AHA Scientific Statement

Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease
A Scientific Statement From the American Heart Association

Benjamin I. Goldstein, MD, PhD, Chair; Mercedes R. Carnethon, PhD; Karen A. Matthews, PhD, FAHA; Roger S. McIntyre, MD; Gregory E. Miller, PhD; Geetha Raghuveer, MD, FAHA; Catherine M. Stoney, PhD; Hank Wasiak, BA, MBA; Brian W. McCrindle, MD, MPH, FAHA, Co-Chair; on behalf of the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young

Abstract—In the 2011 "Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents," several medical conditions among youth were identified that predispose to accelerated atherosclerosis and early cardiovascular disease (CVD), and risk stratification and management strategies for youth with these conditions were elaborated. Major depressive disorder (MDD) and bipolar disorder (BD) among youth satisfy the criteria set for, and therefore merit inclusion among, Expert Panel tier II moderate-risk conditions. The combined prevalence of MDD and BD among adolescents in the United States is ≈10%, at least 10 times greater than the prevalence of the existing moderate-risk conditions combined. The high prevalence of MDD and BD underscores the importance of positioning these diseases alongside other pediatric diseases previously identified as moderate risk for CVD. The overall objective of this statement is to increase awareness and recognition of MDD and BD among youth as moderate-risk conditions for early CVD. To achieve this objective, the primary specific aims of this statement are to (1) summarize evidence that MDD and BD are tier II moderate-risk conditions associated with accelerated atherosclerosis and early CVD and (2) position MDD and BD as tier II moderate-risk conditions that require the application of risk stratification and management strategies in accordance with Expert Panel recommendations. In this scientific statement, there is an integration of the various factors that putatively underlie the association of MDD and BD with CVD, including pathophysiological mechanisms, traditional CVD risk factors, behavioral and environmental factors, and psychiatric medications. (*Circulation*. 2015;132:000-000. DOI: 10.1161/CIR.0000000000000229.)

Key Words: AHA Scientific Statements ■ adolescent ■ atherosclerosis ■ bipolar disorder ■ cardiovascular diseases ■ coronary artery disease ■ depressive disorder, major ■ population at risk

In a 2006 American Heart Association scientific statement on cardiovascular risk reduction in high-risk pediatric patients, a list of 8 pediatric diagnoses associated with elevated cardiovascular risk were identified, and practical management recommendations were generated.[1] In that scientific statement, tier II conditions required "pathophysiological evidence for arterial dysfunction indicative of accelerated atherosclerosis before 30 years of age." In the 2011 "Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents" (henceforth, "Expert Panel"), special risk conditions were identified in accordance with the above definition for tier II (moderate

risk). Specifically, moderate-risk conditions are those for which "the disease process has been shown to be associated with pathologic, physiologic, or subclinical evidence of accelerated atherosclerosis."[2] According to the Expert Panel, tier II included Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease (systemic lupus erythematosus, juvenile inflammatory arthritis), HIV infection, and nephrotic syndrome. Moreover, risk stratification in the Expert Panel indicated that children and adolescents with tier II conditions were to be moved to tier I (high risk) if they had 2 or more of 7 traditional cardiovascular risk factors or comorbidities (obesity, tobacco smoke exposure, hypertension, insulin resistance, dyslipidemia including high levels of low-density lipoprotein cholesterol, high levels of triglycerides, and low levels of high-density lipoproteins). Importantly, in the Expert Panel report, specific cut points and treatment goals were outlined for blood pressure, body mass index, glucose, and lipids, and recommendations were provided regarding lifestyle change and pharmacological treatment.

When the results of several studies to date are considered together, as reviewed in this statement, it can be concluded that the inclusion of adolescent mood disorders on the list of tier II moderate-risk pediatric diagnoses is warranted. Moreover, there is compelling evidence regarding excessive and premature cardiovascular disease (CVD)* among adults with major depressive disorder (MDD) and bipolar disorder (BD). The association between depression and CVD among adults is well known.[3,4] In recent epidemiological studies in the United States, the prevalence of CVD among adults with MDD was nearly 3-fold greater than among adults without mood disorders, and adults with CVD and MDD were ≈7.5 years younger than adults with CVD who did not have mood disorders.[5] Putative pathophysiological mechanisms of the increased risk of CVD among adults with mood disorders include hypothalamic-pituitary-adrenal axis and sympathomedullary hyperactivity, increased platelet reactivity, reduced heart rate variability, vascular inflammation, oxidative stress, and endothelial dysfunction (Figure 1). These processes are likely set into motion in part by adverse lifestyle behaviors that are disproportionate among people with mood disorders. The results of twin studies and molecular genetic studies also implicate shared genetic pathways between depression and CVD.[6,7] There is also preliminary evidence based on adolescents regarding the familial nature of the CVD-depression link. For example, psychiatrically healthy adolescent offspring of parents with MDD have been shown to have increased aortic stiffness and blood pressure, along with decreased insulin sensitivity.[8] Moreover, adolescents with a history of MDD have elevated rates of parental CVD.[9]

The association between BD and CVD appears to be at least as strong as the association with MDD, although this association is less commonly recognized. CVD is the leading cause of death in BD, with a standardized mortality ratio of 1.5 to 2.5.[10,11] Among young adults specifically, the standardized mortality ratio may be as high as 8.[12] By comparison,

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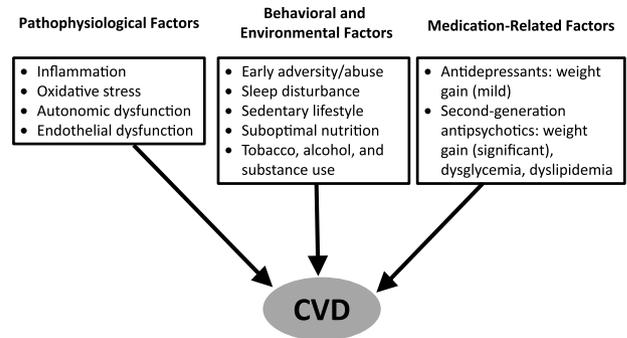
Figure 1. Putative reasons for excessive and premature cardiovascular disease (CVD) among youth with major depressive disorder and bipolar disorder.

although malignancy is the second most common medical cause of death in BD, it does not appear to be more prevalent in BD than in the general population.[10,13] Excess and premature CVD mortality in BD has been documented for >70 years, before the use of mood stabilizers and antipsychotic drugs.[11,14] After control for multiple potential confounders, including medications, symptomatic severity in BD was independently associated with CVD mortality.[15] Adults with BD in the US population have a 5-fold increased risk of CVD and manifest CVD 14 years earlier than adults without mood disorders, despite the fact that approximately half have never received any pharmacological treatment for BD and approximately three-fourths have not received antimanic medication.[5,16,17] The prevalence of CVD among adults with BD is nearly 2-fold greater than among adults with MDD.[5] On the basis of recent genome-wide association studies, calcium channels are implicated in the pathophysiology of BD,[18,19] and these channels also appear to be salient to CVD.[20,21]

MDD and BD are the first and fourth most disabling conditions, respectively, among adolescents worldwide.[22] BD involves repeated episodes of mania/hypomania (elated or irritable mood together with other symptoms) that generally, but not always, alternate with episodes of depression (sadness or lack of interest/pleasure along with other symptoms). MDD involves episodes of depression without mania/hypomania.[23] The diagnostic criteria for mood episodes in MDD and BD are summarized in Table 1; more detailed descriptions and guidelines are available elsewhere.[24–27] In the United States, the prevalence of mood disorders among adolescents is ≈10% (8.7% for MDD, 2.6% for BD).[28] By comparison, the prevalence of the 4 existing Expert Panel tier II moderate-risk conditions ranges from ≈0.5% (chronic inflammatory disease) to <0.05% (HIV, Kawasaki disease, nephrotic syndrome). In other words, MDD and BD together are at least 10 times more prevalent than the 4 previously identified moderate-risk conditions combined. Because mood disorders are highly prevalent among adolescents and are generally amenable to treatment, there could be substantial cardiovascular benefits associated with improved identification, monitoring, and treatment of these conditions, with potential public health implications. Importantly, mood disorders that begin in childhood or adolescence are known to persist into adulthood and are known to be especially pernicious variants of these disorders, with a far greater burden of psychiatric symptoms than adult-onset

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*CVD is used in this statement to denote atherosclerotic/coronary/ischemic heart disease; however, when referencing previous studies that included structural or infectious heart disease within CVD, this statement specifies the term that best reflects the above definition of CVD.

Table 1.   DSM-5 Criteria for Major Depression, Mania, and Hypomania

DSM-5 criteria for major depression: ≥5 of the following symptoms (including depressed or irritable mood or loss of interest/pleasure), lasting at least 2 wk, constituting a change from previous functioning*:

1. Depressed or irritable mood for most of the day, nearly every day

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day

3. Significant weight loss when not dieting or weight gain (eg, a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day

4. Insomnia or hypersomnia nearly every day

5. Observable psychomotor agitation or retardation nearly every day

6. Fatigue or loss of energy nearly every day

7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day (not merely self-reproach or guilt about being sick)

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation with a specific plan, or a suicide attempt or a specific plan for committing suicide

DSM-5 criteria for mania and hypomania: A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, in addition to 3 (if elated/expansive) or 4 (if only irritable) of the following†:

1. Inflated self-esteem or grandiosity

2. Decreased need for sleep (eg, feels rested after only 3 h)

3. More talkative than usual or pressure to keep talking

4. Flight of ideas or subjective experience that thoughts are racing

5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)

6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

Mania

- Episode lasts at least 1 wk (or any duration if hospitalization is necessary), most of the day, every day

- The mood disturbance must be sufficiently severe to cause marked functional impairment (eg, social, academic) or to necessitate hospitalization to prevent harm to self or others, or there must be associated psychotic features (eg, grossly disorganized thinking, hallucinations, and/or delusions)

Hypomania

- Episode lasts at least 4 d, most of the day, every day

- The mood disturbance must be associated with an unequivocal and uncharacteristic change in functioning, and the mood symptoms and change in functioning must be observable by others

- Marked impairment, need for hospitalization, and psychotic features preclude a diagnosis of hypomania

Depression, mania, or hypomania deemed to be caused by the direct physiological effects of a substance (eg, illicit drugs, medications), a medical condition (eg, hyperthyroidism), or somatic treatments such as electroconvulsive therapy or light therapy preclude a diagnosis of bipolar disorder or major depressive disorder. Major depressive disorder is characterized by ≥1 episodes of major depression without episodes of mania/hypomania. Bipolar disorder is characterized by episodes of mania/hypomania, generally alternating with episodes of major depression.

DSM-5 indicates *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.

*The other symptoms must co-occur with depressed or irritable mood or diminished interest/pleasure.

†The other symptoms must co-occur with euphoria or irritability.

mood disorders.[29–36] This increased severity of child- and adolescent-onset mood disorders has been observed in clinical samples[30,31,34] and representative epidemiological samples.[29,32] The high prevalence of mood disorders in adolescents, the biological plausibility of an association between mood disorders and CVD, and the strength of association between mood disorders and CVD justify the need for a scientific statement to address CVD risk among adolescents with mood disorders.

The overall objective of the current statement is to increase awareness and recognition of mood disorders among young people as being moderate-risk conditions for early CVD. To achieve this objective, the primary specific aims of this statement are to (1) summarize evidence that mood disorders (MDD and BD) are Expert Panel tier II moderate-risk conditions associated with accelerated atherosclerosis and early CVD and (2) position MDD and BD as tier II moderate-risk

conditions that require the application of risk stratification and management strategies in accordance with Expert Panel recommendations. In addition, in this statement, the contribution of traditional cardiovascular risk factors (eg, diabetes mellitus, obesity) and lifestyle behaviors (eg, sedentary lifestyle, tobacco smoking) to excessive CVD risk among adolescents and adults with mood disorders is examined. Finally, this statement summarizes the evidence regarding the association of pharmacological treatments commonly used in the treatment of adolescents and young adults with mood disorders (particularly second-generation antipsychotic drugs) with CVD and CVD risk factors. The success of this statement will rely on the extent to which it results in improved CVD risk factor screening, prevention, and intervention among adolescents and young adults with mood disorders and the extent to which it spurs increased collaboration between preventive

cardiology, pediatrics, and psychiatry, together with consumers and other stakeholders, in achieving these goals.

Pathophysiological, Subclinical, and Clinical Evidence of Accelerated Atherosclerosis Among Adolescents and Young Adults With Mood Disorders

The articles reviewed in this section were identified with MEDLINE searches using the following medical subject headings (MeSH) terms and keywords: *major depressive disorder* or *bipolar disorder*, each cross-referenced with *cardiovascular diseases* or *cardiovascular* or *heart disease* or *atherosclerosis* or *coronary disease* or *coronary vessels* or *coronary* or *endothelium* or *endothelial* or *arterial stiffness* or *vascular stiffness* or *arterial pressure*, or *flow mediated dilation*, or *reactive hyperemia*. Articles were selected for inclusion if either all of the participants or a substantial proportion of participants were <30 years of age.

Evidence of Premature Cardiovascular Mortality

Two observational, population-based studies have linked MDD, attempted suicide, BD, and anxiety in children and young adults to increased risk of premature CVD or related deaths. The National Health and Nutritional Examination Survey included 7641 participants 17 to 39 years of age during 1988 to 1994 and performed follow-up of this cohort until 2006 (Table 2).[37] After controlling for Framingham scores, diagnoses of clinical depression, as opposed to high levels of mood symptoms on a checklist, were associated with increased ischemic heart disease (IHD) mortality. The adjusted hazard ratio for IHD mortality was 3.70 (95% confidence interval [CI] 1.32–10.35) for depression (associated with an MDD or BD diagnosis) and 7.12 (95% CI 2.67–18.98) for history of attempted suicide; associations were stronger among women. Further controlling for education, income, body mass index, alcohol intake, and sedentary lifestyle did not affect these findings. The associations were stronger for IHD than for CVD (including endocarditis, myocarditis, heart failure, and cerebrovascular disease). The risk of IHD mortality attributable to MDD or attempted suicide or suicide was 13% among males (fourth strongest risk factor after obesity, smoking, and hypertension) and 65% among females (strongest risk factor).

In a Taiwanese national health insurance study involving >1 million participants of all age groups, including young adults, the association of MDD, BD, and anxiety disorder diagnoses with risk of IHD was examined. The relative risk for IHD among patients <20 years old was 2.19 for MDD, 2.11 for BD, and 9.88 for anxiety.[38] Although the prevalence of IHD increased with increasing age in all diagnostic groups, the excessive relative risk for IHD among patients with MDD, BD, and anxiety was greatest among those <20 years old. Although these findings do not demonstrate causality, they are based on large samples and robust covariate modeling and provide a basis for hypothesizing that the spectrum of BD, MDD, suicide attempts, and even anxiety in adolescents and young adults may confer increased risk of subsequent CVD and cardiovascular mortality.

Increased Carotid Artery Intima-Media Thickness

There is evidence in epidemiological studies of a link between depressive symptoms (even when they are not severe or disabling enough to merit a full clinical diagnosis) and premature vascular aging as measured by carotid artery intima-media thickness (CIMT). Findings from the Cardiovascular Risk in Young Finns study, a population-based longitudinal follow-up study, linked early adult depressive symptoms to increased CIMT in 410 young men.[39] Depressive symptoms in earlier years among men did not predict CIMT after controlling for depressive symptoms concurrent with CIMT assessment. There was no significant association between depressive symptoms and CIMT in women. In a cross-sectional study of 157 black and white 16- to 21-year-olds, depressive symptoms were not correlated with right and left common CIMT.[40] However, higher levels of depressive symptoms were associated with higher pulse-wave velocity, indicative of increased vascular stiffness, independent of covariates (including body mass index, systolic blood pressure, and social class; lipid profiles were not measured). These studies together indicate a plausibly adverse but as yet inconsistent relationship between depressive symptoms and CIMT among adolescents and young adults. Importantly, all of these studies focused on self-reported depressive symptoms. This approach is likely to capture both patients with clinically significant depression and those who are transiently distressed or do not have the degree of functional impairment needed to merit a diagnosis.

Endothelial Dysfunction

One of the earliest signs of risk for CVD is impaired endothelial function, measured by ultrasound-determined brachial artery flow-mediated dilation or by digital pulse-wave amplitude, in which higher values are considered better. There are 6 studies in young adults and adolescents with diagnoses of MDD or depressive symptoms in relation to endothelial function. In 15 young adults with MDD and 15 healthy control subjects, percent change in brachial artery diameter was smaller among those with MDD.[41] Participants with MDD also had elevated monocyte chemotactic protein-1, soluble intercellular adhesion molecule-1, and E-selectin, markers of risk for atherosclerosis. No study participants were taking antidepressant medications or had elevated cardiovascular risk factors. By contrast, in another study of 50 untreated depressed young adults matched to 50 healthy control subjects, there were no group differences in flow-mediated dilation[42]; however, plasma nitrite/nitrate concentrations were lower among the depressed participants, which suggests decreased nitric oxide production. In a small controlled study, participants with BD (n=27), matched with healthy control subjects with regard to tobacco use, age, and sex, did not differ from the control subjects with regard to flow-mediated dilation.[43] Among 248 teenagers, symptom scores for depression, anger, and anxiety were associated with lower pulse-wave amplitude scores among girls only.[44] In a single longitudinal study, 135 female teenagers at high risk for MDD were followed up over a period of 2.5 years, and pulse-wave amplitude was assessed at 12-month intervals.[45] Depressive symptoms were negatively associated with endothelial function at each time period but did not predict endothelial function at later time points. In this

Table 2. Summary of Findings Related to Accelerated Atherosclerosis and Early CVD

Study (Year)	Sample Characteristics	Covariates	Methods	Findings	Limitations
CVD mortality					
Shah et al (2011)[37]	Longitudinal, population-based National Health and Nutritional Examination Survey III (United States). N=7641, mean age, 28.1 y; n=416 MDD, n=122 BD, n=419 history of suicide attempt	Primary analyses controlled for Framingham Risk Score. Sensitivity analyses further controlled for income, education, BMI, sedentary lifestyle, alcohol intake, cocaine use	CVD mortality and IHD mortality determined via death certificates. History of MDD, BD, and suicide attempt via Diagnostic Interview Schedule. Median follow-up of 14.9 y	IHD mortality: adjusted HR (95% CI) for IHD: 3.70 (1.32–10.35) for depression, 7.12 (2.67–18.98) for attempted suicide. Women: adjusted HR 3.20 (1.12–9.17) for CVD, 14.57 (2.65–80.10) for IHD; depression or suicide #1 risk factor for IHD mortality. Men: adjusted HR 2.37 (0.85–6.58) for CVD, 3.52 (1.05–11.76) for IHD; depression or suicide #4 risk factor for IHD mortality	Low event rate. Risk factors measured only at cohort inception. Cause of death based on death certificate
CVD prevalence					
Huang et al (2009)[38]	Taiwanese National Health Insurance Database study including young adults; N=1 031 557 adult patients with MDD, BD, and anxiety disorders (n=76 430 MDD, n=41 557 BD, n=913 570 anxiety); N=21 356 304 without mood or anxiety disorders	All patients with mood and anxiety disorders were taking psychiatric medications	Psychiatric diagnoses and IHD determined via ICD-9-CM codes	Greatest excess of IHD was associated with MDD and BD among patients <20 y old. Among patients <20 y old, relative risk was 2.19 for MDD and 2.11 for BD	Use of health claims data relies on seeking treatment; disparities in seeking/obtaining treatment would bias results. Cross-sectional design
CIMT and endothelial function					
Elovainio et al (2005)[39]	Cardiovascular Risk in Young Finns Study (population based); longitudinal study. N=1126 participants (410 men, 716 women); mean age at enrollment 10 y	Analyses controlled for age, childhood/adolescent CVD risk factors (LDL cholesterol, BMI, and systolic blood pressure), and adult CVD risk factors (LDL cholesterol, BMI, systolic blood pressure, tobacco smoking status)	Self-reported depressive symptoms assessed with a revised version of the Beck Depression Inventory in 1992, 1997, and 2001. Left common CIMT measured via ultrasound in 2001	Men with high depressive symptoms in 2001 had significantly greater CIMT than men with low or moderate depressive symptoms. In women, no significant association was found between depressive symptoms and CIMT	Depression determined by self-report only
Dietz and Matthews (2011)[40]	Cross-sectional; N=157 healthy youth aged 16–21 y, divided into 3 groups: low (n=52), moderate (n=55), and high (n=50) depressive symptoms	Analyses controlled for age, race, sex, BMI, parent education, tobacco smoking status, physical activity, systolic blood pressure, and resting heart rate. Sensitivity analyses further controlled for hostility	Self-reported depressive symptoms assessed with the Center for Epidemiologic Studies Depression Scale. CIMT measured via ultrasound images from right and left common carotid, bulb, and internal carotid arteries. Pulse-wave velocity measured via ultrasound of carotid and femoral arteries	Higher depressive symptoms were independently associated with greater pulse-wave velocity, reflecting greater arterial stiffness; no significant effect on CIMT	Cross-sectional study. Depression determined by self-report only

(Continued)

Table 2.   Continued

Study (Year)	Sample Characteristics	Covariates	Methods	Findings	Limitations
Rajagopalan et al (2001)[41]	N=30, including 15 young adults with MDD (mean age, 29 y) and 15 control subjects (mean age, 31 y)	Variables examined for associations with endothelial function included lipids, BMI, blood pressure, baseline brachial artery diameter, and MDD MDD participants were taking antidepressant medication Groups described as well matched for dietary intake, physical activity, and menstrual phase	Participants met diagnostic criteria for MDD Endothelial function determined via ultrasound measurement of flow-mediated dilation	MDD was the only significant predictor of flow-mediated dilation in univariate and multivariate analyses Nitroglycerin-mediated dilation did not differ between groups	Cross-sectional study Small sample size
Garcia et al (2011)[42]	N=100 Hispanic participants, n=50 with first-episode MDD (mean age, 22.6 y), and n=50 control subjects (mean age, 23.4 y)	MDD participants were medication naïve	MDD determined via structured diagnostic interview Endothelial function determined via ultrasound measurement of flow-mediated dilation	Decreased plasma concentrations of nitric oxide metabolites among participants with MDD vs control subjects No significant between-group differences in endothelial function	Limited generalizability (100% Hispanic, undergraduate university students)
Murray et al (2012)[43]	N=54 Participants, including 27 with BD (mean age, 32.1 y) and 27 control subjects (mean age, 32.4 y)	BD participants were taking psychiatric medications, had greater insulin resistance than control subjects	BD diagnosis determined via chart review, confirmed via clinical interview Flow-mediated dilation and nitroglycerine-mediated brachial artery vasodilation determined via ultrasound	No significant differences were found between groups in endothelial function or arterial stiffness	BD participants were taking medications Small sample size Lack of systematic assessment of control subjects, yielding control subjects with MDD
Osika et al (2011)[44]	N=248 healthy adolescents (mean age, 14 y)	Analyses controlled for age and parental education Participants were not taking psychiatric medications	Self-reported symptoms of depression, anxiety, anger, and disruptive behaviors determined with Beck Youth Inventories Endothelial function assessed with peripheral arterial tonometry reactive hyperemia index	Among girls, lower endothelial function was associated with higher levels of anger, depression, and anxiety symptoms Among boys, higher endothelial function was significantly associated with higher (rather than lower) disruptive behavior symptoms	Cross-sectional study Depression determined by self-report only
Tomfohr et al (2011)[45]	N=135 Healthy female adolescents (mean age, 17.6 y), assessed 3 times over a period of 2.5 y. Participants enrolled on the basis of having high risk for mood disorders by virtue of a first-degree relative with a mood disorder or scoring in the top quartile of 1 of 3 indices of cognitive vulnerability	Analyses controlled for physical activity, alcohol use, smoking, and adiposity No participants were taking antidepressant medication at intake; 2 participants were taking an antidepressant medication at a follow-up visit	Self-reported depressive symptoms assessed with the Beck Depression Inventory Endothelial function assessed with peripheral arterial tonometry reactive hyperemia index	Within-person analyses demonstrated that lower endothelial function was significantly associated with higher levels of depressive symptoms, independent of health practices and adiposity	Depression determined by self-report only Only females included

BD indicates bipolar disorder; BMI, body mass index; CI, confidence interval; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; HR, hazard ratio; *ICD-9-CM*, *International Classification of Diseases, 9th Revision–Clinical Modification*; IHD, ischemic heart disease; LDL, low-density lipoprotein; and MDD, major depressive disorder.

sample of adolescents, endothelial dysfunction and depression symptoms travelled together. Taken together, depressive symptoms may be associated with impaired endothelial function in adolescent and young adult females; the association of MDD and BD with endothelial function is not consistent.

Conclusion

There is evidence from several studies of early CVD mortality, CVD, and imaging proxies for atherosclerosis; however, results are mixed. In most studies, depressive symptoms were determined via self-report; however, the strongest evidence emerged from studies in which mood disturbance was ascertained by use of semistructured research interviews that yielded psychiatric diagnoses. Indeed, the study that yielded the strongest data used the most rigorous assessment of mood (ie, diagnostic interviews) and the most valid cardiovascular outcome (ie, CVD mortality).[37] In a previous meta-analysis, the relative risk of incident CVD in adults conferred by diagnoses of MDD (2.69; 95% CI 1.63–4.43) was meaningfully stronger than the relative risk conferred by symptoms of depression (1.49; 95% CI 1.16–1.92).[46] These differences between diagnoses and symptoms are likely mediated by more severe, persistent, or recurrent elevations in pathophysiological processes discussed in the section "Pathophysiological Processes Bridging Mood Disorders and CVD." Other methodological factors may also have contributed to the inconsistency of findings, including small sample sizes and model overfitting (insufficient power). Sensitivity and reliability are important considerations when using noninvasive vascular imaging[47]; however, most studies reviewed in this section were conducted by groups with expertise in these methods. Future studies with larger sample sizes and research-grade assessment of mood symptoms, as well as psychiatric diagnoses, are warranted to resolve some of the inconsistency in these findings.

Traditional Cardiovascular Risk Factors in Relation to MDD and BD

The metabolic syndrome (MetS) is a clustering of clinical and biochemical risk factors for CVD and type 2 diabetes mellitus (T2DM). Several definitions for metabolic syndrome have been proposed. The most often cited are from the National Cholesterol Education Program, Adult Treatment Panel II, World Health Organization, and International Diabetes Federation.[48] MetS does not have a consensus definition in pediatric populations, although various definitions define risk according to pediatric cut points, most commonly the International Diabetes Federation definition.[49] There is evidence from several studies that the prevalence of MetS among adults with MDD or depressive symptoms is elevated.[50] Similarly, an increased hazard for MetS among people with BD has been documented across continents, countries, and cultures.[51,52] Each MetS component has been documented to be present at a higher rate than with matched people in the general population, with abdominal obesity being the most replicated finding.

Risk of MetS components among adolescents with BD is a major concern that has been the subject of comparatively little research to date.[53–57] No published study could be identified that primarily sought to determine the prevalence of MetS in a pediatric MDD or BD population. Notwithstanding this, data from the South Carolina Medicaid program, covering all medical services and medication prescriptions between January 1996 and December 2005, indicated that children and adolescents with BD are differentially affected by several medical disorders, including but not limited to obesity and T2DM.[58] Moreover, these conditions, including obesity and T2DM, were found to precede diagnoses of BD.[54] Similarly, research based on medical claims data indicated that children and adolescents diagnosed with BD were more likely to access several medical services, including cardiology services.[55] Finnish population-based prospective data indicated that there was a bidirectional association between depressive symptoms and MetS between childhood (mean age, 12 years) and early adulthood (mean age, 33 years).[59]

Obesity

Results from longitudinal studies indicated that pediatric obesity increased the risk for MDD and vice versa.[60,61] Merikangas et al[62] examined the association between MDD and obesity among adolescents 12 to 19 years old in the 2001 to 2004 National Health and Nutritional Examination Survey. MDD was associated with a significantly increased prevalence of obesity among males and among non-Hispanic blacks, whereas in the overall sample, the association of MDD with increased prevalence of obesity was no longer significant after controlling for demographic variables (adjusted odds ratio 1.6, 95% CI 0.9–2.9). There was prior evidence from adults that certain depressive subtypes may confer differential risk of obesity and that these subtypes may have genetic underpinnings[63]; however, this has yet to be examined in youth.†

There has been cross-sectional and longitudinal evidence of a bidirectional association between BD and overweight/obesity.[64] In a large cohort of children and adolescents with BD, 42% of participants were overweight/obese.[53] Because the vast majority of this sample had received prior treatment, analyses could not specifically examine untreated participants. As expected, second-generation (or atypical) antipsychotic drugs were significantly associated with overweight/obesity; however, other variables were also significantly and independently associated with overweight/obesity, including nonwhite race, earlier age of BD onset, and history of physical abuse and psychiatric hospitalization. In South Carolina Medicaid data, adolescent BD was associated with an increased risk of obesity (odds ratio 1.92, 95% CI 1.53–2.40).[54]

Insulin Resistance and Diabetes Mellitus (T2DM)

There is evidence of bidirectional associations between depressive symptoms and T2DM among adults.[65] Moreover, among young adult males in 2 Finnish population samples, severity of depressive symptoms was associated with insulin resistance.[66,67] In meta-analytic findings, depressive symptoms along with other psychological symptoms were more common among children with versus without T2DM,[68] and there was preliminary evidence that the association between depression and T2DM was especially strong in youth.[69] There is pharmacoepidemiological evidence of elevated rates of hyperglycemia and

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† "Youth" is used in this statement as an umbrella term for children, adolescents, and/or young adults (defined here as mean sample age within 1 standard deviation of 30 years).

T2DM in pediatric BD treated with psychotropic medication, although diagnoses of T2DM frequently precede treatment.[54,70]

Dyslipidemia

In pharmacoepidemiological studies, the rate of dyslipidemia in younger populations treated for BD is increased relative to the general population. For example, a retrospective cohort study based on a US health insurance organization examined claims for 17 884 adolescents (13–17 years of age) with BD (or schizophrenia) receiving care from 1997 to 2006.[71] The incidence rate per 100 000 person-years of dyslipidemia was 346.4 (95% CI 274.9–431.0) in this group compared with 86.6 (95% CI 76.4–97.7) in the general population. The adjusted hazard ratio for developing dyslipidemia for the psychiatric cohort versus the general population was 1.66 (95% CI 1.22–2.28).[71] A separate study reported increased prevalence of dyslipidemia (ie, 51% and 48% had elevated triglycerides and low high-density lipoprotein levels, respectively) in a mixed sample (n=95) that included 49 youth with BD.[72]

Hypertension

Hypertension is significantly more prevalent among adults with MDD and BD than in the general population and occurs at younger ages among adults with MDD and BD.[5] No original article was identified that primarily sought to report on the rate of hypertension among youth with MDD or BD. However, South Carolina Medicaid data indicated that hypertension was prospectively associated with an increased risk of incident BD among adolescents.[54]

Conclusion

Findings to date have demonstrated a significantly increased prevalence of traditional CVD risk factors among adults with MDD and BD. Although limited in scope, available findings from youth with MDD and BD are largely convergent with adult findings. The data regarding MDD among youth have included representative population samples, many of whom were medication-naïve. In contrast, most data regarding youth with BD are based on clinical or pharmacoepidemiological data. Future studies based on representative population samples of youth with BD are needed.[28] Prospective studies incorporating repeated measures of mood and traditional CVD risk factors are needed to better understand the bidirectional relationships between these variables among youth with MDD and BD.

Pathophysiological Processes Bridging Mood Disorders and CVD

As described in several comprehensive review articles, multiple systemic processes have been implicated in the association between mood disorders and CVD.[3,4,73,74] Although other processes have also been examined, the sections below highlight inflammation, oxidative stress, and autonomic dysfunction in particular because these arguably have the strongest data thus far.

Inflammation

Over the past 20 years, a rapidly growing body of research supports the role of inflammation in MDD and BD among adults.[75–78] Meta-analytic findings demonstrated increased inflammation in MDD.[79] Similarly, 3 meta-analyses in 2013 yielded generally convergent findings in BD, namely, that there is evidence of a proinflammatory imbalance during symptomatic episodes.[80–82] Preliminary genetic, epigenetic, and neurobiological findings suggest that this process may be part of the pathogenesis of MDD and BD rather than being a secondary epiphenomenon.[83–87]

Given the adult literature on this topic, excessive inflammation could underlie some of the association of depression with cardiovascular risk in youth. Indeed, in a handful of small case-control studies, clinically depressed adolescents have shown higher serum levels of some proinflammatory cytokines (eg, interleukin [IL]-1β and IL-6) than healthy control participants.[88–90] The results of larger studies of community youth have been mixed, with most but not all studies demonstrating graded associations between depressive symptoms and inflammatory biomarkers such as IL-6 and C-reactive protein (CRP).[88,91–93] Findings from adults suggest that inflammation may be particularly salient in early-onset BD,[94,95] and there are preliminary findings from youth with BD. In a high-risk offspring study, an aberrant inflammatory gene expression signature was observed among 88% of adolescent and young adult BD offspring affected with mood disorders versus 19% of control subjects.[96] Finally, in a study of 30 adolescents with BD, manic symptom severity was significantly associated with high-sensitivity CRP (r=0.37, P=0.04).[97] High-risk levels of high-sensitivity CRP (≥2 μg/mL)[98] were observed in 40% of the sample, and mean high-sensitivity CRP (3.1±4.6 μg/mL) was 3-fold higher than normal and nearly as high as in acute juvenile inflammatory arthritis.[99] Because both CRP and IL-6 forecast later CVD risk in apparently healthy people,[100–102] these findings suggest the possibility that low-grade inflammation is part of what underlies the increased risk of CVD in MDD and BD.

The question arises as to the direction of the association between depression and inflammation. From the available cross-sectional data in youth, it is not possible to discern how or why depression and inflammation come to be associated; however, it appears from both animal studies and human studies in adults that a bidirectional relationship exists.[77] Rodents treated with inflammatory cytokines develop "sickness behaviors" that resemble depressive symptoms and can include irritability, anhedonia, loss of slow-wave sleep, reduced food intake, and circadian disruptions (particularly in cortisol release).[103] Parallel symptom profiles often arise in patients treated with adjuvant cytokines for malignant melanoma.[104,105] Consistent with the hypothesis that inflammation may contribute to the pathogenesis of some depressive episodes, a recent randomized controlled trial found that infusion of the tumor necrosis factor-α receptor antagonist infliximab can ameliorate depressive symptoms in patients with low-grade chronic inflammation.[106] Moving in the other direction, depressed patients are prone to smoking, obesity, a sedentary lifestyle, and poor sleep quality,[107,108] all of which foster inflammation.

Two multiwave prospective studies of adolescents have yielded results that are consistent with this bidirectional view. In 1 study, 147 teenaged females at high risk for an initial depressive episode were assessed every 6 months for 2.5 years.[109] The transition to depression was accompanied by increases

in levels of IL-6 and CRP, particularly for participants who had experienced previous childhood adversity. In time-lagged models among participants with previous adversity, high CRP levels persisted even after the depressive syndrome had resolved. These lingering effects were bidirectional. Among the participants with previous adversity, high IL-6 forecast risk of depression 6 months later, independent of inflammation at that time. Another study conducted follow-up of 1420 children from the Great Smoky Mountains Study who were assessed up to 9 times between the ages of 9 and 21 years.[110] In time-lagged models, CRP did not forecast later depression risk; however, over time, CRP levels rose in concert with the number of depressive episodes. Of participants who experienced ≥2 depressive episodes, 42% subsequently exceeded the Centers for Disease Control and Prevention's high-risk cutoff for CRP, which is 3.0 mg/L.[111] In contrast, 9.8% of participants with 0 depressive episodes and 11.4% of participants with 1 depressive episode exceeded the high-risk cutoff.

Oxidative Stress

Oxidative stress comprises a disturbance of increased pro-oxidant to antioxidant ratio, which leads to potential damage in numerous systems.[112] Increased oxidative stress has been linked to endothelial dysfunction.[113] Studies have demonstrated that oxidative stress and endothelial dysfunction contribute to cardiovascular risk factors including hypertension,[114] diabetes mellitus,[115] and dyslipidemia.[116] The confluence of endothelial dysfunction and oxidative stress is implicated in the development of atherosclerosis.[113,117]

Oxidative stress markers are commonly increased in people with MDD and BD.[118–124] The most recent meta-analytic data in MDD, based on 23 studies and 4980 patients, evidenced large elevations of oxidative stress during depression, as well as small to medium elevations in antioxidant markers.[125] In addition, in several prospective studies, reductions in oxidative stress markers corresponded with improvement in psychiatric symptoms.[126–129] Levels of thiobarbituric acid reactive substances and nitric oxide activity may be especially increased in patients with BD.[119,129] Taken together, findings from these studies lend support to the hypothesis that oxidative damage may be involved in the pathophysiology of MDD and BD among adults.

Autonomic Dysfunction

In longitudinal observational epidemiological studies, impaired autonomic nervous system function (defined noninvasively by measures such as heart rate variability) is associated with incident hypertension[130,131] and diabetes mellitus.[132–135] Sympathetic activation plays a critical role in the persistence of hypertension through altered arterial baroreflex receptivity and by the promotion of renal dysfunction.[136] Lower resting heart rate variability is also associated with incident clinical cardiovascular events among adults with and without diabetes mellitus.[137–139] In most studies, there is a stronger association with fatal CHD and sudden cardiac death, which suggests an arrhythmic pathogenesis.[140]

Autonomic dysfunction is a primary pathological factor that relates psychological and neurological functioning to cardiovascular events.[141–148] Under normal conditions, the parasympathetic

division of the autonomic nervous system is responsible for neurovegetative functions (eg, appetite, sleep, energy), whereas the sympathetic division prepares the body to respond to a challenge by promoting coagulation and platelet activation, constricting arteries and vessels, and increasing hepatic production of glucose to transport to the muscles for immediate energy. In population and clinical studies, autonomic dysfunction is typically estimated by use of noninvasive estimates of the beat-to-beat variability in heart rate. Through statistical transformations of heart rate variability, individual contributions from the parasympathetic and sympathetic divisions can be estimated. However, in the absence of a stimulus to elicit sympathetic functioning, parasympathetic inputs are most commonly captured. Consequently, the majority of studies reviewed in this section are based on estimates of low parasympathetic input. Relatively fewer studies have investigated BD in relation to autonomic dysfunction, and those studies that have been conducted have relied on very small sample sizes. The following summary of findings therefore includes both MDD and BD.

Autonomic nervous system dysfunction is common in MDD, having been observed in adults[147,149] and adolescents.[141] In a 2010 meta-analysis of 18 articles,[150] patients who were clinically depressed had significantly less favorable measures of autonomic dysfunction reflecting parasympathetic function than nondepressed patients; moreover, depression severity was correlated with autonomic dysfunction. Some[90,151,152] but not all[153] studies have suggested that autonomic nervous system functioning, most commonly estimated as parasympathetic withdrawal, is worse in patients with BD than in those without. Although autonomic dysfunction has been identified in the pathway between depressive disorders and CVD in adults,[154] autonomic dysfunction is less likely to lead to end-organ damage in adolescents and young adults because of the decades-long process by which CVD develops over time. Rather, the pathway by which CVD risk is enhanced in depression and BD is more plausibly related to the development of CVD risk factors such as hypertension and diabetes mellitus. CVD is a distal consequence that is mechanistically plausible given the association of depressive disorders with numerous pathophysiological changes in the vasculature that result from hypertension and diabetes mellitus. The potential impact of psychotropic medications on autonomic and other findings is discussed in "Psychotropic Medications and Cardiovascular Risk Factors in Youth."

Behavioral and Environmental Factors Contributing to CVD Risk

A number of behavioral and psychosocial characteristics that are disproportionately prevalent among adolescents and young adults with mood disorders are associated with increased CVD risk. Such characteristics include early maltreatment, sleep disturbance, sedentary lifestyle, suboptimal nutrition, and tobacco smoking and substance abuse.

Early Maltreatment

This section focuses on maltreatment specifically, rather than negative life events in general, because the literature is most robust on this topic. Nonetheless, other stressful life events, particularly if severe, recurrent, or persistent, may also contribute to CVD risk. Some portion of the association of depression with cardiovascular risk may reflect a common influence of childhood

maltreatment on the pathogenesis of these conditions. A recent study estimated that 13.7% of children in the United States experience parental maltreatment annually.[155] Maltreatment can take the form of neglect or emotional, physical, or sexual abuse.[155,156]

With regard to depression, children exposed to maltreatment are at increased risk of developing an episode of major depression in their lifetime,[157–160] are prone to residual symptoms of depression once the episode subsides, have frequent depressive recurrences, and are resistant to a variety of frontline treatments.[161] With regard to biology, relative to nonexposed children, maltreated youth demonstrate dysregulation of the hypothalamic-pituitary-adrenal axis,[162,163] higher levels of CRP,[164] and more signs of cardiometabolic risk through early and middle adulthood.[165–168] In samples of clinically depressed adults, the prevalence of MetS and low-grade inflammation is significantly higher among those who were exposed to childhood adversities, including maltreatment, than among those who were not.[109,169,170] With regard to vascular outcomes, lifetime rates of stroke, myocardial infarction, and other forms of CVD are elevated among people who report having been maltreated as children.[109,171,172] However, many of the studies on this topic have used retrospective and unconfirmed reports of maltreatment, which complicates interpretation of their results. Given the above evidence that early maltreatment has been associated with mood disorders and with CVD, continued research bridging these topics, particularly prospective research and research that includes confirmed reports of maltreatment, is warranted.

Sleep Disturbance

Sleep disturbances are included among the diagnostic criteria for both MDD and BD.[23] A variety of sleep disturbances have been associated with symptoms of mood disorders among youth.[152,173,174] One study showed that depressed adolescent boys had short REM (rapid eye movement) latency and more frequent nighttime arousals, although depressed adolescent girls showed the same sleep patterns as their healthy counterparts.[175] Circadian phase shifts can occur before the onset of and during a depressive episode in adults and adolescents. Among children and adolescents, disrupted circadian rhythms also occur among those with mood disorders, resulting in delayed and often shortened sleep. Both short and long durations of sleep can precede mood disorders in adolescents and young adults.[176] Interestingly, short and long sleep duration have also been associated with increased CIMT, increased inflammatory markers, and poor cardiovascular outcomes in adults[177]; short sleep duration has also been associated with obesity and insulin resistance among children and adolescents.[178,179] Although circadian therapies can alleviate depressive symptoms and mood disturbances in adolescents and young adults,[176,180,181] the effect of these therapies on cardiovascular risk factors is not known.

Sedentary Lifestyle

Sedentary behavior increases cardiovascular risk factors and disease among adolescents, young adults, and older adults, and physical activity decreases cardiovascular risk through multiple pathways, including reduced body weight, improved endothelial and immune function, and improved blood pressure.[182] People with MDD or depressive symptoms are more likely to be sedentary relative to those without mood disorders.[183–185] The

association of physical activity with BD is inconsistent. Some studies have demonstrated reduced physical activity and reduced exercise tolerance in BD,[186,187] whereas other studies have demonstrated no significant differences.[188] Although many studies have been cross-sectional, and thus, the relationship may not be causal, prospective data from the National Health and Nutritional Examination Survey I demonstrated that physical inactivity was a significant predictor of the development of depressive symptoms in white women.[189] Similarly, in a prospective study of a Swedish cohort of young males, low fitness related to sedentary behavior was a significant risk factor for later depression.[190] In contrast, in a German population study, regular physical activity among adolescents and young adults predicted an increased incidence of BD at prospective follow-up.[191] However, the extent to which sedentary behavior influences the relationship between depression and CVD is not yet clear.

Nutrition

Nutrition could play a role in the association of depression with cardiovascular risk; however, relatively little attention has been devoted to exploring this hypothesis. A small study reported higher glycemic load and higher scores on Western and modern dietary patterns among women with BD.[192] In a handful of cross-sectional studies with adults, depression has been associated with reduced levels of micronutrients and their metabolites, some of which may be relevant to CVD.[193,194] Disparities in zinc, folate, and vitamins D and E have been reported between depressed and nondepressed adults,[195,196] although as a whole, the findings have been inconsistent and constrained by methodological limitations.[197] In a recent meta-analysis, there were significantly lower blood zinc concentrations among depressed adults (n=1642) than among control subjects (n=804).[198] Greater depression severity was associated with greater zinc deficiency. In 1 prospective study, older adults with low serum vitamin D were at increased risk for developing a depressive episode over the next 3 to 6 years.[199] Low vitamin D has also been reported in depressed adolescents, and with open-label supplementation, these patients' mood symptoms improved significantly.[200] Of note, vitamin D is the only supplement recommended in the recent Expert Panel.[2] Thus far, it is unclear whether micronutrient disparities account for the association of depression with cardiovascular risk.

Fish oils, specifically omega-3 fatty acids, have also received much attention in relation to the link between CVD and mood disorders.[201,202] Observational data suggest that greater seafood consumption is associated with lower rates of BD.[203] Omega-3 deficits have been reported among adults with MDD and BD.[204,205] A small study compared youth with versus without BD and found large between-group differences in red blood cell membrane concentrations of omega-3 levels; however, these were not significant after controlling for dietary intake.[206] However, greater docosahexaenoic acid levels were associated with significantly lower depressive symptoms in the BD group. The Ryukyus Child Health Study (n=3067 boys and 3450 girls, 12–15 years old) examined fish intake and omega-3 levels in relation to depressive symptoms.[207] Higher eicosapentaenoic intake was associated with significantly lower depressive symptoms, and a similar trend was observed for docosahexaenoic intake. Clinical trials of omega-3 supplementation, spurred by these findings,

have yielded positive findings for the treatment of depression among adults with MDD and BD.[208,209] Preliminary studies also suggest potential benefits of omega-3 treatment among youth with BD and MDD.[210–212] Recent studies have drawn into question the role of omega-3 treatment for secondary prevention of CVD in the general population,[213] as well as for adjunctive treatment of depression among adults with CVD.[214] However, given the above findings, future studies examining the impact of omega-3 treatment on CVD-relevant outcomes (eg, endothelial function, inflammation) and mood symptoms among youth with MDD and BD are warranted.

Tobacco Smoking and Substance Use

Cigarette smoking is the most significant behavioral risk factor associated with CVD risk,[215] and the severity of CVD increases as a function of the number of pack-years.[216] Adults with MDD and BD are 2 to 3 times more likely to be smokers and less likely to successfully quit smoking.[217–220] Adolescents with MDD and BD are more likely to begin smoking, and begin smoking earlier, than their nondepressed counterparts,[221–224] a significant association because nearly all adult smokers begin smoking as adolescents. There is some evidence that smoking exacerbates the association between CVD and mood disorders. For example, a recent cross-sectional study found that smoking, in combination with elevated body mass index, increases the risk of CVD among adults with depression, BD, and other mood disorders.[225]

Similar to the data on smoking, adolescents with MDD and BD are at increased risk of alcohol and substance abuse.[226–229] However, little research has examined the contribution of alcohol and substance abuse to the elevated CVD risk among those with mood disorders.

Conclusion

In summary, a variety of behavioral and psychosocial factors may contribute to the increased risk of CVD among youth and adults with MDD and BD, potentially acting through the aforementioned pathophysiological mechanisms (eg, inflammation, oxidative stress) and cardiovascular risk factors (eg, increased blood pressure). Primary among these are childhood maltreatment, sleep disorders, physical inactivity, and smoking. These linkages are in need of further study, particularly among adolescents and young adults with MDD and BD. With that said, many of the studies we reviewed statistically controlled for these lifestyle variables and still found significant associations between mood disorders and cardiovascular risk. As such, lifestyle variables may contribute to but do not fully explain the link between mood disorders and cardiovascular risk.

Psychotropic Medications and Cardiovascular Risk Factors in Youth

We recognize that although there are many unanswered questions regarding the role of psychiatric medications in the association of mood disorders with CVD, this topic is nonetheless timely and salient to this statement. For this reason, and although a systematic review of this topic is beyond the scope of this statement, we offer a brief overview and several tentative conclusions on this topic.

Antidepressant Drugs

There is some evidence to suggest that autonomic dysfunction is attributable to medications used to manage depression[147,230]; however, a meta-analysis[150] concluded that the adverse effect of antidepressant drugs was restricted to adults taking tricyclic antidepressants, and similar findings were recently reported among adults participating in randomized controlled clinical trials.[231] Tricyclic antidepressant drugs are not indicated for the treatment of mood disorders among youth and are not commonly used in this population, whereas selective serotonin reuptake inhibitors (SSRIs) are the pharmacological treatment of choice for depression among youth.[232] The topic of SSRIs and CVD has been examined in great detail among adults, and the current literature suggests that SSRIs may have a salutary effect on CVD (particularly citalopram and sertraline) and are unlikely to have a deleterious effect[231,233]; however, there is evidence that SSRIs may confer a risk of obesity and possibly glycemic control problems.[234,235] This topic has received limited attention among youth to date. In a large study of adolescents with treatment-resistant depression, 12 weeks of treatment with venlafaxine (a serotonin and norepinephrine reuptake inhibitor; n=166) was associated with greater increases in diastolic blood pressure than treatment with SSRIs (n=168).[234] The same study found an ≈2-kg increase in weight for venlafaxine-treated youth and ≈3-kg increase in weight in SSRI-treated youth. Although significant weight gain is not a frequently reported side effect in placebo-controlled clinical trials, most trials have not systematically reported changes in weight/obesity. Moreover, anorexia and weight loss are a common symptom of depression, such that weight gain in itself may reflect symptom improvement and may not be a negative outcome. The association between antidepressant drugs and glycemic control is complex. It remains unclear whether antidepressant drugs have a salutary, neutral, or deleterious effect on glycemic control, because different studies have reported each of these associations.[235–237]

Lithium and Anticonvulsant Drugs

Lithium, carbamazepine, and divalproex are associated with significant weight gain among youth with BD.[56,238,239] The magnitude of this association is significantly smaller than second-generation antipsychotic drug (SGA)–associated weight gain among youth.[240] There is also pharmacoepidemiological evidence that exposure to these medications among youth is associated with hypertension.[241] A recent 8-week study found that in contrast to treatment with risperidone, neither lithium (n=62) nor divalproex (n=78) yielded significant changes in blood glucose.[239] Divalproex does not appear to increase risk of dyslipidemia in clinical studies of youth with BD and may in fact improve lipid profiles to some degree.[239,242] Despite its association with weight gain, observational data in adults with BD suggest that long-term treatment with lithium may attenuate the risk of CVD.[243]

Second-Generation Antipsychotic Drugs

SGAs are highly efficacious for mania, and several have received US Food and Drug Administration approval for the treatment of adolescent BD and are considered first-line treatments.[244,245] Unfortunately, antimanic SGAs (with the exception of ziprasidone) have been shown to negatively impact each of the MetS components in pharmacoepidemiological studies and in controlled trials.[56,240,246,247] Despite metabolic monitoring guidelines (ie, glucose, lipids, weight, blood pressure) for patients treated with SGAs from the American Diabetes Association/American Psychiatric Association[248] and the International Society for Bipolar Disorder,[249] adherence to these monitoring guidelines is poor, particularly among youth.[250,251] Patient-, clinician-, and system-level strategies are warranted to increase the proportion of youth achieving guideline-concordant monitoring benchmarks.

Conclusion

Antidepressant medications (including SSRIs) and mood-stabilizing medications (particularly SGAs) can cause weight gain and may also affect other metabolic parameters among adults and youth. There is no doubt these are undesirable side effects in a population with increased risk of CVD; however, it is important to acknowledge that despite the clear evidence regarding CVD risk factors, evidence that these medications cause increases in CVD or CVD mortality is lacking to date.[231,252] Reasons for this discrepancy are uncertain; however, compelling contradictory findings regarding high-potency statins (decreased risk of CVD despite increased risk of T2DM) suggest that this discrepancy is not unique to psychiatric medications.[253] Pending definitive studies on this topic, one might speculate that the anti-inflammatory effects of these medications, or other yet unknown pharmacological properties, may partially mitigate their adverse effects on traditional CVD risk factors.[96,254–257]

Although it remains possible that psychotropic medications contribute in part to CVD risk in MDD and BD, there are 3 primary reasons to conclude that MDD and BD are moderate-risk conditions independent of the effect of psychotropic medications and that medications should not be the only focus. First, the strongest evidence regarding these medications relates to increased CVD risk factors, and the best available evidence suggests that the association between mood disorders and CVD is independent of CVD risk factors.[37,46,258] Second, the association between mood disorders and excessive CVD risk was described decades before the advent of these medications.[11,14,259] Third, many if not most people in population-based studies on this topic had not received pharmacological treatment for their mood disorders.[5,16,260] This is likely to be particularly true for adolescents, at least 60% of whom do not receive any treatment for their MDD or BD, let alone pharmacological treatment.[261]

Overall Summary and Future Directions

Overall Summary

The central goal of this statement is to position MDD and BD alongside other pediatric diseases previously identified as moderate risk for CVD. Despite some inconsistencies, MDD and BD clearly satisfy the criteria that have been set for tier

II moderate-risk conditions and equal or exceed the evidence for other conditions in this category. Taken together, the evidence reviewed in this statement demonstrates that MDD and BD among youth are tier II moderate-risk conditions that predispose to accelerated atherosclerosis and early CVD. Cardiovascular risk among youth with MDD and BD should therefore be managed in accordance with recent Expert Panel integrated guidelines, applying the same recommendations made for other moderate-risk conditions (Figure 2).[2] The magnitude of increased risk for CVD in adulthood is substantial, most likely because of a combination of factors that include direct effects of MDD and BD through shared pathophysiological processes (eg, inflammation), direct effects of mood disorder symptoms (eg, sleep disruption), indirect effects of mood disorder symptoms (eg, smoking, suboptimal nutrition and physical activity), and accumulation of excessive traditional CVD risk factors. Importantly, there is evidence of clustering of risk factors (eg, smoking, hypertension, obesity, suboptimal nutrition or physical activity) among people, including youth, with MDD and BD. As a result, although MDD and BD warrant inclusion among tier II moderate-risk conditions overall, careful assessment is warranted to additionally identify those youth with risk factor clustering (≥2 risk factors), for whom a tier I high-risk designation would apply.

Future Research Directions

Similar to the association between depression and CVD among adults, future studies are needed to determine whether any potential impact of other psychiatric disorders, such as anxiety disorders, on CVD is independent, cumulative, or synergistic.[262] Several studies discussed in this scientific statement demonstrated sex differences. Therefore, future studies are also needed to achieve a better understanding of sex differences as they relate to the risk of CVD among youth with mood disorders. In addition, although many studies examined mood symptoms rather than diagnoses, the strength of the observed associations was in some instances greater when mood diagnoses were examined. Future studies should therefore ascertain both diagnoses and symptoms and should examine whether the severity, persistence, and recurrence of symptoms impacts CVD risk. There is an unrealized opportunity to increase our knowledge on this topic by incorporating CVD-related measures in studies of youth with MDD and BD. Traditional CVD risk factors and high-sensitivity CRP, as well as ascertainment of CVD-related family medical history, can be readily and inexpensively measured and should be incorporated into large cohort studies of youth with MDD and BD, as well as youth at familial risk for MDD and BD. The converse also holds true: mood symptoms and diagnoses, as well as family psychiatric history, should be incorporated into large cohort studies focused on CVD risk among youth. Approaching the mood-CVD link from these complementary perspectives offers the chance to maximize progress in understanding the epidemiology and familial nature of this link. Finally, no studies have systematically examined integrated treatment strategies among youth, although preliminary approaches to mitigating the effect of mood-stabilizing medications on obesity and T2DM have been described.[263–266] It is therefore unclear whether treatment of the mood symptoms of MDD and BD among youth can reduce the risk of accelerated atherosclerosis and premature
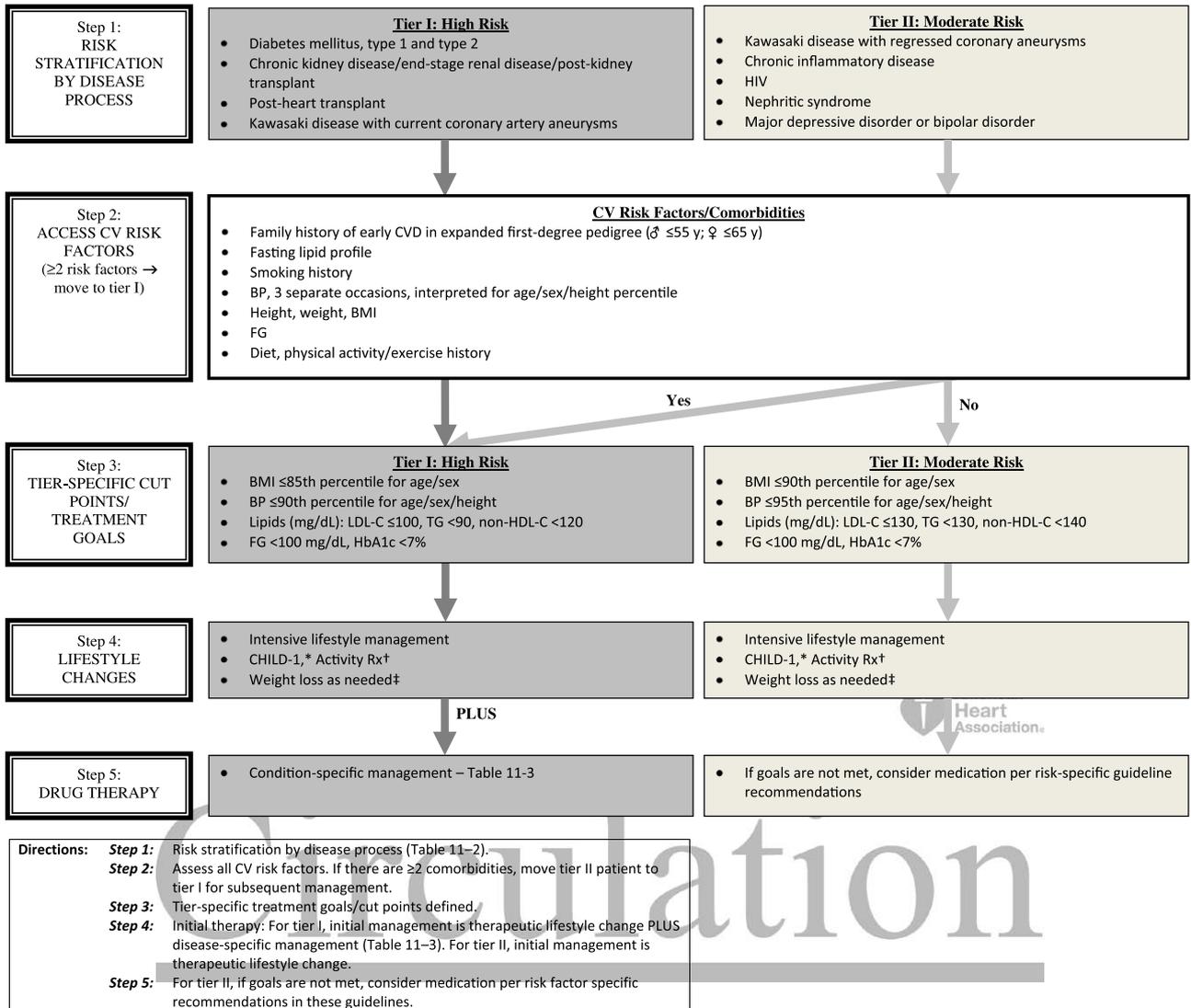
Step 1:
RISK STRATIFICATION BY DISEASE PROCESS

Tier I: High Risk
- Diabetes mellitus, type 1 and type 2
- Chronic kidney disease/end-stage renal disease/post-kidney transplant
- Post-heart transplant
- Kawasaki disease with current coronary artery aneurysms

Tier II: Moderate Risk
- Kawasaki disease with regressed coronary aneurysms
- Chronic inflammatory disease
- HIV
- Nephritic syndrome
- Major depressive disorder or bipolar disorder

Step 2:
ACCESS CV RISK FACTORS
(≥2 risk factors → move to tier I)

CV Risk Factors/Comorbidities
- Family history of early CVD in expanded first-degree pedigree (♂ ≤55 y; ♀ ≤65 y)
- Fasting lipid profile
- Smoking history
- BP, 3 separate occasions, interpreted for age/sex/height percentile
- Height, weight, BMI
- FG
- Diet, physical activity/exercise history

Yes   No

Step 3:
TIER-SPECIFIC CUT POINTS/ TREATMENT GOALS

Tier I: High Risk
- BMI ≤85th percentile for age/sex
- BP ≤90th percentile for age/sex/height
- Lipids (mg/dL): LDL-C ≤100, TG <90, non-HDL-C <120
- FG <100 mg/dL, HbA1c <7%

Tier II: Moderate Risk
- BMI ≤90th percentile for age/sex
- BP ≤95th percentile for age/sex/height
- Lipids (mg/dL): LDL-C ≤130, TG <130, non-HDL-C <140
- FG <100 mg/dL, HbA1c <7%

Step 4:
LIFESTYLE CHANGES

- Intensive lifestyle management
- CHILD-1,* Activity Rx†
- Weight loss as needed‡

- Intensive lifestyle management
- CHILD-1,* Activity Rx†
- Weight loss as needed‡

PLUS

Step 5:
DRUG THERAPY

- Condition-specific management – Table 11-3

- If goals are not met, consider medication per risk-specific guideline recommendations

Directions:
- **Step 1:** Risk stratification by disease process (Table 11–2).
- **Step 2:** Assess all CV risk factors. If there are ≥2 comorbidities, move tier II patient to tier I for subsequent management.
- **Step 3:** Tier-specific treatment goals/cut points defined.
- **Step 4:** Initial therapy: For tier I, initial management is therapeutic lifestyle change PLUS disease-specific management (Table 11–3). For tier II, initial management is therapeutic lifestyle change.
- **Step 5:** For tier II, if goals are not met, consider medication per risk factor specific recommendations in these guidelines.

Figure 2. Risk stratification and management for children and adolescents with conditions predisposing to accelerated atherosclerosis and early CVD. The current statement concludes that major depressive disorder and bipolar disorder among adolescents should be managed as tier II moderate-risk conditions. For Tables 11-2 and 11-3 mentioned in the Figure, please see Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[2] BMI indicates body mass index; BP, blood pressure; CHILD-1, Cardiovascular Health Integrated Lifestyle Diet; CV, cardiovascular; CVD, cardiovascular disease; FG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides. *CHILD 1 (Cardiovascular Health Integrated Lifestyle Diet) per 2011 Expert Panel, Section V. Nutrition and Diet).[2] †Activity Rx – Activity Recommendations per 2011 Expert Panel, Section VI. Physical Activity.[2] ‡Weight loss recommendations per 2011 Expert Panel, Section X. Overweight and Obesity.[2] Modified with permission from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[2] and Kavey et al.[1] Copyright © 2006, American Heart Association, Inc.

CVD, and this is an important question for future research to address. In particular, research regarding the dual mood-related and CVD-related benefits of complementary and alternative interventions such as exercise, mindfulness meditation, antioxidants, and fish oils is warranted. Indeed, future clinical trials would benefit from the incorporation of CVD-related measures and mood-related measures to generate more integrated data regarding the global benefits and risks of interventions.

Future Clinical Directions
Medications used to treat mood disorders among youth, particularly those used to treat BD, confer additional risk of weight gain and other metabolic disturbances. Although the magnitude of the impact of these medications on CVD and CVD mortality has yet to be elucidated, improved metabolic monitoring is warranted to mitigate the accumulation of traditional CVD risk factors. Current guidelines for the treatment of BD among youth acknowledge the importance of metabolic monitoring of those taking mood-stabilizing medications but do not address the importance of metabolic monitoring of youth with BD irrespective of treatment.[26,267] Similarly, current guidelines for the treatment of MDD among youth do not adequately incorporate cardiovascular risk factors.[24,232,268] Future guidelines should integrate cardiovascular risk factor monitoring irrespective of treatment.

A transformational change is required in the management of MDD and BD among youth to meaningfully integrate cardiovascular risk assessment and management into the day-to-day treatment of these conditions. Related changes have begun in the treatment of adults with MDD and BD. Indeed, there is preliminary evidence that integrating cardiovascular risk assessment and management in the treatment of adults with MDD and BD may have salutary effects both on CVD risk and on psychiatric outcomes.[269–271] Although unfortunately, CVD is already highly prevalent by middle age among adults with MDD and BD, there remains a substantial window of opportunity in which to intervene to prevent these outcomes among youth.

To meaningfully change the cardiovascular risk associated with MDD and BD among youth, a concerted effort across stakeholder groups will be required, including pediatricians and other primary care providers, psychiatrists, patients and their families, research funding agencies, and policy makers. Pending the development of evidence-based guidelines that are specific to youth with MDD and BD, it is important that the above stakeholders collaboratively endeavor to ensure that previously described Expert Panel integrated guidelines, with consideration of MDD and BD as additional moderate risk conditions, are consistently applied to these youth.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Benjamin I. Goldstein	Sunnybrook Health Sciences Centre	Depressive and Bipolar Disorder Alternative Treatment Foundation*; Canadian Institutes for Health Research*; Heart and Stroke Foundation†; NIMH†; Ontario Mental Health Foundation*	None	None	None	None	None	None
Brian W. McCrindle	The Hospital for Sick Children	AstraZeneca†; Canadian Institutes for Health Research†; Heart and Stroke Foundation†; Schering Plough†; NIH†	None	None	None	None	Aegerion*; Bristol-Myers Squibb*; Daiichi Sankyo*; Eli Lilly*; Janssen*; Medpace*	None
Mercedes R. Carnethon	Northwestern University	None	None	None	None	None	None	None
Karen A. Matthews	University of Pittsburgh	None	None	None	None	None	None	None
Roger S. McIntyre	University of Toronto	Eli Lilly*; Janssen-Ortho*; Shire*; Astra-Zeneca*; Pfizer*; Lundbeck*; Stanley Medical Research Institute*; National Alliance for Research on Schizophrenia and Depression (NARSAD)*; National Institutes of Mental Health*	None	Janssen-Ortho*; Astra-Zeneca*; Eli Lilly*; Lundbeck*; Merck*; Pfizer*	None	None	Astra Zeneca*; Bristol-Myers Squibb*; France Foundation*; GlaxoSmithKline*; Janssen-Ortho*; Eli Lilly*; Organon*; Lundbeck*; Pfizer*; Shire*; Merck*	Astra Zeneca*; Bristol-Myers Squibb*; France Foundation*; I3CME*; Physicians' Postgraduate Press*; CME Outfitters*; Optum Health*; Merck*; Eli Lilly*; Pfizer*
Gregory E. Miller	Northwestern University	None	None	None	None	None	None	None
Geetha Raghuveer	Children's Mercy Hospitals and Clinics	None	None	None	None	None	None	None
Catherine M. Stoney	NIH/NHLBI	None	None	None	None	None	None	None
Hank Wasiak	University of Southern California	None	None	None	None	None	None	None

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*Modest.

†Significant.

Reviewer Disclosures

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David Brent	University of Pittsburgh School of Medicine	None	None	None	None	None	None	None
Andrea Danese	Institute of Psychiatry, King's College London (United Kingdom)	UK Medical Research Council grants G1002190 and G9806489*	None	None	None	None	None	None
Rae-Ellen W. Kavey	University of Rochester	None	None	None	None	None	None	None
Amit J. Shah	Emory University	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Significant.

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