

Association of Parental Obesity and Diabetes Mellitus With Circulating Adipokines in Nonobese Nondiabetic Offspring

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Background—Adipokines are implicated in the development of obesity-related traits. We hypothesized that nonobese participants without diabetes mellitus (DM) whose parents were obese or had DM would have altered circulating adipokines compared with those without parental history of these conditions.

Methods and Results—Participants in the community-based Framingham Third Generation cohort who were not obese (body mass index <30) and not diabetic with both parents in the Framingham Offspring cohort were included in this analysis (n=2034, mean age 40 years, 54% women). Circulating concentrations of fetuin A, RBP4 (retinol binding protein 4), FABP4 (fatty acid binding protein 4), leptin, LEP-R (leptin receptor), and adiponectin were assayed. Parental DM was defined as occurring before age 60 years, and obesity was defined as body mass index \geq 30 before age 60 years. General estimating equations were used to compare concentrations of adipokines among participants with 0, 1, or 2 parents affected by obesity or DM (separate analyses for each), adjusting for known correlates of adipokines. Overall, 44% had at least 1 parent who was obese and 15% had parents with DM. Parental obesity was associated with higher serum levels of FABP4 and LEP-R in their offspring ($P=0.02$ for both). Parental DM was associated with lower adiponectin but higher RBP4 concentrations in offspring ($P\leq 0.02$ for both).

Conclusions—In our community-based sample, a parental history of DM or obesity was associated with an altered adipokine profile in nonobese nondiabetic offspring. Additional studies are warranted to evaluate whether such preclinical biomarker alterations presage future risk of disease. (*J Am Heart Assoc.* 2017;6:e004973. DOI: 10.1161/JAHA.116.004973.)

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

Obesity predisposes to diabetes mellitus (DM), dyslipidemia, and hypertension¹ and is associated with increased mortality.² The Centers for Disease Control and

Prevention estimate that 1 in 3 Americans is obese, and nearly 60% are overweight.³ Epidemiologic studies have shown that obesity and DM both cluster within families.^{4–6} Consequently, the characterization of biological mediators of the transgenerational transmission of obesity and related traits like DM may help identify the highest risk persons.

Adipose tissue is now understood to be biologically active including the production of circulating compounds (called *adipokines*) such as leptin, its counterregulatory circulating receptor (LEP-R [leptin receptor]), adiponectin, fetuin A, FABP4 (fatty acid binding protein 4), and RBP4 (retinol binding protein 4). Adipokines appear to partially mediate the association between excess adiposity and hyperglycemia, hyperinsulinemia, sympathetic activity, inflammation, and vascular measures.^{7,8} In addition, there is evidence that concentrations of several of these biomarkers are heritable traits.^{9,10} These observations raise the possibility that parental obesity and/or DM may be associated with altered levels of selected adipokine biomarkers in nonobese nondiabetic offspring, antedating the development of obesity and related traits. We hypothesized that among nonobese offspring, those with parental obesity would have higher circulating levels of fetuin A,

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Clinical Perspective

What Is New?

- Given the familial clustering of obesity-related traits like metabolic syndrome, we examined the association between parent obesity or diabetes mellitus and adipokine levels in nonobese offspring as possible mediators of familial aggregation.
- Parental obesity was associated with higher FABP4 and LEP-R (leptin receptor) in adult offspring.
- Parental diabetes mellitus was associated with lower adiponectin but higher RBP4.

What Are the Clinical Implications?

- With future investigation, circulating adipokines may serve to identify offspring at high risk of transgenerational transmission of metabolic syndrome.
- Future studies may also explore the role of adipokines in the transgenerational transmission of metabolic syndrome traits.

FABP4, RBP4, and LEP-R but lower levels of leptin and adiponectin (compared with those without parental obesity). We postulated that a similar pattern would be seen in nondiabetic children of parents with versus without DM. We further hypothesized that offspring adipokine concentrations would change in stepwise fashion with the number of parents with obesity or DM.

Methods

Study Sample

The design and selection criteria of the Framingham Heart Study Third Generation Cohort are detailed elsewhere.¹¹ For the present investigation, participants attending the first examination cycle (2002–2005) and who had both parents in the Framingham Offspring Cohort were eligible. Given the high lifetime risk of developing obesity,¹² we defined parental obesity as a body mass index (BMI) ≥ 30 (calculated as kg/m^2) occurring before age 60 years. Parental DM was also defined as occurring before age 60 years. Of 4095 participants in attendance at examination 1, exclusions were made because of missing parental history of disease ($n=904$), missing adipokine data ($n=161$), prevalent obesity ($n=948$), and prevalent DM (use of antidiabetic agents or fasting plasma glucose ≥ 126 mg/dL; $n=48$). The institutional review board of Boston University approved the study protocol, and all participants provided informed consent.

Clinical Evaluation and Blood Adipokine Measurements

Participants underwent laboratory assessment of risk factors and a routine medical history and standardized physical examination (including blood pressure [BP] measurement and anthropometry) at each Framingham Heart Study examination. After the participant had rested in a seated position for 5 minutes, a physician measured the BP with an appropriately sized cuff on the left arm using a mercury column sphygmomanometer. The average of 2 readings constituted the examination BP. Fasting levels of plasma high-density lipoprotein cholesterol, triglycerides, and glucose were measured using standardized assays. Self-reported use of cigarettes within the year preceding the baseline examination was defined as current smoking.

At the baseline examination, participants had phlebotomy performed after an overnight fast and after they had rested for 5 to 10 minutes in a supine position. Specimens were stored at -80°C without freeze–thaw cycles until assayed. Plasma levels of leptin, LEP-R, RBP4, and adiponectin were measured using ELISA, whereas fetuin A and FABP4 were measured using sandwich ELISA. Baseline fasting plasma glucose and insulin levels were measured during examination cycle 1. The average interassay coefficients of variation for all adipokines were $<5\%$.

Statistical Analyses

Adipokine concentrations were natural logarithmically transformed to normalize their skewed distributions. To compare adipokine levels between Third Generation nonobese, nondiabetic participants with parental obesity or DM versus those with unaffected parents, we used generalized estimating equation models accounting for familial correlations. In addition, we adjusted for known adipokine correlates including the following characteristics of Third Generation participants: age, sex, BMI, systolic and diastolic BP, hypertension treatment, DM, total/high-density lipoprotein cholesterol ratio, and smoking.¹⁰

Parental disease was modeled as an ordinal variable with 0, 1, or 2 affected parents. In multivariable models, BMI was treated as a continuous variable. We examined prespecified interactions by sex that were significant for RBP4 and LEP-R ($P<0.05$ for each), and so sex-specific results are presented; interaction term for continuous BMI was not significant, so results are presented for pooled BMI strata. A 2-sided $P<0.05$ was considered statistically significant, and SAS 9.3 (SAS Institute) was used for all analyses.

Results

Clinical characteristics of our study sample, including mean concentrations of circulating adipokine levels, are shown in

Table 1. Descriptive Characteristics of Study Sample

Characteristics	Women (n=1103)	Men (n=931)
Clinical characteristics		
Age, y	40±8	40±8
Body mass index, kg/m ²	23.4±3.0	25.9±2.5
Systolic BP, mm Hg	110±13	119±12
Diastolic BP, mm Hg	71±9	77±9
Antihypertensive medication, %	4.3	6.8
Serum total cholesterol	182±32	193±38
Serum high density lipoprotein	63±16	48±13
Lipid lowering medication, %	3.5	10.9
Smokers, %	14.1	15.0
Parental disease, n (%)*		
Obesity (BMI ≥30)		
0 parents	605 (54.8)	529 (56.8)
1 parent	409 (37.1)	327 (35.1)
2 parents	89 (8.1)	75 (8.1)
DM before age 60 y		
0 parents	936 (84.9)	789 (84.8)
1 parent	159 (14.4)	138 (14.8)
2 parents	8 (0.7)	4 (0.4)
Circulating biomarkers		
RBP4, μg/mL	36.5 (30.5, 44.7)	43.4 (37.0, 49.9)
FABP4, ng/mL	16.1 (12.1, 21.4)	13.7 (10.1, 17.3)
Fetuin A, μg/mL	421.9 (316.0, 548.8)	408.3 (318.2, 515.9)
Leptin, pg/mL	9349.1 (5045.0, 15 448.6)	3336.2 (2010.2, 5296.6)
LEP-R, ng/mL	20.1 (13.6, 26.1)	19.2 (12.7, 24.8)
Adiponectin, ng/mL	10 826.5 (7507.7, 15 075.8)	5482.3 (3620.9, 8244.2)

Values are mean±SD and adipokine concentrations are expressed as median (Q1, Q3) unless indicated. BMI indicates body mass index; BP, blood pressure; DM, diabetes mellitus; LEP-R, leptin receptor.

Table 1. Men differed from women in BMI, BP, lipids, and several adipokine levels, whereas prevalence of parental obesity and DM was similar between the 2 sexes. Overall, 44% of participants (n=900) had at least 1 obese parent (Table 1), and 15% (n=309) had at least 1 parent with DM. Both obesity and DM occurred in at least 1 parent in 153 participants.

Association of Parental Obesity or DM and Offspring Adipokine Levels

The clinical characteristics in men and women stratified by the presence or absence of parental obesity are shown in Table 2. Clinical characteristics for men and women with or without a history of parental DM before age 60 are shown in Table 3. In multivariable-adjusted models, parental obesity before age 60 years was associated with higher offspring circulating FABP4 and LEP-R concentrations (Table 4 and Figure 1). Sex-stratified multivariable-adjusted analyses were performed that demonstrated women with parental obesity had higher serum levels of RBP4 (men: −0.007 [95% confidence interval (CI), −0.03 to 0.02]; women: 0.02 [95% CI, −0.002 to 0.05]; interaction $P=0.047$) and LEP-R (men: 0.01 [95% CI, −0.04 to 0.05]; women: 0.08 [95% CI, 0.03–0.12]; interaction $P=0.01$). Similarly, in multivariable-adjusted models, parental DM was associated with higher RBP4 but lower adiponectin concentrations (Table 2 and Figure 2). In sex-specific analyses, parental DM was associated with higher RBP4 concentrations in women (men: 0.02 [95% CI, −0.0 to 0.06]; women: 0.06 [95% CI, 0.02–0.1]; interaction $P=0.03$).

Discussion

In our moderate-sized, community-based sample of young to middle-aged adult participants, parental history of obesity or DM was associated with an altered adipokine profile in nonobese nondiabetic offspring. Parental obesity was associated with higher serum levels of FABP4 and LEP-R, whereas parental history of DM was associated with higher circulating RBP4 but lower adiponectin concentrations. Sex modified the effect of parental status on adipokine concentrations. These associations were found to be robust even after adjustment for BMI. Taken together, these findings are consistent with the notion of a transgenerational role linking family history of obesity and DM to key antecedents of these traits in nonobese nondiabetic offspring.

Offspring FABP4, Leptin, and LEP-R and Parental Obesity

We observed a significant association between serum FABP4 and parental history of obesity before age 60 years. We are unaware of previous reports regarding relations of blood FABP4 and familial history of obesity. FABP4 is produced in adipocytes, constituting 1% of soluble proteins in adipose tissue.¹³ Expression of FABP4 is highly induced during adipocyte differentiation and is transcriptionally controlled by key regulators including insulin.¹⁴ After oral glucose tolerance testing, insulin levels increase to inhibit

Table 2. Clinical Characteristics of Participants With and Without Parental History of Obesity Before Age 60 Years

	Women		Men	
	No Parental Obesity (n=605)	≥1 Parent With Obesity (n=498)	No Parental Obesity (n=529)	≥1 Parent With Obesity (n=402)
Age, y	41±8	38±7	41±8	39±8
Smokers, %	11.7	16.9	12.9	17.7
BMI, kg/m ²	22.9±2.9	24.0±3.0	25.4±2.6	26.4±2.4
SBP, mm Hg	110±13	110±13	119±12	119±12
DBP, mm Hg	71±9	71±9	78±9	77±9
Total cholesterol	183±33	181±32	193±34	193±42
HDL	64±16	62±15	48±12	48±13
Antihypertensive medication, %	4.3	4.2	7.0	6.4
Lipid-lowering medication, %	3.8	3.0	10.6	11.2
RBP4, µg/mL	36 (30, 43)	38 (31, 46)	44 (37, 50)	43 (37, 50)
FABP4, ng/mL	16 (12, 21)	17 (12, 23)	13 (10, 17)	14 (11, 18)
Fetuin A, µg/mL	418 (316, 545)	429 (318, 555)	408 (312, 510)	408 (330, 517)
Leptin, pg/mL	8709 (4698, 14 734)	10 133 (5882, 16 363)	3155 (1940, 4939)	3537 (2172, 5744)
LEP-R, ng/mL	20 (13, 26)	20 (14, 26)	20 (13, 25)	19 (13, 25)
Adiponectin, ng/mL	11 487 (8112, 15 214)	10 278 (6821, 14 874)	5513 (3657, 8244)	5454 (3611, 8201)

Values are mean±SD and concentrations are expressed as median (Q1, Q3) unless indicated. BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LEP-R, leptin receptor; SBP, systolic blood pressure.

lipolysis and concomitant FABP4 levels drop.¹⁵ FABP4 appears to be required for adipocyte maturation.¹⁶ Consequently, in participants with family history of obesity,

inherited higher FABP4 may interact with a milieu of insulin resistance and enhanced lipolysis to favor obesity-related traits in offspring.

Table 3. Clinical Characteristics of Participants With and Without a Parental History of DM Before Age 60 Years

	Women		Men	
	No Parental DM (n=936)	≥1 Parent With DM (n=167)	No Parental DM (n=789)	≥1 Parent With DM (n=142)
Age, y	40±8	39±8	40±8	40±7
Smokers, %	11.1	30.5	14.5	17.6
BMI, kg/m ²	23.3±3.0	23.8±3.2	25.8±2.5	26.3±2.6
SBP, mm Hg	110±13	112±14	119±12	120±12
DBP, mm Hg	71±9	71±10	77±9	79±8
Total cholesterol	181±32	186±33	193±38	192±35
HDL	63±16	62±17	48±12	47±14
Antihypertensive medication, %	3.9	5.9	5.8	12.0
Lipid lowering medication, %	3.6	2.4	9.6	17.6
RBP4, µg/mL	36 (30, 44)	39 (33, 47)	43 (37, 50)	43 (37, 52)
FABP4, ng/mL	16 (12, 21)	17 (13.5, 24)	14 (10, 17)	15 (11, 19)
Fetuin-A, µg/mL	418 (314, 545)	472 (337, 571)	411 (321, 516)	397 (318, 512)
Leptin, pg/mL	9021 (4935, 14 926)	10 531 (5882, 18 753)	3317 (1980, 5222)	3467 (2172, 5982)
LEP-R, ng/mL	20 (13, 26)	19 (15, 25)	19 (12, 24)	19 (14, 26)
Adiponectin, ng/mL	11 010 (7748, 15 156)	9468 (6502, 14 195)	5694 (3796, 8438)	4497 (3166, 6814)

Values are mean±SD and concentrations are expressed as median (Q1, Q3) unless indicated. BMI indicates body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; LEP-R, leptin receptor; SBP, systolic blood pressure.

Table 4. Adipokines and Parental History of Obesity or DM Before Age 60

	Parental Obesity				Parental DM			
	Age/Sex-Adjusted		Multivariable-Adjusted		Age/Sex-Adjusted		Multivariable-Adjusted	
	Estimate (SE)	P Value	Estimate (SE)	P Value	Estimate (SE)	P Value	Estimate (SE)	P Value
RBP4	0.0189 (0.0098)	0.05	0.0098 (0.0097)	0.31	0.0563 (0.0170)	0.001	0.0415 (0.0163)	0.01
FABP4	0.0945 (0.0167)	<0.001	0.0344 (0.0147)	0.02	0.0829 (0.0270)	0.002	0.0372 (0.0232)	0.11
Fetuin A	0.0005 (0.0144)	0.97	-0.0029 (0.0147)	0.84	0.0247 (0.0231)	0.29	0.0225 (0.0235)	0.34
Leptin	0.1196 (0.0286)	<0.001	-0.0370 (0.0225)	0.10	0.1096 (0.0516)	0.03	0.0255 (0.0366)	0.49
LEP-R	0.0107 (0.0183)	0.56	0.0407 (0.0180)	0.02	-0.0008 (0.0307)	0.98	0.0135 (0.0296)	0.65
Adiponectin	-0.0329 (0.0250)	0.19	0.0134 (0.0239)	0.57	-0.1298 (0.0417)	0.002	-0.0945 (0.0398)	0.02

Adipokines modeled as continuous, natural logarithm-transformed variables with estimates indicating increase in mean transformed adipokine concentration for each additional parent with obesity or DM (separate analyses for each). Parental disease modeled as an ordinal variable taking on the values of 0, 1, or 2 parents with condition before age 60. Models were adjusted first for age and sex. The multivariable model was adjusted for age, sex, body mass index, systolic BP, diastolic BP, BP treatment, ratio of total/high-density lipoprotein cholesterol, and smoking status. BP indicates blood pressure; DM, diabetes mellitus; LEP-R, leptin receptor.

Leptin is a key long-term energy homeostasis signal with higher energy status marked by lower circulating leptin concentrations.^{17,18} Leptin is well described to affect feeding behaviors and feeding state, likely mediated through its direct central nervous system effects. Circulating LEP-R binds to leptin and reduces its bioavailability.^{17,19} Both markers have been linked to BMI and fat distribution.²⁰ In obesity, paradoxical elevation of leptin occurs due to end-organ leptin resistance^{17,21}; therefore the observed relationship between parental obesity history and higher LEP-R suggests an intriguing hypothesis about the counterregulatory role of LEP-R in affected participants. Higher LEP-R would reduce free

circulating leptin and consequent satiety signaling, which in turn could induce higher energy intake. Soluble LEP-R is upregulated by ≈20-fold in Zucker diabetic obese rats, which may lead to less circulating leptin and consequently less satiety signaling and more calorie intake, perhaps implicating LEP-R in the obesity phenotype of these rats.²²

Offspring RBP4 Levels and Parental DM Status

We observed that elevated serum levels of RBP4 were associated with parental history of diabetes mellitus. RBP4 is a transport protein highly expressed in liver and adipose

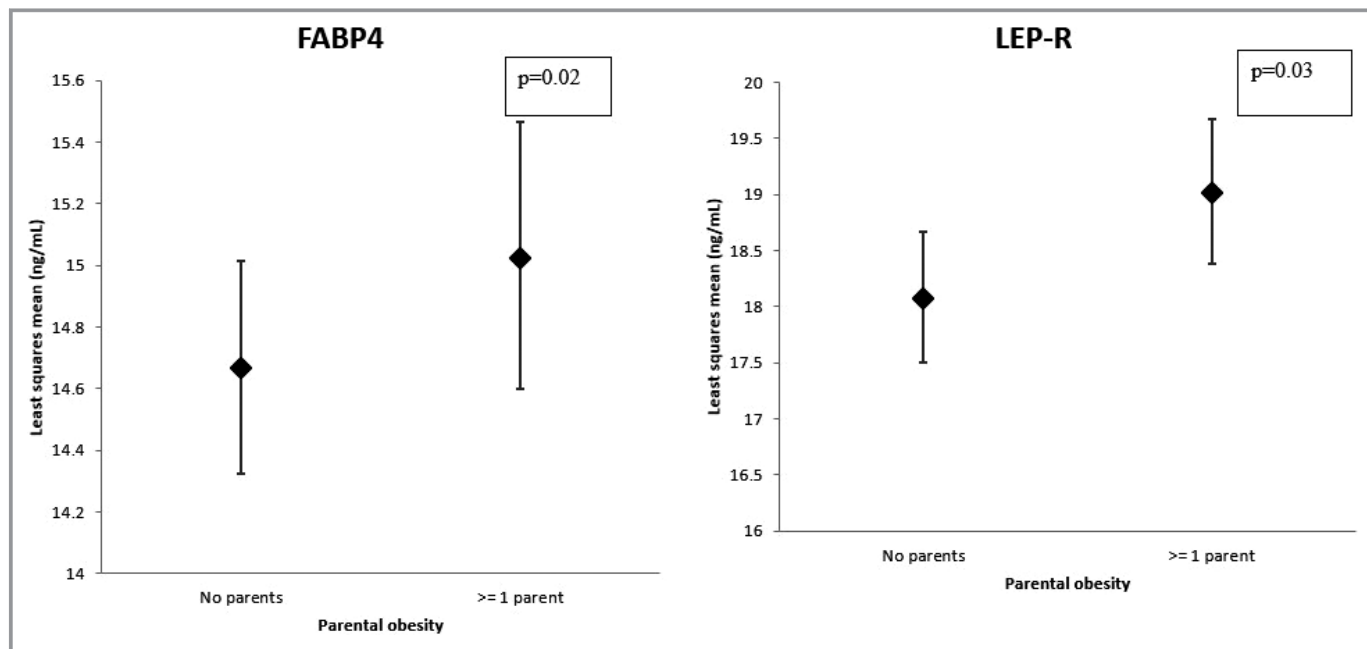


Figure 1. FABP4 and LEP-R (leptin receptor) levels expressed as multivariable adjusted least squares geometric mean and 95% confidence interval error bars (y-axis) according to the presence or absence of parental obesity before age 60 years (x-axis).

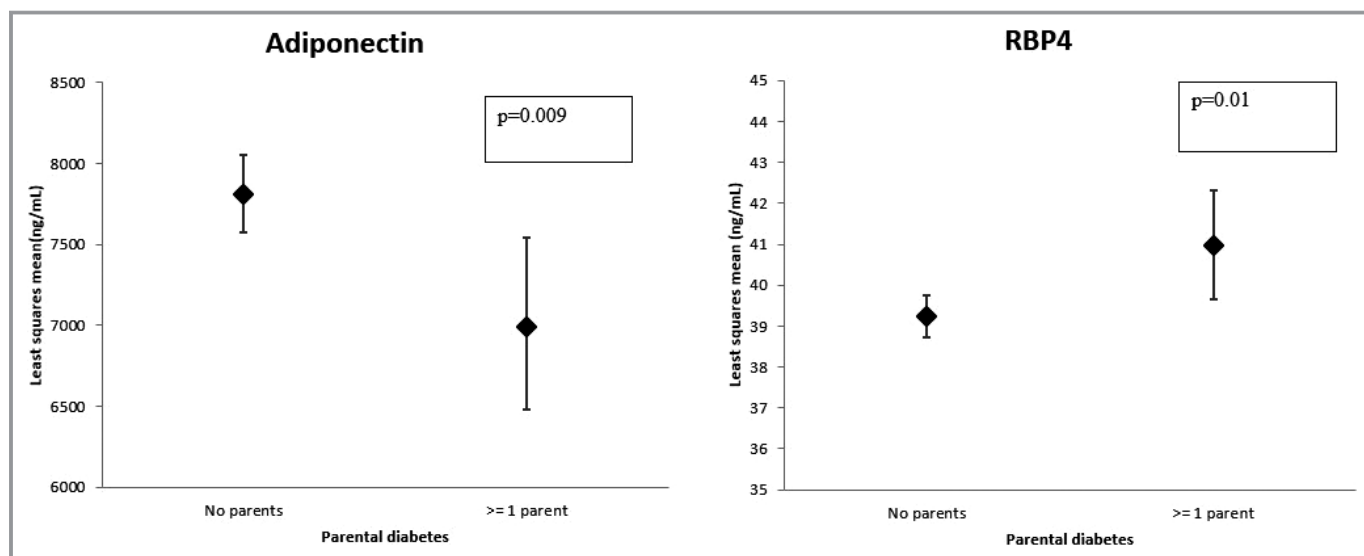


Figure 2. Adiponectin and RBP4 levels expressed as multivariable adjusted least squares geometric mean and 95% confidence interval error bars (y-axis) according to the presence or absence of parental diabetes mellitus before age 60 years (x-axis).

tissue.²³ Overexpression of RBP4 results in insulin resistance, and knockout leads to enhanced insulin sensitivity.^{24,25} A potential association between RBP4 and type 2 DM was initially described in animal models.²⁶ Subsequent work in humans shows that in nonobese normoglycemic participants with at least 1 first-degree relative with type 2 DM, higher RBP4 serum levels were associated with fasting insulin levels. Higher serum RBP4 levels were associated with a poorer rate of glucose disposal, adjusted for age and BMI. Other data from persons before and after modest weight loss suggest that RBP4 may not play a key role in obesity or glucose regulation in humans.²⁷ Nonetheless, our findings suggest that circulating alterations in RBP4 concentrations may be one of several plausible mechanisms for the potential transgenerational transmission of DM.¹⁰

Offspring Adiponectin Levels and Parental DM Status

We observed that lower levels of serum adiponectin in offspring were associated with parental diabetes mellitus. Adiponectin is the most abundant protein secreted by adipose tissue, and plasma levels are correlated negatively with adiposity and type 2 DM.⁹ Previous work on the link between family history of DM and adiponectin is conflicting.^{28,29} Another cohort of nearly 6000 healthy Korean men and women also found family history of DM was associated with lower adiponectin levels.³⁰ Discrepant findings may have been due in part to a nonstandardized definition of family history, geographic or ethnic background and age differences in samples evaluated, and cross-sectional versus longitudinal design.

Limitations and Strengths

Limitations, as with any cross-sectional study, are that we cannot assess the causality of any observed association. Our sample consisted of mostly white participants, so generalizability to other ethnicities is limited. Sex-stratified analyses relating RBP4 to parental obesity or DM status yielded confidence intervals that were overlapping in men versus women (likely due to small sample sizes of individual strata) despite the statistically significant sex interaction term. Moreover, regression coefficients in our analyses were numerically small, often due to the scales of measurement for adipokines. In addition, we did not correct for multiple statistical testing; as such, our findings should be viewed as hypothesis generating and warrant replication in future studies. The strengths of this study include the community-based sample, detailed information on parental obesity and DM occurrence, and the measurement of a comprehensive panel of adipokines.

Our observations of a moderate-sized community-based sample of young to middle-aged adults indicate a transgenerational association between parental history of obesity or DM and circulating levels of key adipokines in offspring, even if they were not obese or diabetic. Additional studies are warranted to evaluate whether such preclinical alterations in adipokine levels presage future risk of obesity or DM.

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Disclosures

None.

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Association of Parental Obesity and Diabetes Mellitus With Circulating Adipokines in Nonobese Nondiabetic Offspring

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