NEW RESEARCH

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Identifying Cardiovascular Disease Risk Endotypes of Adolescent Major Depressive Disorder Using Exploratory Unsupervised Machine Learning

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Objective: Adolescents with major depressive disorder (MDD) are at increased risk of premature atherosclerosis and cardiovascular disease (CVD). The ability to identify adolescents with MDD who are at increased CVD risk would facilitate personalized interventions and advance knowledge regarding the MDD–CVD association. This study aimed to identify adolescent MDD endotypes of increased CVD risk.

Method: Youth with MDD (n = 189; 74% female; mean [SD] age 15.03 [1.85] years) were recruited through an outpatient psychiatry program in a large urban hospital. Individual and family (demographics, depression, anxiety symptoms, family conflict), physical examination (vital signs, body mass index), and laboratory (lipid profile, glucose, C-reactive protein) data were collected. Using demographic, clinical, and laboratory data, k-means clustering was performed; a subsequent model included only lipids. Continuous and categorical measures were compared between clusters.

Results: The model containing all variables yielded 1 high and 1 low CVD risk cluster, which differed significantly in ethnicity, anthropometrics, laboratory data, and family conflict, but not in depression or anxiety severity. The lipid-only model yielded 2 high and 2 low CVD risk clusters that differed significantly in sex, ethnicity, body mass index, lipids, depression, and anxiety severity. Of the 2 CVD risk clusters, one was indicative of increased cardiometabolic risk, while the other comprised adolescents with MDD who had high low-density lipoprotein and no other cardiovascular risk factors.

Conclusion: Endotypes of adolescent MDD associated with varying levels of CVD risk were identified. Results highlight the heterogeneity of adolescent MDD and the need for precision medicine approaches in management of MDD to improve both CVD and depression outcomes.

Plain language summary: This study examined cardiovascular risk factors among adolescents with major depressive disorder (MDD) at the Hospital for Sick Children in Toronto, Canada. Cluster analysis using fasting serum lipid concentrations yielded 4 endotypes of adolescent depression with respect to youth demographic, clinical, and cardiometabolic factors and highlighted different potential mechanisms of increased cardiovascular disease (CVD) risk. Results underscore the heterogeneity of adolescent MDD and the need for precision medicine approaches to improve both CVD and depression outcomes.

Key words: cardiovascular disease; heterogeneity; major depressive disorder; precision medicine

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Depression is a leading cause of disability among youth worldwide.[1] The American Heart Association has identified youth-onset major depressive disorder (MDD) as an independent risk factor for premature atherosclerosis and death from cardiovascular disease (CVD).[2] Previous studies have found that adolescent depression is associated with an increased CVD risk profile.[3–6] Common CVD risk factors reported to be prevalent among adolescents with MDD include a body mass index (BMI) in the overweight or obese range,[2,7–9] increased prevalence of smoking,[8] hypertension,[10,11] lack of physical activity,[12] increased inflammatory markers,[7,13,14] hyperglycemia,[3] and dyslipidemia.[3] Specifically, some studies have found that depressed adolescents have lower high-density lipoprotein (HDL),[4] higher low-density lipoprotein (LDL),[15] and higher triglyceride levels compared with otherwise healthy youth.[3,16] A recent study demonstrated that slightly more than half (52%) of adolescents with MDD exhibit at least 2 CVD risk factors.[6] This highlights the heterogeneity of CVD risk among adolescents with MDD and prompts the question of how we can identify the adolescents with MDD who are at increased CVD risk. Given that CVD risk factors are present

early in the course of MDD, there may be a window of opportunity to prevent future CVD in this high-risk population.

Previous studies have examined the MDD–CVD association by comparing CVD risk factors between depressed adolescents and healthy controls.[4] This approach, however, relies on the assumption that all depressed adolescents experience a similarly heightened CVD risk. Yet ample literature confirms that depression is a heterogeneous illness, in terms of both its clinical presentation and its course. Indeed, in a recent review of this topic, the wide range of symptoms observed in MDD (eg, fatigue, weight gain, hypersomnia) have been attributed to, in part, various alterations in biological pathways.[17] A previous article addressed the difficulties associated with the heterogeneity of psychiatric disorders and commented on the statistical approaches that can be used to overcome the problem by identifying subgroups within a psychiatric population.[18] Indeed, unsupervised machine learning, specifically clustering methods, have recently been used in several studies to better understand the neural and genetic complexities associated with depression.[19] Therefore, a more fruitful approach to understanding the adolescent depression–CVD association may be to identify subgroups of depressed adolescents who demonstrate varying CVD risk. The identification of such subgroups would, in turn, allow for a more personalized approach to managing CVD risk for youth with MDD. The current study aimed to identify and characterize CVD risk endotypes in adolescent MDD using unsupervised machine learning models.

METHOD

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, a tertiary care children's hospital in Toronto, Canada. Youth with relevant reasons for referral (eg, sadness) and increased self-reported depressive symptoms were 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 adolescents younger than 18 years old with MDD.[20] Exclusion criteria included the inability to provide informed consent/assent (eg, psychotic disorder, developmental delay), history of hypomania/mania, and significant chronic medical illness (eg, rheumatologic disease, cancer).

All participants and their guardians provided informed consent for study participation and subsequent dissemination of study results via publication. This study received approval from the SickKids Research Ethics Board.

Clinical Procedure and Measures

Psychiatry Diagnoses. Current and lifetime diagnoses were determined by a standardized semistructured psychiatric interview using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL).[21] The K-SADS depression supplement (Dep-C) was used to assess depressive symptoms for confirmation of MDD diagnosis. The adolescent and their parent(s) both served as informants to provide a more comprehensive understanding of the patient's history. All interviewers had completed a master's degree in a health science field with experience administering standardized semistructured psychiatric interviews and were trained in the K-SADS-PL. After the interview was completed, consensus conferences were held with a child and adolescent psychiatrist blinded to research participation status for diagnostic confirmation. Adolescents also completed the Center for Epidemiologic Studies Depression in Children (CES-DC),[22] a self-reported 20-item questionnaire, using a 4-point Likert scale. Scores range from 0 to 60, with higher scores indicating greater depressive symptoms. In addition to the total score, the CES-DC also yields several subscale scores: somatic (eg, not feeling like eating, sleep disturbances), depressed (eg, unhappy, felt like crying), positive (eg, something good is going to happen), interpersonal (eg, kids not friendly).[23] Anxiety symptoms were assessed using the Screen for Children Related Anxiety Disorders (SCARED), a self-reported 41-item questionnaire using a 3-point Likert scale. Scores range from 0 to 82, with higher scores indicating increased anxiety symptoms. Family conflict was assessed using the Conflict Behavioral Questionnaire parent version (CBQ),[24] a parent-reported 20-item questionnaire in which scores range from 0 to 20, with higher scores indicating greater family conflict.

Cardiovascular Risk Factors. During the in-clinic visit, 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, McCook, Illinois). BMI was computed as weight divided by height squared (kg/m^2) and standardized body mass index (zBMI) (kg/m^2) was calculated using the

World Health Organization growth standards with the anthroplus package in R.[25,26] In keeping with the World Health Organization cutoffs for BMI categories, overweight was defined as a zBMI greater than 1 and less than 2, and obese was defined as a zBMI greater than 2.[27] Systolic and diastolic blood pressure was measured using a Dinamap ProCare DCP 101X-CE automated blood pressure monitor (GE HealthCare, Chicago, Illinois) with the participant resting in the seated position for a minimum of 5 minutes and repeated following a further 5-minute period, with measures averaged across readings and repeated a third time if discrepancies >10 mm Hg in the first 2 readings were present. Laboratory enzymatic colorimetric assays for total cholesterol (TC) (mmol/L), high-density lipoprotein (HDL) (mmol/L), low-density lipoprotein (LDL) (mmol/L), triglyceride (TG) (mmol/L), glucose (mmol/L), and C-reactive protein (CRP) (mg/L) concentrations were measured within 1 hour using an Ortho Vitros instrument (Ortho-Clinical Diagnostics, Rochester, New York).[28] Fasting plasma lipid and glucose concentrations were classified as being acceptable (healthy; TC <4.4 mmol/L, non-HDL <3.11 mmol/L, HDL >1.2 mmol/L, LDL <2.9 mmol/L, TG <1.4 mmol/L), or borderline-high and high as defined by the National Institutes of Health Expert Panel on the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[29] LDL-to-HDL ratio (LDL:HDL) and TG-to-HDL ratio (TG:HDL) were calculated as indirect measures of cardiovascular and cardiometabolic health, respectively.

Data Analysis

Data were summarized by calculating means and standard deviations for continuous variables and counts and percentages for categorical variables. To identify subgroups of adolescent MDD, k-means clustering was performed. The k-means clustering algorithm is an unsupervised machine learning approach that groups data points that are similar into k clusters. The cluster assignment for each data point is performed to minimize the Euclidean distance of that data point to the centroid, or center of the corresponding cluster.

Two k-means clustering models were employed. In model 1, CVD risk factors as determined a priori from extant literature were entered into the model: age; sex; ethnicity; zBMI; blood pressure; heart rate; waist circumference; CES-DC total and subscale scores; SCARED score; and fasting lipid, TG, glucose, and CRP concentrations. This exploratory model aimed to mimic clinical settings where all available data were considered. In model 2, only the lipid profile was entered into the model (n = 181). This parsimonious model aimed to focus on the risk factor that provides the most proximal marker for atherosclerosis and is available in the clinic setting. Moreover, the increased risk of dyslipidemia among individuals with MDD has been previously established.[30] There is value in using all available clinical markers used to evaluate dyslipidemia, despite potential correlations between variables, as they all provide nonredundant information for the models to differentiate clusters. Moreover, it is also possible to test if omitting a highly correlated variable changes the pattern of observed clusters to ensure robustness of results. We tested our models without highly correlated variables and observed the same pattern of clusters, ensuring that our reported results are robust.

Both models used the algorithm of Hartigan and Wong.[31] The optimal number of clusters (k) was selected by using the elbow method, which aims to minimize the total within-cluster variation visualized on scree plots. Each model was set to generate 25 random initial configurations, or centroids, before producing the final output, allowing the identified clusters to stabilize. To reduce all the factors included in the model, principal component analysis (PCA) of a correlation matrix was used. This allowed for the visualization of the clusters in two-dimensional space. As such, only the first two dimensions from the PCA were assessed. To compare measures between the identified clusters, analysis of variance and χ^2 tests were used for continuous and categorical data, respectively. Finally, post hoc t tests were conducted for any relevant comparisons. All models were assessed for normality through visualization of residual plots. Glucose and CRP concentrations failed to meet the normality assumption, as there was very little variability observed in the present sample. Therefore, glucose and CRP were omitted from further analysis. All data processing and analyses were undertaken in RStudio version 1.2.503.[32] Cluster analysis was performed using the stats package, and plots and tables were created using the factoextra[33] and tableone[34] packages, respectively.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the 189 participants are summarized in Table 1. Participants were 74% female with a mean (SD) age of 15.03 (1.85) years. In the present sample, CES-DC had good reliability (α = .86, 95% CI 0.85-0.88). Participants reported a mean (SD) CES-DC score of 37.7 (11.7), indicating high depression severity. More than half of the participants were White (62%), with the remaining participants coming from a

TABLE 1 Participant Demographics and Clinical Characteristics (N =189)

	Value	
	n	(%)
Sex, female (N = 189)	140	(74)
Race/ethnicity (n = 146)		
Black/African American	2	(1)
East Asian	5	(3)
Mixed	28	(19)
Other	9	(6)
South Asian	12	(8)
White	90	(62)
Family income (> CAD $75,000) (n = 145)	87	(60)
Maternal education (n = 143)		
Some/all high school	16	(11)
Some/all postsecondary	83	(58)
Completed postgraduate	44	(31)
	Mean	(SD)
Age, y (n =187)	15.0	(1.8)
CES-DC total (n = 181)	37.7	(11.7)
Somatic	12.9	(4.7)
Depressed	13.4	(5.1)
Positive	7.8	(2.6)
Interpersonal	3.5	(1.9)
SCARED (n = 171)	40.9	(16.1)
CBQ (n = 189)	6.2	(5.9)

Note: CESDC = Center for Epidemiological Studies Depression Scale for Children (0-60); CBQ = Children's Behavior Questionnaire (0-20); SCARED = Screen for Child Anxiety Related Disorders (0-82).

minority ethnic background or mixed ethnic background. The majority of participants' mothers completed at least some postsecondary education.

Model 1: Cluster Analysis of All Factors

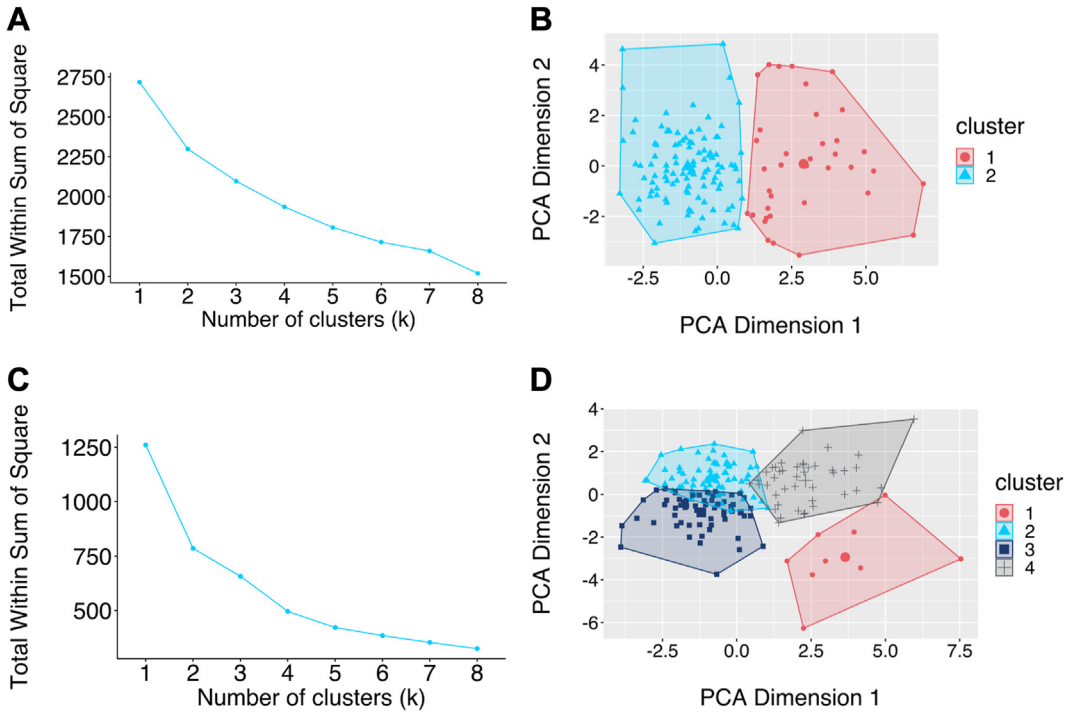
Two subgroups of adolescents were identified from the clustering of all factors using scree plot visualization to determine the optimal k value (Figure 1A). Characteristics of participants in each cluster are summarized in Table 2. With respect to demographics, cluster 1 (n = 37) comprised a lower proportion of White participants compared with cluster 2 ($p < .01$). With respect to individual and family factors, adolescents in cluster 1 also experienced greater family conflict than adolescents in cluster 2 (mean [SD] CBQ 8.0 [5.9] vs 5.7 [6.0], $p = .05$). Adolescents in cluster 1 had higher zBMI, waist circumference, blood pressure, and heart rate than adolescents in cluster 2 ($p < .01$). In laboratory investigations, adolescents in cluster 1 presented with lower fasting HDL and higher fasting non–HDL-C, LDL, TG, LDL:HDL, TG:HDL, and glucose (all $ps < .01$). Adolescents in clusters 1 and 2 did not differ in age, sex, maternal education, depression or anxiety severity, or CRP concentration (all $ps > .05$) (Table 2). Clusters also did not differ with respect to the use of antidepressants ($p > .05$) (Table S1, available online).

PCA reduced all factors included in model 1 to 2 dimensions that explained 23% and 14% of the variance in the original data. As shown in Figure 1B, dimension 1 (labeled CVD risk) distinguished adolescents in cluster 1 from adolescents in cluster 2, whereas dimension 2 (labeled other factors) did not. Given the differences between clusters 1 and 2 (Table 2), it can be inferred that dimension 1 represents CVD risk factors, and dimension 2 represents other characteristics (eg, demographic, clinical). As such, adolescents in cluster 1 are at higher risk for CVD than adolescents in cluster 2, but depression severity is similar in both clusters.

Model 2: Cluster Analysis of Lipid Profile

Four subgroups of adolescents were identified from clustering of all lipid factors using scree plot visualization to determine the optimal k value (Figure 1C). Participant characteristics by cluster are summarized in Table 3. With respect to laboratory markers of CVD risk, clusters differed significantly in lipid profile, including TC, non–HDL-C, HDL, LDL, and TG concentrations (all p values $< .001$). The proportion of participants whose lipid concentrations were outside of the healthy range in each cluster is summarized in Table 4. The majority of participants in clusters 1 and 4 had borderline-high concentrations of TC (56% and 67%, respectively) and non–HDL-C (78% and 81%, respectively). In contrast, only a minority of participants in cluster 2 and no participants in cluster 3 had borderline-high concentrations of TC (25% and 0%, respectively) and non–HDL-C (4% and 0%, respectively). Moreover, adolescents in clusters 1 and 4 had a higher LDL:HDL ratio compared with clusters 2 and 3 (mean [SD] LDL:HDL cluster 1: 2.2 [0.7]; cluster 2: 1.2 [SD]; cluster 3: 1.5 [0.4]; cluster 4: 2.5 [0.5] (all p values $< .001$). These findings suggest that both clusters 1 and 4 are at higher CVD risk, while clusters 2 and 3 are at lower CVD risk. In addition, adolescents in cluster 1 had a higher TG:HDL ratio compared with adolescents in cluster 4 ($p < .001$), while adolescents in cluster 4 had a higher LDL concentration than adolescents in cluster 1 ($p < .001$). This indicates that the mechanism that leads to the heightened CVD risk might differ between adolescents in cluster 1 compared with 4. Clusters did not differ with respect to CRP and glucose concentrations (all p values $> .05$). Clusters also did not differ with respect to the use of antidepressants ($p > .05$) (Table S2, available online).

FIGURE 1 Cluster Analysis of All Factors (Model 1) and Cluster Analysis of Lipid Profile (Model 2)



Note: *(A) Elbow plot to determine the optimal number of clusters in model 1 (B) Identified clusters in model 1 plotted by principal component analysis (PCA) dimensions. (C) Elbow plot to determine the optimal number of clusters in model 2. (D) Identified clusters in model 1 plotted by PCA dimensions.*

With respect to demographics and clinical characteristics, cluster 3 comprised a greater proportion of male participants compared with cluster 2 ($p = .002$). When considering each ethnic category listed in Table 1 individually, differences in ethnic composition between clusters were observed ($p = .04$). However, insufficient numbers of participants within each category precluded further investigation across categories. To address this, further analyses that grouped participants as either White or non-White were conducted, and no significant differences in the proportion of White participants and non-White participants between clusters were observed ($p = .23$; data not shown). Adolescents in cluster 4 experienced greater depression severity than adolescents in cluster 1 (mean [SD] CES-DC 40 [10.9] vs 30.4 [11.6], $p = .04$); however, this difference lost significance after adjusting for familywise error rate ($p = .11$). Adolescents in cluster 4 also experienced higher somatic symptoms compared with adolescents in cluster 1 (mean [SD] somatic subscale score 14.6 [3.9] vs 8.4 [4.4], $p < .01$). Adolescents in cluster 2 experienced greater anxiety symptoms compared with adolescents in cluster 3 (mean [SD]SCARED 43.0 [15.9] vs 34.8 [16.9], $p = .02$). Therefore, the primary clinical difference between the 2 high CVD risk clusters (1 and 4) was somatic symptom severity, while the clinical difference between the 2 low CVD risk clusters (2 and 3) was severity of anxiety symptoms. With respect to anthropometric values, cluster 1 consisted of a high proportion (78%) of overweight and obese adolescents, and adolescents in this cluster had the highest standardized BMI among the 4 clusters.

PCA produced 2 reduced dimensions that explained 49% and 22% of the variance in the original data. In contrast to model 1, both PCA dimensions in model 2 distinguished the 4 clusters (Figure 1D) such that dimension 1 separates clusters 1 and 4 from clusters 2 and 3, while dimension 2 separates clusters 1 and 3 from clusters 2 and 4. When looking at participant characteristics by cluster shown in Table 3, it is possible that dimension 1 represents cardiovascular risk, and dimension 2 represents clinical characteristics. Thus, adolescents in clusters 1 and 4 exhibit higher CVD and cardiometabolic disease risk than adolescents in clusters 2 and 3, and adolescents in clusters 2 and 4 exhibit greater depression or anxiety symptom severity than adolescents in clusters 1 and 3. Observing a dimension related to clinical

TABLE 2 Participant Characteristics by Cluster in Model 1 (n = 144)

	Cluster 1 (n = 37)		Cluster 2 (n = 107)		
	Mean	**(SD)**	**Mean**	**(SD)**	***p***
Demographics					
Age, y	14.87	(1.85)	15.19	(1.75)	.34
	n	**(%)**	**n**	**(%)**	
Sex, female	30	(81.1)	78	(72.9)	.44
Maternal education					.19
Some/all high school	2	(7)	11	(13)	
Some/all postsecondary	22	(73)	48	(55)	
Postgraduate	6	(20)	29	(33)	
Ethnicity					**.007**
Black/African American	1	(3)	1	(1)	
East Asian	0	(0)	4	(5)	
Mixed	6	(20)	19	(21)	
Other	6	(20)	2	(2)	
South Asian	4	(13)	5	(6)	
White	13	(43)	58	(65)	
	Mean	**(SD)**	**Mean**	**(SD)**	
Mental health					
CES-DC total	38.0	(11.9)	37.3	(11.7)	.76
Somatic	13.6	(5.5)	13.12	(4.9)	.64
Depressed	13.3	(5.0)	12.7	(4.5)	.54
Positive	7.6	(2.5)	7.9	(2.6)	.54
Interpersonal	3.5	(2.1)	3.5	(1.9)	.99
SCARED	43.1	(14.5)	38.6	(16.0)	.14
CBQ-P	8.0	(5.9)	5.7	(6.0)	**.05**
Physical examination					
zBMI[a]	26.9	(7.9)	21.1	(3.1)	**<.001**
Waist circumference, cm	88.7	(20.2)	74.4	(11.4)	**<.001**
Systolic BP, mm Hg	117.0	(13.9)	110.6	(11.1)	**.006**
Diastolic BP, mm Hg	65.5	(8.6)	62.1	(7.4)	**.02**
Heart rate, beats/min	79	(12)	74	(14)	**.04**
Laboratory factors					
TC, mmol/L	4.9	(0.8)	3.7	(0.5)	**<.001**
Non-HDL, mmol/L	3.6	(0.7)	2.3	(0.4)	**<.001**
HDL, mmol/L	1.3	(0.3)	1.4	(0.3)	**.01**
LDL, mmol/L	2.9	(0.7)	1.9	(0.4)	**<.001**
LDL:HDL	2.4	(0.7)	1.4	(0.4)	**<.001**
TG, mmol/L	1.5	(0.9)	0.8	(0.3)	**<.001**
TG:HDL	1.2	(0.8)	0.6	(0.3)	**<.001**

Note: Boldface p values are statistically significant. p values for numeric variables indicate statistical significance for t tests, and p values for categorical variables indicate statistical significance for χ^2 *tests. BP = blood pressure; CBQ = Children's Behavior Questionnaire (0-20);CESDC = Center for Epidemiological Studies Depression Scale for Children (scale 0-60); CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LDL:HDL = LDL-to-HDL ratio; SCARED = Screen for Child Anxiety Related Disorders (scale 0-82); TC = total cholesterol; TG = triglyceride; TG:HDL = TG-to-HDL ratio; zBMI = standardized body mass index.*

[a]*zBMI was calculated using World Health Organization growth standards based on age and sex norms.*

characteristics was notable, given that the cluster analysis was based only on lipid factors. These results suggest that there may be latent patterns of lipid factors that are associated with clinical characteristics.

DISCUSSION

This study identified subgroups of adolescents with MDD, first using demographic, mental health, physical examination, and laboratory data and then using only fasting lipid

TABLE 3 Participant Characteristics by Cluster in Model 2 (n = 181)

	Cluster 1 (n = 9)		Cluster 2 (n = 68)		Cluster 3 (n = 61)		Cluster 4 (n = 43)		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	*p*
Demographics									
Age, y	14.2	(1.8)	15.0	(2.1)	15.2	(1.6)	15.2	(1.6)	.477
	n	(%)	n	(%)	n	(%)	n	(%)	
Sex, female	7	(78)	57	(84)	35	(57)	36	(84)	**.002**
Maternal education									.23
Some/all high school	1	(20)	8	(16)	4	(9)	2	(6)	
Some/all postsecondary	4	(80)	30	(59)	23	(49)	23	(66)	
Postgraduate	0	(0)	13	(25)	20	(43)	10	(29)	
Ethnicity									**.04**
Black/African American	0	(0)	1	(2)	0	(0)	1	(3)	
East Asian	0	(0)	2	(4)	2	(4)	1	(3)	
Mixed	0	(0)	15	(29)	6	(13)	6	(13)	
Other	1	(20)	0	(0)	4	(9)	4	(11)	
South Asian	1	(20)	3	(6)	0	(0)	7	(20)	
White	3	(60)	31	(60)	35	(75)	18	(49)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Mental health									
CES-DC total	30.4	(11.6)	39.0	(11.5)	35.2	(11.9)	40.0	(10.9)	**.03**
Somatic	8.4	(4.4)	13.2	(4.9)	11.7	(4.4)	14.6	(3.9)	**<.001**
Depressed	11.6	(5.0)	13.8	(5.0)	12.4	(5.3)	14.0	(4.9)	.24
Positive	7.6	(3.0)	8.1	(2.6)	7.3	(2.7)	7.9	(2.7)	.46
Interpersonal	2.9	(2.2)	3.9	(1.9)	3.2	(2.0)	3.5	(2.0)	.15
SCARED	43.6	(13.8)	43.0	(15.9)	34.8	(16.9)	44.8	(13.6)	**.008**
CBQ	8.1	(6.2)	5.6	(5.7)	6.3	(6.1)	7.3	(5.9)	.42
Physical examination									
zBMI[a]	1.8	(0.9)	0.2	(1.1)	0.5	(1.3)	0.8	(1.5)	**.002**
Waist circumference, cm	88.3	(18.3)	75.1	(12.0)	78.5	(14.6)	78.6	(17.1)	.10
Systolic BP, mm Hg	117.1	(8.1)	110.7	(12.6)	114.4	(12.1)	112.1	(14.8)	.28
Diastolic BP, mm Hg	65.2	(6.5)	61.6	(7.7)	64.2	(8.0)	61.7	(8.4)	.18
Heart rate, beats/min	74.6	(11.2)	75.8	(13.5)	74.9	(15.0)	76.8	(12.9)	.90
Laboratory factors									
TC, mmol/L	4.8	(1.0)	4.1	(0.4)	3.3	(0.4)	4.8	(0.6)	**<.001**
Non-HDL, mmol/L	3.7	(0.8)	2.4	(0.4)	2.1	(0.4)	3.6	(0.5)	**<.001**
HDL, mmol/L	1.1	(0.3)	1.7	(0.2)	1.2	(0.2)	1.3	(0.2)	**<.001**
LDL, mmol/L	2.4	(0.7)	2.0	(0.3)	1.8	(0.4)	3.1	(0.5)	**<.001**
LDL:HDL	2.2	(0.7)	1.2	(0.3)	1.5	(0.4)	2.5	(0.5)	**<.001**
TG, mmol/L	2.9	(0.9)	0.9	(0.4)	0.8	(0.3)	1.0	(0.3)	**<.001**
TG:HDL	2.6	(0.7)	0.5	(0.2)	0.7	(0.3)	0.8	(0.3)	**<.001**

Note: Boldface p *values are statistically significant.* p *values for numeric variables indicate statistical significance for analysis of variance tests, and* p *values for categorical variables indicate statistical significance for* χ^2 *tests. BP = blood pressure; CBQ = Children's Behavior Questionnaire (0-20); CESDC = Center for Epidemiological Studies Depression Scale for Children (scale 0-60); CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LDL:HDL = LDL-to-HDL ratio; SCARED = Screen for Child Anxiety Related Disorders (scale 0-82); TC = total cholesterol; TG = triglyceride; TG:HDL = TG-to-HDL ratio; zBMI = standardized body mass index.*

[a]*zBMI was calculated using World Health Organization growth standards based on age and sex norms.*

concentrations. In the model comprising all variables, a cluster consisting of 37 adolescents with MDD was identified in which participants exhibited several increased CVD risk factors, including overweight or obesity, greater blood pressure and heart rate, and dyslipidemia. In addition, the high CVD risk group consisted of a greater proportion of non-White participants (57%) compared with the low CVD risk group (35%). This finding highlights the possible

TABLE 4 Proportion of Participants With Borderline-High (TC, LDL, Non-HDL, TG) or Borderline-Low (HDL) Lipid Concentrations by Cluster in Model 2

	Cluster 1 (n = 9)		Cluster 2 (n = 68)		Cluster 3 (n = 61)		Cluster 4 (n = 43)		
	n	(%)	n	(%)	n	(%)	n	(%)	p
TC	5	(56)	17	(25)	0	(0)	29	(67)	<.001
HDL	6	(67)	0	(0)	23	(38)	14	(33)	<.001
LDL	3	(33)	1	(2)	0	(0)	30	(70)	<.001
Non-HDL	7	(78)	3	(4)	0	(0)	35	(81)	<.001
TG	9	(100)	16	(24)	16	(26)	20	(47)	<.001

Note: p *values for numeric variables indicate statistical significance for analysis of variance tests. Cutoff values for acceptable lipid concentrations according to the National Institutes of Health Expert Panel on the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: TC <4.4, non-HDL <3.11, HDL >1.2, LDL <2.9, TG <1.4 mmol/L. HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglyceride.*

role ethnicity plays in moderating the depression–CVD risk association among adolescents. Interestingly, while depression severity did not differ between these 2 subgroups, levels of family conflict did, with the increased CVD risk group experiencing higher family conflict. This raises the possibility that family conflict might be an indicating factor for this increased risk endotype, such that regardless of depression and anxiety symptoms, increased family conflict is a pertinent factor associated with increased CVD risk among youth with MDD. Indeed, previous research has identified an association between family conflict and inflammatory levels,[35,36] which is a critical underlying component of the development of atherosclerosis.[37] It is therefore possible that family conflict is associated with increased CVD risk via inflammatory processes. Further investigation into the temporal association of family conflict that is able to consider potential confounding factors (eg, parental mental health) and its role in the development of CVD in adolescents with MDD is needed.

In the lipid-only model, 4 clusters of adolescents with MDD were identified. Cluster 1 consisted of 9 adolescents with increased cardiometabolic risk factors, including overweight and obesity, and dyslipidemia consisting of both increased LDL and hypertriglyceridemia. Furthermore, participants in cluster 1 had an average TG:HDL ratio of 2.6, which was 3 times the ratio found in the other clusters. Previous studies have found that the TG:HDL ratio is a reliable proxy for insulin resistance and that values greater than 2.0 identify children at increased cardiometabolic disease risk and increased arterial stiffnesses, an early sign of atherosclerosis.[38–40] Moreover, a meta-analysis of longitudinal studies found a bidirectional association between adolescent depression and obesity.[41] Specifically, depressed adolescents had a 70% increased risk for obesity, while obese adolescents had a 40% increased risk for depression. This suggests that there is a subgroup of adolescents who experience MDD and comorbid obesity, which is in line with the anthropometric and clinical characteristics of cluster 1. Identifying this subgroup is important in ensuring that both their depressive symptoms and obesity are addressed to improve health outcomes broadly.

This study also identified a cluster of 43 adolescents who were of healthy weight, yet demonstrated dyslipidemia (cluster 4). In fact, 70% of participants in cluster 4 had borderline to high levels of LDL compared with 33% of participants in the cardiometabolic cluster (cluster 1). As such, adolescents in cluster 4 represent a MDD subgroup at increased CVD risk by virtue of their dyslipidemia who appear healthy on physical examination (BMI in the healthy range). This finding has 2 important clinical implications. First, adolescents belonging to this group are more likely to be missed by routine screening using demographic and anthropometric data to determine eligibility for CVD preventive interventions. Therefore, their elevated risk for CVD would remain undetected. Second, these results are consistent with previous research that has identified several underlying mechanisms that may link adolescent depression with increased CVD risk, including, but not limited to, shared genetic variations,[42] MDD and lipidemic-associated inflammatory pathways, and autonomic dysfunction.[2] Emerging data also highlight the possible role of early life conditions via the developmental origins of health and disease hypothesis, which suggests that a suboptimal early life environment leads to developmental adaptations that can have long-lasting effects on growth, physiology, and metabolism.[43] One such early life exposure may include the microbiome. Studies have suggested that gut–brain dysfunction may be a direct cause of both depression[44] and elevated CVD risk.[45,46] It is possible that one or more of these mechanisms distinguish the increased CVD risk observed in cluster 1 compared with cluster 4.

The results of this study highlight the heterogeneity of adolescent MDD and emphasize the need for precision medicine in the field of child and adolescent psychiatry. Current depression diagnoses are made based on depressive symptoms with assessments and management strategies limited to those within the realm of psychiatry.[47,48] As such, adolescents diagnosed with MDD are evaluated and treated similarly, despite having potentially different disease mechanisms.[17,48]

Indeed, previous researchers have argued that it is the lack of personalized approaches that have resulted in the stagnation of treatment advancement for adolescent depression.[49] In the present study, the lipid-only model identified 4 distinct subgroups of adolescent depression, each associated with a unique combination of CVD risk factors, clinical characteristics, and demographics. Two of these subgroups exhibited increased cardiovascular disease risk, but in different ways; while the majority of participants in cluster 1 were overweight and presented with greater cardiometabolic risk factors, the majority of participants in cluster 4 were of healthy weight and had elevated LDL levels despite normal cardiometabolic risk factor levels. Therefore, the results of this analysis have several possible implications for the incorporation of precision medicine in the management of adolescent MDD. First, these findings suggest that there may be a subgroup of adolescents with MDD who require monitoring for the progression of atherosclerosis and CVD, regardless of their body weight. In the present study, this group corresponds to cluster 4, which consists of adolescents who appear healthy on physical examination, but show early evidence of dyslipidemia. Second, our results further highlight the potential benefit of interventions targeting health behaviors (eg, dietary and physical activity interventions) as adjunctive first-line treatments for adolescents with MDD presenting with overweight/obesity and increased cardiometabolic risk, given the overall lower level of depressive symptoms in this study subgroup and the benefits of lifestyle interventions on both depressive symptoms and cardiovascular health.[50,51]

The current study has many strengths, including the use of semistructured diagnostic interviews to determine the diagnosis of MDD; objective and standardized measurement of cardiovascular risk factors, including anthropometrics; and analyses that provide holistic insight to adolescent MDD. Despite this, the study also has several limitations. First, the sample size, although substantial compared with previous research in the field, is small for unsupervised machine learning techniques, such as a cluster analysis. In particular, model 2 yielded a small cluster consisting of 9 participants; therefore, the findings must be interpreted with caution. Moreover, it is possible that further differences between clusters may have been undetected due to a lack of statistical power. That said, previous research has found that unsupervised machine learning analyses with reduced power from a small sample size can be compensated for with the use of high-quality indicators.[52] In the present study, only well-established CVD risk factors were included in the cluster analyses. Therefore, while the findings of this study may be of clinical significance, replication in larger samples is needed. Second, participants were recruited through an outpatient mental health program. Although study participants are broadly representative of the demographics of the province in which the study was conducted, they may not be representative of adolescents with depression generally. According to Statistics Canada 2021 Census, 70% of the population report being White,[52] and 42% of the population report an income greater than CAD $75,000.[53] The present sample consists of 62% White participants and 60% with an income greater than CAD $75,000. Therefore, while the sample is aligned with the diversity of the Canadian population, participants reported a higher mean annual income compared with that of the Canadian population, which may limit generalizability of the study findings to adolescents with MDD from lower-income families. It is therefore unclear whether the results of this study will generalize to the broader population of adolescents with MDD. The lack of a comparator group to assess whether the identified endotypes of CVD risk are specific to adolescents with MDD is also a limitation of the current study. Future studies should include healthy controls to determine if the results of this study generalize to healthy adolescents as well. An additional limitation is that while the data in this study were collected at the time of diagnosis of depression among adolescents, data regarding depression symptom duration were not collected. Prospective studies able to examine the MDD–CVD association from symptom onset are needed to probe the direction of association. A final limitation of this study is the use of a cross-sectional design. Results may also reflect differential mechanisms of MDD–CVD association, including temporal associations; however, the cross-sectional data in our study cannot parse the directionality of the MDD–CVD association in the varying endotypes. Longitudinal studies are needed to advance knowledge regarding pathoetiology, treatment response, and course of illness across identified clusters.

In this study, unsupervised machine learning identified adolescent MDD endotypes that are associated with varying levels of CVD risk factors. Our results underscore the heterogeneity of adolescent MDD with respect to CVD risk and the need for precision medicine approaches in the management of MDD to affect both cardiovascular and mental health outcomes.

CRediT authorship contribution statement

Anisa F. Khalfan: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Susan C. Campisi:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Ronda F.**

Lo: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Brian W. McCrindle:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Daphne J. Korczak:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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The research was performed with permission from the Hospital for Sick Children Research Ethics Board.

Consent has been provided for descriptions of specific patient information.

Data Sharing: Requests for data should be sent to the corresponding author, together with the proposed research aims and analytical plan.

Ronda F. Lo served as the statistical expert for this research.

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