Early Life Adversity Is Associated With Elevated Levels of Circulating Leptin, Irisin, and Decreased Levels of Adiponectin in Midlife Adults

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Context: Early-life adversity, defined as physical, emotional, or sexual abuse and neglect before 18 years of age, is associated with metabolic syndrome, obesity, and type 2 diabetes mellitus in adult life. However, the underlying mechanism is not fully understood, and whether adipomyokines are associated with early-life adversity independent of other factors such as body mass index, psychosocial risks, and health behaviors is not known.

Objectives: The objective of the study was to evaluate the association between early-life adversity and circulating the levels of the adipomyokines such as leptin, adiponectin, and irisin and the inflammatory marker, C-reactive protein (CRP).

Design/Subjects/Setting: This study was a cross-sectional study of 95 adults at a university-based research center. We collected venous blood from participants and analyzed serum for leptin, adiponectin, irisin, and CRP.

Results: Circulating leptin, irisin, and CRP levels were significantly higher in the highest adversity tertile group compared with low and middle tertile groups ($P < .001$ for leptin, $P = .01$ for irisin, and $P = .02$ for CRP). Adiponectin levels were lower in the highest tertile group compared with the low and middle tertile groups ($P = .03$). After adjusting for demographic variables, physical activity, diet, current mental health, and body mass index, the associations between early-life adversity leptin, irisin, and did not change. However, adiponectin and CRP levels were no longer significantly related to early life adversity.

Conclusion: Early-life adversity is directly associated with elevated circulating leptin and irisin, and indirectly associated with elevated CRP and decreased adiponectin. These findings suggest that these adipomyokines may play a role in the pathogenesis of metabolic abnormality in a population with significant early life adversity. **(*J Clin Endocrinol Metab* 99: E1055–E1060, 2014)**

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Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index; CRP, C-reactive protein; HPA, hypothalamic-pituitary-adrenal; MET, metabolic equivalent; T1, tertile 1; T2, tertile 2; T3, tertile 3.

Early-life adversity, defined as physical, emotional, and sexual abuse and neglect before 18 years of age (1), is well known to affect physical health in adulthood including increased risk for obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease, and premature mortality (2, 3).

It has been hypothesized that early-life adversity directly alters the hypothalamic-pituitary-adrenal (HPA) axis, the immune system, and systems of energy/metabolic regulation (4, 5), epigenetic changes (6), and shortening of telomere length (7). Previous studies also have shown that inflammatory markers such as C-reactive protein (CRP) and IL-6 were elevated in young individuals with early-life adversities (8). However, the pathophysiological mechanism underlying the link between early-life adversity and obesity is not fully understood.

Leptin, an adipokine that was initially discovered as a protein that decreases appetite via hypothalamic receptors, is an important determinant in the development of obesity and metabolic syndrome (9). Adiponectin, on the other hand, is an adipokine with insulin-sensitizing effects, and low adiponectin is associated with insulin resistance and type 2 diabetes (10, 11). Irisin is a novel peroxisome proliferator-activated receptor-γ coactivator 1-α (*PGC-1α*)-dependent myokine that is secreted from skeletal muscle after exercise, mediating exercise-related energy expenditure and glucose metabolism (12, 13). Importantly, there are no previous reports on the associations of early-life adversity and these circulating adipomyokines that affect energy homeostasis and cardiometabolic risks.

We aimed to evaluate the associations between adipomyokines and early life adversity in a racially diverse, mixed-risk sample, after adjusting for demographic variables (ie, age, gender, race, education), smoking status, diet, physical activity, and current mental health status. Furthermore, we adjusted for overall obesity [body mass index (BMI)] as a potential mediator of early-life adversity's effects.

Materials and Methods

Study design and participants

This is a cross-sectional study of 95 adults aged 35–56 years who were recruited from the general population of the greater Boston area via advertisements, including newspapers, flyers, and radio, from October 2009 to April 2012. Individuals with a history of myocardial infarction or stroke, an active diagnosis of diabetes mellitus, active iv drug use, hepatitis, cirrhosis, dialysis, long-term steroid use, and/or current treatment for cancer or active infection were excluded from enrollment. A total of 170 participants were enrolled; 95 participants with complete records of early life adversity, diet, and exercise information and at least one biomarker (leptin, adiponectin, irisin) were included in the current analyses. The study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center and the Judge Baker Children's Center (Boston, Massachusetts). Written informed consent was obtained from all participants.

Measurement of adipomyokines

Venous blood samples were collected after overnight fasting from participants at Beth Israel Deaconess Medical Center. Serum and plasma were isolated within 90 minutes of collection and stored at −80°C. Leptin and adiponectin were measured by a RIA (Millipore). Irisin was measured by an ELISA (Phoenix Pharmaceuticals). Inter- and intraassay coefficients of variation were 3.6%–6.2% and 3.4%–8.3% for leptin, 6.9%–9.3% and 1.8%–6.2% for adiponectin, and less than 15% and less than 10% for irisin. Fasting glucose and CRP were measured with the Roche Cobas c311 clinical chemistry analyzer (Roche Diagnostics). Fasting insulin levels were measured by Immulite 1000 chemiluminescence immunoassays (Siemens). Leptin, adiponectin, irisin, CRP, and insulin were measured in serum, and glucose was measured in plasma.

Psychosocial data

Information on early-life adversity and psychosocial measurements was obtained via validated interview and questionnaires at Judge Baker Children's Center by trained interviewers (14). An overall adversity score was created by multiplying the number of adversities × the overall severity of adversity × the overall chronicity of adversity. Severity and chronicity was measured based on the previous report (14). Participants were grouped into tertiles based on the scores.

The Beck Depression Inventory (BDI)-II was used to assess depressive symptoms. Participants with a BDI-II score of 21 or greater were classified as having moderate to severe depressive symptoms (14).

A detailed medication history including psychiatric medications such as antidepressants, psychotropic medications, and anxiolytics was obtained from the medical and psychological interviews.

Dietary quality and physical activity assessment

The Block Food Frequency Questionnaire (NutritionQuest) was used to obtain information about the dietary intake of participants. To assess the quality the nutritional intake, Alternate Healthy Eating Index (AHEI) scores were calculated from the Block Food Frequency Questionnaire (15).

Data on physical activity including the type and typical duration of regular exercise were obtained from self-report questionnaires. Energy expenditure by regular exercise including aerobic and anaerobic exercise was estimated as the metabolic equivalent (MET) hours per week (16).

Anthropometric measurements

Height, body weight, and waist and hip circumferences were measured prior to blood sampling in the fasting state.

Statistical analysis

We performed a two-group analysis: tertile 3 (T3; overall adversity score ≥ 16) vs a combined group of tertile 1 (T1) and tertile 2 (T2; overall adversity score < 16) using the Wilcoxon

rank sum test for continuous variables and χ^2 tests for categorical variables. Spearman correlation analysis was performed for continuous variables. Leptin, adiponectin, irisin, and CRP were logarithmically transformed to achieve a normal distribution. Multiple linear regression analysis was performed to examine the association between adversity and adipomyokines and CRP using a dummy variable for adversity [high adversity (T3) vs no to moderate adversity (T1+T2)]. SPSS version 19.0 and SAS version 9.3 were used for the statistical analysis.

Results

Baseline characteristics

The mean age of the total sample was 45.7 (±3.4) years; 52 participants (54.7%) were female, and 53 (56.4%) were black/African American. There were 61 participants in the T1+T2 group, and 34 in the T3 group.

Comparison between T3 and T1+T2 (Table 1)

There were no significant differences in age or gender between the T3 and T1+T2 groups. T3 had more black/African American participants compared with T1+T2 ($P < .001$). The T3 group had a higher percentage of participants with BDI of 21 or greater and/or on currently on psychiatric medication ($P = .003$). BMI was higher in T3 ($P = .02$). There were no significant differences in diet or physical activity between the groups. T3 had higher levels of leptin ($P = .001$), irisin ($P = .02$), and CRP ($P = .02$) and lower adiponectin ($P = .03$) levels compared with T1+T2 group (Table 1).

Correlations among study variables (Supplemental Table 1)

Raw scores for overall adversity were positively correlated with BMI (r = 0.28, $P = .005$), waist circumference (r = 0.31, $P = .003$), and leptin (r = 0.31, $P = .003$). Conversely, they were negatively correlated with adiponectin (r = −0.28, $P = .007$). There was a marginally significant positive correlation between overall adversity and irisin (r = 0.18, $P = .08$).

Multivariate linear regression analysis: associations among adversity and adipomyokines and CRP

There were strong positive associations between high adversity and leptin ($P = .01$) and irisin ($P = .01$). Adiponectin had a marginally negative association with high

Table 1. Comparison of Patient Characteristics Between T3 (Overall Adversity Score ≥ 16) and T1+T2 (Overall Adversity Score < 16) Groups

	Total Population (n = 95)	T1+T2 (Overall Adversity Score < 16) (n = 61)	T3 (Overall Adversity Score ≥ 16) (n = 34)	*P* Value
Age, y	46 (43–48)	45 (43–47)	47 (43–49)	.21
Female, n, %	52 (54.7)	32 (42.6)	20 (58.8)	.55
Race, African-American, n, %[a]	53 (56.4)	26 (42.6)	27 (81.8)	**<.001**
Smoking, n, %	27 (28.4)	15 (24.6)	12 (35.3)	.27
Bachelor's degree, n, %[b]	28 (31.5)	23 (39.7)	5 (16.1)	**.02**
BDI ≥21 and/or psychiatric medication, n, %[a]	30 (31.6)	13 (22.4)	17 (63.0)	**.003**
BMI, kg/m^{2}[b]	28.9 (25.9–34.5)	28.2 (24.4–33.2)	30.7 (27.3–41.6)	**.02**
Waist to hip ratio	0.88 (0.81–0.93)	0.85 (0.81–0.92)	0.89 (0.82–0.94)	.21
Waist circumference, cm[a]	99.3 (88.0–112.5)	92.8 (86.55–109.3)	104.65 (93.65–118.3)	**.002**
Metabolic syndrome, n, %	25 (26.3)	14 (23.0)	11 (32.4)	.32
AHEI	43.1 (35.1–52.3)	44.6 (35.9–55.8)	42.1 (33.7–49.2)	.16
Physical activity, MET h/wk	11.0 (0–29.3)	13 (0–31.5)	9.3 (0–19.4)	.12
Fasting glucose, ng/mL	90.6 (84.0–96.0)	90.5 (83.3–94.9)	90.8 (84.6–98.3)	.43
Fasting insulin, ng/mL	5.8 (3.2–10.3)	5.1 (3.2–9.1)	7.6 (4.0–11.9)	.22
Leptin, ng/mL[a]	22.8 (6.9–37.0)	14.2 (3.9–34.1)	33.9 (20.1–45.6)	**.001**
Adiponectin, ng/mL[b]	7.5 (4.8–11.9)	9.1 (5.4–13.0)	6.6 (3.8–8.6)	**.03**
Irisin, ng/mL[b]	171.8 (142.5–214.2)	161.2 (137.8–190.4)	203.7 (163.9–220.5)	**.02**
CRP, mg/dL[b]	1.6 (0.6–3.7)	1.2 (0.5–3.0)	2.2 (1.0–4.5)	**.02**

Data are presented in number (percentage) or median (interquartile range); value of $P < .05$ is in bold.

[a] $P < .01$, Wilcoxon rank-sum test for continuous variables, χ^2 test for categorical variables.

[b] $P < .05$, Wilcoxon rank-sum test for continuous variables, χ^2 test for categorical variables.

adversity in an unadjusted univariate regression, but adjusting for age, gender, and race rendered it nonsignificant. CRP was significantly positively associated with high adversity in an unadjusted model ($P = .02$), but it was not independently associated with high adversity when adjusted for age, gender, and race (Table 2).

Discussion

We report that early-life adversity is generally associated with high circulating leptin, irisin, and CRP and low circulating adiponectin levels. The associations between early-life adversity and leptin and irisin remained significant, even after adjusting for potential confounders, whereas for adiponectin and CRP, the associations were nullified in multivariate models. To our knowledge, this is the first report of early-life adversity as predictors of adipomyokines in adult life.

Our results support that leptin and irisin are potential direct mediators of the association between early-life adversity and the pathogenesis of obesity and not simply reflection of current obesity (high BMI) or other factors such as smoking status, quality of diet, exercise, or psychosocial factors linked to health such as depression.

Leptin is known for its strong correlation with BMI and fat mass (9). Hyperleptinemia in obesity is explained by resistance to leptin or alteration of negative feedback mechanisms (9, 17). Stress is known to stimulate the HPA axis and increase the production of glucocorticosteroid in adrenal glands via ACTH (4). Animal studies with rats revealed that glucocorticoids stimulated the release of leptin from adipose tissue but contributed to the development of leptin resistance at the same time (17). Leptin could be a mediator of the effect of childhood adversity on obesity via alteration of the HPA axis.

Adiponectin is an anti-inflammatory adipokine mainly produced by adipocytes. It is inversely correlated with overall and visceral obesity (18). In our study, univariate analysis revealed a negative association between circulating levels of adiponectin and early-life adversity, but multivariate regression analysis including gender and race failed to show a significant association. Levels of adiponectin were lower in the African-American group compared with Caucasians ($P = .005$) and higher in females compared with males ($P = .02$). In our population, circu-

Table 2. Multiple Linear Regression of Association Between Adipomyokines and CRP with T3 (Overall Adversity Score ≥ 16, Reference: T1+T2 − Overall Adversity Score <16)

Dependent (Outcome) Variable	β (95% CI)	Standardized β	SE	*P* Value
Log (leptin)				
Model 1	0.81 (0.35–1.27)	.34	0.23	**<.001**
Model 2	0.68 (0.22–1.13)	.28	0.23	**<.001**
Model 3	0.72 (0.19–1.26)	.29	0.27	**.01**
Model 4	0.71 (0.20–1.22)	.28	0.26	**.01**
Model 5	0.64 (0.16–1.12)	.25	0.24	**.01**
Log (adiponectin)				
Model 1	−0.27 (−0.57 to 0.04)	−.18	0.15	**.08**
Model 2	−0.14 (−0.45 to 0.16)	−.10	0.15	.36
Model 3	−0.02 (−0.37 to 0.33)	−.01	0.18	.91
Model 4	−0.02 (−0.37 to 0.34)	−.01	0.18	.92
Model 5	0.01 (−0.34 to 0.36)	.01	0.18	.96
Log (irisin)				
Model 1	0.17 (0.04–0.31)	.27	0.07	**.01**
Model 2	0.16 (0.01–0.30)	.24	0.07	**.04**
Model 3	0.25 (0.08–0.41)	.37	0.08	**.004**
Model 4	0.25 (0.08–0.42)	.37	0.08	**.004**
Model 5	0.24 (0.08–0.41)	.37	0.08	**.01**
Log (CRP)				
Model 1	0.55 (0.08–1.02)	.24	0.24	**.02**
Model 2	0.33 (−0.17 to 0.82)	.14	0.25	.19
Model 3	0.39 (−0.22 to 0.99)	.16	0.30	.20
Model 4	0.37 (−0.21 to 0.95)	.15	0.29	.21
Model 5	0.24 (−0.25 to 0.73)	.10	0.25	.33

Value of $P < .05$ is in bold. Model 1 is unadjusted comparison between high-adversity group vs low-adversity group. Model 2 is model 1 + adjusted for demographic variables [age (years), gender, and race]. Model 3 is model 2 + adjusted for smoking, education, BDI of 21 or greater or on psychiatric medication. Model 4 is model 3 + adjusted for diet (AHEI), physical activity (MET hours per week). Model 5 is model 4 + adjusted for BMI (kilograms per square meter).

lating adiponectin levels are indirectly associated with early-life adversity via gender and race.

Irisin, a *PGC-1α* dependent myokine, is secreted from muscle in response to exercise in both animal and humans (12, 13). The physiological role of irisin includes the browning effect of white adipose tissue to expend more calories via thermogenesis (12). Although several studies (13, 19) revealed that irisin is secreted from muscle acutely after exercise in humans, there are no reports on the relationship between long-term physical activity and irisin, and the predictors of irisin remain largely unknown.

Our data showed that circulating irisin is significantly elevated in the high-adversity group independently of exercise and BMI. This suggests that systemic regulation of irisin is directly related to early-life adversity and adds to the relatively small literature addressing the role that irisin plays in energy metabolism. Recently irisin is reported to be increased with morbid obesity and metabolic syndrome (20). If early-life adversity alters circulating levels of irisin, then our findings could lead to revealing a novel mechanism in the pathophysiology of obesity.

Alteration of the immune system and inflammation are believed to be involved in disease processes from early-life adversities (1). In addition, CRP is a known inflammatory marker associated with obesity (18). In our study, although CRP was significantly higher in the high-adversity group, early-life adversity was not independently associated with CRP. Adjusting for race rendered the significance negative in our population.

The limitations of this study are its cross-sectional nature and relatively small sample size. With a current sample size of 95, assuming a power (β) of 80%, a correlation coefficient of $r = 0.25$ can be detected as significant at $\alpha = .05$ level. Longitudinal cohort studies as well as well-controlled animal studies to evaluate the effect of early stress on the profiles of adipomyokines will provide more conclusive answers regarding the causal relationship between early-life adversity and adipomyokines.

The strength of this study lies in that it is the first study to show the associations between early-life adversity and adipomyokines as well as CRP, providing more information regarding the pathogenesis of obesity in a population with early-life adversities.

In conclusion, leptin and irisin, but not adiponectin or CRP, are positively and directly associated with early-life adversity, adjusting for important variables that also impact on metabolic systems: obesity, psychosocial factors, and health behaviors. Leptin and irisin likely play an important role in the pathogenesis of obesity and regulation of adiposity in individuals with early-life adversities.

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