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Serum Adiponectin Levels, Neuroimaging, and Cognition in the Mayo Clinic Study of Aging

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Abstract

BACKGROUND—Adiponectin, a protein involved in inflammatory pathways, may impact the development and progression of Alzheimer’s disease (AD). Adiponectin levels have been associated with mild cognitive impairment (MCI) and AD; however, its association with Alzheimer-associated neuroimaging and cognitive outcomes is unknown.

OBJECTIVE—Determine the cross-sectional association between plasma adiponectin and neuroimaging and cognitive outcomes in an older population-based sample.

METHODS—Multivariable adjusted regression models were used to investigate the association between plasma adiponectin and hippocampal volume (HVa), PiB-PET, FDG PET, cortical thickness, MCI diagnosis, and neuropsychological test performance. Analyses included 535 non-demented participants aged 70 and older enrolled in the Mayo Clinic Study of Aging.

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RESULTS—Women had higher adiponectin than men (12,631 ng/mL vs. 8,908 ng/mL, $P < .001$). Among women, higher adiponectin was associated with smaller HVa ($B = -0.595$; 95% CI $-1.19, -0.005$), poorer performance in language ($B = -0.676$; 95% CI $-1.23, -0.121$) and global cognition ($B = -0.459$; 95% CI $-0.915, -0.002$), and greater odds of a MCI diagnosis ($OR = 6.23$; 95% CI $1.20, 32.43$). In analyses stratified by sex and elevated amyloid (PiB-PET SUVR > 1.4), among women with elevated amyloid, higher adiponectin was associated with smaller HVa ($B = -0.723$; 95% CI $-1.43, -0.014$), poorer performance in memory ($B = -1.02$; 95% CI $-1.73, -0.312$), language ($B = -0.896$; 95% CI $-1.58, -0.212$), and global ($B = -0.650$; 95% CI $-1.18, -0.116$) cognition, and greater odds of MCI ($OR = 19.34$; 95% CI $2.72, 137.34$).

CONCLUSION—Higher plasma adiponectin was associated with neuroimaging and cognitive outcomes among women. Longitudinal analyses are necessary to determine whether higher adiponectin predicts neurodegeneration and cognitive decline.

Currently, there is no cure or disease modifying treatment for Alzheimer's disease (AD), which continues to be one of the leading public health challenges in a rapidly aging global population [1]. A number of potentially modifiable conditions including cardiovascular diseases, obesity, and type II diabetes mellitus have been associated with risk of AD through inflammatory pathways and insulin resistance [2, 3]. Adiponectin is a protein that is released from adipose (and other) tissues, and is involved in inflammatory pathways [4, 5], and insulin sensitivity [6, 7]. Perturbations in adiponectin levels have been hypothesized to contribute to the development of AD through metabolic and inflammatory changes including insulin dysregulation, mitochondrial dysfunction [8], and down regulation of brain derived neurotrophic factor [9].

Studies have reported associations between adiponectin and all-cause dementia, AD, or mild cognitive impairment (MCI) [10–13]. A case-control study reported that AD and MCI patients had higher plasma levels of adiponectin compared to cognitively normal individuals. MCI and AD patients also had higher cerebrospinal fluid (CSF) levels of adiponectin compared to cognitively normal individuals, but the difference was only significant between the MCI and cognitively normal groups [12]. A large-scale longitudinal study using the Framingham data found that higher plasma adiponectin levels were associated with risk of developing both all-cause dementia and AD in women, but not men [13]. This latter finding is interesting in the context that women have higher plasma levels of adiponectin than men [14], and that recent studies highlight sex differences in the risk of AD [15].

While previous studies have investigated the association between adiponectin and risk of MCI and dementia [10–13], the relationship between adiponectin and neuroimaging measures of AD pathology have not been examined. AD is accompanied by a number of brain changes and pathologies, including formation of beta-amyloid ($A\beta$) plaques and neurofibrillary tangles, hippocampal atrophy, and cortical thinning in AD signature regions (ie, the entorhinal cortex and inferior temporal cortex) [16]. However, it is not understood whether adiponectin is associated with increasing amyloid or neurodegeneration and how it might be best utilized as a biomarker for AD. In this study, we examined the cross-sectional association between plasma adiponectin and magnetic resonance imaging (MRI) and amyloid- and FDG-positron emission tomography (PET) imaging outcomes, as well as

cognition, among non-demented participants aged 70 and older enrolled in the Mayo Clinic Study of Aging (MCSA).

Methods

Participants

The data utilized for the current analyses included participants enrolled in the MCSA, a prospective population-based study aimed at characterizing the incidence and prevalence of MCI in Olmsted County, Minnesota [17]. In 2004, Olmsted County residents between the ages of 70 and 89 were identified for recruitment using an age- and sex-stratified random sampling design to ensure that men and women were equally represented in each 5-year age strata. The present study included 535 participants aged 70 years and older without dementia, who at a concurrent visit, had plasma adiponectin levels and neuroimaging including MRI, fludeoxyglucose (FDG)-PET, and amyloid PET.

The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

Participant Assessment

MCSA visits included a physician examination, an interview by a study coordinator, and neuropsychological testing [17]. The physician examination included a medical history review, complete neurological examination, and administration of the Short Test of Mental Status [18]. The study coordinator interview included demographic information, medical history and questions about memory to both the participant and an informant using the Clinical Dementia Rating (CDR) scale [19].

The neuropsychological battery was administered by a psychometrist and included nine tests covering four domains: 1) **memory** (Auditory Verbal Learning Test Delayed Recall Trial [20]; Wechsler Memory Scale-Revised Logical Memory II & Visual Reproduction II) [21]; 2) **language** (Boston Naming Test [22] and Category Fluency [23]; 3) **executive function** (Trail Making Test B [24] and WAIS-R Digit Symbol subtest [25]; and 4) **visuospatial skills** (WAIS-R Picture Completion and Block Design subtests) [25].

Diagnostic Determination

For each participant, cognitive performance in each domain was compared with the age-adjusted scores of cognitively normal individuals previously obtained using Mayo's Older American Normative Studies [26]. This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Participants with scores ≥ 1.5 SD below the age-specific mean in the general population were considered for a diagnosis of possible MCI. A final decision to diagnose MCI was based on a consensus agreement between the study coordinator, examining physician, and neuropsychologist who evaluated the participant, after taking into account education, prior occupation, visual or hearing deficits, and reviewing all other participant clinical information [17]. Individuals who performed in the

normal range and did not meet criteria for MCI or dementia, which was diagnosed using DSM-IV criteria [27], were deemed cognitively normal.

Primary Exposure: Laboratory Analyses of Adiponectin

During the in-clinic exam, participants' blood (serum and EDTA plasma) was collected after an overnight fast. The blood was centrifuged, aliquoted, and stored at -80°C . Total adiponectin levels were measured using the Human Adiponectin double antibody radioimmunoassay kit (Linco Research, Inc, St. Louis, MO 63304). Intra-assay coefficients of variability were 17%, 4.7%, and 7.3% at standard levels of 5.1, 29.9, and 119 ng/mL, respectively.

Imaging Outcomes: Amyloid PET, FDG PET, and MRI

Participants completed MRI and PET scans on the same day; CT was obtained for attenuation correction. Amyloid PET images were performed with C11 Pittsburgh Compound B (PiB) [28], and were obtained 40 to 60 minutes after injection. Standardized uptake value ratios (SUVR) were formed from the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate regions of interest (ROIs) normalized to the entire cerebellum [29, 30]. Amyloid PET was examined as both a continuous and dichotomous variable. Elevated amyloid PET was defined as $\text{SUVR} > 1.40$. This cut point was determined using the 90th percentile from a sample of 75 AD dementia subjects from the Mayo Clinic [29].

FDG PET SUVR was formed from the angular gyrus, posterior cingulate, inferior temporal ROIs normalized to the pons and vermis [31]; images were obtained 30–40 minutes after injection. The amyloid PET images were partially volume corrected, while the FDG PET images were not partially volume correct, because previous evidence has shown that these methods improve diagnostic performance [32–34].

All MRI scans were completed on one of three 3T machines, and cortical surface was parcellated using FreeSurfer version 5.3.0 (<https://surfer.nmr.mgh.harvard.edu/>). Hippocampal volume (HVa) was adjusted for total intracranial volume, using our in-house fully automated imaging processing pipeline [30]. The AD-signature cortical thickness measure was formed from the entorhinal, inferior temporal, middle temporal and fusiform ROIs [35, 36].

Assessment of Covariates

Participants' girth (cm) and hip circumference (cm), and height (cm) and weight (kg) were measured during the in-clinic exam. These measures were used to calculate the waist-to-hip ratio (WHR) and body mass index (BMI), respectively. Medical conditions (e.g., hypertension, diabetes, dyslipidemia) were abstracted from the Rochester Epidemiological Project medical records linkage system. Depressive symptoms were assessed using the Beck Depression Inventory [37]; participants with a score of ≥ 13 were considered to have depression. Apolipoprotein E (APOE) $\epsilon 4$ allele genotyping were performed from a blood draw. Plasma levels of interleukin-6 (IL-6) and tumor necrosis factor (TNF)- α levels were

measured using MesoScale Discovery multiplexed electrochemiluminescence assays on a SECTOR Imager 2400.

Statistical Analyses

Total adiponectin levels were log-transformed to normalize the distribution. Student's t-tests and chi-square analyses were used to examine differences between men and women at baseline. All subsequent analyses were stratified by sex because women had higher plasma levels of adiponectin than men, which is consistent with the literature [14]. Using the mean and standard deviation from the MCSA 2004 enrollment cohort, which excluded subjects with dementia, participant's test scores were converted to z-scores [20]. A global cognitive domain score was created using the z-transformation of the average of the four aforementioned domains.

Both linear and logistic regression models were used to determine the cross-sectional association between plasma adiponectin levels and neuroimaging outcomes. Linear regression models were used to determine the association between adiponectin and HVa, log amyloid PET, FDG PET, and cortical thickness. Logistic regression was used to determine if adiponectin levels were associated with increased odds of MCI. Both linear and logistic regression models were adjusted for multiple covariates based on the literature and their association with adiponectin. Model 1 was adjusted for age and education; Model 2 was adjusted for age, education, WHR, diabetes, hypertension, and the APOE ϵ 4 allele. We also stratified by elevated amyloid status in the fully adjusted model to determine whether amyloid modifies the association between adiponectin and either neurodegenerative or cognitive outcomes. All analyses were completed using Stata Version 12.0 (StataCorp, College Station, TX).

Results

Participant Characteristics

Characteristics of the participants at the time of concurrent neuroimaging and plasma adiponectin level measurement, by sex, are shown in Table 1. Briefly, over half of the participants were men (61.3%), median age was 80 years (inter quartile range [IQR] = 77, 84), median education was 14 years (IQR = 12, 16), and median WHR was 0.93 (IQR = 0.87, 0.97) (Table 1). Compared to men, women had significantly higher levels of plasma adiponectin and fewer years of education (Table 1). Women performed better in the memory and attention cognitive domains, while men performed better in the visual-spatial domain. Men had larger HVa and women had greater amyloid deposition. There were no other differences between men and women.

Association Between Adiponectin and Neuroimaging and Cognitive Outcomes by Sex

Among men, higher plasma adiponectin levels were associated with smaller HVa ($B = -0.489$; 95% confidence interval (CI) $-0.884, -0.093$), reduced cortical thickness ($B = -0.103$; 95% CI $-0.186, -0.020$), and reduced cerebral glucose uptake ($B = -0.107$; 95% CI $-0.179, -0.035$) after adjustment for age and education (Table 2). However, after additional adjustment for WHR, diabetes, hypertension, and the APOE ϵ 4 allele in model 2, only the

association between adiponectin and FDG PET ($B = -0.087$; 95% CI $-0.166, -0.008$) remained significant (Table 2). Plasma adiponectin levels were not associated with odds of MCI among men.

Among women, higher adiponectin levels were associated with smaller HVa ($B = -0.595$; 95% CI $-1.19, -0.005$) and poorer cognitive performance in the language ($B = -0.777$; 95% CI $-1.42, -0.138$) and global ($B = -0.729$; 95% CI $-1.40, -0.053$) cognitive domains in multivariate models (Table 2). Higher adiponectin was also associated with greater odds of a MCI diagnosis in the fully adjusted model (OR = 6.23; 95% CI 1.20, 32.43).

Association Between Adiponectin and Neuroimaging and Cognitive Outcomes by Sex and Elevated PiB PET

We next stratified the above analyses by elevated amyloid to determine whether adiponectin was more strongly associated with measures of neurodegeneration or cognition among those with substantial amyloid deposition. Among men, elevated amyloid did not modify the associations between adiponectin and either neuroimaging or cognitive outcomes (Table 3). In contrast, only among women with elevated amyloid was higher plasma adiponectin associated with smaller HVa ($B = -0.723$; 95% CI $-1.43, -0.014$) and poorer scores in the memory ($B = -1.40$; 95% CI $-2.38, -0.422$), language ($B = -1.03$; 95% CI $-1.82, -0.244$), and global ($B = -1.07$; 95% CI $-1.85, -0.288$) cognitive domains. Higher adiponectin was also associated with a greater odds of MCI (OR = 19.34; 95% CI 2.72, 137.34) among women with elevated amyloid, but not among women with lower amyloid levels (OR = 0.112; 95% CI 0.0008, 15.97).

Other Analyses

In sensitivity analyses, we adjusted for BMI instead of WHR and included depression as a covariate but the results not change. We additionally adjusted for two markers of inflammation, IL-6 and TNF α , and similarly found that the results did not change. Lastly, we investigated the interactions between adiponectin and diabetes, adiponectin and the presence of an APOE $\epsilon 4$ allele, adiponectin and obesity, and adiponectin and dyslipidemia. None of these interactions predicted the neuroimaging or cognitive outcomes (results not shown). Diabetes medications were also not associated with adiponectin levels.

Discussion

In this cross-sectional study of participants without dementia, aged 70 and older and enrolled in the MCSA, we found that higher plasma adiponectin levels were associated with neuroimaging markers of neurodegeneration and poorer cognitive outcomes. Notably, there was a sex difference such that higher adiponectin levels were associated with smaller HVa, poorer performance in language, memory and global cognitive domains, and higher odds of MCI among women. Among men, higher adiponectin levels were only associated with reduced cerebral glucose uptake. Further, among women, the adverse effects of high adiponectin had the most detrimental effects on cognition and neurodegeneration among those with elevated amyloid. These results, while cross-sectional, suggest that adiponectin

could be an important predictor of cognitive decline and neurodegeneration among women who are amyloid positive.

Adiponectin, one of the most abundant adipokines in plasma, is a protein that is released from adipose tissue and is thought to play important roles in brain function. It affects inflammatory pathways [4, 5], and is involved in insulin sensitivity and fatty acid catabolism [6, 7]. As such, low blood adiponectin was originally hypothesized to contribute to a reduced risk of AD by regulating metabolic changes including insulin dysregulation, mitochondrial dysfunction [8], and downregulation of brain derived neurotrophic factor [9]. Despite this proposed association, however, high adiponectin levels have been associated with increased mortality and with worse cognition in the elderly, especially among women. For example, the Framingham cohort reported that high baseline plasma adiponectin levels were associated with an increased risk of all-cause dementia and AD over 13 years of follow-up among women [13]. Our results provide further support to these findings, such that elevated adiponectin is associated with worse performance in memory, language, and global cognition, as well as a greater odds of MCI among women. Given the initially proposed benefits of adiponectin, based on cellular and animal studies, one possible explanation for the counterintuitive results is the known elevation of adiponectin levels with weight loss, which typically occurs in the years prior to a diagnosis of dementia. We did adjust for diabetes and WHR or BMI in the models and the results among women remained.

We theorize that the observed sex differences could be related to the interaction between adiponectin and estrogen, which are inversely correlated [38]. Some studies [38], though not all [39], show adiponectin levels increase in post-menopausal women. Due to the neuroprotective role that estrogen plays [40], it may be that this change in balance between adiponectin and estrogen is contributing to the observed association in older women but not older men. Further, evidence suggests that women are more likely to have cognitive impairment than men at the same levels of neuropathology [41]. This may be a reason why we observed an association in women with elevated PiB-PET SUVR, but not men. However, the role of adiponectin in the brain is still not well understood, so additional research must be done to determine the potential mechanisms behind the sex differences observed in this study and others [13].

Few clinical or epidemiological studies have examined the associations between plasma adiponectin and measures of brain amyloid or neurodegeneration. One study of middle- to older-aged type II diabetics found that lower levels of adiponectin were associated with smaller HVa [10]. In contrast, we found that higher levels of plasma adiponectin were associated with smaller HVa among women aged 70 and older. Notably, after stratification by elevated amyloid, the association between higher adiponectin and lower HVa only remained significant among women with elevated amyloid. There was no association between adiponectin and HVa among either men or women with lower amyloid levels. Our results may suggest that the detrimental effects of elevated adiponectin only occur in the presence of substantial amyloid deposition. While replication of this association is clearly needed, this finding could have important implications. First, it could suggest new pathways by which amyloid could be linked to neurodegeneration and cognitive decline. Second, it could also identify when and in whom plasma adiponectin may be best utilized as a

biomarker for AD. Lastly, some studies have proposed adiponectin as a treatment target for AD [42, 43]. The present findings suggest that such a treatment may not be effective after significant brain amyloid deposition, even in the absence of significant cognitive impairment.

This study has many strengths including the large, population-based sample, availability of laboratory measures, and extensive neuroimaging and cognitive measures. However, the findings of this study must be viewed within the scope of its limitations. First, our findings may not be directly generalizable to other populations. In particular, Olmsted County residents are largely of northern European ancestry, thus the reported associations may differ among other racial or ethnic groups. Second, we were only able to measure plasma adiponectin at a single time point. However, previous studies have shown that plasma adiponectin levels are stable over time supporting the measurement of adiponectin at a single visit [44]. Third, we measured total adiponectin, not high molecular weight adiponectin. However, other studies have also measured total adiponectin and found an association between plasma adiponectin levels and cognitive outcomes [13]. Finally, this study was cross-sectional, so causality cannot be inferred. Longitudinal studies are needed to determine the causal association between adiponectin and neuroimaging and cognitive outcomes, and whether amyloid deposition modifies this longitudinal relationship.

Conclusions

Our results, while cross-sectional, suggest that adiponectin could be an important predictor of cognitive decline and neurodegeneration among women who are amyloid positive. Longitudinal studies are needed to further elucidate the temporal association between adiponectin, cognition, and AD pathology. Specifically, to determine at what point in the AD pathological cascade, plasma adiponectin might be most useful as a biomarker of disease progression.

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Table 1

Participant Characteristics

Characteristic	All (n=535)	Men (n=328)	Women (n=207)	P value
Plasma adiponectin, ng/mL, median (IQR)	10 649 (6895, 14 683)	8908 (6070, 13 163)	12 631 (9418, 16 967)	<.001
Age, years, median (IQR)	80 (77, 84)	80 (77, 84)	80 (77, 85)	.16
Waist-to-hip ratio, median (IQR)	0.93 (0.87, 0.97)	0.95 (0.92, 0.99)	0.86 (0.81, 0.92)	<.001
Years of education, median (IQR)	14 (12, 16)	14 (12, 17)	13 (12, 16)	.01
Diabetes, No. (%)	126 (23.6)	84 (25.6)	42 (20.3)	.16
Hypertension, No. (%)	422 (78.9)	262 (79.9)	160 (77.3)	.48
Depression, No. (%)	44 (8)	23 (7)	21 (10)	.19
1 APOE ε4 allele, No. (%)	159 (29.7)	92 (28.0)	67 (32.4)	.29
MCI, No. (%)	150 (28.0)	94 (28.7)	56 (27.1)	.69
Memory, z-score, median (IQR)	0.23 (−0.68, 1.07)	0.005 (−0.81, 0.86)	0.52 (−0.43, 1.30)	.001
Language, z-score, median (IQR)	0.14 (−0.56, 0.75)	0.12 (−0.56, 0.73)	0.17 (−0.60, 0.81)	.26
Attention, z-score, median (IQR)	0.25 (−0.35, 0.86)	0.16 (−0.37, 0.77)	0.39 (−0.32, 1.04)	.04
Visual-spatial, z-score, median (IQR)	0.42 (−0.32, 0.97)	0.51 (−0.19, 1.15)	0.17 (−0.54, 0.78)	<.001
Global, z-score, median (IQR)	0.28 (−0.44, 0.96)	0.31 (−0.47, 0.87)	0.23 (−0.38, 1.09)	.56
HVa, cm ³ median (IQR)	−1.87 (−2.45, −1.21)	−2.03 (−2.62, −1.39)	−1.50 (−2.16, −0.93)	<.001
No. (%) with abnormal Hva	139 (26.0)	108 (32.9)	31 (15.0)	<.001
AD signature thickness, mm, median (IQR)	2.77 (2.65, 2.87)	2.77 (2.65, 2.86)	2.77 (2.64, 2.88)	.83
No. (%) with abnormal AD signature thickness	229 (42.8)	137 (41.8)	92 (44.4)	.58
Amyloid PET, SUVR, median (IQR)	1.51 (1.34, 1.97)	1.46 (1.32, 1.93)	1.59 (1.37, 2.07)	.08
No. (%) with elevated amyloid PET	331 (61.9)	328 (58.5)	139 (67.1)	.046
FDG PET, SUVR, median (IQR)	1.35 (1.25, 1.46)	1.34 (1.25, 1.45)	1.36 (1.25, 1.46)	.84
No. (%) with reduced FDG PET	241 (45.0)	153 (46.6)	88 (42.5)	.35

Abbreviations: Hva, hippocampal volume, adjusted for total intracranial volume; IQR, inter quartile range; MCI, mild cognitive impairment. Depression was defined by a score of 13 on the Beck Depression Inventory.

Linear Regression: Association Between Plasma Adiponectin Levels and Neuroimaging and Cognitive Outcomes by Sex

Table 2

	Model 1			
	<u>Men</u>		<u>Women</u>	
	B (95% CI)	P value	B (95% CI)	P value
<i>Neuroimaging outcomes</i>				
HVa, * cm ³	-0.489 (-0.884, -0.093)	.016	-0.544 (-1.09, 0.002)	.051
AD signature thickness, mm	-0.103 (-0.186, -0.020)	.015	0.003 (-0.105, 0.111)	.951
Amyloid PET, SUVR	0.037 (-0.068, 0.143)	.487	-0.028 (-0.178, 0.122)	.714
FDG PET, SUVR	-0.107 (-0.179, -0.035)	.004	-0.064 (-0.157, 0.029)	.177
<i>Cognitive outcomes</i>				
Memory domain, z-score	0.041 (-0.455, 0.537)	.871	-0.734 (-1.53, 0.063)	.071
Language domain, z-score	0.033 (-0.382, 0.448)	.877	-0.560 (-1.17, 0.053)	.073
Attention domain, z-score	0.165 (-0.229, 0.559)	.411	-0.060 (-0.676, 0.556)	.847
Visual-spatial domain, z-score	-0.060 (-0.474, 0.354)	.775	-0.172 (-0.818, 0.474)	.600
Global cognition, z-score	0.070 (-0.341, 0.480)	.739	-0.549 (-1.19, 0.097)	.095
	Model 2			
	<u>Men</u>		<u>Women</u>	
	B (95% CI)	P value	B (95% CI)	P value
<i>Neuroimaging outcomes</i>				
HVa, * cm ³	-0.154 (-0.558, 0.249)	.453	-0.595 (-1.19, -0.005)	.048
AD signature thickness, mm	-0.067 (-0.153, 0.020)	.131	-0.023 (-0.134, 0.089)	.689
Amyloid PET, SUVR	-0.040 (-0.151, 0.071)	.476	0.009 (-0.148, 0.166)	.909
FDG PET, SUVR	-0.087 (-0.166, -0.008)	.031	-0.080 (-0.181, 0.021)	.120
<i>Cognitive outcomes</i>				
Memory domain, z-score	0.028 (-0.511, 0.566)	.919	-0.769 (-1.59, 0.051)	.066
Language domain, z-score	0.014 (-0.438, 0.465)	.952	-0.777 (-1.42, -0.138)	.017
Attention domain, z-score	0.137 (-0.284, 0.559)	.522	-0.421 (-1.07, 0.232)	.205
Visual-spatial domain, z-score	-0.133 (-0.584, 0.318)	.562	-0.220 (-0.918, 0.479)	.536
Global cognition, z-score	0.062 (-0.384, 0.509)	.783	-0.729 (-1.40, -0.053)	.035

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Model 1 was adjusted for age and education. Men: HVa, n=322; amyloid and FDG, n=324; cortical thickness, n=321; memory, n=322; language, n=316; attention, n=306; visual-spatial, n=308; global, n=301. Women: HVa and cortical thickness, n=203; amyloid and FDG, n=204; memory, n=203; language, n=196; attention, n=197; visual-spatial, n=196; global, n=193. Model 2 was adjusted for age, years of education, waist-to-hip ratio, current diabetes and hypertension, and APOE ε4 status. Men: HVa, n=311; amyloid and FDG, n=313; cortical thickness, n=310; memory, n=312; language, n=306; attention, n=298; visual-spatial, n=300; global, n=293. Women: neuroimaging outcomes, n=199; memory, n=198; language and visual-spatial, n=191; attention, n=192; global, n=188.

* HVa adjusted for total intracranial volume.

Model 2. Association Between Plasma Adiponectin Levels and Neuroimaging and Cognitive Outcomes by Sex and Elevated (PiB-PET SUVR 1.4) Amyloid Level

	<u>Men with Elevated Amyloid</u>		<u>Women with Elevated Amyloid</u>	
	B (95% CI)	P value	B (95% CI)	P value
<i>Neuroimaging outcomes</i>				
HVa, ^a cm ³	-0.279 (-0.836, 0.278)	.324	-0.723 (-1.43, -0.014)	0.046
AD signature thickness, mm	-0.013 (-0.150, 0.124)	.852	0.100 (-0.067, 0.266)	0.238
FDG PET, SUVR	-0.098 (-0.216, 0.019)	.101	-0.054 (-0.186, 0.079)	0.418
<i>Cognitive outcomes</i>				
Memory domain, z-score	0.020 (-0.739, 0.780)	.958	-1.40 (-2.38, -0.422)	0.005
Language domain, z-score	-0.173 (-0.784, 0.438)	.577	-1.03 (-1.82, -0.244)	0.011
Attention domain, z-score	0.347 (-0.222, 0.915)	.231	-0.654 (-1.45, 0.139)	0.105
Visual-spatial domain, z-score	-0.101 (-0.689, 0.488)	.735	-0.196 (-1.03, 0.640)	0.644
Global cognition, z-score	0.048 (-0.546, 0.642)	.873	-1.07 (-1.85, -0.288)	0.008
	<u>Men with Lower Amyloid Levels</u>		<u>Women with Lower Amyloid Levels</u>	
	B (95% CI)	P value	B (95% CI)	P value
<i>Neuroimaging outcomes</i>				
HVa, ^a cm ³	0.080 (-0.537, 0.696)	.799	-0.458 (-1.63, 0.716)	.438
AD signature thickness, mm	0.010 (-0.017, 0.038)	.467	0.022 (-0.030, 0.073)	.403
FDG PET, SUVR	-0.078 (-0.209, 0.054)	.244	0.026 (-0.209, 0.261)	.826
<i>Cognitive outcomes</i>				
Memory domain, z-score	-0.028 (-0.828, 0.772)	.945	0.639 (-0.981, 2.26)	.433
Language domain, z-score	0.194 (-0.492, 0.880)	.576	-0.635 (-1.73, 0.462)	.251
Attention domain, z-score	-0.256 (-0.902, 0.390)	.434	-0.378 (-1.61, 0.857)	.542
Visual-spatial domain, z-score	-0.349 (-1.09, 0.389)	.351	-0.621 (-2.04, 0.795)	.383
Global cognition, z-score	-0.079 (-0.783, 0.624)	.824	-0.351 (-1.68, 0.977)	.598

Models were adjusted for age, years of education, waist-to-hip ratio, current diabetes and hypertension, and APOE ε4 status. A+ Men: neuroimaging outcomes, n=182; memory, n=181; language, n=176; attention, n=171; visual-spatial, n=171; global, n=166. A+ Women: MRI, n=133; memory, n=132; language, n=128; attention, n=130; visual-spatial, n=128; global, n=126. A- Men: HVa, n=129; FDG PET, n=131; cortical thickness, n=128; memory, n=128; language, n=131; attention, n=127; visual-spatial, n=129; global, n=127. A- Women: neuroimaging outcomes, n=66; memory, n=66; language and visual-spatial, n=63; attention, n=62; global, n=62.

*HV_a adjusted for total intracranial volume.

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