Alzheimer's disease

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Although the prevalence of dementia continues to increase worldwide, incidence in the western world might have decreased as a result of better vascular care and improved brain health. Alzheimer's disease, the most prevalent cause of dementia, is still defined by the combined presence of amyloid and tau, but researchers are gradually moving away from the simple assumption of linear causality as proposed in the original amyloid hypothesis. Age-related, protective, and disease-promoting factors probably interact with the core mechanisms of the disease. Amyloid β42, and tau proteins are established core cerebrospinal biomarkers; novel candidate biomarkers include amyloid β oligomers and synaptic markers. MRI and fluorodeoxyglucose PET are established imaging techniques for diagnosis of Alzheimer's disease. Amyloid PET is gaining traction in the clinical arena, but validity and cost-effectiveness remain to be established. Tau PET might offer new insights and be of great help in differential diagnosis and selection of patients for trials. In the search for understanding the disease mechanism and keys to treatment, research is moving increasingly into the earliest phase of disease. Preclinical Alzheimer's disease is defined as biomarker evidence of Alzheimer's pathological changes in cognitively healthy individuals. Patients with subjective cognitive decline have been identified as a useful population in whom to look for preclinical Alzheimer's disease. Moderately positive results for interventions targeting several lifestyle factors in non-demented elderly patients and moderately positive interim results for lowering amyloid in pre-dementia Alzheimer's disease suggest that, ultimately, there will be a future in which specific anti-Alzheimer's therapy will be combined with lifestyle interventions targeting general brain health to jointly combat the disease. In this Seminar, we discuss the main developments in Alzheimer's research.

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Introduction

Alzheimer's disease is the main cause of dementia and one of the great health-care challenges of the 21st century. In December, 2013, the G8 stated that dementia should be made a global priority and their ambition that a cure or a disease-modifying therapy should be available by 2025. Research since the discoveries of amyloid β (Aβ) and tau, the main components of plaques and tangles respectively, has provided detailed information about molecular pathogenetic events, yet little is known about the cause of Alzheimer's disease and no curative treatments are available. Furthermore, although the presence of Alzheimer's pathological changes are a sine qua non for diagnosis and sufficient to cause symptoms in some patients, several causes are implicated in patients who become symptomatic aged older than 75 years.

With the advent of modern techniques to image and measure brain processes and analyse big data (including genetic and genomic data), and with governments across the world increasingly prioritising dementia in national health-care agendas, there is hope that the rate of scientific progress will increase. In this Seminar, we present novel, promising findings from the rapidly evolving field of Alzheimer's research, which seem to provide a glimpse into a future when Alzheimer's disease might be cured or—perhaps even more likely—prevented. We describe the clinical context of the disease and novel developments in epidemiology, molecular genetics and pathophysiology, fluid biomarkers, imaging biomarkers, and treatment.

Clinical signs and symptoms

In panel 1, we describe two cases, which show the range of Alzheimer's disease in terms of age and clinical presentation. The first case is a typical presentation of dementia (memory impairment and executive dysfunction interfering with daily life activities)—elderly individuals, who are often on their own and increasingly dependent on others for care. The second is an atypical presentation, and all too often such clinical manifestations are not recognised by primary care doctors and others. Atypical presentations include language, visual, practic, or executive problems before—and more pronounced than—memory deficits. Fortunately, increasing attention is being paid to early-onset Alzheimer's disease and its often-atypical presentations.[2–5] In early-onset disease with atypical presentation, diagnostic biomarkers can make all the difference and can guide management and decision making.

Clinical diagnosis of any dementia syndrome depends on taking a history from the patient and their carers, neuropsychological testing, and assessment of symptoms with time. The first set of criteria proposed for diagnosis of Alzheimer's disease was launched in 1984 and focused

Search strategy and selection criteria

Between March 1, and Sept 15, 2015, we searched the Cochrane Library, PubMed, and Embase with the search term "Alzheimer's Disease" in combination with the terms "pathology", "imaging", "diagnosis", "therapy", "trials", "epidemiology", "CSF", and "biomarkers" for articles published in any language since Jan 1, 2010. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. We largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar permits.

Panel 1: **Case vignettes**

Mrs A, a 79-year-old woman, is brought to see a geriatric psychiatrist by her brother because of progressive complaints of memory loss and occasional word-finding difficulties. She has managed the household independently since her husband died 5 years ago, but can no longer do so. She sometimes forgets to cook, skips meals, and pays less attention to her appearance than she used to. She has three children and seven grandchildren, whose names she sometimes mixes up. Her Mini-Mental State Examination (MMSE) score is 23 out of 30, her Cambridge Cognition (CAMCOG) score is 78 out of 104, both below the cutoff for dementia. Because she has a 7 year history of mild hypertension and mild diabetes (both well controlled), the specialist orders an MRI, which shows grade 2 bilateral hippocampal atrophy on the Scheltens scale and grade 1 white matter hyperintensities on the Fazekas scale. The geriatric psychiatrist diagnoses mild Alzheimer's disease, starts Mrs A on an acetylcholinesterase inhibitor, and recommends a daily visit from a home-care nurse.

Mrs B is a highly educated 52-year-old university professor, who presents to the neurologist with gradual progressive loss of sight and problems with identification of objects, which prompted several visits to the ophthalmologist and changing glasses, without success. Her wife and two teenage children are worried: she has been off work for 8 months already with a diagnosis of mild depression, but drugs provided no relief. On examination, her MMSE score is 28 and his CAMCOG score is 93, both within normal range, and routine neurological and laboratory investigations show no abnormal findings. Neuropsychological examination reveals visuoperceptive disturbances and executive dysfunction. MRI shows bilateral parietal atrophy, no hippocampal atrophy, and no vascular changes. Because of her young age, a family history of dementia (her mother, who received her diagnosis at age 76 years), and progressive dysfunction in her job, the neurologist suspects dementia and performs a lumbar puncture. Analysis of cerebrospinal fluid shows an abnormal pattern of low amyloid β1–42 together with increased total tau and phosphorylated tau. A diagnosis of probable Alzheimer's disease with high likelihood of Alzheimer's pathophysiology was made according to the National Institute of Aging–Alzheimer's Association criteria,[3] and Mrs B is included in a clinical trial. An amyloid PET, done as part of the trial, shows abnormal deposition of amyloid in the parietal and posterior cingulate regions. Her university puts her on sick leave.

on clinical symptoms only. At the time, Alzheimer's pathological changes could not be measured in vivo, so disease could be definitively diagnosed only after death. With the advent of MRI and the discovery of cerebrospinal fluid (CSF) biomarkers and amyloid PET, the International Working Group (IWG) proposed new criteria,[6] which formed the inspiration for a subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working groups.[1,7,8] Several important developments are included in these new criteria. A long pre-dementia stage is acknowledged. Mild cognitive impairment is recognised as prodromal Alzheimer's disease in the IWG criteria and in the NIA–AA criteria when supported by biomarkers suggesting the presence of amyloid and neurodegeneration. Biomarker evidence can be used to attribute the clinical syndrome of dementia or mild cognitive impairment to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is Alzheimer's disease) in the NIA–AA criteria. Atypical presentations are acknowledged, such that in the IWG critieria, presence of memory impairment is no longer required for diagnosis, as long as biomarker evidence is available. Preclinical Alzheimer's disease (NIA–AA)[8] and at risk for Alzheimer's disease (IWG)[9] have been accepted and are defined as evidence of Alzheimer's pathological changes in cognitively healthy individuals (panel 2).

Epidemiology

An estimated 40 million people, mostly older than 60 years, have dementia worldwide, and this figure is projected to double every 20 years, until at least 2050.[18] Within these estimates, both the number of people who develop the disease at a specific age and the survival time of those with the disease are assumed to remain stable for a given region. Projected increases in the prevalence of dementia are proportionally much higher for developing countries with young populations than for western Europe and the USA, which already have a much older population. Reliable estimates of the prevalence of early-onset dementia and Alzheimer's disease (before age 65 years) are scarce. The prevalence of dementia before age 50 years is less than 1 per 4000, with roughly 30% of cases being attributed to Alzheimer's disease.[19]

In the past 5 years, several European population-based cohort studies have provided evidence that the age-specific incidence of dementia has decreased in the past 20 years, thereby raising expectations for preventive interventions. In a study[20] in which incidence was directly compared between sub-cohorts, age-specific incidence was 24% lower in the 2000 cohort than in the 1990 cohort. Risk factor profiles and brain imaging scans were also compared: the 2000 cohort had less evidence of generalised brain atrophy and cerebral small vessel disease and their vascular risk factors were better controlled, notwithstanding an overall increase in vascular risk factors (ie, hypertension, diabetes, obesity). In several other European studies[9] in which prevalence in the same areas was compared, with similar methods and diagnostic criteria but years or decades apart, similar conclusions were reached. Long-term monitoring of health-care records and other health survey data suggest similar trends in the USA.[21]

Data for time trends in other regions are limited. Results of a 2013 systematic review[22] suggested that the prevalence of dementia has increased in China, but this notion was challenged by another review in which variation in methods and changing diagnostic criteria were taken into account.[23] A common observation across Asian studies is an apparent shift from vascular dementia, which used to be more common, to Alzheimer's disease, with a resulting disease ratio akin to that in western countries.[24] Demographic and lifestyle changes; changes in vascular background risk, diagnostic methods, and criteria; and adaptation to the more Alzheimer's-focused international research community could all have contributed to this shift.[25]

Lifestyle and vascular risk factors

Alzheimer's disease develops over a long preclinical period of several decades, which raises the question of the extent to which risk factors assessed in late life or shortly before onset of clinical symptoms are a result of developing pathological changes rather than a causal relation. Two different approaches have been taken to address this issue. Studies that were started decades ago and included people in early life or midlife allowed assessment of the relations between early-life or midlife risk factors and cognitive decline and dementia risk later in life. Whereas the results of most studies[26–29] confirmed the relation between vascular health status and risk of later cognitive decline and dementia, an important caveat when interpreting such longitudinal studies is the potential for selective dropout. An alternative, and more specific, approach has focused therefore on intermediate or endophenotypes—particularly brain imaging markers. The challenge of these studies is to avoid potential biases during sampling, particularly for convenience or clinic-based sampling.[30,31] In light of the falling age-specific incidence of dementia, the World Dementia Council declared that dementia risk reduction is crucial to the global dementia agenda, with strong evidence that interventions for cardiovascular risk could improve cognitive health at the population level.

Increasing evidence suggests that many other lifestyle-related factors, including diabetes, obesity, physical and mental inactivity, depression, smoking, low educational attainment, and diet have a role in dementia, and the potential for primary prevention related to such modifiable risk factors is huge but yet to be fully explored.[32] On the basis of the Rotterdam study, it has been modelled that elimination of the seven most important modifiable risk factors would lead to a 30% reduction in dementia incidence.[33] This finding shows both the huge potential of risk-factor reduction, and the need for other therapeutic strategies for the remaining 70% of cases.

Genetic susceptibility

APOE4 is the major genetic risk factor for Alzheimer's disease. Lifetime risk for Alzheimer's disease is more than 50% for *APOE4* homozygotes and 20–30% for *APOE3* and *APOE4* heterozygotes, compared with 11% for men and 14% for women overall irrespective of *APOE* genotype.[34] APOE4 has several effects on Alzheimer's disease. It interferes with Aβ clearance from the brain,[35] and is also processed into neurotoxic fragments.[36] Furthermore, mice that express *APOE4* show disinhibition of a cyclophilin A signalling mechanism in the pericytes of the brain blood vessels, resulting in degeneration of these vessels, leakage of the blood–brain barrier, and neurodegeneration independent of Aβ.[37] The pleomorphic effects of *APOE4* show the complex interplay of mechanisms contributing to sporadic Alzheimer's disease.

Genome-wide association studies have been used to identify more than 20 genetic loci associated with the risk of Alzheimer's disease. The newly identified genes point at pathways implicated in the immune system and

For the **declaration on dementia risk reduction** see http://dementiachallenge.dh.gov.uk/

Panel 2: A shift in diagnostic framework

The field of dementia has changed substantially since the conceptual shift towards the idea that Alzheimer's disease exists before dementia is present. This game-changing notion was needed to boost drug development and advance-care planning. However, the diagnostic criteria of the International Working Group and the National Institute of Aging–Alzheimer's Association still rely on a clinical phenotype combined with biomarker information, mainly driven by amyloid and tau.

The next step that can be envisaged is the development of clinical-label-free protein characterisation for each patient's protein abnormalities—such as amyloid, tau, TDP43, progranulin, α-synuclein, tau species—in combination with appreciation of aggravating risk factors (eg, genetics, vascular risk factors, vascular disease) and protective factors (eg, genetics, healthy lifestyle). Essentially, clinical nosology would be replaced with labels describing pathophysiological processes. This approach has the potential to revolutionise diagnosis by acknowledging that treatment ultimately needs to be directed against the causative proteinopathies and other pathological changes, irrespective of the clinical phenotype. That most patients' dementia has mixed causes is also acknowledged: these patients could thus receive treatment targeted at different aspects of their disease. This approach will fuel and speed up therapeutic development for any neurodegenerative dementia. It will necessitate even closer collaboration between molecular biologists, chemists, engineers, and clinicians. Clinical diagnosis will still be necessary to establish the syndrome diagnosis (ie, severity). Also, better prognostic biomarkers will be needed to determine which patient needs to be treated when (eg, an amyloid-positive individual that will never become symptomatic does not need treatment).

Thus, a focus on preclinical Alzheimer's disease is pivotal. Studies in which cerebrospinal fluid biomarkers and amyloid PET are analysed have shown that roughly a third of elderly people are amyloid positive, and that this amyloid positivity is associated with an increased risk of clinical progression.[10,11] Several important questions will hopefully be answered in the next 5 years. Which factors determine that an individual becomes amyloid positive? Will every amyloid-positive patient develop a dementia syndrome if they live for long enough? If so, which factors determine when a patient will develop dementia? If not, can protective factors be identified? Even if all amyloid-positive individuals were to ultimately develop dementia, there is a difference between hearing at 85 years old that you will be demented in 20 years, or hearing at age 65 years that onset of dementia will happen within the next 2 years. Biomarkers providing this information are absent. A follow-on question would be, do all amyloid-positive patients follow the same route to Alzheimer's disease? The existence of individuals with suspected non-amyloid pathology who progress to Alzheimer's disease already suggests that the order in which events occur (eg, amyloid followed by tau or the other way around) might differ among patients.[12,13]

In addition to the well studied syndrome of mild cognitive impairment or prodromal Alzheimer's disease, the focus of research is now shifting even earlier. Individuals with subjective cognitive decline, which is defined as personal sensation of cognitive decline despite results within healthy limits on cognitive tests might be an excellent population in which to study preclinical Alzheimer's disease.[14] Subjective cognitive decline is associated with an increased risk of progression to dementia, especially when the patient is worried about the decline.[15] Compared with healthy controls, patients with subjective cognitive decline have more brain abnormalities, including hippocampal volume loss and hypometabolism.[16] Furthermore, in patients with subjective cognitive decline, cerebrospinal amyloid β is strongly predictive of subsequent clinical progression.[17]

inflammatory responses, cholesterol and lipid metabolism, and endosomal-vesicle recycling.[38] Some factors could be age related, whereas others could have protective effects; all these factors probably interact with the core mechanisms of the disease. These polymorphisms are frequent in the population but contribute little to the individual risk for disease (figure).[39]

Patients with Alzheimer's disease do not induce expression of *REST*,[40] which exerts cell survival effects and is normally upregulated in the ageing brain.[40] Alterations in other genes and in non-coding RNA, such as microRNA, might also have important roles in disease susceptibility.[41,42] Novel genome-sequencing technologies have been used to identify rare mutations, which convey substantial increases in risk to carriers.[43,44] The best validated are mutations in TREM2, a microglia receptor involved in Aβ clearance.[45] Genome-wide profiling of gene expression in the brains of patients with late-onset Alzheimer's disease supports the hypothesis of an upregulated immune-specific and microglia-specific module with TYROBP as a key regulator.[45,46]

Pathophysiology

The past 30 years of Alzheimer's disease research have produced substantial evidence that accumulation of abnormally folded Aβ and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in patients' brains.[47] Yet observational and pathological studies have generated overwhelming evidence for the complexity and multicausality of dementia.[48] This complexity is increasingly recognised in basic and clinical studies too, and research is moving away from the simple assumption of linear causality as proposed in the original amyloid hypothesis.[49]

The strongest evidence for Aβ and tau as causative comes from studies of familial Alzheimer's disease—cases with mutations in *APP*, *PSEN1*, or *PSEN2*.[39] APP is the precursor of the Aβ peptides and *APP* mutations affect Aβ cleavage and aggregation. PSEN1 and PSEN2 provide the catalytic subunit to the γ secretases, which cleave APP. Originally thought to result in an increase in Aβ42,[50] studies[51] show that *PSEN* mutations cause less efficient

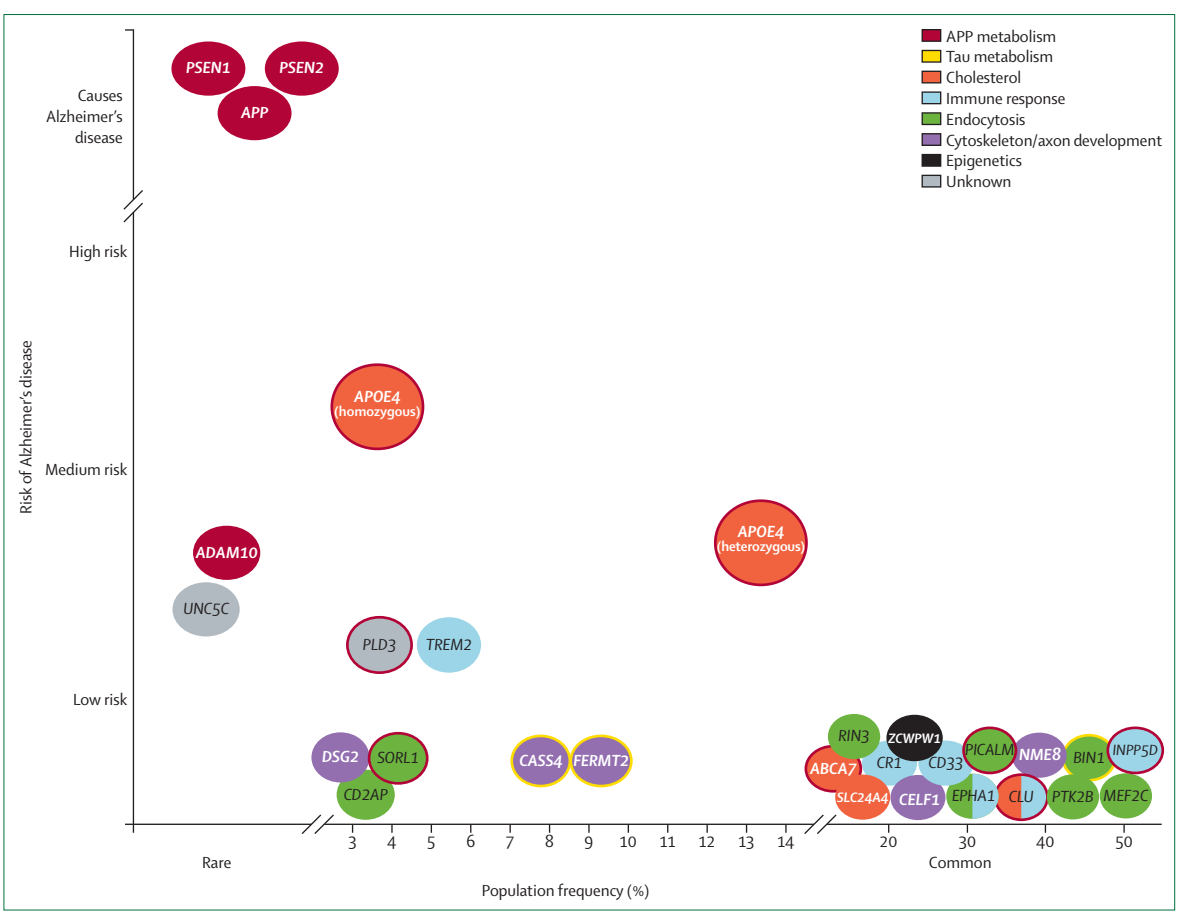

Figure: **Schematic overview of genes linked to Alzheimer's disease**
The colours in the key show the pathways in which these genes are implicated. Genes that are known to affect APP metabolism are circled in red, whereas those that affect the tau pathway are circled in yellow. The interior colours provide further information on what functions the genes have. When there are two colours, the gene might have functional roles in two different biological pathways. Many of the genes have been related to APP processing or trafficking (red or red border), suggesting the central importance of APP metabolism in Alzheimer's disease. The figure was adapted with permission from Karch et al, 2015.[39]

processing of APP and the generation of longer and more hydrophobic Aβ peptides. Aβ is thought to be the trigger, or even the driver, of the disease process, at least in familial cases.[47] Tau is also a prerequisite for diagnosis of Alzheimer's disease, but mutations in the tau gene cause frontotemporal dementia without amyloid plaques—ie, tau can act independently of Aβ to cause neurodegeneration. Although in the amyloid hypothesis, pathological alterations of tau were thought to be downstream events of Aβ deposition, it is equally plausible that tau and Aβ act in parallel pathways causing Alzheimer's disease and enhancing each other's toxic effects.[49]

Analogous with prion disorders, toxic conformations of Aβ or tau, or both, are generated during the disease. These so-called seeds can induce pathological conformations of normal peptides, which can cause spreading of the disease across the brain.[52] Evidence for this idea comes from a pathological study[53] in which pathological changes were noted in four of eight young (<55 years) patients who died from iatrogenic Creutzfeldt-Jakob disease caused by injections from human-pituitary-derived growth hormone. Mutations in *APP*, *PSEN1*, and *PSEN2* probably accelerate the generation of such seeds, whereas in sporadic Alzheimer's disease, decreased clearance of Aβ[54] or oxidative stress[55] might have roles in the accumulation of toxic Aβ species. However, the nature of the pathological conformations (oligomeric or fibrillic, specific post-translational modifications, different strains)[56,57] and the associated mechanisms of toxic effects need to be further elucidated.[58] Aβ oligomers, for instance, seem to bind to various membrane receptors,[59] including the prion protein,[60] but the relative importance of these different interactions to the disease process is unclear.

Because Aβ has such a crucial role, a rational way to treat or prevent Alzheimer's disease would be to block the proteases that generate Aβ. The first cleavage step in the generation of Aβ is mediated by the β-secretase BACE1, which is highly expressed in neurons and cleaves many physiologically important substrates.[61] Mice deficient in BACE1 show complex phenotypes,[62] and BACE1 is involved in synaptic plasticity.[63] Furthermore, inhibition of BACE1 induces alternative processing of APP and generation of synaptically active peptides that are different from Aβ.[64] Inhibitors of β secretase are being tested in clinical trials,[65] and side-effects so far seem surprisingly limited. Inhibitors of the γ secretases, which are implicated in the second cleavage step, were unsuccessful in clinical trials because of side-effects,[66] but to rule out γ secretases as drug targets for Alzheimer's disease would be premature. In the future, their activity could be modulated by compounds called γ-secretase modulators such that shorter, less toxic versions of Aβ are generated. Such modulators, given in combination with a β-secretase inhibitor, could be particularly efficient in reduction of potential side-effects.[67] Structural work with powerful new cryo-electron microscopy techniques has provided the first atomic resolution of the structure of the γ-secretase complex,[68] which will probably revolutionise drug discovery research for this aspect of disease. Better three-dimensional cell culture models that generate plaques and tangle-like pathological changes in vitro will probably speed up drug discovery further.[69]

Fluid biomarkers

Core CSF biomarkers

Core CSF biomarkers for Alzheimer's disease are $A\beta_{42}$, which shows cortical amyloid deposition; total tau (t-tau), which reflects the intensity of neurodegeneration; and phosphorylated tau (p-tau), which correlates with neurofibrillary pathological changes.[70] These core CSF biomarkers have high diagnostic accuracy, with sensitivity and specificity of 85–90%, to identify prodromal Alzheimer's disease in the mild cognitive impairment stage.[71,72] When assessing the diagnostic performance of Alzheimer's disease biomarkers, it is essential to consider that a continuum of pathological changes (eg, plaque counts) exists without any clear distinction between patients with Alzheimer's disease and cognitively healthy elderly people who died from other causes,[73] that clinical diagnoses—often used as a gold standard—are an imperfect criterion,[74] and that elderly patients with Alzheimer's disease often show several pathological changes, including α-synuclein, TDP43, and vascular changes.[75] This pathobiological variance precludes any biomarker from having 100% diagnostic accuracy. Nonetheless, CSF biomarkers can help with diagnostic decision making at memory clinics (panel 1),[76] and have especially good negative predictive value—ie, healthy concentrations of all three biomarkers in a patient with mild memory disturbances almost excludes Alzheimer's disease.

Variability in measurements between clinical laboratories has hampered the identification of uniform cutoffs for CSF biomarkers. This problem stems from differences in analytic procedures for manual ELISA methods between laboratories and variability in reagent quality and manufacturing procedures that results in batch-to-batch variations,[77] and is most pronounced for $A\beta_{42}$. Standardisation efforts have resulted in fully validated mass-spectrometry-based reference measurement procedures for CSF Aβ42,[78] and certified reference materials to serve as gold standards for standardisation of CSF biomarker measurements. Additionally, novel assays have been developed on fully automated laboratory analysers, resulting in very stable measurements between laboratories. Taken together, these standardisation efforts provide the basis for the introduction of uniform cutoffs and more general use of CSF biomarkers for routine clinical diagnosis of Alzheimer's disease.

The frequency of misdiagnosis in clinical trials in which diagnosis is made on clinical grounds alone[79] underscores the need for biomarker-based inclusion criteria. Large clinical studies show high concordance

with identical diagnostic performance for CSF Aβ1–42 and amyloid PET,[80,81] suggesting that these techniques can be used interchangeably for trial enrolment.

Novel CSF biomarkers

Additional objective measures of pathogenetic processes implicated in Alzheimer's disease would help to provide insight into the full range of molecular pathogenesis. Investigation of different biomarkers is at different stages of development. One such biomarker is Aβ oligomers, which are thought to be a toxic form of Aβ that cause synaptic dysfunction.[82] In most studies, an increase in CSF Aβ oligomers is reported in Alzheimer's disease,[83] but overlap with control groups is large. Aβ oligomers are rarely detected in CSF, which limits quantification by ELISA, thus making it unreliable.[84] Encouragingly, novel ultra-sensitive techniques hold the promise of clinically useful tests for Aβ oligomers.[85] Another novel candidate is synaptic biomarkers, such as the dendritic protein neurogranin, which is involved in long-term potentiation and memory consolidation.[86] High CSF concentrations of neurogranin predict progression to Alzheimer's disease in patients with mild cognitive impairment and correlate with rapid cognitive deterioration during clinical follow-up.[87] Concentrations of the presynaptic protein SNAP25 increase substantially during the prodromal stage.[88] Synaptic biomarkers could be a link to both cognitive symptoms and therapeutic response.

Blood biomarkers

Blood is more accessible than CSF, which makes blood biomarkers desirable for use in both primary care and multiple sampling in clinical trials (and perhaps even future population screening). In many studies, combinations of proteins, lipids, metabolites, or other molecules have been used to discriminate patients with Alzheimer's disease from healthy controls, and such panels could represent novel Alzheimer's blood biomarkers.[89,90] These studies are often based on screening of many unselected molecules followed by identification of a combination that shows diagnostic separation when multivariate statistics are used, but overlap for individual molecules is often substantial. Besides patient and control-cohort differences and difficulties with pre-analytic and analytic standardisation,[91] statistical over-fitting of data on the basis of the presence of a combination of molecules unrelated to Alzheimer's disease pathogenesis to a panel in a specific cohort could introduce bias. Thus, the results from these panels often fail to be replicated in independent clinical cohorts,[92] or dissimilar protein biomarker panels are suggested in different studies.[90]

Another approach is to measure CNS-specific proteins; however, it is notoriously difficult because of low concentrations in blood, because these proteins undergo degradation by plasma proteases, and because of the huge amount of matrix proteins in blood that can cause assay interference. Nonetheless, application of novel ultra-sensitive techniques could provide the analytic sensitivity needed to allow accurate measurement of CNS-specific proteins such as tau,[93] but large clinical studies are needed to assess diagnostic performance of this type of blood biomarker.

Imaging

Towards an inclusionary approach

Imaging has a key role in the clinical assessment of patients with suspected Alzheimer's disease. The traditional view that at least one structural scan (either CT or MRI) should be done at least once in every patient with cognitive impairment to rule out intracranial causes (eg, meningioma, subdural haematoma) has been complemented by the notion that the demonstration of regional atrophy in the medial temporal region can provide positive diagnostic information (panel 1).[94] A visual scale rating of medial temporal atrophy is commonly used in the diagnostic work-up of patients with cognitive impairment.[95,96] Hippocampal volumetry might be more accurate,[97] and a protocol for the manual segmentation of the hippocampus has been standardised globally[98,99] but is not easily applicable in routine clinical settings because sophisticated hardware and software are needed. Automated hippocampal segmentation algorithms have been developed and need to be validated against the manual segmentation gold standard.[100] For patients with atypical Alzheimer's disease, such as posterior cortical atrophy, appreciation of atrophy in the parietal region is of the utmost importance. A visual rating scale for this purpose has been developed, helping implementation in clinical practice.[101] Additionally, MRI remains the modality of choice for the assessment of vascular brain changes, such as white matter hyperintensities, lacunes, and microbleeds (which have gained increasing attention because they are frequent side-effects in anti-amyloid trials).[102,103] Novel developments show the need for, and potential of, automated image analysis, multimodal analysis, and computer-aided diagnostics.

PET

The diagnostic work-up of patients with cognitive impairment can be difficult during the early stage, when the differential diagnosis is still wide and includes normal ageing.[7] ^{18}F-fluorodeoxyglucose (FDG) PET measures glucose uptake of neurons and glial cells and is sensitive to synaptic dysfunction. A normal FDG PET virtually excludes a diagnosis of neurodegenerative disease.[104] A positive scan, conversely, suggests Alzheimer's disease if the pattern is temporoparietal and posterior cingulate, and frontotemporal dementia if the pattern is anterior or asymmetric, or both. Ultimately, accurate interpretation of FDG PET in patients with dementia does not rest on the presence or absence of a single region of hypometabolism but rather should take into account the pattern of hypometabolism across the whole cortex.[105]

Consensus is consolidating that visual analysis should be complemented by quantitative operator-independent readouts, such as Statistical Parametric Mapping, Stereotactic Surface Projections, or other commercial products. The resulting maps provide detailed anatomical localisation of dysfunctional brain regions but still need to be interpreted by an expert reader. Pattern recognition classification software, which is based on neural networks or other sophisticated statistical programs (those that analyse differences in grey matter structures on MRI, for instance),[106] might help in the classification. Synaptic dysfunction in the posterior regions (the so-called default mode network) is captured also by network analysis of functional blood-oxygen-level-dependent MRI. However, standardisation and reproducibility issues mean that this technique is not yet useful on an individual level.[107]

The most innovative imaging marker for Alzheimer's disease that is used clinically is PET with ligands for Aβ. Three ligands have been approved for clinical use by the European Medicines Agency and the US Food and Drug Administration: florbetapir, florbetaben, and flutemetamol.[108] These ligands have very high accuracy for cortical amyloidosis, as shown by verification studies of pathological changes in elderly patients scanned just before death.[109] However, because brain amyloidosis is a necessary but not sufficient condition for diagnosis of Alzheimer's disease, the diagnostic value of amyloid PET is more exclusionary (ie, a high negative predictive value) than inclusionary (ie, it has a moderate positive predictive value). A patient with cognitive impairment and negative amyloid PET is unlikely to have Alzheimer's disease, whereas up to 35% of cognitively healthy people older than 60 years have positive amyloid PET scans.[110] Brain amyloidosis was strongly associated with age in a large meta-analysis,[111,112] which also showed that the curve representing the increase of amyloid with age highly resembles that representing the increase in dementia prevalence with age, although the former precedes the latter by at least 20 years.

Increasing evidence suggests that the combination of several markers—ie, hippocampal volumetry, FDG PET, amyloid PET, CSF Aβ42, t-tau, and p-tau, as suggested in the NIA–AA criteria—has good positive and negative predictive value to differentiate Alzheimer's disease from normal ageing in patients with mild cognitive impairment. In a multicentre memory clinic study, patients with mild cognitive impairment with positive results for hippocampal atrophy, temporoparietal hypometabolism on FDG PET, and CSF $A\beta_{42}$, invariably developed dementia at follow-up, whereas those with negative results for all three parameters almost never did.[113] This finding has been supported by the results of larger independent samples.[114]

Fluorinated ligands for tau have been developed, and bind to fibrillary tau aggregates with remarkable accuracy.[115] Tau ligands have shown binding topography that correlates well with the clinical syndrome in Alzheimer's disease and show a better correlation with hypometabolism and atrophy than does amyloid PET.[116] Tau imaging is being used in clinical trials of drugs aiming to delay progression of Alzheimer's disease, but its usefulness for clinical diagnosis remains to be confirmed.

Imaging markers in clinical trials

In clinical trials of drugs that are designed to delay onset of dementia or progression of cognitive impairment in patients with Alzheimer's pathology, imaging is frequently used for inclusion and as a secondary outcome measure. Hippocampal atrophy and amyloid PET have been qualified by the European Medicines Agency to enrich clinical trials at the pre-dementia stage of Alzheimer's disease.[117,118]

Repeated MRI scans sensitive to microbleeds are mandatory in clinical trials of anti-amyloid drugs to monitor amyloid-related imaging abnormalities.[119] These include signal hyperintensities on fluid attenuation inversion recovery sequences, which are thought to represent vasogenic oedema or sulcal effusion, and signal hypointensities on gradient-recalled echo/T2*, which are thought to represent haemosiderin deposits, including microhaemorrhage and superficial siderosis. Amyloid-related imaging abnormalities develop after removal of amyloid from cerebral microvessels, which leads to endothelial damage, increased vascular permeability, and leakage of water or blood in the brain parenchyma.

The road towards full exploitation of imaging biomarkers is still long both in the clinic and in clinical trials. Standardisation of collection and measurement of all biomarkers is mandatory. The added diagnostic value of one biomarker over another should be elucidated to devise parsimonious and cost-effective diagnostic protocols. The individual and societal benefits of an expensive biomarker-based diagnosis should be demonstrated—especially until effective drugs are available. Imaging-based surrogate outcomes of efficacy—analogous to white-matter changes in multiple sclerosis—should be developed to allow clinical trials with small group sizes and in the presymptomatic stage.

Treatment

The mainstay of treatment for Alzheimer's disease is supportive care from family and other caregivers. Patients with dementia have better quality of life in a predictable home environment that meets their daily needs. Familial caregivers need help to learn how to manage the progressive nature of the illness and guidance on how to mobilise the resources needed to maintain care for their loved one while preserving their own wellbeing.

Four drugs are used for the treatment of the dementia phase: the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the glutamate antagonist memantine. Acetylcholinesterase inhibitors tend to

stabilise cognitive performance and daily functioning during the first year of treatment. Further decline ensues, but continued treatment might produce some benefits. Memantine might provide some benefit for patients with moderate-to-severe dementia, either as monotherapy or in combination with a cholinesterase inhibitor.

New treatments that will prevent, delay, or treat the symptoms of Alzheimer's disease are urgently needed. Researchers have focused on anti-amyloid approaches, including active and passive immunisation strategies, γ-secretase and β-secretase inhibitors, and anti-aggregation drugs. Several large phase 3 trials of anti-amyloid approaches in patients with mild-to-moderate Alzheimer's disease have been published, with disappointing results.[66,79,120–123] In an 18-month trial,[79] bapineuzumab, a monoclonal antibody that targets the N-terminus of Aβ, was not associated with any clinical benefit despite a slight decrease in amyloid accumulation and lowering of CSF p-tau in *APOE* ε4 carriers. Dosing was limited because of the development of transient amyloid-related imaging abnormalities.[79,119,124] An 18 month trial[120] of solanezumab, a monoclonal antibody that binds to soluble Aβ, showed no benefit in the primary cognitive clinical outcomes. A secondary analysis of the trial showed a possible slight decrease in the rate of cognitive decline in patients with mild dementia and a new study of solanezumab in patients with mild Alzheimer's disease is ongoing (NCT01900665). As many as 30% of patients who underwent amyloid PET in the bapineuzumab and solanezumab trials had amyloid concentrations below the cutoff for Alzheimer's disease, and this proportion was higher in *APOE* ε4 non-carriers. Disease progressed more slowly in amyloid-negative participants, which raises questions about the validity of the diagnosis.

Anti-amyloid trials have incorporated screening with amyloid biomarkers to ensure that participants have amyloid pathological changes. The unsuccessful trials show the huge need for more basic research in Alzheimer's disease. For instance, passive vaccination strategies against Aβ or tau assume that the antibodies will block or clear various Aβ species, but whether the antibodies bind disease-relevant conformations is unknown. Such knowledge might provide clues as to why the trials with Aβ antibodies failed.[125] Other possible reasons for the disappointing results of anti-amyloid trials include treating too late, poor diagnostic regimens (without amyloid biomarkers) focusing on the wrong target or drug, and insufficient target engagement.

There is a growing consensus that anti-amyloid drugs will probably be most effective early in the disease process. However, results of trials of the monoclonal antibody gantenerumab[126] and the γ-secretase inhibitor avagacestat in patients with prodromal Alzheimer's disease, in which a low concentration of $A\beta_{42}$ in the CSF was an inclusion criterion, were discouraging. On the positive side, an interim analysis of a phase 1b trial of aducanumab, a human monoclonal antibody selective for aggregated forms of Aβ (ie, soluble oligomers and insoluble fibrils), in patients with early Alzheimer's disease (ie, mild cognitive impairment and mild dementia) was associated with a dose-dependent decrease in amyloid uptake and a slower decline in cognition and global functioning. These results have prompted a direct move to a pivotal phase 3 trial in patients with early Alzheimer's disease (table). Blocking the proteases that generate Aβ is another important approach to treat or prevent Alzheimer's disease, and β-secretase inhibitors are in clinical development in phase 2 and 3 clinical trials for early Alzheimer's disease and secondary prevention.

For the **interim trial analysis** see http://www.neuroimmune.com

Secondary prevention, risk reduction, and other approaches

Several major trials investigating how to delay the onset of cognitive decline in individuals at high risk for Alzheimer's disease are underway. The Anti-Amyloid in Asymptomatic Alzheimer's disease (A4) study is testing whether solanezumab given monthly for 3 years could delay cognitive decline in cognitively healthy elderly patients with a positive amyloid PET scan.[127] Four studies aiming to delay cognitive decline in individuals with high genetic risk are underway, two in families with a deterministic Alzheimer's mutation (the Dominantly Inherited Alzheimer's Network–Treatment Unit and Alzheimer's Prevention Initiative–Colombia trials), one in *APOE* ε4 homozygotes, and one in individuals at risk according to an algorithm based on *TOMM40* and *APOE* (the TOMMORROW study).[128–130] These early intervention trials face challenges of widespread screening, a high screening-failure rate, ethical issues in disclosure of genetic and biomarker results, and the need for sensitive outcome measures. The US Food and Drug Administration has issued guidance providing provisional approval for compounds tested in preclinical Alzheimer's disease based on a positive response on a composite cognitive measure, with ongoing monitoring to demonstrate benefits in terms of functional outcomes.[131]

Tau neurofibrillary tangles are closely associated with synaptic loss and cognitive decline, and tau-based immunotherapy and other tau-modulating strategies are in active clinical development. The selective 5-HT_6 receptor antagonist idalopirdine was associated with significant cognitive benefit compared with placebo in mild-to-moderate Alzheimer's disease in combination with donepezil, and phase 3 trials are in progress.[132] Insulin signalling might have a role in pathogenesis of Alzheimer's disease, and a trial of long-acting intranasal insulin is underway in patients with mild cognitive impairment and mild dementia.[133] Deep brain stimulation, which is approved for the treatment of Parkinson's disease, is now being tested in a double-blind trial targeting the limbic memory circuit in patients with mild Alzheimer's disease.[134] The medical food

	Manufacturer	Epitope	Origin	Isotype	Target	Possible mechanism of action	Outcomes in latest stage trial	Amyloid biomarker inclusion criteria in trials	Trials planned or in progress	Rate of amyloid-related imaging abnormalities
Solanezumab (NCT0760005, NCT01900665)	Eli Lilly	Mid-domain	Humanised	IgG1	Soluble, monomeric, non-fibrillar Aβ	Sequestration of soluble monomeric Aβ	Negative clinical outcomes in two phase 3 trials in mild-to-moderate Alzheimer's disease; possible slowing of cognitive decline in mild disease	None	Phase 3 trials underway in mild, preclinical, and autosomal-dominant Alzheimer's disease	Low
Bapineuzumab (NCT00575055, NCT00574132)	Pfizer/Johnson & Johnson	N-terminus	Humanised	IgG1	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in two phase 3 trials despite significant decrease in amyloid PET and phosphorylated tau concentrations in cerebrospinal fluid	None	..	Related to dose and *APOE* ε4 carrier status
Crenezumab (NCT 01397378, NCT01723826, NCT01998891)	Roche/ Genentech	Mid-domain	Humanised	IgG4	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in phase 2 trials in mild-to-moderate Alzheimer's disease; possible cognitive slowing in mild disease in patients given high doses	None in ABBY trial; amyloid PET in BLAZE trial	Phase 3 trial in autosomal-dominant Alzheimer's disease underway	Low
BAN2401 (NCT01767311)	Eisai/Biogen	N-terminus	Humanised	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	No phase 2 trials yet completed	Amyloid PET	Phase 2 trial underway in mild cognitive impairment	..
Gantenerumab (NCT01224106, NCT02051608)	Roche/ Genentech	N-terminus and mid-domain	Human (phage display library and affinity maturation)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Negative clinical outcomes in phase 3 trial for prodromal Alzheimer's disease	Cerebrospinal fluid Aβ	New phase 3 trial in planning phase	Related to dose and *APOE* ε4 carrier status
Aducanumab (NCT02484547, NCT02477800)	Biogen/ Neurimmune	N-terminus	Human (RTM)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Dose-dependent decrease in amyloid PET and cognitive decline in early Alzheimer's disease (mild cognitive impairment and mild disease) in interim analysis of phase 1b trial	Amyloid PET	Phase 1 trial in prodromal or mild Alzheimer's disease and phase 3 trial of early disease underway	Related to dose and *APOE* ε4 carrier status

Aβ=amyloid β. ..=not applicable. RTM=reverse translational medicine.

***Table*: Anti-amyloid monoclonal antibodies in clinical development**

Axona,[135] a formulation of fractionated coconut oil (caprylictrigyceride) that is thought to improve energy supply to the brain, is approved for the treatment of Alzheimer's disease in the USA, and the nutritional formulation Souvenaid,[136] a combination of 11 vitamins and supplements, is approved for early Alzheimer's disease in some European countries, Australia, and China.

Although psychotropic drugs are often prescribed, no treatments are approved for management of behavioural symptoms in dementia. In a trial, the combination of quinidine and dextromethorphan, which is approved for treatment of pseudobulbar affect, decreased agitation in patients with dementia compared with placebo, and the combination is being tested in two phase 3 randomised, placebo-controlled trials for treatment of agitation in Alzheimer's disease (NCT02442765 and NCT02442778).[137] High doses of citalopram, a selective serotonin reuptake inhibitor, reduced symptoms of agitation in a controlled trial[138] but were also associated with an average decline of 1 point on the Mini-Mental State Examination.

In view of the multifactorial nature of Alzheimer's disease, multidomain, long-term interventions targeting several risk factors simultaneously might be needed. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial,[139] elderly patients at risk of dementia were randomly assigned to either a combined regimen of exercise, diet, cognitive training, and close management of cardiovascular risk factors or to standard care; patients in the intervention group did better in tests of executive function and processing speed and had higher total neuropsychological battery scores (but not on memory). In the European PREVENT trial, a similar intervention strategy will be compared with usual care in middle-aged individuals with a parental history of Alzheimer's disease.[140]

Panel 3: Diagnosis and management of early Alzheimer's disease in 2025

To make the postulated changes to the diagnosis and management of Alzheimer's disease a reality by 2025, lots of work is needed. The validity and cost-effectiveness of amyloid and tau imaging need to be shown. Ideally, less invasive and expensive methods will have been developed and become available, such as retinal amyloid imaging or a blood test. Hopefully, more and effective personalised lifestyle recommendations can be provided, perhaps on the basis of individual genetic and environmental characteristics (ie, a personalised risk profile). Effective treatments to reduce Alzheimer's disease burden are urgently needed. An era of discovery is underway to identify drugs targeting the key components of pathogenesis, neuritic plaques, neurofibrillary tangles, inflammation, and neurodegeneration. Open science and a broad alliance of scientific, clinical, public, and private sectors will be needed for treatment breakthroughs. Future treatment will probably involve a combination of two or more drugs with lifestyle and risk-reduction strategies. The development of combination treatments will necessitate adaptive trial designs with early readouts and important safety, dosing, regulatory, and intellectual property challenges will need to be overcome.[141] In 2025, treatment of Alzheimer's disease might have progressed to where some cancer treatments are now—ie, with diagnosis and management based on multimodal information that enables personalised treatment. Research is at a crucial tipping point, and a world in which Alzheimer's disease is a preventable and treatable condition could soon be a possibility.

Conclusions

Alzheimer's research is rapidly progressing. Advances in basic science and molecular diagnostics have provided unprecedented possibilities for drug development. In the aftermath of the G8 statement, there is no time to waste in trying to provide a better future for the patients of tomorrow, although improving care and help for today's patients should always remain a priority.

If progress accelerates as expected, a patient with early symptoms of Alzheimer's disease in 2025 will be treated substantially differently from how they are now (panel 3). They will probably be seen by their primary care doctor in most countries upon first complaints. This doctor will prescribe risk-factor management, treat comorbid disease, and provide personalised advice for lifestyle modification. The patient will also be referred to a specialist and undergo MRI, amyloid and tau imaging, or measurement of cerebrospinal fluid biomarkers, depending on availability of techniques, tradition, training status of clinicians, and financial considerations.[142] If results suggest Alzheimer's disease, the patient might be put on a cocktail of anti-amyloid compounds, anti-tau drugs, synaptic enhancers, repurposed drugs producing small epigenetic changes, and perhaps even gene therapy directed at *APOE4*, and progression to dementia would be monitored. Imaging will be used to monitor the efficacy of the treatment in removing amyloid and tau from the brain and to tailor the treatment regimen, whereas biomarkers will be used to monitor effects on neuronal and synaptic degeneration. As a result of the developments discussed in this Seminar, such novel diagnostic and management strategies are well on the way.

Contributors

PS designed the Seminar outline and invited the other authors to provide parts of the text according to their expertise. PS and WMYdF combined and edited these texts, and did additional searches for references.

Declaration of interests

PS has received research support from Merck, GE Healthcare, Piramal, Alzheimer Nederland, Dioraphte, Stichting VUmc Fonds and Stichting Alzheimer & Neuropsychiatrie; served as a consultant for AbbVie, Avraham, ARC, Janssen Research Foundation, MD Start, Nutricia, Takeda, Probiodrug, and EIP Pharma; and received speaker fees from Piramal and GE Healthcare. He is co-editor-in-chief of *Alzheimer's Research & Therapy* and associate editor of *Alzheimer's Disease and Associated Disorders*. KB has served as a consultant for Eli Lilly, Novartis, Roche Diagnostics, Sanofi-Aventis, Amgen, and IBL International; has received speaker fees from Fujirebio Europe and Lundbeck; and is cofounder of Brain Biomarker Solutions. BdS has received research support from Janssen and served as a consultant for Janssen, Remynd, and Forum. SS has received research support from NIA–ADNI, DIAN, A4, Alz Assoc–DIAN; been involved in clinical trials sponsored by Lilly, Biogen, Genentech, Bayer, Avid, Roche, Merck, and Functional Neuromodulation; served as a consultant for Avid-Lilly, GE, Baxter, Biogen, Roche, Genentech, Forum, Piramal, and Merck; and been on the editorial boards of the *Journal of Neuropsychiatry and Clinical Neurosciences*, *Journal of Prevention of Alzheimer's Disease*, and *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*. WMYdF has received research support from ZonMW, NWO, EU-FP7, Alzheimer Nederland, CardioVascular Onderzoek Nederland, Stichting Dioraphte, Gieskes-Strijbis fonds, Boehringer Ingelheim, Piramal Neuroimaging, Roche, Janssen Stellar, Stichting VUmc Fonds, and Stichting Alzheimer & Neuropsychiatrie, and speaker fees from Boehringer Ingelheim. MMBB and GBF declare no competing interests.

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