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Adiponectin predicts incident hypertension independent of body fat distribution: observations from the Dallas Heart Study

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Abstract

Background—Excess adipose tissue has been implicated in the pathogenesis of insulin resistance and atherosclerosis, and is a key risk factor for blood pressure (BP) elevation. However, circulating levels of adiponectin, a protein produced by adipose tissue and widely implicated in the pathogenesis of insulin resistance and atherosclerosis, are inversely proportional to adiposity. The relationship between adiponectin and incident hypertension has not been determined in the general U.S. population.

Methods—Normotensive participants (n = 1,233) enrolled in the Dallas Heart Study, a multiethnic, probability-based population sample of Dallas County adults were followed for median of 7 years. Retroperitoneal, intraperitoneal, visceral, and subcutaneous adipose tissue were measured at baseline by magnetic resonance imaging. Liver fat content was measured by ^{1}H-magnetic resonance spectroscopy. Relative risk regression was used to determine the association of adiponectin with incident hypertension after adjustment for age, race, sex, BMI, smoking, diabetes, baseline systolic BP, total cholesterol, as well as regional fat depot.

Results—Of the 1,233 study participants (median age 40, 40% black, 56% women), 391 (32%) had developed hypertension over a median follow up of 7 years. Adiponectin levels were associated with reduced risk of incident hypertension (RR 0.81, 95% CI [0.68 – 0.96]) in the fully adjusted model, which included liver fat. Similar results were observed after adjustment for subcutaneous or visceral fat depots when tested individually or simultaneously in the model.

Conclusion—Our study suggested a protective role of adiponectin against incident hypertension independent of body fat distribution.

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Keywords

Hypertension; Adiponectin; Leptin; Visceral Adipose Tissue; Fat; Subcutaneous Adipose Tissue

Introduction

Hypertension is projected to afflict 30% of the global population by the year 2025 [1]. Obesity, particularly visceral obesity, is an increasingly common risk factor for hypertension [2–4]. Adipose tissue secretes a number of proteins and hormones, including adiponectin (APN), leptin, and interleukin-6, which have been implicated in the pathogenesis of insulin resistance and inflammation. Compared with subcutaneous fat tissue (SAT), visceral adipose tissue (VAT) secretes significantly less APN [5–7] and leptin [8, 9] which may explain a greater correlation between these adipokines with SAT than VAT. In preclinical models, APN conveys antihypertensive properties while leptin was shown to have the opposite action [10–12]. High circulating APN is associated with a lower risk of hypertension, while high levels of leptin are associated with increased burden of hypertension in several population-based studies in Europe and Asia[13]. However, none of these studies were conducted in ethnically diverse adults in the United States. Furthermore, the confounding influence of VAT, which may play a direct role in the subsequent development of hypertension or indirectly via altering adipokine secretion, was not determined. Accordingly, we examined the relationship between baseline adiponectin and leptin levels and incident hypertension in participants of the Dallas Heart Study, a multiethnic probability-based population sample of Dallas County adults. We also determined the association between these 2 adipokines and incident hypertension after adjustment for SAT, VAT, and liver fat, using the highly sensitive techniques of magnetic resonance imaging and ^{1}H-magnetic resonance spectroscopy.

Materials and Methods

Study Population

The Dallas Heart Study is a multiethnic, probability-based cohort study of Dallas County adults (ages 18 to 65 years at study entry), with deliberate oversampling of African-American participants[14]. As shown in Figure 1, the current study population was drawn from 2,743 participants who completed DHS phase 1 (DHS-1) from 2000 to 2002, which included blood pressure (BP) measurements, laboratory testing, abdominal magnetic resonance imaging (MRI), and ^{1}H-magnetic resonance spectroscopy. Those with baseline hypertension, defined as systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg, or on antihypertensive treatment for hypertension, were excluded. Participants with borderline BP elevations at baseline (SBP ≥ 130 or DBP ≥ 85 mm Hg) were also excluded to avoid minimal increases in BP meeting the incident hypertension definition. Participants with baseline known CVD were excluded. After these exclusions, 1774 participants were eligible for follow-up. Of these, 1,233 completed all 3 visits of DHS-1 and returned for DHS phase 2 (DHS-2), which consisted of follow-up studies during a single visit between 2007 and 2009. This comprised the current study population. There were no significant differences in medical history, demographics, or biomarker data between eligible participants who did and did not complete DHS-2[15]. All

participants provided written informed consent, and the University of Texas-Southwestern Medical Center institutional review board approved the protocol.

Hypertension Definition

Trained professionals obtained BP measurements after 5 min of rest in the seated position using an automated oscillometric device (Series #52,000, Welch Allyn, Arden, North Carolina). The last three of five total measurements were averaged. In both phases of the DHS, hypertension was defined as SBP ≥140 mm Hg, DBP ≥ 90 mm Hg, or the participant taking any antihypertensive medications.

Abdominal Fat Quantification

All participants in our current cohort (n = 1233) were scanned at their baseline exam by a 1.5-T MRI scanner (Intera, Philips Healthcare, Best, the Netherlands). Retroperitoneal, intraperitoneal, and SAT abdominal fat masses were quantified by a single MRI slice taken at the L2–L3 level as previously described [16]. Areas were converted to mass (kg) as previously described [17]. VAT was defined as the combination of both retroperitoneal and intraperitoneal fat masses to express the total intra-abdominal fat mass[15, 18]. A subset of our subjects (n = 1101) also underwent ^{1}H-magnetic resonance spectroscopy for hepatic triglyceride quantification, as previously described [19].

Biomarker Analysis

Fasting blood samples were collected in tubes containing EDTA and were maintained at 4°C for <4 h. Plasma aliquots were then removed and stored at −80°C until assays were performed. Samples were analyzed for high-sensitivity C-reactive protein (hs-CRP), MMP 9 (matrix metallopeptidase 9), sRAGE (soluble receptor of advanced glycation end products), VEGF (Vascular endothelial growth factor) interleukin (IL)-6, cystatin-C, N-terminal pro–B-type natriuretic peptide (NT-pro-BNP), adiponectin, leptin, fasting glucose, and insulin levels (supplemental appendix).

Statistical Analysis

Baseline demographic, clinical, laboratory, and imaging variables are expressed as mean ± standard deviation, median (25th, 75th percentile) or proportions, as appropriate. Differences in characteristics between participants who remained normotensive and those who developed hypertension were compared using chi-square tests or the Wilcoxon rank sum test. Multivariable relative risk regression models with a log link and binomial error distribution were created to analyze associations between baseline adiponectin as well as leptin and incident hypertension while adjusting for age, sex, race/ethnicity, history of smoking, diabetes mellitus, baseline SBP and individual measures of adiposity. Race and sex-specific adiponectin (supplemental appendix table 2) and leptin levels were used in quintile analysis. Correlation coefficients for select confounding variables are shown in the online appendix. Interactions were also tested in the fully adjusted model to assess for differential relationships between adiponectin and incident hypertension by sex (male vs female), and race (black vs. non-black). Two-sided p values <0.05 were considered significant. All analyses were performed using SAS version 9.4 (SAS Corporation, Cary, North Carolina).

Results

Among 1,233 initially normotensive participants (median age, 40 years at study entry; 56% women; 40% black), 391 (32%) had developed hypertension after a median follow up of 7 years. Baseline characteristics of participants who remained normotensive (NT, n=842) and those who became hypertensive (HT, n=391) are shown in Table 1. Compared with the NT group, participants who developed hypertension at follow up were older, had higher SBP, DBP, BMI, WC, fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), VAT, SAT and Liver fat (Table 1). Median adiponectin among NT subjects was 7.7μg/ml and among those who developed hypertension was 6.7 μg/ml ($p < 0.05$). Median leptin was 9.5ng/ml among NT subjects and 15.7 ng/ml among those who developed hypertension Table 2 shows baseline characteristics stratified by adiponectin quintiles. Higher levels of baseline adiponectin were associated with lower levels of leptin, BMI, WC, VAT, SAT, RP fat, IP fat Liver fat, TC, TG, FPG, HOMA-IR, and hs-CRP; and higher age, alcohol use, and levels of NT-proBNP (Table 2). Adiponectin levels were inversely correlated with hs-CRP (supplemental appendix table 1, $r = -0.22$, $p< 0.05$), MMP-9 ($r = -0.15$, $p < 0.05$), and ICAM-1 (-0.07, $p <0.05$); and were positively correlated with NT-proBNP ($r = 0.38$, $p <0.05$) and sRAGE ($r = 0.18$, $p< 0.05$). Adiponectin was not correlated with levels of VCAM-1, leptin, IL-6, or VEGF (supplemental appendix table 1)

Multivariable regression models showed an inverse relationship between baseline adiponectin levels and the risk of incident hypertension after adjusting for potential confounders, including sex, race, baseline age, smoking, diabetes, BMI, total cholesterol, systolic BP, hs-CRP, and NT-pro BNP (model 3, Table 3). This association was also statistically significant in models that added VAT, SAT, IP fat, RP fat, liver fat individually to this baseline model (Table 3 and Fig. 2). When SAT and VAT were simultaneously added to the model 3, the association between adiponectin and incident hypertension remained unchanged (RR 0.84; 95% CI; 0.72 – 0.98). Similarly, when MMP-9, ICAM-1, and sRAGE were simultaneously entered in the model 3 along with VAT, higher levels of adiponectin continued to be associated with lower risk of hypertension (RR 0.79; 95% CI; 0.66 – 0.94). There was a graded reduction in the risk of incident hypertension with increasing race- and sex- specific adiponectin quintiles, which was significant in the fourth and fifth adiponectin quintiles (Fig. 2). In contrast, the association of leptin with incident hypertension seen in the unadjusted model was completely attenuated after adjusting for either BMI or body fat (Table 4 and Fig. 3).

There were no significant subgroup interactions for the association between adiponectin and incident hypertension in subgroups defined by age, sex, race, diabetes, and BMI (All interaction p-values > 0.1 except for age where interaction p-value = 0.09).

Discussion

The major findings from this study are three fold. First, circulating adiponectin levels is associated with reduced risk of future development of hypertension in a multiethnic, probability-based population sample of Dallas county adults. Second, this association persisted after further adjustment for visceral or subcutaneous fat depots, suggesting an

adiposity-independent antihypertensive property of adiponectin. Third, no association with hypertension was seen with leptin, another major peptide produced by adipose.

Adiponectin is secreted by adipose tissue and has been implicated in the pathogenesis of insulin resistance and hypertension[13, 20–23]. Studies in genetically obese KKAy mice demonstrated lower plasma adiponectin levels and higher BP than the control mice. Hypertension in the obese KKAy mice was ameliorated by delivery of adenovirus expressing adiponectin[10]. Adiponectin-deficient mice developed hypertension despite having normal body weight and insulin sensitivity, suggesting direct antihypertensive action of adiponectin independent of obesity[10]. Mechanisms underlying BP lowering effects of adiponectin is unknown but expression of vascular endothelial nitric oxide (NO) synthase (eNOS) and prostaglandin I_2 synthase may play a role[10]. More recently, adiponectin knockout mice were shown to display both elevated resting heart rate and 24-hour urinary epinephrine excretion, suggesting sympatho-inhibitory action of adiponectin[11]. Adiponectin may also protect against incident hypertension through its anti-inflammatory effects [24]. C-reactive protein (CRP), an acute phase reactant, has been shown to increase BP in mice[25, 26] and has been linked to increased risk of incident hypertension in humans[27–30]. Consistent with the anti-inflammatory properties of adiponectin, we found that hs-CRP was inversely correlated with adiponectin in our study ($r = -0.22$, $p < 0.01$).

Despite multiple studies showing a BP lowering property of adiponectin in rodents, the evidence in humans is less consistent. While prospective studies in Chinese and Japanese populations indicated that higher levels of adiponectin were associated with a lower risk of hypertension [31, 32], studies from Denmark [33, 34] and Turkey [35] failed to confirm these findings. The only study conducted in the U.S., the Women's Health Initiative-Observational Study (WHI-OS), showed an inverse relationship between baseline adiponectin level quartiles and incident hypertension in black but not white postmenopausal women after adjusting for body mass index and relevant risk factors[36]. However, none of these previous studies were conducted in an ethnically diverse US adult men and women. Furthermore, none of these previous studies specifically addressed the relationship between adiponectin and BP after accounting for regional fat accumulation. This is knowledge gap is particularly important as a recent analysis indicated that visceral adiposity, but not total or subcutaneous adiposity, was associated with subsequent development of hypertension[37].

Leptin is another major adipokine involved in energy homeostasis. In contrast to APN, leptin levels were increased in human obesity and reduced after weight loss[24, 38]. Leptin promotes hypertension in rodents via stimulation of sympathetic nervous system through activation of leptin receptors in the hypothalamic neurons[11, 12]. Leptin promotes neointimal hyperplasia via vascular leptin receptors, which may further contribute to elevated BP [39, 40]. Like APN, leptin stimulates NO production in the vascular cells by increasing eNOS phosphorylation and activation[41], which may negate its hypertensive action via sympathetic stimulation. Leptin is a significant predictor of incident hypertension in several population studies from Italy and Denmark[33, 34, 42]. Similarly, one study in older Caucasian Americans demonstrated increased odds of incident hypertension after adjusting for age, BMI, systolic BP, total cholesterol, medications, and cardiovascular disease [43]. However, the results of these studies have been challenged by a recent small

study in patients with lipodystrophy showing no significant change in BP after short-term treatment with recombinant human leptin [44]. Our study extends this previous observation in lipodystrophy to a larger and more diverse general population sample, including 40% African Americans, the population with the highest burden of hypertension which has not been examined in prior prospective observational studies.

The strengths of our study include the measurement of adipokines in a large, multiethnic cohort, which significantly improves generalizability to the US population compared with prior studies. The precise measurement of several visceral fat compartments using magnetic resonance imaging and ^{1}H-magnetic resonance spectroscopy allows us to explore the role of these adipokines on incident hypertension beyond measurement of BMI alone. Our study is also limited by several factors. Although adiponectin exists as high molecular weight, low molecular weight, and trimer forms[45–48], only total adiponectin was measured in this study. The observational design precludes any conclusions about causality. Furthermore, adiponectin and leptin were measured only once, limiting any ability to draw conclusions about how longitudinal changes in adiponectin affects incident hypertension. Although our study was not designed with statistical power to formally test for potential interaction by race/ethnicity, the point estimates for association between adiponectin with incident hypertension were similar for Black vs Non-Black participants. Furthermore, the interaction p value for incident hypertension of blacks vs. non-blacks subgroup is not significant ($p > 0.1$). Thus, we believe that the relationship of adiponectin and incident hypertension is independent of race/ethnicity but needs to be further confirmed in the larger cohorts.

In conclusion, our study suggests a protective role of adiponectin against the future development of hypertension, independent of body fat distribution. Further studies are needed to corroborate the findings from this study and to determine whether the association noted is evident as well for incident hypertension defined on the basis of ambulatory blood pressure measurements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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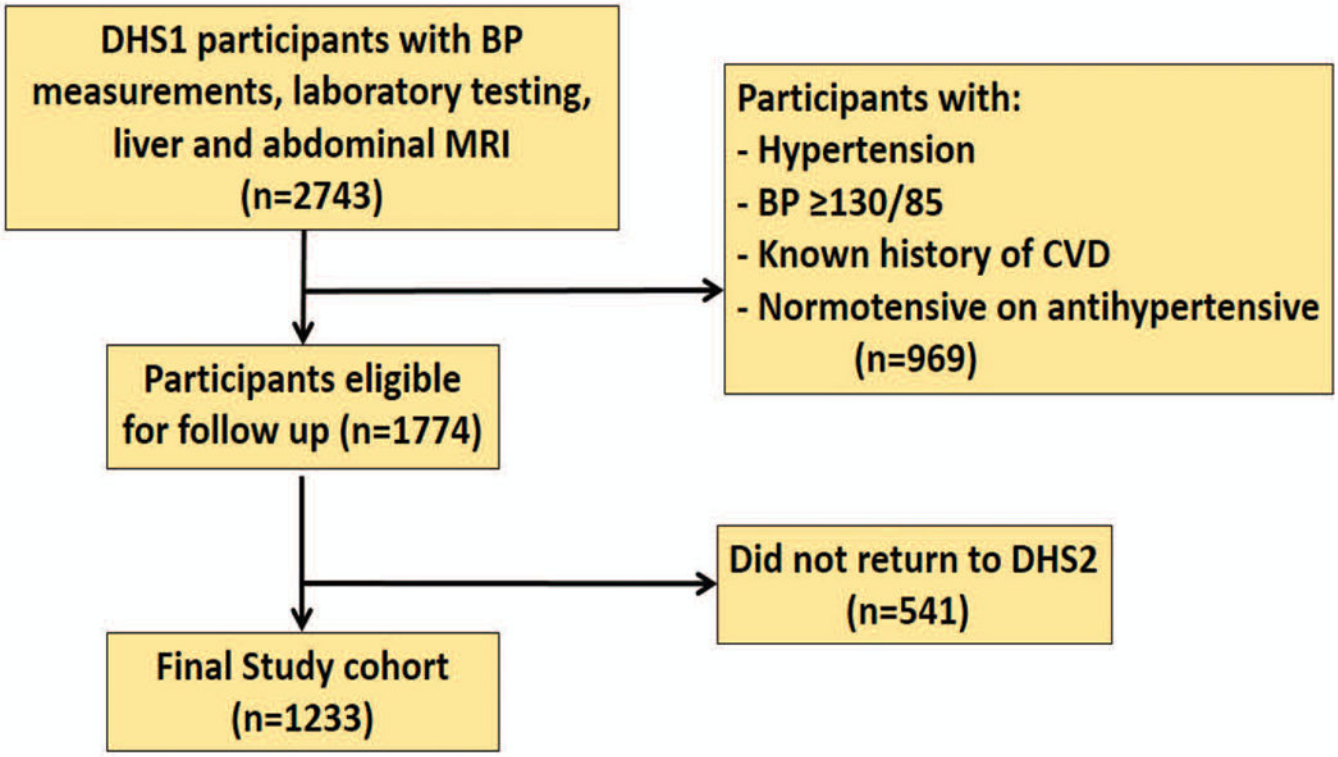

Figure 1.
Flow diagram of study cohort

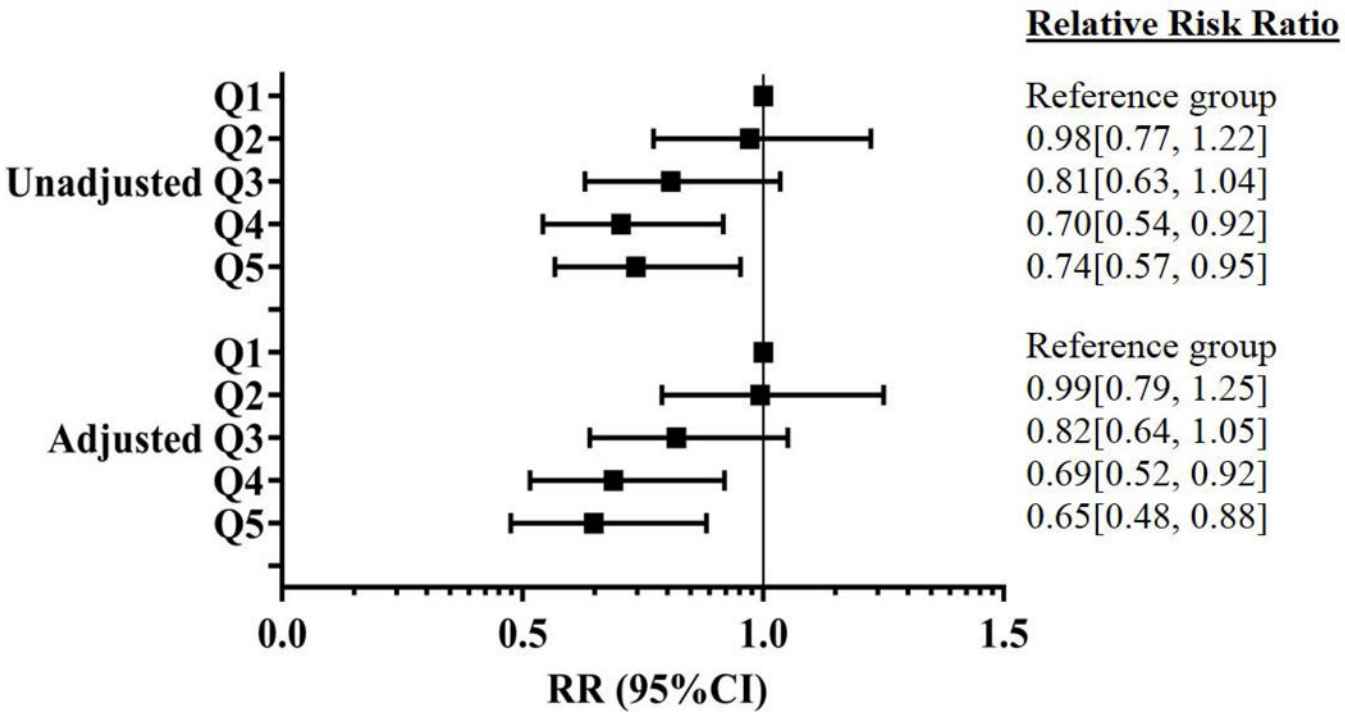

Figure 2.

Forest plot of relative risk for incident hypertension according to baseline adiponectin quintiles in the whole population after adjustment for liver fat, clinical, and relevant variables (Age, smoking, diabetes, BMI, total cholesterol, baseline systolic BP, hs-CRP, NT-pro BNP)

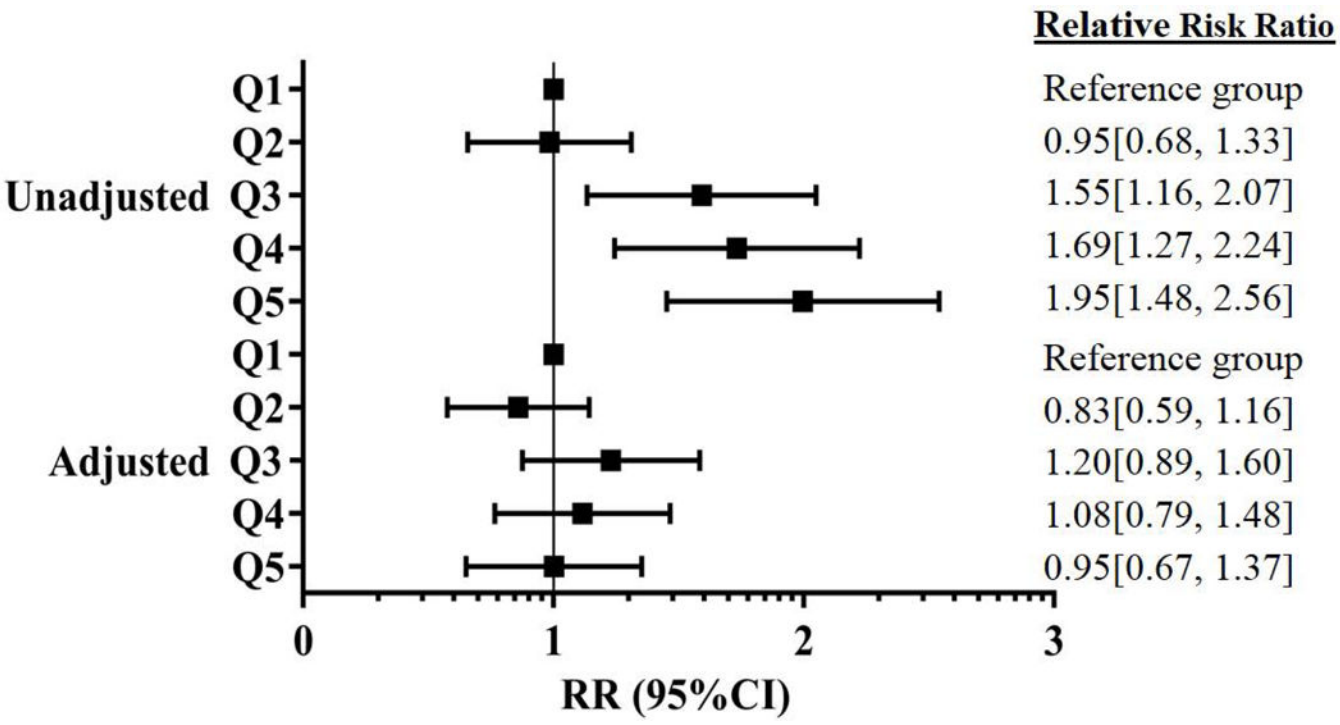

Figure 3.

Forest plot for relative risk for incident hypertension according to baseline leptin quintiles in the whole population after adjustment for liver fat, clinical, and relevant variables (age, sex, race, smoking, diabetes, BMI, HDL cholesterol, total cholesterol, baseline systolic BP, hs-CRP, NT-pro BNP)

Table 1

Baseline Characteristics

Variable	NT (n = 842)	HT (n= 391)	* p value
Adiponectin, (μg/ml) †	7.7 (5.0, 10.6)	6.7 (4.6, 9.2)	<0.01
Leptin, (ng/mL) †	9.5 (4.2, 19.9)	15.7 (6.1, 30.0)	<0.01
Age (yrs)	41±9	45 ± 9	<0.01
Male (%)	45%	40%	<0.01
Black (%)	34%	51%	<0.01
SBP (mmHg)	116 ±10	127 ±12	<0.01
DBP (mmHg)	73± 7	80 ± 7	<0.01
BMI (kg/m^2)	28 ± 6	31 ± 7	<0.01
WC (inches)	93 ±14	100 ±17	<0.01
VAT (kg)	1.9 ± 0.9	2.2 ±1.0	<0.01
RPfat (kg)	0.7 ± 0.4	0.9 ±0.5	<0.01
IP fat(kg)	1.2 ± 0.6	1.4 ±0.8	<0.01
SAT (kg)	4.2 ± 2.5	5.4 ± 3.2	<0.01
Liver fat (%)	4 ± 5	6 ± 6	<0.01
HOMA-IR	3.1 ±3.5	4.2 ± 4.3	<0.01
Fasting glucose (mg/dl)	93 ±28	99 ± 35	<0.01
Total cholesterol (mg/dl)	178 ± 38	182 ± 39	0.09
HDL (mg/dl)	51 ± 6	50 ± 15	0.29
TG, (mg/dL) †	87 (63, 124)	98 (68, 149)	<0.01
hs-CRP (mg/dL) †	1.9 (0.8, 4.4)	2.6 (1.2, 6.9)	<0.01
NT-proBNP (pg/ml) †	26.2 (12.7, 49.5)	25.9 (11.1, 54.4)	0.84
MCP-1 (pg/ml) †	164.7 (121.1, 219.4)	157 (117, 215)	0.12
IL-6 (pg/ml)	16.8 (0, 35.8)	17.0 (0, 32.4)	0.85
IL-18 (pg/ml)	477 (338, 713)	498 (337, 721)	0.62
Alcohol, g/w †	6 (0, 39)	4.3 (0, 39)	0.54
GFR (ml/min)	99 ±20	101 ± 21	0.33

* p value comparing 2 groups

† Median (interquartile range). All other values are mean ± standard deviation or n (%)

BMI = body mass index; DBP = diastolic blood pressure; GFR = glomerular filtration rate; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IHT = incident hypertension; IL-6 = interleukin-6; IL -18 = interleukin 18; IP = intraperitoneal; LDL = low-density lipoprotein; MCP-1 = monocyte chemoattractant protein- 1; NT = normotension; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RP = retroperitoneal; SAT = subcutaneous adipose tissue; SBP = systolic blood pressure, VAT = visceral adipose tissue; WC = waist circumference.

Table 2

Baseline Characteristics by Age and Sex-Specific Adiponectin Quintiles

Variable	Q1	Q2	Q3	Q4	Q5	* p-trend
Adiponectin, ug/ml †	3.45 (2.78, 4.14)	5.3 (4.5, 6.1)	7.1 (6.2, 8.2)	9.2 (8.2,10.6)	13.3 (11.0,17.0)	<0.05
Leptin, ng/mL †	14.9 (6.3,29.3)	13.8 (5.4, 25.7)	11.5 (5.2,3.8)	9.0 (4.1,18.3)	7.8 (3.1, 17.3)	<0.05
Age, yrs	40 ± 9	42 ± 8	42 ± 8	42 ± 9	44 ± 9	<0.05
Male, n (%)	105 (43)	108 (43)	108 (44)	108 (43)	107 (44)	0.9
Black, n (%)	96 (40)	98 (39)	97 (39)	98 (39)	97 (39)	0.9
SBP, mm Hg	120 ± 11	120 ± 12	119 ± 12	119 ± 12	120 ± 13	0.5
DBP, mm Hg	76 ±7	75 ± 8	75 ± 9	75 ± 8	75 ± 8	0.3
BMI, kg/m^2	33 ± 7	31 ± 7	29 ± 7	27 ± 6	26 ± 6	<0.05
WC, cm	102 ± 16	99 ± 15	96 ± 15	91 ± 1.5	88 ± 13	<0.05
VAT, kg	2.4 ± 1.0	2.2 ± 0.9	2.1 ± 1.0	1.8 ± 0.9	1.6 ± 0.8	<0.05
RP fat, kg	0.9 ± 0.5	0.9 ± 0.4	0.8 ± 0.4	0.7 ± 0.3	0.7 ± 0.6	<0.05
IP fat, kg	1.4 ± 0.8	1.4 ± 0.6	1.3 ± 0.6	1.1 ± 0.6	0.9 ± 0.8	<0.05
SAT, kg	5.6 ± 3	5.1 ± 2.8	4.8± 23.0	3.8 ± 2.3	3.5 ± 2.2	<0.05
Liver fat, %	8 ± 7	6 ± 6	5 ± 6	4 ± 4	3 ± 3	<0.05
HOMA_IR	5.1 ± 4.4	3.8 ±3.1	3.4± 3.9	2.6 ± 2.7	2.5 ± 4.2	<0.05
FPG, mg/dL	102 ± 43	97 ± 31	93 ± 17	93 ± 35	90 ±14	<0.05
TC, mg/dL	181 ± 41	181 ± 39	177 ± 36	178 ± 37	180 ± 38	0.9
HDL-C, mg/dL	44 ± 14	46 ± 11	50 ± 13	56 ± 15	59 ± 17	<0.05
TG, mg/dL †	111 (70, 79)	106 (70, 156)	88(64, 122)	81(60,116)	78(56,107)	<0.05
hs-CRP, mg/dL †	3.7 (1.5, 7.4)	2.7(1.1,5.9)	2.2(0.8,5.8)	1.6(0.7,3.8)	1.3(0.6,2.8)	<0.05
NT-proBNP, pg/ml †	17.1 (8.1, 41.3)	23.3 (10.0, 41.2)	24.9 (12.6,44.5)	29.5(14.6,58.9)	39.3(18,76.5)	<0.05
MCP-1, pg/ml †	159 (124, 219)	175 (124, 227)	167 (124, 218)	156 (111, 211)	165(119, 214)	0.4
IL-6, pg/ml †	156 (0, 32.0)	17.3 (0, 30.7)	18.8 (0, 41.1)	16.2(0, 35.8)	17.3 (0, 35.6)	0.17

Variable	Q1	Q2	Q3	Q4	Q5	* p-trend
Alcohol, g/w †	4(0,30)	3(0, 39)	8 (1,39)	8(0,59)	6(0,59)	<0.05
GFR, ml/min	102 ± 20	101 ± 20	97 ± 18	99 ± 21	101 ± 22	0.1

* p trend comparing 5 groups

† Median (interquartile range). All other values are mean ± standard deviation or n

BMI = body mass index; DBP = diastolic blood pressure; FPG = fasting plasma glucose; GFR = glomerular filtration rate; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IHT = incident hypertension; IL-6 = interleukin-6; IP = intraperitoneal; LDL = low-density lipoprotein; MCP-1 = monocyte chemoattractant protein- 1; NT = normotension; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RP = retroperitoneal; SAT = subcutaneous adipose tissue; SBP = systolic blood pressure; TC= total cholesterol; VAT = visceral adipose tissue; WC = waist circumference.

TABLE 3

Relative risk of developing hypertension per 1 S.D. higher baseline adiponectin

	RR (95%CI)	p- value
Unadjusted	0.77 (0.67 – 0.88)	<0.05
Model 1	0.85 (0.73 – 0.99)	<0.05
Model 2	0.83 (0.72 – 0.96)	<0.05
Model 3	0.81 (0.70 – 0.93)	<0.05
Model 4		
RP fat (kg)	0.82 (0.71 – 0.94)	<0.05
IP fat (kg)	0.82 (0.71– 0.95)	<0.05
VAT fat (kg)	0.83 (0.72 – 0.96)	<0.05
SAT fat (kg)	0.81 (0.70 – 0.93)	<0.05
Liver Fat (%)	0.80 (0.68 – 0.94)	<0.05

RR = Relative Risk, CI = Confidence Interval, RP=Retroperitoneal, IP = Intraperitoneal, VAT= Visceral Adipose Tissue, SAT= Subcutaneous Adipose Tissue

Model 1 = age, sex, race, BMI

Model 2 = Model 1 + smoking history, diabetes, baseline systolic BP, total cholesterol

Model 3 = Model 2 + hs-CRP, NT-proBNP

Model 4 = Model 3 + RP fat, IP fat, VAT, SAT, Liver fat added individually

TABLE 4

Relative risk of developing hypertension per 1-S.D. higher baseline leptin

	RR (95%CI)	p- value
Unadjusted	1.25 (1.15 – 1.36)	<0.05
Model 1	1.06 (0.94 – 1.19)	0.33
Model 2	1.06 (0.93 – 1.20)	0.39
Model 3	1.06 (0.93 – 1.21)	0.35
Model 4		
RP fat (kg)	1.05 (0.92 – 1.19)	0.47
IP fat (kg)	1.04 (0.91 – 1.19)	0.57
VAT fat (kg)	1.02 (0.90 – 1.17)	0.72
SAT fat (kg)	1.06 (0.93 – 1.21)	0.39
Liver Fat (%)	1.03 (0.90 – 1.18)	0.68

RR = Relative Risk, CI = Confidence Interval, RP=Retroperitoneal, IP = Intraperitoneal, VAT= Visceral Adipose Tissue, SAT= Subcutaneous Adipose Tissue

Model 1 = age, sex, race, BMI

Model 2 = Model 1 + smoking history, diabetes, baseline systolic BP, HDL cholesterol, total cholesterol

Model 3 = Model 2 + hs-CRP, NT-proBNP

Model 4 = Model 3 + RP fat, IP fat, VAT, SAT, Liver fat added individually