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REVIEW ARTICLE

Depression as an Immunometabolic Disorder: Exploring Shared Pharmacotherapeutics with Cardiovascular Disease

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Abstract: Modern times have seen depression and cardiovascular disease (CVD) become notorious public health concerns, corresponding to alarming proportions of morbidity, mortality, decreased quality of life, and economic costs. Expanding comprehension of the pathogenesis of depression as an immunometabolic disorder has identified numerous pathophysiologic phenomena in common with CVD, including chronic inflammation, insulin resistance, and oxidative stress. These shared components could be exploited to offer improved alternatives in the joint management of these conditions. Abundant preclinical and clinical data on the impact of established treatments for CVD in the management of depression have allowed for potential candidates to be proposed for the joint management of depression and CVD as immunometabolic disorders. However, a large proportion of the clinical investigation currently available exhibits marked methodological flaws which preclude the formulation of concrete recommendations in many cases. This situation may be a reflection of pervasive problems present in clinical research in psychiatry, especially pertaining to study homogeneity. Therefore, further high-quality research is essential in the future in this regard.

Keywords: Depression, cardiovascular disease, chronic inflammation, insulin resistance, oxidative stress, metabolism.

1. INTRODUCTION

In recent years, depression has become one of the most prominent conditions in daily clinical practice and is currently recognized as the leading cause of disability globally, amounting to extremely high direct and indirect financial costs, as well as representing a severe detriment to the quality of life [1]. Interestingly, depression stands alongside cardiovascular disease (CVD) as some of the most prominent problems in public health at present, with CVD being the first cause of mortality and morbidity worldwide [2]. The parallels in the epidemiology of these conditions have sparked abundant research on their interrelated pathophysiology and clinical management.

Although depression is notorious for frequently co-occurring with a myriad of medical comorbidities [3], the link with CVD appears to be particularly powerful, with these entities sharing various risk factors such as chronic stress, physical inactivity, westernized dietary patterns and various metabolic alterations [4] and depression increasing CVD-related mortality by up to 60% [5]. Moreover, they share several pathophysiologic components, including chronic low-grade inflammation, insulin resistance (IR), and dysthrombogenesis [6]. The presence of these shared elements blurs the traditional distinction between mental and physical illness, and could significantly change the management standards of depression and CVD by posing the question: How can the treatment of these conditions be integrated on the basis of their common pathophysiologic components? This review aims to summarize current views on depression as an immunometabolic disorder and its link with CVD, as well as potential novel pharmacological options for their joint management. A literature search was performed on PubMed, EMBASE, Scopus, ISI Web of Science, and Google Scholar databases, from inception to January 2020.

2. REVISITING DEPRESSION AS AN IMMUNOMETABOLIC DISORDER

2.1. From the Sparks to the Flame: Emphasis on Chronic Inflammation

Depression was historically conceived as an illness limited to the brain-mind. However, in recent decades, accumulating evidence has propelled a paradigm shift, where depression is now understood as a systemic disease, with the

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brain-mind and the body sharing a bidirectional relationship [7]. Chronic inflammation (CI) has been identified as a key common component in depression and multiple medical conditions, including CVD, endocrine-metabolic disorders, autoimmune disorders, cancer, and many others [8-11]. Although inflammation is a key physiologic mechanism that aims to preserve homeostasis in the face of injury, it comes at the cost of profound disturbances in the functionality of target tissues [12]. Classic examples of these include vascular changes to allow exudate formation, such as increased endothelial adhesiveness and permeability in response to cytokine signaling [13]. Nonetheless, all tissues are vulnerable to inflammation-induced changes, with each displaying distinct patterns of dysfunction. Thus, systemic CI entails the dysregulation of multiple organ systems [14].

The term "neuroinflammation" has been coined to describe CI in the central nervous system (CNS), which involves activation of microglia, astrocytes and oligodendrocytes, with the release of cytokines, chemokines, acute-phase reactants, and other mediators [15]. Although neuroinflammation may be beneficial in the acute setting, for example, in the limitation of CNS infections; its persistence results in hyperactivation of microglia and neurotoxicity [16, 17]. As with all forms of CI, it is hypothesized to stem from the conflation of extrinsic and intrinsic proinflammatory factors (Fig. **1**) [18, 19].

A great body of research has documented the presence of elevated circulating biomarkers of inflammation in participants with depression, including IL-1β, IL-6, IFNγ, TNFα and acute-phase reactants, especially high-sensitivity C-Reactive Protein (hs-CRP), among others [20, 21]. Neuroinflammation and chronic stress are both powerful inducers of the neuroendocrine changes typical of depression, especially sustained activation of sympathetic autonomous signaling and the hypothalamus-pituitary-adrenal axis (HPAA) [22]. Notably, in non-depressed participants, acute and chronic stress, as well as increased inflammatory biomarkers have been associated with "sickness behavior", which features many depressive characteristics, such as low mood, anhedonia, fatigue, and feeding and sleep disorders [18,23]. Indeed, neuroinflammation can significantly disrupt the metabolism and signaling of monoamines serotonin, norepinephrine and dopamine the central neurotransmitters involved in the neurobiology of depression [24].

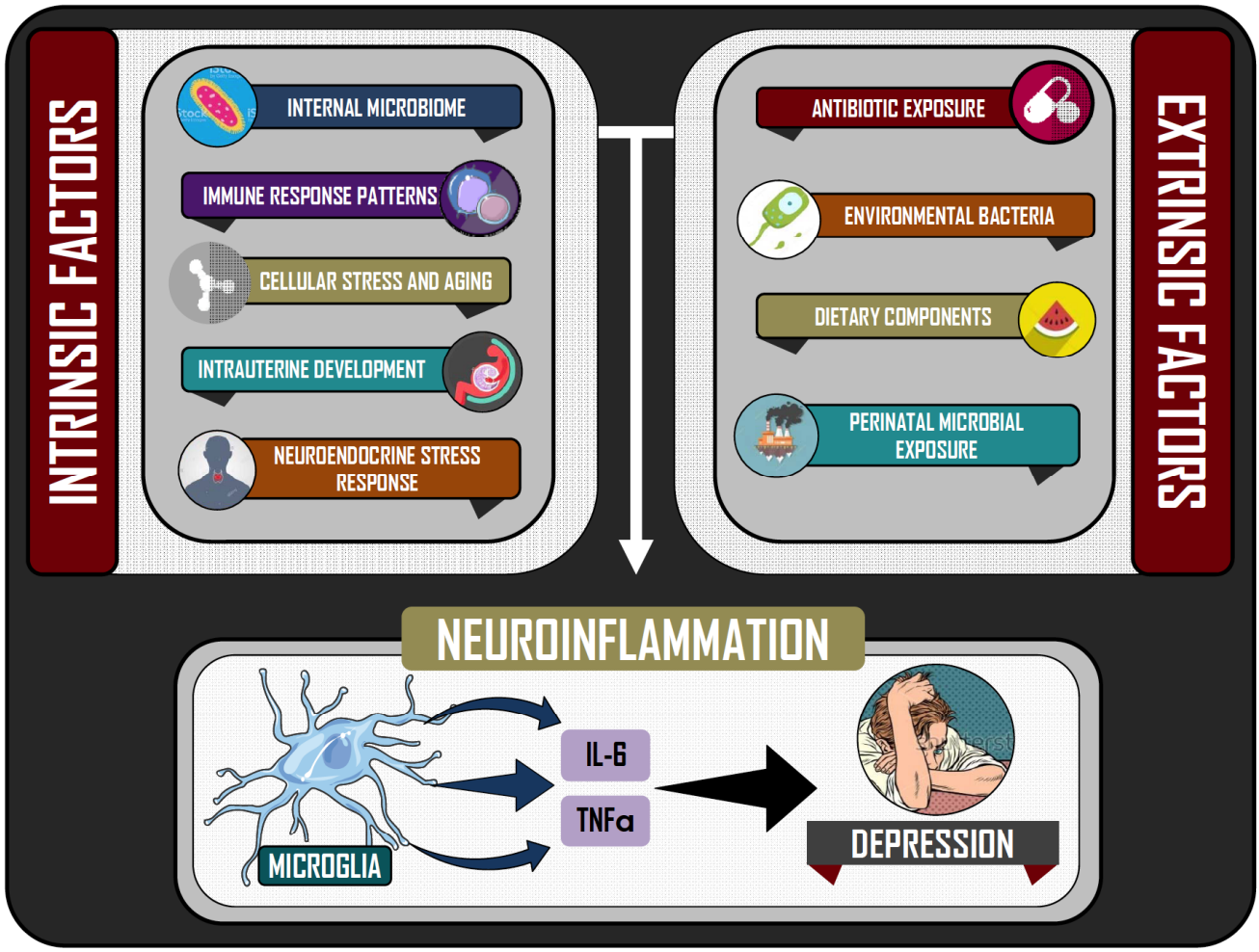

Fig. (1). Intrinsic and extrinsic etiologic factors of neuroinflammation. The additive and synergic effects of various intrinsic and extrinsic factors results in chronic inflammation. Neuroinflammation in particular is associated with depression and other neuropsychiatric disorders. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

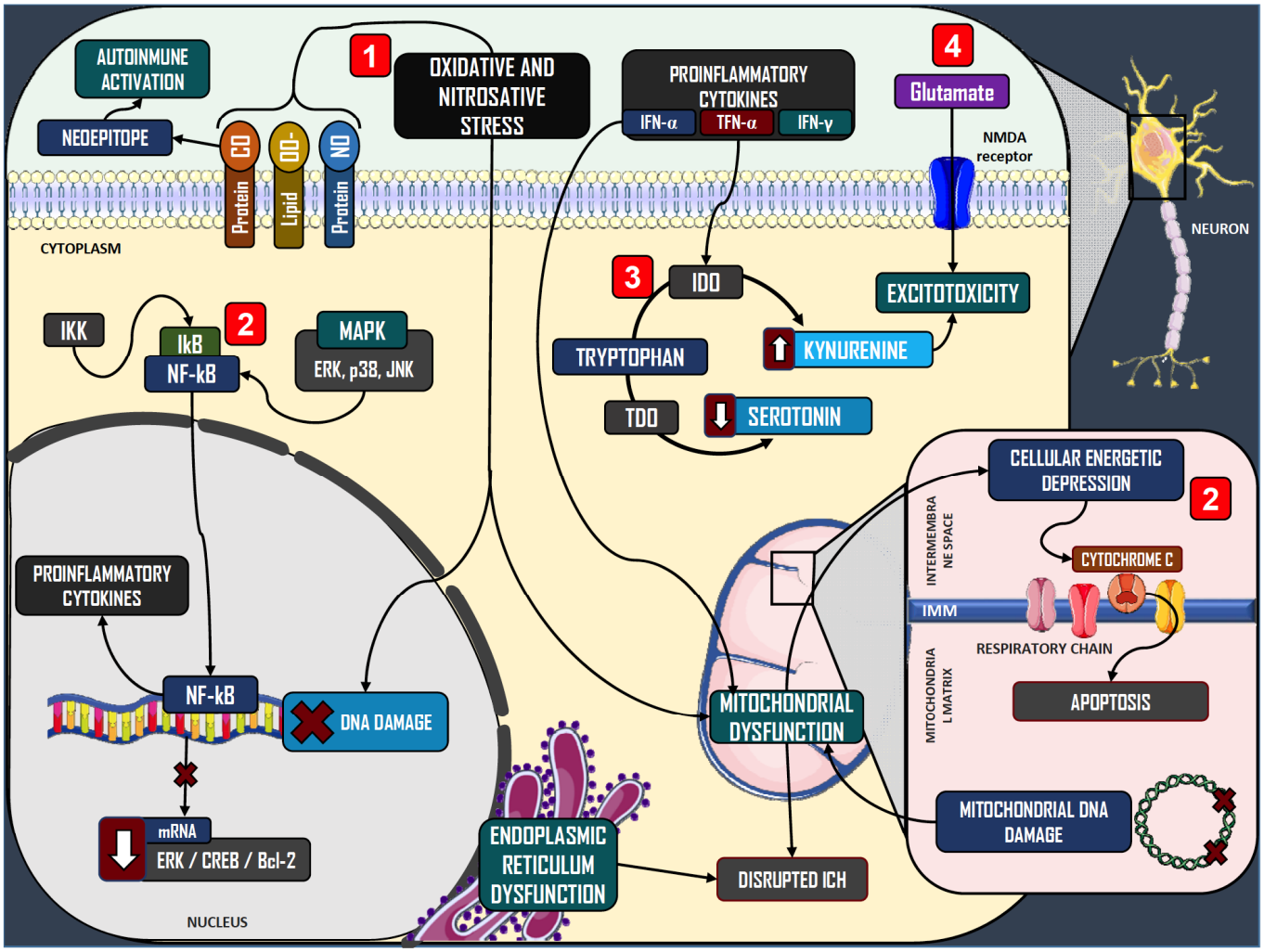

Fig. (2). Molecular events associated with chronic inflammation in neurons. In neurons, chronic inflammation is associated with four major pathophysiologic components: 1) Increased oxidative and nitrosative stress, which is associated with protein carbonylation and nitrosylation as well as lipid peroxidation, which results in formation of neoepitopes and favors autoimmunity. Oxidative stress and nitrosative stress also damages nuclear DNA and induces mitochondrial dysfunction. 2) Activation of stress-related intracellular signaling pathways, which promote apoptosis and disruptions in intracellular calcium homeostasis, worsen inflammation and oxidative stress, and impair neurotrophic signals. 3) Disruptions in monoamine metabolism, through activation of IDO, leading to kynurenine synthesis, which decreases serotonin availability and promotes excitotoxicity. 4) Excitotoxicity, promoted by kynurenine, disrupted calcium metabolism, and increased glutamate signaling from glial cells. Abbreviations: Protein-CO: Protein carbonylation. Protein-NO: Protein nitrosylation. Lipid-OO-: Lipid peroxidation. IKK: I kappa B Kinase. IkB: inhibitor kB protein. NFkB: Nuclear factor kappa B. MAPK: Mitogen-activated protein kinases. ERK: Extracellular signal-regulated kinase. JNK: Jun N-terminal kinase. CREB: Cyclic AMP responsive element binding protein. Bcl-2: B-cell lymphoma-2. IDO: Indoleamine 2,3-dioxygenase. TDO: Tryptophan 2,3-dioxygenase. ICH: Intracellular calcium homeostasis. IMM: Internal mitochondrial membrane. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

At the molecular level, oxidative stress (OS), alterations in intraneuronal signaling, disruptions in monoamine metabolism and excitotoxicity are the major pathophysiologic phenomena induced by CI in the context of depression (Fig. **2**). Oxidation of inflammatory mediators such as arachidonic acid and its precursor, linoleic acid, entails increased production of reactive oxygen species (ROS) [25-27], which can cause membrane lipid peroxidation, DNA damage and protein carbonylation in neurons [28]. Patients with depression may be especially vulnerable to OS, with lower levels of antioxidant molecules such as glutathione, coenzyme Q10, and possibly zinc, vitamin A and vitamin D; as well as decreased expression of superoxide dismutase and glutathione peroxidase [29, 30]. CI also involves hyperactivity of inducible nitric oxide synthase (iNOS) with increased production of nitric oxide and nitrosative stress (NS) by nitrosylation of proteins, membrane lipids and DNA [29, 31].

Proinflammatory cytokines, OS and NS act as alarm signals and can activate cellular stress-related kinases such as JNK, p38 and IKK-kinase. These promote the nuclear translocation of NF-κB, a potent proinflammatory transcription factor, thus worsening CI in a positive feedback loop [32-34]. Furthermore, patients with depression have been described to exhibit significantly higher levels of IgM antibod-

ies against neoepitopes produced from CI, OS and NS [35]. Neuronal stress also potentiates signaling of the ERK/CREB/Bcl-2 pathway, which promotes apoptosis, alterations in intracellular calcium traffic, and release of cytochrome C [36-38]. Neurons in the prefrontal cortex, anterior cingulate cortex, amygdala and hippocampus may be particularly susceptible to these changes in depression [38-42]. Guan *et al*. reported prenatally stressed offspring rats to display the decreased expression of these proteins in the prefrontal cortex and hippocampus, in association with depression-like behavior [38]. Conversely, patients with depression may have impaired activity of Nrf-2, a transcription factor that promotes the expression of cytoprotective enzymes such as thioredoxin reductase, glutathione peroxidase, glutathione-S-transferase, haeme oxygenases, and others [43-45]. Indeed, imaging and postmortem studies have identified neuronal and glial modifications, as well as volumetric changes in the hippocampus, amygdala, basal nuclei, the prefrontal cortex, and the anterior cingulate cortex, in association with cognitive impairment [46-48]. This structural neurodegeneration is thought to be due to decreased signaling by neuroprotective mediators, such as the brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF) [49-51]; which in turn are disrupted by the damaging environment promoted by CI and OS [52-54]. These alterations in neurotrophic signaling may be reversible by antidepressant treatment [55, 56]; and BDNF levels have been observed to rise in parallel with the improvement of depressive symptoms in a clinical study by Piccinni *et al*. [57].

Finally, in neurons, IFN-α, IFN-γ and TNF-α can activate indoleamine 2,3-dioxygenase (IDO), which synthesizes kynurenine (KYN) from tryptophan, the precursor to serotonin, thus implicating decreased production of this monoamine. In addition, the metabolism of kynurenine yields quinolinic acid and kynurenic acid (KA), both of which promote excitotoxicity by binding to NMDA receptors and promoting glutamate release in glial cells [58]. Furthermore, KA may impair dopamine release [59,60]. In patients with hepatitis C undergoing therapy with IFN-α for 24 weeks, this treatment was associated not only with increased depressive symptoms, but also increased KYN/tryptophan ratios, reflecting higher IDO activity, as well as increased KYN/KA ratios, corresponding to the degree of neurotoxicity involved [61].

2.2. Feeding the Fire: Proinflammatory Neuroendocrine Signaling

Certainly, the impact of CI on depression is hardly limited to changes in the brain; it is widely recognized as a pivotal pathophysiologic component in atherosclerosis, by potentiating vascular chemotaxis, release of growth factors, and proliferation of vascular smooth muscle cells, among other mechanisms. This underlines the shared mechanisms underlying the pathogenesis of depression and CVD [62]. Participants with depression also appear to have increased expression of VCAM-1 and other vascular adhesion and thrombogenic molecules in endothelial cells [63-67]. Hyperactivation of the HPAA and hypercortisolemia have been related to the downregulation of endothelial nitric oxide synthase (eNOS), impairing relaxation of vascular walls [68, 69]. Other possible alterations of vascular tone in depression include decreased vagal tone with sympathetic hyperactivation, with increased non-selective α-adrenergic and β-adrenergic activity in the cardiovascular system [70, 71]. Platelet dysfunction has also been described in depression, including augmented intraplatelet traffic of calcium and other disruptions in signaling, upregulation of α-adrenergic and 5HT2A receptors, P-selectin, glycoprotein IIb/IIIa and β-thromboglobulin, and downregulation of serotonin transporters [72-74]. Indicators of endothelial dysfunction in depressed patients may improve with antidepressant therapy. López-Vílchez *et al*. found participants with depression to display higher levels of circulating endothelial cells, VCAM-1 and soluble von Willebrand factor, which decreased gradually along 24 weeks in treatment with escitalopram [63].

In addition, IR is a pivotal mediator between CI, CVD and depression. IR, defined as decreased peripheral tissue responsivity to insulin signaling [75], is promoted by proinflammatory mediators, particularly by inducing serine phosphorylation of IRS-1 [76], as well as ectopic fat deposition in the liver and muscle tissue [77]. Typical hormonal changes of depression, such as increased catecholamine and glucocorticoid signaling, can also promote IR. This impact may be most marked regarding the cognitive symptoms of depression, as described by Austin *et al*. in a cohort of 328 patients [78]. This reduced sensitivity entails hyperinsulinemia, which in turn yields deleterious effects on all organ systems, and predisposes to numerous cardiometabolic disturbances such as obesity, hyperglycemia, dyslipidemia and hypertension, among others [79]. In turn, these are all promoters of CI, thus constituting a vicious cycle involving depression, CI, and IR (Fig. **3**) [80].

Obesity is a powerful enhancer of IR and all its associated disturbances. Adipose tissue has been recognized as an immunologically active organ, through the secretion of proinflammatory cytokines and adipokines: leptin, resistin and adiponectin [81]. Leptin plays a physiological role, where it promotes satiety in accordance with increasing adipose tissue deposits. However, in obesity, leptin resistance is a frequent finding, favoring an energetic imbalance towards excess [82]. Leptin also intervenes in the pathogenesis of depression by potentiating HHPA activation [83] and promoting the expression of IL-6 and TNFα [84]. Resistin and adiponectin display opposite effects regarding CI and energetic homeostasis, with the former being proinflammatory and upregulated in obesity, and the latter being anti-inflammatory and upregulated by weight loss, with decreased expression in obesity [85]. Although the role of resistin in depression remains obscure; adiponectin expression has been found to be downregulated by glucocorticoid signaling, which could further favor obesity and CI in depression [86]. Altered adipokine levels have been widely reported in depressed patients, especially increased leptin and decreased adiponectin [87]. These mediators have been proposed as putative biomarkers for depression, though variables such as the severity of depression and obesity may be important confounders in this context as determined in a systematic review and meta-analysis by Carvalho *et al*. [88]. Adipokines may be predictors of antidepressant therapy outcomes, although similar concerns remain [89]. Because IR is a natural stepping stone in the development of Type 2 Diabe-

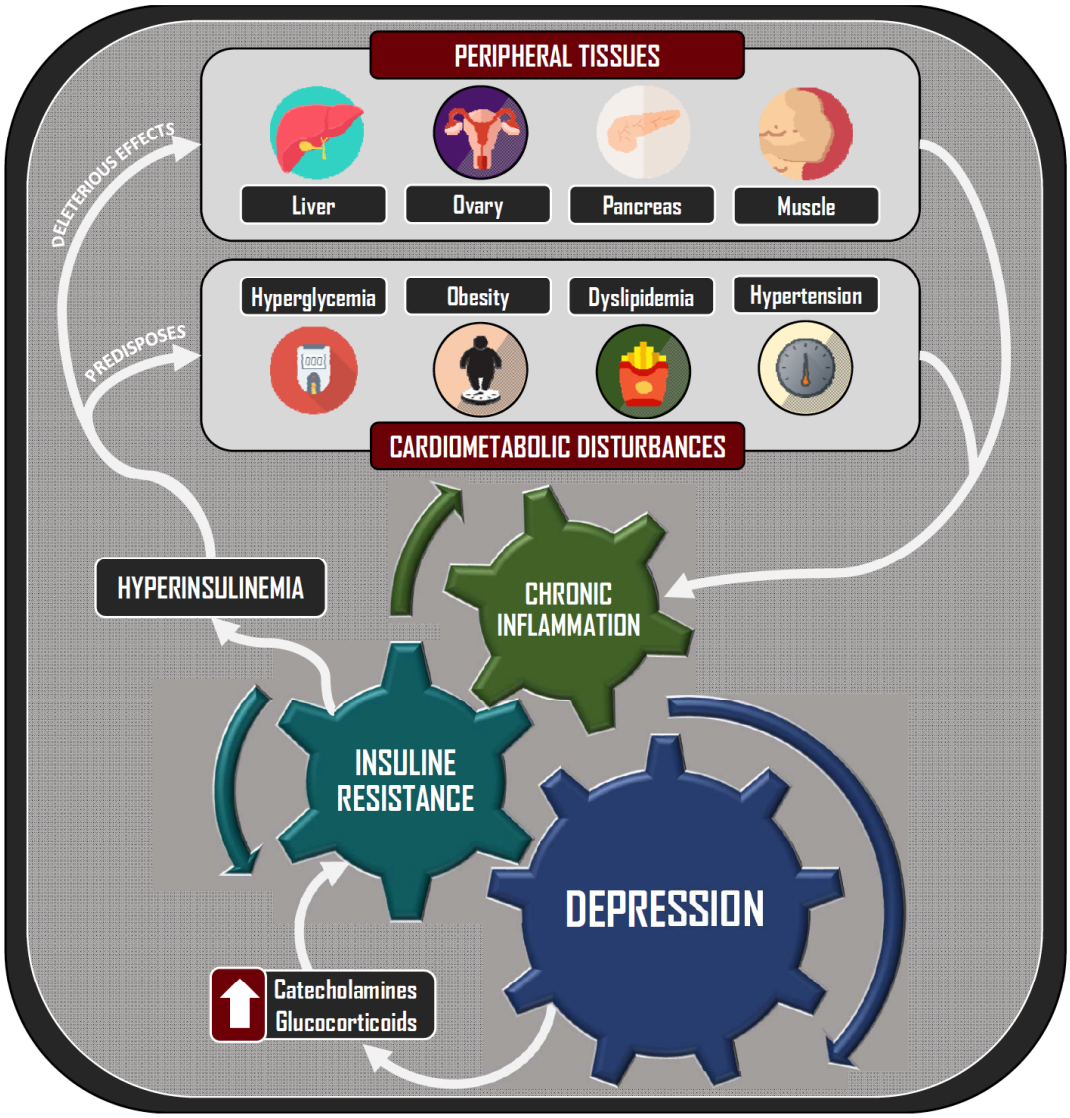

Fig. (3). Relationship between chronic inflammation, insulin resistance and depression. Chronic inflammation, insulin resistance and depression constitute a positive feedback loop, each worsening each other through diverse disruptions in peripheral tissues and various cardiometabolic disturbances. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tes Mellitus (DM2), and owing to the added psychosocial challenges by the disease [90], it is unsurprising that the prevalence of depression is two to three times greater in diabetic patients [91]. DM2 majorly enhances all pathophysiologic components related to IR, CI, and obesity [92], which leads to potentiated neuroinflammation through the increased OS and deleterious microvascular and macrovascular changes [93]. Notoriously, brain structures involved in circuits related to suicidal behavior may be especially susceptible to damage in DM2 [91, 94, 95]. Hypertension is also closely related to IR: Angiotensin II, a key mediator in the renin-angiotensin-aldosterone system (RAAS) has been reported to modulate neuroprotection *via* AT2 receptors in neurons [96-100]. In addition, activation of AT1 receptor favors CI and OS by triggering the release of TNFα and other cytokines, activation of the NADPH-oxidase complex and NF-κB, and expression of iNOS and cyclooxygenase-2 (COX-2) [101-103].

The sum of these CI- and IR-related risk factors results in endothelial dysfunction [104], which has also been associated with depression. Measures of endothelial dysfunction such as intima-media thickness and flow-mediated dilation have been inversely correlated with the severity of depression [105, 106]; highlighting the progressive impact of the immunometabolic disturbances in the evolution of depression.

3. IMPACT OF ESTABLISHED TREATMENTS FOR CARDIOVASCULAR DISEASE IN THE MANAGEMENT OF DEPRESSION

There have been significant advances in the elucidation of the mechanistic interplay between depression and CVD [4], and the effect of antidepressants on discrete cardiometabolic variables has been outlined [107]. Nevertheless, the effects of antidepressants on specific cardiovascular outcomes remain undetermined [108]. The same is true for the

Table 1. Summary of key evidence regarding established treatments for cardiovascular disease in the management of depression.

Class	Compounds (REF)	Methodology	Relevant Results
Non-steroidal anti-inflammatory drugs	NSAIDs, cytokine inhibitors (113)	Systematic review and meta-analysis on 14 trials (6262 participants), 10 with NSAIDs and 4 with cytokine inhibitors assessing their use for depression and depressive symptoms.	Anti-inflammatory treatment was associated with reduced depressive symptoms (SMD, -0.34; 95% CI, -0.57 to -0.11; I2=90%). This was most prominent for celecoxib (SMD, -0.29; 95% CI, -0.49 to -0.08; I2=73%) on remission (OR, 7.89; 95% CI, 2.94 to 21.17; I2=0%) and response (OR, 6.59; 95% CI, 2.24 to 19.42; I2=0%).
	ASA + SSRI (117)	Pilot open-label trial which included 24 patients with major depression who had not responded to treatment during at least 4 weeks with an SSRI, and received add-on ASA 160 mg/day during 4 weeks.	Of the 21 patients who completed the study, 52.4% showed a significant response to the ASA + SSRI combination; and 82% achieved remission by the end of the study. Significant changes were observed in the HDRS ratings, with a baseline mean of 29.3±4.5 points, which decreased to 14.0±4.1 points by day 7 (P<0.0001). This trend persisted until the end of the study on day 28.
Statins	Lovastatin + Fluoxetine (124)	Randomized, placebo-controlled trial which included 68 patients with major depressive disorder who received up to 40 mg/day of fluoxetine + lovastatin 30 mg/day or fluoxetine + placebo for 6 weeks.	Both groups obtained a significant reduction in HDRS scores, although this was greater in the fluoxetine + lovastatin group. The fluoxetine + lovastatin group had a baseline mean HDRS score of 28.9±6.86 points, which decreased to 16.3±5.03 by week 6 (P<0.05).
	Simvastatin + Fluoxetine (125)	Double-blind, placebo-controlled trial which included 48 patients with moderate-severe depression which received fluoxetine 20-40 mg/day + simvastatin 20 mg/day or fluoxetine + placebo for 6 weeks.	Patients treated with fluoxetine + simvastatin had a significantly greater reduction in HDRS scores in comparison with the fluoxetine + placebo group. The reductions in HDRS scores for the former were of 8.04±4.09 by week 2 (P<0.01), 13.45±4.58 by week 4 (P<0.02), and 18.5±7.1 by week 6 (P<0.02). No adverse effects were reported during the study.
Antidiabetic drugs	Various (128)	Systematic review and meta-analysis on 19 trials (3369 participants), 9 with thiazoldinediones, 5 with metformin, 2 with thiazolidenediones against metformin, 2 with incretin-based therapies and 1 with insulin, assessing their impact on depressive symptoms.	Pioglitazone was associated with reduced depressive symptoms compared to controls (pooled effect size = -0.68 (95% C.I. -1.12 to -0.24), p = .003, $N_{studies}$ = 8, I^2 = 83.2%); while metformin was compared to controls. Female sex was a predictor for improvement of depressive symptoms with pioglitazone.
	Pioglitazone (131)	Meta-analysis with 4 randomized controlled trials comprising 161 patients with a major depressive episode.	In comparison with controls, pioglitazone was associated with increased remission rates (27% versus 10%, I^2=17.3%, fixed-effect model: [OR] =3.3, 95% confidence interval [95% CI; 1.4; 7.8], *P*=0.008).
	Metformin (138)	Double-blind, randomized, placebo-controlled trial which included 58 patients with depression and DM2 who received metformin 1-2 g/day or placebo for 24 weeks.	Administration of metformin was associated with a decrease in MADRS (F1,112 = 26.43, p < 0.001) and HDRS-17 (F1,112 = 27.61, p < 0.001) scores compared to baseline. In addition, at week 24, patients on metformin showed a significant improvement in cognitive function; with improved WMS-R scores in the verbal memory index (F1,112 = 22.19, p < 0.001), visual memory index (F1,112 = 10.53, p < 0.01), general memory index (F1,112 = 4.27, p <0.05), attention and concentration index (F1,112 = 12.62, p < 0.01), and delayed memory index (F1,112 = 19.84, p < 0.001).
Antihypertensive drugs	Irbesartan + Fluoxetine (145)	Preclinical study on rats subjected to an unpredictable mild stress protocol which were treated with irbesartan 40 mg/kg and/or fluoxetine 25 mg/kg in monotherapy or combination. Behavioral responses were assessed with MFST and TST at week 6.	Treatment with Irbesartan + Fluoxetine decreased immobility time (166s, p<0.001) in the TST, whereas it increased swimming (184.16s, p<0.001) and climbing times (184.16s, p<0.001) and decreased immobility time (8.5s, p<0.001) in the MFST.

(Table 1) contd….

Class	Compounds (REF)	Methodology	Relevant Results
Polyunsaturated fatty acids	Omega-3 Fatty Acids (161)	Meta-analysis which included 13 randomized, placebo-controlled trials with a total of 1233 adults with major depressive disorder who received supplemental omega-3 fatty acids. A meta-regression was performed to evaluate the effects of the supplement according to several variables.	Omega-3 fatty acids appear to ameliorate depressive symptoms in patients with MDD, especially at high doses, and in patients who receive treatment with antidepressants. The overall SMD was 0.172 (95% CI 0.018, 0.325; P=0.028) when compared with placebo. Studies on participants with MDD employing ⩾60% EPA yielded a highly significant SMD of 0.892 (95% CI 0.543, 1.241; P<0.001), compared to those with <60% EPA, which showed no effect.

Abbreviations: NSAIDs: Non-steroidal anti-inflammatory drugs; ASA: Acetylsalicylic acid; SSRI: Selective serotonin reuptake inhibitor; HDRS: Hamilton depression rating scale; DM2: Type 2 diabetes mellitus; MADRS: Montgomery-Asberg depression rating scale; HDRS: Hamilton depression rating scale-17 items; WMS-R: Wechsler memory scale-revised; MFST: Modified forced swim test; TST: Tail suspension test; MDD: Major depressive disorder; EPA: Eicosapentaenoic acid.

effects of cardiometabolic treatments on depression [109, 110], remaining an equally provoking, yet uncertain field of research (Table **1**).

Non-steroidal anti-inflammatory drugs (NSAIDs) have been posited as potentially useful modulators of CI in depression due to their relatively selective pharmacodynamics [111, 112]. Selective COX-2 inhibitors may be the most promising in this regard. In a systematic review and meta-analysis, celecoxib appeared to significantly decrease depressive symptoms without notable adverse effects, in contrast with other NSAIDs and cytokine inhibitors [113]. Similar findings have been supported by multiple trials [114-116]. However, different NSAIDs appear to yield different results in depression. In a pilot study on patients with treatment-resistant depression (TRD), 52.4% of participants responded positively to the coadministration of acetylsalicylic acid with a selective serotonin reuptake inhibitor (SSRI) [117]. In contrast, other studies with differing combinations of non-selective NSAIDs and SSRIs have failed to obtain similar results [118-121]. At any rate, these findings should be interpreted with caution, as the available trials were short and executed on younger participants. Indeed, the need for optimization and uniformity of trial methodology is a recurring theme in the assessment of NSAIDs and several other treatments for depression.

Empirical evidence shows that the use of statins is associated with a decreased risk of depression in adults [122]. This effect has been hypothesized to be mediated by the reduction of excitotoxicity and OS through antagonism of NMDA receptors and IDO [123]. Several small, short, placebo-controlled trials have reported improved antidepressant responses in participants treated with fluoxetine + lovastatin [124], fluoxetine + simvastatin [125], and citalopram + simvastatin [126]. Yet, again, future trials require larger samples and longer duration to better ascertain the efficacy of statins as antidepressant adjuvants. Clinical research on other hypolipidemic drugs in depression is scarce, and preclinical findings seem discouraging [127].

A variety of antidiabetic drugs have also been evaluated in depression [128]. Most research has focused on thiazolidinediones, which have powerful anti-inflammatory activity *via* activation of PPAR-γ and downregulation of eNOS [129] and have shown antidepressant activity in rat and mouse models [130]. In a meta-analysis, these drugs displayed a pooled effect size of −0.68 (95% C.I. −1.12 to −0.24) for symptom amelioration in depression [128]; and another supports the role of pioglitazone in improving the probability of remission [131]. Indeed, numerous studies have reported favorable results for the use of pioglitazone as an adjuvant to antidepressants [132-134]. Indeed, there is evidence that the antidepressant effect of pioglitazone is more perdurable when compared with other similar adjuvants, with trials as long as 24 weeks returning positive results [135]. However, it should be noted that these studies mostly included individuals with obesity, DM2 and other established metabolic disorders. Thus, the effects of pioglitazone in depression in more metabolically healthy participants remain to be ascertained.

Metformin also has notorious anti-inflammatory activity, by decreasing expression of NF-κB *via* AMPK-dependent and independent pathways, as well as improving energetic balance irrespective of the presence of DM2 and other metabolic disturbances [136, 137]. In a 24-week double-blind, placebo-controlled, randomized clinical trial of patients with DM2, the administration of metformin significantly improved depressive symptoms in comparison to placebo [138]. However, these results are not consistent across trials [139]; and pioglitazone may be a superior alternative: In a 6-week double-blind study on obese patients with depression and polycystic ovary syndrome and depression, monotherapy with pioglitazone granted greater improvement in depressive symptoms than monotherapy with metformin [140]. Similarly to pioglitazone, the antidepressant potential of metformin in metabolically healthy participants remains rather unexplored. Research on other antidiabetic drugs including glibenclamide [141], liraglutide [142], and sitagliptin [143] for depression remains chiefly in preclinical stages.

Concerning antihypertensive drugs, amounting preclinical and clinical evidence suggests a link between modulation of the RAAS to intervene in the pathophysiology of depression [144-150]. Angiotensin-converting enzyme inhibitors (ACEI), and angiotensin-receptor blockers (ARB) may impact depression by reducing CI and OS, and promoting neurogenesis [148]. Out of all classes of antihypertensive drugs, only ACEI and ARB were associated with decreased risk for hospitalization related to a mood disorder in a large retrospective study by Boal *et al*. [149]. Likewise, in the HUNT study from Norway, hypertensive patients treated with ACEIs had lower odds of displaying symptoms of depression [150]. However, future studies accounting for confounders

such as disease severity, comorbidities and polypharmacy should clarify the true role of antihypertensive drugs as antidepressant adjuvants.

Finally, in recent decades, omega-3 fatty acids received widespread acceptance as augmenting agents for antidepressant therapy [151-154]. These molecules have been recognized due to their direct anti-inflammatory and antioxidant properties [155]. They may also participate in the neurobiology of depression by modulating the expression and functionality of serotonin and dopamine receptors [156]. Nevertheless, more recent meta-analyses have reframed the role of these molecules for depression, with reports of small, non-significant effect sizes [157-159]. The variable concentrations of eicosapentaenoic acid (EPA) in omega-3 preparations may be an important intervening factor in this scenario [160]. A meta-analysis by Martins *et al*. [161] found omega-3 fatty acids to enhance antidepressant response, yet with great variability depending on EPA contents: Only studies with EPA contents ≥60% showed significant antidepressant effects, in contrast with studies using EPA contents <60%. This highlights the importance of continuous evaluation of novel antidepressant alternatives in clinical settings.

4. POTENTIAL PHARMACOLOGICAL CANDIDATES FOR THE JOINT MANAGEMENT OF DEPRESSION AND CARDIOVASCULAR DISEASE

In addition to the use of antidepressants for CVD and the use of cardiometabolic treatments for depression, other pharmacological options have been studied in an effort to attack both problems simultaneously. CI remains a prime

Table 2 Summary of key evidence regarding new pharmacological candidates for the joint management of depression and cardiovascular disease.

Class	Compounds (REF)	Methodology	Relevant results
Interleukin antagonists	Ustekinumab (164)	Multicentric, double-blind, randomized, placebo-controlled trial where 1230 patients with psoriasis who received ustekinumab 45 mg, ustekinumab 90 mg, or placebo for 24 weeks, and had their depressive and anxious symptoms evaluated.	At week 12, treatment with ustekinumab was associated with significant reductions in HADS scores both in patients who received 45 mg (-1.7 ± 3.1) and 90 mg (-2.1 ± 3.4); P<0.001.
	Dupilumab (165)	Double-blind, randomized, placebo-controlled trial with 380 patients with atopic dermatitis who were treated with dupilumab 100 mg, 200 mg or 300 mg, or placebo for 16 weeks, and had their depressive and anxious symptoms evaluated.	A significant reduction in depressive and anxious symptoms was observed at 16 weeks in patients treated with dupilumab (P<0.001), with 66.7-75% reductions in the treated groups vs 22.2% in the placebo groups.
	Infliximab (166)	Double-blind, randomized, placebo-controlled, 12-week trial with 60 patients with major depression who received three infusions of infliximab (5 mg/kg, at baseline and weeks 2 and 6) or placebo.	Of patients with high-sensitivity C-reactive protein levels >5 mg/L, 62% showed an improvement of ≥50% in depressive symptoms as assessed with the HDRS.
Antioxidants	NAC (171)	Systematic review including 65 studies on the use of NAC for various neuropsychiatric disorders, of which 2 were on depressive disorder.	The grade of recommendation for depressive disorder was B. Authors highlight the need for further controlled studies and longer follow-up for assessing consistent improvement.
Vitamins	Various (174)	Systematic review and meta-analysis with 40 studies on various nutraceuticals, including 9 on folate, folinic acid, methylfolate, or a combination of folic acid with vitamins B6 and B12.	The pooled effect size was 0.49 inconsequential, with a non-significant difference between folic acid and placebo (p=50.23; z=51.19, 95% confidence interval [CI], –0.31 to 1.29). Similarly, isolated analysis of methylfolate yielded a non-signifcant effect (p=50.25; z=51.15, 95% CI, –0.22 to 0.83).
	L-Methylfolate (175)	Naturalistic clinical trial with 554 patients, of which 502 received L-methylfolate as adjunctive therapy, and 52 as monotherapy.	A mean reduction of 8.5 points (58.2% decrease) was found in patients' PHQ-9 score (mean baseline PHQ-9 score= 14.6, mean follow-up PHQ-9 score= 6.1; *P* = .000). In addition, 376 patients (67.9%) showed treatment response, while 253 (45.7%) achieved remission after an average of 95 days in treatment.
Nutritional supplements	SAMe (185)	Double-blind, randomized, placebo-controlled, 12-week trial on 189 patients with MDD who were treated with SAMe 1600-3200 mg/d, escitalopram 10-20 mg/d or placebo.	All treatment arms showed a significant reduction in HDRS scores (p<0,001); with a reduction of mean scores from 18.98 ± 5.09 to 12.79 ± 7.38 (p < 0.001) in the group treated with SAMe. Remission rates were 28% for SAMe, 28% for escitalopram, and 17% for placebo.

Abbreviations: HADS: Hospital anxiety and depression scale; HDRS: Hamilton depression rating scale; NAC: N-acetylcysteine; PHQ-9: Patient Health Questionnaire-9; SAMe: S-adenosylmethionine; MDD: Major depressive disorder.

therapeutic target in this context, with numerous other forms of anti-inflammatory agents being studied in these circumstances (Table **2**) [119]. Immunotherapy may be a frontrunner in this regard, as it has been ascertained to diminish cardiovascular risk in patients with rheumatoid arthritis and other similar conditions [162, 163]. Immunotherapy may also be useful in depression: in a randomized, double-blind, placebo-controlled, 24-week trial carried out on 1230 patients with moderate-severe psoriasis, treatment with ustekinumab, an IL-12 and IL-23 antagonist, was associated with significant improvement of anxious and depressive symptoms [164]. In a similar study on 380 patients with severe atopic dermatitis, the administration of dupilumab, an IL-4 antagonist, was also associated with a significant reduction of anxious and depressive symptoms [165]. Indeed, to date, improvement of depression is a secondary outcome in most trials assessing immunotherapeutics. Nevertheless, a small randomized, double-blind, placebo-controlled, 12-week trial by Raison *et al*. [166] evaluating the use of TNFα antagonist infliximab for TRD reported more promising results. In this study, participants in the control group with initial hs-CRP levels >5 mg/L showed >50% improvement of depressive symptoms. Future studies should explore more in-depth the utility of immunotherapy in populations with depression without other inflammatory comorbidities.

Various nutritional supplements have also been studied in the management of depression. N-acetylcysteine (NAC) has particularly ignited research interest given its role as an antioxidant by replenishing glutathione levels, as well as being an immunomodulator, and regulator of glutamate and dopamine neurotransmission [167, 168]. Its antioxidant properties have proved useful in the management of CVD [169, 170]. Current clinical evidence on NAC for depression is considered only preliminary, with further confirmatory research required, especially on the exploration of optimal dosing schemes and candidate selection, as determined in a systematic review by Deepmala *et al*. [171]. Indeed, clinical outcomes remain equivocal, with trials reporting improvement of depressive symptoms without changes in inflammatory biomarkers [172]; or major uncertainty in regards to sufficient and optimal duration of administration [173].

Finally, folate has also been studied substantially in the context of depression. A large systematic review and meta-analysis concluded that available data assessing folate, folinic acid and methylfolate on this matter are contradictory, without any determinant evidence in favor of folate, and relatively more positive results for methylfolate [174]. Interestingly, in isolated clinical trials methylfolate appears to be beneficial both alone and as adjunctive therapy [175, 176]. This should warrant further investigation, as in the National Health and Nutrition Examination Survey (NHANES), Americans with low serum folate were found to be at increased risk for depression [177]. Future continued investigation is essential, as folic acid derivates may aid in the prevention of CVD by intervening in the metabolism of homocysteine, a known biomarker for cardiovascular risk [178].

Research on the use of other supplements with joint effects on depression and CVD, such as zinc and various vitamins, is currently underway [179, 180]. In this setting, S-adenosylmethionine (SAMe) represents a peculiar case, as it has raised concerns of increased cardiovascular risk, due to being a precursor of homocysteine [181]. In animal models, SAMe has been shown to increase the synthesis of monoamines, modulate neurotransmission and improve membrane fluidity [182]. Although current findings suggest SAMe to be innocuous regarding cardiovascular risk [183], evidence regarding its efficacy for depression is inconsistent, and numerous studies have failed to show significant benefits to its use [184, 185].

CONCLUSION

The integration of the management of depression and CVD on the basis of their shared pathophysiologic components is an attractive prospect. However, great gaps in currently available preclinical and clinical knowledge preclude the introduction of novel alternatives in this regard at this time. CI is undoubtedly the most appealing target in this context. Although the need for further clinical investigation is indisputable, researchers should mind the common research design problems frequently seen in clinical psychiatry. Indeed, beyond the necessity for more homogenized methodology and clear study outcomes, a wide spectrum of questions must be addressed earnestly, ranging from the practical, in population selection and follow-up duration; to the conceptual, including the very definition of TRD, remission and relapse [186, 187].

The resolution of these conundrums is necessary to improve the quality of research in clinical psychiatry, and consequently facilitate the introduction of revolutionizing therapeutic measures in depression, CVD, and other associated conditions. In the meantime, lifestyle recommendations, in the form of sufficient physical activity and dietary modifications, may be invaluable, safe and useful tools in the treatment of depression, CVD, and many related immunometabolic disorders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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