Published in final edited form as:
Gastroenterology. 2008 April ; 134(4): 953–959. doi:10.1053/j.gastro.2008.01.037.

Parental Obesity and Offspring Serum Alanine and Aspartate Aminotransferase Levels: the Framingham Heart Study

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Abstract

Background and Aim—Obesity is an important correlate of serum alanine (ALT) and aspartate (AST) aminotransferase levels. We sought to examine the relations between parental obesity and the serum ALT and AST levels among offspring in a community-based sample.

Methods—Participants (n=1732) of the Framingham Offspring Study (50% women, mean age 42 years) who had serum ALT and AST measurements and both parents in the Framingham Original cohort, were studied. Study participants were grouped into early-onset parental obesity [n=193] (at least one parent obese), later-onset parental obesity [n=460], and no parental obesity [n=1079] subgroups. The association between elevated ALT or AST and parental obesity was tested using generalized estimating equations to account for familial correlations.

Results—In multivariable analysis including adjustment for offspring obesity, significantly higher ALT was observed among individuals with paternal early-onset obesity as compared to those without paternal obesity (p-value=0.02). Offspring with early-onset paternal obesity were more likely to have elevated ALT levels compared with those without paternal obesity (odds ratio [OR] 1.75 (95% CI 1.06–2.89; p=0.03). There was no association with elevated ALT among offspring with maternal

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Conflict of interest: None disclosed.

early-onset obesity (OR 1.10, 95% CI 0.76–1.59; p=0.61). There was no association between parental obesity and serum AST levels.

Conclusion—Early-onset paternal obesity, but not maternal obesity, increases the odds of elevated serum ALT levels in the offspring, suggesting a predisposition to developing elevated serum ALT levels that may be mediated through familial early-onset obesity.

Keywords

Obesity; premature; family history; nonalcoholic fatty liver disease; non alcoholic steatohepatitis; alanine aminotransferase; aspartate aminotransferase; genetic susceptibility; epidemiology; early-onset; Framingham Heart Study

Introduction

Obesity is an important global public health problem (1–4), and is a modifiable risk factor for morbidity and mortality(5,6). National statistics demonstrate continued increases in overweight and obesity among adults and children over the past three decades (3,7), and currently two-thirds of adults are either overweight or obese (7). Obesity is an important correlate of elevated serum alanine (ALT) and aspartate aminotransferase (AST) levels (8), markers of liver injury in the general population.

Based on the National Health and Nutrition Examination Survey (NHANES) data, up to 7% of the adult US population has unexplained elevated ALT levels (9), most likely due to nonalcoholic fatty liver disease (NAFLD) (9). NAFLD is a spectrum of liver disease ranging from benign steatosis to nonalcoholic steatohepatitis (NASH), a progressive form of NAFLD that may lead to chronic hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) (10). The association between elevated ALT levels, obesity, and metabolic risk factors including diabetes has been recognized (11–13), suggesting that these conditions may share a common pathogenesis.

Obesity is a heritable condition with a strong underlying genetic component (14). In addition, there are strong ethnic associations to elevated serum ALT levels and NAFLD (12,15,16). Familial clustering of fatty liver, NASH and cryptogenic cirrhosis has been reported, further suggesting that genetic factors may play a role in the pathogenesis of NAFLD (17–19). Data from a Danish twin study suggests that the heritability estimate of ALT is between 0.33 and 0.48, which is independent of BMI and alcohol consumption (20).

Therefore, the goal of this study is to examine the association of parental obesity with serum levels of ALT and AST in the offspring. To evaluate the contribution of genetic factors, we investigated whether early-onset parental obesity is associated with elevated ALT and AST levels. We hypothesize that offspring of parents with early-onset or general obesity are more likely to have higher ALT or AST levels than offspring of non-obese parents.

Methods

Study Sample

The Framingham Heart Study (FHS) is a prospective epidemiologic study of cardiovascular disease and its risk factors that was started in 1948 by recruiting 5209 men and women between the ages of 30 and 62 from the residents of Framingham, Massachusetts. Participants are followed up with biennial examinations (21). In 1971, 5124 offspring and offspring spouses were recruited as an extension of the FHS, and classified as the Framingham Offspring Study (FOS) Cohort (22).

The study participants for the current study were derived from the FOS. Written informed consent was obtained from all the participants and the Institutional Review Board of Boston Medical Center approved the research protocol. The details of the cohort, selection criteria, and purpose of the FOS have been published previously (22).

Only offspring participants with data available for both parents were included in order to minimize misclassification of parental obesity status. Offspring participants with both parents in the cohort were similar to offspring without both parents in the cohort with the exception of age, as participants with both parents in the cohort were on average 4 years younger ($p < 0.001$). Among offspring participants who attended the second offspring examination (1978–1982; n=3867), 1887 had both parents as members of the original cohort of the FHS. Additionally, we excluded 155 participants for the following reasons: unavailability of serum ALT or AST levels (n=89), serum ALT or AST greater than 120 IU/L (n=13), body mass index (BMI) less than 18.5 kg/m^2 (n= 29), missing covariate data (n=18), and parents with maximum BMI less than 18.5 kg/m^2 (n=6).

Parental Obesity History

Parental obesity was defined as a body mass index (BMI) of 30 kg/m^2 or more on at least two occasions during the entire follow-up of the Original cohort. Early-onset parental obesity was defined empirically as the 25th percentile of the age at the first obesity among these obese fathers and mothers (41 years in men and 45 years in women). The study participants were hence grouped into three categories: 1) early-onset parental obesity; 2) later-onset parental obesity; 3) no parental obesity.

Serum ALT and AST Levels

Serum ALT and AST were measured on fasting morning samples using the Kinetic method (Beckman Liquid-Stat Reagent Kit) (23). Coefficients of variation for ALT and AST were 8.3 and 10.7%, respectively. We defined elevated ALT using the cut-point of serum ALT ≥30 IU/L in men and ≥19 IU/L in women as suggested by Prati et al (24,25). We used the same cut-off level for serum AST.

Covariate and Risk Factor Assessment

Details regarding the methods of risk factor measurement and laboratory analysis have been described elsewhere (21). Body mass index (BMI) was defined as weight (kilograms) divided by square of the height (meters). Participants with systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 (average of 2 readings recorded by a study investigator) or receiving medications for the treatment of hypertension were classified as hypertensive. Fasting lipid measures included serum triglyceride, total and HDL cholesterol. Diabetes was defined as a fasting plasma glucose ≥7 mmol/L (126 mg/dl) or treatment with either insulin or a hypoglycemic agent. Participants who reported smoking during the previous year before the exam were reported as current smokers. Excess alcohol use was defined as 7 or more drinks a week in women or 14 or more drinks a week in men. In addition, an intensive chart review of all subjects was used to identify key words suggesting alcohol dependence or other alcohol abuse. Cardiovascular disease (CVD) was defined by standard Framingham Heart Study criteria as any of the following: new onset angina, fatal and non-fatal myocardial infarction or stroke, transient ischemic attack, heart failure, or intermittent claudication.

Statistical Analysis

Logarithmically transformed serum ALT and AST levels were used in the analyses because of their skewed distributions. Generalized estimating equation (GEE) model was used to account for familial correlation. The statistical significance of differences in ALT and AST values

among the three exposure groups (early-onset parental obesity; later-onset parental obesity; no parental obesity [referent]) was tested using GEE, by generating least square means of the log-transformed ALT or AST levels. We also grouped individuals by having elevated ALT or AST levels and applied GEE using multivariable logistic regression to generate the odds of elevated ALT and AST levels in individuals with early-onset parental obesity or later-onset parental obesity relative to those without a parental history of obesity (referent group). In addition to parental obesity, the significance of the association for obesity in fathers (paternal history of obesity) or mothers (maternal history of obesity) was examined. We tested the hypothesis by adjusting for: 1) age and sex; and 2) multiple covariates including age, sex, diabetes, BMI, systolic blood pressure, hypertension treatment, total/HDL cholesterol ratio, triglycerides, smoking status, total alcohol consumption (drinks/week), and prevalent CVD.

Secondary analyses were conducted by excluding offspring participants with obesity (n=158) to assess whether the observed findings were independent of offspring obesity. Offspring with excess alcohol use (n=190), as defined by more than 7 drinks/week (men) or 14 drinks/week (women) or indication of alcohol dependence or abuse identified from an extensive chart review, were also excluded.

A two-sided p-value of <0.05 was consider significant. SAS version 8.1 (SAS Institute, Cary NC) was used for all analyses.

Results

A total of 1732 offspring cohort participants were included in this study with a mean age of 42 years, and half were women. Nearly one-tenth had a history of early-onset parental obesity (n=193), and 27% had a history of later-onset parental obesity (n=460); study participant characteristics are presented in Table 1. Offspring in the early-onset parental obesity were younger, had higher BMI, higher serum triglyceride and serum ALT, and lower serum HDL levels as compared to offspring without parental obesity, whereas few differences existed for later-onset obesity as compared to no parental obesity.

In offspring with early-onset parental obesity, 41% had paternal obesity, 64% had maternal obesity, and 6% had both. In offspring with later-onset parental obesity, 46% had paternal obesity, 69% had maternal obesity, and 0% had both maternal and paternal obesity. The Pearson correlation coefficient between maternal BMI and paternal BMI was 0.35.

Serum ALT and AST Levels By Parental History of Obesity

Age-sex adjusted log ALT levels were higher among participants with at least one early-onset obese parent (Table 2) as compared to those without parental obesity (3.21 ± 0.04 vs. 3.08 ± 0.02, p-value = 0.001). Age-sex adjusted log ALT levels remained statistically significant when participants with early-onset maternal or paternal obesity were compared to those without paternal or maternal obesity. The multivariable adjusted log ALT levels were significantly higher only among participants with paternal obesity as compared to those without paternal obesity (3.21 ± 0.06 vs. 3.08 ± 0.01, p-value = 0.02). Similar comparison with respective referent groups for maternal and at least one parent obese models did not achieve statistical significance. No significant differences were observed in any of the models when participants with later-onset obesity were compared to those without parental obesity. No significant differences in AST levels in any of the models in the three exposure categories were observed.

Age-sex adjusted odds ratio (OR) of elevated serum ALT was higher in offspring with both paternal early-onset obesity as compared to no paternal obesity (Table 3; OR 2.04, 95% confidence interval (CI) 1.29–3.24, p-value = 0.005), and early-onset obesity in at least one parent compared to no parental obesity (OR 1.52 (95% CI 1.13–2.06, p-value=0.006).

However, statistical significance was not observed in models examining maternal early-onset obesity as compared to no maternal obesity (OR 1.33 (95% CI 0.95–1.85, p-value=0.09). In multivariable models, participants with paternal early-onset obesity had higher serum ALT levels (Table 3; OR 1.75, 95% CI 1.06–2.89, p-value=0.03) relative to those without paternal obesity. Early-onset paternal obesity was associated with ALT elevation independent of maternal obesity in multivariable-adjusted models (OR 1.72, 95% CI 1.02–2.69, p-value=0.03). Those with a history of maternal obesity or at least one obese parent did not have elevated ALT levels OR 1.10 (95% CI 0.76–1.59; p=0.61), and 1.25 (95% CI 0.90–1.74; p=0.18), respectively, when compared to offspring without maternal obesity or those without either parent with obesity, respectively. There were no significant differences in the odds of elevated ALT levels in participants with later-onset parental obesity when compared to offspring without parental obesity (Table 3). The odds of elevated serum AST levels in the offspring did not differ in the exposure groups (early-onset parental obesity and later-onset parental obesity), when compared to the offspring without parental obesity.

Secondary Analyses

After excluding obese offspring, the overall findings were essentially unchanged, although in these secondary analyses the multivariable-adjusted odds ratios were somewhat strengthened for the association between paternal early-onset obesity and ALT (**Online Supplemental Table**). Among individuals without excess alcohol consumption or abuse, the results were not substantially different (data not shown).

Discussion

Principal Findings

In this community-based sample of white adults, we found that a paternal history of early-onset obesity is associated with a higher odds ratio of elevated serum ALT levels in offspring. This relation is independent of the offspring body mass index and persists among non-obese offspring. Moreover, early-onset paternal obesity but not maternal obesity was associated with elevated serum ALT levels in the offspring. On the contrary, serum AST levels were not associated with parental obesity status.

In the Context of Current Literature

NAFLD is now considered to be the most common cause of serum ALT elevations in the US population (9). Previous studies have shown that there is familial clustering of factors that may predispose to the development of NAFLD, NASH, and cryptogenic cirrhosis (18,19,26). Struben et al reported increased prevalence of NASH or cryptogenic cirrhosis or both in seven of eight kindreds (18). Willner and colleagues demonstrated that the prevalence of NAFLD is higher in first-degree relatives of NASH patients (19). Both of these findings suggest that NAFLD and elevated serum ALT levels may have an underlying genetic susceptibility, particularly in the setting of obesity (27,28). A recent study by Kazumi and colleagues showed an association between parental BMI and elevated serum ALT levels in their male offspring (29). Contrary to our findings, this study reported that maternal rather than paternal BMI was associated with elevated ALT levels in Japanese men. The primary difference between this prior study and ours, in addition to being conducted in a sample of men from Japan, classified parental BMI exposure based on offspring recall. In our study, detailed information regarding measurement of parental BMI during a physician visit was obtained. Previous studies have shown that patient recall can lead to misclassification of exposure status. Therefore, differences in age, sex, race, and parental BMI may contribute to the disparate findings between these studies.

Mechanism

Our findings suggest that there may be a familial component to ALT levels, and in particular, this predisposition may be mediated through early-onset familial obesity. Obesity has a strong familial and genetic component (14). Early-onset or premature occurrence of a disease condition may be more associated with an underlying genetic susceptibility. Therefore, these data support a potential mechanism of elevated ALT.

Several genes have been implicated in the development of early-onset obesity. A missense mutation in human pro-opiomelanocortin (POMC) gene (30) and single-nucleotide polymorphisms (SNPs) in melanin-concentrating hormone receptor 1 (MCHR1) have been associated with development of early obesity (31). It is known that mutations in the leptin gene lead to a severe form of early onset obesity (32). Leptin is thought to be an important regulator of fat and energy metabolism (33). and several studies have shown that leptin may play a key role in regulating hepatic fibrosis (34,35) and progression of NASH (36). Our findings raise the possibility that genes involved in the pathogenesis of early-onset obesity may also be associated with abnormal ALT levels. However, we can not rule out the possibility that shared environmental and unmeasured behavioral practices could have contributed to this finding.

Our findings were also notable for a stronger effect in the presence of a paternal history of early-onset obesity. One potential explanation may be that serum ALT is linked to genes on the Y-chromosome or X-linked conditions. An additional explanation may have to do with gene imprinting or telomere length, both of which have been suggested as a mechanism of paternal mode of inheritance (37,38). However, these hypotheses are speculative and need to be explored in future studies.

Our results demonstrated association for ALT and not AST. This was not entirely surprising because ALT has been shown to correlate better with obesity (39). Furthermore, elevations of serum AST are more sensitive to alcohol consumption as compared to ALT, which is usually associated with NAFLD (40). Lastly, serum ALT is a more specific marker of liver injury than serum AST (41,42).

Strengths and Limitations

Strengths of our study include the use of a well-characterized large community-based sample. Parental adiposity status was obtained from routine Framingham Heart Study clinic examinations and was not based on offspring self-report. We were able to account for potentially important confounding variables that are known to be related to elevated serum ALT levels. Our study has several limitations. First, our sample was exclusively white, thus the generalizability of these findings to other races or ethnic groups is uncertain. Second, the study sample included only offspring with both parents in the Framingham Heart Study. This was necessary to minimize bias due to misclassification of parental obesity status. Third, parental serum ALT and AST levels were not measured. Therefore, we can not exclude the possibility that parents with early-onset obesity also had abnormal ALT or AST levels. Information on other liver diseases, such as viral hepatitis, autoimmune or metabolic liver disease and their risk factors, was not available and therefore these conditions could not be excluded as a cause of ALT elevations. To limit potential bias, we excluded individuals who might have these conditions by restricting our study sample to offspring with ALT and AST < 120 IU/L. These individuals were excluded because higher levels of serum ALT and AST are more likely to be associated with acute liver injury that may be related to factors such as drug-induced liver injury, acute viral hepatitis, and not NAFLD. Nonetheless, inclusion of these individuals in our study would result in misclassification and would bias the results towards the null hypothesis. Therefore, it is unlikely that this issue contributes to our findings.

Lastly, we did not have information on central obesity or measures of insulin resistance, two factors that could potentially mediate our findings.

Implications for Further Research

Our findings support the hypothesis that familial factors may play a role in the risks of elevated serum ALT levels in the general population. Further, this association may be mediated through early-onset obesity. It is possible that genes that associate with early-onset obesity may also be associated with elevated ALT levels. Future studies should specifically examine the relations of potential candidate genes, elevated ALT levels and NAFLD. However, it is important to recognize that our findings do not establish a causal relationship between genetic factors and the development of elevated serum ALT levels or NAFLD.

These results support the need for further studies to establish whether individuals with early-onset parental obesity and elevated serum ALT levels are at a higher risk of developing progressive liver disease such as NASH. Further research will also be important to identify whether these individuals are also at increased risk of developing metabolic complications of both obesity and NAFLD. These results need to be validated in other family studies to further understand the role of genetic and shared environmental factors on susceptibility to developing elevated serum ALT levels.

Conclusion

A history of early-onset paternal obesity, but not general parental obesity, increases the odds of elevated serum ALT levels in offspring, suggesting a genetic predisposition to developing elevated serum ALT levels, and perhaps NAFLD. Familial factors may be involved in the pathogenesis of elevated serum ALT.

Acknowledgments

The authors would like to thank Dr. John G. McHutchison for providing insightful comments on study results, and Dr. Jordan Feld for helpful discussions and critical review of the manuscript.

NIH Funding Support: This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (N01-HC-25195), K-24-HL-04334 (VR) and the intramural training program of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Role of Funding Agencies: No role in data analysis or reporting.

Abbreviations

ALT
: alanine aminotransferase

AST
: aspartate aminotransferase

BMI
: body mass index

NAFLD
: nonalcoholic fatty liver disease

NASH
: nonalcoholic steatohepatitis

FHS

Framingham Heart Study

OR

odds ratio

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Table 1

Characteristics of offspring participants by parental obesity status based upon at least one obese parent.

	Early-onset parental obesity	Later-onset parental obesity	No parental obesity (Referent group)	p-value[§]	p-value[#]
	N = 193	**N = 240**	**N = 1079**		
Age (years)	38 (7)	42 (10)	43 (9)	<0.001	0.19
Women (%)	46	52	51	0.21	0.80
BMI (kg/m^2)	27.1 (5.2)	26.1 (4.5)	25.0 (3.8)	<0.001	<.001
Systolic Blood Pressure (mm Hg)	119 (14)	121 (16)	121 (16)	0.39	0.47
Total Cholesterol (mg/dl)	196 (34)	199 (37)	201 (38)	0.45	0.70
HDL Cholesterol (mg/dl)	47 (13)	48 (13)	49 (13)	0.03	0.38
Total/HDL cholesterol ratio	4.6 (1.6)	4.5 (1.6)	4.4 (1.6)	0.03	0.27
Triglyceride (mg/dl)	135 (79)	131 (70)	128 (73)	0.03	0.23
Alcohol intake (drinks/wk)	3.2 (4.1)	3.8 (5.8)	3.9 (5.2)	0.38	0.83
Diabetes (%)	0	2	2	n/a	n/a
Hypertension treatment (%)	6	10	7	0.21	0.03
Current smoking (%)	43	38	35	0.17	0.39
Cardiovascular Disease (%)	6	4	3	0.05	0.16
ALT[*] (IU/L)	25 (19–35)	22 (16–31)	22 (16–32)	0.01	0.23
AST[*] (IU/L)	20 (12–26)	19 (14–25)	19 (14–25)	0.43	0.31
Elevated ALT[**] % (n)	52 (100)	42 (195)	43 (459)	0.006	0.96
Elevated AST[**] %(n)	30 (58)	26 (119)	27 (291)	0.18	0.68

P value was abstracted from GEE model adjusted for age, sex and familial correlation comparing participants with parental (early or later-onset) obesity to those without parental obesity.

[§] p-value: Early onset parental obesity vs. no parental obesity

[#] p-value: Later-onset parental obesity vs. no parental obesity

Data presented as mean (standard deviation) for continuous variables or % (n) for categorical variables.

Abbreviations: BMI=body mass index; HDL=high density lipoprotein; n/a = not applicable

[*] ALT and AST presented as median and [25th, 75th percentiles]

[**] Elevated ALT or AST is defined as ≥30 IU/L in men and ≥19 IU/L in women.

Table 2

Log transformed ALT and AST values by parental history of obesity.

	Early-onset parental obesity	Later-onset parental obesity	No parental obesity (Referent Group)	p-value**	p-value§
	N = 193	N = 460	N = 1079		
ALT					
Father					
Age-sex model	3.27 (0.06)	3.10 (0.03)	3.08 (0.02)	0.001	0.44
Multivariable model*	3.21 (0.06)	3.08 (0.03)	3.08 (0.01)	0.02	0.99
Mother					
Age-sex model	3.19 (0.04)	3.07 (0.03)	3.08 (0.02)	0.02	0.72
Multivariable model*	3.15 (0.04)	3.05 (0.03)	3.10 (0.02)	0.22	0.14
At least one affected parent					
Age-sex model	3.21 (0.04)	3.06 (0.03)	3.08 (0.02)	0.001	0.39
Multivariable model*	3.17 (0.03)	3.03 (0.03)	3.10 (0.02)	0.07	0.05
AST					
Father					
Age-sex model	3.00 (0.05)	2.93 (0.03)	2.91 (0.01)	0.06	0.41
Multivariable model*	2.99 (0.05)	2.92 (0.03)	2.91 (0.01)	0.10	0.63
Mother					
Age-sex model	2.94 (0.04)	2.92 (0.03)	2.91 (0.01)	0.51	0.70
Multivariable model*	2.93 (0.04)	2.91 (0.02)	2.90 (0.01)	0.69	0.83
At least one affected parent					
Age-sex model	2.96 (0.03)	2.91 (0.02)	2.90 (0.02)	0.15	0.72
Multivariable model*	2.95 (0.03)	2.90 (0.02)	2.91 (0.02)	0.30	0.77

Least square of mean (standard error) of log transformed serum ALT and AST values are presented above

Results obtained from GEE adjusted for familial correlation.

*Age, sex, diabetes, BMI, systolic BP, hypertension treatment, total cholesterol/HDL ratio, triglyceride, smoking status, total alcohol consumption, and cardiovascular disease.

**p-value comparing early onset parental obesity vs no parental obesity

§p-value comparing later-onset parental obesity vs no parental obesity

Table 3

Odds ratio of elevated ALT and AST levels with or without adjustment grouped by parental obesity status.

	Early-onset vs. no parental obesity		Later-onset vs. no parental obesity	
	OR (95% CI)	**p-value**[**]	**OR (95% CI)**	**p-value**[§]
	ALT			
Father				
Age-sex model	2.04 (1.29–3.24)	0.005	1.05 (0.79–1.39)	0.76
Multivariable model[*]	1.75 (1.06–2.89)	0.03	0.93 (0.68–1.27)	0.66
Mother				
Age-sex model	1.33 (0.95–1.85)	0.09	1.05 (0.82–1.35)	0.68
Multivariable model[*]	1.10 (0.76–1.59)	0.61	0.91 (0.70–1.18)	0.49
At Least One Affected Parent				
Age-sex model	1.52 (1.13–2.06)	0.006	1.01 (0.80–1.26)	0.97
Multivariable model[*]	1.25 (0.90–1.74)	0.18	0.88 (0.69–1.12)	0.29
	AST			
Father				
Age-sex model	1.26 (0.78–2.04)	0.34	0.94 (0.69–1.29)	0.71
Multivariable model[*]	1.18 (0.73–1.91)	0.49	0.91 (0.65–1.26)	0.56
Mother				
Age-sex model	1.24 (0.81–1.74)	0.28	0.95 (0.72–1.26)	0.73
Multivariable model[*]	1.14 (0.75–1.71)	0.54	0.86 (0.65–1.16)	0.33
At Least one Affected Parent				
Age-sex model	1.28 (0.92–1.80)	0.15	0.95 (0.73–1.23)	0.68
Multivariable model[*]	1.17 (0.82–1.66)	0.39	0.87 (0.66–1.14)	0.32

The analysis is based upon GEE model adjusted for familial correlation.

The referent group is either offspring without a paternal, maternal, or parental history of obesity for Father, Mother, and At least One Affected Parent model, respectively.

[*] Age, sex, diabetes, BMI, systolic BP, hypertension treatment, total cholesterol/HDL ratio, triglyceride, smoking status, total alcohol consumption (drinks/week), and cardiovascular disease.

[**] p-value comparing early onset vs. no parental obesity

[§] p-value comparing later onset vs. no parental obesity