Relation of Serum Leptin to Blood Pressure of Japanese in Japan and Japanese-Americans in Hawaii

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Abstract—Data from animal studies clearly indicate an association between leptin and hypertension; results of human studies are less concordant. We investigated the role of leptin in obesity-related higher blood pressure (BP) in Japanese Americans living in Hawaii and Japanese in Japan. Serum leptin and BP were examined by standardized methods in men and women ages 40 to 59 years from 2 population samples, one Japanese American in Hawaii (88 men and 94 women) and the other Japanese in central Japan (123 men and 111 women). Multiple linear regression models were used to assess role of leptin in obesity-related higher BP. Across quartiles of leptin, there were significantly higher mean body mass index levels, systolic BP, and diastolic BP for both sexes and sites (P<0.01 to 0.02). In multivariate regression analyses using all of the data combined, relations of body mass index and leptin to systolic BP and diastolic BP remained significant with the interaction term (body mass index×log-leptin) in the models (P<0.01 to <0.05). These findings are consistent with the inference that leptin may be an independent mediator for obesity-related elevations in BP. (Hypertension. 2009;54:00-00.)

Key Words: leptin ■ Japanese in Japan and Hawaii ■ obesity ■ body mass index ■ mediator ■ blood pressure

Obesity is associated with increased cardiovascular morbidity and mortality, in part through its relation to adverse blood pressure (BP) levels. Leptin, named after the Greek leptos meaning thin, was identified by positional cloning of the mouse obese (ob) gene; it is regarded as a key molecule in the physiological regulation of body weight and energy balance.1 Leptin is produced and secreted mainly by adipocytes. It acts on the hypothalamus, altering energy intake by decreasing appetite and increasing energy expenditure via sympathetic stimulation of several tissues.2 Obese persons, however, remain hyperphagic despite their high circulating leptin concentrations, indicating hypothalamic insensitivity to leptin.3 Despite hypothalamic leptin resistance, the sympathoexcitatory effect of leptin is manifested after systemic or central neural administration of leptin.4 These findings led to the concept of selective leptin resistance.5 Mechanisms of obesity-related cardiovascular diseases are not fully understood; leptin effects on the cardiovascular system may play a role.

The International Study of Macro/Micronutrients and Blood Pressure (INTERMAP), Japan and Hawaii, investigated coronary heart disease risk factors in 4 Japanese population samples in Japan and a Japanese-American population sample in Hawaii.6,7 In this, we hypothesized that the relation of obesity to higher BP may be explained (at least partially) by a role played by leptin. Our samples, including Japanese in Japan and Japanese Americans in Hawaii, enable consideration in an ethnically homogenous cohort of whether serum leptin modifies the body mass index (BMI)-BP relationship in people with a wide range of BMIs (from 17.2 to 47.0 kg/m²) attributed to differences in lifestyle-related factors.

Methods
Detailed methods of the INTERMAP Study have been described.8,9 They are summarized here. Two standardized BP measurements were made on each of 4 different days; medical and lifestyle information and 2 timed 24-hour urine collections were obtained for each participant. In addition, nonfasting blood was drawn from the participants.6,7 We used data on analytes measured in these samples, as well as other data from INTERMAP.

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Participants
INTERMAP, Japan and Hawaii, participants ages 40 to 59 years were from 5 INTERMAP population samples: 4 in Japan and 1 in Hawaii.6,7 For the present study, serum leptin concentrations were measured on individuals from 2 of these samples, 1 from Japan and 1 from Hawaii. The 2 populations samples were Japanese residents in Aito Town, a rural town in Shiga prefecture, central Japan (129 men and 129 women), and third- and fourth-generation offspring of Japanese emigrants living in Honolulu (100 men and 106 women).6,8 Participants in Honolulu were asked about the ethnicity of their mother and father; those included in the study responded 100% Japanese to both. Aito Town was chosen because it was the only Japanese community sample; the other 3 samples were of factory workers. Although Aito Town is a rural community, only ~15% of residents are engaged in farming and fishing; 43% are involved in manufacturing and 42% in commerce and services. They were not significantly different from the other 3 samples in Japan in terms of BMI. There were only small differences in dietary and other lifestyle traits among the 4 samples in Japan; differences of those variables across Japan and Hawaii were larger.8 Among those in these 2 samples, 48 persons (24 Japanese and 24 Japanese Americans) were excluded because the volume of their stored serum specimen was not enough to measure leptin, leaving 234 Japanese individuals (123 men and 111 women) and 182 Japanese Americans (88 men and 94 women).

Ethics committees of the Shiga University of Medical Science, the Pacific Health Research Institute, and Northwestern University approved the study protocol. Written informed consent was obtained from all of the participants.

Anthropometric and Lifestyle Assessment
Participants visited the research centers 4 times on 2 pairs of consecutive days on average 3 weeks apart. Height and weight with light clothes were measured at each visit. Using a questionnaire, trained observers inquired about physical activity, smoking status, previous medical history of cerebrocardiovascular diseases/diabetes mellitus, use of medication (including antihypertensive medication), and so forth. BMI was calculated as weight divided by height squared (kilograms per meter squared).

Biochemical Measurements
Nonfasting blood was drawn on the second day of the first 2-day visit pair. Serum and plasma were obtained by centrifugation within 30 minutes of blood drawing and immediately refrigerated. Within 24 hours, all of the specimens were frozen and stored locally at ~70°C. Samples from the Hawaiian and Japanese centers were shipped to a central laboratory in Japan on dry ice. Individual samples from the 2 centers were randomly allocated for analysis to avoid systematic measurement bias. Serum leptin concentrations were measured by immunoassays from Linco Research (Millipore). Postprandial stability of leptin also has been shown in normal and obese persons, as well as in patients with type 2 diabetes mellitus.11,12

Data Analyses
SAS version 9.1 for Windows (SAS Institute) was used. Because the distribution of serum leptin was positively skewed, a logarithmic transformation was used to normalize the distribution (log-leptin). Sex- and site-specific participant characteristics by quartile of serum leptin concentration were analyzed. The Mantel-Haenszel chi-squared statistical test for nominal variables and the “contrast” option for ANOVA for continuous variables were performed to assess whether there was a significant trend across quartiles of leptin concentration. Partial correlation coefficients among BMI, age, log-leptin, systolic BP (SBP), and diastolic BP (DBP), adjusted for sex, were obtained using all of the sex/site data combined.

Multiple linear regression analysis with adjustment for confounders was used to examine the influence of leptin on the relation of BMI to SBP and DBP. Sex-site–specific analyses and analyses for all of the data combined were performed. Model 0 included age and log-leptin. Model 1 included age and BMI. Model 2 included model 1 covariates and whether subjects were on antihypertensive medication. Model 3 included model 2 covariates and alcohol consumption (grams per day), smoking (cigarettes per day), and urinary sodium and potassium excretions (millimoles per 24 hours). Model 4 included model 3 covariates plus log-leptin. Model 5 included model 4 plus an interaction term (BMI×log-leptin). Sex and an indicator for site (Hawaii=1 and Japan=0) were added in analyses using all of the data combined. Percentage reduction in the BMI coefficient was calculated to assess influence of the added leptin variable on the relation of BMI to SBP and DBP. In addition, a formal statistical comparison of the BMI-BP models with and without leptin to quantify the extent to which adding leptin to the models attenuates the BMI-BP relationship was done. Logistic analysis was done with hypertension as the dependent variable (defined as either drug treatment, SBP ≥140 mm Hg, or DBP ≥90 mm Hg) and BMI, log-leptin, site, age, and the interaction term (BMI×log-leptin) as covariates.

With a level at 0.05, number of predictors (as in model 4) at 10, the anticipated overall variance of the model (R²) at 0.20, and an addition to R² when the variable is entered last (ΔR²) at 0.02, calculated minimum required sample size for regression analysis was 172.13 Therefore, our sample size of 416 was ample for this study when all of the data are combined. All of the P values were 2-tailed. P<0.05 was considered significant.

Results
Characteristics of Participants by Quartile of Serum Leptin Concentration
Sex-specific characteristics of Japanese participants in Japan by quartile of serum leptin concentration are shown in Table 1. Mean BMI, SBP, and DBP were significantly greater in the higher leptin concentration groups in both men and women (all P values <0.01). The percentage of participants on antihypertensive medication was significantly greater in the higher leptin concentration groups in men (P=0.04). Prevalence of current smokers, mean cigarettes smoked per day, and urinary potassium excretion per day were significantly lower in the higher leptin concentration groups in men (P values of 0.01 to 0.02).

Sex-specific characteristics of participants of Japanese ethnicity living in Hawaii by quartile of serum leptin concentration are shown in Table 2. Mean BMI, SBP, DBP, urinary sodium excretion per day, and percentage of participants on antihypertensive medication were significantly greater in the higher leptin concentration groups in both men and women (P values <0.01 to 0.02).

For all of the participants combined, partial correlation coefficients adjusted for sex of BMI with log-leptin, SBP, and DBP; those of log-leptin with SBP and DBP were all statistically significant (all P values <0.01; Table 3). Partial correlation coefficient of age with SBP (P<0.01) and of SBP with DBP (P<0.01) were statistically significant.

Relation of BMI and Log-Leptin to SBP
Table 4 gives coefficients from multiple linear regression models used to examine relations of BMI and log-leptin to SBP for sex/site-specific strata and for all of the partici-
pants combined. With all of the data combined, log-leptin was significantly related to SBP (model 0), as was BMI (model 1). The addition to model 1 of possible confounding factors (antihypertensive treatment, alcohol intake, smoking, urinary sodium, and potassium excretion) reduced the coefficient for BMI modestly (18.2% in model 2 and 16.9% in model 3); the contribution of BMI to SBP remained significant (P<0.01). The addition of log-leptin to model 3 reduced the coefficient for BMI substantially by 54.8%; the relation of BMI to SBP was no longer significant (P=0.11) but the relation of log-leptin remained significant (P<0.01; model 4). Addition of the interaction term (BMI×log-leptin) to model 4 increased both coefficients for BMI and log-leptin (P values of 0.01 and <0.01; Model 5). The coefficient for the interaction was inverse, at 0.82 (P=0.04). Comparison of model 3 and model 4 BMI-SBP coefficients showed that BMI greater by 1 kg/m² was associated in model 3 with an SBP higher by 0.81 mm Hg (95% CI: 0.47 to 1.14) and in model 4 by 0.36 mm Hg (95% CI: 0.08 to 0.81; the latter 54.8% less). Sex/site-specific data were basically similar to those for all of the participants combined.

Relation of BMI and Log-Leptin to DBP

Table 5 gives coefficients from multiple linear regression models used to examine relations of BMI and log-leptin to DBP in sex/site-specific data and for all of the participants. In the latter analyses, log-leptin was significantly related to DBP (model 0), as was BMI (model 1). The addition to model 1 of possible confounding factors influenced the coefficient for BMI only slightly (models 2 and 3); the relation of BMI to DBP remained significant (P<0.01). The addition of log-leptin to model 3 reduced the coefficient for BMI greatly (46.1%); the relation of BMI and log-leptin to DBP both remained significant (P=0.03 for BMI; P=0.01 for log-leptin; model 4). The addition of the interaction term (BMI×log-leptin) to model 4 increased both coefficients for BMI and log-leptin (both P values <0.01; model 5). The

Table 1. Participant Characteristics by Quartile of Serum Leptin: 123 Men and 111 Women of Japanese in Aito Town (1997–1999 INTERMAP, Japan and Hawaii Study)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>Trend P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese, men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin range, ng/mL</td>
<td>2.7 to 4.9</td>
<td>5.1 to 7.0</td>
<td>7.2 to 10.3</td>
<td>10.4 to 28.9</td>
<td></td>
</tr>
<tr>
<td>N (subtotal=123)</td>
<td>26</td>
<td>29</td>
<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>49.5±5.6</td>
<td>49.1±6.6</td>
<td>51.5±6.1</td>
<td>49.6±6.3</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.1±1.8</td>
<td>22.5±2.1</td>
<td>23.8±1.4</td>
<td>25.6±3.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>114.2±10.6</td>
<td>115.0±9.1</td>
<td>115.6±11.7</td>
<td>124.0±14.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>69.3±5.9</td>
<td>70.9±8.0</td>
<td>71.2±7.7</td>
<td>75.5±9.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension Rx, %</td>
<td>7.7</td>
<td>6.9</td>
<td>7.1</td>
<td>14.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Alcohol consumers, %</td>
<td>92.3</td>
<td>93.1</td>
<td>85.7</td>
<td>85.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Alcohol intake, all, g/d</td>
<td>0.6±2.1</td>
<td>1.2±2.4</td>
<td>0.4±0.7</td>
<td>0.5±0.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>3.9</td>
<td>0.0</td>
<td>3.6</td>
<td>0.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Smoking, all, cigarettes per day</td>
<td>0.1±0.6</td>
<td>0.0±0.0</td>
<td>0.0±0.2</td>
<td>0.0±0.0</td>
<td>0.23</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>199.2±39.4</td>
<td>189.1±39.2</td>
<td>204.3±57.3</td>
<td>195.6±53.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Urinary potassium, mmol/24 h</td>
<td>51.4±14.9</td>
<td>51.4±15.9</td>
<td>49.0±15.3</td>
<td>51.6±15.4</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless otherwise described. Trend P values are for the relationship between the variables listed on the left and quartile of leptin, obtained by the Mantel-Haenzel χ² test and the “contrast” option for ANOVA. BMI indicates body mass index (range: 17.2 to 39.0 kg/m²); hypertension Rx, on antihypertensive medication.
coefficient for the interaction was inverse, at \(-0.56\) (\(P=0.06\)). In a comparison of model 3 and model 4 BMI-DBP coefficients, BMI higher by 1 kg/m² was associated with DBP higher in model 3 by 0.66 mm Hg (95% CI: 0.40 to 0.91) and in model 4 by 0.37 mm Hg (95% CI: 0.03 to 0.71; the latter 43.9% less).

**Relation of BMI and Log-Leptin to Hypertension**

Significant independent contributors to hypertension by logistic analysis were BMI (coefficient \(\beta=0.41\); \(P<0.01\)), log-leptin (\(\beta=6.98\); \(P<0.01\)), and the interaction term (BMI \(\times\) log-leptin, \(\beta=0.24\); \(P<0.01\)). Site, age, and sex were not significant.

**Discussion**

Using 2 population samples of common genetic background and diverse lifestyles, Japanese Americans in Hawaii and Japanese in Japan, with widely ranging BMIs, we showed that BMI and log-leptin related significantly to SBP and DBP.

It has been suggested that increased sympathetic nervous system activity plays a major role in the mechanism of obesity-associated adverse BP levels. In animal studies, leptin increases sympathetic nerve activity to the kidneys, hind-
Table 4. Relation of Variables to SBP: 416 Participants (211 Men and 205 Women), Japanese in Alto Town and Japan and Japanese Americans in Honolulu (INTERMAP, Japan and Hawaii Study)

<table>
<thead>
<tr>
<th>Model</th>
<th>All</th>
<th>JM</th>
<th>JW</th>
<th>HM</th>
<th>HW</th>
<th>% Change in BMI Coefficient From Model 1, All</th>
<th>% Change in BMI Coefficient From Model 3, All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 0</td>
<td>16.8†</td>
<td>16.8†</td>
<td>19.3†</td>
<td>12.9†</td>
<td>21.0†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.97†</td>
<td>1.44†</td>
<td>1.58†</td>
<td>0.83†</td>
<td>0.82†</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>0.79†</td>
<td>1.32†</td>
<td>1.47†</td>
<td>0.71†</td>
<td>0.63*</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>0.81†</td>
<td>1.45†</td>
<td>1.47†</td>
<td>0.55</td>
<td>0.54</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>0.36</td>
<td>0.99</td>
<td>0.83</td>
<td>0.24</td>
<td>0.30</td>
<td>62.4</td>
<td>54.8</td>
</tr>
<tr>
<td>Model 5</td>
<td>1.22†</td>
<td>2.06</td>
<td>1.35</td>
<td>0.50</td>
<td>2.93</td>
<td>30.6†</td>
<td>59.3</td>
</tr>
</tbody>
</table>

Results are for site- sex-specific and combined data analyses. Coefficients for BMI and log-leptin in multiple linear regression models were used to examine relations of variables to SBP in men (123 in Japan and 88 in Hawaii) and women (111 in Japan and 94 in Hawaii). Covariates in model 0 are age and log-leptin; model 1 covariates are age and BMI; model 2 covariates are model 1 + hypertension Rx; model 3 covariates are model 2 + alcohol, smoking, and urinary sodium and potassium excretions; model 4 covariates are model 3 + log-leptin; model 5 covariates are model 4 + interaction term (BMI × log-leptin). Sex and an indicator for site (Hawaii = 1 and Japan = 0) were added in sex- and site-combined analyses. Percentage changes in BMI coefficient from model 1 and model 3 of combined analyses are also shown. Ranges of other P values were as follows: site (<0.01), sex (<0.01 to 0.09), hypertension Rx (<0.01), alcohol (0.17 to 0.20), smoking (0.06 to 0.13), urinary sodium excretion (0.14 to 0.51), and urinary potassium excretion (0.15 to 0.34) in combined analysis. JM indicates Japanese men living in Japan; JW, Japanese women living in Japan; HM, men of Japanese ethnicity living in Honolulu; HW, women of Japanese ethnicity living in Honolulu; Hypertension Rx, on antihypertensive medication; alcohol, alcohol consumption (grams per day), smoking (cigarettes per day); log-leptin, log-transformed serum leptin concentration. Urinary sodium and urinary potassium were in millimoles per 24 hours. P values are indicated by *P < 0.05 and †P < 0.01.

Table 5. Relation of Variables to DBP: 416 Participants (211 Men and 205 Women), Japanese in Alto Town and Japan and Japanese Americans in Honolulu (INTERMAP, Japan and Hawaii Study)

<table>
<thead>
<tr>
<th>Model</th>
<th>All</th>
<th>JM</th>
<th>JW</th>
<th>HM</th>
<th>HW</th>
<th>% Change in BMI Coefficient From Model 1, All</th>
<th>% Change in BMI Coefficient From Model 3, All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 0</td>
<td>12.0†</td>
<td>18.2†</td>
<td>10.6†</td>
<td>10.8†</td>
<td>10.5†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.68†</td>
<td>1.59†</td>
<td>0.95†</td>
<td>0.58†</td>
<td>0.47†</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>0.64†</td>
<td>1.51†</td>
<td>0.94†</td>
<td>0.62†</td>
<td>0.36*</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>0.66†</td>
<td>1.60†</td>
<td>0.99†</td>
<td>0.62†</td>
<td>0.34</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>0.37†</td>
<td>1.24†</td>
<td>0.74†</td>
<td>0.29</td>
<td>0.27</td>
<td>5.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Model 5</td>
<td>0.95†</td>
<td>1.51</td>
<td>0.56</td>
<td>0.43</td>
<td>2.33*</td>
<td>20.6†</td>
<td>20.5</td>
</tr>
</tbody>
</table>

Results are for site- sex-specific and combined data analyses. Coefficients for BMI and log-leptin in multiple linear regression models were used to examine relations of variables to DBP in men (123 in Japan and 88 in Hawaii) and women (111 in Japan and 94 in Hawaii). Covariates in model 0 are age and log-leptin; model 1 covariates are age and BMI; model 2 covariates are model 1 + hypertension Rx; model 3 covariates are model 2 + alcohol, smoking, and urinary sodium and potassium excretions; model 4 covariates are model 3 + log-leptin; model 5 covariates are model 4 + interaction term (BMI × log-leptin). Sex and an indicator for site (Hawaii = 1 and Japan = 0) were added in sex- and site-combined analyses. Percentage changes in BMI coefficient from model 1 and model 3 of combined analyses are also shown. Ranges of other P values were as follows: site (<0.01), sex (<0.01 to 0.09), hypertension Rx (0.16 to 0.18), alcohol (0.09 to 0.10), smoking (0.51 to 0.76), urinary sodium excretion (0.73 to 0.84), and urinary potassium excretion (0.08 to 0.19) in combined analysis. JM indicates Japanese men living in Japan; JW, Japanese women living in Japan; HM, men of Japanese ethnicity living in Honolulu; HW, women of Japanese ethnicity living in Honolulu; Hypertension Rx, on antihypertensive medication; alcohol, alcohol consumption (grams per day), smoking (cigarettes per day); log-leptin, log-transformed serum leptin concentration. Urinary sodium and urinary potassium were in millimoles per 24 hours. P values are indicated by *P < 0.05 and †P < 0.01.
independent of age, BMI, abdominal adiposity, and fasting plasma insulin. In contrast, no association was found between leptin and BP in a study by Almeida-Pititto et al 21 of centrally obese Japanese-Brazilian women.

The present study takes advantage of the unusual opportunity to assess 2 population samples of common genetic background and diverse lifestyles, Japanese Americans in Hawaii and Japanese in Japan, with widely ranging BMIs, reflecting differences in lifestyles. The same samples were used previously to study the relation of long-chain n-3 polyunsaturated fatty acid intake to serum high-density lipoprotein cholesterol and the relation of dietary and other lifestyle traits to serum adiponectin concentration.10 A few other studies used similar settings to examine questions in cardiovascular epidemiology.22,23 In the present study, BMI and log-leptin, considered separately, had significant associations with SBP and DBP. When BMI and log-leptin were entered concomitantly with the interaction term (BMI×log-leptin) in multiple regression models, coefficients for relations of both BMI and log-leptin to SBP and to DBP became greater and were significant. The negative value of the interaction term (BMI×log-leptin) indicates that, when BMI is larger, relations of log-leptin to SBP and to DBP are less strong; when BMI is higher, relations of BMI to SBP and to DBP are less strong. These findings are consistent with the inference that leptin is an independent mediator for obesity-related higher SBP and DBP. Hemodynamic determinants of mean arterial pressure include cardiac output and systemic vascular resistance. Cardiac output is increased in obese adults.24 Leptin increases systemic vascular resistance via sympathetic tone. These mechanisms may account for our finding that both leptin and BMI remained significantly associated with SBP and DBP.

The main strengths of the present study are its population-based samples, standardized collection of high-quality BP and blood data, and use of multiple procedures for quality control. The study was limited by its 2-sample cross-sectional design. Findings may or may not be generalizable to all Japanese and to other populations. Additional studies are indicated on other mechanisms for obesity-related adverse BP and also genetic analyses on leptin genes to enable the use of mendelian randomization.25

**References**


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