Ushering in the study and treatment of preclinical Alzheimer disease

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Abstract | Researchers have begun to characterize the subtle biological and cognitive processes that precede the clinical onset of Alzheimer disease (AD), and to set the stage for accelerated evaluation of experimental treatments to delay the onset, reduce the risk of, or completely prevent clinical decline. In this Review, we provide an overview of the experimental strategies, and brain imaging and cerebrospinal fluid biomarker measures that are used in early detection and tracking of AD, highlighting at-risk individuals who could be suitable for preclinical monitoring. We discuss how advances in the field have contributed to reconceptualization of AD as a sequence of biological changes that occur during progression from preclinical AD, to mild cognitive impairment and finally dementia, and we review recently proposed research criteria for preclinical AD. Advances in the study of preclinical AD have driven the recognition that efficacy of at least some AD therapies may depend on initiation of treatment before clinical manifestation of disease, leading to a new era of AD prevention research.

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Introduction

Alzheimer disease (AD) is the most common cause of dementia in older people, and takes a devastating toll on patients and families.[1] Owing to the growing number of people living to older ages, a considerable increase is expected in the number of older adults with AD[2–4] unless effective treatments can be found. Concern is increasing that AD treatments in development may need to be started early—that is, before clinical onset when extensive evidence of disease pathology already exists—to exert their most profound benefit.[5] This concern, together with recent efforts to detect and track cognitive, clinical and biomarker changes associated with the preclinical stages of AD, has contributed to the interest in evaluation of preclinical AD treatments.[6–10] We have previously defined[6] such treatments as "interventions that are started in the absence of mild cognitive impairment (MCI) or dementia and intended to postpone the onset, reduce the risk of, or completely prevent the clinical stages of AD."

The pathogenic cascade of AD is thought to begin at least one to two decades prior to cognitive impairment, starting with accumulation of the amyloid-β_{42} ($A\beta_{42}$) peptide (the major constituent of neuritic plaques) into oligomeric and fibrillar assemblies. The cascade eventually leads to neuroinflammatory changes, synaptic dysfunction and loss, accumulation and phosphorylation of microtubule-associated protein tau (the main constituent of neurofibrillary tangles) and, ultimately, to neuronal degeneration.[11] Research has also suggested that some of these processes can be assessed using brain imaging and fluid biomarkers.[12,13] Recent studies, however, have indicated that other changes might precede Aβ accumulation. Such studies found evidence of mitochondrial dysfunction, accumulation tau pathology at young ages,[14–16] and reduction of temporal cortex grey matter and smaller hippocampi in infants at increased genetic susceptibility for AD, raising the possibility that some changes linked to initiation of AD may be developmental,[17] perhaps providing a starting point for the cascade noted above.

The International Working Group for New Research Criteria for the Diagnosis of AD[18] and, more recently, working groups from the National Institute on Aging (NIA) and Alzheimer's Association (AA) have championed efforts to reconceptualize AD as a progressive

Competing interests
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Key points

- The pathogenic cascade of Alzheimer disease (AD) is thought to begin at least one to two decades prior to cognitive impairment
- Disappointing results of several AD drugs in late-stage trials have suggested the need for early therapeutic intervention, calling for development of biomarkers and sensitive cognitive measures of preclinical disease
- The best established measurements for detection and tracking of preclinical and clinical AD include MRI, fluorodeoxyglucose PET, amyloid PET, and cerebrospinal fluid measures of amyloid-$\beta_{42,}$ total tau, and phospho-tau
- Studies of individuals with inherited AD can provide insights into cognitive and biomarker changes that precede clinical manifestation of AD, and are suitable candidates for ongoing monitoring and early-intervention strategies
- We are entering an era of AD prevention research, with a number of preclinical AD treatment trials in the planning stages or under way for several at-risk, cognitively unimpaired populations

sequence of pathophysiological stages (Figure 1), some of which can be assessed using biomarkers, and which roughly correspond to preclinical, MCI and dementia stages. The NIA-AA proposed revised criteria for clinical diagnosis of MCI[19] and dementia due to AD,[20] and research criteria were proposed for the preclinical stages of AD.[21] These provisional, hypothesis-driven research criteria include three staging categories (Table 1) and are intended to provide a common language for researchers, to facilitate comparison of findings from different laboratories, and to help set the stage for evaluation of preclinical AD treatments. Approximately one-third of cognitively normal older adults over 70 years of age have been suggested to meet NIA-AA criteria for preclinical AD (stages 1–3).[22] Of these individuals, approximately 10% progress to a diagnosis of MCI or dementia within 1 year, and of those in stage 3 disease, 43% progress to MCI or dementia in this time frame.[23]

Brain imaging and other biomarker measures have had a considerable influence on the study of AD, and are expected to have an important role in the effort to find effective preclinical AD therapies. In this article, we review well-established cognitive, brain imaging, and fluid biomarkers for preclinical detection and tracking of AD. We also discuss studies in genetic at-risk groups as well as longitudinal studies examining progression to the clinical stages of AD. Finally, we note how these efforts are helping to accelerate evaluation of preclinical AD treatments in cognitively unimpaired individuals who are at increased risk of AD according to genetic or biomarker findings.

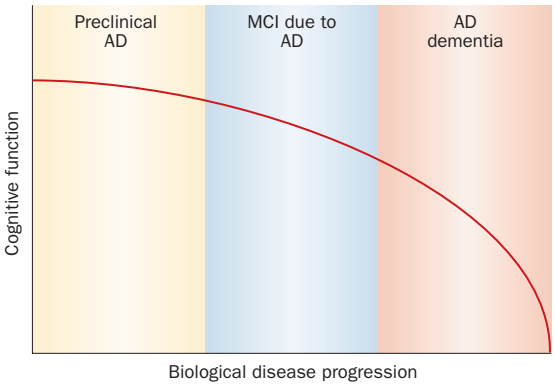

Figure 1 | Stages of Alzheimer disease. AD encompasses a continuum, from asymptomatic individuals with biomarker evidence suggestive of pathological AD-related changes (preclinical AD), to subtle cognitive decline including subjective report of memory decline (MCI), to AD dementia. Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.

Established AD biomarkers

To date, the most well-established measurements for detection and tracking of the preclinical and clinical stages of AD (Box 1, Figure 2) include structural MRI measurements of regional and whole-brain tissue shrinkage, fluorodeoxyglucose (FDG) PET measurements of decline in regional cerebral metabolic rate for glucose (CMRgl), PET measurements of fibrillar Aβ burden, and cerebrospinal fluid (CSF) measures of $A\beta_{42,}$ total tau (t-tau) and phospho-tau (p-tau).[24,25] Other increasingly well-studied AD biomarkers include functional connectivity MRI (fcMRI) and task-related functional MRI. Notably, information provided by these and other biomarker measures depends not only on the modality used, but on the manner in which the data are acquired and analysed.

Structural MRI

Structural MRI has been the most extensively used brain imaging method in the detection and tracking of AD, and shows establishment of brain atrophy at the time of diagnosis of dementia due to AD. These measurements also reveal that patients with MCI and dementia due to AD have accelerated rates of atrophy of the hippocampus, entorhinal cortex, regional grey matter, and whole brain.[26,27] Many of these measurements correlate with clinical severity,[28,29] subsequent clinical decline,[29,30] and neuronal loss.[31] Moreover, these MRI changes are apparent before onset of clinical symptoms, with hippocampal volumes reduced by approximately 10% at least 3 years prior to diagnosis of dementia due to AD, and atrophy beginning at least 5 years prior to the diagnosis.[27,32]

FDG PET

AD is associated with preferential CMRgl reductions in the precuneus, posterior cingulate, and parietotemporal cortex, some of which are apparent prior to onset of dementia, and extend to the frontal cortex and whole brain as disease progresses.[33] CMRgl abnormalities could be related to reductions in activity or density of terminal neuronal fields or perisynaptic glial cells,[34,35] metabolic dysfunction,[36,37] or a combination of these factors. CMRgl reductions are progressive, correlate with clinical severity and are predictive of subsequent clinical decline.[38]

Fibrillar Aβ PET

PET measurements of fibrillar Aβ deposition could help to advance the study of AD by enabling *in vivo* measurement of fibrillar amyloid in the brain.[39] Clinically affected patients with AD show fibrillar Aβ deposition in the precuneus, posterior cingulate, parietal, temporal

and frontal cortices, which mostly occurs in early disease stages, with fibrillar Aβ levels probably stabilizing later in the disease.[40] Cortical fibrillar amyloid seen with PET imaging correlates closely with amyloid pathology at autopsy.[41,42]

Functional connectivity MRI

Resting state fcMRI allows characterization of neural network activity when an individual is not completing a task. The default mode network (DMN) represents a cluster of brain regions—predominantly consisting of midline and lateral frontal regions, and medial and lateral parietal regions extending into the posterior cingulate–retrosplenial cortex—that have elevated activity in states of relative rest.[43,44] Such regions seem to be suppressed during various cognitive activities, including encoding of new memories.[45,46] Reduced resting state connectivity[47] and alterations in task-induced deactivation responses on functional MRI have been identified in normal ageing,[48,49] MCI[46,50] and AD[43,49] compared with younger, healthy controls.

The DMN overlaps anatomically with brain regions that have Aβ deposition,[51–53] regional atrophy and areas of reduced white matter integrity as measured on MRI,[54] and reduced CMRgl as measured using FDG PET.[47] Moreover, the DMN overlaps with brain regions that rely on glucose beyond its usual role, referred to as 'aerobic glycolysis' in adequately oxygenated tissue.[55] The spatial distribution of aerobic glycolysis in young adults (age 20–33 years old) overlaps with PET measurements of fibrillar Aβ deposition,[55] which suggests that aerobic glycolysis could have a role in preclinical AD, although the biological processes remain to be clarified.

Cerebrospinal fluid measures

Measurement of CSF $A\beta_{42,}$ particularly when combined with t-tau or p-tau_{181} measures, is useful for establishment of a diagnosis in people with MCI or very mild dementia, and for prognostication.[56] Clinically affected patients with AD have abnormally low CSF $A\beta_{42}$ levels, and elevated p-tau_{181} and t-tau levels.[57,58] The reduction in CSF $A\beta_{42}$ may seem counterintuitive, but is thought to result from sequestration of $A\beta_{42}$ in amyloid plaques in the brain.[56] CSF changes precede clinical onset by over a decade,[59–61] and are associated with smaller whole-brain volumes in cognitively healthy adults.[60] Although CSF $A\beta_{42}$ levels are well-established in detection and differential diagnosis of AD,[62] this measure is not well-correlated with disease duration or clinical severity.[63] Similarly, elevated t-tau is consistently reported in patients with clinical AD but is not closely associated with severity of dementia.[56,64]

Detecting the earliest brain changes

Several AD-associated biomarkers show changes years before onset of symptoms in individuals at increased genetic risk of AD (for example, carriers of the ε4 allele of the apolipoprotein E [*APOE*] gene[65] and individuals with gene mutations that cause early-onset AD[59]) and those with Down syndrome,[66] as well as cognitively normal individuals who subsequently progressed to clinical AD (Figure 3).[67,68] Considerable research is this area has been done to date, although the need remains for continued cohort studies with large sample sizes, and head to head comparisons of identified biomarkers, in conjunction with development of new biomarkers, to determine the extent to which these measurements, alone or in combination with other factors, predict subsequent rates of clinical decline.

Table 1 | Staging of preclinical Alzheimer disease[21]

Stage	Pathological features	Biomarkers		
		Amyloid-β (PET or CSF)	Neurodegeneration (tau, FDG, MRI)	Cognitive change
1	Asymptomatic amyloidosis	Present	Absent	Absent
2	Asymptomatic amyloidosis and neurodegeneration	Present	Present	Absent
3	Asymptomatic amyloidosis, neurodegeneration and subtle cognitive decline	Present	Present	Present

Abbreviations: CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose.

The sequence of biomarker changes

The hypothetical sequence of biomarker changes are thought to begin about 10–20 years prior to clinical onset with biomarker evidence of amyloid plaque deposition (reduced CSF $A\beta_{42}$ levels and increased fibrillar Aβ PET measurements; Figure 4).[12,13,59,61,69] Other elements of the pathobiological cascade, however, might exist that have yet to be discovered. These changes are probably followed by biomarker evidence of neuronal dysfunction and synaptic loss, such as regional reductions in cerebral glucose metabolism as measured on PET, altered patterns of functional connectivity, alterations in regional brain activity during memory encoding and novel viewing tasks, and reductions in grey matter and cortical thickness as measured on MRI. Biomarker evidence of tau pathology, neurofibrillary tangles, neuronal degeneration, and neuronal loss seem to follow in the sequence of biomarker changes. These changes include elevated CSF t-tau and p-tau levels, and hippocampal atrophy on MRI.

The exact timing of biomarker changes can depend on many factors, including the analytical tools used, the

Box 1 | Biomarkers of Alzheimer disease

Markers of amyloid-β accumulation
- Amyloid-β in cerebrospinal fluid
- PET amyloid imaging using ^{11}C-Pittsburgh compound B or ^{18}F radiotracers to bind to fibrillar amyloid-β

Markers of neurodegeneration
- Tau and phospho-tau in cerebrospinal fluid

Markers of neuronal activity
- Functional MRI measures of task-based neuronal activation, and resting neuronal connectivity

Markers of neuronal loss
- MRI measures of cortical thinning, hippocampal volume, and whole-brain volume

Markers of synaptic dysfunction
- ^{18}F-fluorodeoxyglucose PET

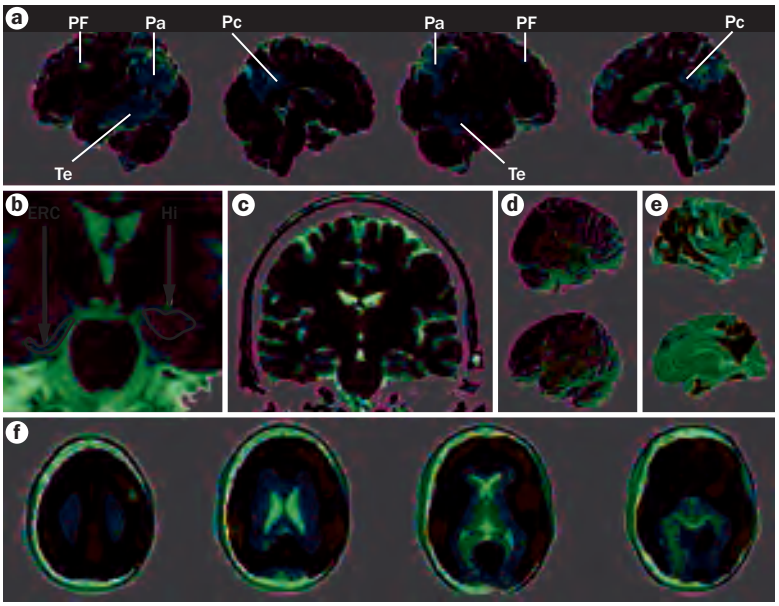

Figure 2 | Selected brain imaging approaches for detection of AD. **a** | Statistical brain maps from FDG PET imaging show characteristic and progressive declines in regional CMRgl (blue) in various cortical regions in AD dementia compared with controls. **b** | Structural MRI studies find brain shrinkage in AD dementia, including accelerated rates of atrophy in hippocampus and ERC; **c** | accelerated rates of whole-brain atrophy using sequential MRI scans (red); **d** | characteristic and progressive loss of grey matter (red), as shown in statistical brain map comparing AD dementia with controls; and **e** | characteristic and progressive cortical thinning (yellow and red), as shown in statistical brain map comparing AD dementia with controls. **f** | Statistical comparison of PiB PET measurements of fibrillar amyloid-β show increased brain amyloid load in AD dementia compared with controls; other radioligands for fibrillar amyloid-β PET imaging are now under investigation. Abbreviations: AD, Alzheimer disease; CMRgl, cerebral metabolic rate for glucose; ERC, entorhinal cortex; FDG, fluorodeoxyglucose; Hi, hippocampus; Pa, parietal; Pc, precuneus; PF, prefrontal; PiB, Pittsburgh compound B; Te, temporal. Part a reproduced with permission from Massachusetts Medical Society © Reiman, E. M. *et al. NEJM* **334**, 752–758 (1996). Part d reproduced with permission from Elsevier Ltd © Baron, J. C. *et al. Neuroimage* **14**, 298–309 (2011). Part e reproduced with permission from Oxford University Press © Du, A. T. *et al. Brain* **130**, 1159–1166 (2007).

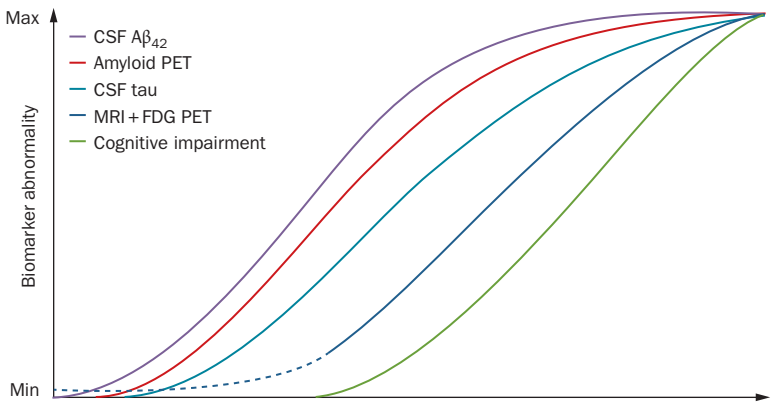

Figure 3 | Dynamic biomarkers of the AD pathological cascade over time. Abnormality in levels of CSF $A\beta_{42}$ is hypothesized to be the first biomarker to show change in patients with AD, being the most abnormal at any given time during disease progression. Such changes are closely followed by those of amyloid PET, then CSF tau. MRI and FDG PET measures (depicted together), are the last biomarkers to become abnormal. Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose. Permission obtained from Elsevier Ltd © Jack, C. R. *et al. Lancet Neurol.* **12**, 207–216 (2013).

underlying pathobiology, and the age at which participants are studied.[17] We and others have characterized early biomarker and cognitive changes associated with preclinical AD by studying individuals with different risk of AD on the basis of genetic background, biomarker evidence of AD, or other factors. As part of these studies, the apparent longitudinal trajectory of cognitive and biomarker changes in these at-risk groups was mapped as the individuals progressed to clinical stages of AD or estimated on the basis of years from anticipated age at clinical onset. A number of other important risk factors for AD—including but not limited to age, family history, cardiovascular disease and diabetes—exist, but are beyond the scope of this Review, given its focus on at-risk groups for preclinical treatment trials.

Identification and study of at-risk individuals

Apolipoprotein E

APOE is the major susceptibility gene for late-onset AD. Compared with individuals with the ε3ε3 genotype, the ε2 allele is associated with decreased risk of late-onset AD and older age at dementia onset. By contrast, possession of one copy of the ε4 allele, which is found in about 25% of the population and about 60% of patients with AD dementia, is associated with higher risk of late-onset AD and younger age at dementia onset, and individuals with two copies of this allele have an especially high risk of AD.[176,177] The number of other confirmed AD susceptibility genes continues to grow, but these genes are associated with comparatively modest effects on AD risk.[70–74]

As each *APOE* genotype is associated with a different level of risk of AD, detection and tracking of cognitive and biomarker changes in individuals with these different genotypes can provide researchers with initial information about which preclinical AD biomarker (baseline measurement or change in measure) or combination of biomarkers is related to subsequent clinical onset, without having to wait several years to obtain such information in unselected populations.

Studies of cognitively unimpaired individuals who carry at least one copy of the *APOE* ε4 allele show considerable differences in AD biomarkers compared with noncarriers, including MRI-measured accelerated cortical thinning,[75] lower grey matter density,[76] and accelerated brain atrophy.[77] Some changes in brain structure are apparent during infancy in ε4 carriers,[17] although the relationship between such changes and development of AD dementia remains unknown. FDG PET studies of cognitively unimpaired *APOE* ε4 carriers reported reduced CMRgl in the same posterior cingulate, precuneus, parietal, temporal and frontal regions as in AD dementia.[78–83] Some of these changes are apparent almost 50 years prior to the expected onset of symptoms,[84] are progressive,[85] and are correlated with ε4 allele dose.[86] Recent evidence suggests that preclinical hypometabolism in the posterior cingulate precedes hippocampal volume loss associated with *APOE* ε4 allele dose,[87] and some findings in cognitively normal older adults (average age 75 years) with greater amyloid deposition and in patients with MCI and Down syndrome,

suggest that hypermetabolism may precede metabolic decline in certain brain regions, irrespectively of *APOE* genotype.[88–90]

A study of adult (49–79-year-old) *APOE* ε4 carriers reported a pattern of reduced deactivation compared with noncarriers in brain regions consistent with the DMN during a semantic categorization task, although no allele dose effect was observed.[91] Similarly, relative to age-matched noncarriers, differences in resting state connectivity were detected in both older adult (50–65-year-old)[92] and young (20–35-year-old)[93] *APOE* ε4 carriers.

Amyloid PET studies of cognitively unimpaired adult *APOE* ε4 carriers found substantial fibrillar Aβ deposition in brain regions affected by AD pathology, including frontal, temporal, posterior cingulate–precuneus, and parietal regions compared with noncarriers.[69,94–99] Fibrillar Aβ deposition is correlated with ε4 allele dose,[94] is apparent approximately 10–15 years prior to estimated onset of AD dementia, and might be associated with greater cognitive impairment in ε4 carriers.[95,100,101] Differences in CSF measures of Aβ and tau have been reported, with *APOE* ε4 carriers having reduced $A\beta_{42,}$[83,99,102–104] elevated $A\beta_{40}$:$A\beta_{42}$ ratios,[105] and higher t-tau and p-tau_{181}[104,106,107] compared with noncarriers.

In addition to tracking biomarker changes in cognitively unimpaired *APOE* ε4 carriers, we and others have also examined the cognitive differences between carriers and noncarriers. Differences have not been consistently identified in early life[108] but, starting in late-middle age, decline in long-term recall memory performance is more prominent in *APOE* ε4 carriers[109–112] and is associated with ε4 allele dose,[113,114] despite affected individuals having no apparent clinical symptoms.

Autosomal dominant AD

More than 200 mutations of the presenilin 1 (*PSEN1*), *PSEN2,* and amyloid precursor protein (*APP*) genes have been shown to cause autosomal dominant AD (ADAD).[115] As carriers of mutations in these genes will almost certainly develop AD, they provide a unique group in which to characterize the trajectory of preclinical AD changes in relationship to their family's estimated age at clinical onset.[116] ADAD differs from the more common, late-onset form of AD in several respects—for example, by a generally younger age at clinical onset and overproduction rather than reduced clearance of $A\beta_{1\text{-}42}$,[117,118] although the question of overproduction versus clearance is still under study.[119] The two forms of AD do, however, have common features, particularly in regard to clinical phenotype.[120,121] Investigation of ADAD, therefore, provides another approach to preclinical study of AD.

Autosomal dominant versus sporadic AD

Findings from biomarker studies of cognitively unimpaired ADAD mutation carriers are generally consistent with those from cognitively unimpaired *APOE* ε4 carriers, although the exact timing and patterns of pathological changes, such as fibrillar Aβ deposition, can differ. Comparison between ADAD and groups who are genetically at-risk of sporadic AD—in this case, *APOE* ε4 carriers—is important for determination of how findings from trials in ADAD carriers relate to sporadic AD, given the planned preclinical treatment trials, discussed below.

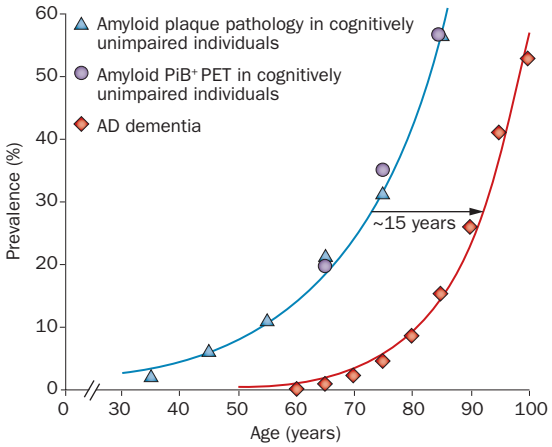

Figure 4 | Temporal link between amyloid deposition and onset of AD dementia. Graph shows the age-related prevalence of: amyloid plaque deposition detected at postmortem in cognitively unimpaired individuals (blue triangles); fibrillar Aβ deposition as measured by high PiB PET signal in cognitively unimpaired individuals from the Australian Imaging, Biomarkers and Lifestyle cohort (purple dots); and AD dementia in the general population (red diamonds). Taken together, the data suggest that amyloid-β deposition precedes diagnosis of AD dementia by approximately 15 years. Abbreviations: AD, Alzheimer disease; PiB, Pittsburgh compound B. Permission obtained from Elsevier Ltd © Rowe, C. C. *et al. Neurobiol. Aging* **12**, 1275–1283 (2010).

Cognitively unimpaired, young adult ADAD mutation carriers can have reduction in grey matter volume (as measured by voxel-based techniques)[122,123] in the same brain regions that are preferentially affected by AD, even before CSF or PET evidence of $A\beta_{42}$ deposition.[61] Reductions in hippocampal volume are apparent approximately 15 years before expected symptom onset[59,124] and continue to decline over time.[125] Research by the Dominantly Inherited Alzheimer Network (DIAN) will be crucial in teasing apart the timing and trajectory of MRI changes, although to date it has only reported findings in regard to hippocampal volume.[59] Studies in ADAD mutation carriers have also reported CMRgl reductions in the posterior cingulate, precuneus, parietal, and temporal cortex at least 10 years prior to expected symptom onset.[59,126–128]

Findings in amyloid PET studies to determine the pattern and timing of preclinical fibrillar Aβ deposition are generally similar in ADAD mutation carriers and *APOE* ε4 carriers, with deposition apparent approximately 10 years prior to the expected age at clinical onset.[59,61] Some studies, however, have reported preferential deposition in the striatum in carriers of certain ADAD mutations.[129,130] A notable difference, highlighted by data from DIAN, is that in clinically affected ADAD mutation carriers, fibrillar Aβ deposition may continue to rise after clinical onset of AD. Conversely, this finding has not been replicated in a large kindred with ADAD

caused by an Glu280Ala mutation in the *PSEN1* gene,[61] perhaps owing to the difference in fibrillar Aβ patterns observed with different ADAD mutations.

In cognitively unimpaired ADAD mutation carriers, the direction of CSF Aβ differences between carriers and noncarriers seems to depend on the age of participants, although the assay and grouping of samples probably also have an important role. For example, in a recent study by our group, young adult *PSEN1* Glu280Ala mutation carriers had significantly higher CSF $A\beta_{42}$ levels and significantly lower CSF t-tau:$A\beta_{42}$ and p-tau:$A\beta_{42}$ ratios compared with kindred noncarriers,[123] in contrast to most findings reported in older preclinical individuals and in the clinical stages of late-onset AD and autosomal dominant AD.[63,131] Findings from the DIAN study, which involved a larger number of individuals with different mutations and at different ages, have suggested that CSF $A\beta_{42}$ levels begin to decline 25 years before their estimated age at clinical onset. The researchers did not, however, detect differences in CSF, plasma, or brain imaging measures between the 13 carriers and 13 noncarriers who were studied more than 20 years before their estimated age at clinical onset, perhaps owing to the small sample size.[59] Similar to findings in *APOE* ε4 carriers, cognitive decline—including changes in memory, visuospatial and executive function—was reported in ADAD mutation carriers despite ongoing normal clinical status.[132–136]

Other at-risk individuals

Individuals with biomarker evidence of AD pathology but no clinical symptoms represent another group in which to track the trajectory of preclinical AD. Amyloid PET studies suggested that approximately one-third of cognitively unimpaired older adults have marked fibrillar Aβ deposition, which is consistent with intermediate or high likelihood of pathological AD,[69,96,137–139] with most of the rise in deposition occurring during the preclinical stage of AD.[140] Notably, most studies report that cognitive function is normal or only mildly affected in older individuals with PET evidence of Aβ deposition,[96,141–143] and that Aβ deposition could be more closely associated with longitudinal cognitive decline in older adults, particularly in regard to episodic memory.[144–147]

Predicting clinical progression

Retrospective and longitudinal studies have been helpful for tracking of changes that occur during progression from preclinical AD to AD dementia. For example, retrospective analyses of individuals who eventually progressed to AD dementia have generally reported decline in memory—particularly episodic, semantic and working memory—to be a defining feature of preclinical AD,[148,149] with the rate of cognitive decline and affected domains greatly accelerating 5–6 years prior to diagnosis of dementia.[150] Importantly, cognitive decline in older age may be specific to those who progress to MCI or AD dementia and might not be an inevitable part of ageing *per se*,[150] supporting the utility of cognition as a predictive marker of clinical progression. We and others have been particularly interested in determining the optimal combination of cognitive assessments for tracking cognitive decline prior to clinical progression of AD.[151–153]

Non-biomarker-enriched populations

AD biomarkers could be useful for prediction of clinical AD progression in populations who are not selected on the basis of AD biomarker profiles. For example, people with MCI who subsequently progress to probable AD dementia show significantly greater declines in CMRgl (measured on FDG PET) in AD-related brain regions than do individuals with MCI who remain stable during the same time interval.[154,155] MRI-measured reductions in hippocampal and entorhinal cortex volume parallel very early memory decline and are associated with subsequent progression to MCI or AD dementia.[30,156,157]

Functional connectivity MRI could also be useful in predicting conversion from MCI to AD dementia.[158,159] Increased activity in 'task-positive' networks (as opposed to brain networks that deactivate during tasks, such as the DMN) in patients with MCI or AD dementia have been interpreted as attempts at compensation, although this hypothesis remains to be demonstrated conclusively. Alternative explanations include dedifferentiation of cortical function and aberrant excitation—a finding that has also been seen in animal models of AD.[160] In addition, lifelong patterns of increased brain activity might themselves predispose an individual to Aβ deposition.[161] The latter hypothesis is intriguing, particularly given that Aβ deposition, as measured by amyloid PET, is associated with longitudinal cognitive decline in some cognitively normal adults and with progression to AD dementia.[68,96] As clinical progression occurs, however, Aβ accumulation slows[96,157] and probably plateaus by the time of diagnosis of AD dementia.[162] Similar to functional MRI, elevated ratios of CSF tau:$A\beta_{42}$ and p-tau:$A\beta_{42}$ are predictive of subsequent clinical progression in preclinical AD or MCI to AD dementia.[63,163] Together, positivity for PET and CSF measures of Aβ seem to confer a threefold to fivefold higher likelihood of progression from preclinical AD or MCI to AD dementia.[164–169]

Biomarker-enriched populations

Several studies have examined clinical outcomes in individuals with biomarker evidence of AD pathology. Multiple positive AD biomarkers might have additive predictive value. For instance, in people with MCI, presence or absence of abnormal CSF t-tau and p-tau concentrations and hippocampal atrophy predicted time to AD dementia.[170] Similarly, lower CSF $A\beta_{42}$ concentration, hypometabolism as measured on FDG PET, and hippocampal atrophy were associated with a faster time to AD dementia in people with MCI,[171] supporting the hypothetical dynamic biomarker model discussed previously.[12,13] Moreover, in the latter study, people with MCI who were positive for all of the three AD biomarkers consistently progressed to AD dementia during a

3-year period, whereas those with no positive biomarkers were unlikely to progress. These findings in MCI are supported by findings in cognitively normal individuals in which abnormal amyloid levels on PET imaging and CSF biomarkers, when examined together, are associated with faster time to cognitive impairment, whereas no differences were identified in the predictive value of individual biomarkers.[172]

Preclinical AD populations

In preclinical AD populations, high Aβ levels on PET imaging correlates with decreased performance on episodic memory and language assessments[146] and increased hippocampal atrophy rate[173] over 18 months. Additional follow-up is needed to assess the predictive value of abnormally high amyloid levels on PET imaging in cognitively healthy individuals for progression to MCI or AD dementia.

An important related issue is determination of the cut-off value that defines 'amyloid positivity'. A level could be selected that is consistent with an intermediate to high likelihood of AD pathology, or one that signifies the presence of any Aβ above that observed in low-risk individuals (that is, young *APOE* ε4 noncarriers).[174] The optimal approach probably depends on the question being explored. An intermediate value between these two cut-offs could be a suitable approach for tracking change over time—something that is particularly important as the field begins preclinical AD treatment trials in biomarker-enriched populations—but researchers will need to ensure that this cut-off is associated with a high likelihood of progression to AD.

Needs, challenges and opportunities

Biomarkers of preclinical-treatment response

As growing evidence from natural history studies indicates that brain imaging and other biomarker measurements begin to change years before clinical symptoms emerge, it is plausible that these measures could have a role in evaluation of preclinical AD treatments. However, as we enter this era in AD prevention research and treatment trials, it is important to examine how biomarkers behave in response to treatment, irrespective of what is suggested by longitudinal data in observational studies. Prominent examples of unexpected biomarker responses to experimental treatment include MRI-measured brain shrinkage in response to the anti-Aβ vaccination AN-1792 (despite possible cognitive benefit on a subset of memory measures)[175] and in response to the passive Aβ immunotherapy bapineuzumab. Crucially, therefore, trials should incorporate all established AD biomarker measures to determine how they behave in response to treatment.

Refining and expanding biomarker knowledge

Observational longitudinal cohort studies stand to make important contributions to the field of preclinical AD biomarkers. For example, they are needed to improve our understanding of the trajectory of biomarker changes, enabling determination of the accuracy of prevailing hypotheses regarding the sequence of biomarker changes, and identification of which biomarkers, alone or in combination, predict subsequent clinical course. Additionally, new biomarkers are needed to detect other aspects of disease pathology and process and, if developed, could help in evaluation of potential treatments throughout the disease spectrum. Examples of needed biomarkers include those for assessment of oligomeric Aβ species, tau burden, and neuroinflammation, and more-specific measures of synaptic density.

Preclinical treatment trials

A number of preclinical treatment trials are in the planning stages or are already under way in several at-risk populations of cognitively unimpaired individuals—namely, individuals with biomarker evidence of Aβ as measured by amyloid PET, individuals who carry ADAD mutations, those who are homozygous for the *APOE* ε4 allele, and individuals with variable-length polymorphisms in *TOMM40*. Although observational studies conducted to date have been valuable in preparing researchers for preclinical treatment trials, an important point to consider is that prevalence estimates of factors such as amyloid burden in older adults, which are derived from population-based studies, might not be observed in clinical trials owing to recruitment biases.

Over the next several years, the field will certainly see more trials as a result of initiatives including, but not limited to, the National Alzheimer's Project Act, the French Alzheimer Plan, and Alzheimer Europe. These prevention trials, which will embed currently available AD biomarkers and sensitive composite cognitive test scores, are designed to show that the treatment effects on biomarker measures are reasonably likely to predict clinical benefit, with the intent that one or more of these biomarkers may receive regulatory agency qualification as a surrogate end point for use in preclinical AD treatment trials.[5–7] In some cases, all of the data and biological samples will be made available to the scientific community following trial completion, with the aim of accelerating development of new biomarkers and sensitive data analysis methodologies. Moreover, these trials should provide a better test of the amyloid hypothesis than do trials in AD dementia or MCI.

Conclusions

The pathogenic cascade of AD is thought to begin at least 10–20 years prior to cognitive impairment, and AD biomarkers have played a crucial role in detection and tracking of preclinical and clinical stages of AD. As we begin this era of AD prevention research, biomarkers and sensitive cognitive measures are poised to continue to make important contributions. For example, AD biomarkers, alone or in combination, could provide scientific advances and could help to accelerate regulatory approval for treatments in development. Although there is no guarantee that treatments in the development pipeline will be effective, interest is growing in evaluation of these treatments in the preclinical stage of AD. Given the potential benefits to society if an effective

AD or preclinical AD treatment is found, researchers and other involved parties should have a sense of urgency. Moreover, this enthusiasm needs to be shared with the general public, informing them how to volunteer in prevention-focused research, given the likelihood that for every prevention trial, thousands of individuals will need to be screened in order to find enough eligible participants. With these factors in mind, we will be better prepared to deal with the complexities and uncertainties that lie ahead.

Review criteria

We searched PubMed using the terms "Alzheimer disease", "preclinical Alzheimer disease", "dominantly inherited Alzheimer disease", "autosomal dominant Alzheimer disease", "early-onset Alzheimer disease", "cognition", "cerebral spinal fluid", "MRI", and "PET" for articles published in English from January 1980 until February 2013. We selected full-text research articles and reviews. We also reviewed the reference lists of the identified papers for further leads.

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Author contributions
J. B. Langbaum, K. Chen, N. Ayutyanont, F. Lopera, Y. T. Quiroz, R. J. Caselli and E. M. Reiman researched data for the article. A. S. Fleisher, P. N. Tariot and E. M. Reiman made substantial contributions to discussion of the content. J. B. Langbaum, P. N. Tariot and E. M. Reiman wrote the article. J. B. Langbaum, A. S. Fleisher, P. N. Tariot and E. M. Reiman contributed to review and/or editing of the manuscript before submission.

CORRECTION

Ushering in the study and treatment of preclinical Alzheimer disease

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In the version of this article initially published, in the second sentence of the section 'Identification and study of at-risk individuals', incorrect references were cited and the appropriate references were omitted. The references that should have been cited are:

Corder, E. H. *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921–923 (1993).

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The error has been corrected for the HTML and PDF versions of the article.