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Association between leptin levels and severity of suicidal behaviour in schizophrenia spectrum disorders

Gohar SM, Dieset I, Steen NE, Mørch RH, Vedal TSJ, Reponen EJ, Steen VM, Andreassen OA, Melle I. Association between leptin levels and severity of suicidal behaviour in schizophrenia spectrum disorders.

Objective: Associations between suicidality and lipid dysregulation are documented in mental illness, but the potential role of leptin remains unclear. We examined the association between leptin and suicidal behaviour in schizophrenia, together with the influence of other clinical and biological indices.
Method: We recruited a sample of 270 participants with schizophrenia spectrum diagnoses. Blood samples were analysed for leptin, while symptom severity was assessed by Positive and Negative Syndrome Scale (PANSS) and Inventory of Depressive Symptomatology (IDS-C). Patients' history of suicidal behaviour was categorized into three subgroups based on IDS-C suicide subscale: No suicidal behaviour, mild/moderate suicidal behaviour and severe suicidal behaviour with/without attempts.
Results: Mild/moderate suicidal behaviour was present in 17.4% and severe suicidal behaviour in 34.8%. Both groups were significantly associated with female gender (OR = 6.0, $P = 0.004$; OR = 5.9, $P = 0.001$), lower leptin levels (OR = 0.4, $P = 0.008$; OR = 0.5, $P = 0.008$) and more severe depression (OR = 1.2, $P < 0.001$; OR = 1.1, $P < 0.001$) respectively. Smoking (OR = 2.6, $P = 0.004$), younger age of onset (OR = 0.9, $P = 0.003$) and less use of leptin-increasing medications (OR = 0.5, $P = 0.031$) were associated with severe/attempts group, while higher C-reactive protein CRP (OR = 1.3, $P = 0.008$) was associated with mild/moderate group.
Conclusion: Lower leptin levels were associated with higher severity of suicidal behaviour in schizophrenia.

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Key words: suicide; schizophrenia; depression; leptin; lipid

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Significant outcomes

- After adjusting for potential confounding factors (i.e. age, sex, BMI, smoking, and medications), the association between leptin and severity of suicidal behaviour remained significant. The finding suggests potential biological mechanisms in the development of suicidal behaviour that should be followed up in future studies.
- Increased risk of suicidal behaviour (both moderate and severe groups) was associated with female gender, smoking, early age of onset and severe depression.
- Lower use of psychotropic medications that are known to increase leptin levels (i.e. clozapine, olanzapine, quetiapine and mirtazapine) was associated with severe suicidal behaviour.

Limitations

- The study was observational with a cross-sectional design, and we can neither assume the direction of the association between leptin and suicidal behaviour nor conclude regarding causality.
- The lack of a detailed psychometric test assessing suicidality prevents us from in-depth exploration of associations to other phenomena, such as the risk of violent suicide.
- We have not included a healthy control group since suicidal behaviour is sporadic in the healthy general population.

Introduction

Patients with schizophrenia have significantly higher mortality rates than the general population (1), with a recent systematic review estimating an average of 14.5 years of potential life lost (2). Lifetime suicide risk in schizophrenia is estimated to be around 4.9% (3). The proportion of increased mortality rates attributable to suicide, however, varies across different studies, from 0% to 46% of all causes of death (4). Since suicidal behaviour is highly complex phenomenon, many studies have investigated both clinical and biological risk factors for suicide in this patient group.

Interestingly, some clinical risk factors for suicide were found to be disease-specific while others were similar to those found in the general population (5). The systematic review of Hor and Taylor (6) identified 51 studies concerning risk of suicide in schizophrenia published since 2004. The authors highlighted several common and disease-specific clinical factors with strong evidence of increased risk, and these included depressive symptoms, the presence of active positive symptoms, lower level of negative symptoms, the presence of insight, comorbid substance use, past individual and family history of suicide.

Studies of potential biological risk factors for suicide in general over the last two decades have included investigations of the role of inflammatory cytokines and lipid dysregulation. A recent systematic review of 22 studies indicated that elevated interleukin-6 (IL-6) and reduced IL-2 were observed in patients with suicide attempts (7). Wu and colleagues conducted a meta-analysis including 65 studies, highlighting the potential role of lipid dysregulation. The authors found significantly lower serum levels of total cholesterol (TC) and low-density lipoproteins (LDL) in suicidal patients compared to non-suicidal patients and healthy controls (8). These findings highlight the possible underlying role of lipid disturbances in the pathophysiology of suicide in schizophrenia.

Leptin is a peptide hormone synthesized mainly from adipose tissue. From its discovery by Zhang and colleagues (9) in 1994, the effects of leptin on the brain were initially seen as limited to the homeostatic regulation of feeding and energy consumption through its action on hypothalamus (10, 11). Recently, it has become clear that leptin has many other brain regulatory functions that also involve neuroendocrine, neuroinflammatory and neurodevelopmental processes (12–14). These functions are mainly mediated through the widely distributed leptin receptors in the human brain, located in the hypothalamic nuclei, hippocampus, amygdala and cortex (15). Leptin receptors are also present throughout the hypothalamic–pituitary–adrenal (HPA) axis, an important area for regulation of stress and emotional response (16). Moreover, leptin has been hypothesized to exert modulatory actions on both dopaminergic and serotonergic systems (17, 18).

These emerging findings from preclinical studies have encouraged research on potential links between leptin dysregulation and clinical psychopathology (19), including studies of the association between serum leptin levels and symptom profiles of schizophrenia. The results are however conflicting. A few studies show that leptin levels are increased, not only in patients using atypical antipsychotics (20) but also in drug-free (21) and drug naive subjects (22). However, another study reported decreased leptin levels in patients with schizophrenia, particularly in patients with severe suicidal behaviour i.e. suicide attempts (23). The role of leptin, a potential lipid-regulation associated biomarker, has however been infrequently investigated in suicide research.

Aims of the study

The current study has the primary aim to investigate the association between leptin levels and suicidal behaviour in a representative clinical sample of patients with schizophrenia spectrum disorders, to test the hypothesis that lower levels of serum leptin are associated with increased severity of suicidal behaviour. A secondary aim is to assess other potential clinical and biological indices that could be associated with suicidal behaviour in the sample.

Material and methods

Participants

Subjects were recruited through the ongoing Norwegian Thematically Organized Psychosis (TOP) study. The project started in 2003 as a multicentre study involving the major hospitals of greater Oslo and is approved by the Regional Committee for Medical Research Ethics. Inclusion criteria are being 18–65 years of age, meeting the diagnostic criteria for schizophrenia and bipolar disorders according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) and being able and willing to give a written informed consent to participate. Participants with a history of significant head injury, neurological

disorder, mental retardation and autoimmune disease were excluded.

For the present study, we included only subjects with a diagnosis of schizophrenia and other psychotic disorders diagnosed according to DSM-IV with available serum leptin measurements. We then excluded patients with C-reactive protein (CRP) above 10 mg/L (n = 31) and with missing data for the main research question of the study (i.e. symptoms scales and information about suicidal behaviour) from the analyses. The final sample consisted of 270 participants with the following diagnostic distribution: schizophrenia (n = 145), schizoaffective disorder (n = 43), schizophreniform disorder (n = 13) and psychosis not otherwise specified (NOS; n = 69).

Clinical variables

Sociodemographic and clinical data were collected from clinical interviews and medical records. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used to confirm the diagnosis (24). We calculated duration of illness as the age at time of the inclusion minus the age of onset of the first psychotic episode. Standardized procedures were used for physical examination that included height, weight and body mass index (BMI). The following psychometric rating scales were used to assess symptom severity: the Structured Interview for the Positive and Negative Syndrome Scale (PANSS) (25) and clinician-rated Inventory of Depressive Symptomatology (IDS-C) (26). The grouping of patients based on the severity of suicidal behaviour was derived from IDS-C item 18 on suicide with the addition of information about a history of at least one-lifetime suicidal attempt from the clinical interviews and hospital records.

Item 18 of IDS-C measures suicidal severity using a four-point scale (0–3). Here, (0) is scored for those who do not think of suicide or death; (1) is scored for those who feel that life is empty or is not worth living; (2) is scored for those who thinks of suicide/death several times in a week; and finally, (3) is scored for those who thinks of suicide/death several times a day, or has suicidal plans or suicidal attempts. Based on this and lifetime history of attempts, we categorized the patients into three subgroups: no suicidal behaviour (score = 0 on IDS-C/item 18 and no history of attempts), mild to moderate suicidal behaviour (score from 1 to 2 on IDS-C/item 18 and no history of attempts) and severe suicidal behaviour with or without attempts (score = 3 on IDS-C/item 18 and at least one history of attempt) henceforth 'severe suicidal behaviour'.

Biochemical variables

Fasting venous blood samples were obtained in the morning. Measurement and analysis of total cholesterol (TC), triglyceride (TG), low-density lipoproteins (LDL) and standard C-reactive protein (CRP) were conducted at the Department of Medical Biochemistry, Oslo University Hospital. Leptin concentrations were measured using ^{125}I-labelled human leptin radioimmunoassay (HL-81K Kit; EMD Millipore Corporation) and analysed at the Hormone Laboratory, Department of Endocrinology, Aker University Hospital.

Medications

Studies have reported that psychotropic medications may increase leptin levels, in particular, olanzapine, clozapine, quetiapine and mirtazapine (27–29). In order to adjust for potential confounding effects of psychotropic medications in the statistical analysis, we used data from the clinical interview and medical records together with measurements of the serum level of different antipsychotic drugs. Based on this, we dichotomized the sample into two subgroups: the group using psychotropic medications affecting leptin (olanzapine, clozapine, quetiapine and mirtazapine) vs. the group using other psychotropic medications/not using any psychotropic medications.

Statistical analysis

The data were analysed using the statistical package for Social Sciences (IBM Corp. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp., 2016). The statistical significant level was preset to $P < 0.05$ (two-tailed). Variables were presented as numbers (percentages) or means ($\pm$ standard deviation) as appropriate. Substitution with mean was used for missing data for years of education (five patients missing this information). Leptin levels were log-transformed for all analyses due to markedly skewed distribution. To investigate the association between leptin and suicidal behaviour, with other sociodemographic, clinical and biochemical characteristics, we started out investigating their bivariate associations using Pearson's r for normally distributed continuous variables as shown in Table 2. We then used multivariate multinomial logistic regression to estimate the odds ratio (OR) of being in the mild to moderate or the severe suicidal groups respectively, compared to the no suicidality group. We included all potential covariates with known clinical associations to suicidal behaviour or to

variation in leptin levels according to previous studies, in addition to those showing significant bivariate associations with both leptin and suicidal behaviour in our current sample. (i.e. age, gender, daily tobacco smoking, BMI, age of onset, medication affecting leptin, IDS – C total score without suicide item 18 and CRP; Table 3). Lipid measures (i.e. TC, TG and LDL) were not entered into the multivariate analysis to avoid potential multicollinearity issues since they were highly correlated with BMI and CRP. We then added (log) leptin levels at the last step of the multivariate analysis. To illustrate the distribution of (log) leptin levels across groups, adjusted for covariates, we used an analysis of covariance (ANCOVA) to produce adjusted means for the error bar graph shown in Fig. 1.

Results

Two hundred seventy patients with schizophrenia spectrum disorders were participated, out of whom 161 (59.6%) were male. Mean age was 30.7 (±10.1) and duration of illness was 8.2 (±8.4) years. Around half of the patients (52.2%) had either mild or severe suicidal behaviour. Their demographic, clinical and biochemical characteristics are shown in Table 1.

In the bivariate analyses, we found serum leptin levels to be positively and statistically significantly correlated with female gender ($r = 0.5$, $P < 0.001$), BMI ($r = 0.5$, $P < 0.001$), lipid levels [TC ($r = 0.2$, $P < 0.001$); LDL ($r = 0.2$, $P = 0.004$); TG ($r = 0.2$, $P = 0.001$)] and CRP ($r = 0.4$, $P < 0.001$). Severity of suicidal behaviour was positively correlated with female gender ($r = 0.2$, $P = 0.011$), daily tobacco smoking ($r = 0.2$, $P = 0.002$), positive symptoms ($r = 0.2$, $P = 0.001$), depression ($r = 0.3$, $P < 0.001$), negatively correlated with age of onset ($r = -0.3$, $P < 0.001$) and use of psychotropic drugs that are known to increase leptin level ($r = -0.1$, $P = 0.019$) (Table 2).

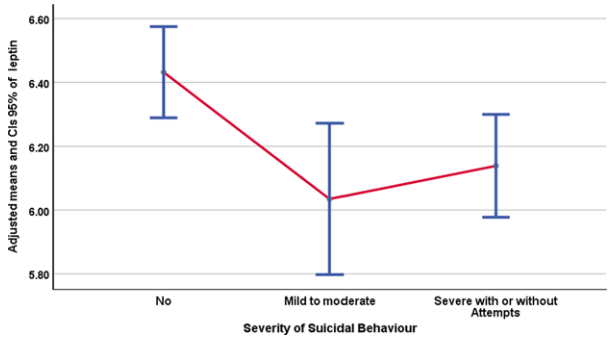

Fig. 1. Error bar graph of adjusted leptin levels in relation to severity of suicidal behaviour.

Table 1. Descriptive characteristics of the sample

	$N = 270$
Age (years), *M* (SD)	30.7 (10.1)
Male sex, *n* (%)	161 (59.6)
Education (years), *M* (SD)	12.8 (2.9)
Caucasian ethnicity, *n* (%)	218 (80.7)
Daily tobacco smoking, *n* (%)	157 (58.1)
Age of onset (years), *M* (SD)	22.6 (8.6)
Schizophrenia spectrum diagnoses, *n* (%)	
Schizophrenia	145 (53.7)
Schizophreniform	13 (4.8)
Schizoaffective	43 (15.9)
Psychosis NOS	69 (25.6)
Psychotropic medications, *n* (%)	
Use on regular basis	328 (88.2)
Psychotropic medications affecting leptin*	141 (37.9)
PANSS – positive, *M* (SD)	15.1 (5.1)
PANSS – negative, *M* (SD)	15.8 (6.4)
IDS-C total, *M* (SD)	19.3 (12.6)
Suicidal behaviour†, *n* (%)	
No	129 (47.8)
Mild to moderate	47 (17.4)
Severe with or without attempts	94 (34.8)
BMI (kg/m^2), *M* (SD)	26.1 (5.1)
Total cholesterol (mmol/l), *M* (SD)	5.3 (1.1)
LDL (mmol/l), *M* (SD)	3.2 (1.0)
Triglyceride (mmol/l), *M* (SD)	1.5 (0.9)
Leptin‡(mg/l), *M* (SD)	6.3 (1.0)
CRP (mg/dl), *M* (SD)	3.3 (2.8)

BMI, body mass index; CRP, C-reactive protein; IDS-C, Inventory of Depressive Symptomatology clinician-rated; LDL, low-density lipoproteins; *M*, mean; NOS, not otherwise specified; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

*Psychotropic medications affecting leptin are clozapine, olanzapine, quetiapine and mirtazapine.

†Suicidal behaviour is classified according to item 18 in IDS-C and lifetime history of suicidal attempts.

‡log-transformed leptin score.

The multivariate multinomial logistic regression analysis showed that female gender (OR = 6.00, 95% CI = 1.8–20.5; OR = 5.9, 95% CI = 2.2–16.0 respectively) and higher depressive symptoms (OR = 1.2, 95% CI = 1.1–1.2; OR = 1.1, 95% CI = 1.0–1.1 respectively) statistically significantly increased the risk of being in the mild to moderate or severe suicidal behaviour groups (compared to the no suicidal behaviour group).

Importantly, lower levels of leptin also significantly increased the risk of being in the mild to moderate or severe suicidal behaviour groups (OR = 0.4, 95% CI = 0.2–0.8; OR = 0.5, 95% CI = 0.3–0.8 respectively). In addition, higher CRP levels (OR = 1.3, 95% CI = 1.1–1.5) increased the risk of being in the mild to moderate suicidal behaviour group, while daily tobacco smoking (OR = 2.6, 95% CI = 1.4–5.1), younger age of onset (OR = 0.9, 95% CI = 0.9–1.0) and less use of medications affecting leptin (i.e. clozapine, olanzapine, quetiapine or mirtazapine; OR = 0.5, 95% CI = 0.3–0.9) increased the risk of

Table 2. Bivariate associations of leptin and suicide

	Leptin†	Suicidal behaviour‡
Age	0.1	−0.1
Female sex	0.5**	0.2*
Daily tobacco smoking	−0.1	0.2**
Medication affecting leptin§	0.0	−0.1*
BMI	0.5**	−0.1
Age of onset	−0.0	−0.3**
PANSS – positive	−0.1	0.2**
PANSS – negative	−0.0	0.0
IDS – C¶	0.1	0.3**
TC	0.2**	−0.1
LDL	0.2**	−0.1
TG	0.2**	0.0
CRP	0.4**	0.0

BMI, body mass index; CRP, C-reactive protein; IDS-C, Inventory of Depressive Symptomatology clinician-rated; LDL, low-density lipoprotein; PANSS, Positive and Negative Syndrome Scale; TC, total cholesterol; TG, triglyceride.

*$P < 0.05$, **$P < 0.01$

†log-transformed leptin score.

‡Suicidal behaviour is classified according to item 18 in IDS-C and lifetime history of suicidal attempts.

§Psychotropic medications affecting leptin are clozapine, olanzapine, quetiapine and mirtazapine.

¶IDS – C total score without suicidal ideation item 18.

Table 3. Multinominal logistic regression analysis

	B (SE)	Wald	Odds Ratio	95% CI Lower	95% CI Upper
Suicidal behaviour (mild to moderate) vs. None					
Intercept	0.2 (1.7)				
Age	−0.0 (0.0)	0.7	1.0	0.9	1.0
Female sex	1.8 (0.68)	8.2**	6.0	1.8	20.5
Daily tobacco smoking	0.2 (0.4)	0.1	1.2	0.5	2.8
BMI	0.0 (0.1)	0.6	1.1	0.9	1.2
Age of onset	0.0 (0.0)	0.1	1.0	1.0	1.1
Medication affecting leptin	−0.7 (0.4)	2.8	0.5	0.2	1.1
CRP	0.2 (0.1)	7.0**	1.3	1.1	1.5
IDS-C total (without suicide item 18)	0.1 (0.0)	47.7**	1.2	1.1	1.2
Leptin	−0.9 (0.4)	7.0**	0.4	0.2	0.8
Suicidal behaviour (severe and/or attempts) vs. None					
Intercept	1.9 (1.3)				
Age	0.0 (0.0)	0.1	1.0	1.0	1.1
Female sex	1.8 (0.5)	12.1**	5.9	2.2	16.0
Daily tobacco smoking	1.0 (0.3)	8.1**	2.6	1.4	5.1
BMI	0.1 (0.1)	1.1	1.1	1.0	1.2
Age of onset	−0.1 (0.0)	8.8**	0.9	0.9	1.0
Medication affecting leptin	−0.7 (0.3)	4.7*	0.5	0.3	0.9
CRP	0.1 (0.1)	1.2	1.1	0.9	1.2
IDS-C total (without suicide item 18)	0.1 (0.0)	18.5**	1.1	1.0	1.1
Leptin	−0.7 (0.3)	7.0**	0.5	0.3	0.8

$R^2 = 0.4$ (Cox & Snell), 0.4 (Nagelkerke). Model χ^2 (18) = 127.2, $P < 0.001$

BMI, body mass index; CRP, C-reactive protein; IDS-C, Inventory of Depressive Symptomatology clinician-rated.

*$P < 0.05$, **$P < 0.01$

being in the severe suicidal behaviour group. The pseudo-R^2 (Cox and Snell) for the analysis was 0.38, and the detailed regression weights are found in Table 3.

Finally, participants with both mild to moderate and severe suicidal behaviour had significantly lower adjusted levels of leptin compared to participants with no suicidal behaviour [F (2, 260) = 4.75, $P = 0.009$, partial $\eta^2 = 0.035$]. Adjusted means and 95% CIs error bar of adjusted leptin levels for the suicide severity groups are shown in Fig. 1.

Discussion

The main finding of the current study is that lower levels of leptin were associated with increased risk of suicidal behaviour in schizophrenia spectrum patients, also after adjusting for age, sex, smoking, BMI and psychotropic medications affecting leptin. This finding is in line with previous findings of Atmaca and colleagues, who reported lower levels of leptin in schizophrenia patients with suicidal attempts, compared to patients without attempts (23) and in patients with severe mental disorders and suicide attempts compared to healthy controls (30) respectively.

The contradictory findings concerning leptin levels and suicidal behaviour in schizophrenia from other previous studies could be explained by the potential confounding influence of factors (i.e. age, sex, BMI, dietary habits, smoking, age of onset and duration of illness) that may act on leptin levels in both mentally ill patients and healthy individuals (31–34). We here, however, found that lower leptin levels were significantly associated with moderate and severe suicidal behaviour (compared to no suicidal behaviour) also after adjustments for these factors.

A relationship between depression, suicidal behaviour and low brain leptin has previously been found in analyses of cerebral venous blood in patients with major depressive disorders and mRNA from post-mortem CNS tissue from patients with completed suicide (35). Recent and emerging evidence supports the notion that leptin could be an essential component of the pathophysiology of depression and suicide (36). First, the presence of leptin receptors in brain areas closely related to depression neurobiology such as the amygdala and the hippocampus, together with the potential hippocampal synaptic neuroplasticity induced by leptin documented in recent animal studies, supports this hypothesis (37). Second, it has been suggested that leptin has a modulatory

effect on HPA axis activity in the hypothalamus and subsequently affect response to stress (16). Third, evidence from animal studies shows a potential modulatory role of leptin on serotonin through its action on nitric oxide synthase (NOS) and nitric oxide (NO) production, which could affect serotonin reuptake (38) and activation (39). In addition, NO levels are found to be high in schizophrenia (40). The lack of inhibitory effects of leptin on NO could aggravate the serotonin dysregulation in schizophrenia in turn affecting mood, impulsivity and self-regulation. Thus, the serotonergic pathway, in particular, could be considered the main pathophysiological link between leptin, mood, psychotic disorders and associated suicidal behaviour (41).

Furthermore, the interaction between adiposity and inflammation has been linked to leptin in several studies on depression (42). Interestingly, our finding supports this potential link and extends it to suicidal behaviour. We found that leptin levels were significantly positively correlated with CRP and BMI, and that CRP was associated with mild to moderate suicidal behaviour. The lack of any direct association between suicidal behaviour and BMI in our sample could be understood in terms of the recent findings of population-based studies. These studies indicated that suicidal behaviour is higher among underweight individuals (BMI < 20 kg/m^2) and people with extreme obesity (BMI ≥ 35 kg/m^2) which indicate a U-shaped or curvilinear relationship (43, 44). This complex type of relationship is difficult to investigate in our sample, which mainly comprised individuals with an average BMI with a few overweight exceptions.

It is noteworthy that the use of specific psychotropic medications (i.e. clozapine, olanzapine, quetiapine and mirtazapine) could increase leptin levels (28, 29). One of the interesting findings from our analyses is that less use of these medications was associated with severe suicidal behaviour. Clozapine is the only antipsychotic drug that has US Food and Drug Administration (FDA) approval for treatment of suicidal behaviour (45), at the same time as clozapine use is associated with weight gain and increased leptin levels (46). This finding raises the possibility of a potential pathophysiological role of leptin in suicidal behaviour processes, linked to other underlying mechanisms such as adiposity and inflammation, which needs further investigation.

Major strengths of this study include the well-characterized and representative sample of schizophrenia spectrum disorders patients, together with the detailed clinical, biochemical and medication records that allowed us to adjust for potential confounders adequately. Major limitations are the cross-sectional design that does not allow us to conclude about the directionality of the association between leptin and suicidality. Moreover, the lack of specific psychometric assessment of suicidality and its related aspects prevent us from exploring in-depth associations including the use of violent means in attempts (30). Finally, we did not include healthy controls in the current study, as they have very low levels of suicidal behaviour and the main research question is targeting the association between leptin levels and suicidal behaviour.

In summary, this study indicates an inverse association between leptin and severity of suicidal behaviour in schizophrenia. Proper assessment of depression together with the use of psychotropic drugs affecting leptin could have a beneficial role in the management of suicide risk. Future studies should explore the interaction between leptin and inflammation, and its potential link to suicide, with particular emphasis on the role of depressive symptomatology. A better understanding of the complex phenomenon of suicidal behaviour is essential to improve prognosis and long-term outcome of schizophrenia spectrum disorders.

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Declaration of interest

OAA has received speaker's honorarium from Lundbeck. All other authors declare no conflicts of interest.

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