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The Association between Major Depressive Disorder in Childhood and Risk Factors for Cardiovascular Disease in Adolescence

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Abstract

Objective—Depression in adults is associated with risk factors for cardiovascular disease (CVD). It is unclear, however, when the association between clinical depression and cardiac risk factors develops, or how early in life this association can be detected.

Methods—In an ongoing study of pediatric depression, we compared CVD risk factors, including smoking, obesity, physical activity level, sedentary behavior, and parental history of CVD, across three samples of adolescents: probands with established histories of childhood-onset major depressive disorder (MDD; N=210), never-depressed siblings of probands (N=195), and controls with no history of any major psychiatric disorder (N=161).

Results—When assessed during adolescence, 85% of the probands were not in a major depressive episode. Nevertheless, at that assessment, probands had a higher prevalence of regular smoking ([odds ratio [OR] 12.54, 95% confidence interval [CI] = 4.36–36.12) and were less physically active than controls (OR .59, CI = .43–.81) and siblings (OR .70, CI = .52–.94), and had a higher rate of obesity than did controls (OR 3.67, CI = 1.42–9.52). Parents of probands reported high rates of CVD (significantly higher than did parents of controls), including myocardial infarction and CVD-related hospitalization (ORs 1.62–4.36; CIs = 1.03–15.40). Differences in CVD risk factors between probands and controls were independent of parental CVD.

Conclusions—Major depression in childhood is associated with an unfavorable CVD risk profile in adolescence, and risks for pediatric depression and CVD may coincide in families.

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Effective prevention and treatment of childhood depression may be a means to reduce the incidence of adult CVD.

Keywords

Depression; cardiovascular disease; risk factors; adolescence

Cardiovascular disease (CVD) is a leading cause of mortality worldwide and accounts for approximately 30% of all deaths (1). Depression in adults has been identified as an independent risk factor both for incident coronary heart disease and cardiac events among patients with established heart disease (2, 3, 4). Repeated exposure to major depression has been associated with measures of *preclinical CHD*, such as coronary artery calcification (CAC) both cross-sectionally, and longitudinally (5–6). Moreover, well-established risk factors for CVD tend to be more common and more severe in depressed than in nondepressed adults: Depressed adults are more likely to smoke (7), have a higher body mass index (BMI) (8), and be more sedentary (9) than their nondepressed counterparts.

Critically, because research linking depression to CVD risk factors has typically involved middle-aged and older adults, it is unclear when in the life course clinical depression first becomes associated with traditional risk factors for CVD. Most research linking depression to established CVD risk factors has involved middle-aged and older adults. There are some indications that this association may be detectable with childhood or adolescent samples. (10, 11, 12, 13, 14), although most studies have examined a single CVD risk factor in isolation. The clearest evidence for childhood or adolescent depression contributing to future elevation on a CVD risk factor is obesity (see 15–16 for reviews). For example, a follow up of a sample of children and adolescents, psychiatrically diagnosed with major depression at ages 6–17 years, found that childhood depression predicted adult BMI about 10–15 years later (17). However, most studies of youths have relied on self-rated, questionnaire measures of depression, which typically assess current symptom levels only and are likely to underestimate true effect sizes. Further, such questionnaires do not provide information about whether an individual has a history of a diagnosable depressive disorder.

The present report is based on data from an ongoing study of the outcome and emotional functioning of youngsters who were identified in a prior investigation as having had major depressive disorder. The current project includes adolescent probands with childhood-onset major depressive disorder, never-depressed siblings of probands, and healthy controls. Although the project was not designed as a study of CVD risk factors, the protocol included variables relevant to this topic. We enriched the project dataset for this report by collecting supplemental information about parental history of CVD.

Using the available data, we sought to determine whether a carefully-established history of major depression in childhood is associated with selected cardiovascular risk factors in adolescence, even after adjustment for parental history of CVD (18). Probands in our sample were, on average, 9-years old at onset of their first depressive episode. Clinically manifest CVD is extremely rare at that age. Thus, this data set provided an opportunity to evaluate the relationship between depression and traditional CVD risk factors, without confounding by clinically manifest CVD.

METHODS

SAMPLES

Three groups of adolescents were studied: probands with childhood-onset depression (COD; N=210), never-depressed siblings of COD cases (SIBS; N=195), and normal control youth without any major psychiatric disorder (N=161). COD probands and siblings were part of 723 families that had been recruited from 2000 and 2006 for a molecular genetic study of childhood-onset depression (19). Beginning in 2011, a new project began data collection with a subset of cases from the original genetic study, enrolling families who resided within commuting distance of three research hubs. (Funding constraints did not permit us to follow all families). On average, probands and siblings entered the original genetic study seven years before the current assessment, and enrollment data on some CVD risk variables (i.e., smoking history) were available on them.

For the ongoing study, a group of normal controls was recruited from public schools in neighborhoods attended by probands. Research staff gave presentations at routine parents' meetings at these schools, seeking volunteers for the study. Potential control subjects and parents were invited to participate in diagnostic evaluations; only children free of major psychiatric and medical disorders were recruited into the study as controls.

The depressed probands were recruited from 24 child mental health facilities across Hungary based on the following criteria: (i) current or recent DSM-IV defined major depressive disorder, (ii) 7–14-years old at the initial screen, (iii) no evidence of mental retardation or major systemic medical disorder, (iv) had at least one biological parent available to participate, and (v) had at least one full biological 7–18 year-old sibling. As described previously (20–21), caseness for each proband was established via two standardized psychiatric diagnostic evaluations by different interviewers about 1 month apart, followed by independent verification of the diagnosis by the consensus best-estimate diagnostic procedure (22).We used the Interview Schedule for Children and Adolescents - Diagnostic Version (ISCA-D), a semi-structured psychiatric interview (for more detail, see 20), which is an extension and modification of an earlier semi-structured Interview (23); parent and child each separately served as informants. Siblings and controls were interviewed once with the ISCA-D, and diagnostic outcomes were independently verified. Evaluations were conducted by child psychiatrists and clinical psychologists who were trained in standardized psychiatric evaluation. Siblings received a psychiatric evaluation at enrollment but the presence of depression or other forms of psychopathology was neither an exclusion nor an inclusion factor. For the current study, only never-depressed siblings were evaluated. A sibling was considered never-depressed if he or she had no lifetime history of depression as ascertained by the most recent psychiatric evaluation.

The research was approved by the institutional review boards of the University of Pittsburgh and the Hungarian clinical research sites. All parents provided written informed consent, and depending on their ages, participating youth provided either assent or consent.

ASSESSMENT OF CVD RISK FACTORS AND PARENTAL CVD HISTORY

Information on demographics and smoking was gathered by clinicians using standardized, pre-coded forms. Height and weight, measured on standard medical scales, were used to compute body mass index (BMI). The BMI value was converted into age- and sex-standardized z-scores (24). The BMI z-score was treated as a continuous measure and also categorized based on recommended percentile cut-offs of the standard normal distribution (25). The participants completed an 8-item Physical Activities History questionnaire (adapted from the Youth Risk Behavior Surveillance-United States, Centers for Disease Control and Prevention), which included questions about the average amount of time per day spent in sports, aerobic exercise, and various sedentary activities.

History of CVD in mothers and fathers was assessed by a self-report questionnaire that was mailed to each family. The questionnaire focused on objective events, such as having been diagnosed with heart disease by a physician, having been prescribed cardiac medications, and cardiac hospitalizations. Diagnosis and treatment of diabetes were also included in the parental questionnaire because diabetes is a major risk factor for CVD. For practical reasons, we asked one parent —usually the mother—to complete the questionnaire about herself and the subject's father.

STATISTICAL ANALYSIS

Descriptive statistics were computed in SAS v. 9.2. All other analyses were conducted with Mplus v. 6.12. (26). Missing values comprised less than 4% of the data, with the exception of the Parental History of CVD questionnaire, which was returned by 173 proband/sibling families (60%) and 141 control families (88%). In modeling the outcomes of interest, sensitivity analyses (27) found no substantive differences between results using complete-case and Robust Full Information Maximum Likelihood (MLR) methods. Therefore, MLR estimation was used in all regression models (28). Comparative Fit Index (CFI) values of .95 or greater and Root Mean Square Error of Approximation (RMSEA) values of .06 or lower were regarded as indicating excellent model fit for exploratory and confirmatory factor analyses (29).

In analyzing the Physical Activities History questionnaire, two items considering days per week walking or bicycling over 30 minutes were discarded (one due to low correlations with other scale items, typically $r < .10$, and the other due to systematic age effects). Exploratory and confirmatory factor analyses (CFA) of random-split halves of the remaining items ($N_{1\ \&\ 2} = 286$) found that 4 loaded on a latent physical activity factor, leaving two sedentary behavior items that quantified the number of hours spent watching TV and playing on computers on school days, respectively (CFA: CFI = 1.00, RMSEA = .004). The items on the Parental History of CVD questionnaire were analyzed individually in the whole sample and were reduced with hierarchical CFAs into four latent factors (CFI = .99, RMSEA = .03). Maternal diabetes and paternal diabetes were each comprised of 3 items concerning the presence of high blood sugar, blood sugar medication, and diagnosed diabetes. Maternal heart disease and paternal heart disease were each comprised of 11 items concerning the presence of high blood pressure, blood pressure medications, high cholesterol/triglycerides, stroke, heart attack, angina, "weak" heart, heart disease medication, cardiac-related

hospitalization, cardiac-related invasive procedure, and death of close relatives from heart disease. The four factors explained a notable portion of variance in their item-level indicators (maternal diabetes: λs =.94–.96, R^2 = .89–.93; paternal diabetes: λs=.98 R^2 =.96; maternal heart disease: λs =.42–.92, R^2 = .18–.85; paternal heart disease: λs =.45–.96, R^2 = .20–.91), and were used to fit a second a second-order Composite Parental CVD factor (CFI = .98, RMSEA = .04; λs =.67–.76, R^2 = .45–.58). The means of the Parental History Factor Scores can be thought of as Z-scores. The interest is in the mean differences between groups.

Group differences in CVD risk variables were first tested via multinomial logistic regression. Youth group membership was the dependent variable and the adolescent CVD risk variables were the independent variables. These analyses first were performed without adjustment for covariates. The final models (see Table 1) were adjusted for age, sex, and parental education because these variables have all been shown to be related to cardiovascular health (30, 31, 32) and because there were significant across-group differences (see below) in the sample. With respect to age and sex (the proband sample was somewhat older and had more boys than the controls). With respect to parental educational level, which served as a surrogate for socioeconomic status (control parents were better educated than were proband parents). When probands and siblings were compared, Taylor Series linearization was employed to account for within-family dependence (26). Finally, we assessed whether any proband-control group differences on risk behaviors were independent of parental CVD. Thus, the final multiple logistic regression model (Table 3) included the Composite Parental CVD History variable and tested whether elevations on CVD risk factors continued to be associated with proband status, after controlling for parental CVD history.

RESULTS

Demographic and Clinical Characteristics of the Samples

Probands were about 1 year older (17.0±1.4 years) than siblings (15.9±2.1 years) and controls (15.8±2.1years); $F(2, 563) = 22.2$, $p<.001$. There were more boys (63.3%) than girls (37.7%) among the probands, which is typical of clinical COD cases (33). The control group (64.6% boys) was sex-matched to the probands, but the sibling group (45.6% boys) was not , $\chi2=17.5$, $p<.001$. The overall sample was predominantly Caucasian (97.0%) and the remaining participants were minorities (Roma; African). A significantly higher portion of control mothers (52.2%) had college level or higher education than did mothers of probands/siblings (15.1%; $\chi2=69.5$, $p <.001$); this was also the case for fathers of controls vs. probands (44.4% vs. 11.1%, $\chi2=63.1$, $p < .001$). Maternal ages of probands/siblings and of controls were comparable (44.1 ± 5.1 years, and 43.6 ± 4.7 years, respectively), as were paternal ages (47.7 ± 6.5 years, and 46.7 ± 6.2 years, respectively).

The mean age at onset at the first MDD episode in probands was 9.1 years ±1.9. By the time of the current assessment in adolescence, 59.0% of the probands had one MDD episode, 31.9% had two episodes, and 9.0% had three or more episodes. Paralleling well-replicated findings in COD (33), the most common psychiatric comorbidities were anxiety disorders (38.6%) and disorders of behavior, such as attention-deficit-hyperactivity disorder (36.2%).

At the time of the current assessment, 14.8% of the probands were in a major depressive episode, and 3.8% reported current psychotropic medication use.

Adolescent Risk Factors for CVD

Table 1 presents odd ratios and the prevalence or mean value of risk factors in the 3 groups of adolescents. Despite no overall group difference in mean BMI, more probands than control youth were classified as obese or overweight after correcting for age- and sex using the Center for Disease Control weight classification categories (24). All of the other risk factors were significantly more prevalent, or had higher levels, in probands than controls. In general, the values for the never-depressed siblings fell roughly midway between the values for the controls and the probands. Specifically, as shown in Table 1, probands reported lower levels of regular physical activity than did siblings and controls, while both probands and siblings reported spending more time in sedentary activities (TV and computer use) than did controls. Finally, more probands than siblings were regular smokers (33.5% vs 13.6%, respectively, Wald $\chi^2 = 9.27$, $p = .002$), but both the proband and sibling groups had a higher proportion of regular smokers than controls (Wald χ^2: probands: 21.96, p<.001; siblings: 8.59, $p = .003$).

Parental History of CVD

History of CVD was reported more often by one or both parents of proband/sibling families than by control families (Table 2). This pattern was evident in eight out of the ten items concerning manifestations of CVD, including heart attacks and CVD-related hospitalizations. Greater CVD history in proband/sibling than control families was reflected in higher CVD factor scores for mothers and for fathers, as well as in the Composite Parental CVD Factor score.

A multiple logistic regression analysis was conducted to determine whether the across-group differences in risk factors (identified in univariate analyses, see Table 1) were independent of parental CVD and one-another. As shown in Table 3, parental CVD did not account for the elevations on CVD risk factors among proband offspring. Proband status continued to be associated with elevated CVD risk factors after controlling for parental CVD history, as well as for subjects' age, sex, and parental education level.

DISCUSSION

There is a compelling body of evidence that depression is associated with cardiac risk factors in older adults with CVD (2–4), but less is known regarding risks posed by depression in individuals who do not yet have clinically manifest CVD.. This study demonstrates that childhood-onset major depressive disorder is associated with a pattern of elevated CVD risk factors during adolescence, long before the development of manifest CVD. Our study thus fills an important gap in knowledge about the developmental precursors of risk factors for CVD using a uniquely large sample of psychiatrically diagnosed youngsters.

The findings suggest that CVD risk factors are affected by both depression and family membership. While adolescent probands with depression histories had the highest rates of

CVD risk factors, their never-depressed siblings scored between probands and unrelated control adolescents on several risk indices, suggesting a risk gradient. That probands smoked more regularly and were less physically active than never-depressed siblings suggest that a history of pediatric depression may confer added CVD risk, even above the risk associated with parental history of CVD.

The high rates of cardiovascular disease among mothers and fathers in COD families were unexpected because the parents were relatively young (mean ages of 44 years and 48 years, respectively). This finding is also striking because COD families were not originally ascertained in connection with cardiovascular disease, but rather on the basis of depression in their child. While a positive parental history of CVD puts a child at high risk for eventual CVD, it is also important to note that parental cardiovascular problems did not account for the elevated CVD risk factors among proband youths, nor did several other potential confounds, including subjects' age, sex, and parental education level. Overall, the clustering of CVD history in parents and CVD risk factors in offspring may reflect a common genetic vulnerability to depression and CVD and/or the effects of unhealthy lifestyles operating within the family environment (34).

The vast majority (85%) of our probands were not in a depression episode when they exhibited elevated rates of CVD risk factors in adolescence, which likely lessened response biases that are known to be associated with depression. Possibly, the high rates of risk factors in question, such as smoking or sedentary behavior, may be consequences of depression the probands had experienced earlier. Indeed, data from the enrollment assessments for the original genetic study support this possibility. From among those probands identified as regular smokers in the present report, only 1 (1%) was a regular smoker at enrollment in the original study about 7 years earlier, on average. Of the 19 probands who were classified as obese in the present report, 9 (47%) were obese 7 years earlier. In light of these facts, we repeated the multivariate logistic analysis, excluding probands who smoked or who were obese when they entered the genetic study. Odds ratios were in all cases substantially unchanged, suggesting that the high rates of CVD risk factors we detected in adolescents were not accounted for by children who had some of those same risk factors earlier while they were depressed. The present results are thus consistent with the possibility that depression may aggravate CVD risk factors (5, 12).

Overall, given their histories of depression, the elevated rates of several CVD risk factors, and the high prevalence of CVD in their parents, our probands have a notable CVD risk profile. According to a recent meta-analysis, elevations on *multiple* CVD risk factors are associated with substantial increases in subsequent lifetime risk of cardiovascular disease (35). Based on their profile, our probands are on a hazardous developmental trajectory, one that is more likely to result in early preclinical signs of CVD, and eventually in clinically manifest CVD (36–37).

Limitations and Conclusions

Our investigation has several unique features as well as some weaknesses. Although analyses controlled for parental education, which was an observed difference between proband and control families, probands and control families were originally recruited at

different times and places; thus, we cannot rule out the possibility that selection bias may have weakened our comparisons between proband and control children. Because the study did not originally focus on CVD, we lacked information on several biological CVD risk factors, including lipid abnormalities, inflammation, and elevated blood pressure and the number of missing values for the Parental History of CVD questionnaire was high. Also, we employed one parent as an informant on the CVD history questionnaire for both parents. While the family history method has established validity (38), direct assessments of both parents would have been advantageous. Finally, our study was conducted in Hungary. However, the correlates of CVD are similar across many nations, and epidemiological data suggest this sample has characteristics typical of depressed children in Western countries (39).

Findings from this study have clinical implications. While links between depression, risk factors, and CVD have collectively been established by this study and in the wider literature, it is not known whether the link between depression and CVD operates predominantly through CVD risk factors. Although the mechanisms through which depression increases the risk for CVD need further investigation, the results of this study suggest the possibility that depression may first give rise to these CVD risk factors, which may in turn lead to manifest CVD later in life. In any case, depressed children and adolescents should be monitored for signs of CVD risk behaviors and factors, which may be more amenable to be corrected at younger (rather than older) ages. Ultimately, it may be valuable to determine whether treating depression in children can prevent the emergence of preclinical CVD, and ultimately, of manifest CVD. Effective prevention and treatment of childhood depression episodes may be one means to reduce the long-term burden of CVD.

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Glossary

CVD	Cardiovascular disease
BMI	body mass index
COD	probands with childhood onset depression
SIBS	never depressed siblings
MLR	Robust full information maximum likelihood
CFA	confirmatory factor analysis
CFI	comparative fit index
RMSEA	root mean square error of approximation
MDD	major depressive disorder

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Table 1

Adolescent Cardiovascular Risk Factors in Control, Proband, and Sibling Groups

Variable	Control (n=161)	Proband (n=210)	Sibling (n=195)	χ^2 Statistic‡	Odds Ratio (95% CI) P v C.	S v C.	P v S.
Body Mass Index Z-Score	−0.16 (± 1.07)	−0.05 (± 1.26)	−0.14 (± 1.15)	1.14	1.11 (.90–1.36)	1.03 (.85–1.25)	1.08 (.91–1.28)
Weight Status Category§ (%-ile):				11.59			
Healthy (5th-<85th)b	81.4	67.1	75.4		---	---	---
Underweight (<5th)	7.5	10.5	6.7		1.95 (.77–4.97)	1.13 (.42–3.05)	1.73 (.78–3.86)
Overweight (85th–95th)	6.8	12.9	10.8		2.13** (1.00–4.56)	1.78 (.81–3.92)	1.20 (.64–2.23)
Obese (>95th)	4.3	9.5	7.2		3.67** (1.42–9.52)	2.11 (.79–5.64)	1.74 (.81–3.73)
Physical Activities							
Factor Score	0.26 (± 0.66)	−0.09 (± 0.79)	0.11¥ (± 0.79)	11.81*	.59*** (.43–.81)	.85 (.62–1.15)	.70* (.52–.94)
TV/School day (hours)	1.14 (± 1.13)	2.03 (± 1.50)	1.89 (± 1.35)	29.09**	1.68*** (1.37–2.06)	1.50*** (1.23–1.84)	1.12 (.97–1.29)
Computer use/day	1.46 (± 1.39)	2.07 (± 1.72)	1.99 (± 1.53)	17.12**	1.33*** (1.12–1.57)	1.37*** (1.16–1.61)	.97 (.85–1.11)
Cigarette Smoking (%)				36.87**			
None[a]	92.40	52.90	80.10		---	---	---
Occasionally	5.10	13.60	6.30¥		2.65** (1.01–6.95)	1.13 (0.38–3.37)	2.34* (1.08–5.11)
Regularly	2.50	33.50	13.60¥		12.54*** (4.36–36.12)	5.29** (1.74–16.09)	2.37** (1.37–4.12)

Figures represent mean (± SD) unless otherwise indicated.

‡Likelihood Ratio Test, accounting for dependence within families. Group effect adjusted for age, sex, and parental education. Significant ($p<.05$) *post-hoc* differences vs. controls -- after adjustment -- are underlined.

¥Significant ($p < .05$) *post-hoc* difference between siblings vs. probands after adjustment.

*p<0.05

**p<0.01,

***p<0.001

§USA Centers for Disease Control (http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html)

P = proband, S = siblings, C = controls, P v C. & S v C. = Control group used as reference category for Odds Ratios, P v S = Siblings used as reference category for Odds Ratios.

[a] Reference category for Odds Ratios.

Table 2

Parental History of Cardiovascular Problems in Proband/Sibling and Control Families.

Variable	Control Fam. (n=141)	Proband/Sibling Fam. (n=175)	O.R. (95% C.I.)†	Wald χ^2
Positive History in Either Parent (%)				
High Blood Sugar	15.6	23.1	1.63 (0.91, 2.89)	2.8
Blood Sugar Medication	9.9	12.1	1.25 (0.61, 2.56)	0.4
Diabetes	11.4	14.0	1.27 (0.64, 2.49)	0.5
High Blood Pressure	39.3	51.2	1.62 (1.03, 2.55)	4.4*
Blood Pressure Medication	32.6	47.4	1.86 (1.17, 2.95)	7.0**
High Cholesterol/triglycerides	25.7	37.1	1.70 (1.04, 2.78)	4.5*
Heart Attack	4.3	12.2	3.13 (1.23, 7.98)	5.7*
Angina	7.9	20.8	3.06 (1.46, 6.26)	9.3**
Cardiovascular Invasive Procedure	1.4	2.9	2.08 (0.40, 10.88)	0.8
Stroke	2.1	8.7	4.36 (1.24, 15.40)	5.3*
“Weak Heart”	5.7	11.1	2.05 (0.87, 4.82)	2.7
CVD Medication	17.0	33.7	2.48 (1.44, 4.26)	10.8***
CVD-Related Hospitalization	10.6	22.0	2.36 (1.24, 4.51)	6.8**
Close Relative Died of Heart Disease	25.0	32.2	1.42 (0.86, 2.34)	1.9
Parental History Factor Scores (Mean ± S.D.)‡				
Maternal Diabetes	0.14 ± 0.79	0.42 ± 0.86	1.52 (1.14, 2.02)	8.3**
Paternal Diabetes	0.14 ± 0.93	0.49 ± 1.00	1.46 (1.15, 1.86)	9.5**
Maternal CVD	−0.02 ± 0.90	0.41 ± 1.10	1.53 (1.21, 1.93)	12.7***
Paternal CVD	−0.03 ± 0.95	0.40 ± 1.15	1.47 (1.18, 1.83)	11.8***
Composite Parental CVD	0.04 ± 0.61	0.32 ± 0.69	1.93 (1.36, 2.75)	13.3***

Notes:

† Univariate logistic regression odds ratio (and 95% confidence interval) of depression given history of disease in mother or father, or unit increase in factor score.

‡ Scores computed via confirmatory factor analysis of family history items categorized by diabetes vs. heart disease in mother vs. father.

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$

Table 3

Multiple Logistic Regression Model ofRisk Factors for CVD Predicting Proband Status.

Variable	O.R. (95% C.I.)†	Wald χ^2 or Z-score
BMI Weight Classification (vs. Healthy)		6.60
Obese	4.77 (1.33, 17.11)	
Overweight	1.69 (0.70, 4.11)	
Underweight	1.54 (0.51, 4.66)	
Physical Activity Factor Score	0.42 (0.20, 0.86)	−2.36*
TV per School day (hour)	1.53 (1.19, 1.95)	3.38***
Computer per School day (hour)	1.31 (1.05, 1.62)	2.44*
Smoke (vs. Never)		17.31***
Sometimes	2.17 (0.73, 6.43)	
Regularly	16.20 (4.21, 62.36)	
Age of youngster (Years)	1.13 (0.91, 1.40)	1.10
Sex of youngster (Male)	0.77 (0.39, 1.54)	−0.73
College Degree or Higher Education of:		
Biological Mother	0.32 (0.16, 0.62)	−3.33***
Biological Father	0.60 (0.28, 1.30)	−1.30
Composite Parental CVD Factor Score	2.19 (1.08, 4.45)	2.17*

Notes:

†Multiple logistic regression odds ratio and 95% confidence interval of depression estimated with full-information likelihood (i.e., 160 controls vs. 203 probands with complete continuous variables) with all factors simultaneously in the model.

*p<0.05,

**p<0.01,

***p<0.001