

Early onset of Alzheimer's is on the rise - Evidence and Implications

Aldan K. Joseph

Abstract:

The prevalence of early-onset Alzheimer's Disease (AD) and Major Depressive Disorder (MDD) has demonstrated an escalating trajectory. This warrants an investigation into their intricate connections. This review will assess the relationship among AD, MDD, and their associated medication, specifically Selective Serotonin Reuptake Inhibitors (SSRIs). The overarching hypothesis suggests that diet significantly contributes to depression by modulating tryptophan metabolism, and SSRIs can significantly stunt AD progression. Therefore, this review will examine three aspects: the biochemistry of depression and how it relates to the progression of AD; how diet is linked to MDD and whether this is predominant in a younger age range; and the potential effectiveness of the SSRIs fluoxetine (FLX) and citalopram as a treatment to inhibit AD pathology.

Introduction.

Alzheimer's disease (AD) is a neurodegenerative disease stemming from neuronal damage within the temporal lobe, resulting in memory loss and poor judgment (1). AD is characterized by the progressive deterioration of an individual's memory, cognition, and social behavior (2). AD is the most prevalent form of dementia (3,4), and it often advances to levels of severity that impair the daily activities and functional capability of the affected individuals (5). The pathogenesis of AD revolves around abnormal protein buildups in neuronal synapses, predominantly on the postsynaptic side. Amyloid beta ($A\beta$) protein plaques and tau protein tangles are key contributors researched in AD (1,4). Although AD predominantly manifests in the elderly population, it can manifest in individuals as young as their 30s or 40s (6). This early manifestation of AD in individuals under the age of 65 is known as 'early-onset' or 'younger-onset' AD (7).

During the last decade, there has been a notable increase in the prevalence of depression across demographically diverse populations (8). In the aftermath of the Coronavirus (COVID-19) pandemic, a substantial proportion of the American population, nearly 1 in 10 individuals, and particularly 1 in 5 young adults, exhibited manifestations of depressive disorders (8). Depressive disorder has demonstrated a capacity to induce structural modifications within the gray and white matter of the hippocampus, thalamus, and amygdala (9). Notably, these regions overlap with those susceptible to early-onset AD (1). Gray and white matter serve as essential substrates for interregional neural communication and information exchange within the brain (10). Alterations in the composition and structural integrity of these neural constituents may provide a plausible explanation for select AD symptoms, such as memory loss (11).

AD progresses due to the enzymatic breakdown of amyloid precursor proteins (APP), culminating in their degradation and recycling (12). Dysregulations in the process of breaking down APP give rise to irregularities, precipitating the formation of $A\beta$ plaques (13). $A\beta$ proteins constitute a pivotal factor in AD, orchestrating the agglomeration into $A\beta$ plaques, thereby disrupting neuronal signaling processes (14,15). This dysregulation is implicated in the compromise of specific cerebral functions, like memory loss (16). Tau proteins, situated within

neurons, reside on microtubules, where they play an integral role in the maintenance of the cytoskeleton (17). The disruption of Tau protein functionality is catalyzed by the enzyme Asparagine endopeptidase (AEP), inducing alterations and subsequent aggregation into Tau tangles (18). These Tau tangles exhibit pathological similarities with A β plaques, thereby substantiating their involvement in the cognitive deterioration characteristic of AD.

Specific dietary patterns have demonstrated an impact on the prevalence of depressive symptoms, a factor pertinent to AD (19). Prominent dietary regimens, including the Mediterranean and Paleolithic diets, have exhibited favorable outcomes for mental well-being and the mitigation of anxiety-related conditions (20,21). The diagnosis criteria for depression involve the examination of vitamin B-12 levels, blood alcohol, and electrolytes including calcium, phosphate, and magnesium (22). These are all measurements that diets tend to influence.

Fluoxetine and Citalopram represent commonly prescribed antidepressant medications that exert their therapeutic effects through the inhibition of serotonin reuptake within neuronal synapses (23). These SSRIs travel to the presynaptic neuron after serotonin transportation takes place in the synapse. It then occupies the area on the presynaptic neuron that would reuptake serotonin for other purposes and inhibits the reabsorption, which results in an increased level of serotonin to aid with a depressed individual's lack of serotonin (24)(25). Notably, these SSRIs have demonstrated the capacity to enhance metabolic rates in individuals, thus prompting consideration of a plausible link between their metabolic effects and their potential utility in the context of AD intervention. The augmentation of metabolic processes may contribute to more efficient clearance mechanisms for A β protein plaques, a hallmark of AD pathology that precipitates cognitive decline, potentially yielding therapeutic benefits in mitigating the severity of AD in affected patients (26).

Mechanisms & Epidemiology of MDD and AD.

The prevalence of MDD has exhibited a steady increase with approximately 17.5 million cases in the US as of 2018 compared to 13.7 million in 2005 (27). This upward trend in MDD has coincided with societal advancement and witnessed a notable surge, particularly among individuals below the age of 65 (8).

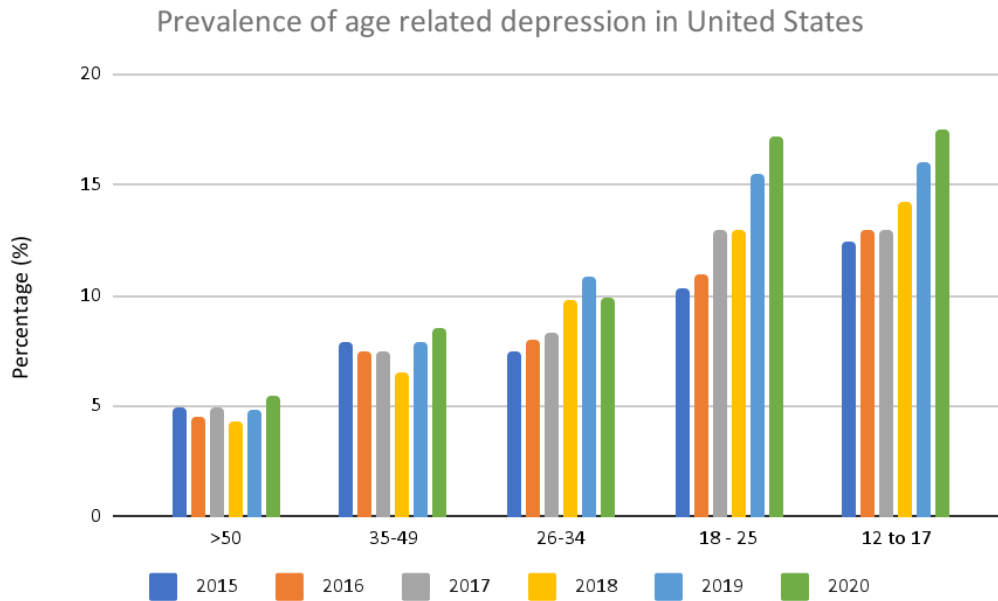


Figure 1: The increases in depression rates from 2015-2020 by age ranges (8).

There are roughly 6.5 million Americans aged 65 and above with AD, with numbers estimated to reach upwards of 13 million cases in 2060 (28)(29). Early-onset AD only made up approximately 5% of cases as of 2017 (7). Although Alzheimer’s is most prevalent in people over 65, early-onset Alzheimer’s has spiked in recent years.

MDD is characterized by imbalances of neurotransmitter levels, notably serotonin and norepinephrine. These imbalances arise from intricate environmental, genetic, and biological determinants (30)(31). An examination of MDD in the context of AD is imperative due to the impact MDD has on brain regions involved in memory regulation, notably the hippocampus (32). MDD is susceptible to being modulated by psychosocial adversity streaming from stressful life circumstances (31). MDD’s symptoms include a depressed mood, disturbed sleep, and impaired cognitive function (31). MDD affects the amygdala, hippocampus, and thalamus by decreasing their structural capacity and limiting their function (33). Functional MRI scans of depressed individuals have additionally revealed a reduction in gray matter volume within the left middle frontal gyrus of the cerebral cortex (34).

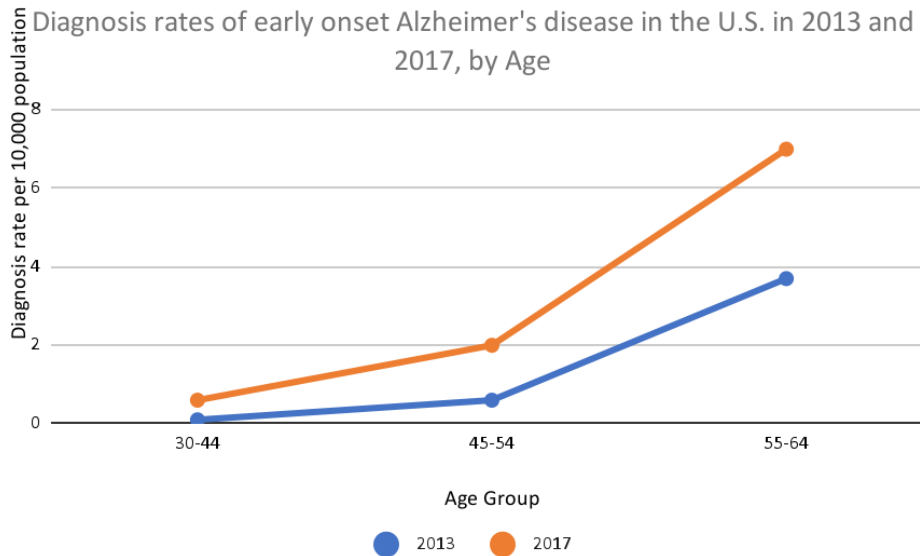


Figure 2: Demonstrates the increases in early-onset AD from 2013 to 2017 (6).

AD represents a neurodegenerative disease characterized by a progressive decline in an individual's cerebral functionality and capacity over time (35). AD pathogenesis is centered around aberrant protein deposits in areas of the brain that affect memory, most notably the hippocampus (4). The primary proteinaceous aggregation consists of extracellular A β plaques, which are formed when irregularities regarding APP processing take place (36). APP, localized within neuronal membranes, serves as a protein essential for neuronal growth (37). Via the amyloidogenic pathway, alpha-secretase and gamma-secretase break down APP, resulting in the generation of A β monomers comprised of amino acid sequences ranging from 37 to 49 amino acid residues (38). In AD there is an elevated production of A β monomers associated with a compromised capacity for their degradation. These surplus A β monomers traverse to the neural synaptic junction, where they can assemble into oligomers, protofibrils, and fibrils, culminating in the formation of aggregates commonly referred to as plaques. These plaques block the synaptic transmission of neurotransmitters between neurons, which limits the conveyance of information in hippocampal brain regions, impacting memory processing (39).

Another manifestation of the proteinaceous aggregation associated with AD involves the formation of intracellular tau protein tangles, commonly referred to as neurofibrillary tangles (NFTs) (40). Neurons rely on microtubules for the intracellular transport of various materials, facilitating the trafficking between the soma and axon terminal (41). Tau proteins play a pivotal role in microtubule stabilization, and their phosphorylation is initiated by the activation of kinase enzymes due to the presence of A β monomers (42). In a hyperphosphorylated state, Tau proteins disengage microtubules, subsequently aggregating into structures known as NFTs (40). In congruence with the extracellular obstruction posed by A β plaques, the presence of NFTs further exacerbates the impairment of intracellular transport mechanisms, culminating in neural degeneration (40). In the absence of functional tau proteins, microtubules undergo

destabilization and subsequent fragmentation, resulting in the cessation of intracellular transport processes (17).

MDD may constitute a conceivable risk factor for the onset and progression of AD (43). Research in the field of AD has unveiled instances of cerebral atrophy affecting the hippocampus, thalamus, and entorhinal cortex. These particular regions control an individual's memory capacity and relay motor signals to the cerebral cortex (44). Similarly, individuals diagnosed with MDD have displayed discernible structural and functional alterations within the hippocampus, thalamus, and amygdala (34). AD manifests clinical symptoms of memory impairment, with concurrent evidence of structural degradation in the hippocampus, which is similarly susceptible to the impact of MDD. This shared vulnerability suggests a potential association between the two conditions. Moreover, observed trends reflecting an elevated incidence of depression among younger and middle-aged adults correspond with an increased prevalence of early-onset AD, thereby reinforcing the possible link between AD and MDD. It is noteworthy that, as of 2014, MDD was reported in approximately 50% of patients diagnosed with AD (45).

How do dietary regimens affect MDD predispose AD?

MDD may potentially be associated with specific dietary patterns. A substantial portion of the United States population consumes diets characterized by a high consumption of nutritionally unfavorable items, including processed foods, sugar-laden products, and fast foods (46). Studies from 2015-2018 revealed that a significant proportion of dietary intake among US adults, as measured by Chilean dietary criteria, came from sources characterized as junk food, corresponding to 47% of energy, 75% of total sugar, 46% of sodium, and 48% of saturated fat consumption (47). Other studies ranging from 2001 to 2018 indicated a substantial proportion of the sample, encompassing 92.7% of US children aged 2-19 and 86.0% of US adults aged 20 and above, reported some degree of junk food consumption on any given day, with children displaying a relatively higher average consumption rate (48). The repercussions of these dietary patterns are evident in individuals diagnosed with MDD, as they often exhibit deficiencies in essential nutrients including calcium, folate, vitamin D, magnesium, and vitamin B12 (49). These nutritional deficits have been shown to exert detrimental effects on individuals' mental well-being (49). In contrast, diets that provide robust nutrients may aid against MDD's pathology. Other dietary regimens prevalent in Western society, such as Mediterranean and Paleolithic diets, have garnered attention for their potential to alleviate certain manifestations of MDD (20).

Mediterranean diets, which originate from regions such as southern Spain, Italy, and Crete, are dietary patterns characterized by a high consumption of vegetables, legumes, fruits, nuts, grains, fish, seafood, extra virgin olive oil, and a moderate intake of red wine (50). Scientific research underscores the favorable benefits of the Mediterranean diet, revealing its efficacy in reducing the increase of conditions including obesity, hypertension, metabolic syndrome, and dyslipidemia (50). The dietary components comprising the Mediterranean diet revealed promising results regarding the reduction of total caloric intake, the augmentation of overall phytochemical consumption, and the restriction of amino acid and saturated fatty acid intake (50). Notably, Mediterranean diets incorporate polyphenols, naturally occurring compounds found in plants recognized for their antidepressant properties (51). Adverse body image

perceptions have demonstrated an association with MDD, with individuals exhibiting a more favorable body image perception tending to report fewer depressive symptoms (52). Remarkably, Mediterranean diet patterns have been correlated with weight loss ranging from 3.8 to 10.1kg and improved body image perceptions compared to other diets (53). Consequently, this dietary regimen holds the potential to address MDD from both biochemical and psychosocial perspectives. Negative body image perceptions have also been linked to MDD, as patients with a more positive body image perception showed fewer reported depressive symptoms (53).

Paleolithic diets, often referred to as the caveman diet, seek to emulate dietary practices from the Stone Age. The diet emphasizes the consumption of lean meats, nuts, olive oil, fresh vegetables, and fruits. Like the Mediterranean diet, the Paleolithic diet has been associated with several beneficial outcomes, including enhanced glucose tolerance, weight loss, and a diminished risk of cardiovascular symptoms (54)(55). Therefore, it is conceivable that the cultivation of improved body image perceptions and the ingestion of polyphenols inherent in the foods of the Paleolithic diet may confer anti-depressive benefits (51)(52).

An examination of individuals diagnosed with MDD reveals a notable deficit in a specific amino acid, namely L-tryptophan (56). Tryptophan is an essential amino acid that is not endogenously synthesized by humans but assumes a vital role in the subsequent biosynthesis of serotonin (57). Tryptophan is present in Paleolithic and Mediterranean diets but not so much in traditional Western diets (58). Serotonin is a neurotransmitter that modulates mood, and low neuronal serotonin concentrations are correlated with depressive conditions. L-tryptophan is hydrolyzed into L-5OH-tryptophan, which is further enzymatically modified by aromatic decarboxylase (DDC) to produce serotonin (59). Approximately 95% of biologically available serotonin is synthesized by enterochromaffin cells in the gastrointestinal tract, with the remaining amounts synthesized by raphe neurons in the brain stem (60)(61). Subsequently, serotonin travels through the peripheral circulation before reaching the central nervous system. A comprehensive understanding of this biochemistry exemplifies the imperative role of dietary sources abundant in tryptophan in modulating neuronal serotonin concentrations (56). Therefore, an individual's diet is paramount to the reduction of depression. Tryptophan is typically found in foods such as bananas, dried prunes, milk, tuna fish, cheese, bread, chicken, turkey, peanuts, and chocolate (62). These observations support the notion that adherence to an unhealthy traditional Western Diet may predispose individuals to MDD, concurrently influencing the progression of early-onset AD. This relationship exists as individuals with early onset of AD often manifest impairments within their serotonergic systems (63).

SSRIs as a possible treatment for AD:

The research inquiry that investigated the association between AD and MDD also examined the impact of dietary constituents on MDD's prevalence. The study findings revealed that dietary regimens deficient in the precursors required for serotonin neurotransmission were associated with an elevated tendency for the manifestation of MDD in individuals, thereby substantiating the relationship between MDD incidence and the progression of AD, and possibly early onsets of AD (64). SSRIs (selective serotonin reuptake inhibitors) function to augment intraneuronal serotonin levels, thereby promoting an improved emotional state. While SSRIs are primarily

employed to treat MDD, their therapeutic effects have garnered attention as a prospective intervention for AD (65).

Serotonin is transported within synaptic vesicles within the presynaptic neuron of the central nervous system, subsequently being transported to the synaptic cleft and ultimately reaching the postsynaptic neuron (25). Serotonin's release occurs when an action potential stimulates a calcium-dependent exocytotic release from the presynaptic neuron to the synaptic cleft. Serotonin is then absorbed by HTR1 receptors on the postsynaptic neuron (25). A small portion of the serotonin that was discharged from the presynaptic neuron undergoes reuptake rather than engaging directly with the postsynaptic neuron to modulate neurotransmitter concentrations (25). SSRIs are typically administered orally. Following ingestion, SSRIs undergo absorption in the gastrointestinal tract entering the bloodstream and crossing the blood-brain barrier to reach presynaptic neurons (25). SSRIs exert their therapeutic action by augmenting the synaptic concentration of serotonin. They inhibit the small amount of serotonin that undertook its reuptake, which results in an increased availability of serotonin to bind with postsynaptic neurons, thereby enhancing serotonin signaling. Consequently, SSRIs often have therapeutic benefits for individuals with MDD by restoring their diminished synaptic serotonin levels (24)(66).

Studies have investigated the potential neurogenic effects of SSRIs in the hippocampal region of the brain (67). It is noteworthy that SSRIs may require a period of up to six weeks to manifest their therapeutic effects (68). Treatment with SSRIs can be accompanied by a spectrum of side effects, encompassing symptoms such as nausea, vomiting, insomnia, drowsiness, headaches, and decreased libido (69). Excessive usage of SSRIs may result in serotonin syndrome, a critical medical condition stemming from an excessive accumulation of serotonin within neural synapses (70).

One of the most prescribed SSRIs, Fluoxetine (FLX), has demonstrated potential in mitigating the formation of A β plaques associated with AD (25,64,70). Research by Mdawar et al. revealed that the administration of FLX leads to a significant reduction in the accumulation of A β plaques within the interstitial fluid of the brain tissue of mice. Additionally, it was observed that Fluoxetine administration enhances the degradation of neurofibrillary tangles. Notably, dosages ranging from 5 to 10 mg/kg of FLX exhibited a substantial reduction in the levels of soluble A β 40 and A β 42, as well as decreased APP phosphorylation in mice (65). Further investigations involving depressed rodents subjected to FLX treatment have similarly demonstrated notable reductions in A β and Tau protein production. Depression was induced in the rats through self-isolation, and their depressive-like behavior was compared to a control group. The results yielded in favor of FLX treatment, as the self-isolated rats were shown to have a statistically significant deterioration of depressive-like behavior when treated with 10 mg/kg FLX per day (26). Furthermore, FLX has exhibited the capacity to enhance memory and cognitive function in limited sample groups, potentially fostering neurogenesis within the hippocampus. This experiment had 58 people randomly assigned to FLX or a placebo perform a mini-mental status examination that showed an increase in score with patients who were assigned FLX as a treatment (71).

Citalopram, another widely recognized SSRI, has also exhibited the potential to attenuate A β plaque levels in individuals diagnosed with AD (71,72,73). A study was conducted to explore the protective mechanisms of citalopram against impaired mitochondrial dynamics and synaptic dysfunction in hippocampal cells expressing mutant APP mutations. The findings made through immunoblotting, quantitative RT-PCR, and transmission electron microscopy methods revealed that citalopram effectively mitigates the toxicities associated with mutant hippocampal APP, A β accumulation, and mitochondrial dysfunction (72). Furthermore, investigations involving AD mouse models subjected to citalopram treatment have shown reductions in cognitive decline, A β levels, and synaptic toxicities. These tests were run on 12-month-old wild-type mice and age-matched transgenic APP mice that were on citalopram. A combination of rotarod tests, immunoblotting, and cognitive behavioral assessments indicated increased levels of mRNA associated with increased mitochondrial fusion and biogenesis (73). Citalopram treatments have also been associated with an enhancement of non-amyloidogenic APP processing. ADAM10, a protein that reduces the generation of A β , was shown to have increased activity in PSEN1 cells treated with citalopram (74). Collectively, these studies suggest that the administration of SSRIs confers beneficial effects on the pathogenesis of AD.

Discussion:

Herein, we have provided a considerable amount of evidence linking MDD and AD. Evidence points to a link between MDD and AD, as they both affect similar portions of the brain, and both follow similar trends of prevalence. It is also notable to understand that trends in younger populations may contribute to increased severity as individuals age. This topic would play a vital role in understanding why early-onset AD has become increasingly prevalent. Understanding other causes of MDD may also be another topic of interest when exploring further causes of AD.

Diets play a vital role in determining an individual's outlook when diagnosed with MDD. High-tryptophan diets promote higher serotonin production, which has been shown to be ameliorative towards MDD. This may suggest that natural remedies, potentially as simple as an individual's diet, can completely change how they respond to MDD, and this may combat the early onset of AD as individuals with the disease tend to show a lack of synaptic serotonin. This leads to the assumption that a healthy diet is part of a healthy lifestyle and is a combative measure against neurodegenerative disease. When individuals follow certain dietary regimens, like Mediterranean or Paleolithic diets, they take steps to prevent harmful diseases. This signifies the importance of a diet, as it can dictate an individual's overall health.

Although SSRIs are typically used to combat MDD, the link between MDD and AD allows the application of SSRIs as a possible treatment for neurodegenerative disease. SSRIs block the reuptake of serotonin in the synapse, causing more serotonin to be absorbed post-synoptically. It has been established that individuals with MDD and AD lack serotonin, so the application of SSRIs seems logical. Although research on these applications is limited, there have been positive results drawn from the application of Fluoxetine and Citalopram. These results indicate a reduction in A β production in mice, but human trials have yet to show any statistical significance. This opens the field for lots of incoming research, as these anti-depressants can possibly combat the progression of AD. The importance of these results should be focused on early-onset AD. As the risk for early-onset AD is low, cases have been on the rise, like trends in

MDD. The aim should be to apply treatments to younger populations to reduce the progression of AD into more serious neurological degeneration.

Other scientific procedures, such as AI applications to detect AD risk, also provide an interesting opportunity to increase awareness of early-onset AD. These applications utilize digital biomarker prognostic models to assist in screening for early signs of cognitive decline throughout populations(75). AD's genetic causes may introduce CRISPR gene editing to modify APOE genes that predispose individuals to AD. Medications such as Lecanemab (BAN2401) which acts as an A β antibody, should also be studied as possible advances for a cure for AD. Overall, much more experimentation and human trials over wide populations are required to determine the effectiveness of specific dietary regimens and the application of SSRIs as treatments to combat AD.

Conclusion

Based on the epidemiological evidence reviewed, it appears plausible that MDD may be associated with an increased risk of developing early-onset AD. This link is further suggested by the overlapping brain regions affected and common symptoms, such as memory loss, observed in both disorders. Nutritional deficits, particularly in the essential amino acid tryptophan, have been implicated in the predisposition to both MDD and AD. Tryptophan is a precursor to serotonin, a neurotransmitter that is typically deficient in individuals with MDD and potentially in those with AD. Diets rich in tryptophan, like the Mediterranean and Paleolithic diets, are associated with enhanced serotonin production and may offer protective effects against MDD.

SSRIs such as fluoxetine and citalopram aim to increase serotonin levels in synaptic gaps and have been used in the treatment of MDD, with some research suggesting potential benefits in AD management. While these SSRIs are widely prescribed as antidepressants and have shown promise in countering AD, the research on their effectiveness is not uniformly conclusive.

Despite generally positive findings, the effectiveness of specific dietary regimens and SSRIs has been variable across different studies and participant samples. Consequently, larger studies with diverse populations and a range of treatment approaches are needed to corroborate the results suggested in this review. It is imperative that future research continues to explore these findings to better understand the mechanisms and potential interventions for MDD and early-onset AD.

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