ORIGINAL RESEARCH

Prospective Relation of Circulating Adipokines to Incident Metabolic Syndrome: The Framingham Heart Study

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***Background*—**Adipokines are elaborated by adipose tissue and are associated with glycemic, lipid, and vascular traits. We hypothesized that in a cross-sectional analysis circulating adipokines are altered among subsets of obesity stratified by presence versus absence of metabolic syndrome (MetS) and prospectively predict the incidence of MetS.

***Methods and Results*—**Participants in the community-based Framingham Third Generation Cohort who attended examination cycle 1 were included in the study (2002–2005; N=3777, mean age, 40 years; 59% women). Circulating adiponectin, leptin, leptin receptor, fetuin-A, fatty acid–binding protein 4, and retinol binding protein 4 were assayed and related to incident MetS in follow-up (mean 6 years). The adipokines were compared among individuals with excess body weight (body mass index ≥25 kg/m^2) and prevalent MetS, excess body weight without MetS (metabolically healthy obese), and normal-weight with MetS (metabolically obese, normal-weight) with normal-weight participants without MetS as a referent. Metabolically healthy obese individuals (n=1467) had higher circulating levels of fetuin-A and fatty acid–binding protein 4 but lower levels of leptin, leptin receptor, and adiponectin (P<0.001 for all). The adipokine panel was associated with incident MetS (263 new-onset cases; P=0.002). Higher circulating concentrations of retinol-binding protein 4 and fetuin-A were associated with incidence of MetS (odds ratio per 1-SD increment log marker, 1.21; 95% CI, 1.03–1.41 [P=0.02] and 1.17; 95% CI, 1.01–1.34 [P=0.03], respectively).

***Conclusions*—**In our community-based sample of young to middle-aged adults, metabolically healthy obese individuals demonstrated an adverse adipokine profile. Higher circulating levels of retinol-binding protein 4 and fetuin-A marked future cardiometabolic risk. **(*J Am Heart Assoc*. 2017;6:e004974. DOI: 10.1161/JAHA.116.004974.)**

Key Words: adipokine • epidemiology • metabolic syndrome • obesity • risk factor

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Metabolic syndrome (MetS) is associated with an increased risk of diabetes mellitus (DM) and cardiovascular disease (CVD), likely attributable to its constituent constellation of risk factors.[1,2] In addition, there is significant variation in cardiometabolic risk among individuals with similar body mass index (BMI). While some persons with excess weight may have profound metabolic derangements, nearly 40% of obese individuals have a normal metabolic profile (so-called metabolically healthy obese [MHO]).[3] Conversely, some normal-weight persons may have substantial metabolic derangements (termed metabolically obese, normal weight [MONW]). Since BMI alone cannot consistently predict cardiometabolic risk, researchers have focused on variations in adipose tissue endocrine function to understand the pathogenesis of cardiometabolic risk in obese individuals.[4,5] Adipokines are biologically active compounds elaborated by adipose tissue, with examples including leptin, its counter-regulatory circulating receptor (LEP-R), adiponectin, fetuin-A, fatty acid–binding protein 4 (FABP4), and retinol-binding protein 4 (RBP4).[6] Investigators have reported that some adipokines individually predict cardiometabolic risk, but, to our knowledge, the prospective association of a panel of adipokines for MetS in both MHO and MONW groups has not been previously evaluated.[6] We hypothesized that in a cross-sectional analysis both MHO and MONW individuals have an altered circulating

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Clinical Perspective

What is New?

- Since the association between obesity and MetS traits is variable, we explored the association between circulating adipokines and future incidence of MetS.
- We observed that higher levels of RBP4 and fetuin-A were associated with future incidence of MetS.

What are the Clinical Implications?

- With future investigation, circulating adipokines may serve to identify persons at high risk of MetS.
- Future studies may also explore the role of adipokines in the pathophysiology of MetS and the association between MetS and atherosclerotic events.

adipokine profile compared with a referent group with normal BMI (<25 kg/m^2) and without MetS. We also postulated that in a prospective analysis, an adipokine profile characterized by higher circulating levels of fetuin-A, FABP4, RBP4, and LEP-R but lower concentrations of adiponectin and leptin will be prospectively associated with a greater incidence of MetS. We tested these hypotheses using a multimarker adipokine panel in a community-based sample of young to middle-aged adults.

Methods

Study Procedures

The design and the selection criteria of the Third Generation Cohort of the Framingham Heart Study have been detailed elsewhere.[7] The institutional review board of Boston University approved the study protocol, and all study participants provided written informed consent. At each Framingham Heart Study examination, attendees underwent a routine medical history with a standardized physical examination including anthropometry and blood pressure (BP) measurement. After the participant rested in a seated position for 10 minutes, a physician measured the participant's BP using a standardized protocol with mercury column sphygmomanometer and an appropriately sized cuff. The average of 2 readings constituted the examination BP. Self-reported use of cigarettes within the year preceding the baseline examination was defined as current smoking.

Attendees underwent laboratory assessment of other risk factors in a fasting state. Phlebotomy was performed after participants rested for 10 minutes in the supine position. Specimens were stored at −80°C without freeze-thaw cycles until assay. Fasting levels of plasma high-density lipoprotein cholesterol, triglycerides, insulin, and glucose were measured using standardized assays. Plasma levels of fetuin-A and FABP4 were measured using sandwich ELISA (BioVendor Reasearch and Diagnostic Products). Plasma levels of leptin, LEP-R, RBP4, and adiponectin were measured using ELISA (R&D Systems). The average interassay coefficients of variation for the biomarkers were as follows: leptin 4.97%, LEP-R 4.01%, FABP4 2.38%, RBP4 2.18%, fetuin-A 2.52%, and adiponectin 2.23%.

Study Samples

For the present study, participants who attended the first examination cycle (2002–2005) were eligible. Of 4095 participants who attended the first baseline examination, 221 individuals were excluded for having missing adipokine data, 53 for missing covariates, 44 for prevalent CVD (defined as coronary heart disease, congestive heart failure, intermittent claudication, or cerebrovascular disease), and one for missing serum creatinine. The remaining 3777 participants (sample 1) were included in the cross-sectional adipokine analyses (Figure 1).

For the prospective analyses, we used a 2-step analysis where longitudinal associations were identified between adipokines and incident MetS at the follow-up examination in participants without MetS at the baseline examination. Adipokines identified at this step were examined for longitudinal associations with individual change in components of MetS measured between the baseline and follow-up examinations. Of examination cycle 1 attendees, 2669 participants

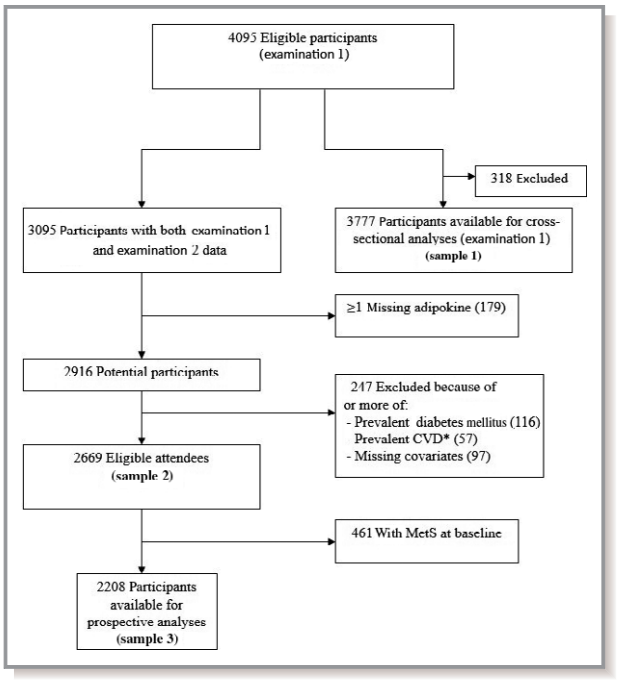


Figure 1. Flow diagram of respective sample inclusion/exclusion criteria. CVD indicates cardiovascular disease; MetS, metabolic syndrome.

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subsequently attended examination cycle 2 (2008–2011), a mean of 6 years after the baseline examination (sample 2), and were examined for associations with the individual MetS traits. Of sample 2, a total of 461 participants were excluded for prevalent MetS at the baseline examination, prevalent CVD, prevalent DM (use of antiglycemic agents or fasting plasma glucose ≥100 mg/dL), serum creatinine >2.0 mg/dL, missing adipokine data, or missing covariates, leaving 2208 participants (sample 3) eligible for analyses relating adipokine concentrations to the incidence of MetS.

Outcome Definition

Using the National Cholesterol Education Program Adult Treatment Panel III guidelines, MetS was defined as the presence of 3 or more of the following: elevated BP (≥130 mm Hg systolic, ≥85 mm Hg diastolic) or treatment for high BP; hypertriglyceridemia (≥150 mg/dL) or treatment with lipid-lowering treatment; low high-density lipoprotein cholesterol (<40 mg/dL in men, <50 mg/dL in women); hyperglycemia (fasting glucose ≥100 mg/dL) or treatment with oral hypoglycemic agents or insulin; and increased waist circumference (≥102 cm for men, ≥88 cm for women).[1,2]

Statistical Analyses

Adipokine concentrations were standardized within sex (mean=0, SD=1) to account for sex differences in their distributions. Pairwise Pearson correlation coefficients were calculated to assess the relations among the adipokines. The homeostasis model assessment insulin resistance index (HOMA-IR) was calculated using the formula: fasting insulin×fasting glucose/22.5.[8]

Cross-sectional analyses

Participants were grouped according to BMI <25 kg/m^2 versus ≥25 kg/m^2 (normal weight and overweight, respectively). Participants were divided into 4 groups: (1) absence of MetS and BMI <25 kg/m^2; (2) presence of MetS and BMI <25 kg/m^2 (MONW); (3) absence of MetS and BMI ≥25 kg/m^2 (MHO); and (4) presence of MetS and BMI ≥25 kg/m^2 (at risk for overweight). Using the absence of MetS and BMI <25 kg/m^2 as the referent group, we compared the mean levels of adipokines among the 4 groups.

Longitudinal analyses: multimarker panel and incidence of MetS

We used a conservative 2-step multimarker strategy to relate the adipokines (modeled as sex-standardized continuous variables) to the incidence of MetS in participants in sample 3. First, we used multivariable logistic regression to relate the entire panel of adipokines to incident MetS. We adjusted for age, sex, and baseline MetS component levels, which included waist circumference. We estimated a chi-square test–derived global *P* value using a likelihood ratio test examining the difference between the −2 log-likelihood models of clinical covariates alone versus clinical covariates plus all adipokines as a panel. If the panel global *P* value was <0.05, we then used backward elimination (threshold of *P*<0.05 for retention in the model) to select a final parsimonious set of "informative" adipokines.

In secondary analyses, to explore whether the association of adipokines with incident MetS was confounded by insulin resistance, HOMA-IR was added as an additional covariate to the multivariable model. A receiver operator curve comparing the models with versus without HOMA-IR in the prediction of MetS at follow-up examination was constructed. The MetS prediction C statistic (area under the receiver operating characteristic curve) for participants missing HOMA-IR data was not significantly different than those with HOMA-IR (0.82 versus 0.83), therefore participants with missing HOMA-IR data were included to maximize statistical power. We also used age and sex interaction terms to examine effect modification on the biomarker-MetS relationship. To ascertain nonlinearity in the adipokine-MetS association, we constructed restricted cubic splines with 3 knots corresponding to quartile cut points. We assessed the conjoint influence of informative adipokines on incident MetS by cross-classifying participants according to sex-standardized median values and determining whether individuals with values above the median ("high") for ≥1 adipokines had a greater risk of developing MetS compared with those with the concentrations of the informative adipokines at or below the median ("low"). These models were adjusted for age, sex, baseline BMI (except for models with waist circumference as the dependent variable), and baseline level of the individual risk factor analyzed.

Longitudinal analyses: adipokines and longitudinal changes in MetS components

Finally, the association between the baseline informative adipokine levels (modeled together as continuous variables) with longitudinal changes in the levels of individual MetS components separately were examined in the 2669 participants from sample 2, excluding participants using BP- or lipid-lowering treatment at baseline for BP and triglyceride analyses, respectively. In sex-pooled multivariable logistic regression models, the change in each MetS component was the dependent variable (separate analysis for each component) and informative sex-standardized, natural logarithmically transformed adipokines as the independent variables. For waist circumference, change was sex-standardized. For systolic BP, diastolic BP, plasma glucose, and log-triglycerides, we used censored normal regression to account for

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Table 1. Baseline Characteristics of Study Sample 1

	Sample 1 (n=3777)		Sample 2 (n=2669)		Sample 3 (n=2208)	
Clinical Features	Men (n=1747)	Women (n=2030)	Men (n=1202)	Women (n=1467)	Men (n=907)	Women (n=1301)
Age, y	40.1±837	40.0±8.8	40.2±8.5	40.1±8.7	39.3±8.6	39.5±8.6
Systolic BP, mm Hg	120±13	113±14	120±12	113±14	118±11	111±12
Diastolic BP, mm Hg	78±9	73±9	78±9	72±9	76±9	71±9
BP ≥130/85 or treatment, %	36	19	18.3	9.8	9.5	5.9
Hypertension, %	12.0	7.8	19.0	10.0	9.5	6.1
Treatment for hypertension, %	9.4	7.0	8.0	5.3	3.2	3.4
BMI, kg/m²	27.8±4.6	26.0±6.1	27.7±4.4	25.5±5.5	26.5±3.7	24.6±4.7
BMI ≥30 kg/m², %	25.0	20.1	23.8	17.9	13.6	12.8
Weight, kg	88.1±15.8	70.0±16.7	87.6±15.0	68.7±15.2	83.9±13.0	66.4±13.1
Waist circumference, cm	98.1±12.6	88.4±15.7	97.6±12.0	87.1±14.3	94.2±10.4	84.8±12.5
Elevated waist circumference, %*	32.5	41.4	31.0	39.0	17.4	31.7
Plasma total cholesterol, mg/dL	193±37	185±34	194±36	184±32	191±36	183±32
Plasma triglycerides, mg/dL	134±108	97±63	129±92	92±52	104±62	82±35
Elevated triglycerides, %†	29.4	13.0	27.3	10.7	12.7	4.3
Plasma HDL-C, mg/dL	47±12	61±16	47±12	62±16	50±11	64±15
Low HDL-C, %‡	28.7	23.9	27.5	21.8	14.6	15.5
Change in weight, kg§	NA	NA	3±7	3±7	3±6	3±7
Smoking, %	15.9	14.3	15.6	13.4	15.8	12.2
Fasting plasma glucose, mg/dL	98±17	92±18	96±8	90±8	94±7	89±7
Impaired fasting glucose, %‖	3.32	1.92	0.3	0.1	0.1	0.1
HOMA-IR	1.4±1.2	1.1±0.9	1.3±0.9	1.0±0.7	1.0±0.5	0.9±0.5
Biomarkers, median (quartile 1–3)						
CRP mg/L	0.90 (0.4–2.1)	1.21 (0.5–3.4)	0.88 (0.4–2.0)	1.1 (0.4–3.2)	0.7 (0.3–1.6)	1.0 (0.4–2.7)
Leptin, ng/mL	6.0 (2.3–7.4)	18.0 (6.5–23.5)	4.1 (2.4–7.1)	11.6 (6.2–22.1)	3.4 (2.0–5.5)	10.2 (5.7–19.3)
Leptin receptor, ng/mL	18.9 (12.7–23.5)	19.9 (13.0–25.0)	17.4 (11.9–22.9)	18.3 (12.3–24.7)	18.5 (12.3–23.6)	18.9 (12.6–25.3)
Fetuin-A, ng/mL	442.5 (325.1–524.1)	469.1 (337.3–570.4)	409.3 (321.2–521.4)	438.6 (329.1–571.2)	408.3 (323.9–516.5)	434.4 (325.7–571.4)
RBP4, ng/mL	43.9 (39.6–49.6)	38.2 (30.6–44.7)	42.8 (36.9–49.4)	36.6 (30.6–44.6)	42.2 (36.4–48.1)	36.1 (30.3–43.6)
FABP4, ng/mL	16.6 (10.9–19.9)	21.7 (13.2–25.9)	14.7 (10.6–19.3)	17.5 (12.8–24.6)	13.2 (9.9–17.6)	16.6 (12.3–22.2)
Adiponectin, μg/mL	6.1 (3.3–7.9)	10.9 (6.5–14.6)	5.3 (3.4–8.0)	10.3 (6.9–14.7)	5.9 (3.9–8.5)	10.7 (7.6–15.1)

Values for clinical features are means±SD or percentages and for adipokines are median and 25%–75% interquartile range. BMI indicates body mass index; BP, blood pressure; CRP, C-reactive protein; FABP4, fatty acid–binding protein 4; HOMA-IR, homeostasis model assessment insulin resistance index; NA, not available; RBP4, retinol-binding protein 4.

*Waist circumference ≥40.2 inches (102 cm) in men, ≥34.6 inches (88 cm) in women.

†Triglycerides ≥150 mg/dL or treatment.

‡High-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men, <50 mg/dL in women.

§Change in weight from examination 1 to examination 2.

‖Glucose ≥100 mg/dL.

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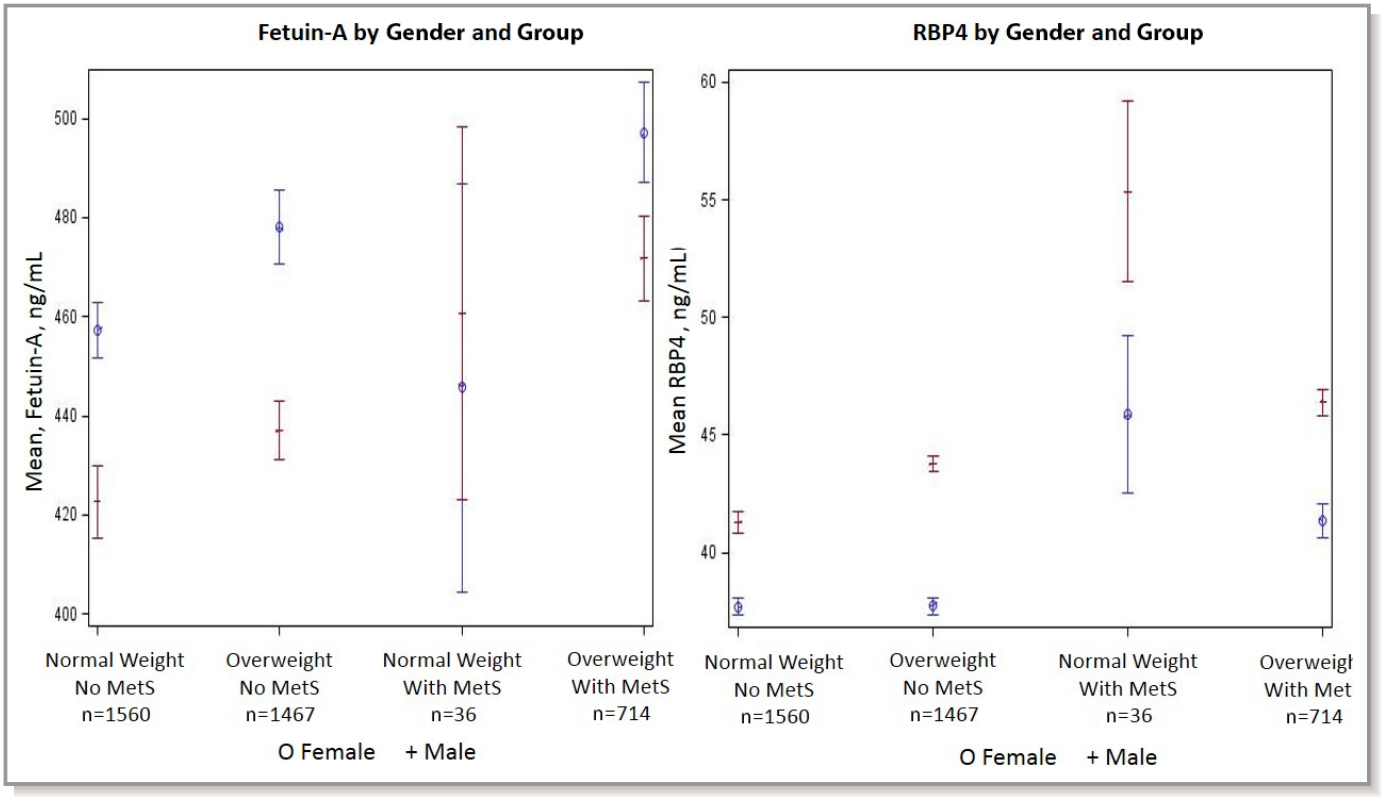


Figure 2. Least square mean and standard error of plasma fetuin and retinol-binding protein 4 (RBP4). The *x* axis represents different subgroups (presence/absence of metabolic syndrome [MetS] and normal/overweight). The *y* axis represents least square mean for fetuin and RBP4.

initiating treatment of high BP, DM, or dyslipidemia by the follow-up examination.[9] For all analyses, a 2-sided *P* value of <0.05 was considered statistically significant. All analyses were performed with SAS (version 9.2, SAS Institute) and R (version 2.12).

Results

Baseline Adipokines and Clinical Characteristics

Baseline clinical characteristics of samples 1, 2, and 3 are shown in Table 1. Mean values of circulating leptin, adiponectin, and FABP4 were higher in women than in men. Mean values of fetuin-A and RBP4 according to sex and age younger than 40 or 40 years and older among BMI and MetS groups are seen in Figure 2. Compared with nonattendees, sample 2 participants generally had lower BP, rates of obesity, triglyceride levels, proportion of smoking, and blood sugar (Table 2). Modest pairwise correlations were noted among the adipokines (r=−0.30 to +0.55; Table 3). Stronger correlations were demonstrated for leptin and HOMA-IR or FABP4 (r=0.55 for both).

Cross-Sectional Findings

Baseline characteristics according to presence/absence of MetS and by BMI group are summarized in Table 4. Participants with normal weight represented roughly 41% of sample 1, 19% had MetS, 39% were MHO, and 1% were MONW. In age- and sex-adjusted models, leptin, fetuin-A, RBP4, and FABP4 were higher in the MHO group (compared with the referent group; *P* value for all <0.01). Leptin-R and adiponectin were significantly lower in the MHO group than in the referent group (*P* value for both *P*<0.001).

Relation of the Adipokine Panel to Incident MetS

A total of 263 participants (113 women) in sample 2 developed new-onset MetS on follow-up. The panel of biomarkers was associated with incidence of MetS (global test, *P*=0.004). On multivariable logistic regression with backward elimination of adipokines and adjusted for baseline MetS component levels, higher plasma RBP4 (adjusted OR per 1-SD increment, 1.21; 95% CI, 1.03–1.41 [*P*=0.02]) and fetuin-A (1.17; 95% CI, 1.01–1.34 [*P*=0.03]) were significantly associated with development of new-onset MetS. Table 5 shows quartile-based analyses where circulating RBP4 was associated with a 17% increased risk of MetS per quartile increment, whereas fetuin-A increased risk of future MetS by 16% per quartile increment. Restricted cubic splines demonstrating the association between fetuin-A or RBP4 and future development of MetS is seen in Figure 3. Analysis of incident MetS risk among binary categories of RBP4 and fetuin-A

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Table 2. Baseline Characteristics of Participants in Study Sample 2 vs Nonattendees

Clinical Features	Men Attending Examination 2 (n=1202)	Men Not Attending Examination 2 (n=710)	*P* Value	Women Attending Examination 2 (n=1467)	Women Not Attending Examination 2 (n=716)	*P* Value
Age, y	40.2 (8.5)	40.5 (9.4)	0.481	40.1 (8.7)	39.9 (9.1)	0.751
Systolic BP, mm Hg	120.0 (12.1)	122.2 (13.3)	0.001	112.8 (14.0)	114.1 (15.1)	0.050
Diastolic BP, mm Hg	78.0 (9.2)	79.0 (9.4)	0.025	72.3 (9.2)	73.4 (9.2)	0.009
Hypertension, %	19.0	27.3	<0.0001	10.0	16.3	<0.0001
Treatment for hypertension, %	8.0	14.1	<0.0001	5.3	11.2	<0.0001
BMI, kg/m^2	27.7 (4.4)	28.4 (5.2)	0.002	25.5 (5.5)	27.2 (7.1)	<0.0001
BMI ≥30 kg/m^2, %	23.8	29.5	0.005	17.9	26.9	<0.0001
Weight, kg	87.6 (15.0)	89.4 (17.4)	0.017	68.7 (15.2)	72.9 (19.4)	<0.0001
Waist circumference, cm	97.6 (12.0)	99.5 (13.7)	0.002	87.1 (14.3)	91.5 (18.0)	<0.0001
Total cholesterol, mg/dL	193.7 (36.2)	191.9 (38.9)	0.335	184.3 (32.2)	187.0 (34.5)	0.092
Triglycerides, mg/dL	128.7 (91.9)	149.2 (135.5)	0.001	91.8 (50.6)	109.5 (80.3)	<0.0001
HDL-C, mg/dL	46.9 (11.9)	46.5 (13.4)	0.508	61.9 (15.8)	59.0 (16.3)	<0.0001
Current smoker, %	15.6	23.4	<0.0001	13.4	21.9	<0.0001
Fasting plasma glucose, mg/dL	95.9 (7.6)	103.6 (27.6)	<0.0001	89.8 (7.5)	96.9 (29.3)	<0.0001

Values for clinical features are means±SD or percentages. BMI indicates body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment insulin resistance index.

dichotomized at the median shows that the individuals with levels of both RBP4 and fetuin-A above the median experienced a higher risk compared with the group with both adipokines at or below the median (Table 5).

Circulating RBP4 and Fetuin-A and Longitudinal Tracking of MetS Components

In multivariable-adjusted logistic regression models, circulating RBP4 and fetuin-A were associated with longitudinal changes in systolic BP and borderline statistically significant associations with higher fasting glucose (Table 6). In addition, blood RBP4 was significantly associated with an increase in diastolic BP (*P*=0.007).

Discussion

We evaluated circulating concentrations of a panel of adipokines in younger adults with normal weight, MONW individuals, and MHO individuals cross-sectionally, and the incidence of MetS prospectively. Overall, MHO participants exhibited an abnormal adipokine profile and MONW participants also had trends toward abnormal adipokine profile. Circulating RBP4 and fetuin-A were associated with incident MetS and longitudinal increase in systolic BP, while RBP4 was associated with significantly higher diastolic BP and a trend toward higher fasting glucose. Overall, our data extend to young to middle-aged adults in previous work associating certain adipokines to one or more metabolic traits in middle to older adults.[10,11]

Table 3. Adipokine Intercorrelations

	Leptin	Leptin Receptor	Fetuin-A	RBP4	FABP4	Adiponectin	CRP	HOMA-IR
Leptin	1.00	−0.21*	0.07*	0.04	0.55*	−0.18*	0.29*	0.55*
Leptin receptor		1.00	−0.04*	0.11*	−0.12*	0.17*	−0.09*	−0.17*
Fetuin-A			1.00	0.06*	0.04*	−0.02	0.05*	−0.10*
RBP4				1.00	0.07*	0.003	−0.04*	0.05*
FABP4					1.00	−0.22*	0.21*	0.40*
Adiponectin						1.00	−0.12*	−0.30*
CRP							1.00	0.24*
HOMA-IR								1.00

CRP indicates C-reactive protein; FABP4, fatty acid–binding protein 4; HOMA-IR, homeostasis model assessment insulin resistance index; RBP4, retinol-binding protein 4.
*Values are Pearson correlation coefficients (n=2416) for sex-standardized, age-adjusted adipokines in natural units.

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Table 4. Baseline Examination Characteristics Cross-Classified by Weight vs MetS Category

Clinical Features	Absence of MetS		Presence of MetS	
	BMI <25 (n=1560)	MHO Participants (n=1467)	MONW Participants (n=36)	BMI ≥25 (n=714)
Age, y	38.4	39.8	43.0	43.7
Systolic BP, mm Hg	111	117	125	128
Diastolic BP, mm Hg	71	76	81	83
BP ≥130/85 mm Hg or treatment, %	13.0	20.3	77.8	74.1
Hypertension, %	13.0	20.3	77.8	74.1
Treatment for hypertension, %	3.5	3.5	22.2	17.1
BMI, kg/m^2	22.2	29.0	23.5	32.8
BMI ≥30 kg/m^2, %	0	27.5	0	61.8
Weight, kg	63	85	68	98
Waist circumference, cm	80	98	90	110
Increased waist circumference, %*	5.4	48.0	33.3	85.2
Total cholesterol, mg/dL	180	192	202	202
Triglycerides, mg/dL	82	103	252	202
High triglycerides, %†	11.1	20.0	66.7	72.3
HDL-C, mg/dL	54	54	45	42
Low HDL-C, %‡	14.0	17.5	77.8	66.7
Smoking, %	14.8	13.1	22.2	19.2
Fasting plasma glucose, mg/dL	90	64	102	108
Impaired fasting glucose, %§	0.51	0.89	5.56	10.36
Biomarkers, mean (95% CIs)				
HOMA-IR	0.86	1.16	1.29	2.21
Leptin, ng/mL	4.1 (3.7–4.5)	16.4 (15.7–17.1)	7.8 (5.7–9.9)	22.8 (21.6–24.0)
Leptin receptor, ng/mL	22.1 (21.5–22.6)	18.4 (18.0–18.8)	20.4 (18.4–22.4)	16.5 (16.0–17.1)
Fetuin-A, ng/mL	439.4 (430.5–488.2)	458.8 (449.4–468.2)	455.6 (399.8–511.4)	490.2 (476.7–503.6)
RBP4, ng/mL	39.7 (39.1–40.2)	40.6 (40.1–41.1)	50.1 (45.1–55.1)	43.6 (42.7–44.5)
FABP4, ng/mL	13.5 (13.1–13.9)	21.3 (20.8–21.8)	21.7 (18.0–25.4)	28.2 (27.2–29.3)
Adiponectin, μg/mL	10.4 (10.1–10.7)	8.2 (8.0–8.5)	6.1 (4.9–7.4)	5.8 (5.5–6.1)

Values for clinical features are means or percentages, biomarkers are age and sex adjusted means with 95% CI. BMI indicate body mass index; BP, blood pressure; FABP4, fatty acid–binding protein 4; HOMA-IR, homeostasis model assessment insulin resistance index; MetS, metabolic syndrome; MHO, metabolically healthy obese; MONW, metabolically obese, normal-weight; RBP4, retinol-binding protein 4.

*Waist circumference ≥40.2 inches (102 cm) in men, ≥34.6 inches (88 cm) in women.

†Triglycerides ≥150 mg/dL or treatment.

‡High-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men, <50 mg/dL in women.

§Glucose ≥100 mg/dL.

Cross-Sectional Data on Adipokine Concentrations in Subsets of Obesity

It is estimated that 28% of the US population older than 20 years is MHO, while the prevalence of MONW is 8.1%.[3] The prevalence of metabolically healthy obesity was 39% in our current study, similar to US, Swedish, and prior Framingham estimates, while our rate of MONW was roughly 1%.[12,13] The CVD risk of these respective categories is somewhat controversial. Some studies identify an elevated risk of CVD events in obese persons without cardiometabolic risk factors, while other studies have found no elevated risk.[14–16] These conflicting results may be explained by different follow-up periods and event rates between studies. On the other hand, there is evidence that persons with cardiometabolic risk factors in the context of normal body weight have an elevated risk for both experiencing a CVD event and developing DM.[15]

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Table 5. Logistic Regression Analysis Examining Biomarkers in Quartiles and in Combinations to Incidence of MetS

	No. of Cases/ No. of People at Risk*	Unadjusted Incidence Rates % (95% CI)	Multivariable Adjusted† OR (95% CI)	*P* Value
RBP4				
Quartile 1	47/591	8.0 (5.7–10.2)	Referent	
Quartile 2	64/568	11.3 (8.5–14.0)	1.39 (0.90–2.16)	0.14
Quartile 3	70/552	12.7 (9.7–15.7)	1.25 (0.81–1.94)	0.32
Quartile 4	82/497	16.5 (12.9–20.1)	1.75 (1.12–2.78)	0.02
Trend	…	…	1.17 (1.01–1.35)	0.03
Fetuin-A				
Quartile 1	50/559	8.9 (6.5–11.4)	Referent	
Quartile 2	68/557	12.2 (9.3–15.1)	1.28 (0.84–1.96)	0.25
Quartile 3	69/550	12.5 (9.6–15.5)	1.47 (0.97–2.24)	0.07
Quartile 4	76/542	14.0 (10.9–17.2)	1.59 (1.05–2.42)	0.03
Trend	…	…	1.16 (1.02–1.33)	0.03
Marker combination				
Both ≤ median	42/579	7.3 (5.1–9.4)	Referent	
Either RBP4 or fetuin-A below median	134/1050	12.8 (10.6–14.9)	1.48 (1.01–2.22)	0.05
Both above median	87/579	15.0 (11.9–18.2)	1.70 (1.10–2.65)	0.02

OR indicates odds ratio for log-transformed adipokine; RBP4, retinol-binding protein 4.
*Excludes participants with metabolic syndrome (MetS) at baseline, and uses sex-standardized biomarkers (which explains why the number at risk differs for each quartile).
†Multivariable models are adjusted for age, sex, baseline body mass index, sex-standardized waist circumference, systolic and diastolic blood pressure, high-density lipoprotein cholesterol, glucose, and log of triglycerides.

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Metabolically abnormal profiles appear to be more frequent with advancing age (10% among persons aged 20 to 34 years; 56% among persons aged 80 years or older), suggesting that metabolically healthy obesity may be an early phenotype that can worsen to greater cardiometabolic risk over time.[3] In a Finnish population, 20% of men and 24% of women were MONW, possibly reflecting ethnic differences in the proportion of metabolic derangement compared with our

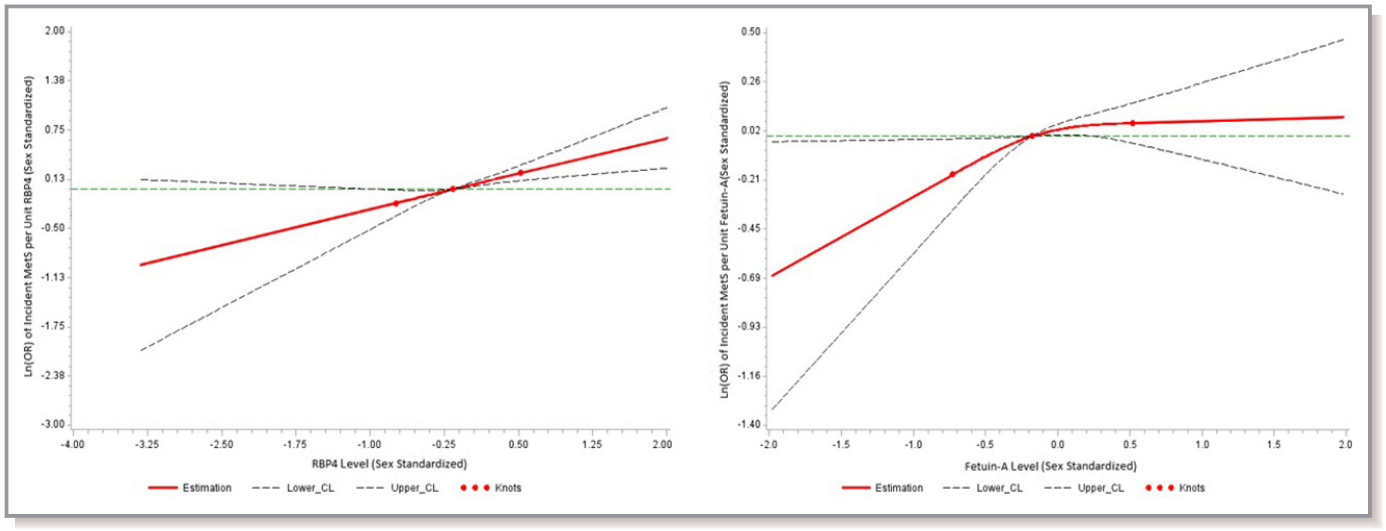


Figure 3. Association between fetuin-A or retinol-binding protein 4 (RBP4) and incident metabolic syndrome (MetS) using restricted cubic splines with 3 knots. Knots represent the first, second (median), and third quartile values, with the reference as the first (or lower) quartile value. The *x* axis represents the range of values for each respective adipokine and the *y* axis represents the log (odds ratio [OR]) for a 1-unit increase in the sex-standardized adipokine. CL indicates 95% confidence limit.

Table 6. Logistic Regression Analysis Examining the Incidence of Individual Risk Factors From Baseline Examination to Follow-Up Examination According to Biomarkers (Modeled Together)

			RBP4		Fetuin-A	
Δ MetS Component	No.	Incidence Proportion, %	Multivariable Adjusted* OR (95% CI)	*P* Value	Multivariable Adjusted* OR (95% CI)	*P* Value
Waist circumference	2208	916/2208 (41.5%)	1.05 (0.93–1.18)	0.42	1.04 (0.92–1.18)	0.5
Fasting glucose	2207	369/2208 (16.7%)	1.13 (0.99–1.28)	0.06	1.03 (0.90–1.17)	0.07
Systolic BP	2206	411/2206 (18.6%)	1.22 (1.06–1.39)	0.004	1.14 (1.00–1.30)	0.04
Diastolic BP	2206	394/2206 (17.8%)	1.19 (1.04–1.13)	0.007	1.08 (0.95–1.22)	0.26
Triglycerides	2206	441/2206 (20.0%)	1.08 (0.96–1.23)	0.19	0.99 (0.88–1.11)	0.80
HDL-C	2208	238/2206 (10.8%)	1.05 (0.89–1.22)	0.58	1.09 (0.94–1.26)	0.26

BP indicates blood pressure; HDL-C, high-density lipoprotein cholesterol; RBP4, retinol-binding protein 4.
*Multivariable-adjusted beta for change (Δ) in components of metabolic syndrome (MetS) are adjusted for age, sex, baseline body mass index (except waist circumference model), and baseline level of the individual component, and values are per SD increment of log biomarkers.

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cohort.[17] Beyond epidemiological differences, our data suggest key biological distinctions between MHO and MONW groups. The leptin pathway and adiponectin appeared to track with participants with obesity in that the MHO pattern was associated with higher leptin and lower LEP-R in participants with normal weight. The MONW participants appeared to be intermediate between metabolically healthy obesity and normal weight in leptin and LEP-R, while overweight participants with MetS had the highest levels of leptin and lowest LEP-R and adiponectin. Therefore, the monotonically higher free leptin that can be inferred by the gap between measured leptin and LEP-R levels among categories of normal weight, MONW, metabolically healthy obesity, and overweight with MetS may reflect the dominant role played by weight in driving leptin pathway levels. In contrast, adiponectin levels were highest in normal-weight individuals, lower in MHO individuals, and lowest in MONW and overweight individuals with MetS, suggesting it may be a strong driver of cardiometabolic risk in these individuals. Comparable levels of fetuin and FABP4 were shown in MHO and MONW persons, which were higher than those in normal-weight persons but lower than those in overweight individuals with MetS, suggesting a codependent pattern where cardiometabolic risk or excess weight each drive abnormalities in these adipokines. Finally, RBP4 showed a pattern of elevation more consistent with cardiometabolic risk rather than with weight per se, since circulating concentrations in metabolically healthy obesity and normal weight were largely similar.

RBP4 and Risk of MetS

We observed that higher plasma RBP4 concentrations were not only associated with cross-sectional presence of MetS but also prospectively associated with incident MetS. Higher circulating RBP4 concentrations were specifically associated with higher systolic and diastolic BPs and with borderline higher fasting glucose level on follow-up. These findings are consistent with previous reports linking RBP4 to dysglycemia, vascular properties, and hypertension.[18–20] RBP4 may be an intriguing predictor of cardiometabolic risk, especially given that serum levels of RBP4 have appeared to be independent of obesity and previously noted to be elevated in nonobese, insulin-resistant patients.[20,21] RBP4 is a transport protein highly expressed in liver and adipose tissue.[22,23] Overexpression of RBP4 results in insulin resistance, while, conversely, knockout of the protein translates into enhanced insulin sensitivity.[20,24] Serum RBP4 levels have previously been inversely correlated with insulin sensitivity in nondiabetic patients and are increased in patients with impaired glucose tolerance, type 2 DM, fatty liver, cerebral infarction, and components of MetS, particularly triglycerides.[20,25–27] RBP4 has been shown to be a relevant marker for the prediction of prevalent MetS in cross-sectional, community-based samples of elderly patients, although less is known about its effects on younger patient populations or in prospective studies.[25,28] Our data clarify and extend previous observations to younger adult populations.

Fetuin-A and Risk of MetS

In our sample, plasma fetuin-A levels were positively associated with MetS cross-sectionally and with greater risk of incident MetS longitudinally, specifically with elevation in systolic BP and trends toward higher fasting glucose on follow-up, consistent with previous reports. Fetuin-A inhibits insulin receptor signaling in liver and muscle via tyrosine kinase activity, thereby promoting hepatic and skeletal muscle insulin resistance.[29–31] Fetuin-A knockout mice have been shown to have enhanced insulin sensitivity, resistance to weight gain, and lower triglyceride levels.[30] Higher serum fetuin-A levels have been associated with risk of type 2 DM,

myocardial infarction and ischemic stroke, MetS, and specific components of MetS.[10,32–35]

Study Strengths and Limitations

The strengths of our investigation include the moderately sized community-based sample, the routine assessment of several circulating adipokines in a younger adult sample, a design that included cross-sectional and longitudinal components, the adjustment for several standard clinical covariates in multivariable analyses, and the assessment of the conjoint associations of several adipokines. These adipokines may provide novel insights into the pathophysiological progression to MetS.

The limitations of our investigation include the "single occasion" measurement of adipokines that may not adequately capture their biologic activity or variability over time. The sample size of the MONW group was small (n=36), limiting our statistical power to assess associations for this group. Our sample consists of mostly white participants, therefore generalizability to other ethnicities is limited. The differences between included participants and nonattendees may also limit generalizability of our findings to persons with higher CVD risk. Lastly, the follow-up period in the current study was 6 years, and we may have underestimated the long-term metabolic risks associated with adipokine profiles. This, in part, may explain why both circulating RBP4 and fetuin-A concentrations demonstrated borderline statistically significant associations with fasting blood glucose concentrations.

Conclusions

In our community-based sample of young to middle-aged adults, distinctive cross-sectional patterns of adipokine elevations were observed in normal-weight, overweight with MetS, MHO, and MONW participants. Longitudinally, circulating fetuin-A and RBP4 concentrations were associated prospectively with the incidence of MetS and of specific MetS components, even after adjustment for baseline MetS component levels. Additional studies of other age groups and multiethnic samples are warranted to confirm the role of these adipokines in the incipient MetS and cardiometabolic consequences. Future work may identify adipokines as screening tools to identify persons at high risk for MetS and CVD events.

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Disclosures

None.

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Prospective Relation of Circulating Adipokines to Incident Metabolic Syndrome: The Framingham Heart Study

Justin P. Zachariah, Rene Quiroz, Kerrie P. Nelson, Zhaoyang Teng, John F. Keaney, Jr, Lisa M. Sullivan and Ramachandran S. Vasan

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