The Interconnected Complexity of Diabetes and Depression

Elizabeth A. Beverly[1,2] and Jeffrey S. Gonzalez[3,4,5]

[1]Department of Primary Care, Ohio University Heritage College of Osteopathic Medicine, Athens, OH; [2]Ohio University Diabetes Institute, Ohio University Heritage College of Osteopathic Medicine, Athens, OH; [3]Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY; [4]Departments of Medicine, Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY; [5]New York-Regional Center for Diabetes Translation Research, Bronx, NY

Diabetes and depression have a bidirectional relationship, with negative impacts on glycemia, self-care, long-term complications, quality of life, and mortality. This review highlights key aspects of the interconnected and complex relationship between diabetes and depression, including how it affects health outcomes, depression duration and recurrence, age-specific manifestations, and recommendations for screening and nonpharmacological treatment.

Diabetes is a significant and growing public health problem, affecting 11.6% of people in the United States, or 38.4 million people (1). In the United States, diabetes accounts for one of every four health care dollars spent, with total annual costs exceeding $412 billion (2). Diabetes treatment plans involve complex self-care behaviors, including weight management, healthy eating, regular physical activity, medication-taking, frequent glucose monitoring, daily foot care, and attendance at medical appointments (3). These behaviors can be time-consuming and difficult to integrate into daily life (4,5). Moreover, people with diabetes frequently experience numerous psychosocial factors that affect their self-care, health outcomes, and psychological well-being (6).

Major depressive disorder (MDD) and elevated depressive symptoms are the most studied behavioral health condition in people with diabetes. Both MDD and elevated depressive symptoms are more prevalent in people with type 1 or type 2 diabetes and parents/caregivers of youth with diabetes (7–9). A 2022 systematic review and meta-analysis of 44 studies found the prevalence of depression and elevated depressive symptoms was significantly higher in people with type 1 diabetes (22 vs. 13%, odds ratio [OR] 2.10, 95% CI 1.23–3.52) and type 2 diabetes (19 vs. 11%, OR 1.76, 95% CI 1.55–2.01) compared with people without diabetes (10). Similarly, a 2023 systematic review and meta-analysis of 22 studies found that the pooled prevalence of depression and depressive symptoms among parents of youth with type 1 diabetes was comparable to that of people with type 1 or type 2 diabetes (22.4%, 95% CI 17.2–28.7%) (11).

Considering the high prevalence of diabetes along with comorbid depression and depressive symptoms, health care professionals (HCPs) should be aware of the unique challenges and outcomes this population faces. Below, we highlight key aspects of the relationship between diabetes and MDD and elevated depressive symptoms, including its bidirectional nature, impact on health outcomes, duration and recurrence, and age-specific manifestations, as well as recommendations for depression screening and nonpharmacological treatment.

Overview: MDD and Elevated Depressive Symptoms

MDD is a serious mood disorder that affects an estimated 8.3% of all U.S. adults, or 21 million people (12). MDD is characterized by symptomatic episodes of 2 weeks' duration or longer defined by a loss of interest or pleasure in all or almost all activities and/or a depressed mood for most of the day nearly every day (13). The loss of interest or pleasure and/or depressed mood must be present along with four or more somatic, psychological, and cognitive symptoms for the diagnosis of MDD. These symptoms include appetite disturbance or weight loss, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, feelings of worthlessness and guilt, diminished concentration or indecisiveness, and recurrent suicidal ideation (13). Not all people will meet the criteria for MDD per the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5); however, that does not diminish the seriousness of elevated depressive symptoms.

For the remainder of the article, MDD and elevated depressive symptoms will be referred to as depression.

Corresponding author: Elizabeth A. Beverly, beverle1@ohio.edu

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Bidirectional Relationship

Diabetes and depression have a bidirectional relationship, such that a preexisting history of depression increases the risk of type 2 diabetes, and a diagnosis of type 1 or type 2 diabetes increases the risk of depression (14,15). Several systematic reviews and meta-analyses have documented this bidirectional relationship. A 2008 systematic review and meta-analysis of 13 studies representing 6,916 cases found that people with depression had a 60% increased risk of developing type 2 diabetes (15). Similarly, a 2017 meta-analysis of 32 studies with 1,274,337 participants showed that people with depression were at 34% higher risk for type 2 diabetes compared with people without depression (16). This systematic review and meta-analysis also pooled data from 24 studies with 329,658 participants and found a 28% increased risk of developing depression in people with diabetes compared with those without diabetes (16). This finding is comparable to another 2010 systematic review and meta-analysis of 11 longitudinal studies involving 172,521 participants that found people with type 2 diabetes had a 24% increased risk of incident depression compared with those without diabetes (17).

A complex interplay of biological, behavioral, and psychosocial mechanisms contributes to the bidirectional relationship between diabetes and depression. Proposed biological mechanisms include inflammation, the hypothalamic-pituitary-adrenal (HPA) axis, and neurotransmitter imbalances. A 2015 meta-analysis of 58 studies found significantly elevated levels of C-reactive protein (CRP) and interleukin-6 in people with depression (18). A 2014 prospective cohort study of 4,955 community-dwelling adults found that type 2 diabetes incidence was highest among participants with elevated depressive symptoms and high CRP levels, which signal inflammation, even after adjusting for age, sex, comorbidities, and BMI (adjusted hazard ratio 2.03, 95% CI 1.14–3.61) (19). Another study from 2017 observed that the severity of depressive symptoms was positively associated with serum high-sensitivity CRP ($P < 0.01$) and the high-molecular-weight [HMW]-to-total adiponectin ratio in adults with type 2 diabetes ($P < 0.01$) (20). Adiponectin is a hormone produced from adipocytes that plays a role in the metabolism of glucose and lipids (21). It circulates in human serum as low-molecular-weight, medium-molecular-weight, or HMW forms, with low referring to a smaller, simpler form of adiponectin and high referring to a larger, more complex form. HMW adiponectin is the most biologically active form, and high circulating levels are associated with improved insulin sensitivity and reduced inflammation (22). Although the observed association between increased depressive symptoms and HMW-to-total adiponectin ratio may seem counterintuitive, a higher ratio may also signal that the body is under chronic stress and working to counterbalance the inflammation and insulin resistance of type 2 diabetes. In this same study, no association was observed between depressive symptoms and HMW-to-total adiponectin ratio in adults with type 1 diabetes; however, a positive association was observed between depressive symptoms and soluble intercellular adhesion molecule-1 (sICAM-1) levels in adults with type 1 diabetes ($P = 0.035$) (20,23). sICAM-1 is a protein involved in inflammation and the immune response, both of which are independently associated with type 1 diabetes (24) and depression (25).

Evidence also supports the involvement of the HPA axis. The HPA axis is a neuroendocrine system responsible for regulating the body's response to stress (26). Its main function is to release glucocorticoids, primarily cortisol, to activate the body's short-term stress response. During a stressful situation, the autonomic nervous system signals the hypothalamus to release corticotropin-releasing hormone (CRH). CRH then activates the pituitary gland to release adrenocorticotropic hormone, which subsequently triggers the adrenal cortex to release cortisol (26). Cortisol mobilizes energy during stress by raising blood glucose levels. However, chronic HPA axis activation, often resulting from prolonged stress, can lead to sustained high levels of cortisol. This chronic elevation of cortisol disrupts neurotransmitters, including serotonin and dopamine, both of which regulate mood and are linked to depression (27). In relation to diabetes, chronic elevation of cortisol levels can redistribute fat from peripheral to visceral depots and increase both the number and size of adipocytes (fat cells) (27). Cortisol also stimulates lipolysis, releasing fatty acids into the bloodstream, which contributes to insulin resistance (28). A 2014 study of 3,508 participants, including 238 participants with type 2 diabetes, showed that having diabetes was associated with a flatter decline in cortisol across the day (95% CI 0.001–0.007, $P = 0.014$) and raised cortisol levels at bedtime (95% CI 0.010–0.117, $P = 0.020$) (29). These findings contrast with cortisol's typical diurnal pattern, which is characterized by high levels upon waking, a peak 30–45 minutes later, followed by a decline throughout the day (30). Another 2014 study with 196 participants with type 1 diabetes found that participants with self-reported depression had high midnight salivary cortisol levels ($\geq$9.3 nmol/L) (31). These studies demonstrate how dysregulation of the HPA axis and altered cortisol patterns are associated with both diabetes and depression.

Behavioral mechanisms in the relationship between diabetes and depression emphasize the role of health behaviors. Findings from a 2019 longitudinal study of 47,671 adults showed that unhealthy behaviors such as tobacco and alcohol use, eating behaviors, and BMI moderated the relationship between depressive symptoms and type 2 diabetes (32). Another

2008 longitudinal study of 4,847 adults found that baseline depressive symptoms predicted rates of new-onset type 2 diabetes; however, after controlling for demographic factors and health behaviors (i.e., smoking status, daily caloric intake, physical activity, and alcohol consumption), the increased risk for type 2 diabetes was no longer significant (14). This finding lends support to the contribution of behavioral mechanisms in the relationship between diabetes and depression.

Finally, psychosocial mechanisms may also explain the relationship between diabetes and depression. A 2007 longitudinal study with 4,747 participants assessed depressive symptoms among adults with normal fasting plasma glucose (FPG), impaired FPG, undiagnosed type 2 diabetes, and diagnosed type 2 diabetes. Findings revealed that participants with impaired FPG and undiagnosed type 2 diabetes did not have an increased risk of depressive symptoms, whereas those with diagnosed type 2 diabetes had a 1.7 times increased risk of elevated depressive symptoms compared with participants with normal FPG (33). This finding suggests that the psychosocial burden of diagnosed diabetes is a risk factor for depression.

Clinical Impact

The clinical implications of depression are substantial. In adults with type 2 diabetes, depression is associated with hyperglycemia (34), higher systolic blood pressure (35,36), higher levels of LDL cholesterol (36), lower levels of HDL cholesterol (36), and higher triglyceride levels (37). Consequently, adults with depression are at significantly higher risk for adverse macrovascular outcomes, including cardiovascular, cerebrovascular, and peripheral vascular disease (38,39), and microvascular outcomes, including retinopathy, nephropathy, and neuropathy, even after adjusting for demographic and clinical variables (38,39). Moreover, depression is associated with decreased engagement in diabetes self-care, specifically appointment-keeping, healthy eating, medication-taking, regular exercise, and glucose monitoring (40). Further complicating clinical status, adults with depression are more likely to experience comorbid psychosocial concerns, including diabetes distress (41), anxiety (42,43), binge eating disorder (44), night eating syndrome (45), suicide risk (46), serious mental illness (47), and cognitive impairment (48). All of these factors contribute to decreased health-related quality of life (HRQoL) (49), increased functional disability (50,51), increased use of medical services (50), higher total health care costs (50), and increased risk of all-cause mortality (52,53).

In adults with type 1 diabetes, depression is associated with higher mean A1C (54), severe hyperglycemia (55), severe hypoglycemia (55), higher total cholesterol (56), and lower HDL cholesterol (57). These metabolic changes contribute to an increased risk for macrovascular complications (58,59) and microvascular complications (54). Furthermore, depressive symptoms are associated with decreased self-care behaviors in adults with type 1 diabetes, including performing physical activity (60), monitoring blood glucose (61), bringing blood glucose meters to medical appointments (61), and using continuous glucose monitoring devices (61). Adults with comorbid depression are more likely to experience multiple psychosocial concerns, including diabetes distress (60), anxiety (62), disordered eating and eating disorders (63,64), suicide risk (46,65), and cognitive impairment (66,67). Overall, depression negatively affects HRQoL (68), health care utilization (50), total medical costs (69), and all-cause mortality (53,70,71).

Recurrent Episodes of Depression

Recurrence of depression is a crucial aspect of the psychosocial care of people with diabetes and depression. A 2016 study of 50 participants with type 2 diabetes and depression examined the history of depressive disorders at baseline, post-intervention, and 3-month follow-up (72). Findings included a mean number of lifetime episodes of depression of 1.8 ± 0.8 (range 1.0–4.0), a mean episode duration of 23.4 ± 31.9 months (range 0.5–231.3 months), and a mean lifetime exposure to all depression diagnoses of 43.1 ± 46.5 months (range 0.5–231.3 months) (72). Additionally, the time between episodes became shorter, with the median time to the second recurrence much shorter than the time to first recurrence (66.0 vs. 128.5 months, $n = 32$) and the median time to the third recurrence much shorter than the time to the second recurrence (18.0 vs. 62.0 months, $n = 19$). These findings are consistent with prior research documenting the course of depression in adults with type 1 or type 2 diabetes (73–75).

Of particular importance, the course of depression in adults with diabetes is of long duration. As noted above, the average duration of depressive episodes in adults with diabetes was 23.4 months, whereas in the general population, depressive episodes average ~3 months (76,77). This considerable discrepancy highlights the need for screening protocols and early intervention, when indicated. Without intervention, people with diabetes and comorbid depression are at higher risk for negative health outcomes, decreased quality of life, and increased mortality.

Age-Specific Manifestations

HCPs should be aware that depressive symptoms may manifest differently across the life span. In children with diabetes,

depressive symptoms may present as somatic complaints (e.g., headaches and stomachaches), behavioral changes (e.g., irritability, mood swings, crying, and tantrums), decreased energy, decline in academic performance, and social withdrawal from friends and activities (78,79). Some symptoms overlap in children and adolescents, including behavioral changes (e.g., mood swings and irritability), academic decline, withdrawal from peers and social activities, and fatigue (79,80). New symptoms in adolescence may include disturbances in sleep patterns and engagement in risky behaviors such as substance use and/or not performing diabetes self-care behaviors (80,81). One of the strongest risk factors for depression in youth with diabetes is parental depression, which occurs in ~22% of parents (11). Thus, parental depression should be considered an essential component of diabetes-related psychosocial care in youth with diabetes.

Adults with diabetes tend to show depressive symptoms more consistent with the DSM-5 criteria, including persistent sadness, loss of interest in activities once enjoyed, fatigue, difficulty concentrating or making decisions, and physical complaints such as aches and pains (82). Older adults with diabetes may also show a loss of interest in activities and physical complaints; however, the physical complaints may be more frequent and more severe. Additionally, older adults may show a noticeable slowing down in speech and body movements, increased memory problems and confusion, preoccupation with their mortality, and denial or lack of sadness (83). Importantly, older adults with depression are at increased risk for suicidal thoughts and actions. The most common risk factors for suicide in older adults are the recent death of a loved one, social isolation and loneliness, a major change in a social role, a decline in physical health, and a perception of poor health (83). Understanding how depressive symptoms may differ across different age-groups can enhance the accuracy of diagnoses and ensure the provision of more appropriate treatments.

Depression Screening Recommendations

The American Diabetes Association (ADA) recommends at least annual screening for depressive symptoms in all people with diabetes and more frequent screening in those with a history of depression (3). Other crucial times for screening include at the diagnosis of complications and when there are significant changes in medical status (3). The U.S. Preventive Services Task Force (USPSTF) also recommends screening for depression in the adult population, including older adults ≥65 years of age, and adolescents aged 12–18 years (84,85). HCPs should use age-appropriate standardized and validated tools to screen for elevated depressive symptoms and depression and, when indicated, should refer to a qualified behavioral health professional with experience in evidence-based treatment approaches for depression (3).

Depression Screening Tools

Selecting the appropriate screening tool involves careful consideration of several key factors, including validity and reliability, sensitivity and specificity, suitability for the person with diabetes, language availability, integration within the health care system, and cost. Table 1 provides a list of recommended screening tools.

A 2012 systematic review (86) and a 2018 systematic review (87) of screening tools for measuring depression in people with type 1 or type 2 diabetes concluded that the Center for Epidemiological Studies Depression Scale (CES-D) (88) was the best-supported tool for measuring depressive symptoms in people with diabetes. Specifically, the CES-D had the best ability to discriminate between depressive symptoms and nondepressive symptoms, which is crucial given the high rates of comorbid psychosocial concerns in people with diabetes (89). Furthermore, the CES-D demonstrated strong evidence for internal consistency, structural validity, and construct validity and moderate evidence for positive criterion validity, and it has been used in people with diabetes in multiple languages and cultures (e.g., Chinese, English, Indian, Malaysian, Spanish, and Turkish) (87). The Patient Health Questionnaire-9 (PHQ-9) is also recommended. The PHQ-9 demonstrates good internal consistency, criterion validity, and construct validity. It has been used in people with diabetes in five languages (Chinese, Dutch, English, Mirpuri, and Sylheti) (87). For adults ≥60 years of age, the Geriatric Depression Scale-15 (GDS-15) is recommended. This tool focuses on psychiatric rather than somatic symptoms (e.g., weight loss and sleep disturbances), which can be related to the aging process (90). The GDS-15 can be completed in 5–7 minutes, which is ideal for people who fatigue easily or have a limited ability to concentrate for long periods. For youth, the Center for Epidemiologic Studies Depression Scale for Children (CES-DC) (91) and the PHQ-9 Modified for adolescents (PHQ-A) (92) are recommended. The USPSTF notes that both screening tools have been well studied and are widely used (84).

Referrals to Behavioral Health

A positive screen indicates that a person with diabetes has depressive symptoms, but it does not confirm a diagnosis of depression. Individuals with a positive screen should be referred to a qualified behavioral health professional, ideally one with experience in diabetes, for further assessment. If a person expresses suicidal thoughts or plans during the

TABLE 1 Recommended Depression Screening Tools

Tool	Construct Measured	Target Population	Reliability/ Validity, α	Sensitivity, %	Specificity, %	Items, *n*	Score Range	Cut Points	Time, minutes	Cost
Adults										
CES-D	Level of depressive symptoms	Adults	0.60–0.93	60–100	61–87	20	0–60	≤16: no to mild depression; 17–23: moderate depression; ≥24: severe depression	5–10	Free
PHQ-9	Symptoms of major depressive disorder	Adults	0.86–0.89	66–100	52–85	9	0–27	0–4: no depression; 5–9: minimal depression; 10–14: mild depression; 15–19: moderate depression; 20–27: severe depression	2–5	Free
Older Adults										
GDS-15	Mild and major depression	Adults ≥60 years of age	0.92	92	89	15	0–15	0–4: no depression; 5–8: mild depression; 9–11: moderate depression; 12–15: severe depression	5–7	Free
Youth										
CES-DC	Level of depressive symptoms	Youth 6–17 years of age	0.89	71	57	10	0–60	≥15: clinically elevated depressive symptoms	5–10	Free
PHQ-A	Symptoms of major depressive disorder	Adolescents 11–17 years of age	0.89	84–95	68–95	9	0–27	0–4: no depression; 5–9: minimal depression; 10–14: mild depression; 15–19: moderate depression; 20–27: severe depression	2–5	Free

screening process, a suicide risk assessment should be performed. Specific questions to ask may include, "Do you have thoughts of harming yourself?" If the individual responds yes, ask, "Do you have a plan to hurt yourself?" If they respond yes, immediate intervention is necessary.

Assessment Considerations

Diabetes and depression share confounding symptoms (e.g., fatigue, appetite disturbance, and disrupted sleep), which makes accurate assessment of depression difficult. For this reason, self-reported screening measures may result in false positives and, in turn, overdiagnosis and overtreatment (82). Overtreatment with antidepressants in people with diabetes can lead to a range of issues, including weight gain (93), hypoglycemia (94,95) and/or hyperglycemia (95), increased health care costs (96), medication burden (97), and polypharmacy (98). Importantly, the impact of each antidepressant medication can differ greatly depending on individuals' unique characteristics. Furthermore, depressive symptoms often overlap with other psychosocial concerns such as diabetes distress (41,99), which means that accurate diagnosis of depression requires a clinical evaluation. The ADA provides a list of behavioral health professionals who have specialized training in psychosocial concerns related to diabetes (https://my.diabetes.org/health-directory).

Nonpharmacological Evidence-Based Treatment Recommendations for Depression

Multiple psychosocial interventions, including cognitive behavioral therapy (CBT), collaborative care, mindfulness, and exercise, have demonstrated improvements in depressive symptoms. CBT is an evidence-based form of psychotherapy that uses goal-oriented techniques to identify and change negative thought patterns and behaviors (100). A 2022 systematic review and meta-analysis of 32 randomized controlled trials (RCTs) with 7,006 participants (n = 3,603 in intervention groups and n = 3,403 in control groups) used CBT in adults with type 1 diabetes, type 2 diabetes, or gestational diabetes (101). Twenty of the studies evaluated CBT as monotherapy, and 12 evaluated CBT in combination with motivational enhancement therapy, lifestyle intervention, or aerobic exercise. The CBT-based interventions reduced A1C by −0.14% (k = 22, 95% CI −0.25 to −0.02%, P = 0.020), fasting blood glucose levels by −15.48 mg/dL (k = 4,

95% CI −30.16 to −0.81 mg/dL, P = 0.040), diastolic blood pressure by −2.88 mmHg (k = 4, 95% CI −4.08 to −1.69 mmHg, P <0.001), scores for depressive symptoms by −5.67 (k = 21, 95% CI −9.52 to −1.82, P = 0.04), scores for anxiety symptoms by −1.46 (k = 8; 95% CI −2.53 to −0.39, P = 0.008), and scores for sleep quality by −2.14 (k = 3, 95% CI −4.15 to −0.14, P = 0.04) (101). Two RCTs using Web-based CBT also demonstrated improvements in depressive symptoms for people with diabetes. A 2017 trial randomized participants with type 1 or type 2 diabetes to either the 10-week Web-based lessons in CBT skills (n = 49) or treatment as usual (n = 57) (102). It found that the Web-based CBT program was more effective in reducing depressive symptoms than usual care postintervention, with a moderate between-group effect size (Cohen d = 0.78) (102). Similarly, a 2023 trial randomized participants with type 1 diabetes to either a 9-week Web program with weekly sessions based on CBT (n = 35) or a control group (n = 30), which served as a waiting list for the Web-based program (103). Compared with the control group, the Web-based CBT program demonstrated greater improvements in depressive symptoms (P = 0.001) but not A1C (P = 0.576) at the end of the intervention (103).

RCTs using the collaborative care model, an integrated approach to health care that brings together primary care and behavioral health, show improvements in both A1C and depressive symptoms. A 2014 systematic review and meta-analysis of seven collaborative care interventions found a − 0.33% reduction in A1C (n = 1,556, 95% CI −0.66 to −0.00%) and a − 0.32 reduction in standardized depressive symptoms (n = 1,895, 95% CI −0.53 to −0.11). Likewise, mindfulness-based interventions have also shown improvements in A1C and depressive symptoms. These interventions are designed to help people with diabetes manage the physical and psychosocial demands of a chronic, progressive condition. Specifically, mindfulness-based interventions focus on stress reduction, emotion regulation, mindful eating, body awareness, and improvement in self-care behaviors (104). A 2021 systematic review and meta-analysis of eight RCTs with 659 participants (n = 297 in intervention groups and n = 362 in control groups) with type 1 or type 2 diabetes showed a −0.25% reduction in A1C (k = 6; 95% CI −0.43 to −0.07) and a −0.56 reduction in standardized depressive symptoms (k = 8, 95% CI −0.82 to −0.30) (104). Finally, exercise interventions (aerobic, resistance, or combined) with and without nutrition counseling also show improvements in A1C and depressive symptoms. A 2022 systematic review and meta-analysis of 17 RCTs with 2,127 participants (n = 1,164 in intervention groups and n = 963 in control groups) with type 2 diabetes documented an A1C reduction of −0.51% (k = 7, 95% CI −0.97 to −0.04%, P = 0.03) and a standard mean difference of −0.65% (k = 11, 95% CI −1.03 to −0.28%, P <0.001) in depressive symptoms (105). Notably, only the meta-analysis of exercise interventions demonstrated a clinically significant reduction in A1C (≥0.5%), a threshold associated with decreased risk of diabetes-related complications (106). Taken together, this evidence supports multiple psychosocial interventions for people with diabetes and depression.

Conclusion

The complex relationship between diabetes and depression presents a significant challenge to the health and quality of life of people with diabetes. The bidirectional nature of these conditions, coupled with their long duration and frequent recurrence, necessitate vigilant screening, early intervention, and evidence-based treatment. This review highlighted nonpharmacological evidence-based treatments. Psychosocial interventions, including CBT, collaborative care, mindfulness, and exercise, have demonstrated effectiveness in improving both glycemic outcomes and depressive symptoms. As the prevalence of diabetes and comorbid depression continues to rise, HCPs must address these interconnected conditions with person-centered and comprehensive care.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

E.A.B. led the conception and design of the review, conducted the literature search, and wrote the manuscript. J.S.G. reviewed and edited the manuscript and contributed to discussion. Both authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring its integrity and accuracy. E.A.B. is the guarantor of this work and, as such, had full access to all the literature reviewed and takes responsibility for the integrity of the data presented and the accuracy of the conclusions drawn from the reviewed studies.

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