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Association between Leptin, Cognition, and Structural Brain Measures among "Early" Middle-Aged Adults: Results from the Framingham Heart Study Third Generation Cohort

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Abstract

Background: There is growing interest in the pathophysiological processes of preclinical Alzheimer's disease (AD), including the potential role of leptin. Human studies have shown that both low and high levels of leptin can be associated with worse neurocognitive outcomes, suggesting this relationship may be moderated by another risk factor.

Objective: We examined the association between plasma leptin levels and both neuropsychological test performance and structural neuroimaging and assessed whether body mass index (BMI) is an effect modifier of these associations.

Methods: Our study sample consisted of 2223 adults from the Framingham Heart Study Third Generation Cohort (average age = 40 years, 53% women).

Results: Among the entire sample, there was no association between leptin and any of the neuropsychological domain measures or any of the MRI brain volume measures, after adjustment for BMI, APOE4, and other clinical factors. However, we did observe that BMI category was an effect modifier for the association between leptin and verbal memory (p-value for

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interaction=0.03), where higher levels of leptin were associated with better performance among normal weight participants (BMI 18.5–24.9) kg/m^2 (beta=0.12, p-value=0.02). No association was observed between leptin level and verbal memory test performance among participants who were overweight or obese.

Conslusions: These findings suggest that the association between leptin and cognitive function is moderated by BMI category. Prospective examination of individuals transitioning from middle age to older adulthood will help to clarify the contribution of leptin to AD and other neurodegenerative conditions.

Keywords

Alzheimer's disease; cognition; aging; leptin; obesity; neuroimaging

Introduction

Preclinical Alzheimer's disease (AD) refers to the time period during which the pathophysiological processes underlying AD are identifiable, but symptoms are not yet present [1]. A growing number of physiological processes have been implicated in this pathology, including metabolic dysregulation, inflammation, and obesity [2] [3] [4] [5] [6] [7]. These factors are associated with increased risk for AD and other causes of dementia later in life [8] [9] [10], as well as structural abnormalities on neuroimaging [11] [12] [13] and neurofibrillary tangles (NFT) [14] [15].

Leptin may be an important biomarker for and protective factor against AD. Leptin is a hormone secreted by adipose tissue that aids regulation of appetite and satiety [16]. Higher endogenous levels of leptin have been associated with increased risk for obesity, insulin resistance, and neuroendocrine function [17]. In animal models, injection of leptin into the brain has been shown to slow neurodegeneration [18], increase beta amyloid clearance [19], and improve hippocampal neuron survival [20]. Leptin is found in high doses in the hippocampus where it appears to promote synaptic plasticity [21] and acts in the hypothalamus and throughout the central nervous system (CNS) to aid regulation of homeostasis and weight [22].

Given these effects, there has been greater interest in clarifying the possible association between leptin and cognitive function in preclinical stages. However, findings for the relationship between leptin and neurocognitive function in human studies are mixed. Low levels of leptin and leptin deficiency [23] have been associated with increased risk of mild cognitive impairment (MCI) and dementia in some samples [24] [25]. In contrast, other studies have shown higher circulating levels of leptin are associated with *worse* performance on tasks of executive function in older adults, including those with type 2 diabetes (T2D) [26] [27].

The exact reason for the inconsistent findings across studies is unclear, though may be related to the impact of body mass index (BMI) on both leptin and cognitive function. Persons with obesity have higher endogenous levels of leptin, are more likely to develop leptin resistance [17], and exhibit cognitive impairment and greater risk for dementia relative

to their normal weight peers [27] [28] [8] [29]. Some evidence for an interaction between leptin and BMI has been found in older adults, as higher leptin levels were associated with better cognitive function over time in non-obese persons, but unrelated to cognitive function in obese participants [30] [31] [25].

Little is known about the impact of leptin on neurocognitive function in pre-clinical populations, especially in younger middle-aged adults. As AD pathology is believed to start many years prior to the onset of clinical symptoms [1] [32], there have been increased efforts to identify risk factors early in the neurodegenerative process. As the Framingham Heart Study Third Generation Cohort study has previously identified associations between obesity markers with cognitive function and brain volume [33] [34], it provides a unique opportunity to further examine the association between leptin and cognitive function and structural markers of brain integrity among an early middle-aged study sample, where the mean age is ~40 years at the time of leptin measurement. Our objective was to examine the association between leptin and cognitive function and neuroanatomical markers using MRI, and whether these associations are modified by BMI, using a sample of neurologically-healthy, early middle-aged adults.

Methods

Participants and Design

The FHS is a longitudinal community-based study that began in 1948 [35]. It involves serial examinations of the Original 1948 cohort, as well as serial exams of cohorts comprised of the original cohort participants' children (i.e., Generation 2, "Offspring Cohort") [36] and grandchildren (i.e., Generation 3, "Third Generation Cohort") [37]. The current sample included participants from the Third Generation cohort. The FHS Third Generation cohort has been described in detail elsewhere [37] [38]. The first clinic examinations for Generation 3 occurred between 2002 and 2005 (N=4,095, 53.3% women, mean [SD] age=50 [9]) [38] and included detailed medical and physical examinations, collection of fasting blood samples, as well as laboratory tests. Participants who then attended examination 2 (n = 3,411) between 2008 and 2011 underwent a preliminary self-reported cognitive screening and were re-invited to participate in a detailed cognitive evaluation and MRI brain imaging.

The present analysis is based on the 2,326 participants who had available leptin measurements during Examination 1 and who completed neuropsychological testing during Examination 2. We excluded participants with a history of stroke (n=10) or other neurological conditions (n=44), which may have affected their cognitive ability, and those with missing covariates (n=17). Additionally, given our interest in examining the interaction between leptin and BMI category, we excluded 32 participants who were underweight (BMI<18.5 kg/m^2) since the sample size was too small for a meaningful subgroup analysis. Thus, the final analytic sample size for the NP outcomes was 2,223. A subset of 2,011 of the 2,223 participants also underwent MRI during examination 2 and were included in the analysis of brain volume outcomes. The sample size was lower for MRI due to refusal to complete MRI or MRI contraindication. The mean time between leptin measurement and NP/MRI was 7.8±1.1 years. The FHS research protocol has been approved by the Boston

Medical Center and Boston University Medical Campus Institutional Review Board and all participants have provided written informed consent.

Neuropsychological Testing

Participants were administered a neuropsychological battery by a trained psychometrician who used standard administration protocols. Beginning in 2011, approximately eight years after the first Third Generation Cohort examination, participants were administered a detailed neuropsychological battery that assessed pre-morbid intelligence, attention and executive function, verbal and visual learning and episodic memory, language, and visuospatial abilities. The following neuropsychological tests were examined in the present study: 1) Wechsler Memory Scale (WMS) Logical Memory Delayed Recall (LMD) involving auditory presentation of brief stories and delayed free recall 20–30 minutes later; 2) WMS Visual Reproductions (VR) Delayed Recall involving presentation of a series of five, visual designs and free recall after time delay; 3) Wechsler Adult Intelligence Scale (WAIS) Digit Span Forward (DSF) and Backward (DSB) involving auditory presentation of a series of numbers progressively increasing in serial length and requiring immediate recall of the numbers, either in forward or backward organization; 4) Trail Making Test Parts A (TrA) and B (TrB) involving connecting a series of visually presented numbers or numbers and letters on a page while preserving accuracy and speed; 5) WAIS Similarities (SIM) involving auditory presentation of multiple two-word pairings requiring verbal explanation of how they are conceptually alike; 6) Hooper Visual Organization Test (HVOT) involving visual presentation of sections of line drawings of familiar objects rotated in various directions requiring identification of the names of the objects; 7) Boston Naming Test-30 item version (BNT) involving identification of visually presented pictures of common objects.

Each NP test score was individually regressed onto age and education group (≤high school degree, some college, ≥college degree) to obtain age- and education-adjusted residuals. The residuals were then standardized to z-scores. The z-scores for Trails A and B were multiplied by −1 so that higher scores indicated better performance, to be consistent in direction with the other NP tests. The z-scores for the NP tests were summarized into four domains: 1) verbal memory (LMD), 2) visual memory (VRd, HVOT), 3) attention, psychomotor speed, and executive function (DSF, DSB, TrB – TrA, SIM), and 4) language (BNT30). For domains represented by more than one NP test, the average of the z-scores was used. Verbal and visual memory were examined separately consistent with past findings of differential prediction [39] [40].

Magnetic Resonance Imaging

Participants underwent MRI on a 3.0-T Siemens Avanto scanner at or near the time that the neuropsychological tests were administered. Three sequences were acquired, including a 3D T1-weighted coronal spoiled gradient-recalled echo acquisition, fluid-attenuated inversion recovery (FLAIR), and diffusion tensor imaging (DTI). For the present study, total brain volume, gray matter volume, white matter volume, hippocampal volume, and white matter hyperintensities volume were considered as outcome variables. Aside from white matter hyperintensities, all brain volume measurements were expressed as a percentage of total

intracranial volume, to account for individual differences in head size. Each brain volume measure was individually regressed onto age and age-squared and the residuals were standardized to z-scores.

Several iterative methods were used to calculate the structural MRI indices. All images were skull-stripped using an atlas-based method [41] followed by manual edits. Structural MRIs were then non-linearly registered to a minimal deformation template (MDT) synthetic brain image [42] [43]. Inhomogeneity biases were then corrected [44] in order to improve the template-to-image deformation. Gray, white and CSF measurement were then determined using an Expectation-Maximization (EM) algorithm that produces outputs that are most consistent with input intensities from the native-space T1 images [45] [46]. The initial estimates for the EM algorithm were produced from previously segmented images that were in template space. Mean and standard deviations of image intensities for each tissue type were then determined. These values served as the initial parameters for a Guassian model of image intensity for each tissue class that were then iteratively used for segmentation. The segmentations were refined using a Markov Randon Field model. The newly refined segmentations were used to compute new Gaussian intensity models for each tissue class; Gaussian appearance models and MRI-based segmentation were iteratively repeated until convergence. The MRF-based segmentation at the final iteration served as the final output segmentation.

Hippocampal volume was segmented using automated methods that use a standard atlas based diffeomorphic approach [47] with minor modification of label refinement. This approach was also modified to include the EADC-ADNI harmonized hippocampal masks for atlas registration to each participant [48] [49] [50] [51] [52]. Atlas fusion was performed using MALF [53] [54], which was then followed by intensity-based label refinement.

Using FLAIR and 3D-T1 images, volume of WMH was determined using a Bayesian probability structure that is based on a previously published method of histogram fitting [55]. Prior probability maps were created for more than 700 individuals with semi-automatic detection of WMH followed by manual editing. Probability likelihood values of WMH at each voxel in the WMH were determined and then thresholded at 3.5 SD above the mean to create a binary WMH mask. Additional segmentation was based on a modified Bayesian approach that combined image likelihood estimates, spatial priors, and tissue class constraints.

Leptin Measurement

Measurement of leptin occurred at the first Third Generation Cohort examination for participants who provided a plasma sample at Examination 1. Leptin concentration was measured using a commercially-available immunoassay kit (Quantikine Human Leptin Immunoassay, R&D Systems, Inc, Minneapolis, MN). The inter-assay coefficient of variation ranged from 3.5–5.4%. The minimum detectable concentration of leptin was <7.8 pg/mL.

Covariate Measurement

All covariates were measured during Examination 1 of the Third Generation Cohort. Blood glucose and insulin levels were measured using fasting morning blood samples, if available. Diabetes was defined as a non-fasting blood glucose ≥200 mg/dL or fasting blood glucose (FBG) ≥126 mg/dL or use of an antidiabetic therapy [56]. BMI was defined as weight (kg) divided by the square of height (m). BMI category was defined using cutpoints defined by the NHLBI (2007): normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Waist circumference (cm) was measured at the participant's umbilicus while standing. Current smoking status, antihypertensive treatment use, and education level were determined by participant self-report. Educational achievement was coded as a 3-category variable (high school degree or less, some college, or college degree or more). *APOE ε*4 carrier status was defined based on whether or not a participant had one or more apolipoprotein *ε*4 alleles.

Statistical Analysis

Descriptive statistics were calculated for all variables using means (SD, standard deviation), medians (interquartile range), or frequency counts and percentages, as appropriate. Any variable with a skewed distribution was natural log (ln) transformed prior to analysis. Serum leptin (pg/mL) measurements were natural log (ln) transformed and then standardized within each sex (mean=0, standard deviation=1), due to the large difference in mean leptin values between women and men. Additionally, leptin was categorized into sex-specific quartiles. Differences in study sample characteristics by sex-specific leptin quartile were compared using either Chi-square, ANOVA, or Kruskall-Wallis tests.

Linear regression models were constructed to examine the association between sex-standardized log-leptin and each of the neuropsychological domain scores and MRI-derived volumetric measures. Model 1 was adjusted for age at neuropsychological testing (years), education (≤High school degree, some college, ≥college degree), systolic blood pressure (mm Hg), insulin (pM/L), fasting blood glucose (mg/dL), and years between clinic exam and NP. For the MRI outcomes, Model 1 was adjusted for age at MRI, age at MRI-squared (due to the non-linear association between age and brain volume measures; [57], systolic blood pressure (mm Hg), insulin (pM/L), fasting blood glucose (mg/dL), and years between clinic exam and MRI. Model 2 was adjusted for model 1 covariates plus BMI (kg/m^2). Model 3 was adjusted for the covariates in Models 1 and 2 plus *APOE ε* 4 genotype. Due to the high collinearity between BMI and waist circumference, we opted to include only BMI as a measure of adiposity in the models.

The presence of effect modification by BMI category (18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2) on the association between leptin and each outcome was assessed by including a cross product term in the linear regression models (model 1). Since BMI category was represented by indicator variables, the statistical significance of the cross-product terms was assessed using a two degree of freedom Type III test. Linear regression models stratified by BMI category were constructed for any model that showed a statistically significant interaction. All analyses were performed using SAS 9.4 (Cary, NC). A p-value of <0.05 was considered statistically significant.

Results

Study sample characteristics stratified by sex-specific leptin quartile are presented in Table 1. Overall, participants in the highest (4^{th}) leptin quartile were older, had a lower level of education, and had higher levels of BMI, waist circumference, fasting blood glucose, and insulin as compared to participants in the lowest (1^{st}) quartile.

Table 2 presents the linear regression results for the association between leptin levels and cognitive domains. There were no statistically significant associations observed between sex-standardized log leptin and any of the cognitive domains. Table 3 presents the linear regression results for the association between leptin levels and MRI brain volume measurements. There were no statistically significant associations between sex-standardized log leptin and any of the MRI outcomes.

In examining the presence of effect modification by BMI category for the association between leptin and each of the cognitive domains and MRI outcomes, we observed a statistically significant interaction only for verbal memory (p-value for interaction=0.03; Table 4). Among normal weight participants (BMI 18.5–24.9 kg/m^2), a one standard deviation increment of log-leptin was associated with higher verbal memory scores (beta=0.12, p-value=0.02). There was no association observed in either the overweight (BMI 25.0–29.9 kg/m^2; beta=−0.060, p-value=0.27) or obese (BMI≥30 kg/m^2; beta=−0.095, p-value=0.20) subgroups for log-leptin.

Discussion

The current study shows a complex association between leptin levels and verbal memory performance in a sample of neurologically healthy middle-aged adults. To our knowledge, this is one of the first studies to explore this association in a younger adult study sample with a mean age of 40. For the study sample as a whole, we did not observe any statistically significant association between leptin and any of the cognitive domains after controlling for BMI. However, we did observe that the association between leptin and verbal memory was modified by BMI group. Among participants with lower BMI (18.5–24.9 kg/m^2), higher levels of leptin were associated with improved verbal memory test performance. No association was found between leptin and memory performance in participants who were overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI≥30 kg/m^2). Leptin was not associated with any of the MRI brain volume measures.

The current findings suggest an association between leptin and cognitive function in neurologically-healthy, middle-aged adults with normal weight. Elevated BMI is an independent risk factor for adverse neurological outcomes, including accelerated cognitive decline, abnormalities on functional and structural neuroimaging, and dementia incidence [58] [59] [6]. Much work has examined the contribution of insulin resistance to obesity-related cognitive impairment [60] [61] [62], but the current findings suggest leptin may also play an important role in the interactions underlying the associations between weight and cognitive function. Interestingly, the association between leptin levels and verbal memory was not identified in overweight persons or persons with obesity. This pattern is consistent

with the interaction between leptin and BMI found in older adult participants from the Framingham Heart Study, Sacramento Area Latino Study on Aging, and the Study of Osteoporotic Fractures [31] [30]. As suggested in these previous studies, the cognitive benefits imparted by leptin may be disrupted in the presence of obesity, potentially due to increased risk for leptin resistance leading to reduced leptin crossing the blood-brain barrier [63] [64] and/or due to increased inflammatory biomarkers interefering with leptin receptors [65]. As such, the current findings may further suggest an optimal range of leptin values that differs across individuals, protecting against the harmful effects of both leptin deficiency [66] and the elevated amounts of leptin found in obesity indicative of metabolic dysfunction or leptin resistance [67] [68] which may also impair brain health [69] [70]. Prospective studies will help to clarify this possibility as individuals transition from pre-clinical stages of AD into older adulthood.

Whereas previous research has examined the influence of BMI on leptin and cognition in persons with obesity [71], metabolic disorders [72], and older adults [73], the current study included a largely healthy sample of early-middle-aged adults. Finding higher leptin levels were associated with better memory performance in normal-weight persons, even in a pre-clinical sample, raises the possibility of leptin as being a protective factor against future neurodegenerative disease [31] [25]. Low leptin levels may be a marker of subclinical metabolic dysfunction [74] or an independent contributor to cognitive function through a yet-to-be understood pathway. As above, prospective studies may help to clarify these findings, particularly in samples with known changes in leptin levels and cognitive function. For example, work in a middle-aged sample of bariatric surgery patients (average age = 43 years) revealed higher leptin levels are associated with poorer cognitive function prior to surgery, but that post-operative reductions in leptin were associated with improved cognitive test performance [75]. Similarly, older adults that exhibit unintentional weight loss are at elevated risk for incident MCI and dementia [76] [77] [78] and weight loss is associated with acute reductions in leptin levels in this age range [79] [80]. Investigation of the covariation among leptin, BMI, and cognitive function in other cohorts will help to clarify their relationship.

Limitations of the current study warrant brief discussion, particularly in regards to the distribution of BMI within the current sample. Approximately 40% of participants exhibited normal BMI (18.5–24.9 kg/m^2), 37% met criteria for overweight (BMI 25.0–29.9 kg/m^2), and 23% for obesity (BMI≥30 kg/m^2). Although this prevalence of obesity is representative for Massachusetts (25.7%) [81], it is lower than that found in the general population (39.8% obesity) [82] and included few persons with severe obesity (3%; i.e. BMI ≥40). A similar phenomenon may account for the lack of association between leptin levels and MRI indices. Past work shows higher leptin levels are associated with greater neurogenesis [18] and synaptic plasticity [21], with especially strong effects in older adults (i.e. >65 years) [83] [31]. Though helping to clarify the early relationship between leptin and neurocognitive function, recruitment of a healthy and younger sample may limit current findings, as such individuals are unlikely to exhibit significant atrophy or white matter changes on MRI. BMI is also a crude metric of adipose tissue and measurement error is a potential limitation of our findings. Further, as composite scores for cognitive domains were created to reduce the number of comparisons, it is possible that associations between leptin and BMI with some

individual neuropsychological tasks were obscured (e.g., executive functions vs attention). Future work should further investigate these specific effects. Leptin assessment and covariate measurement also occurred on average eight years prior to neuropsychological and MRI testing. Although this is beneficial for assessing the temporality of the association, we are unable to determine the effects of changes in leptin levels over time. Though past research suggests that genetic factors may lead to overall stability of leptin levels over time [84] [85], future studies examining similar associations would likely benefit by measuring similar markers of interest concurrently over multiple time points. Lastly, the current sample included participants from the FHS Third Generation Cohort who are predominantly white and were recruited from one geographic region. The present findings need to be externally validated in other population-based cohorts.

Conclusions

The present study examined the association between leptin, neurocognitive function, and neutoanatomical correlates in a sample of neurologically-healthy early middle-aged adults. Higher levels of leptin were associated with better performance on a test of memory only among participants with normal BMI 18.5–24.9 kg/m^2. No association was observed between leptin and memory test scores among participants who were overweight or obese. Such findings are consistent with work in older adults and suggest the neurocognitive impact of leptin is moderated by BMI. Prospective studies are needed to further clarify the interaction between leptin and BMI on neurological outcomes, particularly in prospective samples in which participants exhibit changes in both cognitive function and weight status.

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Table 1.

Study sample characteristics.

	All Participants	Leptin, pg/mL** [Median (Minimum-Maximum)]				P-value†
		Quartile 1 [Females: 4365 (793–6873) Males: 1633 (322–2445)]	Quartile 2 [Females: 9420 (6898–12,443) Males: 3365 (2445–4358)]	Quartile 3 [Females: 16,746 (12,445–23,620) Males: 5551 (4369–7735)]	Quartile 4 [Females: 36,175 (23,654–101,539) Males: 11,407 (7771–64,214)]	
	N=2223	N=555	N=556	N=557	N=555	
Female sex	1169 (52.6)	292 (52.6)	292 (52.5)	293 (52.6)	292 (52.6)	0.99
Age at clinic exam, years	40.4 (8.6)	38.7 (8.0)	39.7 (8.7)	40.8 (8.8)	42.3 (8.4)	<0.0001
Age at NP/MRI, years	48.2 (8.7)	46.4 (8.4)	47.5 (8.8)	48.6 (8.9)	50.1 (8.6)	<0.0001
Years between clinic exam and NP/MRI	7.8 (1.1)	7.8 (1.0)	7.7 (1.0)	7.8 (1.1)	7.8 (1.1)	0.73
Education level						
High school degree or less	324 (14.6)	73 (13.2)	80 (14.4)	70 (12.6)	101 (18.2)	0.0004
Some college	531 (23.9)	111 (20.0)	124 (22.3)	139 (25.0)	157 (28.3)	
College degree or more	1368 (61.5)	371 (66.9)	352 (63.3)	348 (62.5)	297 (53.5)	
APOE4, n (%)	471 (22.2)	113 (21.7)	117 (21.7)	113 (21.3)	128 (24.3)	0.63
Systolic blood pressure, mm Hg	117 (14)	112 (12)	115 (13)	118 (13)	123 (15)	<0.0001
Hypertension treatment	174 (7.9)	13 (2.3)	30 (5.4)	44(7.9)	87 (15.8)	<0.0001
Current smoker	297 (13.4)	87 (15.7)	75 (13.5)	57 (10.2)	78 (14.1)	0.06
Body mass index, kg/m^2	27.0 (5.3)	22.9 (2.5)	24.9 (3.1)	27.2 (3.3)	32.9 (5.6)	<0.0001
BMI category, n (%)						
18.5–24.9	891 (40.1)	433 (78.0)	299 (53.8)	140 (25.1)	19 (3.4)	<0.0001
25.0–29.9	832 (37.4)	122 (22.0)	229 (41.2)	314 (56.4)	167 (30.1)	
≥30.0	500 (22.5)	0 (0.0)	28 (5.0)	103 (18.5)	369 (66.5)	
Diabetes	54 (2.4)	5 (0.90)	11 (2.0)	9 (1.6)	29 (5.2)	<0.0001
Waist circumference, in	36.3 (32.5, 40.0)	32.0 (29.8, 34.8)	34.5 (31.5, 37.3)	37.3 (34.8, 39.8)	42.3 (38.8, 45.8)	<0.0001
Fasting blood glucose, mg/dL	92 (87, 98)	90 (85, 94)	91 (87, 97)	94 (89, 99)	96 (91, 103)	<0.0001
Insulin, pM/L	23.9 (17.0, 35.6)	16.4 (12.2, 21.9)	21.5 (16.3, 28.4)	26.9 (20.2, 36.7)	38.3 (26.8, 53.2)	<0.0001
Leptin, pg/mL	7498 (3760, 15,123)	2343 (1590, 4472)	7031 (3420, 9480)	12,966 (5588, 17,028)	25,074 (11,564, 38,570)	---

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	N=2223	**N=555**	**N=556**	**N=557**	**N=555**	
Neuropsychological test score						
Logical Memory - Delayed	11.5 (3.7)	11.4 (3.8)	11.6 (3.8)	12.0 (3.7)	11.1(3.6)	0.0008
Visual Reproductions - Delayed	8.9 (2.6)	9.2 (2.5)	9.0 (2.6)	8.8 (2.7)	8.5 (2.7)	0.0002
Hooper's Visual Organization Test	27.0 (25.5, 28.0)	26.5 (25.5, 28.0)	27.0 (25.5, 28.0)	27.0 (25.5, 28.0)	27.0 (25.5, 28.0)	0.65
Digit Span Forwards	6.9 (1.3)	6.9 (1.2)	7.0 (1.3)	6.9 (1.3)	6.7 (1.3)	0.03
Digit Span Backwards	5.1 (1.3)	5.3 (1.3)	5.1 (1.3)	5.1 (1.3)	5.1 (1.3)	0.01
Trails B – Trails A	0.53 (0.38. 0.73)	0.53 (0.38, 0.73)	0.52 (0.38, 0.70)	0.53 (0.38, 0.73)	0.56 (0.41, 0.73)	0.16
Similarities	17.3 (3.1)	17.4 (3.0)	17.5 (3.0)	17.2 (3.1)	17.1 (3.2)	0.08
Boston Naming Test (30 item)	28.0 (27.0, 29.0)	28.0 (27.0, 29.0)	28.0 (26.0, 29.0)	28.0 (27.0, 29.0)	28.0 (27.0, 29.0)	0.81
MRI Brain Volume Measures	**N=2011**	**N=523**	**N=505**	**N=504**	**N=497**	
Total cerebral brain volume*, %	79.0 (1.9)	79.2 (1.8)	79.1 (1.7)	79.0 (2.0)	78.8 (2.1)	0.003
Total gray matter volume*, %	49.9 (2.0)	50.1 (2.1)	50.1 (2.1)	50.0 (1.9)	49.6 (2.1)	0.002
Total white matter volume*, %	40.9 (2.1)	41.0 (2.1)	40.9 (2.1)	40.9 (2.2)	40.8 (2.2)	0.83
Hippocampal volume*, %	0.54 (0.045)	0.54 (0.044)	0.54 (0.045)	0.54 (0.045)	0.55 (0.045)	0.36
White matter hyperintensities, cm^3	0.41 (0.21, 0.86)	0.36 (0.18, 0.74)	0.38 (0.20, 0.79)	0.43 (0.23, 0.86)	0.48 (0.24, 1.03)	0.0001

Note: The numbers in the table represent mean (SD) for continuous, normally distributed variables, median (25^{th}, 75^{th} percentile) for continuous non-normally distributed variables, and n (%) for categorical variables.

*Expressed as a percentage of total cranial volume.

**Sex-specific quartiles of natural log-transformed leptin.

†Calculated using a Chi-square test (categorical variables), ANOVA (continuous, normally distributed variables), or Kruskall-Wallis test (continuous, non-normally distributed variables)

Table 2.

Linear regression results for the association between leptin and cognitive domains.

Cognitive Domain (per SD)	Model 1*		Model 2**		Model 3***	
	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Verbal memory†	−0.00026 (0.027)	0.99	0.035 (0.033)	0.29	0.044 (0.034)	0.19
Visuo-spatial memory	0.019 (0.022)	0.40	0.024 (0.028)	0.39	0.033 (0.029)	0.25
Attention, Psychomotor speed, & Executive function	0.0075 (0.017)	0.66	0.031 (0.021)	0.15	0.033 (0.022)	0.13
Language	0.025 (0.027)	0.35	0.037 (0.034)	0.29	0.044 (0.035)	0.21

Abbreviations: SD, standard deviation; SE, standard error

Note: Leptin is natural log-transformed and standardized within each sex. Cognitive domains are expressed per standard deviation increment of age/education-adjusted residuals. The interaction between leptin and BMI for each outcome was assessed using Model 1.

*Adjusted for age at NP, sex, education group (≤High school degree, some college, ≥college degree), systolic blood pressure, ln-insulin, ln-fasting blood glucose, and years between clinic exam and NP.

**Adjusted for model 1 covariates plus body mass index (kg/m^2).

***Adjusted for model 2 covariates plus APOE4.

†P-value for interaction between leptin and BMI group <0.05

Table 3.

Linear regression results for the association between leptin and MRI brain volume measures.

Brain Volume Measure (per SD)	Model 1*		Model 2**		Model 3***	
	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Total cerebral brain, %	0.029 (0.028)	0.31	0.036 (0.035)	0.30	0.039 (0.036)	0.28
Total gray matter, %	−0.0023 (0.027)	0.93	0.043 (0.034)	0.21	0.045 (0.035)	0.20
Total white matter, %	0.025 (0.028)	0.38	0.016 (0.035)	0.66	0.018 (0.036)	0.61
Hippocampus, %	0.0017 (0.028)	0.95	−0.0039 (0.035)	0.91	−0.028 (0.036)	0.43
White matter hyperintensities, cm^3 (ln-transformed)	0.020 (0.028)	0.49	−0.042 (0.035)	0.23	−0.044 (0.036)	0.23

Abbreviations: SD, standard deviation; SE, standard error

Note: Leptin is natural log-transformed and standardized within each sex. Brain volume measures are expressed per standard deviation increment of age and age-squared-adjusted residuals. The interaction between leptin and BMI for each outcome was assessed using Model 1. There are no statistically significant interactions between leptin and BMI category for any of the brain volume outcome measures.

*Adjusted for age at MRI, age-squared, sex, systolic blood pressure, ln-insulin, ln-fasting blood glucose, and years between clinic exam and MRI.

**Adjusted for model 1 covariates plus body mass index (kg/m^2).

***Adjusted for model 2 covariates plus APOE4.

Table 4.

Linear regression results for the association between leptin and verbal memory, stratified by BMI category.

Body Mass Index	N	Beta (SE)	P-value	P-value for interaction between leptin and BMI category
18.5–24.9 kg/m^2	708	0.12 (0.052)	0.022	0.028
25.0–29.9 kg/m^2	740	−0.060 (0.054)	0.27	
≥30 kg/m^2	466	−0.095 (0.075)	0.20	

Abbreviations: SE, standard error; kg, kilogram; m, meter

Note: Leptin is natural log-transformed and standardized within each sex. Verbal memory is expressed per standard deviation increment of age/education-adjusted residuals. Models are adjusted for age at NP, sex, education group (≤High school degree, some college, ≥college degree), systolic blood pressure, ln-insulin, ln-fasting blood glucose, and years between clinic exam and NP.