Is Anxiety a Prodromal Symptom Contributing to The Development of Alzheimer's Disease? A Thematic Literature Review

Ariana L. Herrera Delfino

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Background: Existing studies show that there is a correlation between anxiety disorders and Alzheimer's disease, but the research is limited. These studies have found this relationship by comparing anxiety symptoms to mild cognitive impairment, amyloid-beta production, and genetic susceptibility. Acknowledging these studies' findings could result in a positive improvement for Alzheimer's disease research and prevention.
Objective: The main objective of this thematic review is to investigate the relationship between Alzheimer's disease and neuropsychiatric symptoms, specifically anxiety disorder symptoms and diagnosis, so this data could be used to improve knowledge about Alzheimer's risk factors and risk population groups.
Method: A thematic literature review was performed using PubMed and Google Scholar. After including 17 articles, four themes were selected so the studies can be thoroughly analyzed.
Results: Results of the three studies reviewed showed that the anxiety identified is related to mild cognitive impairment and later Alzheimer's disease. The correlation was significant between anxiety symptoms and clinical anxiety diagnosis. This link was further supported by analyzing the relationship of Alzheimer's disease with neuropsychiatric symptoms, neurobiological mechanisms of anxiety, and genetic susceptibility.
Conclusion: According to the studies reviewed, there seems to be an important correlation between anxiety and Alzheimer's disease, making it possible to consider anxiety as a prodromal factor of Alzheimer's, but not entirely proven. This needs to be researched more as it can be used to help with Alzheimer's disease prevention by the risk population.

Introduction

Alzheimer's disease (AD) is currently the most common type of dementia worldwide, with the prevalence continuing to grow due to environmental factors of modern society and the aging world population[1]. This type of dementia causes a decline in cognitive function, consequently interfering with a patient's daily life. Due to its devastating effects on individuals and their families and communities, researchers are investigating ways to identify early symptoms of AD with the hope of preventing the disease[2]. Many attempts to identify early AD include measures of cognition, function, brain imaging, and fluid biomarkers[3]. However, other indicators can be used to predict later AD, such as neuropsychiatric diseases. For instance, there have been many studies presenting a correlation between depression and AD. Fewer studies have linked anxiety disorders to AD, even though it has been discovered that there is a possible connection between the two that could improve its diagnosis and prognosis. Some systematic reviews and meta-analyses synthesizing data from prospective longitudinal studies have shown that anxiety in midlife and older age is associated with an increased risk of all-cause dementia, AD[4,5], and vascular dementia[6].

The presence of neuropsychiatric symptoms (NPS), such as anxiety, occurs in up to 75% of AD patients. This is supported by studies such as Sturm et al. (2013)[7], which measured emotional contagion in 237 participants: 111 healthy controls, 62 patients with mild cognitive impairment (MCI), and 64 patients with AD. The analysis of covariance between groups found significantly higher emotional contagion at each stage of participants with AD (75%). Additionally, Sturm et al. (2013) used neuroimaging to show that atrophy in the anterior temporal lobe and amygdala are associated with heightened emotional contagion. These regions are crucial for emotional regulation and salience progressing. This suggests that structural brain changes could lead to the presence of NPS, further strengthening the link with AD. This study further demonstrates how emotional symptoms can precede overt memory decline, suggesting they might be early behavioral indicators of underlying pathology. Similarly, Scarimazza et al. (2019)[8] demonstrated that neuropsychiatric symptoms NPS showed AD pathology studying the ratio between cerebrospinal-fluid (CSF) tau and β-amyloid42 (Aβ42) levels in MCI compared to AD patients. Consistently, t-tau/Aβ42 ratio correlated with NPS in all the MCI and AD patients, showing that NPS shows AD pathology, as MCI is often recalled as an early stage of AD; then NPS has a less prevalent occurrence in AD because it can be inter-

preted as a prodromal symptom, which explains why it is more prevalent in the early stages. NPS can also lead to the development of chronic anxiety, causing neurotic stress and potentially leading to neuronal damage via glucocorticoid pathways. This can be caused by the disruption of synaptic plasticity caused by elevated cortisol levels in chronic anxiety[9,10]. Damage of the via glucocorticoid can lead to a prolonged glucocorticoid elevation, which eventually leads to a structural degeneration in brain regions implicated in both anxiety and AD[11], such as the hippocampus.

Among the many NPS presented in AD, anxiety is often overlooked, even if it has been shown to have a great influence on the development of AD. Studies have shown that anxiety is observed in approximately 40% of people with AD. It is primarily present in the early stages of AD and during MCI. In some cases, anxiety has been observed to appear before a significant memory decline, suggesting that it may serve as a prodromal feature of AD[12]. This was demonstrated by studying the amyloid scans of demented patients: in a comparison of 118 cognitively unimpaired and MCI patients followed on the Hospital Anxiety and Depression Scale (HADS-Anxiety), anxiety was related to amyloid-β (Aβ) deposition on flutemetamol amyloid positron emission tomography (PET) imaging, suggesting that the presence of anxiety predicted a cognitive decline and interacted with amyloid status to predict faster cognitive deterioration[13]. Furthermore, the link between AD and anxiety can also be found by studying genetic susceptibility. APOE ε4 allele is the most widely studied genetic risk factor. Studies show that people with one copy have 3 higher risk of developing AD, as shown by studying interactions between multiple genetic risk factors and environmental or physiological stressors in the Korgan et al. study (2020)[14]. In this thematic analysis literature review, the different relationships between anxiety and AD with factors such as NPS and genetic susceptibility will be analyzed to identify if anxiety is a prodromal symptom contributing to the development of AD.

1 Methods

A. Search Strategy

A comprehensive search was conducted using PubMed and Google Scholar. Searches were done by keywords: (Alzheimer's disease OR mild cognitive impairment OR prodromal dementia OR amyloid beta OR hyperphosphorylated tau OR cognitive decline) AND (Anxiety OR prodromal symptoms OR GAD-7 OR HAM-A OR STAI OR genetic susceptibility OR neuropsychiatric symptoms OR NPS OR APOE).

Inclusion and Exclusion Criteria

The inclusion criteria included: a) content - they need to specifically associate anxiety disorders with cognitive decline; b) keyword - needed to contain the keywords mentioned before; c) method - they needed to include a cognitive outcome or a neurobiological mechanism or a genetic moderator.

After evaluating the initially screened studies based on the inclusion criteria, additional exclusion criteria were determined: a) if only discussing biomarkers without association to cognition, then exclude; b) if focused only on depression or non-Alzheimer's dementias, then exclude; c) if lacking primary data, then exclude; d) if not being able to read the paper freely, then exclude.

The studies identified by the search query on PubMed and Google Scholar were first screened using the title and the abstract. No language restriction has been used, but only full free articles were screened. Studies were included or excluded based on the criteria defined above.

Potential risk bias

There is the possibility of showing certain systematic errors or distortions in how studies are designed, conducted, or interpreted could skew the overall conclusions of the thematic review. For instance: a) publication bias - positive results are more likely to be published than null/negative findings; b) selection bias - only certain types of participants were included, mostly AD patients or/and APOE ε4 carriers; c) influence external factors other factors such as the presence of other mental disorders (e.g. depression), the difference in education, or the use of medication may influence both anxiety and cognitive outcomes; d) measurement bias - variability in anxiety assessment tools (e.g., self-report, clinician-administered scales) may affect the results.

Results

An initial pool of 243 studies was identified by using the keywords. By doing title and abstract screening, only 72 were considered relevant because of the inclusion and exclusion criteria. Using the previously mentioned inclusion and exclusion criteria and after selecting studies based on the relevance of the thematic objective and after doing a full-text screening of the text, a sample of 24 studies was considered relevant to mention throughout the thematic analysis, while, by mapping the themes, only 17 were identified to fit under the themes selected.

The reasons of exclusion of the full-text screening of 48 research studies were: a) lacked outcome linkage to cognition - 18 studies; b) focused only on depression or non-AD dementias - 12 studies; c) lack of primary data in narrative reviews - 8 studies; d) articles behind paywalls - 10 studies.

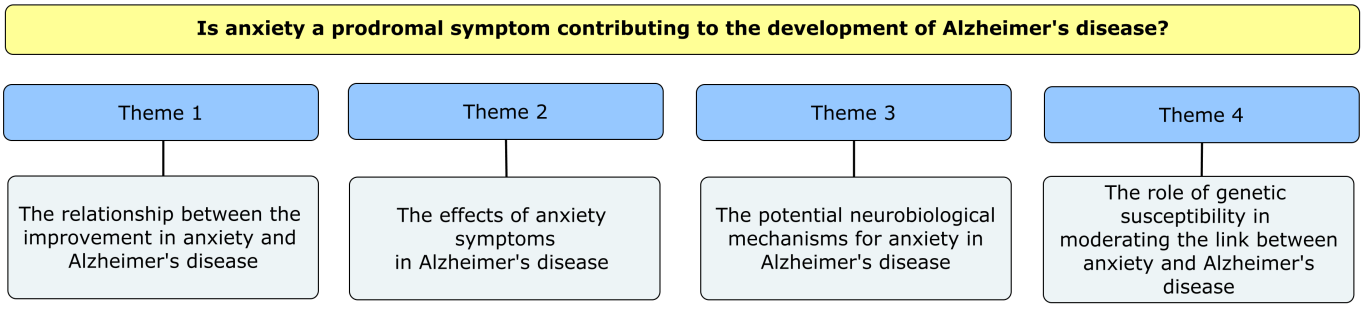

Fig. 1 Comprehensive diagram to present the themes. The diagram demonstrates the four themes that are going to be explored in this thematic review.

Thematic Analysis Approach

The themes selected were not predefined but rather emerged inductively from the literature analyzed. A thematic analysis approach was used to synthesize and group different findings, making it easier to understand the relationship between anxiety and AD. The studies were grouped by identifying which type of relationship between AD and anxiety was described. Following this process, articles were grouped into four major themes, as shown in Fig. 1.

Thematic Analysis

1. The relationship between the improvement in anxiety and Alzheimer's disease

Even if not prioritized in research, the study of the potential relationship between improvement in anxiety and AD can be a crucial part for understanding what can be done to increase the improvement in AD patients. Some studies can build bridges and connect anxiety and AD, opening the possibility to other studies to investigate the relationship. For example, it is important to cite Stott et al. (2022) prospective cohort study [15], which showed how treatments for anxiety such as psychological therapy could be used to mitigate the risk of AD diagnosis, preventing the suffering of many prospect patients and families. Stott et al. (2022) used data from nationally provided psychological therapy services in England to examine data from 2012 to 2019 patients with a probable anxiety disorder and no other previous current diagnosis of dementia. A sample of 128,077 patients was initially selected, but after many exclusion criteria (e.g., missing data, presence of dementia diagnosis) the sample was reduced to 107,448. After using Cox proportional hazard models and ICD-10 dementia codes from Hospital Episodes Statistics, Mental Health Services Dataset, and mortality data, the study revealed valuable results linking the relationship between anxiety and AD. The results from Cox proportional hazard models showed that people who showed reliable improvement in anxiety had lower rates of later dementia diagnosis (39%) than those who did not show reliable improvement (51%). Consequently, Stott et al. (2022) describes the association between treatment of anxiety disorders through psychological interventions and a lower incidence of dementia. The acknowledgment of this information could benefit the knowledge of AD pathology, prevention, and treatments, as it shows how AD risks can be reduced.

However, there are some irregularities in Stott et al. (2022) study which could have potentially changed the results. In Stott et al. (2022) a large number of patients, specifically 16,119, were excluded due to missing data. According to the data stated in the study, more than 10% of data were missing for psychotropic medication use and long-term health conditions. Consequently, it is unclear whether excluding those patients altered the findings. This could also be a subject of biased exclusion, but we cannot confirm it due to a lack of information. Nevertheless, it seems less likely that this was a biased exclusion because of the exclusion criteria stated in the methods section. It is important to note these possible biased decisions so that future research takes carefully the factors analyzed, but this does not mean that results from this study should be overlooked.

2. The effects of anxiety symptoms in Alzheimer's disease

The relationship between anxiety and AD can also be found by researching the effects of the disorder's symptoms in patients with AD. Examining the effects of anxiety symptoms on patients with AD may provide valuable insights on the identification of a possible risk population regarding AD. One important symptom of anxiety is worry, a popular symptom on the AD-anxiety link discussion. Hence, it is important to mention the 2-year prospective cohort study by Pietrzak et al. (2012) [16], which associates mild worry symptoms with learning and memory decline in healthy older adults that leads to later hypothesis on how we can use this data to prevent later-life AD development. This study included 263 community-dwelling adults in Melbourne, Australia. The study used multiple tests to measure the population's visual attention, recognition and working memory,

psychomotor skills, and visual learning such as the Continuous Paired Associate Learning Test (CPAL), the One-Card Learning (OCL) task, and the International Shopping List Test (ISLT). Ulterior Multivariate analysis of covariance (MANCOVA) and Mediational analysis were conducted to analyze the relationship between worry symptoms, ISLT performance, and performance on complex measures of cognition. The results showed that older adults with mildly elevated worry symptoms at baseline performed worse than older adults with minimal worry symptoms on measures of visual and paired associate learning and the study concluded that assessment of worry symptoms, even mild levels, may have utility in predicting early cognitive decline in healthy, community-dwelling older adults. Worry symptoms can later grow to an anxiety disorder, thence identifying the prodromal nature of anxiety in its relationship with AD.

On another hand, anxiety has been linked to MCI, which in most cases potentially evolves to AD. Studies identified anxiety disorders as a transitional stage between age-related memory decline and AD. A perfect example of this is Devier et al. (2009)[17]. This study was conducted to assess the impact variables in predicting AD conversion by systematically assessing 148 patients with MCI. Devier et al. (2009) measured anxiety in patients by using the Spielberger State-Trait Anxiety Inventory (STAI) with the help of the Memory Disorders Clinic run by the departments of Psychiatry and Neurology at New York State Psychiatric Institute, the Center for Memory and Behavioral Disorders in the Department of Neurology, and Columbia University. The study included patients between 41 and 85 years old that showed anxiety symptoms, mainly memory complaints without dementia. Participants were excluded if previously diagnosed with dementia, schizophrenia, current major affective disorder, active alcohol/substance dependence, clinical history of stroke, cortical stroke or infarct $\geq$2cm in diameter based on MRI, cognitive impairment secondary to medications, or other major neurological illness, for example, Parkinson's disease.

After using an extensive neuropsychological test battery, STAI Inventory (STAI), a Cox Proportional Hazards Regression survival analysis, the One-way analysis of variance (ANOVA), and Chi-square (2) tests; the study found that higher STAI State and trait scores showed significant correlation with poorer performance on the Folstein MiniMental State Examination (MMSE), meaning they have poorer orientation, memory, registration, recall, calculation, and language performance. Also, higher STAI Trait scores ($>$ 30) were significantly associated with a lower risk of developing AD. Additionally, the clinical-based sample showed that MCI patients had higher levels of both state and trait anxiety compared to controls. Highlighting this type of study is important, as it prioritizes the use of the STAI scale and shows how results shown by this anxiety inventory can contribute to identifying the possibility of later AD, as the identification of trait anxiety can be considered a prodromal symptom for AD.

Another research paper that relates anxiety symptoms to AD is Pink et al. (2021)[18] longitudinal study, as it investigates how anxiety symptoms relate to amyloid-β deposition and MCI, a prodromal stage of Alzheimer's disease (AD). The paper included 1440 community-dwelling and cognitively unimpaired adults starting from the age of 50, which were studied throughout the span of 5.5 years. The study further explores whether anxiety is a risk indicator or an early symptom of dementia, especially in those who are PiB+ (i.e., have elevated brain amyloid). This aligns directly with how anxiety symptoms manifest or contribute to dementia-related processes. Cortical amyloid beta (Aβ) was measured by Pittsburgh compound B positron emission tomography (PiB-PET) and elevated deposition (PiB+) was defined as standardized uptake value ratio $\geq$ 1.48. The results showed a relationship between anxiety and MCI as PiB-PET+ PiB+ participants with clinical anxiety (HR [95% CI], 6.77 [3.58, 12.79], P $<$ .0001) had an increased risk of incident MCI compared to the reference group. Additionally, there was a statistically significant additive interaction between amyloid positivity and clinical anxiety (P = .0310) in increasing the risk of incident MCI. However, the last result was only verified when adjusting sex, education, and medical comorbidity. Also, it is not a fact that MCI will develop to AD in all cases; however, it is important to have these results into consideration to have a more structural and concrete idea of the AD risk population. In addition, other parts of the results showed that PiB+ patients without clinical anxiety had an elevated risk of developing dementia, showing how additional studies need to be done to identify the exact relationship between anxiety and MCI. Pink et al. (2021) suggest that studies involving biomarkers will be crucial to pave the way to understanding the mechanism linking anxiety with the risk of dementia.

Finally, there are two studies that discuss anxiety symptoms in AD: Mah et al. (2015)[19], which discusses how anxiety has been associated with alterations in the mesial temporal lobe, and Karim et al. (2022)[20], which associates greater brain age with greater worry, an anxiety symptom. Mah, Binns, & Steffens (2015) created a longitudinal Magnetic Resonance Imaging (MRI) study that analyzed 376 participants with amnestic cognitive impairment (aMCI) using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). This way, the study identified the progression of aMCI to AD. Results showed that higher anxiety severity scores on the ADNI were associated with faster progression from aMCI to AD, independent of depression or memory impairment, and greater rates of atrophy in the entorhinal cortex (EC), a critical mesial temporal lobe structure heavily implicated in early AD, over a 3-year follow-up period. The EC is integral to memory encoding, emotional regulation, and stress responses. Atrophy here may also reflect on increased oxidative stress and neuroinflammation, anticipating the importance of neurobiological mechanisms in the AD and anxiety link. In the same conversation, Karim et al. (2022) recruited 78 participants with the minimum age of 50 along a wide range of worry

severity. By collecting imaging data and computed voxel-wise gray matter, the researchers conducted a multivariable linear regression between brain age and other factors like age, sex, education, worry, anxiety, depression, stress. It is important to study worry, as it is an important anxiety symptom that, in great quantities, can make it possible to develop an anxiety disorder. Results from the study found that, primarily in the male sex, worry and rumination were associated with accelerated aging in late life, and expressive suppression may have a protective effect. These results provide evidence for the transdiagnostic model of negative repetitive thoughts, which are associated with cognitive decline, amyloid, and tau. Nevertheless, limitations of these studies still need to be considered as they may have influenced the results. Such limitations include sample size (too small), missing biomarkers (e.g., amyloid beta), not only focus on anxiety, and the causal directionality between anxiety and neurodegeneration..

3. The potential neurobiological mechanisms for anxiety in Alzheimer's disease

In this section, the objective is to discuss the potential neurobiological mechanisms that might explain the observed associations, such as stress hormones, inflammation, and neurodegeneration. Reviews such as De Felice et al. (2015)[21] and Numakawa & Kajihara (2023)[22], are important to continuing this discussion. De Felice et al. (2015) focused on metabolic stress paradigms, including ER stress, eIF2αP signaling, insulin resistance, oxidative stress, and how these molecular stress pathways trigger synaptic impairments and drive AD neurodegeneration. Results showed that the combination of inflammation, neuronal insulin resistance, oxidative/ER stress and translational repression might generate a noxious scenario of brain metabolic stress to mediate and propagate synapse defects, resulting in cognitive deficits. Some neurobiological mechanisms mentioned, such as stress, are connected directly to anxiety. Likewise, Numakawa & Kajihara (2023) explored how chronic stress and hypothalamicpituitaryadrenal (HPA) axis disruption reduces via glucocorticoid-mediated gene repression (BDNF), impair synaptic plasticity, elevated the production of reactive oxygen species (ROS), and mitochondrial dysfunction. The review concluded that low BDNF, inflammation, oxidative stress, and synaptic dysfunction (driven by stress hormones) are implicated in both anxiety symptoms and early AD changes.

Moving into research papers, Hashimoto et al. (2006)[23] studied 41 patients diagnosed with AD recruited from the VA Greater Los Angeles Health Care System and with the help of University of California, Los Angeles. Each participant underwent through a very detailed clinical evaluation where each patient's history was examined to review the presence of psychiatric symptoms. This was supported by structural neuroimaging studies. Hashimoto et al. (2006) used positron emission tomography (PET) imaging of cerebral metabolic activity to study fluorodeoxyglucose PET (FDG-PET) values to compare glucose metabolism to the Neuropsychiatric Inventory (NPI) anxiety item score. Results found that higher anxiety levels in AD patients correlated with reduced glucose metabolism in specific brain regions: the bilateral entorhinal cortex, the bilateral anterior parahippocampus gyrus, the left anterior superior gyrus, and the left insula. The regions of the brain stated are critical nodes in the brain's limbic system, which modulates fear, emotional memory, and threat processing. This way, using FDG-PET imaging, the researchers demonstrated that higher anxiety levels in patients with AD were significantly associated with reduced glucose metabolism in key brain regions involved in emotional regulation, memory, and interoceptive awareness, including in the areas of the brain stated before. However, the interpretation of the results of this study is limited because of the small and uneven sample size (35 men, 6 women).

Further into the discussion, the results from the Tsang et al. (2008)[24] study cannot be obviated. The mentioned study aims to correlate several glutamatergic measures with chronic anxiety and AD by studying a cohort of 21 patients assessed by NPI and divided into two subgroups: low anxiety (LA) and high anxiety (HA). Subjects were recruited and assessed at the University of California, Los Angeles Alzheimer Disease Research Center (UCLA-ADRC). The study measured glycine recognition sites (GlyRS) of N-methyl-d-aspartate (NMDA) receptors by brain homogenate binding with [^{3}H]MDL105,519 and [^{3}H]MK-801, respectively. Additionally, the study analyzed the densities of NMDA receptors NR2A, NR2B, and NR1 subunits by immunoblotting. Results found that the binding affinity to GlyRS was higher in HA compared to LA. In addition, the magnitude of NR2A reduction was strongly correlated with higher scores on NPI for anxiety. These results are important to the thematic review because they propose a possible link between chronic anxiety in AD via effects on GlyRS function. Furthermore, the NR2A subunit plays a key role in fast synaptic transmission and regulating neuronal excitability as its loss suggests compromised excitatory signalinga hallmark of early AD and associated cognitive impairment. However, this result can also be limited by the small sample size of the study.

Continuing with the stress factor is the Daniilidou et al. (2023) study[25], which links salivary cortisol to biomarkers of neurodegeneration and cognitive decline. The cross-sectional analysis studied collected data from 158 memory clinic patients with subjective cognitive decline (SCD, n=55), MCI (n=62), and AD (41) from the Karolinska University Hospital in Sweden. To measure salivary cortisol both glucocorticoid-mediated gene repression (BDNF) serum mBDNF and proBDNF were used, and for neuroinflammation, synaptic degeneration, and AD pathology the chinitinase-3-like protein 1 (YKL-40); synaptotagmin-1, neurogranin and SNAP-25); and Aβ1-42, t-tau and p-tau markers were used, respectively. The results showed that salivary

cortisol levels correlate with markers of tau (t-tau, p-tau), synaptic degeneration (neurogranin, SNAP-25), and lower peripheral proBDNF, suggesting that cortisol hypersecretion is tied to synaptic dysfunction in people with memory symptoms or AD. Hence, cortisol levels have been found to be a central mechanism influencing AD-related pathology. This possibly correlates to anxiety because anxiety is often associated with chronic stress and HPA-axis overactivity, which provoke elevated cortisol levels. However, the study does not focus on an anxiety link, so interpretation of the results regarding it must be carefully considered. Likewise, the role of cortisol in chronic stress and neurodegenerative disorders has been studied in the Knezevic et. al (2023)[26] review, which argues that chronic cortisol may contribute to dysfunctional microglia, impaired phagocytosis of amyloid beta, chronic cytokine release, activation of NLRP3 inflammasome, and in turn further amyloid beta/tau progression and synaptic damage. In particular, the review presented how reduced neurotrophic support causes the cortisol to suppress of the expression of BDNF. This finding is incredibly significant as low BDNF correlates with both synaptic loss and anxiety.

4. The role of genetic susceptibility in moderating the link between anxiety and Alzheimer's disease

To begin explaining the role of genetic susceptibility in the link between AD and anxiety is first needed the clarification of the initial relationship between AD and gene susceptibility. The gene analyzed is the apolipoprotein E (APOE) ε4 allele. The meta-analysis conducted by Bailey et al. (2024)[27] discusses the mentioned relationship. Based on this review, APOE ε4 allele is a known genetic factor that increases the risk of AD, contributing to more severe brain atrophy. Bailey et al. (2024) successfully studied the impact of APOE ε4 allele gene on brain atrophy in MCI as a transitional stage of AD by performing a meta-analysis of voxel-based morphometry (VBM) studies to identify the pattern of grey matter atrophy in APOE ε4 carriers and non-carriers. Furthermore, the objective was obtained by collecting the data of a coordinate-based structural MRI for 1,135 from 12 studies on PubMed and Google Scholar. Results found that APOE ε4 carriers had significant non-healthy atrophy in the hippocampus and parahippocampus compared to non-carriers. This way, Bailey et al. (2024) managed to link APOE ε4 allele to hippocampal atrophy in both AD and MCI emphasizing the allele's critical influence on neurodegeneration, especially in the hippocampus. Additionally, another study correlates APOE ε4 to the development of AD. Bonham et al. (2016)[28] studied the presence of APOE ε4 in preclinical AD, showing APOE ε4 as a possible prodromal factor of AD. The study used fata from 5,381 cognitively normal older adults and, using the Cox proportional hazards models, elongated the effects of APOE ε4 on progression from normal cognition to MCI or AD in ages between 60 and 85. Boham et al. (2016) hypothesized that APOE genotype would predict progression to MCI and AD. Results from the study showed that APOE ε4 carrier status and dosage significantly influenced progression to MCI or AD in all age groups studied, but the risk was greater between ages 70 and 75. This results showed how APOE ε4 status significantly predicts progression to MCI or AD across older adulthood and that this risk varies with age, giving useful information to future research studying AD pathology.

Having recognized the previously mentioned information, it is of great significance that we mentioned studies that correlate these results to anxiety. The cross-sectional study of Dar-Nimrod et al. (2012)[29], which primarily tested if neuroticism could moderate the association between APOE genotype and cognitive function and AD. The study sampled 602 older adults with mean age of 78 and measured the presence of the APOE ε4 allele and its association with AD by using the NEO-Five Factory Inventory and the Alzheimer's Disease Assessment Scale-cognitive (ADAS-COG), which was measured every 6 months for 6.5 years. Results showed that neuroticism, moderates the relationship between APOE ε4 genetic risk and cognitive decline and AD in older adults. The study, while stating neuroticism also highlighted trait anxiety, an aspect of neuroticism. Thence, Dar-Nimrod et al. (2012) concluded that phenotypic personality dimensions, primarily neuroticism, moderate the relationship between APOE ε4 genotype and cognitive outcomes in later-life. Nevertheless, future research is needed to further identify the physiological processes involved in the interactions listed.

More recent studies have also shown the association between genetic susceptibility, AD-related phenotypes and psychiatric diseases. For instance, Xu et al. (2023)[30] studied a total of 1,382 subjects with the mean age of based on data collected from the Texas Alzheimer's Research and Care Consortium (TARCC, n=1320) and the Initial Study of Longevity and Dementia from the Rio Grande Valley (ISLD-RGV, n=62). By studying the effects of APOE ε4 in the participants, results showed that in 31.2% of the cases the APOE ε4 allele was associated with AD, while its relationship with normal cognition was only of 18.1% ($p<0.0001$). Furthermore, APOE ε4 allele was also associated with anxiety ($p<0.0001$) and depression ($p=0.0004$). Therefore, this study showed that APOE alleles show increased risk for anxiety and depression. However, the interpretations of this study can be limited by the fact that participants were only Hispanic; any other ethnicity was not included. Moreover, 921 (69.8%) of the subjects were females, and 399 (30.2%) of the subjects were males, which shows further nonuniform population characteristics. Another relevant and even more recent study was conducted by Dang et al. (2025)[31], which found anxiety as one of the stress-related psychiatric disorders sharing genetic risk variants with AD while also suggesting overlapping with genetic susceptibility. Researchers studied the risk variants and genetic etiology underlying AD and three stress-related psychiatric disorders: post-traumatic stress disorder (PTSD), anxiety

disorder, and major depressive disorder. The study investigated global genetic correlations using linkage disequilibrium score regression, genetic covariance analysis, and high-definition likelihood recruiting 501,457 participants aged 37-73 years in the United Kingdom between 2006 and 200. Association analysis based on subsets and cross-phenotype association revealed thirteen risk variants in six genes shared between AD and post-traumatic stress disorder; seven risk variants in four genes shared between AD and anxiety disorder; and 23 risk variants in four genes shared between AD and major depressive disorder. These studies advance the knowledge of the shared genetic origins of comorbidities and advance prevention of stress-related AD. However, the study is limited because only White or British ethnic backgrounds were selected and, because of the exclusion criteria, only 199,125 participants remained on the analysis.

Conclusion

This thematic analysis reviewed the complex relationship between anxiety and AD, focusing on four themes: the relationship between improvement in anxiety and AD risk reduction, the effects of anxiety symptoms in AD, the neurobiological mechanisms linking anxiety to AD, and the role of genetic susceptibility in associating anxiety and AD. Across these themes, the studies highlighted how anxiety could act as a contributing factor in the onset progression of AD. Some key findings suggest that improvement in anxiety symptoms is associated with reduced dementia, worry, entorhinal atrophy, and chronic stress-related biological pathways (e.g., cortisol). Additionally, other studies have found that genetic risk factors like the APOE $\varepsilon 4$ allele may heighten vulnerability to both anxiety and AD, further complicating the disease trajectory.

These studies hold importance in both clinical practice and future research. For instance, recognizing anxiety (e.g., trait anxiety, chronic worry) as a prodromal symptom of AD may aid in the earlier identification of individuals at elevated risk of cognitive decline. In addition, results suggest that anxiety treatment may serve as a factor for improvement in AD. From a biological standpoint, mechanisms such as synaptic dysfunction, oxidative stress, and HPA-axis dysregulation may represent shared targets for therapeutic intervention in both anxiety and AD. The research proposed here encourages a more integrative understanding of mental health symptoms in older adults, emphasizing their significance beyond quality-of-life concerns and positioning them as indicators of underlying neurodegeneration. Research institutes and hospitals should take this information into consideration so they have a proper definition of risk population of AD and can increase the possibility of MCI patients acquiring anxiety disorders' psychological treatment as they are often not given this service. Further investigating the relationship between anxiety disorders and AD needs to be researched, as it could change many patients' outcomes, AD research and treatments, and AD care accessibility.

The objective of this thematic review was to determine whether anxiety can be considered a prodromal symptom of AD and to explore the mechanisms that might manifest this association. The findings support this hypothesis, showing that anxiety often precedes measurable cognitive decline, correlating with structural and functional brain changes commonly seen in early AD, and overlaps with the disease's genetic risk structure. Despite promising associations, the current body of research remains preliminary and marked by notable limitations. Many studies are cross-sectional or retrospective in nature, making it difficult to infer causality. Several suffer from small sample sizes, uneven demographic representation, or reliance on self-reported anxiety measures that may not distinguish between transient emotional states and clinically significant anxiety disorders. The exclusion of certain populations (e.g., non-White ethnicities, men in smaller proportions) also raises questions about generalizability. Additionally, while neurobiological mechanisms such as BDNF depletion and NMDA receptor dysfunction are proposed, few studies have directly linked these pathways to both anxiety and AD in the same cohorts. Therefore, future research must prioritize longitudinal designs, standardized anxiety assessment tools, and biomarker-based approaches to better understand the temporal and causal dynamics of this relationship.

In conclusion, this thematic review does not only have the purpose of notifying readers about possible AD risk factors but also has the purpose of calling upon research institutes to follow and concentrate on anxiety and AD correlation research. Thereafter, if done correctly hospitals could identify risk population of AD, giving them major accessibility to treatment. As science continues to uncover the biological threads connecting mental health and neurodegeneration, the research direction of identifying the potential role of anxiety as a prodromal symptom of AD may hold transformative implications for both prevention and personalized care in aging populations. Hence, understanding this link offers a unique opportunity to bridge psychiatry and neurology, shifting how we detect, treat, and perhaps even prevent AD. This thematic analysis hopes to redirect AD pathology research to its associations with anxiety and other neurological disorders.

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