# Leptin, Abdominal Obesity, and Onset of Depression in Older Men and Women

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**ABSTRACT**

***Objective:*** The mechanisms that underlie the association between abdominal obesity and depression risk in older persons are not well known, but the "leptin hypothesis" of depression suggests that leptin resistance may be involved in mood regulation. We tested whether high circulatory concentration of leptin, alone and in combination with visceral adiposity, is associated with onset of depression in a sample of older persons.

***Method:*** Participants were 1,220 men and 1,282 women aged 70–79 years and enrolled in the Health, Aging, and Body Composition study. Serum concentration of leptin and abdominal visceral fat, ascertained by computed tomography, were assessed at baseline (April 1997–June 1998). Onset of depression, the primary outcome measure, was defined as a Center for Epidemiologic Studies-Depression Scale 10-item score ≥ 10 and/or new antidepressant medication use at any annual visit over a 5-year follow-up.

***Results:*** Higher leptin level was associated with the risk of depression onset in men with high levels of visceral fat (hazard ratio [HR] = 1.25; 95% CI, 1.06–1.46; $P = .01$) but not in those with normal visceral fat (HR = 0.98; 95% CI, 0.80–1.19; $P = .80$) (leptin-by-visceral fat, $P = .04$). No interaction between leptin and visceral fat was detected in the analysis focusing on women ($P = .90$).

***Conclusions:*** In older men, high leptin level was associated with an increased onset of depressive symptoms, especially in the presence of abdominal obesity, suggesting that underlying leptin resistance may play a role in this link. Differences in visceral fat levels and metabolic consequences may explain the absence of this association in women. These findings suggest a potential biological link between depression, obesity, and their joint association with negative health outcomes.

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Increasing evidence suggests a causal link between adiposity, particularly abdominal obesity, and depression.[1–3] White adipose tissue produces leptin, initially identified as an antiobesity hormone operating as a negative feedback to control energy homeostasis.[4,5] The "leptin hypothesis of depression" contends that leptin contributes to regulation of affective status.[6] In animal models of depression, leptin has been shown to improve cognition and mood.[7] However, clinical studies in humans have had conflicting results,[6,8] which may be partly explained by the complexity of leptin response in obese persons,[9,10] who often have high, not low, levels of leptin. The lack of inhibition of food intake in obese persons is thought to be caused by a mechanism of physiological leptin resistance, similar to the one that links type 2 diabetes mellitus and insulin resistance, that blunts leptin central action despite increasing concentrations.[9–11] On the basis of these observations, it has been hypothesized that it is not the absolute serum leptin concentration but rather its impaired central action that is correlated with mood.[6,8]

Data from the Health, Aging, and Body Composition (Health ABC) study showed that visceral fat, independent of overall obesity, was a risk factor for depression onset in older men.[3] We used longitudinal data from the same cohort of men and women aged 70–79 years to test whether serum leptin in older adults may represent a mechanism relating abdominal adiposity with increased risk of developing relevant depressive symptoms. Since the presence of hyperleptinemia in obese persons may be considered an indicator of leptin resistance,[6] we hypothesized that risk of depression onset would be especially increased for participants with high levels of leptin and visceral fat.

## METHOD

### Study Population

Participants were part of the Health ABC study, a cohort study consisting of 3,075 initially well-functioning, 70- to 79-year-old black and white men and women. Participants were identified from a random sample of white Medicare beneficiaries and all age-eligible community-dwelling black residents in designated areas surrounding Memphis, Tennessee, and Pittsburgh, Pennsylvania. Participants were eligible if they reported no difficulty in walking one-quarter of a mile, going up 10 steps without resting, or performing basic activities of daily living. Exclusion criteria were a history of active treatment for cancer in the prior 3 years, plans to move out of the study area in the next 3 years, or participation in a randomized trial of a lifestyle intervention. Baseline data (April 1997–June 1998) included an in-person interview and clinic-based examination, with evaluation of body composition, diseases, and physical functioning.

For the present analyses, we initially retained 2,802 participants free of depression at baseline, as indicated by a Center for Epidemiologic Studies-Depression scale (CES-D)[12] score below the clinical cutoff and

no reported use of antidepressants. We then excluded 143 participants because of missing data on baseline leptin and visceral fat levels and 157 subjects without follow-up data on depressive symptoms. Those lost to follow-up, as compared to those available, were more often male and black, had poorer cognitive function, were more likely to have diabetes and cardiovascular disorders, and had higher depressive symptoms. The primary sample for analyses included the remaining 2,502 participants. Participants were assessed annually over a median follow-up of 4.9 years (range, 0.9–5.6); 8.4% of the participants died during follow-up period.

### Leptin

Measures for leptin were obtained from serum samples collected at baseline. Fasting blood samples were obtained in the morning, and, after processing, the specimens were aliquoted into cryovials, frozen at −70°C and shipped to the Health ABC study core laboratory. Leptin concentrations were measured in duplicate by using the Sensitive Human Leptin RIA Kit (Linco Research, Inc, St Charles, Missouri). The minimum concentration detectable was 0.05 ng/mL. Intraassay coefficients of variation were 3.7%–7.5%, and interassay coefficients of variation were 3.2%–8.9%. For 155 participants, leptin concentrations were outside of the linear range of the assay and were not on the linear portion of the standard curve. These numerical values were not recorded by the laboratory and were recoded as 52 ng/mL (upper limit of the curve specified by Linco Research, Inc). In addition to continuous measures (per SD increase), sex-specific quartiles of leptin levels were constructed, and dichotomous variables compared persons in the highest quartiles versus persons in quartiles 1–3. High leptin levels were > 10.1 ng/mL for men and > 28.9 ng/mL for women.

### Depressive Symptoms

Depressive symptoms were evaluated at baseline by using the CES-D and at selected follow-up visits (after 2, 3, 4, and 5 years) by using the CES-D, 10 item (CES-D10),[13] which is derived from a 10-item subset of the standard CES-D. The properties of the CES-D10 show satisfactory test-retest correlations and good predictive accuracy compared with the standard CES-D.[13] Baseline prevalence of significant depressive symptoms was defined by the established cut point of ≥ 16 on the CES-D, which is equivalent to a cut point of ≥ 10 on the CES-D10.[13] In addition, at baseline and at follow-up (after 1, 2, 4, and 5 years), antidepressant use (with depression/mood as self-reported reason) was coded according to the Iowa Drug Information System.[14] Consistent with previous articles from the Health ABC study,[3,15] depression onset, the primary outcome measure, was operationally defined by relevant depressive symptoms (CES-D10 score ≥ 10) or antidepressant use at follow-up. Following the procedures used by Vogelzangs et al,[3] 2 alternative definitions of depression onset were also tested. One used CES-D10 scores only and the second had the additional requirement of a minimum increase of 3 points on the CES-D10.

**Clinical Points**

- Obesity, in particular abdominal adiposity, is a risk factor for depression.
- Leptin impaired central action (resistance) may represent a biological mechanism relating abdominal adiposity with depression onset in obese persons.
- In obese depressed patients, the development of therapeutic interventions on leptin downstream pathways should target leptin central resistance rather than leptin itself.

### Abdominal Visceral Fat

Computed tomography scanning was performed at the fourth and fifth lumbar vertebrae to measure visceral fat ($cm^2$) by using a Somatom Plus 4 (Siemens, Erlangen, Germany) or a Picker PQ 2000S (Marconi Medical Systems, Cleveland, Ohio) scanner in Memphis and a 9800 Advantage scanner (General Electric, Milwaukee, Wisconsin) in Pittsburgh. Scans were conducted at 120 kilovolt (peak) and 200–250 mA/s, with a slice thickness of 10 mm. Areas were calculated by multiplying the number of pixels of a given tissue type by the pixel area using Interactive Data Language software (Research Systems Inc, Boulder, Colorado). Abdominal visceral fat was manually distinguished from subcutaneous fat by tracing along the fascial plane defining the internal abdominal wall. For consistency with the previous article by Vogelzangs et al,[3] visceral fat was considered both as a continuous measure and as a categorical variable defined by the highest sex-specific quartile (men > 195.6 $cm^2$; women > 165.9 $cm^2$).

### Covariates

Covariates were a priori selected on the basis of previously reported associations with leptin and depression. The following were assessed at baseline: age, sex, race, education level, and smoking status (nonsmoker/former/current smoker). Alcohol consumption was assessed by using a standardized questionnaire[16] and was categorized as former drinker, never or < 1 drink/wk, 1–7 drinks/wk, and > 7 drinks/wk. Physical activity during the week that preceded the baseline visit was expressed as kcal/kg/wk. According to time/intensity spent on physical activities, metabolic equivalent values were assigned,[17] summed, and multiplied by body weight. Cognitive function was measured by the Modified Mini-Mental State examination,[18] with a maximum score of 100. Total number of chronic conditions (peripheral arterial disease, cancer, lung disease, osteoarthritis, osteoporosis, gastrointestinal disease, prostate disease, thyroid disease, Parkinson's disease, and kidney disease) was calculated. Since leptin is associated with cardiovascular diseases (heart failure, stroke, myocardial infarction, angina pectoris, coronary angioplasty or coronary artery bypass grafting) and diabetes,[19–21] these conditions were specifically addressed. Presence of diabetes and cardiovascular disease was adjudicated by using standardized algorithms, considering various sources of

**Table 1. Characteristics of the Study Population**

| Characteristic[a] | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Normal Leptin Level (n = 920) | High Leptin Level[b] (n = 300) | *P*[c] | Normal Leptin Level (n = 947) | High Leptin Level[b] (n = 335) | *P*[c] |
| Age, mean ± SD, y | 73.7 ± 2.9 | 73.7 ± 2.8 | .96 | 73.6 ± 2.9 | 73.3 ± 2.7 | .19 |
| Race (black), % | 40.9 | 19.7 | < .0001 | 45.0 | 46.0 | .76 |
| Education, % | | | .16 | | | .001 |
| Less than high school | 26.6 | 22.0 | | 19.9 | 28.6 | |
| High school | 24.5 | 29.0 | | 39.6 | 39.8 | |
| Postsecondary | 48.9 | 49.0 | | 40.6 | 31.6 | |
| Alcohol intake, % | | | .52 | | | .63 |
| Never or < 1 drink/wk | 62.2 | 58.7 | | 79.1 | 81.5 | |
| 1–7 drink/wk | 25.8 | 28.9 | | 17.5 | 15.5 | |
| > 7 drink/wk | 12.0 | 12.4 | | 3.5 | 3.0 | |
| Smoking status, % | | | .002 | | | .04 |
| Nonsmoker | 31.3 | 29.0 | | 59.4 | 53.4 | |
| Former smoker | 11.4 | 5.0 | | 9.0 | 7.5 | |
| Current smoker | 57.3 | 66.0 | | 31.7 | 39.1 | |
| Physical activity, mean ± SD, kcal/kg/wk | 87.0 ± 71.4 | 79.6 ± 68.8 | .12 | 85.7 ± 71.8 | 80.1 ± 66.9 | .19 |
| 3MS score, mean ± SD | 89.5 ± 8.9 | 90.2 ± 7.1 | .002 | 91.4 ± 7.0 | 90.6 ± 8.7 | .002 |
| No. of chronic diseases, mean ± SD | 1.4 ± 1.0 | 1.5 ± 1.1 | .09 | 0.9 ± 0.9 | 1.1 ± 1.1 | .007 |
| Diabetes, % | 22.8 | 37.3 | < .0001 | 14.8 | 34.0 | < .0001 |
| Cardiovascular disease, % | 20.8 | 28.7 | .005 | 11.5 | 16.7 | .01 |
| Interleukin-6, median (IQR), pg/mL | 1.8 (1.4) | 2.1 (1.7) | < .0001 | 1.5 (1.4) | 2.2 (1.6) | < .0001 |
| C-reactive protein, median (IQR), μg/mL | 1.4 (1.6) | 1.8 (1.9) | .01 | 1.6 (2.1) | 2.9 (3.3) | < .0001 |
| BMI, % | | | < .0001 | | | < .0001 |
| Normal | 38.0 | 4.7 | | 43.2 | 3.0 | |
| Overweight | 49.5 | 47.0 | | 37.1 | 41.5 | |
| Obese | 12.5 | 48.3 | | 19.8 | 55.5 | |
| Body fat, mean ± SD, % | 28.1 ± 4.5 | 33.0 ± 4.1 | < .0001 | 39.5 ± 5.7 | 43.9 ± 4.3 | < .0001 |
| Abdominal visceral fat, mean ± SD, $cm^2$ | 123.1 ± 39.9 | 253.5 ± 52.3 | < .0001 | 103.8 ± 35.1 | 212.47 ± 41.9 | < .0001 |

[a]Categorical and continuous variables were reported as percentage or mean ± SD as appropriate. Variables with a skewed distribution were presented as median (IQR) and were log-transformed for the analyses.
[b]High leptin level is defined as >10.1 ng/mL in men and > 28.9 ng/mL in women.
[c]Based on $\chi^2$ for categorical variables and independent *t* test for continuous variables.
Abbreviations: 3MS = Modified Mini-Mental State examination, BMI = body mass index, IQR = interquartile range.

information, including self-report, medications, clinical findings, and medical claims data from the former Health Care Financing Administration. Body mass index (BMI) was calculated as $kg/m^2$ and categorized as normal (BMI < 25), overweight (25–29.99), and obese (BMI ≥ 30). Percentage of body fat was determined by using fan-beam dual-energy x-ray absorptiometry (QDR 4500A; Hologic Inc; Waltham, Massachusetts). Levels of interleukin-6 and C-reactive protein were measured in duplicate from stored serum by enzyme-linked immunosorbent assay kits (interleukin-6: R&D Systems, Minneapolis, Minnesota; C-reactive protein: Calbiochem, San Diego, California). Interassay coefficients of variation were 10.3% for interleukin-6 and 8.0% for C-reactive protein.

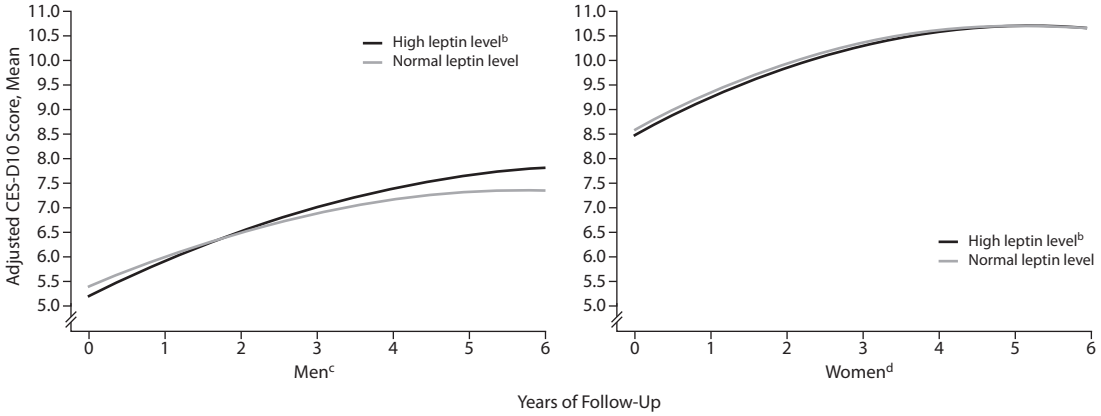
### Statistical Analyses

Variables were reported as percentage, mean ± SD, or as median and interquartile range (IQR), as appropriate. Because differences between men and women in body composition, leptin levels, and prevalence of depression have been established in the literature and because sex differences in the relationship between obesity and depression have been observed in the present sample,[3] all results are shown for men and women separately. Differences in baseline characteristics were tested according to leptin categories by using descriptive statistics. Fat levels across sexes were compared by using analysis of covariance. Trajectories of depressive symptoms over time were estimated by using random coefficient analyses with random intercept. This method handles missing values, different spacing of measurement observations, and correlation between multiple observations per subject. Multivariate Cox proportional hazards model was used to compare risk of depression onset over the follow-up period associated with leptin. Participants who survived without developing depressed mood were censored at the date of the last follow-up. The proportional hazards assumption was checked by including a time-to-event–by-leptin interaction term and was met in all analyses. To test whether visceral fat and leptin had an interacting association with depression onset, we entered leptin-by-visceral fat interaction terms in the regression models including the visceral fat term. Leptin-by-race interaction terms were tested but were not statistically significant. All analyses were performed by using SAS, version 9.1, (SAS Institute Inc, Cary, North Carolina). Significance level was set at $P < .05$.

## RESULTS

Participants' mean ± SD age at baseline was 73.6 ± 2.9 years, 51.1% were women, and 40.5% were black. The median (IQR) levels of leptin were 6.1 (6.6) ng/mL for men and 18.5 (19.2) ng/mL for women. Characteristics of participants according to sex and leptin groups are reported in Table 1. Overall, participants with high leptin levels were more likely to be

**Figure 1. Trajectories[a] of CES-D10 Scores During Follow-Up According to Baseline Leptin Level**




[a]Estimated trajectories are adjusted for age, race, education level, alcohol consumption, smoking status, physical activity, Modified Mini-Mental State examination score, number of chronic diseases, cardiovascular disease, diabetes, visceral fat, (log)interleukin-6 and (log)C-reactive protein.
[b]High leptin level was > 10.1 ng/mL in men and > 28.9 ng/mL in women.
[c]Main effect: high leptin, $P = .40$; time, $P < .0001$; time$^2$, $P < .0001$. Interaction term: high leptin by time, $P = .02$.
[d]Main effect: high leptin, $P = .58$; time, $P < .0001$; time$^2$, $P < .0001$. Interaction term: high leptin by time, $P = .68$.
Abbreviation: CES-D10 = Center for Epidemiologic Studies-Depression scale, 10 item.

**Table 2. Risk of Depression Onset According to Baseline Levels of Leptin**

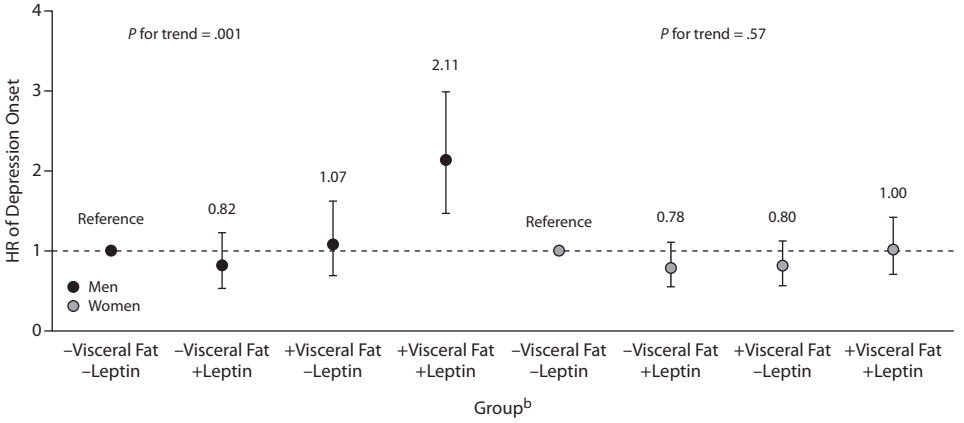
| | Leptin Level in Men | | | | | | | Leptin Level in Women | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Per SD Increase[a] | | | High vs Normal[b] | | | | Per SD Increase[a] | | | High vs Normal[b] | | |
| | n/n | HR | 95% CI | *P* | HR | 95% CI | *P* | n/n | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Total Sample | 245/1,220 | | | | | | | 352/1,282 | | | | | | |
| Adjustment | | | | | | | | | | | | | | |
| Sociodemographic[c] | | 1.17 | 1.05–1.31 | .01 | 1.32 | 1.00–1.74 | .047 | | 0.99 | 0.89–1.11 | .90 | 1.01 | 0.79–1.29 | .94 |
| + Lifestyle and health[d] | | 1.17 | 1.05–1.31 | .01 | 1.29 | 0.97–1.71 | .08 | | 0.94 | 0.83–1.06 | .32 | 0.94 | 0.73–1.21 | .60 |
| + Visceral fat | | 1.11 | 0.97–1.26 | .12 | 1.10 | 0.81–1.49 | .56 | | 0.95 | 0.84–1.08 | .41 | 0.95 | 0.73–1.24 | .72 |
| Leptin-by-visceral fat | | | | .04 | | | .046 | | | | .90 | | | .30 |
| Normal visceral fat | 170/920 | | | | | | | 254/947 | | | | | | |
| Adjustment | | | | | | | | | | | | | | |
| Sociodemographic[c] | | 0.96 | 0.79–1.17 | .71 | 0.87 | 0.58–1.30 | .50 | | 0.94 | 0.81–1.09 | .42 | 0.86 | 0.62–1.19 | .36 |
| + Lifestyle and health[d] | | 0.98 | 0.80–1.19 | .80 | 0.84 | 0.56–1.27 | .41 | | 0.91 | 0.78–1.07 | .25 | 0.81 | 0.58–1.15 | .25 |
| High visceral fat[e] | 75/300 | | | | | | | 98/335 | | | | | | |
| Adjustment | | | | | | | | | | | | | | |
| Sociodemographic[c] | | 1.25 | 1.08–1.45 | .003 | 1.87 | 1.14–3.06 | .01 | | 0.99 | 0.89–1.11 | .90 | 0.94 | 0.83–1.06 | .32 |
| + Lifestyle and health[d] | | 1.25 | 1.06–1.46 | .01 | 1.93 | 1.14–3.28 | .02 | | 1.01 | 0.79–1.29 | .94 | 0.94 | 0.73–1.21 | .60 |

[a]Leptin per SD increase: 7.0 ng/mL in men and 15.1 ng/mL in women.
[b]High leptin level was > 10.1 ng/mL in men and > 28.9 ng/mL in women.
[c]Adjusted for age, race, education and baseline Center for Epidemiologic Studies-Depression scale.
[d]Additionally adjusted for alcohol intake, smoking status, physical activity, Modified Mini-Mental State examination, number of chronic diseases, diabetes, cardiovascular disease, log(interleukin-6) and log(C-reactive protein).
[e]High level of visceral fat was > 195.5 cm$^2$ in men and > 165.9 cm$^2$ in women.

smokers and obese and to have diabetes and cardiovascular disease, and they had a higher number of chronic diseases and higher level of total percentage body fat, visceral fat, and inflammatory markers. In age- and race-adjusted analyses, men, as compared to women, were less likely to be obese (21.3% vs 29.1%; $P = .001$) and had lower mean ± standard error (SE) total percentage body fat (29.3 ± 0.2 vs 40.6 ± 0.2%; $P < .0001$); in contrast, men had higher abdominal visceral fat (cm$^2$) in the whole sample (154.2 ± 1.9 vs 133.1 ± 1.8; $P < .0001$) and in the subgroup of participants with high leptin (252.1 ± 2.8 vs 213.7 ± 3.0; $P < .0001$). Figure 1 shows CES-D10 mean scores over the follow-up period adjusted for age, race, education level, alcohol consumption, smoking status, physical activity, Modified Mini-Mental State examination score, number of chronic diseases, cardiovascular disease, diabetes, (log) interleukin-6, (log) C-reactive protein, and visceral fat. In both men and women, depressive symptoms were not different across leptin levels at baseline (leptin: $P > .40$) and significantly increased over time (time: $P < .0001$). Men with high levels of leptin had an increase in CES-D10 score of 0.11 points/y higher than those with normal levels (leptin-by-time: $\beta = .11$, SE = 0.05, $P = .02$). The inclusion of BMI or total percentage body fat in the models, which already included visceral fat, did not change the results, and these variables were not significantly associated with change in CES-D10 scores; therefore, these adjustments were not retained in the analyses.

During follow-up, depression onset emerged in 20.1% of men and 27.5% of women. Table 2 shows the risk of depression onset according to baseline leptin and in subgroups

**Figure 2. Risk of Depression Onset Across Baseline Levels of Leptin by Visceral Fat[a]**




[a]Hazard ratios and 95% CIs are adjusted for age, race, education level, alcohol consumption, smoking status, physical activity, Modified Mini-Mental State examination score, number of chronic diseases, cardiovascular disease, diabetes, visceral fat, (log)interleukin-6 and (log)C-reactive protein.
[b]+Visceral fat = high visceral fat (> 195.5 $cm^2$ in men and > 165.9 $cm^2$ in women); –visceral fat = normal visceral fat; +leptin = high leptin (> 10.1 ng/mL in men and > 28.9 ng/mL in women); –leptin = normal leptin.
Abbreviation: HR = hazard ratio.

stratified by visceral fat. After full adjustment plus baseline CES-D10 scores were factored, we found that risk of developing depression in men was significantly associated with higher leptin (hazard ratio [HR] = 1.17; 95% CI, 1.05–1.31; $P = .01$). The strength of this association was substantially reduced after additional adjustment for visceral fat (HR = 1.11; 95% CI, 0.97–1.26; $P = .12$). In women, no significant associations were detected (HR = 0.94; 95% CI, 0.83–1.06; $P = .32$). In men, a significant leptin-by-visceral fat association was found ($P = .04$). Higher leptin level was significantly associated with the risk of depression onset in men with high visceral fat level (HR = 1.25; 95% CI, 1.06–1.46; $P = .01$) but not in those with normal visceral fat level (HR = 0.98; 95% CI, 0.80–1.19; $P = .80$). No leptin-by-visceral fat interaction was detected in the analysis focusing on women ($P = .90$). Analyses distinguishing participants with high versus normal leptin obtained the same results. To further illustrate the interaction between leptin and visceral fat, Figure 2 shows that the fully adjusted HR of developing depression was higher among men with both high visceral fat and leptin levels as compared to all other groups.

Similar results were found when alternative operational definitions of depression onset were used: in men with high levels of visceral fat, higher leptin levels were associated with depression onset defined only by CES-D10 (70/300 cases; HR = 1.24; 95% CI, 1.05–1.46; $P = .01$) or when a requirement of a minimum 3-point increase on the CES-D10 was incorporated (72/300 cases; HR = 1.24; 95% CI, 1.07–1.46; $P = .01$). Considering the whole sample, a significant leptin-by-sex interaction ($P = .002$) was observed, confirming the differential association between leptin and depression by sex.

Finally, similar results were obtained in sensitivity analyses performed after the exclusion of 231 men and 158 women who developed incident diabetes or cardiovascular disease before depression onset (data not shown).

## DISCUSSION

In community-resident older men, but not women, high serum levels of leptin and abdominal obesity had an interactive effect on the onset of depressive symptoms over a 5-year period. In general, men with a high level of leptin, as compared to those with normal levels, had a steeper increase, although of small relevance, of depressive symptoms over time. However, the impact of high serum levels on depression onset was especially evident in men with abdominal obesity. The latter may suggest that in older men leptin resistance may contribute to alterations of affective status as proposed by the leptin hypothesis of depression.[6]

The sex specificity of the present findings deserves further comment. Consistent with the established literature, we found that men, as compared to women, had lower levels of leptin and lower percentages of depression onset. On the basis of the finding above, we may expect a stronger association of leptin with depression in women than in men. However, the present findings highlighted the interactive effect of leptin and visceral fat in predicting depression onset. If the presence of the specific combination of both high leptin and visceral fat levels is important for depression to emerge, this combination may be a less important contributing factor for depression in women due to differences in visceral fat levels and related metabolic consequences. Indeed, it has been consistently shown also in the present study that women, as compared to men, have higher measures of body fat but less visceral adiposity.[22,23] Visceral adiposity is associated with metabolic disturbances and increased inflammatory response that, in turn, have been linked to depression and development of leptin resistance.[22–28] Finally, in women depression may have a more complex etiology, and other biological (eg, estrogen) and/or psychosocial (eg, social support, stressful life events)[29–31] factors may have a stronger role than leptin.

Nevertheless, the reasons for this sex-specific interaction remain unknown, and further research comparing men and women is needed.

Leptin is synthesized in white adipose tissue and exerts its homeostatic function by interacting with hypothalamic arcuate nucleus.[32] Recently, several peripheral and extrahypothalamic effects of leptin have been described.[7] Leptin receptors are expressed in limbic substrates related to mood regulation, such as the hippocampus and amygdala.[32] In animals, leptin has been shown to affect hippocampal and cortical structure,[33] to exert antidepressant effects, and to improve learning and memory in behavioral and cellular assays.[34–36] Moreover, accumulating evidence shows that leptin modulates hypothalamus-pituitary-adrenal axis, which has been implicated in depression and obesity.[37] However, the few clinical studies in depressed patients showed conflicting findings, with studies showing increased, decreased, or no differences in leptin.[38–45] The phenomenon of leptin resistance may explain similar conflicting results. Obese individuals commonly display hyperleptinemia associated with central leptin resistance due to impaired transport across the blood-brain barrier, reduced function of the leptin receptor, and defects in leptin signal transduction,[9,10] which ultimately weaken leptin's central effect despite increasing circulating levels. A recent study[11] showed that leptin effect was impaired in the hippocampus of diet-induced obese mice, resulting in a severe depressive state despite hyperleptinemia.

When proposing the leptin hypothesis, Lu[6] underscored the need for future studies to clarify the role of leptin insufficiency versus leptin resistance in depression. We believe our findings provide support for the second mechanism proposed. Thus, the key to understanding the pathophysiology of leptin may lie in its function and its impaired central action and not merely in its circulating level. Therefore, in obese depressed patients, therapeutic interventions on leptin downstream pathways should target leptin central resistance rather than leptin itself.[6–8,46]

Limitations of the present study should be considered. First, depression was not confirmed by a clinical diagnosis, and data on psychiatric comorbidity were not available. The study design did not allow detection of depressive episodes that started and remitted between subsequent follow-up visits. Another limitation is the loss of participants to follow-up, who were slightly less healthy than the participants who remained in this study; this aspect may limit the generalizability of the findings. Moreover, the detected associations could have been driven by variables related to adipokine and depression, such as diabetes and cardiovascular disease.[19–21] However, in this sample, accounting for baseline diabetes and cardiovascular disease and excluding participants who developed these disorders during follow-up did not change the association. Moreover, adjustment for confounders decreased the possibility that factors such as physical inactivity, alcohol consumption, smoking, and inflammation may have driven the observed associations. Another limitation is that the sample was not adequately sized to test for the interactive effect of leptin and visceral fat on persistent depression. Finally, the observational nature of the present study restricts the ability of drawing definite causal inferences. Further studies in larger samples well characterized in terms of psychiatric diagnoses are needed to sustain the hypothesis of a causal pathway.

In conclusion, we believe our findings suggest that in older men leptin may represent a mechanism relating abdominal adiposity with depression onset. These results expand the body of evidence on the involvement of new biological factors in the pathophysiology of depression. Moreover, by demonstrating the reciprocal interaction between leptin and visceral fat, the present findings suggest a potential common shared biological link between depression, obesity, and their association with negative outcomes.

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