How do lipids influence risk of violence, self-harm and suicidality in people with psychosis? A systematic review

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Abstract

Objectives: Low cholesterol has been linked with violent and suicidal behaviour in people with schizophrenia. This association, if consistently present, may be a promising biological marker that could assist clinicians in decision making regarding risk and treatment. We conducted a systematic review to assess whether there is a reliable association between lipid profile (total cholesterol, high- and low-density lipoprotein cholesterol, and triglycerides) and aggression, self-harm or suicide in people with schizophrenia, and whether effects are similar in males and females.

Method: Relevant databases were searched to identify primary research studies (up to November 2020) that (1) involved adults (some samples also included 16- to 18-year olds) with a confirmed diagnosis of schizophrenia, schizoaffective disorder or psychosis; and (2) included a standardised assessment of verbal aggression, physical aggression against objects, physical aggression against self (including suicide) or others. The search yielded 23 studies eligible for inclusion following a quality appraisal.

Results: Suicidality was the most commonly assessed subtype of aggression (20 studies). For suicidality, about half the studies, including the study with the largest sample size, found a link with total cholesterol. An association between low total cholesterol and violence towards others was found in six of nine studies that investigated this. The evidence for a link with violence was the strongest for total cholesterol, followed by low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, and the weakest for triglycerides. Only a few studies investigated sex differences and yielded mixed evidence. Studies focussed on self-harm as well as involving females in forensic settings were lacking.

Conclusion: There is encouraging evidence of an association between low total cholesterol and aggression towards others as well as suicidality in schizophrenia. Future studies should systematically explore this association in people with schizophrenia who have a significant history of violence, suicidality and self-harm, both inpatients and community, and also investigate underlying mechanisms.

Keywords
Cholesterol, aggression, suicide, schizophrenia, sex

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Introduction

The majority of patients in forensic psychiatric services have schizophrenia (Fleischman et al., 2014; Silverstein et al., 2015) or personality disorder (PD), often presenting comorbidly (Arseneault et al., 2000). There is considerable evidence of an association between interpersonal violence and schizophrenia (Fleischman et al., 2014; Silverstein et al., 2015; Walsh et al., 2002). Violent crime has been shown to be up to 10 times more common in people with schizophrenia than matched populations (Fazel et al., 2009). A growing body of evidence (review, Sedgwick et al., 2016) suggests that several neurobiological measures are aberrant in forensic psychiatric populations. Some of these aberrations, if reliably associated with risk or outcomes, could assist clinicians to make decisions about treatment planning, risk and discharge (Sedgwick et al., 2016). One such promising biological marker could be the lipid profile, particularly serum cholesterol.

A link between low levels of cholesterol and violent behaviour in forensic psychiatric populations has been suggested for over 25 years (Boston et al., 1996; Douglas and Nasrallah, 2019; Sedgwick et al., 2016). Low cholesterol may also be linked to suicidality (Asellus et al., 2010; Lee and Kim, 2003; Wu et al., 2016). Low cholesterol has been discussed as a biomarker for suicide since the early 1990s when meta-analytic evidence associated the use of statins (cholesterol-lowering drugs) with an elevated risk of death by suicide, despite these drugs lowering the risk of death by coronary events (Muldoon et al., 1990). A significant relationship between low serum cholesterol levels and suicide in psychiatric disorders, including psychosis, has also been reported (Kulak-Bejda et al., 2021). Furthermore, low cholesterol has been linked to inpatient suicidal and violent behaviour, and with 3-month post-discharge violent behaviour in non-forensic patient populations (Roaldset et al., 2016), as well as with criminal violence in the general population (Golomb et al., 2000). However, some studies indicate that low cholesterol-aggression association may be true only for men (Tomson-Johanson and Harro, 2018), and a few studies failed to observe this association (Deisenhammer et al., 2004; Roy et al., 2001). To what extent this association is influenced by sex or reliably present in people with schizophrenia remains unclear.

The main aim of this review, therefore, was to systematically investigate possible associations between lipid profile, as indexed by the levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG), and specific dimensions of aggression and violence in adult patients with schizophrenia. For the purpose of this review, aggression was defined as any behaviour falling under verbal aggression, physical aggression against objects, physical aggression against self (including suicide) or physical aggression against others, in line with the Modified Overt Aggression Scale (MOAS) (Sorgi et al., 1991). Our secondary aim was to consider potential sex differences in these associations wherever possible.

Methods

Information sources and search

We followed the guidelines detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009) for literature search. An extensive search of PubMed, PsycINFO, Academic Search Complete, CINAHL Plus, MEDLINE, Scopus and Web of Science databases was carried out in the first week of December 2020. A combination of the following search terms was used: (cholesterol* OR high density lipoprotein OR low density lipoprotein OR LDL OR triglycerides OR lipid profile) AND (schizoph* OR psychosis OR schizoaffective*) AND (violence OR aggression* OR assault OR suicide* OR self-harm* OR self-mutilation). Other studies were located through hand searching of relevant publications and reference lists.

Screening and selection

Articles were selected using the following pre-formed inclusion and exclusion criteria: (1) patients must have a diagnosis of schizophrenia, schizoaffective disorder or psychosis stated through either a DSM (Diagnostic and Statistical Manual of Mental Disorders) or ICD (International Classification of Diseases) classification; (2) participants must be adults, aged 18 years and over, unless unavoidable (i.e. studies where the vast majority of participants were over 18, but included some participants between 16 and 18 years, were included); (3) aggressive behaviour described must fall under at least one type stated in the MOAS – verbal, physical against objects, physical against self, physical against others; (4) level of cholesterol must be specified with units; (5) access to full published text and methodology must be available (excluding review articles, editorials and data from conference publications); and (6) articles must be available in English. Two blinded reviewers (P.S. and D.A.) independently made the study selection according to these criteria. Both reviewers had to agree with the articles selected.

Quality appraisal and data extraction

The quality of the selected studies was then assessed using The Joanna Briggs Institute (JBI) Critical Appraisal Tools for cross-sectional, case–control and case series studies (Zeng et al., 2015). One point was granted for meeting each of the criteria. Articles scoring less than 80% were excluded. Each criterion was graded as ‘yes’, ‘no’, ‘unclear’ or ‘not applicable’. One point was granted for scoring ‘yes’ on...
each of the criteria, and then all points added to derive the total score, expressed in percentage, for each study. Studies assessed ranged in score from 71.4% to 100% (Tables 1–3). Articles scoring less than 80% were excluded. The mean score of papers included in the review following quality appraisal was 94.2%.

Case–control studies were scored out of 10, based on the following criteria: were the groups comparable, other than the presence of disease in cases or the absence of disease in controls; were cases and controls matched appropriately; were the same criteria used for identification of cases and controls; was exposure measured in a standard, valid and reliable way; was exposure measured in the same way for cases and controls; whether confounding factors were identified; whether strategies to deal with confounding factors were stated; whether outcomes were assessed in a standard, valid and reliable way for cases and controls; was the exposure period of interest long enough to be meaningful; and whether appropriate statistical analyses were used.

Similarly, case series studies were scored out of 10. A point was given if: there were clear criteria for inclusion in the case series; the condition was measured in a standard, reliable way for all participants included; valid methods were used for identification of the condition for all participants included; the case series had consecutive inclusion of participants; the case series had complete inclusion of participants; there was clear reporting of the demographics of the participants in the study; there was clear reporting of clinical information of the participants; the outcomes or follow-up results of cases were clearly reported; there was clear reporting of the presenting site/clinic demographic information; and statistical analysis chosen was appropriate.

Finally, cross-sectional studies were scored out of 8, based on criteria assessing whether: the inclusion criteria were clearly defined; the study subjects and setting were described in detail; the exposure was measured in a valid and reliable way; objective, standard criteria was used for measurement of the condition; confounding factors were identified; strategies to deal with confounding factors were stated; the outcomes were measured in a valid and reliable way and appropriate statistical analysis was chosen. Studies excluded at this stage consistently lacked the identification of confounding factors and strategies to handle them appropriately. A list of articles with reasons for exclusion following quality appraisal is provided in Tables 1–3.

A data extraction table was created with the final selection of articles (Table 4), compiling data on: the first author’s name, year of publication, location of the study, study design, psychiatric conditions included in the study, the diagnostic classification used, sample size (and sex distribution), the number of schizophrenia, schizoaffective and psychotic patients included (and sex distribution), details of the case and control groups, form of cholesterol examined (TC, LDL, HDL, TG), findings classified by each aggression type (physical against self, physical against others, physical against objects, verbal) and any other findings (see Table 4).

Results

Our literature search produced 29 articles for quality appraisal, of which 23 were deemed eligible for inclusion (Figure 1).

Studies on suicide

In total, 20 studies (see Table 4) examined attempted suicide and suicidal behaviour, and some of these studies considered violent suicide attempts in inpatients with schizophrenia.

Eight of these 20 studies (Kavoor et al., 2017; Marcinko et al., 2005, 2007, 2008; Repo-Tiihonen et al., 2002; Ruljancic et al., 2007; Sankaranarayanan et al., 2020; Tripodianakis et al., 2002) concluded that relatively lower levels of cholesterol were associated with suicidality in patients with schizophrenia. Additionally, one of these studies (Repo-Tiihonen et al., 2002) found relatively lower TC (below 5.3 mmol/L) to be a marker of violent and suicidal behaviour. Apart from TC, low levels of HDL were associated with suicidality in three studies (Kavoor et al., 2017; Marcinko et al., 2008; Sankaranarayanan et al., 2020), of which one study was on males with schizoaffective disorder (Marcinko et al., 2008). Two of these studies also showed a link of suicidality with low LDL (Kavoor et al., 2017; Marcinko et al., 2008). Of these eight studies, one small sample study (Marcinko et al., 2005) showed that patients with a violent suicidal attempt had significantly lower TC levels than patients with non-violent attempts and non-suicidal controls but another study (Tripodianakis et al., 2002) with a far larger sample size found no such difference. Yet another study (Ruljancic et al., 2007) found a link between relatively low cholesterol and non-violent suicidal attempts (across several disorders) when compared to those without a suicidal attempt but did not report on such a link specifically for schizophrenia, schizoaffective disorder or psychotic disorder.

A total of seven studies (Capuzzi et al., 2018; Cariou et al., 2018; Gohar et al., 2019; Huang and Wu, 2000; Kunugi et al., 1997; Park et al., 2013; Shrivastava et al., 2017) did not find any link between lipid profile and suicidality in schizophrenia. In addition, one study (Chen et al., 2015) that examined the four types of aggression did not report findings on suicidality. One study (Misiak et al., 2015) found the opposite link, where relatively higher TC was associated with suicidal ideation in females with first-episode schizophrenia, thus demonstrating the complexity of the link. Finally, one study (Kim et al., 2002) found a link between relatively low TC and suicidality for major depressive disorder and personality disorder, but not for schizophrenia.
With regard to TG, seven studies (Capuzzi et al., 2018; Gohar et al., 2019; Kavoor et al., 2017; Marcinko et al., 2007; Misiak et al., 2015; Park et al., 2013; Sankaranarayanan et al., 2020) explored TG and suicidality, and none found an association. All these studies were spread over a time period of more than two decades between 1997 and 2020. Sample sizes varied widely, from 31 to 802, though the smaller studies targeted patients admitted to hospital following a suicidal attempt. It is interesting to note, however, that the study (Sankaranarayanan et al., 2020) with the largest sample size ($n=802$) did find a link between lipid profile and suicidality.

**Studies on aggression against others**

A total of nine studies (Cariou et al., 2018; Chakrabarti et al., 2004; Chen et al., 2015; Eriksen et al., 2017, 2018; Hjell et al., 2020; Huang and Wu, 2000; Repo-Tiihonen et al., 2002; Turkoglu et al., 2009) explored the link between lipid profile and violence against others, of which six studies found a link. However, there were some variations in the findings. One group of researchers (Eriksen et al., 2018) did not find a link with TC but with HDL, and only for men and not for women. The same authors, while studying violence in the first 3 months after discharge, also found HDL to be inversely associated with violence in men only (Eriksen et al., 2017). One study (Repo-Tiihonen et al., 2002) tried to identify a cut-off point for low TC levels to be a marker for violence, measured by frequency of seclusion, finding the cut-off level to be 5.3 mmol/L. Another researcher group (Kavoor et al., 2017) found a correlation with TC and LDL but not with HDL for measures of psychopathology, impulsivity and aggression (and suicidality).

One study (Cariou et al., 2018) retrospectively evaluated hospitalised patients over the course of a year and found a link between low plasma concentration of LDL and hetero-aggression. The group with low LDL also had a higher
Table 1. The Joanna Briggs Institute (JBI) quality appraisal ratings for included and excluded studies: case–control studies.

| Study | Study design | Comparable groups other than the presence or absence of the disease | Appropriate matching of cases and controls | Same criteria used for identification of cases and controls | Standard, valid and reliable measurement of exposure | Exposure measured in same way for cases and controls | Identification of confounding factors | Strategies to deal with confounding factors stated | Outcomes assessed in a standard, valid, reliable way | Exposure period of interest long enough to be meaningful | Appropriate statistical analysis used | Score (%) | Overall appraisal |
|-------|--------------|---------------------------------------------------------------|-------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------|--------------------------------------|------------------------------------------|----------------------------------------------|-----------------------------------------------|-----------------------------------------------|----------|-------------------|
| Turkoglu et al. (2009) | Case control. Categorical observation between schizophrenia patients with and without a record of crime | Participants all male. Comparable in age: mean (SD) of crime group = 36.52 (8.48); mean (SD) of control group = 35.36 (7.74) | 50 male schizophrenia patients with at least one crime record matched with 50 male schizophrenia patients without a crime record. No significant differences in mean age, height or weight between groups | Schizophrenia diagnosis made according to DSM-IV in both cases and controls | Blood samples for TC, TG and ghrelin collected between 08.00 a.m. and 11.00 a.m. TC and TG levels were measured by Olympus Biochemical Autoanalyser, by spectrophotometric method using Olympus brand kits | Blood samples collected and examined for all subjects in the case and control group | Medication and diet identified as potential confounders | No strategy for dealing with confounders | Patients grouped into those with a criminal record and without a criminal record | Blood samples collected between 08.00 a.m. and 11.00 a.m. | t-test used | 90 | Include |
| Marcinko et al. (2005) | Case control. Categorical observation between schizophrenia patients with violent, non-violent and no suicidal attempts (control group) | Participants all male. No significant differences in age, BMI, marital, family or employment status | 31 male schizophrenia patients with a suicide attempt matched with 15 male schizophrenia patients with no history of suicide | Schizophrenia diagnosis made according to ICD-10 in both cases and controls | Blood samples were collected at 7.00 a.m. after overnight fasting. TC determined enzymatically, immediately after blood collection. Assays done with commercial kits on Olympus AU 600 automatic analyser | Blood samples were collected from all subjects in the case and control group | Age and BMI identified as confounders | Confounders controlled in ANCOVA analysis | Patients grouped into those admitted following a suicide attempt and those without a history of suicide attempt | Blood samples collected after overnight fasting | ANOVA and ANCOVA used | 100 | Include |
| Chakrabarti et al. (2004) | Case control. Categorical observation between psychotic patients with a history of violent crime and without a history of violent crime | Participants all male diagnosed with a psychotic illness | 30 inpatients with a psychotic illness with a history of violent crime matched through age, sex and BMI to 30 male psychotic inpatients without a history of violent crime | All psychotic illnesses diagnosed according to ICD-10 in both cases and controls | Blood sample obtained after a 12-hour overnight fasting. Biochemical assay used. TC, TG triglycerides and HDL-cholesterol were estimated by colorimetric method. VLDL and LDL cholesterol were calculated from Friedewald and Friedrickson's formulas | Blood sample obtained from each person selected for the study | Medication identified as potential confounder | No strategy for dealing with confounders | Patients grouped into those with a history of violent crime, which included homicide, rape, arson and grievous injury as per the Criminal Procedure Code of the Indian Law, and those without a history of violent crime | Blood sample obtained after a 12-hour overnight fasting | Pearson correlation coefficients used | 90 | Include |

(continued)
Table 1. (continued)

| Study                        | Study design                                                                 | Comparable groups other than the presence or absence of the disease | Appropriate matching of cases and controls | Same criteria used for identification of cases and controls | Standard, valid and reliable measurement of exposure | Exposure measured in same way for cases and controls | Identification of confounding factors | Strategies to deal with confounding factors stated | Outcomes assessed in a standard, valid, reliable way | Exposure period of interest long enough to be meaningful | Appropriate statistical analysis used | Score (%) | Overall appraisal |
|------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------|--------------------------------------------------------|-----------------------------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------|-------------------|
| Tripodianakis et al. (2002)  | Case control. Categorical observation between patients and healthy controls (no psychiatric history), matched for age and sex | Suicide and non-suicide attempt groups were age matched according to sex – male controls were age matched to male attempters and female controls matched to female attempters | Case group, admitted after suicide attempt, consisted of 35 males and 76 females. Control group, with no psychiatric history or history of suicide attempt, consisted of 31 males and 31 females. Ages of control subjects matched according to sex | n/a – control group did not have a psychiatric diagnosis | Blood and urine samples taken within 24 hours of admission at 8:00 in the morning. Total cholesterol was estimated in plasma samples using commercially available kits | Blood and urine samples taken within 24 hours of admission from all the patients | Age identified as confounder | Confounders controlled in ANOVA | Age identified as confounder | Severity of the suicidal intent was estimated with SIS | Blood and urine samples taken within 24 hours of admission | 100 | Include |
| Repo-Tiitinen et al. (2002)  | Case control. Categorical observation between patients who had been sequestered involuntarily (for violent acts, for suicidal acts) and patients who had not been sequestered | Participants all males diagnosed with a psychotic illness | All psychotic illnesses diagnosed according to ICD-10 in both cases and controls | The serum samples for assaying TC levels were collected always in the morning after 10 to 12 hours’ fast. The method for assaying was enzymatic | Blood samples taken in the morning after 10–12 hour fast | States that BMI did not explain differences in TC, suggesting that this may have been a potential confounder | No strategy for dealing with confounders | ‘Violent and dangerous’ psychiatric patients sent to his hospital by municipal psychiatric hospitals | Blood samples taken in the morning after 10–12 hour fast | Mann–Whitney U-test used | 80 | Include |
| Mufti et al. (1998)          | Case control. All participants admitted during the same 2-month period in early 1995 | All participants admitted during the same 2-month period in early 1995 | Case group consisted of 17 African Americans and control group consisted of 16 African Americans | Not specified | Method of measuring TC and TG not stated | TC and TG obtained from medical chart review for all patients | Age, sex and race identified as confounders | Confounders controlled in ANCOVA and logistic regression | Patients grouped into those who were violent, were sequestered or restrained, and those who did not receive seclusion or restraint | Selcution or restraint within 3-month period | ANCOVA and logistic regression used | 80 | Exclude |

SD: standard deviation; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.); TC: total cholesterol; TG: triglyceride; BMI: body mass index; ICD-10: International Classification of Diseases, 10th Revision; ANCOVA: analysis of covariance; ANOVA: analysis of variance; HDL: high-density lipoprotein; VLDL: very low-density lipoprotein; LDL: low-density lipoprotein; SIS: Scale for Impact of Suicidality.
Table 2. The Joanna Briggs Institute (JBI) quality appraisal ratings for included and excluded studies: Case series studies.

| Study | Study design | Clear criteria for inclusion in case series | Condition measured in standard, reliable way for participants in case series | Valid methods used for identification of condition for participants in case series | Consecutive inclusion of participants in case series | Complete inclusion of participants in case series | Clear reporting of demographics of participants | Clear reporting of clinical information of participants | Outcomes or follow-up results of cases clearly reported | Clear reporting of presentation site/clinic demographic information | Appropriate statistical analysis | Score (%) | Overall appraisal |
|-------|--------------|--------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|-----------------------------|---------------|-------------------|
| Chen et al. (2015) | Case series. Correlational observation | Inclusion criteria: schizophrenia patients over the age of 16 who were admitted to the acute psychiatric ward in National Taiwan University Hospital | DSM-IV criteria used Psychotic symptoms assessed weekly by psychiatrists using the Comprehensive Psychopathological Rating Scale for inpatients with severe mental disorder | DSM-IV classification used. | Patients were recruited in succession from April 2002 to March 2003 | Yes, n = 107 | Age, gender, education, unemployment and being single all reported | Positive symptoms scores, negative symptoms scores, age at onset and BMI reported | Tables reporting relationships between schizophrenia and violence and explained in text. | p values reported | Logistic regression analysis used | 90 | Include |
| Ruljancic et al. (2007) | Case series. Categorical observation between psychiatric patients | Inclusion criteria: all patients admitted to Sveti Ivan Psychiatric Hospital were included. Exclusion criteria: Patients with psychiatric diagnosis of low prevalence were excluded | ICD-10 criteria used | ICD-10 classification used. | All patients admitted from January 2005 to April 2005 | Yes, n = 677 | Age: 17–89 262 females, 415 males Geographic region: Zagreb, Croatia | Schizophrenia, n = 136 Schizoaffective disorder, n = 64 Psychotic disorders, n = 47 | Table shows mean and SD of TC in patients and explained in text. | p values reported | ANOVA test used | 90 | Include |
| Huang et al. (2000) | Case series. Categorical analysis – between paranoid and non-paranoid schizophrenic patients | Inclusion criteria: all patients admitted to the Chang Gung Memorial Hospital Exclusion criteria: no comorbid illness | DSM-III-R criteria used | DSM-III-R classification used. | All patients admitted from January to December 1995 | Yes, n = 213 | Mean age 10.8 ± 47 months, 59 females Geographic region: Kaohsiung, Taiwan | Mean BMI = 23 Paranoid and non-paranoid schizophrenia, n = 106 | Table shows mean and SD of TC in patients and explained in text. | p values reported | t-test used | 90 | Include |

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.); BMI: body mass index; ICD-10: International Classification of Diseases, 10th Revision; SD: standard deviation; TC: total cholesterol; ANOVA: analysis of variance; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders (2nd ed., rev.).
| Study | Study design | Inclusion criteria clearly defined | Study subjects and setting described in detail | Exposure measured in a valid and reliable way | Objective, standard criteria used for measurement of condition | Confounders identified | Strategies to deal with confounders | Outcomes measured in a valid way | Appropriate statistical analysis | Score (%) | Overall appraisal |
|-------|-------------|----------------------------------|---------------------------------------------|-----------------------------------------------|-------------------------------------------------|---------------------|-------------------------------|-------------------------------|--------------------------------|----------|-----------------|
| Sankaranarayanan et al. (2020) | Cross-sectional | Not clearly defined. Descriptive characteristics and ICD classification given but no distinct inclusion criteria | Age, sex, education, employment and marital status given. Sample collected from a database of Australians with psychotic disorders | Fasting levels of TC, HDL, LDL and TG were collected and analysed | ICD-10 classification of schizophrenia and schizoaffective disorder used | Age, sex, smoking status, cannabis use, dysphoria and BMI identified as potential confounders | Potential confounders controlled in logistic regression | Suicidal ideation assessed using the Diagnostic Interview for Psychosis | Multivariable logistic regression used | 87.5 | Include |
| Hjell et al. (2020) | Cross-sectional | Inclusion criteria: a diagnosis within the schizophrenia or bipolar spectrum, age between 18 and 65 years, ability to give informed consent, and Norwegian language skills sufficient for valid assessments. Exclusion criteria: marked cognitive deficit (IQ scores below 70), neurological disorder and history of severe head trauma | Age, sex, race, smoking status and medication given. Study formed part of the TOP study, where patients with severe mental disorders were recruited from psychiatric inpatient and outpatient clinics of the major hospitals in Oslo, Norway | Venous blood samples were collected in the morning after an overnight fast of at least 8 hours. Levels of TC, LDL and HDL were measured | DSM-IV classification of psychiatric disorders used. The Positive and Negative Syndrome Scale (PANSS) used to measure severity of symptoms | Age, sex, BMI and medication identified as confounders | Aggression measured using PANS Excited Component. Impulsivity measured using Barratt Impulsiveness Scale | Multinomial logistic regression used | 100 | Include |
| Gohar et al. (2019) | Cross-sectional (with correlational analysis) | Inclusion criteria clearly defined: 18–65 years of age, DSM-IV criteria for schizophrenia and psychotic disorders, have available serum leptin measurements and able to provide consent to participate. Participants with a history of significant head injury, neurological disorder, mental retardation and autoimmune disease were excluded | Age, sex, ethnicity, education, smoking status and age of onset recorded. Subjects were recruited through the ongoing Norwegian TOP study | Fasting venous blood samples were obtained in the morning. Measurement and analysis of TC, TG, LDL and standard C-reactive protein were conducted | DSM-IV classification of psychiatric disorders used. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) used to confirm the diagnosis | Age, sex, BMI, dietary habits, smoking, age of onset and duration of illness identified as confounders | Severity of suicidal behaviour measured using item 18 of IDS-C | Multinomial logistic regression used | 100 | Include |

(continued)
| Study                      | Study design | Inclusion criteria clearly defined | Study subjects and setting described in detail                                                                 | Exposure measured in a valid and reliable way | Objective, standard criteria used for measurement of condition | Confounders identified | Strategies to deal with confounders | Outcomes measured in a valid way | Appropriate statistical analysis | Score (%) | Overall appraisal |
|---------------------------|--------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------|------------------------|----------------------------------|---------------------------------|----------------------------------|----------|-------------------|
| Goel et al. (2019)        | Cross-sectional | Inclusion criteria clearly defined: patients of either sex and those patients or accompanying relatives willing to give written informed consent for participation in study. Exclusion criteria: patients having comorbid physical disorders | Age, sex, and marital status recorded. Patients recruited from inpatient and outpatient of AvBR Hospital | Blood sample for total cholesterol level was taken immediately after admission in psychiatry ward or on OPD basis | No DSM or ICD classification used for diagnosis | Mental illness, medication and dietary factors were identified as confounders | Patients grouped into recent suicide attempt, suicidal ideations but no attempts and no suicidal ideation or attempt | Chi-square test used | 75                  | Exclude |
| Shaﬁ et al. (2019)        | Cross-sectional | Inclusion criteria clearly defined: all registered inpatients with suicidal behaviour (successful suicide and attempted suicide, in total), during the last 60 months | Age, sex, marital status and employment recorded. Setting described in detail: Razi psychiatric hospital, as the largest psychiatric hospital in the Middle East, five acute academic wards, which are speciﬁed for admission of ﬁrst episode adult psychiatric patients, and ﬁve acute non-academic wards, speciﬁed for admission of recurrent episode adult psychiatric patients | Serum lipids, including TC, TG, LDL and HDL were analysed, having being collected as part of routine laboratory tests for all patients upon admission | DSM-IV classification of psychiatric disorders used | Confounders, such as age, sex, BMI and involuntary admission, were not identiﬁed | T-test used | 75                  | Exclude |
| Cariou et al. (2018)      | Cross-sectional | Induction criteria clearly defined: admitted in the Psychiatry department in the course of the year 2014, to be aged 18 and older, and to have had a lipid panel test. Exclusion criteria: patients admitted in the eating disorders unit | Age, sex, weight, height, BMI, medication, history of diabetes, liver diseases and cardiovascular risk factors recorded. Recruited from the psychiatry department of Nantes University Hospital, France | Lipid panel test was done and TC, HDL, and TG were collected and analysed. LDL was calculated according to the Friedewald formula. | ICD-10 classification of psychiatric disorders used | Medical cause of HBL identified as confounder | Patients with medical cause of HBL excluded | Mann–Whitney tests for quantitative variables and Fisher tests for the qualitative variables | 100                  | Include |

(continued)
### Table 3. (continued)

| Study | Study design | Inclusion criteria clearly defined | Study subjects and setting described in detail | Exposure measured in a valid and reliable way | Confounders identified | Strategies to deal with confounders | Outcomes measured in a valid way | Appropriate statistical analysis | Score (%) | Overall appraisal |
|-------|--------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|------------------------|-------------------------------|---------------------------------|---------------------------------|-----------|------------------|
| Eriksen et al. (2018) | Cross-sectional with longitudinal component | Inclusion criteria: all patients admitted to the acute psychiatric ward at Oslo University Hospital, Norway, between 21 March 2012 and 20 March 2013 | Age, gender, education, marital status recorded; Acute psychiatric ward at Oslo University Hospital admits adults (18 years or older) from a catchment area of 204,000 people | Serum measures of TC and HDL in millimoles per litre (mmol/L) were obtained from routine blood tests at admission and analysed with 'enzymatic colorimetric method' for TC and 'homogeneous enzymatic colorimetric method' for HDL ('Cobas 8000 c702', Roche Diagnostics, Oslo, Norway) | ICD-10 classification of psychiatric disorders used | Involuntary admission and age identified as confounders | Confounders controlled in logistic regression | Violent behaviour measured using SOAS-R. Association between cholesterol and suicide attempt measured using appropriate statistical analysis | 100 | Include |
| Capuzzi et al. (2018) | Cross-sectional | Inclusion criteria: patients admitted between January 2012 and December 2017, to Psychiatric Inpatient Unit (Desio Hospital, ASST Monza, Italy), psychiatric diagnosis classified by ICD-10, aged between 18 and 65 years, medically stable, not needing treatment for any physical condition. Exclusion criteria: subjects suffering from other mental disorders or mental retardation, serious physical illnesses or treated with thyroid hormone, antidiabetic, anticoagulant, anti-platelet, urate- and lipid-lowering agents | Age, sex, smoking status, BMI, and medication recorded; Psychiatric Inpatient Unit at Desio Hospital, ASST Monza, Italy | Information on TC, LDL and TG retrieved from routine blood samples drawn at approximately 8.00 a.m., after an overnight fasting. Blood tests carried out within 24 hours after hospitalisation | ICD-10 classification of psychiatric disorders used | Age and sex identified as confounders | Confounders controlled in logistic regression | Standard definitions used to distinguish violent (firearm, hanging, cutting, jumping, car exhaust, other violent methods) from non-violent (drug overdose and poisoning) attempt methods | 100 | Include |
| Study                      | Study design                                      | Inclusion criteria clearly defined                                                                 | Study subjects and setting described in detail                                                                 | Exposure measured in a valid and reliable way | Objective, standard criteria used for measurement of condition | Confounders identified                                                                          | Strategies to deal with confounders                                                                 | Outcomes measured in a valid way | Appropriate statistical analysis                                                                 | Score (%) | Overall appraisal |
|---------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------|------------|-------------------|
| Eriksen et al. (2017)     | Cross-sectional with a longitudinal component    | Inclusion criteria: all patients admitted from 21 March 2012 to 20 March 2013 from Oslo University Hospital Exclusion criteria: incomplete serum-lipid samples | Age, sex, involuntary admission, employment, education status and marital status recorded Acute psychiatric ward at Oslo University Hospital has five units (45 beds) for emergency psychiatric admissions from a catchment area of about 200,000 persons older than 18 years | Serum measures of TC and HDL in millimoles per litre (mmol/L) were obtained from routine blood tests at admission and analysed with "enzymatic colorimetric method" for TC and "homogeneous enzymatic colorimetric method" for HDL | ICD-10 classification of psychiatric disorders used | Male gender, involuntarily admitted and psychosis identified as potential confounders | Violent behaviour measured using SOAS-R Association between cholesterol and suicide attempt measured using appropriate statistical analysis |       | Multivariate binary logistic regression used                                      | 100        | Include           |
| Shrivastava et al. (2017) | Cross-sectional, cohort study, Categorical observation | Inclusion criteria: age 18–30, schizophrenia diagnosed by DSM-IV-TR, inpatients in the first episode of the illness and consent Exclusion criteria: organic psychiatric conditions, other major psychiatric disorders, substance abuse (excluding nicotine dependence), and major medical or surgical illnesses | Age, sex and duration of illness recorded A tertiary general psychiatric centre (hospital name not provided), in India | TC collected from routine blood investigation. Data TC were retrieved from the biochemistry database of the facility | DSM-IV-TR classification of schizophrenia used | Differences in socioeconomic status, metabolic profiles and dietary differences identified as confounders | No strategy to deal with confounders SIS-MAP used to measure severity of suicidal behaviour |       | Pearson correlation analysis used                                               | 87.5       | Include           |
| Study          | Study design   | Inclusion criteria clearly defined | Study subjects and setting described in detail | Exposure measured in a valid and reliable way | Objective, standard criteria used for measurement of condition | Confounders identified | Strategies to deal with confounders | Outcomes measured in a valid way | Appropriate statistical analysis | Score (%) | Overall appraisal |
|---------------|----------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------------------------------|------------------------|-------------------------------|-------------------------------|---------------------------------|----------|------------------|
| Kavoor et al. (2017) | Cross-sectional. Categorical observation compared to age, sex and ethnicity matched healthy controls | Inclusion criteria: schizophrenia diagnosed with ICD-10 classification, antipsychotic-drug naïve or antipsychotic-drug free for at least 4 weeks (oral medication) or 8 weeks (depot medication), educated to at least class 5. Exclusion criteria: diagnosis of substance dependence, other psychiatric or eating disorders, comorbid neurological disorder or medical conditions and taking oral contraceptives and beta blockers. | Age, sex, education, religion, marital status, family history and BMI recorded. Tertiary-level referral centre and a post graduate teaching hospital in western Uttar Pradesh. | Venous blood samples (5 mL) were drawn on weekdays between 7 and 9 a.m. after the participants had fasted for at least 12 hours. Samples were immediately delivered to the hospital laboratory and analysed for TC, HDL, LDL, VLDL and TGs using enzymatic auto-analyser. | ICD-10 classification of schizophrenia used. Substance abuse, nutritional status and use of historical indices of violence identified as confounders. | No strategy to deal with confounders. | MOAS, IRS and BSI were used to quantify impulsivity, aggression and suicidality, respectively. | Age, sex, education, religion, marital status, family history and BMI recorded. Tertiary-level referral centre and a post graduate teaching hospital in western Uttar Pradesh. | Pearson's correlation analysis used. | 87.5 | Include |
| Mensi et al. (2016) | Cross-sectional. Unclear inclusion criteria – stated that patients included met the inclusion criteria but did not specify the nature of the criteria. | Inclusion criteria: schizophrenia diagnosed with DSM-IV classification. | Age, sex, BMI smoking status and alcoholic status were recorded. Recruited from the University Hospital of Monastir, located in the Mid-eastern part of Tunisia. | Venepuncture was performed for all subjects between 8 and 9 a.m. after a 12-hour overnight fast. Approximately 5 mL of blood was collected. Immediately after collecting blood samples, serum concentration of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG) were determined using enzyme methods on COBAS 6000 automats analyser, and low-density lipoprotein cholesterol (LDL-c) was calculated with the Friedewald equation. | DSM-IV classification of schizophrenia used. Medication identified as a potential confounder. | No strategy to deal with confounders. | Suicide attempts divided into two groups: lifetime suicide group (who had attempted suicide for more than 2 months) and recent suicide group (who had attempted suicide for less than 2 months). | Chi-square test and independent sample t test used. | 75 | Exclude |
### Table 3. (continued)

| Study                  | Study design          | Inclusion criteria clearly defined | Study subjects and setting described in detail | Exposure measured in a valid and reliable way | Objective, standard criteria used for measurement of condition | Confounders identified | Strategies to deal with confounders | Outcomes measured in a valid way | Appropriate statistical analysis | Score (%) | Overall appraisal |
|-----------------------|-----------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------------------------------|-----------------------|-----------------------------------|---------------------------------|---------------------------------|-----------|------------------|
| Misiak et al. (2015)  | Cross-sectional cohort study | Inclusion criteria: schizophrenia diagnosis based on DSM-IV and confirmed using OPCRIT checklist, admitted to Lower Silesian Center of Mental Health (Wrocław, Poland) Exclusion criteria: mental retardation and/or general brain disorder, supplementation of folic acid or vitamins B, medications influencing lipid profile, positive urine screening for illicit drugs, alcohol or drug abuse/dependence during 1 year prior to the onset of psychosis and severe somatic comorbidities | Age, sex, education, marital status, employment, weight, height, and BMI recorded. Lower Silesian Center of Mental Health (Wrocław, Poland) Blood samples were obtained between 7.30 and 8.30 a.m. after at least 10 hours overnight fasting from the antecubital vein. TC determined using a Cobas 6000 analyser. Enzymatic methods used also to measure TC, HDL and TG. LDL was calculated using the Friedewald equation | DSM-IV classification of schizophrenia used | Age, BMI, chlorpromazine dosage and treatment duration identified as confounders | Confounders controlled in general linear model | Patients divided into two subgroups based on those who had a lifetime experience of suicidal ideation and those who did not. Subgroups derived based on OPCRIT checklist | General linear model and two-way ANOVA used | 100       | Include          |
| Ainiyet et al. (2014) | Cross-sectional       | Inclusion criteria: schizophrenia diagnosed by at least two psychiatrists according to DSM-IV criteria (SGID), acute exacerbation of schizophrenia Exclusion criteria: severe somatic illness, drug and/or alcohol abuse/dependence, comorbid eating disorder, and using low-fat diet, lipid-lowering drugs or hormonal therapy | Age, sex and duration of illness recorded. Inpatient clinic at the Department of Adult Psychiatry, Poznan University of Medical Sciences Fasting blood was drawn at 800 a.m. within 24–72 hours of admission to the outpatient clinic. Laboratory measures included concentrations of the following lipids: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and total lipids | Schizophrenia diagnosis by at least two psychiatrists according to DSM-IV criteria (SGID) | Potential confounder, such as age, smoking, involuntary admission and a previous history of suicide attempt, not identified | No strategy for dealing with confounders | Non-paired t-test used | 75       | Exclude          |
### Table 3. (continued)

| Study                  | Study design                        | Inclusion criteria clearly defined                                                                 | Study subjects and setting described in detail                                                                 | Exposure measured in a valid and reliable way                                                                 | Objective, standard criteria used for measurement of condition | Confounders identified | Strategies to deal with confounders | Outcomes measured in a valid way                                                                 | Appropriate statistical analysis                  | Score (%) | Overall appraisal |
|----------------------|-------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------|---------------------------------|-----------------------------------------------------------------|-----------------------------------------------|-----------|------------------|
| Park et al. (2013)   | Cross-sectional                     | Inclusion criteria: schizophrenia, bipolar affective disorder or major depressive disorder, based on ICD-10, aged over 18 | Age, sex, number of admissions, BMI, socioeconomic status and comorbid disease recorded. Recruited from a psychiatric ward at a university hospital in Seoul, Korea | TC, HDL and TG were recorded at time of admission. ICD-10 classification of schizophrenia used | Previous history of suicide attempt identified as a potential confounder | No strategy for dealing with confounders | Patients grouped into two categories: patients who died by suicide and patients that did not | Nonparametric Spearman correlation coefficient test used | Independent t-test for continuous variables and a chi-square test for categorical variables | 85.7 | Include |
| Marcinko et al. (2008) | Cross-sectional                    | Inclusion criteria: male schizoaffective patients whose biochemical analyses from the time of admission were available, treated at Department of Psychiatry, University Hospital Zagreb, during the period of 18 months | Age, BMI, previous hospitalisation and duration of illness recorded. Department of Psychiatry, University Hospital Zagreb | Venepuncture was performed for all subjects between 8 and 9 a.m. after 12-hour overnight fast. Immediately after collecting blood samples, TC, HDL and triglycerides were determined using enzyme method and commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on Olympus AU 600 automated analyzer | ICD-10 classification used | Poor physical health, dietary habits, social and economical conditions identified as potential confounders | No strategy for dealing with confounders | Patients suicidal at hospital admission if suicidal ideation, suicide attempt, or both, was present. Suicidality was assessed positive if item 3 of the Hamilton Depression Rating Scale (HDRS-17) scale was scored positively. Severity of suicidality was measured by SSI at the time of admission | Nonparametric Spearman correlation coefficient test used | 85.7 | Include |
| Marcinko et al. (2007) | Cross-sectional with longitudinal follow-up over 12 months | Inclusion criteria: male patients diagnosed with Psychotic Disorder Not Otherwise Specified, admitted to Department of Psychiatry, University Hospital Zagreb, during the period of 12 months | Age, BMI, family status. Church attending, and family history of suicide or suicide attempt recorded. Department of Psychiatry, University Hospital Zagreb | Blood samples were collected from all subjects at 8:00 a.m. after an overnight fasting. TC was determined enzymatically, immediately after the blood collection, using commercial kits | DSM-IV classification used | Age and BMI identified as confounders | Confounders controlled in ANCOVA test | ANOVA and ANCOVA | 100 | Include |
Table 3. (continued)

| Study                     | Study design | Inclusion criteria clearly defined | Study subjects and setting described in detail                                      | Exposure measured in a valid and reliable way | Objective, standard criteria used for measurement of condition | Confounders identified | Strategies to deal with confounders | Outcomes measured in a valid way | Appropriate statistical analysis | Score (%) | Overall appraisal |
|--------------------------|-------------|-----------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------|------------------------|----------------------------------|---------------------------------|---------------------------------|-----------|------------------|
| Kim et al. (2002)        | Cross-sectional | Inclusion criteria: patients admitted to Korea University Medical Center emergency room consecutively after suicide attempt between January 1994 and July 2000 Exclusion criteria: panic disorder | Age, sex and BMI reported Korea University Medical Center emergency room All subjects fainted overnight. Samples of blood were drawn from the antecubital vein in a sitting position using a tourniquet between 7 a.m. and 8 a.m. For the suicidal patients, blood was collected within 48 hours after the suicide attempt. Five millilitres of blood was collected into a vacuum tube with no additives. Total serum cholesterol levels were measured by enzymatic procedures using a Hitachi 717 analyser | DSM-III-R classification used Age, gender and BMI identified as confounders | Confounders controlled in ANOVA analysis | The severity of suicide attempt was evaluated according to the degree of resulting medical injury on the 5-point Medical Lethality Rating Scale (A.T. Beck, unpublished) | ANOVA and t-test used | 100 | Include |
| Steinert et al. (1999)   | Cross-sectional | Unclear, only ‘patients on general psychiatric admission unit’ stated Age, age at admission, sex recorded General psychiatric admission unit in Germany | Blood samples taken within first 3 days after admission under sober conditions in the morning. TC determined in an external laboratory centre providing continuous quality controls | ICD-10 classification used Potential confounding factors, such as BMI, smoking, medication, involuntary admission, not identified | No strategy for dealing with confounders | Aggression assessed after discharge using MOAS, SDAS, SOAS, and VS | Spearman’s rank for correlations used | 62.5 | Exclude |

(continued)
| Study                | Study design        | Inclusion criteria clearly defined                                                                 | Study subjects and setting described in detail                                                                 | Exposure measured in a valid and reliable way                                                                 | Objective, standard criteria used for measurement of condition | Confounders identified                                      | Strategies to deal with confounders                      | Outcomes measured in a valid way | Appropriate statistical analysis | Score (%) | Overall appraisal |
|---------------------|---------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------|-------------------|
| Kunugi et al. (1997) | Cross-sectional    | TC measured immediately after admission (within 24 hours), blood sampling carried out in the morning of the day following admission, total protein level and red blood cell count simultaneously measured. Exclusion criteria: diagnosis of substance abuse or organic brain syndrome. | Age, sex, psychical condition (injury, burn, intoxication or hypoxia) reported. Emergency ward at Teikyo University Hospital, Tokyo, Japan. | TC measured immediately after admission (within 24 hours), blood sampling carried out in the morning of the day following admission. | DSM-III-R classification used | States that 'potential confounders were adjusted for' but no specification of what these were. | Confounders controlled in ANCOVA analysis                       | Cases consisted of suicide attempters that were discharged alive. | ANCOVA and Student's t-test used | 87.5            | Include          |

ICD: International Classification of Diseases; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; ICD-10: International Classification of Diseases, 10th Revision; BMI: body mass index; TOP: Thematically Organised Psychosis study; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.); IDS-C: Inventory of Depressive Symptomatology; HBL: hypobetalipoproteinaemia characterised by LDL lower than fifth percentile for age and sex; SOAS-R: Staff Observation Aggression Scale–Revised; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.); SIS-MAP: Scale for Impact of Suicidality – Management, Assessment and Planning of Care; VLDL: very low-density lipoprotein; LPT: Lipid panel test.
| Study                                      | Location                                                                 | Study design                        | Psychiatric conditions included in study          | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) | Cholesterol measures examined in relation to aggression | Findings classified by aggression type | Other findings                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------|-------------------------------------|------------------------------------------------|---------------------------|-----------------------------------------|---------------------|------------------------------|----------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------|
| Sankarana-rayanan et al. (2020)           | Database of patients with psychotic disorders from Australia             | Cross-sectional                     | Schizophrenia, schizoaffective disorder         | ICD-10                    | 802 (540 males, 262 females)            | 591 schizophrenia 211 schizoaffective disorder | Cases – patients with schizophrenia or schizoaffective disorder Controls – values from the normal population | 37.72 ± 10.92                             | TC HDL LDL TG Mean TG/HDL ratio | Low HDL more likely to report current suicidal ideation (OR = 0.375, 95% CI = [0.14, 0.99]) | Confounders like psychological stress, impulsivity or serum cortisol were not included in the analysis. The HDL significance could be a type I error. The study was conducted predominantly on community-dwelling patients with schizophrenia, not on acutely ill or inpatients with schizophrenia |
| Hjell et al. (2020)                       | Inpatient and outpatient clinics of major hospitals in Oslo, Norway      | Cross-sectional                     | Schizophrenia spectrum disorder Bipolar spectrum disorder | DSM-IV                    | 1001 (525 males, 476 females)           | Cases – patients with schizophrenia spectrum disorder Controls – values from the normal population | >18 Median age for patients with no aggressive symptoms (NAS) 30. Median age for patients with medium level aggressive symptoms (MLAS) 29. Median age for patients with high level aggressive symptoms (HLAS) 25 | No relationship between TC, LDL or HDL and aggression, as measured by PANSS-EC (sum of items measuring excitement, hostility, tension, uncooperativeness and poor impulse control) | TC LDL HDL | Highest levels of aggression scarcely represented among study participants. Median age of patients in sample was 29, below the recommended age of 40 for initiation of cardiovascular disorder risk evaluation and statin therapy initiation |
Table 4. (continued)

| Study | Location | Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) Range and mean ± SD (if available) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type |
|-------|----------|--------------|------------------------------------------|--------------------------|---------------------------------------|---------------------|---------------------------------------------------------------|----------------------------------------------------------|---------------------------------------|
| Gohar et al. (2019) | Major hospitals in Oslo, Norway | Cross-sectional (with correlational analysis) | Schizophrenia, Schizoaffective disorder, Schizophreniform disorder, Psychosis NOS | DSM-IV | 270 (161 males, 109 females) | Cases: patients with mild/moderate suicidal behaviour and severe suicidal behaviour with/without suicide attempts Controls: patients without suicidal behaviour | 18–65 years 30.7 ± 10.1 | TC LDL TG | Physical against self Physical against others Physical against objects Verbal Other findings |

(continued)
### Table 4. (continued)

| Study          | Location Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Number of schizophrenia/schizoaffective/psychotic patients and gender distribution (male:female) | Case control groups | Findings classified by aggression type |
|----------------|-----------------------|------------------------------------------|---------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------|---------------------|---------------------------------------|
| Cariou et al. (2018) Nantes University Hospital, France | Cross-sectional | Schizophrenia, schizotypal and delusional disorders Organic mental disorder Mental disorders due to psychoactive substance use Unspecified psychosis Affective disorders Neurotic disorders Disorder of adult personality and behaviour Pervasive and specific developmental disorders | ICD-10 | 837 (of 839, 2 patients excluded due to secondary causes of HBL) (495 males, 342 females) | 300 (male:female ratio not provided) | Cases: patients Controls: values from the normative population | Age of participants (years) Range and mean ± SD (if available) | Cholesterol measures examined in relation to aggression |
|                |                       |                                           |                           |                                         |                                                                                               |                     | Physical against self Physical against others Physical against objects Verbal Other findings |
| Eriksen et al. (2018) Oslo University Hospital, Norway | Cross-sectional with longitudinal component | Psychosis Bipolar disorder Substance abuse Depression Anxiety Personality disorders | ICD-10 | Inpatient sample: 348 (156 males, 192 females in inpatient sample) | Psychosis Group: Inpatient: 102, follow-up: 29 | Cases: patients admitted to an acute psychiatric ward Controls: values from the normal population | Inpatient: 18-83 Follow-up sample: 20-75 | TC HDL |
|                |                       |                                           |                           |                                         |                                                                                               |                     | TC link with violence was non-significant for men and women for inpatients. HDL contributed to violence risk for men in the inpatient sample even when controlled for other variables (p = 0.032) but not women |
| Findings classified by aggression type |   |   |   |
|-------------------------------------|---|---|---|
| Physical against self               |   |   |   |
| Physical against others             |   |   |   |
| Physical against objects            |   |   |   |
| Verbal                              |   |   |   |

**Number of schizophrenia/schizoaffective/psychotic patients and gender distribution (male:female)**

- Capuzzi et al. (2018) - 195 Cases – patients with schizophrenia
  - Controls – values from the normal population
  - Most subjects were treated with pharmacological agents, including antipsychotics, mood stabilizers and antidepressants, which might influence lipid profile and its relationship with suicidal behavior.

**Other findings**

- No association between recent suicide attempts and TC ($p=0.841$), LDL ($p=0.682$) and TG ($p=0.515$) in patients with schizophrenia.

**Table 4.** (continued)

- Most subjects were treated with pharmacological agents, including antipsychotics, mood stabilizers and antidepressants, which might influence lipid profile and its relationship with suicidal behavior.

**Number of suicide attempts was relatively small.**

**Most subjects were treated with pharmacological agents, including antipsychotics, mood stabilizers and antidepressants, which might influence lipid profile and its relationship with suicidal behavior.**
| Study | Location | Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) | Range and mean ± SD (if available) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type |
|-------|---------|-------------|------------------------------------------|---------------------------|----------------------------------------|--------------------|---------------------------|-------------------------------|----------------------------------|----------------------------------------|
| Eriksen et al. (2017) | Oslo University Hospital, Norway | Cross-sectional with a longitudinal component | • Psychosis  
• SubSTANCE abuse  
• Bipolar disorder  
• Depression  
• Anxiety  
• Personality disorders | ICD-10 | 362 inpatients (158 males, 204 females); of these, 99 followed up at 3 months after discharge | NA | > 18  
18-95 Baseline inpatient sample: Mean = 41  
Follow up outpatient sample (outpatients) Mean 38 | TC HDL | Not assessed | 59 (16%) inpatients 26 (26%) post-discharge |
| | | | | | | | | | | Physical against self  
Physical against others  
Physical against objects  
Verbal | Other findings |
| | | | | | | | | | Physical against self  
Physical against others  
Physical against objects  
Verbal | Other findings |
| | | | | | | | | | Physical against self  
Physical against others  
Physical against objects  
Verbal | Other findings |
| | | | | | | | | | Physical against self  
Physical against others  
Physical against objects  
Verbal | Other findings |
| | | | | | | | | | Physical against self  
Physical against others  
Physical against objects  
Verbal | Other findings |
| | | | | | | | | | Physical against self  
Physical against others  
Physical against objects  
Verbal | Other findings |
| | | | | | | | | | Physical against self  
Physical against others  
Physical against objects  
Verbal | Other findings |

At inpatient assessment, a statistically significant association, OR [95% CI] = 0.52 [0.28, 1.0], p = 0.049 between low HDL and aggression (physical against others and verbal assessed together). 
At post-discharge assessments, no association across the entire sample (p = 0.186) but a significant association between low HDL and post-discharge violence, OR [95% CI] = 0.099 [0.010, 0.95], p = 0.045 when examined in men. 
For psychosis (baseline inpatient assessment) and HDL, for inpatients, OR [95% CI] = 1.35 [1.28, 1.43], p < 0.001. 
No statistically significant association found between TC and aggression.
| Study | Location | Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type |
|-------|----------|--------------|------------------------------------------|--------------------------|----------------------------------------|---------------------|-----------------------------|-------------------------------------------------|----------------------------------|
| Shrivastava et al. (2017) | A tertiary general psychiatric centre (hospital name not provided), in India | Cross-sectional, cohort study, Categorical observation | Non-affective schizophrenia | DSM-IV | 60 (41 males, 19 females) | NA | 18–39 | TC | Lower levels of TC ($p=0.047$) in female patients with moderate suicidality ($n=9$) compared to those with low ($n=6$) or high suicidality ($n=4$) |

**Findings classified by aggression type**

- **Physical against self**: Not assessed
- **Physical against others**: Not assessed
- **Physical against objects**: Not assessed
- **Verbal**: An association was not found for men between low TC and suicidality. No association for the whole sample between low TC and suicidality. Even for females, no association was found with suicidality, but this could be due to low numbers with high suicidality. Correlation between TC and SIS-MAP scales (Scale for Impact of Suicidality - Management, Assessment, and Planning of Care) was non-significant ($r=0.203$, $p=0.119$). This study suggests that the relationship between TC and suicidality may not be necessarily linear. The sample size, however, was really small, even for moderate suicidality.
Table 4. (continued)

| Study | Location | Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) | Number of schizophrenia/schizoaffective/psychotic patients and gender distribution (male:female) | Cholesterol measure/s | Findings classified by aggression type |
|-------|----------|--------------|---------------------------------|--------------------------|----------------------------------------|---------------------|--------------------------|--------------------------------|-----------------|-------------------------------------|
| Kavoor et al. (2017) | Tertiary level referral centre and post-graduate teaching hospital in western Uttar Pradesh, India | Cross-sectional. Categorical observation compared to age, sex and ethnicity matched healthy controls | Paranoid and undifferentiated schizophrenia | ICD-10 | 120 (92 males, 28 females) | Cases: 60 adult schizophrenia patients (60 age- and sex-matched healthy controls) | 32.40 ± 6.6 | Controls: 32.42 ± 6.7 | TC, TG, HDL, VLDL | A negative trend-level correlation ($r = -0.183$) between TC and suicidal aggression assessed through the MOAS score, though not statistically significant. Negative correlation between TC and impulsivity assessed using the IRS ($r = 0.517$, $p < 0.01$). Negative correlation between LDL and impulsivity (IRS) ($r = 0.307$, $p < 0.01$) but not aggression (MOAS) ($r = 0.092$). There was also a negative correlation between TG and IRS-assessed impulsivity ($r = 0.282$, $p < 0.05$). |
| | | | | | | | | | | Findings not stated |
| | | | | | | | | | | Findings not stated |
| | | | | | | | | | | TC was significantly lower in the patient group compared to healthy controls ($p < 0.001$). HDL and LDL were also significantly lower in the patient group ($p < 0.005$ and $p < 0.009$). VLDL was also lower but not to statistical significance ($p = 0.119$ and $p = 0.068$). Male schizophrenia patients additionally had lower TG levels than the healthy male control group ($p = 0.025$). TC showed negative correlation with impulsivity ($r = 0.517$, $p < 0.01$) and suicidality ($r = 0.303$, $p < 0.05$). |
### Table 4. (continued)

| Study          | Location                          | Study design               | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Number of schizophrenia/schizoaffective/psychotic patients and gender distribution (male:female) | Case control groups | Age of participants (years) Range and mean ± SD (if available) | Cholesterol measure(s) examined in relation to aggression | Findings classified by aggression type | Findings not stated | Physical against self | Physical against others | Physical against objects | Verbal | Other findings |
|----------------|-----------------------------------|----------------------------|-------------------------------------------|----------------------------|------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------|----------------------|------------------------|------------------------|---------|----------------|
| Chen et al. (2015) National Taiwan University Hospital, Taiwan | Case series Correlational observation | Schizophrenia DSM-IV | 107 (33 males, 74 females) | NA | >16 | 33.4 (11.9) | TC TG LDL HDL | Findings not stated | Findings not stated | The major manifestation of violence in this study was verbal aggression towards others | Cases with an increased level of overall aggression exhibited a trend towards smaller proportion of high LDL level (p = 0.06). Female gender and low TC levels (along with early onset, higher scores of positive symptoms and lower scores of negative symptoms) were found to be predictors of violence with a predictive accuracy of 0.85 [95% CI] = [0.72, 0.97], p < 0.0001. Smaller sample sizes in the higher violence trajectory classes (3 and 4) might have prevented their association with lipid levels reaching statistical significance |
Table 4. (continued)

| Study | Location | Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Number of schizophrenia/schizoaffective/psychotic patients and gender distribution (male:female) | Number of suicidal ideation cases and controls in male:female | Age of participants (years) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type |
|-------|----------|-------------|------------------------------------------|--------------------------|---------------------------------------|---------------------|------------------------------------------------------------------------------------------------|-----------------------------|--------------------------|------------------------------------------|-----------------------------------|
| Misiak et al. (2015) | Lower Silesian Centre of Mental Health, Wroclaw, Poland | Cross-sectional cohort study | Schizophrenia | DSM-IV | 100 (53 males, 47 females) | 100 | Cases – 30 first-episode schizophrenia with lifetime experiences of suicidal ideation Controls – 70 first-episode schizophrenia patients with no lifetime experience of suicidal ideation | | Range: 18–43 | TC (mg/dL) LDL (mg/dL) HDL (mg/dL) TG (mg/dL) | Association found between higher TC and suicidal ideation in females \(p = 0.012\), and between higher LDL and suicidal ideation in females \(p = 0.020\). This was based on group differences between cases and controls. No such differences found in males. This is offering a finding which is an opposite result to other studies mostly showing an association between low TC and suicidal risk, thus suggesting that the nature of lipid metabolism in patients experiencing suicidal ideation might be complex. |
| Park et al. (2013) | Psychiatric ward at University Hospital in Seoul, Korea | Cross-sectional | Schizophrenia Bipolar affective disorder Major depressive disorder | ICD-10 | 516 (males 252, females 264) | 246 | Cases – patients with schizophrenia who died by suicide Controls – with schizophrenia who were non-suicidal | | TC TG HDL | No difference between patients who died by suicide and controls in schizophrenia, including TC, triglyceride and HDL cholesterol. No standardised procedure for arriving at diagnoses Information on other risk factors like symptomatic characteristics and poor adherence to medication not available. |
Table 4. (continued)

| Study | Location      | Study design                                           | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) | Range and mean ± SD (if available) | Cholesterol measure/s examined in relation to aggression | Physical against self | Physical against others | Physical against objects | Verbal | Other findings |
|-------|---------------|-------------------------------------------------------|------------------------------------------|----------------------------|----------------------------------------|---------------------|----------------------------|----------------------------------|------------------------------------|-----------------------|---------------------|------------------------|--------|-----------------|
| Turkoglu et al. (2009) | Elazig Mental Hospital, Turkey | Case control. Categorical observation between schizophrenia patients with and without a record of crime | Schizophrenia | DSM-IV | 100 (all male) | 100 (all male) | Cases – 50 male, criminal schizophrenia patients Controls – 50 male, non-criminal schizophrenia patients | 19-59 | TC | Ghrelin | Not assessed | 72% of crime included in the study were physical aggression against others, including homicide, assault and battery. Levels of serum TC were numerically lower in the schizophrenia patients who had committed a crime compared to those who had not but the difference was not statistically significant. (p > 0.05; exact value not reported). Serum TG levels and ghrelin were higher in the offender group, compared to the non-offender group. (p < 0.001) | 14% of crime included damage to public property | Not assessed |
### Table 4. (continued)

| Study | Location | Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) | Range and mean ± SD (if available) | Cholesterol measure(s) examined in relation to aggression | Findings classified by aggression type | Other findings |
|-------|----------|--------------|------------------------------------------|---------------------------|----------------------------------------|---------------------|-----------------------------|----------------------------------|----------------------------------|-----------------------------|----------------|
| Marcinko et al. (2008) | University Hospital Zagreb, Croatia | Cross-sectional | Schizoaffective disorder | ICD-10 | 60 (all males) | 40 (20 with suicidal and 20 non-suicidal) | Cases – consecutively admitted patients with schizoaffective disorder with suicidal behaviour and consecutively admitted patients with schizoaffective disorder without suicidal behaviour | >18 | TC | Suicidal patients: 28.90 ± 8.76 Non-suicidal patients: 37.35 ± 12.21 Controls: 29.85 ± 7.57 | Physical against self: Suicidal patients had significantly lower levels of TC (p = 0.000) and LDL (p = 0.001) than non-suicidal patients. TG and HDL values were also lower but without a statistically significant difference. | The authors claimed that this was the first study to show the relationship between reduced TC and suicidality in schizoaffective disorder. |
| Study                  | Location                          | Study design                                      | Psychiatric conditions included in study                                                                 | Diagnostic classification | Total sample size (gender distribution) | Number of schizophrenia/schizoaffec-tive/psychotic patients and gender distribution (male/female) | Case control groups | Age of participants (years) Range and mean ± SD (if available) | Cholesterol measure examined in relation to aggression | Findings classified by aggression type                  |
|------------------------|-----------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------|----------------------------------------|-------------------------------------------------------------------------------------------------|---------------------|-----------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| Ruljancic et al. (2007)| Sveti Ivan Psychiatric Hospital, Croatia | Case series. Categorical observation between psychiatric patients | • Schizophrenia • Schizoaffective disorder • Psychotic disorder • Dependence Syndrome • Depressive disorder • Stress reaction • Personality disorder • Non-violent suicidal attempt (drug poisoning) • Violent suicidal attempt (hanging, suffocation, sharp object) | ICD-10                   | 677 (415 males, 262 females)           | Schizophrenia: 136 (58 females, 78 males) Schizoaffective: 64 (49 females, 15 males) Psychotic disorders: 47 (19 males, 28 females) | NA                  | 17-89 TC                                                        | Patients with a history of non-violent suicidal attempt (drug poisoning) had significantly lower serum TC than those with schizophrenia (p=0.039) or schizoaffective disorder (p=0.019) | Physical against self Not assessed Physical against others Not assessed Verbal Other findings There was a similar difference between non-violent suicidal attempters and depressive disorder, stress reaction and personality disorders. This study did not examine TC levels in relation to any history of violence within schizophrenia, schizoaffective/psychotic disorder groups |
| Marcinko et al. (2007) | Clinical Hospital Centre, Zagreb, Croatia | Cross-sectional with longitudinal follow-up over 12 months | Psychotic Disorder Not Otherwise Specified (first episode of psychosis) | DSM-IV-TR                | 81 (all males)                        | 27 Cases – 27 consecutively admitted suicidal men in the first episode of psychosis and 27 consecutively admitted men in first episode of psychosis without suicidal behaviour Controls – healthy males with no history of psychiatric illness and suicidal behaviour | Suicidal patients: 29.70 ± 7.22 Non-suicidal patients: 29.56 ± 8.67 Healthy controls: 30.33 ± 3.13 | TC levels were significantly reduced in suicidal when compared to non-suicidal or healthy subjects, even after controlling for age and BMI (p=0.028) | TC levels were significantly reduced in suicidal when compared to non-suicidal or healthy subjects, even after controlling for age and BMI (p=0.028) | Platelet 5-HT concentration was significantly lower in suicidal than in non-suicidal patients or healthy controls (p < 0.001 and p= 0.002, Scheffe’s test, respectively) |
### Table 4. (continued)

| Study                     | Location                      | Study design                      | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Age of participants (years) Range and mean ± SD (if available) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type |
|---------------------------|-------------------------------|-----------------------------------|------------------------------------------|---------------------------|-----------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------|
| Marcinko et al. (2005)    | Clinical Hospital Centre, Zagreb, Croatia | Case control                     | Schizophrenia                            | ICD-10                    | 46 (all males)                          | Cases – 31 males suffering from schizophrenia, admitted after suicide attempt (15 non-violent attempters, 16 violent attempters) Controls – 15 schizophrenia non-suicidal male patients | TC Serum cortisol                                    |
|                           |                               |                                   |                                          |                           |                                         | Cases: 32.02 ± 8.21 Controls: 30.95 ± 9.03 | Not assessed                                                | Physical against self: significantly lower TC in violent attempters compared to non-violent attempters (p < 0.01) and compared with no suicide controls (p < 0.01). No significant difference between the non-violent suicide attempters and no suicide controls | Serum cortisol concentration significantly higher (p < 0.01) in violent compared to non-violent suicide attempters, and no suicide attempters |

(continued)
| Study | Location | Study design | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) Range and mean ± SD (if available) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type |
|-------|----------|--------------|------------------------------------------|--------------------------|----------------------------------------|---------------------|---------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------|
| Chakrabarti et al. (2004) Central Institute of Psychiatry, Ranchi, India | Case control Categorical observation between psychotic patients with a history of violent crime and without a history of violent crime | Schizophrenia (paranoid and undifferentiated) Bipolar affective disorder Recurrent depressive disorder ICD-10 | 46 – 23 in case group and 23 in control group, as the control group was matched to the case group by diagnosis (all males) | Cases – 30 male inpatients diagnosed with a psychotic illness with a history of violent crime Controls – 30 age and BMI matched psychotic inpatients with no history of violent crime | TC HDL LDL VLDL TG Apolipoprotein A1 Apolipoprotein B | Cases: 33.17 ± 7.53 Controls: 32.43 ± 9.14 | TC <p>0.001</p> LDL <p>0.001</p> VLDL <p>0.001</p> TG <p>0.003</p> Apolipoprotein A1 <p>0.021</p> | Physical against self: Violent crime was assessed in this study and included homicide, rape, arson and grievous injury. Group with a history of violent crime showed significantly lower TC (p = 0.001) and lower LDL (p < 0.001) compared to group without a history of violence | Findings not stated | Not assessed | Physical against others: Though there was no significant association between higher HDL and TC in this study, higher HDL is known to be associated with lower total cholesterol Grandiosity (p = 0.012), elated mood (p = 0.039), motor hyperactivity (p = 0.031) and distractibility (p = 0.033) showed a negative correlation with APA1. Higher APA1 is associated with lower total cholesterol |

(continued)
| Study               | Location               | Study design                  | Psychiatric conditions included in study                                                                 | Diagnostic classification | Total sample size (gender distribution) | Number of schizophrenia/schizoaffective/psychotic patients and gender distribution (male/female) | Case control groups | Age of participants (years) | Cholesterol measure’s examined in relation to aggression | Findings classified by aggression type                      | Physical against self | Physical against others | Physical against objects | Verbal | Other findings |
|---------------------|------------------------|-------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------|----------------------------------------|------------------------------------------------------------------------------------------------|--------------------|--------------------------|----------------------------------------------------------|-----------------------------------------------------------------|-----------------------|------------------------|--------------------------|--------|---------------------|
| Tripodanakis et al. | Evangelismos General Hospital, Greece | Case control Categorical observation between patients and healthy controls (no psychiatric history), matched for age and sex | Schizophrenia, Adjustment disorder, Depression, Personality disorder, All admitted to medical wards after a suicidal attempt | DSM-IV/R                  | 173 (66 males, 107 females)           | Cases – 111 (35 males, 76 females) Controls – 62 healthy controls (no psychiatric history or history of suicide attempt) (31 males, 31 females) | Schizophrenia group: 30.4 ± 9.9 Controls: 31.6 ± 8.1 | TC                       | Violent suicide attempters had a significantly lower TC level compared to controls (p = 0.041) and so did non-violent attempters (p = 0.0004) | The difference between violent and non-violent suicide attempters was not significant (p = 0.94) |
| Niuvanen et al.     | Hospital, Finland       | Case control Categorical observation between patients who had been secluded involuntarily (for violent acts, for suicidal acts) and patients who had not been secluded | Schizophrenia, paranoid and other types Personality disorder Other | ICD-10                    | 409 (all males)                       | Cases – male secluded patients (207 total, of which 165 schizophrenia patients) Controls – male non-secluded patients (202 total, of which 61 schizophrenia patients) | IS-71               | TC                       | Low (below 5.3 mmol/L) TC level was deemed to be a marker (p = 0.01) for increased risk of violent and suicidal behaviour in these forensic patients | Findings not stated | Findings not stated | Findings not stated | Patients who had been secluded as a result of violent behaviour (p = 0.001) and suicidal acts (p = 0.026) had significantly lower TC levels than those who had not been secluded |

(continued)
### Table 4. (continued)

| Study            | Location              | Study design       | Psychiatric conditions included in study                                                                 | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type | Other findings |
|------------------|-----------------------|--------------------|----------------------------------------------------------------------------------------------------------|---------------------------|----------------------------------------|---------------------|-----------------------------|---------------------------------------------------------|--------------------------------------|----------------|
| Kim et al. (2002) | Korea University Medical Centre, Korea | Cross-sectional    | Schizophrenia, Bipolar disorder, Personality disorder, Major depressive disorder | DSM-III-R                | 693 (327 males, 366 females)           | Cases: suicide attempters with schizophrenia (n=231) Controls – non-suicidal psychiatric inpatients (n=231) and normal healthy controls (n=231) | Cases: age not specified but mean age for the whole patient group 38.1, with SD 17.0 Controls: age not specified but mean age for psychiatric controls 38.2 ± 15.4; normal control: 38.2 ± SD 16.3 | TC Risk to self – no significant difference in serum TC levels found in suicide attempters with schizophrenia compared to non-suicidal attempts as well as normal controls | Total serum TC levels among suicide attempters was significantly lower (p < 0.001) in patients with major depressive disorder and personality disorder, but not also in bipolar disorder |
| Huang et al. (2000) | Chang Gung Memorial Hospital, Kaohsiung, Taiwan | Case series, Categorical analysis – between paranoid and non-paranoid schizophrenic patients | Schizophrenia, Bipolar I disorder (mania), Major depression, Organic mental disorder, Drug dependence, Alcohol dependence, Delusion disorder, Others | DSM-III-R                | 213 (gender distribution not specified) | Cases: psychiatric patients with any kind of diagnosis Controls – normal population | 30.6 ± 10.8 TC | No significant differences (p > 0.08) in the serum TC levels between patients who had (n=104) or had not made a suicidal attempt (n=92) | No significant differences (p = 0.8373 > 0.05) in the serum TC levels between patients with physical violence (n=22) and without (n=84) | Not assessed | No significant difference (p = 0.96) in mean serum TC levels between men and women No significant differences (p > 0.24) in mean serum TC between paranoid and non-paranoid sub-types Serum TC levels were lower (p < 0.001) in psychiatric inpatient group compared to controls |
| Study                  | Location                  | Study design       | Psychiatric conditions included in study | Diagnostic classification | Total sample size (gender distribution) | Case control groups | Age of participants (years) Range and mean ± SD (if available) | Cholesterol measure/s examined in relation to aggression | Findings classified by aggression type | Other findings                  |
|-----------------------|---------------------------|--------------------|------------------------------------------|---------------------------|-----------------------------------------|---------------------|-----------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------|----------------------------------|
| Kunugi et al. (1997)  | Tokyo University Hospital, Tokyo | Cross-sectional | Schizophrenia spectrum disorders          | DSM-III-R                 | 173 (99 males, 74 females)              | 66                  | Cases – patients with schizophrenia admitted with suicide attempt Controls – patients with schizophrenia without suicide attempt | 37 suicide attempters: age not specified but mean age for whole sample: 40 ± 16.7 29 non-suicide attempters: age not specified but mean age for whole sample 39.6, with SD 15.5 | TC                                | No significant difference in TC levels between suicidal and non-suicidal groups in schizophrenia spectrum disorders | Significantly lower TC in suicide attempters than controls with mood disorders and with personality or neurotic disorders |

ICD-10: International Classification of Diseases, 10th Revision; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; OR: odds ratio; CI: confidence interval; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.); LDL: low-density lipoprotein; HBL: Hypobetalipoproteinaemia characterised by LDL lower than fifth percentile for age and sex; VLDL: very low-density lipoprotein; BSI: Beck Scale for suicidal ideation; MOAS: Modified Overt Aggression Scale; IRS: Impulsivity Rating Scale; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.); BMI: body mass index; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders (3rd ed., rev.); APA I: Apolipoprotein A1; PANSS-EC: Positive and Negative Syndrome Scale–Excited Component.
frequency of schizophrenia, thus reinforcing the link between low LDL levels, psychiatric disorders and aggression (Cariou et al., 2018).

Serum TG was explored in five studies (Cariou et al., 2018; Chakrabarti et al., 2009; Chen et al., 2015; Kavoor et al., 2017; Turkoglu et al., 2009) involving violence to others, with one finding a clear link between low TG and violence (Cariou et al., 2018), one between high TG and violence (Turkoglu et al., 2009), with the other three studies finding no significant link, but a trend towards a link between low TG and violence (Chakrabarti et al., 2009; Chen et al., 2015; Kavoor et al., 2017).

Two studies (Hjell et al., 2020; Huang and Wu, 2000) did not find a link between measures of serum cholesterol and violence in schizophrenia patients. Of these, the largest and most recent study (Hjell et al., 2020) had a large sample size ($n=1001$) and examined all patients with schizophrenia recruited from inpatient and outpatient clinics of major hospitals in Oslo, Norway, between the years 2002 and 2017. It had 601 patients with schizophrenia spectrum disorders, and the measure of aggression was the PANSS Excited Component (PANSS-EC; Kay et al., 1987). This scale has items on excitement, hostility, tension, uncooperativeness and poor impulse control. Impulsivity was measured with the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995).

There were no significant associations between TC, LDL, HDL and aggression or impulsivity in patients with schizophrenia spectrum disorders. The other study (Huang and Wu, 2000) examined paranoid and non-paranoid schizophrenia patients and did not find significant differences in serum cholesterol levels between patients with and without physical violence and patients who had or had not made a suicidal attempt. This study was on an exclusively inpatient sample.

The studies were again spread over a time period of almost two decades, between 2002 and 2020. Sample sizes varied widely, the largest study with a sample size of 1001 (Hjell et al., 2020), medium level studies with sample sizes of 409 and 348 (Eriksen et al., 2018; Repo-Tiihonen et al., 2002) and the smallest with a sample size of 60 patients (Chakrabarti et al., 2009).

**Studies assessing sex differences**

For the studies on suicidality, there were only three studies and these were exclusively single sex, for males (Marcinko et al., 2005, 2007, 2008). One found a link between low TC, low LDL and low HDL (but not low TG) and suicidality in schizoaffective disorder (Marcinko et al., 2008), one found a link between low TC and suicidality in first-episode psychosis (Marcinko et al., 2007) and the third study found low TC in patients with violent suicidal attempts as opposed to non-violent suicidal attempts and controls (Marcinko et al., 2005).

For the studies exploring link between cholesterol levels and violence, there were three studies exclusively on males (Chakrabarti et al., 2004; Repo-Tiihonen et al., 2002; Turkoglu et al., 2009), all involving forensic populations. These studies all found a significant association between relatively low TC and violence, except one (Turkoglu et al., 2009), where the association did not reach statistical significance. With regard to the studies which found a positive link between low TC and suicidality, one study (Misiak et al., 2015) which had both males and females in it found a link between relatively higher TC and LDL levels with suicidal ideation in female, but not in male first-episode schizophrenia patients. One problem with this study, however, was the relatively low overall prevalence of suicidal ideation. The authors themselves advise caution in the interpretation of the study results.

With regard to the studies examining the link between lipid profile and violence, one study (Eriksen et al., 2018) found low HDL to be contributing significantly to the model for violence risk assessment in males, but not females. In another report from the same group (Eriksen et al., 2017), low HDL level was significantly correlated with violence for males but not females in the first 3 months following discharge. However, another study (Chen et al., 2015), where sex distribution was 33 male and 74 female schizophrenia patients, found female sex and low dichotomised TC levels as two of five variables (others being early onset, higher scores of positive symptoms and lower scores of negative symptoms) which could be used as predictors of violence, with a predictive accuracy of 0.85 (95% CI = [0.72, 0.97]).

The studies which exclusively examined male populations were all in forensic patients and all suggested a link between lower TC and violence (Chakrabarti et al., 2004; Repo-Tiihonen et al., 2002; Turkoglu et al., 2009). However, there have been no recent studies on forensic populations, and none involving female forensic populations.

A study of 41 male and 19 female schizophrenia patients (Shrivastava et al., 2017) observed that females with moderate but not low or high suicidality had lower cholesterol levels to statistical significance, but such a link was not found for males. However, sample sizes were really low ($n=4–9$ per subgroup in female participants) in this study.

Overall, the link between lipid profile and violence seems to be slightly stronger for males than females, but that might well be because males have been studied more often than females. There is also some inconclusive evidence to suggest that the relationship might be different for females and males, both for violence and suicidality.

**Discussion**

There were three main findings in relation to the primary objectives of this systematic review.

First, there were many more studies which reported on a link between low cholesterol and violence to others than those which did not find a link. All researchers investigating
forensic samples found such a relationship. However, the relationship was not only with low TC but also with other parameters of the lipid profile, such as low LDL and low HDL. It is thus important not just to collect data on TC, but LDL and HDL as well. The evidence was weaker for the link between TG and violence, with only two studies finding a link, but one with high TG, the other with low TG. It is to be noted that the study with the largest sample size failed to find a link (Hjell et al., 2020). However, one of the issues in this study was the relatively low rate of baseline violence in the study population, thus offering some indication that the link is likely to be more valid in groups where there is a greater prevalence of violence (i.e. forensic populations).

The biological mechanism behind cholesterol–violence association has been hypothesised to involve serotonin. Animal studies have found an increase in violent behaviour in monkeys assigned to a low-cholesterol diet (Kaplan et al., 1991, 1994). Kaplan et al. (1991) suggested that low cholesterol may reduce cell viscosity and reduce serotoninergic receptor activity. This may lead to a depressive state (Marcinko et al., 2005), increased impulsivity (Carver and Miller, 2006; Paaver et al., 2007) and aggressive behaviour (Chakrabarti et al., 2004). This finding was observed in Kaplan et al. (1994), where monkeys with experimentally lowered cholesterol had higher concentrations of serotonin metabolites than monkeys given high-cholesterol diets. However, the exact biological mechanism underlying cholesterol–violence (towards self/others) association in humans is still unclear.

Second, there was mixed evidence for a link between low cholesterol and suicidality in schizophrenia, with almost equal number of studies in favour and against such a link. The majority of studies used suicide as the method of assessing aggression. Eight studies found a statistically significant association between low cholesterol and suicide attempts, two of which only found this association in females (Misiak et al., 2015; Shrivastava et al., 2017). Seven studies failed to find a link. However, the study with the largest sample size (Sankaranarayanan et al., 2020) did find a link, thus suggesting that methodological flaws, particularly low power, might have contributed to the variation in findings.

The evidence for a specific relationship between lipid profile and violent suicidal attempts was even more mixed. Rutljaniec et al. (2007) found a significant association between cholesterol and non-violent suicide attempts, in contrast to two other studies (Marcinko et al., 2005; Tripodianakis et al., 2002), reporting an association between low cholesterol and violent suicide attempts. While the two studies showing a positive association had smaller sample sizes, such findings are supported by other literature (Garland et al., 2000; Vevera et al., 2003). A meta-analysis found 50% more violent deaths in males with relatively low cholesterol than in participants with higher levels of cholesterol (Jacobs et al., 1992). This meta-analysis also found a higher prevalence of depressive symptoms in males with low serum cholesterol.

An association between low cholesterol and depression has frequently been observed (Grussu et al., 2007; Ploecckinger et al., 1996; Troisi et al., 2002). It is plausible that the causal pathway from low cholesterol to suicidality in schizophrenia patients involves depression. Kunugi et al. (1997) did not find a significant difference in cholesterol level between suicidal and non-suicidal inpatients with schizophrenia spectrum disorders. However, significantly lower cholesterol levels were found in suicide attempters with mood disorders compared with controls. Similarly, Modai et al. (1994) found a significant association between lower cholesterol and suicidality in patients with depression, but not in schizophrenia patients. Around 40% of people with schizophrenia have depression, with depression being the most significant factor in completed suicide (Upthegrove et al., 2016). People with schizophrenia and comorbid depression also have a significantly increased risk of violence and suicidality (Conley et al., 2007) and poorer clinical outcomes (Gardsjord et al., 2016; Upthegrove et al., 2009). The studies included in this systematic review did not control for depressive symptoms in schizophrenia patients. Although findings of low cholesterol and depression are inconsistent, with a number of researchers not finding a significant association (Cepeda et al., 2020; Van Dam et al., 1999), it is plausible that suicidality seen in schizophrenia patients with low cholesterol may be a consequence of depressive symptoms.

Third, most of the studies had similar findings for males and females. However, low HDL was seen in two studies to be a better predictor of violence than low TC for males (Eriksen et al., 2017, 2018). Another study found female sex and low TC levels could be used, in part, as predictors of violence in patients with schizophrenia (Chen et al., 2015). One study found higher TC and LDL levels to be associated with suicidality in females but not males with first-episode schizophrenia, thus suggesting that the link between lipids and violence is somewhat complex (Misiak et al., 2015). Future studies need to be designed to explore the nature of the link separately for females and males. All studies (Chakrabarti et al., 2004; Marcinko et al., 2005, 2007, 2008; Repo-Tiihonen et al., 2002) investigating only male schizophrenia patients found a significant association between low cholesterol and suicidality, except one group (Turkoglu et al., 2009) who did not report a significant association. On the contrary, three study authors observed an association only in female participants: two for suicidality (Misiak et al., 2015; Shrivastava et al., 2017) and one for violence towards others in patients with schizophrenia (Chen et al., 2015). However, one study (Eriksen et al., 2017) did not find this specific correlation in female participants.

Thus, it can be concluded that cholesterol levels could be used, in part, as predictors of violence in patients with schizophrenia. The evidence for a clear link with sex remains
inconclusive. This is an important area for further work given that rates of violence in psychiatric patients following discharge tend to be higher in men than in women (Robbins et al., 2003). In addition, the neurobiology of violence, factors like body mass index (BMI), incidence of metabolic syndrome following antipsychotic medication and the effects of cholesterol are different between men and women, suggesting that discrete effects may occur in each sex (Golomb, 1998).

Limitations

There were several limitations regarding the studies reviewed. First, in many of the studies reviewed, the main focus was on suicide and physical aggression to others. As a result, most patients observed were clinically ill enough to warrant inpatient treatment. Few studies evaluated aggression as physical against property and verbal, potentially deemed less severe and more likely to be seen in community or outpatient-based studies. A representative view of schizophrenia patients of all severities, including inpatients and outpatients, was therefore not specifically assessed in this review. Second, confounding factors, including sex, medication and age, may have affected the findings of this review. According to the Gender Paradox in Suicide, men are more likely to die by suicide than women, while women are more likely to engage in suicidal behaviour and deliberate self-harm (Canetto and Sakinofsky, 1998). However, self-harm was not frequently assessed in these studies. There is some indication of a link between low TC, HDL, LDL and impulsivity, which could translate into risk of self-harm, but this link needs to be explored through studies in populations with higher self-harming behaviours, like inpatient female wards. Medication, such as certain antipsychotics like risperidone, stimulate serotonergic output in cortical and subcortical areas more than other antipsychotics (Amato, 2015), and this may contribute to changes in aggressive behaviour independent of cholesterol level. In addition, with age comes a natural variance in cholesterol level, with a tendency of increased serum cholesterol with increasing age (Morgan et al., 2016). Aggressive behaviour may be independent of low cholesterol in younger participants as they, typically, would have a lower cholesterol level when compared to older patients. The effects of age as well as medication were not accounted for in a number of studies. Finally, the lack of statistical analysis using a 95% confidence interval in a number of studies (see Table 4) limited the review by making it difficult to assess precision and risk in data obtained.

In addition, there are limitations to the review itself. First, the review may have been limited by only allowing diagnosis of schizophrenia by a variant of DSM or ICD classifications. This excluded foreign classifications such as T-SCL-90-R. Second, selection bias arose when only considering studies reported in English. The inclusion and exclusion criteria stated that participants must be adults only, unless unavoidable. As a result, three included studies (Chen et al., 2015; Repo-Tiihonen et al., 2002; Ruljancic et al., 2007) had some participants below the age of 18, leading to wide variations in the age range of the study participants.

Conclusion

This systematic review presents encouraging evidence of low cholesterol showing promise as a biomarker of risk in patients with schizophrenia. The majority of studies (around 70%) did find an association between low cholesterol and violence towards others, as well as about half of the studies with suicidal behaviour. However, studies specifically focusing on males and females with schizophrenia were lacking, along with relatively small sample sizes for some studies. Future studies need to be carried out focused exclusively on participants with a diagnosis of schizophrenia, and with histories of violent, self-harming and suicidal behaviours. These studies need to be longitudinal, exploring measures of self-harm, suicidality and aggression in male and female patients, both inpatients and outpatients, while taking age, medication history and any comorbidities into account, to explore patterns of link with lipid profiles including TC, LDL and HDL. Preferably, these studies should also include patients with other diagnoses as comparison groups. Such research would be essential to explore how a relatively commonly assessed measure like serum cholesterol along with high- and low-density lipoprotein could be incorporated into calculations of risk for any patient with schizophrenia, whether it is risk to others or to self.

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Author Contributions

P.S. and V.K. contributed to conception of the review; P.S. and D.A. led the literature search, quality appraisal and data extraction from the eligible studies; V.K. contributed to review of data from the eligible studies; P.S. and D.A. wrote first draft of the paper; A.I.B. and V.K. critiqued the output for important intellectual content. All authors contributed to and approved the final version.

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**Data Accessibility Statement**
All data supporting this review will be made available through Brunel University London research repository.

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