Low cholesterol level as a risk marker of inpatient and post-discharge violence in acute psychiatry – A prospective study with a focus on gender differences

Bjørn Magne S. Eriksen[a,b,*], Stål Bjørkly[c,d], Øyvind Lockertsen[a,e], Ann Færden[a], John Olav Roaldset[c,f,g]

[a] Oslo University Hospital, Division of Mental Health and Addiction, Acute Psychiatric Section, Oslo, Norway

[b] University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Oslo, Norway

[c] Oslo University Hospital, Centre for Research and Education in Forensic Psychiatry, Oslo, Norway

[d] Molde University College, Molde, Norway

[e] Oslo and Akershus University College of Applied Sciences, Faculty of Health Sciences, Department of Nursing and Health Promotion, Oslo, Norway

[f] Ålesund Hospital, Møre & Romsdal Health Trust, Psychiatric Department, Ålesund, Norway

[g] The Norwegian University of Science and Technology, NTNU, Trondheim, Norway

[*] Corresponding author at: Oslo University Hospital, Division of Mental Health and Addiction, Acute Psychiatric Section, P.O. Box 4956 Nydalen, N-0424 Oslo, Norway. Tel: +4722118420, Fax: +4722118470, Mob: +4797068315

E-mail address: b.m.s.eriksen@medisin.uio.no

Abstract

Several studies indicate an association between low levels of serum cholesterol and aggressive behaviour, but prospective studies are scarce. In this naturalistic prospective inpatient and post-discharge study from an acute psychiatric ward, we investigated total cholesterol (TC) and high-density lipoprotein (HDL) as risk markers of violence. From March 21, 2012, to March 20, 2013, 158 men and 204 women were included. TC and HDL were measured at admission. Violence was recorded during hospital stay and for the first 3 months post-discharge. Univariate and multivariate binary logistic regression were used to estimate associations between low TC and low HDL and violence. Results showed that HDL level was significantly inversely associated with violence during hospital stay for all patients. For men, but not for women, HDL level was significantly inversely associated with violence the first 3 months post-discharge. Results indicate that low HDL is a risk marker for inpatient and post-discharge violence in acute psychiatry and also suggest gender differences in HDL as a risk marker for violence.

Keywords: HDL, total cholesterol, violence, risk assessment, emergency psychiatry, biomarkers

1. Introduction

Potential biological markers associated with psychiatric disorders, like mood disorders or psychotic disorders, or different types of aggressive behaviours (like violence or self-harm) have been identified during the last couple of decades (Kalia and Costa, 2015; Siever, 2008). Two examples of potential risk markers associated with violence are low levels of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL). TC is a measure of all the cholesterol transported in the blood stream and consists of cholesterol particles like HDL, low-density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons (Fielding and Fielding, 2008).

A positive association between low levels of TC and violence has been found in most previous studies, e.g. in a meta-analysis of 32 studies with different design (Golomb, 1998), in a large community cohort study (Golomb et al., 2000), and in studies from different areas of psychiatry (Asellus et al., 2014; Paavola et al., 2002; Roaldset et al., 2011a). When it comes to HDL, results have been more conflicting. In a study on personality disordered male cocaine addicts, significantly lower levels of HDL were found in patients with a history of aggression (Buydens-Branchey et al., 2000). In another study on 20 young adult males with a history of aggression and 40 controls, correlations between lower levels of antiatherogenic lipoproteins (HDL and Apo A-I) and aggression were found in the aggressive subjects, and between atherogenic lipoproteins (LDL and Apo-B) and aggression in the controls (Troisi and D'Argenio, 2006). In two of the studies mentioned earlier, Roaldset et al. (2011a) found a significant association between low HDL and post-discharge violence in acute psychiatry, while Paavola et al. (2002) found higher HDL in violent patients compared to controls in a study from forensic psychiatry. A recent study on schizophrenia inpatients found no significant associations between HDL and violence (Chen et al., 2015). Our literature search

on studies on TC, HDL and other cholesterol particles as risk markers for violence showed that prospective studies were rare.

Mechanisms of a possible connection between low levels of TC or other cholesterol particles and violence are not fully known. One main hypothesis of a possible biological mechanism which might explain the association is that low cholesterol levels in the central nervous system (CNS) may contribute to reduced transportation of serotonin through cholesterol-containing cell membranes. This may result in low levels of serotonin in the CNS and insufficient top-down control from the prefrontal cortex to the limbic structures of the brain, resulting in increased risk of affective and impulsive aggression (Engelberg, 1992; Siever, 2008; Wallner and Machatschke, 2009). Associations between low cholesterol levels and impulsivity in patients with mood symptoms were found in a recent study (Troisi, 2011). Buyidens-Branchery et al. (2000), who found an association between low HDL and a history of aggression, identified a significant association between low HDL and impulsivity in the same investigation.

Methods for violence risk assessments among psychiatric patients in use today consist solely of psychosocial risk factors and do not take knowledge of potential biological markers of aggression into account. Examples of psychosocial risk factors are psychotic disorders and symptoms, personality disorders, psychopathic traits, previous violence, low education level, violence-prone living conditions and unemployment. Two examples of existing methods in violence risk assessments are the Historical Clinical Risk Management-20 (HCR-20) Version 3 (Douglas et al., 2013), mainly used in forensic and long-term settings, and the Violence risk screening - 10 (V-RISK-10) (Hartvig et al., 2011; Roaldset et al., 2011b) used in acute and general settings. Singh and co-workers (2011) emphasized the need for research on alternative risk factors and risk markers for violence, including the use of potential biological markers of violence like TC and HDL, to improve existing risk assessment methods (Singh et al., 2011).

Acute settings are characterised by high patient turnover, short stays and time pressure, which underlines the importance of developing simple and rapid procedures for risk assessments. Taking a blood sample is often a routine procedure at admission, and results normally appear within a day. Using potential risk markers like TC or HDL to supplement existing procedures for violence risk assessments may therefore be quite easily integrated in the clinic's work. This underlines the need for prospective studies on the possible association between low cholesterol and future violence, especially from acute settings.

Violence is more common among men than women. One possible biological explanation is that male brains are larger and therefore they have been evolutionarily more vulnerable to low levels of serum cholesterol than female brains (Wallner and Machatschke, 2009). This may strengthen the link between low cholesterol levels and violence in men. A recent study of V-RISK-10 indicated that there may be gender differences concerning psychosocial risk factors of violence in acute psychiatry (Eriksen et al., 2016). In our literature search on studies of associations between different types of cholesterol and violence among psychiatric patients, we found only two studies that addressed gender differences (Asellus et al., 2014; Chen et al., 2015). Asselus and co-workers found no gender differences with respect to low TC levels as a risk marker of violence when examining association between exposure to childhood violence and violent behaviour as an adult. Chen et al. found that low TC levels in women added significant incremental validity to a psycho-social model of risk factors for violence.

In sum, research findings indicate that there may be an association between low levels of TC, and possibly also subtypes of cholesterol like HDL, and violence. Still, there seems to be a lack of prospective studies on this topic. Studies that have investigated gender differences concerning cholesterol levels as a potential risk marker of violence are scarce. Hence, our main objectives in this study from acute psychiatry were to investigate (1) the predictive

accuracy of TC and HDL recorded at admission as risk markers for violence during hospital stay and the first 3 months after discharge and (2) possible gender differences in TC and HDL recorded at admission as risk markers for violence during hospital stay and the first 3 months after discharge.

2. Methods

2.1. Design

This was a naturalistic prospective inpatient and outpatient observational study. The research was approved by the Regional Committee for Medical and Health Research Ethics. The approval granted exemption from asking for patients' informed consent to be included, but all patients could at any time withdraw from the project. Approval of access to police records for additional post-discharge recordings of violent behavior was given by the National Police Directorate.

2.2. Setting and participants

Oslo is the capital of Norway with a total population of 650,000. The acute psychiatric ward at Oslo University Hospital has five units with a total of 45 beds for all emergency psychiatric admissions from a catchment area of about 200,000 persons older than 18 years. Patients are first admitted to the Emergency Unit (7 beds), where they stay for a maximum of 3 days. Then they are either discharged or transferred to one out of four specialized units.

All patients admitted during one year, from March 21, 2012, to March 20, 2013, were included, resulting in a total of 558 patients with 755 hospital stays. Thirty patients used their right to withdraw from participation and were excluded. Another 166 patients were excluded due to missing or incomplete serum-lipid samples. The inpatient study sample then included recordings of 362 patients, 158 men and 204 women (counted with only one hospital stay

each; see 2.3. Procedure). The 3-months follow-up sample included recordings of 61 patients in outpatient clinics, 32 when readmitted to the ward, 3 from police records and 3 from hospital records: in total, 99 patients, comprising 46 men and 53 women (see 2.3. Procedure).

2.3. Procedure

All patients were informed verbally and in writing about the project. Routine blood samples (to measure TC and HDL) were taken by nurses at the ward the morning after admission, in most cases the patients had not been fasting. When patients were admitted on weekends or public holidays, the blood sample was given on the first regular working day. As part of the routine examinaton at admission, the physician on duty measured height and weight and performed an overall clinical judgment of the general condition ("*impaired general condition*" or "*normal general condition*").

Violent episodes during hospital stay were recorded by nursing staff using the Staff Observation Aggression Scale-Revised (SOAS-R) (Nijman et al., 1999). Additional information about inpatient violent episodes, including any use of protocols of coercive measures, was gathered from hospital records by the researchers. Violent episodes during the first 3 months after discharge were coded in a recording sheet by the patient's therapist at three collaborating outpatient clinics (see 2.5. Outcome measure). If a patient had been discharged and then admitted again to the acute ward during the project, outpatient violence for that post-discharge period was recorded in the recording sheet by the hospital staff. Additional information about episodes of post-discharge violence was collected by the researchers from out-patient hospital records and police records.

If a patient was readmitted to the ward during the project period, his or her previous post-discharge follow-up period was ended. The patient was then re-included with a new file number. Patients who had more than one hospital stay with recordings of TC and HDL during

the project period were only counted once in the analyses. For patients with recorded violence in more than one hospital stay or post-discharge period, the stay with the earliest violent episode was chosen. For non-violent patients, the first stay was chosen.

2.4. Baseline measures

Serum measures of TC and HDL in millimoles per liter (mmol / L) were obtained from routine blood tests at admission and analyzed at the Department of Medical Biochemistry at Oslo University Hospital with "enzymatic colorimetric method" for TC, and "homogeneous enzymatic colorimetric method" for HDL ("Cobas 8000 c702", Roche Diagnostics, Oslo, Norway). The analyses only included TC and HDL, not LDL or other cholesterol particles. Demographic variables and height, weight, general physical condition and ICD-10 diagnosis (WHO, 1992) were gathered from hospital records.

2.5. Outcome measure

The outcome measure was violent behaviour, including light/moderate and severe physical violence and threats of violence. *Violence* was defined in accordance with previous studies: *Physical violence* was defined as a physical act against another person, involving the use of body parts or objects, with a clear intention to cause physical injury on that person. *Verbal threats* were defined as verbal communications that conveyed a clear intention to inflict physical injury on another person (Dean et al., 2006; Monahan et al., 2005; Swanson et al., 2006).

During hospital stay, the SOAS-R was used to record violence to others (Nijman et al., 1999). Nurses were instructed to record only physical violence or threats against other persons according to the definition of violence. SOAS-R had been used in the ward the entire year before in another project. The nurses were therefore familiar with the form.

Post-discharge violence was coded in a recording sheet. Violent behaviours were categorized into (1) violent threats, (2) light/moderate violent acts (e.g. punches and kicks without serious injury) and (3) severe violent acts (e.g. use of weapons, sexual violence, or other violence with intent to inflict serous injury on another person). The recording options for each category were “no occurred episodes”, “yes, episodes have ocurred” or “don’t know if episodes have occurred”. The sheet also contained a short guideline on how to categorize violent episodes. Prior to the project’s start, the therapists were briefed in how to record violent behaviour.

2.6. Statistics

The data were analyzed using SPSS version 23.0. *Don’t know* recordings of outcome measures were treated as missing and excluded. To increase statistical power, verbal threats and categories of physical violence (regardless of frequency of episodes) were combined into one dichotomous outcome variable, “any violence”.

To test differences between groups of patients, the Mann-Whitney *U* test and *t*-test were used for continuous variables. Chi-square tests were used for categorical variables. Pearson’s Correlation Coefficient (Pearson’s *r*) was used to estimate associations between two continuous variables.

Univariate binary logistic regression analyses were conducted to estimate effect sizes (odds ratio, OR) for HDL and TC and to identify other variables associated with violence**.** Associations between TC and HDL levels as continuous variables, and violence were analyzed separately for the inpatient and post-discharge settings, and for each gender. Interaction analyses were performed to test the significance in gender differences.

NCSS PASS version 15 was used for post-hoc analysis of statistical power. The purpose was to estimate the sample sizes that would have been required to obtain significant

associations between predictors (HDL and TC) and outcome (violence) at a 0.5 significance level. To obtain 80% power, required samples sizes for analyses of TC for the whole sample were *n*=3174 in the inpatient and *n*=22196 in the post-discharge setting, for men: *n*= 47769 in the inpatient and *n*=1613 in the post-discharge setting, and for women *n*=1762 in the inpatient and *n*=9600 in the post-discharge setting. For HDL, required sample sizes for the whole sample were *n*=136 in the inpatient and *n*=89 in the post-discharge setting, for men *n*= 38 in the inpatient and *n*=8 post-discharge setting, and for women *n*=2623 in the inpatient and *n*=5853 in the post-discharge setting.

We also did an additional univariate analysis of TC/HDL ratio as a continuous variable. To specifically look at those patients with the lowest levels of TC and HDL, we dichotomized the lowest 25 percentiles of TC and HDL = 1, and those with higher levels = 0, and did the same univariate analysis for all patients, both settings and gender.

Multivariate binary logistic regression with a block enter procedure was used to control for other variables. The variables *unemployed* and *only primary school* were excluded from multivariate analyses due to a considerable number of missing cases: 34 (9.4%) and 32 (8.8%), respectively. Only potential confounders, that is, variables with a significant association ($p < 0.05$) both with the univariate significant TC or HDL and with violence, were chosen as control variables. *Male gender*, *involuntarily admitted* and *psychosis* remained as potential confounders, and were controlled for in multivariate analysis (see 3.5. Multivariate ORs for HDL, other variables, and violence).

Analysis of the area under the curve (AUC) of the receiver operating characteristic (ROC) was performed to assess the overall predictive accuracy. The AUC value ranges from 0 to 1, where an area of 0.5 equals chance and 1.0 equals a perfect prediction. To scrutinize the results, further statistical analyses were also performed to estimate (1) sensitivity, (2) specificity, (3) positive predictive value (PPV), (4) negative predictive value (NPV), (5)

number needed to assess (NNA, how many patients were needed to be assessed to identify one true violent patient, which is equal to 1/PPV) and (6) the likelihood ratio (LR). The LR determines the extent to which the odds of an outcome (e.g. violence) increases when a test is positive (LR+) and decreases when a test is negative (LR–). For example, an LR+ value of 2 signifies a 2-fold increase in the likelihood of violence when the test is positive. For tests with only two outcomes, the LR+ can be expressed as sensitivity/(1 – specificity) and LR– as (1 - sensitivity)/specificity (Deeks and Altman, 2004).

3. Results

3.1. Demographics with comparison of included and missing patients

See Table 1. In the inpatient sample, included patients had longer hospital stays and more depression and psychosis, while more of the missing patients had personality disorders and other or no diagnosis. In the follow-up sample, included patients had longer hospital stays and more depression, while more of the missing patients had *other* or *no* diagnoses.

3.2. Recorded violence

During hospital stay, 59 patients (16%) were violent. There was no significant difference from the missing sample. Men were more violent than women: 38 (24%) vs. 21 (10%), χ^2 (*df*) = 12 (1), $p < 0.001$.

Twenty-six (26 %) patients were violent during follow-up. This was not significantly different from the missing sample. There were no significant gender differences. Of the 26 violent patients, 7 (27%) were recorded in outpatient clinics, 13 (50%) when readmitted to the ward, 3 (11.5 %) in police records and 3 (11.5 %) in hospital records.

3.3. Variables associated with TC and HDL levels

To answer main objective one about the predictive accuracy of TC and HDL as risk markers for violence, we also looked at which baseline variables were associated with TC and HDL. As can be seen in Table 2, *male gender* was significantly associated with lower levels of TC, and increasing *age* and *BMI* were associated with higher TC levels. *Male gender*, *involuntarily admitted*, *unemployed*, *only primary school* and *psychosis* were associated with lower levels of HDL, and *alcohol abuse* and increasing *age* were associated with higher HDL levels.

3.4. Univariate ORs for TC and HDL and violence

Results are displayed in Table 3. No significant ORs were found for TC for any violence, and TC was therefore not entered into further analysis. HDL was significantly inversely associated with violence during hospital stay. For men, HDL was significantly inversely associated with violence 0-3 months after discharge.

Analyzing dichotomous variables with the lower 25 percentiles of TC and HDL = 1 gave a significant OR for HDL for all patients during hospital stay (HDL below 1.16 mmol/L, n=87, 21 violent): OR = 2.0, 95 % CI = 1.1 – 3.6, p = 0.025, while the other results for TC and HDL were non-significant. Analyzing TC / HDL ratio as baseline variable gave only non-significant ORs in both settings across gender.

Interaction-analyses for HDL to test significance in gender differences as a risk marker of violence gave non-significant results with p = 0.083 in the inpatient setting and p = 0.064 in the post-discharge setting.

3.5. Multivariate ORs for HDL, other variables and violence

See Table 4, which also displays inpatient univariate ORs for the variables used in multivariate analyses. None of the variables associated with HDL had significant ORs for

post-discharge violence. The variables associated with HDL with significant ORs for inpatient violence were therefore also used in the post-discharge analysis for men (see 2.6. Statistics).

In the inpatient multivariate analysis, HDL became non-significant whereas *male gender* and *involuntarily admitted* remained significant. In the post-discharge multivariate analysis for men, HDL remained borderline significant, while the other variables were non-significant.

We also did a multivariate analysis of the significant univariate finding for the lower 25 percentile of HDL for all patients during hospital stay (see 3.4. Univariate ORs for TC and HDL and violence), and controlled for the same variables as in Table 4. HDL then also became non-significant; OR = 1.4, 95% CI = 0.74-2.8, $p = 0.278$. *Male gender*; OR = 2.2, 95 % CI = 1.2-4.1, $p = 0.016$, and *involuntarily admitted*, OR = 5.7, 95% CI = 2.8-11, $p < 0.001$, remained significant.

3.6. ROC-AUC and other predictive measures of HDL for violence

The AUC-value for inpatient violence for the whole sample was 0.59, 95% CI = 0.51-0.67, $p = 0.035$, and for violence among men 0-3 months post-discharge, 0.70, 95 % CI = 0.53-0.86, $p = 0.037$. The other predictive values were based on the mean value of HDL in the whole sample (= 1.49 mmol/L). Values equal to mean or lower were defined as a *positive test.* For inpatient violence, sensitivity was 0.68, specificity 0.45, PPV 0.19, NPV 0.88, NNA = 5.3, LR+ = 1.2 and LR- = 0.71. For post-discharge violence in men, sensitivity was 0.86, specificity 0.34, PPV 0.36, NPV 0.85, NNA 2.8, LR+ 1.3 and LR- 0.41.

4. Discussion

4.1. Main findings

TC was not associated with inpatient or post-discharge violence across gender. Low HDL was associated with violence during hospital stay for the whole sample. However, the association became non-significant in multivariate analysis. For men, low HDL was associated with violence the first 3 months after discharge. The association remained borderline significant in multivariate analysis. HDL levels were not associated with violence in women.

4.2. Clinical and ethical implications

Unlike findings from other studies (Asellus et al., 2014; Paavola et al., 2002; Roaldset et al., 2011a), any inpatient or post-discharge associations between low levels of TC and violence were non-significant. The same goes for separate analysis of patients with the lowest levels of TC, and tests of the HDL/TC ratio. HDL is part of TC, and although our analyses did only include TC and HDL, negative findings for TC and positive findings for HDL might indicate that HDL, but not LDL or other types of cholesterol, is associated with violence in our population.

The finding of low level of HDL as a potential risk marker for future violence is in line with findings from another prospective study from acute psychiatry that found significant associations between low HDL and violence at 3 and 12 months post-discharge (Roaldset et al., 2011a). The findings indicate a stronger association between HDL and violence the first 3 months post-discharge for men when compared to the inpatient setting. In contrast to inpatient findings, the post-discharge OR for men remained borderline significant in multivariate analysis ($p = 0.052$). A significant AUC of 0.70 in this subgroup also offers preliminary support for this association. An increased violence risk in some groups of male patients with a history of violence, for instance, those with drug abuse and some subgroups of psychotic patients, is well recognized in psychiatric wards. The weaker HDL-violence link in the

inpatient setting may therefore be explained by higher risk awareness and more efficient preventive measures for these patients during hospital stay, turning true positives into “false positives”. Despite this possible bias, the findings, if replicated, might also indicate that low HDL is a better marker for violence risk for men during the first period after discharge from acute care than during their inpatient period. The fact that a majority of the post-discharge violence happens during this period of time emphasizes the need for further research (Monahan et al., 2001; Roaldset et al., 2011b; Tardiff et al., 1997).

Positive likelihood ratios (“ruling in”) of 1.2-1.3 indicate only a 1.2-1.3 – fold increased likelihood of becoming violent with a HDL score at cut-off or below, and low positive predictive values of 0.19 (inpatient) and 0.36 (for men post-discharge) indicate a high rate of false positives (see 3.6. ROC-AUC and other predictive measures of HDL for violence). Obviously, to make a clinical decision about a person’s risk of violence based on this risk marker alone would be unethical and a clinical hazard. However, using low HDL values together with a structured risk assessment tool may strengthen the predictive accuracy of the risk estimate. In the follow-up sample for men (n = 46), a negative predictive value of 0.85 and a negative likelihood ratio (“ruling out”) of 0.41, indicating a 2.5 - fold increased likelihood of not being violent if scoring higher than cut-off, indicate better properties for identifying those without violence risk.

Asellus et al. (2014) found that low TC had a modifying effect on “the cycle of violence”; they found a significant correlation between exposure to violence as a child and expressed violence as an adult, but only in patients with serum TC below median. Further investigation on the “Gene x Environment” effect might contribute to the understanding of the association between cholesterol levels and aggressive behavior. One should also have in mind the possibility of explaining the link between low cholesterol levels and violence by other psychological factors not controlled for in our study, such as impulsivity (Pozzi et al., 2003;

Troisi, 2011), anhedonia (Loas et al., 2016) and impaired psychological health (Sahebzamani et al., 2013).

In gender stratified analyses of post-discharge violence, HDL was a significant risk marker for future violence for men, but not for women. Although the inpatient OR for men was only borderline significant, an OR of 0.38 for men ($p = 0.063$), as opposed to 1.2 for women ($p = 0.623$), indicates the possibility that the same gender differences also might exist for inpatient violence. Despite the different results for men and women for HDL, the gender difference was non-significant in the interaction analyses, but might still show a trend towards significant gender differences with p=0.083 in the inpatient setting and p=0.064 in the post-discharge setting. Low n in the follow-up sample might also increase the probability of making a Type II error in this analysis. We didn't find other studies in our literature search specifically targeting gender differences in HDL as a potential risk marker of violence. However, two of the investigations reported earlier with findings of associations between low HDL and aggression, only included male patients (Buydens-Branchey et al., 2000; Troisi and D'Argenio, 2006). In a previous study from the same patient population, we found differences between men and women concerning psychosocial risk factors of violence, and a higher explained variance in these factors for men (Eriksen et al., 2016). Our findings may indicate that such differences also exist for HDL, supporting the hypothesis that men might be more vulnerable than women to low cholesterol levels (Wallner and Machatschke, 2009). One may also hypothesize that cholesterol is associated with different types of aggression, like suicidal behaviour, in women compared to men. A previous study on female patients found lower cholesterol levels in women with violent suicide attempts compared to women with non-violent suicide-attempts and controls (Vevera et al., 2003). Other studies have found associations between low HDL and suicide attempts in women (Emet et al., 2015; Zhang et al., 2005). Our study did not include suicidal behaviour as an outcome. Even when taking these

aspects into consideration, the findings suggest a stronger association between low HDL and violence for men than for women.

Research on biological risk markers for different psychiatric conditions or behaviour among psychiatric patients is a developing field (Kalia and Costa, 2015). The findings for HDL in our study, and also for other types of cholesterol in previous studies, are only contributions to this important field of research, but hopefully such findings will contribute to a broader understanding of psychiatric diseases and behaviour among mentally ill patients. With respect to violence risk, the use of potential biological risk markers like HDL may contribute to better violence risk assessments and thereby better prevention of incidences of violence and aggression in psychiatric wards and also after discharge from hospital.

4.3. Strengths and limitations

The prospective naturalistic design might increase the external validity of the study. Still, the fact that data were gathered in only one hospital is a limitation to the generalizability. Another strength is the use of multiple statistical methods to nuance the results in line with recent recommendations for risk assessment studies (Singh et al., 2015). Under-recording of violence is known from other studies using SOAS-R (Hvidhjelm et al., 2014; Nijman et al., 2005). The use of multiple sources of information in the recording of violence (staff, therapists, inpatient and outpatient hospital records, police records) may have contributed to reducing possible under-recording. Another limitation is the heterogeneous patient population in acute psychiatric settings with its wide spectrum of diagnoses and other factors which may contribute to violence risk. This makes interpretation of the impact of risk factors and risk markers, such as HDL, difficult on an individual level.

The study had a considerable number of missing patients (31% in the inpatient sample and 81% in the post-discharge sample). One possible explanation is that missing patients had

significantly shorter hospital stays and thereby less time and opportunity to give blood samples. Only a small proportion of the patients were re-admitted or went for further treatment in the outpatient clinics. The fact that re-admissions and outpatient clinics were our main sources for post-discharge recordings might explain some of the even larger number of patients missing from the post-discharge sample.

Type I errors and random findings cannot be completely ruled out, but are less likely in this study due to a limited number of subgroups and a limited number of baseline variables in multivariate analyses. Investigating only one outcome (violence), and only two main objectives in the study, also mitigate this risk.

Post-hoc power calculations showed that analyses had sufficient power to identify results of clinical significance, except for the non-significant OR of 0.38 for HDL for men during hospital stay, which is still somewhat surprising. Despite sufficient power, the possibility of Type II errors in some of the non-significant results can still not be completely ruled out, because post-hoc calculations are also subject to considerable uncertainty (Hoenig and Heisey, 2001; Yuan and Maxwell, 2005).

When blood samples were taken, patients had not necessarily been fasting. Although we cannot rule out that this to some degree could have influenced the non-significant results for TC, this seems less likely, because levels of TC and HDL are not normally affected by meal intake (Nakamura et al., 2016; Weidner et al., 2009). Cholesterol values could have been influenced by other factors, such as smoking, somatic diseases (e.g. diabetes), and use of statins or other medications. Despite these potential biases, the relatively young mean age makes use of statins less likely among the majority of the patients. Furthermore, statins and diabetes did not influence the results significantly in another similar study from acute psychiatry (Roaldset et al., 2011a).

4.4. Conclusions

Results indicate that HDL has the potential of becoming a useful risk marker for violence among acute psychiatric patients, especially for men during the first 3 months after discharge. The findings should be interpreted with caution due to some methodological shortcomings, especially the low *n* in some analyses. Because results were non-significant for women, the study raises questions concerning gender differences in biological risk markers of violence. Future studies should examine whether biological markers such as HDL may add incremental validity to structured risk judgments. Because this would be a time- and resource-effective measure, it would be of particular relevance for short-term risk assessments in acute psychiatry.

Acknowledgements

We acknowledge the nursing staff, physicians, psychologists and administrative staff at the Acute Psychiatric Section, Southern Oslo DPS, Nydalen DPS and Section of Early Psychoses Treatment, Oslo University Hospital, and especially the coordinators Kate Storm, Øyvind Ohnstad, Ingunn Verdal, Suraj Bahadur Thapa, Anniken Eid and Marit Forthun Vågsnes for their help with data collection and recordings. We would like to thank professor Petter Laake at the University of Oslo, Department of Biostatistics, for valuable statistical advice and also the head of the Division of Mental Health and Addiction, Marit Bjartveit, and the head of the Acute Psychiatric Section, Thorbjørn Harald Sundin, for their support for the project.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Asellus, P., Nordstrom, P., Nordstrom, A.L., Jokinen, J., 2014. Cholesterol and the "cycle of violence" in attempted suicide. Psychiatry Research 215 (3), 646-650.

Buydens-Branchey, L., Branchey, M., Hudson, J., Fergeson, P., 2000. Low HDL cholesterol, aggression and altered central serotonergic activity. Psychiatry Research 93 (2), 93-102.

Chen, S.C., Chu, N.H., Hwu, H.G., Chen, W.J., 2015. Trajectory classes of violent behavior and their relationship to lipid levels in schizophrenia inpatients. Journal of Psychiatric Research 66-67, 105-111.

Dean, K., Walsh, E., Moran, P., Tyrer, P., Creed, F., Byford, S., Burns, T., Murray, R., Fahy, T., 2006. Violence in women with psychosis in the community: prospective study. British Journal of Psychiatry 188, 264-270.

Deeks, J.J., Altman, D.G., 2004. Diagnostic tests 4: likelihood ratios.[comment]. BMJ 329 (7458), 168-169.

Douglas, K.S., Hart, S.D., Webster, C.D., Belfrage, H., 2013. HCR-20V3: Assessing risk of violence – user guide. Burnaby, Canada: Mental Health, Law, and Policy Institute, Simon Fraser University.

Emet, M., Yucel, A., Ozcan, H., Akgol Gur, S.T., Saritemur, M., Bulut, N., Gumusdere, M., 2015. Female attempted suicide patients with low HDL levels are at higher risk of suicide re-attempt within the subsequent year: a clinical cohort study. Psychiatry Research 225 (1-2), 202-207.

Engelberg, H., 1992. Low serum cholesterol and suicide. Lancet 339 (8795), 727-729.

Eriksen, B.M.S., Bjorkly, S., Faerden, A., Friestad, C., Hartvig, P., Roaldset, J.O., 2016. Gender differences in the predictive validity of a violence risk screening tool: a

prospective study in an acute psychiatric ward. International Journal of Forensic Mental Health 15 (2), 186-197.

Fielding, C.J., Fielding, P.E., 2008. Dynamics of lipoprotein transport in the circulatory system. Vance, D.E., Vance, J.E. (Ed.), Biochemistry of Lipids, Lipoproteins and Membranes (Fifth Edition). Elsevier, San Diego, pp. 533-553.

Golomb, B.A., 1998. Cholesterol and violence: is there a connection? Annals of Internal Medicine 128 (6), 478-487.

Golomb, B.A., Stattin, H., Mednick, S., 2000. Low cholesterol and violent crime. Journal of Psychiatric Research 34 (4-5), 301-309.

Hartvig, P., Roaldset, J.O., Moger, T.A., Ostberg, B., Bjorkly, S., 2011. The first step in the validation of a new screen for violence risk in acute psychiatry: the inpatient context. Eur Psychiatry 26 (2), 92-99.

Hoenig, J.M., Heisey, D.M., 2001. The abuse of power. The American Statistician 55 (1), 19-24.

Hvidhjelm, J., Seestoft, D., Bjørner, J.B., 2014. The Aggression Observation Short Form identified episodes not reported on the Staff Observation Aggression Scale-Revised. Issues in Mental Health Nursing 35, 464-469.

Kalia, M., Costa, E.S.J., 2015. Biomarkers of psychiatric diseases: current status and future prospects. Metabolism: Clinical and Experimental 64 (3 Suppl 1), S11-15.

Loas, G., Dalleau, E., Lecointe, H., Yon, V., 2016. Relationships between anhedonia, alexithymia, impulsivity, suicidal ideation, recent suicide attempt, C-reactive protein and serum lipid levels among 122 inpatients with mood or anxious disorders. Psychiatry Research 246, 296-302.

Monahan, J., Steadman, H., Silver, E., 2001. The MacArthur study of mental disorder and violence. Oxford University Press, New York.

Monahan, J., Steadman, H.J., Robbins, P.C., Appelbaum, P., Banks, S., Grisso, T., Heilbrun, K., Mulvey, E.P., Roth, L., Silver, E., 2005. An actuarial model of violence risk assessment for persons with mental disorders. Psychiatric Services 56 (7), 810-815.

Nakamura, A., Monma, Y., Kajitani, S., Noda, K., Nakajima, S., Endo, H., Takahashi, T., Nozaki, E., 2016. Effect of glycemic state on postprandial hyperlipidemia and hyperinsulinemia in patients with coronary artery disease. Heart and Vessels 31 (9), 1446-1455.

Nijman, H.L., Muris, P., Merckelbach, H.L.G.J., Palmstierna, T., Wistedt, B.r., Vos, A.M., van Rixtel, A., Allertz, W., 1999. The Staff Observation Aggression Scale-Revised (SOAS-R). Aggressive Behavior 25 (3), 197-209.

Nijman, H.L.I., Palmstierna, T., Almvik, R., Stolker, J.J., 2005. Fifteen years of research with the Staff Observation Aggression Scale: a review. Acta Psychiatrica Scandinavica 111 (1), 12-21.

Paavola, P., Repo-Tiihonen, E., Tiihonen, J., 2002. Serum lipid levels and violence among Finnish male forensic psychiatric patients. Journal of Forensic Psychiatry 13 (3), 555-568.

Pozzi, F., Troisi, A., Cerilli, M., Autore, A.M., Lo Castro, C., Ribatti, D., Frajese, G., 2003. Serum cholesterol and impulsivity in a large sample of healthy young men. Psychiatry Research 120 (3), 239-245.

Roaldset, J.O., Bakken, A.M., Bjorkly, S., 2011a. A prospective study of lipids and serotonin as risk markers of violence and self-harm in acute psychiatric patients. Psychiatry Research 186 (2-3), 293-299.

Roaldset, J.O., Hartvig, P., Bjorkly, S., 2011b. V-RISK-10: validation of a screen for risk of violence after discharge from acute psychiatry. Eur Psychiatry 26 (2), 85-91.

Sahebzamani, F.M., D'Aoust, R.F., Friedrich, D., Aiyer, A.N., Reis, S.E., Kip, K.E., 2013. Relationship among low cholesterol levels, depressive symptoms, aggression, hostility, and cynicism. Journal of Clinical Lipidology 7 (3), 208-216.

Siever, L.J., 2008. Neurobiology of aggression and violence. American Journal of Psychiatry 165 (4), 429-442.

Singh, J.P., Serper, M., Reinharth, J., Fazel, S., 2011. Structured assessment of violence risk in schizophrenia and other psychiatric disorders: a systematic review of the validity, reliability, and item content of 10 available instruments. Schizophrenia Bulletin 37 (5), 899-912.

Singh, J.P., Yang, S., Mulvey, E., 2015. Reporting guidance for violence risk assessment predictive validity studies: the RAGEE statement. Law and Human Behavior 39, 15-22.

Swanson, J.W., Swartz, M.S., Van Dorn, R.A., Elbogen, E.B., Wagner, H.R., Rosenheck, R.A., Stroup, T.S., McEvoy, J.P., Lieberman, J.A., 2006. A national study of violent behavior in persons with schizophrenia. Archives of General Psychiatry 63 (5), 490-499.

Tardiff, K., Marzuk, P.M., Leon, A.C., Portera, L., 1997. A prospective study of violence by psychiatric patients after hospital discharge. Psychiatric Services 48 (5), 678-681.

Troisi, A., 2011. Low cholesterol is a risk factor for attentional impulsivity in patients with mood symptoms. Psychiatry Research 188 (1), 83-87.

Troisi, A., D'Argenio, A., 2006. Apolipoprotein A-I/apolipoprotein B ratio and aggression in violent and nonviolent young adult males. Journal of Psychiatric Research 40 (5), 466-472.

Vevera, J., Zukov, I., Morcinek, T., Papezova, H., 2003. Cholesterol concentrations in violent and non-violent women suicide attempters. Eur Psychiatry 18 (1), 23-27.

Wallner, B., Machatschke, I.H., 2009. The evolution of violence in men: the function of central cholesterol and serotonin. Progress in Neuro-Psychopharmacology and Biological Psychiatry 33 (3), 391-397.

Weidner, G., Connor, S.L., Gerhard, G.T., Duell, P.B., Connor, W.E., 2009. The effects of dietary cholesterol-lowering on psychological symptoms: a randomised controlled study. Psychology, Health & Medicine 14 (3), 255-261.

WHO, 1992. The ICD-10 classification of mental and behavioural disorders, clinical description and diagnostic guidelines. World Health Organization, Geneva.

Yuan, K.-H., Maxwell, S., 2005. On the post hoc power in testing mean differences. Journal of Educational and Behavioral Statistics 30 (2), 141-167.

Zhang, J., McKeown, R.E., Hussey, J.R., Thompson, S.J., Woods, J.R., Ainsworth, B.E., 2005. Low HDL cholesterol is associated with suicide attempt among young healthy women: the third national health and nutrition examination survey. Journal of Affective Disorders 89 (1-3), 25-33.

Table 1

Demographics with comparison of included and missing patients

	Study sample				Follow-up			
	Included (*n* = 362)	Missing (*n* = 166)	Test Value	*p*	Included (*n* = 99)	Missing (*n* = 429)	Test value	*p*
Mean age (range)	41(18-95)	40(18-84)	0.97[e]	0.334	38 (20-75)	42 (18-95)	-1.9[e]	0.061
Male gender	158 (44%)	76 (46%)	0.21 (1)[f]	0.646	46 (47%)	188 (44%)	0.23 (1)[f]	0.633
Stay days mean/median	20 / 11	9 / 1	- 8.8[g]	<0.001	23 / 16	15 / 3.0	- 4.0[g]	< 0.001
Involuntarily admitted	160 (44%)	68 (41%)	0.49 (1)[f]	0.486	42 (42%)	186 (43%)	0.029 (1)[f]	0.866
Unemployed[a,b]	228 (70%)	108 (73%)	0.43 (1)[f]	0.510	68 (72%)	268 (70%)	0.20 (1)[f]	0.652
Only primary school[a]	107 (32%)	43 (33%)	0.007 (1)[f]	0.934	31 (33%)	119 (33%)	0.0 (1)[f]	0.983
Not in relationship[a]	249 (72%)	120 (76%)	0.97 (1)[f]	0.325	67 (70%)	302 (74%)	0.65 (1)[f]	0.421
F10-19 substance abuse	52 (14%)	34 (21%)	3.1 (1)[f]	0.077	12 (12%)	74 (17%)	1.6 (1)[f]	0.213
F20-29 psychosis	104 (29%)	27 (16%)	9.5 (1)[f]	0.002	28 (28%)	103 (24%)	0.79 (1)[f]	0.375
F30-31 bipolar disorder	47 (13%)	14 (8.4%)	2.3 (1)[f]	0.129	13 (13%)	48 (11%)	0.30 (1)[f]	0.586
F32-39 depression	55 (15%)	12 (7.2%)	6.5 (1)[f]	0.011	21 (21%)	46 (11%)	8.0 (1)[f]	0.005
F40-49 anxiety	48 (13%)	21 (13%)	0.037 (1)[f]	0.847	10 (10%)	59 (14%)	0.94 (1)[f]	0.331
F60 personality disorders	28 (7.7%)	22 (13%)	4.0 (1)[f]	0.044	10 (10%)	40 (9.3%)	0.057 (1)[f]	0.812
Other or no diagnoses	28 (7.7%)	36 (22%)	21 (1)[f]	<0.001	5 (5.1%)	59 (14%)	5.7 (1)[f]	0.017
Total cholesterol (range)	5.00 (1.80-10.6)	-	-	-	5.12 (2.50-8.50)	4.97 (1.80-10.6)	1.1[e]	0.285
HDL[c] (range)	1.49 (0.55-3.44)	-	-	-	1.50 (0.72-3.08)	1.48 (0.55-3.44)	0.32[e]	0.750
BMI[d] (range)	25(16-42)	26(17-52)	-0.90[e]	0.367	26 (16-39)	25 (16-52)	1.4[e]	0.155
Impaired general condition[a]	79 (22%)	40 (25%)	0.36 (1)[f]	0.550	18 (19%)	101 (24%)	1.3[f]	0.252

Note. Proportions or means are calculated from the valid *n* for variables with missing cases.

[a]Missing cases (2.8-13%)

[b]Not working (excluding age retirement)

[c]High Density Lipoprotein Cholesterol

[d]Body Mass Index, kg/m^2. Missing cases (44%)

[e]Independent samples *t*-test (*t*-value)

[f]Chi-square test, χ^2 (*df*)

[g]Mann-Whitney *U* test (*Z*-value)

Table 2

Associations for different variables with TC and HDL: Mean values for categorical variables and correlations for continuous variables

	TC				HDL			
	Yes mmol/L (95%CI)	No mmol/L (95%CI)	Test value	*p*	Yes mmol/L (95%CI)	No mmol/L (95%CI)	Test value	*p*
Mean values:								
Male gender	**4.83 (4.64-5.02)**	**5.12 (4.96-5.29)**	**-2.3[a]**	**0.021**	**1.32 (1.25-1.38)**	**1.62 (1.55-1.69)**	**-6.3[a]**	**<0.001**
Involuntarily admitted	4.88 (4.70-5.06)	5.09 (4.92-5.26)	-1.7[a]	0.092	**1.41 (1.35-1.48)**	**1.55 (1.47-1.62)**	**-2.6[a]**	**0.011**
Unemployed	5.01 (4.86-5.17)	5.07 (4.83-5.32)	-0.40[a]	0.691	**1.41 (1.35-1.47)**	**1.63 (1.52-1.73)**	**-3.6[a]**	**<0.001**
Only primary school	4.89 (4.67-5.11)	5.05 (4.88-5.21)	-1.1[a]	0.266	**1.29 (1.22-1.37)**	**1.56 (1.49-1.63)**	**-5.4[a]**	**<0.001**
Not in relationship	5.00 (4.86-5.14)	5.00 (4.73-5.26)	0.024[a]	0.981	1.47 (1.41-1.53)	1.53 (1.43-1.63)	-1.0[a]	0.296
Alcohol abuse (F10)	5.10 (4.65-5.55)	4.99 (4.86-5.12)	0.46[a]	0.647	**2.01 (1.76-2.27)**	**1.45 (1.40-1.50)**	**4.5[a]**	**<0.001**
Drug abuse (F11-19)	4.79 (4.32-5.27)	5.02 (4.89-5.15)	-1.1[a]	0.265	1.45 (1.33-1.58)	1.49 (1.44-1.55)	-0.49[a]	0.623
Psychosis	4.88 (4.67-5.10)	5.04 (4.89-5.19)	-1.2[a]	0.243	**1.35 (1.28-1.43)**	**1.54 (1.48-1.61)**	**-3.8[a]**	**<0.001**
Bipolar disorder	5.06 (4.67-5.45)	4.99 (4.86-5.12)	0.40[a]	0.689	1.59 (1.45-1.73)	1.47 (1.42-1.53)	1.6[a]	0.120
Depression	5.03 (4.72-5.34)	4.99 (4.85-5.13)	0.23[a]	0.816	1.51 (1.36-1.66)	1.48 (1.43-1.54)	0.38[a]	0.703
Anxiety	5.02 (4.73-5.31)	4.99 (4.86-5.13)	0.13[a]	0.900	1.56 (1.40-1.73)	1.48 (1.42-1.53)	1.2[a]	0.248
Personality disorders	4.99 (4.60-5.38)	5.00 (4.87-5.13)	-0.033[a]	0.974	1.45 (1.28-1.63)	1.49 (1.44-1.54)	-0.38[a]	0.706
Impaired general condition	4.93 (4.64-5.23)	5.03 (4.89-5.17)	-0.66[a]	0.513	1.44 (1.33-1.54)	1.51 (1.45-1.57)	-1.2[a]	0.222
Correlations:								
Age	-	-	**0.23[b]**	**< 0.001**	-	-	**0.15[b]**	**0.004**
BMI	-	-	**0.24[b]**	**0.001**	-	-	-0.029[b]	0.671

Note. TC = total cholesterol. HDL = high-density lipoprotein cholesterol. Yes = Patients with variable. No = Patients without variable. Significant *t*-tests and correlations in bold.

[a]Independent samples *t*-test (*t*-value)

[b]Pearson's *r*

Table 3

Univariate ORs of TC and HDL values

			TC		HDL	
	N	violent (%)	OR (95% CI)	*p*	OR (95% CI)	*P*
All patients						
Inpatient	362	59 (16%)	0.87 (0.68-1.1)	0.249	**0.52 (0.28-1.0)**[a]	**0.049**
Post-discharge	99	26 (26%)	0.95 (0.66-1.4)	0.784	0.50 (0.18-1.4)	0.186
Men						
Inpatient	158	38 (24%)	0.97 (0.71-1.3)	0.829	0.38 (0.14-1.1)	0.063
Post-discharge	46	14 (30%)	0.84 (0.49-1.5)	0.549	**0.099 (0.010-0.95)**	**0.045**
Women						
Inpatient	204	21 (10%)	0.82 (0.53-1.3)	0.353	1.2 (0.52-2.9)	0.623
Post-discharge	53	12 (23%)	1.1 (0.67-1.8)	0.697	1.1 (0.32-4.0)	0.835

Note. OR = odds ratio, TC = total cholesterol. HDL = high-density lipoprotein cholesterol. Significant ORs in bold.

[a]95% CI = 0.276-0.996

Table 4

Univariate and multivariate ORs of HDL and other variables

	Univariate				Multivariate					
	Inpatient (*N* = 362)				Inpatient, all (*N* = 362)		Post-discharge, men (*n* = 46)			
	n	Violent (%)	OR (95% CI)	*p*	OR (95% CI)	*p*	*n*	Violent (%)	OR (95 % CI)	*p*
HDL	362	-	0.52 (0.28-1.0)	0.049	0.85 (0.42-1.7)	0.653	46	-	0.090 (0.008-1.0)	0.052
Male gender	158	38 (24%)	2.8 (1.5-4.9)	0.001	2.3 (1.2-4.3)	0.011	46	14 (30%)	-	-
Involuntarily admitted	160	47 (29%)	6.6 (3.4-13)	<0.001	5.6 (2.8-11)	<0.001	24	9 (38%)	1.4 (0.35-5.7)	0.628
Psychosis	104	26 (25%)	2.3 (1.3-4.0)	0.005	1.3 (0.67-2.4)	0.467	17	5 (29%)	0.60 (0.14-2.5)	0.481

Note. OR = odds ratio. HDL = high-density lipoprotein cholesterol