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Research paper

The association between adolescent depression and dyslipidemia

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ABSTRACT

Background: Children and adolescents with major depressive disorder (MDD) are at increased risk for premature cardiovascular disease (CVD). Whether adolescents with MDD manifest evidence of dyslipidemia, a key risk factor for CVD, is unknown.

Methods: Youth recruited through an ambulatory psychiatry clinic and the community, were categorized following diagnostic interview as MDD or as healthy controls [HC]. CVD risk factors including high density lipoprotein (HDL), low density lipoprotein (LDL), and triglyceride concentrations were collected. Depression severity was measured using the Center for Epidemiological Studies Depression Scale for Children. The associations of diagnostic group as well as depressive symptom severity with lipid concentrations were examined using multiple regression analyses. Models were adjusted for age, sex, and standardized Body Mass Index.

Results: Participants ($n = 243$) were 68 % female with a mean age of 15.04 ± 1.81 years. MDD and HC participants had comparable levels of dyslipidemia (MDD: 48 %, HC: 46 %, $p > .7$) and hypertriglyceridemia (MDD: 34 %, HC: 30 %, $p > .7$). Among depressed adolescents, greater depressive symptoms were associated with higher total cholesterol concentrations in unadjusted models only. Greater depressive symptoms were associated with higher HDL concentrations and a lower triglyceride-to-HDL ratio, after adjusting for covariates.

Limitations: Cross-sectional design.

Conclusions: Adolescents with clinically significant depressive symptoms manifested similar levels of dyslipidemia as healthy youth. Future studies examining the prospective trajectories of depressive symptoms and lipid concentrations are needed to determine the point at which dyslipidemia emerges in the course of MDD, and the mechanism of the association that imparts increased CVD risk for depressed youth.

1. Introduction

Over the last decade, there has been a rising increase in the number of people who experience depressive symptoms (Twenge et al., 2018). Depression is currently the leading cause of disability globally ("Adolescent mental health," 2021). Adolescence is a particularly vulnerable period for developing depression (Avenevoli et al., 2015; Mullen, 2018). In 2019, a study of 95,856 youth found that 12.9 % of adolescents exhibited clinically significant depressive symptoms for at least a 12-month period (Lu, 2019). Further, a meta-analysis of 80,879 youth conducted during the first year of COVID-19 concluded that the global prevalence of youth experiencing clinically significant depressive symptoms increased to 25 % (Racine et al., 2021). Adolescents experience a multitude of symptoms during depression episodes, including persistent sadness, weight change, loss of energy, and insomnia (Rice et al., 2019). However, adolescent depression is also associated with many lasting physical health problems (Korczak et al., 2013; Naicker et al., 2013; Rhew et al., 2017; Weavers et al., 2021). Consequently, it is of utmost importance to understand the pathophysiology underlying adolescent depression, and how it relates, or possibly leads to, long-term health effects.

Adolescent depression is associated with an increased likelihood of

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experiencing cardiovascular events (Franco et al., 2015). According to the American Heart Association, depression is considered to be a tier II risk factor for early cardiovascular disease (Goldstein et al., 2015). Indeed, a small body of research demonstrates that adolescents with depression begin to manifest biological processes subserving cardiovascular disease (CVD) at an early age, including increased markers of inflammation (Colasanto et al., 2020; Copeland et al., 2012; Giollabhui et al., 2020), increased systolic and diastolic blood pressure (Klakk et al., 2018; Olive et al., 2020; Waloszek et al., 2015), greater prevalence of overweightness and obesity (Carney et al., 2021; Goldstein et al., 2015; Goldstein and Korczak, 2020), and early evidence of arterial stiffening (Goldstein et al., 2015; Goldstein and Korczak, 2020). Dyslipidemia is also an established, potentially modifiable, risk factor for CVD (e.g., Pires et al., 2016). However whether adolescents with depression evidence lipid abnormalities early in the course of illness is unclear.

Previous research on the relationship between serum lipid profiles and depression are inconsistent. Low-density lipoprotein (LDL)-cholesterol accumulates in blood vessels and increases the risk of coronary artery disease and high-density lipoprotein (HD) cholesterol transports other forms of cholesterol out of the blood stream and is inversely related to coronary artery disease risk (Wilson, 1990). Adults with depression demonstrate specific changes in serum lipid profiles, including increased (Shin et al., 2008) and decreased levels of HDL (Bharti et al., 2021; Bot et al., 2020; Cepeda et al., 2020; Enko et al., 2018; Sadeghi et al., 2011; Zhang et al., 2020), and increased levels of LDL (Enko et al., 2018; Klakk et al., 2018; Sadeghi et al., 2011; Tedders et al., 2011; Wagner et al., 2019) and triglycerides (Bharti et al., 2021; Bot et al., 2020; Cepeda et al., 2020; de Kluiver et al., 2021; Enko et al., 2018; Koponen et al., 2015; Segoviano-Mendoza et al., 2018). Study findings of total cholesterol (TC) levels among adults with depression are mixed, with both increased (Cepeda et al., 2020; Enko et al., 2018; Koponen et al., 2015; Sadeghi et al., 2011) and decreased (Bharti et al., 2021; Segoviano-Mendoza et al., 2018) levels reported. Studies among adults with major depressive disorder (MDD) have further observed that the magnitude of dyslipidemia and hypertriglyceridemia is significantly associated with increasing depressive symptom severity (Enko et al., 2018; van Reedt Dortland et al., 2010; Wagner et al., 2019), including suicidality (Oh and Kim, 2017; So et al., 2018). Research examining the causal relationship between lipid levels and depression is scant, however, with one study of 601 adults with MDD (mean age 40.9) observing that a high TG:HDL ratio increased the risk of developing MDD over a nine year follow up period (Watson et al., 2021), and in doing so raised the question of whether an adult's lipid profile can be used as a biomarker of depressive disorders (Walther et al., 2018).

In contrast, only a small number of studies have examined the association between depression and lipids early in the course of illness, among adolescents, when the presence of confounding comorbidities (e.g., obesity, type 2 diabetes mellitus) are less likely to obscure the association. Among published studies, findings are mixed. Studies of adolescents with depression have reported lower HDL (Barinas-Mitchell et al., 2021), lower (Karadeniz et al., 2020) and higher LDL (Kim et al., 2019), higher TG (Elovainio et al., 2010; Waloszek et al., 2015) and no association of lipids with MDD (Karadeniz et al., 2020; Katrenčíková et al., 2020). Moreover, studies to date have been conducted primarily among non-clinical samples. As the increased risk of CVD is described for individuals with clinically significant depression symptoms, this is an important distinction. Thus, the aim of the current study was to determine the association of lipid levels with depressive symptoms among adolescents with MDD, as compared with healthy youth. We hypothesized that adolescents with MDD would demonstrate greater levels of dyslipidemia (i.e., lipids at unhealthy levels) compared to healthy youth, based on the evidence among depressed adults. Further, we hypothesized that higher clinically significant depressive symptoms would be associated with higher LDL, TG, and TC concentrations, and with lower HDL concentrations.

2. Methods

2.1. Participants

Participants in the depression group [MDD] were recruited from a child and adolescent psychiatry clinic for youth with MDD at The Hospital for Sick Children (SickKids), a tertiary care children's hospital in Toronto, Canada. Youth with relevant reasons for referral (e.g., sadness) and increased self-reported depressive symptoms are referred via the departmental centralized intake system, which receives referrals from a wide variety of clinicians and settings, including family physicians, pediatricians, nurse practitioners, emergency medicine clinicians, and psychiatrists. Participants were children under the age of 18 years old with MDD as defined by the Diagnostic and Statistical Manual for Mental Disorders 5th edition (Arlington, 2013). Exclusion criteria included inability to provide informed consent/assent (e.g., psychotic disorder, developmental delay), history of hypomania/mania and significant chronic medical illness (e.g., rheumatologic disease, cancer).

Healthy control [HC] participants were recruited through community advertisements (e.g., coffee shops, public schools). HC participants did not have any active psychiatric disorders within the previous 6 months, no lifetime mood or anxiety disorders, and no maternal history of depression.

All participants and their guardians provided informed consent. This study received approval from the Hospital for Sick Children Research Ethics Board.

2.2. Clinical procedure and measures

Psychiatry diagnoses: Current and lifetime diagnoses were determined by standardized semi-structured psychiatric interview using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (Kaufman et al., 1997). The KSADS MDD-C was used to assess depressive symptoms in current and previous depressive episodes for confirmation of depressive diagnosis. Youth with the following diagnoses were included: Major Depressive Disorder, Major Depressive Episode, Persistent Depressive Disorder. Youth and parent each separately served as informants with information incorporated from each informant. All interviewers had completed a master's degree in a health science field with experience administering standardized semi-structured psychiatric interviews and were trained in the KSADS-PL. After the interview was completed, consensus conferences were held with a child-adolescent psychiatrist (D. K.) blinded to research participation status for diagnostic confirmation. Youth also completed the Centre for Epidemiologic Studies of Depression in Children (Radloff, 1977), a self-reported 20-item questionnaire using a 4-point Likert scale. Scores range from 0 to 60, where higher scores indicate greater depressive symptoms. A threshold score of 25 on the CES-DC was used for referral to the outpatient program, consistent with research reporting the need for employment of higher thresholds in clinical vs. community samples (Chabrol et al., 2002; Radloff, 1977). In the present sample, CES-DC had good reliability ($\alpha = 0.86$, 95 % CI: 0.85 to 0.88). In addition to the total CES-DC score, the following previously established subscale scores were calculated: Somatic (e.g., anorexia, sleep disturbance), Depressed (e.g., unhappy, felt like crying), Positive Affect (e.g., something good is going to happen), Interpersonal (e.g., kids are not friendly to me) (Barkmann et al., 2008).

Cardiovascular Risk Factors: Cardiovascular risk factors were assessed during the morning of initial assessment. Trained research staff measured height and weight in light clothing to the nearest 0.1 cm and 0.1 kg, respectively, using a Health o meter Professional stadiometer (Sunbeam Products, Inc). Body Mass Index (BMI) was computed as weight divided by height squared (kg/m2) and standardized body mass index (zBMI, kg/m^2) was calculated using the WHO growth standards with the Anthro Plus package in R (de Onis et al., 2007; Schumacher, 2021). Overweight was defined as BMI greater than the 85th and less

than the 95th percentile; obese was defined as BMI equal to or greater than the 95th percentile, in keeping with recommendations of the National Institute of Health Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (NIH-EP-CVH) (Adolescents, 2011). Systolic and diastolic blood pressure (BP) was measured using a DINAMAP ProCare DCP101X-CE automated blood pressure monitor (GE Healthcare) with the participant resting in the seated position for a minimum of 5 min and repeated following a further 5 min period, with measures averaged across readings and repeated a third time if discrepancies >10 mmHg in the first two readings were present. Blood pressure percentile was calculated based on age, sex and height-based norms (Flynn et al., 2017). Youth were also asked to report ("yes" or "no") if they are currently smoking cigarettes. Laboratory enzymatic colorimetric assays for total cholesterol (TC; mmol/L), high-density lipoprotein (HDL; mmol/L), low-density lipoprotein (LDL; mmol/L), and triglyceride (TG; mmol/L) concentrations were measured within 1 h using an Ortho Vitros instrument(Sapan et al., 2010). Fasting plasma lipid (total cholesterol, low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, triglyceride [TG]) concentrations were classified as being acceptable (healthy), borderline-high, or high as defined by the NIH-EP-CVH (Adolescents, 2011). Given the overall low prevalence of high lipid concentrations, the borderline-high and high categories were combined. Furthermore, here, the overall prevalence of dyslipidemia is defined as having at least one of the above lipid concentrations outside the acceptable range. Non-HDL, LDL-to-HDL ratio (LDL:HDL), and TG-to-HDL ratio (TG:HDL) were calculated from the fasted values.

2.3. Data analysis

Descriptive statistics, including *t*-tests for continuous variables and chi-square tests for categorical variables, were used to compare demographic and descriptive variables between the HC and MDD groups. For our primary analyses, we employed linear regression. First, we examined the association between clinical status (MDD, HC) and lipid variables. Next, we examined the association between total CES-DC scores and lipid variables among the MDD group. Lastly, we examined the association between the lipid variables that were significantly associated with the total CES-DC score, and each CES-DC subscale score (somatic, depressed, positive, interpersonal) among the MDD group. Regression models were conducted examining the association of depression with the following lipid concentrations: TC, HDL, LDL, LDL:HDL, non-HDL, TG, and TG:HDL. All models were adjusted for sex, age, and zBMI. Analyses were undertaken using R Studio, version 1.2.5033 (RStudio Team, 2019).

3. Results

Participants ($n = 243$) were 68 % female with a mean age of 15.0 ± 1.8 years. Demographic information is summarized in Table 1.

The majority of participants in both the MDD and HC group had lipid concentrations within the acceptable range (Table 2). No group differences in lipid concentrations were observed between the MDD and HC groups (Fig. 1). Depression status was not associated with any lipid concentration after adjusting for age, sex, and zBMI (Appendix Table 1). Sex was associated with TC, HDL, LDL, and non-HDL (all $ps < 0.001$); therefore, the models were re-run with the inclusion of clinical status × sex interaction term, and then with zBMI. In both models, clinical status was not associated with any lipid concentration following adjustment for covariates.

The association of depression symptom severity with fasting lipid levels was examined after adjusting for age, sex, and zBMI. Higher depressive symptoms were associated with increased HDL concentrations ($\beta = 0.23$, $SE = 0.08$, $p = .004$) in adjusted models (Fig. 2). Higher depression symptoms were also negatively associated with TG:HDL ratio ($\beta = -0.17$, $SE = 0.08$, $p = .03$) (Fig. 2). In addition, higher depression symptoms were initially observed to be associated with greater TC concentrations in unadjusted models ($\beta = 0.18$, $SE = 0.07$, $p = .02$). However, the association was no longer statistically significant ($\beta = 0.11$, $SE = 0.08$, $p = .15$) following adjustment. Depression severity was not associated with LDL, TG, non-HDL, or LDL:HDL concentrations (Appendix Table 2).

Table 1
Participant characteristics by diagnostic group.

	Healthy controls ($n = 57$)	Major Depressive Disorder (MDD) ($n = 186$)	*p*
Age (mean (SD))	15.1 (1.7)	15.0 (1.9)	0.84
Sex (n,%)			**0.001**
Female	28 (49)	134 (74)	
Male	29 (51)	48 (27)	
BMI (mean (SD))	21.3 (3.4)	22.3 (5.3)	0.19
zBMI (mean (SD))	0.3 (1.0)	0.5 (1.3)	0.43
BMI category (n,%)			0.08
Normal weight	38 (67)	127 (71)	
Obesity	2 (3)	21 (12)	
Overweight	17 (30)	31 (17)	
Heart rate (mean (SD))	69 (10)	76 (14)	**0.001**
Systolic BP (mean (SD))	112.5 (11.4)	112.5 (12.7)	0.99
Diastolic BP (mean (SD))	61.4 (7.3)	62.8 (8.0)	0.24
Depression (CESDC [mean (SD)])	8.3 (4.5)	37.5 (12.0)	**<0.001**
Race/ethnicity (n,%)			0.62
White/Caucasian	33 (61)	89 (62)	
Mixed	7 (13)	27 (19)	
East/South Asian	9 (17)	17 (12)	
Other	5 (10)	11 (7)	
Living situation (n,%)			0.13
Both biological parents	44 (82)	92 (64)	
Both biological parents, joint custody	4 (7)	15 (1)	
Single biological parent	3 (6)	33 (23)	
Other	3 (6)	4 (3)	
Father employed (n,%)	45 (88)	128 (93)	0.39
Mother employed (n,%)	50 (93)	116 (81)	0.08
Household income (n,%)			
< 75,000 CAD/year	8 (15)	35 (25)	0.29
> 75,000 CAD/year	38 (7)	85 (59)	
Prefer not to answer	8 (15)	23 (16)	
Smoking (n, %)	0 (0)	10 (6)	0.15

Abbreviations: Dx = diagnosis; zBMI = body mass index z-scores, standardized for age and sex using the World Health Organization's 2007 AnthroPlus software in R studio; CES-DC = Center for Epidemiologic Studies Depression Scale for Children.
Bolded p values indicates statistical significance ($p < .05$).

Within the MDD group, multivariable linear regression analyses were performed with CES-DC subscales to examine associations with HDL and TG:HDL, as these were the only lipids significantly associated with the depression (CES-DC) total score. All models were adjusted for age, sex, and zBMI. Higher Depressed and Interpersonal subscale scores were significantly associated with higher HDL concentrations ($\beta = 0.20$, $SE = 0.08$, $p = .01$; $\beta = 0.27$, $SE = 0.08$, $p < .001$, respectively) in adjusted models. Increased interpersonal difficulty was also associated with decreased TG:HDL ratio ($\beta = -0.18$, $SE = 0.08$, $p = .03$) after adjusting for covariates. We did not observe any other associations between depression subscales and remaining lipid concentrations (see Table 3).

4. Discussion

This study compared serum lipid concentrations among youth with MDD at the time of diagnosis with those of healthy youth, and examined the association between depression severity and lipid concentrations for youth with MDD. No differences in mean lipid levels were observed among MDD and non-MDD control adolescents. In addition, there were no differences in the proportion of adolescents with borderline-high

Table 2
Lipid concentrations by diagnostic group.

	Healthy controls (n = 57)	Major Depressive Disorder (MDD) (n = 186)	p
Total cholesterol (mean (SD); mmol/L)	3.96 (0.73)	4.08 (0.79)	0.31
Acceptable (< 4.40; n (%))	42 (77.8)	128 (71.1)	0.43
Borderline-high (≥ 4.40; n (%))	12 (22.2)	52 (28.9)	
HDL (mean (SD); mmol/L)	1.40 (0.49)	1.40 (0.33)	0.92
Acceptable (> 1.16; n (%))	41 (75.9)	138 (76.7)	1.0
Borderline-low (≤ 1.16; n (%))	13 (24.1)	42 (23.3)	
LDL (mean (SD); mmol/L)	2.22 (0.61)	2.22 (0.65)	0.96
Acceptable range (< 2.85; n (%))	48 (83.3)	152 (81)	0.85
Borderline-high (≥ 2.85; n (%))	9 (16.7)	34 (19)	
LDL:HDL (mean (SD))	1.70 (0.61)	1.68 (0.65)	0.80
Non-HDL (mean (SD); mmol/L)	2.56 (0.87)	2.67 (0.75)	0.59
Acceptable range (< 3.11; n (%))	43 (79.6)	134 (74.4)	0.55
Borderline-high (≥ 3.11; n (%))	11 (20.4)	46 (25.6)	
Triglycerides (mean (SD); mmol/L)	0.88 (0.38)	0.99 (0.59)	0.20
Acceptable range (< 1.01; n (%))	41 (70.4)	119 (66.5)	0.71
Borderline-high (≥1.01; n (%))	16 (29.6)	60 (33.5)	
TG:HDL	0.69 (0.35)	0.76 (0.55)	0.36

Abbreviations: Dx = diagnosis; HDL = high density lipoprotein; LDL = low density lipoprotein; LDL:HDL = LDL-to-HDL ratio.

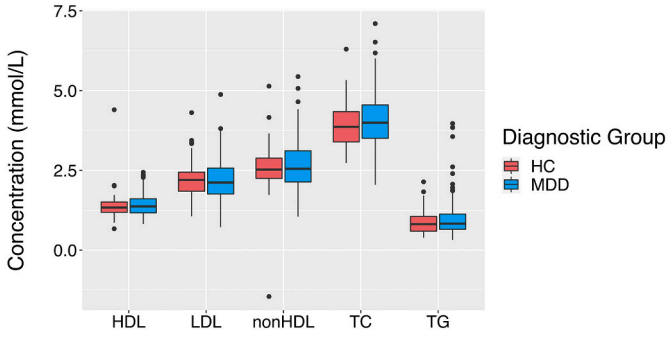

Fig. 1. Lipid levels by diagnostic group; [n = 243].

lipid concentrations between diagnostic groups. This study also finds that among youth with MDD, greater depressive symptoms were associated with higher HDL levels and a lower TG:HDL ratio after adjusting for sex, age, and zBMI.

The results of the current study are consistent with those of Katrenčíková et al. (2020) yet in contrast to findings among adult samples that have consistently reported an association between clinically significant MDD and dyslipidemia (Bharti et al., 2021; Enko et al., 2018; Wagner et al., 2019). Given that previous work identifies youth-onset depression as a risk factor for premature atherosclerosis and ischemic heart disease, our findings raise the possibility that prolonged symptoms of depression may also increase lipid concentrations via indirect mechanisms. For example, children and adolescents with depression report lower levels of physical activity than peers (Korczak et al., 2017; Rodriguez-Ayllon et al., 2019), eat less healthy foods than controls (Korczak et al., 2021b), and report a greater number of sleep problems, including nonrestorative sleep and insomnia (Urrila et al., 2012). Thus, children and adolescents with depression may also present indirect risk factors for premature CVD in adulthood (Goldstein et al., 2015). Indeed, Barinas Mitchell et al. (2021) found that those with child-onset depression had higher TG and lower HDL concentrations, as measured in adulthood, compared with healthy controls (Barinas-Mitchell et al., 2021), where both observations are a critical component of metabolic syndrome (Wilson and Grundy, 2003). As the current study included adolescents at the time of MDD diagnosis, the null findings suggest that the lipid concentrations may be a more distal marker of increased CVD risk among depressed youth.

Previous research has proposed several biological mechanisms linking MDD with premature CVD. For example, systemic inflammatory pathways have been implicated as a mechanism by which MDD may incur increased risk of CVD among depressed adults (Bivanco-Lima et al., 2013; Messay et al., 2012). These findings are consistent with those of a recent meta-analysis (including 20,791 participants) examining the prospective association of adolescent depression with inflammation, reporting that increased depressive symptoms is associated with increased pro-inflammatory cytokines (e.g., CRP and IL-6) in longitudinal studies and conversely, that increased pro-inflammatory cytokines also predict future depression among adolescents, thereby highlighting the bidirectional nature of the association (Colasanto et al., 2020).

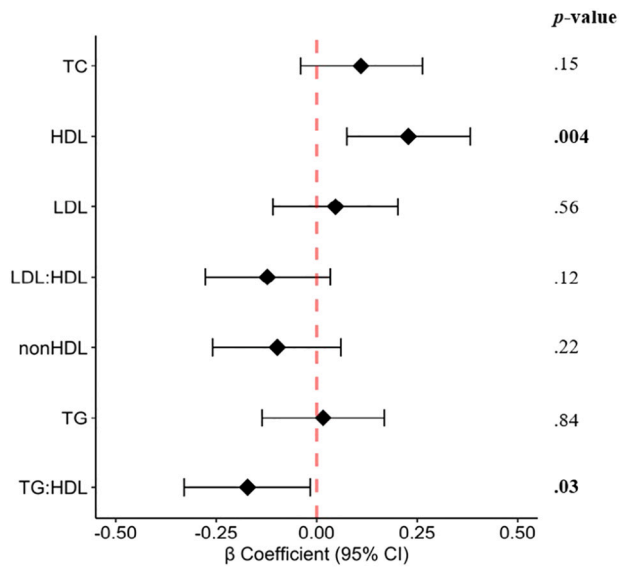

Fig. 2. Association of depression severity with blood lipid concentrations among youth with MDD (n = 170). Reported standardized coefficients are adjusted for sex, age, and zBMI score.
Abbreviations: TC = total cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; TG = triglyceride; MDD = Major Depressive Disorder, zBMI = standardized Body Mass Index.

Table 3
Association of depression severity subscales blood lipid concentrations among youth with MDD (n = 170). All models are adjusted for sex, age, and BMI z score.

	Predictor	b	β	SE	95 % CI		p
					Lower	Upper	
HDL	Somatic	0.01	0.11	0.08	−0.05	0.27	0.17
	Depressed	0.01	0.20	0.08	0.05	0.35	**0.01**
	Positive	0.02	0.12	0.08	−0.03	0.27	0.11
	Inter-personal	0.05	0.27	0.08	0.12	0.42	**0.00**
TG:HDL	Somatic	−0.01	−0.15	0.08	−0.28	0.04	0.13
	Depressed	−0.01	−0.14	0.08	−0.29	0.02	0.09
	Positive	−0.02	−0.08	0.08	−0.23	0.08	0.32
	Inter-personal	−0.05	−0.18	0.08	−0.33	−0.02	**0.03**

Abbreviations: HDL = high density lipoprotein; TG: triglyceride. For HDL, R^2 for each model is 0.07, 0.09, 0.07, and 0.13, respectively. For TG:HDL, R^2 for each model is 0.06, 0.06, 0.05, 0.07.
Bolded p values indicates statistical significance (p < .05).

Taken together, this suggests a role for inflammation in the MDD-CVD association at both early and later points of illness.

Another potential mechanism by which MDD may confer increased risk of CVD is via disruption to autonomic nervous system activity. The autonomic nervous system, consisting of the sympathetic and parasympathetic nervous system, has a regulatory effect on several organs, with dysregulation leading to systemic effects on the body (McCorry, 2007). It has been theorized that autonomic nervous system dysfunction, defined as increased sympathetic and decreased parasympathetic output, yields a pro-inflammatory and hypercoagulable state that acts to accelerate atherosclerosis, thereby conferring increased CVD risk (Tonhajzerova et al., 2020). Several previous studies support this mechanism. Wang et al. (2013) found that adults with MDD demonstrated greater autonomic dysfunction, which was significantly correlated with depression severity. These findings were also consistent with those of Kop et al. (2010) in the examination of the combined impact of inflammation and autonomic dysfunction on the prevalence of cardiovascular mortality in adults. However, together, these two measures only explained a small portion of the depression-cardiovascular mortality association, indicating that additional factors remain unexplained. Similarly, elevated autonomic nervous system activity has also been reported among adolescents with MDD (Goldstein et al., 2015). As the current study suggests that lipid concentrations may be a more distal marker of increased CVD risk among depressed youth, more proximal mechanistic investigations, such as those of inflammatory markers and autonomic nervous systemic activity, may be more productive in determining the early pathway by which youth-onset MDD increases the risk of CVD.

Indeed, although the mechanism(s) by which depression confers increased CVD risk have yet to be definitively established, it is evident that MDD youth do manifest several early risk factors for CVD. A recent study of youth with a clinical diagnosis of MDD found that over half the participants exhibited two or more CVD risk factors (Korczak et al., 2021a). Previous research has also consistently shown the prevalence of other CVD risk factors is significantly greater among depressed young adults than that seen in the general population, including obesity, nicotine and alcohol use, insulin resistance, and hypertension (Carney et al., 2021; Chaplin et al., 2021; Klakk et al., 2018). These factors require varying degrees of chronicity before reaching clinical significance. Findings from the current study suggest that dyslipidemia observed in studies of depressed adults may similarly emerge with greater duration of illness than we observed in this clinical population of adolescents early in the course of illness.

Results of this study also show a positive association between HDL and depression severity among MDD adolescents, which is in contrast with the inverse relationship observed by Katrenčíková et al. (2020) in their smaller study of 80 adolescents (58 adolescents with a depressive disorder and 20 control youth). In contrast, no association between depressive symptoms and HDL concentrations were observed in the HC group. While the smaller HC sample may have resulted in a lack of power to detect the association, we also note the gender differences between the MDD group (75 % female) and the HC group (50 % female) in the current study, and consider our findings in the context of those of a previous meta-analysis, in which a positive association between HDL and depressive symptoms were noted only in adult women (Shin et al., 2008). Currently, leading hypotheses fail to account for this potential gender-specificity in the depression-CVD association. Taken together, results of the current study support the need for further examination of the relationship between gender, depression, and cholesterol.

5. Strengths and limitations

This study contains several strengths, including use of a clinical MDD population early in the course of illness and prior to the emergence of the commonly comorbid cardiometabolic conditions (e.g. obesity, type 2 diabetes mellitus) that can serve as confounders in the MDD-CVD relationship. In addition, this study included a non-MDD adolescent comparison group. Importantly, the MDD sample included in the present study, to our knowledge, is the largest to examine the association of depressive symptoms with lipid concentrations among a clinical population of youth. Despite these strengths, however, several limitations are noted. First, the sample size of the HC comparator group, while larger than those of similar studies published previously (Katrenčíková et al., 2020) is smaller than the MDD group. Thus, while it is possible that the smaller HC sample size contributed to the null findings of the current study it is unlikely, as the lipid concentrations exhibited by this group are similar to those reported in a previous study ($N = 2141$) examining reference values for lipid concentrations in Caucasian children and adolescents (Nielsen et al., 2017). Furthermore, post-hoc power analysis revealed that given the total sample size of 243 adolescents, the present study had >90 % power to detect a medium effect size. That said, replication of the null association of clinical status with lipid concentration in larger samples is important. Second, the mean CES-DC score among healthy youth was 8.3, with a standard deviation of 4.5, as compared to the mean CES-DC score of 37.5 (SD 12) among MDD youth, limiting the variance in depression severity over which an association may be detectable, and contributing to the null association among healthy children found in the current study. Finally, the cross-sectional design of the current study precluded examination of the prospective, directional association between MDD and serum lipid concentrations, and specifically between depression severity and HDL levels. Future research examining the longitudinal course of depression and lipid trajectories are needed in order to determine both the directionality of effects as well as the point at which dyslipidemia noted in adult studies emerges.

6. Conclusions

The findings of the current study suggest that adolescents with depression do not exhibit clinically significant dyslipidemia at the time of diagnosis. Results suggest that early onset MDD provides a window of opportunity to mitigate the increased CVD risk associated with dyslipidemia. Findings of the current study further support the need for longitudinal studies examining the trajectories of potential CVD risk factors, such as dyslipidemia, in tandem with those of depressive symptoms to more accurately characterize the potentially dynamic mechanism underlying the MDD-CVD association, and determine points of potential preventive intervention.

CRediT authorship contribution statement

AFK conceptualized and designed the study, assisted in data collection, conducted initial analyses, and drafted the initial manuscript. SCC assisted with the conceptualization, data collection, and interpretation of the findings. RFL assisted with the analyses. BWM contributed to the conceptualization and interpretation of the findings. DJK contributed to the conceptualization, data collection, and interpretation of the findings. All authors critically reviewed and approved the final manuscript.

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Declaration of competing interest

The authors have no potential conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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References

Adolescent Mental Health, 2021. https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health. (Accessed 31 December 2023).

Arlington, V., 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association.

Avenevoli, S., Swendsen, J., He, J.-P., Burstein, M., Merikangas, K., et al., 2015. Major depression in the National Comorbidity Survey- Adolescent Supplement: prevalence, correlates, and treatment. J. Am. Acad. Child Adolesc. Psychiatry 54, 37–44.e2. https://doi.org/10.1016/j.jaac.2014.10.010.

Barinas-Mitchell, E., Yang, X., Matthews, K.A., et al., 2021. Childhood-onset depression and arterial stiffness in young adulthood. J. Psychosom. Res. 148, 110551 https://doi.org/10.1016/j.jpsychores.2021.110551.

Barkmann, C., Erhart, M., Schulte-Markwort, M., BELLA Study Group, 2008. The German version of the Centre for Epidemiological Studies Depression Scale for Children: psychometric evaluation in a population-based survey of 7 to 17 years old children and adolescents–results of the BELLA study. Eur. Child Adolesc. Psychiatry 17 (Suppl. 1), 116–124. https://doi.org/10.1007/s00787-008-1013-0.

Bharti, V., Bhardwaj, A., Hood, K., et al., 2021. A systematic review and meta-analysis of lipid metabolomic signatures of Major Depressive Disorder. J. Psychiatr. Res. 139, 197–205. https://doi.org/10.1016/j.jpsychires.2021.05.036.

Bivanco-Lima, D., de Souza Santos, I., Vannucchi, A.M.C., et al., 2013. Cardiovascular risk in individuals with depression. Rev. Assoc. Med. Bras. 59, 298–304. https://doi.org/10.1016/j.ramb.2012.12.006.

Bot, M., Milaneschi, Y., Al-Shehri, T., et al., 2020. Metabolomics profile in depression: a pooled analysis of 230 metabolic markers in 5283 cases with depression and 10,145 controls. Biol. Psychiatry 87, 409–418. https://doi.org/10.1016/j.biopsych.2019.08.016.

Carney, R., Firth, J., Pedley, R., et al., 2021. The clinical and behavioral cardiometabolic risk of children and young people on mental health inpatient units: a systematic review and meta-analysis. Gen. Hosp. Psychiatry 70, 80–97. https://doi.org/10.1016/j.genhosppsych.2021.03.007.

Cepeda, M.S., Kern, D.M., Blacketer, C., Drevets, W.C., 2020. Low levels of cholesterol and the cholesterol type are not associated with depression: results of a cross-sectional NHANES study. J. Clin. Lipidol. 14, 515–521. https://doi.org/10.1016/j.jacl.2020.06.001.

Chabrol, H., Montovany, A., Chouicha, K., Duconge, E., 2002. Study of the CES-D on a sample of 1,953 adolescent students. Encephale 28, 429–432.

Chaplin, A.B., Daniels, N.F., Ples, D., et al., 2021. Longitudinal association between cardiovascular risk factors and depression in young people: a systematic review and meta-analysis of cohort studies. Psychol. Med. 1–11 https://doi.org/10.1017/S0033291721002488.

Colasanto, M., Madigan, S., Korczak, D.J., 2020. Depression and inflammation among children and adolescents: a meta-analysis. J. Affect. Disord. 277, 940–948. https://doi.org/10.1016/j.jad.2020.09.025.

Copeland, W.E., Shanahan, L., Worthman, C., et al., 2012. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. Biol. Psychiatry 71, 15–21. https://doi.org/10.1016/j.biopsych.2011.09.023.

de Kluiver, H., Jansen, R., Milaneschi, Y., et al., 2021. Metabolomic profiles discriminating anxiety from depression. Acta Psychiatr. Scand. 144, 178–193. https://doi.org/10.1111/acps.13310.

de Onis, M., Onyango, A.W., Borghi, E., et al., 2007. Development of a WHO growth reference for school-aged children and adolescents. Bull. World Health Organ. 85, 660–667. https://doi.org/10.2471/blt.07.043497.

Elovainio, M., Pulkki-Råback, L., Kivimäki, M., et al., 2010. Lipid trajectories as predictors of depressive symptoms: the Young Finns Study. Health Psychol. 29, 237–245. https://doi.org/10.1037/a0018875.

Enko, D., Brandmayr, W., Halwachs-Baumann, G., et al., 2018. Prospective plasma lipid profiling in individuals with and without depression. Lipids Health Dis. 17, 149. https://doi.org/10.1186/s12944-018-0796-3.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute, 2011. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 128, S213. https://doi.org/10.1542/peds.2009-2107C.

Flynn, J.T., Kaelber, D.C., Baker-Smith, C.M., et al., 2017. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 140, e20171904. https://doi.org/10.1542/peds.2017-1904.

Franco, S., Hoertel, N., Peyre, H., et al., 2015. Age at onset of major depression and adulthood cardiovascular risk. Psychiatry Res. 225, 736–738. https://doi.org/10.1016/j.psychres.2014.12.022.

Giollabhui, N.M., Swistun, D., Murray, S., et al., 2020. Executive dysfunction in depression in adolescence: the role of inflammation and higher body mass. Psychol. Med. 50, 683–691. https://doi.org/10.1017/S0033291719000564.

Goldstein, B.I., Korczak, D.J., 2020. Links Between Child and Adolescent Psychiatric Disorders and Cardiovascular Risk | Elsevier Enhanced Reader [WWW Document]. https://doi.org/10.1016/j.cjca.2020.06.023.

Goldstein, B.I., Carnethon, M.R., Matthews, K.A., et al., 2015. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation 132, 965–986. https://doi.org/10.1161/CIR.0000000000000229.

Karadeniz, S., Yaman, H., Bilginer, Ç., et al., 2020. Serum nesfatin-1, ghrelin, and lipid levels in adolescents with first episode drug naïve unipolar depression. Nord. J. Psychiatry 74, 613–619. https://doi.org/10.1080/08039488.2020.1772363.

Katrenčíková, B., Vaváková, M., Waczulíková, I., et al., 2020. Lipid Profile, Lipoprotein Subfractions, and Fluidity of Membranes in Children and Adolescents with Depressive Disorder: Effect of Omega-3 Fatty Acids in a Double-Blind Randomized Controlled Study. Biomolecules (Basel, Switzerland), vol. 10. https://doi.org/10.3390/biom10101427, 1427-.

Kaufman, J., Birmaher, B., Brent, D., et al., 1997. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36, 980–988. https://doi.org/10.1097/00004583-199707000-00021.

Kim, E.J., Hong, J., Hwang, J.-W., 2019. The association between depressive mood and cholesterol levels in Korean adolescents. Psychiatry Investig. 16, 737–744. https://doi.org/10.30773/pi.2019.03.24.

Klakk, H., Kristensen, P.L., Andersen, L.B., et al., 2018. Symptoms of depression in young adulthood is associated with unfavorable clinical- and behavioral cardiovascular disease risk factors. Prev. Med. Rep. 11, 209–215. https://doi.org/10.1016/j.pmedr.2018.05.017.

Kop, W.J., Stein, P.K., Tracy, R.P., et al., 2010. Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. Psychosom. Med. 72, 626–635. https://doi.org/10.1097/PSY.0b013e3181eadd2b.

Koponen, H., Kautiainen, H., Leppänen, E., et al., 2015. Association between suicidal behaviour and impaired glucose metabolism in depressive disorders. BMC Psychiatry 15, 163. https://doi.org/10.1186/s12888-015-0567-x.

Korczak, D.J., Lipman, E., Morrison, K., et al., 2013. Are children and adolescents with psychiatric illness at risk for increased future body weight? A systematic review. Dev. Med. Child Neurol. 55, 980–987. https://doi.org/10.1111/dmcn.12168.

Korczak, D.J., Madigan, S., Colasanto, M., 2017. Children's physical activity and depression: a meta-analysis. Pediatrics 139, e20162266. https://doi.org/10.1542/peds.2016-2266.

Korczak, D.J., Cleverley, K., Birken, C.S., et al., 2021a. Cardiovascular disease risk factors among children and adolescents with depression. Front. Psych. 12.

Korczak, D.J., Perruzza, S., Chandrapalan, M., et al., 2021b. The association of diet and depression: an analysis of dietary measures in depressed, non-depressed, and healthy youth. Nutr. Neurosci. 0, 1–8. https://doi.org/10.1080/1028415X.2021.1918981.

Lu, W., 2019. Adolescent depression: national trends, risk factors, and healthcare disparities. Am. J. Health Behav. 43, 181–194. https://doi.org/10.5993/AJHB.43.1.15.

McCorry, L.K., 2007. Physiology of the autonomic nervous system. Am. J. Pharm. Educ. 71, 78.

Messay, B., Lim, A., Marsland, A.L., 2012. Current understanding of the bi-directional relationship of major depression with inflammation. Biol. Mood Anxiety Dis. 2, 4. https://doi.org/10.1186/PREACCEPT-14614937596285.

Mullen, S., 2018. Major depressive disorder in children and adolescents. Ment Health Clin. 8, 275–283. https://doi.org/10.9740/mhc.2018.11.275.

Naicker, K., Galambos, N.L., Zeng, Y., Senthilselvan, A., Colman, I., 2013. Social, demographic, and health outcomes in the 10 years following adolescent depression. J. Adolesc. Health 52, 533–538. https://doi.org/10.1016/j.jadohealth.2012.12.016.

Nielsen, T.R.H., Lausten-Thomsen, U., Fonvig, C.E., et al., 2017. Dyslipidemia and reference values for fasting plasma lipid concentrations in Danish/North-European White children and adolescents. BMC Pediatr. 17, 116. https://doi.org/10.1186/s12887-017-0868-y.

Oh, J., Kim, T.-S., 2017. Serum lipid levels in depression and suicidality: the Korea National Health and Nutrition Examination Survey (KNHANES) 2014. J. Affect. Disord. 213, 51–58. https://doi.org/10.1016/j.jad.2017.02.002.

Olive, L.S., Abhayaratna, W.P., Byrne, D., et al., 2020. Depression, stress and vascular function from childhood to adolescence: a longitudinal investigation. Gen. Hosp. Psychiatry 62, 6–12. https://doi.org/10.1016/j.genhosppsych.2019.10.001.

Pires, A., Sena, C., Seiça, R., 2016. Dyslipidemia and cardiovascular changes in children. Curr. Opin. Cardiol. 31, 95. https://doi.org/10.1097/HCO.0000000000000249.

Racine, N., McArthur, B.A., Cooke, J.E., et al., 2021. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis. JAMA Pediatr. 175, 1142. https://doi.org/10.1001/jamapediatrics.2021.2482.

Radloff, L.S., 1977. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. https://doi.org/10.1177/014662167700100306.

Rhew, I.C., Fleming, C.B., Vander Stoep, A., et al., 2017. Examination of cumulative effects of early adolescent depression on cannabis and alcohol use disorder in late adolescence in a community-based cohort: depression and substance use disorders. Addiction 112, 1952–1960. https://doi.org/10.1111/add.13907.

Rice, F., Riglin, L., Lomax, T., et al., 2019. Adolescent and Adult Differences in Major Depression Symptom Profiles | Elsevier Enhanced Reader [WWW Document]. https://doi.org/10.1016/j.jad.2018.09.015.

Rodriguez-Ayllon, M., Cadenas-Sánchez, C., Estévez-López, F., et al., 2019. Role of physical activity and sedentary behavior in the mental health of preschoolers, children and adolescents: a systematic review and Meta-analysis. Sports Med. 49, 1383–1410. https://doi.org/10.1007/s40279-019-01099-5.

RStudio Team, 2019. RStudio: Integrated Development Environment for R.

Sadeghi, M., Roohafza, H., Afshar, H., et al., 2011. Relationship between depression and apolipoproteins A and B: a case-control study. Clinics (Sao Paulo) 66, 113–117. https://doi.org/10.1590/s1807-59322011000100020.

Sapan, C.V., Lundblad, R.L., Price, N.C., 2010. Colorimetric protein assay techniques [WWW Document]. https://iubmb.onlinelibrary.wiley.com/doi/abs/10.1111/j.1470-8744.1999.tb00538.x. (Accessed 26 May 2022).

Schumacher, D., 2021. anthroplus: Computation of the WHO 2007 References for School-Age Children and Adolescents (5 to 19 Years). R package version 0.9.0.
Segoviano-Mendoza, M., Cárdenas-de la Cruz, M., Salas-Pacheco, J., et al., 2018. Hypocholesterolemia is an independent risk factor for depression disorder and suicide attempt in Northern Mexican population. BMC Psychiatry 18, 7. https://doi.org/10.1186/s12888-018-1596-z.
Shin, J.Y., Suls, J., Martin, R., 2008. Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors. Ann. Behav. Med. 36, 33–43. https://doi.org/10.1007/s12160-008-9045-8.
So, H.-C., Chau, C.K., Cheng, Y., et al., 2018. Causal relationships between blood lipids and depression phenotypes: a Mendelian randomization analysis (preprint). Genetics. https://doi.org/10.1101/363119.
Tedders, S.H., Fokong, K.D., McKenzie, L.E., et al., 2011. Low cholesterol is associated with depression among US household population. J. Affect. Disord. 135, 115–121. https://doi.org/10.1016/j.jad.2011.06.045.
Tonhajzerova, I., Sekaninova, N., Bona Olexova, L., Visnovcova, Z., 2020. Novel insight into neuroimmune regulatory mechanisms and biomarkers linking major depression and vascular diseases: the dilemma continues. Int. J. Mol. Sci. 21, 2317. https://doi.org/10.3390/ijms21072317.
Twenge, J.M., Joiner, T.E., Rogers, M.L., et al., 2018. Increases in depressive symptoms, suicide-related outcomes, and suicide rates among U.S. adolescents after 2010 and links to increased new media screen time. Clin. Psychol. Sci. 6, 3–17. https://doi.org/10.1177/2167702617723376.
Urrila, A.S., Karlsson, L., Kiviruusu, O., et al., 2012. Sleep complaints among adolescent outpatients with major depressive disorder. Sleep Med. 13, 816–823. https://doi.org/10.1016/j.sleep.2012.04.012.
van Reedt Dortland, A.K.B., Giltay, E.J., van Veen, T., et al., 2010. Associations between serum lipids and major depressive disorder: results from the Netherlands study of depression and anxiety (NESDA). J. Clin. Psychiatry 71, 729–736. https://doi.org/10.4088/JCP.08m04865blu.
Wagner, C.J., Musenbichler, C., Böhm, L., et al., 2019. LDL cholesterol relates to depression, its severity, and the prospective course. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 92, 405–411. https://doi.org/10.1016/j.pnpbp.2019.01.010.
Waloszek, J.M., Byrne, M.L., Woods, M.J., et al., 2015. Early physiological markers of cardiovascular risk in community based adolescents with a depressive disorder. J. Affect. Disord. 175, 403–410. https://doi.org/10.1016/j.jad.2015.01.008.
Walther, A., Cannistraci, C.V., Simons, K., et al., 2018. Lipidomics in major depressive disorder. Front. Psych. 9.
Wang, Y., Zhao, X., O'Neil, A., et al., 2013. Altered cardiac autonomic nervous function in depression. BMC Psychiatry 13, 187. https://doi.org/10.1186/1471-244X-13-187.
Watson, K.T., Simard, J.F., Henderson, V.W., et al., 2021. Incident major depressive disorder predicted by three measures of insulin resistance: a Dutch cohort study. Am. J. Psychiatry 178, 914–920. https://doi.org/10.1176/appi.ajp.2021.20101479.
Weavers, B., Heron, J., Thapar, A.K., et al., 2021. The antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories: a longitudinal, population-based English study. Lancet Psychiatry 8, 1053–1061. https://doi.org/10.1016/S2215-0366(21)00281-9.
Wilson, P.W.F., 1990. High-density lipoprotein, low-density lipoprotein and coronary artery disease. In: The American Journal of Cardiology, A Symposium: The Significance of High-Density Lipoprotein Cholesterol in the Prevention of Coronary Artery Disease, 66, pp. A7–A10. https://doi.org/10.1016/0002-9149(90)90562-F.
Wilson, P.W.F., Grundy, S.M., 2003. The metabolic syndrome. Circulation 108, 1537–1540. https://doi.org/10.1161/01.CIR.0000089506.12223.F1.
Zhang, C., Yang, Y., Zhu, D.-M., et al., 2020. Neural correlates of the association between depression and high density lipoprotein cholesterol change. J. Psychiatr. Res. 130, 9–18. https://doi.org/10.1016/j.jpsychires.2020.07.012.