Metabolic syndrome among young adults at high and low familial risk for depression

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Abstract

Background. Our study examined whether the early-onset depression phenotype among young adults (probands) is associated with the metabolic syndrome (MetS) and its components, and if MetS characterizes unaffected but high-risk siblings of probands.

Methods. We studied three groups of young adults (*M* age = 25 years, s.d. = 3.84 years): probands with histories of childhood onset depression – i.e. early-onset phenotype – (*n* = 293), their unaffected siblings (high-risk siblings, *n* = 273), and healthy controls (*n* = 171). Participants completed a full psychiatric interview, physical and laboratory assessments, and self-rating scales. MetS was defined using the criteria of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001).

Results. Early-onset depression phenotype and being a high-risk sibling were associated with higher MetS composite scores relative to that of controls, but did not differ from one another. With regard to MetS components: Probands and siblings had similarly larger waist circumference and lower HDL than did controls, while siblings and controls had lower triglyceride levels than did probands but did not differ from one another. Groups did not differ on glucose levels and SBP.

Conclusions. Our study extends the literature on the association between MetS and depression and underscores the importance of depression phenotypes: failure to account for the clinical heterogeneity of depression may partly underlie the inconsistent findings regarding its relation to MetS. The results also suggest that, in depression-prone populations, MetS may predate and possibly function as a risk factor for eventual depression.

Introduction

Clinical depression is known to be an independent risk factor for cardiovascular disease (CVD) (Goldstein et al., 2015). Clinical depression is also associated with the metabolic syndrome (MetS), which itself is an established risk factor for multiple indices of cardiovascular morbidity (such as coronary heart disease, heart failure, and stroke) and mortality (Galassi, Reynolds, & He, 2006; Gami et al., 2007; Tune, Goodwill, Sassoon, & Mather, 2017). Indeed, it has been proposed that MetS is one of the pathways whereby depression leads to cardiovascular problems (e.g. Marazziti, Rutigliano, Baroni, Landi, & Dell'Osso, 2014; Vaccarino et al., 2008).

In the literature on the co-occurrence of depression and MetS, depression has been most commonly indexed via the number of depressive symptoms, or an overall symptom severity score, both derived from self-rated questionnaires (see also Akbaraly et al., 2009, 2011; for reviews, see Marazziti et al., 2014; Pulkki-Råback et al., 2009; Vaccarino et al., 2008; Vogelzangs et al., 2011). However, self-rated depression questionnaires (e.g. BDI-II: Beck, Steer, & Brown, 1996) typically mirror only current (past 1–2 weeks) symptom levels. To determine a person's history of exposure to depression requires a psychiatric evaluation via a standardized semi-structured interview that covers the lifespan (e.g. SCID: First, Williams, Karg, & Spitzer, 2015).

While the literature reveals some variation in how MetS has been defined, there is consensus that it includes multiple components, most commonly: abdominal obesity or high body mass index, elevated blood pressure (BP), dyslipidemia, and abnormal insulin levels or glucose regulation. Clinical criteria for each component have been offered by various professional organizations: in the USA the diagnosis of MetS is made when the patient meets criteria on three or more components (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). According to a US survey, the prevalence of MetS is substantial in the general population at the rate of 34% (Aguilar, Bhuket, Torres, Liu, & Wong, 2015).

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There is considerable evidence of an association between depression and MetS. Using various definitions of depression (including symptom counts and diagnoses), several meta-analyses and reviews concluded that depressed individuals have higher rates of MetS than do non-depressed controls (Ghanei Gheshlagh, Parizad, & Sayehmiri, 2016; Marazziti et al., 2014; Repousi, Masana, Sanchez-Niubo, Haro, & Tyrovolas, 2018). Focusing on psychiatric interview-based major depressive disorder (MDD), reported in 18 studies with more than 5500 clinically referred subjects (mean age of 45.5 years), Vancampfort et al.'s meta-analysis (2014) found that depressed participants had 1.5 times higher odds of having MetS compared to general population controls. While much of this work has targeted middle-aged and older adults (e.g. Repousi et al., 2018; Vancampfort et al., 2014), recent studies have extended the findings to younger age groups. For example, a large national survey found that 17- to 39-year-old women (but not men) with a history of at least one major depressive episode were twice as likely to have MetS than those with no history of depression (Kinder, Carnethon, Palaniappan, King, & Fortmann, 2004). Focusing on 24- to 30-year-olds in a population-based sample with a clinically diagnosed current depressive episode, Moreira et al. (2017) likewise reported a higher prevalence of MetS among them compared to population controls.

However, a closer look at the findings suggests notable inconsistencies, including highly variable effect sizes (for a review, see Pan et al., 2012). Some studies have reported a lack of association between depression and MetS in diverse samples, including those in the community (Demirci, Cinar, & Bilgel, 2011; Foley et al., 2010) and in a university setting (Lin, Liang, Liao, & Tsay, 2014). Further, in some studies, only some MetS components (but not the overall syndrome) correlated with depression (Bakhtiari et al., 2018; Muhtz, Zyriax, Klähn, Windler, & Otte, 2009). Indeed, in their meta-analysis, Vancampfort et al. (2014) concluded that fasting blood glucose and triglyceride levels (rather than BP, high-density lipoprotein cholesterol (HDL-C), and waist circumference) are the MetS components most likely to differentiate clinically depressed patients from controls. Yet, in still other studies, apparent associations between MetS components and depression disappeared after controlling for covariates (e.g. Herva et al., 2006; Lin et al., 2014; Yu, Yang, Guo, Zheng, & Sun, 2017).

As noted by reviewers, one factor that may account for the equivocal findings in the literature is that depression has been defined and assessed in various ways; self-rated v. clinically diagnosed depression, for example, may identify different individuals (for a review, see Pan et al., 2012). Yet another important source of variability in the findings is the apparent lack of attention paid to the heterogeneity of clinically defined depression phenotypes. If some depression phenotypes are associated with MetS, but others are not, or if various phenotypes are associated with variable rates of MetS, then studies with different depression samples will yield equivocal findings.

One example of a clinical phenotype that has been studied in connection with MetS is 'atypical depression', which is characterized by reverse physiological symptoms (hyperphagia and hypersomnia). For example, in a sample of men in Japan, those with atypical depression were almost four times as likely to suffer from MetS than those whose depression reflected the more prevalent physiological symptoms (Takeuchi, Nakao, Kachi, & Yano, 2013). Among participants in a large study in the UK, the rate of MetS was almost twice as high among those with lifetime atypical MDD than among participants with non-specific MDD histories (Brailean, Curtis, Davis, Dregan, & Hotopf, 2020).

Further, according to Lasserre et al. (2017), only the atypical but not various other (e.g. melancholic and unspecified) depression phenotypes prospectively predicted MetS and several of its components.

Another important phenotype that has not yet been examined in relation to MetS is the early-onset (pre-adult- or juvenile-onset) depression phenotype. Depression that onsets during childhood and adolescence can be clearly distinguished from adult-onset depression (e.g. Jaffee et al., 2002), is prevalent and persistent (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012), recurrent (e.g. Kovacs, Obrosky, & George, 2016), with adverse health outcomes (Keenan-Miller, Hammen, & Brennan, 2007), and a worse clinical course than is later-onset depression (Zisook et al., 2007). In other words, depression that first declares itself during childhood or early adolescence signals a greater illness burden (Zisook et al., 2007) and a particularly severe form of depression (Wilson, Hicks, Foster, McGue, & Iacono, 2015). Given the evidence that both depression and MetS often originate early in life (for a review, see Richards, 2011; also see Retnakaran, Zinman, Connelly, Harris, & Hanley, 2006), pre-adult or early-onset depression is a particularly relevant clinical phenotype, and yet, little is known about its association with MetS.

Another unresolved issue in the literature is the direction of the depression–MetS relationship. In a meta-analysis of cross-sectional and longitudinal epidemiologic studies, Pan et al. (2012) concluded that the association between MetS and depression is bi-directional. However, some of Pan et al.'s (2012) conclusions are questionable. For example, it is unclear if MetS predicts depression in never depressed adults because Pan et al.'s analyses of nine studies, which addressed depression as the outcome of MetS, included studies that did not control for (or exclude) individuals with earlier histories of depression. One way to examine whether a presumably causal factor may be implicated in a particular outcome is to study samples at high risk for the outcome. For example, if, compared to healthy controls, those not yet depressed but at elevated risk for depression (such as the offspring or sibling of depressed individuals) have significantly higher rates of MetS, that finding would provide initial support for MetS as predating and being a plausible risk factor for eventual depression. While it has been reported that, relative to the offspring of non-depressed parents, young and healthy offspring with a parent who had depression manifested changes in insulin sensitivity and BP regulation, which can be plausibly related to MetS (Mannie et al., 2013), we found no publications specifically focused on MetS in populations at high-risk for depression. We sought to fill this gap in the literature by examining individuals at high familial risk for depression because they had siblings with documented histories of depression.

The high-risk family study is used in psychiatry to estimate the familiarity of a given disorder and better understand its transmission, to identify pre-morbid risk factors that can inform prevention, or to refine subtypes (Avenevoli & Merikangas, 2006). While in the present study, our primary goal was to examine whether MetS is a risk factor for eventual depression, it also is of clinical interest how high-risk, never depressed sibs and probands compare on the targeted outcomes. In a prior study, which used the current sample to examine behavioral risk factors for CVD, the rates of most risk factors among never depressed siblings were intermediary to the rates among probands and controls (Rottenberg et al., 2014). Relatedly, it has been reported that the number of risk factors for the MetS increased gradually across categories of increasing depression severity (Vaccarino et al.,

2008). Because probands had experienced the burden of depression, which is known to have adverse effects on a broad range of functions, they should manifest MetS at higher rates than their never depressed siblings (although both groups should be at greater risk for this outcome than healthy controls).

In light of the literature just summarized, our study sought to determine whether the early-onset depression phenotype is associated with MetS and if MetS characterizes individuals at high risk for but not yet manifesting depression. We examined three groups of young adults: (a) probands with childhood-onset depression (COD; mean onset age of 10 years), who exemplified the early-onset phenotype, (b) full biological siblings of probands unaffected by depression (high-risk siblings), and (c) healthy control peers. Our main hypothesis was that subjects with the early-onset depression phenotype (probands) and never depressed (high-risk) siblings of probands are more likely to manifest MetS and its components than are control peers. Our secondary hypothesis was that probands are more likely to manifest MetS and its components than are never depressed high-risk siblings. Given that education, level of physical activity, and smoking may confound the effects of group membership on the outcomes of interest, we adjusted for them in our models.

Methods

Participants

Our study included probands with COD ($n = 293$), never-depressed siblings of COD probands ($n = 273$), and controls without a history of major psychiatric disorder ($n = 171$). Probands were originally recruited as part of a genetic investigation in a national sample of children in Hungary that took place during the years 2000–2008: cases were accessed through 23 child mental health facilities and were 7–14 years of age at that initial ascertainment. Original study inclusion required current or recent depressive disorder per the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000), absence of mental retardation and major systemic medical disorder, and availability of at least one full biological 7- to 18-year-old sibling. During 2010–2014, probands and siblings who resided near three major university centers in Hungary were enrolled in a subsequent study of depression and a control group was recruited from public schools in the same neighborhoods as the participating probands (Rottenberg et al., 2014). At the conclusion of that project, available probands, siblings, and controls were enrolled in the present study of risk factors for eventual CVD.

General procedure

The study was conducted in three cities in Hungary (Budapest, Szeged, and Pécs). Subjects participated in a laboratory session early in the morning, which included collection of a fasting blood sample, vital signs, and physical phenotype measurements. Subjects were asked to refrain from eating, smoking, or caffeine intake overnight and reported the time interval since their last meal, caffeine intake, and smoking. Following the completion of the laboratory assessment, subjects participated in a psychiatric interview and completed self-rated questionnaires.

MetS components

The laboratory session included an assessment of the following MetS components:

BP was assessed via an Omron M6 BP Monitor with a memory function. There were three measurements per participant. Subjects sat comfortably in a chair and were asked to relax for 5 min before the first measurement. Then twice in a row, the cuff was loosened, and a 5 min break was provided before the next measurement. In our modeling procedures, we used the mean of the three systolic BP (SBP) values. Because we approached the analysis with standardized data and not the classic definition of MetS (with clinical cutoffs), we chose SBP because it tends to be a more powerful predictor of CVD (Borghi, Dormi, Ambrosioni, & Gaddi, 2002).

Waist circumference was measured according to a standard protocol. Subjects removed unnecessary upper clothing and emptied their pockets, were asked to stand, raise their shirt, blouse, or T-shirt, and breathe normally. A tape measure was placed around mid-distance between the upper edge of the hip (iliac) bone and the lowest rib, touching but not indenting the skin, and, while exhaling, the circumference to the nearest 0.1 cm was recorded.

Fasting blood draw was performed by a certified phlebotomist when subjects arrived in the laboratory in the early morning hours after having refrained from eating overnight. The samples were processed at the University Research Laboratory in Budapest according to accepted international standards and yielded the following:

Glucose level (100 μL of the sample) was determined by an enzymatic method based on Bondar and Mead (1974), and utilizing the coupled reactions catalyzed by hexokinase and glucose-6-phosphate dehydrogenase. Intra-assay coefficient of variation (CV %) was 2.91%.

HDL-C level (100 μL of the sample) was determined via a two-reagent method using reagents obtained from Vital Diagnostics (Lincoln, RI). The intra-assay CV% was 4.07%.

Triglycerides level (100 μL of the sample) was determined enzymatically using the procedure of Bucolo and David (1973). The intra- and inter-assay CV% was 4.75%.

Standardized z-scores were computed for each measure so that the MetS components could be compared on the same continuous scale of increasing pathology. The population mean and variance were estimated by regressing measurements from this study on a mixed-effect model of the grand mean with a random family intercept. Due to skewness, triglyceride values were log-transformed before standardization. Since lower HDL confers a higher risk of CVD, its standard score was reversed. For waist circumference and HDL, separate models were estimated for males and females due to documented sex differences in these two measures (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

The resulting standardization formulas were computed as the original score, minus the mean score, divided by the standard deviation: SBP: (mmHg, 111.77)/11.54; waist circumference: males: (cm, 86.61)/11.58, females: (cm, 76.74)/12.63; glucose: (Mmol, 4.95)/0.42; HDL: males: $-1 \cdot$(Mmol, -1.22)/0.25, females: $-1 \cdot$(Mmol, -1.50)/0.36; and triglycerides: [ln(Mmol), -0.09]/0.47. Finally, we modelled the sum of standardized components to create a standardized MetS z-score: (sum of component z-scores, -0.003)/2.88.

Psychiatric evaluation

As described previously (Kiss et al., 2007), the original study entry diagnoses (at enrollment into the initial genetic study) were established via two standardized psychiatric diagnostic evaluations

completed by different interviewers about 1 month apart, followed by independent verification of the results by the consensus best-estimate diagnostic procedure (Maziade et al., 1992). We used the Interview Schedule for Children and Adolescents – Diagnostic Version (ISCA-D), a semi-structured psychiatric interview, which is an extension of an earlier semi-structured interview (Sherrill & Kovacs, 2000), with satisfactory inter-rater reliabilities (Kiss et al., 2007). The ISCA-D, which was administered in childhood by trained clinical interviewers, requires two informants: the parent informs about the child and the child informs about him or herself: the interviewer integrates the sources of information and generates diagnoses that mirror DSM-IV criteria (Kiss et al., 2007).

Subjects eventually participated in other studies and were assessed via modified versions of our interviews that were suitable for young adults. Specifically, for the current study, subjects were administered by trained clinicians the semi-structured Interview Schedule for Young Adults – Follow-up Version (ISYA-FU), which is part of our suite of psychiatric diagnostic interviews (e.g. Kiss et al., 2007) and includes most DSM Axis-I diagnoses: it queries about symptoms since the subject's last research evaluation. The ISYA-FU results are part of each subject's record of lifetime diagnoses starting at the time that subjects were first interviewed at younger ages (see Sherrill & Kovacs, 2000). Presumably unaffected siblings without prior psychiatric assessment were administered a lifetime version of our interview schedule. As part of the assessment, subjects also provided information about current prescribed psychotropic and non-psychotropic medication and health behaviors (e.g. smoking). Based on the results, the clinician generated the appropriate DSM-IV diagnoses, including the onset and offset dates of disorder episodes, which were approved by a senior supervisor. Additional levels of subsequent reviews were conducted by senior diagnosticians who finalized the diagnoses using clinical consensus. Siblings who were found to have a history of affective disorders or controls who had any psychiatric disorder were excluded from the current analysis.

Self-rated physical activity

We used the seven-item version of the International Physical Activity Questionnaire (IPAQ) to quantify the level of physical activity. The IPAQ has been validated in several countries (Craig et al., 2003). It quantifies vigorous activity, moderate activity, walking and sitting time over the course of the past week and yields a continuous value expressed as metabolic equivalent minutes per week (MET-min/week) for each activity.

Data analysis

Statistical analyses were undertaken using SPSS version 24.0 and SAS version 9.4. Available data from 737 probands, unaffected siblings, and controls were used. Raw differences between groups were tested via ANOVA or χ^2 tables as appropriate. To account for family dependencies and covariates, group differences were examined using a mixed-model ANCOVA for each standardized component and the composite score. In addition to indicator variables (no/yes = 0/1) for probands and siblings (to yield group comparisons vs. controls in one-sided tests), each model had a random family intercept and covariates for study site, age, sex, and fasting compliance (<8, 8–11, 12 h, or longer). Because there were significant differences in two mean MetS

components based on study site (glucose, SBP), we controlled for the effect of site in our models.

Next, we examined whether years of schooling, physical activity, and smoking status may confound the effect of group on our outcomes. We therefore ran three additional models for each outcome measure, separately adjusting for these three variables. Control, proband, and unaffected sibling least squares means (LSM) were compared in one-sided tests adjusted for three-group comparison (Tukey). Model assumptions were examined, and no major violations were detected.

Results

Characteristics of the samples

Table 1 presents selected characteristics of the initial samples. As can be seen, controls were, on average, younger than were siblings and probands. There were more males in the control group relative to the sibling group. Controls and siblings were better educated than were probands. Controls, relative to siblings and probands, were less likely to report that they were regular smokers. Furthermore, siblings relative to probands were less likely to report being regular smokers. However, there were no group differences in excessive consumption of alcohol, use of cardioactive medications, or physical activity.

There were 285 probands with full MetS information (see Table 2). For these subjects with pediatric-onset depression, mean age at onset of first episode of MDD was 10.6 years (S.D. = 2.4 years). The modal age at onset of first depression was 8.6 years. At the time of the laboratory evaluation, altogether 21 probands were in a depressive episode.[†][1]

Table 2 presents the MetS values (z-scores) for cases with complete data on all five MetS components (total $N = 718$). We deleted from the analyses altogether 19 subjects: two had missing values on all MetS components, 15 had missing blood serum data, one had erroneous glucose data, and one had technical problems during BP assessment. We thus excluded <3% of the overall samples, including three controls, eight siblings, and eight probands (excluded cases did not significantly differ across groups, $\chi^2 = 0.69$, $p = 0.71$). As can be seen in Table 2, the final sample included 285 probands with COD, 265 never-depressed siblings of COD probands, and 168 controls.

Looking at the unadjusted values in Table 2, we find that the MetS composite scores of both probands and siblings were higher than were the scores of controls ($d = 0.35$). Considering the MetS components without statistical adjustment for covariates, proband and sibling mean waist circumference values were larger and their mean HDLs were lower than for controls ($d > 0.32$). Probands' mean triglycerides levels were elevated relative to the values for controls and siblings ($d = 0.29$). There were no group differences in BP and glucose.

MetS and depression risk

Table 3 displays the y-standardized group differences, adjusted for covariates, on MetS composite scores and their components. The

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[†]The notes appear after the main text.

[1]Looking at the unadjusted values of the composite MetS score and its components for remitted probands ($n = 264$) versus currently depressed probands ($n = 21$), we found there were no significant differences between groups ($p > 0.20$). We also re-examined group differences using mixed-model ANCOVAs for each standardized component and the composite score excluding currently depressed subjects from the proband group. Patterns of significance were unchanged.

Table 1. Selected characteristics of the samples

	Controls ($n = 171$)	Siblings ($n = 273$)	Probands ($n = 293$)	Statistics
Age, M (s.d.), years	21.66 (1.54)[a]	25.05 (4.99)[b]	25.52 (2.57)[b]	$F = 70.56$***
Sex (male), n (%)	105 (61)[a]	125 (46)[b]	158 (54)	$\chi^2 = 10.60$**
Education, M (s.d.), years	13.84 (1.66)[a]	12.94 (2.26)[a]	12.51 (2.62)[b]	$F = 17.99$***
Currently smoking, n (%)	42 (25)[a]	109 (40)[b]	160 (55)[c]	$\chi^2 = 41.76$***
Current cardioactive medication, n (%)	3 (2)	9 (3)	14 (5)	$\chi^2 = 3.01$
Excessive alcohol consumption (%)	1 (1)	3 (1)	7 (2)	$\chi^2 = 2.88$
Physical activity (MET), M (s.d.)	4383.61 (3426.48)	4725.36 (4047.19)	5134.06 (4572.65)	$F = 1.85$

Note: Current cardioactive medication = current intake of cardioactive (e.g. diabetes, BP) medication. Excessive alcohol consumption = daily consumption of raw spirits, alcohol and/or wine is above 1 dL.
[a,b,c]Different superscripts denote groups that are significantly different at $p < 0.05$.
*$p < 0.05$, **$p < 0.01$, ***$p \leqslant 0.001$.

Table 2. Raw and *z*-score means for the MetS score and its components (M; s.d.) for subjects with complete data

	Controls	Siblings	Probands	
Variable	$n = 168$	$n = 265$	$n = 285$	Statistics (unadjusted)
SBP (mmHg)	111.65 (12.00)	112.91 (11.60)	113.89 (12.76)	$F = 1.98$
Z	−0.01 (1.04)	0.10 (1.01)	0.18 (1.11)	
Waist circumference (cm)	79.73 (10.65)	84.03 (13.83)	84.12 (13.83)	$F = 13.45$***
Z	−0.26 (0.76)[a]	0.23 (1.07)[b]	0.17 (1.08)[b]	
Glucose (Mmol)	4.99 (0.39)	4.99 (0.41)	5.00 (0.49)	$F = 0.23$
Z	0.09 (0.92)	0.08 (0.97)	0.10 (1.15)	
HDL (Mmol)	1.39 (0.33)	1.32 (0.30)	1.31 (0.35)	$F = 9.22$***
Z	−0.23 (1.00)[a]	0.16 (0.90)[b]	0.13 (1.09)[b]	
Triglycerides (Mmol)	0.93 (0.43)	1.00 (0.57)	1.13 (0.65)	$F = 7.26$***
Z	−0.15 (0.89)[a]	−0.06 (1.03)[a]	0.19 (1.04)[b]	
Composite *z*-score	−0.18 (0.86)[a]	0.19 (1.03)[b]	0.28 (1.14)[b]	$F = 11.00$***

Note: Triglycerides raw values were log-transformed before analyses or *z*-score transformation. HDL was reversed before *z*-score transformation (see text for formulas).
[a,b]Different superscripts denote groups that are significantly different at $p < 0.05$.
*$p < 0.05$, **$p < 0.01$, ***$p \leqslant 0.001$.

findings support the hypothesis that subjects with early-onset depression phenotype (probands) and never depressed siblings at high risk for depression are more likely to manifest MetS and several of its components than are healthy control peers.

Specifically, the composite MetS score is elevated in probands and high-risk siblings relative to the score of controls (*LSM differences* from 0.25 to 0.36, $p < 0.02$). Regardless of covariates, probands' triglyceride levels are elevated compared to controls' by about ¼ s.d. (*LSM differences* from 0.23 to 0.30, all $p < 0.02$). Probands and siblings, relative to controls, have larger waist circumferences (*LSM differences* from 0.28 to 0.35, all $p < 0.03$), apart from the model adjusting for years of schooling (*LSM differences* = 0.21, $p = 0.07$). Similarly, probands and siblings, relative to controls, have worse – i.e. lower raw, higher *z*-score – HDL (*LSM differences* from 0.27 to 0.39, all $p < 0.01$). However, regardless of which sets of covariates are used, probands and siblings do not differ from controls in SBP and glucose levels (*LSM differences* from −0.10 to 0.16, all $p > 0.09$).

The findings do not support our second hypothesis that subjects with early-onset depression phenotype (probands) are more likely to manifest MetS and several of its components than are their never depressed siblings. Regardless of which sets of covariates are used, subjects with early-onset depression and their siblings do not differ in MetS composite score and most MetS components (*LSM differences* from −0.08 to 0.04, all $p > 0.4$). However, probands' triglyceride levels are significantly higher than are the levels obtained for siblings (*LSM differences* from 0.23 to 0.26, all $p < 0.01$).

Discussion

The main purpose of the current study was to contribute to our understanding of the relations of MetS and depression by examining whether the early-onset depression phenotype is associated with MetS. The answer is an 'unequivocal yes': our probands with early-onset depression had significantly higher MetS scores than did normal controls even after we controlled for several potential confounds or covariates. In further support of our first hypothesis, we found that high-risk siblings also had significantly higher MetS composite scores than did controls. We also found strong

Table 3. Adjusted group differences (±s.ε.) on MetS components and the composite score

Covariates group	Dependent variable (Least squares mean difference in *z*-score[a])					
	SBP	Waist circumference	Glucose	HDL	Triglycerides	Composite
A: sex, site, age, and fasting compliance						
Probands *v.* controls	0.14 ± 0.09	0.29 ± 0.11**	−0.03 ± 0.11	0.38 ± 0.11***	0.28 ± 0.11*	0.35 ± 0.11**
Siblings *v.* controls	0.15 ± 0.09	0.35 ± 0.11**	0.00 ± 0.11	0.38 ± 0.11***	0.04 ± 0.11	0.32 ± 0.11**
Probands *v.* siblings	−0.02 ± .07	−0.05 ± .07	−0.03 ± .07	0.00 ± .07	0.25 ± .08**	0.03 ± 0.07
B: A and years of schooling						
Probands *v.* controls	0.11 ± 0.10	0.21 ± 0.11	−0.10 ± 0.11	0.27 ± 0.11*	0.28 ± 0.11**	0.25 ± 0.11*
Siblings *v.* controls	0.13 ± 0.09	0.28 ± 0.11*	−0.05 ± 0.11	0.30 ± 0.11**	0.03 ± 0.11	0.25 ± 0.11*
Probands *v.* siblings	−0.02 ± 0.07	−0.08 ± .07	−0.05 ± 0.08	−0.03 ± 0.07	0.24 ± 0.08**	0.01 ± 0.08
C: A and physical activity						
Probands *v.* controls	0.12 ± 0.09	0.28 ± 0.11*	−0.03 ± 0.11	0.39 ± 0.11***	0.30 ± 0.11**	0.36 ± 0.11**
Siblings *v.* controls	0.13 ± 0.09	0.34 ± 0.11**	−0.01 ± 0.11	0.39 ± 0.11***	0.04 ± 0.11	0.32 ± 0.11**
Probands *v.* siblings	−0.01 ± 0.07	−0.05 ± 0.07	−0.03 ± 0.08	−0.01 ± 0.07	0.26 ± 0.08**	0.04 ± 0.07
D: A and smoking status						
Probands *v.* controls	0.15 ± 0.09	0.32 ± 0.11**	0.02 ± 0.11	0.31 ± 0.11**	0.24 ± 0.11*	0.35 ± 0.11**
Siblings *v.* controls	0.16 ± 0.09	0.36 ± 0.11**	0.02 ± 0.11	0.34 ± 0.11**	0.02 ± 0.11	0.32 ± 0.11**
Probands *v.* siblings	−0.01 ± 0.07	−0.04 ± 0.07	−0.01 ± 0.07	−0.03 ± .07	0.23 ± 0.08**	0.03 ± 0.08

*$p < 0.05$, **$p < 0.01$, ***$p \leqslant 0.001$ one-sided test.
[a]In mixed effect models (A, B, C, and D) of each dependent variable adjusted for covariates and random family intercept.

differences between groups in some MetS components. Specifically, regardless of covariates used in the models (apart from years of schooling), probands and siblings had larger waist circumference than did controls. Also, regardless of all covariates used in the models, probands and siblings had lower HDL levels than did controls, and probands had elevated triglyceride levels relative to the levels manifested by controls. However, there were no significant group differences in any models of BP and glucose level. Regarding our second hypothesis, probands and their siblings did not significantly differ in MetS composite scores and most MetS components. However, regardless of the covariates used in the models, probands had elevated triglyceride levels relative to their siblings' levels.

Past studies have reported that the *atypical subtype* of depression is associated with and predicts MetS, whereas the usual typical type of depression does not (Brailean et al., 2020; Lasserre et al., 2017; Takeuchi et al., 2013). Our work extends this literature by having documented that the *early-onset depression phenotype* also plays a role in the depression and MetS comorbidity. Importantly, these depression subtypes are sufficiently prevalent to affect a study's results. According to Lasserre et al.'s (2017) study, 6.4% of the cases positive for depression met the criteria for atypical depression; in a very large community sample in the UK, 6.2% of those with lifetime MDD had the atypical phenotype (Brailean et al., 2020). In a clinical sample with major depression (Zisook et al., 2007), 12% of the participants dated the onset of their first depression to childhood (earlier than 12 years of age), while an additional 25% estimated that their first depression occurred during adolescence (between 12 and 17 years of age). Therefore, in so far as the depression–MetS relationship reflects the effects of atypical and early-onset depression phenotypes, studies that fail to include the expected phenotype portions are unlikely to generate positive results. Thus, because most studies have not subtyped participants' depressions, unknown and variable proportions of atypical and early-onset depression phenotypes across samples probably account for some of the equivocal findings in the literature.

How can we explain the links between depression phenotypes and MetS? While several propositions have been put forth in regard to atypical depression and MetS that focus on the effects of increased appetite (hyperphagia) on glucose metabolism and waist circumference (e.g. Lasserre et al., 2017), those arguments do not apply to the early-onset phenotype. We propose an alternative explanation in regard to both phenotypes, namely, that the early-onset and the atypical depression forms both signify particularly malignant versions of depression and are surrogates for some underlying dimension of illness severity. Indeed, there is evidence that the juvenile-onset phenotype has a more severe course than does depression that onsets later in life (Zisook et al., 2007). Additionally, a large population-based study has documented that atypical depression is associated with earlier onset, longer and more recurrent episodes (worse course), and multiple additional adversities (Brailean et al., 2020). Thus, future studies should examine the features of atypical and early-onset depression, which may point toward processes that influence illness severity.

Although abdominal obesity is often regarded as a key component of MetS (Carr et al., 2004) and previous reports have suggested that waist circumference might be the most important MetS component in relation to depression (Dunbar et al., 2008; Skilton, Moulin, Terra, & Bonnet, 2007; Takeuchi, Nakao, Nomura, & Yano, 2009), atypical depression has been also linked to increased glucose level (Lasserre et al., 2017). However, we

found that, for the early-onset depression phenotype, all MetS components, except SBP and glucose, are in the direction of maladaptive values. Therefore, atypical and early-onset depression may present different MetS components profiles, a possibility, which should be examined in future studies.

Our finding that probands with early-onset depression, compared to controls, exhibit higher rates of MetS as a full syndrome, and on several MetS components, is in line with much of the literature (for reviews, see Ghanei Gheshlagh et al., 2016; Repousi et al., 2018; Vancampfort et al., 2014). Equally important is our finding that siblings of probands, who did not experience depression in their lifetime, also differed from healthy controls in MetS full syndrome and some of its components. This finding provides initial support for MetS as predating and a plausible risk factor for eventual depression and is in line with previous work showing that young offspring at high familial risk for depression exhibit compromised physiological functioning (for a review, see Kovacs & Lopez-Duran, 2010). The elevated rates of MetS among our high-risk siblings could mirror adverse life events, which are prevalent in high-risk families (Daches, Vine, George, & Kovacs, 2019) and have been shown to predict several components of MetS (McIntyre et al., 2012). Relatedly, a history of childhood adversity has been reported to increase the risk of obesity (one component of MetS) in adults by 20–40% (Thomas, Hyppönen, & Power, 2008).

How can we explain the finding that probands and siblings had comparable rates of MetS and most MetS components (differing only on triglyceride levels)? As Avenevoli and Merikangas (2006) explicitly stated, a high-risk family study design (such as ours) cannot distinguish between genetic and environmental risks as etiologic factors. However, the broader literature suggests that shared adverse environment (contextual factors) may be at play. Such an explanation is implied by a twin study, which found that the co-occurrence of depressive symptoms and MetS was not explained by genetic vulnerability (McCaffery, Niaura, Todaro, Swan, & Carmelli, 2003). It is also consistent with the results of other twin studies, which revealed that the association between physiological variables and mood disorders is due to a shared environment (e.g. Padmos et al., 2009).

The finding that triglyceride level was the only component of MetS that differentiated probands with depression histories from unaffected siblings is consistent with reports that triglyceride levels are positively associated with depression (Enko et al., 2018; Huang & Chen, 2004; Liu et al., 2016; Sevincok, Buyukozturk, & Dereboy, 2001; Shao et al., 2017). Given the role of triglycerides in cognitive functioning (De Frias et al., 2007; Morley & Banks, 2010), higher triglyceride levels in depression-prone individuals may mirror residual cognitive impairment (Shao et al., 2017). Thus, triglyceride levels may have the potential to serve as a biomarker of depression.

Our study has several limitations. First, due to the study's cross-sectional nature, the findings cannot inform about the temporal association between early-onset depression and MetS. Second, we did not consider the effects of psychiatric comorbidity on MetS or its components. Third, our study was conducted in Hungary and thus the overall sample was predominantly Caucasian. Because the prevalence of MetS varies by race and ethnicity (Ervin, 2009), it would be important to replicate our findings with a non-predominantly Caucasian sample. Fourth, we only studied the early-onset phenotype of depression and thus cannot generalize our findings to all depression phenotypes.

Yet, several strengths of our study make the results compelling. We focused on the pediatric-onset phenotype of depression, thus

controlling for age at onset, which is a key contributor to the heterogeneity of clinical depression. Furthermore, the use of a high-risk, but not yet affected sample allowed us to look at the temporal precedence of MetS in depression risk. Finally, the association between depression and MetS in our sample held up against rigorous statistical controls for confounding risk factors such as education, physical activity, and smoking. Therefore, we are confident that the age of onset of depression plays an important role in the occurrence of MetS, an association that may be influenced by environmental factors.

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