How to Mitigate Risk of Premature Cardiovascular Disease Among Children and Adolescents with Mental Health Conditions

Lulu Xu1 · Martha Zimmermann1 · Heather Forkey2 · Jessica Griffin1,2 · Caitlin Wilds1,3 · Wynne S. Morgan1 · Nancy Byatt1 · Catherine J. McNeal4

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Abstract

Purpose of Review The goal of this article is to characterize the myriad of ways that children with mental health conditions can be at risk for premature cardiovascular disease (CVD) and various modalities to ameliorate this risk in childhood in order to improve the life course of these children.

Review Findings Child and adolescent mental health conditions are a common yet underrecognized risk factor for premature CVD. The American Heart Association has recently included psychiatric conditions as a CVD risk factor (CVDRF) and the evidence linking childhood adversity to cardiometabolic disease. There are bidirectional and additive effects from the intrinsic emotional dysregulation and inflammatory changes from the mental health condition, the associations with risky health behaviors, and in some cases, metabolic side effects from pharmacotherapy. These pathways can be potentiated by toxic stress, a physiologic response to stressors from childhood adversity. Toxic stress is also associated with development of mental health conditions with epigenetic effects that can result in transgenerational inheritance of cardiometabolic risk. Exposure to toxic stress and mental health conditions in isolation sometimes compounded by pharmacotherapies used in treatment increase the risk of cardiometabolic diseases in childhood. The multiple pathways, which adversely influence cardiometabolic outcomes, encourage clinicians to consider strategies to mitigate these factors and justify the importance of early screening and treatment for CVDRFs.

Summary Mental health, health behaviors, and environmental factors co-occur and intersect in complex pathways that can increase CVD risk over the lifespan. Early detection and response can mitigate the risks associated with premature development of CVD.

Keywords Cardiovascular disease · Cardiometabolic · Mental health conditions · Toxic stress · Pharmacotherapy

Introduction

Approximately one in every three to four youth meet criteria for a mental health condition as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) [1, 2]. Mental health conditions common among children and adolescents include, but are not limited to, anxiety disorders, major depressive disorder (MDD), eating disorders, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and alcohol and substance misuse. This article is part of the Topical Collection on Children/Adolescents/Young Adults and Atherosclerosis

1 Department of Psychiatry, UMass Chan Medical School, Worcester, MA 01655, USA
2 Department of Pediatrics, UMass Chan Medical School, Worcester, MA 01655, USA

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use disorders. Co-occurring conditions are common, with approximately 40% of adolescents meeting criteria for one mental health condition also meeting criteria for a second disorder [3].

Child and adolescent mental health conditions are a common yet underrecognized risk factor for premature cardiovascular disease (CVD) [4]. Evidence increasingly suggests a relationship between mental health conditions and both CVD and CVDRFs such as hypertension, type 2 diabetes (T2D), obesity, and dyslipidemia [4, 5•, 6, 7]. Causes include emotional dysregulation seen with many mental health conditions and their association with risky health behaviors [8]. Some pharmacotherapy of mental health conditions (e.g., atypical antipsychotics) may also increase risk for CVD [5•]. Indeed, a longitudinal study found that children exhibiting emotional or behavioral problems associated with mental health conditions at age six demonstrated increases in cardiometabolic dysfunction by age 10 [9]. There is also considerable evidence linking adverse childhood experiences (ACEs) with subsequent cardiometabolic diseases [6].

It is important to note that mental health conditions in childhood can result from prolonged or repetitive exposure to toxic stress. Toxic stress is a physiologic response to severe physical or emotional stress in the absence of sufficient buffering. This can cause emotional dysregulation and mental health conditions including sleep disorders, major depression, anxiety, and PTSD, which respond differently to treatment than these conditions in the absence of toxic stress [10–13]. There is also evidence that the pathways that explain the relationship between mental health in childhood and incident CVD may be accelerated or more potent in the context of ACEs [6, 14]. It is thus vital for healthcare providers to recognize the increased risk for developing CVRFs and subsequent premature CVD in children and adolescents with exposure to significant adversity in addition to those with known mental health conditions.

The purpose of this review is to comprehensively describe the cardiometabolic risks for premature CVD in youth with mental health conditions and the extent to which they are exacerbated by toxic stress. We also describe strategies that providers can use to mitigate this risk.

### Risk Factors for Premature Cardiovascular Disease

#### Mental Health Conditions and Emotional Dysregulation

Mental health conditions are associated with an increased risk of CVD in youth even after controlling for sociodemographic factors [15], biological risk factors, and health risk behaviors [16]. This may be due to the emotional dysregulation [17] and general psychological distress that is characteristic of some mental health conditions that are associated with an increased risk of developing CVD [18, 19]. Though negative emotions may be adaptive in the short-term in those that are otherwise healthy, they can negatively impact health if unregulated or if chronically experienced. Emotional states linked to development and progression of CVD include anger, hostility, and anxiety, as well as those typical of depression (e.g., sadness and hopelessness) [19, 20].

Data from adults suggest that emotional dysregulation can cause changes in the autonomic system, immune system, and neuroendocrine system [17]. These changes include reduced parasympathetic cardiac control and amplified sympathetic nervous system functioning, inflammation, and hypothalamic–pituitary–adrenal axis activity [17]. Anger and hostility may increase autonomic nervous system dysregulation, inflammation (noted by increased interleukin-6 (IL-6) and C-reactive protein), fibrinogen, and cortisol [20]. It has also been suggested that negative emotionality may increase cardiovascular activity generally and impact insulin resistance, endothelial and platelet dysfunction, hypertension risk, and brain plasticity [8]. These changes may in turn be related to CVD risk [21, 22]. Brain imaging studies have suggested overlapping circuitry identified in the amygdala, anterior cingulate and medial prefrontal cortices, and insula that may be responsible for both negative emotions and CVD risk [17]. More research is needed to examine causal pathways that originate from pediatric mental health to ameliorate the risk of CVD across the lifespan.

#### Mental Health Conditions and Behavioral Risk Factors

Mental health conditions in childhood and adolescence are associated with behavioral risk factors for CVD [5•]. Physical inactivity, poor diet, substance use, and poor sleep quality or inadequate sleep [8, 23] are all associated with the altered decision-making, perception of risk, memory bias, and social dysfunction that are seen in many mental health conditions [19]. Paradoxically, health risk behaviors may both increase the risk for some mental health conditions in youth and result from those same conditions [24]. For example, frequency and quantity of alcohol use in adolescence is associated with depression, and alcohol misuse may result from high-risk behavior associated with depression [24]. A third possibility is that of shared risk for both developing mental health disorders and engaging in health risk behaviors. For instance, temperament, genetic, or environmental factors may increase risk for both anxiety disorders and substance use [25].
Physical Inactivity

Physical activity among youth with ADHD, ASD, MDD, anxiety disorders, and bipolar disorder has been demonstrated to be lower than in matched peers [5, 26, 27]. It is generally thought that physical activity and sports participation may buffer negative effects of mental health conditions through neurobiological pathways (e.g., anti-inflammatory responses and hypothalamic pituitary (HPA) axis regulation) and psychosocial pathways (self-efficacy, social relationships) [28]. Physical inactivity is associated with higher body fat and overall higher composite risk factor scores for CVD in children [29, 30]. There is also mixed evidence of insulin resistance associated with physical inactivity [31].

Diet

A high quality diet, as defined by consumption of nutrient-rich food (e.g., vegetables, fruits, whole grains, and low saturated fat), has been associated with more positive mental health among children and adolescents, while unhealthy dietary patterns (e.g., higher intake of saturated fat, refined carbohydrates, and processed foods) are associated with poorer mental health [32]. This relationship appears to be stronger for unhealthy dietary patterns, and some evidence suggests a prospective relationship between mental health and unhealthy dietary patterns [24]. Mechanisms linking diet to mental health include inflammation, oxidative stress, and structural changes in the brain related to diet [28]. For example, dietary patterns in adults have been linked with hippocampal volume [33]. In addition to dietary patterns, behavioral characteristic of mental health conditions such as impulsivity may be related to diet, such as an increased impulsive eating among youth with ADHD [5•].

Substance Use

Substance use initiation often occurs during adolescence and has known impacts on blood pressure and hypertension with increased risk of stroke [34]. While the relationship between substance use and mental health is complex and likely multidirectional, research has suggested that for many youth, mental health conditions precede alcohol, nicotine, and drug use [35, 36]. Smoking in particular is widely recognized as a CVDRF. The presence of any psychiatric disorder in adolescence or young adulthood is associated with increased risk of nicotine dependence [35]. Smoking is more common among youth with depression, anxiety, and bipolar disorder although not among youth with ASD [5•, 37]. Youth are also increasingly consumers of other emerging tobacco products such as noncombustible electronic cigarettes [38].

Sleep Disturbance

Sleep disturbance commonly co-occurs with mental health conditions in youth [39], and is an underrecognized risk factor for CVD [40]. Meta-analyses suggest that sleeping more than 8–9 h/night or fewer than 5–6 h/night is associated with greater CVD risk in adults [41], and especially hypertension [40]. Sleep disturbance impacts critical hormones regulating appetite, insulin resistance, and leptin and ghrelin which in turn affect appetite and caloric intake and physical activity levels in adults [42, 43]. Prospective studies suggest a relationship between insomnia disorder and incident CVD [44].

Mental Health Conditions and Pharmacotherapy

Though rarely considered first-line treatments, pharmacologic agents are, in some cases, used to treat mental health conditions in children or adolescents. Fortunately, there is little metabolic risk for the majority of common medications used in children (Table 1). Both direct cardiovascular risk and the risk for T2D and weight gain were found to be small in children newly prescribed selective serotonin reuptake inhibitors (SSRIs), a medication class which can be used for treatment of depression or anxiety [45, 46]. In contrast, other medications have greater association for CVDRFs. For example, stimulants, which are prescribed for ADHD, while shown to decrease obesity in children [47], can increase blood pressure and heart rate [48]. On rare occasions, other medications like mood stabilizers have been associated with more direct cardiac risks such as arrhythmias or sudden cardiac death; these are noted in Table 1. There continues to be a need for systemic investigation into the long-term metabolic effects of psychiatric medication commonly prescribed to children.

Second-generation antipsychotics (SGAs), also known as “atypical antipsychotics,” are the class of psychiatric medications most commonly associated with CVDRFs. More specifically, they have been associated with metabolic syndrome, including weight gain, T2D, and dyslipidemia further [49–53] increasing the risk of earlier adult onset of CVD [54, 55]. A small proportion of youth are screened for their metabolic side effects [56], as recommended by clinical guidelines published more than a decade ago [57]. These drugs are in fact so obesogenic that they are used to treat malnutrition and cachexia as an appetite stimulant [58]. The mechanisms for these metabolic effects appear to be multifactorial including the genetic profile of the patient, altered metabolic control, and blockage of several neurotransmitter pathways and not all children who take an SGA experience the adverse cardiometabolic effects [52, 59]. Increased risks of adverse metabolic effects have also been associated with young age and simultaneous prescription of multiple medications in children [60, 61]. While not all are approved by the United States
Food and Drug Administration (FDA) for use in children some SGAs have been approved for the treatment of bipolar disorder, schizophrenia, irritability with autistic disorder, and Tourette’s disorder in children [52, 62]. Although these conditions are not as prevalent as other mental health conditions seen in children, SGAs are increasingly prescribed off-label for more common mental health conditions with behavioral symptoms including ADHD with aggressive symptoms, ODD, and conduct disorder (CD) [63, 64].

Despite these cardiometabolic and cardiovascular risks, it is important to recognize that pharmacotherapy can be essential to improving the lifestyle and health benefits of some children with mental health conditions which in turn can decrease the risk for development of CVDRF. As these medications can be lifelong, providers must be aware of these risks to facilitate early identification and treatment of the potentially adverse metabolic side effects.

### Mental Health Conditions and Toxic Stress

As noted above, a recent American Heart Association (AHA) Scientific Statement highlighted the evidence linking the effects of ACEs and childhood adversity on the

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### Table 1  Pediatric psychiatric medications and CVD risk generic drug name (brand name)

| Class of drug                        | Examples                                                                 | CVD risk                                      |
|--------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------|
| **ADHD medications**                 |                                                                          |                                               |
| Stimulants                           | Dextroamphetamine (Dexedrine, Adderall, Procentra), Lisdexamphetamine (Vyvanse) | Tachycardia, hypertension, arrhythmia, sudden death |
|                                      | Methylphenidate (Concerta, Daytrana, Metadate, Ritalin), Dexmethylphenidate (Focalin) |                                               |
| Norepinephrine transporter inhibitor | Atomoxetine (Strattera)                                                  | Tachycardia, hypertension, arrhythmia, sudden death |
| Alpha agonist                        | Citalopram (Tenex, Intuniv), Clonidine (Kapvay)                          |                                               |
|                                      |                                                                          |                                               |
| **Antidepressant medications**       |                                                                          |                                               |
| Selective serotonin reuptake inhibitors (SSRIs) | Fluoxetine (Prozac), Sertraline (Zoloft), Fluvoxamine (Luvox), Escitalopram* (Lexapro) | Minimal cardiovascular effects                |
| Serotonin norepinephrine reuptake inhibitors (SNRIs) | Duloxetine (Cymbalta)                                                     | Mild tachycardia and hypertension             |
| Tricyclic antidepressants (TCAs)     | Clomipramine* (Anafranil)                                                | Arrhythmia, orthostatic hypotension, tachycardia, weight gain |
| **Antipsychotic medications**        |                                                                          |                                               |
| First-generation antipsychotic medicatons (FGA) | Chlorpromazine* (Thorazine), Thioridazine* (Mellaril), Trifluoperazine* (Stelazine), Thiothixene (Navane), Pimozide* (Orap), Haloperidol (Haldol) | Arrhythmias, sudden cardiac death             |
| Second-generation antipsychotic (SGA) | Olanzapine (Zyprexa), Quetiapine (Seroquel), Asenapine (Saphris), Paliperidone (Invega), Risperidone (Risperdal), Lurasidone (Lutada), Aripiprazole (Abilify) | Weight gain, type 2 diabetes mellitus, dyslipidemia, hypertension |
| **Mood stabilizers**                 |                                                                          |                                               |
| Lithium                             | Lithium (lithium carbonate, Eskalith, Lithobid), Valproic Acid (Depakote, Depakene), Carbamazepine (Tegretol), Lamotrigine (Lamictal), and Oxcarbazepine (Trileptal) | Arrhythmias                                  |
| **Anti-anxiety medications**         |                                                                          |                                               |
| Benzodiazepines                      | Lorazepam (Ativan), Diazepam (Valium), Clonazepam (Klonopin)             | Minimal cardiovascular effects                |
| Non-Benzodiazepine hypnotics         | Zolpidem (Ambien)                                                        | Minimal cardiovascular effects                |
| Atypical anti-anxiety medications    | Buspironine (BuSpar)                                                     | Minimal cardiovascular effects                |

*Risk of QT prolongation.
development of cardiometabolic risk factors [6]. ACEs include potentially traumatic stressors within the household, including abuse, neglect, or witnessed domestic violence [65]. Almost 2/3 of surveyed American adults have experienced an ACE [65]. Childhood adversity is an even broader term that also encompasses stressors outside of the home. When the normal mechanisms to mediate childhood adversity are thwarted, consequent overactivity of the stress response results in disruptions to the physiology of the rapidly developing brain and body known now as toxic stress. Toxic stress is associated with the development of mental health conditions [66, 67] as well as behaviors as a response to trauma that can be incorrectly identified as symptoms of ADHD, depression, aggression, or other mental health conditions [68]. In fact, toxic stress can cause disruptions in brain architecture and function, immune and endocrine systems, and at the epigenome [14, 69•]. Those impacted by early adversity thus experience challenges to emotional and psychological functioning and are in a state of persistent inflammation even when controlling for body mass index (BMI) and smoking [70•]. Susceptibility to cardiovascular disease likely is due to mental health and behavioral factors as well as direct sympathetic, inflammatory, and neuroendocrine effects [71]. And importantly, epigenetic changes can result in lifelong and even transgenerational inheritance of cardiometabolic risk, especially with respect to obesity [72, 73]. For these reasons, children that experience toxic stress without proper support are at risk for developing CVD.

Direct Impact on CVDRF

Sympathetic and inflammatory consequences of toxic stress that directly impact cardiovascular risk factors include (1) an increased heart rate suggesting hyperkinetic circulation, likely resulting from the increased sympathetic activity; this is noted in children and adolescents [74] and (2) hypertension which may be related to increased sympathetic activity, and/or obesity. This is not usually seen until later adolescence or young adulthood [75]. (3) Increased circulating levels of endothelin-1 (ET-1) have been noted in rats and youth over age 12 exposed to early life stress. ET-1 is an endothelium-derived peptide which is a potent vasoconstrictor. Elevated levels are associated with elevated blood pressure, decreased cardiac output, and arterial stiffness [76].

Indirect Impact on CVDRF

Indirect effects on cardiovascular health from toxic stress include insulin resistance, T2D, accelerated aging, and obesity including increased body mass index and increased waist circumference [69•, 71, 74, 77]. Children exposed to ACEs were found to have increased levels of soluble urokinase plasminogen activator receptor (sLuPAR), a new biomarker of chronic inflammation [70•]. Elevated baseline sLuPAR level was associated with an increased risk of CVD and T2D [78]. The gut microbiome is also sensitive to the systemic inflammation, and disruptions of microbial colonization of mucosal tissues are also being investigated as a pathway for cardiovascular and mental health consequences from early adversity [79]. Furthermore, symptoms from emotional dysregulation are sometimes diagnosed as symptoms due to a mental health condition [10, 68]. These children can be prescribed psychiatric medications including SGA’s even though response to treatment in the setting of toxic stress may vary from the response to treatment absent toxic stress [10–13, 80].

Toxic Stress and Health Risk Behaviors

Psychological consequences of early adverse experiences (impulsivity, compulsivity, limited executive function) and efforts to reduce stress can result in adoption of health risk behaviors (smoking, substance misuse, physical inactivity, overeating) or self-harming behaviors which further jeopardize both mental and physical health [79, 81, 82]. Early adversity can alter stress reactivity and responsivity leading to difficulty with emotional regulation and a focus on present challenges rather than long-term outcomes. This can further limit the ability to adopt healthier lifestyles or maintain medication adherence [71, 83, 84].

Social Support

Furthermore, a dose–response relationship has been found between social support and CVD [8]. Meta-analytic results suggest a relationship between structural social support or lack thereof (i.e., social isolation, social networks, and social integration) and CVD [85]. Impacts on social functioning and lack of social support are often features of mental health conditions. Depression, for instance, is associated with less social support among children and adolescents, and social support is thought to confer benefit for affected youth [86]. This is particularly relevant for many children who experience household dysfunction or who are removed from their home and placed into foster care.

Synergy Between Risk Factors

The synergy, bidirectionality, and additive effects of these multiple CVDRF associated with childhood mental illness contribute to the consequent risk of premature CVD (Fig. 1). Childhood adversity in the absence of sufficient emotional support and consequent chronic toxic stress can lead to risky behavior choices, emotional dysregulation, or mental
health conditions which have independent association with CVD. Exposure to toxic stress and mental health conditions in isolation are additionally associated with CVDRFs. Furthermore, psychiatric medications such as SGAs which are prescribed for children and adolescents with mental health conditions and/or the emotional dysregulation associated with trauma are also associated with CVDRFs. These multitudes of factors contributing to CVD make its prevention a challenge for providers.

**Mitigating CVD Risk Factors**

***Use a Trauma-Informed Approach***

With an understanding of how CVDRFs are acquired, healthcare providers can potentially mitigate the impact of mental health disorders on CVD risk by several approaches. All providers should be encouraged to use trauma-informed care (TIC) in their practice to address the significant health risks associated with adversity. Instead of simply asking “what is wrong” instead, consider “what happened” to the patient. TIC requires an awareness of protective factors that can buffer the impact of trauma and adversity. Many studies have shown that the best way to mitigate the consequences of ACEs and improve outcomes is through safe, stable, and nurturing relationships with caregivers [14, 87, 88]. This highlights the important role that health providers can play in educating caregivers, including foster parents, to effectively recognize the health consequences from toxic stress and the importance of support from the caregiver. Thus, providers need to understand the impacts of trauma, collect thorough child and family experience as part of the medical and social history, and refer youth to mental health colleagues if necessary.

***Treat Mental Health Conditions with Optimal Pharmacotherapy***

Mental health conditions need to be properly identified and properly treated to mitigate CVD risk. If pharmacotherapy is used, providers should keep in mind the variable risks associated with CVD when prescribing medications for patients, particularly since medications may be used for an extended period of time. For example, among SGAs that are FDA-approved for the pediatric population, olanzapine has significantly higher risk of metabolic effects than others such as aripiprazole and lurasidone [49, 50, 89–92]. It is also important to recognize that although some psychiatric medications can increase risk of cardiovascular disease, the lifestyle and health benefits

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![Diagram of overlapping pathways of mental health, health behaviors, and environmental factors that increase risk for CVD](image)

**Fig. 1** Overlapping pathways of mental health, health behaviors, and environmental factors that increase risk for CVD

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associated with treating the mental health condition can outweigh the risks of cardiovascular disease from the medication. It is thus important that the treatment plan be completed with the help of a child psychiatrist who can advise on the best pharmacotherapy and reduce polypharmacy.

**Consistent Screening for CVDRF**

Recognizing the challenges of preventing all the factors that can cause CVD risk, it is vital for providers to properly screen for the development of CVDRFs. This is already recommended in all youth less than 18 years of age by the AHA and American Academy of Pediatrics (AAP) [93] and is summarized in Table 2; however, more scrutiny to risk factor screening is warranted in children with mental health conditions. There are additional guidelines for providers prescribing SGAs for adults or children due to potential metabolic syndrome [53]. This includes an understanding of the patient’s family history and a baseline screening of BMI, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile. Despite these guidelines, many children treated with SGAs are not properly assessed or monitored for metabolic and cardiac risk factors [52, 57, 94, 95]. Providers must be aware of these guidelines to ensure early interventions to mitigate risk exposure. Cardiometabolic effects need to be tracked and followed through the length of the treatment and assessed at regular intervals. More important than screening are early treatment interventions; however, options are limited and often challenging because of underlying behavioral problems and/or the context of the environment the child lives in which may not promote or prioritize healthy lifestyle habits.

**Future Directions**

Mental health conditions in youth and the extent to which they are exacerbated by childhood adversity and toxic stress may be underrecognized as risk factors for premature CVD. This is all the more essential to consider in the context of the ongoing COVID-19 pandemic as negative mental health impacts have been seen with youth in prolonged social isolation and without sufficient caregiver buffering [96–98]. Early intervention in particular is crucial, as mental health comorbidity increases with age [3], and health impacts of mental health conditions may occur early in life [9]. Future research should focus on several areas discussed in the following sections.

**Identifying Biomarkers of Toxic Stress**

Ideally, biomarkers can be used to identify children who are at risk for premature CVD as a consequence of symptoms of childhood adversity or of an undiagnosed mental health condition. Biomarkers of these stressors could allow us to identify these children objectively. Yet, no single biomarker has yet been identified which is consistently useful in the pediatric clinical setting. This is in part because the age of exposure to adversity, the type of adversity, and manner of measurement affect results. Suggested markers include markers of endocrine function such as cortisol [69•]; markers of inflammation and immune function including C-reactive protein, IL-6, natural killer cell response, tumor necrosis factor alpha, or suPAR; markers of autonomic nervous function: respiratory sinus arrhythmia reactivity (a measure of vagal tone); markers of genetic impacts — telomere length [69•, 70•, 99–101]; or markers of genetic susceptibility to stress (multiple) [79]. Additional research needs to be

**Table 2** Screening periodicity and suggested treatment of cardiovascular disease risk factors

| Risk factor or behavior | Measure | Timing of assessment | Abnormal value |
|------------------------|---------|----------------------|---------------|
| Obesity                | Height, weight, and BMI percentile | At each clinical encounter starting at age 2 years | BMI > 85th percentile or crossing 2 centiles |
| Dyslipidemia           | Fasting lipid panel | Selective screening starting at age 2 years | Total cholesterol > 200 mg/dL, LDL-C > 130 mg/dL, triglyceride > 100 (0–9 years), > 130 mg/dL (10–19 years) |
|                        | Nonfasting lipid panel | Universal screening considered for 9- to 11-year-old and 17- to 21-year-old youths | Systolic or diastolic BP > 90th percentile for age, height, and gender |
| Hypertension           | Blood pressure | At least annually ≥ 3 years < 3 years in high-risk infants/toddlers | Fasting blood glucose > 100 mg/dL or A1C > 5.6% |
| Insulin resistance/DM  | Fasting glucose (A1C) | Screen at-risk youth starting at 9–11 years of age | |
| Family history of ASCVD and risk factors | History | Update at each clinical encounter | |
| Physical activity      | History | Each clinical encounter | |
| Tobacco use            | History | Each clinical encounter | |

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conducted to reliably identify levels of these biomarkers in children experiencing toxic stress.

**Optimizing Pharmacotherapy with the Collaboration of Child Psychiatrists**

It can be challenging for providers who are not formally trained as mental health specialists to choose the optimal pharmacotherapy if that is required as part of treatment. Pediatricians have been increasingly likely to identify and treat mental health conditions despite varying degrees of comfort with psychiatric diagnosis and treatment [102, 103]. Reasons include lack of availability of child psychiatrists [104] and distrust or logistical barriers from the family [105]. The development of child psychiatry access programs can be particularly helpful [106–108]. These are programs that allow providers to consult child psychiatrists by telephone and/or in-person clinical consultations regarding medication choices, identification of community resources, or diagnostic specificity [109]. This is a structural solution to the limited number of child psychiatrists. Implementation studies are needed to understand the best ways to adapt these access program models to unique settings, and better describe patient outcomes [110].

**Pharmacotherapy to Mitigate Risks**

Truncal obesity, insulin resistance (characterized by an elevated fasting glucose level and often accompanied by acanthosis nigricans), dyslipidemia (elevated triglycerides, low high-density lipoprotein-cholesterol), and an elevated blood pressure are the major components of metabolic syndrome (MetS) in youth and adults; other problems including sleep disturbances, nonalcoholic fatty liver disease, polycystic ovarian syndrome, and hyperuricemia often cluster with MetS. These many cardiometabolic abnormalities commonly precede the development of T2D and are associated with premature CVD. Because obesity and insulin resistance are prevalent in youth with mental health conditions, early treatment can be helpful to prevent progression to T2D. There is no doubt that dietary modification and increased physical activity constitute the first step and most common treatment, but these changes are often difficult to implement in youth (or their parents). Providers should consider referring children to a pediatric dietician as soon as MetS components are present, or as a preventative measure in children at risk of developing MetS components. To date, the only FDA-approved drugs for weight loss in the pediatric population are orlistat (≥16 years) and phentermine (≥16 years). Topiramate and zonisamide have been suggested but are not approved as adjunctive medications in children with psychiatric conditions and SGA-induced weight gain [111].

Although no drug has been approved to reduce insulin resistance in youth, metformin is often used. Although it is a glucose-lowering drug for T2D in children ≥10 years, it can be used without concern for symptomatic hyperglycemia. It has been studied in obese, insulin-resistant youth with some success [112], and, to a greater extent, significantly reduces the risk of developing T2D in adults [113]. Among the potentially most promising pharmacologic approaches for obesity and T2D is the use of a glucagon-like peptide-1 (GLP-1) analogue. This class of drugs is FDA-approved for weight loss and T2D in adults (lariuglutide and semaglutide) as well as T2D in children ≥10 years (only lariuglutide). Mechanistically, endogenous GLP-1 levels are increased to oppose weight gain. A large pediatric study recently found that GLP-1 is substantially higher in overweight/obese youth and levels also positively correlate with cardiometabolic factors [114]. This may prove to be a robust biomarker to identify high-risk youth. Mechanistically, there is also a potential link with toxic stress via an IL-6-induced GLP-1 secretion and its action at area of the brain involved with stress response and emotion regulation resulting in improved and psychological well-being [115].

In conclusion, the current evidence suggests that exposure to toxic stress, and mental health conditions in isolation, and the pharmacotherapies used in treatment increase the risk of cardiometabolic diseases in childhood through complex pathways that can also increase CVD risk over the lifespan. Important knowledge gaps exist with respect to the identification of toxic stress and potential pharmacological approaches to ameliorate this risk early in life before risk factors are entrenched with the inexorable progression contributing to premature CVD.

**Compliance with Ethical Standards**

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The other authors declare that they have no conflict of interest.
Human and Animal Rights and Informed Consent. This article does not contain any studies with human or animal subjects performed by any of the authors.

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