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**Issue coordinated by** Peter Falkai and Michael Davidson
Dialogues in Clinical Neuroscience is a quarterly publication that aims to serve as an interface between clinical neuropsychiatry and the neurosciences by providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects. Each issue addresses a specific topic, and also publishes free contributions in the field of neuroscience as well as other non–topic-related material. All contributions are reviewed by members of the Editorial Board and submitted to expert consultants for peer review.

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Editorial

Is dementia a preventable disease?
Michael Davidson, MD; Florence Thibaut, MD, PhD, Editor in chief

There currently exists evidence of moderate quality that cognitive training, blood pressure management, and physical activity can delay onset or slow progression of AD. All other preventive interventions have either produced negative and controversial results or are still under investigation. This issue will present reviews on both established preventive interventions and those under investigation.

The prospect of being affected by dementia, in general, and by Alzheimer disease (AD) in particular, is a source of worry for many of us as individuals and as a society. These worries are enhanced by knowing an affected individual whether genetically related to us or not and, by the self-realization that as we age the frequency of memory lapses increases.

Research during the 1980s and 1990s was dominated by the optimistic, yet biologically naïve notion that pharmacological enhancement of the activity of a single or a few neurotransmitters would ameliorate the ravages of AD. The ability to visualize with the help of positron emission tomography (PET) the pathognomonic marker of AD, the amyloid deposit, has led to a plethora of trials since the beginning of 2000, targeting the amyloid deposits. However, like the neurotransmitter enhancing strategy, the anti-amyloid strategy yielded negative results. Since AD is characterized by progressive degeneration of neurons and synapses in key brain areas, a plausible explanation for these treatment failures would postulate that by the time the disease is clinically manifested, considerable tissue damage has already occurred; damage which cannot be reversed. Therefore, much of the current research efforts have been switched from treatment to prevention. If indeed the amyloid plaque and the tangles which are present 5 to 10 years before clinical manifestation are on the pathophysiological pathway to the disease and not just an innocent marker, then a wide window for prevention exists.

Like most diseases, AD is the result of genetic predisposition interacting with mutable factors, some of which have already been identified - hence, candidates for prevention. Prevention can consist of pharmacological/medical interventions and/or in risk-reducing lifestyle. However, to institute effective prevention programs, it is essential to accurately define the population at risk and to quantify the risk. Pharmacological/medical interventions must be safe and well-tolerated and lifestyle interventions must be readily applicable and nonintrusive. To prevent disappointment and subsequent noncompliance, it is essential to communicate clearly to the health professionals and to the public the experimental background supporting the available preventive interventions and their inherent limitations.

In our State of the art article, Is Alzheimer disease a failure of mobilizing immune defense? (p 7), Katsel and Haroutunian compare post-mortem data from a cohort of very old (>80 y/o) nondemented individuals with a cohort of demented individuals to explore the role of microglia modulation on the pathophysiology of AD. In a related article by Arad and Schwartz, Potential immunotherapy for Alzheimer disease and age-related dementia (p 21) the authors propose a treatment strategy by which the naturally occurring inhibitory mechanism of the immune system is blocked with the help of a systemically injected antibody. This in turn opens the blood-brain barrier, thus activating the central nervous system (CNS) “aging” immune system of AD patients. In turn, the CNS-activated immune system cleaves the plaques and other related debris and, in the AD-engineered rodent improves cognitive abilities. In sum, although we are far from full elucidation on which intervention is beneficial, there are some hints that...
Editorial
Is dementia a preventable disease? - Davidson and Thibaut

Lifestyle changes might reduce the risk for AD. Observational data collected over the last 5 years reveal a reduction in AD incidence which can be attributed to better lifestyle.\(^1\)\(^,\)\(^2\) Due to the fact that drug development for AD currently is unsuccessful, validated targets and validated biomarkers are of utmost importance. Lewczuk et al\(^4\) reviewed in 2017 cerebrospinal fluid and blood biomarkers for neurodegenerative dementias.

Jessen focuses on methodology in *What are we trying to prevent in Alzheimer disease?* (p 27) discusses the trial design, the functional and biomarkers outcome measurements, and the regulatory environment for prevention trials. In *Cognitive stimulation, training, and rehabilitation* (p 35), Kurz concludes, based on randomized controlled trials (RCTs), that nonspecific cognitive-enhancing activities or cognitive stimulation produce small benefits in healthy elderly, mild cognitive impairment (MCI), and early dementia. Cognitive training which is based on the repetition of a particular cognitive activity produces benefits on the specific activity, but it is not clear if the benefits translate beyond that specific activity. Cognitive rehabilitation focuses on task rather than a specific cognitive activity and when the benefit is achieved it can delay dependency and institutionalization. The reader is encouraged to scrutinize the claim of effectiveness advertised by some internet-based programs for proof of efficacy. In *Dementia treatment versus prevention* (p 43) and *Dementia prevention and reserve against neurodegenerative disease* (p 53), Perneczky reviews the mutable and immutable risk factors and elaborates on the notion that brain reserve might reduce risk for AD. Also, he reviews the interactions between life-long education, occupation, and genetics of IQ versus AD risk. Finally, he suggests that better education might reduce risk for AD. Lautenschlager et al, in *Physical activity for cognitive health* (p 61), assert that sedentary lifestyle increases the risk for dementia and that prospective trials indicate that physical activity (PA) benefits cognitive functioning in healthy elderly, MCI, and mild-to-moderate AD patients. They then review the impediments towards regular aerobic exercise in the elderly and provide specific guidelines on how to overcome the impediments.

Scarmeas and Vlachos, in *Dietary intervention in MCI and dementia* (p 69) identify folate, vitamin E, Ω-3 fatty acids, and certain multi-nutrient formulations as potential additives benefiting dementia. However, the authors warn against a large number of potential confounders such as variability in supplement dosage and duration of administration, different chemical composition of the additive, previous and concomitant dietary habits to name only a few.

Bendlin in *Antidiabetic therapies and Alzheimer disease* (p 83) first reviews the observational studies linking type 2 diabetes (T2D) to AD clinical manifestation but not the amyloid deposits suggesting that antidiabetic medication might suppress the formation of the amyloid plaque, hence explaining the apparent discrepancy. However, observational studies of treatment with antidiabetic drugs produced inconclusive results ranging from benefits to no effect or damage. The large number of drugs used to treat T2D, variability in length of treatment, the effect of diabetic illness itself on AD, and the degree of the T2D control by the drugs are only some of the confounding variables that might explain the inconsistent results of the observational studies. Similar to observational studies, prospective trials have produced inconclusive and mainly negative results. Yet investigators continue to research brain insulin signaling and the effect of T2D on brain vasculature in an attempt to elucidate the undisputable link between T2D and risk for AD. Beeri, in *Prevention of dementia presents a potentially critical platform for improvement of long-term public health* (p 93) first provides a model to assess the impact of AD prevention/delay on public health. Then she lists the large multidomain prevention trials. Finally, she speculates on the effect of monitoring and disclosing the risk of AD on compliance with preventive activities.

Finally, in *Ethical issues in early diagnosis and prevention of Alzheimer disease* (p 101), Whitehouse discusses the ethical issues related to AD prevention, touching upon prevention in general, the role of science in society, and AD prevention versus the rest of the competing priorities in the provision of health care.

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Disease-Modifying Therapy in Dementia

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State of the art

Is Alzheimer disease a failure of mobilizing immune defense? Lessons from cognitively fit oldest-old

Pavel Katsel, PhD; Vahram Haroutunian, PhD

Multifaceted evidence supports the hypothesis that inflammatory mechanisms contribute to Alzheimer disease (AD) neuropathology and genetic association of several immune-specific genes (REM2, CR1, and CD33) suggests that a maladaptive immune response may be pivotal drivers of AD pathogenesis. We reviewed microglia-related data from postmortem AD studies and examined supporting evidence from AD animal models to answer the following questions: i) What is the temporal sequence of immune activation in AD progression and what is its impact on cognition? ii) Are there discordant, “primed,” microglia responses in AD vs successful cognitive aging? iii) Does central nervous system (CNS) repair in aging depend on recruitment of the elements of cellular adaptive immune response such as effector T cells, and can the recruitment of system ic immune cells ameliorate AD neuropathology? iv) How effective are the immune-system-based therapeutic approaches currently employed for the treatment of AD?

Keywords: Alzheimer disease; gene expression; immune response; inflammation; macrophage; microglia; oldest-old; T cell

Integration of the immune response in the central nervous system

Vigilant immune defenses against infection and injury ensure the endurance of the organism by setting in motion a discrete, localized inflammatory response to thwart a variety of pathogenic and pathophysiological threats. These responses must be tuned and scaled precisely, because insufficiency or excesses of responses such as prolonged inflammation can cause morbidity and mortality, shortening lifespan and compromising health. Homeostasis and health are restored when inflammation is resolved by rapid and reversible anti-inflammatory responses. Derailed resolution of inflammation is accompanied by impaired antigen clearance, persistence of inflammatory triggers, activated macrophages, and the development of maladaptive immunity.

The mammalian nervous system integrates inflammatory responses by gathering information about invasive events, mobilizing defenses, and restoring homeostasis, and creates immune memory to improve likelihoods of survival. Microglia, derived from primitive myeloid progenitors that populate the developing brain during mid-embryogenesis, are the resident immune/inflammatory cells of the central nervous system (CNS). Additional subtypes of macrophages (reviewed in ref 3) are positioned at brain boundaries and show diverse transcriptional profiles. These cell populations include perivascular, subdural, and choroid plexus macrophages which are distinct from parenchymal microglia and are likely derived from hematopoietic precursors during development. Throughout this review we will discuss brain injury responses of adult microglia, the functions of which may be inherently different from the role(s)
of microglia during prenatal periods when microglia regulate the wiring of brain circuits, influence the outgrowth of dopaminergic axons, impact the laminar positioning of subsets of neocortical interneurons, and effect functional connectivity.6

Under homeostatic conditions microglia are ramified cells with multiple branches and processes. Microglia extend processes to contact neurons, macroglia (astrocytes and oligodendrocytes), and blood vessels and constantly monitor and respond to injuries or inflammatory stimuli and are characterized by enlarged cell bodies and shortened processes with restricted coverage. Ameboid morphology is associated with phagocytosis and proinflammatory functions. Additional differently shaped activated microglia are recognized (e.g., bipolar, rod-shaped etc) possibly reflecting their diverse responses and movement toward injury or “toxic” stimuli.

Activated parenchymal and perivascular microglial cell populations express variable levels of extracellular markers of myeloid lineage in which some resemble tissue macrophages attesting to microglial heterogeneity.7 It remains unclear whether hematopoietic-derived progenitors contribute to the expansion of adult parenchymal microglia-like cells when homeostasis is disrupted, such as during brain injury, or whether microglia can maintain and transform their function independently of hematopoietic-derived progenitors throughout adult life in the absence of temporary disruption of the blood-brain barrier (BBB). Activation of some microglia is essential in resolving injury and maintaining normal self-tolerance. Resident microglia are believed to be restricted by the BBB and cannot progress into the cell cycle program. However, resident microglial progenitors provide a rapid mechanism for mobilizing defense responses, rather than recruitment of systemic bone marrow-derived precursors, which is believed to be restricted by the BBB when intact.9 Therefore, the robust mitotic potential of microglia in advanced age may be among the critical factors for tissue repair and preservation of cognitive function in healthy aging.19 whereas replicative senescence (please see below) may contribute to pathological aging.

Advanced age is the greatest risk factor in AD and is associated with replicative senescence (loss of mitotic ability after repeated rounds of replication) in myeloid cells

Under the inflammatory conditions of an active immune response, microglia must moderate the potential damage to the nervous system by supporting tissue repair and remodeling, including the maintenance and restoration of synaptic connections. Microglia achieve neuroprotection by clearing debris, suppressing inflammation, restoring BBB integrity20 and promoting cortical synaptogenesis/neurogenesis by stripping inhibitory synapses.21 To protect from attacking its own antigens/proteins microglia must also maintain natural self-tolerance. To induce central systemic self-tolerance, resident dendritic cells must present self-antigens from circulating dying cells to T cells. It is not clear how microglia maintain self-tolerance of neural cell types. How ever, examination of the effector function of acrophages derived from microglia in animal models of autoimmune disease has shown that microglia-derived acrophages were protective and oriented toward resolving neuroinflammation, whereas monocytoid microglia were highly phagocytic and proinflammatory suggesting that self-immune tolerance may be an inherent feature of microglia.
Additionally, it has been shown that locally secreted immuno-suppressive cytokines (e.g., TGFβ, G-CSF, and IL-10) by im mune cells may promote immune tolerance to self-associated antigens. It is plausible that self-tolerance mechanisms may contribute to the accumulation of toxic signals in neurodegenerative disorders such as AD.

We will discuss whether the engagement of systemic adaptive immune responses can overcome self-tolerance suppression of the brain immune response in order to ameliorate AD neuropathology. We will additionally sum arize microglia-related data from postmortem AD studies and examine supporting evidence from AD animal models to answer the following questions: i) What is the temporal sequence of immune activation in AD progression and what is its impact on cognition? ii) Are there discordant, "primed," microglia activation states revealed by transcriptomics approaches? iv) How effective are the immune system-based therapeutic approaches currently employed for the treatment of AD?

Brain inflammatory response – relevant factor in Alzheimer disease and successful cognitive aging: evidence from neuropathology and molecular studies

Alzheimer disease and its associated dementia is the most common type of neurodegenerative disorder, with age and aging representing the greatest risk factors. The neuropathological hallmarks of AD include neuronal loss, abnormal neuronal cytoskeletal changes, known as neurofibrillary tangles (NFT), and extracellular protein deposits called neuritic amyloid β plaques (NPs). In addition to the NFTs and NPs, evidence from multiple models support the hypothesis that inflammatory responses contribute to AD neuropathology. Elevated levels of the inducers of acute phase response, such as inflammatory cytokines and acute phase reactants, are identified in CSF, plasma, and in am yloid-laden plaques; the presence of reactive microglial cell clusters around senile plaques and com plement components of the immune response are well-documented in postmortem studies of individuals with AD. Additionally, changes in gene expression of inflammatory signaling pathways and regulatory gene networks have been consistently found in brains of individuals with AD.

Given the evidence of genetic linkage of several immune-specific genes (TREM2, CR1, and CD33), the immune response may be pivotal drivers of AD pathogenesis. This model proposes that im mune-inflammatory processes may be pivotal drivers of AD pathogenesis. This model proposes that inflammatory-immune mechanisms would drive toxic inflammatory responses and promote memory loss and neurodegeneration. It is plausible that inflammation-immune mechanisms would drive toxic inflammatory responses and contribute to AD neuropathology. Elimination of chronically activated microglia in AD mice (5xFAD) prevented neuronal and synaptic loss and improved memory function in the absence of any change in their Aβ levels or plaque load. Sim ilarly, immune system impaired models of AD showed improved memory function in the absence of any change in their Aβ levels or plaque load.

Despite their potential lack of construct validity, studies in AD transgenic animal models demonstrated that reactive immune responses in microglia are sufficient to stimulate neuronal degeneration and targeting the reactive microglia alone can relieve cognitive decline in these mouse models. For instance, reactive microglial cells were sufficient to promote the self-amplifying cycle of microglia in AD. This model proposes that im paired clearance of amyloid deposits and apoptotic cellular material as a result of persistent microglia dysregulation would drive toxic inflammatory responses and promote memory loss and neurodegeneration. It is plausible that inflammatory-immune mechanisms would drive toxic inflammatory responses and contribute to AD neuropathology. Elimination of chronically activated microglia in AD mice prevented neuronal and synaptic loss and improved memory function in the absence of any change in their Aβ levels or plaque load.

Extrapolating from these admittedly imperfect model systems to AD suggests that elucidation of specific microglial responses to CNS insults may be imperative for understanding and potentially treating the contribution of inflammation to processes of neurodegeneration and impaired cognitive function in AD. Recent imaging studies aiming to assess longitudinal changes in microglial activation and function.
amloid deposition in mild cognitive impairment and AD provided some clues regarding the temporal sequences and trajectories of microglia activation in the progression of AD. Initial activation during mild cognitive impairment followed by longitudinal (>14 months) reduction of microglial activation was observed during prodromal AD. A second wave of activation of microglia was observed in individuals with definite AD, suggesting the prevalence of proinflammatory phenotype of microglia in advanced stages of AD. The vulnerability of cholinergic neurons, cholinergic atrophy, and decline of acetylcholine release in AD may be at least in part responsible for proinflammatory phenotype in definite AD as acetylcholine directly modulates immune responses by acting on the α7 nicotinic acetylcholine receptor and suppressing the proinflammatory response in microglia and in blood-borne macrophages.

Acquired anti-inflammatory protective phenotype during prodromal AD may be tied to self-tolerance mechanisms; or it may exemplify chronic para-inflammatory response (low-grade inflammation) switched on due to cellular stress associated with aging and gene-by-exposome interactions such as age-associated low level of physical activity, high-calorie diet, and environmental toxin exposure, rather than tissue injury/infection. Divergent immune responses along with age-related immune responses may suppress the anti-inflammatory phenotype of microglia during the prodromal phase of AD and enable progression to frank dementia, synaptic loss, neurodegeneration, and AD. Inarguably, microglia activation will demand high rate of metabolic activity necessary for synthesis and degradation of toxic molecules and Aβ deposition. Evaluation of the microglial transcriptome in healthy adult mice showed that during physiological aging the microglial transcriptome undergoes disproportionate downregulation of genes involved in sensing endogenous ligands and upregulation of genes associated with alternative neuroprotective microglial priming states suggesting that aging is associated with the microglial transcriptome signature shifting toward neuroprotection by downregulating debris-sensing receptor signaling. Thus, it can be argued, and studied further, that neuroprotection processes assisted by activated microglia are likely central to the cognitive resilience. The presence of ubiquitin-immunoreactive dystrophic neurites in the neocortex of nonagenarians (90+ years old) humans and granular degeneration of myelin in white matter in the absence of amyloid deposition and neocortical neurofibrillary degeneration support activation of immune responses. However, extrapolation from mouse to human must be approached with caution. A recent purified microglia study in human brains found little overlap between genes differentially expressed during aging in humans and those of the mouse brain suggesting that the microglia of physiologically aged mice are not necessarily recapitulated in human aging.

Extrapolating to the CNS microglia and successful cognitive aging, one may hypothesize that robust immune responses involving ubiquitination may promote intact cognitive function in extreme age and protect against accumulation of toxic molecules and Aβ deposition. Evaluation of transcriptional profiles from human postmortem brains...
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show support for contribution of immune activation to the cognitive resilience in aging. Direct comparison of neocortex transcriptomes from young-old (64 to 86 years old) and oldest-old (87 to 103 years old) cognitively normal and demented individuals suggest that inability to scale up robust immune activation that typify oldest-old individuals who evaded dementia (Figure 1) may be directly associated with cognitive decline in the oldest-old.1 Additional examination of transcriptional changes in cognitively normal oldest-old compared with younger individuals found evidence for the upregulation of genes involved in sensing extracellular signals released during tissue injury, including LPAR5, GPR34, TREM2, CSF1R and P2RY12 (Figure 1). Uproregulation of genes involved in host defense and phagocytosis including antigen presentation, Fc receptors, and complement cascade support engagement of ent of inflammation response and phagocytosis in cognitively normal elderly. Given that microglia and complement cascade mechanisms are intimately involved in synaptic pruning and neuronal loss,50 the next generation of studies of the role(s) of microglia in cognition in Alzheimer disease must clarify the mechanisms that simultaneously avert synaptic loss while allowing for amplified expression of phagocytosis and host defense genes, including engagement of the complement cascade. One working hypothesis may be that successful aging is associated with an enhanced immune response resulting from priming of microglia, similar to the mechanisms known to occur in peripheral macrophages.54 The “primed” microglia would respond to triggering stimuli more rapidly and to a greater degree than would be expected from non-primed microglia presumably by modulating accessibility of microglia-specific transcriptional enhancers and promoters (work in transgenic mice suggests that senescent-like dysfunctional neurons are sufficient to induce progressive priming responses in microglia). This hypothesis stands in contrast to, and is underscored by, the fact that there is general consensus that acute and chronic systemic inflammation is detrimental to brain function,78 impedes adult neurogenesis,80 and is associated with cognitive decline in AD.76 This “paradox” may be more apparent than real, however, and may be a result of a too-simplistic or too-binary model of microgliosis and neurodegeneration, while in the alternative primed state microglia release anti-inflammatory immunomodulators associated with neurodegeneration. As we have discussed above, microglia assume diverse phenotypes and can promote both harmful and advantageous/neuroprotective outcomes. Findings in animal models show that upon receiving triggering stimuli, microglia in their classical primed state will release excessive concentration of inflammation cytokines (IL-1B, IFNG, TNFA etc) associated with neurotoxicity and neurodegeneration, while in the alternative primed state microglia release anti-inflammatory cytokines.
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with protection and neuroplasticity. Transcription study of isolated microglia in rodents suggested that during aging the m icroglial phenotype shifts toward an alternative neuroprotective prim ing state. Survey of protein levels of 30 cytokines in cortical grey m attre of nondem ented oldest-old when com pared with cognitively intact younger individuals showed that only a sm all set of cytokines (G-CSF, IL-6, 8, and 15) were significantly upregulated in tissue hom ogeneates (Brodm ann area 22) from nondem ented oldest-old (refer to ref 74 for unpublished data derived from the same dataset). At least two of these factors (IL-6 and IL-15) can be considered to elicit both pro- and anti-inflamm atory responses im plying that this sim plistic subdivision of cytokine responses m ay also be inadequate to classify their function and necessitate further examination with respect of neuronal and glial responses in the hum an CNS.

It is critical to keep in m ind that m icroglia and the other cell-types of the CNS do not function independently. Rather, neurons, microglia, astrocytes, oligodendrocytes, and m icrovascular endothelial cells interact extensively and function in unison. Notably, the m ost upregulated cyto kine in the brain of nondem ented oldest-old is granulocyte-colony stim ulating factor (G-CSF) which has been shown to induce neurogenesis, neuroplasticity to counteract apoptosis, and is known as a factor involved in vasculogenesis. G-CSF is currently under investigation for the development of treatments of neurological diseases such as acute cerebral ischem ic stroke. In this respect, participation of brain m icrovascular endothelial cells in inflam m atory responses is highly critical as they can initiate the release of cytokines/chem okines, reactive oxygen species capable of inducing neurotoxicity, expression of antigen presentation m olecules (MHC class II), phagocytosis-related Fc receptors, and m atrix m etallopeptidases. In contrast, M2 (a,b,c) phenotypes are central for inflam m atory reso lution, imm unom odulation, angiogenesis, tissue repair/remo deling and associated with release of neurotrophic/pro-survival factors and anti-inflamm atory cytokines. These phenotypes are not static, however, and exhibit dynamic changes at different ages, stages of evolution of diseases such as AD, and in response to different environmental stimuli. Novel approaches such as single-cell and cell-type-specific transcriptomics have revolution ized modern immunology and suggests that classification systems such as M1 and M2 phenotypes may be inadequate for the advanced understanding of m icroglia diversity in health and disease. Recent advances in next-generation sequencing and single-cell transcriptomics show that m icroglia activation states associated with development, aging and different neuropa thologies are varied, display unique m ultiple transcription signatures that are not only distinct from myeloid cells/m acrophages in peripheral tissue, but also m uch m ore complex than those im pled by M1 vs M2 dichotomy imm unox genic vs/tau antagonism. For exam ple, a comprehensive m apping of all im mune cell clusters in AD m oscue brains revealed novel neurodegenerative disease associated m icroglial subtypes localized in proxim ity to neuritic plaque foci m ore of which appear to have the potential to restrict/confine AD neuropathology. Another intriguing finding

Microglia plasticity - different states of activation and altered immune cell composition in Alzheimer disease

Activation of m icroglia is frequently categorized by the M1-classical and M2-alternative phenotypes sim ilar to the categorizations attributed to m acrophages. The M1 phenotype is considered a proinflamm atory state char acterized by elevated levels of cytokines/chem okines, reactive oxygen species capable of inducing neurotoxicity, expression of antigen presentation m olecules (MHC class II), phagocytosis-related Fc receptors, and m atrix m etallopeptidases. In contrast, M2 (a,b,c) phenotypes are central for inflam m atory resolution, imm unom odulation, angiogenesis, tissue repair/remo deling and associated with release of neurotrophic/pro-survival factors and anti-inflamm atory cytokines. These phenotypes are not static, however, and exhibit dynamic changes at different ages, stages of evolution of diseases such as AD, and in response to different environmental stimuli. Novel approaches such as single-cell and cell-type-specific transcriptomics have revolutionized m odern imm unology and suggests that classification systems such as M1 and M2 phenotypes may be inadequate for the advanced understanding of m icroglia diversity in health and disease. Recent advances in next-generation sequencing and single-cell transcriptomics show that m icroglia activation states associated with development, aging and different neuropathologies are varied, display unique multiple transcription signatures that are not only distinct from m yeloid cells/m acrophages in peripheral tissue, but also much more complex than those implied by M1 vs M2 dichotomy immunogenic vs/tau antagonism. For example, a comprehensive mapping of all immune cell clusters in AD mouse brains revealed novel neurodegenerative disease associated microglial subtypes localized in proximity to neuritic plaque foci some of which appear to have the potential to restrict/confine AD neuropathology.
of that analysis was the identification of TREM2-dependent activation of gene networks specific to the novel disease-associated microglial subtype, which is consistent with genetic evidence of TREM2 polymorphism and dysregulation associated with increased risk of AD.45,98 Recent meta-analysis of myeloid transcriptional responses from the fusiform gyrus of individuals with AD and controls, and animal models of different pathological states provided additional information about m icroglial population-wide transcriptional changes indicating upregulation of not only the TREM2-dependent core neurodegeneration-related subtype, but also additional cell-type clusters including phenotypes related to neutrophil/m onocyte, which were absent in AD mouse models and a subtype related to the phenotypes related to neutrophil/monocyte, which were absent in AD mouse models and a subtype related to the acute response to endotoxin lipopolysaccharide.9 It is not clear whether multiple m icroglial cell clusters represent various dynamic phenotypes of activated m icroglia, such as phagocytic, antigen presenting cells (APC), and/or whether they include CNS-infiltrating m onocyte-derived m acrophages and Aβ-reactive T cells. What these m ore recent studies reveal is a remarkable diversity in m icroglial cell phenotypes that requires reassessment of functional distinctions and perhaps even a new taxonomy.

While the functions of m icroglia as APC for adaptive immune responses has not been characterized in AD, the appearance of perivascular and intraparenchymal dendritic cells (DC) - classical APCs - has been demonstrated in brains of patients suffering from epilepsy and encephalopathies.100 These findings are consistent with data acquired in adult transgenic m ice showing pronocit appearance of DCs in CNS regions exhibiting plasticity and adult neurogenesis with the m orphologic characteristics of immune/microglia cells.101 However, these CD11c-positive DC cells express low levels of MHC class II genes suggesting that their function as APC m ay be flawed or that within the CNS their functions m ay be different or possess features in addition to classical antigen presentation. It is possible that these DC-like cells within the CNS m ay not infiltrate from the periphery. It has been suggested that adult m icroglial progenitors m ay differentiate into m ature DCs in the presence of granulocyte-m acrophage colony-stimulating factor and express extracellular m ark ers distinct from the rest of microglia.9,100 These DC-like cells can m ature fully into DC upon CD40 ligation.100 Consistent with this hypothesis, T cell-based vaccination in AD m ice induced the appearance of a DC-like CD11c m icroglia phenotype which was associated with increased neurogenesis and m proved spatial learning and m em ory suggesting that DC-like m onocytes m ay be of benefit to the brain’s resistance to AD by aiding T helper cells to induce T cell activation as APC.

Lim ited work in postmortem human brains also suggests elevated appearance of T cells (T cell receptor expressing m ature T lymphocytes are part of the adaptive immune system) in the brain parenchyma of elderly and individuals with AD.104-106 More comprehensive tissue immunochemical staining using m ultiple T cell m ark ers have confirmed increased frequencies of T cells in the hippocampus, the entorhinal cortex and associated brain regions of individuals with AD compared with other types of dem entia and controls.107 These observations have supported the view that brain parenchymal T cells are likely m em ory T cells rather than naïve T cells based on the cell-surface m ark ers staining.107 The absence of the IL-2 receptor subunit (CD25), proliferation m ark ers, and CD11b staining in CD8+ cells argues against clonal expansion of T cells in AD brains, and their complete differentiation into effector cells.107 Taken together, these findings suggest ineffective activation of T lymphocytes or a brain-specific T lymphocyte phenotype in AD brain.

A subtype of T cells, regulatory/suppressor T cells (Tregs), is another component of the immune system, critical for the modulation of inflammatory responses, and usually difficult to distinguish from effector T cells. Modulation by Tregs of overall systemic inflammation, m atory status m ay also translate into differential activation and functional differentiation of parenchymal m icroglia. The m echanism involved in this interaction and the infiltration of circulating immune cells into the CNS is a controversial topic and a question that needs to be addressed with high priority. It has been hypothesized that elevated activity of Tregs, key m unsuppressors, and protectors of systemic immune tolerance, is permissive of cerebral plaque pathology and cognitive decline in AD, and m ay contribute to the limited efficacy of anti-inflammatory m atory treatment trials of AD.24,108 Under neurodegenerative condition CNS recruitment of circulating immunoregulatory cells, such as T cells, m ay be critical for m oderating m icroglial m ediated neuroinflammation m atory response. In support of this hypothesis, tem porary reduction of Tregs restored system immune suppression and boosted accumulation of inflammation m ation-resolving cells in the brain parenchyma, which was...
associated with reduced brain protein levels of soluble β amyloid and reversed cognitive decline in transgenic AD mice.\textsuperscript{24,108} Similarly, early vaccination experiments with CNS antigens showed enhanced recovery after axonal injury\textsuperscript{109} and subsequently boosting levels of CNS-specific circulating T cells facilitated the recruitment of monocyte-derived macrophages from the periphery to the CNS sites of injury where they differentiate locally into resolving macrophages.\textsuperscript{110} The blood-CSF barrier of the choroid plexus is a likely candidate for a selective site of monocyte CNS infiltration and is characterized by distinct population of effector-memory T lymphocytes expressing T-cell receptors specific for CNS antigens.\textsuperscript{111} The cellular composition of CSF is different from that of peripheral blood and constitutively predisposed towards a tissue injury healing, pro-resolving, environment characterized by elevated levels of anti-inflammatory cytokines, which may act as a permissive mechanism allowing leukocyte infiltration through the choroid plexus.\textsuperscript{112} Blocking of brain IFN-I signaling improved neurogenesis and partially restored cognitive function in aging mice.\textsuperscript{113} Commencing murine studies have reported strong increases of the subset of Tregs negative for the immunosuppressive programmed death receptor 1 in individuals with mild cognitive impairment.\textsuperscript{114} Studies in humans have shown that age-induced dysfunction of the choroid plexus and cognitive decline are associated with elevated expression of IFN-I responses interfering with IFN-type II regulation of leukocytes homing, rolling, and migration, which may act as a permissive mechanism allowing leukocyte infiltration through the choroid plexus.\textsuperscript{115} Thus, a more thorough understanding of cells with Treg phenotype is required for disentangling these diverse findings.

The exposome, its individual constituents, and sex are additional factors influencing adult microglia and need special attention. Ex vivo and in vitro experiments show profound variability in microglial phenotype at different stages of AD progression.\textsuperscript{116} Different pathological states of microglia, their phenotypic diversity and the myriad roles and responses of microglia and the ways in which they influence and modulate the functions of other cells of the CNS. As daunting a task as this may seem, recent advances in cell-type specific omics provides the light at the end of the tunnel.

**Challenging immune responsiveness in central nervous system – therapeutic approaches to Alzheimer disease**

Current immunotherapeutic approaches to AD aim to reduce amyloid burden and reduce or slow the rate of cognitive decline by increasing amyloid β clearance and microglial phagocytic activity, while dampening pro-inflammatory cytokine production. Suppression of inflammation alone through non-steroidal anti-inflammatory drug therapy has been disappointing, or had adverse effects in advanced AD. With hindsight, this is not surprising given that, as described above, microglial activation phenotypes are contextually different and evolve at different stages of AD progression (reviewed in ref 118 and ref 119). The anti-inflammatory agent, prednisone, was explored in a randomized, multi-center trial\textsuperscript{120} with no positive outcome and with some adverse reactions. Minocycline-antibiotic immunomodulation, neuroprotective in neurodegenerative models and with an unknown mechanism of action, showed reduced production of proinflammatory cytokines, while showing promising results for amyloid clearance.\textsuperscript{121-123} Recent clinical trial in patients with moderate-severe traumatic brain injury showed detrimental effects of chronic phase minocycline treatment, increasing neurodegeneration, while decreasing inflammation.\textsuperscript{124}
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One line of defense against toxic amyloid subspecies could be natural neutralizing antibodies, which can be expanded upon imunization with Aβ peptides (active vaccination). The first active vaccine (AN1792, consisting of pre-aggregate Aβ Elan Pharamaceutical) was term inated because it induced autoimmunity in hum ans. Postrm m rine tissue exam ination showed T cell infiltration and inflammatory around leptomeningeal blood vessels, near vascular amyloid and infiltration of microglia in white matter. Despite these negative consequences, imunized patients also showed improved in am amyloid clearance and reduced amyloid plaques and microglial markers reminiscent of the phagocytic phenotype.

Another approach has focused on passive vaccination by administering antibodies against Aβ. Several anti-Aβ monoclonal antibodies (eg, bapineuzumab, solanezumab and mAb158) have been developed. The cognitive benefits of the initial clinical studies with bapineuzumab are still unclear and concerns on the safety of these antibodies have been raised. Solanezumab, a humanized monoclonal antibody directed against the middle region of the Aβ peptide, was shown to neutralize soluble Aβ. Initial evaluation from two pooled phase III studies suggest a positive trend toward slowing of cognitive decline in the mild AD subgroup.

A monoclonal antibody, mAb158 has high selectivity for soluble Aβ protofibrils, which are toxic to neurons. A humanized version of mAb158, BAN2401, has now entered a clinical phase IIb trial for Aβ immunotherapy in early AD with some positive outcomes. Despite these encouraging trends, none of the trials to date have led to meaningful and substantial clinically significant outcomes.

Experimental approaches toward utilizing cellular mechanisms of adaptive immune responses against Aβ are supported by detection of elevated levels of amloid beta-reactive T cells in healthy elderly and individuals with AD suggesting that either these cells are either positively selected, or that they have escaped central and peripheral tolerance. A recent animal study provided convincing evidence that activated CD4 positive T cells polarized toward the Th1 phenotype (but not Th2 or Th17 subsets) and injected into the lateral ventricles can effectively migrate and target amyloid plaques in the hippocamal region and the cerebral cortex improving neurogenesis and alleviating amyloid burden. Interestingly, T cell function and migration within the brain parenchyma was dependent on IFN-gamma signaling in neural tissue, which is consistent with IFN-gamma regulation of adhesion and migration, which may act as a permissive mechanism allowing immune cells infiltration through the choroid plexus. T cells migration was associated with upregulation of MHC class II molecules in choroid plexus revealing that MHC-T cell receptor interactions may be a prerequisite for T cell transmigration to the CNS and agrees with hypotheses that suggest that Aβ induces adaptive immune response in the periphery. While the exact source and functional characteristics of CNS perivascular antigen presenting dendritic cells remains elusive in human studies, animal studies favor the recruitments of blood-derived monocytes and their differentiation into dendritic cells.

Hyperphosphorylation of tau at specific sites transforms normal tau into misfolded tau within paired helical filaments and leads to the canonical NFTs of AD. When secreted by affected neurons, misfolded tau may propagate pathology by inducing tau aggregation in neighboring neurons. Preclinical studies suggest that active immunization may be effective against misfolded tau in AD animal models. Very few preclinical studies of passive immunization against hyperphosphorylated tau protein are currently available. Exam ination of two Ig isotype antibodies specific to human tau pathological phosphorylation site pS404 showed that IgG2a/kappa, but not IgG1/kappa antibody, reduced hyperphosphorylation of tau and NFT burden in two independent mouse models of tau pathology.

Despite the meager effects of current clinical trials of Aβ immunization and anti-inflammatory treatment, the prospect for effective immune system-based approach for treatment of AD will be enhanced as we expand our knowledge of microglia-mediated immune responses, their phenotypic and functional diversity, and their role(s) in modulating cognition, successful aging, and cognitive decline during AD progression.

Disclosure/Acknowledgements: The authors have no conflict of interest to declare.
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Potential immunotherapy for Alzheimer disease and age-related dementia

Michal Schwartz, PhD; Michal Arad, PhD; Hila Ben-Yehuda, PhD

Emerging results support the concept that Alzheimer disease (AD) and age-related dementia are affected by the ability of the immune system to contain the brain’s pathology. Accordingly, well-controlled boosting, rather than suppression of systemic immunity, has been suggested as a new approach to modifying disease pathology without directly targeting any of the brain’s disease hallmarks. Here, we provide a short review of the mechanisms orchestrating the cross-talk between the brain and the immune system. We then discuss how immune checkpoint blockade directed against the PD-1/PD-L1 pathways could be developed as an immunotherapeutic approach to combat this disease using a regimen that will address the needs to combat AD.

Keywords: Alzheimer disease; immune checkpoint; immunotherapy; macrophage; microglia

Introduction

Alzheimer disease (AD) is a devastating age-related neurodegenerative disorder, and the most frequent cause of senile dementia.1 The appearance of cognitive decline is associated with accumulation of misfolded proteins, as well as the presence of several additional toxic agents.2 Among the common neuropathological features found in AD are synaptic and neuronal loss, intracellular neurofibrillary tangles, elevated levels of the toxic form of amyloid beta (Aβ),4-42 and the accumulation of extracellular senile plaques containing misfolded Aβ peptide.2-4 Local inflammatory responses as well as uncontrolled astrocyte reactivity are often observed in the brains of AD patients and in animal models; these processes are not necessarily the primary causes of the disease, but are considered to be key factors in disease progression and escalation.5,7 The accumulated misfolded proteins and the neuroinflammatory response have led to numerous attempts over the years to arrest disease progression, either using treatments that are directed against the misfolded proteins to arrest plaque burden,8,9 or using systemic anti-inflammatory drugs to arrest the brain inflammation. Inconsistent and even conflicting results were obtained, and none of the drugs tested thus far have proven effective in reversing or arresting cognitive loss in patients.10-16

The failure of treatments directed at Aβ to arrest or reverse cognitive loss could reflect the fact that by the time Aβ plaque burden is high, rem oval of plaques, while still important, may be insufficient to modify disease because numerous collateral disease-escalating factors enter into a vicious cycle and continue even after the plaques are removed. Such factors might include immune-related molecules and cells. In apparent support of such a view are, recent results dem onstrating that resolution of inflammation is an active mechanism mediated by recruitment of circulating immune cells to sites of brain pathology.17-19

Here, we will discuss the role of brain immune communication in brain homoeostasis and repair. In addition, we will discuss if and how activating the immune system by immune checkpoint blockade can contribute to disease modification.
Systemic leukocytes are essential players in central nervous system repair

For decades, it was commonly assumed that the brain is unable to tolerate immune cell entry, mainly due to beliefs that it is a tissue behind barriers, and considered an immune privileged site. In animal models of acute central nervous system (CNS) injuries, both monocyte-derived macrophages and CD4+ T cells recognizing brain antigens, are needed for coping with and helping heal parenchymal damage. Moreover, T cells present in the periphery facilitate recruitment of monocyte-derived macrophages to the CNS. Such macrophages play a role in supporting neuronal survival and axonal regrowth, by resolving the local inflammatory response and facilitating local scar removal. Additional studies revealed that systemic T cells not only participate in CNS repair, but are also needed for life-long brain plasticity.

Independent attempts were made to understand how T cells support healthy brain plasticity while they are excluded from the brain parenchyma, how they facilitate recruitment of monocyte-derived macrophages, and how such monocytes can gain access to the CNS without breaching the blood-brain-barrier (BBB). Such attempts have suggested that the brain’s barriers, including the meningeal barrier and the blood-cerebrospinal fluid barrier (BCSFB) can serve as a key compartment for immune-brain crosstalk in health and disease.

The BCSFB, which is comprised of the tightly connected choroid plexus (CP) epithelial cells, along with the accumulated evidence that immune cells are needed for brain maintenance and repair, led us to suggest that the CP is a physiological gateway that enables selective immune cell access, depending on the needs of the CNS.

The paradoxical fate of the “leukocyte gate” to the brain in Alzheimer disease models

Several independent studies in animal models have shown that recruitment of circulating monocyte-derived macrophages, possibly together with additional immune regulatory leukocytes, can modify AD pathology. Such cells can help remove misfolded protein including Aβ-plaques, balance the local inflammatory milieu, reduce gliosis, and protect synaptic structures.

AD is a devastating age-related neurodegenerative disorder, and the most frequent cause of senile dementia

Analyzing the fate of the CP with respect to its ability to support leukocyte trafficking revealed that its activity is impaired in animal models of brain aging and AD. It was further discovered that reducing systemic immune suppression in AD animal models, by transiently depleting peripheral Foxp3+ regulatory T cells has a beneficial effect in mitigating disease pathology. These results are consistent with an independent observation, showing that the adaptive immune system plays an important role in the progression of AD in animal models. For example, it was demonstrated that genetic ablation of B, T, and natural killer cells in the 5xFAD mouse model by crossing these mice with Rag2/Il2rc double knockout animals (Rag-5xFAD), resulted in increased plaque load and increased soluble Aβ levels.

Importantly, immunoregulatory T cells and anti-inflammatory cells are needed in the brain as a source of anti-inflammatory cytokines for reducing the inflammatory response. Homing of such immunomodulating cells requires well-controlled boosting, rather than suppression of systemic immunity. Accordingly, special care must be taken when viewing immunosuppressive cells (such as FoxP3) as uniformly beneficial or harmful in neurodegenerative diseases, without considering their localization and kinetics.

Taken together, the results summarized above created the basis for our approach of empowering the systemic immune system, by transiently blocking inhibitory immune checkpoints, to drive a cascade of immune events that starts outside the brain, induces activation of the CP, and culminates in immune-dependent brain repair processes.

Immune checkpoint blockade for mitigating Alzheimer disease pathology

Inhibitory immune checkpoints restrain the activity of memory T cells, mainly those directed against self-compounds, to avoid autoimmune diseases. Among such checkpoints are the programmed cell death protein 1...
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(PD-1), a member of the B7-CD28 family, expressed by a variety of activated effector memory immune cells, including CD4+ T cells.65 The PD-1 ligand is expressed by dendritic cells and regulatory T cells,66 as well as by non-immune cells such as endothelial and epithelial cells,67,68 and astrocytes.66 The interaction between PD-1 and PD-L1 suppresses memory T-cell responses, including proliferation, and cytokine production.65,66 Blocking the PD-L1/PD-1 pathway potentially results in an increase in T cell activation.70-72 Based on our new understanding, we envisioned that targeting systemic PD-1/PD-L1 might be a way to activate such a protective/reparative immune response.

Our studies using anti-PD-1 or anti-PD-L1 antibody in the 5xFAD mouse model of AD, as well as in a dementia model of tau pathology, revealed that such treatments are effective in helping and even reversing cognitive impairments and reducing disease pathology. This process was associated with monocyte-derived macrophages homing to the brain.61,62 These macrophages locally express numerous molecules including scavenger receptors for removal of dead cells as well as misfolded or aggregated proteins, anti-inflamm atory cytokines, and growth factors.61,64 Importantly, a single injection of antibody directed against either PD-1 or PD-L1 initiated a chain of events that started outside the brain, and led to alterations in several processes within the brain that together resulted in disease modification.64 Notably, in most mouse models of AD, disease symptoms begin earlier in females than in males. In humans there is no clear scientific consensus regarding gender differences in AD, though most studies have shown that men and women exhibit differences in the development and progression of the disease.73 Generally, women are considered at greater risk and show more rapid progression.74 Notably, both female and male mice of tau-driven models of dementia and amyloid β-driven pathology similarly responded to treatment with m un ano logical events that start outside the brain, and, in synergy with inflammatory signals emerging from the diseased brain, restore the immune unbalance between the brain and the immune system? The resulting m odification of the im muno logic m ilieu of the brain culminates in reduction of cognitive deficits and disease pathological manifestations. The treatment protocol going forward to clinical trials will require intermittent administration of the antibody. Such a protocol is likely to reduce adverse immunological effects. Moreover, since the treatment is not directed against a single factor within the brain that contributes to disease escalation, but rather affects common immunological pathways, it is expected to have a higher efficacy than past attempts, and to overcome disease heterogeneity and some translational obstacles.

Conclusion
In conclusion, results from animal studies suggest that treatment with PD-1/PD-L1 blockade evokes a series of immunological events that start outside the brain, and, in synergy with inflammatory signals emerging from the diseased brain, restore the unbalanced unbalance between the brain and the immune system? The resulting modification of the immune milieu of the brain culminates in reduction of cognitive deficits and disease pathological manifestations. The treatment protocol going forward to clinical trials will require intermittent administration of the antibody. Such a protocol is likely to reduce adverse immunological effects. Moreover, since the treatment is not directed against a single factor within the brain that contributes to disease escalation, but rather affects common immunological pathways, it is expected to have a higher efficacy than past attempts, and to overcome disease heterogeneity and some translational obstacles.

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What are we trying to prevent in Alzheimer disease?

Frank Jessen, MD

Within aging societies, the number of individuals suffering from Alzheimer disease (AD) is consistently increasing. This is paralleled by intense research aimed at improving treatment options and potentially even fostering effective prevention. The discussion on relevant outcomes of such interventions is ongoing. Here, different types of currently applied outcomes in the treatment of AD at the dementia stage, but also at the pre-dementia stages of mild cognitive impairment (MCI) and asymptomatic preclinical AD are discussed. Regulatory agencies require effects on the clinical measures of cognition and function. In novel disease-modifying therapy trials, biological markers are used as secondary and exploratory outcomes. Additional outcomes of great relevance for the individual patients are neuropsychiatric symptoms, quality of life, and goal attainment. In addition, costs and cost-benefit ratios are of interest for the reimbursement of interventions.

Keywords: Alzheimer disease; clinical trial; dementia; disease modification; mild cognitive impairment; outcome; preclinical Alzheimer disease; symptomatic treatment

Background

Alzheimer disease (AD) is the most common cause of dementia. According to current concepts, AD refers to a pathological brain process, which extends over several years to decades. Core pathologic features are aggregation of the amyloid-β (Aβ)-peptide, which originates from the amyloid-precursor protein (APP) and aggregation of the neuronal tau protein tau. These processes are accompanied by synaptic dysfunction, inflammatory reactions, neurodegeneration, and related molecular mechanisms. The accumulation of pathology evolves over many years within the preclinical phase, during which the individual does not experience any symptoms or functional effects of this process. Subsequently, symptoms develop slowly over many years. Longitudinal studies suggest that around 10 years before the stage of dementia, subtle cognitive decline begins, which is often accompanied by the subjective experience of cognitive worsening. This stage may also be accompanied by mild behavioral symptoms such as depression, anxiety, apathy, and sleep disturbances. Once the dysfunction in cognition becomes apparent and detectable on neuropsychological testing, the stage of mild cognitive impairment (MCI) is reached. MCI is defined by objective cognitive dysfunction with still fully intact functioning and independence in daily living. After the MCI stage, which may also last for a number of years, dementia gradually develops. Dem entia is defined by substantial impairment in cognitive capacities, which causes functional disabilities (eg, severe memory impairment, orientation deficits, language comprehension problems, apraxia) with the requirement for support in everyday life. The dementia stage can be divided into a mild, a moderate, and a severe stage. The latter is characterized by full dependency on care and the inability to perform basic activities of
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daily life. This is often accompanied by severe language impairment, full loss of memory, and motor symptoms. Behavioral neuropsychiatric symptoms often occur, sometimes at a severe degree. Such symptoms include, but are not limited to, delusions, hallucinations, agitation, severe apathy, depression, anxiety, and severe sleep disturbances. Care demands usually increase, with the progression of cognitive and functional decline reaching the maximum at the severe dementia stage. The late stage is also associated with higher costs and with frequent institutionalization. Caregiver's burden and health risks are significant throughout the dementia stage of AD. Death occurs after a limited number of years within the dementia stage of AD is reached. Neuropathologic changes are progressive and extended brain tissue loss with a particular focus on medioperiodal regions and cortical areas occur in the late stage of the disease. Based on this disease course, different aims of treatment and prevention have been developed over the past decades.

Treatment goals of symptomatic therapy

In the late 1980s and early 1990s, the currently licensed drugs for symptomatic treatment of either mild-to-moderate (acetylcholinesterase inhibitors) or moderate-to-severe (memantine) Alzheimer dementia were developed. Since then, the US Food and Drug Administration (FDA) and the European Medical Agency (EMA) have required the proof of efficacy on two parallel end points, namely global cognition (both) and global clinical change (FDA) or activities of daily living (EMA) for such symptomatic treatment at the different dementia stages. In the trials for regulatory approval of such drugs, proof of AD pathology in the individual patient is usually not required. The label is formulated based on the clinical syndrome of dementia.

The gold standard for testing cognition in the symptomatic treatment of Alzheimer dementia is the Alzheimer’s Disease Assessment Scale, cognitive part (ADAS-Cog) of which different versions are available. Within the ADAS-Cog, different domains of cognition are tested in a paper-pencil approach. A total score is calculated. For cognition at the advanced dementia stage, the Severe Impairment Battery (SIB) is available. Global clinical change, which is the additional FDA requirement, is assessed with physician-based rating scales. The second end point, which is required by the EMA, refers to the ability in performing activities of daily living (ADL). A number of different ADL scales are in use in clinical trials. For both, clinical change and ADL capacities ratings, information provided by the caregivers is incorporated.

All currently licensed drugs for the treatment of Alzheimer dementia showed superiority against placebo on both of these end points in at least two independent 6-month trials. The effect size of the drugs on the respective outcomes are small to moderate and range between a Cohen's of 0.3–0.5. Clinical trials show that on average a slight improvement in performance is observed for a period of 3 to 6 months. After that, further decline occurs. If these drugs are stopped even at the stage of progressive worsening, decline is accelerated. Thus, many guidelines propose to continue such drugs long-term, beyond the 6-month period, which is the basis for licensing. Novel symptomatic treatments are currently tested as an add-on to the licensed medication using the same end points and trial durations.

There have been extensive debates on whether effects on cognition per se are relevant patient-related outcomes and whether the effect size of such drugs is sufficient to provide and adequate benefit-risk ratio. At present nearly all international guidelines on the treatment of Alzheimer dementia have concluded that these drugs are of benefit and are recommended for treatment. The clinical benefit is supported by the effect on the clinical change and ADL scales, which reflect outcomes related to daily functioning.

Symptomatic outcomes for the pre-dementia state of Alzheimer disease

With the development of novel drugs, which aim at slowing disease progression, and with the failure of such drugs in clinical trials in mild to moderate dementia, research has moved the field of pre-dementia disease...
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Detection and intervention. The target population for most current trials is patients with MCI and combined groups of MCI and mild dementia, in whom cerebrospinal fluid (CSF) biomarkers or positron emission tomography (PET) indicate the presence of amyloid pathology. In such target populations, cognitive performance is the main outcome. The ADAS-Cog is optimized for the mild to moderate dementia stage. Therefore, additional, more demanding cognitive test batteries have been generated mainly from observational cohort studies in these patients groups. One of these cognitive test sets is referred to as the neuropsychological test battery (NTB). At present, there is not yet a specific cognitive test battery, which could be considered the gold standard in the MCI/mild dementia population. Until now, there have been no drug trials which showed an effect on these cognitive scales as a primary outcome. This may be due to the lack of efficacy of the respective compounds, but may also be at least partly caused by insufficient sensitivity for change of the current instruments.

Patients at the MCI/mild dementia stage only show minor or no impairment of ADL scales, which are used in mild-to-moderate Alzheimer dementia clinical trials. Scales for the assessment of complex instrumental ADL are under development and provide evidence for subtle impairment in functioning already in this patient group. To date, however, such scales are not used as primary end points in clinical trials.

Due to the subtlety of effects in this patient group on standard scales for Alzheimer dementia clinical trials, the FDA and the EMA have recently agreed upon accepting a single primary end point in MCI/mild dementia clinical trials, which usually have a duration of 12 to 24 months. The currently proposed single primary end point for such trials is the Clinical Dementia Rating Scale (CDR). This instrument rates cognitive and functional capacities based on a physician interview with the patient and the caregiver. Besides a global score, which can be used for classification of patients into different stages of the cognitive impairment, it also provides a continuous measure (CDR sum of boxes, CDR-SOB). The CDR-SOB is considered to reflect a clinically meaningful combined assessment of cognition and function. Up to now, however, studies in the respective target population have failed to demonstrate an effect on the CDR-SOB as a primary end point. Once first compounds achieve this goal, the effect size will guide the discussion on clinical relevance.

Measuring cognitive change at the pre-mild cognitive impairment stage of Alzheimer disease

A few clinical trials aim at impacting on the disease course and on cognition even in the pre-MCI stage of AD. Examples of such studies are the A4 trial in amyloid positive cognitively normal individuals as well as the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) and the Autosomal Dominant Alzheimer’s Disease (ADAD) Trial, which perform studies in cognitively normal individual with causal monogenic mutations. In these long-term studies, which may exceed a number of years, sensitive cognitive batteries, also derived from observational cohorts, are employed to detect subtle change in cognitive performance over time as the primary end point. One example of such instruments is the Preclinical Alzheimer Cognitive Composite (PACC). At present all of these studies are ongoing and results are to be expected within the next few years.

Alzheimer disease biology as an outcome of treatment

The leading concept of recent drug development in AD is disease modification. This refers to impacting on the core molecular pathology of the disease plus achieving a slowing of symptom progression. The main current molecular target is the deposition of amyloid. Several trials in different patient populations have been performed or are ongoing. Molecular effects are measured by biomarkers. In phase 2 and 3 clinical trials, such biomarker outcomes are measured as secondary or exploratory end points in addition to the cognitive and functional primary outcomes.

Anti-amyloid approaches are capable of reducing cerebral amyloid load and Aβ production. Amyloid plaque reduction by monoclonal antibodies against amyloid has been demonstrated with PET. Postmortem analysis of individuals who received active immunization against amyloid showed a correlation between the antibody titer and the reduction of amyloid plaque load.
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<td><strong>Cognitive tests</strong></td>
<td></td>
</tr>
<tr>
<td>Alzheimer Disease Assessment Scale, cognitive part (ADAS-Cog)</td>
<td>Global cognition, required by EMA and FDA in mild-to-moderate AD trials, different versions available</td>
</tr>
<tr>
<td>Severe impairment battery (SIB)</td>
<td>Global cognition in moderate-to-severe dementia</td>
</tr>
<tr>
<td>Neuropsychological test battery (NTB)</td>
<td>Global cognition and individual cognitive domains, optimized for mild cognitive impairment (MCI)</td>
</tr>
<tr>
<td>Preclinical Alzheimer cognitive composite (PACC)</td>
<td>Global cognition and individual cognitive domains, optimized for preclinical Alzheimer disease</td>
</tr>
<tr>
<td><strong>Clinical ratings</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical dementia rating scale (CDR)</td>
<td>Rating of cognition and function in different domains, often single primary end point in MCI/mild AD trials</td>
</tr>
<tr>
<td>Clinician’s interview-based impression of change with caregiver input (CIBIC-plus)</td>
<td>Rating of the overall status of the patient in comparison to an earlier time point</td>
</tr>
<tr>
<td>Alzheimer’s Disease Cooperative Study/ activities of daily living scale (ADCS/ADL)</td>
<td>Assessment of functional capacities in activities of daily life (ADL), all dementia stages, distinction between instrumental and basic ADL, several other ADL scales available</td>
</tr>
<tr>
<td><strong>Behavioral symptom assessments</strong></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric inventory (NPI)</td>
<td>Quantitative rating of twelve different behavioral domains, caregivers' burden rating included, short version available</td>
</tr>
<tr>
<td>Cornell scale for depression in dementia (CSDD)</td>
<td>Measures symptoms of depression</td>
</tr>
<tr>
<td>Cohen-Mansfield agitation inventory (CMAI)</td>
<td>Measures agitation and aggression in dementia</td>
</tr>
<tr>
<td>Dementia care mapping (DCM)</td>
<td>Observation-based assessment of mood and well-being in severe dementia</td>
</tr>
<tr>
<td><strong>Additional outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Quality of life in Alzheimer’s disease scale (QoL-AD)</td>
<td>Assesses different aspects of quality of life in dementia, other scales available</td>
</tr>
<tr>
<td>Goal attainment scale (GAS)</td>
<td>Develops individual goals of an intervention in a hierarchical fashion</td>
</tr>
<tr>
<td>Resource utilization in dementia (RUD)</td>
<td>Measures the quantity of used health care resources in a defined timeframe</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>Time to nursing home placement</td>
</tr>
<tr>
<td><strong>Biological markers</strong></td>
<td></td>
</tr>
<tr>
<td>Amyloid</td>
<td>Aggregated amyloid can be measured with positron emission tomography (PET), Aβ42 can be quantified in the cerebrospinal fluid (CSF)</td>
</tr>
<tr>
<td>Tau, phosphorylated tau (ptau)</td>
<td>Both can be quantified in the CSF, Tau indicates neuronal injury, ptau indicates AD-related modification of Tau</td>
</tr>
<tr>
<td>Neurofilament light (NFL)</td>
<td>Can be measured in the CSF and in the blood, corresponds to neurodegeneration</td>
</tr>
<tr>
<td>Hippocampal volume, whole brain volume</td>
<td>Can be measured with magnetic resonance imaging</td>
</tr>
</tbody>
</table>

Table 1. Examples of different types of outcomes in clinical trials in Alzheimer disease.
inhibition of the β-secretase with respective inhibitors leads to a significant reduction in Aβ42 reduction in the brain.28 Thus, it is possible to impact on specific molecular mechanisms related to AD and to measure such effects. At present however successful lowering of cerebral amyloid has not been associated with a slowing of symptom progression, which is an unexpected outcome of the majority of recent trials.27,29 In one small study with the monoclonal antibody Aducanumab, however, reduction of amyloid as detected with PET was accompanied by a dose dependent slowing of disease progression as measured with the CDR-SOB as an exploratory outcome over 12 months in mild Alzheimer dementia.30 This promising compound is currently being tested in two phase 3 international clinical trials.

There is a growing number of clinical trials with anti-tau compounds.31 At present, however, data is too limited to understand the effects of anti-compounds on biomarker of total tau, phosphorylated tau (ptau) or tau-PET as well as on clinical outcomes.

An unspecific marker of neurodegeneration, which also occurs as a core feature in AD, is the volume reduction of brain tissue as detected with magnetic resonance imaging (MRI). In trials with active and passive anti-amyloid immunization, the hippocampus and other measures of brain volume, such as whole brain volume and ventricular size, were used as indicators of the impact of amyloid-lowering on neurodegeneration. To general surprise, the volume reduction of the hippocampus was accelerated within the verum groups in comparison with the placebo groups in a number of trials.32,33 This finding, however, was not accompanied by accelerated cognitive decline. The cause of accelerated brain volume loss in anti-amyloid treatment is not resolved at present.

Trials with other compounds, which potentially stimulate neuroplasticity to a certain extend, provide opposite results. In a placebo-controlled trial with donepezil, a slowing of volume reduction of the hippocampus in prodromal AD as the primary outcome was observed. This was, however, not associated with cognitive effects.34 In a placebo-controlled trial with the medical food Fortasyn Connect®, slowing of hippocampal volume reduction was also observed as a secondary end point in a 12-month trial. This effect was paralleled by a slowing of decline on the CDR-SOB. The primary cognitive end point of that study, however, was negative.35 Overall, established biomarkers, which are used to identify AD pathology, have provided evidence for molecular target engagement of novel compounds. The relationship with symptoms and thus, the potential usefulness of a surrogate marker of treatment effects in AD is unclear.

Novel biomarkers are under development. As an example, Neurofilament Light Chain (NFL) has been identified as a marker of axonal injury and neurodegeneration in CSF and plasma.36 In multiple sclerosis, there is promising evidence that NFL may serve as a meaningful marker of disease-modifying treatment.7 Trials in AD are ongoing. Overall, the need for biomarkers, which serve beyond diagnostics and extend to treatment monitoring and outcome prediction is substantial.

**Additional outcomes related to patient benefit**

From the very beginning of cognitive decline up to severe dementia, patients experience neuropsychiatric symptoms (NPS), which include, but are not limited to depression, anxiety, apathy, agitation, hallucinations, delusions, and sleep disorders.7 In the majority of current clinical trials effects of drugs or interventions on these symptoms are measured as secondary end points. The most commonly used instrument is the Neuropsychiatric Inventory (NPI), which cover all NPS domains quantitatively and also assesses the associated caregivers’ burden.38 Currently licensed drugs for the treatment of mild, moderate, and severe Alzheimer dementia have shown modest positive effects on such symptoms on a global level.39,40 There is no clear evidence yet that such symptoms are affected by novel disease-modifying approaches.

There are many studies which apply specific drugs from psychopharmacology, such as antipsychotics and antidepressants to improve single NPS (eg, depression, psychosis, agitation).41,42 Often specific scales exist for such individual symptoms, such as the Cornell Scale for Depression in Dementia (CSDD)43 or the Cohen-Mansfield Agitation Inventory (CMAI).44 Overall, some antipsychotics show benefits on specific target symptoms.41 At the same time, these drugs are associated with increased mortality rates and other side effects in
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dementia.\textsuperscript{41,45} Thus, the use should be limited to cases with very clear indication and the treatment duration should be as short as possible. Antidepressants have a more favorable side effect profile. However, their efficacy in reducing symptoms of depression seems to be lower than in patients with depression, but without dementia.\textsuperscript{42} Greater improvement of NPS than with medication is achieved by nonpharmacological interventions, in particular by those, which focus on communication and environment. A number of instruments are available to measure quality of life (QoL) in patients with dementia.\textsuperscript{46} One main challenge in assessing QoL in dementia is cognitive impairment, particularly in the domains of memory and language, which interferes with the report on QoL as a highly subjective construct by the patient him- or herself. In particular, if symptoms of anxiety and depression occur inconsistently, the overall report by the patient at a given time point may be of insufficient validity. Due to the subjective nature of QoL, study partners or caregivers cannot easily serve as substitutes. One approach of assessing QoL in dementia indirectly, is by constant observation as developed in nursing science via Dementia Care Mapping (DCM). In DCM, patients with severe dementia are observed over a long period of time and their emotional expressions are constantly recorded. Based on such very extended assessment it is possible to estimate the patient’s well-being and to guide and modify interventions.\textsuperscript{47}

A highly patient-centered outcome is the goal attainment approach.\textsuperscript{48} Here, individual goals related to a specific intervention are defined within a clinical interview with the patient and the caregiver. These goals are ranked in order of importance. At follow-up visits, it is discussed with the patient and the caregiver, if steps towards this goal were achieved or not. The meaningfulness of this outcome is significant, as it is individually tailored. The Goal Attainment Scale (GAS) has been used in randomized controlled clinical trials in Alzheimer dementia.\textsuperscript{49} However, challenges with regard to standardization of the method and the interpretation of data have to be acknowledged.

Cost-related outcomes

Due to the extensive costs generated by AD, particularly at the late disease stages, there is a high interest in the potential of cost reduction by individual interventions.

The Resources Utilization in Dementia (RUD) instrument is most commonly used in clinical trials.\textsuperscript{50} It measures all costs related to care over the previous weeks. As yet, however, efficacy of interventions on the RUD has not yet been solidly shown.

Another frequently assessed outcome is institutionalization, referring to transition from the home environment to a nursing home. Since institutionalization is associated with increased cost, it can be considered a health economic outcome. In prospective randomized clinical trials, institutionalization is not a common outcome, because in mild dementia or pre-dementia stages, at which most trials are performed, it is a rare event. Institutionalization was assessed in the DOMINO trial (donepezil and memantine in moderate to severe AD) in the United Kingdom (UK), which tested the impact of randomized withdrawal of the acetylcholinesterase inhibitor donepezil after long-term treatment in patients with moderate to severe dementia, who showed cognitive decline. The study found a significantly lower rate of institutionalization within the first 6 months in those who were randomized to treatment continuation in comparison with those who were discontinued.\textsuperscript{51}

It has to be acknowledged that institutionalization and other measures of cost are very much dependent on the health care system of the respective countries and regions. Thus, conclusions on cost savings of interventions cannot easily be transferred between health care systems.

Conclusion

Alzheimer disease is a very complex condition with very many facets and many potential goals of intervention. The majority of drugs currently under development are focusing on disease modification by targeting key molecular mechanisms of the disease such as amyloid deposition and tau aggregation. Biomarkers provided evidence of target engagement of such compounds. So far, however, none of these novel compounds has shown a robust effect on the clinical symptomatology of the patients. In the current absence of effective prevention of dementia, it is crucial to further develop pharmacological and nonpharmacological interventions, which aim at improving and stabilizing symptoms at all disease stages, such as cognition and ADL function, but also neu-
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ropropsychiatric symptoms and quality of life of patients and caregivers. Once novel drugs have shown efficacy, effect sizes, patient-related benefit, and cost-benefit evaluations will guide the discussion on reimbursement and ultimately decide on access to such innovations for the patients. In the end, we will hopefully achieve successful early treatment development with pharmacological and lifestyle-based interventions, which will significantly delay disease progression and will keep patients independent for prolonged periods of time.

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Cognitive stimulation, training, and rehabilitation

Alexander Kurz, MD, PhD

Cognition-focused interventions for people with cognitive impairment including mild-to-moderate dementia may be classified into three categories: cognitive stimulation, training, and rehabilitation. Cognitive stimulation, consisting of nonspecific cognition-enhancing activities often in group format, produces small improvements on some aspects of cognitive ability which can be accompanied by gains in quality of life, everyday functioning, and social interaction. Cognitive training which involves repeated practice of tasks that target specific cognitive functions, often using computers, provides improvements on trained tasks that usually do not translate to nontrained tasks and have little impact on real life. Cognitive rehabilitation represents an individual approach that focuses on disability rather than cognition per se and is helpful in terms of reaching personally relevant goals and improving day-to-day performance. Data are largely lacking to support commercial claims regarding the efficacy of video games or virtual reality and augmented reality devices. There is insufficient evidence from randomized controlled trials whether cognition-focused interventions can delay or prevent cognitive decline. However, data from prospective cohort studies strongly suggest that late-life cognitive activity is associated with a reduced risk of dementia.

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Keywords: cognitive; dementia stimulation; mild cognitive impairment training; rehabilitation; video game; virtual reality

Introduction

Cognitive impairment is a key feature of dementia. The most frequent underlying causes are progressive neurodegenerative diseases. Since these pathologies affect multiple brain regions and neuronal networks, cognitive deficits are not limited to single domains such as memory, language, or perception (as in pure amnesia, aphasia, or agnosia) but simultaneously involve several functions, both on basic (attention, speed) and higher levels (executive function, social cognition). Nonpharmacological interventions that target cognitive functions address different populations, pursue different aims, and use different strategies. Prevention of cognitive decline and dementia involves asymptomatic people who are at risk of developing dementia due to age, family history of dementia, or subjective cognitive complaints. The hypothesis here is that cognitive engagement strengthens the brain’s resilience (“brain reserve” or “cognitive reserve”) against neurodegenerative damage. Enhancement or maintenance of cognitive function is an important goal in people who already have some degree of cognitive impairment. The underlying assumption is that cognitive exercises improve trained functions and may transfer to nontrained domains. The practicing of compensatory strategies attempts to bypass impaired cognitive functions using internal (eg, mnemonic devices) or external (eg, memory aids, action prompters) tools. The concept is that people with dementia can adopt alternative strategies to reach personally important goals. Cognitive intervention strategies are usually classified into cognitive stimulation,
cognitive training, and cognitive rehabilitation.\textsuperscript{1} Although this classification has been called into question because the three categories are vaguely defined and many interventions comprise components of more than one category\textsuperscript{2} it will be used for structuring the present article. Innovative cognitive strategies that take advantage of advanced information and computer technology and represent a rapidly growing market include video games, virtual reality, and augmented reality. Drawing mainly on systematic reviews and meta-analyses, the present article aims to provide an overview of cognition-focused interventions in cognitively healthy individuals and in people with mild cognitive impairment and dementia, and to discuss practical implications. Intervention effects are summarized in Table I.

**Table I. Effects of cognitive interventions.** CF: cognitive function; ADL: activities of daily living; QoL: quality of life; PB: problem behaviors.

### Cognitive stimulation

This is a nonspecific approach where a range of different activities, usually in group format, are used to engage and stimulate the individual in order to enhance cognitive, social, and communicative functioning. Interventions often include components of reminiscence therapy, reality orientation, social activity, and sensorimotor exercises. Emphasis is on the involvement of multiple cognitive domains rather than the targeting of one specific cognitive function.\textsuperscript{1}

#### Cognitively healthy older adults

A review that did not clearly distinguish between cognitive stimulation and training showed that most studies targeted memory; other areas of exercise were attention and executive function. There was a large heterogeneity among interventions with regard to format (group, individual, computerized), intensity, and duration. Sample sizes were usually small. All interventions produced some significant improvements at least on single cognitive functions but had no impact on activities of daily living or quality of life.\textsuperscript{3}

### People with mild cognitive impairment

A meta-analysis on 17 studies concluded that cognitive stimulation programs provided significant post-treatment benefits in overall cognition and episodic memory, as well as smaller, nonsignificant gains on executive function, semantic memory, attention and processing speed, visuospatial ability, and language.\textsuperscript{4} The positive effects of cognitive interventions in people with mild cognitive impairment are retained for 3 to 4 months after treatment initiation.

### People with dementia

A Cochrane review and meta-analysis of 15 randomized controlled trials (RCTs) with varying duration and intensity, including a total of 718 participants who had mild-to-moderate stages of dementia, revealed a clear, consistent benefit of cognitive stimulation on cognitive function with a moderate effect size. The benefits of cognitive stimulation enhanced those of medication. The cognitive improvement was evident at follow-up 1 to 3 months after the end of treatment. Benefits of moderate size were also noted on self-reported quality of life. Participants were reported to communicate and interact better than previously. No differences between treatment groups were observed.
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regarding mood, activities of daily living, or problem behaviours. The results of the Cochrane review were confirmed by a more recent meta-analysis which showed a moderately sized effect of cognitive stimulation on general cognitive ability, a small benefit on quality of life but no impact on problem behaviors or activities of daily living. Maintenance cognitive stimulation for 24 weeks resulted in improvements of self-rated and proxy-rated quality of life and activities of daily living. The above findings were expanded in another recent meta-analysis on 33 studies involving people diagnosed with dementia. Post-intervention, a significant pooled effect size was found for cognitive stimulation versus nonactive controls using the Mini Mental State Exam (MMSE) as a measure, corresponding to a group difference of 1.78 points. A smaller but still significant pooled effect size was seen versus active controls. On the Alzheimer’s Disease Assessment Scale, cognitive part (ADAS-Cog), the pooled effect size was smaller, even compared with nonactive controls. The conservative threshold for clinical significance of two points on the MMSE was only reached in about half of the studies involving nonactive controls and only in two of nine studies using active controls. According to a small number of studies the favorable effects on cognitive ability were maintained at 3 months and 6 months after the end of the intervention.

Cognitive training

Interventions of this kind involve guided practice of a standardized task targeting a specific cognitive function, typically without explicit teaching of memory techniques (mnemonics) or problem-solving strategies. The assumption is that repeated exercise will lead to an improvement in the cognitive domain trained, and may generalize to nontrained cognitive functions. Cognitive training is usually delivered individually, may be computerized or non-computerized, and is often adaptive, allowing an increase in task difficulty as expertise develops. Since computer-based cognitive interventions are more cost-effective than traditional face-to-face formats, and adjusted to individual performance, and overcome mobility barriers, they have gained considerable attention and have triggered a “brain training” business.

Cognitively healthy older adults

A systematic review of 34 RCTs concluded that training in a particular cognitive domain using classic cognitive training tasks or neuropsychological software has the potential to improve performance in that domain compared with inactive or active control conditions. According to the ACTIVE Study such effects may persist over 2 years or even longer. However, benefits of cognitive training do not translate into gains on nontrained functions. This also applies to computer-based online and performance-adaptive training using working memory, logic, and planning games (30 minutes per day, 5 days a week). In a systematic review, 38 studies on computer-based cognitive training programs in healthy older adults were evaluated. Moderate-to-large effect sizes were found on standard neuropsychological tests for attention, reaction time, speed of processing, working memory, executive function, and visuospatial abilities. Training sessions lasted from 2 weeks to 24 weeks, ranging from daily to three times weekly sessions. The studies suggest that classic cognitive training tasks are most likely to improve working memory, executive function, and processing speed. On the other hand, neuropsychological software appears to be most effective in the domains of memory and visuospatial ability. These studies also suggest that older adults do not need to be technologically savvy to benefit from computerized cognitive training.

People with mild cognitive impairment

A review of computerized cognitive training found more derate but statistically significant effects on global cognition, verbal learning, verbal memory, nonverbal learning, working memory, attention, and psychosocial functioning. These results indicate a beneficial therapeutic role for computerized cognitive training in this population. No significant results were found for executive function (which may have been insufficiently trained), information processing.

Innovative cognitive strategies that take advantage of advanced information and computer technology and represent a rapidly growing market include video games, virtual reality, and augmented reality.
speed, visuospatial skills, language, or instrumental activities of daily living. There was no difference across studies with active or passive controls.\textsuperscript{11} These findings were confirmed and complemented by another recent systematic review showing that technology-based cognitive training in people with mild cognitive impairment (MCI) can provide benefits on noncognitive domains including reduced depression and anxiety. Immediate effects of activities of daily living or quality of life were only observed in single studies.\textsuperscript{15} According to another meta-analysis, computerized cognitive training in people with MCI does not impact measures of activities of daily living, whereas therapist-led interventions provide benefits in this regard, particularly if compensatory strategies are taught.\textsuperscript{16}

**People with dementia**

A recent systematic review included 31 RCTs and a total of more than 2000 participants with a clinical diagnosis of Alzheimer disease (AD), mostly of mild severity. The review concluded that cognitive training, alone or when combined with other intervention methods, improved at least one cognitive outcome in 2/3 of the trials. Higher intensity (twice weekly or more) and intensity of training (24 sessions or more) were associated with greater benefits. Positive results were most often observed in global cognition (e.g., assessed using the MMSE), but were rarely observed in specific cognitive domains. Many trials reported improvement limited to tasks in the same domain as training, but only three studies found a generalization of effects to other domains than trained. Effects on activities of daily living or quality of life were not reported. No clear evidence was found that combinations of cognitive training with other strategies are superior to cognitive training alone.\textsuperscript{17} A review focusing on computerized cognitive training identified 12 studies encompassing 389 participants with dementia. The overall effect on global cognition was weaker in this group than in individuals with MCI and was statistically nonsignificant. Interestingly, clinically meaningful effects were found only for studies that used non-traditional approaches to cognitive training such as virtual reality and exergaming (see opposite page).\textsuperscript{11}

**Cognitive rehabilitation**

This is a more individualized approach to helping people with cognitive impairments. Cognitive rehabilitation does not set out to train or improve cognition but uses a goal-oriented approach to facilitate the management of functional disability.\textsuperscript{18} This type of intervention has only been used in people with mild-to-moderate dementia.

**People with dementia**

In people with early dementia in AD eight individual sessions consisting of personalized interventions to address pre-defined relevant goals supported by compensatory strategies significantly improved goal performance but had no effect on measures of cognition.\textsuperscript{19} In a small group of people with mild to moderate dementia training of instrumental activities of daily living (twice weekly for 6 months) which incorporated techniques of error-free learning and spaced retrieval resulted in significant improvement of activities of daily living which were maintained after 3 months. The intervention had no effects on general cognitive ability, everyday quality of life, or behavior.\textsuperscript{20} In another study on a small sample of people with early-stage Alzheimer disease, 8 sessions of cognitive rehabilitation (60 minutes per session, once weekly) were compared with an active control condition. The intervention resulted in significant improvement on pre-defined individuals goals, general cognitive ability (MMSE), and self-rated quality of life.\textsuperscript{21} In a large, long-term RCT individualized cognitive rehabilitation was compared with cognitive training using standard tasks, reminiscence, and a passive control condition. Interventions were provided in small group format (exception: cognitive rehabilitation) in weekly sessions over 3 months followed by maintenance sessions every 6 weeks for 21 months. After 2 years, cognitive training and reminiscence had no effect on cognition, activities of daily living, behavior, quality of life, or depression. On the contrary, the individualized cognitive rehabilitation therapy provided modest but clinically significant improvement; in particular, it reduced functional disability and delayed institutionalization.\textsuperscript{22}

**Video games**

Most video games have not been designed to improve cognition and are not targeted towards specific cognitive domains. A review of 8 studies on commercially available video games in cognitively healthy older adults found low-to-moderate effects on global cognition, reaction time, processing speed, executive function, and attention. Exercises lasted for 2 to 11 weeks and from 2 to 5 hours per week. Thus, video game training appears to have an impact on
measures of reaction time and processing speed with less consistent results regarding measures of executive function and memory. In people with mild dementia, benefits of video games have also been reported on mood and behavior. The combination of games and physical exercises has been termed “exergaming.” A very small number of studies have been conducted to explore virtual reality interventions in people with dementia have shown small effects of such combined interventions on episodic memory, instrumental activities of daily living, and physical performance. There are no data regarding the comparison of video games and other cognitive interventions.

Virtual reality

This technology is defined as interactive virtual image displays to convince users that they are immersed in a synthetic space. The technology has been suggested for use in the areas of diagnosis and training for people with cognitive disorders and dementia. Virtual reality applications focus on navigation, orientation, face recognition, and instrumental activities of daily living. A characteristic which is particularly helpful in people with cognitive impairment is the high level of interaction that can be achieved using devices such as joysticks, gloves, and surfaces. Most current virtual reality systems for training concentrate on performing activities that are related to autobiographical memory or instrumental activities of daily living. A characteristic which is particularly helpful in people with cognitive impairment is the high level of interaction that can be achieved using devices such as joysticks, gloves, and surfaces. Most current virtual reality systems for training concentrate on performing activities that are related to autobiographical memory or instrumental activities of daily living.

Augmented reality

This technology enhances a real environment by superimposing synthetic elements into the user’s perception. In contrast to virtual reality systems, users of augmented reality applications face real physical locations upon which additional virtual elements are introduced. To date, only a few systems have been developed to assist people with cognitive impairment. An example is an ambient annotation system which notifies persons with dementia of digital tags or notes placed on objects or furniture by their carers.

Does cognitive training or stimulation prevent cognitive decline or dementia?

According to prospective cohort studies, cognitively stimulating activities are associated with a reduced risk of dementia, while randomized controlled trials have demonstrated that cognitive stimulation or training provides cognitive long-term improvements. Therefore it is tempting to assume that continuous cognitive activity or training may delay or even prevent cognitive decline and dementia. A putative neurobiological mechanism is that cognitive engagement may increase the brain’s resilience against neurodegenerative disease (“brain reserve” or “cognitive reserve”). However, there is currently insufficient evidence regarding whether cognitive stimulation or training reduces the risk of future cognitive impairment or dementia.

In a nonrandomized 3-year study on cognitively healthy older adults, habitual levels of cognitive activity in combination with any degree of physical activity—but not without physical activity—were associated with a reduced incidence of MCI after 3 years. A randomization comparison of physical activity, cognitive activity, the combination of both, and social activity as an active control several times per week over 1 year in older adults with MCI showed significant cognitive improvement in all four groups at study end point, but no differences between groups with regard to overall cognitive status or instrumental activities of daily living. The prospective randomized FINGER Study started cognitively unimpaired older adults on a combination of cognitive training with other lifestyle modifications (diet, exercise) and vascular risk monitoring which improved executive functions and processing speed, but not memory, at 2-year follow-up. The recently completed randomized MAPT Study compared a nutritional program with a multi-component intervention including group cognitive training with placebo in a large sample of nondemented older adults with cognitive complaints. The rate of cognitive decline after 3 years did not differ between the groups. These findings confirm that cognitive activity, alone, or in combination with other intervention modalities, may preserve or even improve cognitive functions over extended periods of time. There is insufficient
evidence to date, however, that cognitive interventions have a potential to delay or even prevent the incidence of cognitive impairment or dementia.

**Discussion**

Cognitive stimulation, ie, nonspecific cognition-enhancing activities, produces small improvements on some aspects of cognitive ability in cognitively healthy older adults, in people with mild cognitive impairment and in people with mild to moderate dementia. These gains are maintained for 3 to 6 months post-intervention. While the clinical significance of the effects of short-term cognitive stimulation remains questionable, maintenance cognitive stimulation over longer periods has been shown to enhance quality of life and activities of daily living. Because cognitive stimulation is usually performed in group form at, it also provides benefits in social interaction and reduces unification. Therefore, cognitive stimulation is recommendable as part of the management of people with any level of cognitive impairment or dementia, except for advanced dementia, in different settings. In contrast, cognitive training, ie, repeated practice of tasks that target specific cognitive functions that is often computer-based, provides improvements on nontrained tasks which do not translate to gains on nontrained tasks and usually have no impact on everyday performance or quality of life. The poor ecological validity could be due to the fact that cognitive training commonly addresses memory, speed, or perception, whereas everyday functioning is most closely associated with executive abilities such as inductive reasoning, and self-rated or carer-rated quality of life is not predicted by memory or other cognitive abilities. There are no data showing that cognitive training is superior to cognitive stimulation in people with cognitive impairment. Cognitive rehabilitation is a therapist-intensive individual approach which targets disability rather than cognition per se. It improves the attainment of personally relevant goals as well as performance on day-to-day tasks in people with dementia, and may even delay institutionalization, but has little impact on cognitive abilities. There are no convincing data on the efficacy of video games, virtual reality, and augmented reality in people with cognitive impairment. Therefore, commercial claims regarding the benefits of these kinds of interventions must be met with caution. As yet, there is also no evidence from randomized controlled trials that cognitive interventions can delay the onset of cognitive impairment or dementia in people at risk. Randomized and controlled studies with long follow-up intervals are needed to demonstrate such preventive effects. Since it is not clear whether treatment programs combining multiple modalities are likely to provide additional benefits over single-component strategies, interventions in preventive trials need not be limited to complex variables. While conclusive evidence from randomized trials is still awaited, a large body of data from prospective cohort studies shows that greater participation in late-life cognitive activities is associated with a lower incidence of dementia. This strongly suggests that a cognitively active lifestyle including cognitive stimulation or training may offer some reduction in risk of dementia. More research is needed to better characterize the type, duration, intensity, and timing of cognitive activities before more specific recommendatons can be developed.

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**Original article**

**Dementia treatment versus prevention**

Robert Perneczky, MRCPsy, MBA

Alzheimer disease (AD) and dementia are becoming increasingly prevalent due to the aging of the global populations. Currently available treatment options, including acetylcholinesterase inhibitors and memantine, only have symptomatic effects and no drugs with disease-modifying properties are available. Research on the amyloid cascade indicates that amyloid-β (Aβ) clearance from the brain may be the main pathophysiological change in late-onset AD and the key driver of neurodegeneration, which ultimately results in progressive cognitive deterioration and dementia. Most new AD drug candidates target different aspects of Aβ clearance, eg, using passive anti-Aβ immunization, but so far, all efforts to develop more effective drugs have failed. In parallel, nonpharmacological prevention trials are being conducted to modify dementia risk associated with known epidemiological risk factors. Some initial results are promising, but replication across independent cohorts remains a challenge.

**Keywords:** Alzheimer disease; biomarker; clinical trial; dementia; epidemiology; mild cognitive impairment; prevention; prognosis; public health; treatment

**Introduction**

Due to the aging of the global populations, chronic disorders are becoming increasingly prevalent. This includes dementia, which in 2015 affected 47 million people worldwide and is expected to affect twice as many people 20 years from now. Most late-onset dementia cases are related to Alzheimer disease (AD) pathology, but mixed etiologies are more prevalent in older populations. Amloid-β (Aβ) plaques and tau neurofibrils, the two pathological hallmarks of AD, have less impact on cognitive performance in the oldest-old compared with younger individuals, and “pure” AD cases are also less frequent in older patients, who mostly have additional neuropathological lesions, including vascular changes. Also, significant Aβ pathology is not only found in individuals with dementia but is also prevalent in cognitively intact individuals, and age is a main predictor of Aβ plaques, even in the absence of relevant cognitive decline.

In neuropsychiatric tradition, AD was conceptualized as a clinicopathological duality, ie, a diagnosis was only possible in the presence of an amnestic-type progressive dementia syndrome and the exclusion of alternative etiologies. This simple set of criteria is not particularly sensitive for early changes nor is it specific enough for AD pathophysiology. Therefore, in the last 10 years evolving sets of new AD criteria were proposed by different international expert groups, aiming to steer the dementia field towards a more biologically oriented disease concept, similar to other areas of medicine, such as cancer, where biomarkers are used to define diseases. This paradigm shift is fuelled by the urgent desire to develop more effective, ie, disease-modifying rather than purely symptomatic, treatment options. Being able to identify a disease in its pre-symptomatic or prodromal stage would open new opportunities to prevent or slow pathophysiological processes rather than merely trying to retard the worsening of symptoms. The development of biomarkers which are more sensitive for the early stages of AD is a...
prerequisite for a successful transformation of the diagnostic approaches.

Individuals at risk of cognitive deterioration and dementia, who are still asymptomatic, would probably benefit most from intervention strategies aimed at prevention of further neuronal loss. If no or only minimal symptoms are present, effective disease modification could help the target population to maintain their independence, fulfillment of social roles, and ability to work for a longer period of time.

Biomarkers of AD pathophysiology may improve diagnosis and prognosis in early AD cases; also, surrogate end points are required to ensure that only individuals with a high a priori likelihood of the target pathology are included in interventional studies and to avoid exposing individuals to potentially significant side effects who are unlikely to benefit from the treatment. Biomarker-based endophenotypes are also required to prove the feasibility of large-scale prevention studies aimed at exploring the effectiveness of factors derived from epidemiological research, such as obesity, diabetes mellitus, and physical inactivity. Due to the decades-long silent, pre-clinical stage of AD, prevention trials would have to be conducted over extended periods to be able to reliably assess their effectiveness. Using imaging or other biomarkers to identify eligible study participants and to demonstrate effectiveness of the new intervention would significantly reduce sample size and study length. However, so far it has not been possible to replace traditional clinical study end points by biomarker-derived surrogates.

Early diagnosis

Early diagnosis is essential in chronic disorders if disease-modifying treatment options are available, which can alter disease trajectories, and which offer meaningful benefits to the affected individuals. For AD, all available treatments ie, cholinesterase inhibitors and memantine, only have symptomatic effects, which on average offer comparably small clinical benefits. Since all efforts to develop more effective, disease-modifying drugs have so far been unsuccessful, the future availability of these drugs is currently a far-fetched argument in support of the early recognition of AD. In contrast, providing individuals and their families with reliable information about the underlying causes of cognitive and functional decline and behavioral change can reduce uncertainty and conflicts and may therefore be a valid reason for early diagnosis in certain situations. Furthermore, individuals at increased risk for short-term cognitive deterioration may benefit from early diagnosis if it enables them to make important decisions affecting their future lives, such as making a will, as long as their decision-making capacity is still preserved. However, only a few patients seem to use the early diagnostic information to initiate advance care planning, indicating that there is either no great demand for this information, or that improved counseling is required in these situations.

There are also certain disadvantages and risks associated with receiving information about a diagnosis of early AD. Without effective treatment options, affected individuals are confronted with the prospect of inevitable loss of cognitive abilities and independence, while no countermeasure is available. The ambiguous prognosis associated with currently available biomarkers may have significant psychological consequences, including stress, despair, depression, or even suicide in extreme cases. Negative effects on employment or interpersonal relationships may also occur.

Most studies concur that currently available AD biomarkers perform remarkably well in situations when prodromal AD cases need to be separated from “normal” aging or when progression from minor cognitive complaints to full-blown dementia has to be predicted. However, even in specialist settings, in which AD cases are preselected and relatively “pure,” at least 30% of individuals with full-blown AD-type dementia have normal biomarker findings. Current biomarkers show better sensitivity than specificity; therefore, ruling in AD as the main cause of cognitive complaints is more difficult and inaccurate than ruling it out.

Biomarkers with improved specificity and sensitivity for early AD may be available in the near future.
ally, they will not only offer better diagnostic and prognostic value, but will also be less invasive than current biomarkers, which require a lumbar puncture for CSF protein assessment or the application of a radioactive tracer for positron emission tomography (PET) studies. Blood-based markers, for example, would facilitate large-scale screening efforts and the inclusion of a large number of individuals at risk for future cognitive decline in prevention studies. An improved biomarker could potentially be used in a two-stage screening approach, with an initial pre-screening step using affordable, low-invasive techniques to identify individuals with Aβ pathology, followed by more expensive and invasive testing only in a subset of participants. Using traditional technology such as enzyme-linked immune sorbent assays (ELISA) to measure Aβ in blood was associated with insufficient accuracy.13 Using a new generation of high-sensitivity technology, more accurate measurement of blood biomarkers appears to be possible.14,15

Pathomechanisms

The most influential model of AD pathophysiology, and therefore the most frequently targeted mechanisms in AD drug development, is the amyloid cascade hypothesis, which was originally derived from findings in rare autosomal dominant mutation carriers.16 Briefly, amyloid precursor protein (APP) is cleaved by either α-secretase, resulting in soluble non-amyloidogenic products, or β- and γ-secretases, which results in the Aβ peptide, which initially aggregates to form soluble oligomers, and subsequently insoluble fibrils, later found in the typical senile plaques. The soluble Aβ aggregates may be the main drivers of synaptic and neuronal loss, rather than the insoluble, fibrillar deposits.17

The importance of soluble forms of Aβ in the pathological AD cascade is underlined by the toxic effects of small peptide complexes on synapses and mitochondria.18 Respiratory chain defects and autophagic degradation are central mitochondria-related pathomechanisms in AD,19 which contribute to the release of toxic oxygen species, impair energy production and related axonal transport, and interfere with calcium homeostasis.20 Aβ also leads to a local inflammatory response, which involves microglia clusters, upregulated acute phase proteins and other mediators of an inflammatory response.21 Microglial activation and neuroinflammation may be beneficial and neuroprotective in the early stages of AD, but overactivation of the cerebral immune system may be a harmful driver of neurodegeneration in later disease stages.21

It was repeatedly demonstrated that the number of senile plaques is not the main structural correlate of cognitive deficits in AD; loss of synapses and neurons in the neocortex and hippocampus is much closer correlated with the deterioration of cognitive performance.22 An imbalance of Aβ is most likely the main driver of protein accumulation in the brain. Overproduction of Aβ is likely the key pathomechanism in early onset autosomal dominant cases, but Aβ production in late-onset sporadic disease is only slightly higher than in age-matched control subjects.23 Therefore, Aβ clearance from the brain is probably a major contributor to cerebral peptide accumulation.

A number of different mechanisms for Aβ clearance have been described. This includes active, receptor-mediated transport across the blood-brain barrier (BBB) by the receptor for advanced glycation end products (RAGE) from blood to brain24 and by a soluble form of the low-density lipoprotein receptor related protein 1 (LRP1) from brain to blood.23 Until recently, transport across the BBB was considered to be the main mechanism for Aβ removal from the brain; however, findings from the past few years support the existence of additional important mechanisms.25 Bulk-flow of interstitial fluid (ISF) mediated by astroglia (ie, the glymphatic system) and recently discovered lymphatic vessels in the meninges may also make a meaningful contribution to Aβ clearance.26 The degradation of Aβ by cleaving enzymes such as neprilysin and insulin-degrading enzyme may also play an important role.27 Since the different clearance systems probably act together to drive Aβ from the brain, any change in their function could contribute to AD. It is therefore key to prove our mechanistic understanding of Aβ clearance, which may be used to develop improved approaches to reduce excess Aβ deposits and delay, or prevent, AD onset.

Previously, it was thought that about 75% of Aβ is cleared by BBB transport and only 10% by the glymphatic system. However, recent photon imaging studies in mice, using microscopy with fluorescent tracers, have suggested that the glymphatic system contributes to a larger part...
to Aβ clearance than previously thought. Water channels called aquaporin 4 (AQP4) on the vascular end feet of astrocytes facilitate convective flow out of the pararterial space and into the interstitial space. Mislocation of AQP4 water channels may contribute to neurodegenerative disease progression.

During wakefulness, the interstitial volume is more contracted, which increases resistance to convective flow and cerebrospinal fluid (CSF) movement. During sleep, the interstitial space increases in volume, which facilitates convective flow, CSF-to-ISF turnover and thus glymphatic clearance. Choroid plexus functioning and arterial pulsatility determine the CSF dynamics and for instance regulate CSF influx through the perivascular space and are the driving forces of the glymphatic system. Factors influencing arterial pulsatility, such as vessel stiffness and heart rate, affect the amount of waste clearance. Arterial pulsatility decreases due to processes such as metabolic syndrome, hypertension, hyperlipidemia, diabetes, or aging. Arterial stiffness and increased pulsatility of cerebral blood flow potentially damage small vessels and may indirectly affect glymphatic clearance and can possibly lead to neurodegeneration.

Besides BBB disruption, inflammation can also contribute to glymphatic dysfunction. Inflammation slows down the convective flow, decreases CSF-to-ISF turnover, and impairs glymphatic clearance. A schematic representation of clearance pathways is provided in Figure 1.

The exact pathophysiological link between Aβ and the second pathological hallmark of AD, hyperphosphorylated tau, is still largely unknown. At the same time, there is a growing body of evidence suggesting that tau hyperphosphorylation and form ation of neurofibrils are secondary events, which are catalysed by Aβ. In vitro experiments using different cell types (for example, primary cortical or hippocampal neurons and hippocampal organotypic cultures) support the notion of Aβ-induced changes of tau. For example, there is evidence that Aβ oligomers promote tau phosphorylation and induce oxidative damage. An increasing number of animal experiments are also in support of tau pathology induced by Aβ. Even though initial AD mouse models express mutant APP without overexpression of tau did not have significant tau aggregation or neurofibrils, subtle changes of endogenous tau related to increased Aβ included hyperphosphorylated tau. Moreover, mouse AD models with high senile plaque load consistently showed dystrophic neurites with hyperphosphorylated tau around the plaque edges.

**Current treatment options**

Treatments used for specific disorders reflect the pharmacological and pathophysiological understanding of their time, and AD is no exception in this regard. Initial attempts to treat AD were not related to any of the currently known core pathophysiological abnormalities, but were merely targeting unspecific suspected disease mechanisms, including brain metabolism and perfusion. Subsequently, drugs were developed, constituting the current generation of treatment options, which aim at rectifying the biochemical consequences of nerve cell loss in specific neuron populations, still without any impact on the underlying pathophysiology.

Neurodegeneration in AD involves subcortical brain regions, which includes the locus coeruleus, the dorsal raphe nuclei, and the basal forebrain; the associated loss of neurons results in deficits of the neurotransmitters acetylcholine, serotonin, and norepinephrine, contributing to the progressive impairment of higher functions such as memory, attention, behavior, and mood. Currently, two symptomatic treatment approaches are available for AD. Acetylcholinesterase inhibitors (tacrine, donepezil, galantamine, and rivastigmine) aim to improve the cortical function by blocking the breakdown of acetylcholine, allowing the neurotransmitter to persist longer in the synapse. The other class of treatments, called NMDA receptor antagonists, targets glutamate receptors that are involved in synaptic plasticity and learning. This helps preserve the remaining healthy neurons and improves cognitive function.
concentration of acetylcholine, which is reduced due to loss of neurons in the basal forebrain nuclei (nucleus basalis Meynert).41 Similar effects are seen in nicotinic acetylcholine receptor sensitizers (galantamine).42 The symptomatic effect of memantine is ascribed to a different mechanism of action, which targets the excessive release of glutamate occurring as a result of cortical neuronal loss, by improving the signal to noise ratio of glutamatergic transmission and potentially protecting neurons to a certain degree from the toxic effects of chronically increased exposition to glutamate.43 The clinical benefits of these drugs are related to a delay of progression of symptoms over several months, but an inconsistent impact on everyday function44 and other relevant outcome measures such as behavioral and psychological symptoms of dementia (BPSD).45 Furthermore, effectiveness has only been shown in the dementia stage of AD, not in prodromal stages.46 New symptomatic drugs are still being developed and a combination of disease-modifying and symptomatic treatments may be an effective means in the future in individuals already suffering from minor AD symptoms. A review of the 2018 drug development pipeline for AD showed that most compounds currently being scrutinized in clinical trials have disease-modifying properties (63%) across phases 1 to 3, followed by cognitive enhancers (23%), and drugs targeting BPSD (12%).

**Novel drugs**

A recent analysis of studies available on www.clinicaltrials.gov shows that in 2018 the current AD drug development pipeline across all study phases encompasses 112 compounds,7 including 23 agents in 25 phase 1 trials, 63 agents in 75 phase 2 trials, and 26 agents in 35 phase 3 trials. This includes eight new drugs in phase 1, 14 in phase 2, and four in phase 3 compared with an analysis conducted in 2017.47 Biomarkers, mainly indicating Aβ status, are increasingly being used as study entry criterion, particularly for studies on disease-modifying agents. There is also a trend towards targeting earlier disease stages, ie, prodromal or preclinical AD.

Most studies (14 phase 3 trials in 2018) target Aβ, but an increase of non-Aβ m echanism s of action of com pounds in earlier stages of development is noted.

Among the different approaches targeted at Aβ, immunization remains the best developed strategy, particularly passive immunization with monoclonal antibodies. Other strategies are being explored, including efforts to inhibit the activity of the APP cleaving enzymes β- and γ-secretase or Aβ aggregation, among others. Immunization trials had an ill-fated start with AN1792 (active immunization with full-length Aβ42), for which the development was terminated prematurely because of T cell mediated meningoencephalitis in 6% of the treated study population.48 Second-generation active vaccines use antibodies restricted to the N-term inus of Aβ, avoiding T cell epi topes at the C-terminus. So far only CAD106 has advanced to phase 3 clinical development and is being studied in the Alzheimer Prevention Initiative study in homozygous carriers of the apolipoprotein E (APOE) ε4 risk allele.49

Because of the better risk-benefit profile, passive anti-Aβ immunization appears to be more promising. Passive immunization allows antibody titers to be more stable and treatment can be stopped if severe adverse events occur. However, monoclonal antibodies are relatively expensive to produce and have to be administered repeatedly.50 Bapineuzumab (AAB-001) was the first m onoclonal antibody that entered human studies, and the first passive immunization attempt that failed. Bapineuzumab is a hum anized im m unoglobulin G1 anti-Aβ m onoclonal antibody, which binds the five N-term inal residues and clears both fibrillar and soluble Aβ. Bapineuzumab was generally safe and well-tolerated, but some participants receiving higher doses developed transient vasogenic edema, now referred to as ARIA (amyloid-related imaging abnormalities).51 All bapineuzumab trials were terminated in 2012 because no clinical effectiveness could be shown,52 despite reduction of fibrillar Aβ in PET and CSF studies in patients with AD receiving the drug.53 Further failures of m onoclonal antibody studies followed in the subsequent years (eg, solanezumab)54 supporting the assumption that treatment should have been commenced earlier in the disease course, administered in higher doses, or that the wrong Aβ species were targeted. Ongoing research tries to remedy the shortcomings of previous studies by, for example, targeting preclinical AD populations to prevent neurodegeneration and associated symptoms.55 Im proved Aβ clearance from the brain is a major aim of most ongoing trials.56

In addition to Aβ, tau remains an important treatmen t target for disease m odification. Early attempts to influence tau aggregation largely failed, but some are currently...
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being reevaluated. Similar to immunization targeted at Aβ, immunotherapy studies against tau have reached early clinical development phases. Unknowns remain, including which tau epitope to target, the question of extracellular vs intracellular tau and the level of required target engagement. A growing number of compounds are aiming at targets related to tau, including neurofibrillary tangles consisting of microtubule associated hyperphosphorylated tau aggregates. The effectiveness of these strategies remains to be shown.

Prevention trials

A number of large cohorts have been established over the last decades in Europe and globally to prospectively study the effects of aging and neurodegeneration. Many of these studies collect important data on potentially modifiable risk factors of cognitive impairment and dementia, which are supported by epidemiological evidence. The available information includes lifestyle and clinical information and in some cases neuroimaging and other biomarker data and biomaterial from large numbers of relevant individuals collected at various points in life. Continuing to follow up these individuals and harmonize data collection and analysis for relevant outcome measures (eg, genome-wide data, environmental exposures, neuromaging data, blood and CSF proteins, etc) across individual cohorts is a powerful approach to fill existing knowledge gaps related to risk and protective factors and how they can be influenced by new intervention and treatment strategies. Examples of large-scale initiatives to effectively integrate information from diverse cohorts include the European Medical Information Framework for AD, the Dementias Platform UK, and the EU Joint Program for Neurodegenerative Disease Research (JPND) longitudinal cohort studies action group.

Given the complex structure of risk and etiological factors of AD, a multimodal prevention approach seems advisable. Thirty-five percent of the dementia risk is attributable to the nine most important environmental risk factors, which are all potentially modifiable. Several of these factors have been studied in prevention trials aiming to reduce risk associated with physical inactivity, suboptimal diets, and limited cognitive stimulation, for example. Overall results were mixed, and the field has since moved to investigating the effectiveness of complex interventions, addressing several risk factors concurrently in the same study.

Examples for large ongoing dementia prevention initiatives, which apply a multidomain approach, include preDIVA (Prevention of Dementia by Intensive Vascular Care), MAPT (Multidomain Alzheimer Preventive Trial), FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability), and HATICE (Healthy Ageing Through Internet Counselling in the Elderly). While, for example, FINGER showed positive effects of a 2-year multidomain intervention (consisting of diet, exercise, cognitive training, and vascular risk monitoring) on cognitive performance compared with general health advice, in preDIVA intensive vascular care was not proven to effectively prevent dementia, except in a posthoc analysis of a subgroup with untreated hypertension, and in MAPT a multimodal lifestyle intervention combined with a nutritional supplement for dementia prevention was unsuccessful as well. It still has to be clarified if certain lifestyle interventions are biologically ineffective or if lack of efficacy is caused by inappropriate methods, particularly related to participant selection, intervention intensity, and adherence.

Conclusions

Despite the disappointment associated with the failed AD treatment trials, the field has learned significant lessons in the last few years. It is now clear that monoclonal antibodies vary considerably in how they interact with Aβ forms. These characteristics impact on Aβ clearance across the BBB and are also important for potential side effects such as ARIA. Starting trials earlier in the disease course, when neurodegenerative damage is absent or minimal, will open a window of opportunity for preventive interventions; this approach will be aided by biomarkers with improved sensitivity in preclinical disease stages, which are ideally associated with less invasive procedures and lower costs. Initial encouraging results with high dose Aducanumab indicate that higher antibody doses may offer promise. Clinical effects of titration dosing seem to be equivalent to fixed dosing, but with a better safety profile with lower incidence of ARIA.

A concern with the current AD drug development pipeline is that the strong focus on the early disease stages
has resulted in a lack of new compounds targeting the later (dementia) stages.\(^7\) Only a few ongoing studies allow the inclusion of individuals with moderate AD dementia. The availability of disease-modifying drugs will not completely eliminate the need for symptomatic treatment options, which can also be used in more advanced disease stages. Otherwise, millions of people worldwide will be left to suffer from dementia without any prospect for improved care.

The lack of appropriate surrogate biomarker end points, which could be used to substitute clinical end points, is a major problem both for pharmacological and nonpharmacologic intervention studies. Misdiagnosis rates in AD trials can reach 20% of all included cases,\(^6,7\) which have probably contributed to previous failed trials. A surprisingly high percentage of currently recruiting treatment trials do not employ biomarker inclusion criteria or biomarker (secondary) end points. Several new research frames for AD classification have recently been proposed, which all have a strong emphasis on biomarkers. However, the clinical utility of those criteria has yet to be proven.\(^68\) Due to the decades-long preclinical stage of AD, surrogate biological end points are also urgently needed to make lifestyle intervention studies more feasible, which would otherwise have to be conducted over many years and result in high costs.

The success of treatment trials depends on the effectiveness of recruitment strategies, and the requirement for effective recruitment has become even more acute for large-scale prevention studies, which include large numbers of cognitive intact individuals followed longitudinally. Different types of clinical readiness registries, which collect different amounts of health-related data, have been established in the last few years.\(^69\) The overarching purpose of these registries is to identify interested individuals who can be assessed for appropriateness for clinical trials and enlist them if they have the prespecified biomarker profile required for trial participation. Optimizing the use of registries to enhance trial recruitment will be among the important lessons from studying the current registries.

Nonpharmacological prevention studies use more sophisticated methods than in the past, including evidence-based multimodal intervention programs. However, results so far have been mixed and it is not clear if reduced vascular risk scores, for example, also reduce risk for cognitive decline and dementia. Ongoing research on the biological effects of the studied interventions may help to improve the design of the prevention trials.

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The challenges of aging societies

According to the World Health Organisation’s (WHO) definition, healthy aging is “the process of developing and maintaining the functional ability that enables wellbeing in older age.”1 The new concept of decline of intrinsic capacities, comprising “the mental and physical capacities that a person can draw on [including] their ability to walk, think, see, hear, and rem em ber,” necessitates a repositioning of prevention efforts in the dementia space. The traditional definition of healthy aging as years lived free from disease is replaced by a concept focusing on a process that allows individuals to maintain their normal function as they age. This is in stark contrast to the usual health care and public health approaches, which mostly aim at identifying and treating acute illnesses rather than maintaining the intrinsic capacities throughout the life course. This paradigm shift in the definition of healthy aging will have to be followed by a process of redesigning the global health care systems with a stronger focus on preserving function for a longer period of time.

Treatment and prevention of dementia have long been considered impossible, but emerging evidence suggests that certain lifestyle choices are related to reduced risk, and that modification of lifestyle factors could be used to implement effective public health policies that promote healthy aging. A 2017 systematic review, commissioned by the US National Institutes on Aging, found that there is currently not enough evidence to justify large investments in public health initiatives geared to prevent dementia.2 The report found a mix of negative and positive effects for differ
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Dementia prevalence and costs

The increase in life expectancy is one of the major achievements of modern societies. Global health care systems, however, are confronted with new challenges due to the constantly increasing number of older people. Age-associated chronic diseases are becoming more prevalent and lead to increased suffering for the affected individuals and their families and a higher financial burden for the community. Dementia is among the most prevalent and there are imminent chronic disorders in older people; most cases are related to Alzheimer disease, but other copathologies such as cerebrovascular lesions also play an important role and dementia is mostly caused by a mix of different pathologies in people over the age of 75 years. According to estimates, 47 million people worldwide were affected by dementia in 2015 and this number is expected to double every 20 years (all things being equal). Therefore, 74 million people would be affected in 2030 and over 131 million in 2050. In terms of the costs of dementia, over 1 trillion USD was spent in 2018 in the USA alone. Only 15% of the costs is caused by medical care, the remaining 85% is related to social and family care. New healthcare models and public health approaches may replace at least some of the informal care, leading to reduced overall costs.

Even though dementia incidence and prevalence are on the rise globally, significant regional differences have been described, with a much stronger increase in low-income vs high-income countries. Currently about 58% of the global population live in low-income countries according to the WHO classification; this proportion is expected to increase to 63% in 2050, which will contribute to the global burden of dementia cases. Reliable data show an increase in the age-associated incidence of dementia in lower income regions in Latin America, Asia, and Africa, whereas the incidence are stable or decreasing in higher income regions, such as Europe and the USA. Similar trend reversals are known from other areas of medicine, for example, cardiovascular disease, cancer, and diabetes mellitus, and are frequently related to improved prevention and treatment approaches.

It is important to highlight that many of the described protective factors are interrelated.

The term inology and definitions of Alzheimer disease (AD) and dementia are currently undergoing a transformation process, which is important to define disease categories based on biological evidence which can be targeted in treatment and prevention trials. However, constantly changing definitions make it difficult to compare studies and, at least in a transition period, make it more difficult to compare results. Also, there are different definitions of prevention and it is therefore crucial to agree on a common only accepted term inology and aim to maximize the use of sparse research funding to conduct better studies. The total cost of developing an AD drug is estimated at over 5 billion USD, comparable with less than 1 billion for cancer and the pharmaceutical industry average of under 3 billion. The high costs and high failure rate associated with AD drug development has already resulted in some pharmaceutical companies focusing on more promising fields.

Intensive Vascular Care study (preDIVA),

...
It is important to point out though that the decreasing age-associated dementia incidence and prevalence in high-income countries does not equal a lower overall number of dementia cases, which is still increasing due to the higher average life expectancy.

**Risk and protective factors**

The observation that the overall dementia risk is decreasing in Europe and other more developed countries leads to the important question about the underlying reasons. Similarly to other complex diseases, the etiology of dementia is multifactorial and determined by complex gene-environment interactions. Genetic susceptibility is innate and nonmodifiable (except for epigenetic changes, which are related to environmental factors), but risk which is attributable to external parameters can potentially be modified and targeted by lifestyle intervention approaches aiming at preventing or slowing neurodegenerative changes (or its symptomatics). Many of the currently known lifestyle-related risk factors of dementia are linked to factors such as vascular disease, obesity, and diabetes mellitus, which all are potentially amenable to modification. In addition to risk factors, protective factors are increasingly receiving attention, including strategies to strengthen the reserve against neurodegenerative diseases, for example, by enhancing physical, social, and cognitive activities to enhance the resilience against dementia-related deterioration.

A recently published expert consensus (The Lancet Commission on Dementia Prevention, Intervention, and Care) suggests that about 35% of dementia can be explained by a set of nine risk factors in early, mid, and late life, including in descending order of importance, hearing loss, education to a maximum of age 11 to 12 years, smoking, late-life depression, physical inactivity, social isolation, midlife hypertension and diabetes mellitus, and midlife obesity. The magnitude of the overall dementia risk conferred by the identified, potentially modifiable risk factors is striking, in particular compared with the estimated 7% reduction in dementia incidence related to the complete elimination of the apolipoprotein E (APOE) ε4 allele, the major genetic susceptibility factor for AD.

Schooling is used in many studies as a proxy measure of reserve because of its association with lower dementia risk and because it is a readily available outcome measure in clinical and epidemiological settings. School achievement is related to a diverse array of factors, which include genes, prenatal and early childhood development, socioeconomic and cultural parameters, and personality traits. There is also some conflicting evidence on the moderating effects of schooling on the lifetime rate of cognitive deterioration and some studies suggest that education in different life stages may have differential effects on sustained cognitive performance and reserve. Since education is closely associated with the performance on the psychometric tests which are typically used to diagnose dementia, better performance may simply mirror formal education and not the degree of reserve against cerebral pathology.

Education (and related reserve proxies such as IQ or occupation) is influenced by characteristics of the environment. For individuals with only limited access to formal education, other measures (such as literacy) may better correspond to their educational experiences. In many Asian and African countries, for example, schooling is determined by socioeconomic variables (e.g., the parent’s income) rather than individual abilities and talents. Quality of education is another important aspect, which is not appropriately captured by a simple measure such as years of schooling.

The list of modifiable dementia risk factors indicates that relatively simple measures would potentially be effective dementia prevention tools. Better schooling, for example, is frequently associated with lower dementia risk and higher reserve against cognitive deterioration. The fact that formal education is typically completed by late childhood or early adulthood could suggest that...
reserve is determined early in life and cannot be modified thereafter. However, several other mid- and late-life factors have also been identified, which appear to provide reserve against neurodegeneration. Working demands a large proportion of an adult’s time and energy, and there is ample evidence that occupational attainment and certain job characteristics are associated with dementia risk. Intellectually demanding occupations, for example, appear to provide reserve against AD and FTD similar to the musculoskeletal and vascular reserve provided by long-term physical activity. A large body of evidence confirms the link between occupation attributes and risk for cognitive deterioration and dementia, and studies suggest that engagement in leisure and social activities may also be protective concerning future deterioration. It is important to mention that the beneficial effects of active lifestyles are not limited to early and mid-life. Studies suggest that lifestyle changes in later life may also contribute to better cognitive outcomes.

In addition to intellectual activities, there is evidence in support of the protective effects of noncognitive activities, suggesting that physically active individuals are at lower risk of cognitive deterioration and dementia compared with their less active counterparts. Biomarker studies indicate that the beneficial clinical effects of physical activity can also be demonstrated on a biological level, for example, by providing evidence in support of a hypothalamic-pituitary-adrenal axis response or cerebrospinal fluid AD marker changes in relation to aerobic exercise in individuals with mild cognitive deficits.

Interestingly, a decreased risk for cognitive decline has not only been shown for strenuous but also for only moderate physical activity, and it has been suggested that motor function per se has a reserve component too.

Genetic structure of reserve

Lifetime environmental exposures play an important role in determining the individual risk for cognitive decline and dem entia, but nonenvironmental factors also have to be considered, including genetic and epigenetic parameters. Also, certain reserve-related factors are usually considered environmental, even though they are also influenced by genetic characteristics. For example, single nucleotide polymorphisms (SNP) have recently been discovered which are associated with education and IQ. Maximum adult head size, estimated by head circumference or intracranial volume is an important brain structural measure of reserve, which is associated with the perinatal environment but also with genetic variation. Research on the genetic underpinnings of reserve has only recently been made possible by using genomewide association studies (GWAS) to discover SNPs associated with risk and protective factors in increasingly large cohorts, required to be able to identify genetic variants with study-wide statistical significance. Large national resources such as the German National Cohort or UK Biobank will fuel further genetic research in the years to come.

GWAS have helped to discover important associations between reserve and dementia, including that dementia shares a substantial genetic basis with reserve. Also, some of the shared SNPs appear to be related to effects already present in early life or even in utero. The importance of early-life development is underlined by studies showing a reduced risk of dem entia and a smaller impact of neurodegeneration-related changes on cognitive performance in AD in individuals with larger vs smaller head size. Brain growth is largely complete by the age of six years and brain size is the main determinant of head size, measures related to head size therefore reflect brain development early in life. An optimal brain growth therefore appears to be important for reserve against neurodegeneration and dementia decades later. Brain development is affected, in addition to genes, by external factors such as infections, nutrition, and perinatal injury. Large brains may simply contain more large neurons or synapses, but functional advantages may also play a role, such as better connectivity. But irrespective of the underlying mechanism, early-life brain development seems to play a major role in providing reserve against age- and disease-associated brain changes; hence, public health measures to promote healthy brain growth are pivotal in terms of dementia prevention.

Interventions for dementia prevention

It is important to highlight that many of the described protective factors are interrelated. For instance, education and other environmental factors strongly influence literacy, and intelligence has a strong effect on school
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achieved. The level of schooling is associated with occupational attainment, but occupations are also a form of lifelong education. Socioeconomic factors in general are also relevant determinants of education, occupation, leisure, and social activities. Individuals with protective lifestyles are less likely to drink alcohol and smoke and are more likely to be physically active and have better diets. Genetic factors also seem to (co) determine many behavioral choices such as daily physical activity, smoking, and eating habits. This underlines that studying reserve-related factors in isolation may not be the appropriate approach. Studies need to adopt a more inclusive strategy, taking into consideration that epidemiological risk and protective factors may represent interrelated constructs to a certain degree.

These considerations emphasize the need for life course research to capture a multitude of variables from birth and onward. For lifestyle interventions aimed at improved dementia prevention, multidimensional approaches may be more appropriate than strategies only targeting a single candidate lifestyle factor. The development of effective lifestyle-modifying interventions is methodologically challenging because of the slowly progressive nature of most late-onset neurodegenerative diseases, including AD, with a clinically silent stage over many years (or even decades) before the first symptoms appear. Therefore, studies either have to run over many years, limiting their feasibility, or surrogate markers have to be used to measure effectiveness, such as imaging or other biological measures. So far, using surrogate endophenotypes as primary outcomes has not been successfully implemented in prevention trials, but some encouraging results have still been reported.

The first nonpharmacological intervention trials emerged in the early 2000s. Most of them concentrated on a single modality, for example, testing the effects of aerobic exercise, cognitive training, or nutritional counselling on relevant outcomes such as vascular disease. Overall, results were mixed, and the field developed towards conducting multidomain interventions, combining the individual interventional strategies which had previously been developed and investigated. The initial findings from these more recent dementia prevention studies indicate that multidomain interventions may offer certain benefits in older individuals at risk for cognitive decline. At the same time, findings from individual studies have not been consistently replicated so far in independent cohorts, and some trials show no effects of multidomain approaches. Also, it is questionable whether the same interventions can be expected to affect different disorders, for example AD and FTD. The existing data also does not allow differentiating between neuroprotective and symptomatic effects of the interventions. More biologically rooted concepts are therefore needed. However, irrespective of the exact mechanisms, even small symptomatic effects may suffice on a population level to result in meaningful reduction of dementia cases.

Conclusions

Dementia risk is determined by a complicated interplay of factors (both environmental and genetic), some of which are modifiable and amenable to lifestyle interventions. The dementia field is currently undergoing a major paradigm shift towards more biologically oriented definitions and disease concepts (such as the 2018 National Institute on Aging – Alzheimer's Association research framework) and clinical trial design, including nonpharmacological trials, will have to adapt to these changes. The urgent desire to develop more effective, ie, disease-modifying, drugs is the main driver for the conceptual changes; however, some recent trials were able to show significant positive effects on secondary biomarker study end points, while at the same time failing to show clinically meaningful effects on cognition or daily function. Those studies emphasize the need to identify relevant pathophysiological targets is important, but showing clinically meaningful benefits for affected or at risk of dementia populations is even more important. The same notion applies to both pharmacological and nonpharmacological strategies.

There is sufficient evidence to substantiate that AD-type pathology is the most prevalent cause of dementia in older individuals. At the same time, studies also suggest that the association between AD pathophysiological changes and cognitive performance is attenuated in the oldest-old. This suggests that other pathologies may play an increasingly important role as people are getting older, and the strict categorization of dementia subtypes based on the underlying pathological changes is called into question. On the one hand, a substantial proportion of

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seemingly “pure” AD cases have mixed pathologies at autopsy (cerebrovascular lesions in many cases); on the other hand, AD-typical Aβ plaques are frequently found in cognitively intact older individuals.\(^{21}\)

Epidemiological studies highlight the importance of lifestyle-related and environmental protective and risk factors. It may be particularly important to try to improve unhealthy lifestyles during midlife, with a focus on vascular health.\(^{22}\) Improved education, reduced vascular burden and other positive, for example societal, changes during the last 20 to 30 years have probably led to a decreasing dementia risk. However, this claim only holds true for high income countries\(^{17,23}\) while dementia incidence and prevalence are on the rise in poorer countries,\(^{14}\) further increasing the economic burden and inequality between the developed and developing world. To design and implement more effective dementia prevention strategies and programs, which also involve low income regions, the fragmented population-based research landscape has to be aligned more closely. Research should account for the differences between global regions (for example concerning the educational system) and relevant associations between dementia risk factors on different levels (biological, societal, psychological) have to be studied more closely. Research should also cross the traditional boundaries between the disciplines and disease entities, for example, applying similar approaches to study AD and other dementias or unrelated neurological and psychiatric disorders.

Apparently, close collaboration between groups and comparison and contrasting of data and results will be required to develop more effective treatment and prevention options. Due to the high heterogeneity of human environment and genetic data, harmonized approaches which help reduce unwanted variation and noise are required to make progress. The pooling of data and open access to the relevant resources is also key to motivate more researchers globally to work together, including those who do not have the financial resources or infrastructure to establish their own cohorts. Databases such as the International Alzheimer’s and Related Dementias Research Portfolio (https://iadrp.nia.nih.gov/about), which aim to collect and categorize information about the major funding organizations’ portfolios, are helpful in streamlining funding strategies and maximizing resources to increase the positive impact of research on public health and to avoid duplication of activities. Such efforts, however, will need to be proceeded by the establishment of appropriate ethical, legal, and social rules and agreements accepted across regional boundaries, as advocated by the World Dementia Council, for instance (https://worlddementiacouncil.org/our-work).

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Original article
Reserve and dementia prevention - Perneczky


Introduction

This clinical research review aims to give an overview of current evidence whether and how physical activity (PA), as a protective lifestyle factor, might protect cognition in older adults who experience either subjective changes to their cognition (subjective cognitive decline; SCD) and/or objective changes (mild cognitive impairment; MCI). Based on the currently available knowledge, we were interested to determine what advice, based primarily on clinical trials, could be given in clinical settings to those groups of patients in relation to PA.

Subjective cognitive decline and mild cognitive impairment in older age

SCD describes a condition where an older person expresses persistent concerns about their cognition with experiencing a subjective decline in comparison to their usual baseline cognitive abilities. Individuals with SCD, when assessed with neuropsychological measures, show intact performance for age, gender, and education—that is, their cognition is within normal limits. Various underlying causes can contribute to the experience of SCD, such as emerging neurodegenerative diseases or

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Physical activity for cognitive health: what advice can we give to older adults with subjective cognitive decline and mild cognitive impairment?

Nicola T. Lautenschlager, MD; Kay L. Cox, PhD; Kathryn A. Ellis, PhD

Subjective cognitive decline (SCD) and mild cognitive impairment (MCI) are common conditions in older age and are associated with an increased risk of future cognitive decline and dementia. As there is currently no effective pharmacological treatment available for SCD and MCI, modifiable risk factors for cognitive decline and dementia have received increasing attention in the literature as a focus for clinical trials. Physical activity (PA) is one of the strongest protective lifestyle factors. This clinical review aims to highlight the accumulating evidence about the benefits of PA for SCD and MCI. Whilst there is agreement that at least 150 minutes of moderate aerobic PA per week in combination with additional resistance training is necessary to support brain health in people with SCD and MCI, future research is required to help inform specific advice on type of exercise, intensity, “dose” and effective strategies to encourage behavior change.

Keywords: Alzheimer disease; dementia; dementia risk reduction; exercise; mild cognitive impairment; physical activity; prevention; subjective cognitive decline
other dementia pathologies, cerebrovascular pathology, mental health or physical health problems, cognitive changes related to normal aging, personality traits, stressors, medication, and substance use, to name just a few.\(^1\) Not surprisingly the prognosis of SCD varies depending on the underlying causes. Statistically there is a 1.5- to 3-fold increased risk that individuals with SCD will develop MCI or dementia at some stage in the future, but courses over time are often difficult to predict.\(^2\) MCI differs from SCD in that objective cognitive impairment is present, but not to a level which would be required for a dementia diagnosis. For MCI, either the person themself or someone who knows them well needs to have noticed cognitive decline, but activities of daily living are still preserved, except for minimal impairment in more complex activities of daily living.\(^3\) There is still no undisputed international agreement about the exact criteria for both SCD and MCI for either research or clinical practice, which leads to various research criteria being used and makes comparison of research findings often challenging. For clinical practice, MCI could be considered as comparable to the World Health Organization (WHO) International Classification of Diseases (ICD-10) category of “Mild cognitive disorder.” In the Diagnostic and Statistic Manual of Mental Disorders (DSM 5) MCI may reflect a diagnosis of “mild neurocognitive disorder.”\(^4,5\) However it falls even better under the term “cognitive impairment not dem entia” (CIND) as CIND allows for multiple causes and conditions contributing to the condition, which reflects better clinical reality.\(^6\) MCI is often described as a transitional period between normal cognition and dementia, but this is more accurate for those cases where MCI occurs due to Alzheimer disease (AD) pathology, now often called “prodromal AD” or “MCI due to AD.” Due to the heterogeneity of underlying causes, a stable presentation or even reverting back to normal cognition are also possible outcomes. Meta-analysis data suggest progression rates to dementia after 3 to 10 years\(^7\) follow-up differ depending on the sample, with progression rates in population-based studies of 22% and in clinical settings of 39%\(^8\) compared with 1% to 3% in the normal population.\(^9\) Due to the variety of criteria used for classification of SCD and MCI, exact prevalence rates are difficult to determine. A recent harmonization effort based on data from geographical diverse cohorts lead to suggestions of a MCI prevalence rate for people of 60 and older of between 6% and 12%.\(^10\) Accurate prevalence rates for SCD are difficult to determine due to the heterogeneity between studies in characterizing the condition.\(^11\) The United States Center for Disease Control and Prevention (CDC) used a random digit dialed telephone survey across 49 States to assess SCD rates, and found 9.9% in adults aged 64 to 74, increasing to 14.3% in adults aged 75 years and older, experienced SCD.\(^12\) Prevalence rates were higher in a recent Chinese study of 2689 participants, with SCD observed in 18.8% of adults aged 60 to 80 years.\(^13\) Clearly, the prevalence of SCD is higher than of MCI, and both are more common than dementia. It is estimated that 47 m illion people live with dementia around the globe and that this number will increase to 47.7 m illion by 2030 and 131.5 m illion by 2050.\(^14\) These estimated increases in prevalence rates reflect primarily the increases in population longevity seen around the world, but these estimates might need to be adjusted given a number of recent publications demonstrating lower incidence rates than expected.\(^15\) The most common cause of dementia is AD, however there are many causes and the older a person is when developing dementia, the more likely that a mix of pathologies is responsible.\(^16\) Whilst estimates of the economic cost of dementia are frequently reported, this is much less clear for SCD and MCI. Increased health care utilization and health care costs have been reported for people with SCD and MCI or those who are one year away from their dementia diagnosis.\(^17,18\) As is the case for dementia, MCI is associated with lower levels of PA and an increased risk of balance and mobility problems as well as falls.\(^20-23\) With the current global knowledge base, effective dementia prevention is not yet a reality. Whilst this might change at some stage in the future, for example via advances in pharmacological research, in the meantime there is an increasing call to focus on potentially protective lifestyle factors to reduce the risk of cognitive decline and dementia in the aging population.\(^24\) Including in people with SCD and MCI. One of the strongest protective lifestyle factors is PA and it has been estimated that targeting physical inactivity could contribute to delaying or preventing a third of all dementia cases.\(^16\)
Physical inactivity in older age

In many countries, the main contributors to the burden of morbidity and mortality are changing, with noncommunicable diseases (NCD), such as type 2 diabetes, cardiovascular, and neurodegenerative diseases, becoming more relevant compared with infectious diseases.\(^{25}\) Physical inactivity is frequently a significant contributing component in the development of NCD and is currently estimated to be the fourth leading risk factor for global mortality.\(^{26}\)

PA can be defined as “any movement by skeletal muscles that leads to energy expenditure.” Sub-groups of PA can be grouped under occupational, household, conditioning, and sports. Exercise in this context is targeted PA, which has the aim to improve or maintain physical fitness. For this review we will focus on the subcategories of aerobic exercise and resistance training, as they have demonstrated cognitive benefits for these clinical groups.

Not surprisingly, older people are often more sedentary than younger adults. Recent systematic reviews demonstrated that sedentary lifestyle is associated with poorer cardiovascular and cognitive health and faster decline of cognitive performance.\(^{28,29}\) However, the intensity of PA, especially when it comes to potential cognitive benefits, plays an important role. For example, whilst walking is one of the most popular ways for older adults to perform PA, many people reduce their walking speed with increasing age. A large Canadian longitudinal study with 2876 older adults aged 70 to 79 years reported recently that a slowing down of walking speed in individuals predicted future decline in PA and this finding was independent of baseline physical health. Furthermore, reduced walking speed in older age has been associated with an increased risk of future cognitive impairment and mortality.\(^{30,31}\)

Physical activity trials in subjective cognitive decline and mild cognitive impairment

Most clinical trials with aerobic PA interventions for participants with SCD or MCI have an intervention duration of 6 m onths with a few offering 12 m onths or longer\(^{22-24}\). Trials demonstrating significant benefits for cognition usually aimed for at least 150 m inutes PA/week, but lower doses (120 and 90 minutes/week) were also reported\(^{35,36}\). The intervention intensity was either moderate or vigorous which was frequently defined as a percentage of maximum heart rate, heart rate reserve, or oxygen uptake (VO\(_2\) max). Although still less commonly conducted, there are now trials with resistance training reporting cognitive benefits. Resistance training occurred at least twice a week over a 6-m onth intervention duration\(^{35,37,39}\).

Significant benefits for global cognition, for example ple m a su red with the Clinical Dementia Rating Scale (CDR), the Mini Mental State Examination Test (MMSE), or the Alzheimer’s Disease Assessm ent Scale-cognitive subscale (ADAS-Cog), have been reported in the majority of PA intervention trials,\(^{30-40}\) with only a few negative exceptions.\(^{42,43}\) These findings were confirmed in a recent meta-analysis of 11 randomized controlled trials (RCT) of aerobic PA in MCI.\(^{44}\) Benefits in global cognition were also reported in trials employing multi-modal intervention where aerobic PA and resistance training were combined,\(^{45-47}\) or for specific exercises like tai chi\(^{48,49}\) or handball.\(^{50}\) Results for executive functions were more inconsistent, with reported benefits\(^{32,37,40,43,49,51}\) but also frequent negative findings.\(^{32,40,41,48}\) The same applied to memory functions, with positive\(^{32,35,37,40,43,48,49}\) as well as negative\(^{32,33,37,38,41,51}\) results. The previously mentioned meta-analysis by Zheng et al also reported small benefits for the memory domain.\(^{44}\)

Biomarker evidence

The last decade has seen a paradigm shift towards biomarker-based definitions of AD that have supported intervention and observational research in PA and other domains. The National Institute of Ageing and Alzheimer’s Association research framework (NIA-AA framework), first introduced in 2011, defines AD based on underlying pathology (eg, \(\beta\) amloid deposition, pathologic tau, and neurodegeneration) rather than clinical consequences of the disease.\(^{52}\) Jack and colleagues have further refined biomarker classification of AD by introducing the A/T/N classification scheme that provides a biomarker category agnostic to the temporal ordering of mechanisms underlying AD pathogenesis but characteristic of an individual’s current biomarker AD status across the three key AD biomarkers: “A” (Am yloid-\(\beta\); PET or CSF), “T” (CSF phospho tau, or tau PET), and “N,” (biomarkers of neurodegeneration or neuronal injury, ie, [\(18F\)]-fluorodeoxyglucose–PET, structural MRI, or CSF total tau).\(^{53}\) These
biomarker paradigms enable research to examine effects of interventions such as PA on the underlying biological causes of AD dementia.

Whilst there is a wealth of publications exploring biomarker evidence to determine the underlying mechanisms how PA protects brain health in animal models and healthy people, much fewer papers have reported this in SCD and MCI. The most commonly used biomarker to date is structural and functional MRI. In a Canadian RCT with 86 female participants diagnosed with MCI, a 6-m onth resistance training intervention resulted in increased activation in three strategic cortical regions (right frontal pole, right occipital-fusiform gyrus, and right lingual gyrus) while performing an associative memory task. In the Australian SMART trial with 100 participants with MCI, 6 m onths of progressive resistance training was associated with improved global cognition, a reduced progression of white matter lesions on MRI as well as positive gray matter changes in the posterior cingulate. Finally, in a Canadian RCT with 70 older adults with mild vascular cognitive impairment a 6-m onth aerobic PA intervention improved global cognitive function measured with the ADAS-Cog, physical fitness measured with the 6-m in walking test, and diastolic blood pressure compared with usual care with education, were observed. In a substudy of this trial, employing functional MRI, reduced activation was reported in the PA group compared with the control group in the left lateral occipital cortex as well as the right superior temporal gyrus which indicates an improvement of neural efficiency. These trial results are supported by cross-sectional evidence in MCI where PA was associated with greater hippocampal volume and fewer cerebrovascular pathology. Other studies reported increases in brain derived neurotropic factor (BDNF), reduction in inflammatory markers (TNF-α and IL-6), and improved insulin sensitivity or cortisol regulation. Whilst these findings support interesting hypotheses about the underlying mechanisms how PA might impact on cognitive health in people with MCI, future replications of findings in larger studies are needed.

**Strategies for clinical advice**

When aiming to suggest behavior change in a clinical setting in relation to lifestyle factors such as PA, it is important to reflect on the potential enablers and barriers for behavior change in this specific population. Whilst there is a healthy body of literature when it comes to PA for older adults in general, much less is known in relation to SCD and MCI specifically. Individuals with SCD and MCI have been reported more frequently than healthy older adults of experiencing loss of self-confidence, reduced well-being, and increased perceived stress levels. These findings suggest that any older adults with SCD and MCI might experience more barriers due to their more vulnerable mental health and potentially reduced resilience. There are examples in the literature where studies adapted motivational strategies used with people with dementia for individuals with MCI. These strategies included adapting the communication style when explaining the PA, providing written handouts, use of behavioral strategies, including pleasurable activities, involving a family member or friend in the activities, etc. Other suggestions included, for example, individual tailoring of the PA program to adjust for cognitive impairment, incorporating more social interaction, carefully considering safety issues, allowing for longer learning periods with more feedback and the use of video recording and music, use of multimodal memory aids, increased interpersonal support with a focus on supervision, and encouragement. Qualitative research in the form of focus groups demonstrated that depending on the degree of the cognitive impairment as well as gender and personality, preference when considering PA could differ quite significantly. The response to PA interventions may differ with gender, with men compared with women observed to achieve 14% higher adherence to a 6-m onth predom inantly walking progra m whereas in a structured lifestyle intervention women adhered better than men. Liu-Ambrose et al highlighted in a recent review that in general, gender factors in PA are highly under-researched, and more specifically when exploring the efficacy of exercise in relation to biological sex.

Most of the PA interventions to date have been supervised, group, or center-based with few utilizing a home-based approach, however the uptake and adherence to the PA has been good with similar results for both approaches. Lam et al noted from a systematic review of exercise training and physical function in individuals with cognitive impairment and dementia that not all studies report adverse events and in those that have...
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Recommendation 1: Older adults who have MCI or SCD should participate in aerobic PA of moderate intensity for at least a total of 150 minutes/week, or vigorous intensity for at least a total of 90 minutes/week. This recommendation is in addition to incidental light intensity activities of daily living.

Recommendation 2: In addition to aerobic PA (as outlined in recommendation 1), older adults with MCI or SCD should engage in progressive resistance training (PRT) activities on at least 2 days per week. This is in addition to continuing incidental activities that help with strength.

Recommendation 3: Older adults with MCI or SCD should engage in activities that help to improve or maintain balance. This is particularly important, as older adults with MCI or SCD often have poorer balance and mobility as well as an increased falls risk, compared with older adults without MCI or SCD.

Recommendation 4: PA and exercise should be individually tailored, with consideration given to factors such as health problems, physical capacity and environment. Older adults with MCI or SCD are advised to consult with their health care professional for advice before undertaking PA and exercise.

Box 1. PA guidelines recommendations for people with SCD and MCI. MCI, mild cognitive impairment; SCD, subjective cognitive decline.

The authors of this review recently contributed to an international and multidisciplinary effort to produce the first PA guidelines for people with SCD and MCI. These guidelines reviewed the specific evidence on PA for people with SCD and MCI in the literature and adapted the existing Canadian Physical Activity Guidelines for Older Adults according to the methodology outlined by the Guideline Adaptation Resource Toolkit (ADAPTE) and the Appraisal of Guidelines for Research Evaluation (AGREE II). This led to four recommendations (Box 1).

These guidelines were developed with the hope that clinicians of various backgrounds who engage with people with SCD and MCI might find them useful when trying to communicate the benefits of PA. A short lay version of the guidelines was specifically developed for the consumer and could function as a starting point to talk about the topic PA or as a reminder and motivator.

While there is now evidence that PA supports health in SCD and MCI, PA is only one component of a healthy lifestyle. A number of large multimodal intervention trials that include PA have been undertaken worldwide, including the worldwide FINGER network based on the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER trial; www.fingers.com), the French Multidomain Alzheimer Preventive Trial (MAPT), the Netherlands Prevention of Dementia by Intensive Vascular Care (preDIVA trial), the European Healthy Ageing Through Internet Counselling in the Elderly (HATICE), and the Australian Maintain Your Brain (MYB) study. Such large-scale multi-modal intervention trials in populations at risk of dementia provide exciting opportunities to examine the utility of health lifestyle interventions that could be implemented at the population level to decrease dementia risk. However further research into strategies, particularly those employing behavioral change theories and practices to enhance the uptake and maintenance of PA in this target group, is needed for the potential of PA to have an impact on reducing the risk of cognitive decline and dementia is to be fully realized.
Conclusion

Whilst this area of research is still in its infancy, the accumulating evidence about the benefits of PA for SCD and MCI starts to appear in clinical recommendations and practice guidelines. Two examples are the clinical review in JAMA by Langa and Levine which gives dialogue examples on how to counsel patients with MCI on protective behaviors, such as exercise,72 the other is the practice guideline update for MCI from the American Academy of Neurology, which suggests that, despite limited evidence, exercise is likely to provide benefit in MCI.73 When advising patients with MCI on the protective lifestyle factors for brain health, might they benefit from a personalized medicine approach? Barha et al promote, in their recent review paper, the need for personalizing exercise recommendations when it comes to brain health.74 Many more research avenues need to be explored before we can be certain which type of exercise, at what level of intensity is best suited for each patient with MCI. However knowledge has advanced to a degree where some basic information on the cognitive benefits of PA can be communicated to patients with MCI in clinical settings and the recently released PA guidelines for people with SCD and MCI17 should assist with this. ■

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Original article

Dietary interventions in mild cognitive impairment and dementia

George S. Vlachos, MD; Nikolaos Scarmeas, MD, PhD

Dietary intervention is an enticing approach in the fight against cognitive impairment. Nutritional supplements and dietetic counseling are relatively easy and benign interventions, but research has not yet yielded irrefutable evidence as to their clinical utility. Heterogeneity in the results of available clinical studies, as well as methodological and practical issues, does not allow replication and generalization of findings. The paper at hand reviews only randomized clinical trials of single nutrients, multi-nutrient formulations and dietary counseling in mild cognitive impairment and dementia of the Alzheimer’s type focusing on both cognitive and functional outcomes. Thus far, folate, vitamin E, Ω-3 fatty acids, and certain multi-nutrient formulations have shown promising preliminary results; larger, well-designed trials are needed to confirm these findings before nutritional elements can be incorporated in recommended clinical guidelines.

Key words: Alzheimer disease; controlled clinical trial; diet; mild cognitive impairment; nutrition; treatment

Introduction

Dementia is almost always relentless, irreversible, and incapacitating for the patient, as well as having an equally burdensome impact on the patient’s social surroundings. Dementia is projected to be a top public health, social, and fiscal concern in the decades to come, as the positive effect of enhanced preventive strategies and public awareness may be offset by global population growth – driven mainly by its increase in low-income countries – and by population aging in the “developed” world.

Evolution of pharmaceutical treatments is costly and requires extensive funding. Additionally, it has been proven to be an extremely challenging task. In contrast, prevention strategies are a lower-cost approach and can be implemented on a larger scale. Nutrition ranks very highly amongst such strategies and it has the added benefit of being acceptable by the majority of the public as more “benign” and potentially free of side effects.

Nutritional preventive measures range from supplementation of the everyday diet with specific nutrients, to changes of dietary habits (ie, enrichment with or avoidance of certain food groups/beverages) to compliance with whole dietary patterns. Evidence for the importance of nutrition in cognitive function as a lifelong modifiable factor arises from animal models, observational studies, and clinical trials. Longitudinal studies account for the bulk of available data on the relationship between nutrition and cognition, but they are commonly observational. Additionally, many of them focus mostly on cognitively normal elderly adults, examining nutrition as a preventive measure of future cognitive decline, with relatively
fewer investigating potential associations with prognosis in already cognitively impaired populations. Beyond observational studies, clinical trials of dietary interventions as a treatment for cognitive impairment are scarce. However, they are instrumental in shaping the clinicians’ opinion on the potential of nutrition to be considered in the therapeutic armamentarium. The paper at hand is an attempt to review and summarize selected high-level scientific evidence on the topic of dietary interventions towards combating established cognitive dysfunction.

**Method**

Literature on dietary treatment for neurodegenerative disorders other than Alzheimer disease (AD) and its prodromal stage, mild cognitive impairment (MCI), is quite limited. There is some evidence on the role of dietary intervention in cognitive symptoms after stroke or coinciding with diseases increasing vascular risk (eg, diabetes mellitus), but the anticipated complex interplay between degenerative, inflammatory, and vascular mechanisms might prevent any attempt to coalesce data into meaningful conclusions. We therefore decided to focus on cognitive impairment due to clinically suspected underlying AD pathological changes.

A large part of published data in the field comes from observational and retrospective studies; we opted to restrict our search to controlled clinical trials reported in English, with an initial sample of at least 50 subjects with MCI or AD and an intervention spanning at least 24 weeks in duration, as neurodegenerative processes evolve slowly and nutritional treatment effects are expected to be low in magnitude. In order to collect evidence with as high practical value as possible, we encompassed only trials with clinical, neuropsychological, or functional end points and not biochemical or neuroimaging changes, as correlation of such changes with everyday outcomes is often indistinct. No limit was imposed on publication year.

We included in our search all types of intervention (eg, ingestion of a certain nutrient/food as well as dietary counseling/training and adherence to a certain diet). Nutritional intervention as both single and “add-on” treatment was accepted. Only therapeutic attempts related to chemical compounds found in food were included, eg, vitamins, minerals, antioxidants as well as whole foods/food groups. “herbal remedies,” or other supplements that are not part of routine diet (eg, gingko biloba) were excluded.

Relevant literature was identified through the PubMed search engine in October 2018; the list of located papers is by no means exhaustive, even though every effort was made toward that end. When the results of a specific trial were reported in more than one paper, we focused on the seminal publication or the one discussing outcomes of a more clinical/neuropsychological nature.

**Results**

Scientific papers fulfilling the criteria outlined above are presented in Tables Ia and Ib in detail. The earliest identified papers date back as far as 1991, albeit in recent years larger and better designed studies have emerged.

Almost all identified random ized controlled trials (RCTs) were double-blind and compared an intervention against a placebo group; eighteen trials tested the therapeutic effect of nutrition on (usually mild-to-moderate) AD and ten on MCI. Diagnosis was established according to various sets of international criteria, although in some studies diagnostic methodology and baseline sample characteristics are not clearly presented. About half of the studies involved a single micronutrient and the rest a micronutrient combination. We did not detect any RCTs with the aforementioned characteristics on the effect of trace elements, vitamin D, coenzyme Q10, curcumin, caffeine, olive oil, whole foods, food groups, or whole diets on cognitive impairment.

A summary of the main findings of the studies by intervention category

**B vitamins**

B vitamins are usually studied as a complex related mainly to energy production in neurons and lowering of homocysteine levels. The B-complex has been studied in MCI in two RCTs. A study from the United Kingdom reported cognitive improvement mainly in those with high baseline homocysteine; further analysis showed an interaction with baseline Ω-3 fatty acid plasma concentrations: only those with higher initial Ω-3 levels benefited from B vitamin supplementation. A Dutch study examined a possible effect in quality of life (QoL) and reported essen-
Dietary interventions for cognitive impairment - Vlachos, Scarmeas

In AD there is one study in subjects with mild-to-moderate AD (and normal baseline vitamin B12 and folate levels) that did not find any effect; oddly, depression was more common in the active treatment group.

Folate has been studied as a solitary intervention: cognitive improvement in general intelligence, attention span, and visuospatial metrics within 6 months has been reported in MCI; two studies on patients with AD under acetyl-cholinesterase inhibitors (AChEI) reported either an increase in Mini-Mental State Examination (MMSE) with no change in Activities of Daily Living (ADL) or the exact opposite result regarding MMSE and ADL.

Antioxidants
Chemical compounds characterized as antioxidants are a diverse group. Vitamins C and E were studied in a simple study in subjects with MCI for 1 year; no difference in MMSE was noted.

Vitamin E has been studied extensively. One study in AD concluded that vitamin E resulted in an MMSE increase in subjects who “responded” to it (ie, showed reduced glutathione oxidation – a marker of oxidative stress), but could even be detrimental in “non-responders.” Vitamin E has also been studied against active comparators: in a large study against donepezil for 3 years in subjects with amnestic MCI, time to progression to AD was not different in either treatment group compared with placebo, even though vitamin E exerted a positive effect on language and overall cognition in the first half of the study period. Two other large studies examined the effect of vitamin E on progression rate in AD against placebo and memantine or selegiline for up to 4 years and showed slower functional decline with focus on the ADL, even though no effect was observed on cognitive measures.

Omega-3 fatty acids
Omega-3 fatty acids are credited with anti-inflammatory and neuroprotective properties. Three studies from China and Australia reported positive cognitive outcomes in subjects with MCI. Two studies were conducted in mild to moderate AD: one Swedish study showed a small benefit only in the population with very mild cognitive dysfunction (slower decline); less agitation was reported in APOE-ε4 carriers and a lower depression score in non-APOE-ε4 carriers in the same study. Another study from the United States reported improved cognitive metrics only in non-APOE-ε4 carriers (APOE: apolipoprotein E).

Phosphatidylserine
Phosphatidylserine, a component of cell membranes, has been studied in two diverse populations: a somewhat poorly designed study in people with at least moderate cognitive decline reported cognitive benefits, while another study in mild to moderate AD that evaluated phosphatidylserine plus cognitive training as part of a multidomain intervention reported only transient cognitive amelioration.

Multi-nutrient formulations
Two distinct multi-nutrient formulations have failed to yield positive cognitive effects: one trial enrolled subjects that were normal or diagnosed with MCI and another one patients with AD and normal baseline vitamin B12 and folate levels.

Other relatively large studies examined the effect of a patented formulation called Fortasyn Connect. In subjects with MCI, no change in a composite neuropsychological score was proven; nonetheless subjects with higher baseline MMSE showed some clinical benefit in the form of Clinical Dementia Rating (CDR) stabilization. One study in drug-naïve patients with mild AD showed improvement in a memory composite score persisting during an open-label, 24-week extension, while in patients with mild-to-moderate AD under standard treatment no cognitive effect was shown. This formulation has also been shown to increase the body mass index (BMI) of patients with mild AD and improve everyday function in those with lower baseline BMI. The safety profile was favorable.

Dietary counseling
One study aimed to identify functional and cognitive benefits of dietary counseling provided to AD patients’ physicians and caregivers and failed to show any change; nonetheless the risk of malnutrition was reduced.
## Dietary interventions for cognitive impairment - Vlachos, Scarmeas

### Table 1a. Randomized clinical trials on the therapeutic effect of dietary interventions on mild cognitive impairment (see abbreviations at end of Table).

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>POPULATION</th>
<th>INITIALLY RANDOMIZED SAMPLE SIZE</th>
<th>DIAGNOSIS (METHOD)</th>
<th>INTERVENTION (DAILY DOSAGE)</th>
<th>DURATION OF INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bo et al (2017)</td>
<td>≥60 yr (m ean: 71 yr), Chinese, community-dwelling</td>
<td>86</td>
<td>MCI according to the modified Petersen criteria (MMSE, CDR, ADL)</td>
<td>480 mg DHA &amp; 720 mg EPA vs placebo (550 mg oleic acid)</td>
<td>6 mo</td>
</tr>
<tr>
<td>Ma et al (2016)</td>
<td>≥65 yr, Chinese, community-dwelling</td>
<td>180</td>
<td>MCI according to the modified Petersen criteria (MMSE &amp; ADL)</td>
<td>Folic acid 400 μg vs conventional treatment</td>
<td>6 mo</td>
</tr>
<tr>
<td>Zhang et al (2017)</td>
<td>≥65 yr, Chinese, community-dwelling</td>
<td>240</td>
<td>MCI according to the modified Petersen criteria (MMSE, ADL)</td>
<td>DHA 2 g vs placebo</td>
<td>12 mo</td>
</tr>
<tr>
<td>de Jager et al (VITACOG, 2011)</td>
<td>≥70 yr, English</td>
<td>271</td>
<td>MCI (TICS-M &amp; category fluency ± MMSE, subjective memory complaints &amp; ADL)</td>
<td>Folic acid 0.8 mg, vitamin B6 20 mg &amp; vitamin B12 0.5 mg vs placebo</td>
<td>2 yrs</td>
</tr>
<tr>
<td>Sinn et al (2012)</td>
<td>&gt;65 yr, Australian, community-dwelling</td>
<td>50</td>
<td>MCI (MMSE, Verbal Paired Associates Task)</td>
<td>EPA 1.67 g &amp; DHA 0.16 g vs DHA 1.55 g &amp; EPA 0.40 g vs placebo</td>
<td>6 mo</td>
</tr>
<tr>
<td>Soininen et al (LipiDiDiet, 2017)</td>
<td>50-86 yr (m ean: 71 yr), Finnish, German, Dutch &amp; Swedish, outpatients</td>
<td>311</td>
<td>MCI (prodromal AD) according to the IWG-1 criteria</td>
<td>125 mL of Fortasyn Connect (DHA 1200 mg, EPA 300 mg, uridine monophosphate 625 mg, choline 400 mg, vitamin E 40 mg, folic acid 400 μg, phospholipids 106 mg, selenium 60 μg) vs placebo</td>
<td>24 mo (+12 mo optional double-blind extension)</td>
</tr>
<tr>
<td>Baleztena et al (2018)</td>
<td>≥75 yr (m ean: 86.9 yr), Spanish, institutionalized</td>
<td>99</td>
<td>normal/MCI (MMSE &amp; Global Deterioration Scale)</td>
<td>DHA 250 mg, EPA 40 mg, vitamin in E 5 mg, phosphatidylserine 15 mg, tryptophan 95 mg, vitamin in B12 5 mg, folate 250 μg &amp; ginkgo biloba 60 mg vs placebo</td>
<td>1 yr</td>
</tr>
<tr>
<td>Naeini et al (2014)</td>
<td>60-75 yr, Iranian</td>
<td>256</td>
<td>MCI (MMSE)</td>
<td>Vitamin in E 300 mg &amp; vitamin in C 400 mg vs placebo</td>
<td>1 yr</td>
</tr>
<tr>
<td>Petersen et al (ADCS, 2005)</td>
<td>55-90 yr (m ean: 72.9 yr), US, outpatients</td>
<td>769</td>
<td>amnestic MCI (delayed recall score, CDR, MMSE)</td>
<td>Vitamin E 2000 IU vs donepezil 10 mg vs placebo; all groups additionally received vitamin in E 15 IU</td>
<td>3 yrs</td>
</tr>
<tr>
<td>van Uffelen et al (2007)</td>
<td>70-80 yr (m ean: 75 yr), Dutch, community-dwelling</td>
<td>179</td>
<td>MCI according to the Petersen criteria (MMSE, TICS, WLT, Groningen Activity Restriction Scale)</td>
<td>For the vitamin intervention: folic acid 5 mg, vitamin in B12 0.4 mg, vitamin in B6 50 mg vs placebo</td>
<td>1 yr</td>
</tr>
<tr>
<td>MAIN OUTCOME (MOSTLY PRIMARY)</td>
<td>TYPE OF MAIN OUTCOME</td>
<td>RESULT</td>
<td>POSITIVE/NEGATIVE STUDY</td>
<td>OTHER FINDINGS/COMMENTS</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
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<td>-------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Differences in BCAT</td>
<td>Cognitive</td>
<td>Improvement in total BCAT scores, perceptual speed, spatial imagery, working memory</td>
<td>+</td>
<td>Olive oil as placebo. BCAT scores improved in both groups; working memory not changed in females</td>
<td></td>
</tr>
<tr>
<td>Difference in IQ &amp; WAIS-RC scores</td>
<td>Cognitive</td>
<td>Improvement in Full Scale IQ, Digit Span &amp; Block Design</td>
<td>+</td>
<td>Unblinded RCT</td>
<td></td>
</tr>
<tr>
<td>Difference in WAIS-RC</td>
<td>Cognitive</td>
<td>Greater increase in Full-Scale IQ, Information &amp; Digit Span scores</td>
<td>+</td>
<td>Corn oil as placebo</td>
<td></td>
</tr>
<tr>
<td>Changes in cognitive and clinical status</td>
<td>Cognitive &amp; functional</td>
<td>No effect for MMSE, HVLT-DR, category fluency or CDR, IQCODE; stabilization of CLOX scores</td>
<td>±</td>
<td>In subjects with high baseline total homocysteine, improvement in all metrics</td>
<td></td>
</tr>
<tr>
<td>Difference in GDS, QoL, cognition (focusing on memory &amp; executive function)</td>
<td>Cognitive &amp; QoL</td>
<td>Improvement in Initial Letter Fluency in the DHA group &amp; in GDS in both active treatment groups</td>
<td>±</td>
<td>LA 2.2 g as placebo</td>
<td></td>
</tr>
<tr>
<td>Difference in composite NTB score</td>
<td>Cognitive</td>
<td>NS</td>
<td>±</td>
<td>Reduced increase in CDR-SoB in the active treatment group; the effect was more pronounced in those with higher baseline MMSE. The control group had slower cognitive decline than anticipated in this study</td>
<td></td>
</tr>
<tr>
<td>Difference in MMSE</td>
<td>Cognitive</td>
<td>NS</td>
<td>–</td>
<td>Improvement in memory subscale of MMSE in well-nourished subjects</td>
<td></td>
</tr>
<tr>
<td>Difference in MMSE</td>
<td>Cognitive</td>
<td>NS</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to conversion to AD (according to the NINCDS-ADRDA criteria)</td>
<td>Cognitive &amp; functional</td>
<td>NS for all time intervals</td>
<td>–</td>
<td>Positive effect of vitamin E on the executive, language &amp; overall cognitive scores for the first 18m o (The risk of progression to AD was lower in the donepezil group than in the placebo group in the first 12 m o; this effect was evident for the whole 3 yr in APoe-e4 carriers)</td>
<td></td>
</tr>
<tr>
<td>Difference in D-QoL &amp; SF-12 scores (overall &amp; health-related QoL)</td>
<td>QoL</td>
<td>NS</td>
<td>–</td>
<td>The same subjects were randomized to a parallel exercise intervention. No cognitive outcomes. Baseline QoL scores above the general population average. Detrimental effect of vitamin supplementation on D-QoL-belonging</td>
<td></td>
</tr>
</tbody>
</table>
Table 1b. Randomized clinical trials on the therapeutic effect of dietary interventions on Alzheimer disease (see abbreviations at end of Table).
## Dietary Interventions for Cognitive Impairment - Vlachos, Scarmeas

<table>
<thead>
<tr>
<th>Table 1: Summary of Main Outcomes and Results</th>
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<tr>
<td><strong>Main Outcome</strong></td>
</tr>
<tr>
<td>Differences in Plutchik Geriatric Rating Scale (behavior) and the Buschke Selective Reminding Test (cognition)</td>
</tr>
<tr>
<td>Difference in ADCS-ADL</td>
</tr>
<tr>
<td>Time to the occurrence of death, institutionalization, loss of the ability to perform basic ADL or CDR of 3</td>
</tr>
<tr>
<td>Difference in &quot;trajectory of change&quot; of the memory function domain z-score of the NTB</td>
</tr>
<tr>
<td>Difference in neuropsychological &amp; clinical measures</td>
</tr>
<tr>
<td>Difference in MMSE &amp; ADL</td>
</tr>
<tr>
<td>Number of good responders per NICE (difference in MMSE, behavioral &amp; functional assessments)</td>
</tr>
<tr>
<td>Difference in MMSE &amp; ADAS-cog</td>
</tr>
<tr>
<td>Differences in neuropsychological battery scores focusing on memory &amp; executive function</td>
</tr>
<tr>
<td>PUBLICATION</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Lloret et al (2009)</td>
</tr>
<tr>
<td>Aisen et al (ADCS, 2008)</td>
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<tr>
<td>Heiss et al (1994)</td>
</tr>
<tr>
<td>Quinn et al (ADCS, 2010)</td>
</tr>
<tr>
<td>Salva et al (NutriAlz, 2011)</td>
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<tr>
<td>Shah et al (S-Connect, 2013)</td>
</tr>
<tr>
<td>Sun et al (2007)</td>
</tr>
</tbody>
</table>

Table Ib. Randomized clinical trials on the therapeutic effect of dietary interventions on Alzheimer disease (see abbreviations at end of Table).
### Dietary interventions for cognitive impairment - Vlachos, Scarmeas

<table>
<thead>
<tr>
<th>MAIN OUTCOME (MOSTLY PRIMARY)</th>
<th>TYPE OF MAIN OUTCOME</th>
<th>RESULT</th>
<th>POSITIVE/NEGATIVE STUDY</th>
<th>OTHER FINDINGS/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in MMSE, BDS, Clock Drawing Test</td>
<td>Cognitive &amp; functional</td>
<td>Increased MMSE score in respondents vs non-respondents, reduced in non-respondents vs placebo</td>
<td>±</td>
<td>No difference in other scores</td>
</tr>
<tr>
<td>Difference in ADAS-Cog</td>
<td>Cognitive</td>
<td>NS (incl. secondary outcomes measures)</td>
<td>–</td>
<td>Adverse events involving depression more common in the active treatment group</td>
</tr>
<tr>
<td>Difference in MMSE &amp; other neuropsychological tool scores</td>
<td>Cognitive</td>
<td>Transient positive effects at 8 wks, mainly in the phosphatidylserine group</td>
<td>–</td>
<td>Unblinded RCT</td>
</tr>
<tr>
<td>Rate of change in ADAS-Cog &amp; CDR-SoB</td>
<td>Cognitive &amp; functional</td>
<td>NS</td>
<td>–</td>
<td>Corn or soy oil as placebo. APOE-ε4 noncarriers showed benefit in ADAS-Cog &amp; MMSE scores</td>
</tr>
<tr>
<td>Difference in ADL-IADL scores</td>
<td>Functional</td>
<td>NS</td>
<td>–</td>
<td>Unblinded RCT. No difference in secondary cognitive outcomes</td>
</tr>
<tr>
<td>Difference in ADAS-Cog</td>
<td>Cognitive</td>
<td>NS</td>
<td>–</td>
<td>Good safety &amp; tolerability, high compliance to treatment</td>
</tr>
<tr>
<td>Difference in ADAS-Cog</td>
<td>Cognitive</td>
<td>NS (incl. secondary outcomes measures)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

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Discussion

Given the body of evidence briefly delineated above, no firm guidance or even recommendation can be offered about any of the proposed dietary interventions for cognitive dysfunction. Indeed, several high-quality systematic reviews and meta-analyses found no or insufficient evidence of benefit.\textsuperscript{34-44} Be that as it may, folate, vitamin E, ω-3 fatty acids, and certain multi-nutrient formulations appear to be the best nutritional candidates for further investigation of potential efficacy in MCI or mild AD. The verdict is still open, as in many cases similar studies result in inconsistent results or a newer study does not replicate the findings of a previous one. The complex and still debatable pathophysiological mechanisms of cognitive dysfunction in AD may be among the main reasons for conflicting results. There are also multiple methodological and practical issues possibly...
Dietary interventions for cognitive impairment - Vlachos, Scarmeas

A main observation involves the significant differences in diagnostic methodology, set or version of diagnostic criteria used, and dementia stage classification across studies. In virtually all cases, diagnosis and staging were mostly clinical, with limited use of objective AD neuroimaging/neurochemical biomarkers. Heterogeneous (community-dwelling elderly, memory clinic outpatients, participants in day care programs, residents of institutions, etc) and ethnically diverse populations were studied. These issues hinder generalization of findings.

Regarding study design, we noted generally small sample sizes and perhaps not long enough duration of the interventions, sometimes accompanied by high dropout rates. Neurodegeneration evolves very slowly, so treatment effects can be expected to be modest at best; large samples and sufficient follow-up are needed to ascertain clinically and statistically important differences (to place findings from this literature in perspective, many novel drug trials in this population exceed a sample size of 2000 participants and, in several cases, last for as long as 2 years). In some trials, biochemical, neurochemical, or neuroimaging parameters were selected as primary outcomes; such trials may not be adequately powered to reveal subtle differences that may exist in secondary cognitive and functional outcomes, which we consider more relevant in everyday clinical practice. To further complicate matters, some of the findings we report here were derived from post hoc analyses. Moreover, in some studies with relatively short follow-up periods and consequently frequent visits, apparent stabilization in neuropsychological scores might be the result of a learning effect that keeps differences under the statistical significance threshold. Various cognitive assessment tools and functional scales were used as outcome measures; some of them may have not been sensitive enough to detect small changes of mental/functional capacity or QoL in the population with mildly affected cognition. Daily variation of cognition is probably larger than nutritional treatment effects, thereby potentially rendering cognitive tests insensitive to them.

Studying patients with overt dementia may prevent unveiling of the beneficial effect of a nutrient, as the neuropathologic process may already have been so advanced that all available intervention may be futile. Despite that, positive results were not more common in studies on MCI than on AD, highlighting perhaps the utility of applying our intervention at an even more prodromal stage of neurodegeneration, if possible.

Great variability was noted in supplement dosage and duration of administration; different chemical compounds were often used for a certain vitamin. Furthermore, results may have been confounded by previous dietary habits or concurrent intake of the studied nutrient in food. In some studies, olive/corn oil were used as placebo, although they contain unsaturated fatty acids that may exert positive effects on cognition. In certain Western countries, folic acid fortification programs may complicate detection of a...
Dietary interventions for cognitive impairment - Vlachos, Scarmeas

relationship between folate status and cognitive impairment. Also, most studies do not report baseline vitamin levels, which may influence the effect of supplemented vitamins on cognition, ie, deficient individuals might show greater benefit. Moreover, in many studies, data on concomitant use of drugs commonly prescribed for AD were not provided. These issues, in addition to the omnipresent risk of publication bias (which is commonly more of a concern for studies of relatively smaller size and power), make interpretation of the results much harder.

It seems reasonable to expect that multi-nutrient formulations may be more potent; conversely, multi-nutrient or whole-diet interventions do not allow identification of the specific action of each component with a possibility of unidentified synergistic, neutral, or even antagonistic effects between them. Theoretically, such interventions might be easier and less expensive, as they do not entail any manufacturing costs, but only advice/counseling and close follow-up of the subjects’ compliance. It should be noted, though, that RCTs (with the characteristics we specified in “Methods”) studying whole foods or diets as treatment for cognitive impairment have not been identified; perhaps the scientific community opts for simpler, straightforward experimental designs or the practical difficulties of implementing such a trial in the elderly population with cognitive dysfunction are hard to overcome. Nonetheless, the existing body of evidence for the potential preventive benefits of the Mediterranean diet, in particular, against cognitive impairment in normal cohorts is substantial; data originating from both RCTs [PREDIMED (on subjects at high cardiovascular risk)] and observational studies show reduction in the rate and risk of cognitive decline. More data are certainly needed in MCI and AD, but until then patients and caregivers can be encouraged to follow the Mediterranean diet.

Evidence shows that the BMI decreases prior to AD onset and remains stable or increases afterwards. Reasons for weight loss in the preclinical stage of AD comprise pathological changes in brain areas that regulate weight, disruption in hormone and neuropeptide levels, apathy, reduced olfaction, eating difficulty, and inadequate nutrition due to cognitive impairment itself. Conversely, it is possible that weight loss might also be a potential risk factor for developing AD, via, for example, a deficiency of biologically important micronutrients and antioxidative compounds. Body weight changes before and after dementia diagnosis highlight the importance of acknowledging the full interplay between nutrition and cognitive function; in fact, nutrition is just one of many potentially modifiable determinants of future cognitive decline.

Indeed, recently, interest in more holistic approaches has increased; multidomain interventions attempt to impact many lifestyle aspects that have been hypothesized to benefit cognition. Such interventions encompass not only nutritional guidance for a healthy diet, but also coaching on modulation of other important factors (eg, physical activity), cognitive training, and control of cardiovascular risk. Some of the large multidomain interventions (preDIVA, MAPT, and FINGER) may have included some subjects who could be categorized into MCI; nevertheless, they mostly focused on prevention, which is out of scope for this manuscript. In the future such approaches in patients with MCI or dementia may yield significant results.

As single nutrients may not be potent enough to produce clinically significant benefits, perhaps future research should steer toward multi-nutrient, whole-diet and multidomain interventions. Recent technological breakthroughs might become invaluable aids to such research, as sensors on portable hand-held/wearable devices and social media-embedded applications could assist in recording dietary habits and even collection of biomarkers. Innovative techniques, such as metabolomics and cerebrospinal fluid neurobiology, or investigation of novel aspects of
nutrition (including hydration status and chronobiology of food intake) may further unravel hidden associations between nutrition and cognitive dysfunction.

Conclusions

Nutrition is an important lifestyle factor related to cognitive impairment. Clinical studies of the potential utility of dietary intervention in ameliorating mild cognitive impairment and dementia are certainly warranted. Thus far, folate, vitamin in E, Ω-3 fatty acids, and certain multi-nutrient formulations have shown some initial promise; larger, well-designed trials with robust methodology may hopefully corroborate some of these findings.

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References

Original article

Dietary interventions for cognitive impairment - Vlachos, Scarmeas

Antidiabetic therapies and Alzheimer disease

Barbara B. Bendlin, PhD

Given current lack of therapies for dementia, there is substantial interest in identifying potentially modifiable risk factors. Clarifying the potential of these factors to mitigate risk as well as determining the mechanisms that link these factors to dementia is expected to lead to new approaches for both preventing and treating neurodegenerative diseases such as Alzheimer disease. Modifiable factors include cardiovascular risks as well as related lifestyle-centric factors such as diet and physical activity (reviewed in this issue). Given reports that type 2 diabetes and associated features increase the risk for developing dementia, there has been tremendous interest in exploring whether use of antidiabetic medications may impact the risk of dementia, as well as whether antidiabetic medications could be used to prevent or treat dementia, particularly Alzheimer disease. This review will briefly cover the known links between diabetes and risk for dementia, the state of evidence linking antidiabetic treatments with either protection against dementia or possibly increased risk for cognitive dysfunction, and provide a brief overview of what has been learned from clinical trials testing antidiabetic treatments in Alzheimer disease.

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Keywords: Alzheimer disease; APOE ε4; biomarker; clinical trial; dementia; metformin; risk; type 2 diabetes

Introduction

Type 2 diabetes (T2D) affects 422 million adults worldwide. The number of individuals affected by T2D in the future is expected to rise, as several factors which confer risk for T2D are also increasing, including over- and undernutrition, declining physical activity, increased stress, and presence of adverse socioeconomic and environmental factors. This health crisis is occurring simultaneously to another looming health epidemic, namely an increase in the incidence of dementia, especially the Alzheimer clinical syndrome.

Considerable evidence indicates that type 2 diabetes (T2D) and related features such as insulin resistance are associated with increased risk for dementia. Consequently, there has also been a great deal of interest in determining to what extent antidiabetic treatments may either protect against dementia or be used as treatments for cognitive dysfunction. This review will provide a brief overview of studies that link T2D with dementia, and in particular the Alzheimer clinical syndrome, describe the state of the evidence linking antidiabetic treatments with Alzheimer disease (AD) prevention or possibly increased risk for cognitive dysfunction, and finally, consider the evidence offered by clinical trials testing antidiabetic treatments in Alzheimer disease.

Type 2 diabetes and dementia

In addition to the well-known risk factors for AD, including age, apolipoprotein (APOE) ε4 genotype, and parental history of AD, there has been a long-standing interest in determining the risk conferred by vascular risk factors, and...
especially T2D. Population-based studies largely support an association between T2D and elevated dementia risk. The Rotterdam study was among the first to show an elevated risk of dementia with T2D, including vascular dementia and AD. Both the Hisayama study in Japan and the Vantaa 85+ study in Finland found a doubling of dementia risk with T2D. Among participants in the Religious Orders Study, T2D was associated with a 65% increase in the risk of developing AD compared with those without T2D. The Kungsholmen Project, a longitudinal population-based study based in Stockholm, found that T2D as well as pre-diabetes accelerated the progression from mild cognitive impairment (MCI) to dementia by 3.18 years. The Cache county study also found an increased risk of dementia among individuals with T2D, although the effect was restricted to women. Similarly, the Framingham study found that the risk for dementia conferred by T2D may be restricted to subgroups, including younger participants (<75 years of age), and individuals who do not carry the AD risk gene APOE ε4 genotype. The increased association between T2D and dementia appears to be stronger when T2D is present in midlife rather than older age, with some suggestion that diabetes-related abnormalities occurring as early as young adulthood may impact later cognitive function.

**Type 2 diabetes and the pathology of Alzheimer disease**

There are several potential mechanisms by which T2D may impact risk for dementia. Vascular mechanisms are likely, given the well-known adverse effects of T2D on vascular health; T2D is associated with cardiovascular disease, lower cerebral perfusion, small-vessel disease, and stroke. T2D-associated abnormalities in insulin are also plausible contributors to dementia risk. Periperal insulin resistance has been associated with several brain differences, including lower cerebral glucose uptake, reduced cerebral perfusion, and atrophy. In addition to the peripheral insulin abnormalities that are present in T2D, central insulin resistance—characterized by downregulation of insulin receptors, lowered binding of insulin, and abnormal insulin signaling—is also a feature of the AD brain.

As covered elsewhere in this issue, AD is defined by the presence of β-amyloid plaques, neurofibrillary tangles, and ultimately, neurodegeneration. However, the extent to which T2D can be directly related to the cardinal features of AD is unclear, particularly in human studies. Animal studies are supportive of a link, demonstrating that T2D can exacerbate AD pathology, including development of amyloid plaques, tau pathology, and neurodegeneration. Some human evidence also points toward a link between T2D and AD pathology; Matsuzaki et al examined lab and autopsy information for 135 individuals and found that antemortem plasma glucose, fasting insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR) were associated with increased risk for amyloid plaques post mortem, especially among individuals with APOE ε4 genotype.

More often, however, human studies examining the link between T2D and AD pathology have been negative, particularly with regard to amyloid. Heitner et al compared 49 diabetics to 52 age-matched controls and did not find elevated AD pathology. In a larger study of 1037 subjects examined at autopsy, T2D (n=279) was not associated with plaque and tangle burden, although APOE ε4 moderated the association such that carriers had higher odds of accumulating tangles. Alafuzoff et al examined 701 brains, where 134 were from individuals who were diabetic, and did not find an association between T2D and AD pathology. Similarly, in vivo studies using positron emission tomography (PET) or CSF analysis suggest that T2D is not associated with greater amyloid accumulation, although Moran et al found a relationship between T2D and higher tau pathology as measured in CSF. One possibility that has been advanced is that antidiabetic treatment among individuals with T2D could mitigate AD pathology. Beeri et al examined brain autopsy data derived from 248 subjects, half with T2D and half non-T2D
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patients matched on age, sex, and postmortem interval. Examining medication usage specifically, individuals with a history of combined use of insulin and oral antidiabetic medication (n=18) had significantly fewer amyloid plaques in all brain regions assessed, suggesting a possible beneficial effect of therapy on AD pathology.

Thambisetty et al are among the few who—like Beeri et al—also examined medication usage in relation to AD pathology as assessed with PET or post mortem assessment of AD pathology. They found that T2D was not associated with AD pathology, and that among the subset taking antidiabetic medications, there was no difference in level of AD pathology. Unlike the study by Beeri et al, however, combination therapy was not examined and the number of individuals who were taking insulin was small. A couple of studies have also found that individuals with T2D have lower AD pathology compared to controls. Ahtiluoto et al found that the proportion of individuals with β-amyloid plaques measured on autopsy was significantly lower among diabetic compared to non diabetic individuals. Likewise, Nelson et al observed significantly lower neurofibrillary counts in the subiculum and lower amyloid plaque count in temporal lobe among diabetics compared with non diabetics. However, these latter two studies did not examine the impact of medication specifically, and in light of the largely mixed literature on the relationship between T2D and AD pathology, it is almost impossible to draw conclusions on the impact of medications from observational studies alone.

Medications for type 2 diabetes and risk for dementia
Determining whether antidiabetic medications mitigate risk for dementia is complicated. Among individuals with T2D, observational studies are confounded by the fact that the effect of antidiabetic medication is not easily separated from the presence of T2D. Furthermore, there are multiple approaches to treating T2D. In addition to recommendations pertaining to diet, physical activity, and other lifestyle factors, treatment of T2D may involve several drug classes, including metformin, sulfonylureas, thiazolidinediones (TZDs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, alpha-glucosidase inhibitors, glucagon-like peptide 1 (GLP1)-based therapies (GLP-1 agonists and dipeptidyl peptidase-4 inhibitors), and insulin. Only a subset of these have been examined in relation to dementia in observational studies (as either monotherapy, or as part of combination therapies), and even fewer have been tested in human clinical trials for AD.

Metformin is typically the first medication prescribed for T2D, reducing the production of glucose in the liver, increasing uptake of glucose by the periphery, and improving insulin sensitivity. In a study of records from individuals 50 years of age or older in Taiwan’s National Health Insurance database, where n=25 393 had a diagnosis of T2D and n=101 816 did not have a diagnosis of T2D, Hsu et al found that dementia was increased 2.6-fold among individuals with T2D. Encouragingly, use of metformin reduced the risk of dementia by 24% compared with no use of antidiabetic medication. Sulfonylureas—which trigger release of endogenous insulin by binding to and closing ATP-sensitive K+ channels on the cell membrane of pancreatic β-cells—reduced dementia risk by 15%. When used in a combined regimen, these two oral antidiabetic agents decreased the risk of dementia in patients with T2D by 35% over 8 years. Adjusting for cerebrovascular disease did not change the association, suggesting that the reduced risk may occur independently from vascular mechanisms.

Heneka et al examined the association between pioglitazone and incidence of dementia utilizing data from a mandatory German public health insurance company. Data included longitudinal observations from 145 928 subjects who were 60 years of age or older and free of dementia and insulin-dependent diabetes at baseline. Subjects were either nondiabetics, diabetics who did not use pioglitazone, diabetics treated with pioglitazone for shorter periods (less than 8 calendar quarters of use), or diabetics treated for longer periods (eight or more quarters of pioglitazone use). Controlling for age, sex, use of rosiglitazone or metformin, and cardiovascular comorbidities, a diagnosis of diabetes without pioglitazone treatment was associated with a 23% increased risk for dementia. In turn, long-term use of pioglitazone was associated with a lower dementia incidence, while shorter-term pioglitazone use was associated with a dementia risk comparable to that of nondiabetics.

Utilizing data from the Sacramento Area Latino Study on Aging (SALSA Study), Wu et al examined the longitudinal association between antidiabetic medications and physical and cognitive functioning among older
community-dwelling Mexican Americans. Antidiabetic drugs included insulin in addition to oral glucose-lowering agents comprising metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and meglitinides. Among 1789 study participants, 585 (32.7%) were identified as having T2D at baseline. There was a positive effect of antidiabetic medication on both physical and cognitive function, with combination therapy of two or more antidiabetic agents resulting in a lower risk than monotherapy.

However, associations between antidiabetic medication and dementia are not uniformly in the direction of increased protection. A case-control study of 14 172 participants aged 65 years and older found that metformin was associated with an increased risk of AD dementia. In the Rotterdam Study, risk of incident dementia was highest among patients treated with insulin. Likewise, a Taiwanese study found that combination therapy with insulin was associated with greater risk of AD. It is possible in these studies that T2D or the severity of T2D—not medication—confounded the increased risk, although controlling for time since diagnosis (which was done in Huang et al) may approximate disease severity.

**Antidiabetic medication as an intervention for dementia**

Despite the mixed findings of observational studies, a large body of literature and several compelling hypotheses still suggest that antidiabetic therapies hold potential as treatments for dementia. Of particular interest, are observations that T2D and AD appear to share mechanisms in common, including abnormalities in insulin signaling, mitochondrial dysfunction, abnormal energy homeostasis, and neuroinflammation, abnormal energy homeostasis, and neuroinflammation, abnormal energy homeostasis, and neuroinflammation, abnormal energy homeostasis, and neuroinflammation. Hundreds of studies have examined the extent to which antidiabetic medications may impact brain pathology—particularly features of AD—with the majority of animal studies pointing toward potential benefits on amyloid pathology, tau pathology, synapses, oxidative stress, neurogenesis, and cognitive function.

However, human clinical trials—such as observational studies—show mixed findings. Promising effects of antidiabetic medications have been observed in relatively smaller trials. In a promising small trial, Luchsinger et al tested the effects of metformin among 80 participants with amnestic MCI and no diagnosis of T2D and found a beneficial effect of metformin on verbal memory. A small placebo-controlled crossover study randomized twenty nondiabetic participants with MCI or mild AD dementia to metformin followed by placebo or vice versa for 8 weeks and found a significant positive effect of metformin on executive function, specifically Trials B. In addition to metformin, sm all trials of TZDs have also shown beneficial effects. A small pilot study which randomized patients with AD/amnestic MCI to oral rosiglitazone or placebo for 6 months found better delayed recall at both 4 and 6 months, as well as better selective attention at 6 months. Pioglitazone was tested among 42 individuals with mild AD and an accompanying diagnosis of T2D and found a benefit of pioglitazone compared with control on MMSE and the Japanese version of ADAS-Cog scores. However, a caveat was the open-label study design.

Larger trials have been routinely negative. An efficacy and tolerability study of rosiglitazone randomized 518 patients with mild-to-moderate AD to various doses of rosiglitazone (2, 4, or 8 mg) or placebo. No effects were observed at 24 weeks on the primary end points including change from baseline in ADAS-Cog or the Clinician’s Interview-Based Impression of Change Plus Caregiver Input. In a follow-up phase 3 study with the same outcomes, 693 participants were stratified by APOE genotype. Again, no significant effects of pioglitazone were observed in either the overall sample or within APOE4 subgroups at week 24.

In the largest trial of its kind to date, a global, phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial evaluated the efficacy of low-dose pioglitazone as a treatment to delay onset of MCI in cognitively unimpaired individuals who were identified as high risk by a genetic risk algorithm. In addition to examining cognitive outcomes, an additional aim of the study was to qualify the genetic biomarker risk algorithm for assigning 5-year risk for developing MCI due to AD. The study—which involved 50 clinical sites and screening of 25 000 people—enrolled 3494 cognitively unimpaired participants who were screened on APOE and TOMM40 genotype. The trial ended early following an interim futility analysis, which showed an inadequate treatment effect of 0.8 mg of sustained release pioglitazone in delaying the onset of MCI due to AD.
Given observed abnormalities in insulin receptor density and insulin signaling in AD, a novel approach to therapy tested in several small and larger trials involves intranasal delivery of insulin. Intranasal delivery tempers the risks that would be involved if insulin were delivered peripherally, including insulin resistance and hypoglycemia. Early results from intranasal insulin trials were promising. For example, an early pilot trial tested a 3-week intervention comparing intranasal insulin with placebo in 24 individuals with amnestic MCI or mild AD and found positive impacts on verbal memory and attention.\[^{55}\] In a separate trial that examined differing doses of intranasal insulin among 33 people with amnestic MCI/early AD and 59 cognitively unimpaired adults, beneficial effects were observed on verbal memory specifically among amnestic MCI/early AD and found positive impacts on verbal memory and attention.\[^{55}\] In a separate trial that examined differing doses of intranasal insulin among 33 people with amnestic MCI/early AD and 59 cognitively unimpaired adults, beneficial effects were observed on verbal memory specifically among amnestic MCI/early AD and found positive impacts on verbal memory and attention.\[^{55}\]

Aβ42 remained stable in the treated group but increased in the control group. The import of these findings is unclear given the small Ns and limited validation of plasma amyloid assays as markers of CNS amyloid. Markers of amyloid and tau pathology have also been evaluated in cerebrospinal fluid as part of single center and larger multisite trials of intranasal insulin. Insulin has been found to lower ptau/Aβ42 in at least one study,\[^{71}\] although another single site study from this same group\[^{72}\] did not show an effect, and early results from SNIFF did not suggest an effect on CSF biomarkers.

**Considerations for the future**

Given the evidence that links T2D with dementia risk, pathophysiological similarities between T2D and AD, as well as promising small trials, why are medications targeting these mechanisms ineffective in larger trials? An issue that has plagued prior trials concerns the timing of interventions in relation to disease course: are treatments initiated when a disease process is already substantially underway and thus less effective? Among individuals with AD, and even MCI, by definition there is usually substantial plaque and tangle burden apparent, as well as neurodegeneration. With regard to testing medications which act on insulin, the issue of timing may also extend beyond cognitive severity or degree of amyloid and tau pathology. For example, activity of the enzymes phosphodiesterase, glycogen synthase kinase 3β, and insulin degrading enzyme, are altered in T2D as well as AD, linking the two diseases, but abnormalities may occur upstream of the development of AD pathology, such that interventions may need to be initiated earlier to be effective. Furthermore, consider the example of hormone therapy as tested in the Women’s Health Initiative study. After risks of hormone therapy such as coronary heart disease, breast cancer, and cognitive decline were discovered, the suggestion was offered that initiating hormone therapy several years postmenopause onset was a poor strategy.\[^{73}\] Therapies targeting the hormone insulin may need to be equally sensitive to timing issues, as age and disease associated changes to insulin receptors evolve and may differ among individuals.

Are trials enrolling participants who are most likely to benefit? For example, in the case of treatments tested as...
Interventions for AD, do the participants harbor AD pathology, or is it a heterogeneous group with various pathologies? Given the unique targets of T2D medications, it may be further necessary to refine the selection of participants to those with metabolic abnormalities. For example, while a phase 3 trial of azeliragon—which inhibits the receptor for advanced glycation end products—was terminated after it was found that patients with mild AD taking azeliragon did not improve on cognition or functional outcomes compared with placebo,74 a subgroup of AD patients with diabetes and high HbA1c did appear to benefit.75 Likewise, insulin sensitizers may need to be selectively tested among individuals who have confirmed central (or possibly peripheral) insulin resistance. Genotype will also play a role, as has become clear with multiple studies of T2D, insulin resistance, and trials of antidiabetic medications; in particular, there is substantial accumulating data pointing toward APOE4 as a critical variable in studies relating to energy metabolism and metabolic dysregulation. Unfortunately, despite the many studies suggesting its importance, how it should be handled in clinical trials is not precisely clear. In at least one study, it appears that carriers benefit from treatment,6 while in other cases, the evidence suggests noncarriers benefit.50,51 Similarly, inconsistencies are apparent with regard to T2D and how it associates with dementia or AD neuropathology; in some cases T2D or related features are associated with pathology or dementia to a greater degree among APOE4 carriers,79,80 and in other studies the opposite appears to be true.51,82 Severity of the clinical syndrome, and by extension level of disease pathology may also be an important factor. In the case of peripheral insulin levels for example, there is some evidence that elevated insulin levels impart increased risk early in the disease process, but by later stages, the relationship flips such that depressed levels may contribute to greater dysfunction.83

It may also be the case that T2D therapies, while having beneficial effects on certain aspects of disease, may exacerbate other disease features if unopposed. Human, rodent, and cell model studies cumulatively suggest that combination therapy could be preferable to monotherapy.37,41,84,85

Other factors that are difficult to parse are whether the impact of T2D directly impacts the brain through an insulin-mediated mechanism, or whether risks for dementia are due to accompanying factors such as obesity, dyslipidemia, hypertension, or the impact of advanced glycation end-products, all of which may have independent or synergistic impacts on the brain. A beneficial approach may be to consider treatment of T2D as part of a broader strategy to control vascular risk factors to attenuate cognitive decline.86

Conclusion

Despite several epidemiologic studies, animal studies, and small trials, there are no gold-standard studies that have unequivocally sealed the case between T2D and AD, or the impact of T2D medications. A number of issues confound the interpretation of observational studies, including the co-occurrence of T2D, treatment for T2D, and comorbidities. A major gap at present for testing anti-diabetic therapies in AD is that the mechanisms which tie T2D to the Alzheimer clinical syndrome are not entirely known and may not be via AD-specific pathology, or they may be upstream phenomena, preceding pathology. Mitigating instigators of pathology may require treating individuals early, prior to development of extensive amyloid and tau tangle burden for maximum effectiveness.

Strategies for optimizing treatment trials are still needed, including improved patient selection, determining the correct timing of treatment in relation to disease course, and identification of suitable biomarkers for evaluating therapies that currently have multifactorial or perhaps even unknown mechanisms of action. Indeed, a major advancement in the field of AD clinical trials has been the improved precision by which individuals with disease pathology can be identified, especially prior to developing cognitive dysfunction. As the field moves toward ever better biomarkers of disease processes, testing and developing drugs related to the specific processes that connect T2D with AD remain a viable area of inquiry and development.

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Original article
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Prevention of dementia presents a potentially critical platform for improvement of long-term public health

Michal Schnaider Beeri, PhD

With the aging of the population, Alzheimer disease (AD) has become an epidemic and a major public health threat. Hundreds of molecules tested in clinical trials in the last decade to treat AD have failed, moving the field to examine the clinical and neurobiological value of prevention of cognitive decline and AD. This short review describes recently finished or currently ongoing clinical trials for prevention of AD, both their main outcomes and secondary outcomes. In addition, the potential modifying effects of age and of genetics as important factors that may affect the design of future clinical trials is discussed. Finally, we discuss the development of new molecular imaging and of digital technologies as a means to disclosure of dementia-related risk and disease progress, and their potential importance as contributors to adherence to healthy lifestyle for the prevention or delay of AD onset.

Keywords: Alzheimer disease; clinical trial; dementia; prevention; risk factor

Introduction

After several decades without successful dementia drug discovery, prevention or delay of cognitive decline is a public health priority. Findings from numerous prospective longitudinal observational studies have identified seven major, potentially modifiable, risk factors that show consistent association with Alzheimer disease (AD) (midlife diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment). The combined population-attributable risk for these modifiable risk factors is 30%, which suggests that prevention or good control of these risk factors may postpone the onset and reduce substantially the incidence of dementia. Postponement of AD onset by 5 years has been estimated to decrease its prevalence by up to 50% in 50 years, effectively targeting these risk factors may have a major public health benefit. Assuming that there is a causal relationship between the risk factors and dementia, and that they are treated in midlife, when evidence suggests they affect brain health most, it is estimated that relative reductions of 10% per decade in each risk factor could reduce the prevalence of AD in 2050 by 8.3% globally. If no effective interventions are developed, about 130 million individuals will suffer from dementia worldwide. An 8.3% reduction in prevalence concretely translates into preventing 11 million individuals from developing dementia.

The focus of this short review will be multidomain clinical trials that target the most well-established risk factors associated with cognitive decline, AD, and dementia, and on factors that might affect the potential effectiveness of such clinical trials. Dementia is a disease of multiple etiologies, but the currently available diagnostic and prognostic tools are not able to pinpoint the etiologies for a
particular individual. Thus, multidomain prevention interventions provide a broader opportunity for targeting at least some of the etiologies of individuals at high dementia risk, thus slowing the disease process.

**Clinical trials for the prevention of Alzheimer disease**

There have been numerous single domain randomized clinical trials for the prevention of cognitive decline, including the OPAL,\(^3\) ACTIVE,\(^4\) LIFE,\(^5\) and IHAMS\(^6\) studies and some with promising results, such as the ACTIVE trial, where the improvements of the targeted cognitive function (reasoning, speed of processing, and memory) were retained after 5 years.\(^4\) However, a recent extensive literature review of randomized control trials on single lifestyle interventions for AD yielded inconsistent results\(^7\) (in the ACTIVE trial itself, incident dementia after 5 years did not decrease in the intervention groups). The positive results of the multidomain lifestyle model FINGER\(^9,10\) study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) brought some optimism which was accompanied by the disappointing results of the multidomain preDIVA\(^11,12\) (Prevention of Dementia by Intensive Vascular Care) and MAPT\(^13,14\) (Multidomain Alzheimer Prevention Trial) studies, raising concerns regarding the multidomain approach.

**A summary and discussion of results of each of the prevention trials**

**FINGER\(^9\)**

This double-blind controlled trial enrolled 1260 individuals between the ages 60 and 77 with a CAIDE (Cardiovascular Risk Factors, Aging and Dem entia) Dem entia Risk Score of at least 6 points (ie, excluding individuals with very low dem entia risk based on this scoring system) and cognition at mean level or slightly lower than expected for age. The intervention targeted several domains (diet, exercise, cognitive training, and vascular risk monitoring) through meetings with relevant professionals who provided specific guidance and information, and lasted 2 years. For example, the nutritional intervention included three individual meetings with a nutritionist and nine additional group sessions. The control group received general health advice. The primary outcome was cognitive decline. The intervention group had significantly less overall cognitive decline than the control group. The main cognitive drivers for these differences in decline were executive functions and processing speed but not episodic memory. The FINGER study results suggest that a multidomain intervention approach may be effective in delaying the onset of the disease for individuals with high dementia risk due to a relatively high load of dem entia-related risk factors. Several replication trials around the world have been launched.\(^15\) Such multidomain recommendations are already applied in the cardiovascular disease field.\(^16\) Beneficial results remaining consistent and similar to those of the original FINGER study would strongly suggest the need for significant involvement of public health decision-makers and policies to broaden multidomain recommendations to delay the onset of dementia.

**preDIVA\(^12\)**

This was a prevention randomized clinical trial with a 6-year follow up of 3700 participants between the ages of 70 and 78, assessing the effect of nurse-led intensive vascular care to decrease dementia incidence and reduce disability. The intervention included treatment of hypertension, hypercholesterolemia, and diabetes; reduction of weight and smoking; and stimulation of physical activity. The intervention consisted of visits every 4 months for 6 years (18 visits) to a nurse in general practice, who assessed the participant’s cardiovascular risk factors (smoking habits, diet, physical activity, weight, and blood pressure), and gave individually tailored lifestyle advice. The primary outcomes were incident dementia and disability score. The only exclusion criteria were dementia and other disorders likely to hinder successful long-term participation in the study, such as terminal illness and alcoholism, so the study did not specifically recruit individuals with a high profile of cardiovascular risk factors related to dementia. The intervention did not reduce the incidence of

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**The impact of midlife risk factors on dementia risk is stronger than the effect of late-life risk factors**

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all-cause dementia. However, secondary analyses showed a beneficial effect for a subgroup of individuals who had untreated hypertension at baseline, raising the possibility that for those carrying risk factors, such an intervention may confer dementia risk benefit. Interestingly, the intervention was associated with decrease in white matter hyperintensities (WMH) volumes in those initiating the study with high (but not low) volumes of WMH.17

*MAPT*
This randomized placebo-controlled superiority trial of 1680 participants had four arms:
1) Multidomain intervention (43 group sessions and three preventive consultations integrating cognitive training, physical activity, and nutrition) plus omega 3 polyunsaturated fatty acid (two capsules a day for a total of 800 mg decosahexaenoic acid and 225 mg eicosapentaenoic acid)
2) Multidomain intervention plus placebo
3) Omega 3 polyunsaturated fatty acids alone
4) Placebo alone. Intervention was for 3 years

Participants were 70 years of age or above, all non-demented community dwelling, who reported either subjective memory complaint, limitations in one instrumental activity of daily living (such as ability to use the phone or shop) and slow gait (below 0.8 m/s, ie, more than 5 seconds to walk 4 m eters). The primary outcome was change from baseline to 36 months in a composite z-score combining four cognitive tests covering episodic memory, orientation in time and space, speed of processing, and verbal fluency. There were no significant differences between any of the three intervention groups compared to the placebo group. However, posthoc analyses combining groups showed significantly less decline in the combined multidomain intervention groups compared with those who did not receive multidomain intervention. In addition, in secondary analyses of the orientation cognitive domain, the combined multidomain intervention groups declined significantly slower than the placebo group. Moreover, among participants with a CAIDE score of 6 or greater, the combined multidomain intervention groups had less cognitive decline than the placebo group. Importantly, a subsample (n=269) of the MAPT study underwent amyloid PET scan. Among those who had a positive amyloid scan, slower cognitive decline was found in the combined multidomain intervention groups, as well as in multidomain intervention plus placebo, than in placebo alone.

*HATICE* *(Healthy Ageing Through Internet Counselling in the Elderly)*
In addition to these studies that have ended, the ongoing HATICE study aims at improving the cardiovascular profile of 2500 com m unity dwelling participants above the age of 65 who are at increased risk for cardiovascular disease due to two or more cardiovascular risk factors (hypertension, dyslipidemia, overweight, active smoking, lack of physical exercise). The intervention is for 18 months and focuses on promoting awareness and self-management of these risk factors. Participants on the treatment arm will be exposed to a supportive, interactive, internet-based coach platform. Participants can set personal goals for lifestyle change through the platform, make action plans, monitor goals by entering data such as blood pressure, and communicate with a trained coach through messaging within the platform. Control participants will be exposed to a static platform providing general health information. The study is taking place in Finland, France, and the Netherlands. Its overall aims are to optimize the self-management of cardiovascular risk factors, improve the cardiovascular risk (CVR) profile, and reduce the risk of cardiovascular disease, cognitive decline, and dementia.

Although the FINGER study raises some optimism in the potential value of multidomain interventions to delay the onset of dementia by slowing cognitive decline, the overall negative results of the other trials raise concerns about the benefits of the approach. This is apparently surprising as there is a large body of observational and animal evidence supporting the potential effectiveness of such an approach. It seems that one common characteristic of the three prevention trials is that the focus has to be on individuals who are at high dementia risk, primarily cardiovascular high risk per se: the preDIVA secondary results for less incident dementia in those with untreated hypertensive participants, and the MAPT secondary results of beneficial effects of the multidomain intervention in those with a CAIDE score above 6 support such an argument. However, to complicate matters, in the preDIVA study, the LIBRA modifiable dementia risk score (an index that includes depression, hypertension,
Obesity, diabetes, smoking, renal dysfunction, physical inactivity, alcohol use, age, and education) did not identify a high-risk group for whom the multidomain intervention was effective in preventing dementia or cognitive decline. In addition, although in a small subsample, the MAPT results on AD neuropathology suggest that a multidomain intervention may have a better chance to maintain cognition among individuals whose brain has already some neuropathological compromise. Similarly, the preDIVA study suggests that the intervention could be effective in persons with high WMH volumes. Such results support the view that the intervention affects the disease biology thereby benefiting cognition.

Two additional important factors may have affected the results of these clinical trials—age and genetic background.

Age is a major modifier of associations of cardiovascular risk factors with cognitive outcomes

The impact of midlife risk factors on dementia risk is stronger than the effect of late-life risk factors. A recent study showed that two or more cardiovascular risk factors in midlife (but not late life), predicted amyloid aggregation. In fact, in the oldest old, many of the associations are “reversed,” such that high levels of the risk factors (eg, hemoglobin A1c (HbA1c), cholesterol, homocysteine) are associated with lower risk for dementia and cognitive impairment. Additionally, the neurodegenerative changes in AD begin decades before dementia and cognitive impairment. Theoretically, the ultimate personalized medicine model adapts the intervention according to each person’s genetic background. In the context of cognition and AD, much scientific progress is needed for this approach to become relevant and effective.

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The associations of several modifiable risk factors with cognition, and with brain-related outcomes associated with AD, are stronger (or exclusively significant) among APOE4 genotype carriers. These include obesity, type 2 diabetes, glycemic control, blood pressure, and physical activity. In contrast, some studies suggest associations of cholesterol and physical activity with AD-related cognitive outcomes among APOE4 noncarriers, but no associations among APOE4 carriers. Additionally, some evidence suggests that treatments for certain cardiovascular risk factors have a beneficial effect on cognition of APOE4 noncarriers, with no effect on APOE4 carriers—for example, angiotensin-converting enzyme inhibitors, the insulin sensitizer rosiglitazone, and intranasal insulin. A few studies (ref 40 provides a good example) did not find a modulating role for the APOE4 genotype on the relationships of modifiable risk factors with cognitive and brain outcomes related to AD.

APOE4 is the most consistently found and replicable risk genotype for AD, and the large body of evidence for differential effects in observational studies, as well as in clinical trials strongly suggests that it should be accounted for in prevention clinical trials as well. Supporting this view are the results of the FINGER study, where the effect of the multidomain lifestyle intervention for prevention of cognitive decline was stronger (albeit not statistically significantly) in APOE4 carriers than in non-carriers. The (non-significant) trend was the same for the MAPT study.
Beyond effects of APOE4, there are recent findings suggesting that for specific conditions that increase the risk of dementia, such as type 2 diabetes, related genes may modulate the effect on dementia. For example, haptoglobin, a gene whose effects on diabetes complications have been well-established, have been recently associated with poorer cognitive functioning and greater cognitive decline among elderly individuals. Moreover, the hapten genotype modulated the association of glycemic control with cognition and with hippocampal volume in cognitively normal type 2 diabetic elderly, such that among those carrying the 1-1 genotype, these associations were strong, while among noncarriers, they are essentially nonexistent. This implies greater susceptibility of the brain of haptoglobin 1-1 carriers to the deleterious effects of poor glycemic control and the potential of this subgroup to benefit from glycemic control-related interventions. These results suggest investigating the potential effects on outcomes of dementia-related genes other than APOE.

Dementia-related risk disclosure and digital technologies may become important contributors to adherence to healthy lifestyle for the prevention of dementia

Another issue of substantive relevance to dementia-related clinical trials is the identification of the factors enhancing adherence to the intervention. Risk disclosure may become a critical factor. For example, there is initial evidence individuals who proactively seek AD genetic risk assessments use results to inform behavioral changes. Risk disclosure of the APOE4 genotype was associated with greater intake of dietary supplements in APOE4 carriers—but not in noncarriers—in the REVEAL trial.

Importantly, disclosure of APOE4 genotype does not seem to increase distress. The disclosure of amyloid PET results is only now evolving, so little evidence is available on behavioral/lifestyle effects. One small study has shown that disclosure of PET amyloid status did not significantly impact mood, but that subjects with increased amyloid burden were more likely than those whose amyloid PET scan was negative to make positive changes to their lifestyle, such as engaging in more exercise and changing their diet. Disclosure of amyloid status was not a barrier to recruitment in preclinical AD clinical trials. The combination of little emotional distress, improved recruitment, and improved response to intervention suggest the potential of risk disclosure as an important contributor to better outcomes in prevention clinical trials.

Finally, the massive development of wearables and smartphone applications may open new prospects for lifestyle improvements and better long-term adherence to these changes. Speech-to-text capabilities may improve participants’ adherence, as “talking out loud one’s own risk factors” might increase awareness and improve engagement in the intervention process. Furthermore, in contrast to “classic” clinical trials, where intermittent “little data” is collected sporadically, use of mobile technologies can create “big data” of continuous risk factor management. Mobile phones are used by most adults, even in developing countries, so preventive intervention using mobile technology to maintain long-life cognitive health should be investigated.

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Ethical issues in early diagnosis and prevention of Alzheimer disease

Peter J. Whitehouse, MD, MA (Bioethics), PhD

This paper considers ethical issues related to early diagnosis and all forms of prevention of Alzheimer disease and related conditions. It offers a critical view of the current state of scientific, clinical, and social responses to the growing number of older people with cognitive challenges, and suggests how priorities going forward should be different from those receiving most attention today. We begin with a review of global policy efforts, consider the fundamental goals of prevention, examine issues surrounding early diagnosis, explore more deeply values associated with efforts to prevent age-associated cognitive decline, and conclude by considering often unexplored ethical issues that contextualize the field and should influence our approaches to the future.

Keywords: Alzheimer disease; dementia; diagnosis; ethics; prevention

Introduction

This paper considers ethical issues related to early diagnosis and all forms of prevention of Alzheimer disease (AD) and related conditions. It offers a critical view of the current state of scientific, clinical, and social responses to the growing number of older people with cognitive challenges, and suggests how priorities going forward should be different from those receiving most attention today. Such future thinking needs to be based on stronger, more open and just ethical foundations than those currently underlying the field. We begin by summarizing activity in the policy domain as an illustration of current global priorities, challenge some of the underlying assumptions in these efforts, review what should be the goals of diagnosis and prevention, and consider contemporaneous efforts to achieve them. We conclude by exploring deeper ethical issues, such as those associated with the role of science in society and competing health priorities that should contextualize future priority setting.

Current policy development priorities and issues

One manifestation of the growing concern about the impact of age-related cognitive challenges in the world is the development of national and global strategies to address dementia. International organizations such as Alzheimer’s Disease International and the World Health Organization, as well as a growing number of countries, have developed comprehensive plans. Virtually all strategies advocate early diagnosis, education of the public, improving care, and research to develop more effective treatments for AD and related conditions. Increasing attention is also being paid in policy statements to the public health aspects of dementia and on prevention, rather than just focusing on finding a medical cure. Many plans and policies are focusing broadly on dementia rather than just AD. This is in part because AD is now being seen as a heterogeneous spectrum of conditions, and there is a growing recognition that public responses need to address the wide range of persons with cognitive...
impairment who often have similar needs regardless of specific diagnosis. Often forgotten in policy efforts (like Dementia Friendly Community efforts) is that dementia affects people of all ages, not just adults.

These policies are emerging in concert with other scientific and social trends relevant to addressing the challenges of dementia. First, despite billions of dollars being invested in finding cures and other biological interventions, no new therapies have been found or seem to be emerging, and the field is in some degree of disarray regarding future directions. Major pharmaceutical companies are beginning to disinvest, as evidenced most recently by Pfizer discontinuing its research and development in AD and Parkinson disease. Second, psychosocial interventions (so-called “nonpharmacological” approaches) are being demonstrated to be valuable in improving quality of life for those affected by dementia. Finally, evidence is emerging that community and public health interventions (eg, increased access to education and health care, removal of lead from gasoline, etc) may actually be reducing rates of dementia over time. So how is policy development tracking these trends?

What are some of the ethical presumptions in these policies? The first presumption is that we understand enough about the conditions themselves to prioritize our approaches to addressing the challenges. What are we researching, and what are we telling people about what we know and do not know? For example, AD, which receives much of the attention as the most common cause of dementia, has been found genetically, pathologically, and clinically to be quite heterogeneous. Is it a single condition? With this unfounded assumption of diagnostic clarity, a challengeable corollary emerges that early diagnosis is preferable to a delayed diagnosis. The various different forms of AD likely have important clinical differences such as rates of progression and prognosis. By using a single label, AD, are we misleading people by forgetting how much we do not know about the underlying conditions, by suggesting people have a similar course, and by implying that ultimately a singular (or any) cure for unitary AD is even possible?

The second major presumption is that more medical research will lead to more effective therapies and that these medications will save money. For example, the Alzheimer’s Association issued a report that claimed that such a medication could save trillions of dollars over the decades to come. However, they assumed in their model that the promised drug would have a cost of “zero.” Such claims are irresponsible in my view. Public health interventions are likely to be more effective, including less costly, than drugs and will improve the health of people with various other conditions, besides dementia.

The final assumption is that the approaches advocated for in the international and national plans represent a reasonable use of social resources given other huge competing health and social problems, such as environmental degradation and social injustice. What are the opportunity costs of investing so much in dementia, particularly in biomedical approaches? Climate change and poverty, through the intervening variables of environmental and social determinants of health, are existential threats to our communities and even civilizations and species.

Goals of prevention and related ethical issues

Prevention is often described as primary, secondary, or tertiary depending on when the intervention is offered during the course of the illness and what the expected outcome is. In primary prevention, the intention is to stop the condition from appearing in the first place. In secondary and tertiary, the condition will have manifested but the aim is to delay or arrest the condition (secondary) or any other health and functional consequences that might be associated with the main illness (tertiary).

Fundamentally, the goal of prevention is to improve length, but particularly quality of life. Here, a challenge is that the cognitive difficulties of a person with dem entia may limit their ability to report the subjective aspects of quality of life that are critical in this measurement. As a result, clinical trials often focus on activities of daily living or mood as important components of quality of life, although most believe that quality of life encompasses more than function and mental health, including one’s own personal interpretation of the quality of one’s own life. These issues link to surrogate decision-making. When someone becomes cognitively impaired enough to impair their judgment about their own health, they will need someone else to make or assist in decisions. Should the patient’s repre-
sentative make their decision and assessment of quality of life using substituted judgement based on a sense of the likely choice of the person with dementia (perhaps guided by an advanced directive) or best interests as perceived by the surrogate?24 People with any degree of cognitive impairment (and even those with normal intelligence) have difficulty making decisions about clinical issues and research participation. Who fully understands genetic risks or the likelihood of the success or dangers associated with medicines in early or even late stages of development? Quite clearly the experts do not, and worse, they have an intrinsic bias towards encouraging people to participate in trials. In general, the best ethical standard is to reflect the voice of the affected person in the decision-making conversation space, realizing that people’s views of cognitive impairment change as their symptoms progress. Open and appropriate communication strategies sensitive to levels of education and degree of intellectual impairment are key.

In addition to the effects of individuals directly impacted by the diagnosis, others in society may also be affected. Given that social resources employed to address one particular condition, like dementia, might not be available for other health priorities, like vaccination or eradicating lead poisoning in children, the allocation of resources in one domain of medicine will potentially affect the quality of life of people with other conditions. Balancing priorities is key, as well as looking for win-win situations. Eliminating the brain damage associated with lead poisoning would help children, and, from a long-term perspective, help them become brain healthier elders. Allocations to social programs such as dementia and age-friendly community development could actually make communities friendlier for children and in fact all of us, for instance by creating better signage, safer and healthier public spaces, and easier to navigate public transportation systems. Currently however, it is not clear that synergies will emerge because of the narrow foci of groups and lack of coordination involved in community transformation. Moreover, most such efforts ignore the deteriorating natural environment due, for example, to cli image change or land misuse (eg, fracking, urban sprawl).

Scientists and clinicians often ask for more resources to support their own activities. Researchers almost invariably conclude papers with a statement such as “more research is needed.” Often ignored is that interventions in non-health domains may have longer enduring effects. For example, artists and musicians are frequently ignored in advocacy and funding efforts, even though evidence suggests that people with dementia can benefit from their approaches. And besides, if we wish to “normalize” people with dementia and reengage them in the community as fellow human beings, how much evidence do we need that people with dementia—who have spent lifetimes enjoying aesthetic experiences—are stimulated by such activities just as the rest of us are?25 The spectrum of cognitive impairment from subjective cognitive impairment (SCI), though mild cognitive impairment (MCI) to activities-of-daily living impairing dementia also challenges this idea that one day you are just enjoying art and music and then you become eligible for art and music therapy and special programs.

The nature of evidence to change clinical practice and policy is a central challenge. Medical professions assert the value of basic medical research such as animal models and randomized controlled trials (RCTs).20 Animal models have had limited predictive value about the effects of biological interventions, and it has often been the case that drugs that cure so-called “Mouse-heimer’s” fail to make an impact in human beings.21 Billions of dollars have been spent trying to prove the value of drugs and biologics through RCTs. Yet the epistemological and practical limitations of this dominant epistemology are often neglected; for example, limits in the generalizability of the results of RCTs, the small all clinical value of some research outcomes, and the relative neglect of long-term safety. Data does not “speak for itself,” as is sometimes asserted, and those who produced or stand to benefit from positive data are often biased in their interpretation, even as they promote “scientific objectivity.” Trials supported by industry are more likely to favor their potential product.22
to study but ultimately less worthwhile, while ignoring those that do not have the resources or even appropriate methodologies to assess and which, like art and music, might prove ultimately highly impactful.

**Diagnosis of what and how early is early?**

In early diagnosis, the question of what specific conditions one is trying to diagnose becomes critical.\(^{24,25}\) Lack of clarity can lead to misunderstanding and longer periods of potential anguish over any misapplied label. Moreover, not often asked is how a label affects the person so diagnosed in terms of providing information (or not) that might lead to changes in perception of and action in one’s life. Those who favor the early diagnosis of AD are commonly confused by changing disease concepts and terminology themselves.\(^{24,26,27}\) For example, genetic, pathological, and clinical research of the last several decades have shown considerable heterogeneity in what we continue to singularly label as “Alzheimer disease,” as well as great difficulty in differentiating “normal” aging from pathological conditions.\(^{28-31}\) The grand quest for subtypes that might respond differently to different therapies has mostly been a failure. Mixed-cause dementia, which features not only plaques and tangles, but other pathologic features such as vascular changes and Lewy bodies, is the most common form. Personalized medicine based on genetics seems an elusive goal and may in fact dehumanize people through its biological determinism. Was it a political success, but ultimately a clinical and scientific problem, to label senile dementia (after age 65) as “Alzheimer disease” when this classification was originally reserved for the rare early onset (before 65) dementia that was frequently caused by autosomal dominant genes? This decision in the 1970s has effectively created an epidemic of AD and fostered expectations of a single cure.

And if we are to diagnose early, how early should we test? Should we test fetuses for the presence of autosomal dominant mutations?\(^{32}\) Should we inform those over 18 who carry a deterministic mutation or even a susceptibility gene like \(APOE4\)? The latter is a risk factor relevant to every human being since we all carry genes for \(APOE\), as a protein involved in normal cholesterol metabolism. Moreover, \(APOE4\) is pleiotropic, meaning it alters risk for a variety of neurological and cardiovascular conditions in addition to so-called AD.\(^{33}\) Research has shown that people find genetic risk information difficult to understand and often revert to their perceived risk prior to testing, throwing into question the utility of genetic tests in the clinical setting.

The lessons from another autosomal dominant dementia, Huntington disease, have taught us that even diagnostic disclosure of causative genes are fraught with challenges. People sometimes do not want to know their gene status. And discrimination against asymptomatic people on the basis of their genetic is still possible despite legislative efforts to protect such information from disclosure to others such as employers or long-term care insurance vendors.

Other forms of degenerative diseases that are mistaken for AD clinically are less well-known, such as hippocampal sclerosis. As noted above, considerable overlap occurs among different forms of degenerative diseases including Parkinson disease, frontal lobe dementia, and AD. Our understanding of the relationships between vascular dementia and degenerative dementias are now less clear than we thought 25 years ago.\(^{26,34}\)

Even when symptoms become manifest how early should we push our diagnostic labels?\(^{6,35}\) SCI requires only the complaint that one’s memory or other intellectual abilities are getting worse over time. Aging Associated Memory Impairment (AAMI) and Age Associated Cognitive Decline (AACD) were invented concepts representing earlier stages of loss where some cognitive impairment can be found on neuropsychological testing.\(^{24,36}\) Finally, we get to the most common pre-dementia label—early and late MCI. Depending on how one defines them statistically in relationship to so-called norm ality, the label MCI could be applied to millions more people. Yet studies have shown considerable variability in how experts use the term, how people respond to this statistically precise but conceptually vague term, and how they progress once labeled.\(^{30,35}\) MCI is said to affect function not at all or only a little. But to what degree is still controversial? Does early diagnosis mean using all these labels?

The word “timely” diagnosis is often used to replace “early” in discussing the diagnostic process. Timely means occurring at a favorable or useful time. But whose favor or usefulness is being considered here—the doc-
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Diagnosis is often linked to conversations about existing or promised future therapies. All patients should get advice about lifestyle regardless of diagnosis or not. It is possible that people with a diagnostic label are more likely to actually implement lifestyle changes, but this is not certain. Moreover, do we have to label people as sick before we encourage healthy prevention-oriented strategies like changes in diet, exercise, and so on? It is often said that we diagnose early to encourage people to enroll in trials. But is this ethical? Clinical and research domains should remain separate. Controversy about whether amyloid plaques or tau tangles are the essential pathological features leads to considerable confusion about what the therapeutic target really ought to be and in the end to failure in clinical trials.37-41

Experts would like to have more biomarkers to employ, like blood, CSF, or imaging measurements.42 In fact, they surmise that a panel of biological tests will eventually be needed for diagnosis in the future. Clinical diagnostic assessment such as memory testing is seen as too insensitive and variable. Biological measures are often believed on faith to be more objective, reliable, and real. Various CSF markers and neuroimaging techniques are already being used in research. It is ethically unfortunate, however, that research tools are often brought into clinical practice before their validity and utility have been demonstrated. Amyloid imaging in the United States is a case in point; yet the scans are of unclear benefit. Scans are reported as “positive or negative,” even though more quantitative information is available than just a report of “yes or no” suggests. This method of feedback creates considerable confusion amongst those who receive the label of having a positive amyloid scan and are thus placed at “elevated” risk for dementia. (How increased is elevated, one wonders). Recent research diagnostic criteria go even so far as to make a diagnosis of AD possible without any clinical features being present, based exclusively on biomarkers.43 This approach may create easier drug targets for the pharmaceutical industry, but will it benefit patients to acquire a stigmatizing “disease” label in the absence of any symptoms? And we must remember there is growing considerable controversy about whether the amyloid therapeutic strategy makes sense in the face of uncertain science and failed trials.

Ethical issues in prevention
The biomedical orientation towards precise and specific diagnosis steers us towards targeted drug and biologic therapies, for treatment and prevention.44 However, there is much we can do to promote health that does not require specifically identifying diseases. Brain health has become a popular term that focuses people’s attention on what they can do to prevent cognitive decline, not to mention motoric and other functional neurological and psychological declines.6,45 This form of health practice is based around diet, physical exercise, social engagement, cognitive stimulation, as well as treating medical risk factors, is not really specific to the brain. General body health can be supported through these activities as well.46-48

Lifestyle variables, such as lack of exercise and poor diet, have been relatively easy to identify but harder to modify. We need more research on how to modify individual behaviors and how cognitive impairment affects such approaches. However, it may be more effective to change communities and culture through educating groups of people rather than focusing on individuals. Safe green spaces in which families can walk together may be better investments of resources than personal exercise programs, for example.

The one area of health enhancement that could be said to be specific to “brain” is cognitive and social activity. Here we find another vast space of commercial and scientific interest in prevention, namely the brain fitness and neurotechnology space.23 Proponents of these approaches argue for keeping one’s mind active by using digital devices such as computer games or mobile apps. The literature here is large and of variable quality. There is some evidence that one can improve performance on the specific task featured in the game itself, but evidence for generalizability beyond the specific fitness game task to overall cognitive abilities and especially to slowing decline is just not there, despite the lofty claims made by marketing departments.23
Of course, the traditional way that we have kept ourselves cognitively active is through learning, both in formal and informal settings.\textsuperscript{45,46} The two main consistently identified factors that relate to preventing dementia include age and level of education. Level of education is a complex variable because of covariates, such as income, diet, and environmental factors like quality of the community.\textsuperscript{13,49} It is unclear whether people who are born with brains that are more resistant to cognitive aging get more education, or whether education through schooling and work and other activities itself builds so-called brain or cognitive reserve. Cognitive reserve is a poorly understood concept that tries to capture the variability in how people with similar degrees of brain pathology function more or less well. Education and exposure to lifelong intellectual challenges are said to build so-called cognitive or brain reserve.\textsuperscript{6}

Measuring the impact of educational interventions is difficult.\textsuperscript{45} That said, there is some evidence that keeping cognitively active improves quality of life. One such study involved observing the effects of people with mild to moderate dementia volunteering in a public intergenerational school in which elders worked one-on-one with young students on tasks such as reminiscence and reading.\textsuperscript{23} It is reasonable to think that purposeful and meaningful activities that create a legacy of having contributed to the lives of children might have a profound effect on people’s lives including their brains.

We have known for some time that brains can change because people can learn. Yet, neuroscientists have aggressively promoted neuroplasticity as a major discovery. Yes, the newfound m echanism s, eg, new neuronal growth in the adult brain, are exciting but are of limited value in actually fostering psycho or social plasticity, ie, behavior and cultural change. We need broader models of health such as ecopsychosocial approaches in order to ask how relevant are specific diagnoses and what the best ways of approaching brain and cognitive health are.\textsuperscript{6} The prefix “eco” turns us towards the issues of preventing dementia by examining environmental effects on cognitive health. Unfortunately, long-standing examples exist in the case of pollution with heavy metals such as lead, mercury, and arsenic. Yet perhaps the greatest threat to the quality of life of people with dementia, and in fact all of us, is ultimately global climate change.\textsuperscript{6,45} Drought, floods, fires, and other environmental disasters affect individuals with cognitive impairment more than others because they cannot plan for the disasters and avoid the danger and as well as those who are cognitively intact. My own belief is that educating people together across the life course about our responsibilities for future generations and about what we can all do to address climate change may be the best long-term way of preventing cognitive impairment.\textsuperscript{6,45} And in that process we might all recognize that we ourselves have difficulties with remembering the past, planning for the future and with our basic and instrumental activities of the living, such as finding healthy food and dealing with our biological and industrial waste products. We need to learn to appreciate limits to our individual and collective behavior. Perhaps a degree of wisdom might be achieved if we recognized some “dementia” in all of us.

Deeper ethical issues

Ethics is not monolithic. Some bioethicists focus on principles like autonomy, beneficence, and justice, others on analysis of narrative,\textsuperscript{52} some on empirical findings, and more rarely, others emphasize virtue and the character of individuals and groups, such as organizations of professions. Even more rarely, bioethicists will question their own roles and moral standards.\textsuperscript{18,53-55}

However, most ethicists would agree that the field has a responsibility to surface value-related issues for discussion and assist in their analysis and action. Traditional biomedical ethical issues well represented in the literature relate to early diagnosis and prevention and include topics such as informed consent, which in turn includes research issues like assessment of likely risk and benefit, and clinical issues related to care, for example surrogate decision-making and end-of-life care.\textsuperscript{18,54} But there are deeper bioethical issues that also require examination.\textsuperscript{55}

One particular prominent issue today is the role of science in society and the potential dangers of unbridled faith in science, so-called scientism.\textsuperscript{2,56} Alzheimer experts have been saying for decades that the cure or at least more effective therapies will be available shortly. Yet this has not happened. Is this excited messaging largely to promote professional fame and fortune allied with the pharmaceutical industry or is it a characteristic...
and justifiable zeal for the potential of scientific and technological breakthroughs? Despite many changes in rules and regulations to govern the relationships between professional and industry, conflicts of interest still abound between clinical scientists as detached experts with a moral responsibility to guide the public and as private individuals enhancing their own financial interest (often not fully disclosed) that bring personal and/or organizational gain.23

Moreover, increasing attention is being paid in science to the problem of replication of results.23 The pressure to publish has increased for career advancement, as has the encouragement from media relations offices in universities to promote academic discoveries very early in their development. The Alzheimer's field is full of unreplicated results and unfulfilled promises.2,46 We have had many triumphantly announced “breakthroughs” in the press that lead to little or nothing of clinical or social value. Maybe so many unfulfilled breakthroughs represent a breakdown in scientific process and public trust. For example, the Alzheimer’s Association in the United States claims that we could save trillions of dollars over the next few decades if we develop an effective medicine by 2025 that they predict will occur if we invest enough in research. One might imagine that they might include some estimate of the cost of the drug. However in their pharmacoeconomic model, the cost of such a promised drug (but as yet undelivered drug) was set at zero, ie, a free drug. Is this a responsible way to try to influence policy?24 Science has come to be dominated by market capitalism, that will either enhance or destroy future life on this our only planet.

Dementia and AD as social phenomena are much more important cultural issues than just the challenges faced by these clinical conditions.44 If we were to address dementia through appropriate community and environmental approaches, we could address the overall health of the human population, as well as other living creatures. If we could truly see the limitations of our current molecular reductionist obsession with cure and rise above our self-serving values to a sense of responsibility for investing and innovating for the future, we might actually survive and flourish as a species. We are living in a time of great derangements in our collective thinking and distortions in our values. Dementia is one such domain in which our promises and expectations are mismatched with our actual deliveries and the real constraints of the world in which we live. It is time to rethink what it means to be a caring human being who ages and dies, perhaps with cognitive impairments at the end, but leaves a legacy both as an individual and as a member of a generation that will either enhance or destroy future life on this our only planet.

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