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# Preclinical Alzheimer disease: identification of cases at risk among cognitively intact older individuals

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## Abstract

Since the first description of the case of Auguste Deter, presented in Tübingen in 1906 by Alois Alzheimer, there has been an exponential increase in our knowledge of the neuropathological, cellular, and molecular foundation of Alzheimer's disease (AD). The concept of AD pathogenesis has evolved from a static, binary view discriminating cognitive normality from dementia, towards a dynamic view that considers AD pathology as a long-lasting morbid process that takes place progressively over years, or even decades, before the first symptoms become apparent, and thus operating in a continuum between the two aforementioned extreme states. Several biomarkers have been proposed to predict AD-related cognitive decline, initially in cases with mild cognitive impairment, and more recently in cognitively intact individuals. These early markers define at-risk individuals thought to be in the preclinical phase of AD. However, the clinical relevance of this preclinical phase remains controversial. The fate of such individuals, who are cognitively intact, but positive for some early AD biomarkers, is currently uncertain at best. In this report, we advocate the point of view that although most of these preclinical cases will evolve to clinically overt AD, some appear to have efficient compensatory mechanisms and virtually never develop dementia. We critically review the currently available early AD markers, discuss their clinical relevance, and propose a novel classification of preclinical AD, designating these non-progressing cases as 'stable asymptomatic cerebral amyloidosis'.

**Keywords:** Alzheimer disease, asymptomatic, cerebral amyloidosis, cognition, compensatory phenomena, dementia

## Introduction

In 1906, Alois Alzheimer documented the case of Auguste Deter, a patient with a combination of cognitive deficits, psychiatric symptoms, and macroscopic and microscopic brain lesions [1,2]. This histopathological and clinical constellation was first designated by Emil Kraepelin as Alzheimer's disease (AD), and later on as dementia of the Alzheimer-type (AD-type dementia). Since this first definition, an impressively broad spectrum of mechanisms have emerged, including genetic vulnerability, and the molecular, cellular, and neurochemical abnormalities closely related to AD pathogenesis [3-5]. Some examples illustrate the diversity of the field and the

difficulty in formulating and following up a unique causal hypothesis for such a heterogeneous disorder. Initially, abnormal protein filaments were described structurally in amyloid plaques (APs) and neurofibrillary tangles (NFTs) [6,7], and more than 200 large clinicopathological studies in hospital-based and community-based series have shown the differential effects of fibrillar amyloid deposits and NFT formation on cognitive performances across the age spectrum [8-11]. Following the pioneering observations of Tomlinson and coworkers, which indicated the presence of substantial AD lesion densities in cognitively intact older people [12], the systematic work of Braak and collaborators showed the stepwise progression of amyloid deposits and NFTs in brain aging and AD [13,14]. Amyloidogenic fragments (monomers, dimers, oligomers) were soon purified from AD-affected brains, and tau protein was identified as the main constituent of NFT [15-17]. Yankner and coworkers then identified the

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neurotoxic properties of the amyloid beta (A $\beta$ ) protein [18]. In the 1970s, the cholinergic hypothesis of AD emerged and growing interest was raised with the identification of the first therapeutic targets for drug development [19-21]. In the early 1980s, medial temporal lobe subdivisions became the focus of interest, following the detailed description of atrophy patterns in association with progressive memory loss in mild and prodromal forms of AD [22-25]. In the early 1990s, the first genes conferring a risk for early-onset (amyloid beta (A4) precursor protein (APP) and presenilin (PSEN)1 and 2) and late-onset (apolipoprotein (APO) $\epsilon$ 4) AD were identified [26-29]. Recently, these discoveries have been followed by identification of polymorphisms in other genes, probably involved in A $\beta$  processing and clearance. Large genome-wide studies have identified associations between late-onset AD and polymorphisms in the genes *clusterin*, *CRI* (complement receptor 1), *SORCS1* (sortilin-related VPS10 domain containing receptor 1) and *PICALM* (phosphatidylinositol binding clathrin assembly protein) [30-32], observations that were subsequently confirmed by other groups in diverse ethnic cohorts [33-40]. Stemming from these milestones in the understanding of AD pathology, the past decade saw the development of animal models and clinical trials with immunization-based therapeutic strategies [41-49]. Despite these efforts, numerous crucial questions remain unanswered. Why are only some brain regions and neuronal types preferentially affected? Why, despite the presence of A $\beta$  deposits, do some individuals not present clinically overt dementia? Is there any natural compensatory mechanism(s) that might counterbalance the toxic effect of A $\beta$ ? Is AD an age- or aging-related pathology?

The major recent conceptual evolution has been the conversion from a 'static and defensive' view of AD pathogenesis to one that is 'dynamic and compensatory'. According to the first model, AD lesions chronically attack the human brain, leading to synaptic and neuron loss before cognitive breakdown. Whether and when this occurs depends mainly on the severity of the external aggression and on the structural reserve [50-52]. The second model suggests that the clinical expression of the disease may vary widely over time, depending on individual vulnerability to the initial phases of the degenerative process, the severity of the AD pathological process at the molecular and cellular levels, and the efficiency and evolution over time of compensatory brain mechanisms.

According to this dynamic model, future curative treatments should be administered long before the emergence of clinically overt symptoms, either to counterbalance the biological compromise that precedes the cognitive breakdown or to promote functional compensation [53]. The limited therapeutic efficacy of the first vaccination trials in moderate AD may have reflected the irreversible brain

damage that had already taken place in these cases. This is also supported by some data from animal models, which showed that the efficacy of  $\beta$ -amyloid<sub>1-42</sub> (A $\beta$ 42) immunization was largely reduced in mice with significant amyloid deposition [54]. In line with these findings, clinical trials using acetylcholinesterase inhibitors in patients with mild cognitive impairment (MCI) all failed to show any clear benefit [55,56]. In fact, more recent evidence has shown that all of the major pathophysiological processes associated with AD have already occurred by the time MCI is diagnosed, introducing the notion that patients with clinically early AD may display substantial biological deficits [57-62]. Consequently, in order to set up true secondary prevention in AD, it is crucial to identify cognitively intact individuals at risk for AD, working on the assumption that some objectively measurable AD markers exist that precede clinical symptoms by several years and define a stable 'pre-AD' stage.

#### **Preclinical Alzheimer disease**

AD was perceived for the first time more as a dynamic process than a stationary state in the late 1980s, and the idea that the pathological process begins long before clinical symptoms become apparent has gained increasing interest [63]. Even though normal brain aging and AD-type dementia are both associated with loss of neurons and accumulation of APs and NFTs, the extent and distribution of the lesions is not the same in both cases [51,52,63]. In non-demented older individuals, NFTs are mainly found in the hippocampus, whereas in the course of dementia a progressive spread of NFTs into the temporal neocortex is seen. It has been shown that the total NFT counts in the hippocampus, entorhinal cortex and prefrontal area 9 is strongly predictive of cognitive status [9,64]. Moreover, the neuron loss and its spatial distribution in normal aging is also qualitatively and quantitatively different from that in AD, where a massive loss of pyramidal neurons takes place mainly in the cornu ammonis (CA)1 field of the hippocampus [9,65-67]. The differences between normal aging and AD were recently clarified and formalized by Dubois and colleagues, who proposed a novel classification of AD, which distinguishes three stages of the disease: preclinical AD, prodromal AD (equivalent of MCI), and dementia [68]. In this review, we focus on preclinical AD cases by addressing the clinical relevance of biomarkers that could predict their cognitive evolution.

#### **Biomarkers of preclinical Alzheimer disease**

##### **CSF markers**

Even though a definite diagnosis of AD can be formulated only neuropathologically, CSF markers play an important supportive role in the clinical diagnosis of probable AD [68]. The levels of A $\beta$ 42 in the cerebrospinal fluid (CSF) are inversely correlated with AP burden,

and the CSF tau levels reflect the progression of tau-related pathology within the cerebral cortex [69]. Low levels of A $\beta$ 42, together with increased levels of phosphorylated (p)-tau and total (t)-tau, identify AD with good accuracy, and can be useful in the differential diagnosis of dementia [70-73]. However, these markers are not specific for dementia. Low levels of A $\beta$ 42 appear early in the course of AD, and have been shown to predict conversion from MCI to AD [74]. Other authors have shown that abnormalities in CSF levels of A $\beta$ 42 and tau can be detected even earlier, in people who are still cognitively normal (CN), preceding MCI by several years [75-83].

Low CSF A $\beta$ 42 levels in CN older adults correlate with whole-brain volume [76], atrophy rate [66], and cortical amyloid load [75,77]. CN carriers of the APO $\epsilon$ 4 allele, which confers a risk for late-onset AD, and is associated with slightly lower cognitive function in adulthood [84], also have lower CSF A $\beta$ 42 levels [83,85]. Contrastingly, an increase in CSF tau and p-tau in cognitively intact individuals correlates with cortical amyloid load [75] and cerebral hypometabolism in the posterior cingulate, precuneus, and parahippocampal regions [79]. Interestingly, a high CSF tau:A $\beta$ 42 ratio in CN adults is related to cortical lesions and pathological changes in the white-matter microstructure, which probably precede structural alterations in the cortex [83,86].

The exact timing of the appearance of these CSF markers is still a matter of debate. Even though it seems that a decrease in CSF A $\beta$ 42 concentrations precedes elevation of tau levels [75], both parameters can be considered as early hallmarks of AD. Reduction in CSF A $\beta$ 42 levels was shown to precede cognitive decline in non-demented subjects for as long as 8 years, and a combination of CSF A $\beta$ 42 and p-tau might further increase its sensitivity and specificity in prediction of dementia [82,87]. Indeed, high CSF tau:A $\beta$ 42 and p-tau:A $\beta$ 42 ratios were shown to be a powerful predictive factor for the conversion of normal cognition to dementia, preceding the conversion by years [77,80-82]. These observations are further supported by independent studies of familial AD, in which decreased levels of A $\beta$ 42 and increased levels of tau and p-tau in the CSF were found in asymptomatic carriers of *PSEN1* and *APP* pathogenic mutations, more than 10 years before the clinical onset of the disease [88-90].

**Positron emission tomography with Pittsburgh compound B**  
Positron emission tomography (PET) imaging of the amyloid-binding agent Pittsburgh compound B (PET-PiB) allows for semiquantitative *in vivo* analysis of the brain A $\beta$  load and its spatial distribution. Like CSF A $\beta$ 42 levels, PET-PiB is a valuable marker in the differential diagnosis of dementia [91]. It is closely correlated with amyloid plaque burden at autopsy [92], and is inversely related to CSF A $\beta$ 42 levels [75,77,93]. However, it is not

specific to dementia; up to 20% of CN people have a considerable PiB load in the brain, falling into a 'PiB-positive' category [91,94-97]. However, though still within the normal cognitive range, these PiB-positive controls have slightly lower cognitive performance compared with PiB-negative people [98]. They have a very subtle episodic memory impairment [96,99], smaller hippocampus volume [99], and accelerated rate of cortical atrophy [100]. The conversion from a PiB-negative to a PiB-positive state reflects a very early step in AD development [95]. These PiB-positive individuals clearly represent a subpopulation at risk for dementia [93,101,102]. For instance, there is a higher prevalence of PiB positivity among CN subjects with known genetic AD risk factors, and CN carriers of APO $\epsilon$ 4 have an increased incidence rate of conversion from PiB-negative to PiB-positive status, many years before the clinical onset of AD [95]. Similarly, asymptomatic carriers of pathogenic *PSEN1* or *APP* mutations, responsible for early-onset AD, have increased PiB retention in the cortex and striatum [103-105]. Together, these data support the idea that increased PiB load may serve as a predictive factor of AD-type dementia in healthy older individuals [100,106,107]. Whether measurement of PET-PiB levels is a better predictive factor than CSF A $\beta$ 42 levels remains unclear [75,108-111].

Individual risk estimation solely on the basis of PiB status remains difficult because many CN individuals have a brain PiB load practically indistinguishable from patients with overt dementia [101]. These 'PiB-high' subjects have a more rapid increase in PiB brain load over time than do PiB-positive individuals with relatively lower PiB signal, and are thought to be at higher risk for AD-type dementia than 'PiB-low' individuals [107,112]. However, not all 'PiB-high' individuals evolve to dementia; in longitudinal studies, some remained CN for at least 4 years [107]. Moreover, even in cases of monozygotic twins with increased PiB load, cognitive discordance (one twin demented and the other one CN) has been described [113], suggesting that environmental and epigenetic factors modulate the effects of A $\beta$  on cognition.

#### **Fluro-D-glucose positron emission tomography**

PET imaging with 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose as a tracer (FDG-PET) measures cerebral glucose metabolism, which reflects the level of synaptic activity. Perturbations in glucose metabolism have been repeatedly reported in AD [114-117]. In order to investigate whether the synaptic dysfunction seen with FDG-PET precedes the clinical symptoms in AD, numerous studies have been performed in CN individuals at risk of AD, all of which documented hypometabolism in the regions typically affected in AD [118-131]. A substantial reduction in glucose metabolism in the posterior cingulate, precuneus, parietal, and prefrontal cortex was shown in middle-aged CN carriers of

the APO $\epsilon$ 4 allele [120,124], and this observation was recently reproduced in Latino populations [123]. A gene-dosage effect was documented in this context, with a more pronounced reduction in glucose metabolism in CN APO $\epsilon$ 4 homozygotes than in heterozygotes [122]. Interestingly, this brain hypometabolism in APO $\epsilon$ 4 carriers is a gradually progressing process that leads to a further decline after a 2-year period, as shown in follow-up studies [121,125]. It is thus likely that the brain hypometabolism in posterior cortical areas represents a valuable preclinical AD biomarker, preceding overt dementia by several years [121,125]. Confirming this viewpoint, Reiman and colleagues showed that low glucose metabolism in the posterior cingulate, parietal, temporal, and prefrontal cortex of CN APO $\epsilon$ 4 carriers can be detected as early as the third decade of life [118] preceding clinical disease onset as much as 40 to 50 years. This unexpected observation (in view of the extremely long preclinical period) is consistent with the substantial NFT formation in brains of young (less than 40 years old) CN APO $\epsilon$ 4 carriers [132].

However, the exact pathophysiological significance of the reduced cerebral glucose metabolism in CN individuals remains unclear. Although it may represent an indirect marker of cortical vulnerability to the degenerative process, it does not determine the occurrence of dementia; for instance, reduction in glucose metabolism in temporal cortex was found in cognitively discordant monozygotic twins [126,127]. The link with APO $\epsilon$  genotype is also difficult to interpret. Even though predominantly studied in the context of APO $\epsilon$ 4 carriers, this hypometabolism seems to be an integral element of AD pathogenesis, without a strict association with a single genetic risk factor. In fact, hypometabolism in parietotemporal, posterior cingulate, and medial temporal cortex was reported in CN individuals with a family history of AD independent of their APO $\epsilon$  genotype [129,133], and also in asymptomatic individuals carrying pathogenic mutations in the *APP* gene [130,131].

#### **Structural MRI**

Even though structural brain changes are usually preceded by alterations in PET and CSF markers, abnormalities in structural MRI become detectable well before the first clinical signs of the disease, and thus might serve as a marker of preclinical AD. The exact hierarchical patterns of cortical atrophy vary greatly over time, but there is broad consensus that the atrophy of the medial temporal lobe (particularly the hippocampus) and cortical thinning in certain AD-vulnerable regions are the first MRI signs of emerging AD [134-142].

In asymptomatic individuals at risk for early-onset familial AD (those carrying a pathogenic APP mutation), volumetric MRI analysis identified decreased hippocampus

volume 2 to 3 years before dementia onset [143]. Other authors have reported that decreased hippocampus volume in community-based older individuals precedes dementia by as much as 6 years [134-138], which fits well with the neuropathological findings [144]. Further subregional analyses have shown that in CN subjects, the volume of restricted parts of the hippocampus (the CA1 and subiculum) is more closely associated with conversion to MCI than is the total hippocampus volume [136,139]. The volume loss in these regions precedes cognitive decline and conversion to MCI by a few years, and was able to discriminate cognitively stable from declining individuals with up to 93% accuracy, especially when combined with neurocognitive testing [136,139]. Using high-dimensional diffeomorphic transformations, Csernasy and colleagues evaluated the surface of the hippocampus, and found that inward deformation of the left hippocampal surface within the CA1 field is an early predictor of the conversion to dementia in CN older subjects [135].

Volume reduction in other medial temporal lobe subdivisions besides the hippocampus, and acceleration of ventricular volume expansion [145], have also been described in CN individuals at risk for AD [136,143,146-148]. Decreased entorhinal cortex volume was shown to precede significant cognitive decline by 4 years and, together with hippocampus volume, to predict cognitive decline in CN subjects with an accuracy reaching 80% (up to 90% when combined with decreased hippocampus volume) [136]. Similar results were reported for the reduced volume of the anteromedial temporal cortex [146,147], the prediction accuracy of which was further improved when neuroimaging data were combined with neuropsychological testing [136,146].

Recently, early structural abnormalities in the neocortex have aroused growing interest [143,146,149,150]. Decreased gray-matter volume in the parietal lobe, notably in the angular gyrus, has been described in CN individuals in advance of MCI development [146]. Moreover, prefrontal cortex atrophy in CN individuals was found to precede dementia onset over a 6-year period, and appeared to be even a more sensitive predictive factor than hippocampal volume [149]. Dickerson *et al.* reported that the analysis of multiple regions preferentially affected in mild AD (referred to as the 'cortical AD signature') could be useful in predicting AD conversion in CN individuals [140-142]. Subtle cortical thinning in a set of seven to nine preselected neocortical regions was shown to be associated with increased risk for AD development, and it preceded loss of hippocampus volume [140,142,151]. Notably, atrophy in these regions was detectable more than 10 years before clinical onset of the disease, and correlated with the CSF A $\beta$ 42/tau ratio and amyloid load measured by PiB binding [142,150,152].

### **Functional MRI**

Functional connectivity between different brain regions is disrupted early in the course of AD [153-156], possibly reflecting the deleterious effects of A $\beta$  on synapses and glucose metabolism. At the whole-brain level, such early dysfunctions trigger multiple compensatory functional rearrangements of the neural networks to preserve cognitive performance [157-164]. Using functional (f)MRI, it was shown that in CN APO $\epsilon$ 4 carriers, the magnitude of brain activation in the parietal and prefrontal regions during memory tasks is higher than in controls, and the extent of brain activation correlates with subsequent memory decline in these subjects [157-160]. This extensive extrahippocampal activation may represent an attempt to counterbalance subtle deficits in hippocampal function, and is thought to represent an early functional sign of emerging AD in CN individuals [161]. The same kind of overactivation in the frontal and temporal lobes during memory encoding has been seen in older people at high risk for late-onset AD, independently of their APO $\epsilon$  genotype, as much as 10 years earlier than the estimated AD onset [162]. Interestingly, such a functional reorganization is not limited to the memory-related tasks, but has been also reported in the parietal lobes during a mental rotation test [163], and in the medial temporal lobe, posterior cingulate cortex, bilateral thalamus, and caudate nucleus, during divided-attention tasks [164].

### **The dynamic cascade in preclinical AD**

Accumulating data on preclinical AD markers obliges us to revisit the traditional view of the degenerative process and its temporal evolution in brain aging. Jack and coworkers recently proposed such a hypothetical model, which defines ordered, sequential appearance of early markers during preclinical phase of AD [165]. According to this model, the markers related to amyloid formation, namely decreased CSF A $\beta$ 42 levels and increased PiB-PET A $\beta$  brain load, become detectable first. Later on, the markers of synaptic dysfunction and neurodegeneration, such as abnormalities in FDG-PET and fMRI patterns, appear followed by an increase in CSF tau protein levels. At more advanced stages, structural brain changes, such as cortical atrophy and decreased hippocampus volume, can be detected by MRI. All of these markers become positive before the first signs of cognitive decline. These authors suggested that the changes in these preclinical markers gradually increase over time, probably following a sigmoid trajectory [165], an idea that has been partly confirmed by recent experimental studies [166].

This model cannot be seen as definitive, and several issues remain to be addressed. For instance, abnormal brain glucose metabolism is seen as early as the third decade of life, and is the earliest detected change in

individuals at risk for late-onset AD [118]. Whether A $\beta$  could also be detected in these subjects if sufficiently sensitive techniques were available remains unknown. Certainly, the exact order of marker appearance depends on the accuracy of the diagnostic techniques, and thus is likely to change as new developments arise. Nevertheless, the concept surrounding this model is innovative, because it describes AD as a dynamic and biologically unstable process, rather than a stable nosological condition, and takes into account sequential marker changes during preclinical stages. In line with this model, new diagnostic research guidelines have recently been formulated, discriminating three stages of preclinical AD [167]. Stage 1 refers to asymptomatic brain amyloidosis, and is based on positive amyloid markers (PiB-PET and/or low CSF A $\beta$ 42 levels). Stage 2 encompasses brain amyloidosis accompanied by markers of neurodegeneration (abnormalities in FDG-PET/fMRI or high CSF t-tau and p-tau levels or atrophy on structural MRI). Stage 3, which refers to brain amyloidosis with signs of neurodegeneration as specified for stage 2, is accompanied by a subtle cognitive decline that does not yet fulfill the criteria for MCI. In population-based studies, 43% of CN older subjects had none of the early AD markers, while 16% met the criteria for stage 1, 12% for stage 2, and 3% for stage 3. Notably, 23% of subjects were not compatible with any of the stages and were defined as 'suspected non-AD pathophysiology' [97]. Interestingly, the transition through these preclinical stages (stage 1 to stage 2 to stage 3) was associated with an increased risk of conversion to MCI or dementia [168], suggesting that this classification adequately reflects the natural course of the disease.

### **Presymptomatic or asymptomatic Alzheimer disease: what exactly do we detect?**

Different terms have been proposed to label these symptom-free individuals, who are positive for one or more early AD biomarkers. Most commonly, this phase of the disease has been called 'preclinical', 'presymptomatic', or 'asymptomatic' AD. In their recent recommendations, the National Institute on Ageing and the Alzheimer's Association workgroup have advocated the term 'preclinical' as the one that 'was felt to best encompass this conceptual phase of the disease' [167]. Even if these terms are still applied interchangeably, their use could reflect different viewpoints about the natural course of AD and the clinical significance of the early markers. Terms such as 'presymptomatic' or 'preclinical', in contrast to 'asymptomatic', imply that early markers not only indicate increased risk of AD-type dementia but that they precede and predict, at the individual level, clinical disease onset. It is now widely accepted that a morbid process that conveys transition from asymptomatic cerebral amyloidosis to AD-type

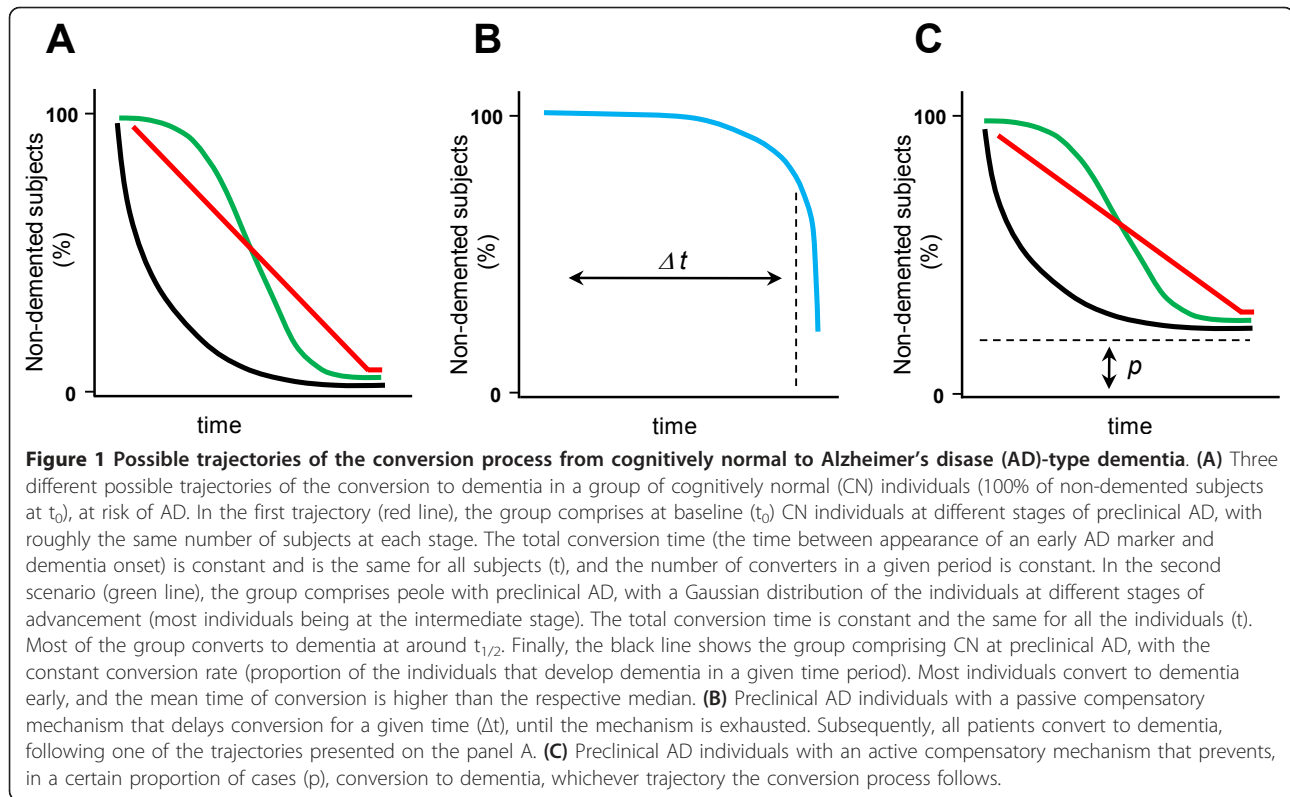
dementia takes on average about 10 years [167]. There is indirect evidence in support of this point of view. At the population level, there is a lag of 10 years between the first detectable A $\beta$  deposits (at autopsy) and dementia onset. In fact, the prevalence of CN people with A $\beta$  deposits in their sixth decade of life is roughly the same as the prevalence of AD-type dementia one decade later [167]. However, such estimation is uncertain in the absence of definitive data on the dynamics of conversion to dementia of the CN population at risk of AD. Theoretically, various trajectories are possible. The conversion of CN to AD could be a linear process, with a steady cognitive decline and a constant number of converters over a given period [169]. In this case, the group at risk of AD would include CN individuals with a more or less advanced morbid process, which lasts a constant period of time. All of the CN individuals would convert to AD, and the more advanced the process in a given subject, the smaller the lag time to AD conversion. If the group comprised roughly the same number of individuals at each preclinical stage (1, 2 or 3), the process would be linear, but if the distribution of the different stages were Gaussian (most people being at the intermediate advanced stage), the conversion process would be better represented by a sigmoid curve (Figure 1A). Alternatively, conversion from preclinical AD to MCI/dementia could be determined by a purely stochastic process, with a constant percentage of individuals converting in a given period. This may correspond to a 'two-hits model', where the first hit (represented by the presence of a first preclinical AD marker) generates vulnerability, which increases at a constant rate the risk for a second hit and conversion to AD-type dementia. In this scenario, most people would convert to MCI/dementia early, and the median of the conversion time would be much shorter than with the linear or sigmoid models (Figure 1A). However, the recent data of Knopman and coworkers, showing a gradual increase in risk of conversion to MCI/dementia across the preclinical AD stages, do not support this possibility [168].

Independently of the dynamics involved, the conversion of the CN population at risk for AD to dementia may be influenced by compensatory mechanisms. Numerous data from both fMRI (for example, extensive extrahippocampal activation during memory activation tasks [157]) and biochemical studies (for example, increased choline acetyltransferase activity and the level of neurotrophic factors [170,171]) seem to support the idea that functional compensation is a major event in the course of AD. These compensatory mechanisms could be 'passive' or 'active'. A 'passive' compensatory process, referring to the notion of cognitive reserve, may only delay the conversion to dementia (Figure 1B). In agreement with this possibility, the cognitive decline preceding AD-type dementia fits a bi-logistic model with a plateau phase, and thus favorsthe

idea of such compensation [172]. On the other hand, an 'active' and potentially inexhaustible compensatory mechanism could stop the progression of the disease at the preclinical phase, and prevent conversion to dementia. The efficiency of such active compensatory mechanisms is of key importance, as they may prevent the development of clinically overt dementia in some carriers of early AD marker(s) (Figure 1C).

The existence of effective compensatory mechanisms and the fate of cognitively intact individuals carrying an early AD marker is a matter of debate, and some authors believe that all individuals with an ongoing AD morbid process will inevitably progress to AD-type dementia if they were to live long enough [106,167]. In the absence of long-term longitudinal studies, the issue remains unresolved; however, certain lines of evidence challenge this idea. For instance, in an 8-year longitudinal study, Fagan and coworkers reported that only some CN older individuals with increased CSF tau/A $\beta$ 42 ratio converted to dementia [77]. Similarly, only a small number of CN individuals with increased PiB load converted to MCI or AD within 3 years [107]. Of course, it cannot be formally excluded that at least some of these CN individuals would eventually develop dementia if they were followed up for a sufficiently long period. However, the curve representing the conversion of CN individuals at risk for AD to dementia is strikingly biphasic. Some individuals convert to dementia rapidly within the first 3 years, whereas others remain cognitively stable over at least 8 years [77]. It is thus likely that some of the preclinical AD cases do not progress to dementia because they have efficient compensatory mechanisms. In line with this presumption, it has been shown that some CN subjects can maintain or even decrease their A $\beta$  burden over time. Most interestingly, even those patients with high A $\beta$  load, indistinguishable from the ones with AD-type dementia, can remain cognitively stable [95,107].

Several medical conditions share with AD the long clinical evolution and presymptomatic phase. It has been suggested that preclinical AD markers play a similar role in the early detection of AD as do increased blood glucose level or preclinical tumor markers in the early diagnosis of type II diabetes or cancer, respectively, for instance [167]. However, it needs to be kept in mind that in contrast to asymptomatic hyperglycemia or carcinoma *in situ*, which, if not treated, will inevitably progress to clinically overt disease, there is to date insufficient evidence to assert that preclinical AD imposes such determinism. Thus, any reliable predictions at the individual level on the basis of available preclinical AD markers are still very difficult. This, in turn, might raise important ethical concerns about disclosure of the information based on biomarker status and pre-AD state [173], especially in view of the current lack of curative treatments.



#### Alzheimer disease-related neurodegeneration: *in vivo* indices of compensatory mechanisms

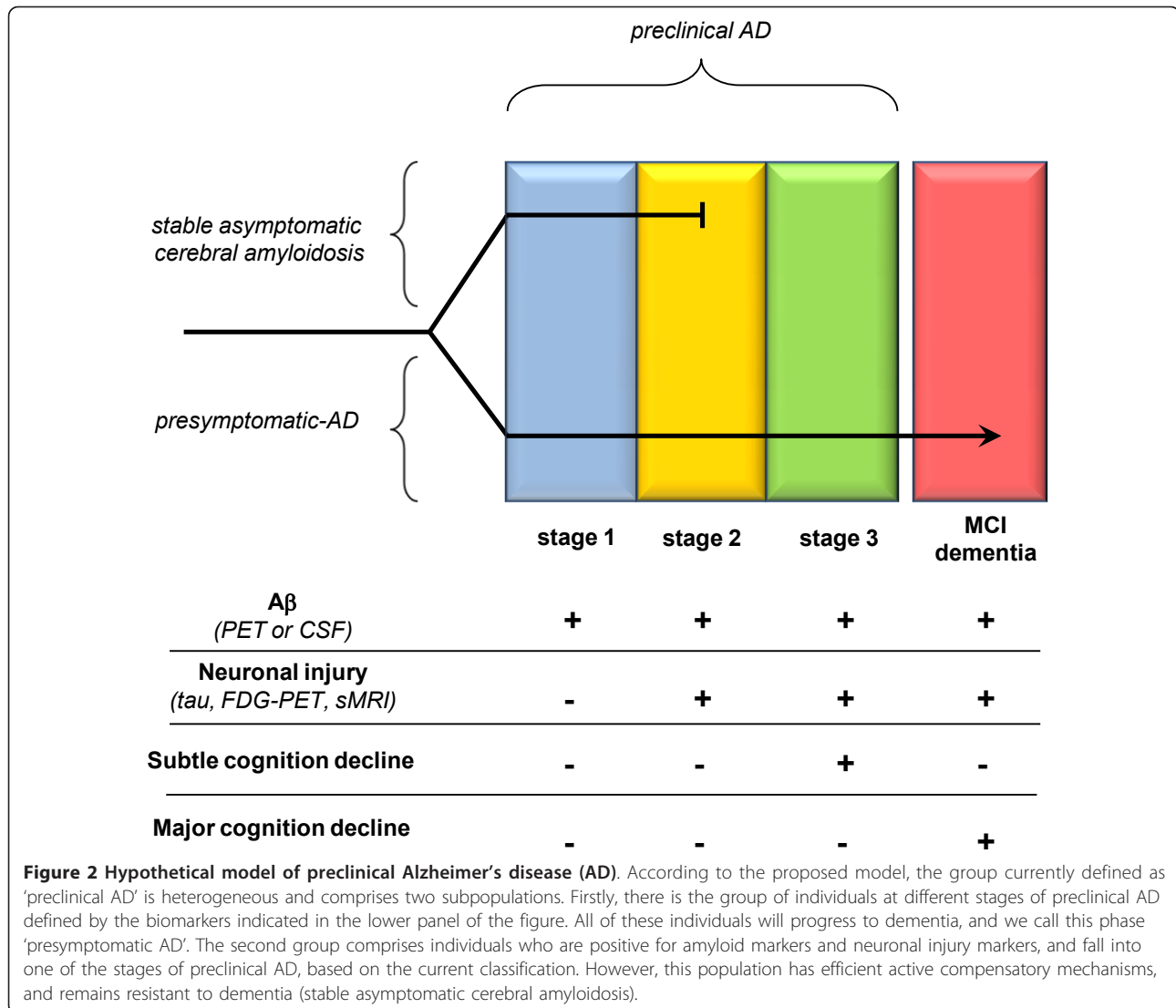
It is commonly believed that curative interventions in AD, especially those targeting  $A\beta$ , might be most effective when applied at the preclinical phase, because this precedes irreversible brain lesions [53,174]. However, the preclinical phase of AD could also be seen as a unique therapeutic window because at this stage the brain compensatory mechanisms are still efficient. Regardless of its exact molecular substrates, AD-type dementia may be viewed as a failure of these compensatory mechanisms in the course of progressive cerebral amyloidosis. One attractive scenario would be to treat AD not only by decreasing  $A\beta$  or tau brain load, but also by preserving these natural compensatory mechanisms. However such approaches remain purely speculative, as our understanding of the compensatory mechanisms is still very limited. Nevertheless, some evidence sustains the presence of active compensatory mechanisms in AD. For instance, there is a differential sensitivity of neurons to  $A\beta$  oligomers toxic effect. Although  $A\beta$  deposits are often localized in the striatum in both familial and sporadic AD cases, they are not associated with neuron loss in this brain region or with extrapyramidal symptoms [103,175]. Moreover, the *APOE*  $\epsilon 3$  genotype, which in contrast to the *APOE*  $\epsilon 4$  allele, decreases the risk of AD, has been shown to protect neurons from hyperexcitability

[176,177], further supporting the notion that active neuroprotection plays an important role in cell vulnerability in AD.

#### Conclusions

Preclinical AD markers may represent a double-edged sword. On the one hand, they make it possible to define a group at risk for AD-type dementia (in terms of disease prevalence), but on the other hand, this group may comprise an increased proportion of 'resistant' individuals, who do not develop dementia despite substantial brain cerebral amyloidosis. Within the preclinical AD spectrum, the first group includes presymptomatic individuals who are positive for at least one amyloid marker (for example, PiB-PET, low  $A\beta 42$  CSF levels) and correspond to stages 1, 2 or 3 as defined by the recommendations from the National Institute on Aging and Alzheimer's Association workgroups [167]. Virtually all of these subjects will convert to MCI or AD-type dementia within 8 to 10 years. A second group includes individuals with stable asymptomatic cerebral amyloidosis, who will remain cognitively stable indefinitely, even though they have positive amyloid marker(s) and would fall into the stage 1 (or even stage 2) of preclinical AD (Figure 2). Defining distinct biomarkers for these stable cases would enable more reliable predictions of clinical evolution at the individual level. Moreover, comparative analysis of





these two groups could allow better insight into the nature of compensatory mechanisms and into the reasons for their failure, which marks the beginning of AD-type dementia.

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#### Authors' contributions

MJL and PG performed the literature search, formulated the present hypothesis, and compiled the first draft of the manuscript. MJL created the figures. PRH and CB participated in the conceptualization and writing of the paper. All authors have read and approved the final manuscript.

#### Competing interests

The authors report no biomedical financial interests or potential conflicts of interest.

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#### References

1. Alzheimer A: Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtlich Medizin* 1907, **64**:146-148.
2. Maurer K, Volk S, Gerbaldo H: Auguste D and Alzheimer's disease. *Lancet* 1997, **349**:1546-1549.
3. Jellinger KA: Alzheimer 100-highlights in the history of Alzheimer research. *J Neural Transm* 2006, **113**:1603-1623.
4. Hodges JR: Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain* 2006, **129**:2811-2822.
5. Goedert M, Spillantini MG: A century of Alzheimer's disease. *Science* 2006, **314**:777-781.
6. Kidd M: Paired helical filaments in electron microscopy of Alzheimer's disease. *Nature* 1963, **197**:192-193.
7. Terry RD, Gonatas NK, Weiss M: Ultrastructural studies in Alzheimer's presenile dementia. *Am J Pathol* 1964, **44**:269-297.
8. Roth M, Tomlinson BE, Blessed G: Correlation between scores for dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects. *Nature* 1966, **209**:109-110.

9. Giannakopoulos P, Gold G, Kövari E, von Gunten A, Imhof A, Bouras C, Hof PR: **Assessing the cognitive impact of Alzheimer disease pathology and vascular burden in the aging brain: the Geneva experience.** *Acta Neuropathol* 2007, **113**:1-12.
10. Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ, Davies P, Del Tredici K, Duyckaerts C, Frosch MP, Haroutunian V, Hof PR, Hulette CM, Hyman BT, Iwatsubo T, Jellinger KA, Jicha GA, Kövari E, Kukull WA, Leverenz JB, Love S, Mackenzie IR, Mann DM, Masliah E, McKee AC, Montine TJ, Morris JC, Schneider JA, et al: **Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature.** *J Neuropathol Exp Neurol* 2012, **213**:362-381.
11. Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, Abner EL, Smith CD, Van Eldik LJ, Kryscio RJ, Scheff SW: **Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies.** *Acta Neuropathol* 2011, **121**:571-587.
12. Tomlinson BE, Blessed G, Roth M: **Observations on the brains of non-demented old people.** *J Neurol Sci* 1968, **7**:331-356.
13. Braak H, Braak E: **Neuropathological staging of Alzheimer-related changes.** *Acta Neuropathol* 1991, **82**:239-259.
14. Braak H, Braak E: **Staging of Alzheimer's disease-related neurofibrillary changes.** *Neurobiol Aging* 1995, **16**:271-278.
15. Glenner GG, Wong CW: **Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein.** *Biochem Biophys Res Commun* 1984, **120**:885-890.
16. Roher A, Wolfe D, Palutke M, Kukkuraja D: **Purification, ultrastructure, and chemical analysis of Alzheimer disease amyloid plaque core protein.** *Proc Natl Acad Sci USA* 1986, **83**:2662-2666.
17. Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM: **Microtubule-associated protein tau. A component of Alzheimer paired helical filaments.** *J Biol Chem* 1986, **261**:6084-6089.
18. Yankner BA, Dawes LR, Fisher S, Villa-Komaroff L, Oster-Granite ML, Neve RL: **Neurotoxicity of a fragment of the amyloid precursor associated with Alzheimer's disease.** *Science* 1989, **245**:417-420.
19. Drachman DA, Leavitt J: **Human memory and the cholinergic system. A relationship to aging?** *Arch Neurol* 1974, **30**:113-121.
20. Bowen DM, Smith CB, White P, Flack RH, Carrasco LH, Gedye JL, Davison AN: **Chemical pathology of this organic dementias. II. Quantitative estimation of cellular changes in post-mortem brains.** *Brain* 1977, **100**:427-453.
21. Bowen DM, Smith CB, White P, Goodhardt MJ, Spillane JA, Flack RH, Davison AN: **Chemical pathology of organic dementias. I. Validity of biochemical measurements on human post-mortem brain specimens.** *Brain* 1977, **100**:397-426.
22. Hyman BT, Van Hoesen GW, Damasio AR, Barnes CL: **Alzheimer's disease: cell-specific pathology isolates the hippocampal formation.** *Science* 1984, **225**:1168-1170.
23. Butters N, Albert MS, Sax DS, Miliotis P, Nagode J, Sterste A: **The effect of verbal mediators on the pictorial memory of brain-damaged patients.** *Neuropsychologia* 1983, **21**:307-323.
24. Kopelman MD: **Rates of forgetting in Alzheimer-type dementia and Korsakoff's syndrome.** *Neuropsychologia* 1985, **23**:623-638.
25. Moss MB, Albert MS, Butters N, Payne M: **Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome.** *Arch Neurol* 1986, **43**:239-246.
26. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J: **Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease.** *Nature* 1991, **349**:704-706.
27. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, Tsuda T, Mar L, Foncin JF, Bruni AC, Montesi MP, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Polinsky RJ, Wasco W, Da Silva HA, Haines JL, Pericak-Vance MA, Tanzi RE, Roses AD, et al: **Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease.** *Nature* 1995, **375**:754-760.
28. Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Mar L, Sorbi S, Nacmias B, Piacentini S, Amaducci L, Chumakov I, Cohen D, Lannfelt L, Fraser PE, Rommens JM, St George-Hyslop PH: **Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene.** *Nature* 1995, **376**:775-778.
29. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA: **Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families.** *Science* 1993, **261**:921-923.
30. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskva V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsis P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, et al: **Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease.** *Nat Genet* 2009, **41**:1088-1093.
31. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, European Alzheimer's Disease Initiative Investigators, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, et al: **Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease.** *Nat Genet* 2009, **41**:1094-1099.
32. Laumet G, Chouraki V, Grenier-Boley B, Legry V, Heath S, Zelenika D, Fievet N, Hannequin D, Delepine M, Pasquier F, Hanon O, Brice A, Epelbaum J, Berr C, Dartigues JF, Tzourio C, Campion D, Lathrop M, Bertram L, Amouyel P, Lambert JC: **Systematic analysis of candidate genes for Alzheimer's disease in a French, genome-wide association study.** *J Alzheimers Dis* 2010, **20**:1181-1188.
33. Corneveaux JJ, Myers AJ, Allen AN, Pruzin JJ, Ramirez M, Engel A, Nalls MA, Chen K, Lee W, Chewning K, Villa SE, Meechoovet HB, Gerber JD, Frost D, Benson HL, O'Reilly S, Chibnik LB, Shulman JM, Singleton AB, Craig DW, Van Keuren-Jensen KR, Dunckley T, Bennett DA, De Jager PL, Heward C, Hardy J, Reiman EM, Huentelman MJ: **Association of CR1, CLU and PICALM with Alzheimer's disease in a cohort of clinically characterized and neuropathologically verified individuals.** *Hum Mol Genet* 2010, **19**:3295-3301.
34. Carrasquillo MM, Belbin O, Hunter TA, Ma L, Biscoglio GD, Zou F, Crook JE, Pankratz VS, Dickson DW, Graff-Radford NR, Petersen RC, Morgan K, Younkin SG: **Replication of CLU, CR1, and PICALM associations with Alzheimer disease.** *Arch Neurol* 2010, **67**:961-964.
35. Lee JH, Cheng R, Barral S, Reitz C, Medrano M, Lantigua R, Jiménez-Velázquez IZ, Rogaeva E, St George-Hyslop PH, Mayeux R: **Identification of novel loci for Alzheimer disease and replication of CLU, PICALM, and BIN1 in Caribbean Hispanic individuals.** *Arch Neurol* 2011, **68**:320-328.
36. Wijmsman EM, Pankratz ND, Choi Y, Rothstein JH, Faber KM, Cheng R, Lee JH, Bird TD, Bennett DA, Diaz-Arrastia R, Goate AM, Farlow M, Ghetti B, Sweet RA, Foroud TM, Mayeux R: **Genome-wide association of familial late-onset Alzheimer's disease replicates BIN1 and CLU and nominates CUGBP2 in interaction with APOE.** *PLoS Genet* 2011, **7**:e1001308.
37. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carrasquillo MM, Lambert JC, Harold D, Schrijvers EM, Ramirez-Lorca R, Debette S, Longstreth WT Jr, Janssens AC, Pankratz VS, Dartigues JF, Hollingworth P, Aspelund T, Hernandez I, Beiser A, Kuller LH, Koudstaal PJ, Dickson DW, Tzourio C, Abraham R, Antunez C, Du Y, Rotter JJ, et al: **Genome-wide analysis of genetic loci associated with Alzheimer disease.** *JAMA* 2010, **303**:1832-1840.
38. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buross J, Gallins PJ, Buxbaum JD, Jarvik GP, Crane PK, Larson EB, Bird TD, Boeve BF, Graff-Radford NR, De Jager PL, Evans D, Schneider JA, Carrasquillo MM, Ertekin-Taner N, Younkin SG, Cruchaga C, Kauwe JS, Nowotny P, Kramer P, Hardy J, Huentelman MJ, Myers AJ, Barmada MM, Demirci FY, Baldwin CT, et al: **Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease.** *Nat Genet* 2011, **43**:436-441.
39. Reitz C, Tokuyama S, Clark LN, Conrad C, Vonsattel JP, Hazrati LN, Palotás A, Lantigua R, Medrano M, Z Jiménez-Velázquez I, Vardarajan B, Simkin I, Haines JL, Pericak-Vance MA, Farrer LA, Lee JH, Rogaeva E, George-Hyslop PS, Mayeux R: **SORCS1 alters amyloid precursor protein processing and variants may increase Alzheimer's disease risk.** *Ann Neurol* 2011, **69**:47-64.
40. Wang HF, Yu JT, Zhang W, Wang W, Liu QY, Ma XY, Ding HM, Tan L: **SORCS1 and APOE polymorphisms interact to confer risk for late-onset**

- Alzheimer's disease in a Northern Han Chinese population. *Brain Res* 2012, **1448**:111-116.
41. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandeventer C, Walker S, Wogulis M, Yednock T, Games D, Seubert P: **Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse.** *Nature* 1999, **400**:173-177.
  42. Frenkel D, Katz O, Solomon B: **Immunization against Alzheimer's beta-amyloid plaques via EFRH phage administration.** *Proc Natl Acad Sci USA* 2000, **97**:11455-11459.
  43. Janus C, Pearson J, McLaurin J, Mathews PM, Jiang Y, Schmidt SD, Chishti MA, Horne P, Heslin D, French J, Mount HT, Nixon RA, Mercken M, Bergeron C, Fraser PE, St George-Hyslop P, Westaway D: **A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease.** *Nature* 2000, **408**:979-982.
  44. Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, Arendash GW: **A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease.** *Nature* 2000, **408**:982-985.
  45. Hock C, Konietzko U, Papassotiropoulos A, Wollmer A, Streffer J, von Rotz RC, Davey G, Moritz E, Nitsch RM: **Generation of antibodies specific for beta-amyloid by vaccination of patients with Alzheimer disease.** *Nat Med* 2002, **8**:1270-1275.
  46. Bayer AJ, Bullock R, Jones RW, Wilkinson D, Paterson KR, Jenkins L, Millais SB, Donoghue S: **Evaluation of the safety and immunogenicity of synthetic Abeta42 (AN1792) in patients with AD.** *Neurology* 2005, **64**:94-101.
  47. Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo JM: **Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial.** *Neurology* 2005, **64**:1553-1562.
  48. Hock C, Konietzko U, Streffer JR, Tracy J, Signorell A, Müller-Tillmanns B, Lemke U, Henke K, Moritz E, Garcia E, Wollmer MA, Umbricht D, de Quervain DJ, Hofmann M, Maddalena A, Papassotiropoulos A, Nitsch RM: **Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease.** *Neuron* 2003, **38**:547-554.
  49. Fox NC, Black RS, Gilman S, Rossor MN, Griffith SG, Jenkins L, Koller M: **Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease.** *Neurology* 2005, **64**:1563-1572.
  50. Yankner BA, Mesulam MM: **beta-Amyloid and the pathogenesis of Alzheimer's disease.** *N Engl J Med* 1991, **325**:1849-1857.
  51. Arendt T, Bigl V: **Alzheimer's disease as a presumptive threshold phenomenon.** *Neurobiol Aging* 1987, **8**:552-554.
  52. Mann DM: **The pathogenesis and progression of the pathological changes of Alzheimer's disease.** *Ann Med* 1989, **21**:133-136.
  53. Golde TE, Schneider LS, Koo EH: **Anti- $\alpha\beta$  therapeutics in Alzheimer's disease: the need for a paradigm shift.** *Neuron* 2011, **69**:203-213.
  54. Das P, Murphy MP, Younkin LH, Younkin SG, Golde TE: **Reduced effectiveness of Abeta1-42 immunization in APP transgenic mice with significant amyloid deposition.** *Neurobiol Aging* 2001, **22**:721-727.
  55. Farlow MR: **Treatment of mild cognitive impairment (MCI).** *Curr Alzheimer Res* 2009, **6**:362-367.
  56. Popp J, Arlt S: **Pharmacological treatment of dementia and mild cognitive impairment due to Alzheimer's disease.** *Curr Opin Psychiatry* 2011, **24**:556-561.
  57. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L: **Mild cognitive impairment represents early-stage Alzheimer disease.** *Arch Neurol* 2001, **58**:397-405.
  58. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Smith GE, Jack CR Jr: **Mild cognitive impairment: ten years later.** *Arch Neurol* 2009, **66**:1447-1455.
  59. Petersen RC: **Mild cognitive impairment: current research and clinical implications.** *Semin Neurol* 2007, **27**:22-31.
  60. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P, Winblad B: **Mild cognitive impairment.** *Lancet* 2006, **367**:1262-1270.
  61. Petersen RC, Morris JC: **Mild cognitive impairment as a clinical entity and treatment target.** *Arch Neurol* 2005, **62**:1160-1163.
  62. Dubois B: **'Prodromal Alzheimer's disease': a more useful concept than mild cognitive impairment?** *Curr Opin Neurol* 2000, **13**:367-369.
  63. Brayne C, Calloway P: **Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum?** *Lancet* 1988, **1**:1265-1267.
  64. Imhof A, Kövari E, von Gunten A, Gold G, Rivara CB, Herrmann FR, Hof PR, Bouras C, Giannakopoulos P: **Morphological substrates of cognitive decline in nonagenarians and centenarians: a new paradigm?** *J Neurol Sci* 2007, **257**:72-79.
  65. West MJ, Coleman PD, Flood DG, Troncoso JC: **Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease.** *Lancet* 1994, **344**:769-772.
  66. West MJ: **Regionally specific loss of neurons in the aging human hippocampus.** *Neurobiol Aging* 1993, **14**:287-293.
  67. Price JL, Davis PB, Morris JC, White DL: **The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease.** *Neurobiol Aging* 1991, **12**:295-312.
  68. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P: **Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria.** *Lancet Neurol* 2007, **6**:734-746.
  69. Seppälä TT, Nerg O, Koivisto AM, Rummukainen J, Puli L, Zetterberg H, Pyykkö OT, Helisalmi S, Alafuzoff I, Hiltunen M, Jääskeläinen JE, Rinne J, Soinen H, Leinonen V, Herukka SK: **CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings.** *Neurology* 2012, **78**:1568-1575.
  70. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, Herukka SK, van der Flier WM, Blankenstein MA, Ewers M, Rich K, Kaiser E, Verbeek M, Tsolaki M, Mulugeta E, Rosén E, Aarsland D, Visser PJ, Schröder J, Marcusson J, de Leon M, Hampel H, Scheltens P, Pirttilä T, Wallin A, Jönköping ME, Minthon L, Winblad B, Blennow K: **CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment.** *JAMA* 2009, **302**:385-393.
  71. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L: **Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study.** *Lancet Neurol* 2006, **5**:228-234.
  72. Schoonenboom NS, Reesink FE, Verwey NA, Kester MI, Teunissen CE, van de Ven PM, Pijnenburg YA, Blankenstein MA, Rozemuller AJ, Scheltens P, van der Flier WM: **Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort.** *Neurology* 2012, **78**:47-54.
  73. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E: **Alzheimer's disease.** *Lancet* 2011, **377**:1019-1031.
  74. Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O: **Cerebrospinal fluid levels of b-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia.** *Arch Gen Psychiatry* 2012, **69**:98-106.
  75. Fagan AM, Mintun MA, Shah AR, Aldea P, Roe CM, Mach RH, Marcus D, Morris JC, Holtzman DM: **Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease.** *EMBO Mol Med* 2009, **1**:371-380.
  76. Fagan AM, Head D, Shah AR, Marcus D, Mintun M, Morris JC, Holtzman DM: **Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly.** *Ann Neurol* 2009, **65**:176-183.
  77. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM: **Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults.** *Arch Neurol* 2007, **64**:343-349.
  78. Schott JM, Bartlett JW, Fox NC, Barnes J: **Increased brain atrophy rates in cognitively normal older adults with low cerebrospinal fluid A $\beta$ 1-42.** *Ann Neurol* 2010, **68**:825-834.
  79. Petrie EC, Cross DJ, Galasko D, Schellenberg GD, Raskind MA, Peskind ER, Minoshima S: **Preclinical evidence of Alzheimer changes: convergent cerebrospinal fluid biomarker and fluorodeoxyglucose positron emission tomography findings.** *Arch Neurol* 2009, **66**:632-637.
  80. Li G, Sokal I, Quinn JF, Leverenz JB, Brodey M, Schellenberg GD, Kaye JA, Raskind MA, Zhang J, Peskind ER, Montine TJ: **CSF tau/Abeta42 ratio for increased risk of mild cognitive impairment: a follow-up study.** *Neurology* 2007, **69**:631-639.

81. Skoog I, Davidsson P, Aevansson O, Vanderstichele H, Vanmechelen E, Blennow K: **Cerebrospinal fluid beta-amyloid 42 is reduced before the onset of sporadic dementia: a population-based study in 85-year-olds.** *Dement Geriatr Cogn Disord* 2003, **15**:169-176.
82. Gustafson DR, Skoog I, Rosengren L, Zetterberg H, Blennow K: **Cerebrospinal fluid beta-amyloid 1-42 concentration may predict cognitive decline in older women.** *J Neurol Neurosurg Psychiatry* 2007, **78**:461-464.
83. Bendlin BB, Carlsson CM, Johnson SC, Zetterberg H, Blennow K, Willette AA, Okonkwo OC, Sodhi A, Ries ML, Birdsill AC, Alexander AL, Rowley HA, Puglielli L, Athana S, Sager MA: **CSF T-Tau/Aβ(42) Predicts White Matter Microstructure in Healthy Adults at Risk for Alzheimer's Disease.** *PLoS One* 2012, **7**:e37720.
84. Izaks GJ, Gansevoort RT, van der Knaap AM, Navis G, Dullaart RP, Slaets JP: **The association of APOE genotype with cognitive function in persons aged 35 years or older.** *PLoS One* 2011, **6**:e27415.
85. Sunderland T, Mirza N, Putnam KT, Linker G, Bhupali D, Durham R, Soares H, Kimmel L, Friedman D, Bergeson J, Csako G, Levy JA, Bartko JJ, Cohen RM: **Cerebrospinal fluid beta-amyloid1-42 and tau in control subjects at risk for Alzheimer's disease: the effect of APOE epsilon4 allele.** *Biol Psychiatry* 2004, **56**:670-676.
86. O'Dwyer L, Lambertson F, Matura S, Scheibe M, Miller J, Rujescu D, Prvulovic D, Hampel H: **White matter differences between healthy young ApoE4 carriers and non-carriers identified with tractography and support vector machines.** *PLoS One* 2012, **7**:e36024.
87. Stomrud E, Hansson O, Blennow K, Minthon L, Londos E: **Cerebrospinal fluid biomarkers predict decline in subjective cognitive function over 3 years in healthy elderly.** *Dement Geriatr Cogn Disord* 2007, **24**:118-124.
88. Ringman JM, Younkin SG, Pratico D, Seltzer W, Cole GM, Geschwind DH, Rodriguez-Agudelo Y, Schaffer B, Fein J, Sokolow S, Rosario ER, Gyls KH, Varpertian A, Medina LD, Cummings JL: **Biochemical markers in persons with preclinical familial Alzheimer disease.** *Neurology* 2008, **71**:85-92.
89. Ringman JM, Schulman H, Becker C, Jones T, Bai Y, Immermann F, Cole G, Sokolow S, Gyls K, Geschwind DH, Cummings JL, Wan H: **Proteomic changes in cerebrospinal fluid of presymptomatic and affected persons carrying familial Alzheimer disease mutations.** *Arch Neurol* 2012, **69**:96-104.
90. Moonis M, Swearer JM, Dayaw MP, St George-Hyslop P, Rogava E, Kawarai T, Pollen DA: **Familial Alzheimer disease: decreases in CSF Abeta42 levels precede cognitive decline.** *Neurology* 2005, **65**:323-325.
91. Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, Cowie TF, Dickinson KL, Maruff P, Darby D, Smith C, Woodward M, Merory J, Tochon-Danguy H, O'Keefe G, Klunk WE, Mathis CA, Price JC, Masters CL, Villemagne VL: **Imaging beta-amyloid burden in aging and dementia.** *Neurology* 2007, **68**:1718-1725.
92. Ikonomic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, Lopresti BJ, Ziolk S, Bi W, Paljug WR, Debnath ML, Hope CE, Isanski BA, Hamilton RL, DeKosky ST: **Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease.** *Brain* 2008, **131**:1630-1645.
93. Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, LaRossa GN, Spinner ML, Klunk WE, Mathis CA, DeKosky ST, Morris JC, Holtzman DM: **Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans.** *Ann Neurol* 2006, **59**:512-519.
94. Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolk SK, James JA, Snitz BE, Houck PR, Bi W, Cohen AD, Lopresti BJ, DeKosky ST, Halligan EM, Klunk WE: **Frequent amyloid deposition without significant cognitive impairment among the elderly.** *Arch Neurol* 2008, **65**:1509-1517.
95. Vlassenko AG, Mintun MA, Xiong C, Sheline YI, Goate AM, Benzinger TL, Morris JC: **Amyloid-beta plaque growth in cognitively normal adults: longitudinal [11C]Pittsburgh compound B data.** *Ann Neurol* 2011, **70**:857-861.
96. Pike KE, Savage G, Villemagne VL, Ng S, Moss SA, Maruff P, Mathis CA, Klunk WE, Masters CL, Rowe CC: **Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease.** *Brain* 2007, **130**:2837-2844.
97. Jack CR Jr, Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, Ivnik RJ, Roberts RO, Rocca WA, Boeve BF, Petersen RC: **An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease.** *Ann Neurol* 2012, **71**:765-775.
98. Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA: **Cognition, reserve, and amyloid deposition in normal aging.** *Ann Neurol* 2010, **67**:353-364.
99. Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, Koeppe RA, Mathis CA, Weiner MW, Jagust WJ: **Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects.** *Brain* 2009, **132**:1310-1323.
100. Chételat G, Villemagne VL, Villain N, Jones G, Ellis KA, Ames D, Martins RN, Masters CL, Rowe CC: **Accelerated cortical atrophy in cognitively normal elderly with high b-amyloid deposition.** *Neurology* 2012, **78**:477-484.
101. Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, Klunk WE, Mathis CA, DeKosky ST, Morris JC: **[11C]PiB in a nondemented population: potential antecedent marker of Alzheimer disease.** *Neurology* 2006, **67**:446-452.
102. Villemagne VL, Pike KE, Darby D, Maruff P, Savage G, Ng S, Ackermann U, Cowie TF, Currie J, Chan SG, Jones G, Tochon-Danguy H, O'Keefe G, Masters CL, Rowe CC: **Abeta deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease.** *Neuropsychologia* 2008, **46**:1688-1697.
103. Klunk WE, Price JC, Mathis CA, Tsopelas ND, Lopresti BJ, Ziolk SK, Bi W, Cohen AD, Ikonomic MD, Saxton JA, Snitz BE, Pollen DA, Moonis M, Lippa CF, Swearer JM, Johnson KA, Rentz DM, Fischman AJ, Aizenstein HJ, DeKosky ST: **Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees.** *J Neurosci* 2007, **27**:6174-6184.
104. Villemagne VL, Ataka S, Mizuno T, Brooks WS, Wada Y, Kondo M, Jones G, Watanabe Y, Mulligan R, Nakagawa M, Miki T, Shimada H, O'Keefe GJ, Masters CL, Mori H, Rowe CC: **High striatal amyloid beta-peptide deposition across different autosomal Alzheimer disease mutation types.** *Arch Neurol* 2009, **66**:1537-1544.
105. Schöll M, Almkvist O, Axelman K, Stefanova E, Wall A, Westman E, Långström B, Lannfelt L, Graff C, Nordberg A: **Glucose metabolism and PiB binding in carriers of a His163Tyr presenilin 1 mutation.** *Neurobiol Aging* 2011, **32**:1388-1399.
106. Morris JC, Roe CM, Grant EA, Head D, Storandt M, Goate AM, Fagan AM, Holtzman DM, Mintun MA: **Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease.** *Arch Neurol* 2009, **66**:1469-1475.
107. Villemagne VL, Pike KE, Chételat G, Ellis KA, Mulligan RS, Bourgeat P, Ackermann U, Jones G, Szoeke C, Salvado O, Martins R, O'Keefe G, Mathis CA, Klunk WE, Ames D, Masters CL, Rowe CC: **Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease.** *Ann Neurol* 2011, **69**:181-192.
108. Forsberg A, Engler H, Almkvist O, Blomquist G, Hagman G, Wall A, Ringheim A, Långström B, Nordberg A: **PET imaging of amyloid deposition in patients with mild cognitive impairment.** *Neurobiol Aging* 2008, **29**:1456-1465.
109. Koivunen J, Pirttilä T, Kempainen N, Aalto S, Herukka SK, Jauhianen AM, Hänninen T, Hallikainen M, Nägren K, Rinne JO, Soininen H: **PET amyloid ligand [11C]PiB uptake and cerebrospinal fluid beta-amyloid in mild cognitive impairment.** *Dement Geriatr Cogn Disord* 2008, **26**:378-383.
110. Forsberg A, Almkvist O, Engler H, Wall A, Långström B, Nordberg A: **High PiB retention in Alzheimer's disease is an early event with complex relationship with CSF biomarkers and functional parameters.** *Curr Alzheimer Res* 2010, **7**:56-66.
111. Schöll M, Almkvist O, Graff C, Nordberg A: **Amyloid imaging in members of a family harbouring the Arctic APP mutation.** *Alzheimers and Dementia suppl* 2011, **7**:303.
112. Sojkova J, Zhou Y, An Y, Kraut MA, Ferrucci L, Wong DF, Resnick SM: **Longitudinal patterns of β-amyloid deposition in nondemented older adults.** *Arch Neurol* 2011, **68**:644-649.
113. Scheinin NM, Aalto S, Kaprio J, Koskenvuo M, Riihä I, Rokka J, Hinkka-Yli-Salomäki S, Rinne JO: **Early detection of Alzheimer disease: <sup>11</sup>C-PiB PET in twins discordant for cognitive impairment.** *Neurology* 2011, **77**:453-460.
114. Herholz K, Salmon E, Perani D, Baron JC, Holthoff V, Frölich L, Schönknecht P, Ito K, Mielke R, Kalbe E, Zündorf G, Delbeck X, Pelati O, Anchisi D, Fazio F, Kerrouche N, Desgranges B, Eustache F, Beuthien-Baumann B, Menzel C, Schröder J, Kato T, Arahata Y, Henze M, Heiss WD:

- Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. *Neuroimage* 2002, **17**:302-316.
115. Jagust W, Reed B, Mungas D, Ellis W, Decarli C: **What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia?** *Neurology* 2007, **69**:871-877.
116. Heiss WD, Kessler J, Szelies B, Grond M, Fink G, Herholz K: **Positron emission tomography in the differential diagnosis of organic dementias.** *J Neural Transm Suppl* 1991, **33**:13-19.
117. Silverman DH, Small GW, Chang CY, Lu CS, Kung De Aburto MA, Chen W, Czernin J, Rapoport SI, Pietrini P, Alexander GE, Schapiro MB, Jagust WJ, Hoffman JM, Welsh-Bohmer KA, Alavi A, Clark CM, Salmon E, de Leon MJ, Mielke R, Cummings JL, Kowell AP, Gambhir SS, Hoh CK, Phelps ME: **Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome.** *JAMA* 2001, **286**:2120-2127.
118. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J: **Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia.** *Proc Natl Acad Sci USA* 2004, **101**:284-289.
119. Mosconi L, De Santi S, Brys M, Tsui WH, Pirraglia E, Glodzik-Sobanska L, Rich KE, Switalski R, Mehta PD, Pratico D, Zinkowski R, Blennow K, de Leon MJ: **Hypometabolism and altered cerebrospinal fluid markers in normal apolipoprotein E4 carriers with subjective memory complaints.** *Biol Psychiatry* 2008, **63**:609-618.
120. Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minooshima S, Thibodeau SN, Osborne D: **Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E.** *N Engl J Med* 1996, **334**:752-758.
121. Reiman EM, Caselli RJ, Chen K, Alexander GE, Bandy D, Frost J: **Declining brain activity in cognitively normal apolipoprotein E epsilon 4 heterozygotes: A foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease.** *Proc Natl Acad Sci USA* 2001, **98**:3334-3339.
122. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J: **Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism.** *Proc Natl Acad Sci USA* 2005, **102**:8299-8302.
123. Langbaum JB, Chen K, Caselli RJ, Lee W, Reschke C, Bandy D, Alexander GE, Burns CM, Kaszniak AW, Reeder SA, Corneveaux JJ, Allen AN, Pruzin J, Huentelman MJ, Fleisher AS, Reiman EM: **Hypometabolism in Alzheimer-affected brain regions in cognitively healthy Latino individuals carrying the apolipoprotein E epsilon4 allele.** *Arch Neurol* 2010, **67**:462-468.
124. Small GW, Mazziotta JC, Collins MT, Baxter LR, Phelps ME, Mandelkern MA, Kaplan A, La Rue A, Adamson CF, Chang L, Guze BH, Corder EH, Saunders AM, Haines JL, Pericak-Vance MA, Roses AD: **Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease.** *JAMA* 1995, **273**:942-947.
125. Small GW, Ercoli LM, Silverman DH, Huang SC, Komo S, Bookheimer SY, Lavretsky H, Miller K, Siddarth P, Rasgon NL, Mazziotta JC, Saxena S, Wu HM, Mega MS, Cummings JL, Saunders AM, Pericak-Vance MA, Roses AD, Barrio JR, Phelps ME: **Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease.** *Proc Natl Acad Sci USA* 2000, **97**:6037-6042.
126. Järvenpää T, Rähä I, Kaprio J, Koskenvuo M, Laine M, Kurki T, Vahlberg T, Viljanen T, Ahonen K, Rinne JO: **Regional cerebral glucose metabolism in monozygotic twins discordant for Alzheimer's disease.** *Dement Geriatr Cogn Disord* 2003, **16**:245-252.
127. Virta JJ, Aalto S, Järvenpää T, Karrasch M, Kaprio J, Koskenvuo M, Rähä I, Viljanen T, Rinne JO: **Voxel-based analysis of cerebral glucose metabolism in mono- and dizygotic twins discordant for Alzheimer disease.** *J Neurol Neurosurg Psychiatry* 2009, **80**:259-266.
128. Mosconi L, Mistur R, Switalski R, Tsui WH, Glodzik L, Li Y, Pirraglia E, De Santi S, Reisberg B, Wisniewski T, de Leon MJ: **FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease.** *Eur J Nucl Med Mol Imaging* 2009, **36**:811-822.
129. Mosconi L, Mistur R, Switalski R, Brys M, Glodzik L, Rich K, Pirraglia E, Tsui W, De Santi S, de Leon MJ: **Declining brain glucose metabolism in normal individuals with a maternal history of Alzheimer disease.** *Neurology* 2009, **72**:513-520.
130. Kennedy AM, Frackowiak RS, Newman SK, Bloomfield PM, Seaward J, Roques P, Lewington G, Cunningham VJ, Rossor MN: **Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease.** *Neurosci Lett* 1995, **186**:17-20.
131. Wahlund LO, Basun H, Almkvist O, Julin P, Axelman K, Shigeta M, Jelic V, Nordberg A, Lannfelt L: **A follow-up study of the family with the Swedish APP 670/671 Alzheimer's disease mutation.** *Dement Geriatr Cogn Disord* 1999, **10**:526-533.
132. Ghebremedhin E, Schultz C, Braak E, Braak H: **High frequency of apolipoprotein E epsilon4 allele in young individuals with very mild Alzheimer's disease-related neurofibrillary changes.** *Exp Neurol* 1998, **153**:152-155.
133. Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM: **Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnesic pre-mild cognitive impairment.** *Arch Neurol* 2008, **65**:1231-1236.
134. den Heijer T, Geerlings MI, Hoebeek FE, Hofman A, Koudstaal PJ, Breteler MM: **Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people.** *Arch Gen Psychiatry* 2006, **63**:57-62.
135. Csernansky JG, Wang L, Swank J, Miller JP, Gado M, McKeel D, Miller MI, Morris JC: **Preclinical detection of Alzheimer's disease: hippocampal shape and volume predict dementia onset in the elderly.** *Neuroimage* 2005, **25**:783-792.
136. Martin SB, Smith CD, Collins HR, Schmitt FA, Gold BT: **Evidence that volume of anterior medial temporal lobe is reduced in seniors destined for mild cognitive impairment.** *Neurobiol Aging* 2010, **31**:1099-1106.
137. Rusinek H, De Santi S, Frid D, Tsui WH, Tarshish CY, Convit A, de Leon MJ: **Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging.** *Radiology* 2003, **229**:691-696.
138. Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Tangalos EG, Kokmen E: **Rates of hippocampal atrophy correlate with change in clinical status in aging and AD.** *Neurology* 2000, **55**:484-489.
139. Apostolova LG, Mosconi L, Thompson PM, Green AE, Hwang KS, Ramirez A, Mistur R, Tsui WH, de Leon MJ: **Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal.** *Neurobiol Aging* 2010, **31**:1077-1088.
140. Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, Hyman BT, Blacker D, Detorledo-Morrell L: **Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults.** *Neurology* 2011, **76**:1395-1402.
141. Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, Grodstein F, Wright CI, Blacker D, Rosas HD, Sperling RA, Atri A, Growdon JH, Hyman BT, Morris JC, Fischl B, Buckner RL: **The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals.** *Cereb Cortex* 2009, **19**:497-510.
142. Dickerson BC, Wolk DA: **MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults.** *Neurology* 2012, **78**:84-90.
143. Fox NC, Crum WR, Scahill RI, Stevens JM, Janssen JC, Rossor MN: **Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images.** *Lancet* 2001, **358**:201-205.
144. Kaye JA, Swihart T, Howieson D, Dame A, Moore MM, Karnos T, Camicioli R, Ball M, Oken B, Sexton G: **Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia.** *Neurology* 1997, **48**:1297-1304.
145. Carlson NE, Moore MM, Dame A, Howieson D, Silbert LC, Quinn JF, Kaye JA: **Trajectories of brain loss in aging and the development of cognitive impairment.** *Neurology* 2008, **70**:828-833.
146. Smith CD, Chebrolu H, Wekstein DR, Schmitt FA, Jicha GA, Cooper G, Markesbery WR: **Brain structural alterations before mild cognitive impairment.** *Neurology* 2007, **68**:1268-1273.
147. Smith CD, Chebrolu H, Markesbery WR, Liu J: **Improved predictive model for pre-symptomatic mild cognitive impairment and Alzheimer's disease.** *Neurol Res* 2008, **30**:1091-1096.
148. Hall AM, Moore RY, Lopez OL, Kuller L, Becker JT: **Basal forebrain atrophy is a presymptomatic marker for Alzheimer's disease.** *Alzheimers Dement* 2008, **4**:271-279.
149. Burgmans S, van Bostel MP, Smeets F, Vuurman EF, Gronenschild EH, Verhey FR, Uylings HB, Jolles J: **Prefrontal cortex atrophy predicts dementia over a six-year period.** *Neurobiol Aging* 2009, **30**:1413-1419.

150. Desikan RS, Sabuncu MR, Schmansky NJ, Reuter M, Cabral HJ, Hess CP, Weiner MW, Biffi A, Anderson CD, Rosand J, Salat DH, Kemper TL, Dale AM, Sperling RA, Fischl B: **Selective disruption of the cerebral neocortex in Alzheimer's disease.** *PLoS One* 2010, **5**:e12853.
151. Sabuncu MR, Desikan RS, Sepulcre J, Yeo BT, Liu H, Schmansky NJ, Reuter M, Weiner MW, Buckner RL, Sperling RA, Fischl B: **The dynamics of cortical and hippocampal atrophy in Alzheimer disease.** *Arch Neurol* 2011, **68**:1040-1048.
152. Becker JA, Hedden T, Carmasin J, Maye J, Rentz DM, Putcha D, Fischl B, Greve DN, Marshall GA, Salloway S, Marks D, Buckner RL, Sperling RA, Johnson KA: **Amyloid- $\beta$  associated cortical thinning in clinically normal elderly.** *Ann Neurol* 2011, **69**:1032-1042.
153. Drzezga A, Becker JA, Van Dijk KR, Sreenivasan A, Talukdar T, Sullivan C, Schultz AP, Sepulcre J, Putcha D, Greve D, Johnson KA, Sperling RA: **Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden.** *Brain* 2011, **134**:1635-1646.
154. Liang P, Wang Z, Yang Y, Jia X, Li K: **Functional disconnection and compensation in mild cognitive impairment: evidence from DLPPC connectivity using resting-state fMRI.** *PLoS One* 2011, **6**:e22153.
155. Miao X, Wu X, Li R, Chen K, Yao L: **Altered connectivity pattern of hubs in default-mode network with Alzheimer's disease: an Granger causality modeling approach.** *PLoS One* 2011, **6**:e25546.
156. Sanz-Arigita EJ, Schoonheim MM, Damoiseaux JS, Rombouts SA, Maris E, Barkhof F, Scheltens P, Stam CJ: **Loss of 'small-world' networks in Alzheimer's disease: graph analysis of fMRI resting-state functional connectivity.** *PLoS One* 2010, **5**:e13788.
157. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW: **Patterns of brain activation in people at risk for Alzheimer's disease.** *N Engl J Med* 2000, **343**:450-456.
158. Fleisher AS, Houston WS, Eylar LT, Frye S, Jenkins C, Thal LJ, Bondi MW: **Identification of Alzheimer disease risk by functional magnetic resonance imaging.** *Arch Neurol* 2005, **62**:1881-1888.
159. Bondi MW, Houston WS, Eylar LT, Brown GG: **fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease.** *Neurology* 2005, **64**:501-508.
160. Seidenberg M, Guidotti L, Nielson KA, Woodard JL, Durgerian S, Antuono P, Zhang Q, Rao SM: **Semantic memory activation in individuals at risk for developing Alzheimer disease.** *Neurology* 2009, **73**:612-620.
161. Suthana NA, Krupa A, Donix M, Burggren A, Ekstrom AD, Jones M, Ercoli LM, Miller KJ, Siddarth P, Small GW, Bookheimer SY: **Reduced hippocampal CA2, CA3, and dentate gyrus activity in asymptomatic people at genetic risk for Alzheimer's disease.** *Neuroimage* 2010, **53**:1077-1084.
162. Bassett SS, Yousem DM, Cristinzio C, Kusevic I, Yassa MA, Caffo BS, Zeger SL: **Familial risk for Alzheimer's disease alters fMRI activation patterns.** *Brain* 2006, **129**:1229-1239.
163. Yassa MA, Verduzco G, Cristinzio C, Bassett SS: **Altered fMRI activation during mental rotation in those at genetic risk for Alzheimer disease.** *Neurology* 2008, **70**:1898-1904.
164. Rodda J, Dannhauser T, Cutinha DJ, Shergill SS, Walker Z: **Subjective cognitive impairment: functional MRI during a divided attention task.** *Eur Psychiatry* 2011, **26**:457-462.
165. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ: **Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade.** *Lancet Neurol* 2010, **9**:119-128.
166. Jack CR Jr, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Lowe V, Kantarci K, Bernstein MA, Senjem ML, Gunter JL, Boeve BF, Trojanowski JQ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Knopman DS: **Shapes of the trajectories of 5 major biomarkers of Alzheimer disease.** *Arch Neurol* 2012, **69**:856-867.
167. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH: **Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.** *Alzheimers Dement* 2011, **7**:280-292.
168. Knopman DS, Jack CR Jr, Wiste HJ, Weigand SD, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, Ivnik RJ, Roberts RO, Boeve BF, Petersen RC: **Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease.** *Neurology* 2012, **78**:1576-1582.
169. Petersen RC: **Mild cognitive impairment as a diagnostic entity.** *J Intern Med* 2004, **256**:183-194.
170. DeKosky ST, Ikonomic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, Cochran EJ, Kordower JH, Mufson EJ: **Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment.** *Ann Neurol* 2002, **51**:145-155.
171. Peng S, Wu J, Mufson EJ, Fahnestock M: **Increased proNGF levels in subjects with mild cognitive impairment and mild Alzheimer disease.** *J Neuropathol Exp Neurol* 2004, **63**:641-649.
172. Smith GE, Pankratz VS, Negash S, Machulda MM, Petersen RC, Boeve BF, Knopman DS, Lucas JA, Ferman TJ, Graff-Radford N, Ivnik RJ: **A plateau in pre-Alzheimer memory decline: evidence for compensatory mechanisms?** *Neurology* 2007, **69**:1333-1339.
173. Karlawish J: **Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease.** *Neurology* 2011, **77**:1487-1493.
174. Lemere CA, Masliah E: **Can Alzheimer disease be prevented by amyloid-beta immunotherapy?** *Nat Rev Neurol* 2010, **6**:108-119.
175. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergström M, Savitcheva I, Huang GF, Estrada S, Ausén B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Långström B: **Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B.** *Ann Neurol* 2004, **55**:306-319.
176. Aboud O, Mrak RE, Boop F, Griffin ST: **Apolipoprotein epsilon 3 alleles are associated with indicators of neuronal resilience.** *BMC Med* 2012, **10**:35.
177. Caesar I, Gandy S: **Evidence that an APOE4 'double whammy' increases risk for Alzheimer's disease.** *BMC Med* 2012, **10**:36.

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