Decreased serum total cholesterol is associated with a history of childhood physical violence in depressed outpatients

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ABSTRACT

Associations between adverse childhood experiences (ACEs) and cholesterol in depressed patients are unclear. Therefore, we compared 78 adult outpatients with major depressive disorder (MDD) with ($n = 24$) or without ($n = 54$) experiences of physical violence in childhood. Background data were collected with questionnaires, and total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured from fasting blood samples. Patients with a history of childhood physical violence had lower levels of TC than the control group. No differences were observed in HDL-C, LDL-C, or low-grade inflammation levels between the two groups. In multivariate models, decreased levels of TC were associated with childhood physical violence, and these associations remained significant after adjustments for age, gender, lifestyle, metabolic condition, socioeconomic situation, psychiatric status, suicidality, low-grade inflammation, the chronicity of depression, medications used and somatic diseases. At the 8-month follow-up, the results were essentially the same when the Trauma and Distress Scale (TADS) was used as the measure of ACEs. The specific mechanisms underlying cholesterol alterations associated with ACEs are a topic for future studies. Better understanding of these mechanisms might lead to possible new interventions in the prevention of adverse health effects resulting from ACEs.

1. Introduction

Adverse childhood experiences (ACEs) are common in the general population. According to the World Health Organization (WHO), a quarter of all adults have been physically abused as children, and 1 in 5 women and 1 in 13 men have experienced sexual abuse (Child maltreatment fact sheet, World Health Organization, 2016).

The consequences of child maltreatment include permanent adverse physical changes, and adults with a background of childhood maltreatment have a pronounced vulnerability to rapidly increasing health adversities (Rohde et al., 2008). ACEs have previously been linked with major depressive disorder (MDD) (Mandelli et al., 2015), symptoms of anxiety, poor self-rated health (Kamiya et al., 2016), adverse metabolic alterations (Davis et al., 2014), and cardiovascular disease (Loria et al., 2014; Rich-Edwards et al., 2012). MDD patients with ACEs also display an increased likelihood and number of suicide attempts (Tunnard et al., 2014). Wingenfeld et al., (2017) warn that the harmful effects of ACEs can remain latent and manifest decades after

the stressor, even in middle age or in the elderly.

Associations between cholesterol levels and psychological conditions have been a focus of interest ever since Engelberg (1992) hypothesized a link between serum lipid concentrations, depression, and suicidality. Many studies have focused on the associations between cholesterol levels and depression (Maes et al., 1997; Lehto et al., 2008; Lehto et al., 2010; Persons and Fiedorowicz, 2016) and also on the link between depression and ACEs (Dias de Mattos Souza et al., 2016; McCarthy-Jones and McCarthy-Jones, 2014; Rohde et al., 2008; Sacks et al., 2017; Tunnard et al., 2014). Altered levels of circulating lipids have been observed in adults who report ACEs compared to those with no such experiences (Groër et al., 2016; Lodhia et al., 2015). Nevertheless, the evidence concerning cholesterol changes in individuals with ACEs is inconsistent. Compared to US female veterans with no childhood sexual abuse experiences, US female veterans with a history of childhood sexual abuse have displayed higher levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (Groër et al., 2016). In contrast, decreased levels of high-density lipoprotein cholesterol (HDL-C) have been reported in Dutch general population adults with experiences of childhood sexual abuse compared to those with no such experiences (van Reedt Dortland et al., 2012). Lodhia et al. (2015) found that among surgical weight loss patients, those with high ACE scores had higher levels of LDL cholesterol and TC 12 months after the operation than patients with low ACE scores.

Cholesterol level alterations detected in individuals with ACEs may result from differences in cholesterol biosynthesis. Furthermore, cholesterol utilization may be altered, or cholesterol may be further metabolized to steroid hormones or bile acids. Several mechanisms explaining associations between cholesterol alterations and ACEs have been suggested. Firstly, repetitive early life stress alters inflammatory and metabolic functioning (Davis et al., 2014), and ACEs such as separation from parents and sexual or physical abuse have been observed to be associated with elevated low-grade inflammation (Slopen et al., 2012; Lehto et al., 2012). Secondly, chronic stress caused by early adversities may lead to an unhealthy lifestyle and behavior (Boynton-Jarrett et al., 2012). Indeed, a connection between childhood maltreatment and adulthood obesity has been demonstrated in several studies (Rohde et al., 2008; Midei et al., 2010; McCarthy-Jones and McCarthy-Jones, 2014).

ACEs, depression (Mandelli et al., 2015), and suicidality (Tunnard et al., 2014) are closely linked. Lowered levels of cholesterol, particularly LDL-C, are associated with suicidality (Troisi, 2009; Cantarelli et al., 2014). ACEs have predicted suicidality in adulthood (Asellus et al., 2014). Investigating associations between ACEs and lipid changes, as well as the related mechanisms, among depressed patients may provide further insight into the additional influence that ACEs exert on cardiovascular health, which is often compromised in depression. To the best of our knowledge, only two previous studies with different study designs have investigated this association in depressed patients, with contradictory findings. McIntyre et al. (2012) examined 373 patients with MDD or bipolar disorder and observed lower levels of HDL-C in patients with a history of parental loss or any childhood trauma than in patients without ACEs. They presented information on the lifetime number of depressive episodes and the age at which depression first occurred, as well as the number of suicide attempts, but did not use this information as confounders explaining altered lipid levels. Another study by Wingenfeld et al. (2017) focused on women only and used a body mass index over 30 as an exclusion criterion. They compared 80 women with MDD, 33 with ACEs and 47 without ACEs, and observed no differences between the two groups in TC, HDL-C, LDL-C, or triglycerides. ACEs were defined as repeated sexual or physical abuse at least once a month over one or more years before the age of 18. In this study, the suicidality or the chronicity of depression was not reported. Furthermore, neither of the above-mentioned studies adjusted the results for inflammation.

We hypothesized that depressed patients with experiences of childhood physical violence would display decreased levels of TC, and HDL-C in particular, as well as elevated levels of low-grade inflammation. Furthermore, we aimed to examine the effects of lifestyle, psychiatric symptoms, suicidality, and the chronicity of depression on these associations.

2. Methods

2.1. Study sample

The data of the present study, conducted as part of the larger NeuroDep Study, were collected during 2011–2012. The study used a naturalistic sample of patients with MDD, diagnosed using the Structured Clinical Interview for DSM-IV (SCID) (DSM-IV; American Psychiatric Association 1994). The study protocol was approved by the Ethics Committee of Kuopio University Hospital. All participants provided written informed consent before entering the study.

The original sample consisted of 99 outpatients recruited from the Department of Psychiatry at Kuopio University Hospital, Kuopio, Finland. The initial exclusion criteria were a history of epilepsy, bipolar disorder, psychotic disorders, mental symptomology due to substance abuse, and severe current somatic conditions physically preventing participation in the study (i.e., conditions limiting mobility and thus participation in study visits). Furthermore, due to the small group sizes in some ACE categories, we excluded patients who reported experiences of sexual violence during childhood ($n = 5$), both sexual and physical violence ($n = 3$), and abuse between other household members but not directly targeted at the participant ($n = 13$). Thus, we only focused on childhood physical violence at home ("Did you experience physical violence at home?"). 24 participants reported experiences of physical violence at home during childhood. After exclusions, the utilized dataset comprised 78 outpatients aged 20 to 61 years (mean 38.6). Follow-up data were available from 58 of them (mean follow-up time 8 months; range 5–13 months). There were no significant differences between those who decided to continue in the follow-up and those who did not (Ali-Sisto et al., 2016).

2.2. Background data

The following variables were extracted from the questionnaires completed by the participants: 1) regular physical exercise (≥ 1 vs. < 1 time per week); 2) regular smoking (yes vs. no); 3) significant alcohol use (0–5 vs. ≥ 6 portions weekly; 1 portion corresponds to 1 bottle of beer, 1 glass of wine, or 4 cl of spirits); 4) marital status (married or living with a partner vs. living alone), and educational level (university, polytechnic, or college education vs. lower); 5) somatic diseases diagnosed or treated by a physician during the previous 12 months (i.e., coronary/vascular diseases, diabetes, inflammatory diseases, or cancer); 6) medications used by the participant (i.e. cholesterol, diabetes, antidepressant, or antipsychotic medication); 7) the lifetime number of depressive episodes; and 8) the duration of the current depressive episode. Data on the last two variables were collected as part of a SCID interview (DSM-IV; American Psychiatric Association 1994). Suicidal ideation was evaluated using item 9 of the Beck Depression Inventory (BDI-21) (Beck et al., 1961). In order to enhance the informational value, we re-coded question no. 9 from the BDI into a binary variable (No suicidal ideation: "I don't have thoughts of killing myself" vs. suicidal ideation: "I have thoughts of killing myself, but I would not carry them out", "I would like to kill myself", "I would kill myself if I had the chance"). Dissociative symptoms were measured with a 28-item self-report questionnaire, the Dissociative Experiences Scale (DES) (Bernstein and Putnam 1986). At the 8-month follow-up, ACEs were measured with Trauma and Distress Scale (TADS) (Patterson et al., 2002).

2.3. Laboratory analyses

Venous blood samples were taken both at baseline and at the 8-month follow-up after an overnight fast (12 hours). All samples were stored at −70 °C until analyzed in one batch. Blood levels of glycated hemoglobin (HbA1c) were measured according to the routine protocol in the accredited medical laboratory of Kuopio University Hospital. Enzymatic methods (Thermo Electron, Vantaa, Finland) were used for lipid measurements (TC: Konelab Cholesterol, code 981812; HDL-C: Konelab HDL-Cholesterol, code 981655). The total variations of the utilized methods were 1.6% and 3.7% respectively. The samples were analyzed using a Konelab 60i Clinical Chemistry Analyzer (Thermo Electron). The level of LDL-C was calculated according to the Friedewald formula (Friedewald et al., 1972). The analytical protocols have been described in detail elsewhere (Chang et al., 1998; Siekmann et al., 1976).

The level of TNF-α was analyzed by multiplexing with a Luminex xMAP technology-based instrument, Bio-Plex 200 (Bio-Rad Laboratories, Hercules, CA, USA) with a Milliplex Human Cytokine/Chemokine Magnetic Bead Panel (Cat# HCYTOMAG-60K; Millipore Corporation, Billerica, MA, USA). The assay was performed according to the manufacturer's instructions, as described by Johansson-Persson et al. (2014) and Jaurila et al. (2017). The assay conditions were standardized and controlled to ensure optimal reproducibility. Results were calculated with a five-parameter logistic equation in Bio-Plex Manager Software 6.0 (Bio-Rad Laboratories).

2.4. Statistical methods

To analyze the differences between the groups, the chi-squared test and Fisher's exact test were used for categorical variables. For continuous variables, the Student's t-test was used for those with a normal distribution and the Mann-Whitney U test for those with a non-normal distribution of values. Due to the non-normal distribution of some of the values, the correlations between the variables were examined with Spearman's rank correlation coefficient. Effect sizes were estimated with Cohen's d (Cohen, 1988).

Linear regression (method: enter) was used for multivariate analysis, with TC, LDL-C, or HDL-C as dependent variables. The variables for adjustments were chosen based on a possible influence on TC, LDL-C, or HDL-C levels, or as being possible consequences of experiences of physical violence during childhood. Fifteen age- and sex-adjusted models were constructed (Table 3): the basic model (Model 1) was adjusted for age and gender. In the lifestyle model (Hughes et al., 2017) (Model 2), regular smoking, physical exercise, and alcohol use were added to Model 1 to investigate the potential confounding effects of lifestyle factors. In the socioeconomic model (Fry et al., 2018) (Model 3), education and marital status (university, polytechnic, or college education; married or living with a partner) were added to Model 1. In the metabolic model (McCarthy-Jones and McCarthy-Jones, 2014) (Model 4), HbA1c levels were added to the basic model to evaluate the potential confounding effect of the metabolic state. In the inflammation model (Baumeister et al., 2016) (Model 5), TNF-α was added to Model 1 to investigate the potential confounding effect of low-grade inflammation. In the psychiatric model (Mandelli et al., 2015) (Model 6), the BDI scores and DES scores were added to Model 1 to investigate the potential confounding effects of symptoms of depression and dissociation. In the suicidality model (Lester 2002; Tunnard et al., 2014) (Model 7), suicidal thoughts were added to Model 1. In the chronicity of depression model (Lehto et al., 2010) (Model 8), the lifetime number of depressive episodes and the duration of the current depressive episode were added to Model 1 to investigate the potential confounding effects of the duration and re-occurrence of depression. In the cardiovascular disease model (Model 9), hypertension, myocardial infarction, coronary thrombosis, coronary artery disease, or angina pectoris diagnosed or treated during the previous 12 months was added to Model 1 to

investigate the potential confounding effect of cardiovascular diseases. In the inflammatory disease model (Model 10), asthma or pulmonary emphysema and rheumatoid arthritis diagnosed or treated during the previous 12 months were added to Model 1 to investigate the possible confounding effect of inflammatory diseases. In the cancer model (Model 11), the diagnosis or treatment of cancer was added to Model 1 to investigate the potential confounding effects of cancer. In the cholesterol medication model (Model 12), information on the usage of cholesterol medication was added to Model 1 to investigate the potential confounding effects of cholesterol medication. In the diabetes medication model (Model 13), information on the usage of diabetes medication was added to Model 1 to investigate the potential confounding effects of diabetes medication. In the antidepressant medication model (Model 14), information on the usage of antidepressants was added to Model 1 to investigate the potential confounding effects of antidepressant medication. In the antipsychotic medication model (Model 15), information on the usage of antipsychotic medication was added to Model 1 to investigate the potential confounding effects of antipsychotic medication. Furthermore, we repeated these linear regression analyses with the TADS scores from the follow-up (Supplementary Table 3).

We performed moderation and mediation analysis for the variables that had significant correlations with lipid parameters. Possible moderation and mediation was assessed using the modeling tool PROCESS version 2.16.3 for SPSS (Hayes, 2012). All the analyses were performed with SPSS Statistics 24 for Mac statistical software (SPSS Inc., Chicago, IL). Two-tailed p-values below 0.05 were considered to indicate statistical significance.

3. Results

The background characteristics of the subjects are presented in Table 1. Participants who had experienced physical violence during childhood were older and expressed more suicidal ideation compared to controls with no such experiences. Those with experiences of childhood physical violence had lower TC levels (Cohen's d for difference = 0.6) than those who had not experienced violence in childhood. No differences were observed in HDL-C (Cohen's d for difference = 0.04) or LDL-C levels (Cohen's d for difference = 0.27) when comparing the two study groups. Experiences of physical violence in childhood did not associate with low-grade inflammation.

TC correlated positively with the duration of the current depressive episode and inversely with the lifetime number of depressive episodes. There was a positive correlation between TC and LDL-C, and an inverse correlation between LDL-C and HDL-C. Furthermore, there was a positive correlation between age and the duration of the current depressive episode, as well as between age and HbA1c. Participant age did not significantly correlate with TC, LDL-C, or HDL-C (Table 2).

In multivariate models, decreased levels of TC associated with experiences of physical violence during childhood. The association remained significant after adjustments for age, gender, lifestyle, the metabolic state, socioeconomic situation, psychiatric status, suicidality, low-grade inflammation, the chronicity of depression, somatic diseases diagnosed or treated by a physician during the previous 12 months (coronary/vascular diseases, diabetes, inflammatory diseases, or cancer), and the medication used by the participant (cholesterol, diabetes, antidepressant, or antipsychotic medication) (Table 3).

We explored the mediating and moderating effects that the chronicity of depression might have on the association between childhood physical violence and circulating cholesterol levels. Neither the duration of the current depressive episode nor the number of depressive episodes during the patient's lifetime had a significant mediating effect on TC ($b = 0.019$, BCa bootstrapped CI [−0.047, 0.192], and $b = -0.074$, BCa bootstrapped CI [−0.304, 0.019], respectively). Furthermore, no moderating effects were observed (Supplementary Tables 1 and 2).

Table 1
Background characteristics of the study groups. Values are medians (interquartile ranges), unless otherwise stated.

	Physical violence (*n* = 24)	Control group (*n* = 54)	Test value	*p*-value
Age, mean (*SD*)	41.63 (9.7)	37.24 (12.5)	1.68	0.10[a]
Female, *n* (%)	12 (50)	30 (55.6)	0.21	0.65[c]
University, polytechnic, or college education, *n* (%)	12 (50)	16 (29.6)	3.00	0.08[a]
Married or living with a partner, *n* (%)	21 (87.5)	45 (83.3)	–	0.75[d]
Regular smoking, *n* (%)	8 (33.3)	13 (24.1)	0.72	0.40[c]
Significant alcohol use[1], *n* (%)	3 (12.5)	13 (24.1)	–	0.36[d]
Regular exercise[2], *n* (%)	10 (41.7)	26 (48.1)	0.28	0.57[c]
BDI scores, mean (*SD*)	29.83 (11.27)	25.22 (11.8)	−1,61	0.11[a]
DES scores	11.79 (7.50–26.70)	15.00 (8.21–26.07)	−0.20	0.84[b]
Suicidal ideation, *n* (%)	18 (75)	27 (50)	4.26	0.04[c]
Duration of current depression (months)	30 (12.00–36.00)	12 (5.75–36.00)	−1.40	0.16[b]
Number of lifetime depressive episodes	3 (1–4)	1 (1–3)	−1.64	0.10[b]
TC (mmol/l), mean (*SD*)	4.88 (0.92)	5.54 (1.29)	2.55	0.01[a]
HDL-C (mmol/l)	1.40 (1.09–1.87)	1.45 (1.19–1.69)	−0.16	0.87[b]
LDL-C (mmol/l)	2.86 (2.51–3.39)	3.18 (2.43–3.71)	−0.379	0.71[b]
HbA1c (mmol/mol)	5.30 (4.93–5.50)	5.30 (5.10–5.40)	−1.03	0.30[b]
TNF-α (pg/ml)	11.29 (7.97–13.01)	11.80 (8.71–19.28)	−0.70	0.49[b]
Hypertension, *n* (%)	9 (37.5)	16 (29.6)	0.47	0.49[a]
Diabetes, *n* (%)	2 (8.3)	3 (5.6)	–	0.64[d]
Myocardial infarction, coronary thrombosis, *n* (%)	1 (4.2)	0 (0.0)	–	0.31[d]
Coronary artery disease, angina pectoris, *n* (%)	2 (8.3)	0 (0.0)	–	0.09[d]
Cancer, *n* (%)	0 (0.0)	1 (1.9)	–	1.00[d]
Rheumatoid arthritis, *n* (%)	0 (0.0)	1 (1.9)	–	1.00[d]
Asthma or pulmonary emphysema, *n* (%)	4 (16.7)	4 (7.4)	–	0.24[d]
Cholesterol medication, *n* (%)	5 (20.8)	5 (9.3)	–	0.27[d]
Diabetes medication, *n* (%)	0 (0.0)	3 (5.6)	–	0.55[d]
Antidepressant medication, *n* (%)	18 (75.0)	49 (90.7)	–	0.84[d]
Antipsychotic medication, *n* (%)	11 (45.8)	15 (27.8)	2.44	0.12[a]

Abbreviations: BDI = Beck Depression Inventory, DES = Dissociative Experience Scale, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TNF-α = tumor necrosis factor alpha, SD = standard deviation

[a] Student's *t*-test;
[b] Mann-Whitney *U* test;
[c] Chi-squared test;
[d] Fisher's exact test
[1] Significant alcohol use, 6 or more weekly portions (1 portion corresponds to 1 bottle of beer, 1 glass of wine, or 4 cl of spirits)
[2] Regular exercise (once per week or more)

Finally, we explored the associations between cholesterol levels and TADS scores at the 8-month follow-up. In multivariate models, decreased levels of TC associated with the TADS score at the follow-up. The associations remained significant after adjustments for age, gender, lifestyle, the metabolic state, socioeconomic situation, psychiatric status, suicidality, low-grade inflammation, the chronicity of depression, somatic diseases diagnosed or treated by a physician during the previous 12 months (cardiovascular diseases, diabetes, inflammatory diseases, or cancer), and the medication used by the participant (cholesterol medication, diabetes medication, antidepressant medication, or antipsychotic medication) (Supplementary Table 3).

4. Discussion

4.1. Main findings

We observed lower levels of fasting serum TC in MDD patients who had experienced physical violence in their childhood than those who had not. The finding remained significant despite adjustments for age, gender, lifestyle factors, HbA1c, the socioeconomic situation, psychiatric symptoms, suicidal ideation, the chronicity of depression, low-grade inflammation, somatic diseases, and the medications used. Contrary to our hypotheses, experiences of physical violence in childhood did not associate with low-grade inflammation or decreased HDL-C levels. Decreased levels of TC were also associated with the TADS scores in the multivariate models at the 8-month follow-up.

4.2. Comparison with the existing literature

Wingenfeld et al. (2017) found no differences in the levels of TC, HDL-C, or LDL-C between MDD patients with or without experiences of physical or sexual abuse in childhood. We observed that belonging to the group of MDD patients with childhood experiences of physical violence was associated with the decrease in TC levels. In our sample, Cohen's *d* for the difference between groups in TC was 0.6 (medium), whereas in the sample of Wingenfeld et al. (2017) it was 0.14 (small). The participants in our sample were somewhat older and had higher BDI scores. Furthermore, Wingenfeld et al. did not report any measure of the chronicity of depression, which may also contribute to the different findings. In a study comparing the metabolic profiles of patients with mood disorders (MDD and bipolar disorder), lower levels of HDL-C were identified in subjects who had experienced parental loss or any kind of childhood trauma, with a trend among subjects with physical abuse (McIntyre et al., 2012). However, in our study, HDL-C levels did not differ between those who had experienced violence in childhood and those who had not.

There are two major approaches to measure the effect of childhood traumas and ACEs on biological variables: either to measure the cumulative effect of early childhood stressors (Felitti et al., 1998; Miller et al., 2011) or to focus on the different types of maltreatment (Groër et al., 2016). A recent meta-analysis suggested that childhood trauma in general contributes to a pro-inflammatory state in adulthood, while specific inflammatory profiles can be linked to specific types of trauma (Baumeister et al., 2016). To the best of our knowledge, there are no comprehensive data on the possible specific effects of different traumas on lipid profiles. We repeated our analyses with 8-month

Table 2
The correlations between the continuous variables used in the multivariate models measured by Spearman's rank correlation coefficients (p-value).

	LDL-C	HDL-C	Age	BDI	Duration of depression	Number of depressive episodes	DES	TNF-α	HbA1c
TC	**0.871 (0.000)**	−0.029 (0.799)	0.110 (0.338)	0.054 (0.641)	**0.279 (0.013)**	**−0.236 (0.038)**	0.048 (0.684)	−0.019 (0.866)	0.207 (0.069)
LDL-C		**−0.261 (0.009)**	0.102 (0.314)	0.044 (0.667)	0.142 (0.213)	−0.174 (0.125)	0.020 (0.846)	−0.045 (0.660)	−0.122 (0.230)
HDL-C			0.065 (0.572)	−0.129 (0.261)	−0.030 (0.797)	0.101 (0.380)	−0.029 (0.806)	0.034 (0.768)	−0.073 (0.524)
Age			—	−0.035 (0.760)	**0.238 (0.036)**	−0.098 (0.394)	−0.132 (0.261)	−0.124 (0.281)	**0.312 (0.005)**
BDI scores				—	**0.232 (0.041)**	−0.022 (0.851)	**0.448 (0.000)**	−0.051 (0.659)	−0.035 (0.760)
Duration of depression					—	**−0.293 (0.009)**	0.037 (0.752)	0.016 (0.889)	0.166 (0.145)
Number of depressive episodes						—	−0.022 (0.851)	0.045 (0.698)	0.003 (0.977)
DES scores							—	−0.024 (0.835)	−0.021 (0.859)
TNF-α								—	0.025 (0.829)

Abbreviations: BDI = Beck Depression Inventory, DES = Dissociative Experience Scale, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TNF-α = tumor necrosis factor alpha

follow-up data using the TADS scale, which considers different types of traumas. The effects of childhood traumas in general were similar to those observed when utilising the variable focusing on physical abuse. This finding supports the hypothesis that different types of traumas may have similar effects on cholesterol levels.

4.3. Possible mechanisms behind our findings

Several mechanisms may explain our findings, and below we discuss those of most importance.

4.3.1. Suicidality

There is a considerable body of knowledge on associations between suicidality and low levels of TC (Lester, 2002; Wu et al., 2016). We found that the participants with a history of physical violence had lower levels of TC and expressed more suicidal thoughts than the controls without a history of physical abuse. However, suicidality did not explain the association between TC levels and ACEs in the multivariate models.

4.3.2. Chronicity of depression

Based on our observations, it is possible that the chronicity of depression partly contributes to the differences in cholesterol levels between those with and without experiences of physical violence during childhood. In our data, there were seemingly controversial correlations regarding the chronicity of depression and cholesterol. There was a positive correlation between the duration of the current depressive episode and the levels of TC, indicating that the longer the depressive episode had lasted, the higher was the level of cholesterol. Furthermore, we observed an inverse correlation between the number of lifetime depressive episodes and the levels of TC. Persons and Fiedorowicz (2016) suggest in their review article that there may be a U-shaped relationship between serum LDL and depression. Lowered levels of LDL-C may contribute to the onset of depression, whereas chronic depression over the course of decades leads to weight gain and, consequently, metabolic syndrome and high serum LDL-C. Taken together, the chronicity of depression appears to be associated with adverse metabolic changes, as indicated by altered levels of TC and cholesterol fractions. However, based on our findings, consecutive episodes of depression may not have the same effect on cholesterol levels. As major depression is a recurrent disease, the number of lifetime depressive episodes may be related to age: the higher the age, the more likely it is for a patient to have experienced several depressive episodes. However, there were no significant correlations between patient age and cholesterol levels.

In our study, the difference in the level of TC between the participants with a history of physical violence during childhood and the control group was more pronounced in the case of the level of LDL-C than HDL-C. However, the group differences in LDL-C did not reach statistical significance with the existing effect size of 0.27. With the current effect size, alpha-level of 0.05 and power of 0.8, the sample size needed for the difference between the groups to reach statistical significance would have been 358 (Faul et al., 2007). Lehto et al. (2010) observed lowered levels of HDL-C in patients with MDD and a long duration of symptoms (i.e., ≥ 3 years). They also found that MDD patients with a symptom duration of less than three years displayed HDL-C levels similar to those in non-depressed controls (Lehto et al., 2010). In our study, participants with a history of physical abuse had longer depressive episodes than those without such experiences, although the difference did not reach significance. In the sample of Lehto et al. (2010), 43% of patients had depression lasting ≥ 3 years, whereas in our data, only 25% had experienced symptoms for this long. Having fewer participants with a longer symptom duration may explain why we did not observe any association between the duration of depressive symptoms and HDL-C.

Depression is a chronic and remitting disorder in which some people

Table 3

Linear regression models for the likelihood of those with experiences of childhood physical violence having lowered levels of TC, LDL-C, or HDL-C.

	TC			LDL-C			HDL-C		
	Beta	t	p-value	Beta	t	p-value	Beta	t	p-value
Model 1: Basic model	−0.285	−2.562	0.012	−0.165	−1.440	0.154	−0.061	−0.538	0.592
Model 2: Lifestyle model	−0.276	−2.441	0.017	−0.163	−1.392	0.168	−0.168	−0.166	0.869
Model 3: Socioeconomic model	−0.305	−2.651	0.010	−0.183	−1.541	0.128	−0.079	−0.674	0.503
Model 4: Metabolic model	−0.279	−2.434	0.017	−0.168	−1.447	0.152	−0.059	−0.512	0.610
Model 5: Inflammation model	−0.288	−2.571	0.012	−0.168	−1.456	0.150	−0.055	−0.484	0.630
Model 6: Psychiatric model	−0.309	−2.648	0.010	−0.169	−1.414	0.162	−0.043	−0.361	0.791
Model 7: Suicidality model	−0.285	−2.486	0.015	−0.154	−1.308	0.195	−0.045	−0.384	0.702
Model 8: Chronicity of depression model	−0.262	−2.385	0.020	−0.149	−1.276	0.206	−0.052	−0.441	0.660
Model 9: Cardiovascular disease model	−0.232	−2.070	0.042	−0.107	−0.922	0.360	−0.044	−0.371	0.712
Model 10: Inflammatory disease model	−0.280	−2.451	0.017	−0.149	−1.269	0.209	−0.073	−0.631	0.530
Model 11: Cancer model	−0.295	−2.634	0.010	−0.178	−1.542	0.127	−0.054	−0.473	0.638
Model 12: Cholesterol medication model	−0.256	−2.349	0.022	−0.130	−1.177	0.243	−0.081	−0.713	0.478
Model 13: Diabetes medication model	−0.282	−2.496	0.015	−0.179	−1.548	0.126	−0.068	−0.591	0.557
Model 14: Antidepressant medication model	−0.247	−2.165	0.034	−0.136	−1.150	0.254	−0.051	−0.428	0.670
Model 15: Antipsychotic medication model	−0.288	−2.525	0.014	−0.165	−1.440	0.154	−0.062	−0.528	0.986

Model 1: Adjusted for age and gender
Model 2: Model 1 further adjusted for regular smoking, significant alcohol use, and regular exercise
Model 3: Model 1 further adjusted for educational level and cohabitation
Model 4: Model 1 further adjusted for HbAC1
Model 5: Model 1 further adjusted for TNF-α
Model 6: Model 1 further adjusted for BDI scores and DES scores
Model 7: Model 1 further adjusted for suicidal thoughts
Model 8: Model 1 further adjusted for the duration of the current depressive episode and number of previous episodes of major depression
Model 9: Model 1 further adjusted for hypertension, myocardial infarction, coronary thrombosis, coronary artery disease, or angina pectoris diagnosed or treated during the previous 12 months
Model 10: Model 1 further adjusted for asthma or pulmonary emphysema and rheumatoid arthritis diagnosed or treated during the previous 12 months
Model 11: Model 1 further adjusted for cancer diagnosed or treated during the previous 12 months
Model 12: Model 1 further adjusted for cholesterol medication
Model 13: Model 1 further adjusted for the diabetes medication used
Model 14: Model 1 further adjusted for the antidepressant medication used
Model 15: Model 1 further adjusted for the antipsychotic medication used
Abbreviations: BDI = Beck Depression Inventory, DES = Dissociative Experience Scale, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein choles-terol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TNF-α = tumor necrosis factor alpha

reach only partial remission. Therefore, the duration of the current episode and the number of previous episodes may not be purely distinctive measures of the total burden of depression. It is possible that the total accumulative duration of depression over the lifetime could be the crucial factor underlying the association with the altered lipid levels. Individuals with ACEs may be more prone to depressive symptoms from an early age, and their total burden of depression may thus be higher compared to other patients with MDD. Even though the difference in the number of lifetime depressive episodes as well as the duration of the current depressive episode between those who had experienced physical violence during childhood and those who had not was not statistically significant in our data, those with childhood trauma reported more previous depressive episodes and their current depressive episodes had lasted longer than in the control group. Due to the small number of cases, it is possible that we did not have enough statistical power to detect a difference between the groups. However, we did not observe a moderating or mediating effect of the number of lifetime depressive episodes or the duration of the current depressive episode on the association between TC and the experience of physical violence during childhood.

4.3.3. Lifestyle

A connection between childhood maltreatment and adulthood obesity has been observed in several studies (Rohde et al., 2008; Midei et al., 2010). The association between obesity and childhood maltreatment may be mediated to some extent by other factors, such as health behaviors (Boynton-Jarrett et al., 2012). Furthermore, psychological, sexual, and physical abuse have been observed to be associated with lower levels of HDL-C, as well as a higher waist circumference and higher overall metabolic risk (van Reedt Dortland et al., 2012). In our

study, the levels of HbA1c, one of the metabolic risk factors, did not differ between participants with or without experiences of physical violence during childhood.

4.3.4. Inflammation

Evidence from both animal and human studies suggests that inflammation may be a central biological mechanism linking early adversity to a variety of health outcomes (Miller et al., 2009). A recent meta-analysis revealed that childhood trauma contributes to a pro-inflammatory state in adulthood, and specific inflammatory profiles have been suggested to link to specific types of trauma (Baumeister et al., 2016). In a recent review article, Catapano et al. (2017) suggest that increased expression of LDL receptors during inflammation results in a decrease in LDL-C levels and fosters the intracellular accumulation of cholesterol, which might induce inflammasome activation. On the other hand, circulating LDL has an increased susceptibility to oxidation, which may explain the increased plasma levels of oxidized LDL in patients with chronic inflammatory diseases (Catapano et al., 2017). There is a bidirectional relationship between HDL-C and inflammation: the elevation of HDL-C reduces the expression of pro-inflammatory interleukins (Cockerill et al., 2001), and the pro-inflammatory response can lead to lowered HDL-C levels (Maes et al., 1997). Lehto et al. (2010) suggested that the systemic anti-inflammatory effects of a high HDL-C level may also act as a buffer against depression-related pronounced low-grade inflammation during the first years of illness, but this effect may cease during extended periods of depressive symptoms. We observed no differences between the two groups in the level of low-grade inflammation measured by TNF-a.

4.4. Strengths and limitations

The small sample size was the main limitation of this study. It would have been informative to compare the effect of physical abuse on cholesterol levels separately in men and women, but our dataset was not large enough to enable sufficient statistical power for such comparisons. However, we adjusted all the multivariate models for gender, and gender was not significant in these models.

The availability of objective data, such as parental interviews regarding ACEs, would have allowed a more thorough examination of the relationship between adverse early experiences and lipid parameters and added to the reliability of our measures. Nevertheless, both prospective objective data and retrospective self-reports are used to measure childhood adversities. Both have potential limitations, such as underestimation and memory bias (Newbury et al., 2018). A Finnish study (Kauhanen et al., 2006) compared retrospective and objective data on the childhood socioeconomic situation in middle aged men and found that using recalled information on childhood circumstances may underestimate the true impact of the childhood socioeconomic situation. Thus, our results may be liable to type II errors.

There is a possibility that different somatic conditions or medications with some connection to the physical abuse or cholesterol levels would have biased our findings. However, we were able to adjust our results for several somatic conditions and medications that might have affected cholesterol levels. Despite these adjustments, the results remained essentially the same. Thus, our results are unlikely to be biased by the effect of somatic conditions or medications.

As the study subjects were adult patients with MDD, the findings may not be generalizable to the general population or other age groups. Having healthy controls with and without ACEs would have added to the generalizability of the findings. In addition, having healthy controls could have helped us to more specifically differentiate between our groups of interest and a healthy population.

5. Conclusions

Our observations add to the debate on cholesterol and ACEs by showing decreased levels of serum TC in patients with MDD and ACEs compared to MDD patients with no ACEs. Future research in this area is warranted. Alterations in cholesterol levels could be due to lifestyle factors and alterations in cholesterol biosynthesis, and the role of these processes should be investigated in the future. Analyzing these processes could add to understanding of the biochemical mechanisms underlying the alterations in lipid levels in those with ACEs and might lead to possible new interventions to prevent adverse health effects related to ACEs.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.108.

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