

## Advances in the prevention of Alzheimer's Disease

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### Abstract

Alzheimer's disease (AD), the leading cause of dementia, has reached epidemic proportions, with major social, medical and economical burdens. With no currently available curative treatments, both the World Health Organization and the G8 Dementia Summit recently identified dementia and AD prevention as a major public health priority. Dementia and AD have a wide range of risk factors (genetic, vascular/metabolic and lifestyle-related), which often co-occur and thus interact with each other. Previous intervention efforts aimed at preventing dementia and AD focused on the management of single risk factors, with relatively modest findings. Also, the effect of risk factors depends on age at exposure, indicating that the timing of preventive interventions needs to be carefully considered. In view of the complex multifactorial nature of AD, as well as its long pre-clinical (asymptomatic) phase, interventions simultaneously targeting multiple risk factors and disease mechanisms at an early stage of the disease are most likely to be effective. Three large European multidomain prevention trials have been launched with the goal of preventing cognitive decline, dementia and AD in older adults with different risk profiles. Pharmacological trials are also shifting towards prevention of Alzheimer dementia, by targeting at-risk individuals prior to the onset of cognitive symptoms. The current review will summarize and discuss the evidence on risk and protective factors from observational studies, ongoing lifestyle-related and pharmacological randomized controlled trials (RCTs), as well as future directions for dementia and AD prevention.

### Introduction

As the worldwide population ages, dementia has reached epidemic proportions, with major social, medical and economical burdens. Dementia is a syndrome associated with progressive declines in cognitive capacities and impairments that interfere with daily functioning. These conditions are the primary cause of dependency, disability and institutionalization among older populations [1-3]. Cerebrovascular and neurodegenerative diseases account for the majority of dementia cases, while a small percentage is due to potentially treatable illnesses, for example, normal pressure hydrocephalus, human immunodeficiency virus (HIV) infection, and thyroid disorders. AD, a neurodegenerative disorder, is the leading cause of dementia, accounting for 60–70% of cases [2,3],

although increasing evidence shows that mixed brain pathologies (AD and vascular) account for most dementia cases, especially in very advanced age (age 85+) [4,5]. It has been estimated that 44 million people worldwide were living with dementia in 2013 and this number is predicted to double every 20 years, reaching 76 million by 2030, and 136 million by 2050 [3,6]. Annually, there are 7.7 million new cases of dementia globally [2]. The estimated worldwide annual socioeconomic cost of dementia was US\$604 billion in 2010, which was higher than the costs of cancer and cardiovascular disease combined [1]. Currently, there is no cure for dementia and AD, and both the World Health Organization and the G8 Dementia Summit recently identified dementia and AD prevention as a major public health priority [7,8].

Dementia and AD are multifactorial disorders, and evidence from the last decades has revealed that genetic, vascular and lifestyle-related risk factors often co-occur and interact across the lifespan to determine the risk of developing dementia and AD later in life (Figure 1). The frequent co-occurrence of AD and cerebrovascular disease is consistent with the evidence that both disorders share several risk and protective factors, supporting the validity of dementia syndrome as a target for prevention. As many epidemiological findings discussed in this review apply to both dementia and AD, these terms are used interchangeably (dementia/AD) whenever applicable.

While the precise underlying etiology of AD is unknown, extensive knowledge is available regarding its clinical and pathological features. The neuropathological hallmarks of AD involve the formation of extracellular beta amyloid (A $\beta$ ) plaques and intraneuronal neurofibrillary tangles, which are both associated with synaptic and neuronal loss. Various mechanisms have been described to explain

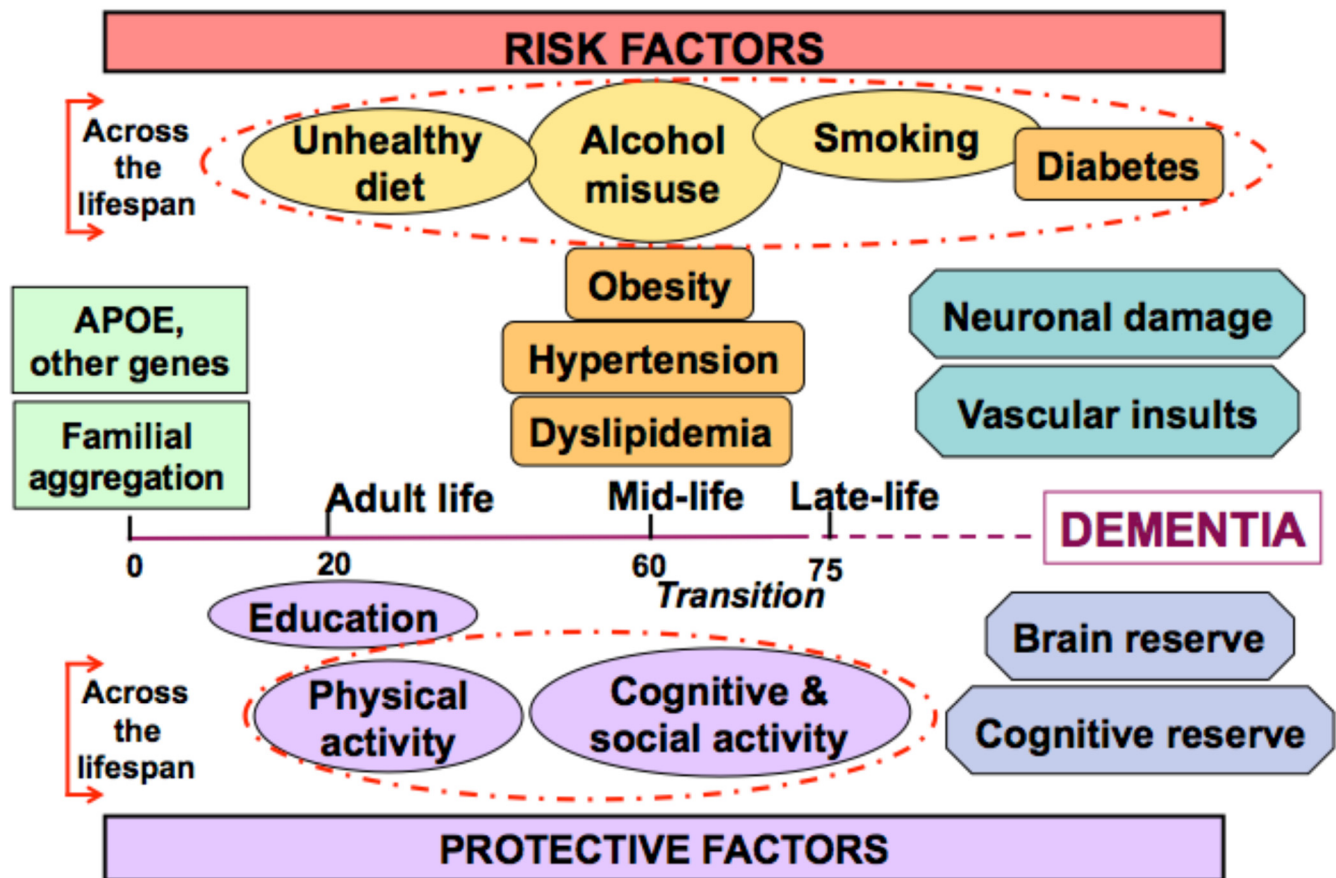
the link between genetic and environmental factors and AD pathophysiology, including oxidative stress, inflammatory and vascular-related pathways [9,10].

To date, preventive interventions to manage vascular and lifestyle risk factors are focusing on late-onset dementia/AD (age  $\geq 65$  years), while pharmacological preventive interventions are mainly targeting early-onset dementia due to AD (age  $< 65$  years). The current review will summarize evidence on dementia risk factors from observational studies, ongoing lifestyle-related and/or pharmacological RCTs, as well as future directions for dementia/AD prevention.

**Observational studies**

Evidence from observational studies has revealed that while some dementia/AD risk factors are non-modifiable, many risk factors are modifiable through lifestyle alterations and/or pharmacological treatment. The most important non-modifiable risk factor is age, and dementia/AD incidence substantially increases with advanced age [2,5].

Figure 1. Risk factors for dementia and Alzheimer’s disease across the lifespan (Figure modified from [51])



Other non-modifiable risk factors for late-life AD are familial aggregation and the apolipoprotein E (*APOE*)  $\epsilon$ 4 allele; the main genetic risk factor for sporadic AD. The *APOE*  $\epsilon$ 4 allele increases the risk for AD in a dose-response manner, where those with homozygous  $\epsilon$ 4 allele (two  $\epsilon$ 4 copies) have a higher risk than individuals with heterozygous  $\epsilon$ 4 allele (a combination of one  $\epsilon$ 4 copy, and an alternative copy:  $\epsilon$ 2 or  $\epsilon$ 3 allele), who in turn have a higher risk than individuals with no  $\epsilon$ 4 copies [11-14]. Moreover, the *APOE*  $\epsilon$ 4 allele reduces the age of AD onset, amplifies the negative effects of lifestyle-related factors and modulates responsivity to interventions [15-20]. It has been estimated that 15 to 20% of dementia and AD are attributable to the *APOE*  $\epsilon$ 4 allele [14,21].

Other genes have been proposed as risk factors for AD (a full meta-analysis can be found on the Alzgene website, [www.alzgene.org](http://www.alzgene.org)), and it has been estimated that about 70% of AD risk can be attributed to genetics [22]. Still, the risk conferred by single genes is small and combinations of risk alleles need to be identified [22]. Genetic causes of AD include autosomal-dominant mutations in

three genes (Presenilin 1 [*PSEN1*], Presenilin 2 [*PSEN2*] and the amyloid precursor protein [*APP*]), which are implicated in early-onset AD and account for approximately 1% of all cases [5,23,24].

Modifiable risk factors for dementia/AD fall into several categories. First, adequate evidence is present for vascular risk factors, including midlife hypertension, diabetes mellitus, smoking, midlife obesity, stroke and cardiovascular disease (Table 1) [25]. Some of these factors increase dementia risk when present in midlife, emphasizing the importance of applying a life-course perspective when examining risk factors and implementing preventive interventions [26-30]. Second, protective nutritional components include omega-3 fatty acids and unsaturated fats, antioxidants, vitamins and moderate alcohol consumption [31-35]. The importance of dietary patterns (e.g. Mediterranean diet) is also recognized, as nutritional components interact to produce synergistic effects (for a review see [36]). Third, lifestyle and psychosocial factors can also modify dementia/AD risk. For example, while living alone, having feelings of loneliness, depression,

**Table 1. Risk and protective factors for late-onset dementia and Alzheimer’s disease (Table adapted from [5])**

Risk factors	Protective factors
<b>Age</b>	<b>Genetic</b>
<b>Genetic</b> Familial aggregation <i>APOE</i> $\epsilon$ 4 Different genes (e.g., <i>CR1</i> , <i>PICALM</i> , <i>CLU</i> , <i>TREM2</i> , <i>TOMM40</i> ) have been proposed ( <a href="http://www.alzgene.org">www.alzgene.org</a> )	Different genes (e.g. <i>APP</i> , <i>APOE</i> $\epsilon$ 2) have been proposed ( <a href="http://www.alzgene.org">www.alzgene.org</a> )
<b>Vascular and metabolic</b> Cerebrovascular lesions Cardiovascular diseases Diabetes mellitus and pre-diabetes <i>Midlife positive association but late-life negative association</i> Hypertension High BMI (overweight and obesity) High serum cholesterol	<b>Psychosocial factors</b> High education and socioeconomic status High work complexity Rich social network and social engagement Mentally stimulating activity
<b>Lifestyle</b> Smoking High alcohol intake	<b>Lifestyle</b> Physical activity Moderate alcohol intake
<b>Diet</b> Saturated fats Homocysteine	<b>Diet</b> Mediterranean diet Polyunsaturated fatty acids and fish-related fats Vitamin B6, B12, folate Antioxidant vitamins (A, C, E) Vitamin D
<b>Others</b> Depression Traumatic brain injury Occupational exposure (extremely low-frequency electromagnetic field, heavy metals) Infective agents (Herpes Simplex Virus 1, <i>Clamydophila pneumonia</i> , <i>Spirochetes</i> )	<b>Drugs</b> Antihypertensive drugs Statins HRT NSAIDs

APP, amyloid precursor protein; APOE, apolipoprotein E; BMI, body mass index; CLU, clusterin; CR1, complement component receptor 1; HRT, hormone-replacement therapy; NSAID, non-steroidal anti-inflammatory drug; PICALM, phosphatidylinositol binding clathrin assembly protein; TOMM40, translocase of outer mitochondrial membrane 40 homolog; TREM2, triggering receptor expressed on myeloid cells 2. A large number of risk and protective factors for dementia and Alzheimer's disease have been investigated, and there are varying degrees of evidence to support these factors.

social isolation and psychosocial stress can increase dementia/AD risk, higher levels of education, engaging in exercise, and cognitively and socially stimulating activities are protective [25,37-39].

Cumulative exposure to risk factors needs to be accounted for, as it impacts the overall risk of late-life dementia/AD. Risk scores have been developed to assess dementia risk and target interventions for at-risk individuals using motivating and educational tools. The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Dementia Risk Score was the first tool developed using midlife risk profiles to predict dementia risk in later life (20 years later) [40]. This validated risk score combines low education with vascular factors (hypertension, obesity, hypercholesterolemia, and physical inactivity) [41]. A mobile application was recently developed for rapid and accessible usage of the CAIDE Dementia Risk score [42,43]. Other risk scores were subsequently developed (for a review see [44]).

A recent estimate took into account the prevalence and co-occurrence of the main modifiable risk factors and investigated combined effects of reducing their occurrence. It showed that up to a third of worldwide AD cases are attributable to seven risk factors (diabetes mellitus, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, low education), and a 10–20% reduction of all these risk factors might decrease AD prevalence by 8–15% in 2050 [45]. These findings further highlight the potential of multimodal preventive interventions—simultaneously addressing multiple risk factors—as preventive measures for dementia and AD. In line with these estimates, recent studies reported that improved lifestyle, medical care, and socioeconomic factors might have contributed to the reduced age-specific incidence of dementia observed during the past two decades [46–50]. However, while the age-specific incidence of dementia has been decreasing in some developed countries, the global occurrence of dementia is continuing to rise, especially considering the worldwide aging population [51].

Collectively, observational evidence provides strong grounds to target vascular and lifestyle-related risk factors that increase dementia/AD risk. Even modest reductions in these factors can considerably mitigate total risk and delay the onset age of dementia/AD [52].

### **Intervention studies**

Based on evidence from observational studies, several intervention studies were designed to prevent or delay dementia/AD onset, including trials testing medications, food supplements, and lifestyle interventions. When

collectively evaluated by the State-of-the-Science Conference held by the National Institutes of Health (NIH), it was concluded that the evidence for preventive interventions of dementia/AD was inadequate, with an exception of adequate evidence for anti-hypertensive medications [53–55]. It is plausible that observed associations from epidemiological studies do not necessarily imply that risk factors can be modified to alter dementia risk. However, inconsistent findings from intervention studies may have also resulted from several methodological issues: a) short intervention durations/follow-up periods may have prevented the observation of time-lagged intervention effects on cognition; b) late intervention timing (after the “window of opportunity” during which interventions have the highest potential for effectiveness); c) small sample sizes (insufficient power); d) considerable diversity in dosages/compounds of nutritional supplements used; e) use of unimodal interventions (e.g. diet or exercise) that are based on unimodal hypotheses, which are unlikely to adequately target the multiple interacting risk factors for multifactorial conditions; and f) the definition of outcome variables, which differs between studies—some studies measured dementia or AD incidence, others measured cognitive performance or decline, rendering comparisons difficult [56–58]. These aforementioned methodological shortcomings may explain the discrepancy in findings and guide in improving future intervention trials.

Several steps have been recently taken in this direction, with expert groups and regulatory authorities, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), providing a new framework for how drugs can be studied in RCTs on early AD. This includes: the development of new diagnostic criteria, which facilitates the identification of the early stages of AD and more homogeneous groups of patients [59–61]; the use of biomarkers, either as enrichment strategies or supportive of a disease-modifying effect [62–64]; and the definition of new trial designs, robust analytical methods, and reliable indicators of clinical efficacy (for a review see [65]). These innovative approaches to RCT design are expected to strengthen the quality of future RCT findings.

### **Ongoing multidomain prevention trials**

Using the cumulative evidence from epidemiological studies, a few research groups have recently taken the aforementioned limitations into account and shifted to conducting multidomain lifestyle RCTs that simultaneously target several modifiable risk factors in order to prevent cognitive impairment and dementia/AD [56]. Currently, there are three ongoing large multidomain



**Table 2. Characteristics of selected RCTs for prevention of cognitive impairment, dementia and Alzheimer's disease based on multidomain interventions (Table adapted from [5])**

RCT	FINGER	MAPT	PreDIVA
Sample size	1260 community dwellers, from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers
Main inclusion criteria	CAIDE Dementia Risk Score >6 and cognition at mean level/slightly lower than expected for age (CERAD test battery)	Frail elderly people, subjective memory complaint, slow walking speed, limitation in IADL (MMSE≥24)	All elderly within GP practices, non demented (MMSE >23)
Age at enrolment	60–77 yrs	≥70 yrs	70–78 yrs
Study design	Multi-center, randomized, parallel-group controlled trial	Multi-center, randomized, controlled trial	Multi-center, cluster-randomized, parallel group controlled trial
Intervention	Multi-domain: nutritional guidance, physical activity, cognitive training, increased social activity and intensive monitoring and management of metabolic and vascular risk factors	Multi-domain: vascular care, nutritional advice, exercise advice, cognitive training, and/or DHA 800 mg/day	Multi-domain: nurse-led vascular care including medical treatment of risk factors, nutritional advice, exercise advice
Duration	2 yrs + 5 yrs extended follow-up	3 yrs + 2 yrs extended follow-up	6 yrs
Outcomes	Primary: change in cognitive function (neuropsychological test battery, Trail Making, Stroop), Secondary: dementia, cardiovascular events, depression, disability, quality of life, health resources utilisation, AD biomarkers change	Primary: change in cognitive function (Grober and Buschke memory test) Secondary: cognition (MMSE, CDR), functional status, depression, health resources utilisation, AD biomarkers change	Primary: dementia, disability Secondary: cognitive decline (MMSE, VAT), depression, cardiovascular events
Status	Intervention was completed in March 2014	Intervention was completed in March 2014	Ongoing, will be completed in 2015

CDR, clinical dementia rating scale; DHA, docosahexaenoic acid; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; GP, general practitioner; IADL, instrumental activities of daily living; MAPT, Multidomain Alzheimer Prevention Study; PreDIVA, Prevention of Dementia by Intensive Vascular Care; VAT, visual association test.

RCTs in Europe: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Multidomain Alzheimer Prevention Trial (MAPT), and the Prevention of Dementia by Intensive Vascular Care (PreDIVA) study (Table 2) [66–69].

FINGER (ClinicalTrials.gov NCT01041989) is a 2-year multicenter RCT aiming to prevent cognitive impairment, dementia and disability in a sample of 1260 community dwelling at-risk older adults (aged 60–77 years), selected according to the CAIDE Dementia Risk Score and the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological test battery [40,70]. Participants were randomly selected from population-based, non-intervention surveys, which provide extensive retrospective information [71]. The multidomain intervention involved nutritional guidance, exercise, cognitive training, social activity, and intensive monitoring/management of metabolic/vascular risk factors (impaired glucose tolerance, obesity, hypertension, and hypercholesterolemia). Participants in the control group received regular health advice. The primary outcome was cognitive performance measured by a comprehensive Neuropsychological Test Battery (NTB) after 2 years [66]. The 2-year intervention was recently finalized (spring 2014). Participants reported positive intervention

experiences, showed high adherence rates and a low dropout rate (11%), demonstrating the feasibility of this type of intervention. After the 2-year program, a significant beneficial intervention effect was seen on global cognition: improvement in NTB total score (pre-specified primary outcome) during 24 months was 25% higher in the intervention than the control group, indicating the possibility of improving/maintaining cognitive functions in older individuals at risk of dementia [72]. Furthermore, the risk for cognitive impairment was 31% higher in the control group compared to the intervention group. To determine the intervention effect on dementia and AD incidence, a 7-year extended follow-up of the study participants started in 2015.

MAPT (ClinicalTrials.gov NCT00672685) is a French, multicenter 3-year RCT, in which 1680 older adults (age ≥70 years) were recruited using a frailty definition that includes three components: memory complaints, limitation in one instrumental activity of daily living, and slow walking speed. Enrolled participants were randomized to four groups: omega-3 supplementation; multidomain intervention; omega-3 plus multidomain intervention; or placebo. The multidomain intervention involved group sessions (cognitive training, nutrition and exercise advice) and personalized consultations to identify and

manage risk factors for dementia and frailty. The study aims to investigate the intervention effects on cognitive changes after 3 years using the Grobe and Buschke Test (memory recall) [68–69]. The 3-year intervention was completed in March 2014, and 5-year extended follow-up will be completed in 2016.

PreDIVA (Controlled-Trials.com ISRCTN29711771) is a cluster-randomized RCT among 3533 Dutch older adults (aged 70–78 years). Participants were recruited from primary care settings, with a follow-up duration of 6 years. The study aims to investigate the effects of nurse-led intensive vascular care on dementia incidence and disability. Intensive vascular care includes consultations with a study nurse and tailored interventions for medical risk factors (diabetes, hypertension, hypercholesterolemia) and lifestyle-related risk factors (diet, body weight, exercise, smoking habits). The control group receives standard care according to Dutch general practice [67].

Considering the similarities between the three aforementioned trials (FINGER, MAPT, and PreDIVA), the trial leaders recently established the European Dementia Prevention Initiative (EDPI) network to promote international collaborations and share/harmonize data analyses [73]. Collectively, the joint analyses within EDPI will demonstrate the extent to which dementia/AD can be prevented by multidomain interventions and the most effective strategies. The EDPI recently launched a collaborative multidomain RCT Healthy Aging Through Internet Counseling in the Elderly (HATICE) to prevent dementia and cardiovascular diseases among 4250 at-risk older adults, recruited in three European countries (Finland, France, and the Netherlands) [74]. Through a user-friendly Internet platform, HATICE participants consult with a coach who offers comprehensive tailored advice to manage vascular and lifestyle risk factors. More recently, EDPI members and other researchers launched the Multimodal Preventive Trials for AD (MIND-AD) project, funded by the Joint Programme - Neurodegenerative Disease Research (JPND) initiative. The MIND-AD project aims to develop effective AD/dementia prevention strategies while harmonizing and optimizing methodologies for multinational and multimodal prevention RCTs across the entire spectrum of AD (that is, from asymptomatic at-risk subjects to early-symptomatic stages of Alzheimer dementia) [75]. This project will build upon experiences and data from all the above-mentioned prevention studies, and it will also investigate for the first time whether a multidomain prevention trial is effective for the prodromal (early stages) of AD through a proof-of-concept multinational pilot trial. If successful, the multimodal intervention strategy can be easily

adapted for different healthcare systems and can thus facilitate the implementation of preventive measures.

### Ongoing trials with potential disease-modifying drugs

Since A $\beta$  is believed to have a key role in AD pathogenesis, many RCTs have tested drugs targeting this protein in subjects with dementia due to AD, with negative findings thus far [65–76–77]. As previously suggested, this may have resulted from starting treatments too late in the disease process among subjects with overt dementia, while a beneficial effect might be achieved if treatments are administered in earlier, asymptomatic (or preclinical) stages of AD [58–78–79]. In order to test this hypothesis, recent prevention trials are focusing on asymptomatic individuals who are at risk of developing dementia/AD, either due to genetic causal factors (carriers of autosomal-dominant mutations: *PSEN1*, *PSEN2*, or *APP*) or brain A $\beta$  accumulation. Currently, there are three ongoing prevention trials that test the safety and efficacy of potential disease-modifying anti-amyloid drugs: the Alzheimer's Prevention Initiative - Autosomal Dominant Alzheimer's Disease treatment trial (API-ADAD), the Dominantly Inherited Alzheimer's Network (DIAN) and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (ADCS-A4) (Table 3). All trials include extensive cognitive assessments, neuroimaging and biomarker measures to track AD onset/progression. These ongoing initiatives are separate, but also interconnected. The Collaboration for Alzheimer's Prevention (CAP) is a consortium including, among others, researchers leading these RCTs, and aims to optimize methodologies, harmonize data collection, and plan future trials based on these aforementioned studies [80]. CAP also provides feedback to regulatory bodies (FDA and EMA) that is used to refine rules supporting preventive RCTs in AD [81]

API-ADAD (ClinicalTrials.gov NCT01998841) is a potentially label-enabling trial testing the anti-amyloid compound crenezumab (Genentech) in 300 asymptomatic members of an extended large family in Colombia with the *PSEN1* E280A mutation, for which the median onset age of mild cognitive impairment (MCI) is 44 years and the onset of dementia is 49 years [82,83]. The goal of the study is to assess whether administration of crenezumab in the preclinical stage can delay or prevent the onset of symptomatic AD. Using a randomized, double-blind, placebo-controlled, parallel group design, participants who are mutation carriers will be randomized to receive crenezumab or placebo. For comparisons with non-carriers of *PSEN1*, the trial will include a cohort of non-carriers who will only receive placebo. The API trial is also due to launch another preventive study in

**Table 3. Characteristics of selected pharmacological RCTs for prevention of Alzheimer's disease using compounds targeting beta-amyloid (Table adapted from [5])**

RCT	Prevention trials based on a genetic risk or an amyloid-beta biomarker risk <b>API</b>	<b>DIAN</b>	<b>ADCS-A4</b>
Sample size	300 members of Colombian families (Antioquia) with early-onset AD. Subjects with no cognitive impairment. A small number of individuals from USA (collaboration with the DIAN network) will also be included	210 members of families with early-onset AD. Subjects can be asymptomatic or have very mild memory and thinking problems including mild dementia	1150 older adults with no cognitive impairment
Main inclusion criteria	Carriers of a mutated <i>PSEN1</i> gene. Non-carriers will also be included, to ensure double-blinding about the genetic status	Carriers (n=105) of mutation in <i>PSEN1</i> , or <i>PSEN2</i> , or <i>APP</i> . Non-carriers (n=105) will also be included, to ensure double-blinding about the genetic status	Evidence of brain amyloid accumulation (PET). Subjects with no evidence of amyloid burden will also be included
Age at enrolment	30-60 yrs	18-80 yrs	65-85 yrs
Study design	Phase II randomized, double blind, placebo controlled trial	Phase II/III randomized, double blind, placebo controlled trial	Phase III randomized, double blind, placebo controlled trial
Intervention	Anti-amyloid monoclonal antibody: Crenezumab (Genentech)	Two anti-amyloid therapies: the anti-amyloid monoclonal antibodies Gantenerumab (La Roche) and Solanezumab (Eli Lilly)	Anti-amyloid monoclonal antibody: Solanezumab (Eli Lilly)
Duration	5 yrs (interim analysis at 2 yrs)	2 yrs + 3 yrs extension	3 yrs + 2 yrs extension
Outcomes	Primary: cognitive function Secondary: AD biomarkers change, including brain amyloid load and brain atrophy	Initial phase (2 yrs): AD biomarkers change, including brain and CSF amyloid, to identify the most promising drug candidate Follow-up phase (3 yrs): cognitive function	Primary: cognitive function Secondary: AD biomarkers change
Status	Started in 2013	Started in 2012	Started in 2014

ADCS-A4, Anti-Amyloid Treatment of Asymptomatic Alzheimer's disease; API, Alzheimer's Prevention Initiative; APOE, apolipoprotein E; APP, amyloid precursor protein; DIAN, Dominantly Inherited Alzheimer Network; PET, positron emission tomography; *PSEN1*, presenilin 1; *PSEN2*, presenilin 1.

2015 (API APOE trial) in which two anti-amyloid drugs (a vaccine and a beta-secretase1 inhibitor) will be tested in cognitively normal subjects who are homozygous APOE  $\epsilon$ 4 carriers and aged 60 to 75 years [84].

DIAN (ClinicalTrials.gov NCT01760005) is an observational study funded by the American National Institute on Aging to develop an international multicenter registry of symptomatic and asymptomatic individuals with genetic mutations for autosomal-dominant AD (*PSEN1*, *PSEN2*, *APP*) [85–86]. Their non-carrier family members are also recruited as controls with similar genetics. The target sample is 400 individuals, and 13 international research institutes are currently involved in the study. The DIAN Trials Unit (DIAN-TU) was recently established to test two anti-amyloid drugs (Solanezumab [Eli Lilly and Company] and Gantenerumab [Hoffmann-La Roche]) among mutation carriers at risk of AD, including 210 asymptomatic or mild symptomatic subjects [87]. Mutation non-carriers are also recruited (placebo arms). The primary outcomes in the DIAN-TU RCT are changes in biomarkers after 2 years. After this period, the agent(s) showing beneficial biomarker effects will be further tested in larger trials with cognitive outcomes.

The ADCS-A4 study (ClinicalTrials.gov NCT02008357) [88] is a placebo-controlled, potential label-enabling

RCT conducted in 1150 asymptomatic individuals (aged 65–85 years) who show brain A $\beta$  accumulation (on positron emission tomography [PET] imaging scans) and are thus considered at risk of AD [80]. The goal is to assess whether administration of anti-amyloid therapy prior to symptoms onset prevents dementia. In this first A4 trial, participants will be randomized to receive solanezumab or placebo, and alternative drugs may be used in future A4 trials. The study will also investigate the impact of disclosing to participants their amyloid status by including psychological assessments and measures of adverse reactions to amyloid status disclosure. Participants without high A $\beta$  levels at initial screening will serve as a comparison group by participating in an observational arm of the A4 study.

Other RCTs among asymptomatic individuals include: the PREVENT Alzheimer Program launched by the Centre for Studies on Prevention of AD (StoP-AD) at the Douglas Mental Health University Institute (Montreal, Canada), which will test preventive interventions (naproxen, nasal insulin or others) in older adults with a family history of AD [89]; and the TOMORROW trial (ClinicalTrials.gov NCT01931566), a multicenter label-enabling trial that tests whether a potential disease-modifying drug (Pioglitazone [Takeda]) can postpone the onset of MCI due to AD, and whether a

genetic-based (using APOE4 and TOMM40) biomarker risk algorithm predicts risk of MCI due to AD. Collectively, the trials will demonstrate whether preventive treatments at the early asymptomatic (or mild symptomatic) stage are effective, and whether alternative drug targets are required.

### Future directions

Due to the worldwide aging population, dementia/AD occurrence will continue to rise. Prevention has been highlighted as one of the key elements in managing the dementia epidemic, in a similar manner to what has been proposed for other major non-communicable diseases. Merely delaying the onset of AD/dementia will considerably alleviate social and economic burdens. Lifestyle-related interventions provide hope to prevent or postpone dementia/AD in the general population. Many experts agree that sufficient evidence is already available to justify immediate action, including prevention/management of vascular and lifestyle-related risk factors (smoking, hypertension, obesity, diabetes mellitus and physical inactivity) [90]. This is particularly important considering the trend towards increased prevalence of diabetes mellitus and obesity, which will impact future dementia/AD prevalence, while reinforcing the need to prevent these risk factors [91–94]. Similar to earlier discoveries that lifestyle-related interventions can protect against cardiovascular diseases, recent evidence confirms the adage “what is good for the heart, is good for the brain”. However, more RCTs are required to refine the knowledge on specific factors that optimize various prevention domains, such as nutrition or exercise. There is also a knowledge gap regarding the window of opportunity for some pharmacological interventions that so far have not been effective in terms of preventing dementia (e.g. statins and hormone replacement therapy) [95–96]. Further evidence is also needed on the underlying mechanisms that reduce dementia risk in prevention trials.

Evidence from the FINGER multimodal prevention trial supports the feasibility and effectiveness of this intervention approach, and the other EDPI trials will provide further insight. These trials will also identify whether barriers to adherence need to be addressed, whether subgroups are most responsive to interventions, and whether windows of opportunity exist for the different intervention types. Such acquired findings will further improve the methods of future trials. Multimodal lifestyle-related preventive strategies have additional benefits as they are not specific to reducing dementia risk; they also prevent chronic conditions including cardiovascular diseases, diabetes and cancer [97]. Translation of these findings will lead to the implementation

of cost-effective interventions at a population level, while tailoring interventions for various sub-populations.

Pharmacological trials were previously conducted in advanced AD stages, showing relatively poor results. The ongoing trials in at-risk subjects will determine whether administering potentially disease-modifying treatments prior to symptoms onset is effective. If findings from the trials are positive, the next task will be to assess whether a similar approach can be adapted for patients at risk for Alzheimer dementia in the general population. It is currently unclear whether interventions and findings from preclinical studies on early-onset AD are generalizable to preclinical stages of late-onset AD, which are more heterogeneous. The two groups of aforementioned trials represent two extremes of the prevention continuum; lifestyle-related prevention trials target large-scale populations with common risk factors, while drug trials focus on highly specific groups with rare genetic mutations or brain A $\beta$  accumulation. Both prevention approaches have benefits for various target populations, however, it will be important for future trials to narrow this gap by combining both approaches and adapting them for various target groups.

It was recently suggested that alternative targeted and adaptive trial designs (which have been used for cancer) might be more effective for complex and heterogeneous diseases such as AD [98]. More optimal designs would test the effects of treatments in heterogeneous samples while simultaneously improving and tailoring the trials for sub-populations as novel biomarkers are identified and validated [98]. Future trials will also benefit from including more enrichment cohorts as well as multitarget therapies, beyond anti-amyloid treatments, with increased collaborations among pharmaceutical companies (“multicompany trials”), as carried out by the DIAN-TU trial [58,99]. It will also be important to establish academic-industrial partnerships such as those developed within the Innovative Medicine Initiative - European Prevention of AD Consortium (IMI-EPAD), the largest public-private partnership in health sciences in Europe [100].

Future successful prevention efforts will require large-scale multinational collaborations. Similar to EDPI and CAP, international umbrella organizations can serve as a model to maximize power and harmonize data collection and analyses among trials. Such initiatives will optimize the use of existing infrastructure, prevent redundant investigations and errors while rapidly improving methodologies and translating findings to clinical practice and the general population in order to successfully prevent dementia/AD.



## Abbreviations

AD, Alzheimer's disease; ADCS-A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease; API, Alzheimer's Prevention Initiative; APOE, apolipoprotein E; APP, amyloid precursor protein; A $\beta$ , beta amyloid; CAIDE, Cardiovascular Risk Factors, Aging and Dementia study; CAP, Collaboration for Alzheimer's Prevention; DIAN, Dominantly Inherited Alzheimer's Network; DIAN-TU, Dominantly Inherited Alzheimer's Network - Trials Unit; EDPI, European Dementia Prevention Initiative; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; HATICE, Healthy Aging Through Internet Counseling in the Elderly; HIV, human immunodeficiency virus; MAPT, Multidomain Alzheimer Preventive Trial; MCI, mild cognitive impairment; MIND-AD, Multimodal Preventive Trials for Alzheimer's Disease; NTB, neuropsychological test battery; PreDIVA, Prevention of Dementia by Intensive Vascular Care; *PSEN1*, presenilin 1; *PSEN2*, presenilin 2; RCT, randomized controlled trial.

## Disclosures

Miia Kivipelto has served on scientific advisory boards for Pfizer Inc., Elan Corporation, Alzheon and Nutricia and received speaker honoraria from Janssen, Novartis, Pfizer Inc., and Merz.

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