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## Association of Plasma Leptin Levels With Incident Alzheimer Disease and MRI Measures of Brain Aging

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**Context:** The adipokine leptin facilitates long-term potentiation and synaptic plasticity in the hippocampus, promotes  $\beta$ -amyloid clearance, and improves memory function in animal models of aging and Alzheimer disease (AD).

**Objective:** To relate baseline circulating leptin concentrations in a community-based sample of individuals without dementia to incident dementia and AD during follow-up and magnetic resonance imaging (MRI) measures of brain aging in survivors.

**Design, Setting, and Participants:** Prospective study of plasma leptin concentrations measured in 785 persons without dementia (mean [SD] age, 79 [5] years; 62% female), who were in the Framingham original cohort at the 22nd examination cycle (1990-1994). A subsample of 198 dementia-free survivors underwent volumetric brain MRI between 1999 and 2005, approximately 7.7 years after leptin was assayed. Two measures of brain aging, total cerebral brain volume and temporal horn volume (which is inversely related to hippocampal volume) were assessed.

**Main Outcome Measure:** Incidence of dementia and AD during follow-up until December 31, 2007.

**Results:** During a median follow-up of 8.3 years (range, 0-15.5 years), 111 participants developed incident dementia; 89 had AD. Higher leptin levels were associated with a lower risk of incident dementia and AD in multivariable models (hazard ratio per 1-SD increment in log leptin was 0.68 [95% confidence interval, 0.54-0.87] for all-cause dementia and 0.60 [95% confidence interval, 0.46-0.79] for AD). This corresponds to an absolute AD risk over a 12-year follow-up of 25% for persons in the lowest quartile (first quartile) vs 6% for persons in the fourth quartile of sex-specific leptin levels. In addition, a 1-SD elevation in plasma leptin level was associated with higher total cerebral brain volume and lower temporal horn volume, although the association of leptin level with temporal horn volume did not reach statistical significance.

**Conclusion:** Circulating leptin was associated with a reduced incidence of dementia and AD and with cerebral brain volume in asymptomatic older adults.

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## Connecting Leptin and Alzheimer Disease

**A**LZHEIMER DISEASE IS THE MOST COMMON cause of late-life dementia and affects more than 35 million people worldwide and 5.5 million in the United States.<sup>1</sup> Alzheimer disease is characterized by progressive loss of memory and cognition. Death typically occurs within 3 to 9 years after diagnosis. The major risk factor for Alzheimer disease is aging; therefore, the current demographics in developed countries with older populations portends dramatic increases in the number of cognitively impaired elderly persons.<sup>1</sup> This poses an enormous burden on families, caregivers, and health care systems. The specific molecular pathogenesis of Alzheimer disease is still unresolved but studies suggest a major role of accumulation of misfolded proteins in the aging brain, which triggers oxidative and inflammatory damage, alteration in energy use, and synaptic dysfunction. Risk factors implicated in Alzheimer disease include midlife obesity and metabolic syndrome.<sup>2,3</sup> The latter is associated with central (visceral) obesity, insulin resistance, type 2 diabetes, hyperlipidemia, hypertension, and increased cardiovascular risk. A study by Lieb et al<sup>4</sup> in JAMA presents

an intriguing link between an adipocyte hormone, leptin, and Alzheimer disease. Leptin is a 16-kDa protein encoded by the *LEP* gene (previously called obese, *OB*). Leptin is produced in adipocytes and then secreted; it circulates in proportion to body fat.<sup>5</sup> Leptin is transported across the blood-brain barrier and acts on hypothalamic neurons to inhibit feeding and decrease body weight and fat.<sup>5</sup> Total absence of leptin signaling, as in congenital leptin deficiency or null mutation of the leptin receptor, culminates in overeating, early-onset obesity, severe insulin resistance, steatosis, and a myriad neuroendocrine defects, notably hypothalamic hypogonadism.<sup>5</sup> Leptin treatment reverses these abnormalities in patients and rodents who lack leptin, consistent with its role as a negative feedback regulator of energy stores. Congenital leptin deficiency is extremely rare, and most obese individuals have high plasma leptin levels and leptin resistance.<sup>6</sup> Studies in diet-induced obese rodents have revealed an impairment of blood-brain leptin transport and induction of suppressors of cytokine signaling 3, which inhibits the ability of leptin to signal through janus kinase signal transducer and activator of

transcription 3 in the hypothalamus.<sup>6</sup> However, whether these mechanisms are important in obese humans is unknown.

Leptin has additional effects on the brain. Brain size is reduced in congenital leptin deficiency in humans and rodents and restored by leptin treatment.<sup>7,8</sup> Leptin regulates neuronal and glial proteins, increases long-term potentiation in the hippocampus and synaptic plasticity in hippocampus and hypothalamus, improves memory in rodents models of aging and Alzheimer disease, enhances the clearance of  $\beta$ -amyloid, and has a neuroprotective effect in stroke and seizure rodent models.<sup>7-12</sup> Although a small cross-sectional study showed that leptin is elevated in midlife obesity and declines during Alzheimer disease,<sup>13</sup> it is uncertain whether leptin reduces the risk of Alzheimer disease. Lieb et al<sup>4</sup> measured plasma leptin concentrations in 785 participants without dementia in the Framingham Heart Study between 1990 and 1994. Total cerebral brain volume and temporal horn volume were measured prospectively in 198 participants without dementia between 1999 and 2005. During a median follow-up of 8.3 years, 111 participants developed dementia and 89 were diagnosed with Alzheimer disease. There was a strong inverse association between the logarithm of leptin concentration and incidence of dementia and Alzheimer disease after adjusting for central obesity (waist to hip ratio) and cardiovascular risk factors. The absolute risk of Alzheimer disease during 12 years of follow-up was 12% for participants with the lowest leptin quartile and 6% for the highest quartile. Higher leptin levels were associated with increased total cerebral brain volume and reduced temporal horn volume. In summary, plasma leptin was strongly associated with reduced incidence of dementia and Alzheimer disease and increased cerebral volume is a cohort of older adults.

The strengths of the study by Lieb et al<sup>4</sup> are the moderate sample size and prospective assessment of cognitive function and brain structure. Overall, the results are consistent with growing evidence that shows beneficial effects of leptin on brain structure and function.<sup>7-12</sup> Leptin receptors are present in the hippocampal cornu ammonis 1 (CA1) region.<sup>10</sup> Leptin stimulates synaptic plasticity and memory function in leptin-deficient rodents.<sup>11</sup> Leptin increases apolipoprotein E-dependent  $\beta$ -amyloid uptake, decreases extracellular  $\beta$ -amyloid levels in the brain, and decreases the hyperphosphorylation of tau protein, a major constituent of neurofibrillary tangles.<sup>14,15</sup> Nonetheless, this community-based, prospective study does not establish a causal role for leptin in Alzheimer disease. High leptin level is often indicative of leptin resistance in obesity; therefore, it is unclear how a high leptin level is capable of signaling in the brain to prevent Alzheimer disease in a subset of apparently leptin-resistant people.<sup>6,16</sup> A major methodological flaw is the reliance on a single baseline measurement of leptin that ignores the fact that leptin is influenced by fat stores as well as changes in energy homeostasis.<sup>5</sup> A better approach is to measure plasma leptin longitudinally in relation to neuropsychiatric evaluation and structural brain assessments. Leptin has circadian and pulsatile rhythms that are disrupted in pathological conditions, eg, amenorrhea and sleep and eating disorders.<sup>17,18</sup> Mea-

asuring these leptin rhythms is impractical in large populations but they may be helpful in small clinical studies. Leptin is present in the cerebrospinal fluid.<sup>19</sup> Perhaps the cerebrospinal fluid to plasma leptin ratio is a better predictor of dementia.<sup>19</sup> Leptin concentration in the cerebrospinal fluid may be related to  $\beta$ -amyloid peptide and tau protein levels. The regulation of leptin is closely associated with insulin, other adipocyte hormones, and cytokines.<sup>20</sup> Based on the complexity of Alzheimer disease and other late-onset dementias, it is doubtful that leptin is solely responsible for the pathology. Rather, it is likely leptin interacts with various humoral factors to affect the structure and function of the cerebral cortex and hippocampus.

Despite these shortcomings, the observation of a strong inverse association of leptin and Alzheimer disease is an important step toward unraveling the complex processes that underlie late-life dementia. Further research is needed to understand how leptin interacts with diabetes and vascular factors to affect Alzheimer disease. The measurement of leptin and other peripheral biomarkers should be incorporated into clinical trials to quantify preventive and pharmacological outcomes. Leptin is inappropriately low in some obese individuals, and partial leptin deficiency predisposes toward obesity.<sup>16,21</sup> It will be interesting to investigate whether patients with midlife obesity and partial leptin deficiency are more prone to Alzheimer disease. Furthermore, the use of leptin mimetic drugs to prevent or treat Alzheimer disease is an attractive therapeutic strategy.

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