Association of Parental Obesity With Concentrations of Select Systemic Biomarkers in Nonobese Offspring

The Framingham Heart Study

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OBJECTIVE—Parental obesity is a risk factor for offspring obesity. It is unclear whether parental obesity also confers risk for obesity-associated conditions (e.g., a proinflammatory or prothrombotic state) in the absence of offspring obesity.

RESEARCH DESIGN AND METHODS—We compared concentrations of multiple biomarkers representing distinct biological pathways (C-reactive protein [CRP], aldosterone, renin, B-type natriuretic peptide, NH_2-terminal proatrial natriuretic peptide, fibrinogen, and plasminogen activator inhibitor-1) in nonobese Framingham Offspring Study participants with no parents ($n = 665$), one parent ($n = 488$), or two parents ($n = 119$) with obesity (BMI ≥30 kg/m^2).

RESULTS—Nonobese offspring with both parents with obesity had higher CRP levels (median 2.16 mg/l) than offspring with one parent (1.58 mg/l) or no parents (1.35 mg/l) with obesity. After multivariable adjustment, a nonlinear relationship with parental obesity became evident: compared with those without parental obesity, CRP levels were higher in offspring with two obese parents ($P = 0.04$) but not in offspring with only one obese parent ($P = 0.76$). Renin levels were more linearly related to parental obesity status, being significantly higher in offspring with one parent ($P = 0.04$) or two parents ($P = 0.09$) with obesity ($P = 0.02$ for trend). The other systemic biomarkers did not vary according to parental obesity status (all $P > 0.05$).

CONCLUSIONS—Our findings suggest that offspring with a high risk of developing obesity have an altered biomarker profile, characterized by systemic inflammation and increased neurohormonal activity, even in the absence of obesity. This is consistent with the notion that parental obesity may confer an increased susceptibility to other adiposity-associated traits. ***Diabetes* 58: 134–137, 2009**

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Obesity is highly prevalent in the U.S. (1) and predisposes to metabolic and cardiovascular diseases (2). Previous studies have documented that excess adiposity is associated with concomitant alterations of several biological pathways, as reflected by the presence of a prothrombotic state (3,4), neurohormonal activation (5,6), and systemic inflammation (7,8).

Obesity clusters in families, and parental obesity substantially increases the risk of obesity in offspring (9). It is, however, less clear whether parental obesity also confers a greater risk for developing a proinflammatory or prothrombotic state, a natriuretic handicap, or increased neurohormonal activation in offspring and whether these conditions may even antedate the occurrence of obesity in these individuals. One way to approach this question is to compare biomarker levels that represent the above-mentioned pathways in nonobese offspring with versus without obese parents.

To the best of our knowledge, no previous study has related circulating levels of a broad panel of biomarkers in nonobese offspring to parental obesity status in a community-based setting. We hypothesized that nonobese offspring with obese parents would have higher levels of C-reactive protein (CRP), renin and aldosterone, plasminogen activator inhibitor (PAI)-1, and fibrinogen but lower levels of B-type natriuretic peptide (BNP) and NH_2-terminal proatrial natriuretic peptide (NT-ANP) than offspring without parental obesity.

RESEARCH DESIGN AND METHODS

A detailed description of the study sample is available in an online appendix (available at http://dx.doi.org/10.2337/db08-0918). Participants of the Framingham Offspring cohort who were nonobese (BMI <30 kg/m^2), were free of prevalent cardiovascular disease at examination cycle 6 (1995–1998), and had both parents in the original cohort were eligible for the present analysis ($N = 1,272$). Offspring who did not have both parents in the original cohort were older and had higher systolic blood pressure and lower total cholesterol levels.

Clinical evaluation and biomarker measurements. Participants underwent a physical examination, anthropometry, laboratory assessment of cardiovascular risk factors, and a medical history at each Framingham Heart Study visit (approximately every 4 years). We analyzed seven biomarkers that have been previously associated with adiposity-related traits or with obesity in our cohort. Details of the different biomarker assays are provided in the online appendix.

Statistical analysis. Baseline characteristics in Table 1 and biomarker concentrations in Table 2 were compared using ordinary linear (normally distributed continuous traits) and logistic (binary traits) regression models as well as median regression models (for continuous traits that were not normally distributed). For the following analyses, biomarkers were natural logarithmically transformed for better symmetry of distributions. Biomarker

TABLE 1
Clinical characteristics of the study sample stratified by parental obesity status

	No parent with obesity	One parent with obesity	Two parents with obesity	*P*
n	665	488	119	
Age (years)	57.8 ± 9.4	57.2 ± 9.4	56.5 ± 10.5	0.13
Sex (% female)	53.8	52.7	51.3	0.56
Systolic blood pressure (mmHg)	126 ± 19	126 ± 19	126 ± 19	0.66
Diastolic blood pressure (mmHg)	75 ± 9	75 ± 9	75 ± 9	0.81
Antihypertensive treatment	21.5	21.3	22.7	0.87
Hypertension	34.4	34.2	34.5	0.97
BMI (kg/m^2)	24.9 ± 2.8	25.8 ± 2.6	26.6 ± 2.5	<0.0001
Total cholesterol (mg/dl)	213 ± 48	205 ± 39	206 ± 37	0.01
HDL cholesterol (mg/dl)	54 ± 17	54 ± 16	51 ± 17	0.11
Current smoker	15.6	14.3	21.0	0.45
Diabetes	6.5	8.8	3.4	0.95

Data are means ± SD or % unless otherwise indicated.

concentrations among offspring of obese parents versus offspring of nonobese parents were compared using generalized estimating equation models (accounting for relatedness among study participants) adjusting for relevant covariates among offspring (age, sex, BMI, systolic and diastolic blood pressure, hypertension treatment, diabetes, total/HDL cholesterol, and smoking—factors known to influence systemic biomarkers). Parental obesity was defined as BMI ≥30 kg/m^2 at any time over a life course as determined by longitudinal examinations of the original cohort of the Framingham Heart Study. We chose this definition because individuals become obese at different ages, but once they are obese, the condition is relatively stable (10). Parental obesity was modeled as a categorical variable (0, 1, and 2 parents with obesity) with 0 parents serving as the referent group.

In additional analyses, we evaluated whether those biomarkers that were related to parental obesity in the primary analyses might be important mediators of the effect of parental obesity on offspring BMI. First, we developed a multivariable model with offspring BMI as the dependent variable and age, sex, smoking status, physical activity index, and caloric intake as the covariates. Next, we analyzed whether parental obesity was significantly related to offspring BMI in the multivariable model using parental obesity as the predictor variable. Third, we omitted the parental obesity variable from the model and added the biomarkers found to be significantly associated with parental obesity in our primary analyses into the multivariable model as the predictor variables, with BMI serving as the dependent variable. Finally, we analyzed whether the regression coefficient for parental obesity (for predicting offspring BMI) was attenuated upon adjustment for the significant biomarker by adding both the biomarker and the parental obesity variable simultaneously into the multivariable model predicting offspring BMI.

The significance level of the attenuation of the regression coefficient was tested using a nonparametric bootstrap with 1,999 replications (11). Thus, we evaluated the following models predicting offspring BMI: *1*) clinical covariates and parental obesity; *2*) clinical covariates and biomarker; and *3*) clinical covariates, parental obesity, and any biomarker related to both parental obesity in the primary analysis and offspring BMI in model 2. For those offspring biomarkers significantly related to parental obesity, we evaluated in secondary exploratory analyses whether paternal or maternal obesity was related to those markers.

RESULTS

Association of parental obesity with offspring biomarker levels. The clinical and anthropometric characteristics of our sample are shown in Table 1. Table 2 displays offspring biomarker levels according to the number of parents with obesity. CRP demonstrated a nonlinear association with parental obesity status. Offspring with two obese parents displayed higher CRP levels than the referent group without parental obesity (Table 2). This association remained significant in multivariable-adjusted models (Table 3). Offspring with a single obese parent did not have higher CRP levels than the referent group.

Offspring with one obese parent had significantly higher renin levels in multivariable-adjusted models (Table 3). Offspring with two obese parents likewise had higher renin levels than offspring without parental obesity, although the association was borderline statistically significant in a multivariable-adjusted model ($P = 0.091$; Table 3). A trend test was statistically significant (regression coefficient for increase in log-renin per parent with obesity $\beta = 0.09$, $P = 0.02$).

In our sample, 335 participants had a history of maternal and 391 of paternal obesity. In exploratory analyses, neither maternal nor paternal obesity demonstrated statistically significant relations to offspring log-CRP ($\beta = 0.03$ [95% CI −0.06 to 0.11] and $\beta = 0.09$ [−0.001 to 0.18], respectively) or offspring log-renin ($\beta = 0.11$ [−0.005 to 0.22] and $\beta = 0.07$ [−0.04 to 0.18], respectively); we cannot exclude associations of a magnitude described by the 95% CIs. The other biomarkers tested did not differ by parental obesity status (Tables 2 and 3).

TABLE 2
Offspring biomarker levels stratified by parental obesity status

	Biomarker concentration			
	No parents with obesity	One parent with obesity	Two parents with obesity	*P*
CRP (mg/l)	1.35 (0.69, 3.51)	1.58 (0.78, 3.55)	2.16 (0.94, 5.12)	0.001
Aldosterone (ng/dl)	10 (7, 15)	10 (7, 14)	10 (7, 14)	1.00
Renin (mU/l)	12 (7, 20)	13 (7, 21)	13 (7, 23)	0.10
BNP (pg/ml)	9.3 (4, 19)	9.2 (4, 21)	8 (4, 17)	0.48
NT-ANP (pmol/l)	322 (230, 451)	325 (239, 463)	311 (193, 463)	0.56
Fibrinogen (mg/dl)	315 (285, 367)	316 (282, 368)	322 (283, 355)	0.75
PAI-1 (ng/ml)	18.8 (11.8, 28.8)	19.1 (12.9, 28.7)	19.8 (11.8, 29.4)	0.43

Data are median (quartile 1, quartile 3). Quartiles 1 and 3 refer to quartile cut points.

TABLE 3
Association of parental obesity status with offspring biomarkers

Log-biomarker	Mutivariable-adjusted model β (SE)	*P*
CRP		
One parent with obesity	0.01 (0.04)	0.76
Two parents with obesity	0.16 (0.08)	0.039
Aldosterone		
One parent with obesity	−0.05 (0.03)	0.14
Two parents with obesity	−0.03 (0.06)	0.58
Renin		
One parent with obesity	0.11 (0.06)	0.037
Two parents with obesity	0.15 (0.09)	0.091
BNP		
One parent with obesity	0.08 (0.05)	0.13
Two parents with obesity	−0.007 (0.08)	0.93
NT-ANP		
One parent with obesity	0.05 (0.03)	0.10
Two parents with obesity	0.03 (0.05)	0.52
Fibrinogen		
One parent with obesity	0.001 (0.01)	0.90
Two parents with obesity	−0.005 (0.02)	0.81
PAI-1		
One parent with obesity	−0.04 (0.03)	0.23
Two parents with obesity	−0.09 (0.05)	0.093

The regression coefficient (β) indicates the increase in log-biomarker per parent with obesity. Thus, having two parents with obesity was associated with an $e^{\beta} = e^{0.16} = 1.17$-fold increase in multivariable-adjusted CRP levels relative to those with no parents with obesity. Multivariable adjustment for age, sex, systolic and diastolic blood pressure, antihypertensive treatment, total-to-HDL cholesterol ratio, smoking, diabetes, and BMI.

Attenuation of relation of parental obesity to offspring BMI upon adjustment for offspring CRP or renin. Parental obesity was a highly significant cross-sectional correlate of offspring BMI (β regression coefficient per one parent with obesity β = 0.86 [SE 0.11], $P < 0.0001$). Likewise, offspring CRP was positively associated with offspring BMI (β per 1-SD increase in logCRP = 0.63 [SE = 0.08], $P < 0.0001$) in a multivariable-adjusted model. The relation of parental obesity to offspring BMI was significantly attenuated upon adjustment for CRP in the model (β = 0.77 [SE 0.11], $P < 0.0001$). The *P* value for this attenuation was 0.0035 using bootstrap with 1,999 replications. In comparison, offspring renin levels were not significantly associated with offspring BMI. Accordingly, additional analyses were not performed with adjustment for log-renin in the models predicting offspring BMI.

DISCUSSION

We analyzed seven systemic biomarker levels in 1,272 nonobese Framingham Offspring Study participants according to the obesity status of their parents. Parental obesity was defined as a BMI ≥30 kg/m^2 at any time over their life course based on biennial examinations of the Framingham Heart Study.

Principal findings. CRP levels demonstrated a nonlinear association with parental obesity status, being significantly higher in nonobese offspring with two obese parents but not in those with one obese parent. Plasma renin levels were more linearly related to parental obesity status; levels were higher in nonobese offspring with one or two parents with obesity in multivariable-adjusted models (*P* for trend = 0.02). Levels of the other offspring biomarkers (aldosterone, BNP, NT-ANP, fibrinogen, PAI-1) did not differ by parental obesity status. These findings indicate that parental obesity may confer risk of a proinflammatory state and neurohormonal activation even in the absence of offspring obesity.

Comparison with the published literature

Obesity and CRP levels. Obesity is a proinflammatory condition (12). Adults and children with obesity have higher CRP levels (7,8). We are not aware of any study that analyzed CRP levels in nonobese offspring of parents with obesity. We observed higher CRP levels in offspring of obese parents even in the absence of offspring obesity. Also, we observed that parental obesity was positively associated with offspring BMI and that this association was attenuated upon adjustment for offspring CRP. These observations indicate that parental obesity is associated with a proinflammatory state in the offspring even in the absence of offspring obesity. Furthermore, the propensity for a proinflammatory state may, in part, mediate the association of parental obesity with offspring BMI (offspring CRP attenuates the regression coefficient for parental obesity). In this context, previous studies have demonstrated that CRP levels predict adiposity-related conditions including diabetes (13) and the metabolic syndrome (14), indicating that a proinflammatory state is not only a consequence of obesity but potentially also a precursor of obesity or adiposity-related conditions. Our observations are consistent with the notion that obesity and inflammation share a common pathophysiological basis that might be transmitted from obese parents to offspring. Interestingly, a recent genome-wide association study for CRP identified nine genetic variants within the leptin receptor gene that reached genome-wide significance for association with CRP levels (15). This finding supports the concept that obesity and inflammation share common genetic influences.

Obesity and the renin-angiotensin-aldosterone system (RAAS). Several lines of evidence indicate an activation of the RAAS in obesity, especially in obesity-related hypertension (16). Clinical studies reported elevated circulating concentrations of elements of the RAAS in individuals with obesity (17). We observed higher renin in nonobese offspring with one or two obese parents. Our data indicate that offspring of obese parents have neurohormonal activation, as evidenced by higher renin levels, even in the absence of offspring obesity.

Obesity and natriuretic peptides. Obesity and BMI have been inversely related to plasma levels of BNP and NT-ANP in independent community-based studies (5,6) and in patients with heart failure (18). However, in the present analyses, we did not observe any association between offspring BNP/NT-ANP levels and parental obesity status.

Obesity and hemostasis. Previous studies documented positive correlations between adiposity traits (e.g., BMI and waist circumference) and PAI-1 in epidemiological (3) and clinical (19) settings. In addition, higher PAI-1 has been shown to predict the development of diabetes (20,21). Likewise, fibrinogen was positively associated with obesity-related measures (3,22). In euglycemic offspring of individuals with diabetes, elevated PAI-1 activity (23) and increased fibrinogen levels (24) have been reported. However, we did not observe any association between offspring PAI-1 or fibrinogen and parental obesity.

Strengths and limitations. The large community-based design, standardized assessment of multiple cardiovascular risk factors, availability of a broad spectrum of biomarkers, and complete ascertainment of obesity in parents all strengthen our investigation. However, some limitations merit consideration. We focused on biomarkers representing key pathways (inflammation, neurohormonal activity, and hemostasis) in obesity-associated conditions that were available in our sample. Other biomarkers might also be related to obesity but were not measured in our sample at this examination. Overall, seven different biomarkers were tested. We did not correct for multiple statistical testing because all tests (and related hypotheses) were specified a priori. However, we acknowledge that our findings need confirmation in other investigations. Also, the cross-sectional design of our study precludes causal interferences. All biomarkers were measured only at one point in time. Intraindividual variability in biomarker levels over time may have limited our ability to discern associations of biomarkers with parental obesity. About one-third of offspring had BNP levels below the detection limit. We therefore also analyzed Tobit models, which confirmed the lack of association between offspring BNP levels and parental obesity status. However, the left truncation of the BNP distribution might have resulted in a random misclassification that may have reduced our power to detect an association between BNP levels and parental obesity status. The exclusion of offspring with obesity at examination cycle 6 may have resulted in excluding some very informative participants, but we chose to do so because presence of obesity profoundly affects several of the biomarkers evaluated. Finally, the generalizability of our findings to other age-groups and ethnicities is not clear because our sample was middle-aged to elderly and almost exclusively white and of European ancestry.

Conclusions. Nonobese offspring of parents with obesity have an altered biomarker profile characterized by higher renin and CRP levels. This is consistent with the concept that obese parents transmit a susceptibility predisposing to systemic inflammation and neurohormonal activation to offspring that is detectable even in the absence or before the development of offspring obesity.

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No potential conflicts of interest relevant to this article were reported.

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