

# Depression in Youth: Investigating the Impact of Obesity, Inflammation and Sleep: A Narrative Review

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## Abstract

**Background:** Depressive disorders in children and adolescents have been associated with lifelong health implications and risk factors. Concurrently, rates of depression, overweight and obesity in pediatrics have markedly worsened since the COVID-19 pandemic. Sleep and inflammation have also been described as altered in depressive and overweight or obese status, suggesting an intertwined relationship. This clinical practice review examines these intertwined roles while exploring health care disparities, holistic care, and interdisciplinary approaches.

**Methods:** The methodology of this review followed a narrative format by examining and summarizing trends related to pediatric depression with existing literature and expert synthesis.

**Results:** Selected articles provided a broad overview of key concepts contributing to a deeper understanding of research topics. Relevant clinical insights into the complex and interwoven concepts of pediatric depression, obesity, and inflammation answered the research question by informing clinical practice with a culturally sensitive, holistic, and integrated health care approach.

**Conclusions:** Significant findings underscored the need for healthcare providers to understand the complex relationships between depression, obesity, inflammation, and sleep, to avoid healthcare disparities and risk for negative lifelong consequences. This article is intended for all the disciplines involved in the care of pediatric populations.

## Introduction

Unipolar depressive disorders have been on the rise and have been significantly impacted by COVID-19. Historically underrecognized, underserved, and underfunded, mental health care challenges were exacerbated by the deleterious effects of the COVID-19 pandemic, considerably worsening the mental health crisis across the nation. Data from previous research suggest that even before the COVID-19 pandemic, rates of pediatric depression were on the rise, with differences noted between genders, ethnicities, and races, and with data suggesting increasing prevalence during childhood<sup>1</sup>. Mental illness is associated with significant impairments in function for individuals and can cause devastating morbidity and mortality outcomes for the individual, family, and society.

Concurrently, and for decades, the American Academy of Pediatrics (AAP) has recognized increasing rates of overweight and obese status among children and adolescents, which are associated with multifactorial and lifelong consequences. The relation between pediatric depression and obesity is well documented, identifying

a need to consider the international factors of these disorders. However, there is limited data to support clinical practice for health care providers working with pediatric populations. Further, in a critical analysis of these factors, there is a need to understand inflammation and its impact on biological response to stress, as there are identified clinical significance and implications for both depression and obesity in pediatric populations.

Sleep is also understood in terms of a critical factor of well-being in pediatric populations, and alterations in sleep are associated with both depression and obesity and are also known to contribute towards both of these disorders. Therefore, there is a critical need for pediatric health care providers to understand the integrated nature of these disorders and consider this knowledge in the assessment, diagnosis, and treatment of pediatric populations.

As treatment of mental health disorders is universally understood and identified as undertreated and underserved, there is also a need to consider the above complex and interrelated disorders in terms of bridging gaps in care and addressing health care disparities. This approach calls for a collaborative, holistic, integrative, interdisciplinary approach and presents the opportunity to review critical aspects of pediatric care for depressive disorders to improve the delivery of care and define the infrastructure required to achieve this goal.

## Methods

The methodology of this review follows a narrative format by examining and summarizing prevalence data related to depression trends among children and adolescents, with synthesis and critical evaluation of existing literature on the complex interrelationships of the confounding impact of overweight and obesity status, systemic inflammation, and sleep. A narrative review was conducted to provide insights on advancing knowledge for the identified topics, drawing on the authors' understanding of the topics as under-researched in the context of the collective, interrelated, and multidirectional factors. Driven by the authors' understanding of the need to promote further development of this knowledge, and clinical practice in this field of study, the authors' selection supported the aim of this review to provide a unique, insightful overview of the topic with wide exploration of data with critical clinical expert analysis and synthesis of information for clinical practice recommendations and considerations of future directions in research. Studies were identified by searching up to currently published peer-reviewed literature.

The authors conducted a structured literature search across multiple databases to identify relevant articles, including PubMed, CINAHL, Cochrane Library, Medline Complete, and Academic Search Premier. Terms used for

the literature search were "pediatric depression," "obesity in youth," "inflammation in depression," "sleep in youth," "pediatric health care disparities," "interdisciplinary treatment planning in youth," "pediatric health care disparities in depression," and "holistic care in pediatric depression." Inclusion criteria for the search were peer-reviewed articles published in academic journals, in the English language, and in pediatrics, including children and adolescents. Exclusion criteria included recognized redundancies, insufficient dominant themes or topic representation, and limited clinical relevance.

The review aims to examine the intertwined roles of obesity, inflammation, sleep, and depression while exploring critical factors of health care disparities, holistic care, and interdisciplinary treatment planning and approaches. An understanding of culturally sensitive descriptors and thoughts about depression or depressive symptomatology may enhance diagnosis and also inform culturally sensitive, holistic care for at-risk populations. While considering the whole individual in assessment, one of the goals of this review is to allow the clinician to consider some underlying biological underpinnings that may be contributing to depression, to enable these factors to be addressed in a whole-person care plan.

Therefore, a rigorous review and interpretation of the data and existing literature was targeted to provide a rich and meaningful examination of this topic. The synthesis of complex issues can provide a wider understanding of interrelated complexities required to provide comprehensive care. This narrative review was built on the following research question: Will exploration of the complex relationships between depression, obesity, inflammation, and sleep with critical expert analysis and knowledge lead to the identification of an improved clinical approach for providers and define essential areas for further research and recommendations for improved clinical practice? The chosen research questions align with the existing literature review approach by integrating evidence-based data and expert clinical experience and knowledge.

## Results

Following a structured literature search using inclusion and exclusion criteria, sixty-one articles were selected, based on the author's in depth expert judgement. The authors analyzed selected articles and found them sufficient based on dominant themes within the identification of key studies to shed light on potential clinical implications contributing to a deeper understanding of the topic. Selection of the articles was further refined through content analysis to enhance the trustworthiness of the study. These articles were examined to provide a broad overview and synthesis of valuable information applicable to pediatric depression and review topics.

The authors' unique understanding of a patient-centered lived experience of the review topics, gained through decades of clinical practice in pediatrics and mental health care, has shaped the authors' interpretations and analysis of selected articles. While this review was not based on an inclusive review of all literature on this topic, the study was conducted based on a need to identify relevant clinical data to inform clinical experts in the field and advance new ideas related to individualized, culturally sensitive, holistic pediatric care with consideration of a team-based interdisciplinary and integrative health care approach.

## Depression Trends Among Children and Adolescents

Depressive disorders are on the rise in children and adolescents and have been further significantly impacted by COVID-19, which may impart lifelong consequences. Depression not only has immediate impacts on sense of self and quality of life, but also on family structure and interpersonal relationships, academic achievement, and, most importantly, on rates of suicide, currently the second most frequent cause of death in children and youth. Long-term, depression in childhood increases the risk of subsequent depressive episodes and may have long-term consequences on the ultimate non-achievement of educational and career goals.

Before the pandemic, Birmaher and Brent reported an increase from 2% in pediatric patients and 8% in adolescents to 8% in children 2 to 17 years and 11% in adolescents<sup>2</sup>. Daly reported an overall 7.7% increase in the presence of a Major Depressive Episode in adolescents aged 12 to 17 years from 2009 to 2019: 8.1% in 2009 to 15.8% in 2019<sup>3</sup>. In this study, using 11 years of the National Survey on Drug Use and Health (N = 167,783), the authors found not only this significant increase in Major Depression but also noted a significant gender difference, with a female increase from 11.4% to 23.4% over this same period<sup>3</sup>. The most significant increases were within the 12–14-year-old subgroup, females, and those identifying as Hispanic<sup>3</sup>. The literature has found as well that pediatric depression is associated with adult depressive disorders, and more recently, a meta-analysis not only reconfirmed this association but also a linkage with adult anxiety disorders<sup>4,5</sup>. Moreover, COVID-19 has demonstrably increased the rates of pediatric depressive disorders significantly to rates reported as high as 25.2% in pooled prevalence data<sup>6</sup>.

Previous studies have demonstrated links between TV and screen time and BMI, as well as with body composition and insulin resistance. One study demonstrated that TV viewing versus physical activity rates were stronger predictors of elevated BMI at six years old than just eating habits alone<sup>7</sup>. Whitaker found a positive association

between TV viewing and childhood obesity<sup>8</sup>. Snitker et al. found that body composition and physical activity are determinants of insulin sensitivity<sup>9</sup>. These examples illustrate the inverse relationship between physical activity and obesity status, with a net positive effect on biological markers of obesity such as insulin resistance, which, in turn, leads to greater adiposity. In conjunction with the effects of body habitus, studies have demonstrated higher rates of affective symptoms with sedentary lifestyles in children. Anton et al. demonstrated that higher reported rates of interpersonal problems and feelings of ineffectiveness on the Children's Depression Inventory (CDI) correlated with sedentary behavior in adolescents aged 11-13 years old<sup>10</sup>. Ybarra et al. found significantly higher self-reports of criteria meeting major depressive disorder or depressive symptomatology that did not meet threshold criteria for major depressive disorders in children and youth aged 10-17 years who used the internet more than 3 hours a day: 34%, significantly higher than pre-pandemic rates of children and youth with depression<sup>11</sup>. Limiting screen time, promotion of physical activity, as well as the promotion of shared family time all can benefit both mood and help to decrease obesity status and the markers of inflammation.

Both obesity and depression may exacerbate sedentary behavior through fatigue, lack of physical activity, increased food consumption, and lack of motivation, thus perpetuating the cycle and promoting self-isolation and negative self-image. A review of 15 randomized controlled trials found that physical exercise significantly reduced adolescent depression with a moderate effect size in both adolescents with depression and with only depressive symptoms<sup>12</sup>. Moderate aerobic exercise of 30 minutes, 4 times a week, showed the best effect on depressive symptoms<sup>12</sup>. Similar findings were reported in a recent meta-analysis of 218 studies demonstrating the benefit of exercise for moderate depression<sup>13</sup>. These data demonstrate the bidirectional relationship between depression and obesity and indicate a need for shared assessment, consideration for addressing directly through education and motivational interviewing, and through continuous monitoring.

## Obesity Trends Among Children and Adolescents

For decades, the American Academy of Pediatrics (AAP) has recognized increasing rates of overweight and obese status among children and adolescents. The AAP estimates that 14.4 million children are affected and recognizes multifactorial and lifelong implications, as well as that there are also communities and populations of at-risk children disproportionately affected<sup>14</sup>. The need for clinical guidelines to help affected individuals has become so great that the AAP published, in February 2023, the first comprehensive clinical practice guidelines for identifying and treating obesity in youth<sup>14</sup>. These guidelines include provider-level and public-level support of policy charges

for prevention strategies; partnering to expand access to evidence-based treatments and the promotion of healthy, active lifestyles; and implementation of formal, provider-level education and training on obesity with its physiological and emotional impact, to incorporate evidence-based management and motivational interviewing<sup>14</sup>. Hu and Staiano, in a longitudinal study of 14,967 children and adolescents aged 2 to 19 years, found the prevalence of obesity increased from 16.9% from 2011 to 2012 to 19.7% from 2017 to 2020, with the greatest increases occurring among boys and children aged 2 to 5 years old<sup>15</sup>. Further, the authors reported significant increased trends for obesity from the 2011 to 2012 to the 2017 to 2020 periods for Mexican American (22.4% to 26.2%) and non-Hispanic Black (20.2% to 24.8%) individuals but not for non-Hispanic White individuals<sup>15</sup>.

During the COVID-19 pandemic, the rates of obesity significantly increased across all age break demographics 2-19 years of age, with rises in BMI noted in clinical settings. Interestingly, across all weight delineations (e.g., underweight, healthy weight, overweight, obese, and morbid obese status), there were noted rises in all measures during and after pandemic lockdown periods, with only relative stability noted in rates of morbid obesity in the 18-20-year-olds<sup>16</sup>. The overall implication of both general trends towards overweight and obesity status, and the sharp rise during pandemic lockdown, is that youth are becoming increasingly unhealthy, likely through multiple mechanisms such as sedentary lifestyles and technology, the effect of prolonged lockdown and isolation, unhealthy food choices, and healthy food scarcity, especially for those in lower socioeconomic strata.

### Proposed Pathophysiological Pathways Between Obesity and Depression

Depression and obesity have shared symptom complexes that may be related to shared pathophysiological mechanisms, such as dysregulated food intake, sedentary behaviors, and sleep problems<sup>17</sup>. Authors have previously found that there are multiple risk factors for obesity, which suggests disparities among populations at risk, such as those with genetic predisposition or lower socioeconomic status, and which may also impact the individual directly with problems with self-esteem, unhealthy physiologic status, and the development of depression<sup>14,17</sup>. One study demonstrated a 2.2 times higher rate of obesity among females with at least one socioeconomic risk factor, including partner violence, maternal depression, maternal substance abuse, food insecurity, housing insecurity, and paternal incarceration<sup>18</sup>. These same factors may also predispose to depression in the same at-risk population, forming a complex potential interaction between depression and overweight or obesity states.

Multiple authors have found associations between obesity status and the development of depression in children and later into adulthood. One meta-analysis of adult studies reported an overall pooled odds ratio of 1.33 for the risk of depression amongst adults with obesity<sup>19</sup>. Sjöberg et al. found that obesity significantly correlated to depression and depressive symptoms, with shaming experiences increasing the odds ratio to 11.3<sup>20</sup>. Studies have identified that adolescent obesity is associated with adult depression, with evidence of a bidirectional relationship as well between obesity and the development of depressive disorders<sup>21</sup>, again suggesting the shared pathophysiological mechanisms. Anderson et al. found that, for females, early childhood depression was associated with higher BMI and higher weight gain than non-depressed females<sup>22</sup>. However, this was not demonstrated in age-matched males<sup>22</sup>. In a prospective study of over 9,000 youth, depressed mood significantly predicted obesity at one-year follow-up, even controlling for baseline BMI, age, race, gender, socioeconomic status, and parental obesity<sup>23</sup>.

Chronic stress, which may be from a combination of physical, psychological, and environmental factors, appears to disrupt homeostasis along metabolic and inflammatory pathways that seem to lead to neuroinflammation and depression<sup>24</sup>. In a study featuring a large cohort of patients in an NIH-funded ECHO program of 50,000 children from 44 states and Puerto Rico, it was found that children born to mothers with high-risk factors of obesity and inflammation had significantly increased odds of their child having behavioral problems independent of the risk of a first-degree relative having a psychiatric disorder<sup>24</sup>. Given these observations, ongoing research has been associated with the shared possible physiological mechanisms, including the derangement or dysfunction of the hypothalamic-pituitary axis, inflammatory markers, and the role of sleep and sleep hemostasis, which are often also affected by chronic stress. Therefore, the link between depression and obesity must also be considered in the context of inflammation and contributing factors.

### Inflammation

#### The Hypothalamic-Pituitary Axis (HPA)

Inflammation is the biological response to stress, which can be both physical, such as that from illnesses and injury, or from environmental stressors, which is meant to heal and protect the body. When this is dysfunctional or in chronic abundance, it can have a deleterious effect on multiple body systems. The hypothalamic pituitary axis is central to the mammalian response to environmental threats and manages metabolic and cardiovascular responses to acute and chronic stress<sup>25</sup>, with cytokines being the messengers to cells to form an immune response. The HPA plays an essential role in the immune response, wherein

proinflammatory cytokines activate the HPA, and HPA dysfunction broadly affects immune function. Cytokines activate the hypothalamus to release corticotropin-releasing hormone (CRH) to the anterior pituitary, releasing adrenocorticotrophic hormone (ACTH) to the adrenal glands. The effect of cortisol, a stress hormone, consequently, affects cardiovascular, liver, metabolic, and immune function. Findings suggest that early life stressors alter HPA function and may have implications for the subsequent development of depressive disorders in at-risk populations. Johnson et al. reported that for toddlers living below the 150% federal poverty level, saliva cortisol levels were higher than those of age-matched controls when there was an insecure attachment to caregivers<sup>25</sup>. Cortisol further induces adiposity, and adipose tissue itself expresses proinflammatory cytokines, which have implications on macrophage function and expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukins, and serum monocyte chemoattractant protein-1 (MCP-1)<sup>26</sup>. Further, it has been found that adipocytes secrete interleukin-6 (IL-6) and TNF- $\alpha$ , and that concentration correlates with the percentage and distribution of fat, as well as that TNF- $\alpha$  and IL-6 influence the amount of the other's secretion<sup>27</sup>. Interleukin-6 (IL-6) has especially been implicated as a potential factor governing depression in multiple studies<sup>26</sup>.

### **The Role of Tumor Necrosis Factor Alpha (TNF- $\alpha$ )**

TNF- $\alpha$  is a multi-functional cytokine that affects physiological and pathophysiologic processes and is created and secreted by macrophages of several cell types, including neurons and supporting glial cells<sup>28</sup>. In this recent review by Uzzan and Azab, the authors remind us that TNF- $\alpha$  directly impacts neuronal function and survival, regulates the production and secretion of neurotransmitters, and increases the permeability of the blood-brain barrier<sup>28</sup>. This alteration of the brain-blood barrier may increase inflammatory mediators in the central nervous system, leading to mood disorders, especially depression. Prolonged exposure to TNF- $\alpha$ , as appears to occur in depression, may contribute to an inadequate response of the HPA axis, resulting in dysregulation of cortisol production and a disruption of the neuroendocrine stress response<sup>29</sup>. A controlled study of adult inpatients with major depressive disorder demonstrated baseline higher levels of TNF- $\alpha$  were observed than in healthy controls, and that after 12 weeks of treatment with antidepressants, there was a strong positive correlation between significant decreases in TNF- $\alpha$  and depressive symptoms, especially in somatic, anxiety, and weight loss metrics<sup>30</sup>. Although biologicals targeting TNF- $\alpha$  exist for various autoimmune conditions such as rheumatoid arthritis and Crohn's disease, meta-analysis has suggested only slight improvement in depressive symptoms with such agents as infliximab and etanercept in patients

with rheumatologic conditions who also presented with depressive symptoms but were not formally diagnosed with a depressive disorder<sup>28</sup>. Given these findings, more research is indicated to better understand the proposed mechanism of action and the potential role in depressive disorders.

### **The Role of Cytokine Interleukin-6 (IL-6)**

Cytokine interleukin-6 (IL-6) has a multiplicity of effects on the body. Mature human IL-6 is a protein consisting of 212 amino acids, encoded from genes at the loci of chromosome 7p15 p2<sup>31</sup>. Mature IL-6 is involved in the production of acute phase proteins in the liver, hematopoiesis, osteoclast activation, proliferation and differentiation of B lymphocytes, and is part of the production of febrile states<sup>31</sup>. IL-6 acts as both a cytokine and myokine in the immune system and is known to have effects in diabetes mellitus, atherosclerosis, prostate cancer, encephalitis, and rheumatoid arthritis, acting as a proinflammatory cytokine reinforcing inflammation<sup>31</sup>.

Human IL-6 is suggested to have neuromodulating effects in the brain and with sleep<sup>32</sup>. Kim et al. found that IL-6 and TNF- $\alpha$  were higher in adult psychiatric inpatients with major depressive disorder as compared with standard controls<sup>33</sup>. In a recent review of IL-6 and depression, authors reported multiple studies showing a correlation between higher plasma levels of IL-6 and depression in both adult and adolescent studies, including predictive studies<sup>31</sup>. Further, findings demonstrated higher levels of IL-6 in studies of melancholic depression, atypical depression, post-partum depression, and depression in older people<sup>31</sup>. In a study comparing patients with treatment-refractory depression compared with standard controls, as well as with euthymic individuals who were previously treatment-refractory, there were higher circulating levels of IL-6<sup>34</sup>. Significant diurnal elevations in plasma IL-6 levels have also been found, and a shift in circadian rhythm in depressed adults compared with tightly matched controls by gender, age, BMI, and menstrual cycle phase<sup>35</sup>. In children, IL-6 plasma levels have been demonstrated to be higher in children diagnosed with obesity than in age-matched standard weight controls, and further studies have demonstrated higher levels of IL-6 predicted depression post-hemopoietic stem-cell transplant in youth<sup>36</sup>.

Based on previously reported data showing that childhood IL-6 levels are associated with depression risk in early adulthood in a dose-response fashion, Foley et al. examined novel biomarkers along the IL-6 signaling and bioavailability pathways<sup>37</sup>. The authors studied three different signaling pathways IL-6 takes via classical interaction with IL-6 receptors (IL-6R) and soluble IL-6 receptors (sIL-6R), and the action on glycoprotein 130, wherein trans-signaling has been shown to cause more

pathological autoimmune effects on the body, such as higher rates of stroke<sup>37</sup>. It was found that higher IL-6 activity/bioavailability was associated with more somatic symptoms of depression, fatigue, and greater depression severity scores amongst study participants<sup>37</sup>.

Considering IL-6 and the signaling pathways as potential targets for adjunctive treatment of depression, mixed results on depression have been found from an IL-6 blocking agent, tocilizumab, a targeted biologic monoclonal antibody approved for treating rheumatoid arthritis. One meta-analysis of 12 published studies found an overall beneficial effect of tocilizumab in preventing depression in a population of those with rheumatoid arthritis<sup>38</sup>. However, another study found that the use of tocilizumab in medically ill patients significantly worsened depression in hemopoietic stem cell transplant recipients<sup>39</sup>. There is an ongoing study in the UK, the Insight study, that is recruiting patients based on a pilot trial for single-dose tocilizumab for depression that showed promise<sup>40</sup>. Thus far, the pilot study, published in 2024, has demonstrated benefits to quality of life, fatigue, C-reactive protein levels, and cognition, but not for depression or hedonic capacity<sup>41</sup>. More research and data are needed to further define a role for these biological agents in the treatment of depression, especially for those who do not have a defined rheumatological process.

Late nocturnal sleep is identified as a period of enhanced IL-6 signaling due to a distinctly enhanced availability of soluble IL-6 receptors<sup>42</sup>. In a small study of 17 healthy male volunteers, intranasal administration of IL-6 during late nocturnal sleep distinctly enhanced the sleep-related consolidation of exposure to emotional text material<sup>42</sup>. This increase in IL-6 may have implications for the development of depression, given that a higher rate of consolidation and storage of emotionally negatively charged memories from the day may perpetuate depression<sup>42</sup>. Taken together, these data demonstrate that inflammation and inflammatory mediators appear to have a significant impact on multiple essential physiological functions, which are both influenced by and directly influence depression and obesity status, and also appears to influence sleep.

### **Pathophysiological Interrelationships of Sleep, Depression, and Obesity**

As identified, sleep alterations within pediatric populations are not only a resulting factor of depression and obesity, but also a contributing factor to these disorders. In adolescent depression, sleep problems or dyssomnias are often prevalent. Data from the Treatment of Adolescent Depression Study (TADS), a pivotal multi-site study, demonstrated that sleep was the most prevalent residual symptom<sup>43</sup>. Adolescents with depression have prolonged sleep latency compared to non-depressed youth, and this same risk factor predicts relapse to depression.

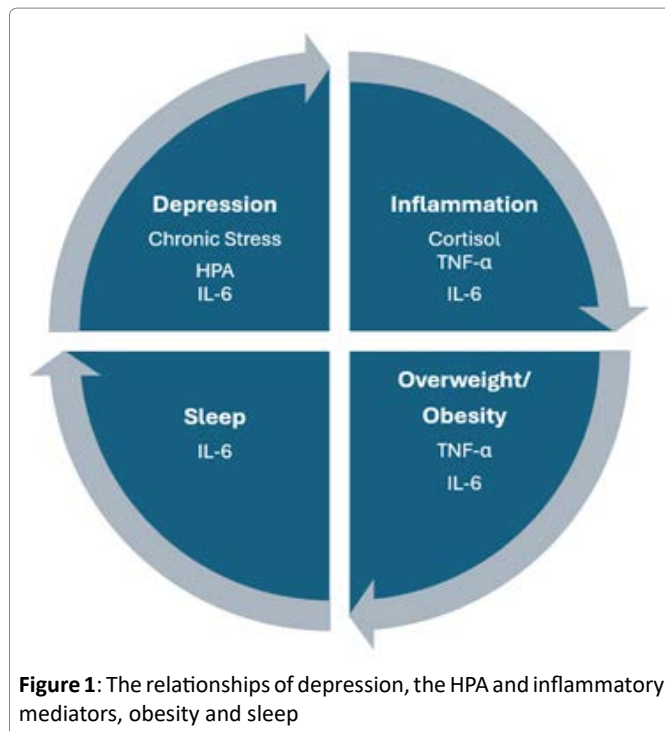
Further, Barbe et al. demonstrated that in children 7 to 17 years old with a diagnosis of major depressive disorder (MDD), insomnia was positively associated with the presence of suicidal ideations<sup>44</sup>. It has been reported that sleep disorders are the most common comorbidity diagnosed with adolescent depression, as well as that more adolescents will report sleep disturbances as a presenting concern than low or depressed mood<sup>45</sup>. Data suggests that there is a bilateral relationship wherein sleep postponement delays the onset of sleep, which restricts sleep opportunity, which, in turn, increases depression symptoms<sup>45</sup>. In concert with this, a physiologic delay in circadian rhythm timing across adolescence exacerbates delayed sleep onset and is consistently associated with increased depression symptoms<sup>45</sup>.

Adding to the physiological changes in sleep architecture during adolescence, overweight or obese status in children is associated with increased risk for sleep apnea and obesity hypoventilation syndrome, which are both associated with daytime somnolence and decreased total sleep time<sup>46</sup>. Another recent study demonstrated that obesity is independently associated with OSA in children after controlling for adenotonsillar hypertrophy, and non-Hispanic Black race and Hispanic ethnicity were identified as independent risk factors for OSA and obesity in the OSA inpatient population<sup>47</sup>.

Further complicating this clinical picture, studies have found that sleep deprivation leads to increased hunger and insulin resistance, which then may exacerbate, or at least sustain, obese status<sup>48</sup>. At least one study has demonstrated an increase in insulin resistance in a study of children with obesity and decreased overall sleep duration by polysomnography<sup>46</sup>. The overall implication suggests this negative feedback of perpetuating or worsening the obese state through a variety of mechanisms, both mechanical and neuroendocrinological, that effect sleep, obese status, and potentially with negative feedback as to mood state and thus a potential risk factor for suicide and suicidality. The lack of sleep at night may also impact daytime somnolence and exacerbate sedentary behaviors, which can, in turn, lead to lower caloric expenditure and drive rates of obesity and insulin resistance. Figure 1 demonstrates these interrelated factors.

### **The Impact of Health Care Disparities**

In identifying the inter-relational health risks associated with depression, obesity, inflammation, and sleep, it is also necessary to consider further risks related to health care disparities that may further exacerbate these factors. Studies of Hispanic populations suggest not only that this population has the highest rates of symptomatology and internalization of depressive symptoms but also higher rates of reported depression, up to 36.2% prevalence,



compared to non-Hispanic White and Black non-Hispanic populations<sup>49</sup>. Further, one in three adolescent Latinx females has seriously contemplated suicide and has higher rates of suicidal thinking and ideation<sup>49</sup>. In a review of data from 2009 to 2019, there was a 119.8% increase in major depressive episodes in the Hispanic population<sup>3</sup>. However, in this survey, there was a much lower rate of reported Major Depressive Episodes in the Hispanic population than previous authors reported, finding the rates similar to that of the overall reported presence in a pooled sample: 8.1% in 2009 to an increase to 17.8% in the 2019 survey sample<sup>3</sup>.

Previous data suggest that there may exist racial bias within data for the prevalence of depressive disorders among Black youth, and data have varied, with some authors suggesting higher rates for Black youth as compared to non-Hispanic White youth, yet other authors reversing this suggestion<sup>50</sup>. However, there have long been concerns that the Diagnostic and Statistical Manual of Mental Disorders criteria for depressive disorders are predicated on descriptors of depressive symptomology for the White population and that the Black population has long been underrepresented in clinical samples, leading to cultural and racial biases in research. These factors may impact the identification and proper treatment of Black youth in clinical settings, suggesting unmet mental health needs and rising rates of impairing disability and potential for suicide<sup>50</sup>. In Daly's study using the National Survey on Drug Use and Health data, the author found a relatively small increase in the presence of significant depression in Black youth, 4.1% between the survey years 2009 and 2019<sup>3</sup>. Though this may seem like a slight increase, it is of

note that the data showed that in a reporting population of those identifying as Black, the rates of adolescent depression in the subpopulation increased from 7.4% to 11.5%<sup>3</sup>. Given the knowledge that depression increased for pediatric populations following the COVID-19 pandemic, the above data demonstrates significant impacts related to health care disparities for underserved populations.

## Discussion

As described, there is a complex relationship between depression, obesity, inflammation, and sleep, which has not yet been fully elucidated given the ever-expanding research and description of very complex mechanisms, some of which have yet to be fully described or understood. Major depression is a heterogeneous disorder, especially in the pediatric population, wherein there is likely to be a multifactorial etiology that should be assessed within the biopsychosocial model, considering the whole child. As rates of depression and depressive disorders have risen in children and adolescents over the past number of years, it is increasingly important to assess not only for the presence of clinically impairing depression across all populations, but also for the clinician to be aware of currently reported trends in special populations who may be more at risk for depression. Data further demonstrate that the increase in pediatric depression is far-reaching and affects all races and ethnicities, though at different rates, but with the same basic message: that depression is on the rise. This trend was demonstrated pre-COVID-19, though the impact of the COVID-19 pandemic has also been clear, with a subsequent and significant rise in the incidence of depression in children and adolescents. Given that mental and behavioral health providers were pre-pandemic in short supply, the gap in provider numbers and those seeking or needing care has only widened<sup>51-52</sup>. Clinicians not only in the field of mental health but also in primary care and other subspecialty care should remain very aware of at-risk populations and various presentations of depression, especially in these more at-risk populations. The review identifies several important recommendations for research and clinical practice.

To avoid the risks associated with health care disparities, there is a significant need to widen access to assessment and diagnosis by improving screening at all opportunities with standardized screens, such as the PHQ-9, during primary care office intakes on both sick and well-child visits, which may help to identify children in need of further diagnostic evaluation. For those clinicians in the mental health field, having an awareness of those populations at risk may help enhance the detection of youth struggling with depression, for which further intervention may be warranted. An understanding of culturally sensitive descriptors and thoughts about depression or depressive symptomatology may also better enhance not

only diagnosis but also inform culturally sensitive, holistic care for at-risk populations. While considering the whole individual in assessment, one of the goals of this review is to allow the clinician to consider some underlying biological underpinnings that may be contributing to depression, to enable these factors to be addressed in unison.

There is also a need for health care providers to use a culturally sensitive evaluation approach to assessment and screening measures. Kaiser et al. identified a lack of culturally responsive mental health assessment tools and significant limitations in the translation of screening tools used in research and practice, placing significant risks for inaccurate and misleading conclusions<sup>53</sup>. The ETHNIC model may help bridge these gaps by serving as an evaluation tool that can be adapted for use in children for mental health diagnosis. It is designed to assist with obtaining an understanding of medical symptoms from a cultural perspective and how parents may perceive symptoms<sup>54</sup>. The American Psychiatric Association (APA), in collaboration with the DSM-5 Cross-Cultural Issues Subgroup (DCCIS) created an evidence-based evaluation tool to assist providers with a person-centered cultural assessment tool: The Cultural Formulation Interview (CFI), a series of 16 questions that can aid providers with gaining appropriate information to inform diagnosis and treatment planning<sup>54</sup>. Existing literature and data identify the essential need for health care providers to use culturally responsive assessment and evaluation methods to avoid the risk of inaccurate diagnosis and missed opportunities for treatment. Further, the ability of health care providers to engage in a culturally sensitive approach to care may serve to break down stereotypes and bias.

While the data support the need for culturally informed holistic care strategies to address multiple attributes associated with pediatric depression, the complexity of the data demonstrate the need for an integrative, multidisciplinary approach. The shortage of mental health providers is particularly acute within underserved populations. In the last decade, primary care providers have been encouraged to participate in integrated models of care to bridge this gap. However, holistic medical and mental health needs remain limited for populations most in need of comprehensive care. The benefit of team-based integrative care to widen access to critical health care services has been defined<sup>55</sup>. Integrative care can support a defined need for public health practice, including fostering an awareness of health care disparities to support comprehensive mental health care and intervention with culturally relevant, evidence-based strategies at individual, interpersonal, and community levels<sup>56</sup>. Collaboration with community resources in the delivery of mental health care should include the formation of partnerships for integrative care as a resource for local primary care providers to assist in the

management of care with targeted health care strategies including crisis management/same day appointments, flexible scheduling which may include weekend availability to increase access to services, continued self-directed learning and review of the literature and research data, and to practice cultural humility<sup>57</sup>.

However, despite the known benefits of integrative health care models in primary care, including mental health and other health care disciplines, challenges in delivering care to manage complex and biopsychosocial mental health care needs remain. Funderburk et al. (2021) identified limitations in clinical skills and expertise, evolving data represented in evidence-based practice, leading to challenges in providing integrative care<sup>58</sup>. These authors identified the benefit of educational opportunities to support integrative care with interprofessional team-based activities to improve competencies in the delivery of care, to support interactive educational opportunities, and to develop opportunities to support complex biopsychosocial care<sup>58</sup>. While there are limitations in the use of integrative care strategies, the data support the need to consider innovative approaches to support further development of interprofessional, integrative care teams. Considering the authors' lived experience and knowledge, fundamental factors to facilitate these teams include the continued support of collaborative care with interdisciplinary consultation in the delivery of complex care needs, including simple strategies such as acute care consultation and continuity of care communication.

This review analyzed the significant risks associated with pediatric depression including overweight and obese status in youth, which, in turn, confers several risk factors for health and mental well-being, including issues with self-esteem and the effect on mood both short and long term; the bilateral relationship with dysfunction of the HPA axis; that obesity is a proinflammatory state that increases systemic cytokines that have known relationships with depression, mainly IL-6 and TNF- $\alpha$ ; and having a deleterious effect on sleep. The data outline the importance of a multidisciplinary approach to informed assessment strategies. For sleep, this includes airway assessment and the need for referral for a sleep study for polysomnography should be considered when indicated, such as those who are snoring loudly and/or most nights; those who might have anatomical differences or known genetic predispositions for OSA (e.g., trisomy 21 or Pierre-Robin sequence); those reporting restless sleep; or children whose parents report odd movements or behaviors at night.

Additionally, collaboration and referral to pediatric pulmonology, otolaryngology, or neurology may be indicated to evaluate for anatomic problems, seizures, REM phenomenon, or other physiologic issues that can negatively impact sleep. Also, consideration of the effect

of allergies, reflux, and itching should be kept in mind to address different medical issues that may alter sleep or sleep architecture, and there should be the consideration to refer back to primary care, or allergists, dermatologists, or pediatric gastroenterologists. These data identify the critical need for enhanced interdisciplinary and integrative treatment planning and approaches, including both non-pharmacological and pharmacological approaches.

Avenues for non-pharmacological interventions provide critical strategies as a fundamental aspect of holistic care and to provide adjunctive support for pharmacological treatment. Culturally responsive therapeutic interventions provide evidence-based treatment and support for depression individualized treatment planning facilitated by the CFI. Therapeutic modalities may include psychoeducation to support wellness, dietary counselling, cognitive behavioral therapy (CBT), group therapy, family therapy, and supportive psychotherapy. As previously discussed, multiple studies have demonstrated that exercise is beneficial for depression in the pediatric population and may certainly help decrease weight and insulin resistance when combined with healthier eating habits. Further, weight loss may be instrumental in improving disordered sleep patterns, especially in those with obstructive sleep apnea or hypopnea. Motivational interviewing has demonstrable benefits and can be implemented during encounters with primary care and with multidisciplinary specialists such as gastroenterologists, pulmonologists/sleep medicine, endocrinologists, therapists, nutritionists, to assist in moving a child and their caregivers/family towards sustainable behavioral change<sup>14</sup>. Other strategies to support with management include maintaining a food diary, providing psychoeducation, promoting stress management and coping skills, utilization of supportive community resources, and therapeutic modalities including family therapy. This last modality further underscoring the importance of including the family in the integrative care process as partners in care and promoting wellness.

Given the complex, interrelated nature of sleep and depression, as well as the natural course of adolescent sleep patterns and circadian rhythm, the clinician should consider a sleep inventory as part of the evaluation to best understand the youth's sleep habits and delays to best address sleep as part of the overall treatment plan. Non-pharmacological interventions include identifying the child's sleep routine and hygiene habits, which should be assessed with a relevant understanding of the child's age and the psychosocial pressures on the child to best counsel on sleep. Though literature is not as robust for the role of cognitive behavioral therapy for insomnia (CBT-I) in pediatrics as there is in adult studies, there are studies that show positive benefits with CBT-I techniques such as teaching relaxation techniques, stimulus control, and

providing psychoeducation to promote sleep<sup>59</sup>. Beyond these non-pharmacologic approaches within a holistic, integrative care plan, there also exists pharmacologic modalities to consider for aiding weight loss, sleep, and for treating depression.

While there are multiple FDA-approved medications for adult weight loss, there are fewer FDA-approved medications for weight loss in children. Understandably, clinicians should begin with counseling for nonpharmacologic means of weight loss. Failing this, given the high burden on health and mental health, and in consideration of these interrelated factors of depression, sleep, and chronic inflammation, clinicians may need to consider treatment with medications to aid weight management. Currently, there are 4 FDA-approved weight loss medications for children 12 years and up: orlistat (Xenical), phentermine-topiramate extended-release (Qsymia), semaglutide (Wegovy), and liraglutide (Saxenda). Clinicians considering prescribing these agents should be aware of potential side effects. They may have variable levels of comfort or knowledge with these agents, and referrals may be indicated to more experienced prescribers or specialists, such as pediatric endocrinology for GLP-1 agents semaglutide and liraglutide. Appreciating the nuances of prescribing medications beyond scope or comfort may limit accessibility to weight loss medications for patients presenting with depression. Consideration of alternate treatments may be indicated for those with experience with specific neurological agents that are employed in mental health, such as topiramate or naltrexone. Though not FDA-approved, there are data to support naltrexone, an opiate blocker that appears to shut down reward pathways and help curb compulsive behaviors<sup>60</sup>. In a study of adolescents with binge-purge behaviors, naltrexone 50mg a day was well tolerated and significantly decreased these behaviors<sup>60</sup>. Significant weight loss could be instrumental in reversing inflammation, achieving better homeostasis of the HPA axis and serum cortisol, having a positive effect on sleep and sleep architecture, and aiding in the overall mood and treatment plan of the depressed youth. Engaging the family in pharmacological psychoeducation is imperative, as well as engagement with primary care in similar supportive motivational interviewing and lab monitoring to enhance and support the holistic, patient-centered approach to care.

As mentioned previously, there is a complex and not yet fully understood relationship between cytokines, chronic inflammation, and depression. Cytokines and inflammatory markers appear elevated in both obesity and in depression states, and may suggest common pathways and a complex interrelationship. However, there is limited positive data with two anti-TNF- $\alpha$  biologicals and mixed results with an anti-IL-6 biological agent. There is not

enough data to support these costly infusions as an adjunct in Major Depressive Disorder in adults, and there are yet no studies in children. Further research into clinically useful biomarkers or treatment agents is needed, and remains a robust field of future research. For now, the role of cytokines may help guide the clinician in screening for autoimmune phenomena and chronic pain issues in the depressed population, especially with those at known higher risk for depression, such as those who have juvenile rheumatoid arthritis, Crohn's disease, psoriasis, or other known autoimmune processes, which can also present in childhood. Further, for those children who may already be in treatment with pediatric gastroenterology, pediatric rheumatology, or dermatology, the clinician may better understand the effect of these biologicals to help inform the overall treatment of depression.

When considering the potential alterations in sleep there is a need to be kept in mind to address different medical issues that may alter sleep or sleep architecture, for example micro arousals related to allergies, reflux, and itching, to either treat as comfortable, for instance hydroxyzine at night for cough or itching, or recommendation of famotidine or omeprazole for reflux. Further, the clinician may need to consider pharmacological intervention with soporifics, even if only short-term, to aid sleep. Though there are no FDA-approved soporifics for children, medicines often employed include over-the-counter melatonin, clonidine, trazodone, doxepin, and mirtazapine<sup>61</sup>. Overall, any pharmacotherapy should be considered in the context of the patient's needs and tailored to the individual as part of a comprehensive treatment plan.

In summary, there is clear need for a collaborative care approach with primary care, mental health specialists, nutritionists, multidisciplinary subspecialists, and counselors, for a team-based approach to yield best results. Having considered all of these factors as previously discussed, there remains the direct treatment of depression itself with a collaborative approach with therapists in first-line treatment with CBT, as well as with FDA-approved, evidence-based treatments with fluoxetine, approved down to the age of 8 years or escitalopram, FDA approved down to the age of 12 years. Please refer to Table 1 for a summary of recommendations.

Finally, it is of critical importance to understand the trends and data identified following COVID-19 lockdown: a sharply increased incidence of depression, and a sharp rise in overweight and obese status concurrently across all ages. With understanding the complex and intertwined nature of the reviewed topics, there is a need to consider the negative contributions of lockdown including social isolation, decreased connections and sense of belonging, decreased access to care, loss of in-school counseling, social and health insecurity, worsening parental mental health,

and rises in abuse and domestic violence. There is a need to consider the powerful impact of stress associated with the HPA axis and its contribution towards depression, especially in the context of pandemic which significantly affected daily life globally, to identify important factors associated with pediatric wellness to predict and perhaps alter response to future high-impact events. The implications of lockdown should continue to be examined in further research to inform improved strategies in the face of natural hazards and disasters to improve health care outcomes for children. These should focus on avoiding isolation, fostering community, supporting connections, and fostering a sense of belonging to prevent or mitigate the deleterious effects on pediatric depression, including the significant risk of suicide, a critical outcome of untreated or undertreated depression, faced by our youth currently.

### Conclusions and Future Directions

Though there is compelling data for the interrelationships between depressive disorders, obesity, inflammation, and sleep, there is still no clear single cause and effect of any one of these factors, thus remaining ripe for further research and exploration. Increasing understanding of complex relationships in physiology and pathophysiology may eventually lead to more targeted treatments and regimens to alleviate the suffering of depression in youth and potentially prevent long-standing adult psychopathology, which confers tremendous burden on the individual and society at large. The complexities of the biological model are likely multifactorial, suggesting an individualized approach to each patient based on the best evidence and considering multiple lifestyle factors. A culturally sensitive, holistic approach to the treatment of pediatric and adolescent depression should consider many factors, including the promotion of proper diet and exercise, understanding of socioeconomic factors that may be propagating stress and obesity, adequate sleep routine and sleep hygiene, and the consideration of the effect of a sedentary lifestyle. Prudent and evidence-based psychopharmacology and non-pharmacologic therapy modalities, such as cognitive-behavioral therapy, may also be beneficial based on the severity and risk of harm to self and should all be part of the broader, comprehensive treatment plan. Because of the multifactorial and complex interactions, a team-based interdisciplinary, integrative approach may be in the individual's best interest to address the multiple factors with guidance from primary care and subspecialty colleagues, nutritionists, therapists, child psychiatrists, and nurse practitioners to address the whole person by bridging gaps in care and improving clinical competencies for health care providers in the delivery of culturally responsive care to avoid the risk of lifelong consequences.

**Table 1:** Summary recommendations

Pediatric Depression Holistic, Interdisciplinary, Culturally Responsive Care			
Depression	Overweight/Obesity	Inflammation	Sleep
Assessment: Biopsychosocial Model			
PHQ-9 Psychiatric Assessment Cultural Formulation Interview ETHNIC Model Framework	BMI calculations Diet history Exercise history Family history Labs	Medical history Review of symptoms Targeted physical exam (if indicated) Labs	Medical history Focused sleep history Collateral informants
Treatment: Integrative Care			
CBT Group Therapy Family Therapy Supportive Psychotherapy Psychoeducation Stress Management Coping Skill Training Sleep hygiene Engagement-Community Resources Interdisciplinary consultation Continuity of care -communication Interprofessional Education Crisis management Flexible scheduling  Pharmacological Management: FDA Approved: • fluoxetine • escitalopram	Psychoeducation Stress Management Coping Skill Training CBT Group Therapy Family Therapy Food diary Engagement-Community Resources  Targeted pharmacological management: FDA Approved: • orlistat (Xenical) • phentermine-topiramate extended-release (Qsymia) • semaglutide (Wegovy) • liraglutide (Saxenda)  Non-FDA Approved: • topiramate • naltrexone	Motivational interviewing Group Therapy Supportive Psychotherapy Psychoeducation Stress Management Coping Skill Training Sleep hygiene Psychiatric treatment	CBT-I Motivational Interviewing Supportive Psychotherapy Stress Management Sleep routine/hygiene Sleep diary Airway assessment if indicated  Targeted pharmacological management: • melatonin • clonidine • trazodone • doxepin • mirtazapine  Pharmacological strategies to support medical issues that may alter sleep or sleep architecture ( e.g. micro arousals related to allergies, reflux, and itching): • hydroxyzine • famotidine • omeprazole
Referral Thresholds/Referrals			
PCP to Psychiatric Services:  • Moderate or higher positive screening for depression • Risk factors of concern • Suicidality • Psychosis	Evaluation/treatment of known medical conditions/comorbidities to obesity status  Refractory states needing more intervention  • Pediatric endocrinology • Nutritionist • Dietitian • Psychiatry • Therapy	Evaluation of comorbid medical conditions, e.g. autoimmune diseases, inflammatory bowel diseases, dermatological diseases such as psoriasis  • Rheumatology • Gastroenterology • Dermatology	Comorbid medical conditions Refractory sleeping problems Diagnostic clarification for such things as anatomic problems, seizures, REM phenomenon:  • Pediatric pulmonology/sleep medicine • Otolaryngology • Neurology • Polysomnography • Allergists

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The authors declare no conflicts of interest.

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