Review Article

Overcoming the Cycle of Mood and Obesity: Metformin's Prospective Contribution

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Abstract: A growing number of Americans will experience the harmful health effects of being overweight and adipose due to the rising rate of obesity in the country, including Type 2 diabetes mellitus (T2DM), cardiovascular disease, and cancers like colorectal, endometrial, and postmenopausal breast cancer. There is growing evidence connecting obesity to cognitive, emotional, and metabolic problems. Clinical results, quality of life, and concomitant illnesses are all negatively impacted by compromised metabolic health and psychological functioning. Metformin presents the fascinating possibility to abrogate the reciprocal association between poor metabolic health and psychological performance because it has both insulin-sensitizing and anti-inflammatory properties. In this study, we review the research on metformin's effects on mood and cognitive performance, look at probable underlying mechanisms, and suggest new lines of inquiry into the drug's potential to improve adherence to advice on healthy behavior.

Keywords: depression, anxiety, mood, cycle, obesity

1. INTRODUCTION

A growing number of Americans will experience the harmful health effects of being overweight and adipose due to the rising rate of obesity in the country, including Type 2 diabetes mellitus (T2DM), cardiovascular disease, and cancers like colorectal, endometrial, and postmenopausal breast cancer [1,2]. The age-adjusted prevalence of obesity in U.S. adults increased from 30.5% to 42.4%, and the age-adjusted prevalence of severe obesity increased from 4.7% to 9.2%, according to data from the National Health and Nutrition Examination Surveys (NHANES) from 1999-2000 through 2017-2018 [3]. The prevalence of obesity was highest among middle-aged individuals (40-59 years) in 2017–2018, at 44.8%; women had a greater prevalence of severe obesity (BMI ≥40 kg/m2) than males, at 11.5% versus 6.9% [3]. People who were non-Hispanic Black had the highest prevalence of obesity, at 49.6%, followed by people who were Hispanic (44.8%) and non-Hispanic White (42.2%) [3]. An urgent call to action has been sent by the continuous increase in obesity over the past 20 years. Healthy nutrition and regular exercise are now recommended weight loss methods. While maintaining an active lifestyle and regular physical activity are...
excellent methods for reducing obesity [4], maintaining these behaviors are notoriously challenging. Short-term studies suggest that those who are overweight or obese can lose weight [5], but NHANES data also show that most people cannot maintain weight loss [6], and fewer adults who are overweight or obese report trying to reduce weight [7]. Numerous factors contribute to this lack of adherence to a healthy lifestyle, including: (1) low tolerance for high-intensity exercise and higher perceived exertion in overweight individuals [8,9,10]; (2) difficulty starting and maintaining healthy lifestyle changes due to emotional and cognitive dysregulation intimately linked to obesity and overweight status [11,12]; and (3) difficulty initiating and maintaining healthy lifestyle changes. Therefore, standard of care recommendations for lifestyle adjustments alone are probably not going to have much of an impact on lowering the risk of obesity in those who are overweight or obese. Despite the strong motivation provided by the health benefits, many adults report having trouble stopping their weight gain by the suggested lifestyle behaviors of exercise and caloric restriction. This suggests a more complicated issue. In the current work, we give a summary of the research indicating the connection between obesity, metabolic dysfunction, mood disorders, and dysregulation of cognitive processes. We next go into the typical pathophysiology that underlies them all. The paper's last part examines human and animal models illustrating the possible impact of the oral hypoglycemic medication metformin on the implaceable cycles of metabolic, mood, and cognitive impairment. We conclude with a discussion and suggestions for additional study.

2. LITERATURE REVIEW

Obesity and excessive fat buildup are caused by a persistent mismatch between energy consumption and energy output. Obesity frequently results in insulin resistance and alterations in how carbs, lipids, and protein are used as fuel, which impairs the uptake of insulin-stimulated glucose by muscle and adipose tissue. When cells stop responding to insulin, hyperinsulinemia results, which promotes an inflammatory environment in adipose tissue with ectopic fat storage and abnormal energy use [13,14]. Excess adiposity, especially visceral adiposity, also promotes chronic low-grade inflammation by macrophage, adipocyte-preadipocyte production of proinflammatory cytokines such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα) and adipokines such as leptin [15,16]; these endocrine effects of adipose tissue inflammation are considered causative of systemic inflammatory pathway activation and lead to insulin resistance. The metabolic syndrome, which is defined as the co-existence of obesity/visceral adiposity, insulin resistance, dyslipidemia, and hypertension, increases the risk of Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and postmenopausal breast cancer [20,21,22]. A vicious loop of dysregulated metabolism involving obesity, proinflammatory signal transduction, and insulin resistance has detrimental implications on health. In a codependent, reciprocal manner, obesity and overweight status are strongly correlated with mood dysregulation [23,24]. Obesity increases the likelihood of mood and anxiety problems by 25% [25]. More often in women than in males, there is a correlation between depression and obesity [26]. Young women who are overweight or obese are more likely to report experiencing a persistent melancholy mood than women who are lean, even after adjusting for racial and socioeconomic factors [27]. Similar to this, population-based research has found an association between depression, as measured by the Major Depression Inventory, and a higher risk of T2DM [28]. It is noteworthy that depression can be identified even at the prediabetes stage, as evidenced by research showing a 37–60% increased future risk of developing T2DM in those with depression [29]. Even in people who do not have abnormal or excessive fat storage, the link between depression and insulin resistance is evident. Children with depression, as determined by the Child Depression Inventory,
develop insulin resistance regardless of changes in BMI, according to a prospective, long-term study [30]. A recent meta-analysis supports these findings by pointing to a weak but significant link between depression and insulin resistance [31]. It should be noted that meta-analyses demonstrating a relationship between depressive symptoms or general distress and T2DM seem strong with both diagnostic (e.g., clinical records) and nondiagnostic (e.g., Centers for Epidemiologic Studies for Depression Scale, General Health Questionnaire) measures of depression [29]. In a similar vein, metabolic health is linked to negative affect in general rather than specifically diagnosed depression [32]. When measured using the Positive and Negative Affect Schedule, higher negative affect or emotional distress (such as anxiety, depression, stress, or sadness) [33] and lower positive affect or pleasant feelings or emotions (such as joy, calmness, interest, or enthusiasm) [34] are linked to higher BMI; for women, the association is stronger [34]. It’s interesting to note that physical poor health seems to be the explanation for the association between lower positive affect and higher BMI [34]. Individuals with mood disorders like depression often have lower energy levels and are therefore less physically active [35], and negative affect is linked to higher intake of sweet, high-fat, and energy-dense foods [36]. Depression may also result in the use of food as a coping mechanism for emotional distress given that food intake corresponds with acute physiological changes (such as increased serotonin, for example). Additionally, studies suggest that sadness was more likely to come before obesity than the other way around [38]. Pharmacological therapies for mood disorders can also cause weight gain [28, 39–41], which has the potential to worsen insulin resistance and the unbreakable cycle of metabolic dysfunction and depressive symptoms [42, 43]. Obese people also have changes in their mood and cognition, particularly in terms of higher level executive functioning [44]. Working memory is the short-term storage of pertinent, immediate information. Inhibitory control is the capacity to regulate one's attention, behavior, thoughts, and/or emotions in order to counteract impulsive or automatic/conditioned responses. Shifting/flexibility is the capacity to adjust behavior and thoughts to new, changing, or unexpected events. Executive function (EF) is a set of higher-order cognitive processes required for goal-directed behavior [45]. EF abilities are essential for controlling and directing behavior, especially in novel or demanding circumstances like starting a health behavior change [49]. The bulk of studies looking at the connection between obesity and EF have concentrated on the differences between obese and normal weight people, while some studies have concentrated on overweight and normal weight people [44]. According to Yang et al.'s meta-analysis [44], several EF tasks have been employed to examine the role of cognitive processes in excessive weight gain. Inhibitory control and planning were the most frequently found cognitive processes. Overall, the findings show that those who are overweight or obese have EF deficiencies. In particular, obese people had poor EF across the board (i.e., working memory, inhibitory control, shifting/flexibility, decision-making, verbal fluency, planning), whereas overweight people only significantly underperformed in these areas compared to normal weight controls [44]. The pattern of results did not appear to be affected by age, BMI, or sex. The type of task seems to matter in terms of working memory and decision-making. The delay discounting or Iowa gambling task and the digit span task had bigger effect sizes for memory evaluation than the letter-numbering sequencing task. The small number of studies that solely looked at those who are overweight (as opposed to those who had obesity) is a key limitation recognized by this meta-analysis. Other limitations include the lack of consideration of antiobesity drug use and the prevalence of a psychiatric disease in many research. Studies evaluating a variety of EF measures have shown mixed findings regarding the link between EF deficits and excessive adiposity/obesity. Regarding the type of cognitive task as well as the correlation between adiposity measurements and cognitive outcomes, the Baltimore Longitudinal Study of Aging found conflicting results [50]. The results of the
study indicate that higher BMI and waist circumference were linked to worse prospective memory; longitudinally, all three measures of adiposity (BMI, waist circumference, and waist-hip ratio, or WHR, defined as the ratio of measurements of the circumferences of the waist and hips) showed declining performance on the Benton Visual Retention test with increasing body size. There were no long-term impacts on either of the language tests (Letter and Category Fluency and Boston Naming), despite cross-sectional studies showing that BMI was linked to noticeably lower performance on the Letter and Category Fluency test [50]. WHR was linked to poorer performance over time in executive function (using the Trail Making B test, assumed to be indicative of working memory and shifting ability) [51]. Unexpectedly, however, obesity was linked to improved attention and visuospatial function. It is challenging to extrapolate the findings to other populations because the sample is older (mean age 55.5, SD: 16.9) and somewhat well-educated (average >16 years of education). In a group of middle-aged adults, the findings on obesity and cognitive function were more consistent. In a group of more than 1800 men and women (aged 40-69) at baseline, the Framingham Heart research focused on BMI and WHR, both of which are risk factors for cardiovascular disease. According to results from the Trails B test, executive function performance was negatively correlated with obesity and hypertension [52]. The authors also discovered that people with obesity experienced more age-related cognitive impairment, and they emphasize the significance of reducing central obesity to stop this process. In the Whitehall II study [53], which measured BMI across the course of the life cycle at 25 years of age, during early midlife (mean age = 44), and late midlife (mean age = 61), the association between BMI and cognition was further investigated. The Mini Mental State Examination (MMSE), a screening tool for general cognition, was used to assess cognition in late middle age, along with measures of short-term memory (a free recall task) and EF (reasoning and verbal fluency). The findings point to a curvilinear association, with both underweight and obese people having worse cognition. The MMSE and measures of memory and executive function were specifically linked to cumulative obesity (obesity at two or three time points), and an increase in BMI from early to late midlife was linked to lower executive function in late midlife [53]. An unfavorable relationship between obesity and a variety of executive functioning tests, including the Wisconsin Card Sorting Test, the Trail Making Test, the Stroop Color-Word Task, the Digit Span Test, and the Delay Discounting Task, was validated by Favaeri et al. in a review of 88 research [11]. These findings reveal that obesity is more than just an illness of disturbed homeostatic controls over food intake. It is also a problem of appetitive motivation. The central melanocortin system's dysfunction, which controls satiety, appetite, energy homeostasis, and body weight, is also linked to the etiology of obesity [54,55]. The mesolimbic dopamine system is stimulated by the impulse to eat particular foods; cognitive processes (such as reward and desire) connected to the mesolimbic pathway are implicated in addiction [56]. However, some researchers contend that these models should also take into account EF processes, including those associated with inhibitory control that are situated in the prefrontal cortex [57]. According to neurobiological and behavioral data, people with lower EF capacities are more likely to consume high-calorie foods and acquire weight [57]. Researchers have proposed that the connections between mood, cognitive performance, and metabolic health are explained by both behavioral and biological factors. According to behavioral research, low mood and negative affect are associated with a greater preference for high-calorie foods, which can be used to control emotions [58]. Furthermore, higher executive functioning abilities that are essential to self-control might be weakened by stress and unpleasant emotions. Finally, from a physiological standpoint, long-term negative affect and/or chronic stress can cause dysregulation in the endocrine and immune systems, which can affect the health of the brain and metabolism and, in turn, affect cognitive and mood disturbances and higher food intake, creating a
vicious, unbreakable cycle. Negative cues make urgent, tangible goals more salient, which makes people prefer decadent over healthful food [60], according to observational studies of stress that use both real-life events and subjective distress scores [59]. Mood dysregulation is linked to unhealthy habits such as binge eating [62], being inactive [61], and consuming more calories [63]. Relatedly, executive functioning skills—which are essential for starting and maintaining healthy behaviors—are impaired by stress/negative affect [64] and depression [65]. This is especially troublesome because EF is necessary for behaviors (such as healthy practices), which have a short-term time and effort cost but long-term health advantages. Evidence suggests that impairments in executive functioning abilities serve as a mediator between the effects of mood/stress on health and health behaviors [66]. The sympathoadrenal system, the hypothalamic-pituitary-adrenal axis, and proinflammatory cytokines are all activated in chronic depression and depressive states [67]. The risk of developing diabetes increases when these systems are dysregulated [67]. By interfering with the neurotransmitter and signaling circuitry in the prefrontal cortex connected to motivation, reward, sadness, and anxiety, a high-fat diet promotes insulin resistance and T2DM [68]. A recognized motivational network in the hippocampus region of the brain called the anterior cingulate cortex, which affects both depression and insulin resistance, is thought to play a role in the relationship between insulin resistance and increased food-seeking behaviors and loss of motivation [69]. The hypothalamic-pituitary-adrenal axis (HPA), one of the major stress response systems, produces cortisol as its byproduct, and research suggests that cortisol is positively correlated with weight gain and increased secretion of proinflammatory hormones and cytokines (adipokines) by adipose tissue depots [70]. Both insulin resistance and T2DM have been linked to proinflammatory cytokines, especially IL-6 and CRP [16]. Depression may be caused by proinflammatory signaling when there is metabolic dysregulation and obesity [71]. As a risk factor, obesity is also connected to mood instability. Chronic inflammation brought on by increased fat mass and metabolic malfunction seems to be linked to mental health issues including anxiety and depression [72]. Participants in a study in the United Kingdom provided data from a mental health questionnaire. Without regard to genetic predisposition to metabolic dysfunction (such as adiposity genetic variants with favorable or unfavorable metabolic profiles based on HDL cholesterol, triglycerides, and T2DM risk), Casanova et al.’s analysis of data from the Biobank (n = 145,668) revealed that higher adiposity increases the odds of depression, the severity of depression, and lower wellbeing [73]. It’s interesting to note that greater levels of the proinflammatory cytokine CRP were linked to the metabolically advantageous obesity variations [73]. In conclusion, mounting data points to an interconnected network that can become implacable and bidirectionally entrained between fat, insulin resistance, and cognitive impairment (Figure 1). Stress and negative affect make people more prone to emotional reactions while also impairing self-control, which increases food intake [74,75] and leads to more sedentary habits [76,77,78]. Over time, these actions may result in decreased functioning in a number of areas of quality of life, maintaining and possibly exacerbating depressive mood. Relatedly, it appears that an increase in mood disorders is connected with metabolic dysfunction, particularly insulin resistance, suggesting convergent and bidirectional effects [23]. Additionally, depression predicts adverse outcomes in a variety of weight loss strategies, including surgical [81] and behavioral [82] procedures, as well as inadequate weight loss maintenance [83]. Higher BMI significantly reduces the effectiveness of antidepressants [79,80]. In fact, even nonclinical measures of mood, such stress (using the Perceived Stress Scale) [84,85] or those who are primarily not depressed (BDI scores of 10) [86], reveal that higher levels predict reduced intervention efficacy, perhaps because of decreased participation [84]. Additionally, studies show that people with depression who are in remission are more likely than those who are not to lose weight as a result of lifestyle changes [86,87], possibly as a result of increased levels
of physical activity [88]. Both academics and physicians must take seriously these findings. Physiological reactions to stressors are intertwined with regulation of appetite because chronic stress and mood dysregulation lead to an increase in demand for foods high in energy [89]. In a comprehensive model that we recently released [90], we make the case that enhancing an individual’s cognitive and emotional capabilities can increase their likelihood of adhering to healthy behaviors. Increased adherence to a lifestyle intervention may result from addressing cognitive and emotional behavior change barriers before putting them into action [90,91]. According to empirical evidence, adopting recommended medical and health behavior is linked to mood improvements [92,93]. Interventions that target mood and higher-order cognitive skills related to self-control may be crucial to enhancing the adoption and adherence of healthy behaviors because (1) they are both impaired in the context of obesity and (2) they share connected pathophysiology [94,95]. Although behavioral interventions such as cognitive training [96] and mindfulness-based therapy [97] can enhance cognition and mood, respectively, they are frequently just as time-consuming as the lifestyle behavior changes themselves, making them difficult to put into practice. Importantly, antidepressant usage is frequently linked to weight increase [98] and a higher risk of developing diabetes [99]. Insulin resistance linked to obesity is decreased with metformin. Metformin, which the Food and Drug Administration initially approved in 1995 for the treatment of T2DM, increases peripheral glucose uptake and utilization while lowering both hepatic synthesis and intestinal absorption of glucose to improve glucose tolerance [100]. Through the activation of AMP-kinase (AMPK), a crucial molecule that shifts substrate use away from glucose and toward fatty acid beta oxidation, metformin appears to lower fasting glucose levels. The liver’s mTOR is inhibited by metformin’s stimulation of AMPK, which has downstream effects that include the reduction of hepatic neogenesis [101]. The blood-brain barrier is crossed by metformin, which may also have anti-inflammatory and neuroprotective properties [102,103]. The drug’s well-established efficacy and safety profile for T2DM and prediabetes permit the prospect of innovative repurposing in addition to its crucial function in modifying metabolic and inflammatory pathways that drive obesity. The literature on metformin’s impact on mood and cognition in both animal and human populations is reviewed here. Metformin may have an effect on mood and cognition, according to a number of preliminary preclinical and clinical investigations. By (1) preventing or treating metabolic dysfunction [104] and (2) acting through cerebrovascular or neurodegenerative processes [105], including reducing advanced glycation end products [106,107] and altering inflammation [108], metformin may improve mood and cognitive performance. Metformin is linked to the amelioration of obesity-associated phenotypes suggestive of mood and cognitive impairment in mouse models of high-fat diet (HFD)-induced obesity. Behavioral tests for mice and rats include the Morris water maze test (109), which measures delayed learning and memory, the tail suspension test (TST), which measures behavioral despair, the sucrose splash test (111), which measures anhedonia/depressive-like behavior, and the elevated plus maze (EPM), which measures anxiety-like behavior. Metformin causes anxiolytic and antidepressant-like behavioral alterations in male C57BL/6 HFD-induced insulin-resistant mice, with increased entry/time in open spaces (EPM) and decreased time of immobility (TST) [113]. The metabolic dysfunction caused by diet-induced obesity and insulin resistance may have been corrected, as seen by the enhanced behavioral effects of both HFD reversal and metformin. The hippocampus, a part of the brain involved in emotional regulation, has lower basal extracellular levels of 5-hydroxytryptamine (5-HT, often known as serotonin), which is interestingly linked to HFD [110]. Behavioral functioning appears to be improved by increased 5-HT neurotransmission in the hippocampus; this effect appears to be partially mediated by lowering the elevated amount of branched chain amino acids (BCAAs) [113]. Particularly noteworthy is the link between elevated BCAA levels and HFD, insulin resistance, and obesity [114].
Metformin may operate to lower circulating BCCA levels [115] and hence promote hippocampal 5-HT neurotransmission in rats fed an HFD, leading to behavioral effects like those of an antidepressant [113]. Metformin improves metabolic irregularities and levels of oxidative stress, which prevents the learning and memory behavioral impairment seen in insulin-resistant HFD-fed rats [109]. In murine models of drug-induced cognitive impairment, pretreatment with metformin significantly alleviated learning and memory deficits via reduced inflammation [118]. Metformin, fluoxetine, and the combination of metformin + fluoxetine reduced depressive symptoms and deficits in spatial memory in a study of rats exposed to chronic restraint stress and HFDS; hippocampus c-jun expression was shown to be downregulated [119]. A recent report of hippocampal spatial memory impairment in mice with streptozocin-induced diabetes suggests that the cognitive decline associated with diabetes and metabolic dysfunction may be partially related to hyperglycemia-induced formation of advanced glycation end products (AGEs) and reactive oxygen species [120]. Metformin has been demonstrated to reduce the mRNA levels of proinflammatory cytokines (such as IL-1, IL-6, and TNF-) in murine macrophages treated with the drug [121]. This is accomplished by inhibiting AGE-induced proinflammatory signal transduction via AMPK activation and the AGE/NF-B receptor. Metformin appears effective in reversing not only the metabolic and psychological dysfunction brought on by HFD-induced models, but also the metabolic dysfunction and depressive-like behaviors mediated by corticosterone [122,123] and the depressive-like behaviors brought on by lipopolysaccharide and linked to aberrant glutamatergic neurotransmission and inflammation-related pathways [124,125]. Chronic stress is linked to increased corticosteroid production and protracted sympathetic nervous system activation, which increases visceral fat and causes metabolic abnormalities such as insulin resistance and T2DM [72, 89]. Female C57BL/6 mice were chronically tested while swimming, and then they were given therapy with particular steroid hormone antagonists, including metformin, an androgen antagonist [126]. The behavior alterations of increased sociability and decreased social novelty were shown to be reversed by metformin [126]. Metformin therapy is also very effective in treating other rodent models of depressed behavior brought on by psychologic stressors, such as chronic social defeat stress (CSDS) and chronic unexpected mild stress (CUMS) [127,128]. BDNF protein levels in the hippocampus did not differ significantly between CUMS vs. control animals in CSDS, despite the possibility that metformin's antidepressant effects in CDS involve enhanced expression of BDNF in hippocampal tissue/cells via AMPK activation [128]. Male C567BL/L6 middle-aged mice were treated with metformin via diets containing 0.1% w/w metformin in comparison to untreated mice, and the results showed improved metabolic parameters, including decreased body weight, an improved metabolic profile (reduced insulin, cholesterol, and HOMA-IR), and the expression of anti-inflammatory genes in liver tissue [129]. Male C567BL/L6 mice were fed either a low fat diet of 4.3% (w/w) or a high fat diet of 34% (w/w) for 10 weeks. The mice on the high fat diet (HFD) had greater levels of fat mass, insulin, and blood glucose, and their adipose tissue had higher levels of the macrophage markers CD11c, MCP-1, CD206, and Arg1 [130]. The shared underlying mechanism for enhanced psychological function in obesity/HFD mouse models of anxiety and depression-like behaviors that involve an obese, HFD-fed phenotype may be an anti-inflammatory mechanism. Notably, male mice have been used in the majority of investigations on obesity and depressive-like behavior in rodents. Future research should focus on the models' sex specificity (for instance, CSDS might only apply to male mice). Studies examining the impact of metformin on human mood and cognition have shown more contradictory, although encouraging, results. An interesting new avenue of research has been highlighted by a recent review indicating antihyperglycemic medications like metformin are effective in reducing depressed symptoms and cognitive impairment [131]. Metformin and sulfonylureas were linked with lower risks ratios for affective
disorders (major and unipolar depression, and bipolar disorders) in people with T2DM, according to observational data from a representative cohort of 800,000 Taiwanese participants [132]. However, due to the high stigma in Asian nations, it is possible that affective illnesses go undiagnosed [133]. Importantly, it is difficult to infer causal relationships from observational data. The Geriatric Depression Scale 1-15 was used in a case-control study of more than 500 elderly T2DM patients, and it was discovered that those taking metformin had a lower risk of depression than those who were not taking any medication [134]. In a study of women with polycystic ovary syndrome (PCOS), metformin was also found, after 6 months of treatment, to improve emotional functioning (as indicated by significant increases in vitality, mental health, and sum scores on the Short Form Health Survey and lower scores on the Symptom Check-List) [135]. A prospective cohort study comparing individuals with PCOS who were treated lifestyle adjustments + metformin with lifestyle modifications alone validated the findings from this observational analysis by finding that those in the metformin group had a 70% decreased probability of experiencing serious depression [136]. In a sample of patients with both depression and diabetes, Guo and colleagues investigated the effects of metformin versus placebo on depression using the Montgomery-Asberg Depression Scale and the Hamilton Scale for Depression [137]. The study’s findings revealed that chronic metformin treatment over a period of 24 weeks resulted in a significant improvement in both depression scales. Importantly, reductions in HbA1c strongly linked with reductions in depression symptoms, indicating that metformin’s anti-diabetic properties may mediate mood elevations. Results showed that metformin significantly reduced both depression (BDI-II) and anxiety (BAI) in a pilot experiment for mood disorders in adolescent and adult women with PCOS [138]. Also improved were body obesity and insulin resistance. It was impossible to evaluate whether changes in metabolic health were responsible for the effects of metformin on mood because of the limited sample size. Notably, the majority of these anxious participants had mild or no depression at baseline, indicating that benefits might still be shown even in the absence of severe sadness [138]. Additionally, metformin is linked to improved mild cognitive impairment [139] as well as better performance on executive function and memory-related cognitive tests [140,141]. A small number of pilot clinical investigations supporting these favorable effects on cognitive function demonstrate that metformin has the potential to enhance a variety of cognitive outcomes. The Wechsler Memory Scale-Revised was used in the trial by Guo et al. to measure improvements in glucose metabolism and cognitive performance in persons with depression and T2DM compared to placebo controls after 24 weeks of metformin treatment [137]. Notably, metformin significantly improved cognitive performance in people (55-90 years old, n = 80) with amnestic mild cognitive impairment and no treated diabetes in a randomized, placebo-controlled trial [142]. Participants (aged 55 to 80) with mild cognitive impairment or early dementia caused by Alzheimer’s disease who had never had diabetes mellitus or prediabetes showed a significant improvement in cognition as measured by executive functioning in the metformin group in a randomized double-blind placebo-controlled crossover study of the drug [143]. The limited study size (n = 20) may have contributed to the lack of significance in learning, memory, and attention improvements [143]. Among those who have survived pediatric brain malignancies, metformin has also been linked to improved declarative and working memory [144]. Nevertheless, the impacts on cognition and mood are not always apparent. Both the exercise and the exercise + metformin interventions showed significant effects on mood as measured by the Profile of Mood States-SF, with large effect sizes for vigor and moderate effective sizes for anger and total mood disturbance in comparison to the metformin group alone in one study comparing exercise, metformin, and exercise + metformin on health-related quality of life measures in participants with T2DM [145]. However, the study’s shortcomings included the small sample size of the
metformin-only group (n = 30) in comparison to the metformin + exercise group (n = 147), nonrandomized design, and senior patient cohort (mean age 70.6). This study demonstrates that metformin with lifestyle modification can considerably enhance mood, despite these constraints making it challenging to interpret the results. Metformin did not lower depression scores in young women with insulin resistance brought on by PCOS and comorbidly diagnosed serious depression in one randomized, double-blind experiment [146]. The small sample size (n = 25 in each group) and high dropout rate (20% did not return after the first post-baseline visit) of this tiny study were its main drawbacks. The treatment period was also much shorter than in previous studies (6 weeks). Notably, metformin had no impact on the HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) scores, which is not unexpected given that metabolic characteristics are thought to be the mechanism by which metformin affects depression. Among patients with PCOS and major depressive disorder, a reduction in depression ratings of 8% from baseline was seen with metformin, but a 38.3% reduction was seen with pioglitazone [146].

Data from the Diabetes Prevention Program (DPP) revealed no changes in depression levels or the percentage of patients taking antidepressants between the intensive lifestyle, metformin, and placebo groups [147]. The initial randomization condition (metformin, lifestyle modification, and placebo) did not significantly differ between the groups in terms of cognitive outcomes such as verbal learning, letter fluency, and the digit symbol substitution tests, according to data from the Diabetes Prevention Outcomes Study [151]. The absence of a baseline cognitive evaluation, the collection of cognitive assessments 12 years after randomization, and the participants' elderly age (mean age = 63 years) are some of the study's weaknesses. Additionally, at the time of the cognitive evaluations, variations in diabetes and glycemia among the intervention groups were also noticeably less. The Diabetes Prevention Outcomes Study results suggest a significant association between higher glycated hemoglobin and lower cognitive performance, which is consistent with data from the Finnish Diabetes Prevention Study [152], despite the apparent lack of effect of metformin exposure on cognition after adjusting for age, sex, education, and randomization arm. Despite earlier findings from the DPP, which shown that weight loss is linked to a decrease in depressive symptoms regardless of randomization [147], the DPP was not intended to examine the impact of metformin on mood. Antidepressant drug use was permitted as part of the DPP eligibility requirements, which may have reduced how much the intervention affected depression levels. Additionally, only 2.7% of individuals reported ratings higher than 16 (moderate depressive symptoms) at the start of the study [99,147]. Intriguingly, however, metformin use was not connected with diabetes risk although severe lifestyle modification was. Metformin's effects on mood and cognition could be influenced by certain molecular targets, which could be tempered by baseline obesity levels. Only in the context of psychological dysfunction brought on by metabolic brain stress, such as T2D, hyperglycemia, and hyperinsulinemia [150], may metformin's cognitive advantage be observed. No significant group differences were detected in one DPP trial, although regardless of the treatment arm, people who were active or who lost weight also had lower levels of depression markers. Increases in total testosterone, however, were linked to declines in anxiety and depressive symptoms in males who were randomly assigned to take metformin [153]. Finally, although these effects were not statistically significant, the positive benefits of metformin versus placebo on cognition (as measured by verbal performance) appear to be greatest for those with a baseline BMI of 35 or higher [154]. In a different study, researchers looked into the effects of metformin as well as compared rosiglitazone and glyburide on cognitive functioning in adults with diabetes but no current depression [155]. Rosiglitazone is an insulin sensitizer that lowers glucose levels by increasing the sensitivity of peripheral and hepatic tissues to insulin, while glyburide lowers glucose levels by enhancing insulin secretion from the pancreas. The
findings showed advantages in both groups, and the size of the effects was connected with reductions in fasting plasma glucose levels but not with circulating insulin or insulin sensitivity [155]. This is in line with research showing that the processes underlying pioglitazone’s effects on depression are mostly unrelated to its ability to increase insulin sensitivity [146].

3. CONCLUSION

Over 40% of American adults are obese, which increases their risk of developing harmful medical disorders like cardiovascular disease, Type 2 diabetes mellitus (T2DM), and cancer. Obesity is a rising and untreated problem globally, but it is especially acute in the United States. The persistence of obesity is reinforced by poor metabolic health and psychologic dysfunction (depressed mood, anxiety, and cognitive impairment) in a positive feedback loop, according to compelling data from epidemiologic, clinical, and basic science investigations. Although treating these mood and cognitive dysregulations with antidepressants may seem like the logical solution, approximately 50% of patients do not respond to therapy with first-line antidepressants [156]. It is crucial to note that antidepressants frequently cause substantial weight gain [157]. Antidepressants may not be desirable for some populations when combined with other potential side effects. Finally, adherence issues can arise even though behavioral therapies seem to be helpful at elevating mood [90]. This is because some populations may find it difficult to make the effort to participate in these programs. Even though it is not intended to be a comprehensive review of the literature, this work highlights the metabolic and psychological abnormalities caused by and encouraging excess adiposity and high BMI as a vicious cycle from which it is challenging, if not impossible, to break free. We carefully studied the literature because there aren’t many studies on metformin, and our work draws on a variety of studies to support our case for breaking the mood-obesity loop. We want to draw attention to the potential of metformin as a tolerable, safe, and affordable intervention that may, at least in some obese people, help break the vicious cycle of excess fat mass, psychological dysfunction, and unbalanced metabolism. We acknowledge the significance of addressing the variety of factors that contribute to the development of obesity. There is strong evidence that metformin may reduce inflammatory and metabolic indicators, which may therefore enhance mood and cognitive function and encourage behavior change. No adequately powered randomized controlled clinical trials have been conducted to far to examine the effects of metformin on mood and cognition. Additionally, preliminary research indicates that metformin may enhance psychological functioning by reducing inflammation and blood sugar levels. If this turns out to be the case, research examining the synergistic effects of metformin prior to or concurrent with a lifestyle intervention may offer a game-changing method for clinicians to encourage behavior change in obese patients. Metformin has the ability to act as a kickstart for those for whom changing their lifestyle may be difficult by addressing mood dysregulation and cognitive deficiencies that make it difficult to begin and sustain balanced diet and activity. The combination of metformin with a lifestyle intervention may also result in an early response (such as a change in behavior) because metformin has a demonstrated strong impact on metabolic health and may also improve mood and cognition. Evidence suggests that people who change their behavior quickly [158] or lose more weight quickly [159] are more likely to maintain their weight loss over the long run.

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