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Unraveling the mechanisms responsible for the comorbidity between metabolic syndrome and mental health disorders

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Abstract

The increased prevalence and high comorbidity of metabolic syndrome and mental health disorders have prompted investigation into the potential contributing mechanisms. There is a bidirectional association between metabolic syndrome and mental health disorders including schizophrenia, bipolar disorder, depression, anxiety, attention deficit/hyperactivity disorder, and autism spectrum disorders. Medication side effects and social repercussions are contributing environmental factors, but there are a number of shared underlying neurological and physiological mechanisms that explain the high comorbidity between these two disorders. Inflammation is a state shared by both disorders, and it contributes to disruptions of neuroregulatory systems, including the serotonergic, dopaminergic, and neuropeptide Y systems, as well as dysregulation of the hypothalamic-pituitary-adrenal axis. Metabolic syndrome in pregnant women also exposes the developing fetal brain to inflammatory factors that predispose the offspring to metabolic syndrome and mental health disorders. Due to the shared nature of these conditions, treatment should address aspects of both mental health and metabolic disorders. Additionally, interventions need to be developed that can interrupt the transfer of increased risk of the disorders to the next generation.

Keywords

obesity; metabolic syndrome; diabetes; schizophrenia; bipolar disorder; depression

Introduction

Interest in the common mechanisms between metabolic and mental health disorders (MHDs) is rising due to increasing prevalence and comorbidity of both. Metabolic syndrome (MetS) is both preventable and deadly. It is currently defined as a set of chronic and associated features that increase risk of cardiovascular disease and type 2 diabetes mellitus, including central obesity, atherogenic dyslipidemia, insulin resistance, and endothelial dysfunction [1, 2]. There are several definitions of childhood MetS, but all contain features of obesity, dyslipidemia, high blood pressure, and impaired glucose metabolism [3]. These childhood

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features are better correlated with waist circumference than BMI, and the cardiovascular risk factors persist to adulthood unless changes in nutrition and physical activity are made [4]. Metabolic and mental health conditions are both impacted by numerous environmental and genetic factors, but this review will focus on the overlapping mechanisms between MetS and MHDs that contribute to the recent increases in prevalence and may explain their comorbidity.

Increased Prevalence and Common Occurrence of both Metabolic Diseases and Mental Health Disorders

The prevalence of MetS and its components is widespread and continuing to rise. Overweight and obese people have an increased risk of developing MetS [1]. In 2010, every state in America had a prevalence of obesity above 20% [5], and one third of the nation is obese [6]. Though rates are plateauing in women, they continue to increase in men and adolescents [7, 8]. Type 2 diabetes is the seventh leading cause of death in the United States [9], and if current trends persist, its incidence will increase to 1 in every 3 by 2050 [10]. Evidence also indicates that maternal obesity and high fat diet consumption during the perinatal period predispose offspring to MetS [11].

MHDs are common: approximately 25% of American adults have a mental health disorder [12]. When delineated further, about 7% of adults suffer from major depressive disorder, about 3% have generalized anxiety disorder, and approximately 4% have attention deficit/hyperactivity disorder (ADHD) [12]. In children, developmental disabilities have increased dramatically (17%) in the last decade, driven largely by increases in ADHD and autism spectrum disorders (ASD) [13]. This increased prevalence has lead to numerous investigations into the environmental risk factors contributing to this recent and rapid rise in childhood neurodevelopmental disorders. Interestingly, the rise in the prevalence of childhood developmental disabilities parallels the increase in adult obesity and several lines of evidence suggest that maternal obesity increases offspring risk for both MetS and MHDs [11, 14, 15].

Metabolic Syndrome and Mental Health Comorbidity

Both MetS and obesity are comorbid with MHDs in 45% of cases [16]. Individuals with schizophrenia, bipolar disorder, depression, anxiety, ADHD, and ASD have a higher prevalence of both obesity and MetS compared to the general population [17, 18]. Evidence linking MetS to specific MHDs will be further outlined in the following sections.

Schizophrenia and Bipolar Disorder

MetS is more prevalent in patients with bipolar disorder or schizophrenia than in the general population. Individuals with bipolar disorder have the highest rates of MetS [17, 19] as well as increased risk for obesity [20] and other metabolic complications [21]. This association is controversial as both typical [22] and atypical [22, 23] antipyschotics are reported to contribute to the increased body weight and MetS. These medications are likely not fully responsible for the association because increased weight and adiposity is also seen in drug-naïve individuals [24] and patients diagnosed with their first-episode of psychosis were also

reported to have increased frequencies of hypertension, diabetes and metabolic syndrome [25].

Depression and Anxiety

Childhood [26, 27] and adult obesity are associated with an increased risk of depression [28–32] and anxiety [28, 29, 31]. Though body weight is a stronger predictor of depression than diabetes [33], evidence shows that diabetes, independent of weight status, is linked with higher rates of depression [33, 34]; some studies report a four-fold risk increase in diabetic patients [35] that increases with symptom severity [34, 36, 37]. Interestingly, a recent study indicates that obesity may only be linked to depression in individuals with a higher socioeconomic status, and depressive symptoms were associated with increased BMI only in Hispanic women [38]. This report and other conflicting reports of the association between affective disorders and obesity indicate that the association is quite complex and is influenced by factors such as socioeconomic status and ethnicity.

ADHD

Children [39], adolescents [39], and adults [40] with ADHD are more likely to be overweight or obese than the general population. Similarly, ADHD is more common in obese teenagers [27, 41, 42]. Bariatric surgery is prescribed to promote weight loss in morbidly obese individuals, and pre-operative evaluations showed rates of ADHD double that of the general population [43].

ASD

Several studies show that obesity is twice as likely in adolescents with ASD [42, 44]. However, others report that the lower nutrient intake experienced by children with ASD is severe enough to counter their obesity and may eventually result in underweight status [45].

Disordered Eating

Obesity and mental health issues are often comorbid in compulsive eating disorders such as night-time eating syndrome and binge eating. Binge eating disorder [46] and night eating syndrome [47] are widespread in the obese population, and night eating syndrome is associated with obesity [48], anxiety [49], and depression [46, 48–50]. Furthermore, obese individuals with ADHD display abnormal eating habits compared to obese patients without ADHD [51], and this is also observed in children with ADHD [41] and ASD [52].

Sex-Dependent Evidence

Many relationships between MetS and MHDs are sex-dependent. There is a stronger association between obesity and psychopathologies in women [29, 53]; only morbidly obese men display an increased risk of depression [54]. Overweight and obese females have increased prevalence of anxiety [53], major depressive disorder [53, 55–62], and both childhood and adult ADHD [63], while obese men did not show the same trends [53, 56, 58, 61]. The risk for generalized anxiety disorder and major depressive disorder is increased six-fold in obese females [64]. Morbidly obese women seeking bariatric surgery were also more

likely to have a history of mood and anxiety disorders [65], and women with type 2 diabetes have higher risk of depression than men [33, 66].

Metabolic Syndrome Increases Risk of Psychopathologies

Beyond comorbidity, several studies highlight that MetS increases the likelihood of developing affective disorders [53], such as depression [67–72] and bipolar disorder [69], due to similar underlying mechanisms. Obesity is not found to increase risk of depression in the general population, but the subset of obese individuals with high socioeconomic status have a doubled risk of depression [38]. The relationship between diabetes and later depressive symptoms has been reported to be modest [73] or weak [74], but the strength of the relationship depends on whether the study used self-reported or diagnostic depressive symptoms [75].

Societal discrimination and stigma against obesity may also increase risk of MHDs [57]. Diabetes may contribute to depression through the fear and lifestyle restriction potentially associated with receiving this diagnosis [73, 75], as well as symptoms like hyperglycemia-induced fatigue [75]. Indeed, there is a peak in antidepressant use after a diagnosis of diabetes [76] and when treatment begins [77].

Psychopathologies Increase Risk of Metabolic Syndrome

Evidence supports the bidirectionality of this association between MetS and MHDs. Adults with ASD have higher risk of developing diabetes [78], and male children with ADHD have a higher risk for adult obesity [79]. Depression similarly increases likelihood of developing diabetes [73] and obesity [68]. Men with depressive symptoms had higher likelihood of developing obesity or MetS in the next decade [80]. Depression during adolescence predicts a higher BMI later in life [61]. This data is not conclusive, however, as other studies do not see an increased risk of obesity with depression [67].

Explanations for this relationship are often accredited to medication side effects or disease-induced lifestyle modifications. Typical and atypical antipsychotics and antidepressants cause dyslipidemia [17], weight gain [22, 81], and glucose dysregulation [81]. Correspondingly, individuals with schizophrenia and bipolar disorder have higher risk for components of MetS [17]. Selective serotonin reuptake inhibitors (SSRIs) do have short-term benefits for glucose regulation, but tricyclics and noradrenergic antidepressants worsen the metabolic state [82]. Indeed, female patients taking antidepressants have higher risk of developing type 2 diabetes than unmedicated patients [66].

Environmental factors increasing risk of MetS may be specific to populations with high risk of MHDs. Reduced access to healthcare in patients with schizophrenia or bipolar disorder may contribute to the development of MetS [17]. The increased sugar and saturated fat intake seen in women with depression and obesity [83] increases the likelihood of weight gain and MetS. Furthermore, depression and emotional dysregulation commonly accompany a preference for sweet and fatty food [84], higher caloric consumption [85], and sedentary behavior [85]. Therefore, MHDs may contribute to developing and maintaining an obese state and may also increase resistance to treatment.

Changes in Metabolic Status Impact Mental Health

Psychopathologies are observed in over half of individuals seeking bariatric surgery [86], but symptomology ratings improve after successful surgery in adults [62, 87, 88] and adolescents [89]. These improvements continue years afterward and are greater in women [90]. An inpatient weight loss program also reported improvements in depression after successful weight loss [55].

In stark contrast, a systematic review of bariatric surgery found an increased risk for suicide completion in patients compared to the general public [91]. Another systematic review found that obese people have lower rates of suicide completion despite higher reports of suicidal ideation [58, 92] and attempts in obese women [92]. Thus, it may be that many bariatric surgery patients have improvements in depressive symptoms, but those that do not are more likely to act on their intrusive thoughts.

Conversely, there is limited evidence that successful treatment of psychiatric disorders improves metabolic functioning. One study reports that glucose metabolism improves after treatment for depression [81].

Maternal Metabolic Disorders and Offspring Mental Health

Maternal metabolic status impacts the neurophysiology of developing offspring; predictably, a relationship between maternal obesity and offspring psychopathology has been observed. Obese mothers are 67% more likely to have a child with ASD [93]. Several studies also identify maternal diabetes as a risk factor for ASD [94, 95] and developmental delays [93]. Additionally, maternal obesity is associated with affective problems in children [96, 97] and adolescents [97], as well as increased ADHD behaviors [98, 99]. Similarly, children with ADHD are twice as likely to have a mother who is obese [100].

Diet-induced maternal obesity in animals shows similar metabolic and behavioral impairments in offspring. Perinatal consumption of a high fat diet leads to mouse offspring with deficits in spatial learning and memory [101] as well as increased aggression and hyperactivity [102]. Rodent [103, 104] and non-human primate [105] offspring from mothers fed a high fat diet show increases in anxious behavior.

Similarly, mouse offspring of depressed mothers have compromised memory, higher emotionality, and decreased neurogenesis [106]. This data provides compelling evidence that maternal metabolic status, and potentially maternal mental health, impacts the outcome for offspring.

Potential Mechanisms for Comorbidity of Mental Health Disorders and Metabolic Syndrome Inflammation

High fat diet consumption and consequent obesity elicit an inflammatory response [107], and key inflammatory cytokines, such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interferon-γ, and interleukin (IL)-6 and -8, are also involved with mood disorders.

IL-6, for example, influences both stress and feeding behaviors [108] and inhibits hippocampal neurogenesis [109], which is involved in schizophrenia and depression [110].

Schizophrenia and Bipolar Disorder

A hypothesis of cytokine-stimulated immune response leading to abnormal brain development is generally accepted for schizophrenia [111]. IL-6 and TNF-α levels are markedly increased in patients with schizophrenia [112–114], and TNF-α is considered a trait marker of the disease [114]. Pathways regulating inflammatory response show alterations in 40% of people with schizophrenia [115]. The cytokine release induced by a toll-like receptor agonist was higher in whole blood from patients with schizophrenia and bipolar disorder [113]. Bipolar patients also show an elevation in IL-6 levels [113].

Inflammation plays such an important role in schizophrenia that this disease is often modeled in rodents by dispensing cytokines and other inflammatory agents to neonates; this results in behavioral abnormalities consistent with human schizophrenia symptoms, and these symptoms respond to antipsychotics [116, 117].

Depression

Increased levels of IL-6 correspond with symptoms of major depressive disorder [112, 118]. Male patients with a history of depression [119] or currently in a depressive episode [120] had higher levels of CRP; this association remained after correction for BMI [120].

Studies examining elderly patients report an association between depression and increased levels of TNF-α [121], CRP [121], and IL-6 [122, 123], though the relationship with IL-6 is stronger in men [121]. Risk for depression in elderly individuals is associated with elevated levels of two of the following pro-inflammatory factors: TNF-α, CRP, and IL-6 [121].

ADHD

Many studies have identified inflammation as a contributing factor for increased risk of ADHD [124]. The brains of individuals with ADHD show higher rates of T cell-induced apoptosis, which is activated by exposure to pro-inflammatory cytokines [125].

ASD

Individuals with ASD present elevated levels of TNF-α [52], IL-1 [52], IL-6 [52, 126], and interferon-γ [127]. Animal studies reveal that overexposure to IL-6 in the brain results in both cellular abnormalities (poor adhesion and migration [126], over-formation of excitatory synapses [126, 128], and abnormal dendritic spines [128]) and behavioral disturbances (learning deficits, low social interaction, and abnormal features of anxiety and habituation [128]) consistent with ASD.

Brain-derived Neurotrophic Factor

Similar to inflammatory cytokines, growth factors such as brain-derived neurotrophic factor (BDNF) are potential mediators of the comorbidity between MetS and MHDs. BDNF is critical in neuron development, differentiation, synaptogenesis, regulation, and survival in

systems critical in regulating cognition and behavior (dopamine and serotonin [129]) and food intake and body weight (pro-opiomelanocortin and agouti-related protein [130, 131] (discussed in the next section). In humans, polymorphisms of BDNF are associated with schizophrenia [132–134], depression [135], anxiety [135, 136], and other mood disorders [136] as well as with obesity [137–140]. Moreover, mice deficient in BDNF display behavioral abnormalities including increased aggression and hyperactivity [141] in addition to obesity [142]. Interestingly, in a mouse model, maternal obesity was associated with decreased hippocampal BDNF and impaired spatial cognitive function [101].

Perturbations in Pathways that Regulate Behavior and Metabolic Status

Perturbations in common neuroregulatory pathways likely contribute to the comorbidity of MetS and MHDs. Neuropeptide systems involved in regulating mental health and metabolic status, such as the serotonin, dopamine, neuropeptide Y (NPY), corticotropin-releasing hormone (CRH), and endocannabinoid systems [143], are likely candidates.

Serotonin

Serotonin is best known for regulating mood and behavior. A suppression of central serotonin synthesis is consistently reported in humans with anxiety [144], depression [145, 146], ADHD [147], and ASD [148, 149]. Serotonin 1A receptors have been identified to play a role in anxiety [144, 150]. Mood disorders are commonly treated with SSRIs, which increase the levels of available serotonin.

The brain serotonin system has also received substantial attention for regulating energy balance. Reduction of serotonin system activity increases food intake [151–154], while drugs that stimulate serotonin release reduce food intake in rats [155, 156], baboons [157], and humans [158, 159]. Of the fourteen subtypes of serotonin receptors, the 1B and 2C subtypes are most strongly implicated in modulating feeding and body weight. These receptors are expressed in hypothalamic regions involved in food intake regulation [160–163]. Furthermore, both 1B and 2C receptor agonists suppress feeding in rodents [164–166], and 2C receptor knockout mice display chronic hyperphagia and obesity [167, 168]. On the other hand, obesity is associated with alterations in the metabolism of tryptophan, the precursor for serotonin synthesis [169].

Dopamine

Recent neuroimaging studies indicate that dopamine synthesis and release is altered in individuals with schizophrenia [170], depression [171, 172], social anxiety [173], ADHD [174], and ASD [175, 176]. Polymorphisms in dopamine transporter are associated with depression [177], social anxiety [178], ADHD [179, 180], and ASD [181]. Also, a polymorphism in dopamine 3 receptors is associated with repetitive behavior in children with ASD [182]. Pharmacological treatment of many MHDs involves modulation of the dopamine system: typical antipsychotic drugs work by blocking dopamine 2 receptors (D2Rs), ADHD is treated using psychostimulants that increase dopamine levels [183], and treatment with a dopamine agonist produces antidepressant effects in treatment-resistant patients with major depressive disorder [184].

Neuroimaging studies provide compelling evidence of the dopamine system's involvement in eating behavior and obesity [185] particularly via dopaminergic projections from the ventral tegmental area to the nucleus accumbens [186]. Additional routes of food intake regulation are dopaminergic projections from the nucleus accumbens to the hypothalamus [187] and dopaminergic neurons in the ventral tegmental area that are impacted by the hormone leptin, which exerts a neurotrophic influence in the development of hypothalamic circuits regulating food intake [186]. Cues associated with food increase dopamine levels [185]. Obese subjects exhibit reduced D2R availability, which likely increases eating in these individuals in order to acutely stimulate underactive reward circuits [188]. This reduction of D2Rs is associated with suppressed metabolism in brain areas involved in self-control and increased metabolism in regions involved in sensory processing of palatability [185, 189]. Interestingly, a recent imaging study of patients recovered from anorexia nervosa indicates that their eating-induced dopamine release may produce anxiety instead of the typical pleasurable response [190].

Mice that lack the gene encoding tyrosine hydroxylase, the enzyme responsible for dopamine synthesis, initially gain weight and feed normally, but, unless dopamine is supplemented, they will stop feeding and die from starvation [191]. Dysfunctional processing of reward-based feeding through the dopaminergic system is a potential contributor to the obesity epidemic and likely contributes to the comorbidity of metabolic and psychiatric disorders.

Hypothalamic Neurotransmitters

Neurons producing NPY/ agouti-related protein and alpha-melanocyte stimulating hormone in the arcuate nucleus are key regulators of body weight and food intake [192]. NPY is also implicated in behavioral regulation, and NPY expression is reduced in schizophrenia [193, 194], bipolar disorder [193–195], and depression [193, 196] and elevated in children with ADHD [197]. Application of a NPY 1 receptor antagonist in rats produces increased anxiety and decreased social interaction [198], and mice given central administration of NPY [199, 200] or lacking NPY 2 receptors display decreased anxiety.

Dysregulation of the Hypothalamic-Pituitary-Adrenal Axis

The role of the HPA axis in MetS is well established. Obese humans with insulin resistance exhibit elevated cortisol [201]. Furthermore, hyperactivation of the HPA axis may increase adiposity by promoting hyperphagia and consumption of palatable foods [84]. Consumption of these "comfort foods" inhibits the HPA axis; thus, overeating may be a compensatory response to temporarily reduce chronic stress [202]. Animal studies demonstrate an acute reduction in anxiety and depressive-like behavior after consumption of palatable food [203]. Cortisol exposure may also impact the reward value of a food item by influencing factors such as leptin, insulin, and NPY [202].

It is also well documented that MHDs are associated with dysregulation of the HPA axis. CRH expressing paraventricular neurons [204] and cerebrospinal fluid CRH levels are increased in individuals with depression [205, 206]. Postmortem analysis of suicide victims reveals a reduction in CRH receptor density [207], which occurs via negative feedback to

compensate for CRH overexposure. There is also evidence that depressed individuals have chronically elevated cortisol that is responsible for increasing MetS symptoms [61, 85].

Mice that overexpress CRH display symptoms of MHDs and MetS including hyperphagia, insulin resistance, increased anxiety, and impaired coping to stress [208–210]. Pharmacological agents used to treat both MetS and MHDs modulate HPA axis activity [211].

Reduction of the Heart Rate Variability

Heart rate variability (HRV) is a non-invasive measurement of cardiac autonomic function that has been considered a valid tool for diagnosis and management of cardiovascular disease [212]. As a number of studies suggest that MetS negatively affects autonomic cardiac control [213, 214], autonomic dysfunction could contribute to an increased risk of subsequent cardiovascular events in individuals with MetS. In general, MetS patients have reduced HRV, suggesting decreased parasympathetic and/or increased sympathetic modulation of the heart [212, 214–217].

This autonomic dysregulation has also been suggested as a possible contributor to the increased cardiovascular risk in patients with psychiatric disorders [218, 219]. Decreased HRV values were found in subjects with depression [220, 221] or schizophrenia [222]. Decreased vagal stimulation was also found in children with ADHD [223]. However, it remains unclear whether mood disorders or medications are driving the autonomic dysregulation found in patients with MHDs. Tricyclic medications and SSRIs were also associated with reduced HRV [224, 225] while non-pharmacological therapies such as physical exercise, meditation, smoking cessation, and dietary changes are associated with increased HRV [224].

Heart rate variability is not the only measurement that highlights the link between components of MetS and MHDs; non-invasive brain stimulation strategies can improve depressive symptoms in patients with depression or bipolar disorder [226] and may be effective in reducing HPA activity [227].

Maternal Metabolic Health Programs Offspring

The mechanisms previously discussed are compounded by the effect of maternal metabolic status. The placenta transfers maternal inflammation to the developing fetal brain, so maternal MetS has additional consequences for offspring metabolic and mental health. In fact, in animal models, perinatal exposure to maternal obesity and a high fat diet has been demonstrated to alter the serotonergic [105] and dopaminergic [228] systems of offspring.

Placental Dysfunction

The placenta is highly sensitive to maternal metabolic status; gestational diabetes [149, 229, 230] and obesity are associated with an inflammatory response in this organ [149, 229–231]. Large animal studies report negative effects of obesity and over-nourishment on the placenta: decreased mass [232], reduced capillary density [232], and reduced uterine blood flow [232, 233].

Poor placental functioning is compounded by the transmission of inflammatory factors. Pregnant women who are obese have system-wide inflammation [229], and increased circulating cytokines further impair placental function [234, 235].

Gestational Exposure to Inflammation

Fetal brain development and neurotransmitter systems essential for behavioral regulation are sensitive to elevated circulating cytokines [236]. Pro-inflammatory factors initiate extensive neuronal plasticity and growth in the fetal brain and contribute to a state of chronic fetal inflammation [237]. Many symptoms of ASD are proposed to result from this early exposure to elevated inflammatory cytokines [237].

High fat diet-induced inflammatory factors are present in both obesity and MHDs. The structural differences of fetal brains exposed to high levels of IL-8 correspond with brain alterations seen in patients with schizophrenia [238]. Additionally, IL-6 has a critical influence on ASD risk in offspring [239]. IL-4 and IL-5 are elevated in mothers of children with ASD [240]. Over-nutrition results in increased levels of inflammatory factors that are also elevated in children with ASD [241, 242].

Alternate Mechanisms of Maternal Programming

Offspring exposed to maternal obesity and high fat diet consumption are exposed to excess levels of nutrients and hormones that are postulated to impact fetal brain development [11]. Maternal glucose passes through the placenta [243], and the pancreatic beta cells of the fetus respond by increasing insulin secretion. As insulin is a critical neural growth factor [244], this hyperinsulinemia during development of neural pathways may predispose the offspring of obese mothers to MetS. For example, rodent studies indicate that insulin administration during development produces obesity [245–247] and risk for diabetes [247] in offspring. In addition, offspring of obese mothers are exposed to elevated levels of leptin [244].

Conclusion

Recent scientific research has identified an association between components of MetS and MHDs, and common underlying mechanisms are credited. A number of lifestyle factors and neurological alterations increase vulnerability to both MetS and MHDs, but the overlapping neurological mechanisms that are implicated in both conditions include changes to neuroregulatory brain pathways, dysregulation of the HPA axis, and a chronic state of inflammation. Additionally, placental dysfunction allows mothers with MetS to transfer the inflammatory state and consequent brain alterations to their developing fetuses.

Psychopathologies have a high comorbidity with obesity and MetS, especially in women, and thus treatment for high body weight should include a therapeutic aspect that is specific to the presented disturbances in the patient. Beyond this holistic approach, it is imperative to prevent transferring these syndromes to the next generation by developing intervention strategies.

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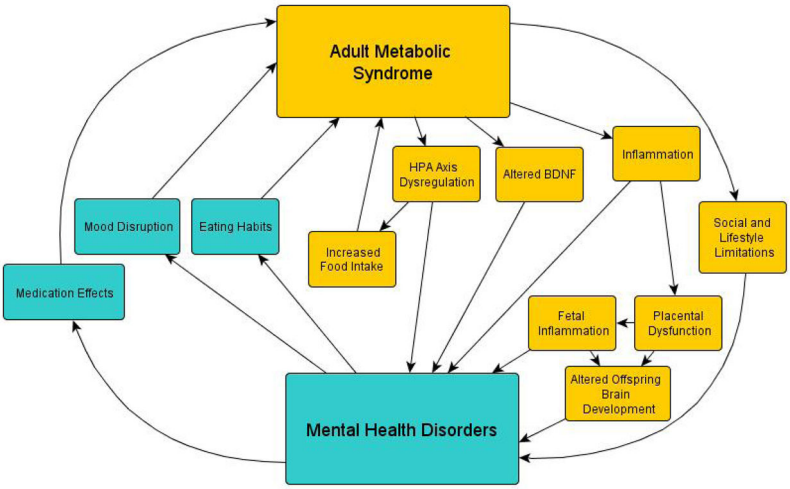

Fig. 1.

The bidirectional relationship and overlapping mechanisms of MetS and MHDs.