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 Meyssami, 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.

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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
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. AD, as the leading cause of dementia, is projected to affect over 150 million individuals worldwide by 2050 with a continually aging population. 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. Depression is the leading cause of disability and loss of productive life years worldwide, currently estimated to affect over 300 million individuals. Depression may affect up to 9.8–13.7% of older adults living in the United States. Obesity is a burgeoning global health epidemic with approximately 36.9% of men and 38.0% of women being obese and overweight globally, 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.

**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. Alternatively late-life depression may represent an early manifestation, or a prodrome, of AD given the strong temporal associations with subsequent development of AD. On the other hand, 23% of obese individuals are estimated to have comorbid depression, while depression increases risk of obesity by 37%.

**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, 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.

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, 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. Larger adipocytes are also more prone to rupture, triggering inflammatory cascades and increased recruitment of M1-type macrophages. 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 NF kappa B (IKKbeta).

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. 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.

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. 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. 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.

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. The central nervous system is no exception, as chronic obesity-derived neuroinflammation likely plays a significant role in neurodegeneration and cognitive decline. 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. The increase in HPA axis activity in obesity has been associated with poorer cognitive performance in obese individuals with type 2 diabetes. Exposure to obesity-
TABLE 1. Summary of Mechanisms Underlying Neuroinflammation

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<td>HPA axis-related mechanisms</td>
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<td>Increased hypothalamic gene expression of IL-6, TNF-alpha, IKKbeta</td>
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<td>Gut Microbiome-related mechanisms</td>
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<tr>
<td>Increased gut microbiome permeability</td>
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<td>Disrupted dendritic cell homeostasis, impaired immune function</td>
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<td>Neurogenesis-synaptic dysfunction</td>
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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 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
HPA axis hyperactivity, a physiologic adaptation in depression to increased psychosocial stressors.\textsuperscript{55}

**Microglia and Astrocyte Activation**

Microglial cell activation, seen in obesity-derived neuroinflammation, is also a key feature of both AD and depression.\textsuperscript{64} During chronic pro-inflammatory states, microglial cells become induced into the M1 subtype,\textsuperscript{65} which have decreased phagocytic activity, diminished expression of beta-amyloid phagocytic receptors, resulting in impaired beta-amyloid clearance,\textsuperscript{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.\textsuperscript{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.\textsuperscript{68–70}

**Insulin Resistance**

Insulin resistance is a potential contributor toward AD pathology.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{77}

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**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.\textsuperscript{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.\textsuperscript{75} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{86} Depressive episodes characterized by weight loss and diminished appetite are associated with increased likelihood of AD.\textsuperscript{86} Unintentional weight loss in late-life is also associated with increased risk for depression.\textsuperscript{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. Interestingly, APOE4 carriers have a lower average Body Mass Index (BMI) compared to APOE3 or APOE2 carriers. Despite this, APOE4 carriers have elevated total cholesterol and low-density lipoproteins compared to other genotypes and are more susceptible to Alzheimer’s disease. 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. 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 with comorbid metabolic abnormalities being associated with worsened clinical outcomes and greater functional impairment. Multiple meta-analyses have demonstrated associations between depression and metabolic abnormalities. 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.

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, there are crucial differences in the study population of Chinese older adults that may potentially explain for these differences. 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. 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. 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.

**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.

Several racial groups, namely, Black, Hispanic, and Pacific Islanders have a much higher rate of obesity. 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.

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. 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). 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 White, 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.

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. 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. Furthermore, physical exercise has been demonstrated to be effective in treating in mild to moderate depression, with increasing anti-inflammatory PGC1α 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. Reductions in inflammatory markers was also correlated with reductions in depressive symptoms in obese individuals after bariatric surgery, 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, lower inflammation, decreased amyloid deposition, and increased BDNF.

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. 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. Reduction of hyperlipidemia with statins is also promising as HMG-CoA reductase inhibitors may reduce pro-inflammatory mediators, decrease ROS, and stimulate eNOS. However, the evidence is mixed as to whether cognitive function may improve in AD. 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. However, previous researchers have noted several limitations, including significant variations in study design, types of NSAID exposure, and lack of control for confounding variables. 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.

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. Similarly, other markers of activated microglial cells have been the subject of interest given their potential as measures for neuroinflammation.

One such target is type 2 cannabinoid receptors (CB2), which are expressed on microglial cells and neurons during neuroinflammation. 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. 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.

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. However, selectivity of radiotracers for COX-2 versus its isofrom COX-1 as well as the high nonspecific binding of these radiotracers remain challenges for future development.

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.

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. 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.

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.

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 neuroinflammation related cellularity that was related to cognitive performance as compared to non-obese healthy controls. 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. 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.

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**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.

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Association between psychosocial risk factors and readmissions

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Association between psychosocial risk factors and readmissions