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Advances in the prevention of Alzheimer's disease and dementia

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Abstract

Definitions and diagnostic criteria for all medical conditions are regularly subjected to reviews and revisions as knowledge advances. In the field of Alzheimer's disease (AD) research, it has taken almost three decades for diagnostic nomenclature to undergo major re-examination. The shift towards presymptomatic and pre-dementia stages of AD has brought prevention and treatment trials much closer to each other than before. Here we discuss: (i) the impact of diagnostic reliability on the possibilities for developing preventive strategies for AD; (ii) the scientific evidence to support moving from observation to action; (iii) ongoing intervention studies; and (iv) the methodological issues and prospects for balancing strategies for high-risk individuals with those for broad population-based prevention. The associations between neuropathology and cognition are still not entirely clear. In addition, the risk factors for AD dementia and the neuropathological hallmarks of AD may not necessarily be the same. Cognitive impairment has a clearer clinical significance and should therefore remain the main focus of prevention. Risk/protective factors for dementia/AD need to be studied from a life-course perspective. New approaches in prevention trials include enrichment strategies based on genetic risk factors or beta-amyloid biomarkers (at least four ongoing pharmacological trials), and multidomain interventions simultaneously targeting various vascular and lifestyle-related risk factors (at least three ongoing

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trials). Experience from prevention programmes in other chronic diseases can provide additional methodological improvements. Building infrastructures for international collaborations is necessary for managing the worldwide public health problem of AD and dementia. The International Database on Aging and Dementia (IDAD) and the European Dementia Prevention Initiative (EDPI) are examples of ongoing international efforts aiming to improve the methodology of preventive studies and provide the basis for larger intervention trials.

Keywords

Alzheimer's disease; biomarkers; clinical trials; dementia; prevention

Introduction

The field of Alzheimer's disease (AD) research has advanced to where it is no longer necessary to justify the importance of prevention as the main therapeutic goal. After nearly two decades of research aimed at AD prevention, there is an abundance ofstudies in support of a number of proposed risk and protective factors [1] (Table 1). The present review was written in response to the evolving changes in the diagnosis and nomenclature of AD. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) was published in May 2013, and the International Classification of Diseases, 11th revision (ICD-11) is expected in 2015. In addition, two new sets of criteria, formulated by an international workgroup and a National Institute of Aging-Alzheimer Association sponsored group, have been proposed and used in AD clinical research [2–6].

Definitions and diagnostic criteria for all medical conditions are regularly subjected to reviews and revisions as new important advances in diagnostic procedures are established. In the field of AD research, it has taken almost three decades for AD nomenclature to undergo a major revision, and several aspects are still under consideration. How much has this interval of 30 years affected prevention research? How will updates in clinical and research criteria influence future prevention studies? And finally, in spite of diagnostic challenges, have we been able to identify any relevant preventive measures? These questions are particularly important considering that diagnostic lexicons mainly have a clinical relevance (i.e. diagnosing individuals for initiating appropriate treatment), whereas the ultimate relevance of prevention is at the population level.

In this review, we will discuss the major impact of diagnostic reliability on the possibility of identifying preventive strategies. We will also review the scientific evidence to support moving from observation to action, and the ongoing intervention studies. We will focus on methodological issues, as well as future perspectives to better balance the individual-based (or high-risk) strategies with population-wide strategies of prevention.

What are we trying to prevent?

A general summary of how research questions about prevention have been addressed so far can be illustrated by a simple PubMed search (Fig. 1). Two main trends have dominated prevention research so far: first, most studies have focused on preventing dementia, the most

severe stage of late-life cognitive impairment, rather than on preventing milder, more common forms of cognitive impairment; secondly, AD dominates dementia prevention research, with less attention given to preventing cognitive impairment of mixed or non-Alzheimer's causes [7]. Such trends are direct consequences of how the criteria for AD were formulated three decades ago: (i) no specific diagnosis is available until the dementia stage; (ii) the diagnosis must be established in two steps, first the dementia syndrome, then the underlying disease; (iii) the dementia syndrome relies heavily on memory impairment, the main feature of AD; and (iv) AD is a diagnosis of exclusion, established when dementia is not due to other brain pathologies. Current updated proposals of new diagnostic criteria address these issues by including diagnoses for milder forms of cognitive impairment, atypical clinical presentations (i.e. language, visuospatial or other non-memory impairments) and criteria related to biomarkers [2–6]. In DSM-5 'dementia' is replaced by 'major neurocognitive disorder', and less severe cognitive impairment is diagnosed as 'mild neurocognitive disorder'; memory impairment is no longer the main focus of these diagnostic criteria [8]. At present, the epidemiology (incidence, prevalence, and risk factors) of these conditions is largely unknown.

Particularly relevant in the context of research addressing prevention is how differently 'disease' is conceptualized in the recently proposed diagnostic criteria: does AD start with the onset of specific pathological changes in the brain [4–6], or does it start with the first appearance of specific clinical symptoms [2, 3, 8]? In other research fields such as cancer, the pathological changes usually define the disease onset. In the dementia field this traditional definition is debatable given that many elderly individuals die with intact cognition but a sufficient number of AD-related pathological signs in their brain to be classified as AD cases [9, 10]. Compared to other factors, age has the strongest effect on the risk of late-life cognitive impairment, and it is not clear whether age-related and pathology-related brain changes are distinct processes [11]. Proper understanding of the biological profile of brain ageing and AD can help to answer a crucial question: should we focus mainly on preventing brain changes, or should we remain focused on preventing cognitive impairment?.

Clinical relevance is the priority—Because clinically manifest dysfunctions are ultimately relevant for the individual, and our current ability to identify specific brain changes at the population level is limited, it seems to be more relevant to focus on preventing cognitive impairment than preventing brain changes that may or may not constitute AD. The intense debate concerning clinical versus neuropathological disease definitions testifies to the fact that the relationships between clinical syndromes, neuropathology and biomarkers are still rather poorly understood.

Despite recent updates, AD remains a diagnosis of exclusion in all proposed criteria. The only exception is AD due to known genetic causes, i.e. mutations in *APP*, *PSEN1* and *PSEN2* genes. These are rare, inherited forms of AD, and they are so specific and different from sporadic AD that they may represent another disease altogether. The great majority of sporadic AD cases are clinically and neuropathologically heterogeneous, which makes it difficult to exclude with certainty the contributions of non-AD pathologies. Too strict exclusions can be counterproductive for prevention strategies at the population level, where

the ultimate goal is to avoid or postpone significant cognitive impairment. This also means that prevention should target not only memory impairment, but impairment in other cognitive domains as well. The most common cognitive impairments in old age probably have mixed aetiologies, and different pathologies (e.g. AD and cerebrovascular disease) also share several risk factors (Table 1), suggesting that combined, multidomain preventive interventions targeting several risk factors simultaneously have the highest likelihood of being effective.

Proposed research criteria for AD acknowledge to a greater extent the 'atypical', non-memory features of the 'clinical Alzheimer syndrome'. Mild and major neurocognitive disorders according to the DSM-5 no longer focus on memory as the compulsory central domain of cognitive impairment, in contrast to the criteria for dementia in the current ICD-10 and previous DSM-IV guidelines. DSM-5 also better emphasizes the role of mixed brain pathologies in cognitive impairment (mild or major neurocognitive disorder due to multiple aetiologies). Major neurocognitive disorder is thus not the exact equivalent of dementia, and mild neurocognitive disorder can potentially include both mild cognitive impairment (MCI) [8], and vascular cognitive impairment [12]. Each of these diagnoses will comprise more heterogeneous groups of patients, and epidemiological research is needed to identify which pathologies are captured by minor (or mild) and major neurocognitive disorders, and their risk factors and prognoses.

The clinical relevance of brain changes—Pathologically, AD is characterized by the deposition of amyloid and accumulation of tangles in neocortical regions of the brain [13]; these processes start decades prior to dementia onset [6, 14]. AD-type brain changes are often found in peoplewith milder cognitive dysfunction, or even without any cognitive symptoms at all [10, 15]. It is clear from clinicopathological studies that not all those with AD-type brain changes will develop overt cognitive impairment. Also, little is known about the time course from the accumulation of these brain changes until the onset of clinical manifestations. Robust evidence requires longitudinal 'pathological' and cognitive data and it is only recently that selected aspects of AD pathology have been detected *in vivo* over time [16]. Such studies have so far mainly confirmed post-mortem data.

The ability of the brain to tolerate or respond to structural changes is known to differ among individuals, and this neural or cognitive reserve [17, 18] can explain why pathological changes can accumulate for a long time without any clinical signs or symptoms [19–23]. In addition, as AD is typically a condition of old age, it is frequently accompanied by other common late-life pathologies, especially cerebrovascular disease (CVD) and Lewy body pathology. Such concurrent pathologies can together lower the threshold for clinical manifestations, making it more likely that an individual will develop cognitive impairment, which will then be clinically diagnosed as AD [24–26].

It is not yet clear to what extent risk factors for clinically diagnosed AD increase the risk of developing the neuropathological hallmarks of AD, or the risk of comorbid conditions contributing to the onset and progression of cognitive impairment. For example, vascular risk factors have been related to the development of 'clinical Alzheimer syndrome', but in clinical-pathological studies they are not consistently associated with AD pathology [27].

Some studies have demonstrated that vascular factors are related to cerebrovascular but not AD changes, while others show conflicting results regarding the type of brain change with which vascular factors are associated. Additionally there is a wide variety of factors that are related to clinical AD without any direct association with pathology, such as education, linguistic ability, cognitive activities, aspects of personality, loneliness, social networks and purpose in life [28–35]. Such factors can also be targets for preventive interventions to reduce the risk of clinical AD through mechanisms that remain unclear.

In summary, it should never be assumed in prevention studies that a risk factor for AD syndrome is automatically a risk factor for amyloid deposition or neurofibrillary tangles. Neither should it be assumed that successful prevention of AD pathology will automatically result in fewer dementia cases as estimated based on the number of persons with clinical AD.

Levels of prevention—Discussions concerning disease definitions have also raised questions about how prevention levels can be defined. The overall goal of primary prevention is to reduce the incidence of disease, by intervening before disease onset through promoting the initiation and maintenance of good health or eliminating potential causes of disease. The goal of secondary prevention is to prevent a disease at very early or preclinical phases from progressing to more overt, manifest disease. Tertiary prevention focuses on managing manifest disease and its complications, and maximizing quality of life. Fig. 2 illustrates how the two alternative definitions of AD onset (disease starting with neuropathological changes, and disease starting with clinical symptoms) lead to different definitions of primary, secondary and tertiary prevention in AD. The different definitions also reduce the separation between prevention and treatment strategies.

This theoretical ‘hair-splitting’ is less relevant if prevention on any level is effective in practice. However, it can eliminate some of the confusion in interpreting epidemiological studies, and facilitate the finding of effective means of prevention. Risk factors for AD-related neuropathological changes are not necessarily the same as risk factors for milder cognitive impairment, or risk factors for dementia. Confusion typically arises in epidemiological studies conducted in older populations, which are a mixture of healthy individuals, those who have ‘silent’ brain changes and those with detected or undetected cognitive impairment of varying severity. Has a specific study really identified risk factors for AD, or just risk factors for dementia? Are these also risk factors for milder cognitive impairment, or for a more accelerated decline from mild impairment to severe dementia? There is no simple answer to such questions, but epidemiological findings are easier to interpret if the choice of the conceptual framework for AD (neuropathological or clinical) is clearly specified, and primary, secondary or tertiary prevention are adequately discussed within the chosen framework.

The search for ‘sufficient evidence’

A large number of risk and protective factors for dementia and AD have been investigated (Table 1). The amount and quality of available evidence varies considerably between these factors. Further, opinions are divided on what should constitute ‘sufficient evidence’ for

prevention recommendations [36]. Randomized controlled trials (RCTs) are usually considered to provide the best evidence that an intervention has clinically meaningful effects. However, conducting traditional RCTs is not always possible. Vascular risk factors cannot be left untreated in the placebo group, and strict double-blinding may not be possible with lifestyle-related interventions. It would also be counterproductive to wait for successful RCTs before implementing every prevention strategy. The relation between smoking and lung cancer is a classic example of observational studies providing enough evidence for prevention.

Since 1965, the nine considerations proposed by Bradford Hill [37] for distinguishing between association and causation have had a major influence on epidemiological thinking. However, there is currently no general agreement on a set of causal criteria in epidemiology, or on how to apply such criteria [38]. There is no generally accepted definition of 'cause', and several conceptual models of disease causation have been developed, each with its own limitations [38]. Bradford Hill avoided an explicit definition of causation, emphasizing instead that in prevention 'the decisive question is where the frequency of the undesirable event B will be influenced by a change in the environmental feature A' [37]. In other words, we need to decide whether intervening to change a modifiable factor (i.e. vascular, metabolic or lifestyle-related) can lead to a reduction in the incidence of AD/cognitive impairment/dementia. From this it also follows that the most appropriate type of intervention(s), timing and target group(s) need to be determined.

Observational studies—The nine considerations were formulated by Bradford Hill in the early years of non-communicable disease epidemiology, when the main challenge was to identify relatively simple and direct-acting causal factors [39]. Because AD and cognitive impairment are multifactorial conditions with a high degree of complexity, it is less appropriate to seek a discrete cause(s) in epidemiological studies, and more appropriate to focus on identifying interrelated and often interacting risk and protective factors for AD/cognitive impairment. Some attempts to apply Bradford Hill's considerations to AD epidemiological research have already been reported [40, 41]. Several issues are important when using these guidelinesin AD prevention studies.

Strength of association: A stronger association is more likely to indicate causation. However, compared to the 20-fold increase in lung cancer risk in smokers versus non-smokers, cited by Bradford Hill in 1965 [37], associations commonly found in contemporary epidemiology are relatively weak [39]. AD prevention studies are no exception. Dementia and AD share several risk factors with cardiovascular and other chronic diseases, and individuals with the highest levels of risk factors may not even survive to older ages when their dementia risk can be studied. Because of competing risks and selective mortality, it is difficult to assess what a 'strong' association should be in AD prevention. In a multifactorial disease, each factor can only explain a small part of the association. Even for the ε4 allele of the apolipoprotein E gene (*APOE*), one of the strongest risk factors for AD, the risk increase is usually about 3- to 4-fold compared to the *APOE* ε3 allele (according to a meta-analysis in AlzGene; www.alzgene.org).

Also, conditions in the population can change dramatically during the course of long-term observational studies. Societal changes occurred during the 20th century in areas such as perinatal care, education, work and retirement conditions, urbanization, housing and hygiene, dietary habits, healthcare and survival. Different birth cohorts are expected to present some differences regarding factors related to dementia/AD. The prevalence of cardiovascular risk factors such as smoking, hypertension and hypercholesterolaemia has decreased, while overweight and diabetes have become more common among middle-aged and older populations between the 1960s and 2000s [42–44]. Interestingly, recent studies indicate that the incidence of dementia might be declining [45, 46], although this needs to be confirmed. Further epidemiological studies are necessary to investigate risk factors for dementia/AD in new generations of older persons. The strength of some associations may change, but even a small effect on a very common risk factor can have an important effect at the population level.

Consistency: A causal explanation is more likely if an association is observed 'by different persons, in different places, circumstances and times' [37]. Unfortunately, one consistent feature of AD prevention research is the use of many different definitions for exposures and outcomes, which makes direct comparisons between studies difficult. There is still a need for (i) more precise, standardized and better validated exposure measures, (ii) more standardized cognitive and functional assessment measures and (iii) more standardized reporting of methods and results [36].

In complex causal mechanisms, several factors may be needed simultaneously to produce an effect. Lack of consistency can indicate that something has been overlooked. Many studies do not investigate gene–environment interactions. In addition, not all potential components of a causal mechanism are considered in all studies. Further, inconsistent results can also be related to the timing of exposure measurement in relation to disease onset (see fourth issue, Temporality, below).

Specificity: The specificity criterion is based on two assumptions: first, a causal factor can only produce a single effect and, secondly, an effect can only have one cause. Neither of these can apply to multifactorial complex diseases such as AD. The presence of AD neuropathology does not necessarily translate into a typical clinically diagnosed AD, and a clinically diagnosed AD is not caused exclusively by AD neuropathology. Many risk and protective factors are related to both dementia/AD and other chronic non-communicable diseases. AD prevention research has benefited enormously from combining efforts with other prevention fields, and taking into account shared risk/protective factors and mechanisms. To date, all long-term, midlife to latelife observational studies focusing on dementia/AD have used cohorts previously enrolled in cardiovascular prevention studies. At the same time, AD as an outcome has enough specific characteristics to warn against copy-pasting criteria from other prevention fields to define 'sufficient evidence for successful prevention'.

Temporality: That exposure must precede the outcome is a necessary, non-arguable criterion. Establishing temporality is one of the most important sources of problems in Alzheimer prevention research, because disease onset (either onset of neuropathology or

onset of cognitive symptoms) is difficult to identify. Most epidemiological studies are conducted in older populations with shorter follow-up times, and there are few large prospective long-term studies starting in midlife or at younger ages when cognitive impairment is less likely to be present already. The effects of midlife risk factors are not necessarily observed at older ages, and findings from late-life studies can even be the mirror image of those from midlife studies (i.e. hypertension, hypercholesterolaemia or obesity in midlife are risk factors for AD/dementia, but at older ages they can appear to 'protect' against AD/dementia) [47, 48]. In recent years, several studies have demonstrated a pattern of more pronounced decline over time in blood pressure, total cholesterol and body mass index (BMI) prior to the development of AD/dementia [48]. This pattern cannot be entirely explained by use of medication or intentional lifestyle changes. Reverse causality is a possible explanation, i.e. a midlife factor increases AD risk, but once the disease starts it affects the same factor that has contributed to it [48, 49].

Another example of the importance of temporality comes from the findings of observational studies of medication effects on AD risk. What appears to be bad in the short-term may be beneficial in the long-term. The results of the Cache County study indicated that hormone-replacement therapy (HRT) (any type) increased AD risk in current users who had been taking HRT for 0–10 years (i.e. a short time before disease onset), but those who had a longer exposure and former users with more than 3 years exposure had a decreased risk of dementia. Lack of effect in the years before dementia onset has also been suggested for non-steroidal anti-inflammatory drugs (NSAIDs). Thus, the timing of potential risk or benefit in relation to disease onset is crucial.

Population-based observational studies starting before midlife are already being planned. A full life-course approach will be implemented for example in the Rhineland Study, a German population-based prospective study on neurodegenerative disorders including 30,000 participants aged ≥30 years [50]. However, studies of older age groups are still needed, especially in those of 85 years and above [51]. Considering the issue of temporality, the concept of 'risk factor' should be used very carefully in such studies. It may be more appropriate to refer to 'risk markers', i.e. factors reflecting the already ongoing disease processes leading to dementia later on.

Biological gradient: Biological gradient refers to an association showing a dose–response relationship. The most clear-cut example is a linear increase in the outcome with increasing exposure dose. However, causal relations do not necessarily have a linear or even a monotonic gradient [38].

The *APOE* ε4 allele is considered a susceptibility gene for AD, and is neither necessary nor sufficient for the development of the disease. The risk of AD increases with increasing number of the ε4 alleles in a dose-dependent manner [3]. U-shaped or J-shaped associations with dementia risk have been described for some factors, such as blood pressure, BMI and alcohol consumption [52]. It is difficult to establish which parts of a U- or J-shaped dose–response curve are causally related to AD/dementia, and which parts merely reflect confounding, reverse causality or other biases. A causal association with AD/dementia could be hypothesized for both extremes of blood pressure (hypo- and hypertension) if temporality

is clearly established. By contrast, the relations between being severely underweight or low/no alcohol consumption and increased dementia risk may be more likely to reflect confounding, reverse causality or other biases.

Plausibility: A causal association needs to be biologically plausible, but this greatly depends on available knowledge at a specific time point. But how much knowledge is needed in order to move from observation to action? Judging an association to be causal must be based on scientific evidence alone, but the decision to act upon a factor associated with AD must also consider the practical consequences of such actions. As Bradford Hill acknowledged, this inevitably leads to the use of different standards for different interventions. More evidence is needed for large-scale prevention trials of, for example, anti-amyloid drugs in asymptomatic, at-risk individuals, than for large-scale prevention trials of lifestyle-related interventions (e.g. physical activity, cognitive training and diet).

Coherence: According to Bradford Hill, a causal association should not fundamentally contradict existing knowledge about disease pathophysiology. It is interesting that the role of vascular factors in AD would not have been recognized during the 1990s if prevention research had avoided contradicting the rigid dichotomy between Alzheimer and vascular dementias. Plausibility and coherence cannot be too strictly imposed.

Analogy: Analogies can at best be useful for formulating hypotheses about associations [38]. A typical example is ‘good for the heart is good for the brain’. However, analogies should not be made at the complete expense of specific characteristics. Adding dementia/AD prevention to the aims of some current cardiovascular prevention strategies is sometimes regarded as redundant. Even dementia prevention studies have highlighted the gap between theory and practice, i.e. many patients fail to meet target levels for risk factors although they receive treatment. Public health and patient education concerning dementia/AD risk in the context of existing vascular prevention strategies could at least narrow this gap.

Experiment: An association is more likely to be causal if it is supported by experimental evidence. Results from experiments in animal models of AD have so far been interpreted exclusively from the perspective of disease treatment, and this field has been separated from prevention research. There are numerous reports of interventions with positive effects on neuropathology and cognitive deficits in transgenic mice [53], but so far none has translated into effective treatments in humans with Alzheimer-related cognitive impairment. This unexpected failure cannot be explained entirely by the inherent differences between rodent and human physiology. Most transgenic mouse models of AD may be more representative of the asymptomatic disease phase than of full-blown dementia [53], and such experimental studies may be better interpreted in the context of AD prevention.

Studies based on animal models of AD use almost exclusively the concept of ‘causal factor’, while ‘risk/protective factor’ is preferentially used in epidemiological research. Behind terminology differences there is a tendency to believe that epidemiological findings can only be suggestive, whereas experimental research on mechanisms in small numbers of selected individuals or in animal models of AD can show cause–effect relations with certainty. However, as causation is not an entity that can be observed and measured in a laboratory or

in a population, even the most carefully controlled laboratory study can only reveal associations between events, although at a greater level of detail and with higher degree of observer control than in epidemiological studies [38]. Yet tight control of the study environment does not automatically exclude errors, and does not automatically guarantee that results (especially from animal models) are applicable to real-life patients with AD.

Experimental Alzheimer research has long been dominated by a simplified concept of causation assuming a one-to-one correspondence between observed cause and effect, i.e. considering each cause as necessary and sufficient in itself to produce the disease. For example, according to the amyloid hypothesis, AD is caused by beta-amyloid deposits (later revised to beta-amyloid oligomers). The tau hypothesis considers instead that tau protein abnormalities initiate the disease process [54]. Results from animal studies are often considered when planning human studies, but not enough attention is paid to results from human studies when designing and interpreting animal models. The heterogeneous and multifactorial nature of AD is widely accepted in prevention research, but combined animal models of AD and other common old age pathologies (e.g. vascular) are only starting to be used.

Randomized controlled trials (RCTs)—The many positive results from observational studies do not necessarily translate into successful prevention strategies in RCTs. In some cases, residual confounding or apparent protective factors in observational studies might actually be markers of an unmeasured risk or protective mechanism. Trials based on the assumption that AD is a one-dimensional entity, with progressive cognitive decline until dementia, have consistently failed to identify effective interventions. A variety of compounds with different mechanisms of action (i.e. NSAIDs, anti-hypertensive agents, HRT, statins, vitamins and ginkgo biloba extract) were tested in prevention RCTs that were often add-ons to trials with other primary outcomes (i.e. cardiovascular or cerebrovascular events) [55]. As the sample sizes and follow-up periods were similar, all the compounds were somehow expected to have the same magnitude of effect on the same outcomes, regardless of inclusion criteria. To date no studies have convincingly shown that the single-drug approach to AD prevention is feasible when the outcome is dementia incidence [56, 57]. Anti-hypertensive drugs represent the only exception, as there is some evidence for these medications of a protective effect against dementia [58]. Also, single lifestyle-related interventions (i.e. physical activity and cognitive training) have had at best only modest or short-term positive results [59].

The importance of intervention timing in relation to disease onset, age and duration of the intervention are emphasized by previous RCT results. For example, the Women's Health Initiative Memory Study (WHI-MS) enrolled women aged 65–79 years, who were given HRT many years after the onset of menopause. The study showed that oestrogen therapy alone or in combination with progestin was associated with a two-fold increased risk of dementia and MCI [60, 61] and increased risk of stroke and heart disease. By contrast, the Kronos Early Estrogen Prevention Study (KEEPS) investigated HRT shortly after menopause onset (enrolment within 3 years; mean age 53 years). HRT use in KEEPS participants was associated with improvement of cardiovascular risk markers, without adverse effects on cognition [62]. It is interesting that the negative short-term effect of HRT

in WHI-MS was especially evident in individuals with lower cognitive functioning at baseline, indicating that HRT may have a negative effect once the disease process has started. A similar situation has been described for NSAIDs [56].

Another example is blood pressure, which seems to decline in the years preceding AD onset [63, 64]. Thus, subjects with higher blood pressure participating in hypertension trials might in fact have a decreased short-term risk for dementia, and those who develop dementia in these trials may have other characteristics compared to individuals with dementia in general [52]. High blood pressure (as well as high cholesterol levels and obesity) in midlife has been linked to an increased risk of dementia and AD 20–30 years later in long-term population-based observational studies [52]. However, conducting such long-term RCTs to verify the effect of interventions is not feasible.

Ongoing dementia prevention studies and initiatives: Several dementia prevention trials have been launched in recent years (Tables 2 and 3), targeting different populations and using different types of lifestyle-related and pharmacological interventions. In contrast to earlier studies, they focus on multiple risk factors simultaneously (multidomain interventions), or employ different forms of disease-risk enrichment. Enrichment can be based on biological markers (genetic and non-genetic) (Table 2) or on the presence of other risk factors (e.g. metabolic or vascular factors) (Table 3). In addition to individual RCTs being conducted, prevention initiative networks serve as a common platform for several RCTs. For example, in the European Dementia Prevention Initiative (EDPI; www.edpi.org) [65, 66], research groups have cooperated from three ongoing prevention RCTs using multidomain vascular and lifestyle-related interventions (preDIVA, FINGER, MAPT; Table 3) [65, 66]. International collaboration between different groups can lead to better use of the available data. Through combined data analyses and sharing of experiences about methodological issues, EPDI aims to improve multidomain preventive strategies that can be tested in larger studies. A step in this direction is the European Union-funded project recently started by the EDPI members: the Healthy Aging Through Internet Counseling in the Elderly (HATICE; www.hatice.eu). HATICE aims to support management of vascular and lifestyle-related risk factors in older adults, through an easily accessible Internet platform, with readily available nurse support. The main goal of HATICE is prevention of dementia and cardiovascular disease in the elderly. An RCT with 4600 elderly participants is planned within HATICE to investigate the efficacy of the platform.

Other ongoing lifestyle-related trials focus on physical activity as the main intervention, and outcomes are cognitive change/functional status and biological markers of AD and cognitive impairment. The PREVENT-Alzheimer programme (Douglas Institute, Montreal, Canada) [67, 68] is planned to include 500 individuals aged ≥55 years, without cognitive impairment but with a family history of AD. Promotion of the Mind Through Exercise (PROMoTE; University of British Columbia, Canada) is targeting 70 participants aged ≥45 years with ischaemic vascular cognitive impairment [69]. The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) [68] is including 150 individuals ≥60 years old, with subjective memory complaints or MCI and at least one cardiovascular risk factor. The Exercise MCI trial, ADCS, USA [70] is targeting 300 sedentary older adults with MCI.

Prevention RCTs using anti-amyloid agents (Table 2) represent a special group of trials because participants are selected based on the presence of brain amyloid on positron emission tomography (PET) scans, genetic risk factors for AD or genetic mutations associated with AD. These studies raise ethical issues concerning the disclosure of dementia risk status, as it is difficult to translate an estimated dementia risk from the group to the individual level. How should patients be informed about their genetic profile or brain amyloid imaging data? Guidelines (Alzheimer's Association and Society of Nuclear Medicine) are being prepared and studies (e.g. REVEAL) are ongoing to evaluate the consequences and impact of disclosing this type of information.

If a genotype of a susceptibility gene is directly linked to the pathophysiological process targeted by a new drug, this could be a potential strategy for selecting the appropriate subjects for an intervention. However, testing for susceptibility genes in asymptomatic individuals is ethically complex. Communicating a genetically increased risk is very different from communicating an autosomal dominant disorder. Also, the relevance of PET amyloid imaging in large populations with no cognitive impairment is unknown. Neuropathological studies have shown that amyloid correlates poorly with cognitive impairment in late-onset dementia, and it is unlikely that this will be a particularly useful biomarker in large unselected populations. However, if anti-amyloid interventions prove effective, then PET scans or risk genes could be used to select those who might benefit from such interventions.

Individuals with an autosomal dominant mutation, which will inevitably cause the clinical syndrome of AD, are selected for the currently ongoing projects Alzheimer's Prevention Initiative; DIAN - Dominantly Inherited Alzheimer Network (API and DIAN)(Table 2). This is a special group of patients who develop dementia at a younger age and who have an essentially different disease compared to the vast majority of those with late-onset dementia, mixed pathology and no genetic mutation. Therefore results from these studies might not be directly applicable at the population level.

Enrichment strategies and surrogate outcomes: the role of biological markers: In the new proposed criteria, genetic, neuroimaging and cerebrospinal fluid markers have an increasingly important role in defining AD. Enrichment strategies may solve some of the previous problems related to the heterogeneity of populations included in RCTs. Highly selected populations can be suitable for very specific prevention strategies targeting a well-defined pathophysiological mechanism (Fig. 3). One disadvantage of enrichment is that generalizability of results is limited. Late-life cognitive impairment is neuropathologically heterogeneous, and any enrichment strategy focusing too heavily on one pathophysiological process will disregard the relevance of many others. Also, AD biomarkers were identified in clinical-based studies, and their test characteristics at the general population level and in different age categories are still not sufficiently well understood. Individuals with cognitive impairment/AD in the general population are usually older compared to those in clinical-based studies, and the predictive value of AD biomarkers at older ages (>75 years) is much reduced [71]. This is not surprising given the large overlap in the presence of Alzheimer pathology (plaques and tangles) between very old subjects with and without cognitive impairment [9, 72]. In addition, currently available biomarkers are measured using

expensive, time-consuming and sometimes invasive procedures (magnetic resonance imaging or PET scans and lumbar puncture), which preclude large-scale use at the population level to select individuals at risk. The identification of appropriate blood biomarkers for easier use is eagerly awaited.

Thus enrichment strategies must be used carefully. Genetic mutations known to lead to AD are one clear means of identifying individuals with a specific type of AD for prevention studies. Also, having a first-degree relative with dementia increases the risk to about the same extent as being a carrier of one APOE ε4 allele [73]. Using family history as an enrichment strategy (a generic and pragmatic risk factor, with no need for ethically complex genetic testing) can make it possible to take into account several potential pathophysiological mechanisms simultaneously when selecting trial participants.

In the context of RCTs, biomarkers are being considered as enrichment strategies for selecting trial participants, or as surrogate endpoints for assessing intervention effects. The Food and Drug Administration (FDA) is currently updating its regulatory framework for RCTs evaluating drugs in early AD, and recently announced the possibility (still under evaluation) of approving the use of AD-related biomarkers. Biomarkers could be used to select subjects with early AD (MCI due to AD or 'prodromal' AD) who can be enrolled in RCTs, and also as secondary outcome measures, in combination with clinical endpoints (cognitive and/or functional) to support a disease-modifying effect. No specific biomarker is recommended and the FDA suggests that biomarker results in RCTs should be interpreted in the context of the state of the scientific evidence [74]. The European Medicines Agency (EMA) does not consider biomarkers (bbeta-amyloid, t-tau and hippocampal atrophy) as diagnostic markers but as enrichment markers for sample selection for trials. According to EMA guidelines, there is not enough evidence for phosphorylated-tau to be used for such purposes [75]. For prevention at the population level, no biomarkers have been shown to adequately predict dementia. As long as no clear correlation between changes in biomarkers and clinically detectable changes have been found, there is no basis for using any of the currently known biomarkers as a surrogate endpoint, or even as an enrichment strategy for large-scale prevention at the population level.

Due to the slowly progressive course of AD, detecting a clinically relevant effect of a prevention strategy can be difficult. So far no biomarker for AD has been validated against clinical measures, and shown to be better than measures of cognitive impairment. As relevant data become available on the translation of surrogate outcomes into clinically relevant ones, these surrogate endpoints can be used in proof of principle studies to decide which interventions should be further explored in large-scale RCTs using clinically relevant outcomes.

The chance of demonstrating efficacy in prevention RCTs can be maximized by using trial endpoints that are more sensitive than 'conversion to dementia'; for example the Neuropsychological Test Battery (NTB) has been proposed for assessing cognitive decline [76]. However it remains a challenge to determine which effects are clinically relevant, and the magnitude of NTB change that can be considered sufficient evidence for intervention efficacy. Cognitive decline is not a linear process and it is difficult to establish to what

extent a difference in rate of decline for example over 6 months is representative of decline over a longer time period.

Documenting the natural course of AD as defined by the proposed new diagnostic criteria, and discovering and validating markers for the earlier and more accurate identification of individuals at risk of AD who can be recruited for prevention RCTs will require large, long-term population-based cohort studies that are culturally and genetically diverse. One approach to launching such an international research resource is the development of the International Database on Aging and Dementia (IDAD) initiative. It is recognized that existing population studies represent an important foundation from which to launch the enterprise [77]. The IDAD initiative will provide a global database that will be useful to: (i) describe the natural history of AD and other chronic brain diseases affecting memory, movement and mood, and (ii) validate the prognostic and disease-monitoring capabilities of putative biomarkers and potential risk factors such as genetic, metabolic, lifestyle and environmental factors on clinical outcomes.

Power calculations: When intervention effects must be powered on data from observational studies, power calculations are particularly difficult. This has been most obvious in lifestyle-related prevention RCTs. Observational studies often have more power due to larger sample sizes and longer follow-up; of note, participants have a wider range of values for the risk factor of interest. Reports of high potential for dementia prevention with up to 50% possible risk reduction have led to high expectations, but such numbers are not realistic considering the effects of prevention strategies in other medical fields [78, 79]. Table 4 shows some examples from cardiovascular disease and cancer prevention compared to dementia prevention. The numbers of participants, duration of RCTs and incidence of outcomes are clear problems in dementia prevention trials. Unrealistic power calculations based on results of larger and longer-term observational studies will lead to underpowered RCTs. How statistical analyses are conducted can also potentially lead to type II errors, i.e. failure to detect a true effect. Due to the exponential increase in incidence of dementia with increase in age, a statistical model assuming proportional risk throughout the follow-up period, as is usually applied, might not be the optimal analysis technique. Alternative statistical methods that can (partly) overcome this issue are available [80].

Conclusions and future directions

Until not so long ago, AD and dementia were not regarded as preventable. The switch from fatalism to larger-scale prevention research in about two decades is a real and important achievement, and the prospect of delaying or preventing the onset of symptoms seems to be within reach [77, 81]. Results from ongoing observational and intervention studies focused specifically on AD/cognitive impairment can contribute to identifying effective preventive strategies tailored to different groups at risk of dementia (i.e. defined according to age, vascular/metabolic/lifestyle profiles, various biological markers and cognitive status). Some of the main barriers to overcome in future studies are summarized in the Panel. These include continually improving and adapting models/criteria/definitions of disease and the need for better research methods and infrastructure. Only a sustained international commitment to solve these problems will accelerate the pace of translating newly emerging

or promising results into practical applications. The success of any campaign to prevent AD will require significant changes in the current philosophy and approach to AD research.

Fundamental questions still remain about the definition of the disease itself. The relation between neuropathological changes and cognitive impairment is not well understood. Which at-risk population should be addressed is highly dependent on the pathophysiological mechanism(s) targeted. Highly specific therapy for selected subjects with, for example, an autosomal dominant form of AD is a very different form of prevention than a population-based strategy in which the target includes a wide range of subjects with increased risk of dementia based on lifestyle.

In multifactorial conditions, a small reduction in multiple risk factors can substantially decrease overall risk. This is important both at the individual and population levels. Incorporation of public health-based research methodology is required in order to reach the impact of prevention strategies targeting many persons with a modestly increased risk. *In silico* experiments using available longitudinal datasets can assist in developing the optimal design of new dementia prevention RCTs.

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Summary panel Main issues and recommendations concerning AD/ dementia prevention

Issue	Recommendations
Alzheimer clinical syndrome and Alzheimer neuropathology do not necessarily have the same risk factors	• Life-course cohorts and neuropathological data clarifying how associations between neuropathology and cognition are modified by comorbidities in different age groups • In prevention studies targeting late-onset AD and dementia, a focus on beta-amyloid and tau should not completely exclude other relevant pathological processes (e.g. inflammation and vascular pathology) • When interpreting epidemiological findings, the choice of AD conceptual framework (neuropathological or clinical) should be more clearly specified; primary, secondary or tertiary prevention should be adequately discussed within the chosen framework
Timing is everything	• Risk/protective factors for dementia/AD should be studied from a life-course perspective • Targeting risk factors for dementia/AD when they have the strongest effect (identifying windows of opportunity for efficient and effective prevention)
Methodological challenges in RCTs of prevention, including: • Recruitment/ enrichment • Power • Duration • Outcome • Ethical issues	• Study recruitment issues - validation of methods and algorithms for identifying asymptomatic individuals with elevated risk • Relevance of biomarkers needs to be validated in the general population; identification of easily available biomarkers and other enrichment criteria • Realistic power calculations; learn from earlier RCTs in dementia and other diseases • Build infrastructure for international collaborations; manage conceptual differences in the design and conduct of clinical trials for prevention versus treatment • Recognize ethical issues for designing RCTs (e.g. vascular risk factors cannot be left untreated in the control group)
Identification of the most effective prevention strategies • Single-domain interventions do not work for AD (heterogeneous condition) • Divided opinions about ‘sufficient evidence’ for AD prevention	• Quality check for AD studies to obtain stronger evidence (i.e. more precise and standardized exposure and outcome measures, more standardized reporting of methods and results) • Multidomain interventions and simultaneous management of various risk factors based on lifestyle changes and pharmacological treatment may be needed for optimal preventive effects • Using experience from previous prevention programmes in other chronic diseases

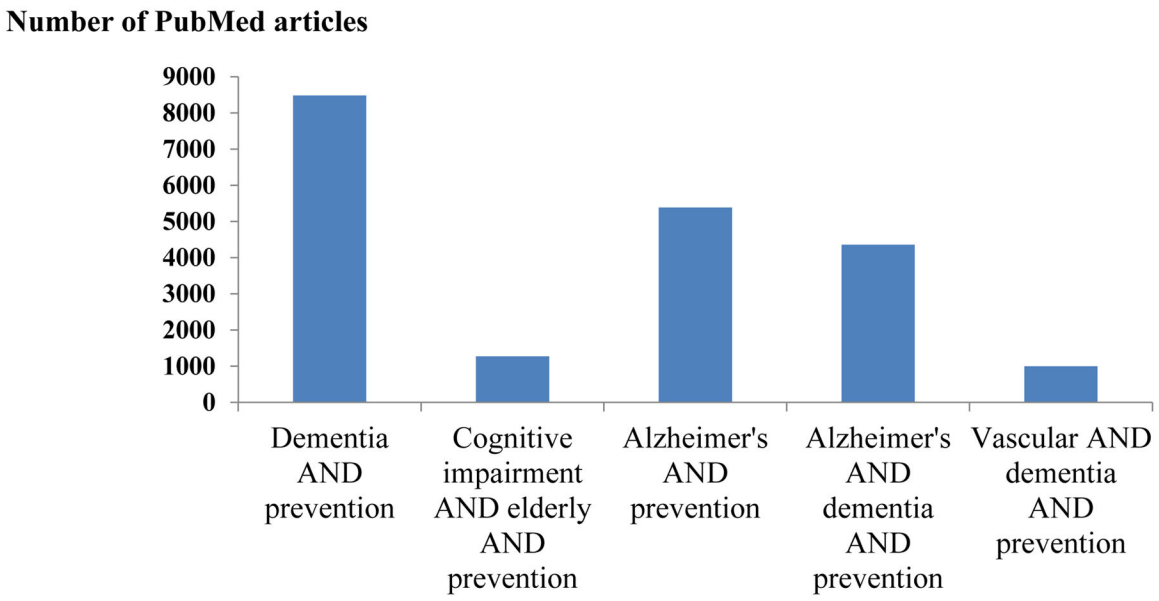

Fig. 1.

PubMed articles with prevention-related keywords, listed up to June 2013, in the field of cognitive disorders in elderly populations.

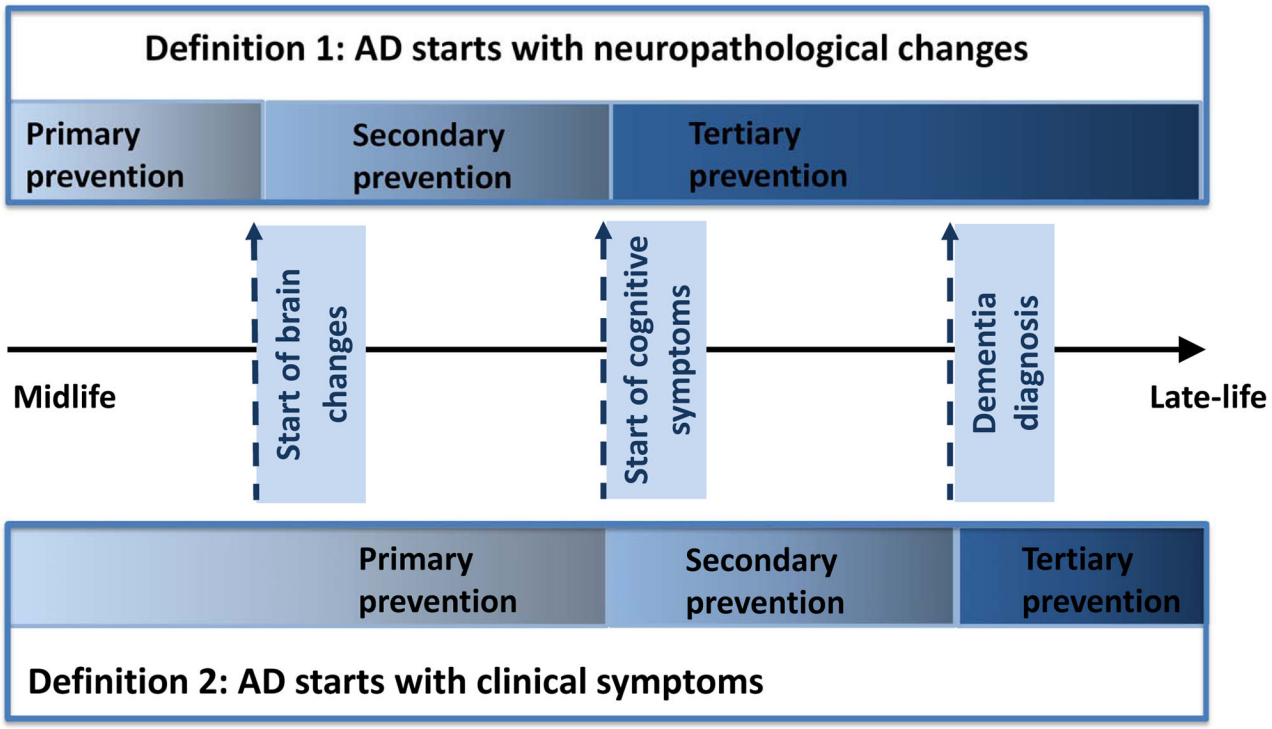

Fig. 2.

Scheme showing how different definitions of AD can lead to different definition of primary, secondary and tertiary prevention in AD. Definition 1, according to the National Institute of Aging-Alzheimer Association workgroup; definition 2, according to Dubois *et al*.[2]

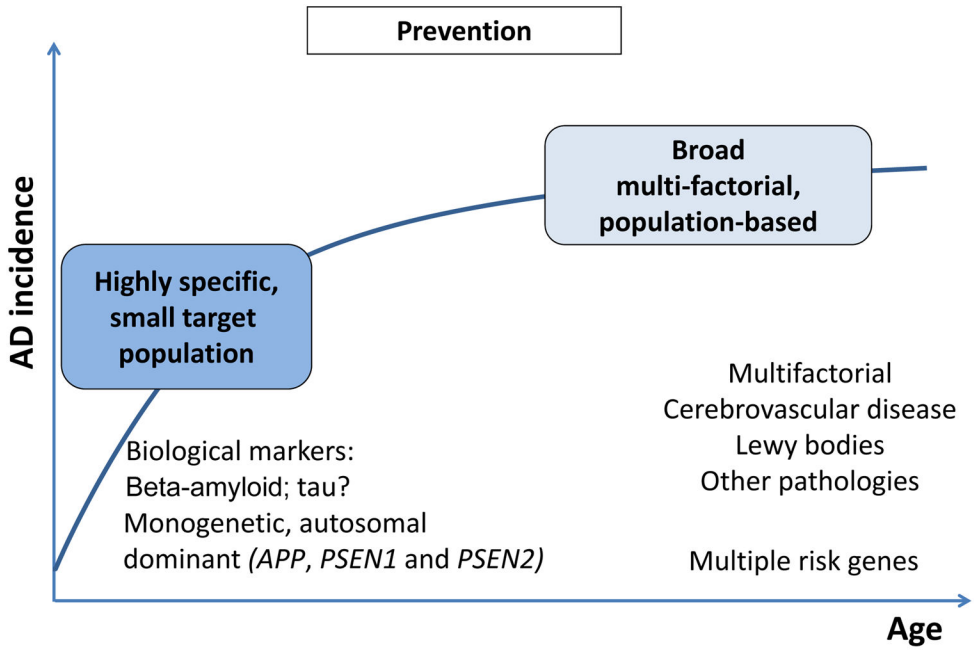

Fig. 3.

Different characteristics can be considered when targeting preventive measures leading to the identification of different populations.

Table 1

Proposed risk and protective factors for late-onset dementia and Alzheimer's disease

Risk factors	Protective factors
Age	**Genetic**
Genetic	Different genes (e.g. *APP*, *APOE* ε2) have been proposed (www.alzgene.org)
Familial aggregation	
APOE ε4	
Different genes (e.g. *CR1*, *PICALM*, *CLU*, *TREM2*, TOMM40) have been proposed (www.alzgene.org)	**Psychosocial factors**
	High levels of education and SES
	High level of complexity of work
Vascular and metabolic	Rich social network and social engagement
Cerebrovascular lesions	Mentally stimulating activity
Cardiovascular diseases	
Diabetes mellitus and pre-diabetes	**Lifestyle**
Midlife positive association but late-life negative association	Physical activity
Hypertension	Moderate alcohol intake
High BMI (overweight and obesity)	
High serum cholesterol	**Diet**
	Mediterranean diet
Lifestyle	PUFAs and fish-related fats
Smoking	Vitamins B_6 and B_{12}, folate
High alcohol intake	Antioxidant vitamins (A, C and E)
	Vitamin D
Diet	
Saturated fats	**Drugs**
Homocysteine	Antihypertensive drugs
	Statins
	HRT
Others	NSAIDs
Depression	
Traumatic brain injury	
Occupational exposure (heavy metals, ELF-EMFs)	
Infective agents (herpes simplex virus type I, *Chlamydophila pneumoniae*, spirochetes)	

Combined effect	
Increased risk	**Decreased risk**
Genetic and environmental factors in midlife	*Genetic and environmental factors in midlife*
APOE ε4 magnifies the effect of high alcohol intake, smoking, physical inactivity and high intake of saturate fat	High education level reduces the negative effect of *APOE* ε4
Vascular and metabolic factors in midlife	Physical activity counteracts the risk due to *APOE* ε4
Co-occurrence of hypertension, obesity, hypercholesterolaemia and/or physical inactivity has an additive effect	*Environmental factors in midlife*

Risk factors	Protective factors
Vascular and metabolic factors/diseases in late-life	High level of complexity of work modulates the increased dementia risk due to low level of education
Higher risk in individuals with brain hypoperfusion profile: chronic heart failure, low pulse pressure, low diastolic pressure	*Genetic and environmental factors in late-life*
Higher risk in individuals with atherosclerosis profile: high systolic pressure, diabetes mellitus or prediabetes, stroke	Active leisure activities or absence of vascular risk factors reduces the risk due to *APOE* ε4

A large number of risk and protective factors for dementia and Alzheimer's disease have been investigated, and there are greater and lesser degrees of evidence to support these various factors.

APP, amyloid precursor protein; *APOE*, apolipoprotein E; BMI, body mass index; *CLU*, clusterin; *CR1*, complement component receptor 1; ELF-EMF, extremely low-frequency electromagnetic field; HRT, hormone-replacement therapy; NSAID, non-steroidal anti-inflammatory drug; *PICALM*, phosphatidylinositol binding clathrin assembly protein; PUFA, polyunsaturated fatty acid; SES socioeconomic status; *TOMM40*, translocase of outer mitochondrial membrane 40 homolog; *TREM2*, triggering receptor expressed on myeloid cells 2.

Table 2

Characteristics of selected RCTs for prevention of Alzheimer's disease (AD), based on compounds targeting beta-amyloid

RCT	ADCS-A4 [82]	API [82]	DIAN [82]	Zinfandel-Takeda prevention study [68, 83]
Sample size	1500 older adults with no cognitive impairment	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	240 members of families with early-onset AD. Subjects can be asymptomatic or have very mild memory and cognitive problems including mild dementia	5000 elderly subjects with no cognitive impairment
Main inclusion criteria	Evidence of brain amyloid accumulation (PET). Subjects with no evidence of amyloid burden will also be included	Carriers of a mutated *PSEN1* gene. Non-carriers will also be included, to ensure double-blinding of the genetic status	Carriers (n = 120) of mutation in *PSEN1*, *PSEN2* or *APP*. Non-carriers (n = 120) will also be included, to ensure double-blinding of the genetic status	Subjects at risk of developing MCI due to AD within 5 years. The risk stratification is based on an algorithm including age and *TOMM40* and *APOE* genotype. Subjects with high and low risk will be included
Age at enrolment	≥70 years	≥30 years	18–80 years	68–83 years
Study design	Randomized, double blind, placebo-controlled trial	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: solanezumab (Eli Lilly)	Anti-amyloid monoclonal antibody: crenezumab (Genentech)	Two anti-amyloid therapies: the anti-amyloid monoclonal antibodies gantenerumab (Hoffmann-La Roche) and solanezumab	Pioglitazone, an oral medication already approved for the treatment of type 2 diabetes (Zinfandel-Takeda)
Duration	3 years + 2-year extension	5 years, (interim analysis at 2 years)	2 years + 3-year extension	5 years
Outcomes	Primary: cognitive function Secondary: change in AD biomarkers	Primary: cognitive function Secondary: change in AD biomarkers, including brain amyloid load and brain atrophy	Initial phase (2 years): change in AD biomarkers, including brain and CSF amyloid, to identify the most promising drug candidate Follow-up phase (3 years): cognitive function	Primary: cognitive function (i.e. time to onset of MCI due to AD) Secondary: qualification (predictive values) of the algorithm based on age and *TOMM40* and *APOE* genotype
Status	Start in 2013	Start in 2013	Start in 2013	Start in 2013

ADCS-A4, Anti-Amyloid Treatment of Asymptomatic Alzheimer's disease; API, Alzheimer's Prevention Initiative; DIAN, Dominantly Inherited Alzheimer Network; MCI, mild cognitive impairment; CSF, cerebrospinal fluid; *APOE*: apolipoprotein E; *APP*, amyloid precursor protein; PET, positron emission tomography; *PSEN1*, presenilin 1; *PSEN2*, presenilin 1; *TOMM40*, translocase of outer mitochondrial membrane 40 homolog.

Table 3

Characteristics of selected RCTs for prevention of cognitive impairment, dementia and Alzheimer's disease (AD) based on multidomain interventions

RCT	FINGER [84]	MAPT [85]	PreDIVA [86]
Sample size	1282 community dwellers, from previous population-based observational cohorts	1680 community dwellers	3534 community dwellers
Main inclusion criteria	Dementia risk score >6 and mild degree of cognitive impairment	Frail elderly individuals (subjective memory complaint, slow walking speed, limitation in IADL)	All elderly within GP practices, non-demented (MMSE >23)
Age at enrolment	60–77 years	≥70 years	70–78 years
Study design	Multicentre, randomized, single-blind, parallel-group trial	Multicentre, randomized, double-blind controlled trial	Multisite, open, cluster randomized, parallel-group trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, increased social activity and intensive monitoring, and management of metabolic and vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training and/or DHA 800 mg/day	Multidomain: nurse-led vascular care including medical treatment of risk factors, nutritional advice, exercise advice
Duration	2 years + 5-year extended follow-up	3 years + 2-year extended follow-up	6 years
Outcomes	Primary: change in cognitive function (neuropsychological test battery, trail making, Stroop test) Secondary: dementia, cardiovascular events, depression, disability, quality of life, health resource utilisation, change in AD biomarkers	Primary: change in cognitive function (Grober and Buschke memory test) Secondary: cognition (MMSE, CDR), functional status, depression, health resource utilisation, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline (MMSE, VAT), depression, cardiovascular events
Status	Ongoing, will be completed in 2014	Ongoing, will be completed in 2014	Ongoing, will be completed in 2015

FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive impairment and Disability; MAPT, Multidomain Alzheimer Prevention Study; PreDIVA, prevention of dementia by intensive vascular care; CDR, Clinical Dementia Rating scale; DHA, docosahexaenoic acid; GP, general practitioner; IADL, instrumental activities of daily living; MMSE, mini mental state examination; VAT, visual association test.

Table 4

Characteristics of selected RCTs for prevention of dementia/Alzheimer's disease (AD) and other disorders

Dementia/AD-related RCTs		RCTs for other disorders	
Prevention of dementia with antihypertensive drugs in subjects with no history of cerebrovascular diseases		**Prevention of coronary heart disease with lipid-lowering drugs**	
4 RCTs in which cognitive measures were secondary endpoints [87, 88]; 15,427 participants	Follow-up: from 2 to 5 years (median 2.9 years); incident cases (treatment/control): 236/259 HR (95% CI): 0.89 (0.74–1.07)	4 RCTs [95]; 21,087 participants	Follow-up: from 5 to 7 years Incident cases (treatment/control): 441/615 OR (95% CI): 0.70 (0.62–0.79)
Prevention of dementia and MCI with oestrogen alone or oestrogen plus progestin in postmenopausal women		**Prevention of cardiovascular and cerebrovascular events with statins in diabetic subjects**	
1 RCT, ancillary to a larger trial; early termination of treatment because overall health risk [60]; 7471 participants	Follow-up: mean 4.4 years (maximum 7 years); incident cases (dementia or MCI: treatment/control):178/132 HR (95% CI) for dementia or MCI: 1.41 (1.12–1.76)	4 RCTs [96]; 10,187 participants	Follow-up: from 3 to 5 years (mean 3.8 years) Incident cases (treatment/control): 434/576 RR (95% CI): 0.75 (0.67–0.85)
Prevention of dementia/AD with naproxen or celecoxib in subjects with normal cognition and family history of AD		**Prevention of cardiovascular and non-cardiovascular outcomes with aspirin**	
1 RCT, early termination of treatment because overall health risk [89, 90]; 2528 participants (1537 for follow-up study)	Follow-up: median 2 years (maximum 3.7 years) + 2-year extended follow-up after treatment cessation Incident cases of AD (treatment/control): 20/5; incident cases of dementia (treatment/control): 23/7; HR (95% CI) for AD with naproxen: 3.57 (1.09–11.7) HR (95% CI) for dementia with naproxen: 2.83 (1.04–7.72) HR (95% CI) for AD with celecoxib: 4.11 (1.30–13.0) HR (95% CI) for dementia with celecoxib: 3.04 (1.13–8.17). Incident cases of AD in follow-up study (treatment/control): 91/70; incident cases of dementia in follow-up study (treatment/control): 102/79; HR (95% CI) for AD with naproxen: 0.92 (0.62–1.35) HR (95% CI) for dementia with naproxen: 0.94 (0.65–1.35) HR (95% CI) for AD with celecoxib: 1.03 (0.72–1.50) HR (95% CI) for dementia with celecoxib: 1.03 (0.72–1.46)	4 RCTs [97]; 102,621 participants	Follow-up: from 3.6 to 10.1 years (mean 6 years) Incident cases of total cardiovascular events (treatment/control): 2107/2171 Incident cases of non-cardiovascular mortality (treatment/control): 1276/1311 OR (95% CI) for cardiovascular events: 0.90 (0.85–0.96) OR (95% CI) for non-cardiovascular mortality: 0.92 (0.85–1.00)
Prevention of dementia with simvastatin		**Prevention of cardiovascular disease with vitamin and antioxidant supplementation**	
1 RCT [91, 92]; 20,536 participants	Follow-up: mean 5 years Incident cases (treatment/control): 31/31 OR (95% CI): 1.00 (0.61–1.65)	50 RCTs: 30 primary and 20 secondary prevention RCTs [98]; 294,478 participants	Follow-up: from 6 months to 12 years Incident cases (treatment/control): 16,571/14,691 RR (95% CI): 1.00 (0.98–1.02)
Prevention of dementia/AD with ginkgo biloba in subjects with normal cognition or MCI		**Prevention of breast cancer with selective oestrogen receptor modulators**	
1 RCT ancillary to a larger trial [93]; 3069 participants	Follow-up: median 6.1 years (maximum 7.3 years) Incident cases of AD (treatment/control): 220/257; incident cases of dementia (treatment/control): 246/277 HR (95% CI) for AD: 1.16 (0.97–1.39) HR (95% CI) for dementia: 1.12 (0.94–1.33)	9 RCTs [99]; 83,399 participants (306,617 women-years of follow-up)	Follow-up: from 4 to 8 years (median 5.5 years) Incident cases (treatment/control): 945/1323 HR (95% CI): 0.62 (0.56–0.69)
Prevention of AD with ginkgo biloba in subjects with memory complaints [57]		**Prevention of cancer with beta-carotene (alone or in combination with other antioxidants) supplementation**	

Dementia/AD-related RCTs		RCTs for other disorders	
1 RCT [57]; 2820 participants	Follow-up: median 5 years Incident cases (treatment/control): 61/73 HR (95% CI): 0.84 (0.60–1.18)	8 RCTs [100]; 180,702 participants	Follow-up: from 4.0 to 12.9 years Incident cases (treatment + control): 10,600 RR (95% CI): 1.01 (0.98–1.04)
Prevention of dementia with α-tocopherol and selenium (alone or in combination) in men		**Prevention of cancer with selenium supplementation**	
1 RCT, ancillary to a larger trial; early termination of treatment due to a futility analysis (prostate cancer outcome), but follow-up is still ongoing [94]; 7547 participants (4246 for the extended follow-up)	Follow-up: ongoing Incident cases after 8 years (treatment + control): 103	9 RCTs: 7 primary and 2 secondary prevention RCTs [101]; 152,538 participants	Follow-up: from 2 to 10 years Incident cases (treatment/control): 1879/1959 RR (95% CI): 0.76 (0.58–0.99)
		Prevention of hip fractures with vitamin D supplementation	
		7 RCTs [102]; 9820 participants	Follow-up: from 1 to 5 years Incident cases (treatment/control): 293/320 RR (95% CI) for vitamin D 700–800 IU/day: 0.73 (0.61–0.88) RR (95% CI) for vitamin D 400 IU/day: 1.15 (0.88–1.50)

AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio; IU, international unit; MCI, mild cognitive impairment; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Except for antihypertensive agents, data for dementia/AD are from individual RCTs, whereas data from trials in other conditions are from meta-analyses; this highlights the lack of RCTs for AD prevention.