Published in final edited form as:

J Alzheimers Dis. 2019 ; 70(4): 995–1004. doi:10.3233/JAD-190092.

Measures of Adiposity and Alzheimer's Disease-Related MRI Markers: The Northern Manhattan Study

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Abstract

Background: Adiposity may increase risk for dementia and Alzheimer's disease (AD), but mechanisms are unclear.

Objective: To examine associations between measures of adiposity with AD-signature region cortical thickness and hippocampal volume.

Methods: We used data from the Northern Manhattan Study, a clinically stroke-free cohort of mostly Hispanic participants. Exposures of interest included body mass index (BMI), waist-hip-ratio (WHR), waist circumference (WC), and adiponectin concentration, measured at study entry. AD-signature region cortical thickness and hippocampal volume were obtained using Freesurfer. We estimated associations using multivariable linear regression, adjusting for sociodemographics and health behaviors. We re-examined estimates after adjustment for *APOE* ϵ 4 allele status or carotid intima-media thickness (cIMT), among those cognitively unimpaired, and after weighting for the inverse probability of selection into the MRI sub-study. We also repeated analyses for cortical thickness in non-AD signature regions.

Results: The sample ($N = 947$, 63% women, 66% Hispanic/Latino, 26% obese) had a mean (SD) age = 63 (8) years. Greater BMI and WC (both z-scored) were associated with thinner AD-signature region cortex (also z-scored) (BMI: β [95% CI] = -0.09 [-0.18 , -0.01], WC: β [95% CI] = -0.11 [-0.20 , -0.02]). We did not find evidence that adiposity was related to hippocampal

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Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/19-0092r2>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-190092>.

volume. Results were consistent after adjustment for *APOE* $\epsilon 4$ allele status or cIMT, after weighting for selection, among those cognitively unimpaired, and for non-AD signature region cortical thickness.

Conclusion: Greater BMI and WC were related to cortical thinning within and outside the AD-signature region, suggesting a global effect not specific to AD.

Keywords

Adiposity; brain aging; epidemiology; neuroimaging; structural MRI

INTRODUCTION

Maintaining brain health is increasingly linked to the management of cardiometabolic disease, including adiposity [1]. Though evidence suggests that adiposity may increase the risk of dementia [2] and Alzheimer's disease (AD) [3], the mechanisms underlying these associations are unclear. Adiposity is related to increased risk for vascular disease, especially hypertension and diabetes, which in turn are related to brain health outcomes [4]. Metabolic changes caused by increased adiposity, such as increased insulin resistance, may explain cortical hypometabolism related to AD risk [5]. Additionally, obesity is associated with a chronic inflammatory state. In particular, adipocytokines are inversely related to body mass index (BMI) and have been shown to exhibit neuroprotective properties [6].

Investigating relationships between different adiposity measures and AD-related imaging biomarkers may provide insight into mechanisms at play, but this literature is limited, especially from large, diverse epidemiologic studies. Data from the Personality and Total Health through Life (PATH) study show that greater adiposity is associated with cortical thinning in AD-related regions [7] and smaller hippocampal volume [8]. However, these data come from a cohort of Australian participants, and thus results may not be generalizable to minority populations in the United States at higher risk for dementia [9].

To examine these associations in a racially/ethnically diverse, US-based, urban sample, we examined the associations between measures of adiposity and AD-signature cortical thickness and hippocampal volume, using data from the Northern Manhattan Study (NOMAS), a diverse, prospective cohort study of brain aging.

MATERIALS AND METHODS

Source and analytic samples

Recruitment of the original NOMAS cohort occurred between 1993 and 2001, as previously described [10]. Potential participants were identified via random digit-dialing and screened for the following eligibility criteria: 1) clinically stroke-free, 2) aged >40 years old, and 3) lived in Northern Manhattan for at least 3 months in a household with a telephone. From 2003 to 2008, participants from the original NOMAS cohort were recruited into the NOMAS Magnetic Resonance Imaging (MRI) Sub-Study. Eligibility criteria for the MRI Sub-Study included: 1) clinically stroke-free, 2) aged >50 years old, and 3) no contraindications to MRI. An additional 199 household members were also recruited. Our

analytic sample consisted of cognitively mixed participants from the NOMAS MRI Sub-Study with cortical thickness and hippocampal volume data ($N = 947$).

Exposures of interest: measures of adiposity

As previously described [11, 12], our four exposures of interest were measured using standardized protocols at study entry and included: BMI, waist-hip-ratio (WHR), waist circumference (WC), and serum adiponectin concentration. BMI was calculated as kilograms divided by height (meters) squared (kg/m^2) and assessed continuously (z-score) and categorically (obese: BMI ≥ 30 , overweight: $25 < \text{BMI} < 30$, and reference: BMI < 25) [13]. Waist and hip circumference was measured in inches with a flexible tape measure as participants stood without wearing heavy outer garments. WC was measured at the level of the umbilicus, while hip circumference was measured at the level of the bilateral greater trochanters. WHR was computed as waist circumference divided by hip circumference. We assessed WC and WHR continuously (z-score) as well as categorically, as presence versus absence of excess central adiposity, defined by WC (WC > 40 inches for men and WC > 35 inches for women [14]) and WHR (men with a WHR > 0.9 and women with a WHR > 0.85 [15]). In a subsample, adiponectin concentrations were measured from stored frozen plasma ($n = 788$) using a commercially available double antibody immunoassay (Linco Research, Millipore, Billerica, MA; Cat # HADP-61HK) [12], and modeled continuously and categorically (reference group: 4th quartile, since adiponectin levels are inversely related to obesity [6]).

Outcomes of interest: Alzheimer's disease-signature region cortical thickness and hippocampal volume

Brain MRIs were obtained at MRI Sub-Study entry on a 1.5T Philips Intera scanner (Philips, Best, the Netherlands) at Columbia University Medical Center and analyzed using Freesurfer version 5.1 (<http://surfer.nmr.mgh.harvard.edu/>). T1-weighted MRIs underwent motion correction, skull stripping, and transformation into Talairach space before segmentation, gray and white matter boundaries identification, and automated topology correction and surface deformation [16]. Cortical parcellation by regions of interest were obtained using the Desikan-Killiany Atlas [17].

Our primary outcomes of interest were AD-signature cortical thickness and hippocampal volume. We computed AD-signature cortical thickness as the mean of the bilateral cortical thickness measurements across the following regions [18] and subsequently z-scored: entorhinal, parahippocampal, inferior temporal, temporal pole, inferior parietal, superior frontal, superior parietal, supramarginal, precuneus, pars opercularis, pars orbitalis, and pars triangularis parcellations. Freesurfer gives an estimate of bilateral hippocampal volume, which we summed and z-scored.

Our secondary outcome of interest was cortical thickness in regions outside the AD-signature. We operationalized non-AD-signature cortical thickness as the mean of the bilateral cortical thickness measurements across the following regions (i.e., regions not included in the AD-signature) and subsequently z-scored: banks of the superior temporal sulcus, caudal anterior cingulate, caudal middle frontal, cuneus, fusiform, isthmus cingulate,

lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, paracentral, pericalcarine, postcentral, posterior cingulate, precentral, rostral anterior cingulate, rostral middle frontal, superior temporal, frontal pole, transverse temporal, and insula.

Measurement of total intracranial volume (TIV) using T1- and fluid-attenuated inversion recovery sequences has been previously described [19]. Briefly, images were sent to the University of California, Davis, and non-brain elements were removed manually by operator-guided tracing of the dura mater within the cranium (including the middle cranial fossa and excluding the posterior fossa and brainstem).

Covariate measurement

Data on medical and risk factor history were obtained using standardized questions adapted from the Behavioral Risk Factor Surveillance System from the CDC [20]. Participants self-identified their race/ethnicity. The difference in years between the NOMAS baseline visit and the MRI visit was computed. Smoking status was self-reported as never (reference), current, or former. Physical activity was measured using a questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics [21]. Moderate-to-heavy physical activity was defined as engaging in one or more physically intense activities within a typical 14-day period as previously described [22]. Moderate alcohol consumption was measured using a modified Block National Cancer Institute Food Frequency questionnaire [23], and defined as current drinking of >1 drink per month up to 2 drinks per day as previously described [24].

Apolipoprotein genotyping was conducted from DNA samples extracted from peripheral white blood cells via *HhaI* digestion and amplified by polymerase chain reaction as previously described [25]. Carotid intima media thickness (cIMT) was measured as previously described [26, 27]. Briefly, cIMT was measured via high-resolution B-mode ultrasound imaging (GE LogIQ 700; 9- to 13 MHz linear-array transducer) by trained and certified sonographers. cIMT was measured in areas without plaque and was calculated as the mean of the maximum measurements at near and far walls of the common carotid artery, bifurcation, and internal carotid artery, bilaterally.

Participants underwent a neurocognitive battery and domain-specific z-scores were computed as previously described [19]. The baseline neuropsychological battery was administered the same day as the cerebral MRI. Executive function was comprised of the Color Trails Forms 1 and 2 [28] (difference in time to complete) and the sum of Odd-Man-Out subtests 2 and 4 [29]. Episodic memory was comprised of scores from three subtests from the Verbal Learning Test: list learning total, delayed recall, and delayed recognition [30]. Semantic memory was comprised of picture naming (modified Boston Naming) test [31], category fluency (Animal Naming) [32], and phonemic fluency test (C, F, L in English speakers and F, A, S in Spanish speakers) [32]. Processing speed was comprised of the Grooved Pegboard task in the non-dominant hand [33] and the Color Trails test Form 1 [28]. Interrelationships between individual neuropsychological test scores were explored using factor analysis and a Scree plot of eigenvalues to determine the number of constructs (i.e., domains) [34]. Raw scores from the neuropsychological battery were transformed into z-

scores using baseline means and standard deviations, and domain-specific composite scores were calculated by averaging these individual z-scores [30, 34]. Cognitive impairment was defined as having at least one domain-specific z-score ≤ -1.5 .

Statistical analysis

This cross-sectional analysis was conducted in SAS 9.4 (SAS Institute, Cary, NC). We compared distributions between those included and excluded from the analysis, between original and household members, and between those with and without adiponectin data using one-way analysis of variance for normally distributed variables, Kruskal-Wallis tests for non-normal variables, and chi-squared tests for categorical variables. We used multivariable linear regression models, adjusting for known confounders of the associations of interest: age, sex, race/ethnicity, years of education, total intracranial volume, years between baseline and MRI, smoking status, moderate-to-heavy physical activity, and moderate alcohol consumption. We further examined potential confounding by *APOE* [H9255]4 allele status or potential mediation by cIMT (as a measure of subclinical atherosclerosis) by adding these covariates to fully-adjusted models. For each outcome, we adjusted confidence intervals for multiple testing using the Bonferroni correction such that the family-wise type I error rate is 5% for each set of hypothesis tests per outcome of interest. Finally, in *post-hoc* analyses, we assessed potential effect modification for our two primary outcomes by race/ethnicity or *APOE* [H9255]4 allele status by adding appropriate two-way interaction terms to fully adjusted models, and stratified analyses if interaction *p*-value < 0.05 .

We ran several sensitivity analyses. First, to evaluate the specificity of our findings to the AD-signature region, we examined the association of adiposity markers with the mean cortical thickness across regions not included in the AD-signature region. Second, since our sample was cognitively mixed, we re-analyzed our data in the sub-sample of cognitively unimpaired participants to account for potential confounding by cognitive status. Third, to account for potential selection bias, we re-ran analyses among original cohort members with generalized estimating equations weighted for the inverse probability of selection into the MRI sub-study. Predicted probabilities of selection were estimated using binary logistic regression models adjusted for the following covariates: age, sex, race/ethnicity, anti-hypertensive medication use, BMI, any physical activity, history of cardiac disease, education level, marital status, diabetes mellitus, hypertension, hypercholesterolemia, diabetes medication use, and cholesterol medication use. Stabilized inverse probability of selection weights were calculated as the predicted probability of selection divided by the predicted probability of selection conditional on covariates and truncated at 1% to further stabilize the weights [35]. Weighted analyses were conducted using generalized estimating equations with an independent correlation structure and robust variance estimators, accounting for the induced within-subject correlation due to the weights [36].

RESULTS

Sample characteristics are displayed in Table 1, stratified by BMI categories. Our analytic sample consisted of 63% women and 66% Hispanics and had a mean age of 63 years (SD =

8) and mean years of education of 10 (SD = 5). Distributions of several exposure, covariate, and outcome variables differed across BMI categories (Table 1). Those excluded from the analysis due to lack of complete imaging data were older, less educated, and generally exhibited worse vascular risk factor burden than those included in the analysis (Supplementary Table 1). Original NOMAS members has slightly lower years of education, a lower proportion of participants with excess adiposity, slightly smaller MRI measures of gray matter metrics and cIMT compared to household members (Supplementary Table 2). Those without adiponectin data had slightly greater years of education, greater proportion of participants with excess central adiposity per WC and who reported moderate alcohol consumption, and slightly greater MRI measures of gray matter metrics and cIMT compared to those with adiponectin data (Supplementary Table 3).

Greater BMI was related to thinner cortices in the AD-signature regions (β [95% CI] = -0.09 [$-0.18, -0.01$]) (Table 2). Similarly, obese and overweight participants exhibited smaller AD-signature cortical thickness, relative to those with BMI <25 (obese: β [95% CI] = -0.20 [$-0.42, 0.03$], overweight: β [95% CI] = -0.12 [$-0.31, 0.08$]), though associations did not reach statistical significance. Associations with BMI differed by race/ethnicity (p for interaction <0.05), and stratified analyses showed that greater BMI was associated with AD-signature cortical thinning particularly in Hispanics and Blacks (Hispanics: β [95% CI] = -0.15 [$-0.23, -0.07$], Blacks: β [95% CI] = -0.11 [$-0.24, 0.03$], and whites: β [95% CI] = 0.04 [$-0.11, 0.19$]).

Greater WC was associated with smaller AD-signature cortical thickness (β [95% CI] = -0.11 [$-0.20, -0.02$]). Additionally, participants with excess central adiposity defined by WC exhibited cortical thinning (β [95% CI] = -0.11 [$-0.29, 0.07$]), though this association did not reach statistical significance. Associations between adiponectin levels or WHR and AD-signature cortical thickness were inconsistent in direction and magnitude and did not reach statistical significance (Table 2). No significant interactions were found with *APOE* $\epsilon 4$ allele status (p interaction >0.05). Estimates were similar to the main analyses when we examined cortical thickness in non-AD-signature regions (Table 2).

Associations between adiposity markers and hippocampal volume were generally close to the null and did not reach statistical significance (Table 2). Estimates were similar to the main analyses after further adjustment for *APOE* $\epsilon 4$ allele status or cIMT (Table 3), in the those without cognitive impairment (Supplementary Table 4), and after re-weighting for selection into the MRI sub-study (Supplementary Table 5).

DISCUSSION

Evidence from the present study shows that greater BMI and WC are associated with cortical thinning in both the AD-signature region and non-AD signature region, suggesting a global effect of adiposity on brain health not specific to AD. Sensitivity analyses among those cognitively unimpaired suggest that confounding by cognitive status is not likely. Finally, sensitivity analyses weighted for inverse probability of selection suggest that selection bias did not substantially affect our results.

Few epidemiologic studies have examined associations between adiposity and AD-specific gray matter structure in the brain, especially cortical thickness. Cortical thickness may be less confounded by surface area than cerebral volume, thus represents a unique biological entity that specifically reflects the number of cells within a neuronal column [37, 38]. Our results are consistent with findings from the PATH study, which found that greater BMI in midlife is associated with thinner cortices in AD-related regions cross-sectionally and over time [7]. However, other studies found opposite associations [39, 40]. One explanation for this difference in findings may be the timing of adiposity measurement, since midlife obesity has been more strongly related to dementia risk compared to late-life obesity [41]. Additionally, the dementia prodrome may be characterized in part by weight loss, further supporting the notion that timing of measurement could explain differences across studies.

Importantly, we also found similar associations when examining cortical thickness in non-AD-signature regions, implying a global mechanism of action, such as vascular or inflammatory disease. These processes would readily explain the global effect of adiposity on cortical structure. Despite the global effect, adiposity appears to still impact cortical thinning in AD-related regions and therefore may impact cognitive impairment and dementia risk. Further, emerging evidence suggests that cardiometabolic disease may directly trigger neurodegenerative processes [42]. Future work should examine whether adiposity contributes to risk of dementia, including but not limited to AD [2].

We did not find evidence of associations with hippocampal volume, which is in contrast to some studies [8, 43–46], but consistent with others [47, 48]. Similarly to cortical thickness, the differences in findings across studies may be due to the timing of adiposity measurement. Additionally, differences between cortical thickness and hippocampal volume findings could indicate that adiposity may specifically affect cortical versus subcortical structures. Finally, differences could also be due to timing of outcome measurement, as the hippocampus is the target of AD pathology and often deteriorates first before global cortical atrophy occurs. The cross-sectional nature of most referenced studies and the present study limits causal inference, and therefore, further work is warranted.

Overall, we did not find evidence that adiponectin were associated with either AD-related MRI marker of interest. This is in contrast to current evidence, especially for hippocampal volume [43, 45, 49–51]. Other adipocytokines, such as leptin, were not examined in this study and might be more related to gray matter atrophy than adiponectin [52]. There is a paucity of epidemiologic studies examining serum levels of adipocytokines and MRI markers of brain aging, so further work is warranted. Differences in findings may be due to differences in cohort characteristics, especially since most previous research has been done in mostly white samples. This may reflect differences in underlying drivers of adiposity, such as diet, metabolism, and genetics. More research is warranted to confirm our findings, especially in diverse samples. Finally, we found the strongest associations with BMI and WC, in contrast to other markers of adiposity like WHR. WHR may be more confounded by height compared to WC [53]. This is relevant for brain aging outcomes, since height as a proxy for early-life health has been related to dementia risk [54].

Several mechanisms may explain our findings. First, obesity is a state of chronic inflammation, and inflammation has been related to brain aging [55]. Inflammation is also implicated in the development of diabetes mellitus and insulin resistance, each of which affect insulin and glucose transport across the blood-brain barrier. Second, adipocytokines likely have varied effects on the brain. For example, an animal study showed that leptin may be neuroprotective through induction of neuronal progenitors in an AD model [56]. Though our findings with adiponectin were largely null, we lacked measures of other important adipokines in this study, and thus this area warrants further investigation. Further, obesity affects cholesterol metabolism that contributes to insulin resistance, which in turn is implicated in cortical glucose hypometabolism that precedes dementia by years and even decades [3].

Importantly, our results represent a mostly Hispanic sample from an urban cohort, and therefore represents a population that is at higher risk for both obesity and dementia compared to non-Hispanic whites [9, 57]. Our interaction analyses suggest that the effect of adiposity on cortical thinning may be worse among Hispanics and Blacks compared to non-Hispanic whites. However, these findings should be considered preliminary, as power to detect differences was limited in this study. Further work is warranted to examine relationships between adiposity, cognitive decline, and dementia risk, as well as whether cortical thickness may mediate these associations in diverse populations.

Limitations of this study should be noted. Selective survival bias may underestimate our associations, though our sensitivity analyses weighted for inverse probability of selection into the study suggests this bias did not substantially affect our results. This is a cross-sectional analysis, and thus causality cannot be inferred. Residual and unmeasured confounding may be present. Lack of multiple repeated measures prohibited us from examining trajectories over time. Reverse causation might be present. Finally, we did not examine burden of cerebrovascular disease specifically in this study, though previous evidence in our cohort did not support the association between adiposity measures and subclinical cerebrovascular disease [58].

Overall, our study suggests that greater BMI and WC are related to cortical thinning in the both AD- signature and non-AD regions. Future work should investigate whether the impact of adiposity on dementia risk is mediated by cortical thickness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We would like to acknowledge the participants of the Northern Manhattan Study for their contributions, as well as the Northern Manhattan Study project manager, Janet DeRosa, MPH. This work was funded by the National Institute of Neurological Disorders and Stroke (R01NS29993, F30NS103462) and the Evelyn F. McKnight Brain Institute.

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Table 1

Sample Characteristics, Stratified by BMI Category ($N = 947$)

	All ($N = 947$)	BMI < 25 ($n = 282$)	BMI 25–<30 ($n = 421$)	BMI 30+ ($n = 244$)
Sociodemographic variables				
Age (y), mean (SD)	63 (8)	64 (9)	63 (8)	62 (8)
Women, n (%)	592 (63)	156 (55)	248 (59)	188 (77)
Years of education, mean (SD)	10 (5)	11 (5)	9 (5)	9 (5)
Race/ethnicity, n (%)				
Non-Hispanic white	145 (15)	65 (23)	53 (13)	27 (11)
Non-Hispanic Black	153 (16)	46 (16)	57 (14)	50 (20)
Hispanic/Latino	628 (66)	161 (57)	304 (72)	163 (67)
Other	21 (2)	10 (4)	7 (2)	4 (2)
Years between baseline and MRI, mean (SD)	6 (3)	6 (3)	6 (3)	6 (4)
Clinical variables				
Body mass index, kg/m^2 , mean (SD)	28 (5)	23 (2)	27 (1)	34 (3)
Adiponectin (mg/dL), median (q1, q3) *	9 (7, 12)	10 (7, 13)	8 (6, 11)	8 (6, 11)
Adiponectin quartiles, n (%) *				
First quartile	239 (30)	49 (20)	118 (33)	72 (38)
Second quartile	236 (30)	68 (28)	111 (31)	57 (30)
Third quartile	192 (24)	68 (28)	77 (22)	47 (24)
Fourth quartile	121 (15)	57 (24)	48 (14)	16 (8)
Waist-to-hip ratio (WHR), mean (SD)	0.90 (0.09)	0.88 (0.10)	0.90 (0.09)	0.90 (0.08)
Excess central adiposity per WHR, n (%)	573 (61)	136 (48)	272 (65)	165 (68)
Waist circumference (WC, inches), mean (SD)	36 (4)	33 (3)	36 (3)	40 (4)
Excess central adiposity per WC, n (%)	345 (37)	16 (6)	125 (30)	204 (84)
<i>APOE</i> $\epsilon 4$ allele status, n (%)	210 (23)	69 (26)	93 (23)	48 (21)
Cognitively impaired, n (%)	124 (13)	27 (10)	56 (13)	41 (17)
Health behaviors				
Smoking status, n (%)				
Current	133 (14)	49 (17)	59 (14)	25 (10)

	All (N = 947)	BMI < 25 (n = 282)	BMI 25–<30 (n = 421)	BMI 30+ (n = 244)
Former	358 (38)	105 (37)	164 (39)	89 (36)
Never	456 (48)	128 (45)	198 (47)	130 (53)
Moderate-to-heavy physical activity, n (%)	109 (12)	40 (14)	49 (12)	20 (8)
Moderate alcohol consumption, n (%)	398 (42)	132 (47)	185 (44)	81 (33)
Imaging variables				
Hippocampal volume (mL), mean (SD)	7.28 (0.93)	7.22 (1.01)	7.32 (0.91)	7.29 (0.86)
AD-signature cortical thickness (mm), mean (SD)	2.43 (0.14)	2.43 (0.15)	2.43 (0.13)	2.43 (0.13)
Non-AD-signature cortical thickness (mm), mean (SD)	2.29 (0.10)	2.30 (0.10)	2.29 (0.09)	2.29 (0.10)
Total intracranial volume (mL), mean (SD)	1149 (120)	1164 (122)	1151 (121)	1127 (114)
Carotid intima-media thickness (mm), mean (SD)	0.92 (0.09)	0.92 (0.09)	0.92 (0.09)	0.92 (0.09)

Presented are means (standard deviations) for normally distributed, continuous variables, medians (with 1st and 3rd quartiles) for skewed continuous variables, and frequencies (with column percents) for categorical variables.

* Missing 159.

Table 2

Cross-Sectional Associations Between Markers of Adiposity, Cortical Thickness, and Hippocampal Volume ($N = 947$)

	AD-Signature Cortical Thickness			Hippocampal Volume			Non-AD-Signature Cortical Thickness		
	β	LCL	UCL	β	LCL	UCL	β	LCL	UCL
BMI (z-score)	-0.09	-0.18	-0.01	0.03	-0.05	0.10	-0.12	-0.21	-0.03
BMI categories									
25<30	-0.12	-0.31	0.08	0.01	-0.15	0.18	-0.17	-0.37	0.03
30+	-0.20	-0.42	0.03	0.05	-0.15	0.24	-0.29	-0.52	-0.05
Adiponectin	-0.01	-0.03	0.01	0.00	-0.02	0.01	0.00	-0.02	0.02
Adiponectin quartiles									
First quartile	0.13	-0.16	0.42	0.06	-0.18	0.31	0.02	-0.28	0.32
Second quartile	0.09	-0.20	0.38	0.12	-0.13	0.36	-0.08	-0.38	0.22
Third quartile	0.15	-0.14	0.45	0.04	-0.21	0.28	0.13	-0.18	0.43
WHR (z-score)	-0.02	-0.10	0.07	0.00	-0.07	0.07	-0.04	-0.13	0.05
Excess central adiposity per WHR	0.02	-0.15	0.19	0.04	-0.11	0.18	-0.06	-0.23	0.12
Waist circumference (z-score)	-0.11	-0.20	-0.02	0.01	-0.07	0.08	-0.15	-0.24	-0.06
Excess central adiposity per WC	-0.11	-0.29	0.07	0.10	-0.05	0.26	-0.20	-0.39	-0.01

* $N = 788$. LCL, lower 95% confidence limit. UCL, upper 95% confidence limit. CIs corrected per outcome via Bonferroni correction for multiple testing. Model adjusted for: age, gender, race/ethnicity, years of education, years between baseline and MRI, total intracranial volume, smoking status, moderate alcohol consumption. BMI categories reference group = BMI <25. Adiponectin quartiles reference group = 4th quartile. Excess central adiposity per WHR or WC reference group = no excess central adiposity.

Cross-Sectional Associations Between Markers of Adiposity and Cortical Thickness and Hippocampal Volume, Adjusted for Additional Covariates ($N=947$)

Table 3

	Full Model + <i>APOE ε4</i> allele status			Full Model + total cMT		
	AD-Signature Cortical Thickness					
	β	LCL	UCL	β	LCL	UCL
BMI (z-score)	-0.10	-0.19	-0.01	-0.09	-0.18	0.00
BMI categories						
25-30	-0.11	-0.31	0.09	-0.12	-0.32	0.08
>30	-0.21	-0.45	0.02	-0.19	-0.42	0.04
Adiponectin	-0.01	-0.03	0.01	-0.01	-0.03	0.01
Adiponectin quartiles						
First quartile	0.15	-0.15	0.45	0.15	-0.15	0.45
Second quartile	0.09	-0.21	0.38	0.10	-0.20	0.40
Third quartile	0.17	-0.13	0.47	0.17	-0.13	0.48
WHR (z-score)	0.00	-0.09	0.09	-0.01	-0.10	0.08
Excess central adiposity per WHR	0.04	-0.14	0.21	0.03	-0.15	0.21
Waist circumference (z-score)	-0.11	-0.20	-0.02	-0.11	-0.20	-0.02
Excess central adiposity per WC	-0.12	-0.30	0.07	-0.12	-0.31	0.07
	Hippocampal Volume					
	β	LCL	UCL	β	LCL	UCL
BMI (z-score)	0.03	-0.05	0.11	0.03	-0.04	0.11
BMI categories						
25-30	0.00	-0.17	0.18	0.00	-0.17	0.17
30+	0.04	-0.16	0.24	0.06	-0.14	0.25
Adiponectin *	-0.01	-0.02	0.01	0.00	-0.02	0.01
Adiponectin quartiles *						
First quartile	0.08	-0.17	0.33	0.06	-0.19	0.31
Second quartile	0.12	-0.13	0.37	0.11	-0.14	0.36
Third quartile	0.05	-0.21	0.30	0.05	-0.20	0.30
WHR (z-score)	0.01	-0.07	0.08	0.00	-0.07	0.08

	Full Model + APOE $\epsilon 4$ allele status			Full Model + total cIMT		
Excess central adiposity per WHR	0.03	-0.12	0.18	0.04	-0.10	0.19
Waist circumference (z-score)	0.01	-0.07	0.09	0.01	-0.06	0.09
Excess central adiposity per WC	0.11	-0.05	0.27	0.10	-0.06	0.26
Non-AD-Signature Cortical Thickness						
	β	LCL	UCL	β	LCL	UCL
BMI (z-score)	-0.12	-0.21	-0.03	-0.11	-0.21	-0.02
BMI categories						
25-30	-0.16	-0.37	0.04	-0.17	-0.38	0.03
30+	-0.29	-0.53	-0.05	-0.28	-0.52	-0.04
Adiponectin	0.00	-0.02	0.02	0.00	-0.02	0.02
Adiponectin quartiles						
First quartile	0.05	-0.26	0.35	0.04	-0.27	0.35
Second quartile	-0.06	-0.36	0.25	-0.07	-0.38	0.24
Third quartile	0.16	-0.15	0.47	0.16	-0.15	0.48
WHR (z-score)	-0.03	-0.12	0.06	-0.04	-0.13	0.05
Excess central adiposity per WHR	-0.04	-0.22	0.14	-0.05	-0.24	0.13
Waist circumference (z-score)	-0.14	-0.24	-0.05	-0.15	-0.24	-0.05
Excess central adiposity per WC	-0.20	-0.39	0.00	-0.20	-0.40	-0.01

* N = 788. LCL, lower 95% confidence limit. UCL, upper 95% confidence limit. CIs corrected per outcome via Bonferroni correction for multiple testing. Model adjusted for: age, gender, race/ethnicity, years of education, years between baseline and MRI, total intracranial volume, smoking status, moderate alcohol consumption, moderate-to-heavy physical activity. BMI categories reference group = BMI <25. Adiponectin quartiles reference group = 4th quartile. Excess central adiposity per WHR or WC reference group = no excess central adiposity.