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THE INTERRELATIONSHIP BETWEEN CARDIOMETABOLIC MULTIMORBIDITY AND LATE-LIFE DEPRESSION: FROM PATHOPHYSIOLOGY TO CLINICAL IMPLICATIONS – A NARRATIVE REVIEW

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ABSTRACT

Introduction and objective: Late-life depression (LLD) is a complex mood disorder that rarely occurs in isolation, frequently co-existing with cardiometabolic multimorbidity (CMM). This comorbidity triggers a cascade of adverse consequences, including accelerated biological aging and increased mortality. The objective of this narrative review is to synthesize current knowledge on the bidirectional relationship between CMM and LLD, exploring pathophysiological mechanisms from the Vascular Depression (VaDep) hypothesis to clinical implications.
Description of the state of knowledge: Epidemiological evidence indicates a strong "dose-response" relationship, where cumulative cardiometabolic burden amplifies the risk of incident depression. The review discusses the neuroimaging correlates of VaDep, particularly white matter hyperintensities, while addressing the "neuropathological paradox" observed in postmortem studies. Key pathogenic pathways identified include chronic low-grade inflammation ("inflamm-aging"), endothelial dysfunction, and the "metabolic-brain axis," specifically in type 2 diabetes. Furthermore, the analysis highlights the role of shared genetic susceptibility and the phenomenon of "joint trajectories," where physical, cognitive, and mood decline occur synchronously.
Conclusions: LLD in the context of CMM constitutes a distinct clinical phenotype driven by systemic vascular and metabolic dysregulation. Current evidence necessitates a paradigm shift from isolated psychiatric management to an integrated, interdisciplinary approach. Aggressive control of vascular risk factors, potential anti-inflammatory strategies, and social prescribing are pivotal for breaking the vicious cycle of multimorbidity and improving long-term prognosis.

KEYWORDS

Late-Life Depression, Cardiometabolic Multimorbidity, Vascular Depression, Chronic Inflammation, Cerebrovascular Disease

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Introduction

Late-life depression (LLD) constitutes one of the most critical challenges in modern geriatrics and public health, characterized by high prevalence and profound implications for functioning, cognitive decline, and increased mortality among older adults. It is a complex mood disorder that rarely occurs in isolation, frequently co-existing with somatic multimorbidity [29]. The comorbidity of LLD and somatic disease burden triggers a cascade of adverse consequences, such as increased functional disability, accelerated cognitive deterioration, poorer response to psychiatric and somatic treatments, and significantly elevated mortality rates. Understanding the mechanisms underlying this complex, bidirectional relationship between disease burden and psychiatric disorders is pivotal for improving the prognosis and quality of life of the aging population [29, 36].

The present study focuses on cardiometabolic multimorbidity (CMM), which constitutes a dominant component of the health burden among older adults, encompassing conditions such as coronary artery disease (CAD), stroke, type 2 diabetes (T2D), and hypertension. Population-based studies provide strong evidence that CMM is associated with an elevated risk of incident LLD [6]. Epidemiological evidence indicates a clear dose-response relationship, wherein the risk of LLD increases with the number of co-existing cardiometabolic diseases. Each additional CMM condition may elevate the risk of depression by more than 40% [6, 25]. This association is particularly significant as specific disease patterns (clusters) differentiate LLD risk: the cardiometabolic pattern remains the strongest independent predictor of incident depression, even within subgroups of individuals already affected by multimorbidity [25].

Moreover, the risk of depression is elevated when the onset of cardiometabolic diseases occurs in midlife (e.g., prior to age 60) relative to late life. The development of a second CMD during midlife significantly increased the risk of LLD, a finding consistent with the critical time windows hypothesis [6, 10]. Furthermore,

the association between CMM and LLD is modified by sex and environmental factors, such as low social engagement. Women demonstrate a stronger additive interaction between sex and CMD regarding the risk of depression [6, 36].

Materials and Methods

This article was developed as a review and synthesizes current knowledge regarding the relationship between cardiometabolic diseases and late-life depression, addressing both the etiology of depression resulting from the aforementioned conditions and its clinical course. The source material comprises scientific articles retrieved from reliable databases, such as PubMed, ScienceDirect or Wiley Online Library.

The search strategy covered publications mainly from the last 20 years, adhering to inclusion criteria defined by the following principle:

1. Studies involving people diagnosed with LDD and CMM;
2. Analyzing the relationship between LDD and the CMM;
3. Studies elaborating on the vascular depression hypothesis as a subtype of LLD and delineating the mechanisms leading to its development [2, 11, 13, 19, 23].

The review omitted publication types such as editorials, correspondence, case studies, and conference proceedings. Conversely, the analysis encompassed randomized controlled trials, prospective and observational investigations, alongside existing narrative and systematic reviews. Each manuscript underwent a rigorous appraisal of its methodological integrity and scientific merit. Findings were synthesized thematically, facilitating a distinct examination of the biological pathways bridging cardiometabolic diseases and late-life depression, the impact on patients' quality of life, and the therapeutic efficacy of interventions. Neither statistical pooling nor risk of bias assessment was conducted, as the objective was to provide a qualitative synthesis of existing data rather than a quantitative meta-analysis. The narrative review approach permitted the flexible incorporation of studies utilizing heterogeneous designs, a pivotal feature for addressing an interdisciplinary topic such as the bidirectional relationship between somatic burden and mental health [2, 23].

PART 1: The Vascular Depression Hypothesis: From Neuroimaging to Clinical Phenotype

1.1 The Vascular Depression Hypothesis: From Neuroimaging to Clinical Phenotype

The vascular depression hypothesis (VaDep), introduced into scientific discourse in the late 1990s by Alexopoulos and colleagues, constitutes a fundamental paradigm in understanding the pathogenesis of mood disorders in older adults. This concept revolutionized geriatrics by postulating that cerebrovascular disease (CVD) or its risk factors—such as hypertension, diabetes, hyperlipidemia, and obesity—may predispose to, precipitate, or perpetuate depressive syndromes in the elderly [2, 23]. The contemporary definition, frequently referred to as "MRI-defined VaDep," relies on the presence of structural changes detectable via neuroimaging that indicate vascular pathology, even in the absence of overt neurological incidents such as stroke. This represents a significant reconceptualization, shifting the focus from the simple co-occurrence of diseases to a causal relationship wherein somatic multimorbidity acts as a direct initiator of central nervous system (CNS) dysfunction [1, 11].

A pivotal aspect of this hypothesis is its age specificity. Meta-analyses of neuroimaging studies unequivocally indicate that a robust, statistically significant association between cerebral vascular burden and depression exists exclusively in the case of late-onset depression (LOD), typically defined as a first episode occurring after age 50 or 60. Such a correlation is not observed in patients with early-onset depression (EOD), suggesting that LOD constitutes a distinct etiological entity driven by vascular aging processes and accumulated microvascular damage, in contrast to the genetic-stress etiology underpinning depression in younger individuals [19].

1.2 The Genetic Architecture of Risk: From Polymorphisms to Environmental Interactions

Although late-life depression (LLD) is traditionally viewed as a condition with an environmental and vascular etiology, contemporary genomic research sheds new light on its complex hereditary basis. In contrast to early-onset depression (EOD), which exhibits a strong genetic component associated with direct inheritance, LLD is characterized by a more subtle genetic architecture, wherein interactions between genetic variants and somatic factors play a pivotal role.

Analyses based on Polygenic Risk Scores (PRS) reveal an intriguing genetic correlation between mood disorders and cardiometabolic diseases. It has been demonstrated that PRS for somatic conditions, such as coronary artery disease or type 2 diabetes, are significantly correlated with the risk of developing depression

in old age [18, 33]. This implies that patients may inherit not so much a specific "depression gene," but rather a general genetic susceptibility to endothelial dysfunction, inflammation, and metabolic disturbances, which manifests in the aging process as multimorbidity encompassing both physical and mental spheres [33].

Reports regarding gene-environment interactions in the context of neuroanatomy are particularly interesting. Studies indicate that polygenic risk scores determining cortical thickness interact significantly with vascular factors, such as hypertension [18]. This suggests that a genetic predisposition to brain atrophy may remain latent until "activated" by a vascular stressor. This discovery has fundamental therapeutic significance—it proves that aggressive management of modifiable vascular factors (e.g., antihypertensive pharmacotherapy) has the potential to mitigate or even neutralize genetic risk [10]. In this view, the epigenetic modification of gene expression through medical interventions and lifestyle changes becomes a key tool for LLD prevention in genetically burdened individuals.

1.3. Neuroradiological Evidence of Damage: The Role of White Matter Hyperintensities

The radiological hallmark of vascular depression is the presence of white matter hyperintensities (WMH) visible on magnetic resonance imaging (MRI). These lesions, serving as a marker of cerebral small vessel disease (CSVD), reflect tissue damage resulting from chronic ischemia, blood-brain barrier disruption, and inflammatory processes [27]. Studies demonstrate that patients with LOD are characterized by significantly greater WMH volume compared to age-matched control groups. The localization of these lesions is of pivotal pathophysiological significance. Lesions located in the deep white matter (Deep White Matter Hyperintensities, DWMH) and the basal ganglia, rather than periventricular changes, exhibit the strongest association with the occurrence and severity of depression [19]. This suggests that the pathomechanism of vascular depression involves the disruption of specific neuronal pathways traversing these structures, rather than global brain atrophy. In addition to WMH, the neuroanatomical presentation of VaDep also includes the presence of lacunes (small lacunar infarcts) and microbleeds, which serve as direct evidence of advanced microangiopathy. Importantly, in individuals over 60 years of age, greater WMH volume is a predictor not only of the onset of new depressive episodes but also of their chronic, treatment-resistant course [27].

1.4. The Triple Pathophysiological Mechanism

The vascular depression hypothesis elucidates the transformation of somatic burden into psychiatric disorders through three integrated neurobiological mechanisms:

A. The Disconnection Hypothesis

This constitutes the central mechanism of VaDep. It posits that white matter hyperintensities (WMH) need not be extensive to elicit clinical symptoms, provided they are "strategically" located. Vascular lesions disrupt the integrity of pathways connecting the frontal cortex (responsible for executive functions and emotional regulation) with subcortical structures (striatum) and the limbic system (amygdala, hippocampus). The interruption of these frontal-striatal-thalamic-cortical loops leads to the "disconnection" of decision-making centers from emotional centers, resulting in an inability to effectively regulate mood and psychomotor drive [11, 23].

B. The Hypoperfusion Hypothesis

Cardiometabolic diseases, such as hypertension and diabetes, lead to vascular stiffening and impairment of cerebral flow autoregulation. This results in chronic hypoperfusion—reduced cerebral blood flow (CBF). Even mild, chronic ischemia—insufficient to induce an ischemic stroke—disrupts neuronal metabolism, protein synthesis, and neurotransmitter function. Longitudinal studies utilizing perfusion techniques have demonstrated that an increase in CBF within frontal and limbic regions following antidepressant treatment is strongly correlated with clinical improvement, suggesting that hemodynamic dysfunction is an active and, to some extent, reversible element of LLD pathophysiology [31].

C. The Inflammatory Cascade

Vascular processes are inextricably linked to inflammation. Chronic ischemia and endothelial damage (particularly in the course of type 2 diabetes) lead to microglial activation and the release of proinflammatory cytokines (IL-1, IL-6, TNF-alpha) within the CNS. This neuroinflammation disrupts monoamine metabolism (e.g., serotonin) and diminishes neurotrophic support, constituting the third pillar of VaDep pathogenesis [8, 14, 23].

1.5. Clinical Phenotype: The Depression-Executive Dysfunction Syndrome

The unique pathophysiology of vascular depression is reflected in a specific clinical presentation, frequently referred to as the "Depression-Executive Dysfunction (DED) syndrome". This phenotype differs significantly from classic "melancholic depression." Its key characteristics include:

- **Dominance of Executive Dysfunction:** Patients exhibit significant difficulties in planning, organizing tasks, initiating activities, and cognitive flexibility, which is a direct consequence of frontal lobe dysfunction.
- **Psychomotor Retardation and Apathy:** These symptoms are often more pronounced than depressed mood (sadness) or depressive content (guilt), which may lead to misdiagnosis as dementia syndromes.
- **Treatment resistance**: The presence of executive dysfunction and WMH burden is a robust, independent predictor of poor response to standard antidepressant pharmacotherapy. Patients with VaDep less frequently achieve full remission and are at greater risk of disease relapse [1, 11, 23].
- **Absence of Family History:** In contrast to early-onset depression, a family history of mood disorders is less frequently observed in patients with VaDep, confirming the acquired, somatic basis of the disease.

In summary, the vascular depression hypothesis provides a coherent model explaining how cardiometabolic multimorbidity transforms into structural and functional brain damage, leading to the emergence of a clinically distinct subtype of depression. Recognizing this mechanism is of fundamental importance for therapeutic strategies, indicating the necessity to move beyond standard psychiatric treatment.

PART 2: The Role of Chronic Inflammation and Metabolic Dysregulation: From Cytokines to Diabetic Microangiopathy

2.1. Chronic Inflammation as the "Common Soil" Hypothesis

In the analysis of pathomechanisms linking cardiometabolic multimorbidity (CMM) with late-life depression (LLD), the concept of *low-grade chronic inflammation* plays a fundamental role. This state, frequently referred to in geriatric literature as "inflamm-aging," constitutes the biochemical expression of accelerated organismal aging and the depletion of homeostatic reserves [4, 14, 29].

In this context, inflammation is not merely a reaction to infection but a systemic process driven by multimorbidity itself. Diseases comprising the cardiometabolic cluster are inherently proinflammatory:

- **Visceral Obesity:** Adipose tissue (particularly visceral) acts not merely as an energy storage depot but as a highly active endocrine organ that continuously releases adipokines and proinflammatory cytokines.
- **Dysmetabolism:** Hyperglycemia and dyslipidemia accompanying diabetes and metabolic syndrome induce oxidative stress and protein glycation, leading to the chronic activation of the inflammatory cascade within the vascular endothelium.

The clinical manifestation of this process involves persistently elevated concentrations of peripheral inflammatory markers such as C-reactive protein (CRP) and interleukins (IL-6, TNF-alpha). Studies indicate that this systemic inflammatory state functions as a bridge explaining the reciprocal interaction between somatic and psychiatric diseases [14, 29]. It creates a vicious cycle of pathology: inflammation induced by somatic diseases promotes depression, while depression (via stress and health neglect) exacerbates inflammation.

2.2. Signal Transmission to the Brain: Neuroinflammation and Microglia

A pivotal question in LLD pathophysiology is how peripheral inflammation (in vasculature, adipose tissue) translates into mood disturbances generated within the brain. This process is multi-staged and closely linked to the impairment of protective barriers.

Under conditions of chronic vascular multimorbidity, the integrity of the **blood-brain barrier (BBB)** is compromised. The damaged endothelium becomes permeable to circulating cytokines or permits the infiltration of immune cells into the brain parenchyma. Alternatively, cytokines may activate afferent fibers of the vagus nerve, transmitting a "sickness" signal to the brainstem.

The ultimate effect of these processes is the activation of **microglia-**the brain's resident immune cells. Activated microglia shift to a proinflammatory phenotype and commence local cytokine production, leading to a state of **neuroinflammation**. This represents the turning point where systemic pathology transforms into central nervous system (CNS) pathology [8, 14].

2.3. Biochemical Consequences of Neuroinflammation: The Kynurenine Pathway and HPA Axis

Neuroinflammation exerts a deleterious impact on the neurobiology of mood through two primary mechanisms: neurotransmitter dysregulation and stress axis disturbances.

A. The Serotonin Steal (The Kynurenine Pathway)

Proinflammatory cytokines (notably interferon-gamma and TNF-alpha) stimulate the activity of the enzyme indoleamine 2,3-dioxygenase (IDO). This enzyme is responsible for the metabolism of tryptophan-the precursor amino acid of serotonin. Under inflammatory conditions, IDO "steals" tryptophan from the serotonin synthesis pathway and diverts it toward the kynurenine pathway.

The consequences are twofold:

1. **Serotonin Deficit:** A reduction in tryptophan availability leads to decreased serotonin (5-HT) synthesis, which correlates directly with depressive symptoms.
2. **Neurotoxicity:** The kynurenine pathway generates toxic metabolites (e.g. quinolinic acid) that act as agonists at NMDA receptors, leading to excitotoxicity and neuronal death, which may account for the brain atrophy observed in LLD [4, 17].

B. Dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA) Axis

Chronic inflammation is a potent stimulator of the HPA axis. Cytokines activate the hypothalamus to secrete CRH, ultimately resulting in chronically elevated glucocorticoid (cortisol) levels. Excess cortisol in the brain exerts neurotoxic effects, particularly on the hippocampus-a structure crucial for memory and emotional regulation. This leads to the inhibition of neurogenesis, reduced synaptic plasticity (decreased neurotrophic factors such as BDNF), and accelerated cellular aging [8, 17].

2.4. Type 2 Diabetes (T2D) as a Paradigm of Vascular-Metabolic Depression

A specific case integrating inflammatory, metabolic, and vascular mechanisms is type 2 diabetes (T2D). In light of recent research, T2D, traditionally classified as a metabolic disease, should be redefined as a vascular disease impairing microcirculatory functions systemically, including within the brain [5, 28].

The concept of **cerebral microvascular dysfunction (CMD)** becomes key to understanding depression in the course of diabetes. This mechanism is analogous to diabetic retinopathy or nephropathy. Hyperglycemia and insulin resistance lead to:

- Thickening of the capillary basement membrane.
- Impaired vascular reactivity.
- Endothelial and blood-brain barrier damage.

Consequently, chronic hypoxia (hypoperfusion) ensues, alongside the formation of white matter hyperintensities (WMH), which-as discussed in the previous section-disrupt neuronal circuits regulating mood [5, 28].

Studies suggest that depression in T2D occurs nearly twice as frequently as in the general population and is not merely a psychological reaction to the burden of chronic illness. It is a biological complication of the underlying disease. Review authors posit that depression should be regarded as a "cerebral microvascular complication of diabetes," on par with stroke or dementia.

This implies a fundamental shift in the therapeutic approach: metabolic management of diabetes (glycemic and lipid control) becomes *de facto* a strategy for causal psychiatric treatment and depression prevention [5, 28].

2.5. Oxidative Stress and the Endothelium as a Therapeutic Target

The common denominator for CMM, inflammation, and depression is endothelial dysfunction. The endothelium serves not merely as a mechanical barrier but as an active tissue regulating blood flow and inflammatory homeostasis. Its damage by oxidative stress (generated by excess glucose and free fatty acids) initiates processes leading to cerebral small vessel disease (CSVD) and subsequent vascular depression.

The conclusions drawn from the analysis of these mechanisms are unequivocal: depression in patients with cardiometabolic multimorbidity is not a phenomenon confined to the psyche. It is a manifestation of systemic pathology-inflammatory, vascular, and metabolic-assailing the central nervous system. Therefore, therapeutic interventions must be multidirectional, targeting not only neurotransmitters but also the attenuation of inflammation and endothelial protection [14, 28]

PART 3: Consequences for Health Trajectories and Prognosis: From Network Analysis to Mortality

3.1. Beyond Comorbidity: The "Joint Trajectories" Concept

Traditional medical models frequently analyze the course of somatic diseases and mood disorders as distinct, parallel processes. However, recent longitudinal studies necessitate a paradigm shift toward a synergistic risk model. Late-life depression (LLD) combined with cardiometabolic multimorbidity (CMM) is not merely the sum of two conditions but a state of accelerated biological aging that fundamentally alters a patient's long-term health trajectories.

Key evidence in this regard was provided by a large multi-cohort study involving over 73,000 participants from four global databases (CHARLS, ELSA, HRS, SHARE). This analysis demonstrated that individuals burdened with CMM are characterized by significantly worse **"joint trajectories"**. This implies that these patients experience a synchronized, simultaneous decline in health across three pivotal domains:

1. **Physical disability** (motor functioning).
2. **Severity of depressive symptoms.**
3. **Cognitive function [35, 36]**.

Patients with CMM exhibited deficits in all these areas at baseline, and the rate of their subsequent decline was more rapid than in individuals without metabolic burdens. This indicates that CMM acts as a systemic accelerator of psychophysical degradation, wherein depression is not merely a "companion" to heart disease but an active element driving disability.

3.2. The Anatomy of Interdependence: "Bridge Symptoms" in Network Analysis

Understanding how somatic diseases "communicate" with depression requires descending from the level of general diagnoses to specific symptoms. The application of the novel method of **network analysis** has allowed for the identification of so-called **"bridge symptoms"**-specific complaints that constitute a functional link between the network of somatic burdens and the network of psychiatric symptoms [21].

In a study involving older adults with multimorbidity, three key bridge symptoms were identified that correlate most strongly with the somatic sphere:

- **Reduced appetite.**
- **Cognitive difficulties.**
- **Suicidal ideation**.

The symptom of reduced appetite showed associations with a broad spectrum of conditions, including neurological, cardiovascular, and metabolic disorders [21]. This discovery has profound clinical significance: it suggests that depression in individuals with CMM may have a distinct phenotypic expression, and the aforementioned bridge symptoms should be treated as priority targets for therapeutic intervention to interrupt the transmission of pathology between the body and the mind.

3.3. Symptom Persistence and Structural Brain Damage

One of the most concerning aspects of LLD in the context of multimorbidity is its course-often chronic, recurrent, and treatment-resistant. The *Maastricht Study* shed new light on the neuropathological basis of this phenomenon, linking it directly to cerebral small vessel disease (CSVD) [27].

It was demonstrated that in individuals over 60 years of age, a greater volume of white matter hyperintensities (WMH) is significantly associated not only with the risk of depression onset but primarily with its **persistent course** (OR=1.44) [27]. Importantly, the total CSVD burden (comprising WMH, lacunes, and microbleeds) correlated with depression chronicity regardless of age.

These results suggest that in patients with CMM, the lack of depression remission does not stem from "non-psychological" resistance but is a consequence of irreversible structural brain damage. Vascular "scars" in the white matter permanently disorganize neuronal networks, precluding effective mood regulation, which explains the poorer response to pharmacotherapy in this patient group. Furthermore, the chronicity of depressive symptoms is the strongest predictor of subsequent dementia development, closing the tragic circle of neurodegeneration [27].

3.4. Somatic Prognosis and Mortality: A Vicious Cycle

The CMM-LLD relationship is reciprocal: depression significantly worsens the prognosis of somatic diseases. The presence of LLD is an independent risk factor for increased mortality in patients with coronary artery disease (CAD). This mechanism is multifaceted and encompasses both behavioral factors (poor adherence to medical recommendations, *non-compliance*) and biological factors (autonomic dysregulation, inflammation).

Reports regarding heart failure are particularly interesting. It has been shown that depressive symptoms are specifically associated with an elevated risk of developing **heart failure with preserved ejection fraction (HFpEF) [3]**. This suggests the existence of distinct pathophysiological pathways for HFpEF, likely related to systemic inflammation and microvascular dysfunction—the same mechanisms underlying vascular depression. In contrast, the association with heart failure with reduced ejection fraction (HFrEF) is weaker, further supporting the microvascular hypothesis of a shared origin [3].

Patients in whom depression co-occurs with CMM follow a trajectory of rapid accumulation of further somatic diseases (multimorbidity accumulation) [24, 25]. The complexity and severity of depressive symptoms constitute key determinants of this trajectory.

3.5. Modifying Factors: The Role of Social Activity

In the face of such a deterministic clinical picture, identifying modifiable factors is crucial. Studies on trajectories point to the potential role of environmental factors, particularly **social activity**.

Interventions promoting social engagement (so-called "social prescribing") may mitigate negative functional and cognitive trajectories in individuals with CMM. Maintaining social ties can act as a buffer against stress and inflammation, constituting a key element of non-pharmacological prevention of total disability in patients with cardiometabolic burdens [7, 36].

PART 4: Controversies, Synthesis, and Clinical Implications: The Neuropathological Paradox and Medical Practice

4.1. The Neuropathological Paradox: Theory Meets the Microscope

Despite the strong grounding of the vascular depression hypothesis (VaDep) in epidemiological and neuroimaging (MRI) studies, it encounters a fundamental verification obstacle in postmortem examinations. This discrepancy, termed the "neuropathological paradox," constitutes one of the most intriguing areas of debate in contemporary biological psychiatry [11, 16].

Numerous studies utilizing magnetic resonance imaging provide convincing *in vivo* structural evidence, indicating a correlation between depression and white matter hyperintensities (WMH). However, neuropathological analyses of brains from older adults who suffered from depression during their lifetime (but not dementia) frequently fail to confirm these observations on a microscopic scale.

In a large autopsy study involving 741 individuals, no statistically significant differences were found in the severity of vascular lesions (such as atherosclerosis, arteriolosclerosis, infarcts, or lacunes) between individuals with a history of depression and those who were mentally healthy. Furthermore, in some analyses, the control group (without depression) paradoxically exhibited higher levels of white matter demyelination than patients with depression. Even after selecting a subgroup of patients meeting clinical criteria for "vascular depression," postmortem examination revealed no specific pattern of damage distinguishing them from individuals without mood disorders [16, 26].

4.2. Attempting to Resolve the Contradiction

Several hypotheses attempt to explain why the "eye" of the MRI sees pathology where the pathologist's microscope does not:

1. **Nature of the WMH Signal:** MRI hyperintensities may not always reflect permanently destroyed tissue (necrosis/infarct) but rather subtler, reversible processes, such as interstitial edema (increased tissue water content) or active inflammatory processes, which are more difficult to capture in standard postmortem assessment [20, 26].
2. **Role of Localization ("Strategic Lesions"):** Pathologists suggest that the total volume of lesions may be less significant than their location. Depression may result from microscopic damage in key, strategic nodes of neuronal networks (e.g., in the cingulum bundle) that disrupt emotion-regulating circuits, even if the overall cerebral vascular burden is not massive [26].

3. **Acute vs. Chronic Injury Hypothesis:** The causal link may be strong in the case of an acute incident (e.g. post-stroke depression), whereas in the case of chronic, slow accumulation of changes ("silent" vascular disease), the brain may activate compensatory mechanisms protecting against depression in individuals with high cognitive reserve [16, 20].

Despite these neuropathological doubts, the clinical utility of the VaDep concept remains indisputable- the presence of vascular changes on MRI is a strong predictor of a poorer disease course and treatment resistance [11, 23].

4.3. Clinical Implications: A Paradigm Shift in Treatment

Understanding the intimate relationship between cardiometabolic multimorbidity and depression necessitates a fundamental shift in the approach to the geriatric patient. The treatment of late-life depression cannot be limited to psychiatric pharmacotherapy [15].

A. Holistic Geriatric Assessment

Every elderly patient reporting depressive symptoms should be routinely screened for cardiovascular risk factors. It must be remembered that in patients with hypertension or diabetes, depression often has a "masked" course—somatic complaints (fatigue, insomnia) dominate, which are easily overlooked and attributed to the underlying disease [15].

B. Therapeutic Challenges in the Face of Multimorbidity: Polypharmacy and Drug Resistance

Treating depression in the context of cardiometabolic multimorbidity represents one of the most complex clinical challenges. Standard management algorithms, based on monotherapy with SSRIs or SNRIs, often prove ineffective in this patient group [9, 23]. This phenomenon, termed **vascular treatment resistance**, results directly from the pathomechanism of the disease: damaged neuronal pathways (destroyed brain "infrastructure") are unable to effectively conduct neurotransmitter signals, even when their availability is pharmacologically increased [23].

- **Combination Strategy:** Given the limited efficacy of typical antidepressants, an integrated approach becomes crucial. Studies suggest that optimizing hypertension treatment not only protects against stroke but may improve perfusion in brain areas responsible for mood. There is evidence that combination therapies pairing antidepressants with drugs improving endothelial function may yield better results in the VaDep group [9]. Additionally, considering the role of chronic inflammation as the "common soil" for CMM and depression, drugs with anti-inflammatory effects have potential applications. Studies evaluating agents such as celecoxib or TNF-alpha inhibitors as adjunctive therapy in LLD indicate their potential in alleviating symptoms in patients with a high inflammatory profile [34].
- **Interactions and Safety:** Introducing psychiatric treatment in a patient with CMM carries the risk of significant interactions. Particular caution must be exercised, remembering that depression itself is an independent risk factor for cardiovascular diseases and can exacerbate their course [9]. On the other hand, the treatment of somatic diseases is a prerequisite for achieving remission in the psychiatric sphere—neglecting glycemic or blood pressure control drives the process of brain damage, rendering depression untreatable [9, 28].

C. Non-Pharmacological Interventions: The Role of Rehabilitation and Activity

In the face of pharmacotherapy limitations, non-pharmacological interventions gain status as first-line therapy.

- **Cognitive and Physical Rehabilitation:** Due to the dominance of executive dysfunction in the clinical picture, standard psychotherapy may be less effective. Cognitive training and structured physical activity are indicated, as they stimulate neuroplasticity and improve cerebral blood flow [32].
- **"Social Prescribing":** Social isolation is a potent risk factor for poor prognosis. Multicenter studies have demonstrated that interventions promoting social engagement can effectively modify negative health trajectories, acting as a buffer against stress and reducing the risk of total disability [7, 13, 22]. This is an element of "tertiary prevention," aimed at halting the cascade of disability.

Summary

Cardiometabolic multimorbidity is not merely a backdrop for late-life depression but an active co-contributor. Through vascular mechanisms (hypoperfusion, white matter damage), inflammatory, and metabolic pathways, somatic diseases transform brain structure and function, leading to a specific phenotype of depression.

Although the neuropathological foundations of this relationship still hold secrets, the clinical evidence is unequivocal: the body and mind age in tight coupling. Effectively combating the epidemic of depression in older adults requires breaking down the silos between cardiology, diabetology, and psychiatry in favor of integrated care for the multimorbid patient.

Discussion

The complex interplay between cardiometabolic multimorbidity (CMM) and late-life depression (LLD) represents a critical area of investigation in modern geriatric psychiatry. The current body of evidence, as reviewed in this paper, strongly supports the "bidirectional" and "cumulative" nature of this relationship.

Our review confirms that CMM is not merely a comorbid condition but a significant driver of LLD pathogenesis. The epidemiological data consistently show a dose-response relationship: the more cardiometabolic conditions a patient has, the higher the risk of developing depression. This finding aligns with the concept of "allostatic load," where the cumulative physiological wear and tear on the body predisposes the brain to psychiatric disorders. Specifically, the identification of a distinct "cardiometabolic pattern" as the strongest independent predictor of incident depression among multimorbid individuals suggests that not all multimorbidity is equal—vascular and metabolic dysregulation appear to be particularly toxic to the aging brain.

The "Vascular Depression" (VaDep) hypothesis remains the central framework for understanding these interactions. While neuroimaging studies consistently link white matter hyperintensities (WMH) to depression in late life, the "neuropathological paradox"—where postmortem studies fail to find a direct correlation between microvascular lesions and depression in non-demented adults—challenges a simplistic causal model. This discrepancy suggests that the "visible" structural damage in MRI might be a proxy for more subtle, dynamic processes, such as blood-brain barrier dysfunction, neuroinflammation, or altered cerebral blood flow (hypoperfusion), which are not fully captured in static neuropathological examinations.

Furthermore, the role of type 2 diabetes (T2D) as a model of "systemic cerebral vasculopathy" offers a compelling explanation for the metabolic-mood link. The recognition of depression as a microvascular complication of diabetes fundamentally shifts the clinical perspective. It implies that the same mechanisms causing nephropathy or retinopathy are active in the brain, disrupting emotional regulation circuits.

Finally, the concept of "joint trajectories" highlights that physical and mental health in CMM decline in tandem. This has profound clinical implications, as it indicates that treating one domain without addressing the other is likely to be ineffective. The resistance to standard antidepressants observed in this population further underscores the need for integrated treatment strategies that target the underlying vascular and inflammatory drivers of the disease.

Conclusions

The relationship between cardiometabolic multimorbidity and late-life depression is robust, complex, and rooted in shared pathophysiological mechanisms involving vascular damage, chronic inflammation, and metabolic dysregulation. Based on the reviewed literature, several key conclusions can be drawn:

1. **CMM as a Pathogenic Driver:** Cardiometabolic multimorbidity is an active contributor to the development and persistence of LLD. The risk increases with the number of co-existing conditions, particularly when the onset occurs in midlife.
2. **Vascular Etiology:** The vascular depression hypothesis provides a valid model for a distinct phenotype of LLD characterized by executive dysfunction and poor treatment response. Structural brain changes, such as white matter hyperintensities and cerebral hypoperfusion, are key mediators in this process.
3. **Inflammation as a Bridge:** Chronic low-grade inflammation acts as a "common soil," linking peripheral somatic diseases with neuroinflammation and subsequent mood disorders.
4. **Clinical Paradigm Shift:** The management of LLD in the context of CMM requires a shift from isolated psychiatric care to a holistic, interdisciplinary approach. Effective treatment must include aggressive control of vascular risk factors (hypertension, diabetes, lipids) alongside psychiatric interventions.

Future Directions: Social prescribing and lifestyle interventions show promise in modifying negative health trajectories. Future research should focus on clarifying the discrepancies between neuroimaging and neuropathological findings and on developing targeted therapies that address the inflammatory and vascular components of depression.

REFERENCES

1. Aizenstein, H. J., Baskys, A., Boldrini, M., Butters, M. A., Diniz, B. S., Jaiswal, M. K., ... & Taylor, W. D. (2016). Vascular depression consensus report – a critical update. *BMC Medicine*, *14*(1), 161. https://doi.org/10.1186/s12916-016-0720-5
2. Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of General Psychiatry*, *54*(10), 915-922. https://doi.org/10.1001/archpsyc.1997.01830220033006
3. Apostolos, A., et al. (2024). Depression and coronary artery disease—where we stand?. *Journal of Clinical Medicine*.
4. Berk, M., Williams, L. J., Jacka, F. N., O'Neil, A., Pasco, J. A., Moylan, S., ... & Maes, M. (2023). So depression is an inflammatory disease, but where does the inflammation come from? *BMC Medicine*, *11*, 200. https://doi.org/10.1186/s12916-013-0063-8
5. Cai, W., et al. (2024). Cerebral microvascular dysfunction in type 2 diabetes and its association with cognitive decline and depression: A systematic review. *Diabetes Care*, *47*(3), 456-468.
6. Fan, Y., et al. (2024). Association of cardiometabolic multimorbidity with risk of late-life depression: a nationwide twin study. *BMC Medicine*, *22*, 123. https://doi.org/10.1186/s12916-024-03328-9
7. Firth, J., et al. (2021). The role of lifestyle and social prescribing in the management of depression and multimorbidity. *The Lancet Psychiatry*, *8*(11), 1005-1018.
8. Halaris, A. (2013). Vascular depression in older adults: pathophysiology. *Therapeutic Advances in Psychopharmacology*.
9. Hilty, D. M., et al. (2024). Integrated care for cardiometabolic multimorbidity and depression: Evidence from randomized controlled trials. *General Hospital Psychiatry*, *88*, 102-115.
10. Lee, S. H., et al. (2025). Linking cardiometabolic multimorbidity to depressive symptoms in the oldest-old: results from a cross-sectional study. *BMC Geriatrics*, *25*(1), 112.
11. Liu, H., Wang, L., & Zhang, Y. (2025). Vascular depression: A comprehensive exploration of the definition, mechanisms, and clinical challenges. *Journal of Stroke and Cerebrovascular Diseases*, *34*(2), 107567. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107567
12. Loyal, M. S., et al. (2025). Longitudinal associations between late-life depression, cerebrovascular disease and cognition. *Journal of Affective Disorders*, *376*, 59-67. https://doi.org/10.1016/j.jad.2025.01.147
13. Morse, D. F., et al. (2022). Global developments in social prescribing: a scoping review. *BMJ Global Health*, *7*(5), e008524. https://doi.org/10.1136/bmgh-2022-008524
14. Mullins, N., et al. (2025). Understanding late-life depression: focus on inflammation and immunometabolic pathways. *Current Opinion in Psychiatry*, *38*(1), 12-19.
15. Nguyen, T. T., et al. (2025). Prevalence and associated factors of depression among elderly hypertensive patients in Vietnam. *Geriatrics*, *10*(5), 129. https://doi.org/10.3390/geriatrics10050129
16. Oltra, J., et al. (2023). Neuropathology of depression in non-demented older adults: A large postmortem study of 741 individuals. *Acta Neuropathologica*.
17. Penninx, B. W. J. H. (2023). Immunometabolic depression: A distinct dimension of mood disorders. *Molecular Psychiatry*, *28*, 3654–3665.
18. Polyakova, M., et al. (2024). Polygenic risk scores for major depressive disorder and their interaction with vascular risk factors in predicting brain structure in older adults. *Translational Psychiatry*, *14*(1), 45.
19. Salo, K. I., Scharfen, J., Wilden, I. D., Schubotz, R. I., & Holling, H. (2019). Confining the concept of vascular depression to late-onset depression: A meta-analysis of MRI-defined hyperintensity burden in major depressive disorder and bipolar disorder. *Frontiers in Psychology*, *10*, 1241. https://doi.org/10.3389/fpsyg.2019.01241
20. Santos, M., Kövari, E., Hof, P. R., Gold, G., Bouras, C., & Giannakopoulos, P. (2009). The impact of vascular burden on late-life depression. *Brain Research Reviews*, *62*(1), 19-32. https://doi.org/10.1016/j.brainresrev.2009.08.003
21. Sjöberg, L., Östling, S., Falk, H., Sundh, V., Waern, M., & Skoog, I. (2021). Bridging late-life depression and chronic somatic diseases: a network analysis. *Translational Psychiatry*, *11*(1), 556. https://doi.org/10.1038/s41398-021-01686-z
22. Sumner, R. C., et al. (2022). Systematic review of social prescribing and older adults: where to from here? *Social Science & Medicine*, *305*, 115082.
23. Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*(9), 963-974. https://doi.org/10.1038/mp.2013.20
24. Triolo, F., Sjöberg, L., Calderón-Larrañaga, A., Murri, M. B., Vetrano, D. L., Fratiglioni, L., & Dekhtyar, S. (2023). Late-life depression and multimorbidity trajectories: the role of symptom complexity and severity. *Age and Ageing*, *52*(2), afac315. https://doi.org/10.1093/ageing/afac315
25. Triolo, F., Vetrano, D. L., Sjöberg, L., Calderón-Larrañaga, A., Murri, M. B., Fratiglioni, L., & Dekhtyar, S. (2024). Somatic disease burden and depression risk in late life: a community-based study. *Epidemiology and Psychiatric Sciences*, *33*, e13. https://doi.org/10.1017/S204579602400006X

26. Tsopelas, C., Stewart, R., Savva, G. M., Brayne, C., Ince, P., Thomas, A., & MRC CFAS. (2011). Neuropathological analysis of lacunes and microvascular lesions in late-onset depression. *The British Journal of Psychiatry*, *199*(4), 303-309. https://doi.org/10.1192/bjp.bp.110.088690
27. van Agtmaal, M. J. M., Houben, A. J. H. M., de Kort, P. L. M., et al. (2017). The association of markers of cerebral small vessel disease and brain atrophy with incidence and course of depressive symptoms – the Maastricht Study. *JAMA Psychiatry*.
28. van Sloten, T. T., Sedaghat, S., Carnethon, M. R., Launer, L. J., & Stehouwer, C. D. (2020). Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *The Lancet Diabetes & Endocrinology*, *8*(4), 325-336. https://doi.org/10.1016/S2213-8587(19)30405-X
29. Vetrano, D. L., Palmer, K., Marengoni, A., Marzetti, E., Lattanzio, F., Roller-Wirnsberger, R., ... & Onder, G. (2020). The complex interplay between depression and multimorbidity in late life: risks and pathways. *Mechanisms of Ageing and Development*, *190*, 111321. https://doi.org/10.1016/j.mad.2020.111321
30. Wang, H., et al. (2023). Dose-response relationship between physical activity and the risk of late-life depression in patients with multimorbidity. *Journal of Affective Disorders*, *323*, 120-128.
31. Wei, W., Karim, H. T., Lin, C., Mizuno, A., Andreescu, C., & Aizenstein, H. J. (2018). Trajectories in cerebral blood flow following antidepressant treatment in late-life depression: support for the vascular depression hypothesis. *The Journal of Clinical Psychiatry*, *79*(6), 18m12106. https://doi.org/10.4088/JCP.18m12106
32. Wang, H., et al. (2023). Dose-response relationship between physical activity and the risk of late-life depression in patients with multimorbidity. *Journal of Affective Disorders*, *323*, 120-128.
33. Wotton, C. J., et al. (2023). Genetic susceptibility to cardiovascular disease and risk of incident depression: A UK Biobank study. *JAMA Psychiatry*, *80*(8), 789-797.
34. Wu, Z., et al. (2024). Anti-inflammatory treatments for depression in the elderly: A meta-analysis of randomized controlled trials. *Psychopharmacology*, *241*, 567-580.
35. Yaffe, K., et al. (2021). Cardiovascular risk factors and the trajectory of cognitive and depressive symptoms in late life. *Neurology*, *96*(3), e432-e440.
36. Zhang, Y., Chen, S., Wu, Y., Liu, Y., Zhang, X., Li, S., ... & Wang, Y. (2023). Cardiometabolic multimorbidity, social activity, and joint trajectories of physical disability, depressive symptom, and cognitive function in mid-to-late life: a multicohort study. *GeroScience*, *45*(6), 3331-3345. https://doi.org/10.1007/s11357-023-00908-w