

Preclinical Alzheimer's Disease

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Review

Preclinical Alzheimer's Disease: Implications for Refinement of the Concept

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Abstract. Increasing interest in clinical trials and clinical research settings to identify Alzheimer's disease (AD) in the earliest stages of the disease has led to the concept of preclinical AD. Individuals with preclinical AD have AD pathology without clinical symptoms yet. Accumulating evidence has shown that biomarkers can identify preclinical AD and that preclinical AD is associated with a poor clinical outcome. Little is known yet about the role of vascular and lifestyle risk factors in the development of preclinical AD. In order to better understand preclinical AD pathology and clinical progression rates, there is a need to refine the concept of preclinical AD. This will be of great value for advancements in future research, clinical trials, and eventually clinical practice.

Keywords: Amyloid, biomarkers, clinical trials, cognition, diagnosis, lifestyle, neuronal injury, preclinical Alzheimer's disease, prognosis, vascular risk

INTRODUCTION

Over the last two decades the developments in biomarkers research have completely altered our perception of Alzheimer's disease (AD). It was shown that amyloid- β ($A\beta$) abnormalities can be observed more than 15 years before clinical symptoms [1–3]. This led to the introduction of the diagnostic category of preclinical AD, defined as individuals with abnormal $A\beta$ but normal cognition. The concept of preclinical AD opens a wide range of possibilities for research of the development of AD and ultimately the prevention of dementia. In this paper, we give an overview of the diagnostic criteria of preclinical AD

and the prevalence, clinical outcome, and risk factors of preclinical AD. We conclude with a discussion of the impact of the concept of preclinical AD on future research, trial design, and clinical practice.

DIAGNOSIS OF PRECLINICAL AD

AD is characterized in the brain by extracellular plaques, resulting from aggregation of the $A\beta$ protein, followed by intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, and brain atrophy. In 2011, a working group of the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed three ordered biomarker-based stages for preclinical AD for cognitively normal individuals with abnormal $A\beta$ [4]. Stage 1 preclinical AD was defined as the presence of only an abnormal $A\beta$ marker, stage 2 as abnormal $A\beta$ and at least one abnormal neuronal injury marker, and stage 3 as

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abnormal A β , neuronal injury, and subtle cognitive changes without impairments.

A β biomarkers

A β aggregation can be measured in cerebrospinal fluid (CSF) or on positron emission tomography (PET). Individuals with AD have lower A β_{42} levels or a lower ratio of A β_{42} to A β_{40} in CSF and an increased PET A β tracer binding [5, 6]. CSF and PET A β measures are not interchangeable as several studies reported discordance in abnormality between both measures in cognitively normal individuals (discordance range 8–21% [7–10], with typically individuals having abnormal CSF A β_{42} but normal A β PET. This suggests that CSF A β_{42} may identify the disease before A β PET binding becomes abnormal. Some studies have demonstrated that the ratio of CSF A β_{42} /A β_{40} may show a better concordance with A β PET, compared to CSF A β_{42} alone, in particular for specific assays [11, 12].

Neuronal injury markers

Tau pathophysiology can be measured in CSF by p-tau levels and recently also on PET by tau PET tracers. Other AD-related neuronal injury markers include medial temporal lobe (MTL) atrophy on magnetic resonance imaging (MRI), hypometabolism on fluodeoxyglucose (FDG) PET, and higher levels of total tau (t-tau) in CSF. Whereas p-tau in CSF and tau on PET are thought to be specific markers of AD pathophysiology, MTL atrophy, hypometabolism on FDG-PET, and higher levels of t-tau are also seen in other conditions and therefore considered non-specific to AD. Also neuronal injury markers are not interchangeable as they measure different processes [9, 13]. This is reflected in the higher discordance in abnormality between these markers. We reported 41% discordance for CSF t-tau and hippocampal atrophy [9], while another study found 15% discordance for CSF t-tau and FDG-PET and 26% for FDG-PET and hippocampal atrophy [10]. When AD-related atrophy patterns were studied, a discordance of 21% with CSF t-tau and 49% with FDG-PET was found, whereas CSF t-tau and p-tau showed a discordance of 49% with FDG-PET [14].

PREVALENCE OF PRECLINICAL AD

Around one-third of individuals in the general elderly population have A β pathology. A recent

worldwide meta-analysis based on over 50 studies showed that A β prevalence increased from age 50 to age 90 from 10% to 44% [3].

The prevalence of preclinical AD NIA-AA criteria stage 1 ranged from 8 to 21%, and of stage 2 from 8 to 34% (Table 1) [2, 14–21]. Differences in prevalence between studies are most likely related to differences in setting, age, kind of biomarkers (e.g., imaging versus CSF markers), and cut-offs that were used. Some studies specifically defined subtle cognitive decline for stage 3 and found a prevalence of 2 to 4% for this stage (Table 1). However, there is no clear consensus yet on defining subtle cognitive change at the preclinical AD stage. In our head-to-head comparison study, using CSF markers for classification resulted in a prevalence of preclinical AD stage 1 of 12%, and stage 2 + 3 of 9%, while with imaging markers the prevalence of stage 1 was 20% and stage 2 + 3 8% [9]. Of the individuals in stage 1 according to CSF biomarkers, 19% were in stage 2 + 3, and 39% were normal according to imaging biomarkers, whereas of the individuals in stage 2 according to CSF biomarkers, 74% were in stage 1, and 11% were normal according to imaging biomarkers.

OUTCOME OF PRECLINICAL AD

Studies examining the relation between A β pathophysiology and longitudinal clinical outcome remain scarce. Overall, A β pathophysiology in cognitively normal individuals has been associated with an increased progression rate to mild cognitive impairment (MCI) and AD dementia [1, 2, 22–24]. Some studies have investigated the association between A β pathophysiology and decline in specific cognitive domains. These findings were examined in a recent meta-analysis (overall $n=14$ studies) and show that A β pathophysiology is associated with a small to moderate decline in global cognition (Cohen's $d=0.30$), with smaller effects for semantic memory, visuospatial function, and episodic memory (Cohen's $d=0.24$), while no such association was found with working memory, processing speed, and executive function [25]. Given the relatively small effects, more sensitive cognitive measures may be needed to capture early cognitive change. The preclinical Alzheimer cognitive composite (PACC) and Alzheimer's prevention initiative cognitive test score (APCC) have been suggested as sensitive tests for global cognitive decline early on in preclinical AD [24, 26, 27] and have been included

Table 1
Prevalence of preclinical AD by NIA-AA stage

Study	N	Setting	Age	Females	APOE ε4	Amyloid marker	Injury marker	Stage 0	Stage 1	Stage 2	Stage 3	Reference
ADC	132	Memory clinic	61.4 y (SD 8.3)	42%	41%	CSF Aβ ₄₂	CSF t-tau or p-tau	61%	8%	8%		Van Harten et al., 2013 [16]
ADNI	326	Clinical trial sites	74.2 y (range 69–85)	47%	27%	CSF Aβ ₄₂	CSF t-tau, HCV	32%	15%	22%	3%	Toledo et al., 2014 [14]
AIBL	573	Community dwelling	73.1 y (SD 6.2)	58%	49%	PiB PET	HCV	54%	15%	9%		Burnham et al., 2016 [18]
BIOCARD	222	Community dwelling via clinical setting	56.9 y (SD 10.1)	60%	33%	CSF Aβ ₄₂	CSF t-tau or p-tau	46%	21%	13%		Soldan et al., 2016 [19]
GEM	140	Clinical trial setting	~86.0 y (SD 2.9)	~41%	~19%	PiB PET	HCV	27%	19%	34%		Zhao et al., 2018 [21]
HABS	166	Community dwelling	74 y (IQR 68–79)	55%	30%	PiB PET	FDG PET or HCV	49%	11%	17%		Mormino et al., 2014 [17]
MCSA	296	Population-based	78 y (IQR 75–82)	44%	25%	PiB PET	FDG PET or HCV	43%	15%	13%	2%	Knopman et al., 2012 [15]
WU-ADRC	311	Community dwelling	72.9 y (SD 6.0)	55%	34%	CSF Aβ ₄₂	CSF t-tau or p-tau	41%	15%	12%	4%	Vos et al., 2013 [2]

Aβ, amyloid-β; AD, Alzheimer's disease; ADC, Amsterdam Dementia Cohort; ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing; APOE, apolipoprotein E; BIOCARD, Biomarkers of Cognitive Decline Among Normal Individuals Study; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; GEM, Ginkgo Evaluation of Memory Study; HABS, Harvard A ging Brain Study; HCV, hippocampal volume; MCSA, Mayo Clinic Study of Aging; PET, positron emission tomography; PiB, Pittsburgh compound B; P-tau, phosphorylated tau; T-tau, total tau; WU-ADRC, Washington University Knight Alzheimer's Disease Research Center.

Table 2
Preclinical AD NIA-AA stages and clinical outcome

Study	N	Setting	Age	Females	APOE ε4	Amyloid marker	Injury marker	Outcome measure	Follow-up time	Overall APR progression	Progression Stage 0	Progression Stage 1	Progression Stage 2	Progression Stage 3	Reference
ADC	132	Memory clinic	61.4 y (SD 8.3)	42%	41%	CSF Aβ ₄₂	CSF t-tau or p-tau	MCI or AD dementia	1.8 y (1.3 SD)	10% overall 5.6% overall APR	3% 1.7% APR	18% 10.0% APR	60% 33.3% APR		Van Harten et al., 2013 [16]
ADNI	326	Clinical trial sites	74.2 y (range 69–85)	47%	27%	CSF Aβ ₄₂	CSF t-tau, HCV	MCI or AD dementia	6 y (IQR 3.0–7.0)	13% overall (6.3% after 3 y and 17.0% after 5 y)	9% Ref	14% HR=2.6	12% HR=1.8	25% HR=11.3	Toledo et al., 2014 [14]
AIBL	573	Community dwelling	73.1 y (SD 6.2)	58%	49%	PIB PET	HCV	MCI or AD dementia	6 y	11% overall 1.8% overall APR	8% Ref	16% HR=2.27 2.7% APR	24% HR=5.60 4.0% APR		Burnham et al., 2016 [18]
BIOCARD	222	Community dwelling via clinical setting	56.9 y (SD 10.1)	60%	33%	CSF Aβ ₄₂	CSF t-tau or p-tau	Cognitive decline; MCI or AD dementia	11 y (0–18; SD 4.1)	23% overall 2.1% overall APR	Similar to stage 1; Tau 20% Ptau 18% Ttau 1.8% Ptau 1.6% APR	Similar to normal group; Tau 20% Ptau 20% Ttau 1.8% Ptau 1.8% APR	Faster decline than other groups; Tau 53% Ptau 53% Ttau 4.8% Ptau 4.8% APR		Soldan et al., 2016 [19]
GEM	140	Clinical trial setting	~86.0 y (SD 2.9)	~41%	~19%	PIB PET	HCV	Cognitive decline	12.2 y (SD 2.2; range 7.2–15.1)	–	Ref.	Faster decline	Fastest decline		Zhao et al., 2018 [21]
HABS	166	Community dwelling	74 y (IQR 68–79)	55%	30%	PIB PET	FDG PET or HCV	Cognitive decline	2.09 y (IQR 1.9–2.3)	–	No decline	No decline	Faster decline than other groups		Mormino et al., 2014 [17]
MCSA	296	Population-based	78 y (IQR 75–82)	44%	25%	PIB PET	FDG PET or HCV	MCI or dementia	1.3 y (range 1.1–5.1)	10% overall	5%	11%	21%	43%	Knopman et al., 2012 [15]
WU-ADRC	311	Community dwelling	72.9 (SD 6.0)	55%	34%	CSF Aβ ₄₂	CSF t-tau or p-tau	CDR ≥ 0.5 DAT	3.9 y (range 1–15)	7.7% overall APR 10% overall	3.8% APR 2% after 5 y Ref	8.5% APR 11% after 5 y HR=4.6 2.2% APR	16.2% APR 26% after 5 y HR=14.3 5.2% APR	33.1% APR 56% after 5 y HR=33.8 11.2% APR	Vos et al., 2013 [2]

Aβ, amyloid-β; AD, Alzheimer's disease; ADC, Amsterdam Dementia Cohort; ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing; APOE, apolipoprotein E; APR, annual progression rate; BIOCARD, Biomarkers of Cognitive Decline Among Normal Individuals Study; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DAT, Alzheimer-type dementia; FDG, fluorodeoxyglucose; GEM, Ginkgo Evaluation of Memory Study; HABS, Harvard Aging Brain Study; HCV, hippocampal volume; HR, hazard ratio; MCI, mild cognitive impairment; MCSA, Mayo Clinic Study of Aging; PET, positron emission tomography; PIB, Pittsburgh compound B; P-tau, phosphorylated tau; T-tau, total tau; WU-ADRC, Washington University Knight Alzheimer's Disease Research Center.

Table 3
Vascular and lifestyle risk factors for preclinical AD

Study	N	Setting	Age	Females	APOE $\epsilon 4$	Risk factor	Amyloid outcome measure	FU time	Predictive accuracy	Reference
Cross-sectional										
ADNI	112	Clinical trial settings	75.7 y (SD 5.2)	50%	23%	(Change in) BMI	CSF A β_{42} , t-tau and PIB PET	-	Lower BMI levels were associated with more CSF A β and tau burden. No association was found with BMI change	Vidoni et al., 2011 [28]
AIBL	116	Community dwelling	70.3 y (range 60–95)	54%	47%	Physical activity	PIB PET	-	Higher exercising $\epsilon 4$ carriers had less A β burden	Brown et al., 2013 [40]
AIBL	162	Community dwelling	~69.8 y (SD 6.8)	~59%	~26%	Dietary protein and fiber intake	PIB PET	-	Higher protein intake was associated with less A β burden	Fernando et al., 2018 [37]
BAC	92	Community dwelling	75.2 y (SD 5.6)	63%	-	Lifetime cognitive activity, current physical activity	PIB PET, combined cortical thickness, FDG-PET and HCV score	-	Higher lifetime cognitive activity was associated with less A β burden	Wirh et al., 2014 [35]
Bonn cohort	87	Memory clinic	67.7 y (SD 9.1)	49%	23%	CSF cholesterol, cholesterol precursors, and cholesterol elimination products	CSF A β_{42} , p-tau	-	Cholesterol elimination products were only associated with p-tau levels	Popp et al., 2013 [32]
DESCRIPA	111	Memory-clinic setting	67.0 y (SD 7.6)	51%	46%	Social activity, cognitive activity, alcohol consumption, current smoking, sleep problems	CSF A β_{42} , t-tau, p-tau and HCV	-	No effect was found	Reijs et al., 2017 [46]
DIAN	139 presymptomatic mutation carriers	Clinical trial settings	34.9 y	58%	28%	Leisure time exercise activity	CSF A β_{42} , t-tau, PIB PET	-	Only in amyloid-positive individuals, higher exercise was associated with less A β on PET. A stronger association was found between A β PET and estimated years of onset in those with lower exercise	Brown et al., 2017 [43]
DIAN	120 presymptomatic mutation carriers	Clinical trial settings	35.3 y (SD 8.0)	73%	-	BMI	PIB PET	-	Lower BMI was associated with less years before estimated symptom onset and more A β burden	Müller et al., 2017 [29]
DIBS	118	Community dwelling	69.5 y (range 47–89 y)	-	23%	Hypertension	Florbetapir PET	-	Hypertension with 1 $\epsilon 4$ allele was associated with more A β burden	Rodrigue et al., 2013 [30]

(Continued)

Table 3
continued

Study	N	Setting	Age	Females	APOE ε4	Risk factor	Amyloid outcome measure	FU time	Predictive accuracy	Reference
FINGER	48	Population-based	52.4 y	~47%	~29%	Blood pressure, BMI, total and LDL cholesterol, and glucose homeostasis	PIB PET (42% abnormal)	-	No effect was found	Kemppainen et al., 2018 [34]
HABS	79	Community dwelling				Social isolation/loneliness	PIB PET	-	Social isolation was associated with more Aβ burden	Donovan et al., 2016 [44]
HABS	186	Community dwelling	74 y (SD 6)	55%	31%	Recent and past cognitive activity, Recent physical activity, Objective recent walking activity	PIB PET, FDG-PET, HCV	-	No effect was found	Gidicsin et al., 2015 [45]
MCSA	430 (of which 38 were cognitively impaired)	Population-based	74.7 y (SD 8.4, range 60-98)	44%	28%	Hypertension, hyperlipidemia, cardiac-arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke	PIB PET, FDG-PET, ERC tau-PET, AD atrophy patterns on MRI	-	Vascular health had direct and indirect impact on neurodegeneration but not Aβ, hyperlipidemia had a direct impact on tau	Vemuri et al., 2017 [33]
NYU-ADC	45	Community dwelling	54 y (SD 11)	71%	42%	Physical activity, Mediterranean diet	PIB PET, FDG-PET, atrophy on MRI	-	Higher physical activity and Mediterranean diet were associated with less AD pathology (Aβ/FDG/MRI). Combined higher physical activity and Mediterranean diet was associated with the least AD pathology	Mathews et al., 2014 [38]
NYU-ADC	52	Community dwelling	54 y (SD 11)	71%	47%	Nutrient patterns	PIB PET, FDG-PET, atrophy on MRI	-	Vitamin B12, vitamin D and zinc were associated with less AD pathology (Aβ/FDG/MRI). Such associations were also found with vitamin E and PUFA (FDG/MRI), anti-oxidants and fibers (FDG). Fats were associated with more abnormal FDG and MRI	Berti et al., 2015 [36]
UCLA	24	Community dwelling SCI	63.1 y (SD 11.6)	67%	33%	Physical activity, BMI, diet	Aβ /tau FDDNP-PET	-	Healthier diet was associated with less Aβ/tau binding	Merrill et al., 2016 [42]
UCSD/UW/OHSU	177	Community dwelling	69.4 y (SD 8.3, range 55-100)	58%	34%	Pulse pressure (systolic-diastolic blood pressure)	CSF Aβ ₄₂ and p-tau	-	Elevated pulse pressure was associated with abnormal p-tau/Aβ ₄₂ and p-tau	Naiton et al., 2013 [31]

(Continued)

Table 3
continued

Study	N	Setting	Age	Females	APOE ε4	Risk factor	Anyloid outcome measure	FU time	Predictive accuracy	Reference
WRAP	186	Population-based	~61 y (SD 6)	~67%	~40%	Current physical activity	PIB PET, FDG-PET, HCV	-	With advancing age, physically active individuals had less AD pathology (Aβ/FDG/HCV) compared to the physically inactive	Okonkwo et al., 2014 [41]
WU-ADRC	165	Community dwelling	65.4 y	68%	34%	Physical exercise	CSF Aβ ₄₂ + PIB PET	-	Lower physical activity was associated with more abnormal Aβ in CSF and on PET; on PET only in APOE ε4 carriers	Head et al., 2012 [39]
Semi-longitudinal (AD biomarkers only assessed at follow-up)										
ARIC	346	Community dwelling	52 y (range 45-64)	58%	31%	Midlife obesity, current smoking, hypertension, diabetes, and total cholesterol	Florbetapir PET (51% abnormal)	Median 23.5 y (IQR 23.0-24.3)	Only midlife obesity predicted Aβ as single factor (OR = 2.06)	Gottesman et al., 2017 [47]
BIOFINDER	318	Population-based	54 y (SD 4.7)	60%	28%	Midlife triglycerides, cholesterol, HDL, and LDL	CSF Aβ ₄₂ and p-tau+ in subset flutemetamol PET (n = 134)	20 y (mean age individuals 73 y)	0 factors Ref; 31% abnormal amyloid I factor OR = 1.88 (NS); 50% abnormal Aβ > = 2 factors OR = 2.88; 61% abnormal Aβ Higher triglycerides levels were associated with abnormal CSF Aβ ₄₂ (OR = 1.34) and Aβ ₄₂ /p-tau (OR = 1.46) higher levels of LDL with abnormal Aβ PET (OR = 2.03-2.12), and higher levels of HDL with less abnormal Aβ PET (OR = 0.25)	Nagga et al., 2018 [49]
FINGER	48	Population-based	52.4 y	~47%	~29%	CAIDE dementia risk score: age, sex, years of formal education, systolic blood pressure, BMI, serum total cholesterol, and physical activity	PIB PET, HCV and MTA on MRI	17.6 y	The CAIDE risk score was only associated with more atrophy (HCV/MTA) at follow-up	Stephen et al., 2017 [50]

(Continued)

Table 3
continued

Study	N	Setting	Age	Females	APOE ε4	Risk factor	Amyloid outcome measure	FU time	Predictive accuracy	Reference
MCSA	942	Population-based	History age 40-64 y	45%	29%	Intellectual enrichment, midlife physical inactivity, ever obesity, ever smoked, diabetes, hypertension, and dyslipidemia, and late life cardiovascular and metabolic conditions	PIB-PET, AD MRI atrophy patterns	Current age 79.7 y (SD 5.9)	Only midlife dyslipidemia was associated with late life Aβ pathology. Obesity, smoking, diabetes, hypertension, and cardiac and metabolic conditions were associated with greater AD-pattern neurodegeneration	Vemuri et al., 2017 [48]
Longitudinal										
ADNI	229	Clinical trial sites	75.1 y (SD 5.0)	48%	27%	Framingham Heart Study risk score: including age, gender, body mass index, blood pressure, smoking, and diabetes	CSF Aβ ₄₂ , FDG-PET, HCV	3.2 y (SD 1.0)	Vascular burden was not associated with cross-sectional and longitudinal changes in Aβ, FDG, or HCV	Lo et al., 2012 [52]
MCSA	393 (of which 53 were cognitively impaired)	Population-based	78.6 y (SD 5.0)	38%	28%	Education, occupation, and reported midlife cognitive activity, exercise activity, and physical activity	PIB PET, FDG-PET, HCV	2.5 y (SD 1.2)	Among highly educated individuals, high midlife cognitive activity was associated with lower (longitudinal) Aβ burden in APOE ε4 carriers	Vemuri et al., 2016 [53]
NYU-ADC	77	Community dwelling	63.4 y (SD 9.4, range 44-86)	60%	30%	Mean arterial pressure in people with (32%) and without hypertension	CSF Aβ ₄₂ , t-tau, p-tau	2.0 y (SD 0.5)	Decreased mean arterial pressure was only related to longitudinal increase in p-tau in people with hypertension	Glodzik et al., 2014 [51]

Aβ, amyloid-β; ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing; APOE, apolipoprotein E; ARIC, Atherosclerosis Risk in Communities Study; BAC, Berkeley Aging Cohort; BIOCARD, Biomarkers of Cognitive Decline Among Normal Individuals Study; BIOFINDER, Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably; BMI, body mass index; CSF, cerebrospinal fluid; DIAN, Dominantly Inherited Alzheimer Network; DESCRIPA, Development of screening guidelines and criteria for predementia Alzheimer's disease; DLBS, Dallas Lifespan Brain Study; ERC, entorhinal cortex; FDG, fluorodeoxyglucose; FINGER = Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; HABS, Harvard Aging Brain Study; HCV, hippocampal volume; MCSA, Mayo Clinic Study of Aging; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; NYU-ADC, New York University Alzheimer's Disease Center; PET, positron emission tomography; PIB, Pittsburgh compound B; P-tau, phosphorylated tau; T-tau, total tau; UCLA, University of California Los Angeles; UCSD/WU/OHSU, collaboration between University of California San Diego, Washington University, and Oregon Health & Science University; WRAP, Wisconsin Registry for Alzheimer's Prevention; WU-ADRC, Washington University Knight Alzheimer's Disease Research Center.

as primary outcome measure in the first clinical trials in preclinical AD. Future research on A β pathophysiology in relation to decline on the APCC and PACC and other cognitive tests will help to better understand the prognosis and outcome of A β pathophysiology in cognitively normal individuals.

Progression rates to cognitive impairment or dementia have been found to increase with advancing NIA-AA preclinical AD stage (Table 2) [2, 14–16, 18, 19]. Reported progression rates to cognitive impairment or dementia were 11–20% in stage 1, 12–26% in stage 2, and 25–56% in stage 3 after an average follow-up of 1 to 11 years (Table 2). Studies that combined stage 2 and stage 3 reported progression rates of 24–60%. A similar trend was found for decline in performance on cognitive testing with more decline in more advanced NIA-AA stages [17, 19, 21]. Moreover, our head-to-head comparison study of AD defined by CSF versus imaging markers (CSF A β_{42} and tau versus amyloid PET and hippocampal atrophy) showed similar progression rates for preclinical AD defined by CSF and imaging markers [9], indicating that both modalities have comparable prognostic value. Together, these findings show that information on neuronal injury can help to further refine the prognosis of cognitively normal individuals with A β pathophysiology.

VASCULAR AND LIFESTYLE RISK FACTORS FOR PRECLINICAL AD

Vascular and lifestyle factors are established risk factors for AD-type dementia but little is known about the role of these factors in the development of AD pathology in cognitively normal individuals. Most previous studies were cross-sectional and findings have been conflicting. Lower BMI [28, 29], hypertension [30] and increased pulse pressure [31] were associated with A β pathology but other studies did not find an association between vascular risk factors and A β pathology [32–34] (Table 3).

Higher cognitive activity [35], a healthy nutrient pattern [36–38], higher physical activity [38–43], and higher social activity [44] were associated with less A β pathology in cognitively normal individuals. However, several studies did not find an association between these lifestyle activities and A β accumulation, e.g., [45, 46].

There are only few longitudinal studies available to date that have examined the relation between risk factors and development of amyloid pathology

(Table 3). Most of these studies lacked a baseline measurement of A β pathology, which limits the interpretation of timing of events. The studies suggested that especially risk factors in midlife (40–65 years) were associated with AD pathology in late life. The ARIC study showed that having 2 or more of the midlife risk factors obesity, smoking, cholesterol, hypertension, and diabetes was associated with a higher prevalence of A β pathology in later life compared to having none of these midlife risk factors (~60 versus 30%) [47]. Another population-based study suggested that midlife dyslipidemia was associated with A β pathology in later life while midlife obesity, smoking, diabetes, and hypertension were associated with AD-related neurodegeneration on imaging [48]. Midlife lipid levels were also found to be associated with late life A β pathophysiology in the BIOFINDER study [49]. The FINGER study reported that a higher midlife CAIDE risk profile (consisting of age, sex, education, blood pressure, cholesterol, body mass index, and physical inactivity) was associated with more pronounced vascular pathology and neurodegeneration on imaging in later life, while no association with A β accumulation was found, although this could be due to the relative small sample size (N = 48) [50]. A study with longitudinal biomarker assessment in individuals in midlife and later life found an association between decreased mean arterial pressure and an increase in p-tau over time but no association with A β changes [51], whereas another study did not find any relation between vascular burden and longitudinal biomarker changes [52]. Furthermore, among highly educated individuals, high midlife cognitive activity was found to be associated with less increased longitudinal A β on PET in APOE ϵ 4 carriers [53]. Although the above findings are inconsistent, lack long-term longitudinal amyloid biomarker measurements, and are based on relatively small samples, they suggest that lifestyle and vascular risk factors may be involved in the development of AD-related pathology later in life.

ONGOING PRECLINICAL AD TRIALS

AD disease-modifying treatment targets are explored in a number of ongoing secondary prevention trials. Secondary prevention trials are testing disease-modifying drugs in individuals with preclinical AD, i.e., individuals with AD pathology but no clinical symptoms yet or presymptomatic mutation carriers. BACE inhibitors are the most commonly

used AD therapy agent and have shown robust reduction in A β pathology. Also immunotherapies, especially monoclonal antibodies, are used in several AD trials [54]. Ongoing trials in preclinical AD include, for example, the Anti-Amyloid treatment for Asymptomatic AD (A4) [55], EARLY, Alzheimer's Prevention Initiative (API) [56], and Dominantly Inherited Alzheimer's Network (DIAN) [57, 58]. The A4 trial and EARLY trial recruit cognitively normal individuals with evidence of A β pathology to test an anti-A β antibody and BACE inhibitor, respectively. The API recruits cognitively normal individuals at high risk of developing symptoms based on their genetic background. The API autosomal-dominant AD trial tests an anti-A β antibody in individuals with presenilin 1 (*PSEN1*) mutations close to their estimated age of onset, while the API *APOE* ϵ 4 trial tests an A β vaccine or BACE inhibitor in cognitively normal homozygous *APOE* ϵ 4 carriers. The DIAN trial tests an anti-A β antibody in autosomal dominant mutation carriers in *APP*, *PSEN1* and *PSEN2* genes. All these ongoing trials use a cognitive composite score as primary outcome measure.

IMPACT OF PRECLINICAL AD ON FUTURE RESEARCH, TRIALS, AND CLINICAL PRACTICE

The concept of preclinical AD has had and will continue to have an enormous impact on developments in research, trials, and clinical practice. Still, the concept of preclinical AD needs to be further refined and several challenges that come with the concept of preclinical AD remain to be tackled.

Need of refinement of preclinical AD

Refinement of the preclinical AD concept is needed in order to capture the earliest changes of AD and understand how the disease unfolds. The proposed ATN classification system forms a first step toward refining preclinical AD by differentiating between several neuronal injury markers [59]. Here the A stands for A β pathology (CSF or PET), the T for tau pathology (CSF p-tau, tau PET), and the N for other forms of neuronal injury (hippocampal volume, CSF t-tau, FDG-PET). This classification system is implemented in the new proposed NIA-AA criteria which state that amyloid pathology is required to be labeled as having AD pathophysiology but evidence of both A β and tau pathology is required in order to be labeled as having AD. The differentiation between

CSF t-tau and p-tau could, however, be questioned as these markers are known to be highly correlated. The high number of resulting subgroup combinations may limit its applicability in clinical research settings.

While A β is considered the core pathology in preclinical AD, we still do not understand the pathophysiology of A β aggregation. To capture the earliest stages of AD, it is crucial to better understand the folding and aggregation of A β monomers into oligomers, protofibrils, and fibrils. Several studies have shown variability between individuals in type of aggregated A β but current assays may not be able to detect these different subtypes of aggregated A β . More knowledge on A β aggregation could shed new light on findings regarding individuals with slightly elevated levels of subthreshold A β who show cognitive decline [17, 60]. It can also help to understand the biomarker and cognitive trajectories of people with neuronal injury in the absence of A β pathology. Currently they are labeled as having Suspected Non-Alzheimer's disease pathophysiology (SNAP) [13], but a subgroup may as well have preclinical AD with a form of aggregated A β that cannot be picked up by current A β assays.

How preclinical AD relates to other AD-related molecular processes is another topic that requires further investigation. Synapse dysfunction, neuroinflammatory responses, and axonal degeneration are known to play a central role in AD, but exact timings are not yet fully understood [61, 62]. Knowledge on these processes in relation to core AD markers could help to identify subtypes of preclinical AD that may benefit from different treatments and improve prognosis in these individuals. Neurogranin [63], YKL-40 [64], and Neurofilament-Light [65] are relatively well-established novel CSF markers that reflect these processes and may be good biomarker candidates for prognosis. Large-scale multimodal omics studies, like the IMI EMIF-AD Biomarker Discovery Study (<http://www.emif.eu/about/emif-ad>), will contribute to the identification of novel genetic and molecular candidates to further refine preclinical AD.

A deeper understanding of the earliest cognitive changes in preclinical AD would be also of great importance for clinical research and AD trials. Studies have shown that composite measures of global cognition may best capture early cognitive changes in preclinical AD (see above) [24, 26]. However, most of the current tests were not developed for identifying AD in cognitively healthy individuals and cognitive norm scores are often based on a cognitively healthy population including also individuals

who have already amyloid pathology. Also the role of subjective cognitive complaints in relation to the earliest cognitive changes should be further clarified.

Key challenges of preclinical AD

Detection and diagnosis

The detection of A β pathology requires a lumbar puncture or PET scan. This complicates screening for preclinical AD among cognitively healthy individuals, as these tools are not yet widely used, more costly, and still considered relatively invasive. To implement screening for preclinical AD on a large scale there is a need for valid easily assessable biomarkers, like blood-based biomarkers. Validated blood-based markers are not yet available, but it is likely that in the future a combined set of blood-based and other markers can serve as signature for preclinical AD or as pre-selection tool for individuals that should undergo assessment of A β pathology by lumbar puncture or PET scan.

Without an available treatment, a diagnosis of AD in the preclinical stage comes with several ethical considerations. A preclinical AD diagnosis can only be considered in relation to clinical trial recruitment, and only with appropriate counseling. Preclinical AD should not be diagnosed in clinical routine as the prognosis is not clear, it may create stigma or induce worries in people who do not have clinical symptoms yet, and because there is no treatment. Nevertheless, there will be people who want to know their risk of progression to dementia. Shared decision-making will then be crucial such that persons understand what the findings can and what they cannot tell regarding diagnosis and prognosis.

Resilience and risk for progression

Not all individuals with preclinical AD will progress to dementia before death. Findings of post-mortem A β plaques in brains of cognitively healthy elderly at death raise the question why some of the individuals with preclinical AD are resilient for cognitive decline. Neuropathological studies suggested that those A β plaques appear to be associated with lower levels of oligomeric A β forms and could therefore be less toxic [66]. Also less neuroinflammation has been reported in brains of these individuals [67]. There are several environmental and lifestyle as well as genetic factors that can influence symptom expression in AD and prevent some individuals from becoming demented. As findings are still inconsistent about the protective role of healthy lifestyle

on core AD pathology (see above), we need a better understanding of the molecular pathways by which cognitive, lifestyle, and genetic protective effects are exerted. Knowledge on factors that promote resilience could lead to novel therapeutic targets for individuals who are at high risk of progression to dementia. Understanding resilience in preclinical AD is also of utmost importance once a cure becomes available in order to avoid treating persons with preclinical AD who may never become demented.

Among individuals with preclinical AD who do progress to dementia there is a large variability in rate of progression. Disease progression may in part depend on the presence of other AD-related pathologies such as synapse dysfunction, neuroinflammation, and axonal degeneration. Preclinical AD manifests at older ages and therefore prognosis may also depend on the presence of age-related comorbid diseases, such as vascular pathology or vascular risk factors [68], which all influence the rate of cognitive decline. This indicates the need of a multidimensional approach to estimate the prognosis of preclinical AD.

Drug trial design

The concept of preclinical AD is very valuable for development of strategies to prevent cognitive impairment. It provides a large time window for disease-modifying treatment, as neurodegeneration is still limited. However, as it reflects a long early stage of the disease, clinically relevant cognitive changes cannot be easily captured. There is a need for cognitive tests that can monitor cognition over time in preclinical AD. Most of the current cognitive tests are rather developed for diagnostic purposes or capture only cognitive changes in more advanced stages of AD. Furthermore, it is not feasible to have treatment trials with a follow-up of more than 5 years. It is therefore essential to be able to translate small cognitive changes in preclinical AD to the expected clinical changes in daily functioning or quality of life in advanced stages of AD by statistical disease modeling. For example, the IMI ROADMAP project (<https://roadmap-alzheimer.org>) aims to develop disease and health-economic models to demonstrate long-term value of treatment in preclinical AD using data of population studies, clinical cohorts as well as EHR datasets that together cover the full AD clinical spectrum.

Timing is everything. Maybe AD can only be stopped before pathology arises such that the preclinical AD stage would already be too late to cure AD. Certain disease-modifying drugs, like drugs targeting

A β production and aggregation, are likely most effective before considerable A β accumulation has taken place. Primary prevention trials would need to test drugs in individuals who are at risk for AD but do not have AD pathology yet. To maximize efficacy in such trials, trial recruitment of cognitively normal individuals could then, besides *APOE* ϵ 4 carriership, be enriched by family history, lifestyle, and vascular risk factors and absence of environmental or genetic factors that point toward resilience.

PRECLINICAL AD: THE FUTURE

The preclinical AD concept has proven to be of tremendous value in understanding AD pathophysiology in the earliest stages of the disease and has obviously advanced drug trials. However, there is still a lot more to learn about preclinical AD and its associated processes. Further refinement of the preclinical AD concept will help us to tackle the current challenges and foster further advancement in research, clinical trials, and eventually clinical practice. Once we move toward primary or secondary prevention of AD, we will be faced with new ethical considerations and challenges regarding detection and diagnosis in primary care settings. For now, it may be useful to promote a healthy lifestyle and treat vascular risk factors in cognitively healthy individuals, already in midlife.

DISCLOSURE STATEMENT

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/17-9943>).

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