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Childhood trauma is associated with increased Body Mass Index and increased C-reactive protein levels in first-episode psychosis patients

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Abstract

Background—The high incidence of metabolic syndrome in patients with psychosis is mainly attributed to antipsychotic treatment. However, it has been suggested that psychological stress also plays a role, by inducing a chronic inflammatory process which may predispose to the development of metabolic abnormalities. We investigated the association between psychosocial stress and inflammatory and metabolic biomarkers in subjects with first-episode psychosis and healthy controls.

Methods—Body Mass Index (BMI), weight and waist circumference were measured in 96 first-episode psychosis patients and 99 healthy controls. High sensitive C-reactive protein (hsCRP) and leptin were measured in a sub-sample of 37 patients and 49 controls. In all the subjects we collected information on childhood trauma and recent stressors.

Results—Only patients with childhood trauma had higher BMI (24.9±0.5 kg/m^2) and higher hsCRP (0.8±0.3 mg/dl) when compared with healthy controls (23.4±0.4 kg/m^2, p=0.018 and 0.2±0.1 mg/dl, p=0.043 respectively). This was specific to childhood sexual abuse; patients who had experienced childhood sexual abuse had higher BMI (26.2±1.0 kg/m^2) and hsCRP (1.9±2.5 mg/dl) not only compared with controls, but also compared with patients who had not experienced childhood sexual abuse (24.3±0.5 kg/m^2, p=0.055; 0.5±0.2 mg/dl, p=0.001).

Conclusions—Childhood trauma is cross-sectionally associated with both increased inflammation and worse metabolic profile in first-episode psychosis. Further studies need to confirm the causal relationship between childhood trauma and higher BMI, and whether this is indeed mediated by the increased inflammation.

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Keywords

metabolic syndrome; inflammation; psychosis; childhood trauma; BMI; sexual abuse; CRP; stress; schizophrenia; weight

Introduction

It is widely acknowledged that, compared with the general population, patients with schizophrenia suffer from higher rates of metabolic syndrome and obesity-related illnesses such as type II diabetes mellitus, dyslipidaemia, hypertension and cardiovascular disease (Heiskanen *et al.*, 2003). The development of metabolic syndrome and other physical illnesses poses a serious health risk for these patients, and it is has been reported that up to 60% of the excess mortality rate in patients with schizophrenia is attributable to physical illnesses (Brown *et al.*, 2000). The treatment of choice in schizophrenia is antipsychotic medications, and these drugs have been associated with weight gain and development of metabolic abnormalities *(*Allison *et al.*, 1999). However, antipsychotics are not the only cause of metabolic abnormalities described in psychosis. In fact, previous studies have also found impaired glucose tolerance and increased visceral fat in drug-naïve first-episode psychosis patients (Ryan *et al.*, 2003, Ryan *et al.*, 2004). Unfortunately, the mechanisms underlying the increased risk of metabolic syndrome in these patients are yet to be understood.

It has been suggested that repeated episodes of psychological stress can induce a chronic inflammatory process, which in turn may predispose to the development of metabolic abnormalities (Black, 2003). In particular, chronic psychosocial stress, including difficult care-giving and hostile marital relationships, has been associated with increased levels of the acute phase protein, C-reactive protein (CRP) (Miller, 2008). Likewise, childhood maltreatment has been associated with increased peripheral blood CRP in a birth cohort study of healthy individuals, independent of co-occurring early life risks, stress or health problems in adulthood (Danese *et al.*, 2007), although it was worse in those with concomitant adult psychopathology (Danese, 2008). Indeed, high levels of stress in both childhood and adulthood have been consistently reported in patients with psychosis, and more recently at the time of the first psychotic episode (Aas *et al.*, 2010, Fisher *et al.*, 2009, Fisher *et al.*, 2010, Mondelli *et al.*, 2010a). However, the possible role of stress in this increased inflammation is unclear.

Previous studies have consistently reported elevated inflammatory markers in patients with chronic schizophrenia (Potvin *et al.*, 2008). More recently, this has been demonstrated in patients with first-episode psychosis (Crespo-Facorro *et al.*, 2008, Fernandez-Egea *et al.*, 2009, Mondelli *et al.*, In Press, Sperner-Unterweger *et al.*, 1999). Furthermore, we have recently demonstrated that childhood trauma and recent life stressors predict lower brain-derived neurotrophic factor (BDNF) expression through an inflammation-mediated pathway in first-episode psychosis patients (Mondelli *et al.*, In Press). Although, there is evidence for increased prevalence of psychosocial stress as well as increased inflammation in this

population, their possible contribution to the development of metabolic syndrome has not been investigated.

The immune response and metabolic regulation are highly integrated, and their proper functioning is interdependent. Indeed, obesity, insulin resistance, and type II diabetes have been shown to be closely associated with chronic inflammation, characterized by activation of inflammatory signalling pathways, and by abnormal cytokine production (Hotamisligil, 2006). Interestingly, even a mild elevation in inflammation levels predicts increased risk of cardiovascular disease in apparently healthy individuals. In particular, high-sensitivity CRP has been recently implemented as an adjunct to traditional risk factor screening for cardiovascular disease (Pearson *et al.*, 2003). Furthermore, a recent study in an obese population, found BMI to be positively correlated with inflammatory makers and adipokines (Capuron *et al.*, 2010). It is currently unclear whether inflammation represents a cause or a consequence of metabolic alterations in patients with psychosis. Since fat tissue is not a simple energy storage organ, but exerts important endocrine and immune functions, it is crucial that anthropometric measures are collected when evaluating inflammatory and metabolic biomarkers.

The aim of this study is to investigate the role of psychosocial stress (childhood trauma and recent stressors) in metabolic and inflammatory abnormalities in first-episode psychosis patients. Given the evidence from previous studies, we hypothesize that the presence of childhood trauma will be associated with increased levels of inflammatory and metabolic markers.

Methods

Subjects

First-episode psychosis patients were recruited from inpatient and outpatient units of the South London and Maudsley (SLAM) NHS Foundation Trust (UK). We recruited subjects aged 18-65 presenting for the first time to these services for a functional psychotic illness (ICD10 F10-19, excluding coding F1x.0 for Acute intoxication; F20-29 and F30-39, psychotic codings) (WHO, 1992). Patients with organic psychosis, learning disabilities or requiring a translator were excluded. Controls were recruited from the same catchment areas as the patients, through local advertisement as well as from existing volunteer databases. Controls were screened using the Psychosis Screening Questionnaire (PSQ) (Bebbington and Nayani, 1995), and excluded if they met criteria for a present or past psychotic disorder. The study was approved by the local Ethical Committee, in accordance with the code of ethics of the World Medical Association, and written informed consent was obtained from all participants.

We recruited and assessed 96 patients with first-episode psychosis and 99 healthy controls. Sixty-three patients received a DSM-IV diagnosis of schizophrenia-like disorder (including schizophrenia, schizophreniform disorder and schizoaffective disorder), 15 of affective psychoses (including major depression with psychotic symptoms and manic episode with psychotic symptoms), 3 of delusional disorder and 15 of psychotic disorder not otherwise

specified. Duration of antipsychotic treatment ranged from 0 to 209 days with a mean duration of 37.0±4.5 days.

The inflammatory markers hsCRP and leptin were measured in a subset of the larger sample, composed of 37 patients and 49 healthy controls. In this subset, 24 patients received a DSM-IV diagnosis of schizophrenia-like disorder, 7 of affective psychoses, 1 of delusional disorder and 5 of psychotic disorder not otherwise specified. Duration of antipsychotic treatment in this subset of patients ranged from 0 to 171 days with a mean duration of 43.7±7.4 days.

Questionnaires and Clinical Assessment

Socio-demographic data were collected using a modified version of the MRC Sociodemographic Schedule (Mallett *et al.*, 2002). Validation of clinical diagnosis was obtained using the Operational Criteria (OPCRIT) (McGuffin *et al.*, 1991), reviewing the case notes in the first month following the first contact with services. The presence or absence of symptoms was measured by the OPCRIT checklist using the strict OPCRIT definitions.

We collected information about stressful life events, in the previous six months, using the Brief Life Events questionnaire (Brugha and Cragg, 1990). This assesses both the number and the emotional impact of life stressors involving moderate or long-term threats, such as illness or injury, death of a close friend or relative, unemployment, financial loss and loss of important relationships. We also measured the perceived stress in the previous month using the Perceived Stress Scale (Cohen and Williamson, 1988). This is a 10-item scale measuring the degree to which situations in one's life are appraised as stressful. Information about childhood trauma were also collected, using a modified version of the Childhood Experience of Care and Abuse (CECA) Questionnaire (Bifulco *et al.*, 2005), including information about loss of parents, separation from parents for more than 6 months, and physical and sexual abuse before the age of 17 years. Cut-off points published by Bifulco et al. *(*Bifulco *et al.*, 2005) were used to dichotomize responses on the physical and sexual abuse variables into severe and non-severe categories. A composite variable was created using the four dichotomized variables considered (loss of parents, separation from parents for more than 6 months, severe physical abuse and severe sexual abuse): the score of this variable ranged between 0 (absence of any childhood trauma) to 4 (presence of all four childhood trauma investigated). This score was then dichotomized again into 0 (absence of any childhood trauma) and 1 (presence of one or more childhood trauma).

Inflammatory and metabolic markers

Weight was measured in subjects while wearing light clothing, to the nearest 0.1 kg, with an analogue floor scale. Height was measured without shoes, to the nearest 0.5 cm using a measuring tape. Body Mass Index (BMI) was calculated as the individual's body weight (in kilograms) divided by the square of their height (in meters). The circumference of the waist was measured using a measuring tape at the narrowest part of the torso.

Blood samples were taken from the antecubital fossa using a BD safety-Lok™ blood collection set. The time of blood collection varied for each subject, and subjects were not fasted before collection. Samples were analyzed at the biochemistry laboratory at King's College Hospital, blind to subjects' status. Glycosilated haemoglobin (HbA1c) was measured using the Primus Ultra 2 boronate affinity HPLC system. Total cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol were all measured using the Bayer Advia 2400 automated system, via an enzymatic assay. Low density lipoprotein (LDL) cholesterol was then subsequently calculated using the Friedwald equation. The high sensitive C-reactive (hsCRP) protein was analyzed using the Cormay hsCRP assay that employed an anti-CRP antibody sensitized to latex particles. The assay was analysed on the Cobas Mira. Leptin was measured with highly sensitive enzyme-linked immunosorbent assay (ELISA) kits.

Data Analyses

Data were analyzed using the Statistical Package for Social Sciences, Version 15.0 (SPSS Inc.). Continuous variables are presented as mean ± standard error mean. Chi-square test was used to compare categorical variables between patients and controls. Independent Samples T-test was applied to test differences in inflammatory markers and metabolic parameters between patients and controls. To test differences associated with childhood trauma variables, analysis of variance with post hoc tests were used between three groups; patients with childhood trauma, patients without childhood trauma and controls. In the group of patients, parametric and non-parametric correlation analyses were used, as appropriate, to test associations between stress variables and the inflammatory and metabolic parameters that were significantly different in the t-test. Further correlation analyses were used to test associations between inflammatory markers and metabolic parameters.

Results

Socio-demographic, anthropometric and stress data of first-episode psychosis patients and healthy controls from the larger sample are shown in Table 1.

Anthropometric Data: Effect of group and childhood trauma

First-episode psychosis patients showed a higher BMI when compared with healthy controls. Consistent with previous data on similar samples (Aas *et al.*, In Press, Aas *et al.*, 2010, Mondelli *et al.*, 2010a) patients also had a higher number of childhood traumatic events, a higher number of recent stressful life events and a higher perceived stress scale score (please see Table 1).

We tested the effects of childhood traumatic events on BMI by analysing the difference among three groups: patients with any trauma, patients without any trauma and controls. There was a significant difference in BMI between the three groups ($F=3.1$, $df=2,191$, $p=0.049$) (Table 2). Post hoc tests revealed that BMI was higher in patients who had experienced childhood trauma when compared with controls ($p=0.018$). When each type of childhood trauma was investigated individually, we found that the association between childhood trauma and BMI was specific for severe sexual abuse. Analysis of variance

showed again that there was a significant difference in BMI between the three groups (F=4.4, df=2,189, p=0.013; (please see Table 2). Post hoc tests revealed that patients who had experienced severe sexual abuse had higher BMI when compared with both healthy controls (p=0.004) and with patients who had not experienced any severe sexual abuse, although this was a trend (p=0.055).

Finally, we investigated whether there was an association between BMI and other measures of psychosocial stress; however, both number of recent stressful life events and perceived stress scale score were not correlated with BMI (Spearman's rho=−0.4 p=0.7 and Pearson r=0.2 p=0.8 respectively).

Inflammatory markers: effect of group and childhood trauma

Socio-demographic, metabolic, inflammatory and stress data of first-episode psychosis patients and healthy controls from the subset of subjects are shown in Table 3.

Levels of hsCRP and triglycerides were significantly higher in patients when compared with controls. Furthermore, levels of hsCRP were correlated with BMI (Spearman's rho=0.49, p=0.012) and also with weight (Spearman's rho=0.47, p=0.012) in the patient group, but not in healthy controls.

When looking at the effects of childhood traumatic events on hsCRP, we again analyzed the difference between three groups: patients with any trauma, patients without any trauma and controls. There was a trend for a difference between the three groups (F=2.5, df=2,70, p=0.089; Table 2). Post hoc tests revealed that hsCRP was higher for patients who had experienced childhood trauma when compared with controls (p=0.043).

Similarly to the results seen for BMI, the association between childhood trauma and hsCRP was specific for severe sexual abuse. There was a significant difference in hsCRP between the three groups (F=8.3, df=2,69, p=0.001; Table 2). Post hoc tests revealed that patients who had experienced severe sexual abuse had higher levels of hsCRP when compared with patients who had not experienced any severe sexual abuse (p=0.001) as well as compared with healthy controls (p<0.001).

Levels of hsCRP did not correlate with either number of recent stressful life events or perceived stress scale scores (Spearman's rho=−0.06 p=0.7 and Pearson r=0.07, p=0.7). This was also true for triglyceride levels (Spearman's rho=0.10, p=0.6 and Pearson r=0.21, p=0.2). Although a difference was found in triglyceride levels between patients and controls, this was not associated with exposure to childhood traumatic events. No differences in triglyceride levels were found between the three groups for any childhood trauma (F=1.9, df=2,69, p=0.2) or for severe sexual abuse (F=1.9, df=2,67, p=0.2).

Potential confounders

To investigate the possible effect of confounding factors on our findings, we tested the difference in duration of antipsychotic treatment, ethnicity and gender between patients with severe sexual abuse and patients without severe sexual abuse. Patients with severe sexual abuse had a shorter duration of treatment compared with patients without childhood trauma

in both the larger sample (22.5±5.8 vs 50.0±9.4 p=0.032) and the subset (24.4±12.3 vs 50.0±9.4 p=0.2). No significant differences were found for ethnicity in either the large sample or the subset (χ^2=0.7, p=0.4 and χ^2=0.05, p=0.1 respectively). Similarly, no significant differences were found for gender in either the large sample or the subset (χ^2=0.2, p=0.2 and χ^2=1.0, p=0.7 respectively). Socioeconomic status as indicated by level of education was also investigated as a potential confounder. Only a small proportion of patients (14%) had no qualifications and this did not have any effect on the metabolic and inflammatory markers. No differences were found for level of education in either the large sample or the subset (χ^2=0.7, p=0.5 and χ^2=0.5, p=0.5 respectively).

Discussion

To our knowledge, this is the first study examining the relationship between childhood trauma, hsCRP and BMI in first-episode psychosis patients. Our results indicate that first-episode psychosis patients show higher BMI as well as higher levels of hsCRP when compared with healthy controls, and that these abnormalities are partially explained by the effect of childhood traumatic events, in particular, severe sexual abuse.

The increased BMI seen in patients with childhood trauma is in keeping with previous studies looking at the effect of childhood adversity on physical health in adulthood, in otherwise healthy individuals. Indeed, studies have shown that childhood adversity can contribute to the development of metabolic problems, as well as to poorer cardiovascular health in the general population (Danese *et al.*, 2009, Lehman *et al.*, 2005, Thomas *et al.*, 2008). Moreover, self-reported abuse in childhood, including sexual, verbal and physical abuse, have been shown to be associated with higher adult BMI and adult obesity (Williamson *et al.*, 2002). Of note, our findings suggest that sexual abuse in particular is associated with increased BMI in adulthood in first-episode psychosis patients. It has been previously demonstrated that childhood sexual abuse is associated with a higher incidence of obesity as well as of type 2 diabetes in adult women (Rich-Edwards *et al.*, 2010, Smith *et al.*, 2010); however, this is the first time this has been shown in first-episode psychosis patients.

There may be several underlying mechanisms driving the association between childhood adversity and poor physical health in adulthood. Our results suggest the involvement of increased inflammatory processes, in particular increases in the inflammatory marker C-reactive protein (CRP). CRP has been consistently associated with an increased risk of diabetes and other metabolic dysfunction (Bassuk *et al.*, 2004), and has also been similarly linked to chronic psychosocial stress (Miller, 2008). Furthermore, recent studies have shown an association between increased levels of CRP and childhood trauma. Work partly conducted in our own research group has demonstrated that maltreated children show a significant increase in CRP levels in adulthood, 20 years later (Danese *et al.*, 2007). In agreement with these findings, we observe the same association between childhood trauma and adulthood CRP in first-episode psychosis patients.

It is also possible that inflammatory processes are not the only mechanism linking childhood trauma and the development of metabolic abnormalities. Other biological systems involved

in the stress response may be over activated, such as the hypothalamic-pituitary-adrenal (HPA) axis. Indeed, hyperactivity of the HPA axis can lead to increased cortisol secretion and this has consistently been demonstrated in first-episode psychosis patients (Aas *et al.*, 2010, Mondelli *et al.*, 2010b). In turn, this increased cortisol secretion can increase glucose levels and visceral fat deposition (Dinan, 2004). Moreover, stress and the HPA axis have been shown to dysregulate food intake and eating behaviour. Clinical evidence has shown that stress can induce increases in the intake of highly calorific food (Dallman *et al.*, 2005), and can precipitate binge eating (Freeman and Gil, 2004). These stress-related changes in diet may play a role in weight gain and in the development of metabolic abnormalities. It has been suggested that adults who have experienced childhood maltreatment exhibit increased HPA axis activity in response to a psychosocial stress test (Heim *et al.*, 2000). However, in our previous study in first-episode psychosis patients, childhood trauma was not associated with HPA axis hyperactivity (Mondelli *et al.*, 2010a). As such, the role of the HPA axis as a possible mechanism for the development of metabolic abnormalities following childhood trauma remains unclear.

If there is indeed a causal relationship between childhood trauma and increases in hsCRP and BMI, this could have significant public health implications. Information about experiences of childhood maltreatment may help to identify individuals with elevated inflammation levels and, thus, at greater risk of developing metabolic abnormalities. This could be used for raising awareness and targeting more vulnerable individuals for prevention and treatment strategies. As it is already well known that individuals with schizophrenia have a higher incidence of metabolic abnormalities, identifying more vulnerable individuals would improve quality of life and decrease poor physical health and mortality rates in these patients.

Some limitations to our study need to be acknowledged. First, the patients in this study were not all drug naïve, and so it is not possible to completely rule out the effect of antipsychotic medications. However, patients who had childhood trauma actually had a *shorter* duration of treatment compared to those patients who had not experienced childhood trauma. This suggests that antipsychotic treatment is not driving the differences seen for BMI and hsCRP between these two groups. Second, patients and controls were not matched for ethnicity. This could be of importance as a recent study demonstrated that hsCRP levels can vary with ancestry (Shah *et al.*, 2010). However, in our sample we did not find any significant differences for ethnicity between patients who had experienced severe sexual abuse compared with patients who had not.

In conclusion, our study shows a role of childhood trauma in the increased prevalence of metabolic and inflammatory abnormalities observed at the onset of psychosis, suggesting that more vulnerable individuals can be identified and targeted among patients with psychosis for preventative treatment strategies that promote better physical health. Future longitudinal studies would need to clarify if the increase in inflammatory markers may, at least in part, mediate the link between early life stress and subsequent metabolic abnormalities in patients with psychosis.

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Table 1

Socio-demographic, anthropometric and stress data of first-episode psychosis patients and healthy controls.

	Patients n = 96	**Controls n = 99**	**Test and Significance**
Age (years)	27.0±0.6	26.3±0.6	t=−0.8, df=1, 193, p=0.4
Gender (% of males)	(62.5%)	(67.7%)	χ^2=0.4, p=0.3
Ethnicity (% of white)	(32.3%)	(53.5%)	χ^2=9.0, **p=0.002**
BMI (kg/m^2)	24.8±0.5	23.3±0.4	t=−2.5, df=1, 193, **p=0.014**
Weight (kg)	72.7±1.4	72.5±1.4	t=−0.1, df=1, 193, p=0.9
Waist (cm)	85.7±1.3	83.0±1.3	t=−1.6, df=1, 174, p=0.1
No. of childhood trauma	1.2±0.1	0.6±0.1	t=−4.3, df=1, 190, **p<0.001**
No. of recent stressful events	2.2±0.2	1.1±1.1	t=−5.0, df=1, 191, **p<0.001**
Perceived Stress Scale	20.3±0.8	12.5±0.7	t=−7.6, df=1, 188, **p<0.001**

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Table 2

BMI and hsCRP in first-episode psychosis patients with childhood trauma, first-episode psychosis patients without childhood trauma and controls.

	Patients with Any Childhood Trauma	Patients without Any Childhood Trauma	Controls	Test and Significance
BMI (kg/m^2)	24.9±0.5	24.6±0.8	23.4±0.4	F=3.1, df=2,191, p=0.049
hsCRP (mg/dl)	0.8±0.3	0.7±0.4	0.2±0.1	F=2.5, df=2,70, p=0.089
	Patients with Severe Sexual Abuse	Patients without Severe Sexual Abuse	Controls	Test and Significance
BMI (kg/m^2)	26.2±1.0	24.3±0.5	23.4±0.4	F=4.4, df=2,189, p=0.013
hsCRP (mg/dl)	1.9±2.5	0.5±0.2	0.2±0.1	F=8.3, df=2,69, p=0.001

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Table 3

Socio-demographic, metabolic, inflammatory and stress data of first-episode psychosis patients and healthy controls from the smaller sample.

	Patients n = 37	Controls n = 49	Test and Significance
Age (years)	28.5±1.1	26.3±0.6	t=−1.8, df=1, 84, p=0.9
Gender (% of males)	(64.9%)	(73.5%)	χ^2=0.4, p=0.3
Ethnicity (% of white)	(24.3%)	(46.9%)	χ^2=4.6, **p=0.026**
BMI (kg/m^2)	25.5±1.2	23.4±0.5	t=−1.8, df=1, 66, p=0.07
Weight (kg)	74.0±3.5	73.7±2.0	t=−0.8, df=1, 69, p=0.9
Waist (cm)	88.5±2.5	83.8±1.6	t=−1.7, df=1, 61, p=0.1
HbA1c (L%)	5.3±0.1	5.2±0.1	t=−1.5, df=1, 82, p=0.1
Triglycerides (nmol/l)	1.5±0.2	1.1±0.1	t=−2.3, df=1, 82, **p=0.023**
Total Cholesterol (nmol/l)	4.8±0.1	4.7±0.2	t=−0.9, df=1, 83, p=0.4
HDL Cholesterol (nmol/l)	1.3±0.1	1.3±0.1	t=0.1, df=1, 82, p=0.9
LDL Cholesterol (nmol/l)	2.9±0.1	2.8±0.2	t=−0.8, df=1, 81, p=0.4
hsCRP (mg/dl)	0.7±0.2	0.2±0.1	t=−2.3, df=1, 84, **p=0.044**
Leptin	17.1±3.4	11.7±3.9	t=−1.0, df=1, 62, p=0.3
No. of childhood trauma	1.0±0.2	0.7±0.1	t=−1.6, df=1, 71, p=0.1
No. of recent stressful events	2.3±0.3	1.3±0.2	t=−2.9, df=1, 77, **p=0.006**
Perceived Stress Scale	20.7±1.4	13.1±1.0	t=−4.6, df=1, 77, p<0.001