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## Abstract

Preclinical Alzheimer's disease (AD) is a relatively recent concept describing an entity characterized by the presence of a pathophysiological biomarker signature characteristic for AD in the absence of specific clinical symptoms. There is rising interest in the scientific community to define such an early target population mainly due to failures of all recent clinical trials despite evidence of biological effects on brain amyloidosis for some compounds. A conceptual framework has recently been proposed for this preclinical phase of AD. However, few data exist on this silent stage of AD. We performed a systematic review in order to investigate how the concept is defined across studies. The review highlights the substantial heterogeneity concerning the three main determinants of preclinical AD: "normal cognition", "cognitive decline" and "AD pathophysiological signature". We emphasize the need for a harmonized nomenclature of the preclinical AD concept and standardized population-based and case-control studies using unified operationalized criteria.

# Introduction

The positivity of biomarkers of Alzheimer's disease (AD) before the occurrence of first clinical symptoms and dementia, supports the concept that AD is a continuum, and that it could be diagnosed before its clinical expression [1]. Intervention at such an early stage of the disease is considered to improve the chance of success because it would target potentially still reversible and less established and extensive pathological processes. The lack of clinical efficacy of trials using monoclonal antibodies targeting amyloid at a mild or moderate stage of the illness is further encouragement to shift the attention to the preclinical stage of the disease.

The concept of a preclinical stage of AD emerged mainly from clinico-pathological studies describing apparently cognitively normal individuals with the possibility of AD hallmark lesions in the brain.[2-5] The International Working Group-2 (IWG-2) and later the National Institute on Aging-Alzheimer's Association (NIA-AA) consortium each proposed a definition of the preclinical stage of AD [6, 7]. The recent release of consensual criteria should facilitate the harmonization and the quality of epidemiological and interventional research on preclinical AD [1].
Until now, little is known about the natural history of the preclinical state. Large epidemiological studies have been conducted or are still ongoing regarding the risk of dementia in the general population, but they are not strictly focusing on AD, and even less on the identification of subjects with the preclinical form of the disease using AD biomarkers (For review see [8] ).

Per definition, people with preclinical AD lack the classical symptoms of the disease. However, the NIA-AA defines a stage of preclinical AD, with "subtle cognitive decline" [7]. This is due to the fact that most longitudinal epidemiological studies show the occurrence of decline, mainly in terms of psycho-motor speed and executive functions, years before the diagnosis of dementia [9, 10]. There is no consensual definition for "subtle cognitive changes" (i.e. "normal cognition" and "cognitive decline"). Likewise, an AD physiopathological biomarker profile was not required for study inclusion in these studies.
The present article, based on a systematic review of the literature on preclinical AD, aims at identifying the diagnostic approaches used by the leading groups in the field at this early stage of the disease. In particular three main issues concerning the concept of preclinical AD must be clarified: 1) the level of cognitive performance considered as "normal cognition" 2) the changes in cognitive performance considered as "cognitive decline", and 3) the best biomarkers or the best combination of them able to identify the "AD pathophysiological signature" in vivo. This review could support future clinical research in the field especially if a disease modifying drug demonstrates its efficacy.

# METHODS:

## Search strategy and selection criteria

The PubMed Database and ClinicalTrials.gov were searched for the terms “Preclinical Alzheimer’s disease”, “Preclinical Alzheimer disease”, “Presymptomatic Alzheimer’s disease”, “Presymptomatic Alzheimer disease”, “Asymptomatic Alzheimer’s disease”, “Asymptomatic Alzheimer disease”, up to June 2016, without any language restriction. The terms had to be in the title or even in the abstract of the manuscript in order to include articles that would only refer to the concept of preclinical AD without studying it.

## Search Strategy Results and further classification of studies

We identified 361 articles reporting “preclinical AD”. They were categorized as “reviews” (for review, conceptual and perspective articles), “out of topic” (when despite the title or abstract of the article, no preclinical AD subject was included in the study), “neuropathological” (when AD diagnosis was pathologically established in subjects who died within one year of a cognitive evaluation considered as unimpaired), “genetic” when the study dealt with cognitively healthy carriers of causative mutations for familial AD, and “biomarker” when they comprised a biomarker based definition of the AD pathophysiology. They were further stratified in “cross sectional” or “longitudinal”. Furthermore, we empirically chose to exclude articles with a sample size below 100 participants in order to focus on the major cohorts allowing for the study of the preclinical AD concept. The search strategy and distribution of the studies are reported in Fig 1. Fifty five studies from the “neuropathological”, “genetic” and “biomarker” groups satisfied the above criteria and have been investigated. From each study, the total number of participants according to their diagnosis (healthy control, preclinical AD, NIA-AA preclinical AD stages and when appropriate mild cognitive impairment (MCI) and AD dementia participants) were extracted as well as their mean age, the percentage of *APOE ε4* carriers and the cohort study from which they derived. As “Suspected non AD Pathophysiology” (SNAP) for biomarker based studies and “Primary age related taupathy” (PART) for neuropathological studies are two concepts that arose from the more systematic use of AD biomarkers and the rising interest in the earlier stages of AD [11], their number in studies on Preclinical AD were also considered. Finally, the way to define “normal cognition”, “cognitive decline” and “AD pathophysiological signature” was analysed in each study. An overview of the studies’ population and methodologies are provided in Tables 1 & 2 respectively. The detailed description of the 55 studies and their methodology are provided in Supplementary Tables 1 and 2.

## Cohorts allowing the study of preclinical AD

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Thirteen different cohorts of cognitively normal individuals for the investigation of preclinical AD were identified from these 55 publications. Nine of them are monocentric and currently recruiting as they were developed in the context of a clinical-research setting with an observational period ranging from 3 to 20 years. Each cohort characteristics were extracted from the published studies and from the cohorts’ websites when available. Specifically, the latest published number of healthy elderly volunteers included in the cohort, the type of follow-up,(clinical routine or research), the mono or multicentric recruitment, the ethnicity and inclusion of minorities, the geographical origin of participants, the male/female ratios, the age of included participants, the selected criteria for normal cognition, the neuropsychological

battery, the existence of cerebrospinal fluid biomarker or blood sampling, MRI, 18FDG-PET, Amyloid-PET and other biomarkers was reported (see Table 3 & Supplementary Table 3). The number of studies in this review categorized by the cohort they emerge from are detailed in Supplementary Fig 1. The diverse cognitive tests are also presented in Fig 2 to clearly depict their frequency of use in the 13 cohorts.

## Clinical trials on preclinical AD

In addition to the observational cohorts described above, the ClinicalTrials.gov website was employed for a detailed research on the drug trials available on the preclinical AD population. All trials mentioning "preclinical AD" as a target population with pathophysiological markers of AD as inclusion criteria in their study design were considered. Three trials were identified, 2 of which concerning familial AD as described in Table 4. This relatively low number of trials is due to the fact that most (8/11) trials listed on the "Clinicaltrial.gov" webpage (but excluded from this review) pertaining to the "preclinical Alzheimer's disease" search terms do not use pathophysiological markers at enrolment, thus being trials on the risk of developing MCI or dementia rather than on the more precise "preclinical AD" concept.

# RESULTS:

## "Normal cognition"

The concept of "normal cognition" is controversial. It is indeed hard to define whether a given individual can be considered as cognitively normal. Usually this is achieved by comparing his psychometric performance to that of a predefined age and educational level matched group on specific tests. In this case, there is no reference to his own cognitive abilities prior to the assessment. This individual factor, requiring longitudinal follow-up prior to inclusion, is almost never accounted for in studies on preclinical AD. Moreover, in the 55 studies selected, five (9.1%) did not clearly specify what was considered as "normal cognition". Twenty-one studies (38.2%) made use of the Clinical Dementia Rating scale (CDR) out of which thirteen (23.6%) used exclusively the CDR score equal to 0 to classify participants as cognitively healthy. The remaining 29 (52.7%) studies relied either on single Mini-mental State Examination (MMSE) or multiple cognitive tests, or on the clinical judgment of one investigators (see Table 2 for details). When cognitive tests were used, the clear definition of what was considered to be "pathological" was not always explicit. By contrast, in some cases it was described thoroughly [12]. MMSE scores when used as cut-off points between normality and impairment varied from 26 [13, 14] to 28 [15]. Interestingly, the MMSE cut-off scores, used in the studies, were higher than those necessary to be included in some of the cohorts (see Table 3 and below). Finally, the 3 clinical trials conducted on preclinical AD used different inclusion criteria (see Table 4).

Concerning the cohorts: The criterion used to define 'normal cognition' was heterogeneous as well. In seven out of the thirteen cohorts, the definition was based on the performance

obtained on standard neuropsychological batteries. In the remaining cohorts, subjects were considered cognitively intact when they had a MMSE scores above 24 with a CDR score equal to 0 in the absence of depressive symptoms. The clinical and neuropsychological assessments were part of the study protocol for all considered cohorts, although the neuropsychological assessment used was not harmonized among cohorts (Fig. 3). The use of core biomarkers of AD was also heterogeneous. In most of the cohorts, the collection of biological and imaging markers was mainly restricted to a subsample of subjects. In addition to the physiopathological biomarkers, three studies collected EEG and three other reported post mortem neuropathological findings.
In terms of open source availability of data collected, not all of these studies are accessible to the scientific community. To our knowledge, the Alzheimer's Disease neuroimaging Initiative (ADNI), the Australian Imaging, the Biomarkers and Lifestyle Flagship Study of Ageing (AIBL), the Harvard Aging Brain Study (HABS), the Charles F. and Joanne Knight Alzheimer's Disease Research Centre (Knight ADRC) at Washington University School of Medicine, the National Alzheimer's Coordinating Centre (NACC) database, and the Wisconsin Registry for Alzheimer's Prevention (WRAP) are the only databases on preclinical AD patients allowing external investigators to access data throughout online available platforms and after appropriate review of projects submitted.

## "Cognitive decline/outcome"

The definition of cognitive decline, as previously emphasized by the NIA-AA guidelines and in clinical trials in preclinical AD descriptions [7, 16-18], also raises some issues: if it is too strict (e.g. going from a CDR equal to 0 to a CDR equal to 1), the number of individuals with "preclinical AD" progressing to "clinical AD" will be very low and will require long-term studies (years if not decades) to draw conclusions on risk factors and progression of preclinical AD. Conversely, if the definition encompasses any slight change in cognition over time (e.g. an increase of a few seconds in a timed psycho-motor speed test), the risk of a low specificity and high number of false positive rises (i.e. temporary cognitive impairment unrelated to AD and disappearing during longer follow-up). In the reviewed studies, the strategy to define cognitive decline was heterogeneous (see table 2 for details). In the three clinical trials, different tests were used to evaluate cognitive decline (see Table 4). Contrarily to the other "determinants" of preclinical AD, the cognitive decline is not mandatory for diagnosis. Both hypothetical frameworks of preclinical AD recognize that the diagnosis can be made when there is 1) a normal cognition and 2) markers of AD pathophysiology [1, 7]. However, evidencing a cognitive decline (even when cognition remains normal with respect to normative data) in an individual is a strong supportive argument of preclinical AD and is the basis on which the clinical trials in preclinical AD are being conducted [18].

## "AD pathophysiological signature"

Three approaches can be of use to search for signs of AD pathophysiology in individuals with a normal cognition. The gold-standard one is the post-mortem brain examination which can be used to directly assess regional Aß and tau pathology loads and provide a neuropathological diagnosis [19, 20]. A limit of this method is that it only allows the study of subjects who died without any clinical impairment but it precludes the study of cognitive

decline. Thus, rather than naming the concept “preclinical AD” in this type of study one could advocate the term “non-clinical AD pathology” or “silent AD pathology” as it is impossible to know if these subjects would have developed clinical symptoms if they have lived for a longer time. This neuropathological validation was performed in 4/55 (7.3%) of this review’s studies. The second method is the identification of a specific Mendelian autosomal dominant genetic mutation for familial AD (FAD). This allows studying preclinical early onset forms of AD as these mutations have a 100% penetrance so that all carriers will develop the disease. Moreover, the age of onset of symptoms in a mutation carrier is approximately the same as that of his parent. Cross sectional studies have been performed in these asymptomatic carriers to analyse the biomarker differences over time and to hypothesize their evolution [21]. A limitation is that the FAD population represents a minor fraction of all AD patients with differences in the expression, progression and pathophysiology of the disease such as the early age of onset. One out of the 55 studies (2%) used this method in our review. The third way to identify the underlying AD physiopathology relies on the use of biomarkers. According to the IWG criteria, only some markers of AD such as CSF biomarkers (Aß, tau or phosphorylated tau) and amyloid and tau positon emission tomography (PET) but not MRI nor functional imaging are considered as pathophysiological markers [6]. In the NIA-AA criteria, brain (especially hippocampal) atrophy on MRI or hypometabolism on $^{18}$FDG-PET are also considered as suitable biomarkers to identify AD as they reflect a neurodegeneration pattern compatible with the disease [7]. In the present review the more restrictive IWG criteria were used so that each of the selected studies can be considered as relying on specific markers to assess an “AD pathophysiological signature” (CSF and/or amyloid and tau PET assessments). However, to date, there is no consensual biomarker-based method universally recognized to define “AD pathophysiological signature”, such as prostate-specific antigen (PSA) values in prostate cancer or glucose values in diabetes [22]. In the studies reviewed herein, fourteen different definitions were applied for CSF biomarkers (CSF collection biomarkers assays, considered markers or panel of markers and cut-offs) and sixteen different definitions for amyloid PET (in terms of tracer, analytical methodology or threshold) out of the fifty biomarker based studies.

## Discussion and strategy for the standardization and harmonization of the Preclinical AD diagnostic and follow-up procedure.

Following the problematic experience with the vastly heterogeneous application of prodromal “MCI” concepts to research studies and drug development programs in AD [23] and failures of recent large-scale trials aiming at slowing down progression of the disease in patients with mild to moderate AD [24, 25], great interest has developed towards the earlier phase of the disease. At present, numerous clinical trials include prodromal AD participants with different definitions [23]. In view of the evolving paradigm change, preclinical AD, a concept that could provide a valuable early time window for therapeutic intervention, is under much scrutiny. The standardization of the neuropsychological and biomarker evaluation required for its diagnosis is an important challenge for future studies [26]. This is supported by converging evidence toward the possible efficacy of disease modifying drugs in the early clinical stage of AD [24, 27]. We propose that three issues should be addressed consistently in upcoming research on preclinical AD: the definition and diagnostic procedures of “normal cognition”, “cognitive decline” and “AD physiopathological signature”. In our review, these three

determinants are largely heterogeneous which contributes among other, less modifiable factors such as geography of recruitment, to a substantial variability from one study population to the other. For instance, the ratio of stage 1 and 2 preclinical AD is of 78 and 22% respectively in one study [28] and of 21 and 79% in another one [29] limiting the generalizability of each study's findings. However, some homogeneity can also be evidenced. The CDR is the most commonly used tool used to define "normal cognition", and frequently used to assess **"**cognitive decline**".** Other endpoints are proposed that rely on various cognitive tests, diagnostic criteria for MCI or prodromal AD and since 2014, various composite cognitive scores. Compared to the CDR, these tests and composite scores offer the advantage of a finer delineation of the subtle cognitive changes that might occur many years before dementia is evidenced. On the other side, they are much more heterogeneous than the universally used CDR. Another issue with composite scores is their multiplicity. In the last two years, at least five different scores have been proposed relying on different methodologies (such as item response theory, or mean-to-standard deviation ratio) and including different tests [30-34]. Also, the use of subjective cognitive decline (SCD) was never considered as a marker of decline, even in studies focusing on memory complaints [15, 35-38] although it has been suggested that it might be a marker appearing late in the preclinical stage of the disease [9]. In fact, the main difference between "normal cognition" and "cognitive decline" could be drawn from differences in terms of relative risks (RR) to develop decline to milestones over time. For instance, an individual with SCD [39] should be considered as cognitively healthy since the RR of decline is low [40] and since the SCD condition is not specific of AD. The same can be said about psychomotor slowing and very mild executive changes which correspond to the "subtle cognitive changes" proposed by the NIA-AA. These symptoms arise many years before the dementia syndrome [9, 10, 38], are also non-specific and can be identified in other conditions such as mild vascular brain lesions [41] frontotemporal dementia [42] or even depression. On the other hand, when an individual has a low free recall in the free and cued selective reminding test (FCSRT) his risk to decline over the next years is high (>10 at 5 years) [43]. The specificity of the amnestic syndrome of the hippocampal type which is identifiable by this test allows for the classification of the subject in the clinical phase of AD (prodromal if it does not impact autonomy or dementia otherwise). This high risk profile and specificity for AD, even at its prodromal stage were the reasons why this test was recommended in the first IWG research criteria for AD diagnosis [44] Likewise, the "subtle cognitive changes", namely attentional/psychomotor speed impairment, mild executive dysfunction should be operationalized as preclinical AD is more and more frequently studied. The chosen tests should be both the most frequently used ones by expert in the field and those which have demonstrated the best sensitivity to change over time in epidemiological studies on cognition in the elderly. The ten most frequently used tests in the 13 analysed cohorts are the Trail Making Test (TMT), Mini Mental State Evaluation (MMSE), Boston Naming Test, Verbal Fluency (animals), Clinical Dementia Rating scale (CDR), Logical Memory Test from the WMS-R, Rey Auditory Verbal Learning Test, Digit Span Forward and Backward from WMS-R, Digit Symbol Substitution Test (DSST) from WAIS-R and Verbal Fluency (letters). Performances below 1 standard deviations (SD) in cognitive tests and the individuals displaying these changes would still not be considered "cognitively impaired" in the absence of more specific symptoms. Studies conducted on the preclinical AD concept could be harmonized by 1) using tests to assess attention and psychomotor speed (such as the Digit Span Forward and DSST), executive functions (e.g. verbal fluencies, Trail making test), questionnaires to assess SCD, episodic memory (FCSRT), and global cognitive functioning (MMSE, CDR) (see table 5) and 2) by repeating these tests over time to identify "cognitive decline". On a schematic point of view, this aspecific/low risk first symptoms vs. high risk/specific impairments can be represented as in Fig 4 and might determine possible

interventions. This appears to be the only way to establish prospectively which test performance(s) is (are) the best specific predictor(s) for the transition from the preclinical to the prodromal stage of the disease. Regarding the "AD pathophysiological signature", methods vary even more. This is most probably due to the recent development of these markers [45]. Of note for further studies, the recommendation to consider preclinical AD only in case of Aß AND tau positive markers points to the need to use either Aß and tau combinations of CSF biomarkers (12/50 studies with biomarkers in this review) or both Aß and tau PET tracers (0 article in this review) [20]. Variability in the choice of cognitive tests and pathophysiological markers as determinants of preclinical AD was maximized when the authors of the studies made use of open-source databases and was reduced in studies focusing on cohorts that were analysed by individual research groups under the supervision of the same principal investigator [46, 47]. The ongoing innovation (e.g. the replacement of $^{11}$C-PiB by $^{18}$Fluor labelled amyloid ligands [48, 49]) renders the process of standardization of biomarker results challenging. There are, however, international efforts to homogenize cognitive [50] and biomarker practice in research studies [51-53]. The specific value of different markers has also been studied [54] but no study combining all these markers with further post-mortem brain examination to determine the individual and combined added values of these marker has, to our knowledge, ever been conducted. The value of downstream topographical biomarkers of progression (brain atrophy on MRI and hypometabolism on $^{18}$FDG-PET) [48] as possible outcomes for decline should also be considered, notably in clinical trials [55]. Of course, it would be simplistic to consider preclinical AD as a homogeneous entity and the idea of proposing a "one size fits all" set of criteria may be problematic. But it is a necessary step to share results from different study groups. A unified definition of preclinical AD would of course not be definite but would evolve as different syndromic entities (eg fast vs. slow decliners) would emerge from ongoing studies. The fast paced innovation of biomarkers in the field also has to be considered. As new markers (such as blood based biomarkers) [56] are discovered and validated, their integration to the diagnostic algorithm of preclinical AD will have to be considered. In the end, a systems biology approach would be needed to propose a comprehensive set of definitions on as many preclinical AD variants as will be identified [57]. Of course, all these diagnostic processes rely on costly and invasive protocols that can, to date, only be proposed in the context of research projects in high income countries. This is reflected by the geographic location of the identified cohorts in this review and the low percentage of ethnic minorities among their participants. When a disease modifying treatment becomes available, the need to devise a pipeline of exams that is both safe and cost effective will be high. Specific neuro-economic studies should be conducted on the balance between the cost and adverse events due to a large scale screening for preclinical AD versus the long term benefit of early intervention at this stage of the disease.

One of the major limitation of this review is that it limits itself to the analysis of studies with more than one hundred participants. This choice was made empirically and the authors of this review recognize that many important insights for the field may be derived from studies with sizes below 100 subjects at this early exploratory and developmental period for the concept of preclinical AD. This choice was mainly made for one reason: to derive robust criteria for a disease or its risk factors you need an epidemiological study with a large number of participants and a long duration of follow-up, much like what the Framingham cohort brought to the cardiovascular field [58, 59]. Our cut-off of 100 participants ensured that we identified some of the preclinical Alzheimer's field experienced centres with a total of 3854 individuals (sum of the total number of included participants in the latest published study of the 11 biomarker cohorts) with a mean (SEM) percentage of preclinical AD among them of 21.5 (2.2). Relatively to cohorts such as Framingham's, the effort to harmonize the definition of preclinical AD in order be able to share information among centres appears even more needed.

In conclusion, even if total standardization of different markers of cognition and AD signature cannot be achieved, the community should agree on the use of some general tools in order to provide robust knowledge on the preclinical AD concept. For instance DSST, CDR, FCSRT for the neurocognitive evaluation, CSF biomarker evaluation adapted to reference analytical procedures such as the Gothenburg measurements [52] and amyloid PET SUVR standardization for instance to a centiloid scale [51]. Also, an operationalized description in these studies of the various subtle cognitive changes occurring in preclinical AD (as proposed in table 5) could lead to a better understanding of the path to decline to be used as markers in clinical trials. As the first important step has been taken when the scientific community agreed on the general principles to define preclinical AD [1], the AD community must take the next step toward a unified procedure to diagnose this disease stage.

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## Figures & Tables

Figure 1: PRISMA (2009) flow diagram of article selection.

Figure 2: Number of studies categorized by the cohort from which they are derived

Figure 3: Presentation of the different cognitive tests used in the thirteen cohorts

Figure 4: Schematic representation of Alzheimer’s disease (AD) clinical spectrum compared to that of Fronto-temporal dementia and Lewy body dementia. The three horizontal lines indicate a change in state from totally asymptomatic preclinical state (lowest quadrant) to preclinical state with subtle cognitive changes to prodromal to dementia (upper quadrant). The initial “preclinical” phase of the disease is represented as a unique triangle encompassing all of the diseases to reflect the difficulty to clinically distinguish one entity from the next at this stage. The five smaller triangles each correspond to one affection. The “…” indicate that the model can be extended with other neurocognitive affections. In the prodromal phase they are well separated as clinical symptoms are often specific of one disease. At the dementia stage, the overlap between these triangles indicate the association of diverse symptoms obfuscating distinct diagnosis. AD physiopathological biomarker status (displayed by the continuity of the yellow dotted line and the yellow triangle) is considered positive from the totally asymptomatic preclinical state to the dementia stage.

Table 1: Description of studies populations

Table 2: **S**tudies methodology

Table 3: Cohorts collecting cognitive and AD pathophysiological markers data in asymptomatic individuals allowing the study of the preclinical AD concept

Table 4: Clinical trials in preclinical AD patients

Table 5: Proposed guidelines and nomenclature to operationalize Preclinical AD stages.

Supplemental Table 1: Detailed Description of studies populations

Supplemental Table 2: Detailed **S**tudies methodology

Supplemental Table 3: Cognitive batteries performed in the different cohorts

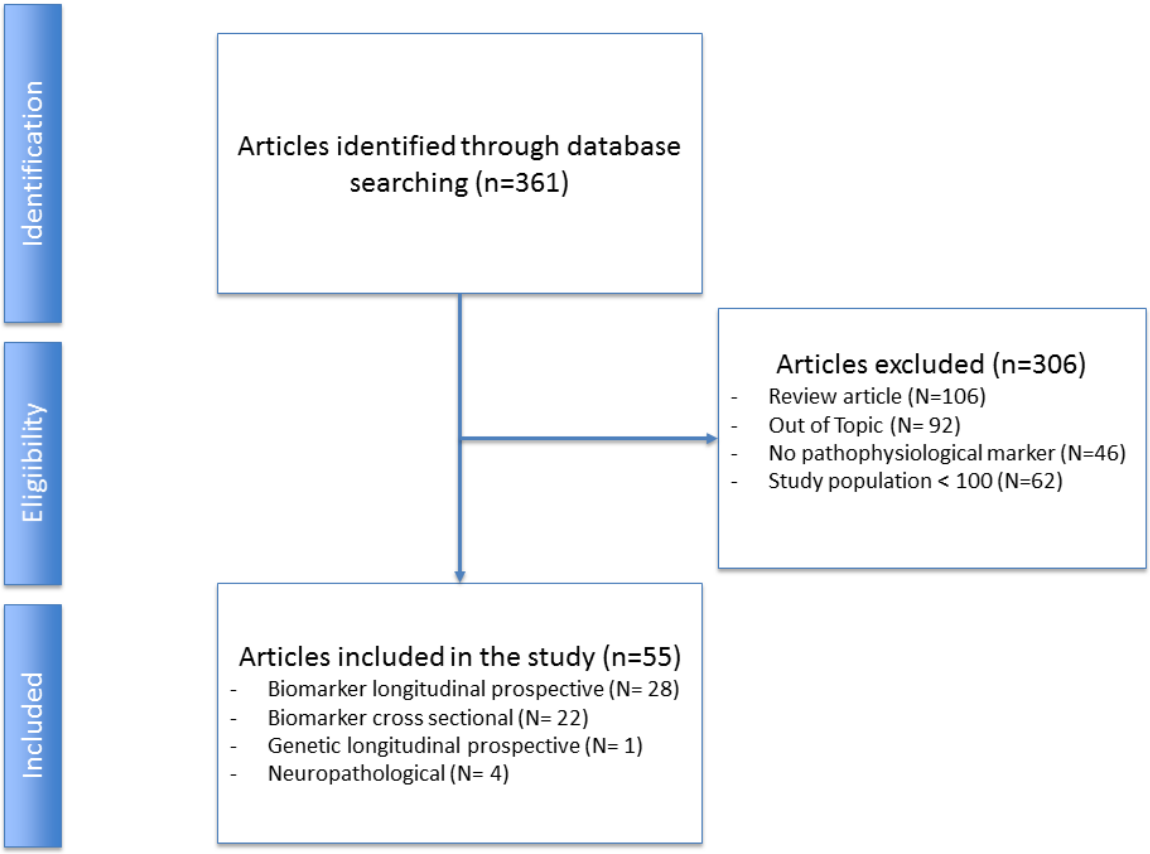


**Figure 1**

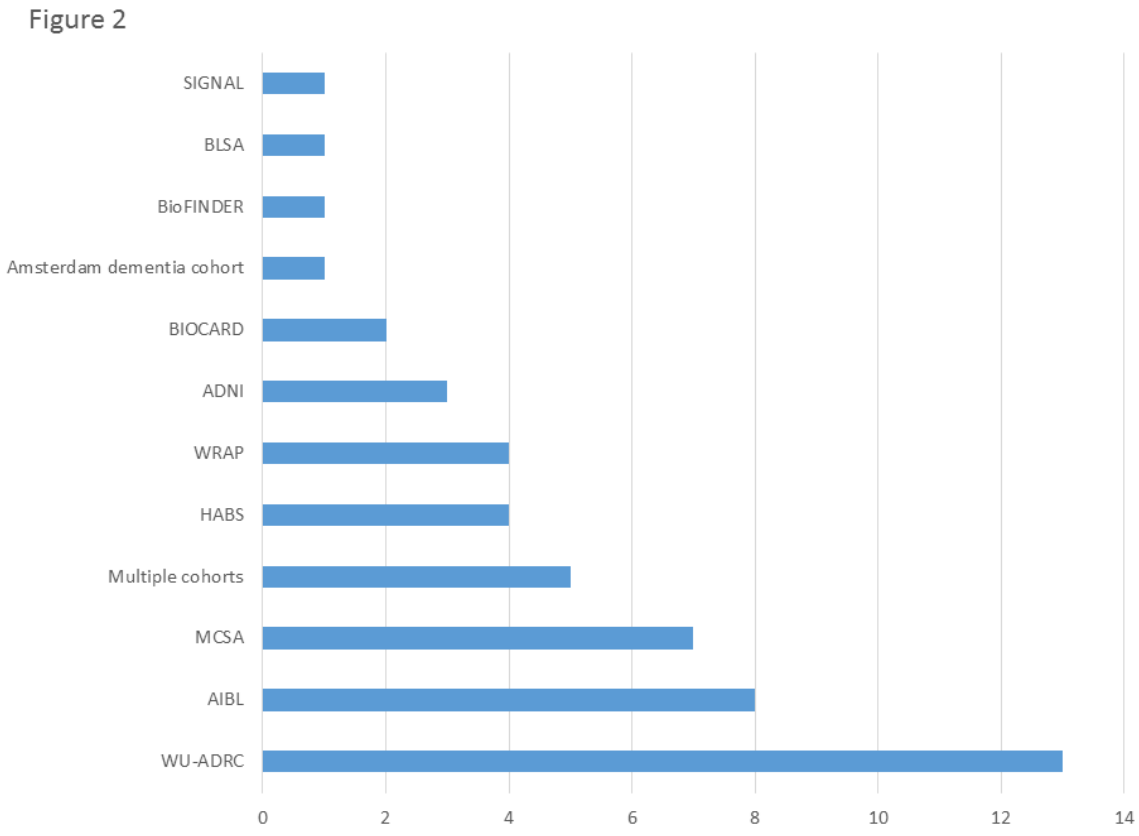
Figure 2
SIGNAL
BLSA
BioFINDER
Amsterdam dementia cohort
BIOCARD
ADNI
WRAP
HABS
Multiple cohorts
MCSA
AIBL
WU-ADRC
0
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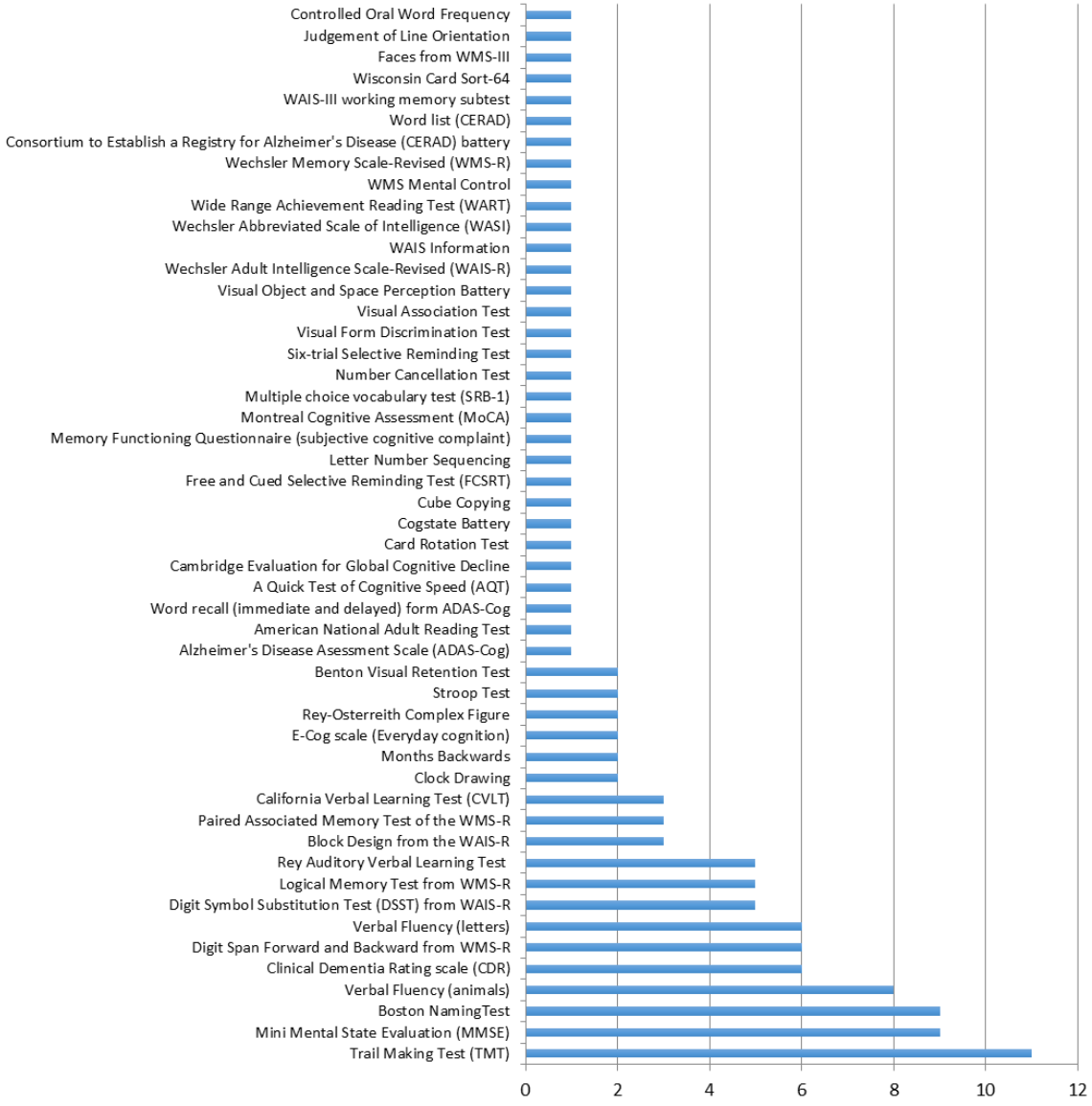
10
12
14

**Figure 2**


Controlled Oral Word Frequency
Judgement of Line Orientation
Faces from WMS-III
Wisconsin Card Sort-64
WAIS-III working memory subtest
Word list (CERAD)
Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery
Wechsler Memory Scale-Revised (WMS-R)
WMS Mental Control
Wide Range Achievement Reading Test (WART)
Wechsler Abbreviated Scale of Intelligence (WASI)
WAIS Information
Wechsler Adult Intelligence Scale-Revised (WAIS-R)
Visual Object and Space Perception Battery
Visual Association Test
Visual Form Discrimination Test
Six-trial Selective Reminding Test
Number Cancellation Test
Multiple choice vocabulary test (SRB-1)
Montreal Cognitive Assessment (MoCA)
Memory Functioning Questionnaire (subjective cognitive complaint)
Letter Number Sequencing
Free and Cued Selective Reminding Test (FCSRT)
Cube Copying
Cogstate Battery
Card Rotation Test
Cambridge Evaluation for Global Cognitive Decline
A Quick Test of Cognitive Speed (AQT)
Word recall (immediate and delayed) form ADAS-Cog
American National Adult Reading Test
Alzheimer's Disease Assessment Scale (ADAS-Cog)
Benton Visual Retention Test
Stroop Test
Rey-Osterreith Complex Figure
E-Cog scale (Everyday cognition)
Months Backwards
Clock Drawing
California Verbal Learning Test (CVLT)
Paired Associated Memory Test of the WMS-R
Block Design from the WAIS-R
Rey Auditory Verbal Learning Test
Logical Memory Test from WMS-R
Digit Symbol Substitution Test (DSST) from WAIS-R
Verbal Fluency (letters)
Digit Span Forward and Backward from WMS-R
Clinical Dementia Rating scale (CDR)
Verbal Fluency (animals)
Boston NamingTest
Mini Mental State Evaluation (MMSE)
Trail Making Test (TMT)
0
2
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6
8
10
12

**Figure 3**

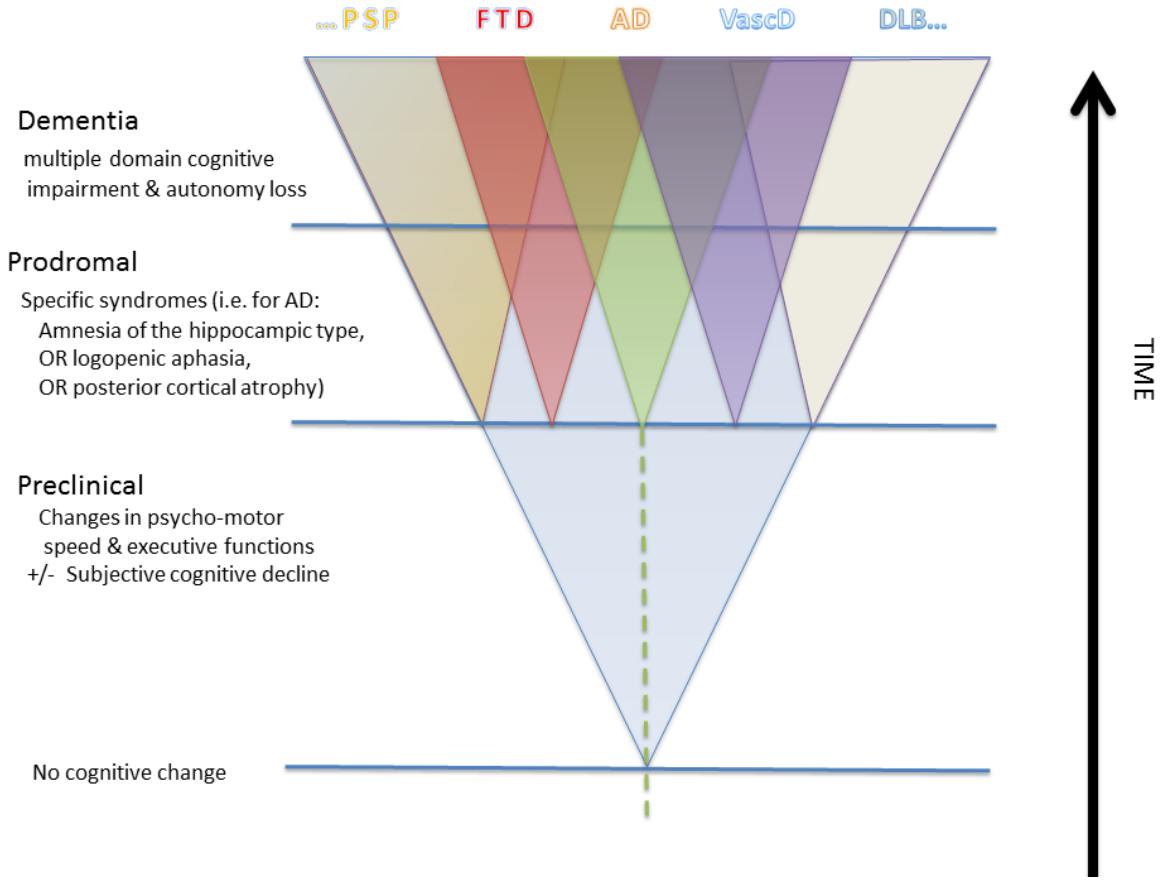
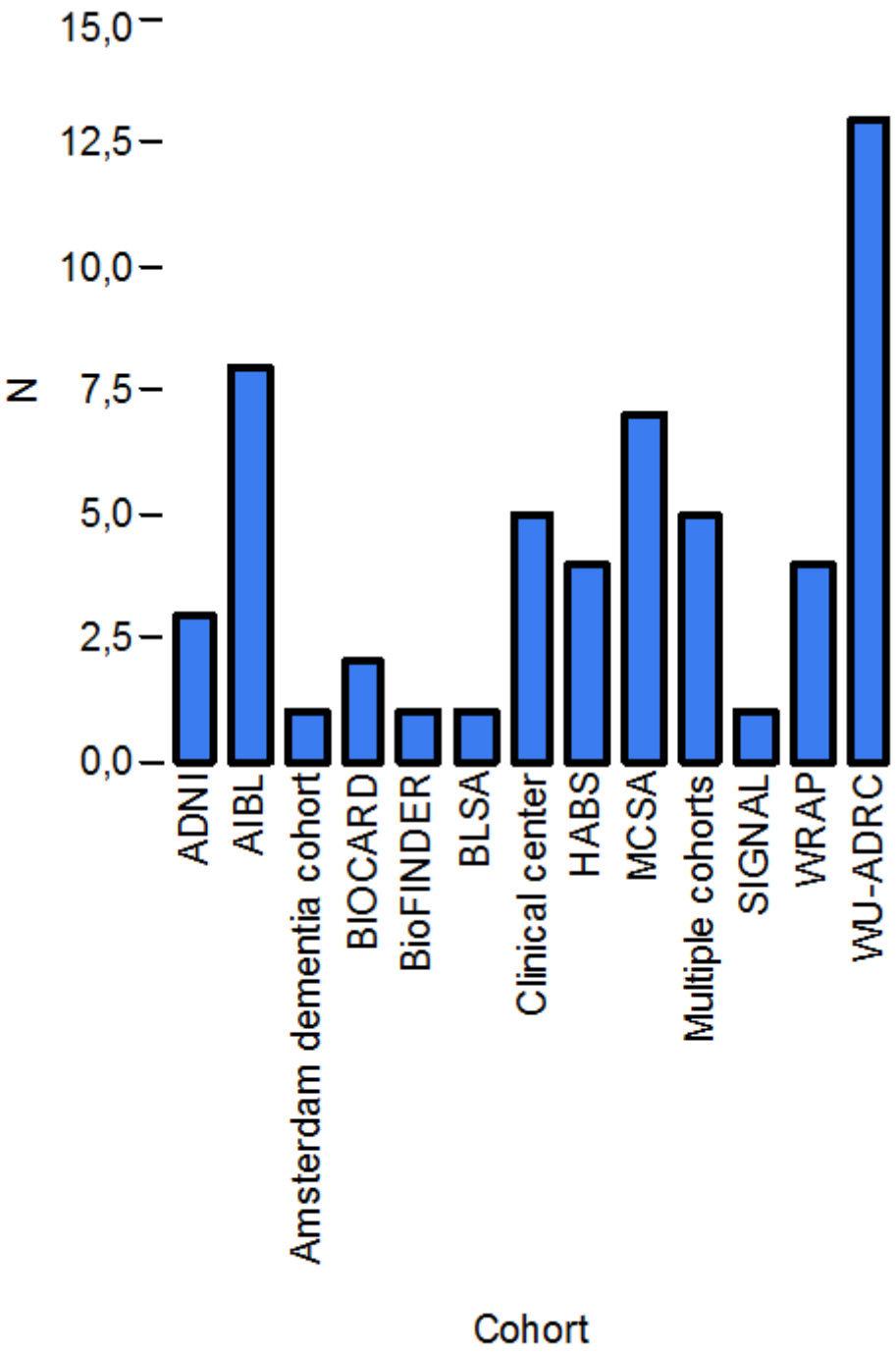

...PSP
FTD
AD
VascD
DLB...
Dementia
multiple domain cognitive impairment & autonomy loss
Prodromal
Specific syndromes (i.e. for AD:
Amnesia of the hippocampic type,
OR logopenic aphasia,
OR posterior cortical atrophy)
Preclinical
Changes in psycho-motor speed & executive functions
+/- Subjective cognitive decline
No cognitive change
TIME

**Figure 4**




**Suppl Figure 1**

TABLE 1 STUDIES POPULATIONS

| *N (%) or Mean (SEM)* | *Cross Sectional studies N=22* | *Longitudinal Studies N=29* | *Neuropathological studies N=4* |
|---|---|---|---|
| *Years of Publication ≥2014* | 13 (59) | 21 (72) | 0 (0) |
| *Study population total size* | 331.5 (48.2) | 261.1 (42) | 866 (550)** |
| *Age* | 71.4 (1,6) | 68.1(1,3) | 78.6 (3.3) |
| *HC* | 158.4 (22.2) | 164.3 (20.2) | 184 (110.3) |
| *HC percentage of total population* | 55.8 (3.6) | 65.2 (3.2) | 58 (8.2) |
| *PC AD* | 83.6 (12.3) | 65.4 (11.2) | 111.3 (68.6) |
| *PC AD percentage of total population* | 27.3 (1.5) | 26.4 (1.4) | 33.7 (5) |
| *NIA-AA PC AD Criteria [1] or [2]* | 8 (36.4) | 7 (24.1) | 1 (25) |
| *N of studies using the conceptual framework (%)* | | | |
| *Stage I** | 54 (5.2) | 53 (5.6) | 24 |
| *Stage II** | 41.4 (6.3) | 43.6 (6.3) | 28 |
| *SNAP percentage of total population* | 20.4 (1.7) | 21.5 (1.6) | 10 |
| *APOE4 percentage of Total population* | 31 (2) | 34.8 (1.5) | 29 (1) |
| *APOE4 percentage of PC AD* | 50.7 (3.7) | 44.1 (3.3) | 32.1 (0.9) |

*% of PC AD. Stage III was only rarely applied (i.e. in 5 of 8 cross sectional studies and 4 of 7 longitudinal studies using this terminology) and so was not included in the table. ** One large study did not give any detail on the number of preclinical AD which accounts for the discrepancy between the Study population total size and the rest of the table figures for the Neuropathology column. PC AD = Preclinical Alzheimer's disease, HC: Healthy control.

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**TABLE 2. STUDIES METHODOLOGY**

| *N (%)* | *Cross Sectional (CS) Studies N = 22* | *Longitudinal (L) Studies N = 29* | *Neuropathology (N) Studies N=4* |
|---|---|---|---|
| ***Criteria for Normal Cognition*** | Available in N= 20 (90.9% of CS studies) | Available in N= 27 (93.1% of L studies) | Available in N= 3 (75% of N studies) |
| *CDR* | 4 (20) | 8 (29.6) | 1 (33.3) |
| *CDR+* | 4 (30) | 4 (14.8) | 0 |
| *Cognitive battery* | 8 (40) | 4 (14.8) | 1 (33.3) |
| *MMSE* | 2 (10) | 10 (37.1) | 1 (33.3) |
| *Clinical Consensus* | 0 | 1 (3.7) | 0 |
| ***Criteria for Cognitive Decline*** | Not applicable | Available in N= 27 (93.1% of L studies) | Available in N= 1 (25% of N studies) |
| *CDR* | - | 6 (22.3) | 1 (100) |
| *CDR+* | - | 1 (3.7) | 0 |
| *Cognitive battery* | - | 3 (11.1) | 0 |
| *Composite scores* | - | 12 (44.4) | 0 |
| *Clinical consensus* | - | 5 (18.5) | 0 |
| ***Criteria for AD pathophysiological signature*** | | | |
| *CSF biomarkers* | 9 (40.9) | 7 (24.2) | 0 |
| *Amyloid PET* | 11 (50) | 17 (58.6) | 0 |
| *Both* | 2 (9.1) | 4 (13.8) | 0 |
| *Mutation* | 0 | 1 (3.4) | 0 |
| *Neuropathology* | 0 | 0 | 4 (100) |

CDR: Clinical dementia rating scale, CDR+: association of a Clinical dementia rating scale and at least one other neuropsychological test, Cognitive battery: association of at least two cognitive test, Clinical consensus: Adjudication by an expert committee of clinicians into one of three categories (normal cognition, mild cognitive impairment or dementia), CSF biomarkers: use of either cerebrospinal fluid $A\beta_{1-42}$, tau, phosphorylated tau concentrations or a combination of these markers. Amyloid PET : use of either PIB, florbetapir or flutemetamol. Mutation : evidence of the presenilin 1 (PSEN1) E280A mutation. Neuropathology: Neuropathological evidence of Alzheimer's disease.

Table 3.

| Cohort | N | Type | Design | Country/state | Ethnicity/minorities | Population (M/F; | Age (Mean +/- SD or Range) | Cognitive Integrity Criteria | Npsy Battery | CSF | MRI sequences | 18FDG-PET | Amyloid PET | Blood | Other Biomarkers | Cohort Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ADNI 1-GO-2** | 145 | R | Multi | USA | Caucasians 93% | M/F=58/42 | 55-90 | MMSE > 24, CDR=0, No-depressed, MCI nor demented | Yes | Subsample | Yes | Subsample | Subsample | Yes | NA | Weiner et al. 2010 |
| **AMSTERDAM Dementia Cohort** | 132 | C | Mono | NL | Not mentioned | M/F = 56/44 | 64 +/- 10 | No CI based on a NRPSY Battery | Yes | Subsample | Subsample | Subsample | Subsample | Subsample | EEG Subsample | van der Flier et al. 2014 |
| **AIBL study (Australian Imaging, Biomarkers and Lifestyle study)** | 423 | R | Multi | Australia | Not mentioned | M/F=42/58 | 70 +/- 7 | No CI based on a NRPSY Battery | Yes | Subsample | Yes | Yes | Yes | Yes | EEG Subsample | Ellis 2009 |
| **BIOCARD (**Prospective Study of Biomarkers for Older Contrls at Risk for Alzheimer's Disease) | 302 | R | Mono | USA, MD | Not mentioned | M/F: 41/59 | Middle-age | Mattis Dementia Rating Scale, Buschke Selective Reminding Test (Buschke, 1973), and Wechsler Memory Scale—Revised (WMS–R; Wechsler, 1987) performance within the | Yes | Yes | Yes | No | Subsample | Yes | postmortem neuropathologic evaluations in a subsamle | Greenwood et al. 2005 |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | normal age-related range of scores | | | | | | | | |
| **BioFINDER** (Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably cognitively healthy cohort) | 352 | R | Multi | Sweden | Not mentionned | M/F: 46/54 | >60 | MMSE 28-30 at screening visit | Yes | Yes | Yes | No | Yes | Yes | Tau PET | http://biofinder.se/biofinder_cohorts/cognitively-healthy-elderly/ |
| **BLSA (Baltimore longitudinal study of Aging)** | 104 | R | Mono | USA, MD. | 73.6% Caucasians | M/F: 50.5/49.5 | Mean 77.3 years | No MCI or dementia by clinical evaluation (i.e. No substantial CI based on mental status screening tests) | Yes | No | Yes | No | Yes | Yes | No | https://www.blsa.nih.gov/ |
| **HABS (Harvard Aging Brain Study)** | 275 | R | Mono | USA, MA | 81% Caucasians | M/F: 41/59 | 62–90 | GDS<11, CDR=0, MMSE >25 and Normal Performances at Logical Memory delayed recall | Yes | Subsample | Yes | Yes | Yes | Yes | NA | Dagley A 2015 |
| **MCSA (Mayo Clinic Study of Aging** | 1331 | R | Mono | USA, MN | 98,6% Caucasians | M/F: 46/54 | 70–90 years | CDR =0 ; Normal functional status ; | Yes | No | No | No | No | Yes | No | Roberts et al., 2008 and 2012 |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **)** | | | | | | | | NRPSY testing within normal limits | | | | | | | | |
| **NACC (National Alzheimer's Coordinating Center database)** | - | R | Mono | USA | 80% Caucasians | M/F: 43/57 | <40->90 years | No CI based on a NRPSY Battery description reported [Weintraub 2009] | Yes | No | Subsample | No | No | Subsample | postmortem neuropathologic evaluations in a subsamle | https://www.alz.washington.edu |
| **Nun Study** | 678 | C | Mono | USA, MN | Ethnicity not mentioned. Specificity of the cohort population: Nuns | M/F: 0/100 | Mean 85 years | NRPSY battery (Delayed Word Recall, Word Recognition; Word List Memory; Verbal Fluency; Construction al Praxis; Boston Naming; MMSE) | Yes | No | No | No | No | Yes | postmortem neuropathologic evaluations | Snowdon et al. 1996 |
| **SIGNAL** | 266 | R | Multi | Spain | Not mentioned | - | 50-75 | MMSE score ≥24 and normal memory performance on FCSRT Significant impairment in other cognitive domains excluded through a formal cognitive evaluation. | Yes | Yes | Yes | No | Optional | Yes | None | Alcolea et al 2015 |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WU-ADRC (Washington University's Alzheimer's Disease Research Center study)** | 340 | R | Mono | USA, MS. | 92% Caucasians | M/F: 45/55 | ≥65 | CDR=0 | Yes | Yes | No | No | No | Yes | No | Vos SJ et al., 2013 |
| **WRAP (Wisconsin Registry for Alzheimer's Prevention)** | 184 | R | Mono | USA, WI. | 98% Caucasians | M/F: 29/71 | 40-65 years | NRPSY battery (Sager 2005) | Yes | No | No | No | No | Yes | No | La Rue A et al., 2008 ; Sager MA 2005 |

R= Research; C=Clinical; Mono= Monocentric; Multi= Multicentric; CI= Cognitive Impairment; GDS=Geriatric Depression Scale; CDR=Clinical Dementia Rating Scale; FCSRT: Free and Cued Selective Reminding Test; NRPSY=Neuropsychological; MMSE Mini Mental State Examination. NA=Not Applicable

For some monocentric studies the name of center is reported as some cohorts may be pooled in the publication.

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2 - van der Flier WM, Pijnenburg YA, Prins N, Lemstra AW, Bouwman FH, Teunissen CE, van Berckel BN, Stam CJ, Barkhof F, Visser PJ, van Egmond E, Scheltens P. Optimizing patient care and research: the Amsterdam Dementia Cohort. J Alzheimers Dis. 2014;41(1):313-27.

3 - Ellis KA, Bush AI, Darby D, De Fazio D, Foster J, Hudson P, Lautenschlager NT, Lenzo N, Martins RN, Maruff P, Masters C, Milner A, Pike K, Rowe C, Savage G, Szoeke C, Taddei K, Villemagne V, Woodward M, Ames D; AIBL Research Group. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. Int Psychogeriatr. 2009 Aug;21(4):672-87.

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.
5 - Palmqvist S, Zetterberg H, Blennow K(2), Vestberg S, Andreasson U, Brooks DJ, Owenius R, Hägerström D, Wollmer P, Minthon L, Hansson O.Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid β-amyloid 42: a cross-validation study against amyloid positron emission tomography. JAMA Neurol. 2014 Oct;71(10):1282-9. doi: 10.1001/jamaneurol.2014.1358.

6 - The Baltimore Longitudinal Study on Aging (BLSA): https://clinicaltrials.gov/ct2/show/NCT00233272

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9 - National Alzheimer's Coordinating Center (NACC) https://www.alz.washington.edu/cgibin/broker93?_service=naccnew9&_program=naccwww.pubrep1.sas&TYPEF=DISPLAYIDS

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11- SIGNAL: http://signalstudy.es/en/objectives.html

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Jul 15.

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| Reference | Cohort(s) used for the study [or center for unnamed monocentric studies)] | N Total | Age | N HC N (% total population) | N PC N (% total population) | stage 1 N (% of PC) | stage 2 N (% of PC) | stage 3 N (% of PC) | N AD N (% of total population) | N SNAP or PART N (% of total population) | N MCI N (% of total population) | N other N (% of total population) | ApoE 4+ in total population N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CROSS-SECTIONAL STUDIES** | | | | | | | | | | | | | |
| (Morris, Roe et al. 2010) | WU-ADRC | 241 | 66,8 | - | 44 (18) | - | - | - | - | - | - | - | 82 (34) |
| (Pike, Ellis et al. 2011) | AIBL | 177 | 70 | 119 (67) | 58 (33) | - | - | - | - | - | - | - | - |
| (Mielke, Wiste et al. 2012) | MCSA | 483 | - | 332 (69) | 151 (31) | - | - | - | - | - | - | - | 121 (25) |
| (Amariglio, Becker et al. 2012) | HABS | 131 | 73,5 | 97 (74) | 34 (26) | - | - | - | - | - | - | - | - |
| (Jack, Knopman et al. 2012) | MCSA | 450 | 78 | 193 (43) | 139 (31) | 70 (50) | 56 (40) | 13 (9) | 42 (9) | 103 (23) | - | 15 (3) | 117 (26) |
| (Harrington, Chiang et al. 2013) | [Pasadena (Cal)] | 149 | 78 | 36 (24) | 34 (23) | - | - | - | 29 (19) | - | 40 (27) | 10 (7) | - |
| (Whitwell, Tosakulwong et al. 2013) | Mayo Clinic ADRC cohort or MCSA | 318 | 80 | 115 (36) | 115 (36) | - | - | - | - | - | 88 (28) | - | - |
| (Ju, McLeland et al. 2013) | WU-ADRC | 142 | 65,6 | 110 (77) | 32 (23) | - | - | - | - | - | - | - | 52 (36.6) |
| (Knopman, Jack et al. 2013) | MCSA | 430 | 78 | 191 (44) | 137 (32) | 68 (50) | 56 (41) | 13 (9) | - | 102 (24) | - | - | 107 (25) |
| (Brier, Thomas et al. 2014) | WU-ADRC | 297 | 68 | 200 (67) | 97 (33) | - | - | - | - | - | - | - | - |
| (Brier, Thomas et al. 2014) | WU-ADRC | 326 | 69 | 132 (40) | 59 (18) | 46 (78) | 13 (22) | - | 31 (9) | - | 90 (28) | 14 (4) | - |
| (Jack, Wiste et al. 2014) | MCSA | 985 | 74 | 503 (51) | 352 (36) | 213 (60) | 130 (40) | - | - | 139 (14) | - | - | 256 (26) |
| (Racine, Adluru et al. 2014) | WRAP | 139 | 60,6 | 112 (81) | 27 (19) | - | - | - | - | - | - | - | - |
| (Fortea, Vilaplana et al. 2014) | ADNI | 145 | 73,4 | 74 (51) | 39 (27) | 8 (21) | 31 (79) | - | - | 32 (22) | - | - | - |
| (Wang, Benzinger et al. 2015) | WU-ADRC | 188 | 73 | - | - | - | - | - | - | - | - | - | - |
| (Doherty, Schultz et al. 2015) | WRAP | 109 | 60,7 | 74 (68) | 35 (32) | - | - | - | - | - | - | - | 45 (41) |
| (Valech, Mollica et al. 2015) | [Barcelona] | 111 | | 59 (53) | 19 (24) | - | - | - | 10 (9) | - | 23 (21) | - | - |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Jack, Wiste et al. 2015) | MCSA | 1331 | 71 | - | - | - | - | - | - | - | - | - | 27 |
| (Alcolea, Martinez-Lage et al. 2015) | SIGNAL | 266 | 58.8 | 203 (76.3) | 36 (13.5) | 26 (72) | <10 (28) | <10 (28) | 0 | 27 (10.1) | 0 | 0 | 67 (25) |
| (Papp, Amariglio et al. 2015) | HABS | 260 | 73 | 126 (48) | 70 (27) | 32 (46) | 38 (54) | - | - | 64 (25) | - | - | - |
| (Hassenstab, Chasse et al. 2016) | WU-ADRC | 264 | 72 | 177 (67) | 87 (33) | - | - | - | - | - | - | - | 83 (31) |
| (Voevodskaya, Sundgren et al. 2016) | BioFINDER | 352 | 72 | 156 (44) | 108 (31) | 59 (55) | - | 49 (45) | - | - | 88 (25) | - | 142 (40) |

**LONGITUDINAL STUDIES**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Morris, Roe et al. 2009) | WU-ADRC | 159 | 71,5 | - | - | - | - | - | - | - | - | - | - |
| (Craig-Schapiro, Perrin et al. 2010) | WU-ADRC | 340 | 71 | - | - | - | - | - | - | - | - | - | - |
| (Desikan, McEvoy et al. 2012) | ADNI | 115 | 76 | 46 (40) | 41 (36) | 20 (49) | 21 (51) | - | - | 19 (17) | - | - | 27 (23.3) |
| (Knopman, Jack et al. 2012) | MCSA | 286 | 79 | 127 (44) | 90 (31) | 41 (46) | 39 (43) | 7 (8) | - | 69 (24) | - | - | 74 (26) |
| (van Harten, Smits et al. 2013) | Amsterdam dementia cohort | 132 | 61 | 80 (60) | 21 (16) | 11 (52) | 10 (48) | - | - | 31 (23) | - | - | 54 (41) |
| (Vos, Xiong et al. 2013) | WU-ADRC | 311 | 72.9 | 129 (41) | 96 (31) | 47 (49) | 36 (38) | 13 (14) | 0 (0) | 72 (23) | - | 14 (5) | 106 (34) |
| (Stark, Roe et al. 2013) | WU-ADRC | 119 | 74.4 | 101 (85) | 18 (15) | - | - | - | - | - | - | - | - |
| (Lim, Villemagne et al. 2013) | AIBL | 165 | 71,4 | 116 (70) | 49 (30) | - | - | - | - | - | - | - | 70 (42,4) |
| (Lim, Maruff et al. 2014) | AIBL | 333 | 70 | 249 (75) | 84 (25) | - | - | - | - | - | - | - | 109 (32,7) |
| (Mormino, Betensky et al. 2014) | HABS | 166 | 74 | 81 (49) | 47 (28) | 19 (40) | 28 (60) | - | - | 38 (23) | - | - | 50 (30) |
| (Donohue, Sperling et al. 2014) | ADNI/AIBL | 97/164 | 75,81/71,37 | 60/114(62/70) | 37/50 (38/30) | - | - | - | - | - | - | - | 24/70 (25/43) |
| (Ayutyanont, Langbaum et al. 2014) | E280A Antioquia cohort | 134 | 44 | 78 (58) | 56 (42) | - | - | - | - | - | - | - | - |
| (Mormino, Betensky et al. 2014) | HABS/ADNI/AIBL | 490 | 75 | 355 (72) | 135 (28) | - | - | - | - | - | - | - | 225 (46) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Pietrzak, Lim et al. 2015) | AIBL | 333 | 70 | 249 (75) | 84 (25) | - | - | - | - | - | - | - | 109 (32,7) |
| (Pietrzak, Lim et al. 2015) | AIBL | 333 | 70 | 249 (75) | 84 (25) | - | - | - | - | - | - | - | 109 (32,7) |
| (Nation, Edmonds et al. 2015) | ADNI | 877 | 72,6 | - | - | - | - | - | - | 167 (19) | 602 (69) | - | 360 (41) |
| (Thai, Lim et al. 2015) | AIBL | 317 | 69.9 | - | 76 (24) | - | - | - | - | - | - | - | 104 (33) |
| (Pettigrew, Soldan et al. 2015) | BIOCARD | 302 | 56.6 | 240 (79) | 62 (21) | - | - | - | - | - | - | - | 94 (32) |
| (Sutphen, Jasielec et al. 2015) | WU-ADRC | 169 | 60.7 | 118 (70) | 51 (30) | - | - | - | - | - | - | - | 61(36) |
| (Papp, Mormino et al. 2016) | HABS | 275 | | 205 (75) | 70 (25) | - | - | - | - | - | - | - | - |
| (Soldan, Pettigrew et al. 2016) | BIOCARD | 222 | 56.9 | 102 (46) | 74 (33) | 46 (62) | 28 (38) | - | - | 46 (21) | - | - | 73 (33) |
| (Racine, Koscik et al. 2016) | WRAP and Wisconsin ADRC | 175 | 59 | 76 (43) | 54 (31) | - | - | - | - | 45 (26) | - | - | 79 (45) |
| (Pascoal, Mathotaarachchi et al. 2016) | ADNI | 120 | 74.9 | - | - | - | - | - | - | - | - | - | - |
| (Vos, Gordon et al. 2016)i | WU-ADRC | 212 | 66.1 | imaging: 127 (60), CSF:114 (54) | imaging: 45 (21), CSF:58 (27) | imaging: 26, CSF:42 | imaging: 19, CSF: 16 | - | - | 40 (19) | - | - | 70 (33) |
| (Bilgel, Prince et al. 2016) | BLSA | 104 | 77 | - | - | - | - | - | - | - | - | - | - |
| (Brier, McCarthy et al. 2016) | WU-ADRC | 157 | 61.6 | 131 (83) | 26 (17) | - | - | - | - | - | - | - | 49 (31.2) |
| (Clark, Racine et al. 2016) | WRAP | 184 | 58.6 | 156 (84.8) | 28 (15.2) | - | - | - | - | - | - | - | 73 (40) |
| (Harrington, Gould et al. 2016) | AIBL | 359 | 69.7 | 278 (77) | 81 (22.6) | - | - | - | - | - | - | - | - |
| (Lim, Snyder et al. 2016) | AIBL | 423 | 69,4 | 326 (77) | 97 (23) | - | - | - | - | - | - | - | 115 (27) |
| **NEUROPATHOLOGICAL STUDIES** | | | | | | | | | | | | | |
| (Jicha, Abner et al. 2012) | UK-ADC (Kentucky) | 126 | 85,1 | 59 (47) | 54 (43) | 13 (24) | 15 (28) | 26 (48) | 14 (11) | 13 (10) | 24 (19) | - | 38 (30) |
| (Abner, Kryscio et al. 2011) | NACC and Nun Study | 2451 | - | - | - | - | - | - | - | - | - | - | - |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Riley, Jicha et al. 2011) | UK-ADC (Kentucky) | 121 | 76 ,1 | 89 (74) | 32 (26) | - | - | - | - | - | - | - | 34 (28,1) |
| (Thal, von Arnim et al. 2013) | Multicentric autopsy study. | 766 | 74 ,7 | 404 (53) | 248 (32) | - | - | - | 114 (15) | - | - | - | - |

TABLE 1. DESCRIPTION OF STUDIES POPULATIONS

ADNI : Alzheimer's Disease Neuroimaging Initiative ; AIBL: Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing; BIOCARD: Biomarkers of Cognitive Decline Among Normal Individuals; HABS: Harvard Aging Brain Study ; MCSA: Mayo Clinic Study of Aging Mayo Clinic ADRC: Mayo Clinic Alzheimer Disease Research Center; NACC : National Alzheimer's Coordinating Center database; SIGNAL study: Spanish project on biomarkers in the preclinical phase of Alzheimer Disease (AD). UK-ADC: University of Kentucky, Alzheimer Disease Center ; BioFINDER: Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably (Sweden); VA SanDiego : Veteran Administration San Diego, CAL ; WU-ADRC : Charles and Joanne Knight Alzheimer's Disease Research Center at Washington University in Saint Louis ; WRAP : Wisconsin Registry for Alzheimer's Prevention. Multicentric autopsy study: All autopsy brains collected from individuals who died in university or municipal Hospitals in Germany (Bonn, Frankfurt/Main, Mainz, Offenbach/Main, Ulm), USA (Little Rock, AR), the United Kingdom (Newcastle upon Tyne), or Austria (Vienna)

HC : Healthy Controls
PC: Preclinical
AD : Alzheimer Disease
MCI : Mild Cognitive Impairment
SNAP : Suspected Non-Amyloid Pathology
PART : Primary Age Related Taupathy
Stage 1-3: according to NIA-AA proposed classification of preclinical AD

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**TABLE 2. STUDIES METHODOLOGY**

| Author and year of publication | Follow-up duration (months) | normal cognition | Cognitive decline/outcome | AD pathophysiological signature | Definition of biomarker |
|---|---|---|---|---|---|
| **CROSS-SECTIONAL STUDIES** | | | | | |
| (Morris, Roe et al. 2010) | - | CDR | - | PET-PIB and CSF | PET-Aß DEFINITION 1: PIB MCBP ≥ 0.18<br><br>CSF DEFINITION 1<br>CSF Aβ42 levels below 500 pg/mL,, tau levels above 500 pg/mL, and Ptau181 levels above 80 pg/mL<br>CSF biomarkers assay Innotest ELISA |
| (Pike, Ellis et al. 2011) | - | Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 2<br>PIB SUVR ≥ 1.5 |
| (Mielke, Wiste et al. 2012) | - | Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 3<br>PIB SUVR > 1.4 and 1.5 |
| (Amariglio, Becker et al. 2012) | - | CDR, MMSE, GDS | - | PET-PIB | PET-Aß DEFINITION 4<br>PIB DVR ≥ 1.25 |
| (Jack, Knopman et al. 2012) | - | Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 2<br>PIB SUVR ≥ 1.5 |
| (Harrington, Chiang et al. 2013) | - | CDR and cognitive battery | - | CSF Aß-42 | CSF DEFINITION 2<br>Aß42/Tau ratio cutoff calculated as 2.7132<br>CSF biomarkers assay Innotest ELISA |
| (Whitwell, Tosakulwong et al. 2013) | - | CDR and Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 2<br>PIB SUVR ≥ 1.5 |
| (Ju, McLeland et al. 2013) | - | CDR | - | CSF Aß-42 | CSF DEFINITION 3<br>A beta 42<500 nmol/mL<br>CSF biomarkers assay Innotest ELISA |
| (Knopman, Jack et al. 2013) | - | CDR and Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 2<br>PiB SUVR ≥ 1.5 |
| (Brier, Thomas et al. 2014) | - | NA | - | CSF Aß or Tau | CSF DEFINITION 4<br>Aβ42 < 500 pg/mL<br>tau > 440 pg/mL<br>NIA AA preclinical AD staging<br>CSF biomarkers assay Innotest ELISA |
| (Brier, Thomas et al. 2014) | - | NA | - | CSF Aß or Tau | CSF DEFINITION 4<br>Aβ42 < 500 pg/mL<br>tau > 440 pg/mL<br>NIA AA preclinical AD staging<br>CSF biomarkers assay Innotest |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | ELISA |
| (Jack, Wiste et al. 2014) | - | Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 5<br>PiB SUVR ≥ 1.4 |
| (Racine, Adluru et al. 2014) | - | Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 6<br>Visual assessment with classification as amyloid negative, positive or indeterminate |
| (Fortea, Vilaplana et al. 2014) | - | MMSE | - | CSF Aß or P-Tau | CSF DEFINITION 5<br>p-tau181p levels >23 pg/ml ; Aβ1-42 levels<192 pg/ml<br>CSF biomarkers assay Luminex |
| (Wang, Benzinger et al. 2015) | - | CDR | - | CSF Aß and Tau | CSF DEFINITION 6<br>CSF Aß42 ≤ 500 pg/mL and CSF tau ≥500 pg/mL, respectively, and negative if CSF Aß42 >500 pg/mL and CSF tau <500 ng/mL<br>CSF biomarkers assay Innotest ELISA |
| (Doherty, Schultz et al. 2015) | - | Cognitive battery | - | PET-PIB | PET-Aß DEFINITION 7<br>Qualitative visual assessment |
| (Valech, Mollica et al. 2015) | - | CDR and MMSE | - | CSF Aβ42 | CSF DEFINITION 7<br>CSF Aβ42≤ 550 pg/ml |
| (Jack, Wiste et al. 2015) | - | Multiple tests | - | PET-PIB | PET-Aß DEFINITION 5<br>SUVR > 1.4 |
| (Alcolea, Martinez-Lage et al. 2015) | - | MMSE, FCSRT and cognitive battery | - | CSF | CSF DEFINITION 8<br>stage 0 (Aß42 ≥ 550 pg/mL, t-tau ≤ 350 pg/mL, and p-tau ≤ 61 pg/mL), stage 1 (Aß42 ≥ 550 pg/mL, t-tau ≤350 pg/mL, and p-tau ≤ 61 pg/mL), stage 2 (Aß42 ≤ 550 pg/mL and either t-tau ≥ 350 pg/mL or p-tau ≥ 61 pg/mL), or stage 3 (stage 2<br>plus subtle cognitive decline, defined as an episodic memory composite<br>score in the lowest 10th percentile).<br>CSF biomarkers assay Innotest ELISA |
| (Papp, Amariglio et al. 2015) | - | CDR, MMSE, GDS, Delayed logical memory recall | - | PET-PIB | PET-Aß DEFINITION 8<br>PIB data were analyzed as standard uptake value ratios (SUVR), and a Gaussian mixture modeling approach was used to classify HABS CNs as Aβ+ or Aβ- (cut-off |

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| | | | | | value=1.20); |
| {Hassenstab, 2016 #23381} | - | CDR | - | CSF and PET-PIB (+ hippocampal volume) | PET-Aß DEFINITION 9<br>PET: mean cortical binding potential> 0.2245;<br>CSF DEFINITION 9<br>CSF: Ab42<459 pg/ml, tau>339 pg/ml |
| (Voevodskaya, Sundgren et al. 2016) | - | MMSE | - | CSF | CSF DEFINITION 10<br>CSF : Aß42≤530 ng/L |
| **LONGITUDINAL STUDIES** | | | | | |
| (Morris, Roe et al. 2009) | 28.8 | CDR | CDR change | PET-PIB | Correlation study (no cut off) |
| (Craig-Schapiro, Perrin et al. 2010) | - | CDR | CDR change | CSF | Correlation study (no cut off) |
| (Desikan, McEvoy et al. 2012) | 6-42 | CDR | MRI | CSF | CSF DEFINITION 5<br>p-tau181p levels >23 pg/ml ;<br>Aβ1-42 levels<192 pg/ml<br>CSF biomarkers assay Luminex |
| (Knopman, Jack et al. 2012) | 12 | Cognitive battery | Cognitive battery | PET-PIB | PET-Aß DEFINITION 2<br>PIB SUVR ≥ 1.5 |
| (van Harten, Smits et al. 2013) | 24 | Cognitive battery | Cognitive battery | CSF Aß/ Tau or P-Tau | CSF DEFINITION 11<br>550 ng/L for Aß42, ,375 ng/L for Tau, and ,52 ng/L for pTau<br>CSF biomarkers assay Innotest ELISA |
| (Vos, Xiong et al. 2013) | 60 | CDR | CDR | CSF Aß/ Tau or P-Tau | CSF DEFINITION 12<br><459 ng/L for Aβ1–42, >339 ng/L for t-tau, and >67 ng/L for p-tau<br>CSF biomarkers assay Innotest ELISA |
| (Stark, Roe et al. 2013) | 12 | CDR | CDR | PET-PIB | PET-Aß DEFINITION 10<br><br>PIB MCBP<br>High and low groups were constructed for all 4 biomarkers and the 2 ratios with the most extreme quartile were assigned as high for that variable |
| (Lim, Villemagne et al. 2013) | 36 | Cognitive batttery | - | PET-PIB | PET-Aß DEFINITION 2<br>PIB SUVR ≥ 1.5 |
| (Lim, Maruff et al. 2014) | 36 | Cognitive batttery | Cognitive battery | PET-PIB or PET florbetapir or PET Flutemetamol | PET-Aß DEFINITION 11<br>PIB SUVR ≥ 1.9<br>Flutemetamol SUVR ≥ 2.19<br>Florbetapir SUVR ≥ 1.29 |

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| (Mormino, Betensky et al. 2014) | 24 | CDR and cognitive batttery | Cognitive battery | PET-PIB | PET-Aß DEFINITION 12<br>PIB SUVR<br>Gaussian Mixture Model: individuals with greater than 50% probability of belonging to their cohort's high Aß distribution were labeled high Aß |
| (Donohue, Sperling et al. 2014) | 36 | CDR | Composite score (ADCS-PACC) | PET-PIB or CSF Aß42 | PET-Aß DEFINITION 2<br>PiB SUVR > 1.5<br>CSF DEFINITION 5<br>Ab42 < 192 pg/ml<br>CSF biomarkers assay Luminex |
| (Ayutyanont, Langbaum et al. 2014) | 24-60 | Clinical | Cognitive battery | E280A PSen 1 mutation | GENETIC DEFINITION 1<br>E280A PSen 1 mutation |
| (Mormino, Betensky et al. 2014) | 18 | CDR, MMSE | MMSE and Logical Memory I and IIa | PET-PIB or Florbetapir | PET-Aß DEFINITION 12<br>PIB or florbetapir SUVR<br>Gaussian Mixture Model: individuals with greater than 50% probability of belonging to their cohort's high Aß distribution were labeled high Aß |
| (Pietrzak, Lim et al. 2015) | 54 | Clinical consensus | Composite score | PET-PIB or PET florbetapir or PET Flutemetamol | PET-Aß DEFINITION 13<br>PIB SUVR ≥ 1.5<br>florbetapir SUVR ≥1.1<br>flutemetamol SUVR ≥ 0.62<br>(pons as reference region) |
| (Pietrzak, Lim et al. 2015) | 54 | Clinical consensus | Composite score | PET-PIB or PET florbetapir or PET flutemetamol | PET-Aß DEFINITION 13<br>PIB SUVR ≥ 1.5<br>florbetapir SUVR ≥1.1<br>flutemetamol SUVR ≥ 0.62<br>(pons as reference region) |
| (Nation, Edmonds et al. 2015) | 28 | - | ADNI criteria for MCI or dementia diagnosis | CSF Aß or P-Tau | CSF DEFINITION 5<br>P-tau levels >23 pg/ml ; T-tau (≥93 pg/ mL ; Aβ1-42 levels<192 pg/ml<br>CSF biomarkers assay Luminex |
| (Thai, Lim et al. 2015) | 18 | - | Cogsate Brief Battery, CVLT-II | PET amyloid | PET-Aß DEFINITION 13<br>several isotopes. SUVR≥ 1.5 for 11C-PiB, SUVR≥1.1 for 18F-florbetapir, and SUVR≥0.62 for 18F-flutemetamol |
| (Pettigrew, Soldan et al. 2015) | 142 | Cognitive battery | Cognitive battery | (study of correlation between CSF tau and cognition) | Correlation study (no cut off) |
| (Sutphen, Jasielec et al. 2015) | 72 | CDR | CDR | CSF CSF Aß (PET-PIB in a subpopulation) | CSF DEFINITION 13<br>CSF Aβ42 cutoff : 1041 pg/mL (INNOTEST kit) |
| (Papp, Mormino et al. 2016) | 19 | MMSE | Letter and category fluencies | PET-PIB | PET-Aß DEFINITION 14<br>Gaussian mixture modeling approach<br>SUVR > 1.2 |

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| (Soldan, Pettigrew et al. 2016) | 132 | Cognitive battery | Cognitive battery | CSF ß-amyloid, tau or p-tau | CSF DEFINITION 14<br>**CSF Aβ1-42 levels in the lower one-third of the distribution of participants (<374.5 pg/mL) or having tau (>74.9 pg/mL) or p-tau (>39.4 pg/mL) levels in the upper one-third of the distribution.** |
| (Racine, Koscik et al. 2016) | 72 | Cognitive battery | Cognitive battery | CSF ß-amyloid and tau | Used to identify clusters, no predefined threshold |
| (Pascoal, Mathotaarachchi et al. 2016) | 24 | CDR and MMSE | - | CSF ß-amyloid and tau, Florbetapir PET SUVR | Correlation study (no cut off) |
| (Vos, Gordon et al. 2016) | 39.6 | CDR, MMSE, cognitive battery | CDR, MMSE, cognitive battery | CSF ß-amyloid and tau, PIB-PET | PET-Aß DEFINITION 9<br>**PET PIB MCBP > 0.2245;**<br>CSF DEFINITION 9<br>**CSF: Ab42<459 pg/ml, tau>339 pg/ml**<br>(CSF definition 9) |
| (Bilgel, Prince et al. 2016) | 39.6 | Clinical MCI and dementia status | Clinical MCI and dementia status | PET-PIB | PET-Aß DEFINITION 15<br>mean cortical<br>DVR threshold of 1.06 |
| (Brier, McCarthy et al. 2016) | 39.5 | CDR | CDR | PET-PIB | PET-Aß DEFINITION 16<br>MC SUVR across the precuneus,<br>prefrontal, gyrus rectus, and temporal FreeSurfer regions of interest (ROIs) > 1.42<br>(equivalent to MCBP values for PIB at or above 0.18) |
| (Clark, Racine et al. 2016) | 92.4 | Cognitive battery | Cognitive Composite scores | PET-PIB | No cut off for PET-PIB (studied across groups of subjects who stay cognitively normal or become MCI) |
| (Harrington, Gould et al. 2016) | 54 | Cognitive batttery | MCI/AD progression | PET-PIB or PET florbetapir or PET flutemetamol | PET-Aß DEFINITION 13<br>several isotopes. SUVR≥ 1.5 for 11C-PiB, SUVR≥1.1 for 18F-florbetapir, and SUVR≥0.62 for 18F-flutemetamol |
| (Lim, Snyder et al. 2016) | 72 | Cognitive batttery | Composite scores (ADCS-PACC/ZAVEN) | PET-PIB or PET florbetapir or PET flutemetamol | PET-Aß DEFINITION 13<br>PIB and flutemetamol SUVR ≥ 1.5<br>florbetapir SUVR ≥ 1.1 |
| **NEUROPATHOLOGICAL STUDIES** | | | | | |
| (Jicha, Abner et al. 2012) | 12 | NACC Cognitive battery | Cognitive battery and NP | NP | NP DEFINITION 1<br>Braak staging and CERAD plaques scores |
| (Abner, Kryscio et al. 2011) | - | MMSE/Clinical dementia status | - | NP | NP DEFINITION 2<br>Braak stages V |

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| (Riley, Jicha et al. 2011) | 900 | CERAD battery | NP | NP | NP DEFINITION 3<br>NIA-Reagan intermediate or high-likelihood of AD |
| (Thal, von Arnim et al. 2013) | - | CDR | CDR | NP | NP DEFINITION 1<br>Thal phases for Aß and Braak/CERAD stages for NFT |

ADCS-PACC: alzheimer disease cooperative study-Preclinical Alzheimer Cognitive Composite
CERAD: The Consortium to Establish a Registry for Alzheimer's Disease
NACC: National Alzheimer's Coordinating Center
NP: Neuropathology
PET: Positon Emission Tomograpy
PIB: Pittsburgh compound B
DVR: regional time-activity curves are analyzed for PIB specific binding by the Logan graphical analysis, using the cerebellum as a reference tissue input function, yielding a tracer distribution volume ratio or DVR.
MCBP: mean cortical binding potential. Regional DVR values are converted in an estimate of binding potential (DVR -1), and averaged to calculate the mean cortical value.
MMSE: Mini-mental State Examination
SUVR: PET standardized uptake value (SUV) data are summed and normalized to the cerebellar cortex SUV, yielding a region-to-cerebellar ratio named SUVR


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Supplementary Table 3

| Cohort | Npsy Battery |
|---|---|
| **ADNI1-GO-2** | ADAS-Cog, American National Adult Reading Test*, AVLT, BNT, Category Fluency, CDR Clock Drawing, Digit Span, DSST, e-Cog* Logical Memory Test II, MMSE, MoCA, Number Cancellation, TMT *(* ADNI-GO and 2 only)* |
| **AMSTERDAM Dementia Cohort** | AVLT, Cambridge Cognitive Examination for Global Cognitive Decline, Digit Span, MMSE, TMT, Verbal Fluency (categories), Verbal Fluency (letters), Visual Association Test, Visual Object and Space Perception Battery |
| **AIBL study (Australian Imaging, Biomarkers and Lifestyle study)** | Cogstate Brief Battery, CDR, CVLT, MMSE |
| **BIOCARD** **(**Prospective Study of Biomarkers for Older Controls at Risk for Alzheimer's Disease) | BNT, Buschke FCSRT, Verbal Fluency (animals), CDR, CVLT, Digit Span, DSST, Lafayette Grooved Pegboard test Letter Fluency, MMSE, Rey-Osterreith Complex Figure, TMT, WAIS-R, WMS-R |
| **BioFINDER** (Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably cognitively healthy cohort) | A Quick Test of Cognitive speed (AQT), AVLT, Block Design, Verbal Fluency (animals), Clock Drawing, DSST, Verbal Fluency (letters), MMSE, Months Backwards, Multiple Choice Vocabulary Test (SRB:1), Rey-Ostereith Complex Figure, Stroop, TMT |
| **BLSA** **(Baltimore longitudinal study of Aging)** | Benton visual Retention Test, Blessed Information- Memory-Concentration Test, BNT, CVLT, Card Retention Test, Verbal Fluency (animals), Verbal Fluency (letters), Digit Span, MMSE, TMT |
| **HABS** **(Harvard Aging Brain Study)** | Benton Visual Discrimimation Test, BNT, CDR, e-Cog, Letter-Number Sequencing, Memory Functioning Questionnaire, MMSE, 6-trial Selective Reminding Test, TMT |
| **MCSA** **(Mayo Clinic Study of Aging)** | AVLT, BNT, CDR, TMT, Verbal Fluency (animals), WAIS-R, WMS-R |
| **NACC** **(National Alzheimer's Coordinating Center database)** | BNT, Digit Span, Logical Memory (WMS-R), MMSE, DSST, TMT, Verbal Fluency (animals), |
| **Nun Study** | CERAD Battery *(i.e.BNT, Constructional Praxis Word List Memory Delayed Recall, Recognition; Verbal Fluency),* MMSE |
| **SIGNAL** | BNT, Buschke FCSRT, Verbal Fluency (animals), Verbal Fluency (letters, Logical Memory (WMS-R), Rey-Osterrieth Complex Figure Test, TMT, Word list (CERAD) |
| **WU-ADRC (Washington University's Alzheimer's Disease Research Center study)** | Paired associate learning (WMS-R), Benton Visual Retention Test, Block Design, Boston Naming Test, CDR, Digit Span, DSST, Information, Logical Memory test (WAIS-R), Verbal fluency (letter), Mental Control, TMT |
| **WRAP** **(Wisconsin Registry for Alzheimer's Prevention)** | AVLT, BNT, COWA, Face Recognition (WMS), Judgement of Line Orientation, Stroop, TMT, WASI, Wisconsin Card-Sort-64, WRAT-3 |

Abbreviations:

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|---|---|
| ADAS-Cog | Alzheimer Disease Assessment Scale-Cognition |
| AVLT | Rey Auditory Verbal Learning Task |
| BNT | Boston Naming Test |
| Benton | Benton Visual Retention Test |
| COWA | Controlled Oral Word Association |
| CVLT | California Verbal Learning Test |
| DSST | Digit Symbol Substitution Test |
| FCSRT | Free and Cued Selective Reminding Test |
| MMSE | Mini-mental State Evaluation |
| MoCA | Montreal Cognitive Assessment |
| TMT | Trail Making Test (Reitan) |
| WAIS | Wechsler Adult Intelligence Scale |
| WART | Wide Range Achievement Reading Test |
| WASI | Wechsler Abbreviated Scale of Intelligence |

| | |
|---|---|
| WMS | Wechsler Memory Scale |