

## Review

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# How to Prevent and/or Revert Alzheimer's Disease Continuum During Preclinical Phases

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**Abstract.** The development of Alzheimer's disease (AD) follows three consecutive phases: namely preclinical, prodromal or mild cognitive impairment (MCI), and dementia. In addition, the preclinical phase can be divided into subphases related to the presence of biomarkers that appear at different points before the onset of MCI. Indeed, an early risk factor could promote the appearance of additional ones through a continuum. The presence of various risk factors may trigger specific biomarkers. In this review, we comment on how modifiable risk factors for AD may be reverted, thus correlating with a possible decrease in the specific biomarkers for the disease. Finally, we discuss the development of a suitable AD prevention strategy by targeting modifiable risk factors, thereby increasing the level of "precision medicine" in healthcare systems worldwide.

**Keywords:** Alzheimer's disease continuum, modifiable risk factors, precision medicine, sleep disturbances

## INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia [1]. It is a silent pathology in which symptoms appear before the clinical diagnosis of dementia [1–4]. Indeed, most researchers in the field hold the view that, when the AD diagnosis has been confirmed, it is too late to repair the damage and reverse the disease. AD is characterized by the appearance of aberrant brain structures, whose components are found in fluids such as cerebrospinal fluid and plasma, a decrease in some brain functions,

and structural changes in the brain, among others [5]. These features could appear through a continuum before clinical diagnosis. The identification of these markers as early as possible would facilitate research into preventing or slowing down the progression of the disease. These features are related to the presence of non-modifiable or modifiable risk factors [6], and from the perspective of prevention, the major goal is to minimize the former or to potentiate the resilience mechanisms or protective factors. However, this field has not been widely explored [7, 8]. Given that non-modifiable risk factors such as genetics cannot be prevented, here we focus on the modifiable ones and how these may correlate with the presence of specific early biomarkers for the disease [9]. For practical purposes, these kinds of studies should be complemented

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with thorough clinical (precision medicine) analysis of patients [10].

In summary, here we discuss whether intervention on risk factors could lead to a decrease in a specific biomarker of the AD continuum and thus ultimately result in the prevention or modification of the progression of the disease.

### **POSSIBLE LINKS BETWEEN EARLY BIOMARKERS AND EARLY RISK FACTORS IN ALZHEIMER'S DISEASE**

#### *Early biomarkers and risk factors in AD*

AD can be considered as the overlapping of two major pathologies, amyloid- $\beta$  (A $\beta$ ) plaques and neurofibrillary tangles, that could be linked due to changes in glial cells [11, 12]. These two pathologies begin in different regions of the brain, and they overlap as the disease progresses, thereby facilitating the onset of dementia.

The presence and spread of aberrant amyloid or tau [13] aggregates occur through different stages: amyloid deposits spread following the stages reported in [14], whereas tau aggregates expand as described in [13]. Amyloid and tau aggregates appear at different times and in distinct regions of the brain during AD. The presence of both structures in distinct regions, for example, amyloid in the cingulate cortex [15], or tau in the entorhinal cortex [16], may manifest in early negative processes, leading to specific cognitive and functional deficits. However, clinical changes appear mainly after stage 3 of these two pathologies, correlating with the onset of dementia, the main disorder related to AD [17]. Glia (microglial cells) have been proposed to play a critical role in this overlap [18, 19].

#### *Additional preclinical markers*

Some studies have examined changes in moral judgment in subjects potentially [20] in the preclinical phase of AD, and the increased tolerance of pain in patients with mild to moderate AD, compared to healthy controls [21, 22]. Also, homocysteine levels in plasma [23], and decreased levels of calcium in bone, which could result in osteoporosis [24], should be taken into account. Thus, given that modifiable risk factors could involve around 40% of the cases of dementia, targeting these factors in the preclinical stage in individuals identified (through longitudinal studies) as having more modifiable risk factors should

bring about the prevention or retardation of the condition [9].

#### *Presence of biomarkers for lesions without clinical symptoms: Resilience*

There is not always a total correlation between the presence of amyloid or tau aggregates with clinical consequences. Indeed, a small proportion of subjects whose autopsies show a high amount of A $\beta$  or tau deposits may have remained cognitively intact until death. In such cases, these subjects may have been protected by resilience mechanisms [25]. These mechanisms are not fully understood and merit further analysis.

#### *Risk factors*

There are risk and protective factors for AD. Here we mainly focus only on the former. Among concepts related with protective modifiable factors; cognitive reserve, brain reserve or maintenance should be included. In this way, a correlation between cognitive reserve and a reduction of risk of developing dementia has been indicated [26]. In addition, the role of brain reserve, cognitive reserve, and maintenance in cognitive disorders like AD, has been widely commented by Dr. Stern [27, 28]. Also, lifestyle (psychical or leisure activity) may supply cognitive reserve [29]. Alternatively, some autoinflammatory agents could act as a possible protective factor for AD [30]. Returning to risk factors, they can be classified into non-modifiable and modifiable. The most relevant non-modifiable ones are aging and genetic factors [31].

Regarding modifiable risk factors, there are discrepancies between the number and incidence of such factors [7–9, 23, 32]. To choose relevant modifiable risk factors, as criteria here we used their prevalence as indicated in the literature [9, 32]. In Fig. 1, we also include factors such as socio-economic status [33], dyslipidemia [34], and nutrition-microbiota changes [35], which were commonly excluded in other reviews. About socio-economic status, we have indicated the impact of individual and neighborhood dimensions of socio-economic status on the presence of mild cognitive impairment (MCI) [33].

Also it has been described that socio-economic deprivation is a risk to develop dementia compared to people with a better economic status, even with a higher genetic risk [36].

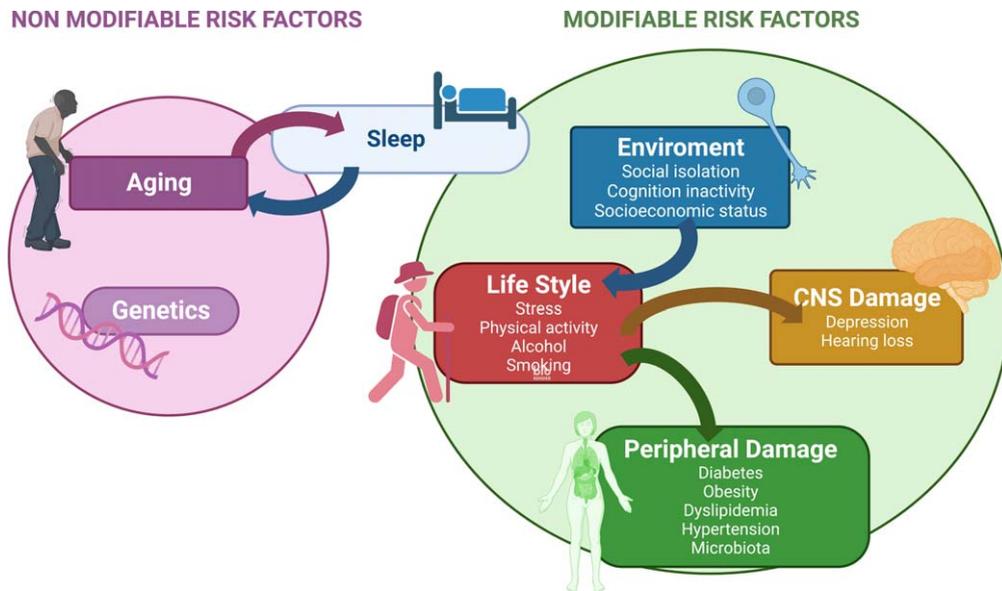


Fig. 1. Modifiable risk factors-Kinetics and links between them. Sleep disturbance is related to increasing age and it could be one of the earlier modifiable risk factors for AD (see text). Other modifiable risk factors related to the environment, lifestyle, or damage to the nervous system, peripheral tissues or organs are indicated. Arrows show the links between these modifiable risk factors.

About microbiota changes, the link between gut microbiota and AD has been reported [35]. Thus, gut microbiota modulation, for example, through probiotics or specific diet, has been suggested as a potential therapy in AD [37, 38].

About nutrition, long term high-fat diet consumption may indicate cognitive decline in aging, as shown in mouse models [39]. In addition, low serum vitamin D status could be associated with the appearance of dementia in the oldest old [40].

As previously indicated [6], some modifiable risk factors for AD can be intervened upon in a preventive manner to delay the development of the disease. It has been reported that modifiable risk factors are associated with the development of the disease in about 40% of dementia cases [9]. Modifiable risk factors also include the following: hypertension, obesity, physical inactivity, chronic stress, depression, and social isolation [6, 41, 42]. During the preclinical phase of AD, various risk factors are activated at different times and some factors that act, early on, may promote the emergence of new ones [43]. For example, chronic stress or social isolation can induce later depression [41, 42], and physical inactivity may lead to subsequent obesity. Thus, the risk factors that are activated at different times during the development of the disease may be linked.

#### *Possible kinetics for risk factors*

MCI is the (late) stage just before the diagnosis of dementia [44, 45]. Thus, it is currently considered a target phase in which intervention on modifiable risk factors may have positive effects on the further progression of the disease [46]. Indeed, a substantial proportion of subjects with MCI could annually revert to a normal cognitive state [47].

Prior to MCI, there is even a previous stage called subjective cognitive decline [48], during which it is also possible to intervene to prevent disorders associated with AD.

#### *Sleep dysfunction as an early risk factor for Alzheimer's disease*

Some modifiable risk factors for AD are the consequences of life changes that occur during aging. It is sometimes difficult to establish whether the decrease in specific functions is the result of aging or, in fact, a preclinical sign of the disease. Sleep disturbances could be related to aging and AD. Indeed, sleep affects several functions related to aging and AD, such as episodic memory consolidation and executive functions [49, 50].

By using the "Slow Oscillation Switch Model", the relationship between sleep and these two domains was explained [49]. Episodic memory is replaced

during sleep through interactions between the hippocampal and neocortical networks. On the other hand, prefrontal-subcortical networks regulate executive functions and working memory [49]. These sleep functions can be disturbed during aging, but dysfunction can also occur earlier, being a very early marker for AD [51]. However, there are some discrepancies in this regard [52]. Sleep deficits have been reported in subjects during the early preclinical phase of AD [53, 54], around (or before) the appearance of amyloid pathology [2, 5, 55]. On the other hand, it has been described that sleep is bidirectionally modified by A $\beta$  oligomers [51, 53, 54]; in a zebrafish model, A $\beta$  reversibly enhances or suppresses sleep as a function of A $\beta$  oligomer length [54]. Short A $\beta$  oligomers facilitate acute wakefulness while long ones induce sleep [54]. During the progression of AD, sleep can be disrupted [51].

In addition, aging and the presence of A $\beta$  aggregates alter circadian rhythms, including sleep regulation. In this regard, a relation between changes in the circadian rhythm and neurodegenerative disorders has been proposed [56].

#### *Could sleep disturbances precede amyloid accumulation?*

Sleep disturbance may be a consequence of claustrum dysfunction [46, 57, 58], which, at the onset of the preclinical phase of familiar AD, could precede amyloid accumulation [58]. Indeed, a link between claustrum deficits and human sleep has recently been described [5, 58]. Therefore, sleep disturbances emerge as a very early risk factor for AD [5, 57] and they may correlate with the presence of A $\beta$  oligomers, which are increased mainly during sleep deprivation [59–61], as also shown by examining these oligomers in soluble fluids (plasma or cerebrospinal fluid) [62]. Although further work is required in this field, treatment of sleep disturbances using medication, psychological strategies, or circadian rhythm treatments could be considered as approaches to prevent the development of AD [63].

Finally, other proteins related to AD, like tau, may play a role in sleep disturbances. In this regard, it has been found that the absence (dysfunction) of tau results in sleep dysregulation [64].

#### *Links between early modifiable risk factors and biomarkers for the preclinical phase of AD*

Given that modifiable risk factors related to lifestyle can often be altered, some studies addressed

whether lifestyle changes could also decrease the level of some AD biomarkers [65, 66].

#### *Increasing physical activity results in a decrease in the level of biomarkers for AD*

An example of a modifiable lifestyle risk factor is physical inactivity. This risk factor can be targeted by doing physical exercise. In this regard, in a mouse model for AD subjected to five months of voluntary exercise showed a decreased level of A $\beta$  deposits in the cortex and hippocampus [67]. Also, long-term treadmill exercise attenuates tau pathology in the P301S-tau transgenic mouse model [68]. In addition, exercise decreases microglia activation in the hippocampus, the levels of cytokines like IL-1 $\beta$  or TNF $\alpha$  being decreased [69]. Thus, there is some evidence that links early modifiable risk factors with a decrease in the level of early markers for the preclinical phase of AD.

In addition, changes in physical activity can also improve functional features like cognitive impairment. Indeed, normal cognitive status has been regained in animal models [66, 70].

In humans, aerobic exercise at early AD stages correlates with an increase in cardiorespiratory fitness that could be linked to an increase in memory function [71]. Also, the effects of different types of physical exercise in humans, have been commented as a possible therapy to prevent neuronal death that could be taken place in neurodegenerative disorders [72].

### **REVERSION OF RISK FACTORS FOR THE PREVENTION AND REVERSION OF PRECLINICAL PHASES OF ALZHEIMER'S DISEASE**

Modifiable risk factors can be targeted when they become activated and, in several cases, the damage they cause, like hypertension, depression, and diabetes, can be decreased by pharmacological therapy, or by psychological strategies that modify lifestyle, for example, by preventing social isolation or depression. Indeed, there is some controversy about the targeting of risk factors to prevent the progression of dementia [7, 8]. Some authors have indicated that such targeting is not a suitable strategy [8]. However, on the other hand, decreasing hypertension by changes in diet could reduce the incidence of AD [71]. Also, analyses performed by the Cochrane Organization examining the effect of hypertension treatments

suggest that such strategies retard dementia [73]. In addition, treatment of depression may enhance cognitive functions [74]. To clarify this controversy, additional analyses that include new relevant modifiable risk factors are required. Thus, it is of interest to collect solid clinical data from patients in the preclinical phase of AD. This could be achieved simply by including additional clinical observations to the previously defined risk factors. In other words, healthcare systems should foster an increased level of “precision medicine” [10, 75].

Finally, cognitive stimulation or lifelong learning have been suggested to improve cognitive functions in people with dementia [76]. In this way, cognitive stimulation therapy has been proposed for treatment of AD [77].

## CONCLUSIONS

In this review, we have addressed the targeting of modifiable risk factors to delay or prevent dementias like AD. However, this strategy depends on the capacity of healthcare systems to monitor changes in these risk factors over several years before a clinical diagnosis is made. However, as indicated in a recent study, vast improvements worldwide are required before these health providers can undertake this task [78]. That study gave examples of countries needing improvement of their systems. However, we question whether any country in the world takes care of brain health in a regular manner like dental health is.

Kerwin et al. [78] highlighted the problems to be tackled in several countries. In this regard, in China, there is a lack of physician training in dementia. In Brazil and Nigeria, socio-economic inequalities are an issue. In Sweden, there is inconsistent use of biomarkers, and in Spain, patient hesitancy, together with an overloaded health care system, are barriers to a proper diagnosis [78]. In conclusion, for more effective clinical management of dementia, healthcare systems worldwide would need to commit to boosting “precision medicine”.

Around this point, the Alzheimer Precision Medicine Initiative (APMI) was launched with collaborations, at the present, from USA, France, Germany, UK, Ireland, Canada, Italy and Switzerland. APMI is at an early development stage [10].

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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