Am J of Geriatric Psychiatry 31:10 (2023) 853–866

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

Clinical Review Article

Neuroinflammation: A Modifiable Pathway Linking Obesity, Alzheimer's disease, and Depression

Maria Ly, M.D., Ph.D.[+], *Gary Z. Yu, M.D., Ph.D.*[+], *Ali Mian, M.D., Austin Cramer, B.A., M.F.A., Somayeh Meysami, M.D., David A. Merrill, M.D., Ph.D., Amjad Samara, M.D., Sarah A. Eisenstein, Ph.D., Tamara Hershey, Ph.D., Ganesh M. Babulal, Ph.D., O.T.D., Eric J. Lenze, M.D., John C. Morris, M.D., Tammie L.S. Benzinger, M.D., Ph.D., Cyrus A. Raji, M.D., Ph.D.*

ARTICLE INFO

Article history:
Received December, 10 2022
Revised May, 31 2023
Accepted June, 1 2023

Key Words:
Neuroinflammation
obesity
Alzheimer's disease
depression
neuroimaging

ABSTRACT

Obesity, depression and Alzheimer's disease (AD) are three major interrelated modern health conditions with complex relationships. Early-life depression may serve as a risk factor for AD, while late-life depression may be a prodrome of AD. Depression affects approximately 23% of obese individuals, and depression itself raises the risk of obesity by 37%. Mid-life obesity independently increases AD risk, while late-life obesity, particularly metabolically healthy obesity, may offer protection against AD pathology.

Chronic inflammation serves as a key mechanism linking obesity, AD, and depression, encompassing systemic inflammation from metabolic disturbances, immune dysregulation through the gut microbiome, and direct interactions with amyloid pathology and neuroinflammation.

In this review, we explore the biological mechanisms of neuroinflammation in relation to obesity, AD, and depression. We assess the efficacy of therapeutic interventions targeting neuroinflammation and discuss current and future

From the Mallinckrodt Institute of Radiology, Washington University in St. Louis, St. Louis, MO; Cramer Performance Institute, St. Louis, MO; Pacific Brain Health Center, Pacific Neuroscience Institute Foundation, Santa Monica, CA; Department of Translational Neurosciences, Saint John's Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA; Department of Neurology, Washington University in St. Louis, St. Louis, MO; Department of Psychiatry, Washington University in St. Louis, St. Louis, MO; Department of Psychological & Brain Sciences, Washington University School of Medicine, St. Louis, MO; Institute of Public Health, Washington University in St. Louis, St. Louis, MO; Department of Psychology, Faculty of Humanities, University of Johannesburg, Johannesburg, South Africa; Department of Clinical Research and Leadership, The George Washington University School of Medicine and Health Sciences, Washington, DC; and the Department of Neurological Surgery, Washington University in St. Louis, St. Louis, MO. Send correspondence and reprint requests to Cyrus A. Raji, M.D., Ph.D., Mallinckrodt Institute of Radiology, Division of Neuroradiology, Washington University in St. Louis, St. Louis, MO 63130. e-mail: craji@wustl.edu

+ These authors contributed equally to this work.

https://doi.org/10.1016/j.jagp.2023.06.001

radiological imaging initiatives for studying neuroinflammation. By comprehending the intricate interplay among depression, obesity, and AD, especially the role of neuroinflammation, we can advance our understanding and develop innovative strategies for prevention and treatment. (Am J Geriatr Psychiatry 2023; 31:853–866)

Highlights

- **What are the primary questions addressed by this study?**
  This narrative review focuses on the mechanisms of neuroinflammation in the pathophysiology of obesity, depression, and Alzheimer's disease (AD), therapeutic interventions reducing neuroinflammation, and neuroimaging initiatives measuring neuroinflammation.
- **What is the main finding of this study?**
  Chronic neuroinflammation induced by obesity is a mechanism that significantly contributes to the pathophysiology of both depression and AD.
- **What is the meaning of the finding?**
  Neuroinflammation plays a crucial role in connecting obesity and AD. As the systemic inflammatory burden associated with obesity and metabolic syndrome primarily builds up during midlife, before AD symptoms appear, targeting this stage for intervention and behavioral changes becomes essential to potentially prevent AD pathology.

INTRODUCTION TO ALZHEIMER'S DISEASE, DEPRESSION, AND OBESITY

Alzheimer's disease (AD), depression, and obesity are three closely interrelated modern major health crises.[1] AD, as the leading cause of dementia, is projected to affect over 150 million individuals worldwide by 2,050 with a continually aging population.[2] Over 6.7 million Americans over age 65 are currently living with AD, representing one in nine individuals, with the prevalence increasing to one in three in those above 85 years.[3] Depression is the leading cause of disability and loss of productive life years worldwide, currently estimated to affect over 300 million individuals.[4–6] Depression may affect up to 9.8% –13.7% of older adults living in the United States.[7,8] Obesity is a burgeoning global health epidemic with approximately 36.9% of men and 38.0% of women being obese and overweight globally,[9] while in the United States, older adults have become increasing obese, affecting up to 42.8% over the age of 60 in 2017–2018 as compared to 23.7 in 1988–1994.[10]

DEPRESSION, A RISK FACTOR AND PRODROME FOR DEVELOPMENT OF AD

Depression represents one of the most common neuropsychiatric comorbidities of AD, yet the relationship is quite complex. Individuals with history of early-life or mid-life depression have been demonstrated to have increased risk for developing AD later in life.[11] Alternatively late-life depression may represent an early manifestation, or a prodrome, of AD given the strong temporal associations with subsequent development of AD.[11–13] On the other hand, 23% of obese individuals are estimated to have comorbid depression, while depression increases risk of obesity by 37%.[14–16]

OBESITY, A MODIFIABLE RISK FACTOR FOR BOTH AD AND DEPRESSION

Obesity in midlife (40–60 years of age) has been shown to be an independent risk factor for AD, while late-life obesity,[17] particularly late-life obesity without metabolic abnormalities (termed "metabolically

healthy obesity"), has also been shown to be protective in late-life against AD pathology. There is growing evidence that the state of chronic inflammation induced by obesity is significant to the pathophysiology of both AD and depression. These mechanisms are diverse and may range from systemic inflammation stemming from metabolic perturbations, to gut microbiome-mediated immune dysregulation, to direct molecular interactions with amyloid pathology and subsequent neuroinflammation.[18–21]

This review aims to 1) discuss the biological mechanisms that underlie neuroinflammation and its role in obesity, AD, and depression, 2) review therapeutic interventions and their efficacies in targeting neuroinflammation, and 3) discuss present and future radiological imaging initiatives on characterizing neuroinflammation for further study.

MECHANISMS OF OBESITY LEADING TO A CHRONIC INFLAMMATORY STATE

Obesity is related to a state of chronic, low-grade inflammation,[18] stemming from the physiologic changes associated with increasing body adiposity, including the formation and hypertrophy of adipocytes, and the deposition of fat outside of adipose tissue. When these changes occur in excess, regulatory mechanisms may become disrupted. For instance, adipose tissue hypertrophy that outpaces blood supply will lack proper tissue perfusion, leading to hypoxia, adipose tissue dysfunction, and inflammation.[22,23] Larger adipocytes are also more prone to rupture, triggering inflammatory cascades and increased recruitment of M1-type macrophages.[24] These adipose tissue macrophages are not only the largest subpopulation of adipose tissue-associated immune cells but are also associated with expression of pro-inflammatory factors including interleukin 1B (IL-1B), IL-6, IL-12, and IL-23, tumor necrosis factor-alpha (TNF-alpha), inducible nitric oxide synthase (iNOS), and inhibitor of NFκB kinase beta (IKKbeta).[25]

In addition, overabundance of diet-derived saturated fatty acids and hyperlipidemic states resulting from adipose tissue dysfunction have been shown to upregulate toll like receptor (TLR)-mediated expression of systemically circulating pro-inflammatory factors including IL-6 and TNF-alpha.[26] Consequently, increased exposure of adipocytes to stressors including oxidative stress, inflammatory cytokines, and hyperlipidemic states also induces pro-inflammatory gene expression through activation of activator protein-1 (AP-1) and NFκB through multiple cellular kinase pathways including mitogen-activated protein kinases (MAPK), IKK beta, mammalian target of rapamycin (mTOR), and various protein kinases C (PKC). Many of these pathways are also involved in insulin resistance and development of subsequent metabolic dysfunction.[18]

Particularly, visceral adiposity has been associated with increased mortality due to being more pro-inflammatory than subcutaneous adiposity for which there are several proposed mechanisms.[27] Visceral fat has been associated with higher production of TNF-alpha, IL-1B, IL-6, and C-reactive protein (CRP) and has also been found to contain higher numbers of macrophages and T lymphocytes.[28] Visceral fat cells have increased likelihood of undergoing lipolysis, thus increasing systemwide free fatty acids triggering inflammation and are more prone to macrophage infiltration, resulting in the release of pro-inflammatory cytokines.[27]

MECHANISMS FOR OBESITY AND NEUROINFLAMMATION

The chronic inflammatory state induced by obesity has been shown to increase susceptibility to a wide range of health issues including cardiovascular disease, type 2 diabetes, and cancer.[29–33] The central nervous system is no exception, as chronic obesity-derived neuroinflammation likely plays a significant role in neurodegeneration and cognitive decline.[34-36] Table 1 summarizes the mechanisms that are reviewed below.

Hyperactivation of HPA Axis

The increased expression of proinflammatory cytokines in obesity, including IL-6 and TNF-alpha, sets off a cascade in of ACTH secretion, HPA axis activation, hypercortisolemia, causing neuronal apoptosis, dendritic atrophy, and reactive gliosis.[37] The increase in HPA axis activity in obesity has been associated with poorer cognitive performance in obese individuals with type 2 diabetes.[38] Exposure to obesity-

TABLE 1. Summary of Mechanisms Underlying Neuroinflammation

Summary of Mechanisms	
HPA axis-related mechanisms	
Increases in TNF-alpha, Increases in IL6, decreases in adiponectin, decrease in nitric oxide, increase in ROS	[37]
Activates Toll-like repector-4 dependent, nuclear factor kappa B	[39]
Increased hypothalamic gene expression of IL-6, TNF-alpha, IKK-beta	[42]
Increased renin-angiotensin-aldosterone system activation	[41]
Gut Microbiome-related mechanisms	
Increased gut microbiome permeability	[41]
Disrupted dendritic cell homeostasis, impaired immune function	[40]
Neurogenesis-synaptic dysfunction	
Decreased expression of mRNA, noncoding RNA related to synaptic plasticity	[43]
Increased AMP-kinase in hippocampus	[44]
Lowered BDNF	[45]
Blood Brain Barrier Permeability	
Decreased expression of tight junction proteins	[48]
Microglia and astrocyte activation	
M1 microglial activation, decreased phagocytic activity, decreased amyloid clearance, iNOS activation	[65]
A1 astrocyte activation, neuronal death	[67]
Insulin resistance	[71]
Activation of glycogen synthase kinase-3	[73–75]

derived hyperlipidemia may directly induce phenotypic changes in microglial cells and astrocytes. Both types of cells have been found to have toll-like receptor-4 (TLR4)-dependent, nuclear factor kappa B (NF-KB)-mediated inflammatory responses to saturated fatty acids.[39]

Synaptic Dysfunction, Impaired Neurogenesis

Multiple studies have demonstrated the impact of diet on potentiating metabolic dysfunction, neuroinflammation, synaptic plasticity, neurogenesis, and the subsequent development of neurological disorders. High fat diets (HFD) have been demonstrated to disrupt dendritic cell homeostasis in obese mice, thus demonstrating critical implications for immunologic function.[40] The western diet has also been shown to contribute to increased renin-angiotensin-aldosterone system activation and increased intestinal permeability with disturbance of the gut microbiota.[41] A study of HFD-induced neuronal injury in rats and mice showed that increases in hypothalamic gene expression of IL-6, TNF-alpha, and IKK-beta occurred as soon as 3 days after exposure to a HFD diet, accompanied by increases in cellular markers of gliosis including CD68, EMR1, Iba1, and GFAP.[42] HFD has been demonstrated to impede neurogenesis in several animal and stem cell studies though several mechanisms: decreased expression of mRNA and non-coding RNA related to neurogenesis, synaptic plasticity, calcium signaling in mice,[43] increased AMP-kinase signaling in the hippocampus which reduced neurogenesis,[44] and lowered BDNF.[45]

Blood-Brain Barrier Permeability

Furthermore, several animal studies with high fat diet have demonstrated increases in blood-brain barrier permeability (BBB) have also been noted in many animal studies of diet-induced obesity,[46,47] secondary to decreased expression of tight junction proteins.[48] Increased BBB permeability can result in increased infiltration of pro-inflammatory cytokines and fatty acids and renders the hypothalamus vulnerable to chronic elevations in insulin and leptin.[49] Chronic microglial activation may result in additional sequelae including more extensive synaptic remodeling and contribution to elevated beta-amyloid and tau pathology.[50,51] These relationships are graphically represented in Figure 1

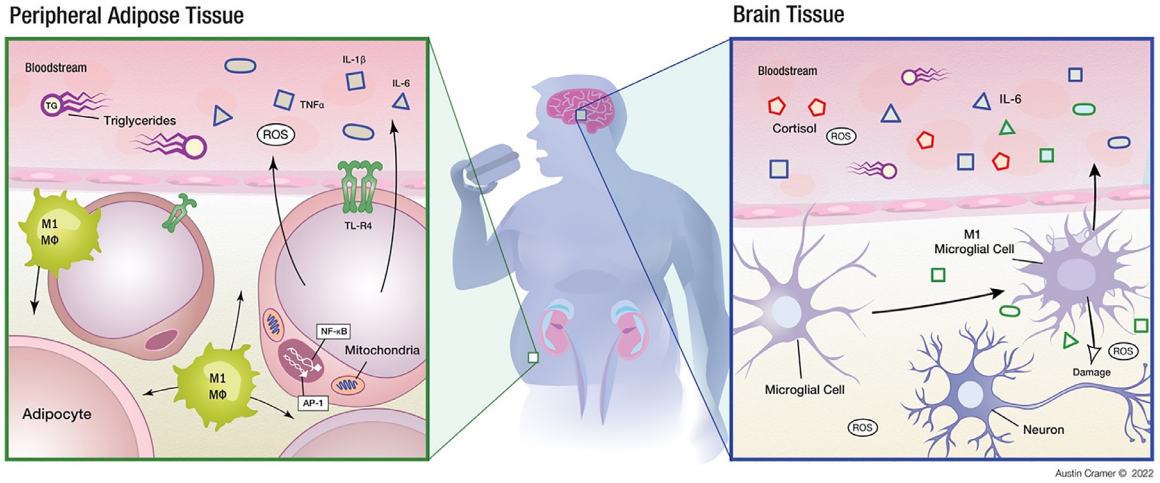
SHARED NEUROINFLAMMATORY MECHANISMS IN AD AND DEPRESSION

Neuroinflammation and its sequelae significantly contribute to the pathophysiology of both AD and depression. Given that these commonalities are found in the chronic inflammatory state of obesity, this is further evidence that obesity has significant mechanistic underpinnings for both conditions.

Oxidative Stress

Oxidative stress is a known hallmark early-stage insult in AD preceding beta-amyloid aggregation and tau deposition[21,52,53] and is also increasingly thought of as a key component of depression.[54,55] Obesity-derived inflammation mediates increased ROS production through mitochondrial dysfunction,[56,57] which may subsequently impair axonal transport and synaptic function, in the CNS especially in hippocampal neurons.[58–60] Regulation of ROS activity is crucial for memory consolidation and long-term potentiation[61] and is further exacerbated by the additional production of ROS by beta amyloid plaques through glutathione depletion and NADPH oxidase activation, emphasizing the interrelated signaling found in obesity and AD.[62,63] Increased oxidative stress is also a result of

FIGURE 1. This illustration depicts the increased peripheral inflammation from adipocytes in an overweight or obese state with macrophage (M1) AP-1 and NF-κB mediated cellular signaling resulting in the release of reactive oxygen species (ROS) within the blood stream in the background of elevated triglycerides (TG). Within the brain, increased ROS and cortisol mediate microglial driven neuroinflammatory changes.



HPA axis hyperactivity, a physiologic adaptation in depression to increased psychosocial stressors.[55]

Microglia and Astrocyte Activation

Microglial cell activation, seen in obesity-derived neuroinflammation, is also a key feature of both AD and depression.[64] During chronic pro-inflammatory states, microglial cells become induced into the M1 subtype,[65] which have decreased phagocytic activity, diminished expression of beta-amyloid phagocytic receptors, resulting in impaired beta-amyloid clearance,[66] and contribute to oxidative stress through increased expression of inducible nitric oxide synthase (iNOS). Through TNF-alpha and IL-1 signaling, M1 microglia may also drive astrocytes into a neurotoxic A1 subtype commonly found in neurodegenerative diseases, inducing neuronal death rather than promoting phagocytosis and synaptogenesis.[67] In addition to significance in AD pathology, pro-inflammatory microglial cells and astrocytes are known to significantly promote depressive-like behaviors through neurogenesis and neuroplasticity and are characteristically found in Major Depressive Disorder.[68–70]

Insulin Resistance

Insulin resistance is a potential contributor toward AD pathology.[71] Insulin receptors facilitate cleavage of beta-amyloid oligomers through insulin-degrading enzyme activity. In turn, beta-amyloid oligomers disrupt insulin receptor function, creating a feedback cycle. Insulin also inhibits glycogen synthase kinase-3 (GSK-3), a key phosphorylator of tau proteins. Activation of GSK-3 disrupts insulin signaling through phosphorylation of insulin receptor substrate-1, perpetuating another feedback cycle. The characteristic features of AD, such as reduced brain glucose metabolism, reduced cerebrospinal fluid (CSF) to plasma insulin ratio, and decreased expression of insulin and insulin receptor genes, further highlight the significance of obesity-related inflammatory signaling in AD pathophysiology.[72] Intranasal insulin administration has shown memory function improvements in individuals with early AD or MCI, adding further support to this connection. In addition, insulin signaling mediated by the GSK-3 pathway is involved in neurogenesis and synaptic plasticity. Disruption of this pathway in insulin resistance has been associated with impaired stress

adaptation and aberrant reward circuitry, both drivers of depressive-like behaviors.[73,74,75]

Numerous studies have delineated the inverse relationships between obesity and cognitive function, independent of cardiovascular and cerebrovascular disease, including in otherwise healthy young adults. Multiple measures of obesity have been investigated in these contexts, including BMI, waist circumference, and waist-to-hip ratio.[76] Cognitive deficits in memory, executive function, and attention may have bidirectional associations, potentially influencing health behaviors that contribute to obesity, such as dietary choices, physical activity, and impulse control.[77]

CLINICAL IMPACT OF OBESITY AS A RISK FACTOR FOR AD AND DEPRESSION

Obesity and Risk for AD

There is increasing evidence that the association between obesity and AD is nuanced according to the trajectory of obesity-related pathology over the individual's lifespan. Recent large cohort studies have demonstrated that there is an increased risk for AD for individuals with midlife (40−60 years of age) obesity. There have also been studies showing that conversely, there is a decreased risk for AD for individuals with late-life obesity.[17]

Although this has been previously deemed paradoxical, more detailed longitudinal results and consideration for underlying pathology may reconcile these differences. One key aspect to this is the trajectory in individual body adiposity over the lifespan. Older individuals are known to develop increased body adiposity as a natural physiologic change. There are already several protective aspects of this adiposity. In addition, the metabolic abnormalities and proinflammatory milieu associated with obesity are known to be chronic conditions developed over decades of an individual's life. Given these aspects, obesity developed in late life may lack these deleterious characteristics which mediate its relationships with depression and AD as previously discussed. Further evidence supporting this is the recognition of metabolically healthy obesity in the elderly as a protective state, which has been proposed to represent a prodromal stage.

In addition to this, studies have shown that in elderly individuals, having decreased body adiposity and being underweight is also a risk factor for AD.[78] With this understanding, it may be more appropriate to attribute the risk for AD with the chronic metabolic and inflammatory derangements characteristic of longstanding obesity rather than the presence of body adiposity alone in late life. Further study of obese mid-life individuals without metabolic abnormalities or significant inflammatory pathology would be warranted to characterize these relationships more fully.

The impact of AD pathology on body adiposity further complicates these relationships as well. For example, weight discrimination has been linked to increased dementia risk and BMI is not always related to performance on cognitive domains.[79,80] Unintentional weight loss is a widely recognized characteristic of AD as well as a prognostic factor of disease progression in individuals with MCI.[81,82] Weight loss may be the result of progressive cognitive deterioration, as individuals with cognitive impairment may have difficulties feeding themselves or remembering to eat.[83] Furthermore, it is possible that with the progression of AD, there may be increased movement due to decreased inhibition, decreased sleep, associated with brainstem dysfunction. In addition, patients with AD are known to have lower concentrations of leptin as compared with amyloid negative participants,[84,85] indicating presence of dysfunctional appetite signaling pathways involving the hypothalamus and central feeding drive. Conversely, nutritional deficiencies present in the underweight state may also significantly impact cognition, creating a feedback cycle. Many of these effects are also present in late-life depression and are interrelated with AD.[86] Depressive episodes characterized by weight loss and diminished appetite are associated with increased likelihood of AD.[86] Unintentional weight loss in late-life is also associated with increased risk for depression.[87]

APOE Genotype and Obesity

While the APOE genotype and obesity each individually contribute to cognitive deficits and Alzheimer's disease, the interplay between these factors is still under investigation. Homozygous APOE4 carriers have a significantly increased risk and earlier

onset of metabolic syndrome, along with higher fasting glucose and insulin levels.[88] Interestingly, APOE4 carriers have a lower average Body Mass Index (BMI) compared to APOE3 or APOE2 carriers.[89] Despite this, APOE4 carriers have elevated total cholesterol and low-density lipoproteins compared to other genotypes and are more susceptible to Alzheimer's disease.[90] Furthermore, APOE4 carriers with a higher waist-to-hip ratio have demonstrated significantly poorer executive and memory functions and have also exhibited a reduced response to insulin therapies compared to non-APOE4 carriers.[91] Collectively, these findings suggest that the relationship between APOE4 carrier status, obesity, and cognitive function may be mediated through metabolic disruptions that contribute to neuroinflammation.

Bidirectional Relationship Between Obesity and Depression

Obesity is a well-recognized risk factor for depression[92–94] with comorbid metabolic abnormalities being associated with worsened clinical outcomes and greater functional impairment.[95] Multiple meta-analyses have demonstrated associations between depression and metabolic abnormalities.[96–98] Similar to the potential temporal significance of obesity on AD, a longitudinal meta-analysis of depression and obesity found that greater temporal exposure to obesity was associated with greater risk for depression than cross-sectional associations.[14,96]

Interestingly, similar to AD, there also exists a paradoxical relationship between obesity and depression when stratified by age. In one study by (Li et al.) of 56,167 elderly Chinese individuals, obesity was associated with lower likelihood of depressive symptoms in both men and women. A similar result was reported in another investigation of 2,516 elderly individuals in Taiwan, where obese and overweight women were less likely to have depressive symptoms than women of normal weight, and underweight men were more likely to have depressive symptoms than men of normal weight.

Although there have been other studies with contradicting results where obesity was positively associated with depressive symptoms,[93] there are crucial differences in the study population of Chinese older adults that may potentially explain for these differences.[15] These include an absence of functional disability (ADL and IADL) in 94.7% of participants and an absence of cognitive impairment in 98.0% of individuals (AMT < 8). Although further metabolic characterization of participants is not provided, only 3% of male and 7% of female participants had BMI of 30 or greater, which is typically lower than that of Western study populations. These results show that late-life overweight in the absence of major cognitive or functional disability is associated with lower risk for depressive symptoms.

Increasing emphasis is being placed on presence of metabolic syndrome and inflammatory markers in late life as modifiable risk factors and predictors for depression rather than body adiposity alone.[99,100] The presence of metabolic and inflammatory abnormalities has also been found to mediate the relationship between depression and frailty, indicating that these abnormalities may have a broader impact on general quality of life than previously expected.[101] As metabolic syndrome is a known repercussion of the chronic inflammatory state arising from obesity, there is a need for improved characterization of obesity-related inflammation and neuroinflammation especially in the contexts of depression and AD.[102]

RACIAL AND SOCIOECONOMIC DISPARITIES IN OBESITY, DEPRESSION, AND AD

There is evidence that the relationships between obesity, AD, and depression may seem to be paradoxical across racial groups.[103]

Several racial groups, namely, Black, Hispanic, and Pacific Islanders have a much higher rate of obesity.[10,103] Inversely, Asian individuals tend to have lower rates of obesity measured at traditional cut-offs but may experience mortality from cardiovascular disease and cancer at a lower BMI than compared with other racial groups.[104,105]

A recent meta-analysis of epidemiological late-life depression studies involving 57,486 older adults demonstrated that the average prevalence was 31.8%, however the pooled prevalence was 40.78% on developing countries as compared to 17.8% in developed countries.[106] A cross-sectional study of 25,503 community-dwelling older adults in the United States as part of the VITAL-D trial demonstrated significant racial disparities with late life depression symptom

severity and care, namely that Black participants tended to have 10% higher severity of PHQ-8 scores and were 61% less likely to have reported receiving any form of symptomatic treatment (after adjustment of sociodemographic, lifestyle, health confounders).[107]

A recent cross-sectional study of 378,615 older adults in the United States investigated the racial disparities in the modifiable risk factors for AD via survey data. 36.9% of AD were hypothesized to be associated with 8 modifiable risk factors, with the three leading factors being midlife obesity (17.7%), physical inactivity (11.8%), and low educational attainment (11.7%). For individuals identifying as American Indians, Alaska Native, Black, and While, mid-life obesity was the most prominent risk factor; for individuals identifying as Hispanic, low educational attainment, and for individuals identifying as Asian, physical inactivity.[108]

INTERVENTIONS REDUCING INFLAMMATION IN OBESITY, DEPRESSION, AND AD

Lifestyle Changes: Caloric Restriction, Diet, Physical Activity, and Bariatric Surgery

Interventions for obesity such as caloric restriction and exercise training may address inflammation in addition to metabolic dysfunction.[23,109] The role of exercise was also emphasized by a study showing additional reduction of circulating inflammatory biomarkers when 6 months of caloric restriction were augmented with aerobic exercise training compared to caloric restriction alone in overweight or obese women.[110] Furthermore, physical exercise has been demonstrated to be effective in treating in mild to moderate depression, with increasing anti-inflammatory PGC1a gene expression, reducing neuroinflammation (Ignacio). Bariatric procedures, previously shown to reduce visceral adiposity, have also been shown to reduce serum CRP in patients after 6 months.[111,112] Reductions in inflammatory markers was also correlated with reductions in depressive symptoms in obese individuals after bariatric surgery,[113] strengthening the role of inflammation mediating the effects of obesity on depression. In AD, aerobic activity and resistance training have been associated with increased cognitive functioning,[114] lower inflammation,[115] decreased amyloid deposition,[116] and increased BDNF.[117]

Pharmacological Interventions

Anti-depressant therapy has been the best understood in the context of depression, and it is hypothesized that except for bupropion and agomelatine, reduce inflammation through regulation of microglial activation and decrease reactive oxide species.[118] Lithium has been demonstrated to reduce GSK3- β pathways involved in neuroinflammation and the pathophysiology of AD: several small studies have suggested that lithium may reduce cognitive decline, but further comparative study is required at this time.[119,120] Reduction of hyperlipidemia with statins is also promising as HMG-CoA reductase inhibitors may reduce pro-inflammatory mediators,[121] decrease ROS, and stimulate eNOS,[122]. However, the evidence is mixed as to whether cognitive function may improve in AD.[123] It is likely that statin use may be more effective in reducing said neuroinflammation at an earlier stage rather than when irreversible cognitive changes have occurred.

Large-scale epidemiological studies and meta-analyses have previously indicated that general NSAID use, not specific to any individual agent, is associated with a decreased risk of Alzheimer's disease.[124,125] However, previous researchers have noted several limitations, including significant variations in study design, types of NSAID exposure, and lack of control for confounding variables.[126] In addition, one randomized control trial of NSAID use versus placebo on Alzheimer disease progression showed no significant slowing of cognitive decline in patients with already-present mild-to-moderate Alzheimer disease.[127]

IMAGING INITIATIVES FOR NEUROINFLAMMATION

Neuroinflammation-focused imaging, centered on the underlying molecular mechanisms of inflammation, is crucial for advancing our understanding of disease pathophysiology and monitoring intervention outcomes. Translocator protein 18 kDa (TSPO), one of the most common positron emission tomography

(PET) imaging biomarkers, is a mitochondrial membrane transporter expressed on the surface of activated microglial cells and astrocytes during neuroinflammation. Increases in TSPO binding have been documented in both AD and major depression episodes, and TSPO uptake in patients with depression has predicted depressive symptom reduction in response to celecoxib, a nonsteroidal anti-inflammatory agent.[128] Similarly, other markers of activated microglial cells have been the subject of interest given their potential as measures for neuroinflammation.[129]

One such target is type 2 cannabinoid receptors (CB2), which are expressed on microglial cells and neurons during neuroinflammation.[130] CB2 expression has also been documented to be elevated in animal models of AD as well as postmortem AD brain tissue, and CB2 activation has been associated with neuroprotective benefits.[131] Specific brain uptake of CB2 radiotracers has been demonstrated in animal models of neuroinflammatory insults. Some investigations for CB2 radiotracers have documented diminished uptake in AD patients compared to healthy controls, but this has been thought to be due to whole brain neuronal loss in late-stage AD.[132]

Another target is cyclooxygenase-2 (COX-2), an enzyme involved in neuroinflammatory pathways mediated by NFκB leading to release of inflammatory cytokines and ROS production. One advantage of targeting COX-2 is its low expression in the brain during healthy conditions, and successful uptake of a COX-2 radiotracer has been demonstrated in a rhesus monkey study of neuroinflammation.[133] However, selectivity of radiotracers for COX-2 versus its isoform COX-1 as well as the high nonspecific binding of these radiotracers remain challenges for future development.[134]

More broadly, as microglial cell activation is also known to affect local microcirculation, arterial spin labeling (ASL) has been used to characterize tissue perfusion as a surrogate measure for neuroinflammation. ASL involves magnetic tagging of arterial blood water content to differentiate blood inflow from a static image and has been shown to correlate well with PET data in neurodegenerative conditions including AD and frontotemporal dementia.[135]

Neuroinflammation and neuronal injury is also associated with decreased glucose metabolism. As such, FDG-PET has also been a known imaging marker for neurodegenerative conditions including AD.[136] Other methods of glucose detection include use of 2-deoxy-d-glucose (2DG) in chemical exchange saturation transfer, which offers the benefit of *in vivo* imaging of glucose metabolism without use of radiotracers.[137]

Brain edema represents a sequela of neuroinflammatory injury. Pathogenesis of brain edema involves BBB disruption such as the increases in permeability resulting from pro-inflammatory cytokine signaling and oxidative stress. Imaging of brain edema is therefore another strategy for detection of neuroinflammation, such as through use of diffusion MR imaging. One recent method for this involves obtaining extracellular water fraction through diffusion-based spectrum imaging.[138,139,140]

Using diffusion-based spectrum imaging, we have demonstrated several notable findings in the context of neuroinflammation in several cohorts of obese individuals. In one study, we demonstrated that young adult obese individuals had significantly lower axonal density, greater neuroflammation related cellularity that was related to cognitive performance as compared to non-obese healthy controls.[141] Furthermore, in midlife obese adults, increased neuroinflammation was found to be associated with smaller caudate volumes and larger nucleus accumbens, providing possible mechanistic suggestions for emotional eating, adiposity, and neuroinflammation. Then, we have demonstrated significant associations between neuroinflammation and obesity in cognitively normal, otherwise healthy older adults, as well as associations between neuroinflammation and decreased brain volumes.[142] Given the significance of obesity-derived neuroinflammation as a risk factor for AD, we have also demonstrated that obesity mediates the relationship between neuroinflammation and biomarkers for AD pathology in individuals with pre-clinical disease (Yu and Ly, in submission). Further investigation of such imaging biomarkers for neuroinflammation in additional patient populations including depression is warranted and will improve earlier detection and prevention of obesity-mediated inflammatory injury.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

In this review we have traversed the landscape of obesity and its impact on AD and depression

through neuroinflammation. By understanding the underlying mechanisms of obesity-mediated inflammation, we may reconcile the differences in disease association between metabolically healthy obesity and obesity with metabolic and inflammatory derangements.

Importance of Intervention and Study During the Mid-Life Period

The process of neuroinflammation is believed to be a long-term, cumulative event that occurs throughout an individual's life. The longer and more intense this inflammatory burden, the more likely it is to result in neurodegeneration. Many current strategies for addressing Alzheimer's disease are often implemented when the disease has already manifested, and dementia is evident. However, this might be too late as the dynamic processes of neurodegeneration may have already reached a point of no return, making the individual unresponsive to therapeutic interventions. Therefore, it is crucial to shift our focus and therapeutic strategies to the earlier stages of this pathology and inflammation. This is particularly important during midlife, a period when metabolic imbalances and the onset of metabolic syndrome, obesity, and systemic inflammation are still developing. During this time, these dynamic processes might still be susceptible to therapeutic interventions, potentially offering a preventive and protective effect against later neurodegeneration.

Racial and Socioeconomic Disparities in Obesity, Depression, and AD

We have reviewed evidence that demonstrate the racial and socioeconomic disparity is significant differences namely in prevalence, symptomatology, and rates of receiving care in obesity, late life depression, and AD. However, this area remains significantly understudied. There are some important other factors that need to be accounted for, such as area deprivation index, intergenerational trauma, racial and ethnic socialization. Furthermore, the relationships between AD, depression and obesity across racial groups are currently not well studied.

Neuroinflammation Imaging and Future Study

Imaging markers for neuroinflammation are continuing to grow increasingly sophisticated, and their application in individuals with obesity may also inform on future risk for development of AD and depression. Additional longitudinal studies on the impact of obesity over the lifespan in conjunction with inflammation imaging will also improve our understanding of the impact that chronic obesity-mediated inflammation may have and aid us in the development of preventative and treatment strategies.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

AUTHOR CONTRIBUTIONS

ML, GY, and CAR drafted the manuscript. All authors reviewed, revised, and provided final approval for the manuscript. AC and AM created the figure.

DISCLOSURES

The authors have no conflicts of interest to declare. This work was funded by grants from the National Institutes of Health (1RF1AG072637-01, P30AG066444, P01AG026276, and P01AG003991). Dr. Raji has consulting relationships with Brainreader ApS, Neurevolution LLC, Apollo Health, the Pacific Neuroscience Foundation, and Voxelwise Consultants.

GM Babulal is funded by NIH grants # grants R01AG056466, R01AG068183, R01AG067428, R01AG074302.

JC Morris is funded by NIH grants # P30 AG066444; P01AG003991; P01AG026276; U19 AG032438; and U19 AG024904. Neither Dr. Morris nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company.

References

1. Zhang X-X, Tian Y, Wang Z-T, et al: The epidemiology of Alzheimer's disease modifiable risk factors and prevention. J Prev Alzheimer's Dis 2021; 8:313–321
2. Patterson C: World alzheimer report 2018. 2018;
3. 2023 Alzheimer's disease facts and figures. Alzheimers Dement 2023; 19:1598-1695
4. Gotlib IH, Hammen CL: Handbook of depression 2008
5. Gutiérrez-Rojas L, Porras-Segovia A, Dunne H, et al: Prevalence and correlates of major depressive disorder: a systematic review. Braz J Psychiatry 2020; 42:657–672
6. Lim GY, Tam WW, Lu Y, et al: Prevalence of depression in the community from 30 countries between 1994 and 2014. Sci Rep 2018; 8:1–10
7. Laborde-Lahoz P, El-Gabalawy R, Kinley J, et al: Subsyndromal depression among older adults in the USA: prevalence, comorbidity, and risk for new-onset psychiatric disorders in late life. Int J Geriatr Psychiatry 2015; 30:677–685
8. Mohebbi M, Agustini B, Woods RL, et al: Prevalence of depressive symptoms and its associated factors among healthy community-dwelling older adults living in Australia and the United States. Int J Geriatr Psychiatry 2019; 34:1208–1216
9. Anand SS, Hawkes C, de Souza RJ, et al: Food Consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system: a report from the workshop convened by the world heart federation. J Am Coll Cardiol 2015; 66:1590–1614
10. Fryar CD, Carroll MD, Afful J: Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats, 2020
11. Barnes DE, Yaffe K, Byers AL, et al: Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Arch Gen Psychiatry 2012; 69:493–498
12. Butters MA, Young JB, Lopez O, et al: Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci 2008; 10:345–357
13. Babulal GM, Ghoshal N, Head D, et al: Mood changes in cognitively normal older adults are linked to alzheimer disease biomarker levels. Am J Geriatr Psychiatry 2016; 24:1095–1104
14. Jantaratnotai N, Mosikanon K, Lee Y, et al: The interface of depression and obesity. Obes Res Clin Pract 2017; 11:1–10
15. Li ZB, Ho SY, Chan WM, et al: Obesity and depressive symptoms in Chinese elderly. Int J Geriatr Psychiatry 2004; 19:68–74
16. Liu JH, Qian YX, Ma QH, et al: Depressive symptoms and metabolic syndrome components among older Chinese adults. Diabetol Metab Syndr 2020; 12:18
17. Sun Z, Wang ZT, Sun FR, et al: Late-life obesity is a protective factor for prodromal Alzheimer's disease: a longitudinal study. Aging (Albany NY) 2020; 12:2005–2017
18. Monteiro R, Azevedo I: Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm 2010: 1–10
19. Amabebe E, Robert FO, Agbalalah T, et al: Microbial dysbiosis-induced obesity: role of gut microbiota in homoeostasis of energy metabolism. Br J Nutr 2020; 123:1127–1137
20. Chen X, Devaraj S: Gut microbiome in obesity, metabolic syndrome, and diabetes. Curr Diab Rep 2018; 18:129
21. Kacířová M, Zmeškalová A, Kořínková L, et al: Inflammation: major denominator of obesity, Type 2 diabetes and Alzheimer's disease-like pathology? Clin Sci (Lond) 2020; 134:547–570
22. Pasarica M, Sereda OR, Redman LM, et al: Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes 2009; 58:718–725
23. You T, Arsenis NC, Disanzo BL, et al: Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. Sports Med 2013; 43:243–256
24. Monteiro R, de Castro PM, Calhau C, et al: Adipocyte size and liability to cell death. Obes Surg 2006; 16:804–806
25. Artemniak-Wojtowicz D, Kucharska AM, Pyrżak B: Obesity and chronic inflammation crosslinking. Cent Eur J Immunol 2020; 45:461–468
26. Xu H, Barnes GT, Yang Q, et al: Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112:1821–1830
27. Ibrahim MM: Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev 2010; 11:11–18
28. Esser N, L'homme L, De Roover A, et al: Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. Diabetologia 2013; 56:2487–2497
29. Rodríguez-Hernández H, Simental-Mendía LE, Rodríguez-Ramírez G, et al: Obesity and inflammation: epidemiology, risk factors, and markers of inflammation. Int J Endocrinol 2013; 2013:678159
30. Manabe I: Chronic inflammation links cardiovascular, metabolic and renal diseases. Circ J 2011; 75:2739–2748
31. Wiebe N, Stenvinkel P, Tonelli M: Associations of chronic inflammation, insulin resistance, and severe obesity with mortality, myocardial infarction, cancer, and chronic pulmonary disease. JAMA Netw Open 2019; 2:e1910456
32. Amin MN, Hussain MS, Sarwar MS, et al: How the association between obesity and inflammation may lead to insulin resistance and cancer. Diabetes Metab Syndr 2019; 13:1213–1224
33. Zatterale F, Longo M, Naderi J, et al: Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Front Physiol 2019; 10:1607
34. Pantoja-Meléndez AMCaLEaCA: Low-grade inflammation and its relation to obesity and chronic degenerative diseases. Revista Médica Hospital Gen México 2017; 80:101–105
35. Furman D, Campisi J, Verdin E, et al: Chronic inflammation in the etiology of disease across the life span. Nat Med 2019; 25:1822–1832
36. Marginǎ D, Ungurianu A, Purdel C, et al: Chronic inflammation in the context of everyday life: dietary changes as mitigating factors. Int J Environ Res Public Health 2020; 17:1–27
37. Ruiz NAL, Del Ángel DS, Olguín HJ, et al: Neuroprogression: the hidden mechanism of depression. Neuropsychiatr Dis Treat 2018; 14:2837–2845
38. Bruehl H, Wolf OT, Sweat V, et al: Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. Brain Res 2009; 1280:186–194
39. Benomar Y, Taouis M: Molecular mechanisms underlying obesity-induced hypothalamic inflammation and insulin resistance: pivotal role of resistin/TLR4 Pathways. Front Endocrinol (Lausanne) 2019; 10:140
40. Chen IC, Awasthi D, Hsu CL, et al: High-fat diet-induced obesity alters dendritic cell homeostasis by enhancing mitochondrial fatty acid oxidation. J Immunol 2022; 209:69–76
41. Malesza IJ, Malesza M, Walkowiak J, et al: High-fat, western-style diet, systemic inflammation, and gut microbiota: a narrative review. Cells 2021; 10:1–9

42. Thaler JP, Yi CX, Schur EA, et al: Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest 2012; 122:153–162
43. Yoon G, Cho KA, Song J, et al: Transcriptomic analysis of high fat diet fed mouse brain cortex. Front Genet 2019; 10:83
44. Wang BZ, Yang JJ, Zhang H, et al: AMPK signaling regulates the age-related decline of hippocampal neurogenesis. Aging Dis 2019; 10:1058–1074
45. Stranahan AM, Norman ED, Lee K, et al: Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus 2008; 18:1085–1088
46. Takechi R, Lam V, Brook E, et al: Blood-brain barrier dysfunction precedes cognitive decline and neurodegeneration in diabetic insulin resistant mouse model: an implication for causal link. Front Aging Neurosci 2017; 9:399
47. Takechi R, Pallebage-Gamarallage MM, Lam V, et al: Aging-related changes in blood-brain barrier integrity and the effect of dietary fat. Neurodegener Dis 2013; 12:125–135
48. Kanoski SE, Zhang Y, Zheng W, et al: The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. J Alzheimers Dis 2010; 21:207–219
49. Klockars A, Levine AS, Olszewski PK: Hypothalamic integration of the endocrine signaling related to food intake. Curr Top Behav Neurosci 2019; 43:239–269
50. Cai D, Liu T: Inflammatory cause of metabolic syndrome via brain stress and NF-κB. Aging (Albany NY) 2012; 4:98–115
51. Miyamoto A, Wake H, Moorhouse AJ, et al: Microglia and synapse interactions: fine tuning neural circuits and candidate molecules. Front Cell Neurosci 2013; 7:70
52. Butterfield DA, Poon HF, St Clair D, et al: Redox proteomics identification of oxidatively modified hippocampal proteins in mild cognitive impairment: insights into the development of Alzheimer's disease. Neurobiol Dis 2006; 22:223–232
53. Nunomura A, Perry G, Aliev G, et al: Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol 2001; 60:759–767
54. Maes M, Galecki P, Chang YS, et al: A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35:676–692
55. Black CN, Bot M, Scheffer PG, et al: Is depression associated with increased oxidative stress? A systematic review and meta-analysis. Psychoneuroendocrinology 2015; 51:164–175
56. Kawasaki N, Asada R, Saito A, et al: Obesity-induced endoplasmic reticulum stress causes chronic inflammation in adipose tissue. Sci Rep 2012; 2:799
57. de Mello AH, Costa AB, Engel JDG, et al: Mitochondrial dysfunction in obesity. Life Sci 2018; 192:26–32
58. Reddy PH, Yin X, Manczak M, et al: Mutant APP and amyloid beta-induced defective autophagy, mitophagy, mitochondrial structural and functional changes and synaptic damage in hippocampal neurons from Alzheimer's disease. Hum Mol Genet 2018; 27:2502–2516
59. Morrison CD, Pistell PJ, Ingram DK, et al: High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. J Neurochem 2010; 114:1581–1589
60. Riemer J, Kins S: Axonal transport and mitochondrial dysfunction in Alzheimer's disease. Neurodegener Dis 2013; 12:111–124
61. Serrano F, Klann E: Reactive oxygen species and synaptic plasticity in the aging hippocampus. Ageing Res Rev 2004; 3:431–443
62. Fernández-Sánchez A, Madrigal-Santillán E, Bautista M, et al: Inflammation, oxidative stress, and obesity. Int J Mol Sci 2011; 12:3117–3132
63. Bondia-Pons I, Ryan L, Martinez JA: Oxidative stress and inflammation interactions in human obesity. J Physiol Biochem 2012; 68:701–711
64. Singhal G, Baune BT: Microglia: an interface between the loss of neuroplasticity and depression. Front Cell Neurosci 2017; 11:270
65. Chylikova J, Dvorackova J, Tauber Z, et al: M1/M2 macrophage polarization in human obese adipose tissue. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2018; 162:79–82
66. Hickman SE, Allison EK, El Khoury J: Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. J Neurosci 2008; 28:8354–8360
67. Liddelow SA, Guttenplan KA, Clarke LE, et al: Neurotoxic reactive astrocytes are induced by activated microglia. Nature 2017; 541:481–487
68. Steiner J, Walter M, Gos T, et al: Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflammation 2011; 8:94
69. Torres-Platas SG, Cruceanu C, Chen GG, et al: Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. Brain Behav Immun 2014; 42:50–59
70. Zhang L, Zhang J, You Z: Switching of the microglial activation phenotype is a possible treatment for depression disorder. Front Cell Neurosci 2018; 12:306
71. Kan C, Silva N, Golden SH, et al: A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care 2013; 36:480–489
72. Hildreth KL, Van Pelt RE, Schwartz RS: Obesity, insulin resistance, and Alzheimer's disease. Obesity (Silver Spring) 2012; 20:1549–1557
73. Jope RS, Cheng Y, Lowell JA, et al: Stressed and inflamed, can GSK3 be blamed? Trends Biochem Sci 2017; 42:180–192
74. Lyra E, Silva NM, Lam MP, Soares CN, et al: Insulin resistance as a shared pathogenic mechanism between depression and type 2 diabetes. Front Psychiatry 2019; 10:57
75. Leonard BE, Wegener G: Inflammation, insulin resistance and neuroprogression in depression. Acta Neuropsychiatr 2020; 32:1–9
76. Miller AA, Spencer SJ: Obesity and neuroinflammation: a pathway to cognitive impairment. Brain Behav Immun 2014; 42:10–21
77. Eirini CSaPDAaANM: obesity, inflammation and cognition. Curr Opin Behav Sci 2016; 9:169–175
78. Gray SL, Anderson ML, Hubbard RA, et al: Frailty and incident dementia. J Gerontol A Biol Sci Med Sci 2013; 68:1083–1090
79. Sutin AR, Stephan Y, Robinson E, et al: Perceived weight discrimination and risk of incident dementia. Int J Obes (Lond) 2019; 43:1130–1134
80. Sutin AR, Stephan Y, Gerend MA, et al: Perceived weight discrimination and performance in five domains of cognitive function. J Psychosom Res 2020; 131:109793
81. Wang PN, Yang CL, Lin KN, et al: Weight loss, nutritional status and physical activity in patients with Alzheimer's disease. A controlled study. J Neurol 2004; 251:314–320
82. Sergi G, De Rui M, Coin A, et al: Weight loss and Alzheimer's disease: temporal and aetiologic connections. Proc Nutr Soc 2013; 72:160–165

83. Cova I, Clerici F, Rossi A, et al: Weight loss predicts progression of mild cognitive impairment to Alzheimer's Disease. PLoS One 2016; 11:e0151710
84. Lilamand M, Bouaziz-Amar E, Dumurgier J, et al: Plasma leptin is associated with amyloid CSF biomarkers and Alzheimer's disease diagnosis in cognitively impaired patients. J Gerontol A Biol Sci Med Sci 2023; 78:645–652
85. McGuire MJ, Ishii M: Leptin dysfunction and Alzheimer's disease: evidence from cellular, animal, and human studies. Cell Mol Neurobiol 2016; 36:203–217
86. Saha S, Hatch DJ, Hayden KM, et al: Appetite and weight loss symptoms in late-life depression predict dementia outcomes. Am J Geriatr Psychiatry 2016; 24:870–878
87. Huffman GB: Evaluating and treating unintentional weight loss in the elderly. Am Fam Phys 2002; 65:640–650
88. Torres-Perez E, Ledesma M, Garcia-Sobreviela MP, et al: Apolipoprotein E4 association with metabolic syndrome depends on body fatness. Atherosclerosis 2016; 245:35–42
89. Tejedor MT, Garcia-Sobreviela MP, Ledesma M, et al: The apolipoprotein E polymorphism rs7412 associates with body fatness independently of plasma lipids in middle aged men. PLoS One 2014; 9:e108605
90. Elosua R, Demissie S, Cupples LA, et al: Obesity modulates the association among APOE genotype, insulin, and glucose in men. Obes Res 2003; 11:1502–1508
91. Zade D, Beiser A, McGlinchey R, et al: Apolipoprotein epsilon 4 allele modifies waist-to-hip ratio effects on cognition and brain structure. J Stroke Cerebrovasc Dis 2013; 22:119–125
92. Stunkard AJ, Faith MS, Allison KC: Depression and obesity. Biol Psychiatry 2003; 54:330–337
93. Roberts RE, Deleger S, Strawbridge WJ, et al: Prospective association between obesity and depression: evidence from the Alameda County Study. Int J Obes Relat Metab Disord 2003; 27:514–521
94. Roberts RE, Kaplan GA, Shema SJ, et al: Are the obese at greater risk for depression? Am J Epidemiol 2000; 152:163–170
95. de Groot M, Kushnick M, Doyle T, et al: Depression among adults with diabetes: prevalence, impact, and treatment options. Diabetes Spectr 2010; 23:15–18
96. Luppino FS, de Wit LM, Bouvy PF, et al: Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010; 67:220–229
97. Mannan M, Mamun A, Doi S, et al: Prospective associations between depression and obesity for adolescent males and females- A systematic review and meta-analysis of longitudinal studies. PLoS One 2016; 11:e0157240
98. Sutaria S, Devakumar D, Yasuda SS, et al: Is obesity associated with depression in children? Systematic review and meta-analysis. Arch Dis Child 2019; 104:64–74
99. Repousi N, Masana MF, Sanchez-Niubo A, et al: Depression and metabolic syndrome in the older population: a review of evidence. J Affect Disord 2018; 237:56–64
100. de la Torre-Luque A, Ayuso-Mateos JL, Sanchez-Carro Y, et al: Inflammatory and metabolic disturbances are associated with more severe trajectories of late-life depression. Psychoneuroendocrinology 2019; 110:104443
101. Kokkeler KJE, Voshaar RCO, Rhebergen D, et al: Frailty measures in immuno-metabolic subtypes of late-life depression; a two-year prospective study. Arch Gerontol Geriatr 2022; 99:104603
102. Felger JC: Imaging the role of inflammation in mood and anxiety-related disorders. Curr Neuropharmacol 2018; 16:533–558
103. Babulal GM, Zhu Y, Roe CM, et al: The complex relationship between depression and progression to incident cognitive impairment across race and ethnicity. Alzheimers Dement 2022; 12:1–10
104. Deurenberg P, Deurenberg-Yap M, Guricci S: Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev 2002; 3:141–146
105. Zheng W, McLerran DF, Rolland B, et al: Association between body-mass index and risk of death in more than 1 million Asians. N Engl J Med 2011; 364:719–729
106. Zenebe Y, Akele B, W/Selassie M, et al: Prevalence and determinants of depression among old age: a systematic review and meta-analysis. Ann Gen Psychiatry 2021; 20:55
107. Vyas CM, Donneyong M, Mischoulon D, et al: Association of race and ethnicity with late-life depression severity, symptom burden, and care. JAMA Netw Open 2020; 3:e201606
108. Nianogo RA, Rosenwohl-Mack A, Yaffe K, et al: Risk factors associated with alzheimer disease and related dementias by sex and race and ethnicity in the US. JAMA Neurol 2022; 79:584–591
109. Johnson JB, Summer W, Cutler RG, et al: Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med 2007; 42:665–674
110. You T, Berman DM, Ryan AS, et al: Effects of hypocaloric diet and exercise training on inflammation and adipocyte lipolysis in obese postmenopausal women. J Clin Endocrinol Metab 2004; 89:1739–1746
111. Pontiroli AE, Frigè F, Paganelli M, et al: In morbid obesity, metabolic abnormalities and adhesion molecules correlate with visceral fat, not with subcutaneous fat: effect of weight loss through surgery. Obes Surg 2009; 19:745–750
112. Chiappetta S, Schaack HM, Wölnerhannsen B, et al: The Impact of obesity and metabolic surgery on chronic inflammation. Obes Surg 2018; 28:3028–3040
113. Emery CF, Fondow MD, Schneider CM, et al: Gastric bypass surgery is associated with reduced inflammation and less depression: a preliminary investigation. Obes Surg 2007; 17:759–763
114. Middleton LE, Barnes DE, Lui LY, et al: Physical activity over the life course and its association with cognitive performance and impairment in old age. J Am Geriatr Soc 2010; 58:1322–1326
115. Hopps E, Canino B, Caimi G: Effects of exercise on inflammation markers in type 2 diabetic subjects. Acta Diabetol 2011; 48:183–189
116. Tapia-Rojas C, Aranguiz F, Varela-Nallar L, et al: Voluntary running attenuates memory loss, decreases neuropathological changes and induces neurogenesis in a mouse model of Alzheimer's disease. Brain Pathol 2016; 26:62–74
117. Reycraft JT, Islam H, Townsend LK, et al: Exercise intensity and recovery on circulating brain-derived neurotrophic factor. Med Sci Sports Exerc 2020; 52:1210–1217
118. Mariani N, Everson J, Pariante CM, et al: Modulation of microglial activation by antidepressants. J Psychopharmacol 2022; 36:131–150
119. Haussmann R, Noppes F, Brandt MD, et al: Lithium: a therapeutic option in Alzheimer's disease and its prodromal stages? Neurosci Lett 2021; 760:136044
120. Matsunaga S, Kishi T, Annas P, et al: Lithium as a treatment for Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2015; 48:403–410
121. Bagheri H, Ghasemi F, Barreto GE, et al: The effects of statins on microglial cells to protect against neurodegenerative disorders: a mechanistic review. Biofactors 2020; 46:309–325

122. Saeedi Saravi SS, Arefidoust A, Dehpour AR: The beneficial effects of HMG-CoA reductase inhibitors in the processes of neurodegeneration. Metab Brain Dis 2017; 32:949–965
123. Majidazar R, Rezazadeh-Gavgani E, Sadigh-Eteghad S, et al: Pharmacotherapy of Alzheimer's disease: an overview of systematic reviews. Eur J Clin Pharmacol 2022; 78:1567–1587
124. Zhang C, Wang Y, Wang D, et al: NSAID exposure and risk of Alzheimer's disease: an updated meta-analysis from cohort studies. Front Aging Neurosci 2018; 10:83
125. Vlad SC, Miller DR, Kowall NW, et al: Protective effects of NSAIDs on the development of Alzheimer disease. Neurology 2008; 70:1672–1677
126. McGeer PL, McGeer EG: NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. Neurobiol Aging 2007; 28:639–647
127. Aisen PS, Schafer KA, Grundman M, et al: Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003; 289:2819–2826
128. Attwells S, Setiawan E, Rusjan PM, et al: Translocator protein distribution volume predicts reduction of symptoms during open-label trial of celecoxib in major depressive disorder. Biol Psychiatry 2020; 88:649–656
129. Meyer JH, Cervenka S, Kim MJ, et al: Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. Lancet Psychiatry 2020; 7:1064–1074
130. Walter L, Stella N: Cannabinoids and neuroinflammation. Br J Pharmacol 2004; 141:775–785
131. Palazuelos J, Aguado T, Pazos MR, et al: Microglial CB2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity. Brain 2009; 132:3152–3164
132. Savonenko AV, Melnikova T, Wang Y, et al: Cannabinoid CB2 receptors in a mouse model of Aβ amyloidosis: immunohistochemical analysis and suitability as a PET biomarker of neuroinflammation. PLoS One 2015; 10:e0129618
133. Kenou BV, Manly LS, Rubovits SB, et al: Cyclooxygenases as potential pet imaging biomarkers to explore neuroinflammation in dementia. J Nucl Med 2022; 63:53S–59S
134. Janssen B, Mach RH: Development of brain PET imaging agents: strategies for imaging neuroinflammation in Alzheimer's disease. Prog Mol Biol Transl Sci 2019; 165:371–399
135. Bambach S, Smith M, Morris PP, et al: Arterial spin labeling applications in pediatric and adult neurologic disorders. J Magn Reson Imaging 2022; 55:698–719
136. Winkeler A, Boisgard R, Martin A, et al: Radioisotopic imaging of neuroinflammation. J Nucl Med 2010; 51:1–4
137. Tolomeo D, Micotti E, Serra SC, et al: Chemical exchange saturation transfer MRI shows low cerebral 2-deoxy-D-glucose uptake in a model of Alzheimer's disease. Sci Rep 2018; 8:9576
138. Wang Q, Wang Y, Liu J, et al: Quantification of white matter cellularity and damage in preclinical and early symptomatic Alzheimer's disease. Neuroimage Clin 2019; 22:101767
139. Cross AH, Song SK: A new imaging modality to non-invasively assess multiple sclerosis pathology. J Neuroimmunol 2017; 304:81–85
140. Assaf Y, Basser PJ: Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain. Neuroimage 2005; 27:48–58
141. Samara A, Murphy T, Strain J, et al: Neuroinflammation and white matter alterations in obesity assessed by diffusion basis spectrum imaging. Front Hum Neurosci 2019; 13:464
142. Ly M, Raji CA, Yu GZ, et al: Obesity and white matter neuroinflammation related edema in Alzheimer's disease dementia biomarker negative cognitively normal individuals. J Alzheimers Dis 2021; 79:1801–1811