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FEATURED ARTICLE

Effects of risk factors on longitudinal changes in brain structure and function in the progression of AD

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Abstract

Introduction: Past research on Alzheimer's disease (AD) has focused on biomarkers, cognition, and neuroimaging as primary predictors of its progression, albeit additional ones have recently gained attention. When turning to the prediction of the progression from one stage to another, one could benefit from the joint assessment of imaging-based biomarkers and risk/protective factors.

Methods: We included 86 studies that fulfilled our inclusion criteria.

Results: Our review summarizes and discusses the results of 30 years of longitudinal research on brain changes assessed with neuroimaging and the risk/protective factors and their effect on AD progression. We group results into four sections: genetic, demographic, cognitive and cardiovascular, and lifestyle factors.

Discussion: Given the complex nature of AD, including risk factors could prove invaluable for a better understanding of AD progression. Some of these risk factors are modifiable and could be targeted by potential future treatments.

KEYWORDS
Alzheimer's disease, APOE, cardiovascular disorders, cognitive decline, disease progression, hypodynamic lifestyle, neuroimaging

1 | INTRODUCTION

Alzheimer's disease (AD) research has shown that it starts years before its clinical manifestation as a preclinical stage comprising individuals with subjective cognitive decline (SCD)[1] and cognitively healthy subjects (CH) with positive AD pathologic markers (cerebrospinal fluid [CSF] or positron emission tomography [PET] Aβ and tau biomarkers).[2] When the disease progresses further, individuals eventually start to exhibit clinical symptoms. Two clinical stages are commonly identified: mild cognitive impairment (MCI) or AD dementia (AD-d).[3] Even though the cause of AD is still debated, many risk factors have been recognized including age, genetics and cardiovascular factors.[4] Recently the Lancet commission published an updated list of modifiable risk factors depicted in Figure 1.[5] Various other factors, perhaps questionable, are assumed to play a protective role against AD development; among these are exercise and Mediterranean diet.[6]

Several excellent cross-sectional reviews[6–10] examined the effects of genetics, cardiovascular diseases, lifestyle, and neuropsychological factors on cognition and neuroimaging parameters. Some of these exhibit a complex interaction between the risk of cognitive decline and AD progression. Because of this, it is imperative to conduct longitudinal research as evidenced by the intensive use of publicly available databases with longitudinal neuroimaging, biological, and behavioral data. Notably, as far as we know, only few review articles focused on longitudinal changes in imaging biomarkers in AD,[11,12] however, they did not address the effect of risk factors on longitudinal changes in brain structure and/or function when it comes to AD progression.

Barbara Hrast and Elvira Khachatryan contributed equally to this work.

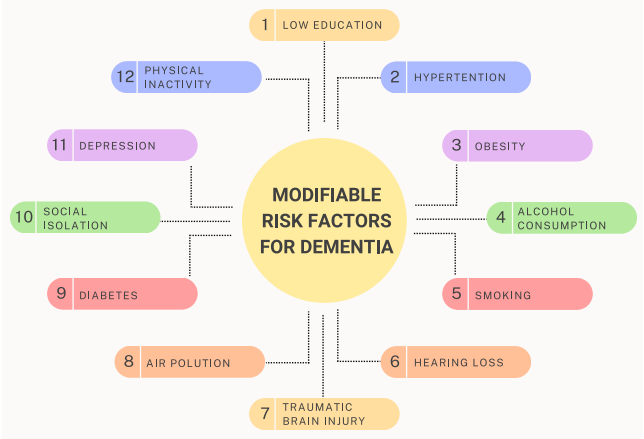

FIGURE 1 List of modifiable risk factors for dementia adapted from 2020 report of the Lancet Commission[5]

In the current review, we address this gap and summarize the results of studies that investigated the effects of different risk/protective factors on longitudinal changes in brain structure or function. In addition to the widely known risk/protective factors, we also included less researched risk factors to widen the pool of factors that could provide valuable insights into the progression of the disease.

RESEARCH IN CONTEXT

1. Systematic Review: The authors conducted a systematic search using traditional and gray literature sources. While longitudinal studies using neuroimaging are on the rise, less is known about Alzheimer's disease (AD) risk/protective factors and their impact on AD progression.
2. Interpretation: Our review looks at well-researched risk factors such as age and sex, cognition, genetics, and cerebrovascular factors and how they impact neuroimaging. However, less researched factors such as neuropsychiatric ones and protective factors such as lifestyle could also be relevant for predicting AD progression. Additionally, the review provides an overview of publicly available longitudinally-collected neuroimaging data.
3. Future Directions: The review hopes to encourage researchers to use publicly available neuroimaging databases and to consider the effect of risk/protective factors in their study designs. Creating effective interventions based on lifestyle factors could not only be more attainable but also avoid many other aversive health conditions and improve the overall quality of life.

2 | METHODS

We conducted a systematic literature search in PubMed, Google Scholar, PsychINFO, and MEDLINE of articles published in English between January 1990 and June 2022. These databases were selected because of their broad coverage of the biomedical science literature and their suitability for conducting systematic literature searches. In addition, Google Scholar was added because it accesses gray literature and can thus be considered a suitable additional source of evidence.

Search terms used included combinations of terms described in the Supplementary Methods. We used MESH terms and Boolean operators and excluded review papers and meta-analyses. Articles that considered longitudinal/serial neuroimaging recordings and protective/risk factors as independent variables were considered and included. For transparency's sake, we adhered to the list of modifiable risk factors published by the Lancet commission (depicted in Figure 1).[5] In addition, we also performed hand searches based on reported citations identified to be of interest. The selection process is illustrated in Figure 2.

All included studies relied on longitudinal neuroimaging, with the majority using magnetic resonance imaging (MRI). For this study, no consent from human subjects was necessary. Demographic and design characteristics of included studies are summarized in Table S1. In addition to neuroimaging biomarkers, other variables were used to explain differences in neuroimaging. Most studies used data from publicly available longitudinal databases. Table S2 lists the longitudinal databases used in these studies, the most popular one being ADNI (Alzheimer's Disease Neuroimaging Initiative) (http://adni.loni.usc.edu/) with various AD biomarkers.

2.1 | Reported risk/protective factors

2.1.1 | Genetic factors

Late-onset (or sporadic) Alzheimer's disease (LOAD[1]) exhibits complex and heterogeneous genetics. More than 10 genes are currently known to increase the risk of LOAD, with the apolipoprotein E (APOE) being the main gene involved in packaging cholesterol and other lipids and transporting them through the bloodstream.[13]

APOE: There is an ongoing debate whether or not APOE-ε2 plays a protective role against LOAD,[14–16] while it has already been proven that APOE-ε4 increases the risk of AD development. Every additional allele of APOE-ε4 increases the risk of AD development by a factor of 3.[16] However, the mechanism behind its effect on AD development is not entirely clear. In addition, the APOE genotype has been shown to modulate the clinical phenotype of AD. The majority of studies, however, stipulate that APOE-ε4 positivity increases atrophy rate in temporal (specifically affecting hippocampus), frontal, parietal, and occipital cortices,[14,17–19] reduces natural hippocampal asymmetry,[14] increases white matter (WM) impairment over time (increase in WM hyperintensities, WMH),[16] especially in amyloid-positive individuals,[20,21] and

[1] From here onwards LOAD, sporadic AD, and AD will be used interchangeably.

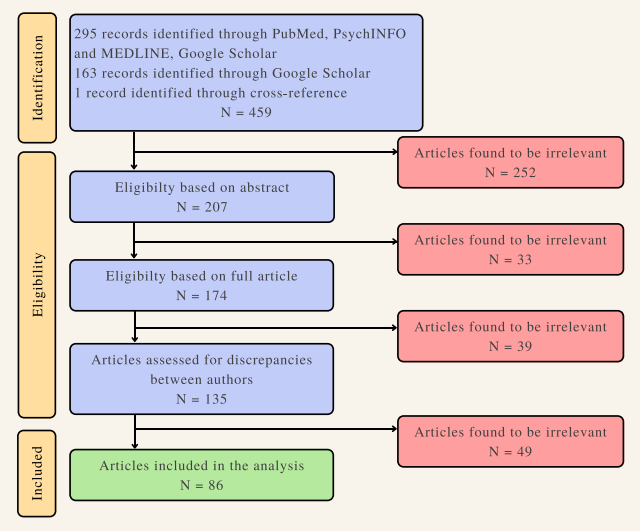

FIGURE 2 Flowchart of selection process. Flowchart showing the article selection process from the identification, the eligibility criteria to the articles included in the review. The used keywords and search terms are listed in the Supplementary Methods – Search Strategy

decreases metabolism in frontal, temporal, and parietal cortices.[22] Furthermore, the effect intensifies with the number of APOE-ε4 alleles present: homozygote APOE-ε4 carriers would have a steeper decline compared to heterozygotes carriers and the latter a steeper decline compared to non-carriers.[19] Soldan et al.[23] also showed that more significant left amygdala volume atrophy was associated with a faster time to onset of clinical symptoms in APOE-ε4 carriers. Amyloid-positive APOE-ε4 carriers also display accelerated medial temporal lobe (MTL) atrophy which is indicative of a faster disease progression. Specifically, MCI patients that progressed to AD-d have significant cortical thinning in regions implicated in AD.[24] Despite acting throughout the entire clinical spectrum (MCI, and AD-d stages), the effect of APOE-ε4 on neuroimaging changes interacts with the clinical manifestation of AD. It has been repeatedly suggested[25–27] that the role of APOE- ε4 positivity in both neuroimaging and clinical changes of AD decreases with the increased severity of the disease. Namely, in the AD-d stage, the difference between neuroimaging changes, specifically hippocampal atrophy in patients with and without APOE- ε4 alleles, is not as pronounced as in CH or MCI patients. That being said, it is important to stress that APOE affects both clinical progression and brain changes in a complex way during all stages of AD, even though for earlier stages more than for later ones.

In addition to APOE, several other genes (described in Supplementary Note 1) influence AD progression.

2.1.2 | Demographic factors

Cross-sectional studies repeatedly showed the effect of demographic variables on both brain structure/function and cognition of individuals.[28] However, their effect on the disease progression rate and the possible conversion from one disease stage to another (e.g., MCI to AD-d) is less investigated, and the results are not always in line.

Age: It has been repeatedly shown that, with age, the brain undergoes atrophy, specifically in medial temporal, prefrontal, and supramarginal cortices and the operculum.[29,30] However, the association between age and atrophy rate is complicated and shown to interact with the individual's sex [15,31] and clinical status.[30,32–35]

Reviewed studies point towards a different relationship between baseline age and structural changes in the brain for MCI and early AD-d patients, compared to CH. A negative correlation between cortical atrophy rate and patient age was observed in MCI and AD-d, the latter to a lesser degree,[30,32–34] while a positive correlation was observed for CH.[32,34] This pattern concerned widespread cortical areas in addition to the hippocampus and amygdala for some studies[30,32,33] while for other studies it was more concentrated in posterior regions.[34] Fiford et al.[34] found that atrophy rate and atrophy pattern differed with age between CH, MCI, and AD-d patients. In particular, greater atrophy rates of the whole brain and the hippocampus were observed in young AD-d patients and greater volume loss in posterior and posteromedial regions compared to older AD-d patients. Older MCI converters displayed 2%-3% faster atrophy rates than non-converters in the temporal lobes.[33] The trend was the opposite for CH, with younger ones exhibiting less hippocampal atrophy than older ones. Similarly, Chang et al.[30] observed a greater atrophy rate in young AD-d patients in the temporal, parietal, and cingulate brain regions than in older AD-d patients. The trend was the opposite for CH, with older ones exhibiting a larger annual atrophy rate than younger ones. Younger age of AD onset is therefore predictive of faster progression of AD.

Sex: The fact that women more frequently suffer from AD compared to men[36] would be suggestive of a higher atrophy rate for women. Even though some extra factors can confound the relationship between sex and AD risk (e.g., women live longer than men), several studies support the claim. For instance, when investigating data from a group combining CH, MCI-, and AD patients, a steeper rate of atrophy in medial temporal lobes was observed across time for women compared to men.[33] Furthermore, for MCI and AD-d patients, the cortical atrophy rate for women was higher than for men except for the hippocampus.[32,37] Interestingly, Spampinato et al.[38] suggested that baseline hippocampal volume and APOE status could predict the conversion of MCI to AD-d with an accuracy of around 72% for women during 3 years of follow-up. During the same follow-up period, but now for men, entorhinal cortex and APOE-status yielded a similar predictive value for AD-d conversion.[38] Furthermore, women with MCI who did not convert to AD-d had the lowest degree of hippocampal loss compared to all other investigated groups (men who did not convert and both men and women who converted into AD-d). These findings provide additional support to previous claims[32,37] on accelerated atrophy of the hippocampus across time for MCI converting women suggesting that it indicates disease progression rather than aging. Furthermore, MCI men with a larger baseline intracranial volume (ICV) showed a more significant atrophy rate of MTL and increased chance of conversion to AD-d than those with smaller ICV. For women, this pattern was reversed, though not in a statistically significant manner.[37]

There are limited data on racial and ethnic disparities in AD development and the effect of menopause on AD progression. The few reports are discussed in Supplementary Note 2.

2.1.3 | Cognitive factors

Given the complex nature of AD, it has proven quite difficult to predict pathological cognitive decline and to distinguish it from age-related cognitive decline. Therefore, the characteristics of AD-d patients, that is, for whom pathological decline is observed, could be considered suitable predictors of future cognitive decline and progression to AD-d in CH that would differ from age-related cognitive decline. Multiple longitudinal studies on CH have tried to see if those factors can predict the pathological decline in cognition and eventually progression towards AD-d. These studies are an important step in AD research, as individuals at risk can be identified at an early stage and start interventions such as cognitive training which have shown some potential to delay the onset of pathological decline.[39,40]

Brain atrophy, especially MTL atrophy, has been observed with increasing age, but also in MCI and AD-d patients, and implicated in the prediction of cognitive decline.[41] Multiple studies[42–44] have consistently shown that anteromedial temporal lobe brain atrophy volume at baseline and higher annual rates of atrophy in left MTL are valid predictors of future episodic memory decline and progression to MCI and AD-d in 5 years. Additionally, the shift of atrophy rate from the anterior part of the left MTL to the left temporoparietal association cortices indicates later clinical diagnosis.[43] Martinez-Torteya et al.[44] looked at the associations between cognitive measures (global cognition, episodic memory, verbal memory, executive function) and cortical atrophy and found that declines in cognitive abilities are concurrent with a decline in the cortical thicknesses of several brain structures but mainly hippocampus and amygdala. When it comes to progression to AD-d, pathological brain changes become apparent along with cognitive symptoms. Studies have shown that hippocampal volume at baseline and tests of episodic memory and processing speed are consistently robust predictors of progression.[45–47] Measures of executive function were associated with the speed of conversion to AD-d[44] and, therefore, could be used as predictors. However, those factors are rarely evaluated jointly for their predictive value. The strongest predictors of MCI to AD-d conversion in a 2-year follow-up were verbal episodic memory measures and left MTL cortical thickness. The decline in Functional Activities Questionnaire (FAQ) and Trail making Test Part B explained approximately 50% of the variance in conversion from MCI to AD-d.[48] With this, the authors argue that AD stage diagnosis might be mainly influenced by functional decline, not necessarily complemented by neurobiological decline.

Structural brain changes involve gray matter (GM) and WM. WMHs in the elderly have been connected with poorer cognitive performance.[49] Pettigrew et al.[50] showed that better reading and vocabulary skills and higher education were associated with lower WMH volumes in CH that eventually progressed to MCI/AD-d, suggesting the effect of cognitive reserve. Changes in myelinization have been shown in the fibers connecting regions structurally affected by AD pathology. Hippocampus-fornix circuitry is essential to episodic memory consolidation and has been implicated in cognitive decline in dementia.[51] Although the integrity of the fornix decreases with age in healthy individuals, it can be used as a predictor of the conversion from MCI to AD-d and even HC to MCI.[52] Older age, lesser fornix integrity, and volume were independently associated with a greater risk of conversion indicated by a decline in cognitive measures.[53] Fornix integrity was also connected to cognitive measures, where low fornix integrity and hippocampal/ICV ratio were predictive of decline in general cognition, verbal episodic, and working memory tests over 2.5 years of follow-up.[54] Additionally, fornix integrity was found to be a better predictor for progression to AD-d than hippocampal volume.[54] Altogether, these findings hint toward possible early-stage degeneration of the broader hippocampus-fornix circuit leading to impairments in memory consolidation.

Functional brain changes in MCI and AD-d have also been observed to reflect neurodegeneration. Changes in the default mode network (DMN) connectivity and connectivity of other regions have been reported in patients with MCI and AD-d.[55] Therefore, combined changes in regional GM volumes and functional brain connectivity indices are a promising approach for assessing AD progression. Serra and colleagues[56] investigated the patterns of structural and functional brain modifications in MCI converters and non-converters over a 2-year interval and showed that both groups have widespread GM atrophy, mainly in the medial temporal lobes and the prefrontal cortex. However, converters had more severe atrophy in prefrontal and temporal areas and in the anterior cingulate cortex, which is consistent with the observed worse executive and visuo-spatial skills.[56] Reductions in functional connectivity in frontal DMN areas were found in all MCI patients but in converters additional reductions in functional connectivity in the posterior cingulate cortex (PCC) were found. There were also some increases in functional connectivity, mainly between the precuneus and other regions of DMN, and angular gyrus and other regions of DMN, hinting at a compensatory mechanism. Overall, combining signs of atrophy in the medial temporal and orbitofrontal structures with functional connectivity changes in the precuneus MCI patients that converted to AD-d in 2 years could be identified. Studies with FDG-PET have indicated that hypometabolism in the posterior associative and/or PCC of patients with MCI is predictive of conversion to AD-d within 1-3 years.[57,58] Hypometabolism in temporal and parietal lobes and verbal episodic memory were identified as predictors that could distinguish between converters and non-converters over 2 years.[59] In contrast, increases in glucose metabolism in parietal and temporal regions were associated with delayed cognitive decline in MCI converters with reduced hippocampal volume and could have a protective effect in at-risk persons (Aβ positive).[60]

By observing how certain biomarkers change in combination with manifested clinical symptoms, we can infer information about the disease trajectory. A study by Han and colleagues[61] using the cascade model of Jack Jr et al.[62] as a basis applied linear mixed models to investigate the temporal relationship between CSF markers, structural MRI, and cognitive measures. They concluded that, in the AD cascade,

cognitive symptoms are preceded by elevated Aβ and tau levels as well as changes in brain function and structure; however, the change in cognition was not related to CSF markers independent of changes in brain function and structure. Therefore, it is clear that elevated levels of Aβ do not provide sufficient evidence of clinical AD since many non-demented, cognitively-intact older adults show CSF, neuroimaging, and autopsy evidence of elevated levels of Aβ.[63] Another study[64] corroborated previous findings showing that, at different disease stages, different biomarkers could be related to cognitive decline, for example, at the MCI stage, Aβ level in CSF, FDG uptake, and hippocampal volume were related to cognitive decline and in AD patients only FDG and hippocampal atrophy were related. Another study[65] came to similar results by showing that longitudinal temporal atrophy was correlated with cognitive impairment in MCI, and a lower baseline score on the delayed logical memory test was correlated with a greater ongoing rate of temporal lobe atrophy, whereas in AD, a greater baseline cognitive impairment correlated with less ongoing atrophy. These findings indicated, on the one hand, that Aβ level in CSF declines prior to the onset of cognitive impairment, while other markers capture the neuronal dysfunction and injury and change with disease stage and severity and, on the other hand, that in AD temporal lobe atrophy already reached a plateau. Because cognition is considered a modifiable factor, some researchers tried to postpone cognitive decline and AD pathology using cognitive training.[66] However, most studies looking at cognitive training consider the outcomes in a shorter time frame than the cognitive factors discussed in this review. The former, therefore, are reported in Supplementary Note 3.

2.1.4 | Neuropsychiatric factors

Usually, AD is considered to be primarily characterized by cognitive impairment, yet neuropsychiatric symptoms (NPS) frequently emerge as well.[67] However, in cohort studies on the AD spectrum, psychiatric patients or patients with NPS are usually excluded.

Depression and apathy: Several longitudinal studies have suggested that depressive symptoms and apathy in CH and patients with MCI are linked to an increased risk of developing dementia.[68] A significant proportion of late-life depression (LLD) patients progresses to dementia, suggesting that a lower hippocampal volume in LLD patients might indicate preclinical AD.[69] In MCI, a greater ongoing rate of temporal lobe atrophy was found to be correlated with a higher baseline depression score.[65] Additionally, more significant hippocampal atrophy and smaller baseline hippocampal volume have been observed in depressed patients,[70–72] which might represent a converging point between depression and AD. Depressed MCI patients also showed earlier onset of progression to dementia compared to non-depressed MCI patients.[73] Comparing both groups of MCI patients, a greater volume loss in the left hippocampus over 2 years was found in depressed MCI patients.[73] These findings imply that depression and smaller hippocampal volume might have a synergetic effect that accelerates progression toward dementia. Additionally, increased frontal lobe and anterior cingulate cortex atrophy rates have been observed in MCI individuals with chronic depressive symptoms compared to non-depressed MCI individuals.[74] They also more frequently progressed to AD-d and had a shorter time to conversion, which was correlated with frontal lobe atrophy. It is speculated that there is a common neurodegenerative pathway (dysfunctional fronto-subcortical circuit) for AD pathology and depression.[74] Depressed MCI patients, positive brain Aβ status and concurrent subsyndromal depression have been shown to have a higher frontotemporal amyloid load and a faster conversion to AD-d than non-depressed MCI individuals, suggesting that the former have a higher risk of developing AD-d.[75] Association between changes in glucose metabolism in medial and lateral parietal regions and apathy across the AD spectrum have also been found.[76] Associations between posterior brain regions and apathy might be more important in earlier stages of AD as opposed to frontal-subcortical structures that appear to be associated with apathy in later stages of AD.[77,78] However, the possibility that depression in AD might not be a risk factor but rather an atypical pattern of neurodegeneration cannot be entirely excluded.[74]

Another neuropsychiatric syndrome commonly present in AD is psychosis.[79] Those findings are described in Supplementary Note 4.

2.1.5 | Cardiovascular and lifestyle factors

It has been repeatedly suggested that cardiovascular pathologies, particularly cerebral small vessel impairment, play a significant role in AD development.[80] However, whether small vessel disease and WMH, often associated with the former,[81] result from AD-pathology, a causing factor, or an accompanying condition is not yet clear. Nevertheless, its role is gaining increased interest in the pathophysiology of AD-development.[50,82,83]

Individuals with cardiovascular risk factors (CVRF) are at higher risk of cerebral small vessel disease,[81] affecting mainly subcortical GM and WM.[84] Research is currently directed towards the longitudinal effects of CVRF on brain structure and metabolism.[82,83] It has been suggested that an increasing number of CVRFs is associated with increased brain damage and progression of the disease. For instance, a widespread reduction in cerebral blood flow (CBF) for AD-d patients[85] and a decreased cortical thickness in the temporal cortex for MCI patients[86] were observed in individuals with multiple CVRFs compared to those with no CVRFs. At the same time, Lin et al.[82] observed a positive association between a combination of several CVRFs that reinforce each other, namely, high body mass index (BMI), triglycerides, high glucose level, and hypertension and WM loss in the left hemisphere of CH and MCI patients, but no association between the metabolic syndrome and the hippocampal atrophy rate for either group. Similar results were reported in Lo et al.[87] where no association was observed between the level of vascular burden and longitudinal change in glucose metabolism in AD-specific brain regions, CSF biomarkers, or hippocampal atrophy across the clinical spectrum of AD. Both studies support the two-hit vascular hypothesis of AD,[88] implying that vascular burden increases the vulnerability to AD pathological changes, leading to cognitive impairment and subsequent AD progression. Specific CVRFs are further discussed in Supplementary Data 5.

Perhaps the most modifiable risk factors for AD are the ones that portray the way we live our lives. When taken into account, they can improve general health and possibly lower the risk for cardiovascular diseases, cognitive decline, and dementia.[89] Two factors addressed by a couple of studies are discussed below, other less studied ones are described in Supplementary Note 5.

Sleep disturbances: Insufficient sleep has been linked to multiple adverse health outcomes, such as cardiovascular morbidity, worse cognitive functions, increased risk for accidents, and worse mental health.[90] Recent laboratory studies point to a connection between impaired glymphatic clearance during sleep and the risk of AD development.[91,92] A population-based study investigating CH with and without obstructive sleep apnea (OSA)[93] supports these results by showing an increased amyloid accumulation in OSA subjects compared to those without OSA.[94] Patients with OSA also had an increased risk and shorter time to progression to MCI and AD-d, especially if they also had Aβ and tau accumulation.[95] The mechanism behind this relationship is unclear, but research suggests sleep fragmentation[93,94] and transient hypoxia[94] during OSA could lead to faster amyloid accumulation in the brain. Sleep disturbances have also been associated with the risk and progression of AD.[96] Nocturnal awakenings have been shown to be connected to lower locus coeruleus structural integrity.[97] This association was especially evident in individuals with elevated tau in plasma, indicating the possible role of the brainstem nucleus in preclinical AD sleep disturbances.[97]

Diet: Diet has been proposed as a risk factor for quite some time, although not many studies address this factor in combination with neuroimaging. Walters et al.[83] investigated adherence to the Mediterranean diet in CH and found that higher adherence correlates with slower rates of decline in glucose metabolism in PCC. This diet, therefore, might have neuroprotective effects in preserving brain metabolic activity.[83] Neth et al.[98] compared the effects of a modified Mediterranean-ketogenic diet (MMKD) and a low-fat American Heart Association Diet in patients with SCD and MCI. After a 6-week dietary intervention, MMKD led to a positive change in CSF AD biomarker profile (increase in Aβ and decrease in tau) and increased CBF mainly in the temporal lobe of both groups, although the effect was greater for the MCI group. Taylor et al.[99] found that a high glycemic diet has some influence on the cortical amyloid burden. Specifically, when assessing preclinical subjects with elevated amyloid, a high glycemic diet was associated with increased amyloid burden in the precuneus, posterior cingulate, and lateral temporal lobe over 1 year. Studies indicate that changes in the diet (reduction of carbohydrates, sugar, and glycemic load) can alter AD biomarkers and therefore influence the progression of the disease. However, future studies need to determine the relationship between diet and AD progression to assess the diets' effectiveness as modifying therapy for AD.

3 | DISCUSSION

This review looked at AD progression, risk factors, and their association with longitudinal neuroimaging indices. Even though publicly available AD databases have contributed significantly to the growing number of neuroimaging studies, longitudinal neuroimaging evidence in conjunction with AD risk factors is still scarce. Most of the studies we reviewed were on cognition, genetics, age, and sex, while research in other areas was sparse. Given the limited number of studies on some risk factors, it is imperative to be cautious with their interpretations.

It is widely accepted that age is a risk factor for AD and the reviewed studies point towards a difference in the effect of age in healthy individuals and individuals on the AD spectrum. Young age in MCI and AD-d patients is associated with an earlier onset and a faster atrophy rate in predominantly MTL regions. On the other hand, in healthy individuals, the relationship is reversed.[30,34] Global and regional (hippocampal) GM atrophy was found in both healthy elderly and individuals on the AD spectrum.[100,101] Because of this overlap between healthy and pathological aging, it is hard to disentangle one process from the other. However, assessing risk factors that show different effects on healthy and pathologic aging could aid in establishing the distinction. Neuroimaging evidence supports the observation of higher incidence of AD in women,[36] showing that they have higher MTL atrophy rate than men.[32,33,37] Moreover, hippocampal atrophy has been further investigated, suggesting that greater hippocampal atrophy in MCI women is linked to progression to AD-d.[38] These findings highlight the need for inclusion of female-specific risk factors, such as menopause, in the studies more often, as they affect AD progression.[102]

Declining cognition, one of the AD symptoms, has been researched extensively. Episodic memory deficits are prevalent in MCI patients, but other cognitive functions are also impaired with disease progression.[44,45] Specifically, the executive function has shown to be a good predictor of the speed of AD conversion.[44,56] Not surprisingly, cognitive decline and progression to MCI and AD-d are tightly linked to temporal lobe atrophy and also to frontal lobe atrophy.[29,41,43,44,103] The most well-established predictor of progression is hippocampus atrophy, although other effective predictors have been proposed, for example, fornix integrity.[53,54] Finding additional relevant predictors could provide insight into AD progression and offer the possibility of an early detection of pathological changes. When considering cognition as a modifiable risk factor, knowledge of the long-term effects of cognitive interventions is lacking. Studies on cognitive training show promising results in slowing down AD progression, especially earlier in the disease[39,40,104] ;however, to chart these benefits, long-term effects need to be studied further, possibly by involving neuroimaging biomarkers.

The vascular hypothesis of AD has played an important role in AD research, and a substantial amount of research has investigated the effects of CVRF on AD risk and progression. Currently, increasing attention is dedicated to specific metabolic markers, not just syndromes (e.g., hypertension). We hope that the detailed mechanisms with which CVRF influences the progression of AD will be uncovered and effective interventions developed. Addressing CVRF could demote other adverse health effects, improving overall health and possible postponing AD progression.

Researchers have by now almost systematically included APOE gene testing in their research on AD, as it has been consistently shown

that APOE-ε4 carriers are at higher risk for AD development and progression than non-carriers. Furthermore, the genetic status has been observed to influence the effect of other AD risk factors (i.e., CVRF), enhancing their effect on AD risk and progression.[105,106] These data led some authors to argue that reporting genetic test outcomes to study participants could empower them to reduce their risk for AD by improving modifiable risk factors such as CVRF.[106] However, relying only on one gene to explain the large variability in AD rate of progression and prognosis is ill-considered, and a few promising SNPs have already been identified as helpful in predicting AD risk and progression. From the reviewed findings, we can conclude that genetic status affects the clinical manifestation of AD and brain changes in complex ways that are still under investigation. An individual's genetic status might play a role in detecting AD progression. However, this role is limited and mainly pronounced in the transitional stages of AD development, such as MCI. Once the process transits to AD-d, genetic status, including APOE-ε4 status, is only of limited value.

From the limited number of longitudinal studies done on NPS and neuroimaging in the AD spectrum, it is clear that not enough attention has been devoted to the research of NPSs as risk factors for AD. The reviewed studies imply that depression and hippocampal atrophy have a synergetic effect on AD progression.[65,71,73] Treating depression also appears to have a beneficial effect on hippocampal atrophy and, therefore, a possible postponement of the onset of AD and progression to AD-d.[107] However, when it comes to psychosis, studies indicate it to be less modifiable than depression when it comes to pharmacological treatment.[108] The lack of studies including NPS is surprising as these symptoms are perceived as a greater burden to patients and caregivers albeit that, in most cases, they can be treated relatively successfully with a beneficial effect on AD progression. All mentioned studies agree that serial neuropsychiatric testing needs to be implemented, especially in MCI individuals at-risk, to monitor and assess disease progression.

By far, the scarcest number of studies are those that address lifestyle factors, such as exercise, diet, sleep, smoking, and substance use. However, in recent decades the interest in these factors has been increasing. Interestingly, our search returned no longitudinal studies on alcohol consumption and AD progression. Alcohol consumption is associated with cognitive impairments, and some longitudinal studies have suggested that heavy alcohol consumption is associated with faster progression of AD.[109] The importance of sleep has been gaining attention recently, and it is not surprising that researchers have looked into the connection between sleep and health outcomes. Findings suggest disturbances directly affect the disease's pathological mechanisms.[94,95] Exercise, physical fitness, and a healthy diet are some of the protective factors linked to better health outcomes. Not surprisingly, when researched in the context of AD, connections between physical fitness and structural brain changes are found.[110] Interventions concerning fitness and diet seem attainable; however, more clinical trials and intervention studies need to be conducted to assess their effectiveness. Creating effective interventions to modify AD risk based on lifestyle factors could also avoid many other aversive health conditions and improve overall quality of life.

3.1 | Future directions

From a methodological viewpoint, there are new developments that might ramify in several areas of AD research. One such development is the use of machine learning/deep learning to unveil potential biomarkers and risk factors as well as patterns or relationships in neuroimaging data. There exist several longitudinal studies that rely on such methods in predating/modeling AD, which are well-presented in a recent review paper.[111] It is expected that such methods can generate complementary or even new evidence to the body of knowledge acquired with traditional statistical methods.

There are two areas of research that seem important in light of the discussed risk factors: temporal dynamics of risk factors and the role of risk factors in disease modifying therapies. The temporal dynamics of biomarkers has been addressed in several studies, and covered in our review, however, the dynamics of how risk factors affect AD progression has been far less researched. We suspect this will become increasingly researched in the near future. Disease modifying therapies for AD is a topic relevant not only for patients but also for researchers. However, because of its recency, not many studies have looked into the involvement of risk factors as research is focusing on the effectiveness of therapies in a clinical setting and on AD biomarkers as they are essential for the early application of such therapies.[112] Given the recent attention on risk factors, we speculate that more insight will be gained in their effect on disease modifying treatments.

4 | CONCLUSIONS

In combination with clinical findings, neuroimaging and risk/protective factors are essential to further our understanding of AD and its progression. Given the complex nature of AD, longitudinal research is best suited to disentangle the relationship between those factors. Additionally, the large cohort databases serve a twofold purpose: they give researchers to access to bigger sample size and improve their findings' reproducibility.

AUTHOR CONTRIBUTIONS

Barbara Hrast: Conceptualization, Methodology, Writing- Original draft preparation, Visualization, Investigation, Writing- Reviewing and Editing; Elvira Khachatryan: Conceptualization, Methodology, Writing- Original draft preparation, Visualization, Investigation; Dušan Šuput: Supervision, Writing- Reviewing and Editing; Marc M. Van Hulle: Supervision, Writing- Reviewing and Editing.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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