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

Lulu Xu[1] · Martha Zimmermann[1] · Heather Forkey[2] · Jessica Griffin[1,2] · Caitlin Wilds[1,3] · Wynne S. Morgan[1] · Nancy Byatt[1] · Catherine J. McNeal[4]

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.

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

---

This article is part of the Topical Collection on *Children/Adolescents/Young Adults and Atherosclerosis*

✉ Catherine J. McNeal
catherine.mcneal@bswhealth.org

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

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

3 Boston Child Study Center, Boston, MA 02116, USA

4 Division of Cardiology, Department of Internal Medicine, Baylor Scott & White Health, Temple, TX 76508, USA

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 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 cortexes, 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, temperamental, 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 hipppocampal 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

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) **Methylphenidate** (Concerta, Daytrana, Metadate, Ritalin), **Dexmethylphenidate** (Focalin)	Tachycardia, hypertension, arrhythmia, sudden death
Norepinephrine transporter inhibitor	**Atomoxetine** (Strattera) **Viloxazine** (Quelbree)	Tachycardia, hypertension, arrhythmia, sudden death
Alpha agonist	**Guanfacine** (Tenex, Intuniv) **Clonidine** (Kapvay)	Bradycardia, hypotension, syncope
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 medications (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** (Latuda), **Aripiprazole** (Abilify)	Weight gain, type 2 diabetes mellitus, dyslipidemia, hypertension
Mood stabilizers		
Mood stabilizers	**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	**Buspirone** (BuSpar)	Minimal cardiovascular effects

*Risk of QT prolongation.

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

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 (suPAR), a new biomarker of chronic inflammation [70•]. Elevated baseline suPAR 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
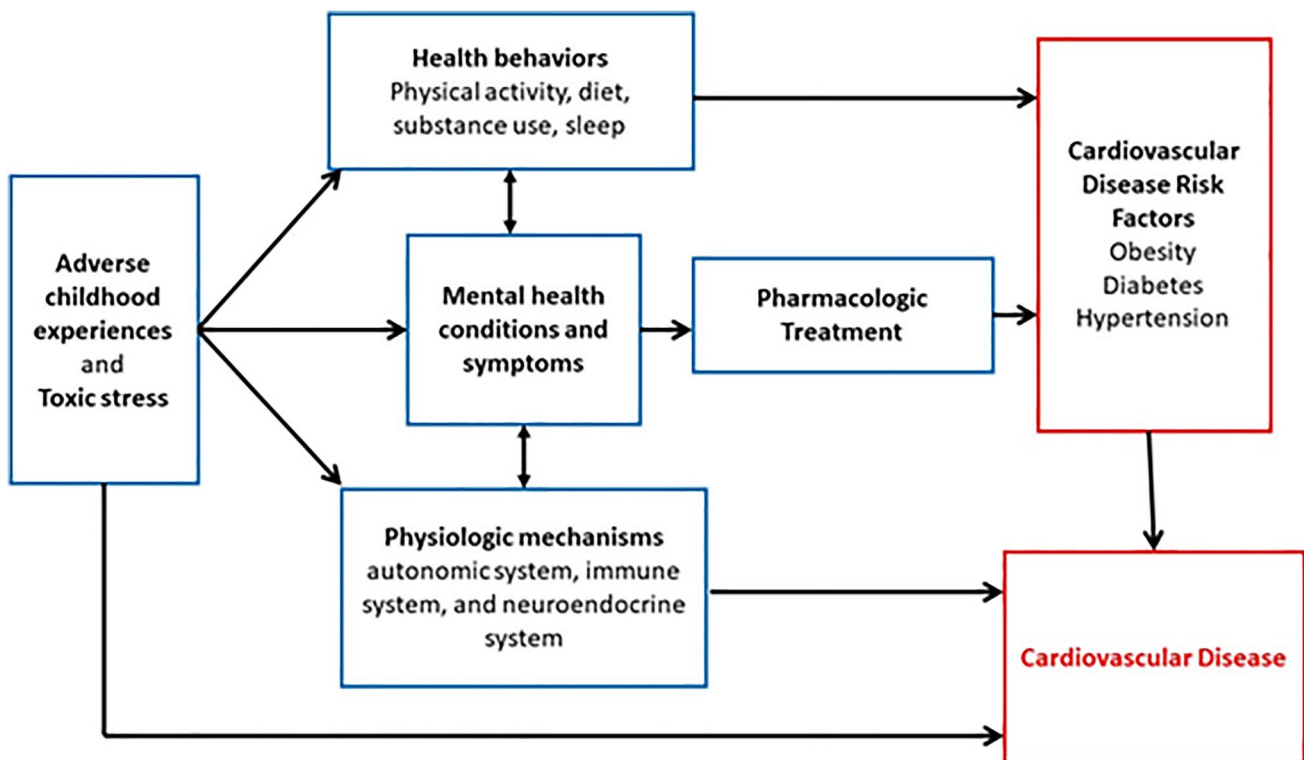

Fig. 1 Overlapping pathways of mental health, health behaviors, and environmental factors that increase risk for CVD

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 paharmacotherapy 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 Nonfasting lipid panel	Selective screening starting at age 2 years Universal screening considered for 9- to 11-year-old and 17- to 21-year-old youths	Total cholesterol > 200 mg/dL, LDL-C > 130 mg/dL triglyceride > 100 (0–9 years), > 130 mg/dL (10–19 years)
Hypertension	Blood pressure	At least annually ≥ 3 years < 3 years in high-risk infants/toddlers	Systolic or diastolic BP > 90th percentile for age, height, and gender
Insulin resistance/DM	Fasting glucose (A1C)	Screen at-risk youth starting at 9–11 years of age	Fasting blood glucose > 100 mg/dL or A1C > 5.6%
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	

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 ($\geq$ 16 years) and phentermine ($\geq$ 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 $\geq$ 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 (lariglutide and semaglutide) as well as T2D in children $\geq$ 10 years (only lariglutide). 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-inducd 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

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.

References

Papers of particular interest, published recently, have been highlighted as: ● Of importance

1. Merikangas KR, Nakamura EF, Kessler RC. Epidemiology of mental disorders in children and adolescents. Dialogues Clin Neurosci. 2009;11(1):7.

2. Association AP. *Diagnostic and statistical manual of mental disorders (DSM-5®).* American Psychiatric Pub; 2013.

3. Merikangas KR, He J-P, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the national comorbidity survey replication–adolescent supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49(10):980–9.

4. Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2015;132(10):965–86.

5.● Goldstein BI, Korczak DJ. Links between child and adolescent psychiatric disorders and cardiovascular risk. Can J Cardiol. 2020;36(9):1394–1405. https://doi.org/10.1016/j.cjca.2020.06.023. **This is a narrative review that examined the connections between several psychiatric disorders commonly seen in childhood with ischemic cardiovascular disease and cardiovascular risk factors.**

6. Suglia SF, Koenen KC, Boynton-Jarrett R, et al. Childhood and adolescent adversity and cardiometabolic outcomes: a scientific statement from the American Heart Association. Circulation. 2018;137(5):e15–28.

7. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and cardiovascular disease risk: a review. Curr Cardiol Rep. 2016;18(12):1–8.

8. Rozanski A. Behavioral cardiology: current advances and future directions. J Am Coll Cardiol. 2014;64(1):100–10.

9. Qureshi F, Derks IPM, Jaddoe VVW, et al. Mental health in early childhood and changes in cardiometabolic dysregulation by preadolescence. Psychosom Med. 2021;83(3):256–64.

10. Gur RE, Moore TM, Rosen AFG, et al. Burden of environmental adversity associated with psychopathology, maturation, and brain behavior parameters in youths. JAMA Psychiat. 2019;76(9):966–75.

11. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10(6):434–45.

12. Flaherty EG, Thompson R, Litrownik AJ, et al. Effect of early childhood adversity on child health. Arch Pediatr Adolesc Med. 2006;160(12):1232–8.

13. Franke HA. Toxic stress: effects, prevention and treatment. Children (Basel). 2014;1(3):390–402.

14. Garner AS, Shonkoff JP. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics. 2012;129(1):e224-231.

15. Tegethoff M, Stalujanis E, Belardi A, Meinlschmidt G. Chronology of onset of mental disorders and physical diseases in mental-physical comorbidity—a national representative survey of adolescents. PLoS ONE. 2016;11(10):e0165196–e0165196.

16. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010;56(1):38–46.

17. Kraynak TE, Marsland AL, Gianaros PJ. Neural mechanisms linking emotion with cardiovascular disease. Curr Cardiol Rep. 2018;20(12):1–10.

18. Rasul F, Stansfeld SA, Smith GD, Shlomo BY, Gallacher J. Psychological distress, physical illness and risk of myocardial infarction in the Caerphilly study. Psychol Med. 2007;37(9):1305–13.

19. DeSteno D, Gross JJ, Kubzansky L. Affective science and health: the importance of emotion and emotion regulation. Health Psychol. 2013;32(5):474.

20. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. J Am Coll Cardiol. 2009;53(11):936–46.

21. De Ferranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. Circulation. 2019;139(13):e603–34.

22. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141(2):122–31.

23. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Part B):2960–2984.

24. Cairns KE, Yap MBH, Pilkington PD, Jorm AF. Risk and protective factors for depression that adolescents can modify: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2014;169:61–75.

25. Garey L, Olofsson H, Garza T, Rogers AH, Kauffman BY, Zvolensky MJ. Directional effects of anxiety and depressive disorders with substance use: a review of recent prospective research. Current Addiction Reports. 2020:1–12.

26. Ahn S, Fedewa AL. A meta-analysis of the relationship between children's physical activity and mental health.

27. Jewell L, Abtan R, Scavone A, Timmins V, Swampillai B, Goldstein BI. Preliminary evidence of disparities in physical activity among adolescents with bipolar disorder. Ment Health Phys Act. 2015;8:62–7.

28. Hosker DK, Elkins RM, Potter MP. Promoting mental health and wellness in youth through physical activity, nutrition, and sleep. Child Adolesc Psychiatr Clin. 2019;28(2):171–93.

29. Dencker M, Thorsson O, Karlsson MK, et al. Daily physical activity related to body fat in children aged 8–11 years. J Pediatr. 2006;149(1):38–42.

30. Tanha T, Wollmer P, Thorsson O, et al. Lack of physical activity in young children is related to higher composite risk factor score for cardiovascular disease. Acta Paediatr. 2011;100(5):717–21.

31. Dencker M, Andersen LB. Health-related aspects of objectively measured daily physical activity in children. Clin Physiol Funct Imaging. 2008;28(3):133–44.

32. O'neil A, Quirk SE, Housden S, et al. Relationship between diet and mental health in children and adolescents: a systematic review. Am J Public Health. 2014;104(10):e31–42.

33. Jacka FN, Cherbuin N, Anstey KJ, Sachdev P, Butterworth P. Western diet is associated with a smaller hippocampus: a longitudinal investigation. BMC Med. 2015;13(1):1–8.

34. Schulte MT, Hser Y-I. Substance use and associated health conditions throughout the lifespan. Public Health Rev. 2013;35(2):3.

35. Griesler PC, Hu MC, Schaffran C, Kandel DB. Comorbid psychiatric disorders and nicotine dependence in adolescence. Addiction. 2011;106(5):1010–20.

36. Swendsen J, Conway KP, Degenhardt L, et al. Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey. Addiction. 2010;105(6):1117–28.

37. Goldstein BI, Birmaher B, Axelson DA, et al. Significance of cigarette smoking among youths with bipolar disorder. Am J Addict. 2008;17(5):364–71.

38. Mermelstein RJ. Adapting to a changing tobacco landscape: research implications for understanding and reducing youth tobacco use. Am J Prev Med. 2014;47(2):S87–9.

39. Blank M, Zhang J, Lamers F, Taylor AD, Hickie IB, Merikangas KR. Health correlates of insomnia symptoms and comorbid mental disorders in a nationally representative sample of US adolescents. Sleep. 2015;38(2):197–204.

40. Gallagher J, Parenti G, Doyle F. Psychological aspects of cardiac care and rehabilitation: time to wake up to sleep? Curr Cardiol Rep. 2015;17(12):1–14.

41. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32(12):1484–92.

42. Spiegel K, Tasali E, Penev P, Cauter EV. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004;141(11):846–50.

43. Spiegel K, Knutson K, Leproult R, Tasali E, Cauter EV. Sleep loss: a novel risk factor for insulin resistance and type 2 diabetes. J Appl Physiol. 2005;99(5):2008–19.

44. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. Eur J Prev Cardiol. 2014;21(1):57–64.

45. Sun JW, Hernández-Díaz S, Haneuse S, et al. Association of selective serotonin reuptake inhibitors with the risk of type 2 diabetes in children and adolescents. JAMA Psychiat. 2021;78(1):91–100.

46. Yekehtaz H, Farokhnia M, Akhondzadeh S. Cardiovascular considerations in antidepressant therapy: an evidence-based review. J Tehran Heart Cent. 2013;8(4):169–76.

47. Cortese S, Castellanos FX. The relationship between ADHD and obesity: implications for therapy. Expert Rev Neurother. 2014;14(5):473–9.

48. Cortese S. Pharmacologic treatment of attention deficit-hyperactivity disorder. N Engl J Med. 2020;383(11):1050–6.

49. Bobes J, Rejas J, Garcia-Garcia M, et al. Weight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol: results of the EIRE study. Schizophr Res. 2003;62(1–2):77–88.

50. Leslie DL, Rosenheck RA. Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. A J Psychiatry. 2004;161(9):1709–11.

51. Hammoudeh S, Al Lawati H, Ghuloum S, et al. Risk factors of metabolic syndrome among patients receiving antipsychotics: a retrospective study. Community Ment Health J. 2020;56(4):760–70.

52. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8(2):114–26.

53. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. 2004;27(2):596–601.

54. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med. 2007;357(23):2329–37.

55. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. Diabetes. 2002;51(1):204–9.

56. Melamed OC, LaChance LR, O'Neill BG, Rodak T, Taylor VH. Interventions to improve metabolic risk screening among children and adolescents on antipsychotic medication: a systematic review. J Child Adolesc Psychopharmacol. 2021;31(1):63–72.

57. Pringsheim T, Panagiotopoulos C, Davidson J, Ho J. Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth. Paediatr Child Health. 2011;16(9):581–9.

58. Nicol GE, Ivanov I. Getting to precision psychopharmacology in child psychiatry: the value of adverse treatment effects. J Child Adolesc Psychopharmacol. 2021;31(1):1–3.

59. Roerig JL, Steffen KJ, Mitchell JE. Atypical antipsychotic-induced weight gain: insights into mechanisms of action. CNS Drugs. 2011;25(12):1035–59.

60. McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. Arch Pediatr Adolesc Med. 2008;162(10):929–35.

61. Correll CU. Multiple antipsychotic use associated with metabolic and cardiovascular adverse events in children and adolescents. Evid Based Ment Health. 2009;12(3):93.

62. Lee ES, Vidal C, Findling RL. A focused review on the treatment of pediatric patients with atypical antipsychotics. J Child Adolesc Psychopharmacol. 2018;28(9):582–605.

63. Rodday AM, Parsons SK, Correll CU, et al. Child and adolescent psychiatrists' attitudes and practices prescribing second generation antipsychotics. J Child Adolesc Psychopharmacol. 2014;24(2):90–3.

64. Crystal S, Olfson M, Huang C, Pincus H, Gerhard T. Broadened use of atypical antipsychotics: safety, effectiveness, and policy challenges. Health Aff (Millwood). 2009;28(5):w770-781.

65. Centers for Disease Control and Prevention. Violence prevention: fast facts. https://www.cdc.gov/violenceprevention/childabuseandneglect/aces/fastfact.html. Published 2020. Accessed2020.

66. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. Am J Prev Med. 1998;14(4):245–58. In.

67. Mwachofi A, Imai S, Bell RA. Adverse childhood experiences and mental health in adulthood: evidence from North Carolina. J Affect Disord. 2020;267:251–7.

68. Siegfried CB, Blackshear K. *Is it ADHD or child traumatic stress? A guide for Clinicians.* Los Angeles, CA & Durham, NC: National Child Traumatic Stress Network;2016.

69.● Oh DL, Jerman P, Silvério Marques S, et al. Systematic review of pediatric health outcomes associated with childhood adversity. *BMC pediatrics.* 2018;18(1):83. **A thorough summary of the many ways that childhood adversity causes changes to physiologic responses that can impact cardiovascular risk factors.**

70.● Rasmussen LJH, Moffitt TE, Arseneault L, et al. Association of adverse experiences and exposure to violence in childhood and adolescence with inflammatory burden in young people. *JAMA pediatrics.* 2020;174(1):38–47. **This paper examines a new biomarker of chronic inflammation (suPAR) that may improve measurement of stress-related inflammation due to childhood adversity.**

71. Su S, Jimenez MP, Roberts CTF, Loucks EB. The role of adverse childhood experiences in cardiovascular disease risk: a review with emphasis on plausible mechanisms. Curr Cardiol Rep. 2015;17(10):88–88.

72. King SE, Skinner MK. Epigenetic transgenerational inheritance of obesity susceptibility. Trends Endocrinol Metab. 2020;31(7):478–94.

73. Hao G, Youssef NA, Davis CL, Su S. The role of DNA methylation in the association between childhood adversity and cardiometabolic disease. Int J Cardiol. 2018;255:168–74.

74. Pretty C, O'Leary DD, Cairney J, Wade TJ. Adverse childhood experiences and the cardiovascular health of children: a cross-sectional study. BMC Pediatr. 2013;13:208.

75. Su S, Wang X, Pollock JS, et al. Adverse childhood experiences and blood pressure trajectories from childhood to young adulthood: the Georgia stress and Heart study. Circulation. 2015;131(19):1674–81.

76. Su S, Wang X, Kapuku GK, et al. Adverse childhood experiences are associated with detrimental hemodynamics and elevated circulating endothelin-1 in adolescents and young adults. *Hypertension (Dallas, Tex : 1979)*. 2014;64(1):201–207.

77. Belsky J. Early-life adversity accelerates child and adolescent development. Curr Dir Psychol Sci. 2019;28(3):241–6.

78. Eugen-Olsen J, Andersen O, Linneberg A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. J Intern Med. 2010;268(3):296–308.

79. Boyce WT, Levitt P, Martinez FD, McEwen BS, Shonkoff JP. Genes, environments, and time: the biology of adversity and resilience. *Pediatrics*. 2021;147(2):e20201651.

80. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. A J Psychiatry. 2013;170(10):1114–33.

81. Cameron JL, Eagleson KL, Fox NA, Hensch TK, Levitt P. Social origins of developmental risk for mental and physical illness. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2017;37(45):10783–91.

82. Sonu S, Post S, Feinglass J. Adverse childhood experiences and the onset of chronic disease in young adulthood. Prev Med. 2019;123:163–70.

83. Danese A, Moffitt TE, Harrington H, et al. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med. 2009;163(12):1135–43.

84. McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. Ann N Y Acad Sci. 2010;1186:190–222.

85. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS medicine*. 2010;7(7):e1000316.

86. Rueger SY, Malecki CK, Pyun Y, Aycock C, Coyle S. A meta-analytic review of the association between perceived social support and depression in childhood and adolescence. Psychol Bull. 2016;142(10):1017.

87. Fisher PA, Gunnar MR, Dozier M, Bruce J, Pears KC. Effects of therapeutic interventions for foster children on behavioral problems, caregiver attachment, and stress regulatory neural systems. Ann N Y Acad Sci. 2006;1094:215–25.

88. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245–258.

89. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. A J Psychiatry. 1999;156(11):1686–96.

90. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302(16):1765–73.

91. Kryzhanovskaya LA, Robertson-Plouch CK, Xu W, Carlson JL, Merida KM, Dittmann RW. The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder: a pooled analysis of 4 clinical trials. J Clin Psychiatry. 2009;70(2):247–58.

92. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020;7(1):64–77.

93. Expert panel on integrated guidelines for cardiovascular H, risk reduction in C, adolescents. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(Supplement 5):S213.

94. Morrato EH, Druss B, Hartung DM, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. Arch Gen Psychiatry. 2010;67(1):17–24.

95. Morrato EH, Nicol GE, Maahs D, et al. Metabolic screening in children receiving antipsychotic drug treatment. Arch Pediatr Adolesc Med. 2010;164(4):344–51.

96. Creswell C, Shum A, Pearcey S, Skripkauskaite S, Patalay P, Waite P. Young people's mental health during the COVID-19 pandemic. The Lancet Child & Adolescent Health. 2021;5(8):535–7.

97. de Figueiredo CS, Sandre PC, Portugal LCL, et al. COVID-19 pandemic impact on children and adolescents' mental health: biological, environmental, and social factors. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2021;106:110171.

98. Loades ME, Chatburn E, Higson-Sweeney N, et al. Rapid systematic review: the impact of social isolation and loneliness on the mental health of children and adolescents in the context of COVID-19. J Am Acad Child Adolesc Psychiatry. 2020;59(11):1218-1239.e1213.

99. Hanssen LM, Schutte NS, Malouff JM, Epel ES. The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis. Health Psychol Res. 2017;5(1):6378.

100. Le-Niculescu H, Roseberry K, Levey DF, et al. Towards precision medicine for stress disorders: diagnostic biomarkers and targeted drugs. *Molecular psychiatry*. 2019.

101. Ridout KK, Khan M, Ridout SJ. Adverse childhood experiences run deep: toxic early life stress, telomeres, and mitochondrial DNA copy number, the biological markers of cumulative stress. *Bioessays*. 2018;40(9):e1800077.

102. Anderson LE, Chen ML, Perrin JM, Van Cleave J. Outpatient visits and medication prescribing for US children with mental health conditions. Pediatrics. 2015;136(5):e1178-1185.

103. Rushton J, Bruckman D, Kelleher K. Primary care referral of children with psychosocial problems. Arch Pediatr Adolesc Med. 2002;156(6):592–8.

104. Thomas CR, Holzer CE 3rd. The continuing shortage of child and adolescent psychiatrists. J Am Acad Child Adolesc Psychiatry. 2006;45(9):1023–31.

105. Hacker K, Arsenault L, Franco I, et al. Referral and follow-up after mental health screening in commercially insured adolescents. J Adolesc Health. 2014;55(1):17–23.

106. Van Cleave J, Holifield C, Perrin JM. Primary care providers' use of a child psychiatry telephone support program. Acad Pediatr. 2018;18(3):266–72.

107. Cama S, Knee A, Sarvet B. Impact of child psychiatry access programs on mental health care in pediatric primary care: measuring the parent experience. Psychiatr Serv. 2020;71(1):43–8.

108. Sullivan K, George P, Horowitz K. Addressing national workforce shortages by funding child psychiatry access programs. *Pediatrics*. 2021;147(1).

109. Sarvet B, Gold J, Bostic JQ, et al. Improving access to mental health care for children: the Massachusetts Child Psychiatry Access Project. Pediatrics. 2010;126(6):1191–200.

110. Bettencourt AF, Plesko CM. A systematic review of the methods used to evaluate child psychiatry access programs. Acad Pediatr. 2020;20(8):1071–82.

111. Shapiro M, Reid A, Olsen B, Taasan M, McNamara J, Nguyen M. Topiramate, zonisamide and weight loss in children and adolescents prescribed psychiatric medications: a medical record review. Int J Psychiatry Med. 2016;51(1):56–68.

112. Masarwa R, Brunetti VC, Aloe S, Henderson M, Platt RW, Filion KB. Efficacy and safety of metformin for obesity: a systematic review. *Pediatrics.* 2021;147(3).

113. Tagi VM, Samvelyan S, Chiarelli F. Treatment of metabolic syndrome in children. Horm Res Paediatr. 2020;93(4):215–25.

114. Stinson SE, Jonsson AE, Lund MAV, et al. Fasting plasma GLP-1 is associated with overweight/obesity and cardiometabolic risk factors in children and adolescents. J Clin Endocrinol Metab. 2021;106(6):1718–27.

115. Guerrero-Hreins E, Goldstone AP, Brown RM, Sumithran P. The therapeutic potential of GLP-1 analogues for stress-related eating and role of GLP-1 in stress, emotion and mood: a review. *Prog Neuropsychopharmacol Bol Psychiatry.* 2021;110:110303.