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Sanborn, Victoria
Preis, Sarah R
Ang, Alvin
et al.

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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

Victoria Sanborn[a,*], **Sarah R. Preis, ScD, MPH**[b,c,*], **Alvin Ang, MD**[b], **Sherral Devine, PhD**[b,d], **Jesse Mez, MD, MS**[b,d,e], **Charles DeCarli, MD**[f], **Rhoda Au, PhD**[b,d,e,g,h], **Michael L. Alosco, PhD**[d,e,*], **John Gunstad, PhD**[*,a]

[a]Department of Psychological Sciences, Kent State University, Kent, OH, USA;

[b]Framingham Heart Study, Boston University School of Medicine, Boston, MA, USA;

[c]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA;

[d]Department of Neurology, Boston University School of Medicine, Boston, MA, USA;

[e]Boston University Alzheimer's Disease Center and Boston University CTE Center, Boston University School of Medicine, Boston, MA, USA;

[f]Department of Neurology, University of California at Davis Health System, Sacramento, CA;

[g]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA;

[h]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, USA

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

Address correspondence to: John Gunstad, 144 Kent Hall, Kent State University, Kent OH 44242; 330-672-2589; jgunstad@kent.edu.

*These authors contributed equally

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.

References

[1]. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 280–292. [PubMed: 21514248]

[2]. Craft S, Watson GS (2004) Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 3, 169–178. [PubMed: 14980532]

[3]. Kroner Z (2009) The Relationship between Alzheimer's Disease and Diabetes: type 3 Diabetes. Altern Med Rev 14.

[4]. Neuroinflammation Working Group (2000) Inflammation and Alzheimer's disease. Neurobiol Aging 21, 383–421. [PubMed: 10858586]

[5]. Bossu P, Ciaramella A, Moro ML, Bellincampi L, Bernardini S, Federici G, Trequattrini A, Macciardi F, Spoletini I, Di Iulio F, Caltagirone C, Spalletta G (2007) Interleukin 18 gene polymorphisms predict risk and outcome of Alzheimer's disease. J Neurol Neurosurg Psychiatry 78, 807–811. [PubMed: 17299019]

[6]. Chuang YF, An Y, Bilgel M, Wong DF, Troncoso JC, O'Brien RJ, Breitner JC, Ferruci L, Resnick SM, Thambisetty M (2015) Midlife adiposity predicts earlier onset of Alzheimer's dementia, neuropathology and presymptomatic cerebral amyloid accumulation. Mol Psychiatry 21, 910–915. doi:10.1038/mp.2015.129 [PubMed: 26324099]

[7]. Anstey KJ, Cherbuin N, Budge M, Young J (2011) Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev 12, e426–e437. [PubMed: 21348917]

[8]. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K (2008) Central obesity and increased risk of dementia more than three decades later. Neurology 71, 1057–1064. [PubMed: 18367704]

[9]. Craft S (2007). Insulin resistance and Alzheimer's disease pathogenesis: Potential mechanisms and implications for treatment. Curr Alzheimer Res 4, 147–152. [PubMed: 17430239]

[10]. Riederer P, Korczyn AD, Ali SS, Bajenaru O, Choi MS, Chopp M, Dermanovic-Dobrota V, Grünblatt E, Jellinger KA, Kamal MA, Kamal W (2017) The diabetic brain and cognition. J Neural Transm 124, 1431–1454. [PubMed: 28766040]

[11]. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, DeCarli C (2011) Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 77, 461–468. [PubMed: 21810696]

[12]. Sala-Llonch R, Idland AV, Borza T, Watne LO, Wyller TB, Brækhus A, Zetterberg H, Blennow K, Walhovd KB, Fjell AM (2017) Inflammation, amyloid, and atrophy in the aging brain: relationships with longitudinal changes in cognition. J Alzheimers Dis 58, 829–840. [PubMed: 28505968]

[13]. Li W, Risacher SL, Huang E, Saykin AJ, Alzheimer's Disease Neuroimaging Initiative (2016) Type 2 diabetes mellitus is associated with brain atrophy and hypometabolism in the ADNI cohort. Neurology 87, 595–600. [PubMed: 27385744]

[14]. Merrill DA, Siddarth P, Raji CA, Emerson ND, Rueda F, Ercoli LM, Miller KJ, Lavretsky H, Harris LM, Burggren AC, Bookheimer SY (2016) Modifiable risk factors and brain positron emission tomography measures of amyloid and tau in nondemented adults with memory complaints. Am J Geriatr Psychiatry 24, 729–737. doi:10.1016/j.jagp.2016.05.007 [PubMed: 27421618]

[15]. Mrak RE (2009) Alzheimer-type neuropathological changes in morbidly obese elderly individuals. Clin Neuropathol 28, 40–45. [PubMed: 19216219]

[16]. Warren MW, Hynan LS, Weiner MF (2012) Leptin and cognition. Dement Geriatr Cogn Disord 33, 410–415. [PubMed: 22814193]

[17]. Friedman J (2016) The long road to leptin. J Clin Invest 126, 4727–4734. [PubMed: 27906690]

[18]. Perez-Gonzalez R, Antequera D, Vargas T, Spuch C, Bolós M, Carro E (2011) Leptin induces proliferation of neuronal progenitors and neuroprotection in a mouse model of Alzheimer's disease. J Alzheimers Dis 24, 17–25. [PubMed: 21335656]

[19]. Fewlass DC, Noboa K, Pi-Sunyer FX, Johnston JM, Yan SD, Tezapsidis N (2004) Obesity-related leptin regulates Alzheimer's Aβ. The FASEB Journal 18, 1870–1878. [PubMed: 15576490]

[20]. Yan BC, Choi JH, Yoo KY, Lee CH, Hwang IK, You SG, Kang IJ, Kim JD, Kim DJ, Kim YM, Won MH (2011) Leptin's neuroprotective action in experimental transient ischemic damage of the gerbil hippocampus is linked to altered leptin receptor immunoreactivity. J Neurol Sci 303, 100–108. [PubMed: 21277586]

[21]. Harvey J, Solovyova N, Irving A (2006) Leptin and its role in hippocampal synaptic plasticity. Prog Lipid Res 45, 369–378. [PubMed: 16678906]

[22]. Harvey J (2007) Leptin regulation of neuronal excitability and cognitive function. Curr Opin Pharmacol 7, 643–647. [PubMed: 18024215]

[23]. Blüher S, Shah S, Mantzoros CS (2009) Leptin deficiency: clinical implications and opportunities for therapeutic interventions. J Investig Med 57, 784–8.

[24]. Johnston JM, Hu WT, Fardo DW, Greco SJ, Perry G, Montine TJ, Trojanowski JQ, Shaw LM, Ashford JW, Tezapsidis N, & Alzheimer's Disease Neuroimaging Initiative (2014) Low plasma leptin in cognitively impaired ADNI subjects: gender differences and diagnostic and therapeutic potential. Curr Alzheimer Rev 11, 165–74.

[25]. Zeki Al Hazzouri A, Stone KL, Haan MN, Yaffe K (2012) Leptin, mild cognitive impairment, and dementia among elderly women. J Gerontol A Biol Sci Med Sci 68, 175–180 [PubMed: 22859388]

[26]. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E (2007) Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr Psychiatry 48, 57–61. [PubMed: 17145283]

[27]. Labad J, Price JF, Strachan MW, Deary IJ, Seckl JR, Sattar N, Reynolds RM, Edinburgh Type 2 Diabetes Study (ET2DS) Investigators (2012) Serum leptin and cognitive function in people with type 2 diabetes. Neurobiol Aging 33, 2938–2941. [PubMed: 22475620]

[28]. Benito-León J, Mitchell AJ, Hernández-Gallego J, & Bermejo-Pareja F (2013) Obesity and impaired cognitive functioning in the elderly: a population-based cross-sectional study (NEDICES). Eur J Neurol 20, 899–e77. [PubMed: 23323838]

[29]. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Yaffe K (2005) Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 330, 1360. doi: 10.1136/bmj.38446.466238.E0 [PubMed: 15863436]

[30]. Zeki Al Hazzouri A, Haan MN, Whitmer RA, Yaffe K, Neuhaus J (2012) Central obesity, leptin and cognitive decline: the Sacramento Area Latino Study on Aging. Dement Geriatr Cogn Disord 33, 400–409. [PubMed: 22814127]

[31]. Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, Harris TB, Roubenoff R, Auerbach S, DeCarli C, Wolf PA, Seshadri S (2009) Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA 302, 2565–2572. doi: 10.1001/jama.2009.1836. [PubMed: 20009056]

[32]. Lane CA, Hardy J, Schott JM (2017) Alzheimer's disease. Eur J Neurol 25. 10.1111/ene.13439

[33]. Debette S, Beiser A, Hoffmann U, DeCarli C, O'Donnell CJ, Massaro JM, Au R, Himali JJ, Wolf PA, Fox CS, Seshadri S (2010) Visceral fat is associated with lower brain volume in healthy middle-aged adults. Ann Neurol 68, 136–144. [PubMed: 20695006]

[34]. Elias MF, Elias PK, Sullivan LM, Wolf PA, & D'agostino RB (2003) Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int J Obes 27, 260.

[35]. Dawber TR, Meadors GF, Moore FE Jr (1951) Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health 41, 279–286.

[36]. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP (1979) An investigation of coronary heart disease in families: the Framingham Offspring Study. Am J Epidemiol 110, 281–290. [PubMed: 474565]

[37]. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, O'Donnell CJ (2007) The third generation cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. Am J Epidemiol 165, 1328–1335. [PubMed: 17372189]

[38]. Weinstein G, Maillard P, Himali JJ, Beiser AS, Au R, Wolf PA, Seshadri S, DeCarli C (2015) Glucose indices are associated with cognitive and structural brain measures in young adults. Neurology 84, 2329–2337. [PubMed: 25948725]

[39]. Bonner-Jackson A, Mahmoud S, Miller J, Banks SJ (2015) Verbal and non-verbal memory and hippocampal volumes in a memory clinic population. Alzheimers Rer Ther 7, 61. 10.1186/s13195-015-0147-9

[40]. Kessels RP, Rijken S, Banningh LWJW, Van Schuylenborgh-Van Es N, Rikkert MGO (2010) Categorical spatial memory in patients with mild cognitive impairment and Alzheimer dementia: positional versus object-location recall. JINS 16, 200–4. doi:10.1017/S1355617709990944 [PubMed: 19883520]

[41]. Aljabar P, Heckemann RA, Hammers A, Hajnal JV, Rueckert D (2009) Multi-atlas based segmentation of brain images: atlas selection and its effect on accuracy. NeuroImage 46, 726–738. 10.1016/j.neuroimage.2009.02.018 [PubMed: 19245840]

[42]. Rueckert D, Aljabar P, Heckemann RA, Hajnal JV, Hammers A (2006) Diffeomorphic registration using B-splines. In International Conference on Medical Image Computing and Computer-Assisted Intervention (pp. 702–709). Springer, Berlin, Heidelberg.

[43]. Kochunov P, Lancaster JL, Thompson P, Woods R, Mazziotta J, Hardies J, Fox P (2001) Regional spatial normalization: toward an optimal target. J Comput Assist Tomogr 25, 805–816. [PubMed: 11584245]

[44]. Fletcher E, Carmichael O, DeCarli C (2012) MRI non-uniformity correction through interleaved bias estimation and B-spline deformation with a template. In 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (pp. 106–109). IEEE. doi: 10.1109/EMBC.2012.6345882

[45]. Rajapakse JC, Giedd JN, DeCarli C, Snell JW, McLaughlin A, Vauss YC, Krain AL, Hamburger S, Rapoport JL (1996) A technique for single-channel MR brain tissue segmentation: application to a pediatric sample. J Magn Reson Imaging 14, 1053–1065. 10.1016/S0730-725X(96)00113-0

[46]. Fletcher E, Singh B, Harvey D, Carmichael O, DeCarli C (2012) Adaptive image segmentation for robust measurement of longitudinal brain tissue change. In 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (pp. 5319–5322). IEEE. doi: 10.1109/EMBC.2012.6347195

[47]. Vercauteren T, Pennec X, Perchant A, Ayache N (2007) Non-parametric Diffeomorphic Image Registration with the Demons Algorithm. In: Ayache N, Ourselin S, Maeder A (eds) Medical Image Computing and Computer-Assisted Intervention – MICCAI 2007. MICCAI 2007. Lecture Notes in Computer Science, vol 4792. Springer, Berlin, Heidelberg. 10.1007/978-3-540-75759-7_39

[48]. Frisoni GB, Bocchetta M, Chételat G, Rabinovici GD, De Leon MJ, Kaye J, Reiman EM, Scheltens P, Barkhof F, Black SE, Brooks DJ (2013) Imaging markers for Alzheimer disease: which vs how. Neurology 81, 487–500. doi: 10.1212/WNL.0b013e31829d86e8 [PubMed: 23897875]

[49]. Boccardi M, Bocchetta M, Apostolova LG, Barnes J, Bartzokis G, Corbetta G, DeCarli C, deToledo-Morrell L, Firbank M, Ganzola R, Gerritsen L (2015) Delphi definition of the EADC-ADNI Harmonized Protocol for hippocampal segmentation on magnetic resonance. Alzheimers Dement 11, 126–138. 10.1016/j.jalz.2014.02.009 [PubMed: 25130658]

[50]. Bocchetta M, Boccardi M, Ganzola R, Apostolova LG, Preboske G, Wolf D, Ferrari C, Pasqualetti P, Robitaille N, Duchesne S, Jack CR Jr (2015) Harmonized benchmark labels of the hippocampus on magnetic resonance: the EADC-ADNI project. Alzheimers Dement 11, 151–160. 10.1016/j.jalz.2013.12.019 [PubMed: 25223727]

[51]. Boccardi M, Bocchetta M, Ganzola R, Robitaille N, Redolfi A, Duchesne S, Jack CR Jr, Frisoni GB, EADC-ADNI Working Group on The Harmonized Protocol for Manual Hippocampal Segmentation and for the Alzheimer's Disease Neuroimaging Initiative, Bartzokis G, Csernansky JG (2015) Operationalizing protocol differences for EADC-ADNI manual hippocampal segmentation. Alzheimers Dement 11, 184–194. 10.1016/j.jalz.2013.03.001 [PubMed: 23706515]

[52]. Frisoni GB, Jack CR (2015) HarP: the EADC-ADNI harmonized protocol for manual hippocampal segmentation. A standard of reference from a global working group. Alzheimers Dement 11, 107–110. doi: 10.1016/j.jalz.2014.05.1761 [PubMed: 25732924]

[53]. Wang H, Suh JW, Das SR, Pluta JB, Craige C, Yushkevich PA "Multi-Atlas Segmentation with Joint Label Fusion," in IEEE Transactions on Pattern Analysis and Machine Intelligence, vol. 35, no. 3, pp. 611–623, 3 2013. doi: 10.1109/TPAMI.2012.143 [PubMed: 22732662]

[54]. Wang H, Yushkevich PA "Dependency prior for multi-atlas label fusion," 2012 9th IEEE International Symposium on Biomedical Imaging (ISBI), Barcelona, 2012, pp. 892–895. doi: 10.1109/ISBI.2012.6235692

[55]. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Garner J, Jack L, Carmelli D (1999) Predictors of brain morphology for the men of the NHLBI twin study. Stroke 30, 529–536. DOI: 10.1161/01.str.30.3.529 [PubMed: 10066847]

[56]. Molenaar EA, Hwang SJ, Vasan RS, Grobbee DE, Meigs JB, D'Agostino RB, Levy D, Fox CS (2008) Burden and rates of treatment and control of cardiovascular disease risk factors in obesity: the Framingham Heart Study. Diabetes Care 31, 1367–1372. [PubMed: 18375414]

[57]. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, Beiser A, D'Agostino R, Wolf PA (2005) Measures of brain morphology and infarction in the Framingham Heart Study: Establishing what is normal. Neurobiol Aging 26, 491–510. [PubMed: 15653178]

[58]. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, Lee S, Hibar D, Dinov ID, Stein JL, Jack CR Jr (2010) Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiol Aging 31, 1326–1339. doi:10.1016/j.neurobiolaging.2010.04.006 [PubMed: 20570405]

[59]. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I (2003) An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 163, 1524–1528. doi:10.1001/archinte.163.13.1524 [PubMed: 12860573]

[60]. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, Holtzman DM (2018) Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol 14, 168–181. [PubMed: 29377010]

[61]. Luchsinger JA, Tang MX, Shea S, Mayeux R (2004) Hyperinsulinemia and risk of Alzheimer disease. Neurology 63, 1187–1192. [PubMed: 15477536]

[62]. Lee J, Kim J, Shin SA, Park S, Yoon DH, Kim H, Kim YK, Moon MK, Koo BK, Lee JY (2018) Moderating effect of insulin resistance on the relationship between gray matter volumes and cognitive function. J Clin Med 7, 413. doi:10.3390/jcm7110413

[63]. Banks WA, Coon AB, Robinson SM, Moinuddin A, Shultz JM, Nakaoke R, Morley JE (2004) Triglycerides induce leptin resistance at the blood-brain barrier. Diabetes 53, 1253–1260. 10.2337/diabetes.53.5.1253 [PubMed: 15111494]

[64]. Steinberg GR, McAinch AJ, Chen MB, O'Brien PE, Dixon JB, Cameron-Smith D, Kemp BE (2006) The suppressor of cytokine signaling 3 inhibits leptin activation of AMP-kinase in cultured skeletal muscle of obese humans. J Clin Endocrinol Metab 91, 3592–3597. [PubMed: 16822822]

[65]. Myers MG, Cowley MA, Münzberg H (2008) Mechanisms of leptin action and leptin resistance. Annu Rev Physiol 70, 537–556. 10.1146/annurev.physiol.70.113006.100707 [PubMed: 17937601]

[66]. McGuire MJ, Ishii M (2016) Leptin dysfunction and Alzheimer's disease: evidence from cellular, animal, and human studies. Cell Mol Neurobiol 36, 203–217. [PubMed: 26993509]

[67]. Maffei Á, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S, Kern PA (1995) Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1, 1155–1161. [PubMed: 7584987]

[68]. Crujeiras AB, Carreira MC, Cabia B, Andrade S, Amil M, Casanueva FF (2015) Leptin resistance in obesity: an epigenetic landscape. Life Sci 140, 57–63. [PubMed: 25998029]

[69]. Bonda DJ, Stone JG, Torres SL, Siedlak SL, Perry G, Kryscio R, Jicha G, Casadesus G, Smith MA, Zhu X, Lee HG (2013) Dysregulation of leptin signaling in Alzheimer disease: evidence for neuronal leptin resistance. J Neurochem 128, 162–172. https://doi-org.revproxy.brown.edu/10.1111/jnc.12380 [PubMed: 23895348]

[70]. Davis C, Mudd J, Hawkins M (2014) Neuroprotective effects of leptin in the context of obesity and metabolic disorders. Neurobiol Dis 72, 61–71. https://doi-org.revproxy.brown.edu/10.1016/j.nbd.2014.04.012 [PubMed: 24780498]

[71]. Tsai CL, Huang TH, Tsai MC (2017) Neurocognitive performances of visuospatial attention and the correlations with metabolic and inflammatory biomarkers in adults with obesity. Exp Physiol 102, 1683–1699. [PubMed: 28983981]

[72]. Yin H, Tian S, Huang R, Cai R, Guo D, Lin H, Wang J, Wang S (2018) Low plasma leptin and high soluble leptin receptor levels are associated with mild cognitive impairment in type 2 diabetic patients. Front Aging Neurosci 10, 132. doi:10.3389/fnagi.2018.00132 [PubMed: 29867443]

[73]. Holden KF, Lindquist K, Tylavsky FA, Rosano C, Harris TB, Yaffe K (2009) Serum leptin level and cognition in the elderly: findings from the Health ABC Study. Neurobiol. Aging 30, 1483–1489. doi: 10.1016/j.neurobiolaging.2007.11.024 [PubMed: 18358569]

[74]. McGregor G, Harvey J (2018) Food for thought: Leptin regulation of hippocampal function and its role in Alzheimer's disease. Neuropharmacology 136, 298–306. 10.1016/j.neuropharm.2017.09.038 [PubMed: 28987937]

[75]. Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Crosby RD, Mitchell JE, Gunstad J (2015) Improved serum leptin and ghrelin following bariatric surgery predict better postoperative cognitive function. J Clin Neurol 11, 48–56. [PubMed: 25628737]

[76]. Alhurani RE, Vassilaki M, Aakre JA, Mielke MM, Kremers WK, Machulda MM, Geda YE, Knopman DS, Petersen RC, Roberts RO (2016) Decline in weight and incident mild cognitive impairment: Mayo Clinic Study of Aging. JAMA neurology 73, 439–446.doi: 10.1001/jamaneurol.2015.4756 [PubMed: 26831542]

[77]. Johnson DK, Wilkins CH, Morris JC (2006) Accelerated weight loss may precede diagnosis in Alzheimer disease. Arch Neurol 63, 1312–1317. [PubMed: 16966511]

[78]. Barrett-Connor E, Edelstein SL, Corey-Bloom J, Wiederholt WC (1996) Weight loss precedes dementia in community-dwelling older adults. J Am Geriatr Soc 44, 1147–1152. [PubMed: 8855991]

[79]. Yukawa M, McCormick WC, Rajan S, Matsumoto AM, Wallace JI, Pearlman RA, Weigle DS (2002) Leptin levels are appropriate for body mass index in older men who experience involuntary weight loss. J Am Geriatr Soc 50, 1566–1571. [PubMed: 12383156]

[80]. Yukawa M, Phelan EA, Callahan HS, Spiekerman CF, Abrass IB, Weigle DS (2008) Leptin levels recover normally in healthy older adults after acute diet-induced weight loss. J Nutr Health Aging 12, 652–656. [PubMed: 18953464]

[81]. Robert Wood Johnson Foundation (2019) The State of Obesity in Massachusetts. Retrieved from: https://stateofchildhoodobesity.org/states/ma/ on November 13, 2019.

[82]. Centers for Disease Control and Prevention (2016) Retrieved from: https://www.cdc.gov/nchs/fastats/obesity-overweight.htm

[83]. Witte AV, Köbe T, Graunke A, Schuchardt JP, Hahn A, Tesky VA, Pantel J, Flöel A (2016) Impact of leptin on memory function and hippocampal structure in mild cognitive impairment. Hum Brain Mapp 37, 4539–4549. [PubMed: 27511061]

[84]. Holm JC, Gamborg M, Ward LC, Gammeltoft S, Kaas-Ibsen K, Heitmann BL, Sørensen TI (2011) Tracking of leptin, soluble leptin receptor, and the free leptin index during weight loss and regain in children. Obes Facts 4, 461–468. 10.1159/000335121 [PubMed: 22248997]

[85]. Narkiewicz K, Szczech R, Winnicki M, Chrostowska M, Pawlowski R, Lysiak-Szydlowska W, Choe I, Kato M, Sivitz WI, Krupa-Wojciechowska B, Somers VK (1999) Heritability of plasma leptin levels: a twin study. J Hypertens 17, 27–31. [PubMed: 10100090]

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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	All Participants	Leptin, pg/mL ** [Median (Minimum-Maximum)]				P-value†
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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.