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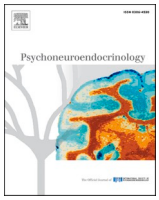

Short communication

Childhood maltreatment and metabolic syndrome in bipolar disorders: In search of moderators

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A R T I C L E I N F O

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A B S T R A C T

As compared to the general population, adult individuals with bipolar disorders (BD) have higher mortality rates due to cardiovascular diseases and higher prevalence of Metabolic Syndrome (MetS). Recent evidence suggests that childhood maltreatment may contribute to the cardiovascular burden in individuals with BD. However, studies are scarce, with limited sample sizes and inconsistent results. We explored the associations between a self-reported history of childhood maltreatment and MetS (and its subcomponents) in a large sample of 2390 individuals with BD. Childhood maltreatment was assessed using the Childhood Trauma Questionnaire and MetS was defined according to the revised criteria of the ATEP III. We suggested associations between childhood maltreatment and the presence of MetS in men and in younger individuals. The association between childhood maltreatment and the presence of MetS in the early onset subgroup was not significant after adjustment for site of recruitment and level of education. Hence, some links between childhood maltreatment and MetS might exist only in specific subgroups of individuals with BD, but confirmation is required in independent and large samples, while taking into account potential confounders. This would help defining how psychosocial interventions that target childhood maltreatment and its consequences may be beneficial for physical health.

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1. Introduction

As compared to the general population, individuals with bipolar disorders (BD) are at higher risk of premature death, this being not exclusively related to suicide. Life expectancy has been estimated to be 10–15 years shorter for individuals with BD (Roshanaei-Moghaddam and Katon, 2009). As compared to the general population, mortality rates due to physical causes (mainly cardiovascular diseases (CVD)) are between 1.5 and 3 times higher in adults with BD, as compared to the general population (Management of Physical Health Conditions in Adults with Severe Mental Disorders, 2018).

Metabolic syndrome (MetS) is recognized as a leading cause of CVD-related mortality in the general population. MetS is highly prevalent in BD, with an estimated global rate of 32.6%, that is two times higher than the rate observed in the general population (Vancampfort et al., 2015). Most common interpretations of this cardiovascular burden in BD are: unhealthy lifestyle (sedentary behavior, harmful use of tobacco, alcohol and illicit drugs), exposure to psychotropic drugs that can induce MetS and a possible genetic overlap between BD and several somatic conditions, including inflammatory conditions (Leboyer et al., 2012). Recent evidence also suggests that childhood maltreatment is a plausible explanation of this greater cardiovascular burden in individuals with BD (Hughes et al., 2017; Quidé et al., 2020). However, the results in the literature are scarce with a few studies, all performed in limited sample sizes and with inconsistent results (Aas et al., 2017; Hosang et al., 2018; Leclerc et al., 2018; McIntyre et al., 2012).

The aim of this study was therefore to test for the associations between MetS and a self-reported history of childhood maltreatment in a large sample of 2390 individuals with BD.

2. Material and methods

2.1. Study population

Individuals were recruited in 12 Centers of Expertize for BD that used the same systematic and standardized clinical assessments. All individuals were stabilized outpatients who were aged 16 years or older, diagnosed with BD (subtypes I, II, and not otherwise specified) according to DSM-IV criteria (American Psychiatric Association, 1994). This cohort have been described in details in previous articles (Henry et al., 2015). Clinical stabilization was defined as the absence of hospitalization and treatment modifications in the 4 weeks before inclusion (but not by the absence of any mood symptoms).

The assessment protocol was approved by the institutional review board (Comité de Protection des Personnes Ile de France IX; January 18, 2010), in accordance with the French laws for non-interventional studies and requires only an information letter for participation.

2.2. Clinical assessment

At inclusion, a specialized team (psychiatrist and psychologist) interviewed the individuals using the SCID (First, 1996) and systematically recorded information about education, marital status, onset and course of BD and psychiatric and somatic comorbidities. Current depressive and hypomanic symptoms were assessed respectively with the Montgomery Asberg Depression Rating Scale and the Young Mania Rating Scale. Childhood maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The CTQ is a 28-item self-report questionnaire that yields a total score.

2.3. MetS definition

MetS was defined according to the revised criteria of the ATEP III (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002), which requires the presence of 3 or more of the following 5 criteria: high waist circumference (>94 cm for men and >80 cm for women), hypertriglyceridemia (≥1.7 mmol/L or on lipid-lowering medication), low HDL cholesterol level (<1.03 mmol/L in men and <1.29 mmol/L in women), high blood pressure (≥130/85 mmHg or on antihypertensive medication), and high fasting glucose concentration (≥5.6 mmol/L or on glucose-lowering medication).

High sensitivity CRP (hs-CRP) was measured in blood samples and an abnormal level was defined as >3 mg/L (Emerging Risk Factors Collaboration et al., 2010).

2.4. Derived metabolic indices

Abdominal obesity was defined by the presence of both hypertriglyceridemia (≥1.7 mmol/L or current treatment by a triglyceride lowering medication) and high waist circumference (>94 cm for male and >80 cm for females) (Després and Lemieux, 2006). Atherogenic index of plasma (AIP) which is considered as a very sensitive predictor of future cardiovascular events was defined as log(triglycerides/HDL cholesterol) (Zhu et al., 2015). Disposition Index (DI) quantifies the nature of the interactions between insulin sensitivity and pancreatic secretion. It is predictive of the development of type 2 diabetes. DI is estimated by the equation log (DI) = 2.449–0.113 × fasting plasma glucose +0.046 × BMI − 0.612 × HDL cholesterol (Lin et al., 2014).

2.5. Statistical analysis

Categorical variables are expressed as numbers and percentages,and continuous variables as mean ± Standard Deviation (SD) values. Associations between childhood maltreatment and MetS or its subcomponents were performed using Mann–Witney *U* tests and analyses of variance. Effect sizes were estimated with Cohen's d. Unadjusted analyses and multivariable analyses adjusted for site of recruitment and level of education were performed. We then used several variables (age, sex, age at onset, type of BD, illness duration, rapid cycling, current use of atypical antipsychotics) as moderators in the analyses, meaning that the associations between CTQ score and MetS were examined separately in each category of a given moderator (for example in females and then in males, when sex was the moderator). Unadjusted analyses and analyses adjusted for site of recruitment and level of education were performed.

Finally, we provided two logistic regression models to test for potential interactions between CTQ total score and moderators (identified in the previous analyses) and using MetS as the dependent variable. These models included the following independent variables: CTQ score, identified moderators and interactions between CTQ score and identified moderators, adjusted for site of recruitment and level of education (model 1), then further adjusted for other clinical variables in a second model (model 2). Statistical analyses were performed with SAS (release 9.4; SAS Statistical Institute, Cary, NC). All statistical tests were two-tailed.

3. Results

This study included a sample of 2390 individuals with BD. Overall, 49.5% of the individuals were diagnosed with BD type I, 40.7% with BD type II, and 9.9% with BD-NOS. The mean age at inclusion was 41.1 (±12.6), 60.5% were women, the mean age at onset was 24.0 (±9.6) years.

The prevalence of MetS was 22.1%. The presence of MetS was associated with male ($p < 0.0001$), older age ($p < 0.0001$), lower education level ($p = 0.0002$), site of recruitment ($p < 0.0001$), longer duration of the illness ($p < 0.0001$), older age at BD onset ($p < 0.0001$) and current use of atypical antipsychotics ($p = 0.0069$) (see Supplementary Table S1), but not with BD subtypes or rapid cycling.

Table 1 shows the univariable associations between childhood

Table 1
Association between metabolic syndrome (and its components) and childhood maltreatment.

	n	Childhood maltreatment mean CTQ score (sd)	ES	Chi-square/F value	DF	P value[a]	P value[b]
Metabolic syndrome							
No	1862	42.6 (14.3)	0.04	0.28	1	0.59	0.29
Yes	528	43.2 (15.2)					
High blood pressure							
No	1620	43.1 (14.6)	0.06	1.76	1	0.18	0.33
Yes	914	42.2 (14.1)					
Low HDL cholesterol or treatment							
No	1556	42.6 (14.4)	0.03	0.55	1	0.45	0.57
Yes	669	43.1 (15.0)					
Hypertriglyceridemia							
No	1864	42.6 (14.4)	0.04	1.29	1	0.25	0.03
Yes	527	43.2 (14.5)					
High Fasting glucose							
No	1932	42.8 (14.6)	0.04	0.12	1	0.72	0.17
Yes	351	42.2 (13.7)					
High waist circumference							
No	896	42.1 (14.4)	0.08	5.74	1	0.02	0.99
Yes	1613	43.3 (14.6)					
Abdominal obesity							
No	706	42.1 (14.6)	0.10	3.41	1	0.06	0.06
Yes	404	43.6 (15.0)					
Body mass index							
<25	1342	42.7 (14.7)	0.03	2.95	2	0.05	0.13
25–30	841	42.2 (13.7)	0.10				
>30	482	44.2 (15.2)					
AIP (>75th)							
No	1777	42.7 (14.5)	0.007	0.19	1	0.66	0.05
Yes	593	42.8 (14.5)					
DI (>75th)							
No	1680	42.9 (14.6)	0.03	0.08	1	0.78	0.54
Yes	559	42.5 (14.2)					
Abnormal CRP							
No	1342	42.1 (14.5)	0.09	3.36	1	0.07	0.61
Yes	513	43.4 (14.7)					

CTQ: Childhood Trauma Questionnaire; MetS: Metabolic Syndrome, Abdominal obesity: defined as having high waist circumference and hypertriglyceridemia; AIP: Atherogenic index of plasma; DI: Disposition Index, HDL High Density Lipoprotein; Abnormal CRP level: defined as >3 mg/L; ES: Effect Size; DF: Degree of freedom.
[a] Mann-Whitney *U* test for the associations between childhood trauma (total score) and dichotomous variables.
[b] Multivariable analysis of covariance adjusted for age, sex, number of education level and site of recruitment.

maltreatment and MetS components. There was no major association between childhood maltreatment (CTQ total score) and MetS, nor with its subcomponents (hypertension, HDL cholesterol, triglycerides, high fasting glucose). An association was observed between a higher waist circumference and a higher CTQ total score ($p = 0.02$), however the effect size was small and the association was no longer significant after adjustment for site of recruitment and level of education. After adjustment for site of recruitment and level of education, some associations

Table 2
Univariable and multivariable associations between metabolic syndrome and childhood maltreatment according to moderators.

	Metabolic syndrome							
	No		Yes					
	n	CTQ Mean (sd)	n	CTQ mean (sd)	Chi-square	P value*	F value	P value**
Male	672	39.5 (11.6)	273	41.6 (13.1)	5.17	**0.02**	**6.48**	**0.011**[a]
Female	1189	44.3 (15.3)	255	44.9 (17.0)	0.01	0.91		
Age <40	1021	40.9 (13.6)	155	44.1 (16.2)	4.30	**0.03**	**6.01**	**0.014**[b]
Age >40	841	44.6 (14.8)	373	42.8 (14.7)	5.29	**0.02**	0.30	0.584[b]
BD type I	848	41.2 (14.0)	262	42.6 (14.5)	2.57	0.10		
BD type II	803	44.1 (14.8)	210	44.4 (16.6)	0.16	0.68		
Illness duration <15 y	951	39.9 (12.0)	185	40.0 (11.5)	0.65	0.42		
Illness duration >15 y	834	45.3 (15.8)	322	44.7 (16.2)	0.87	0.34		
Early onset (<21 y)	903	43.0 (14.9)	195	45.8 (16.5)	4.32	**0.03**	**2.46**	**0.116**[c]
Late onset	885	41.9 (13.6)	312	41.3 (13.4)	0.23	0.62		
Rapid cycling Yes	1366	41.7 (13.6)	369	42.1 (13.7)	0.42	0.51		
Rapid cycling No	264	45.0 (16.6)	84	47.5 (21.0)	0.08	0.78		
Antipsychotic medication Yes	320	41.3 (13.8)	124	41.8 (14.3)	0.09	0.75		
Antipsychotic medication No	1283	42.7 (14.5)	298	43.6 (15.5)	0.65	0.42		

*Mann-Whitney *U* test for each moderator
*** Multivariable analysis of covariance for each moderator
CTQ: Childhood Trauma Questionnaire, BD: Bipolar Disorder, y: years
[a] adjustment for age, education level and site of recruitment
[b] adjustment for sex, education level and site of recruitment
[c] adjustment for age, sex, education level and site of recruitment

were identified between a higher CTQ score, hypertriglyceridemia ($p = 0.03$) and a higher AIP ($p = 0.05$). The associations between the CTQ total score and other indices related to a higher cardio-vascular risk (abdominal obesity, body mass index, abnormal CRP, and DI) were not significant.

We then investigated the associations between CTQ total score and MetS while stratifying analyses on the following moderators: sex, age at inclusion below/above 40 years old, BD subtype, illness duration below/above 15 years, early/late age at onset of BD, presence/absence of rapid cycling, current use of atypical antipsychotics) (see Table 2). After adjustment for potential confounders (education level, site of recruitment, and age and/or sex when appropriate), we observed associations between childhood maltreatment and MetS in men and in individuals aged less than 40 years old. The associations between childhood maltreatment and MetS were not moderated by the other variables (age at onset, current treatment with atypical antipsychotics, rapid cycling, bipolar disorders subtype, and illness duration).

Finally, we performed two logistic regression models with MetS as the dependent variable and the following independent variables: CTQ total score, age, sex and age at onset and the interactions between these three variables and CTQ total score, with an adjustment for site of recruitment and level of education (model 1), and with further adjustment BD subtype, rapid cycling, and current use of antipsychotics (model 2). Model 1 identified an interaction between CTQ total score and sex on the risk of MetS ($p = 0.04$), that was no longer significant when controlled for confounders in model 2 ($p = 0.34$). Both models identified also associations between the risk of MetS and an older age ($p < 0.01$), while model 2 further identified current atypical antipsychotics use as being associated with MetS ($p = 0.02$) (results not shown in details, available upon request from the authors).

4. Discussion

In a large sample of 2390 individuals with BD, we suggested associations between childhood maltreatment and MetS in men, in younger individuals and in individuals with an early onset of the disease. However, most moderation analyses were no longer significant after adjustment for potential confounders.

Association between body mass index or MetS and childhood adversities has previously been explored in the general population, although showing inconsistent results and small effect sizes (Suglia et al., 2018). In individuals with severe mental disorders, and particularly with BD, data are scarce and obtained in small sample sizes. A cross-sectional study (373 adults with major depressive disorder or BD) reported no significant association between childhood maltreatment and obesity after taking into account several potential confounders (McIntyre et al., 2012). A recent study including 271 patients with severe psychiatric disorders (including 123 individuals with BD) showed that childhood abuse was associated with an higher BMI (Aas et al., 2017). Contrary to these results, Leclerc et al., in a sample of 61 individuals with BD, have reported an association between childhood sexual abuse and higher BMI, only in the subgroups of individuals with a late onset of BD (Leclerc et al., 2018). Given these inconsistent results, the links between childhood maltreatment and MetS in BD remain to be clarified.

Several mechanisms have been proposed to explain the association between childhood maltreatment and MetS in individuals with BD. First, many studies have demonstrated that childhood maltreatment may lead to a more severe form of BD that would require more psychotropics use and consequently more exposure to potential side effects leading to MetS. Second, associations between childhood maltreatment and tobacco, alcohol and drugs misuses, which are key risk factors for poor health outcomes, have been largely documented (Agnew-Blais and Danese, 2016). Third, childhood maltreatment has been suggested to modify gene expression and potential underlying epigenetic mechanisms, and is also associated with low grade inflammation (pro-inflammatory cytokines), known to be associated with MetS.

Our study has several strengths, including a large sample of individuals with BD, and a reliable diagnosis. However, because this work is cross-sectional, we cannot establish any causal links, and longitudinal studies are required for this purpose. In addition, even though childhood maltreatment was assessed using an accurate and validated instrument, it is a retrospective questionnaire, and its reliability may be hampered by recall bias.

Combining conflicting results in the literature and results from this study, we cannot support the hypothesis of a strong association between childhood maltreatment and MetS in BD. We suggest that this association may exist only in subgroups of individuals, i.e. in males, in younger individuals or in individuals with an early onset of the disease. However, site of recruitment, level of education and current use of atypical antipsychotics vanished the associations, thus raising some methodological concerns for future studies that should pay attention to these potential confounders. Given their high prevalence in individuals with BD, both MetS and childhood maltreatment should be systematically assessed. More research is needed to clarify the links between childhood maltreatment and cardio-vascular risk in individuals with BD and therefore to further define how psychosocial interventions that target childhood maltreatment and its consequences may be beneficial for physical health.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105327.

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