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Childhood trauma and glucose metabolism in patients with first-episode psychosis

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ABSTRACT

Although the associations between first-episode psychosis (FEP) and metabolic abnormalities on one side, and childhood trauma (CT) and risk of developing psychosis on the other are both well established, evidence on the relationship between CT and metabolic dysregulation in terms of abnormal glucose metabolism is very limited. We tested whether, already at illness onset, FEP patients with a history of CT show dysregulation of a broad range of glucose metabolism markers.

In particular, in 148 FEP patients we evaluated serum concentrations of c-peptide, insulin, plasminogen-activator-inhibitor–1 (PAI-1), resistin, visfatin, glucagon, glucagon-like peptide-1 (GLP-1), gastric-inhibitor-peptide (GIP), leptin, and ghrelin. We also assessed CT with the Childhood Experience of Care and Abuse Questionnaire, and stressful life events (SLEs) with a semi-structured interview. Psychopathology, cannabis and tobacco habits, Body Mass Index (BMI) were recorded. Serum concentrations of markers were analyzed from peripheral blood.

Ninety-five patients (56 % males, mean age 29.5) reported CT. Multivariate models showed that CT is associated only with the concentrations of c-peptide and insulin after adjusting for age, sex, BMI and SLEs. FEP patients who had experienced CT showed higher c-peptide and insulin serum concentrations.

Our study reports that CT might be associated with the metabolic abnormalities in the first stage of psychosis, suggesting that a thorough anamnestic evaluation at psychosis onset that would include the history of CT could be helpful for clinicians in order to implement early programmes of healthy lifestyle education and to guide choice of therapeutic interventions for trauma.

1. Introduction

Individuals with severe mental disorders, including schizophrenia and bipolar disorder, have raised mortality rates, 2–3 times higher than the general population (Reininghaus et al., 2015) turning into a mortality gap of 10–20 years (Lawrence et al., 2013). Epidemiological

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evidence suggests that physical illnesses, including cardiovascular disease and type 2 diabetes, account for most of this increased mortality (Olfson et al., 2015). In particular, individuals with schizophrenia (Mitchell et al., 2013) or bipolar disorder (Vancampfort et al., 2015b) are at higher risk of developing metabolic syndrome than the general population, with a risk of developing type 2 diabetes that is twice as high in individuals with schizophrenia compared to the general population (Stubbs et al., 2015). This association has been interpreted as a result of treatment with antipsychotic medications (Bartoli et al., 2015; Vancampfort et al., 2015a) or the consequence of an unhealthy life style or incorrect dietary regimens associated with the negative symptoms of psychosis (Carra et al., 2014; Samele et al., 2007).

Research in first episode psychosis (FEP) allows the investigation of metabolic alterations that predate long term treatment with antipsychotics. Interestingly, accumulating evidence shows the presence of metabolic dysregulation in terms of abnormal glucose metabolism even in drug-naïve patients with schizophrenia (Fernandez-Egea et al., 2008; Spelman et al., 2007). Specifically, higher levels of insulin (Chen et al., 2013; Pillinger et al., 2017), insulin-resistance (Arranz et al., 2004; Chen et al., 2013; Pillinger et al., 2017; Ryan et al., 2003; Verma et al., 2009; Zhang et al., 2015) and increased levels of insulin-related peptides (Guest et al., 2011, 2010) as c-peptide (Wu et al., 2013) have been found in drug-naïve patients with first episode of schizophrenia relative to controls. We recently reported decreased levels of glucagon and glucagon-like peptide-1 (GLP-1) in FEP patients compared to controls (Bocchio-Chiavetto et al., 2018). Interestingly, a reduction of glucagon and GLP-1 has been reported during the depressive phase of a bipolar disorder, not associated with medications or with the presence of diabetes or metabolic syndrome (Rosso et al., 2015). Since visceral obesity is a key feature of the metabolic syndrome that might both result from, and contribute to insulin resistance (Roberts et al., 2013), several studies have investigated the role of appetite regulating hormones in FEP (Misiak et al., 2019), and found lower levels of leptin in drug-naïve FEP patients compared to controls.

Taken together, this evidence suggests that other factors, apart from antipsychotic medications, can play a role in the metabolic alterations observed at psychosis onset.

Among these, early adversities are important as they have been documented to increase the risk for the onset of both psychosis and metabolic dysfunctions. Specifically, childhood trauma (CT), including physical and sexual abuse, separation from at least one of the parental figures longer than 6 months, and death of a parent, has been the most studied environmental risk factor common to both conditions (Danese and Tan, 2014; Varese et al., 2012). CT acts as a chronic and severe stress that could induce the production of elevated levels of glucose and insulin in blood (Deppermann et al., 2014). In addition, CT appears to induce an over-activation of the Hypothalamus Pituitary Adrenal (HPA) axis (Aas et al., 2011), which interacts with glucose metabolism hormones, like insulin, glucagon, GIP and GLP-1 (Chong et al., 2015; Nussdorfer et al., 2000) increasing the likelihood to develop metabolic dysfunctions. Insulin has an inhibitory activity on HPA axis, while glucagon, GIP and GLP-1 have an enhancing one, inducing the release of corticotrophin release hormone (CRH)/adrenocorticotrophic hormone (ACTH) (Nussdorfer et al., 2000). It is therefore conceivable that CT could lead to the development of the dysfunction in glucose metabolism through the activation of HPA axis (Harris et al., 2013).

Even if association between FEP and metabolic abnormalities (Perry et al., 2016) and between CT and the risk to develop psychosis (Varese et al., 2012) are both well demonstrated, evidence whether childhood trauma is involved in the development of metabolic dysregulation in terms of abnormal glucose metabolism is very limited. This is a key issue to advance knowledge on the potential effects of CT not only on patients' mental but also on physical health. However, to date only one study (Veru-Lesmes et al., 2018) has explored this relationship, reporting higher levels of glycated hemoglobin in FEP patients who were physically abused during childhood compared to those were not. To the best of our knowledge, no study has so far explored the relationship between childhood trauma and the panel of markers involved in the pathway of glucose metabolism regulation.

Here, we tested, in a large sample of FEP patients at their first contact with mental health services, whether patients with a history of CT show, already at illness onset, dysregulation of a broad range of glucose metabolism markers. In particular, we evaluated serum concentrations of c-peptide, insulin, plasminogen-activator-inhibitor–1 (PAI-1), resistin, visfatin, glucagon, glucagon-like peptide-1 (GLP-1), gastric-inhibitor-peptide (GIP), leptin, and ghrelin in order to explore the association between CT and glucose metabolism.

This is a relevant issue in order to deepen our knowledge about the relationship between childhood trauma and metabolic dysfunction in FEP.

2. Methods

This study is part of the "Genetics Endophenotypes and Treatment: Understanding early Psychosis" (GET UP) research program. Details of study design, sample recruitment and clinical assessment have been previously published (Ruggeri et al., 2012, 2015).

Briefly, based on the WHO 10-Country study (Jablensky et al., 1992), the study recruited from patients presenting with psychosis to Community Mental Health Centres (CMHCs) in two Italian regions (Veneto and Emilia-Romagna) and in the urban areas of Florence, Milan, and Bolzano, during the index period (Apr 1, 2010-Mar 31, 2011). Inclusion criteria were: (a) age 18–54 years; (b) residence within the catchment areas of CMHCs; (c) presence of at least one of the following symptoms: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre, or grossly inappropriate behavior; or two of the following symptoms: loss of interest, initiative, and drive; social withdrawal; episodic severe excitement; purposeless destructiveness; overwhelming fear; or marked self-neglect; and (d) first lifetime contact with CMHCs, prompted by these symptoms. Exclusion criteria were: (a) prescribed antipsychotic medication (>3 months) for an identical or similar mental disorder; (b) mental disorder due to general medical condition; (c) moderate-severe mental retardation assessed by clinical functional assessment; and (d) psychiatric diagnosis other than ICD-10 for psychosis. Eligible FEP patients gave written informed consent to the study, after a complete description of the study aims. Ethical approval was obtained by the local Ethics Committee (http://www.ospedaleuniverona.it) (Prot. N. 1682/CE, April 15th 2010).

2.1. Assessment

A comprehensive set of standardized instruments was used to collect clinical and psychosocial information. Participants were assessed by 17 independent researchers who underwent a training on the use of the standardized instruments, and inter-rater reliability exercise to determine consistency of evaluations among investigators. In details, psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), depressive symptoms with the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) and symptoms of mania with the Bech-Rafaelsen Mania Rating Scale (BRMRS) (Bech et al., 1978). Since FEP is generally a phase of high diagnostic instability, the specific ICD-10 codes for psychosis (F1 × .4; F1 × .5; F1 × .7; F20–29; F30.2, F31.2, F31.5, F31.6, F32.3, F33.3) were assigned at 9 months. The best-estimate ICD-10 diagnoses were made by consensus by a panel of clinicians by taking into account all available information gathered from the point of enrolment into the study, as required in the Item Group Checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992). Lifetime and current substance use was assessed using the Cannabis Experiences Questionnaire (Barkus et al., 2006). Subjects were divided into those who had never tried cannabis and those who had tried at least once in

their life.

Information about childhood trauma were obtained using the Childhood Experience of Care and Abuse-Questionnaire version (CECA-Q) (Bifulco et al., 2005). The CECA-Q is a semi-structured interview, and it is designed to elicit information on experiences of childhood adversity that occurred before age 17, including physical and sexual abuse, separation from at least one of the parental figures longer than 6 months, and death of a parent. For this study, we defined childhood trauma (CT) as having experienced at least one event among sexual abuse, physical abuse, separation and/or loss.

The presence of stressful life events (SLEs) was recorded using a semi-structured interview derived from Brown et al. (Brown et al., 1973), which was adapted to the Italian population (Faravelli et al., 1986). This interview recorded events that occurred in the prior year in detail, as well as timing and circumstances in which they occurred. On the basis of these accounts, two assessors, who were blind to the study hypotheses, evaluated the following: a) whether a given event corresponded to any of the events listed in the Paykel scale (Paykel et al., 1971); b) if it was considered severe (i.e., in the top 20 events of the Paykel list). For this study, we considered stressful events as those considered severe and that occurred in the last 12 months, that is death of a family member, sexual or physical abuse, being accused of having committed a crime, sentence of imprisonment, being exposed to war or natural catastrophes, family breakdown, being removed from home, sentimental breakdown, severe physical illness.

Subjects also had a detailed medical examination at first contact with services. Body Mass Index (BMI, kg/m^2) was calculated as following: weight was measured without shoes, and in light indoor clothes, using a balance beam scale; height was measured without shoes using a fixed stadiometer. Smoking habit and current drug therapies were also recorded.

2.2. Biomarker analyses

An anticoagulant-free tube was draw from each participant in the morning after an overnight fast (between 07:00 and 10:00). The tubes were kept at room temperature for 2 h followed by 1 h at 4 °C before serum separation by centrifugation (3000 g for 15 min). Serum samples were then stored at −80 °C until the time of assays.

The concentrations of c-peptide, ghrelin, GIP, GLP-1, glucagon, insulin, leptin, PAI-1 (total), resistin and visfatin were analysed by using the Bio-Plex Pro™ Human Diabetes kit (Bio-Rad, CA, USA). In brief, 12.5 µl of each sample were diluted 1:4 with the sample diluents, and then 50 µl of the diluted sample were incubated in a pre-wet filter plate for 1 h in the dark with the biotinylated detection antibody. Each analyte was detected by the addition of a streptavidin-phycoerythrin solution and quantified using the BioPlex array reader (Bio-Rad, CA, USA). Data acquisition and analysis from the reactions were performed using a Bio-Plex system reader. Standard curves were obtained using the model given by the manufacturer as reference. Single analytes' concentrations were calculated using the Bio-Plex manager software 6.0. All the measurements were double checked, and all the specimens were processed with reference to negative controls.

2.3. Statistical analysis

Data are presented as means (standard deviations) for continuous variables and frequencies (percentages) for categorical variables. Normality assumption of metabolic markers' serum concentration was assessed by Kolmogorov-Smirnov test and all variables resulted positively skewed ($p < 0.05$). Differences between the two groups (No CT vs CT) were evaluated by the non-parametric Mann-Whitney test for continuous variables, while Chi-square test was used for categorical variables. The prediction of each metabolic marker concentration in relation to childhood trauma and a set of potential covariates (age, sex, tobacco use, cannabis use, psychotropic medications, BMI, diagnosis, PANSS, HAM-D, BRMRS and stressful life events) was evaluated by estimating a series of univariate generalized linear models (GLMs) with Gamma family and log link (Goldsmith et al., 2016; Misiak et al., 2019). Final multivariate GLMs were estimated by introducing only those independent variables (CT and covariates) with $p < 0.10$ at the univariate regression.

All p-values were two-tailed with a significance level of 0.05. Statistical analyses were carried out using Stata 13.0 for Windows.

3. Results

A total of 444 FEP patients were recruited in the GET UP Research Project, and out of 201 patients had valid serum concentrations of metabolic markers, 148 (73.6 %) also had information on childhood trauma. These 148 patients were included in further analyses. There were no significant differences in socio-demographic and clinical characteristics between patients with metabolic markers' ($n = 201$) and patients on whom these were not available ($n = 243$) (data available from the Authors). Socio-demographic, clinical characteristics and metabolic markers' serum levels are shown in Table 1.

Among the 148 individuals (56.1 % male, mean age 29.5 years), 25.7 % received an ICD-10 diagnosis of schizophrenia, 45.9 % of non-affective non-schizophrenia psychosis, whereas 28.4 % of affective psychosis. Regarding the medical history, none of the 148 individuals was taking medications for a metabolic disease or had a diagnosis of diabetes. Mean BMI was 23.5 (sd 3.4).

Ninety-five patients (64.2 %) were positive for a history of childhood trauma, while 53 (35.8 %) were negative. There were no significant differences between these two groups in terms of age, gender, smoking and cannabis use, psychotropic medications, diagnosis, psychopathology and BMI. Severe stressful life events (SLEs) in the previous 12 months were more often experienced by patients with a history of CT (41.8 % versus 22.6 %, $p = 0.023$). In terms of metabolic markers, individuals with CT had mean levels of c-peptide and insulin significantly higher than those without CT. The distributions of these markers in the two groups are represented by box-plots (Figs. 1 and 2).

Multivariate generalized linear models (GLMs) with Gamma family and log link estimated the prediction of each metabolic marker by childhood trauma, age, sex, BMI and severe SLEs ($p < 0.10$ in univariate GLMs; data available from the Authors). The multivariate models showed that CT was associated only with the levels of c-peptide and insulin, resistin levels were associated with sex and BMI, while leptin was associated only with sex (Table 2). Visfatin was associated with severe SLEs in the last 12 months.

Specifically, patients with higher c-peptide levels had experienced CT and had higher BMI, with these variables accounting for 17.7 % of the variance. Patients with higher insulin levels had experienced CT, had higher BMI and were younger in age, with these factors accounting for 24.9 % of the variance. Levels of leptin and resistin were higher in female patients and in those with higher BMI, and these factors explained 26.8 % and 11.6 % of the variance respectively. Finally, visfatin was higher in those patients reporting more severe stressful life events in the previous 12 months and this explained 7.3 % of the variance.

No other metabolic markers showed significant associations with childhood trauma and the covariates.

4. Discussion

To the best of our knowledge, this is the first study that investigates the relationship between childhood trauma and the panel of markers involved in the pathway of glucose metabolism (c-peptide, ghrelin, GIP, GLP-1, glucagon, insulin, leptin, PAI-1, resistin and visfatin) in a large sample of patients with first episode psychosis. Our main finding is that only c-peptide and insulin levels are higher in patients reporting a history of childhood trauma, suggesting that hyperinsulinemia occurs early in the course of psychotic disorders. These findings underline the

Table 1
Socio-demographic, clinical characteristics and metabolic markers' serum levels of patients in the whole sample (n = 148) and in subgroups classified by exposure to childhood traumatic events (CT and no CT).

Variable Mean (SD) or N (%)	Total sample	no CT (n = 53)	CT (n = 95)	CT vs no CT p-value
Age at first contact with services (years)	29.5 (9.5)	29.2 (11.0)	29.6 (8.7)	0.780[a]
Gender				
Male	83 (56.1%)	30 (56.6%)	53 (55.8%)	0.924[b]
Tobacco use (17 missing)				
Yes	65 (49.6%)	18 (38.3%)	47 (56.0%)	0.053[b]
Cannabis use (18 missing)				
Yes	18 (13.8%)	6 (12.5%)	12 (14.6%)	0.734[b]
Psychotropic medications (20 missing)				
Yes	117 (91.4%)	44 (91.7%)	73 (91.3%)	0.935[b]
Body Mass Index (BMI) (29 missing)	23.5 (3.4)	23.5 (3.5)	23.4 (3.4)	0.854[a]
Diagnosis				
Affective psychosis	42 (28.4%)	13 (24.5%)	29 (30.5%)	0.732[b]
Non affective psychosis (No schizophrenia)	68 (45.9%)	26 (49.1%)	42 (44.2%)	
Schizophrenia	38 (25.7%)	14 (26.4%)	24 (25.3%)	
PANSS (after clinical stabilization) (1 missing)				
Positive symptoms	2.3 (0.8)	2.3 (0.8)	2.3 (0.8)	0.645[a]
Negative symptoms	2.4 (0.9)	2.4 (1.0)	2.3 (0.8)	0.584[a]
General symptoms	2.3 (0.5)	2.3 (0.6)	2.3 (0.5)	0.918[a]
Total score	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)	0.657[a]
HAMILTON (after clinical stabilization)	17.3 (8.0)	16.6 (6.4)	17.7 (8.8)	0.421[a]
BRMRS (after clinical stabilization) (1 missing)	3.2 (3.7)	2.6 (3.5)	3.5 (3.8)	0.126[a]
Stressful life events (SLEs) (16 missing)				
Yes	45 (34.1%)	12 (22.6%)	33 (41.8%)	0.023[b]
C-peptide ng/ml (3 missing)	0.75 (0.49)	0.58 (0.28)	0.84 (0.55)	0.019[c]
Ghrelin ng/ml (1 missing)	1.34 (0.50)	1.33 (0.56)	1.34 (0.47)	0.958[c]
GIP ng/ml (4 missing)	0.22 (0.50)	0.19 (0.24)	0.24 (0.60)	0.273[c]
GLP-1 ng/ml (2 missing)	0.38 (0.09)	0.37 (0.07)	0.39 (0.09)	0.057[c]
Glucagon ng/ml (2 missing)	0.92 (0.27)	0.91 (0.28)	0.92 (0.27)	0.699[c]
Insulin ng/ml (2 missing)	0.39 (0.28)	0.29 (0.14)	0.44 (0.32)	0.002[c]
Leptin ng/ml (2 missing)	10.65 (8.77)	11.51 (9.60)	10.19 (8.31)	0.753[c]
PAI-1 ng/ml (2 missing)	43.88 (22.52)	41.23 (18.96)	45.34 (24.24)	0.113[c]
Resistin ng/ml (2 missing)	3.77 (2.22)	3.63 (2.52)	3.86 (2.05)	0.059[c]
Visfatin ng/ml (4 missing)	4.66 (5.77)	4.65 (5.28)	4.67 (6.05)	0.751[c]

[a] t Student.
[b] Chi-square.
[c] Mann-Whitney.

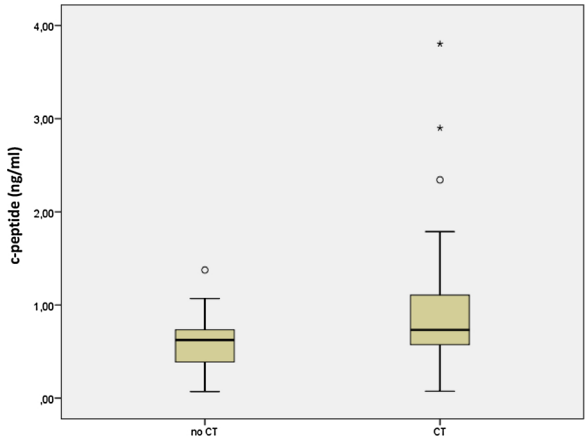

Fig. 1. Box-plots for c-peptide serum concentration distributions in patients who did not experience chilhood trauma (no CT).

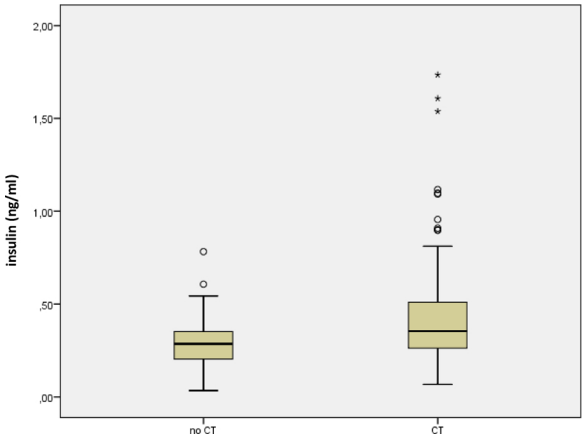

Fig. 2. Box-plots for insulin serum concentration (ng/ml) distributions in patients who did not experience childhood trauma (no CT) and those ones who experienced childhood trauma (CT).

importance of monitoring metabolic alterations from the onset, especially in those patients who report childhood trauma, in order to carry out therapeutic interventions aimed at recovering from the negative outcomes of both hyperinsulinemia and trauma.

The c-peptide is a polypeptide that connects insulin's A-chain to its B-chain in the proinsulin molecule; it is processed and stored in secretory vesicles and released, together with the mature hormone insulin, by β pancreatic cells in response to hyperglycemia. The physiologic role of c-peptide remains to be clarified. The c-peptide has anti-inflammatory (Haidet et al., 2012), vasodilatory (Wallerath et al., 2003) and antioxidant effects (Giebink et al., 2013), exerted both through a direct action on endothelial cells and an indirect action on erythrocytes and immune system cells. Our study provides the first evidence of an association between these two key components of glucose metabolism and childhood trauma already at the time of the first psychotic episode. Our findings on the c-peptide are in line with results from animal data, which have shown a significant association between antenatal stress and higher levels of c-peptide in offspring (Balasubramanian et al., 2015). We also found that insulin levels were

Table 2
Multivariate generalized linear models (GLMs) with Gamma family and log link for metabolic markers significantly associated with at least one independent variable.

	Coefficient (p-value) 95 %CI				
	C-Peptide	Insulin	Leptin	Resistin	Visfatin
Childhood trauma (CT)	0.311 (p = 0.010) 0.075 to 0.548	0.438 (p < 0.001) 0.205 to 0.671	−0.180 (p = 0.311) −0.529 to 0.168	0.129 (p = 0.232) −0.083 to 0.341	−0.140 (p = 0.336) −0.424 to 0.145
COVARIATES[1]					
Age at first contact with services (years)	−0.010 (p = 0.142) −0.024 to 0.003	−0.015 (p = 0.024) −0.028 to −0.002	0.001 (p = 0.917) −0.018 to 0.020	−0.010 (p = 0.109) −0.023 to 0.002	−0.014 (p = 0.100) −0.030 to 0.003
Male sex (Ref.)	−0.148 (p = 0.258) −0.404 to 0.108	−0.194 (p = 0.128) −0.444 to 0.055	−0.824 (p < 0.001) −1.174 to −0.474	−0.399 (p < 0.001) −0.623 to −0.174	−0.211 (p = 0.180) −0.519 to 0.097
BMI	0.066 (p = 0.001) 0.027 to 0.106	0.071 (p < 0.001) 0.035 to 0.108	0.046 (p = 0.066) −0.003 to 0.096	0.052 (p = 0.002) 0.019 to 0.085	0.013 (p = 0.558) −0.032 to 0.059
SLEs	0.063 (p = 0.619) −0.185 to 0.311	−0.043 (p = 0.730) −0.289 to 0.202	−0.101 (p = 0.586) −0.464 to 0.262	−0.021 (p = 0.856) −0.243 to 0.202	0.396 (p = 0.009) 0.098 to 0.695
R-squared %	17.7 %	24.9 %	26.8 %	11.6 %	7.3 %

[1] only variables which resulted significantly associated (p < 0.10) with metabolic markers in univariate GLMs (data available from the Authors).

higher in patients with a history of CT. Insulin, in turn, can be considered the main anabolic hormone of the body and regulates the metabolism of carbohydrates, fats and protein (Voet and Voet, 2010), and exerts an inhibitory activity on the HPA axis (Gallagher et al., 2007; Gunduz-Bruce et al., 2007). A recent metanalysis on FEP patients has reported higher levels of insulin in drug naïve patients compared to controls and highlighted that environmental factors (such as unhealthy lifestyle, incorrect diet regimen) could explain this association (Misiak et al., 2019). Childhood trauma could also represent a negative environmental factor that may affect insulin levels, perhaps through its involvement in the dysregulation of the stress response. Studies in patients with psychosis have shown a hyperactivity of the HPA axis in these patients, including at illness onset (Gallagher et al., 2007; Gunduz-Bruce et al., 2007). It has been suggested that the higher rates of CT in patients with psychosis (Tomassi et al., 2017) might contribute to explain this hyperactivity (Fisher et al., 2009; Read et al., 2005). The alterations observed in the present study may also derive from the interaction between the metabolism and immune response system alterations, another somatic effect of childhood trauma. A recent meta-analysis indicated a relationship between childhood trauma and a pro-inflammatory state in adults (Baumeister et al., 2016). Interestingly, high levels of peripheral inflammation have been found associated with metabolic abnormalities in FEP patients (Chen et al., 2013; Nettis et al., 2019; Pillinger et al., 2017; Russell et al., 2015). These mechanisms might at least partially explain the higher incidence of cardiovascular disease, metabolic and immune system dysfunctions in patients with CT (Pervanidou and Chrousos, 2012).

Thus, the experience of CT could induce alterations of the stress response, and therefore facilitating the development of medical conditions like diabetes, obesity and metabolic syndrome (Berens et al., 2017).

Contrary to our expectations, we did not find any association between the other markers related to glucose metabolism and childhood trauma. Recently, it has been found increased levels of PAI-1 and decreased levels of glucagon, ghrelin, GLP-1 (Bocchio-Chiavetto et al., 2018) and leptin (Misiak et al., 2019) in FEP patients compared to controls. Thus, our negative findings suggest that the dysregulation of biomarkers levels in FEP patients previously reported could be attributed to other factors, rather than to the high rate of childhood trauma.

Conversely, a recent meta-analysis (Misiak et al., 2019) has found that there is no difference between FEP and healthy controls in resistin and visfatin levels, probably since these hormones have been little studied in FEP and never in relation to childhood trauma.

As secondary results, we found that resistin was higher for females and for higher levels of BMI, while leptin was higher only for females. Leptin levels have been demonstrated to be significantly higher in women than in male (Stubbs et al., 2015) and increased leptin levels are present in individuals at risk of psychosis, mostly women (Martorell et al., 2019). Leptin is peptide hormone with several functions, including glucose homeostasis, immune and inflammatory responses, neuroplasticity (Ramos-Lobo and Donato, 2017), modulation of the neuroendocrine axes (Maniam and Morris, 2012).

Finally, we found that visfatin was higher in those patients reporting more severe stressful life events in the previous 12 months. Elevated levels of visfatin have been found in individuals with obesity (Chang et al., 2011) and in patients affected by type 2 diabetes mellitus, independently by BMI (Chen et al., 2006). Consequently, our finding suggests that stressful events in adulthood could lead to an alteration in visfatin, the presence of which has been found associated with the development of metabolic diseases.

This study has several strengths. First, our sample was part of the GET UP Research Project (Ruggeri et al., 2012), conducted in a large catchment area, corresponding to nearly 10 million inhabitants. The lack of significant differences in socio-demographic or clinical characteristics between subjects who had a blood sample and those who did not suggests that our patients were highly representative of the patients treated in “real world” community services, and that our results would be generalizable. Second, we used reliable, internationally validated instruments and adopted conservative cut-off points to identify only the most severe forms of abuse.

Some limitations also need to be acknowledged. First, although our is the largest sample of FEP subjects in which the relationship between childhood trauma and glucose related metabolic markers has been investigated, the association between specific types of trauma exposures (i.e sexual abuse) and metabolic markers’ levels could not be examined due to the small sample sizes for each type of trauma. Second, as for most studies on CT, abuse data rely on retrospective reporting. Nonetheless, the stability of retrospective self-reports of trauma in FEP has been supported (Simpson et al., 2018). Moreover, this limitation has been mitigated by the use of a standardized interview as CECA-Q, which has good reliability and validity both in general (Bifulco et al., 2005) and clinical populations (Brown et al., 2007; Smith et al., 2002). Third, we could not explore the full range of factors known to affect glucose metabolism; for example, we did not have data on diet regime or daily physical activity. Moreover, blood samples were not taken to verify the presence/absence of diabetes by an oral glucose tolerance test (OGTT), so the absence of metabolic disorders has been ascertained only through medical history or routine blood tests. Finally, although details of ongoing psychotropic medications use was not considered, there is evidence that metabolic abnormalities in FEP subjects are independent from medication and predate pharmacological treatment (Perry et al., 2016).

In conclusion, our results suggest a significant association between childhood traumatic experiences and metabolic abnormalities already

in the first stage of psychosis. Individuals with first episode psychosis are known to have an increased risk of developing the metabolic syndrome due to psychopharmacological treatments, high-calories and low-quality diet regime and sedentary lifestyle (De Hert et al., 2011; Fagiolini et al., 2008). Childhood trauma might represent an additional risk factor for metabolic disorders in these patients. Our findings suggest that at psychosis onset a thorough anamnestic evaluation should include the history of traumatic experiences during childhood. This would help clinicians to implement early and assertive programs of food and nutrition education and to guide the choice of medication and specific therapeutic interventions on trauma to reduce the detrimental effects of CT not only on patients' mental but also on physical health.

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Contributors

SaT conceived and designed the present study; interpreted data and wrote the manuscript. ChB performed the statistical analyses and contributed in the interpretation of data; RZ, AM performed the biological analyses; CaB, AD, PS, KF, MI, AP contributed in data collection; SiT, CF, LB-C contributed in the interpretation of data and revised the draft critically. MR and MG, together with AL and LB-C, conceived the GETUP research project design, contributed in the interpretation of data and revised the draft. All authors read and approved the final manuscript.

Declaration of Competing Interest

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.psyneuen.2019.104536.

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