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Authors

Wang, Xin

Sundermann, Erin

Buckley, Rachel

et al.

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Sex Differences in the Associations of Obesity with Tau, Amyloid PET, and Cognitive Outcomes in Preclinical Alzheimer's Disease: Cross-Sectional A4 Study

Xin Wang[a], **Erin E. Sundermann**[b], **Rachel F. Buckley**[c], **Emilie T. Reas**[a], **Linda K. McEvoy**[d,e], **Sarah J. Banks**[a,b,*] **on behalf of the A4 Study Team1**

[a]Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA

[b]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

[c]Department of Neurology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

[d]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA, USA

[e]Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA

Abstract

Background: The association between obesity and Alzheimer's disease (AD) is complex. Recent studies indicated the relationships between obesity and AD may differ by sex, and women may benefit from being overweight in terms of AD risk.

Objective: We investigated whether sex modifies the associations of obesity with tau positron emission tomography (PET), amyloid PET, and cognition in preclinical AD.

Methods: We included 387 cognitively-unimpaired amyloid-positive participants (221 women, 166 men, 87.6% non-Hispanic White) with available ^{18}F-flortaucipir PET, ^{18}F-florbetapir PET, and completed the Preclinical Alzheimer Cognitive Composite (PACC) tests from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study. Participants were categorized based on body mass index (BMI: kg/m^2): normal-weight (BMI: 18.5–25), overweight (BMI: 25–30), and obese (BMI ≥ 30).

Results: Significant sex by BMI category interactions on PACC and its components: Mini-Mental State Examination (MMSE) and Reminding Test–Free+Total Recall (FCSRT96) revealed that overweight and obese women outperformed normal-weight women on FCSRT96, while obese men showed poorer MMSE performance than normal-weight men. These interactions were

*Correspondence to: Sarah J. Banks, University of California, San Diego, 9500 Gilman Drive, m/c 0841, La Jolla, CA 92093, USA. sbanks@health.ucsd.edu.

[1]Full listing of A4 Study team and site personnel available at A4STUDY.org.

CONFLICT OF INTEREST

Erin Sundermann is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. All other authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

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independent of *APOE4*. There were no significant interactions of sex by BMI category on tau and amyloid PET. However, sex-stratified analyses observed obesity was associated with less regional tau and mean cortical amyloid in women, not in men.

Conclusion: This study found that in preclinical AD, overweight and obesity were associated with better verbal memory in women, whereas obesity was associated with worse global cognition among men. Future studies focusing on the mechanism for this relationship may inform sex-specific interventions for AD prevention.

Keywords

Alzheimer's disease; cognition; obesity; overweight; sex differences

INTRODUCTION

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease and one of the leading causes of death in the United States [1]. AD features a decades-long "silent" or preclinical stage when pathological changes are present but clinical symptoms are not yet apparent. Specifically, as amyloid-β aggregates in the form of diffuse interneuronal plaques, pathological tau accumulation in the form of neurofibrillary tangles begins to spread in the medial temporal lobes and beyond [2]. This preclinical period is an important target for interventions aimed at modifiable risk factors of AD before significant cognitive loss.

Obesity is another major health issue in the United States and is associated with many chronic diseases, including diabetes, heart disease, and sleep apnea [3]. The associations between obesity and AD are quite complex. Higher body mass index (BMI) in midlife is associated with greater decreases in cognitive function with age [4], increased cortical thinning in AD-vulnerable regions [5], as well as increased risk of AD in late life [6]. Paradoxically, overweight and obesity in late life have been associated with better cognitive performance [7] and reduced risk of incident AD [8]. Higher late-life BMI has also been associated with lower cortical amyloid burden [9]. These associations have been reported to be related to frailty which is characterized by weight loss [10] and less physical activity [11] and associated with higher incidences of AD and cognitive decline in the elderly [12].

There are important sex differences in obesity and AD. The prevalence of both obesity and AD is higher among older women than older men [13]. Furthermore, in AD, women maintain their advantage in verbal memory performance over men during the prodromal phase of the disease, and lose the advantage only with more advanced AD pathology [14]. Women also exhibit higher regional tau burden than men all along the AD continuum [15, 16]. A few studies have investigated the sex-specific relationships between obesity and AD-related outcomes. In older women, obesity has been associated with slower hippocampal volume loss, ventricle enlargement [17], and lower risk of cognitive impairment [18]. Rahmani and colleagues have reported that with increasing BMI, women showed higher regional white matter (WM) connectivity while men displayed lower regional WM connectivity [19]. Until now, there have been no studies investigating sex differences in the associations of obesity with tau PET and amyloid PET in preclinical AD.

This study aims to investigate potential sex differences in the associations between BMI and AD characteristics including tau PET, amyloid PET and cognitive outcomes among amyloid-positive older adults with unimpaired cognition from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study. We hypothesized that overweight/obese people would show less regional tau PET, cortical amyloid PET or better cognitive performance, and that these associations would be different between men and women. Specifically, we hypothesized that among women, overweight/obesity would be associated with less AD pathology or better cognitive outcomes whereas men would show inverse associations.

METHODS

Participants

We included 389 cognitively unimpaired, amyloid-positive (Aβ+) individuals who had available BMI data, ^{18}F-flortaucipir (FTP) PET data and ^{18}F-florbetapir (FBP) PET data, and completed the Preclinical Alzheimer Cognitive Composite (PACC) tests from the A4 study. Participants completed the PACC at their first visit and then underwent FBP PET scans for the classification of amyloid status before enrollment at their second visit. Tau PET scans were acquired at their fourth visit. BMI was calculated by dividing weight (kg) by the square of height (m^2), measured at the first visit. Participants were categorized based on BMI: normal (BMI: 18.5–25), overweight (BMI: 25–30) and obese (BMI ≥ 30). Two participants (1 woman: age: 66.31, 1 man: age: 79.77) whose BMI was less than 18.5 were excluded, leaving a final analytic sample of 387.

Image processing

The preprocessed FTP PET images were downloaded from the Laboratory of Neuro Imaging website (ida.loni.usc.edu). FTP PET data were acquired at 80–110 min (6 x 5 min frames) after tracer injection. Preprocessed FTP PET images were realigned, summed, and coregistered to the corresponding bias-corrected T1 scans created by Freesurfer (version 5.30). Standardized uptake value ratio (SUVR) images were created using the inferior cerebellum grey matter as the reference region. The entorhinal cortex was the regions of interest (ROIs), because this region shows early signs of tau accumulation. Amyloid PET data were downloaded from the A4 website. Mean cortical amyloid SUVR was calculated using the whole cerebellum grey matter as the reference region. Determination of amyloid eligibility has been described elsewhere [20]. Briefly, it was made using an algorithm incorporating both quantitative (Amyloid SUVR > 1.15) and qualitative (visual read) reviews.

Cognitive tests

The PACC is a composite of multi-domain neuropsychological tests and is the primary outcome of the A4 study. The PACC includes four tests: Mini-Mental State Examination (MMSE, range 0–30), Logical Memory Delayed Recall (LMDR, range 0–25), Digit-Symbol Coding Test (DSC, range 0–93), and the Free and Cued Selective Reminding Test–Free+Total Recall (FCSRT96, range 0–96). The total score is calculated as the sum of the

normalized z-scores of these four measures [21]. The cognitive outcome in this study was PACC and its components.

Statistical analyses

Age and education differences between men and women were compared using independent t-tests. Pearson's chi-squared tests were used to assess sex differences in race, *APOE4* carriership, and BMI category. Sex differences in regional tau SUVR, mean cortical amyloid SUVR, and cognitive outcomes were assessed using multiple linear regression models, adjusting for age, education, and race. Linear regression model was used to assess the associations of BMI category with regional tau SUVR, mean cortical amyloid SUVR, and cognitive outcomes in the whole sample (normal-weight as reference, overweight and obese as two dummy variables), adjusting for sex, age, education, and race. Linear regression models assessed the interaction of sex by BMI category on regional tau SUVR, mean cortical amyloid SUVR, and cognitive outcomes, adjusting for age, education, and race. Significant sex by BMI category interactions were probed by conducting linear regression models in men and women separately, adjusting for age, education, and race. Analyses were repeated with the additional adjustment for *APOE4* carriership after excluding participants with unavailable *APOE* data ($n = 7$).

We performed several sensitivity analyses: 1) including both Aβ+and amyloid-negative (Aβ−) participants, with additional adjustment for amyloid status; 2) restricting the sample to Aβ+non-Hispanic White (NHW) samples, removing race as a covariate, because prior studies have suggested racial differences in obesity and in AD risk factors [22, 23].

In all analyses, we compared tau, amyloid pathology and cognitive function, so p values of < 0.017 (0.05/3) were considered significant following Bonferroni correction for multiple comparisons. All analyses were performed in R (version 4.0.4).

RESULTS

Participants

Men were on average older, more educated, and more likely to identify their race as Asian than women. There were no sex differences in *APOE4* carriership or continuous BMI. The proportion of overweight individuals was higher in men than women whereas the proportions of normal-weight and obese individuals were higher in women than men. Women outperformed men on PACC, MMSE, DSC, and FCSRT96 ($ps < 0.001$) (Table 1).

Association of BMI category with AD biomarkers and cognitive outcomes in the overall sample

Overweight people showed less tau SUVR in the entorhinal region (overweight: β=−0.057, SE = 0.022, $p = 0.010$) compared to normal-weight individuals (Fig. 1A and Supplementary Table 1). Overweight and obese were also associated with low mean cortical amyloid SUVR (overweight: β=−0.056, SE = 0.021, $p = 0.01$; obese: β=−0.061, SE = 0.023, $p = 0.007$) (Fig. 1B and Supplementary Table 1). For cognitive outcomes, we only observed obese people showed better LMDR scores than normal-weight individuals (obese: β=−0.896, SE

= 0.442, $p = 0.043$; Fig. 1E; Supplementary Table 1). However, this association did not survive multiple comparisons correction. After controlling for *APOE4* status, obese people still showed less mean cortical amyloid SUVR than normal-weight people (Supplementary Table 1).

Moderating role of sex in the associations of BMI category with tau, amyloid PET, and cognitive outcomes

We observed significant interaction effects of BMI category and sex on the PACC (obese: interaction β=1.670, SE = 0.662, $p = 0.012$) (Table 2). Specifically, significant interaction effects existed on the components: MMSE (obese: interaction β=0.994, SE = 0.340, $p = 0.004$) and FCSRT96 (overweight: interaction β=1.451, SE = 1.451, $p = 0.004$; obese: interaction β=4.210, SE = 1.562, $p = 0.007$) (Table 2). The results were similar after controlling for *APOE4* status (Table 2).

To interpret the interaction results, we stratified the sample by sex and compared the outcomes among BMI categories. Obese men showed poorer MMSE performance than normal-weight men while there was no difference in MMSE between BMI category among women (Fig. 2D). Overweight and obese women showed better performance in FCSRT96 than normal-weight women and there were no significant differences among men (Fig. 2G). Adjusting for *APOE4* attenuated these associations (Supplementary Table 2). There were no significant PACC differences between BMI categories in either women or men; however, the estimates of overweight and obesity in women were positive while the ones in men were negative (Supplementary Table 2), suggesting being overweight and obese might be trend-associated with higher PACC in women and lower PACC in men.

We did not detect significant interactions of sex and BMI category on tau SUVR in the entorhinal region and mean cortical amyloid SUVR ($ps > 0.05$) (Table 2). However, after sex stratification, we observed that overweight and obese women showed less tau SUVR in the entorhinal region than normal-weight women but no differences among men (Fig. 2A and Supplementary Table 2). Obese women also showed less mean cortical amyloid SUVR (Fig. 2B and Supplementary Table 2). In the sex-stratified analyses, adjustment for *APOE4* attenuated the associations, and only the difference in mean cortical amyloid SUVR between obese and normal-weight women remained significant after multiple comparison corrections (Supplementary Table 2).

Sensitivity analyses

We performed sensitivity analyses by additionally including Aβ− participants (Aβ−: $N = 55$; in total: $N = 442$). The results were similar with significant sex by BMI category interaction effects on PACC, MMSE, and FCSRT96 (Supplementary Tables 3 and 4).

Previous findings have reported the racial and ethical disparities in education, sex proportion, marital status [24], and amyloid burden [25] in the A4 study. We also found racial differences in BMI, with Black ($n = 11$): 30.70 ± 6.38 kg/m^2 > NHW ($n = 339$): 27.66 ± 4.85 kg/m^2 > Asian ($n = 18$): 23.46 ± 2.65 kg/m^2 among Aβ+participants in this study. Thus, we also conducted sensitivity analyses limited to the largest race/ethnicity sample, NHW with Aβ+($N = 339$). Besides the significant interaction effects on MMSE

and FCSRT96, we also found sex by BMI category interaction effects on tau SUVR in the entorhinal region (Supplementary Table 5). However, it did not survive multiple comparison adjustments. The sex-stratified comparison showed that among NHW, obesity was associated with less tau burden in the entorhinal region and less mean cortical amyloid burden only in women, not in men (Supplementary Table 6).

DISCUSSION

The relationship between obesity and AD is complex. In this cross-sectional study, we assessed the sex differences in the association of late-life obesity with AD pathology and cognitive performance in preclinical AD. Firstly, among Aβ+older people with normal cognition, without sex-stratification, we found that overweight/obese individuals showed lower tau PET and less cortical amyloid burden compared to normal-weight people. Next, we found the relationships between obesity and cognitive function differed by sex. Specifically, overweight or obese women showed better verbal memory than normal-weight women. In contrast, obese men performed worse on verbal memory and global cognition compared to normal-weight men. Lastly, we confirmed these findings among cognitively normal aging participants regardless of amyloid status and also restricting NHW individuals with Aβ+. These sex-specific associations are consistent with previous findings that, in women, overweight or obesity has been associated with a lower incidence of dementia (age: 70.2 ± 5.9 years) and better cognitive performance (aged ≥ 65 years) [18, 26]. Additionally, increasing BMI has been associated with higher regional white matter connectivity (age: 69.2 ± 8.3 years) [19]. These results suggest that late-life high BMI might be related to cognitive benefits in women and worse cognitive ability in men. Sex thus appears to be an important modifier in associations of obesity with cognitive function, yet it is often treated as a confounder in research on obesity and AD. This might be one of the reasons for inconsistent findings in the relationship between obesity and AD.

Obesity and AD are both influenced by genetic and environmental factors. A previous study has reported shared genetic variants associated with both cognition and BMI [27]. *APOE4,* the strongest genetic risk factor for sporadic AD, has also been associated with BMI [28]. Multiple studies reported the interaction effects between *APOE4* and obesity on AD [29, 30]. In this study, we did not find significant interaction effects between BMI category and *APOE4* on AD pathologies or cognition. However, all analyses in this study were repeated by additionally adjusting for *APOE4* carriership. Although this attenuated some associations, the interaction effects between BMI category and sex on cognitive outcomes remained significant in this study, suggesting the sex-specific relationships of overweight and obesity with cognition might be *APOE4* independent.

The mechanism of sex differences in the associations between obesity and AD is unknown. Prior research has shown that lower testosterone levels might contribute to higher levels of CSF p-tau and poor cognitive performance [31, 32]. Testosterone is negatively associated with BMI in men but positively associated with BMI in women [33]. The opposite relationships might explain the sex differences in the associations between obesity and AD. Estrogen may also play a role in sex-specific associations. Previous studies have reported that estrogen could protect against cognitive aging in postmenopausal women [34] and

estrone and estradiol levels were about 40% higher in obese versus normal-weight women in postmenopause [35]. Another possible explanation might be related to body fat distribution. Men predominantly store visceral fat [36] which has been associated with high dementia risk [37], while women are more likely to store subcutaneous fat which has been reported to have protective effects for the brain [36, 38]. The post-menopausal increase in metabolic syndrome is a further complication, due to its implications for cerebrovascular health [39]. The paradoxical positive association between obesity and cognition in women is not well understood. The causal relationship between late-life obesity and AD is also unknown. Weight loss has been reported to precede the diagnosis of dementia in women, not in men [40]. Future studies are still needed to explore this.

When restricting to only NHW participants, in addition to the cognitive findings, we also found associations between BMI category and regional tau PET differed by sex. Obese women showed less tau PET signal in the entorhinal cortex than women with normal weight whereas there were no tau PET differences between BMI categories among men. However, these findings must be interpreted cautiously as the interaction effects did not survive multiple comparison corrections. Future studies with larger, more diverse samples are needed to examine the sex-specific associations between obesity and tau findings, and explore possible differences by race/ethnicity.

There were limitations to this study. First, there are no longitudinal data available to detect the causal relationship between BMI and tau PET and cognition. Secondly, BMI is not a perfect measurement for obesity status, other measures assessing obesity such as waist-hip ratio and waist circumstances might be more informative. Furthermore, the BMI data and imaging data collection have several months apart. The associations between them should be interpreted cautiously. Additionally, the participants of this study were predominantly NHW, thus results may not generalize to the overall population. Future studies should examine these associations in other groups. In addition, tau PET data in this study were not corrected for partial volume effects which might decrease the sensitivity of association analysis.

Taken together, we identified sex differences in the associations between overweight/obesity and cognition in preclinical AD. Overweight and obese BMI was associated with better verbal memory in women, whereas obese men were associated with poor cognition. More research is needed to confirm these findings. Future studies focusing on the mechanism for these relationships may inform sex-specific interventions for AD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The A4 Study is a secondary prevention trial in preclinical Alzheimer’s disease, aiming to slow cognitive decline associated with brain amyloid accumulation in clinically normal older individuals. The A4 Study is funded by a public-private-philanthropic partnership, including funding from the National Institutes of Health-National Institute on Aging, Eli Lilly and Company, Alzheimer’s Association, Accelerating Medicines Partnership, GHR Foundation, an anonymous foundation and additional private donors, with in-kind support from Avid and Cogstate. The companion observational Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) Study is funded by the Alzheimer’s Association and GHR Foundation. The A4 and LEARN Studies are led by Dr. Reisa

Sperling at Brigham and Women's Hospital, Harvard Medical School and Dr. Paul Aisen at the Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California. The A4 and LEARN Studies are coordinated by ATRI at the University of Southern California, and the data are made available through the Laboratory for Neuro Imaging at the University of Southern California. The participants screening for the A4 Study provided permission to share their de-identified data in order to advance the quest to find a successful treatment for Alzheimer's disease. We would like to acknowledge the dedication of all the participants, the site personnel, and all of the partnership team members who continue to make the A4 and LEARN Studies possible. The complete A4 Study Team list is available on: a4study.org/a4-study-team.

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DATA AVAILABILITY

Data used in preparation of this manuscript were obtained from the LONI database (ida.loni.usc.edu).

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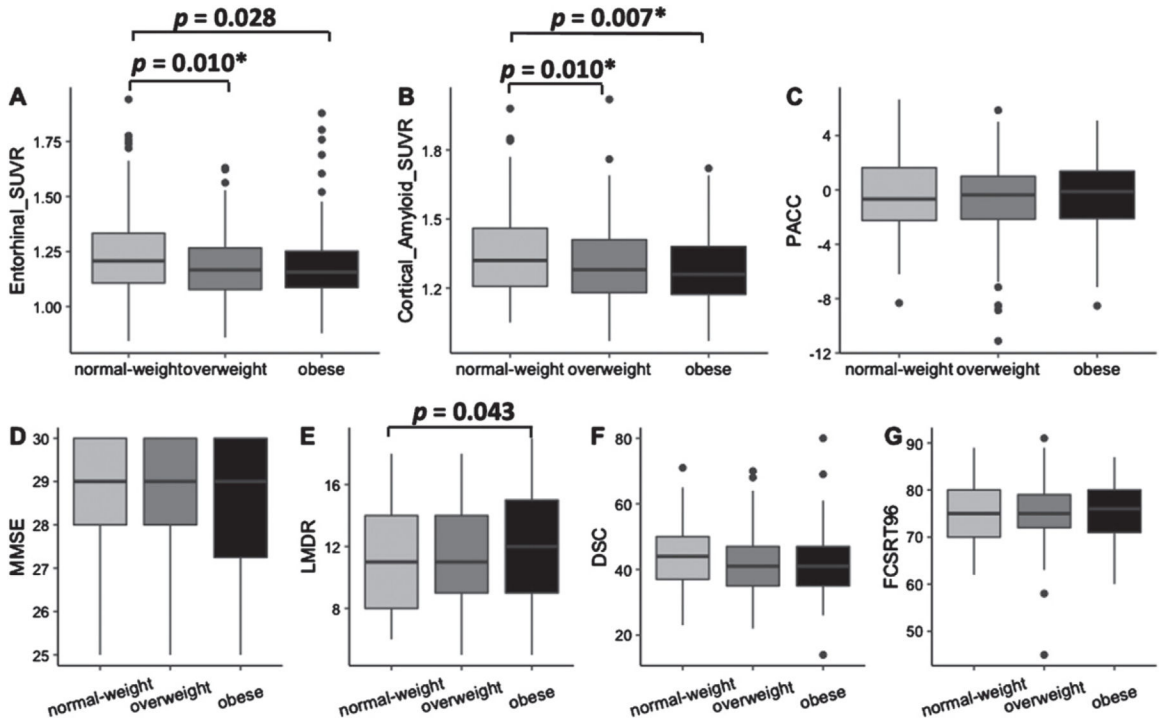

Fig. 1.

Boxplots showing the comparison of A) tau SUVR in the entorhinal region, B) mean cortical amyloid SUVR, C) PACC, D) MMSE, E) LMDR, F) DSC, G) FCSRT96 between BMI category. SUVR, Standardized Uptake Value Ratio; PACC, Preclinical Alzheimer Cognitive Composite; MMSE, Mini-Mental State Examination; LMDR, Logical Memory Delayed Recall; DSC, Digit-Symbol Coding Test; FCSRT96, Free and Cued Selective Reminding Test–Free+Total Recall. $p < 0.05$: bold; *p<0.017; **p<0.005.

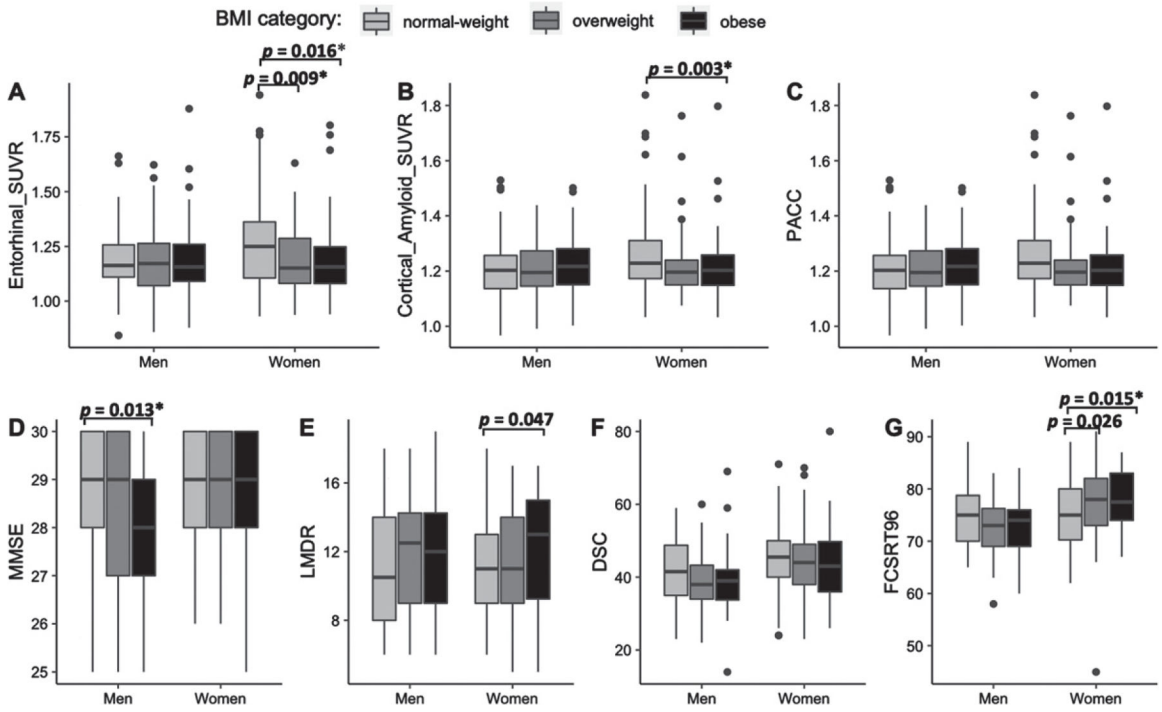

Fig. 2.

Boxplots showing the comparison of A) tau SUVR in the entorhinal region, B) mean cortical amyloid SUVR, C) PACC, D) MMSE, E) LMDR, F) DSC, G) FCSRT96 between BMI category grouped by sex. SUVR, Standardized Uptake Value Ratio; PACC, Preclinical Alzheimer Cognitive Composite; MMSE, Mini-Mental State Examination; LMDR, Logical Memory Delayed Recall; DSC, Digit-Symbol Coding Test; FCSRT96, Free and Cued Selective Reminding Test–Free+Total Recall. $p < 0.05$: bold; *p<0.017; **p<0.005.

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Table 1

Participants characteristics

	All (*N* = 387)		Men (*N* = 166)		Women (*N* = 221)		*p*
Age, mean (SD)	72.2 (4.8)		73.2 (4.9)		71.4 (4.6)		**<0.002** **
Education, mean (SD)	16.1 (2.8)		16.8 (2.9)		15.6 (2.7)		**<0.001** **
APOE4 Carriers, N (%)	380		161		219		0.609
	217 (57.1)		89 (55.3)		128 (58.4)		
Race, N (%)	1	3 (0.8)	1	0 (0.0)	1	3 (1.4)	**0.004** **
	2	18 (4.7)	2	15 (9.0)	2	3 (1.4)	
	3	11 (2.8)	3	6 (3.6)	3	5 (2.3)	
	4	353 (91.2)	4	144 (86.7)	4	209 (94.6)	
	5	2 (0.5)	5	1 (0.6)	5	1 (0.5)	
BMI, kg/m^2	27.7 (5.0)		27.5 (4)		27.8 (5.7)		0.609
BMI_category, N (%)	Normal-weight	132 (34.1)	Normal-weight	50 (30.1)	Normal-weight	82 (37.1)	**0.048** *
	Overweight	141 (36.4)	Overweight	72 (43.4)	Overweight	69 (31.2)	
	Obese	114 (29.5)	Obese	44 (26.5)	Obese	70 (31.7)	
Mean cortical Amyloid SUVR	1.317 (0.176)		1.323 (0.176)		1.313 (0.176)		0.886
Entorhinal_SUVR, mean (SD)	1.205 (0.175)		1.189 (0.163)		1.217 (0.182)		0.064
PACC	−0.60 (2.77)		−1.41 (2.76)		0.01 (2.62)		**<0.001** **
MMSE	28.59 (1.33)		28.34 (1.48)		28.78 (1.18)		**0.001** **
LMDR	11.42 (3.37)		11.42 (3.54)		11.42 (3.25)		0.640
DSC	42.25 (9.27)		39.62 (8.37)		44.23 (9.43)		**<0.001** **
FCSRT96	75.38 (6.32)		73.54 (5.66)		76.76 (6.29)		**<0.001** **

Race: 1: American Indian or Alaskan Native; 2: Asian; 4: Black or African American; 5 = White; 6 = Unknown or Not Reported. BMI, body mass index; SUVR, Standardized Uptake Value Ratio; PACC, Preclinical Alzheimer Cognitive Composite; MMSE, Mini-Mental State Examination; LMDR, Logical Memory Delayed Recall; DSC, Digit-Symbol Coding Test; FCSRT96, Free and Cued Selective Reminding Test–Free+Total Recall.

* $p<0.05$

** $p<0.005$.

Table 2

Interaction coefficients of BMI categories by sex on tau, amyloid and cognitive outcomes

		Not controlling for *APOE4*			Controlling for *APOE4*		
		β	**SE**	***p***	**β**	**SE**	***p***
Tau SUVR (entorhinal region)	Overweight * sex (female)	–0.078	0.043	0.069	–0.070	0.043	0.105
	Obese * sex (female)	–0.087	0.046	0.060	–0.084	0.046	0.068
Mean cortical amyloid SUVR	Overweight * sex (female)	–0.015	0.042	0.721	0.003	0.041	0.938
	Obese * sex (female)	–0.084	0.045	0.064	–0.064	0.044	0.144
PACC	Overweight * sex (female)	1.281	0.615	**0.038**	1.210	0.619	0.051
	Obese * sex (female)	1.670	0.662	**0.012** *	1.634	0.666	**0.015** *
MMSE	Overweight * sex (female)	0.650	0.316	**0.041**	0.551	0.320	0.086
	Obese * sex (female)	0.994	0.340	**0.004** **	0.962	0.344	**0.005** *
LMDR	Overweight * sex (female)	–0.572	0.826	0.489	–0.648	0.836	0.439
	Obese * sex (female)	0.377	0.889	0.672	0.239	0.900	0.791
DSC	Overweight * sex (female)	1.998	2.080	0.337	2.347	2.121	0.269
	Obese * sex (female)	0.192	2.239	0.932	0.374	2.283	0.870
FCSRT96	Overweight * sex (female)	4.147	1.451	**0.004** **	4.116	1.466	**0.005** *
	Obese * sex (female)	4.210	1.562	**0.007** *	4.287	1.578	**0.007** *

SUVR, Standardized Uptake Value Ratio; PACC, Preclinical Alzheimer Cognitive Composite; MMSE, Mini-Mental State Examination; LMDR, Logical Memory Delayed Recall; DSC, Digit-Symbol Coding Test; FCSRT96, Free and Cued Selective Reminding Test–Free+Total Recall. $p < 0.05$: bold

* $p<0.017$

** $p<0.005$.