ORIGINAL RESEARCH

Circulating Galectin-3 Is Associated With Cardiometabolic Disease in the Community

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***Background*—**Circulating Galectin-3 (Gal-3) concentrations are associated with an increased incidence of heart failure, atrial fibrillation, chronic kidney disease, and mortality. Recent evidence suggests that Gal-3 may also be an important modulator of cardiometabolic traits such as adiposity, insulin resistance, and hyperglycemia. We examined the associations of blood Gal-3 concentrations and cardiometabolic disease traits in the Framingham Heart Study.

***Methods and Results*—**In cross-sectional analyses of 2946 Framingham Heart Study participants (mean age 59 years, 55% women), higher Gal-3 concentrations were associated with higher body mass index, waist circumference, and triglycerides ($P<0.0001$ for all). Higher Gal-3 was associated with greater odds of obesity (multivariable-adjusted odds ratio 1.16 per 1-SD increase in log–Gal-3, 95% CI 1.06–1.28, $P=0.002$) and hypertension (odds ratio 1.18, 95% CI 1.07–1.29, $P=0.0006$). In prospective analyses, Gal-3 was associated with incident metabolic syndrome (hazard ratio 1.22, 95% CI 1.10–1.36, $P=0.0002$) and diabetes (hazard ratio 1.21, 95% CI 1.04–1.41, $P=0.02$), in age- and sex-adjusted, but not multivariable-adjusted models.

***Conclusions*—**In this large, community-based sample, circulating Gal-3 was associated with abdominal adiposity, dyslipidemia, and hypertension in cross-sectional analyses, but Gal-3 did not predict incident cardiometabolic disease after adjusting for cardiometabolic risk factors. Future investigations should focus on further elucidating mechanisms linking Gal-3 with cardiometabolic disease and on assessing whether modulation of the Gal-3 pathway might have positive cardiometabolic effects. **(*J Am Heart Assoc*. 2016;5:e002347 doi: 10.1161/JAHA.115.002347)**

Key Words: epidemiology • obesity • prevention

Galectin-3 (Gal-3), a β-galactoside–binding lectin, is expressed in several cell types, including epithelial and inflammatory cells, and is involved in important cellular processes such as adhesion, apoptosis, inflammation, and differentiation.[1,2] Gal-3 also appears to modulate pathways central to numerous disease conditions, including fibrosis, inflammation, cancer progression, and metabolic disorders.[2] Previous studies of Gal-3 in cardiovascular disorders observed higher Gal-3 concentrations to be associated with incident heart failure,[3] atrial fibrillation,[4] chronic kidney disease,[5] atherosclerosis,[6] and mortality[7]; however, the mechanisms linking Gal-3 and cardiovascular disease are not well elucidated.

Cardiometabolic traits such as adiposity, diabetes, hypertension, and dyslipidemia are, in addition to smoking, the dominant modifiable risk factors for cardiovascular disease.[8,9] Recent experimental studies have demonstrated that Gal-3 may be an important regulator of lipogenesis,[1,10] hyperglycemia,[11] and obesity-related inflammation.[12,13] Therefore, Gal-3 may influence cardiovascular disease risk via its potential effects on cardiometabolic pathways. The association of Gal-3 with cardiometabolic disease in humans is not well studied. We hypothesized that higher Gal-3 would be associated with a greater burden of cardiometabolic traits in the community cross-sectionally and with a greater incidence of cardiometabolic traits prospectively. We tested this hypothesis in a large community-based epidemiological cohort in which participants have been well characterized with respect to cardiometabolic traits.

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Methods

Study Sample

The enrollment and characteristics of the Framingham Heart Study (FHS) offspring cohort were reported previously.[14] Briefly, 5124 children of the FHS original cohort and their spouses have been evaluated approximately every 4 years at the FHS research clinic since 1971. For the present investigation, 3532 participants attending the sixth offspring cohort examination cycle (1995–1998) were considered for analysis. Participants were excluded due to offsite visit (n=43), missing Gal-3 measurement (n=41), extreme outlier Gal-3 values (>5 log SDs [1.35 units] above or below the log-transformed mean of 2.63 units; n=5), prevalent heart failure (n=38), prevalent major cardiovascular disease (n=144), stage IV chronic kidney disease (n=7), missing covariates (n=98), or nonfasting laboratory values (n=210), yielding a final sample of 2946 individuals. The Boston University Medical Center Institutional Review Board approved all study protocols, and all participants provided written informed consent.

Laboratory Measures

Fasting blood samples were collected, centrifuged, and immediately stored at −80°C during each examination cycle. Gal-3 concentrations were measured in 2011 on EDTA plasma samples that were obtained during the sixth examination cycle (1995–1998) by using an enzyme-linked immunosorbent assay (BG Medicine), which was previously demonstrated to display within-run and total precision between 2.1% and 5.7% and 4.2% and 12.0%, respectively.[15] The lower detection limit was 1.32 ng/mL and the upper quantification limit was 96.6 ng/mL. Serum triglyceride concentrations and high-density lipoprotein (HDL) cholesterol concentrations were measured by using automated enzymatic assays after precipitation of apolipoprotein B–containing lipoproteins with dextran-sulfate magnesium. Serum glucose was measured at each examination cycle by using a hexokinase reagent. Insulin concentrations were measured during the fifth examination cycle (1991–1995) with a radioimmunoassay (Coat-A-Count Insulin; Diagnostic Products). The Homeostasis Model Assessment of Insulin Sesistance (HOMA-IR) was calculated by the formula: HOMA-IR=fasting plasma insulin [microunits per milliliter]× (fasting plasma glucose [millimoles per liter])/22.5.[16] Insulin resistance was defined as a value above the top quartile of HOMA-IR from the whole FHS Offspring sample free of diabetes [75th percentile of HOMA-IR=2.74 (mg/dL) ×(IU/mL)].[17] C-reactive protein (CRP) was measured at the sixth examination cycle with a Dade Behring nephelometer.

Clinical Assessment and Outcome Definitions

A cardiovascular-focused physical examination, anthropometry, and phlebotomy were performed at each examination cycle at the FHS clinic. Systolic and diastolic blood pressure (BP) measurements were recorded as the mean of 2 physician readings. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertension medications. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and obesity was defined as BMI ≥30 kg/m^2. Diabetes was defined as fasting serum glucose ≥126 mg/dL or receiving drug treatment for elevated glucose. Metabolic syndrome was defined as the presence of any 3 of the following 5 criteria: (1) waist circumference ≥40 inches in men or ≥35 inches in women; (2) triglycerides ≥150 mg/dL; (3) HDL cholesterol <40 mg/dL in men or <50 mg/dL in women; (4) systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or drug treatment for hypertension; and (5) fasting glucose ≥100 mg/dL or drug treatment for elevated glucose.[18] A physical activity index composite score was calculated as the sum of the reported time spent performing specific levels of physical activity during a 24-hour period, weighted by the estimated oxygen consumption for each activity, as described previously.[19] For prospective analyses, incident metabolic syndrome, diabetes, obesity, and hypertension were defined using subsequent clinical assessments during the seventh (1998–2001) and eighth (2005–2008) examination cycles.

Statistical Analysis

Gal-3 was natural log–transformed for all analyses due to a right-skewed distribution. Baseline characteristics were displayed according to sex-specific Gal-3 quartiles. Multivariable linear regression models were used to relate Gal-3 with the following cardiometabolic traits: BMI, waist circumference, triglycerides (log-transformed), HDL cholesterol, fasting glucose, HOMA-IR, and systolic and diastolic BPs. Because HOMA-IR was ascertained at a previous examination cycle, the sample size of eligible participants with available measurements was lower (n=2691). For BP analyses, values were corrected for concomitant antihypertensive treatment by adding 15 mm Hg to the systolic BP and 10 mm Hg to the diastolic BP.[20] Models were first adjusted for age and sex, and then additionally adjusted for systolic BP, antihypertensive treatment status, BMI, diabetes status, current smoking status, physical activity, and triglycerides (log-transformed). We excluded the dependent variable or its close relation for each model (ie, BMI and waist circumference analyses were not adjusted for BMI, fasting glucose and HOMA-IR were not adjusted for diabetes status, systolic and diastolic BP were not adjusted for systolic BP or antihypertensive treatment status).

Multivariable logistic regression models were used to evaluate the associations of Gal-3 with the following cardiometabolic binary traits: metabolic syndrome, diabetes, obesity, hypertension, and insulin resistance. For evaluation of the association of Gal-3 with metabolic syndrome, we included an intermediate model, adjusted for clinical risk factors that are not part of the definition of metabolic syndrome itself: age, sex, physical activity, and smoking.

To evaluate the prospective association of Gal-3 concentrations with incident metabolic syndrome, diabetes, obesity, and hypertension during the 2 follow-up examinations, we used discrete-time Cox proportional hazards regression models. Participants with prevalent disease were excluded for each analysis, yielding different sample sizes for each outcome. We adjusted each model as follows: (1) age and sex and (2) age, sex, smoking status, physical activity, systolic BP, antihypertensive treatment status, fasting blood glucose, HDL cholesterol, triglycerides (log-transformed), and BMI. In addition, for metabolic syndrome analyses, an intermediate model including age, sex, smoking status, and physical activity but excluding variables that are part of the definition of metabolic syndrome was constructed.

Penalized splines were created to test for nonlinearity in the multivariable-adjusted associations of Gal-3 with all outcomes (cross-sectional and prospective). In a sensitivity analysis, models for traits related to dysglycemia and insulin resistance (ie, fasting blood glucose, HOMA-IR, diabetes, and insulin resistance) were repeated after excluding participants with prevalent diabetes. In exploratory analyses, we evaluated the relations of Gal-3 with inflammation as assessed by CRP in the 2852 individuals with both biomarkers measured. CRP was natural log-transformed for these analyses. The correlation between Gal-3 and CRP concentrations was assessed by using the Spearman correlation coefficient. We added CRP to multivariable models to see whether inflammation (CRP) partially explained the relations of Gal-3 with cross-sectional cardiometabolic traits.

For the primary analyses, we tested 5 distinct traits that comprise metabolic syndrome: waist circumference, BP, HDL cholesterol, triglycerides, and hyperglycemia. Therefore, we used a Bonferroni-corrected *P*-value threshold of 0.01 to denote statistical significance and considered $P<0.05$ to be suggestive. For prospective analyses, a *P*-value of 0.05 was considered statistically significant. All analyses were performed using SAS Software version 9.3 (SAS Institute).

Results

A total of 2946 individuals were included, with mean age of 59 years and 55% women. Baseline clinical characteristics by sex-specific Gal-3 quartiles are shown in Table 1. The mean age and proportion of individuals with diabetes, obesity, hypertension, and insulin resistance increased across Gal-3 quartile.

Cross-Sectional Associations of Gal-3 With Continuous Cardiometabolic Traits

The associations of Gal-3 concentrations with continuous cardiometabolic traits are displayed in Table 2. In age- and sex-adjusted analyses, Gal-3 concentrations were positively associated with BMI, waist circumference, serum triglyceride concentrations, HOMA-IR, and systolic and diastolic BP and inversely related to HDL cholesterol ($P<0.0001$ for all). The associations with BMI, waist circumference, and triglycerides persisted after multivariable adjustment ($P<0.0001$ for all). In sensitivity analyses, we examined the relations of fasting glucose and HOMA-IR after excluding those with diabetes, and the results were similar (data not shown).

Cross-Sectional Associations of Gal-3 With Binary Cardiometabolic Traits

Each 1-SD increase in log-transformed Gal-3 was associated with higher odds of having metabolic syndrome in age- and sex-adjusted analyses (odds ratio [OR] 1.29, 95% confidence interval 1.19–1.40, $P<0.0001$), Table 3. When additionally adjusted for smoking and physical activity, Gal-3 remained associated with metabolic syndrome (OR 1.28, 95% CI 1.17–1.39, $P<0.0001$); however, the full multivariable-adjusted model (including covariates used to define metabolic syndrome) was not statistically significant (OR 0.91, 95% 0.80–1.02, $P=0.11$).

In age- and sex- adjusted models, we observed statistically significant direct relations for Gal-3 concentrations with diabetes (OR 1.22, 95% CI 1.06–1.40, $P=0.004$), obesity (OR 1.30, 95% CI 1.19–1.42, $P<0.0001$), hypertension (OR 1.29, 95% CI 1.19–1.41, $P<0.0001$), and insulin resistance (OR 1.25, 95% CI 1.14–1.37, $P<0.0001$), Table 3. The associations with obesity (OR 1.16, 95% CI 1.06–1.28, $P=0.002$) and hypertension (OR 1.18, 95% CI 1.07–1.29, $P=0.0006$) remained statistically significant after further adjustment for cardiometabolic risk factors, whereas the associations with diabetes and insulin resistance were attenuated. Penalized splines did not reveal nonlinearity for any of the significant associations of Gal-3 and cardiometabolic traits.

Associations of Gal-3 With Incident Cardiometabolic Disease

Of the 1612 participants free of metabolic syndrome at the baseline (sixth) examination, 280 developed metabolic syndrome by the seventh examination cycle (1579 [98%]

Table 1. Characteristics of the Study Sample by Gal-3 Quartile

Characteristic	Quartile 1 (n=730)	Quartile 2 (n=746)	Quartile 3 (n=729)	Quartile 4 (n=741)
Age, y	55±9	58±9	60±9	63±9
Women, n (%)	404 (55)	411 (55)	399 (55)	403 (54)
BMI, kg/m^2	26.9±4.8	27.7±5.2	28.2±5.2	28.7±5.2
Waist circumference, cm	37±5	38±5	38±5	39±5
Obesity, n (%)	156 (21)	199 (27)	209 (29)	251 (34)
Heart rate, beats per minute	63±10	63±10	64±10	65±10
Systolic blood pressure, mm Hg	124±18	127±18	130±19	132±20
Diastolic blood pressure, mm Hg	75±9	76±9	76±9	76±10
Antihypertensive medication use, n (%)	107 (15)	161 (22)	201 (28)	305 (41)
Hypertension, n (%)	201 (28)	265 (36)	309 (42)	405 (55)
Smoking, n (%)	102 (14)	116 (16)	119 (16)	98 (13)
Diabetes, n (%)	50 (7)	56 (8)	59 (8)	93 (13)
Fasting blood glucose, mg/dL	100±24	102±26	103±25	105±28
Insulin resistance, n (%)*	139 (19)	187 (25)	211 (29)	245 (33)
HOMA-IR, mg×IU/dL×mL*	2.6±10.4	2.4±3.1	2.5±3.3	3.3±5.5
Triglycerides, mg/dL	118±68	127±78	143±93	158±96
HDL cholesterol, mg/dL	54±17	52±17	51±16	49±15
Metabolic syndrome, n (%)	221 (30)	280 (38)	317 (44)	386 (52)
C-reactive protein, mg/L†	1.5 (0.7, 3.5)	1.7 (0.8, 3.6)	2.5 (1.0, 4.8)	3.0 (1.3, 6.8)
Gal-3, ng/mL‡	10.2 (9.3, 10.9)	12.5 (12.0, 13.2)	14.7 (14.1, 15.6)	18.0 (16.9, 20.0)

Values are mean±SD or median (25th percentile, 75th percentile) for continuous variables, and n (%) for categorical variables. BMI indicates body mass index; Gal-3, galectin-3; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance.

*HOMA-IR measurements were available in 2691 participants.

†C-reactive protein concentrations were available in 2852 participants.

‡Sex-specific Gal-3 values by quartile, in ng/mL, for men: Q1: 3.9 to 10.9; Q2: 11.0 to 12.8; Q3: 12.9 to 15.1; Q4: 15.2 to 54.4; and for women: Q1: 5.0 to 11.9; Q2: 12.0 to 14.2; Q3: 14.3 to 16.7; Q4: 16.8 to 52.1.

participants attended the seventh examination, mean time interval from baseline examination 2.9 years), and 227 developed metabolic syndrome by the eighth examination cycle (1460 [91%] participants attended the eighth examination, mean time interval from baseline examination 9.5 years). In age- and sex-adjusted Cox proportional hazards models,

Table 2. Cross-Sectional Associations of Gal-3 With Continuous Cardiometabolic Traits

Cardiometabolic Trait	Age and Sex Adjusted (β Estimate±SE)	*P* Value	Multivariable Adjusted (β Estimate±SE)	*P* Value
Body mass index, kg/m^2	0.79±0.10	<0.0001	0.47±0.10	<0.0001
Waist circumference, cm	2.18±0.26	<0.0001	1.32±0.25	<0.0001
Triglycerides (log-transformed)	0.10±0.01	<0.0001	0.07±0.01	<0.0001
HDL cholesterol, mg/dL	−2.16±0.29	<0.0001	−0.49±0.26	0.06
Fasting glucose, mg/dL	0.96±0.50	0.05	−1.09±0.49	0.03
HOMA-IR (log-transformed)	0.12±0.02	<0.0001	0.04±0.02	0.03
Systolic blood pressure, mm Hg	1.57±0.38	<0.0001	0.51±0.38	0.18
Diastolic blood pressure, mm Hg	1.03±0.21	<0.0001	0.38±0.21	0.07

Regression coefficients represent the mean change associated with a 1-SD higher log-transformed Gal-3 (0.27 unit), which is equivalent to an increase in Gal-3 from 13.87 ng/mL (the sample mean) to 18.17 ng/mL. Multivariable model adjusts for age, sex, systolic blood pressure (except for systolic blood pressure and diastolic blood pressure), antihypertensive treatment status (except for systolic blood pressure and diastolic blood pressure), body mass index (except for body mass index and waist circumference), diabetes status (except for fasting glucose and HOMA-IR), current smoking, physical activity, and log-transformed triglycerides (except for triglycerides). Gal-3 indicates galectin-3; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance.

Table 3. Cross-Sectional Associations of Gal-3 With Binary Cardiometabolic Traits

	Age and Sex Adjusted		Multivariable Adjusted	
Cardiometabolic Trait	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Metabolic syndrome	1.29 (1.19 to 1.40)	<0.0001	0.91 (0.80 to 1.02)	0.11
Obesity	1.30 (1.19 to 1.42)	<0.0001	1.16 (1.06 to 1.28)	0.002
Diabetes	1.22 (1.06 to 1.40)	0.004	1.01 (0.87 to 1.18)	0.87
Insulin resistance	1.25 (1.14 to 1.37)	<0.0001	1.02 (0.91 to 1.13)	0.77
Hypertension	1.29 (1.19 to 1.41)	<0.0001	1.18 (1.07 to 1.29)	0.0006

OR represent the change associated with a 1-SD higher log-transformed Gal-3. Multivariable model adjusts for age, sex, systolic blood pressure (except for hypertension), antihypertensive treatment status (except for hypertension), body mass index (except for obesity), diabetes status (except for diabetes), current smoking, physical activity, and log-transformed triglycerides. Gal-3 indicates galectin-3; OR, odds ratio.

each 1-SD increase in log-transformed Gal-3 was associated with higher risk of incident metabolic syndrome (hazard ratio [HR] 1.22, 95% CI 1.10–1.36, *P*=0.0002; Table 4). The association persisted after adjustment for age, sex, smoking, and physical activity (HR 1.16, 95% CI 1.04–1.29, *P*=0.007) but was no longer significant after further multivariable adjustment for cardiometabolic risk factors (HR 1.02, 95% CI 0.90–1.16, *P*=0.74).

Among 2513 individuals free of diabetes at the baseline examination, diabetes developed in 72 participants by the seventh examination cycle (2460 [98%] participants attended the seventh examination, mean time interval from baseline examination 2.9 years) and in 115 participants by the eighth examination cycle (2203 [88%] participants attended the eighth examination, mean time interval from baseline examination 9.5 years). In age- and sex-adjusted analyses, each 1-SD increase in Gal-3 was associated with increased incidence of diabetes (HR 1.21, 95% CI 1.04–1.41, *P*=0.02). This association was not statistically significant after multivariable adjustment for cardiometabolic risk factors. Gal-3 concentrations did not predict incident obesity or hypertension.

Relations of Gal-3 and CRP

Gal-3 concentrations modestly correlated with CRP in our sample (Spearman correlation coefficient 0.25, *P*<0.0001). When the multivariable models assessing the associations of Gal-3 with cross-sectional cardiometabolic traits were additionally adjusted for CRP, we observed partial attenuation of the effect estimates. The association of Gal-3 with obesity was no longer statistically significant after further adjustment for CRP (OR 1.08, 95% CI 0.98–1.19, *P*=0.13). The associations of Gal-3 and the continuous variables of BMI (*P*=0.01) and waist circumference (*P*=0.0021) were partially attenuated but remained statistically significant. The relations of Gal-3 with triglycerides (*P*<0.0001) and hypertension (OR 1.15, 95% CI 1.05–1.27, *P*=0.0037) were also partially attenuated by further adjustment for CRP.

Discussion

In our community-based investigation, circulating concentrations of Gal-3 were positively associated with several cardiometabolic traits, including abdominal adiposity, dyslipidemia, and hypertension, in cross-sectional analyses. Prospective associations of Gal-3 with incident diabetes and metabolic syndrome were no longer significant after full adjustment for cardiometabolic risk factors.

The observed relations of Gal-3 with cardiometabolic traits may partially explain the previous reports of associations between Gal-3 concentrations and cardiovascular diseases including heart failure and atherosclerosis.[3–7,21–23] Although

Table 4. Associations of Gal-3 With Incident Cardiometabolic Disease

		Age and Sex Adjusted		Multivariable Adjusted	
Cardiometabolic Trait	No. Events/n at Risk	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Metabolic syndrome	507/1612	1.22 (1.10 to 1.36)	0.0002	1.02 (0.90 to 1.16)	0.74
Obesity	247/1982	1.13 (0.99 to 1.28)	0.07	0.96 (0.82 to 1.13)	0.65
Diabetes	187/2513	1.21 (1.04 to 1.41)	0.02	1.08 (0.88 to 1.32)	0.49
Hypertension	734/1694	1.03 (0.94 to 1.14)	0.51	1.00 (0.90 to 1.12)	0.96

HR represents the hazard ratio for each 1-SD higher log-transformed Gal-3. Multivariable model adjusts for age, sex, systolic blood pressure, antihypertensive treatment status, body mass index, diabetes status, current smoking, physical activity, and log-transformed triglycerides. Gal-3 indicates galectin-3.

not a primary focus, several of these previous studies reported associations of Gal-3 with cardiometabolic traits. For example, in the FHS, Gal-3 concentrations were associated hypertension treatment status and BMI.[3] Similarly in the PREVEND (Prevention of REnal and Vascular ENd-stage Disease) cohort, Gal-3 concentrations were related to BP, BMI, HDL cholesterol, and triglycerides. However, these associations were not evaluated in multivariable models adjusting for other cardiometabolic risk factors.[7]

The role of Gal-3 in cardiometabolic disease has also been evaluated in experimental models of adiposity, insulin resistance, diabetes, and inflammation. In mouse models, Gal-3 promotes adipocyte differentiation through activation of peroxisome proliferator-activated receptor-γ, a nuclear receptor involved in adipogenesis,[1] while Gal-3–deficient mice display accelerated rates of diet-induced obesity, hyperglycemia, insulin resistance, and systemic inflammation.[11,13] Further, Gal-3 expression in adipocytes can be induced by proinflammatory signals such as circulating free fatty acids and interleukin-6.[12] In a study of ≈100 people, Gal-3 concentrations were directly correlated with diabetes status.[24] However, among diabetics, galectin-3 concentrations were paradoxically found to be inversely related to hemoglobin A1c. Whether Gal-3 is a mediator of inflammation and cardiometabolic disease remains unclear. Our exploratory analyses show modest correlation with inflammation, and further studies are needed to explore underlying pathways.

Previous studies have evaluated the associations of novel biomarkers with cardiometabolic traits. In cross-sectional studies, several adipokines (most notably adiponectin and leptin) have been correlated with obesity and hypertension,[25–28] but prospective reports are conflicting.[29] Similarly, although inflammatory markers have been linked with diabetes pathogenesis,[30] a previous report including 2600 FHS participants demonstrated that a panel of 12 inflammatory biomarkers was associated with incident diabetes in age- and sex-adjusted, but not fully adjusted, models.[31] The present investigation, therefore, suggests that Gal-3 may play a similar role as these previous biomarkers in cardiometabolic disease; Gal-3 is related to cardiometabolic traits, but its use as a predictor of future cardiometabolic risk is likely limited. We have previously demonstrated an association of Gal-3 and incident heart failure and all-cause mortality.[3] While Gal-3 remained significantly associated with these clinical outcomes after multivariable adjustment, performance metrics evaluating reclassification showed a limited role for Gal-3 in risk prediction.

Several limitations of our investigation merit consideration. First, although experimental data have demonstrated potential direct effects of Gal-3 on obesity and metabolic disease, causal inferences cannot be drawn from the results of this observational study. Second, Gal-3 concentrations were measured at 1 time point (the baseline examination), whereas changes in this value over time might provide further information. Third, all cross-sectional traits were measured contemporaneously with Gal-3 with the exception of HOMA-IR, which was assessed at the preceding examination cycle, resulting in a reduced sample size. This might introduce bias if the individuals with missing HOMA-IR values differed from the broader sample. The noncontemporaneous measures might also allow for a regression dilution bias, which would likely underestimate a true association. Fourth, our sample was composed primarily of Caucasian individuals of European descent; the generalizability to other population is therefore unknown.

In conclusion, Gal-3 concentrations are associated with cross-sectional measures of abdominal adiposity, dyslipidemia, and hypertension in a large community-based sample. However, Gal-3 did not predict incident cardiometabolic traits after adjusting for traditional clinical risk factors. Therefore, our findings do not support a role for Gal-3 as a clinical biomarker of cardiometabolic risk in the community. Future investigations should focus on elucidating the mechanisms linking Gal-3 to cardiometabolic traits and on examining whether modulation of the Gal-3 pathway might improve cardiometabolic outcomes.

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Disclosures

Galectin-3 assays were provided by BG Medicine (Waltham, MA). BG Medicine had no access to study data and no input into data analyses, interpretation, or preparation of the manuscript. The authors have no other relevant disclosures to report.

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