



# A prospective study of lipids and serotonin as risk markers of violence and self-harm in acute psychiatric patients

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## ABSTRACT

Cross-sectional studies have reported an association between lipids and serotonin levels and aggression, but a literature search revealed a paucity of prospective studies. Subjects of the present naturalistic study were 254 of all (489) involuntary and voluntary acutely admitted patients to a psychiatric hospital during 1 year. Serum lipids and platelet serotonin at admission were prospectively compared with recorded intra-institutional and 1-year post-discharge violence and self-harm. Total cholesterol had a significant negative relationship to inpatient suicidal behaviour and inpatient violent behaviour and to 3-month post-discharge violent behaviour. Triglycerides were a significant marker of inpatient self-mutilation and of self-mutilation in combination with suicidal behaviour at 3 and 12 months of follow-up. High-density lipoprotein (HDL) had a significant negative relationship to violence at 12-months, and to repeated violence in seven patients with two or more admissions. The post-discharge relationships between total cholesterol and violence and between triglycerides and self-harm remained significant even when controlling for other possible explanatory variables in a multivariate model. Results did not change after controlling for current medication at admission. There was no association between platelet serotonin and violence or self-harm. Future research may examine if lipid measurements add incremental validity to established clinical risk assessment procedures of violent and self-harm behaviour.

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## 1. Introduction

A significant association between low cholesterol concentrations and violence has been found across many types of studies (Golomb, 1998; Hillbrand and Spitz, 1999). In a health-screening project, low cholesterol was associated with increased criminal behaviour (Golomb et al., 2000). Studies in psychiatric settings have given similar results (Mufti et al., 1998; Hillbrand et al., 2000; Paavola et al., 2002; Diaz-Sastre et al., 2007). Serum cholesterol has been shown to be lower in suicidal attempters than in non-attempters (Kunugi et al., 1997; Florkowski et al., 2001; Lee and Kim, 2003; Veveva et al., 2003; Peres-Rodriguez et al., 2008) and in violent attempters compared with non-violent (Atmaca et al., 2003; Atmaca et al., 2008). An association between low cholesterol and impulsive violence or impulsive suicidal attempts has been shown by several authors (Paavola et al., 2002; Veveva et al., 2003; Agargun et al., 2004). Increased cholesterol levels have been found in premeditated aggression in contrast to decreased cholesterol in impulsive aggres-

sion and anxiety (Agargun, 2002; Conklin, 2006; Conklin and Stanford, 2008).

Lower cholesterol and platelet serotonin concentrations were found in suicide attempters characterised by violence and impulsiveness (Alvarez et al., 1999; Crowell et al., 2008). In another study, self-harm patients had significantly lower mean total cholesterol than controls, but platelet serotonergic measures did not differ (Garland et al., 2007).

Aggression is often categorised as either 'premeditated' (predatory, instrumental) or 'impulsive' (reactive, affective) (Meloy, 2006; Siever, 2008). Insufficient serotonergic facilitation of 'top-down' control including the 5-hydroxytryptamine<sub>2A</sub> receptors (Coccaro et al., 1997; Krakowski et al., 2006) and 5-HT<sub>2C</sub> receptors (Winstanley et al., 2004), catecholaminergic stimulation, the gamma aminobutyric acid (GABA)-glutamatergic system (Lievig et al., 2008) and pathology in neuropeptide systems (Coccaro et al., 1998; Kirsch et al., 2005; Coccaro et al., 2007a,b; Hermans et al., 2008; Ditzen et al., 2009) may contribute to this. Heredity contributes substantially to impulsive aggression (Beitchman et al., 2006; Marks et al., 2007; Mann et al., 2009). In most hypotheses, low cholesterol is related to low serotonin and, in turn, linked to violence, suicidal behaviour and impulsivity (Siever, 2008).

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A search of the literature revealed that prospective studies are scarce (Deisenhammer et al., 2004; Fiedorowicz and Coryell, 2007) and that there seems, in particular, to be a paucity of studies conducted in acute psychiatric wards (psychiatric emergency wards). The scope of our prospective study was to examine serotonin and lipids as risk markers of violent and self-harm behaviour in patients admitted to an acute psychiatric ward over a 1-year period.

## 2. Methods

### 2.1. Setting and population

The design was a naturalistic observational inpatient and outpatient follow-up study at the acute psychiatric ward at Aalesund Hospital in Norway, with a catchment area of 125 000 persons. All acute admitted involuntary and voluntary patients from 7 March 2006 to 7 March 2007, (489 patients with 716 hospitalisations) were asked to participate. A total of 254 (52%) of these patients gave written consent and were included for the inpatient part of the study, while 199 (41%) were followed up and 55 (11%) were dropouts after discharge. Demographic characteristics are shown in Table 1.

### 2.2. Procedure

Patients were given verbal and written information about the project from the ward staff shortly after admission. Consenting patients gave a fasting blood sample during the following 1–3 days. The ward staff recorded violent and self-harm episodes during the hospital stay.

Follow-up at 3, 6, 9 and 12 months after discharge was carried out by patients' therapists at outpatient psychiatric clinics or at district psychiatric wards. Violent and self-harm episodes were recorded during the 0–3, 4–6, 7–9 and 10–12 months' periods, respectively. Patients discharged to the community were monitored by their psychiatric nurse at the acute ward. Laboratory results were blinded to the recording staff during hospital stay and after discharge. Information was gathered from patients and collaterals, and the research leader systematically obtained information from inpatient and outpatient hospital records. Data of occurred violence were also collected from criminal records. If patients were readmitted to the acute ward during the study period, their trial files were closed after occurred violent and self-harm episodes in that

post-discharge period were recorded. Patients were then included with new file numbers and so on with further re-admissions.

### 2.3. Baseline measures

Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TGs) were measured in mmol l<sup>-1</sup> in fasting blood serum. The fasting period was from 12 PM until blood was drawn at 08–09 AM the next morning. Lipids were analysed at the hospital laboratory with a reflexion photospectrometric method (VITROS 5.1 FS). Platelets in platelet-rich plasma from citrated whole blood were counted before samples were prepared for serotonin determination. Two parallels from each sample of platelet-rich plasma were analysed. The mean of the two parallels was used in further application. Proteins in the samples were precipitated by perchloric acid in 1,4-Dithiothreitol; the supernatant was neutralised with K<sub>2</sub>HPO<sub>4</sub> and kept frozen at –80 °C until liquid-chromatographic analyses for serotonin at Haukeland University Hospital, Bergen (Ingebretsen et al., 1985; Hervig et al., 1999).

Information concerning gender, age, hospital stay, current medication, substance abuse at admittance, judicial status at admission and discharge and International Classification of Diseases (ICD)-10 diagnoses at discharge was obtained from hospital records and included as demographic variables.

### 2.4. Outcome measures

Outcome measures were occurred incidents of violent, suicidal and self-mutilating threats and acts. 'Violent threat' was operationally defined as a verbal or non-verbal communication conveying a clear intention to inflict physical injury upon another person, and 'physical assaults', as the intended infliction of bodily injury upon another person (Monahan et al., 2005; Dean et al., 2006). 'Self-harm' was defined correspondingly: 'suicidal behaviour', to inflict physical injury upon oneself with the intention to kill oneself, and 'self-mutilation', to inflict physical injury upon oneself without the intention to kill oneself (Huth-Bocks et al., 2007). Post-discharge recordings categorised violent and self-harm physical assaults into less severe acts (kicks, blows without injuries and self-harm without need of hospitalisation) and severe acts (weapons use, arson, assaults causing injuries and self-harm followed by hospitalisation or fatality). All were scored as "No occurred episodes", "Yes – episodes have occurred" or "Don't know if episodes have occurred." The recording sheet contained a scoring guide for every item. Prior to the study, staff at all sites was trained in recording violent and self-harm behaviour.

### 2.5. Statistics

Data were analysed by using SPSS version 16.0. Statistics were computed for hospital stay and for discharged patients at the four measurement points at 3, 6, 9 and 12 months. Results are only presented for the 0–3- and 0–12-months' periods because including the second and third measurement points did not significantly change the results.

"Don't know" answers in the recording schemes were handled as missing and excluded. One person could only belong to one category of severity of violence, self-mutilation or suicidal behaviour; if episodes of more than one category were recorded (e.g., threats and less severe acts), the most severe category for each of the three main outcome measures was chosen.

For patients with more than one hospitalisation with blood sampling, the inpatient and post-discharge period with the most severe episode of violence, self-mutilation and suicidal behaviour was chosen. If two or more episodes with similar severity had occurred, the first episode was chosen as a positive identification of violence or self-harm for the analysis.

In each of the main outcome variables (violent behaviour, suicidal behaviour and self-mutilation), the episodes of threats and physical acts were combined into one dichotomous variable to enhance statistical power. Patients were entered into the outpatient part of the project if recorded at least at one of the four follow-up points.

Chi-square tests were used for categorical and *t*-tests and Mann–Whitney tests for continuous variables. The area under the curve (AUC) of the receiver operating characteristic (ROC) analysis was used to assess the predictive validity of lipids and serotonin. The AUC is less dependent on the base rate of the outcome variable and has been considered suitable to validate risk predictions (Rice and Harris, 1995; Douglas et al., 1999; Buchanan, 2008). Logistic regression was used for effect size measures in uni- and multivariate analysis. The 'pseudo R<sup>2</sup>' approximations of Cox and Snell and Nagelkerke were used as lower and upper estimates of the explained variance or 'model fit' (Brace et al., 2006), that is, how much of the total outcome that can be explained by the predictor(s). R<sup>2</sup> estimates in logistic regression are not as accurate as in linear regression, and their use has been questioned. However, they can be used to compare predictors in the same data set (Hosmer and Lemeshow, 2000). Other prediction estimates were positive predictive value (PPV), negative predictive value (NPV) and numbers needed to detain (NND: how many patients have to be detained for every true violent or self-harm patient identified). NND corresponds to number needed to treat. PPVs, NPVs and NNDs were computed for two cut-off values: (1) the mean concentration, and (2) an 'optimal' cut-off using the concentration with the highest (sensitivity + specificity) sum in exploratory ROC analyses.

The project was approved by the Norwegian Social Science Data Services, the Regional Committee for Medical Research Ethics and the Ministry of Health and Care.

**Table 1**

Comparison between inpatients consenting to give a blood sample and non-consenters, and between post-discharge followed up and missing.

	Inpatient = 489			Post-discharge consenting = 254		
	Consent	Not cons.	<i>p</i> -value	Follow-up	Missing	<i>p</i> -value
	<i>n</i> = 254	<i>n</i> = 235		<i>n</i> = 199	<i>n</i> = 55	
Male/female%	54/46	54/46	0.938	52/48	60/40	0.328
Mean age years	43.5	45.6	0.242	42.5	46.9	0.018
Hospital stay, mean/median <sup>1</sup>	20/13	14/5	0.006 <sup>3</sup>	21/14	16/12	0.270
Violent inpatients	6.7%	8.0%	0.328	9.0%	0	0.016
Suicidal inpatients	3.4%	0	0.015	4.4%	0	0.115
Self-mutilation inpatients	2.4%	0	0.062	2.9%	0	0.198
Involuntary admitted	18%	26%	0.035	18%	16%	0.706
Mandatory aftercare	6.3%	10%	0.162	6.7%	5.3%	0.702
F10-19 substance abuse	16%	16%	0.982	15%	16%	0.761
F20-29 psychotic disorders	14%	20%	0.062	16%	7.3%	0.126
F30-31 bipolar disorders	14%	9.3%	0.094	17%	3.6%	0.013
F32-39 <sup>2</sup> depressive disorders	31%	20%	0.004	29%	38%	0.217
F40-49 anxiety disorders	19%	17%	0.453	17%	27%	0.097
F60-62 personality disorders	6.0%	4.7%	0.555	6.1%	5.5%	0.860
Other diagnostic groups	4.0%	15%	<0.001	3.0%	7.3%	0.156

Fx = Main diagnostic groups according to ICD-10 (*The ICD-10 Classification of Mental and Behavioural Disorders, Clinical Description and Diagnostic Guidelines* 1992), <sup>1</sup> All admittances included, <sup>2</sup> F34.0 and F38.0 not included, <sup>3</sup> MannWhitney *U* = 16865.

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