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Longitudinal association between ß-amyloid accumulation and cognitive decline in cognitively healthy older adults: A systematic review

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ABSTRACT

This systematic review examined the longitudinal association between amyloid-β (Aβ) accumulation and cognitive decline in cognitively healthy adults. It was conducted using the PubMed, Embase, PsycInfo, and Web of Science databases. The methodological quality of the selected articles was assessed. In fine, seventeen longitudinal clinical studies were included in this review. A minority (seven out of 17) of studies reported a statistically significant association or prediction of cognitive decline with Aβ change, measured by positron emission tomography (PET; n = 6) and lumbar puncture (n = 1), with a mean follow-up duration of 3.17 years for cognition and 2.99 years for Aβ. The studies reporting significant results with PET found differences in the frontal, posterior cingular, lateral parietal and global (whole brain) cortices as well as in the precuneus. Significant associations were found with episodic memory (n = 6) and global cognition (n = 1). Five of the seven studies using a composite cognitive score found significant results. A quality assessment revealed widespread methodological biases, such as failure to report or account for loss-to follow up and missing data, and failure to report *p*-values and effect sizes of non-significant results. Overall, the longitudinal association between Aβ accumulation and cognitive decline in preclinical Alzheimer's disease remains unclear. The discrepancy in results between studies may be explained in part by the choice of neuroimaging technique used to measure Aβ change, the duration of longitudinal studies, the heterogeneity of the healthy preclinical population, and importantly, the use of a composite score to capture cognitive changes with increased sensitivity. More longitudinal studies with larger sample sizes are needed to elucidate this relationship.

Contents

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1. Introduction

The conceptualization of Alzheimer's disease (AD) has evolved over the past two decades from a clinical concept defined by symptomatology and behavioral manifestations to a biological entity characterized by biomarkers abnormalities [10,20]. Advances in neuroimaging, such as in vivo imaging of pathophysiological changes at different clinical stages, including abnormal deposition of amyloid-β (Aβ) protein, have propelled this transition. According to the amyloid cascade hypothesis, abnormal Aβ accumulation in the brain is not only a marker of AD, but also its initial cause [25]. This theory suggests that significant Aβ accumulation would precede AD-associated cognitive decline by several years, that said Aβ accumulation is closely linked to the clinical progression of AD, and that its effects on cognitive decline would occur before the onset of AD clinical symptoms, making it a central target in AD prevention. As a result, authors have proposed biomarker models of AD, based on the onset of biomarker abnormalities such as elevated Aβ protein levels, to improve early diagnosis of the disease [11,12].

However, the presence of conflicting reports [1,3,15], in addition to the failure of many clinical trials targeting Aβ at early or late clinical stages to demonstrate efficacy in preventing cognitive decline, has raised many questions about the role and effects of Aβ in AD [2]. Furthermore, the relationship between Aβ and cognitive decline in preclinical stages appears to be even less clear.

A narrative review by Rodrigue et al. [24] reported inconsistent findings on the relationship between cognition and Aβ in cognitively healthy older adults and expressed the need to better characterize this relationship across different age groups using longitudinal studies. A meta-analysis of 34 studies by Hedden et al. [8], of which only five had a longitudinal design, showed significant but small effect sizes for the association between Aβ and episodic memory and global cognition in cognitively healthy older adults. The authors highlighted the need to investigate this association with larger sample sizes, while accounting for the multiple sources of variance found across studies. Since then, results from several longitudinal studies have been published. The objectives of this systematic review of longitudinal studies were to update previous findings while assessing the methodological quality of each study, and to expand our knowledge about the nature of the relationship between Aβ accumulation and cognitive decline in cognitively healthy older adults.

2. Methods

2.1. Literature search strategy and sources

This systematic review followed the PRISMA guidelines [21] and was conducted using the PubMed, Embase, PsycInfo, and Web of Science databases for articles published from the inception of the databases through May 15, 2021. Keywords referred to the variables of interest (Aβ accumulation and cognitive decline), the population (cognitively healthy middle-aged and older individuals), and the study design (longitudinal design). The search strategy is presented in the Supplementary Material Table 1.

2.2. Study selection process

Inclusion criteria were established using the PICOS approach [18]. Participants had to be cognitively healthy middle-aged or older adults. Cognitively healthy individuals were defined as those without significant subjective com-

Table 1
Characteristics of selected studies.

#	Study	Age M(SD), y	% Female	Education M(SD), y	Cohort	Time-points (max)	f/u duration, y	n at baseline	n at first f/u
1	[4]	63.2 (13.4)	58.7	15.4 (2.14)	DLBS	2	Cognition: 3.8 PET: 3.6	288	126
2	[5]	76.6 (4.83)	44.7	16.1 (2.93)	ADNI	5	4 (max)	47	46
3	[6]	73.1(6)	58.3	15.6 (3.2)	HABS	Cognition: 8 PET: 5	Cognition: 6.1 PET: 5.1	60	60
4	[7]	67.3 (2.3)	69.2	13.3 (1.25)	Memory clinic, Shonan-Atsugi Hospital	*NR*	3.3	13	*NR*
5	[9]	78.4	47.2	14.4	ADNI, MCSA	4	1.3	540	198
6	[13]	73.9 (6.6)	52.0	16.6 (2.5)	ADNI	Cognition: 9 PET: 6	Cognition: 4.9 PET: 5.3	220	101
7	[16]	74.7 (7)	45.0	16.7 (2.7)	ADNI	Cognition: 5 PET: 4	Cognition: 3.7 PET: 3.9	142	142
8	[17]	76.5 (5.6)	70.4	17.4 (1.8)	Independent	Cognition: 3 PET: 3	Cognition: 2.7 PET: 3.4	45	27
9	[19]	75.1 (5)	48.0	16.0 (2.9)	ADNI	2	3.0	229	36
10	[22]	61.2 (5.58)	66.0	16.6 (2.47)	WRAP	Cognition: 5 PET: 2	2.1	104	78
11	[26]	66.0 (9)	47.8	*NR*	VU University Medical Center, Amsterdam	Cognition: 4 CSF: 2	1.9	23	11
12	[27]	65.5	64.0	17.0	Independent	2	2.0	22	22
13	[29]	73.0 (8)	66.7	*NR*	Memory clinic, Malmo University Hospital	Cognition: 3 CSF: 2	Cognition: 4.5 CSF: 3.9	54	37
14	[31]	73.6 ± 7.3	53.4	13.2 ± 3.5	MHAS	Cognition: 2 PET: 3	1.7	103	103
15	[32]	73.1 ± 7.5	49.1	13.2 ± 3.5	MHAS	Cognition: 2 PET: 3	1.7	106	106
16	[33]	38.3 (11.59)	60.0	14.7 (2.93)	DIAN	*NR*	2.7	188	188
17	[35]	60.5 (8.4)	67.9	16.2 (2.6)	ACS	Cognition: >5 CSF: 4 PET: 5	Cognition: 6.7 CSF: 4.6 PET: 4.7	209	207

Abbreviations: ACS: Adult Children Study, ADNI: Alzheimer's Disease Neuroimaging Initiative, CSF: Cerebrospinal fluid, DIAN: Dominantly Inherited Alzheimer's Network, DLBS: Dallas Lifespan Brain Study, f/u: follow-up, HABS: Harvard Aging Brain Study, M: Mean, MCSA: Mayo Clinic Olmsted Study of Aging, MHAS: Melbourne Healthy Aging Study, NR: not reported, PET: Positron emission tomography, SD: Standard deviation, WRAP: Wisconsin Registry for Alzheimer's Prevention.

plaints about their cognitive functioning or objective cognitive deficits, based on a comprehensible neuropsychological assessment. Participants with familial AD were excluded to focus only on the sporadic form. No other physical and mental status criteria were used. Aβ accumulation was conceptualized as the predictor variable and the cognitive decline variable as the predicted variable. To be included, studies had to report a robust and recognized measure of Aβ change from either lumbar puncture (LP) or positron emission tomography (PET) imaging and at least one measure of cognitive change related to differences in specific cognitive domains, global cognition or cognitive clinical status. As the studies needed to be longitudinal in design, at least two measurements for each variable of interest were required, separated by at least one year. In addition, studies had to report a measure of the association between Aβ accumulation and cognitive decline. Lastly, only original research articles in English or French published in peer-reviewed journals were included.

Articles were selected using the Covidence systematic review software [30] (Veritas Health Innovation). After the initial search, duplicate articles were removed. An initial sorting based on article titles and abstracts was performed, followed by a second sorting based on full-text articles. All articles were evaluated against the inclusion and exclusion criteria, and some articles were excluded accordingly. Screening was performed by two independent reviewers (C.P. and L.S.R.). Articles that were not included by both reviewers were reassessed and included or excluded by consensus. In case of disagreement, a third independent reviewer (C.H.) was consulted.

2.3. Data extraction and quality assessment

Characteristics of the included studies (i.e., authors, year of publication, data sources, sample size at baseline and first follow-up, duration of follow-up, number of measurement time points, and baseline characteristics of the

Table 2
Summary of the Aß measurements, other biomarkers, cognitive domains, and covariates.

Study	Technique	Aß	Other biomarkers	Cognition	Covariates
[4]	**PET** (Florbetapir)	SUVRs: Global, ACC, LPFC, LPC, LOC, LTC, OFC, PCC, Pre	**MRI**: hippocampal, global, and other volumes	**Episodic memory** * (HVLT, CANTAB-VRMT), **Processing speed*** (WAIS (DSST & digit comparison)), **Reasoning*** (RPM, Educational Service Letter Sets)	Age, Sex, APOE e4, Baseline global SUVR, Baseline Episodic memory performance
[5]	**CSF**	Aß 1–42	**CSF**: tau, p-tau **MRI**: volumes, cortical thickness	**Episodic memory** (WMS (logical memory), RAVLT)), **Processing speed** (DSST), **Working memory** (DS)	Age, Gender, Education, p-tau slope
[6]	**PET** (PiB)	SUVRs: ITC, STC, MTC, isthmus cingulate, Pre, fusiform, meta-temporal (global)	**PET**: tau	**Global cognition*** PACC-96* (MMSE, LM, DSST, Free and Cued Selective Reminding Test)	Age, Sex, Education, Baseline AB, Baseline tau, Tau change
[7]	**PET** (PiB & FMM)	SUVRs: LTC, MTC, FC, ACG, PCG, Pre	–	**Episodic memory** (WMS-R (logical memory II), **Global cognition** (MMSE), Clinical (CDR)	*NR*
[9]	**PET** (PiB) & **CSF**	Aß 1–42 SUVRs: PFC, OFC, PC, TC, ACC, PCC, Pre	**CSF**: t-tau **MRI**: hippocampal volume **PET**: FDG	**Clinical**: MMSE, Short Test of Mental Status	Age and Change in age from baseline, Baseline MMSE score and change in MMSE score from baseline, Sex, APOE e4 (separate models)
[13]	**PET** (Florbetapir)	SUVRs: FC, CC, PC, TC (cortical summary)	**MRI**: hippocampal volume **PET**: tau, FDG	**Executive function***, **Episodic memory*** (ADNI neuropsychological battery)	Time, Age, Sex, Education, APOE e4, Baseline AB, AB slope (and interaction effects)
[16]	**PET** (Florbetapir)	SUVRs: FC, CC, PC, TC (cortical summary)	**MRI**: hippocampal volume **PET**: FDG	**Executive function*** (DSST, DS (backwards), TMT (parts A and B), Category Fluency (animal and vegetable), Digit Cancellation, Clock Drawing test), **Episodic memory*** (RAVLT, ADAS-cog (word list learning), MMSE (word recall), WMS-R (Logical Memory I))	Age, Sex, Education, and APOE e4 status, Annualized florbetapir measurements, Baseline florbetapir SUVR, Time, Baseline florbetapir SUVR × time
[17]	**PET** (PiB)	DVRs: FC, CC, PC, TC (global index)	**fMRI**: task-related hippocampal activation	**Episodic memory** (CVLT-II)	Age, Sex, Education, APOE e4, Scanner, Time
[19]	**CSF**	Aß 1–42	**CSF**: t-tau, p-tau **MRI**: hippocampal volume **PET**: FDG, AB	**Global cognition** (ADAS-cog)	Age, Time, Baseline CSF AB42, APOE e4 (separate analysis)
[22]	**PET** (PiB)	DVRs: global composite (derived from 8 ROIs)	**CSF**: AB1-42, t-tau, p-tau, NFL, MCP-1, YKL-40	**Episodic memory** (RAVLT, WMS-R)	Sex, APOE ε4, FH, Interval between first cognitive evaluation and LP, literacy, CSF biomarker level, Time (age at each visit), and the interaction of time + CSF measure (slope)
Sluimer et al., 2008	**CSF**	Aß 1–42	**CSF**: tau, p-tau **MRI**: whole-brain atrophy	**Global cognition** (MMSE)	Age, Sex, Diagnosis
[27]	**PET** (FDDNP)	DVRs: PC, MTC, LTC, FC, PCC	–	**Executive function*** (TMT (B), Stroop (interference)), **Episodic memory** * (WMS-III (Logical memory), BSRT, RCFT), **Language*** (BNT, F-A-S & Animal fluency), **Processing speed & Attention*** (TMT Part A, Stroop (color naming), WAIS-III (DSST)), **Visuospatial*** (WAIS-III (block design), RCFT (Copy))	*NR*
[29]	**CSF**	Aß 1–42	**CSF**: t-tau, p-tau	**Global cognition** (ADAS-cog, (AQT), (Clock drawing test)), **Episodic memory** (ADAS-cog)	Age, Sex, Drop out, APOE e4
[31]	**PET** (PiB)	SUVRs: global	–	**Clinical**: MMSE, CDR, CVLT-II, RCFT, BNT, DS, Category and letter fluency, DSST, Stroop	Age, Gender, Education, PiB status
[32]	**PET** (PiB)	SUVRs: FC, SPC, LTC, LOC, ACC, PCC	–	**Episodic memory** * (RCFT, CVLT), **Non-memory cognition*** (BNT, Category and letter fluency, DS, DSST, RCFT (recognition and trial copy))	Age, Education

Table 2 (*continued*)

Study	Technique	Aß	Other biomarkers	Cognition	Covariates
[33]	**PET** (PiB) & **CSF**	Aß 1–42 SUVRs: PFC, Pre, TC	**CSF**: t-tau, p-tau **MRI**: hippocampal volume **PET**: FDG	**Episodic memory** * (DIAN 16 word-list learning test, WMS-R), **Processing speed & Attention*** (WAIS (DSST)), **Global cognition*** (MMSE)	Gender, Education, Baseline age, APOE e4, Baseline biomarker
[35]	**PET** (PiB) & **CSF**	Aß 1–42 SUVRs: PFC, Pre, TC	**CSF**: tau, p-tau **MRI**: hippocampal volume	**Global cognition***: WMS (Logical Memory, Verbal Paired Associates), Free and Cued Selective Reminding, Animal Naming, TMT (Part A and B)	Familial history, Baseline age, and APOE e4

*Measured with a composite score. Others used individual test scores. **Abbreviations**: Aß 1–42: amyloid beta 1–42 ratio, ACC: anterior cingular cortex, ACG: anterior cingular gyrus, ADAS-cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale, ADNI: Alzheimer's Disease Neuroimaging Initiative, BNT: Boston Naming Test, BSRT: Buschke Selective Reminding Test, CANTAB: Cambridge Neuropsychological Test Automated Battery, CC: cingular cortex, CDR: Clinical Dementia Rating, CSF: cerebrospinal fluid, CVLT: California Verbal Learning Test, DS: Digit Span, DSST: Digit Symbol Substitution Test, DVR: distribution volume ratios, FC: frontal cortex, FDDNP: 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile, FDG: fluodeoxyglucose, HVLT: Hopkins Verbal Learning Test, ITC: inferior temporal cortex, LPFC: lateral prefrontal cortex, LOC: lateral occipital cortex, LTC: lateral temporal cortex, MMSE: Mini-Mental State Examination, MRI: magnetic resonance imaging, MTC: middle temporal cortex, NR: not reported, OFC: orbitofrontal cortex, PACC: Preclinical Alzheimer Cognitive Composite, PC: parietal cortex, PCC: posterior cingular cortex, PCG: posterior cingular gyrus, PET: positron emission tomography, PFC: prefrontal cortex, PiB: Pittsburgh Compound B, Pre: precuneus, RCFT: Rey Complex Figure Test, RAVLT: Rey Auditory Verbal Learning Test, RPM: Raven's Progressive Matrices, ROI: region of interest, SPC: superior parietal cortex, STC: superior temporal cortex, SUVR: standardized uptake value ratios, tau (t-tau, p-tau): protein tau (total, phosphorylated), TC: temporal cortex, TMT: Trail Making Test, WAIS: Wechsler Adult Intelligence Scale, WMS: Wechsler Memory Scale.

participants) were extracted and are shown in Table 1. Information on Aβ accumulation and cognitive decline (i.e., measurement techniques and assessments used) were also extracted (see Table 2), as well as the results of each study (i.e., effect sizes and *p*-values) (see Table 3). The methodological quality of each included study was assessed by two independent reviewers (C.P. and D.P.) with an adapted version of the *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies* (National Institute on Health) (see Supplementary Material Table 2). Studies were assessed for sample size, loss to follow-up, inclusion and exclusion criteria, definition, and measurement of variables of interest and confounding variables, effect size, and *p*-values. Authors of each included study were contacted to provide additional information as needed.

3. Results

3.1. Study selection

On May 13, 2021, 3,968 studies were uploaded to Covidence from the databases (Embase (n = 1,794), PubMed (n = 1,425), Web of Science (n = 471), and PsycInfo (n = 179)). From these 3,968 studies, 1,234 duplicates were removed. From mid-May of 2021 to the end of June 2021, two reviewers (C.P. and L.S.R.) screened the remaining 2,734 titles and abstracts, according to the inclusion and exclusion criteria. A third independent reviewer was not required. In total, 2,466 references were excluded. Full-text screening of the 268 articles resulted in the exclusion of 251 articles. The excluded articles had a single time point for Aβ (n = 101) or cognition (n = 1), did not report a measure of the association between Aβ and cognition (n = 65), did not include cognitively healthy participants at baseline (or participants had the genetic form of AD) (n = 21), had designs that were not longitudinal (n = 14), did not measure Aβ with PET imaging or LP (n = 10), did not report a measure of cognition (n = 1), or the articles were not a peer-reviewed original research articles (n = 38). The final selection for this systematic review included 17 articles (see Fig. 1).

3.2. Data collection

No additional information was collected after contacting the authors of the included studies. Several studies did not report *p*-values, effect sizes or both for the association between Aβ accumulation and cognitive decline, as assessed by one or multiple cognitive domains. This was particularly the case for non-significant results (see Table 3). The non-reporting of *p*-values and effect sizes was part of the quality assessment.

3.3. Study characteristics

Study characteristics and descriptive data are presented in Table 1. The included studies were published between 2008 and 2021. The majority of studies (12/17) used different databanks: Alzheimer's Disease Neuroimaging Initia-

Table 3
Results: Longitudinal association between ß-amyloid accumulation and cognitive decline in cognitively healthy older adults.

#	Study	Amyloid	Cognitive domains assessed	Global cognition *p* (ES)	Executive function *p* (ES)	Episodic memory *p* (ES)	Processing speed *p* (ES)	Visuospatial *p* (ES)	Working memory *p* (ES)	Clinical *p* (ES)
1	[4]	PET	Episodic memory, Processing speed, Reasoning			Global: $p = 0.053/F = 3.820$ ACC: $p = 0.920/F = 0.010$ **PCC: $p = 0.014^*/F = 6.284^*$** **Pre: $p = 0.006^*/F = 7.948^*$** **LPC: $p = 0.014^*/F = 6.211^*$** LOC: $p = 0.082/F = 3.077$ LTC: $p = 0.201/F = 1.655$ OFC: $p = 0.745/F = 0.106$ LPFC: $p = 0.235/F = 1.424$	*n.s.* all *ps* > 0.10			
2	[5]	CSF	Episodic memory, Working memory, Processing speed			*n.s.*	*n.s.*		*n.s.*	
3	[6]	PET	Global cognition	Model 7: $p = 0.31$ (1.75) Model 8: $p = 0.21$ (2.08)						
4	[7]	PET	Episodic memory, Global cognition, clinical	*n.s.*		*NR*				*n.s.*
5	[9]	PET & CSF	Clinical							*n.s.*
6	[13]	PET	Episodic memory, Executive function		*n.s.*	**$p = 0.046^*$, β = 1.50***				
7	[16]	PET	Episodic memory, Executive function		E = −1.909	**$p = 0.031^*$, E = −2.546***				
8	[17]	PET	Episodic memory			**$p = 0.023^*$, E = 20.06***				
9	[19]	CSF	Global cognition	R2 = −0.02						
10	[22]	PET	Episodic memory			*n.s.*				
11	[26]	CSF	Global cognition	*n.s.*						
12	[27]	PET	Episodic memory, Attention/Processing speed, Executive function, Visuospatial		*NR*	**Global: $p = 0.01^*/r = -0.37^*$** **Frontal: $p = 0.01^*/r = -0.37^*$** **PCC: $p = 0.03^*/r = -0.32^*$** NR for other regions	*NR*	*NR*		
13	[29]	CSF	Global cognition, (Episodic memory)	*n.s.* **Patho group (20% decrease): $p < 0.05$**		*n.s.* **Patho group (15% decrease): $p < 0.05$**				
14	[31]	PET	Clinical							*n.s.*
15	[32]	PET	Episodic memory, Non-memory cognition, Clinical	*n.s.*		*n.s.*				**Progressors: $p < 0.05$**
16	[33]	PET & CSF	Episodic memory, Attention/Processing speed, Global cognition	PET: $p = 0.87$ (0.06) CSF Aß 1–42: $p = 0.64$ (0.08)						
17	[35]	PET & CSF	Global cognition: Episodic memory, Working memory, Semantic knowledge, Executive function, Attention, Visuospatial	PET: $r = -0.24$ CSF Aß 1–42: NR						

Abbreviations: Aß 1–42: amyloid beta 1–42 ratio, ACC: anterior cingular cortex, CSF: cerebrospinal fluid, E: Estimate, ES: effect size, LPFC: lateral prefrontal cortex, LOC: lateral occipital cortex, LTC: lateral temporal cortex, NR: not reported, n.s.: not significant, OFC: orbitofrontal cortex, *p*: *p*-values, PCC: posterior cingular cortex, PET: positron emission tomography, PFC: prefrontal cortex, Pre: precuneus.

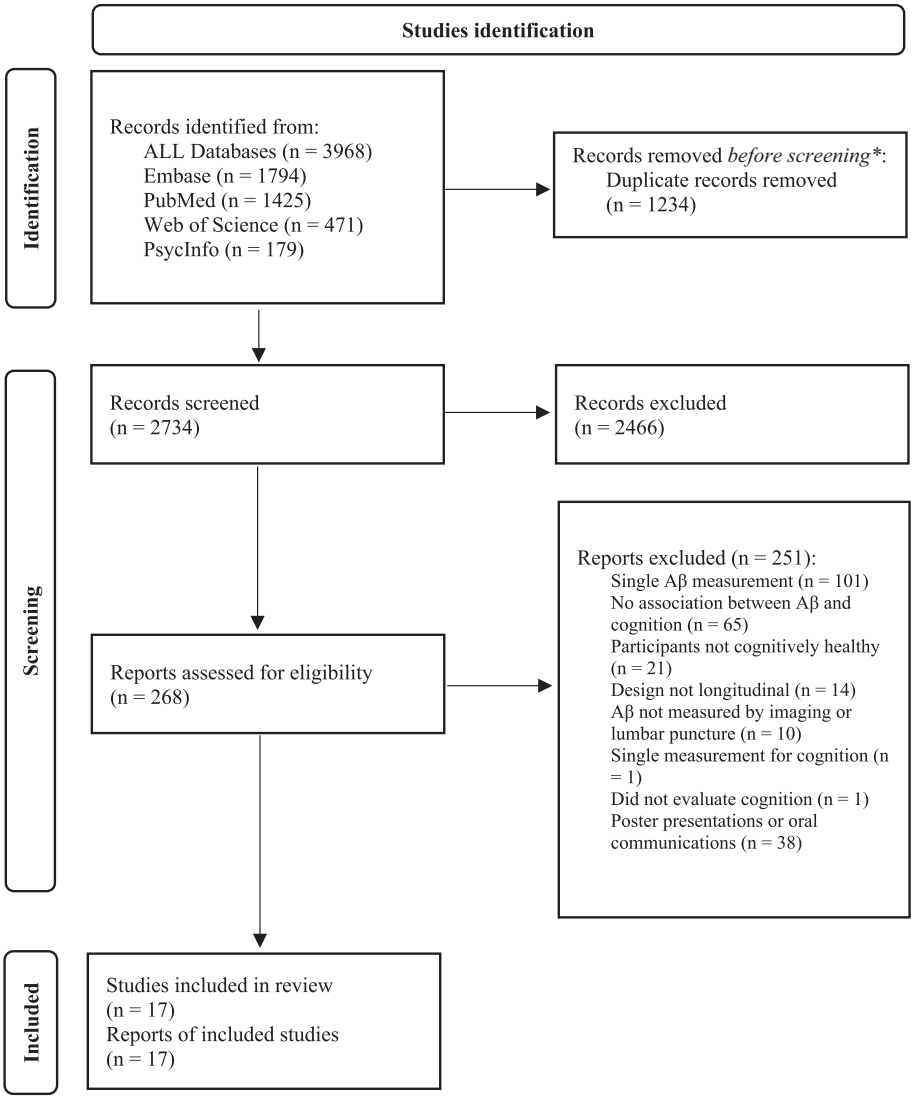

Fig. 1. PRISMA flow chart diagram *All duplicates were removed automatically by the Covidence software.

tive (ADNI) (n = 5), Melbourne Healthy Aging Study (MHAS) (n = 2), Adult Children Study (ACS) (n = 1), Dominantly Inherited Alzheimer Network (DIAN) (n = 1), Dallas Lifespan Brain Study (DLBS) (n = 1), Harvard Aging Brain Study (HABS) (n = 1), and Wisconsin Registry for Alzheimer's Prevention (WRAP) (n = 1). The other five studies recruited their participants through local memory clinics, medical centers, and community advertisements.

The age of participants ranged from 38.3 to 78.4 years (M_{age} = 69.1 years). The percentage of females ranged from 44.7% to 70.4% (M = 54%). The number of years of education ranged from 13.2 to 17.4 years ($M_{education}$ = 15.4 years). At baseline, the sample size ranged from 13 to 540 (mean n = 140). The sample size at the first follow-up ranged from 11 to 207 (mean n = 92.47). Follow-up duration ranged from 1.3 to 6.7 years (M = 3.2 years) for cognition and ranged from 1.3 to 5.3 (M = 3.0 years) for Aβ. Measurement time points ranged from two (baseline and a single follow-up) to nine (M = 4.1 time points) for cognition and ranged from two to six (M = 3.6 time points) for Aβ.

3.4. Measurement of Aβ

Aβ was measured by PET imaging (n = 10), LP (n = 4) or both techniques (n = 3) (see Table 2 for more details). PET studies (n = 13) used the radiotracer Pittsburgh compound B (PiB) (n = 9), Florbetapir (n = 3), and 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene) malononitrile (FDDNP) (n = 1). Units of measurement for Aβ were obtained using standardized uptake value ratios (SUVRs) (n = 10) and distribution volume ratios (DVRs) (n = 3). Seven studies used a global index or composite of SUVRs or DVRs for measuring Aβ in the whole brain, whereas the remaining studies used specific brain regions. Studies using LP (n = 7) used the Aβ 1–42 ratio measure. Other biomarker measures used were: cerebrospinal fluid

(CSF) protein tau (either total tau (t-tau) and/or phosphorylated tau (p-tau)) (n = 8), cerebral volumes with magnetic resonance imaging (MRI) (n = 9) (seven of which specifically measured hippocampal volume), fluorodeoxyglucose (FDG) PET (n = 5), and PET tau (n = 2). Some studies also measured Aβ with PET or LP but did not include these measures in their analyses.

3.5. Cognitive assessment

Cognitive domains assessed (see Table 2 for more details) included episodic memory (n = 12), executive function (n = 4), attention and processing speed (n = 5), working memory (n = 2), language (n = 1), and visuospatial ability (n = 2). Global cognition (n = 7) and clinical status or disease progression (n = 3) were also measured. Cognition was assessed using a composite score (n = 8) or using individual test scores (n = 8). A list of the cognitive tests is presented in Table 2. The most commonly used tests included the Digit Symbol Substitution Test (n = 8), which assesses attention and processing speed, the Wechsler Memory Scale (3rd Edition (WMS-III) or Revised (WMS-R)) (n = 7) which assesses episodic memory, and the Mini-Mental State Examination (MMSE) (n = 6) which assesses global cognition and clinical status.

3.6. Association between Aβ and cognition

Of the 17 studies reviewed, a minority of seven reported (studies' #: 1, 6, 7, 8, 12, 13, 14) a statistically significant association or prediction of Aβ change on cognitive change. A summary of the results of these studies is presented in Table 3. In these seven studies, Aβ was measured using PET imaging (n = 6) and LP (n = 1); follow-up duration was an average of 3.7 years for cognition and 3.8 years for Aβ; and they had an average of 4.4 measurement time points for cognition and 3.5 time points for Aβ. Five of the seven studies used a composite score to measure cognition, two studies used individual test scores, and one study used change in disease progression (clinical status). Six of the seven studies found a significant association between Aβ and episodic memory; one study found a significant association between Aβ and global cognition. These studies also used measures of global cognition (n = 1), executive function (n = 3), episodic memory (n = 1), attention and processing speed (n = 2), and visuospatial ability (n = 1).

Articles reporting an association between Aβ accumulation and cognition include a study by Farrell et al. [4] that reported that in initially Aβ-negative cognitively healthy participants, increased Aβ in global (whole brain), posterior cingular, precuneus and lateral parietal cortices significantly predicted declining performance in episodic memory. In another study, Jagust & Landau [13] reported similar results; such that Aβ slope, as well as age, significantly predicted decreases in episodic memory performance in initially Aβ-negative cognitively healthy participants. Landau et al. [16] and Leal et al. [17] also found similar predictions of episodic memory decline and Aβ accumulation. Small et al. [27] reported a significant negative correlation between Aβ change in the global (whole brain), frontal, and posterior cingular cortex and episodic memory change at follow-up. Stomrud et al. [29] found no significant association between longitudinal Aβ change and cognitive test results at follow-up. However, after a dichotomization of their sample with respect to the presence of pathological changes (i.e., 15% increase in Aβ at follow-up), a statistically significant correlation (positive or negative) was found with episodic memory, and also with global cognition for another pathological subsample of participants (i.e., a 20% increase in Aβ at follow-up). Lastly, Villemagne et al. [32] also initially found no significant correlation between Aβ increases and cognitive change in their cognitively healthy participants sample, but only in their full cohort, which included MCI participants. They then compared the cognitively healthy participants who progressed to MCI or major neurocognitive disorder at follow-up with those who remained cognitively healthy and found that the former had significant increases in Aβ compared with the latter.

No specific association between Aβ accumulation and cognitive decline in cognitively healthy participants was reported in the remaining ten studies (studies' #: 2, 3, 4, 5, 9, 10, 11, 14, 16, 17). Among these 10 studies, three used CSF, four used Aβ PET, and three used both CSF and Aβ PET; follow-up duration was an average of 2.8 years for cognition and 2.5 years for Aβ; and they had an average of 4.0 measurement time points for cognition and 3.6 time points for Aβ. These studies used measures of global cognition (n = 6), episodic memory (n = 3), attention and processing speed (n = 1), working memory (n = 1), and clinical status or disease progression (n = 3), for which the results were not statistically significant. Six studies used individual test scores to measure cognition, three used composite scores and one used clinical status.

One study did not find a significant association between cognitive decline and Aβ accumulation alone, but did find that decline in episodic memory measures was predicted by p-tau slope, and that decline in processing speed measures was predicted by the interaction of p-tau slope and Aβ slope [5]. These authors also sought to compare cognitively healthy participants whose Aβ trajectories differed (was either abnormal at baseline, normal at baseline but declining at follow-up, or normal stable), but found no significant differences in their cognitive trajectories and reported their results for the entire cohort. Jack et al. [9] found no significant results in their cognitively healthy participants sample, but reported significant associations in the whole cohort, which included participants with MCI and dementia. They also reported that their cognitively healthy participants did not show any cognitive decline at follow-up and therefore they could not measure an association with Aβ trajectory. When they pooled all participants, Aβ worsened along with MMSE score only in APOE e4 positive participants. This significant association was not found in clinical subsamples of participants or in APOE e4 negative participants.

The remaining studies did not report a significant association between Aβ accumulation and cognitive decline in cognitively healthy adults. Hanseeuw et al. [6] tested the predictive value of Aβ change, as well as other biomarkers, on cognitive decline. While baseline Aβ and tau change significantly predicted cognitive decline, Aβ change did not.

Hatashita et al. [7] reported no significant association between Aβ and cognition at both baseline and follow-up in cognitively healthy participants, but also in MCI and participants living with a major neurocognitive disorder. Another study reported that no biomarkers (Aβ, glucose metabolism or hippocampal volume) change related to cognitive change in cognitively healthy participants, although glucose metabolism and Aβ were significantly related to cognition at baseline [19]. Racine et al. [22] showed that although CSF ratios of Aβ, t-tau, and p-tau predicted Aβ accumulation at follow-up, none were significantly associated with cognitive decline. Sluimer et al. [26] found an association between whole-brain atrophy rate and cognitive change in their sample (which also included participants living with MCI or major neurocognitive disorder), but Aβ change was once again not associated with cognitive change, and nor was tau change. Villain et al. [31] studied Aβ rates of change in cognitively healthy participants and participants living with MCI or a major neurocognitive disorder. Although they showed a significant increase in Aβ over time, this increase was not significantly associated with cognitive decline. Conversely, Wang et al. [33] reported no change in cognition or Aβ in their cognitively healthy participants, and no significant association between the two variables. Finally, one study reported a significant association between Aβ and cognition at baseline, and between tau and hippocampal volume change and cognitive decline at follow-up, but not with Aβ change [35].

3.7. Methodological quality

The results of the assessment of the methodological quality of the included studies are presented in the Fig. 2. The individual results for each included study are presented in the Supplementary Material Table 2. Twelve studies (studies' #: 1, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 17) reported a sample size justification (mainly data availability). However, none of the studies used a power analysis to determine their sample size. Many studies did not report loss to follow-up or missing data (n = 8; studies' #: 3, 4, 9, 10, 11, 14, 16, 17) and/or did not account for them in their analyses (n = 13; studies' #: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17). Three studies (studies' #: 5, 9, 16) did not provide sufficient information on population eligibility and selection criteria (e.g., lack of detail regarding the selection of cognitively healthy participants). Two studies (studies' #: 2, 5) did not provide sufficient information on the measurement of cognition (i.e., did not clearly describe the tools and methods used to evaluate cognition). Two studies (studies' #: 4, 12) did not mention whether covariates (e.g., age, sex, education, among others) were controlled for in their analyses. All studies reported *p*-values and effect sizes for their statistically significant results. However, they did not report them for all of their results (i.e., those that were not statistically significant) (see Table 3). Studies report the absence of significant effects or associations without reporting the exact effect sizes or *p*-values.

4. Discussion

4.1. Summary of findings

4.1.1. Association between Aβ accumulation and cognitive decline: A mixed picture

To better understand the onset and progression of AD, it is crucial to examine both its putative pathophysiology and its clinical syndrome, as well as their longitudinal relationship at preclinical stages. In this systematic review, we report the results of 17 studies on the longitudinal association between Aβ accumulation and cognitive decline in cognitively healthy adults. A minority of seven of these studies reported a significant association between Aβ accumulation and decline in at least one cognitive domain (episodic memory (n = 6) or global cognition (n = 1)). Only subtle and early changes in episodic memory were observed at this stage. Although episodic memory deficits are known to be an early feature of cognitive decline observed in AD, of the 10 studies that assessed episodic memory, four did not find this association. Similarly, of the eight studies that assessed global cognition, only one reported a significant result. Thus, a test that assesses global cognitive decline may not be sensitive enough in the preclinical stage. Overall, many of the included studies did not observe a significant decline in cognitive performances during follow-up [9,19,29,32,33].

4.1.2. Factors that may influence the association between Aβ accumulation and cognitive decline in cognitively healthy older adults

4.1.2.1. Using composite measures to assess cognitive decline. Significant results were found in five of the seven studies that used a cognitive composite score. Such composite measures were used in only two of the ten studies that found no significant results. Composite measures, which rely on multiple tests and scores, may be a more sensitive and comprehensive measure of cognition and cognitive decline than individual test scores, and may be able to detect these subtle and early changes that would otherwise not be observed [14]. Therefore, the use of multiple measures and composite scores is recommended when assessing early and subtle cognitive changes in cognitively healthy individuals. In this regard, the development of comprehensive cognitive evaluation protocols and new adapted psychometric tools is essential for the study of cognitive decline in preclinical AD.

4.1.2.2. The choice of the neuroimaging technique. In terms of neuroimaging technique, PET imaging (n = 13) was more frequently used than LP (n = 7). Six of the seven studies reporting significant associations used PET, while one used LP. The studies reporting significant results with PET imaging (n = 6) found them in the frontal, posterior cingular, lateral parietal and global (whole brain) cortex as well as in the precuneus, which is consistent with previous findings in the literature [28]. In the early stages of AD, Aβ is expected to initially accumulate in the CSF in its soluble form, which can be observed by LP, before starting to aggregate, as soluble Aβ decreases in the CSF and plaques

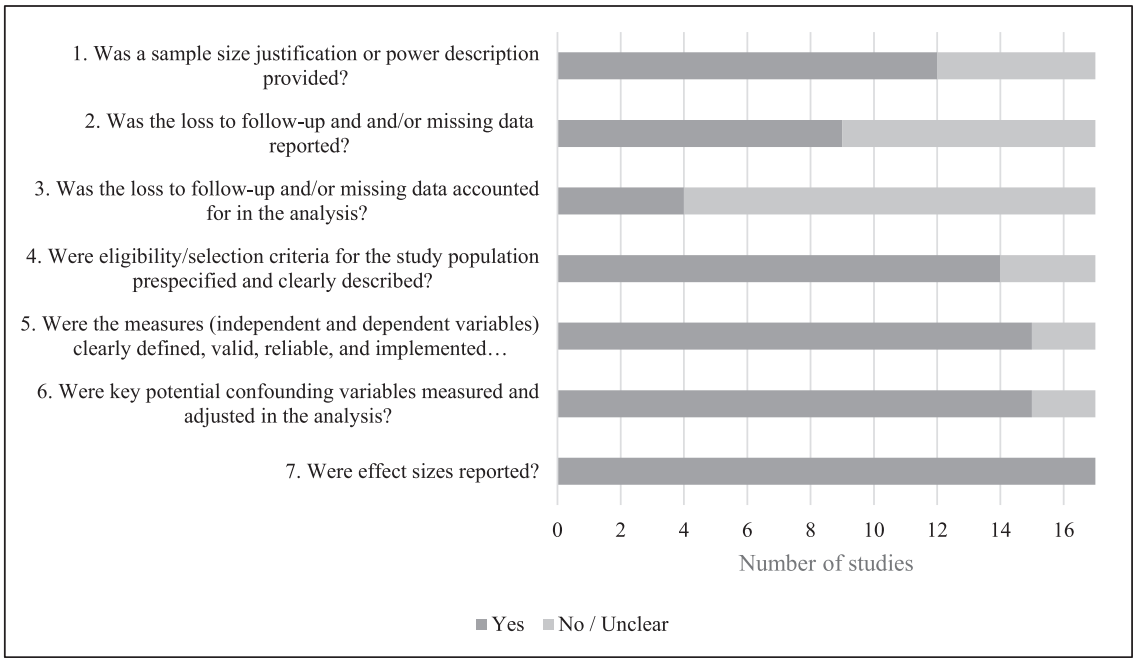

Fig. 2. Results: Methodological quality assessment *The above criteria have been modified from the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Institute on Health, available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

begin to form in the cortex, which can be observed by PET imaging (Jack Jr. et al., 2013). Differences in Aβ measurement techniques may partially explain the discrepancy observed in the present results.

4.1.2.3. The heterogeneity of cognitively healthy individuals in the preclinical stage. Another factor to consider is that the preclinical stage of AD includes individuals who may be at very different and distant stages in the pathophysiological progression of the disease, even though they are all still cognitively healthy. According to the amyloid cascade hypothesis and more recent models, the clinical syndrome appears last in the progression of AD, while multiple pathophysiological changes appear successively before the first cognitive deficits. In our review, the studies reporting significant results with PET imaging may include participants who are in advanced pathophysiological stage of AD and in whom Aβ aggregation has already begun, whereas other studies include participants in whom it is still too early to observe such changes. Therefore, the exact pathophysiological stage at which a cognitively healthy individual may be in at this preclinical stage may vary considerably. This variability may compromise the establishment of a relationship between Aβ accumulation and cognitive trajectories.

4.1.2.4. Other factors and biomarkers. In this review, the included studies analyzed the effect or interaction of a variety of factors other than Aβ on cognitive decline. Age, education and APOE e4 status were examined in most of the included studies. These factors have all previously been shown to have a significant effect on cognitive decline in several studies. Several of the included studies also analyzed other biomarkers for which significant associations and effects were found. Among these, tau protein (either t-tau or p-tau measured in CSF or by PET imaging) and hippocampal volume (measured by MRI) have been reported to be significantly related with cognitive decline [5,6]. Because tau pathology and hippocampal atrophy follow the time course of cognitive decline more closely and strongly than Aβ pathology [24], it's possible that the Aβ-specific contribution to cognitive decline is small, reducing the likelihood of finding statistically significant associations in the present review.

4.1.2.5. The duration of the longitudinal studies. Studies that did not report significant outcomes tended to have slightly shorter follow-up times (mean 2.8 years for cognition and 2.5 years for Aβ) than studies that did report significant outcomes (mean 3.7 years for cognition and 3.8 years for Aβ). Because the disease evolves over decades, during which subtle pathophysiological and clinical manifestations emerge, it is recommended that participants be followed for long periods of time, in order to observe these changes.

4.1.2.6. Cognition and Aβ trajectories during AD progression. Lastly, before examining the association between Aβ accumulation and cognitive decline, it is essential to study the trajectories of both variables independently. Models based on linear regression and correlation are only useful for examining this association if both trajectories are linear in nature and over time. However, previous literature has demonstrated that both cognition and Aβ evolve in nonlinear trajectories during AD progression [23,34]. The onset and pace at which Aβ and cognition

progress during disease are distinct and highly variable, making it difficult to study their association.

4.1.2.7. The methodological quality of the studies. There was no difference in methodological quality between studies that reported significant results and those that did not. However, some studies did not provide enough information to be replicated. Other studies did not report their power analysis, which compromised the investigation of possible associations. The results were not pooled in a meta-analysis, because the reporting of effect sizes for nonsignificant outcomes was incomplete, creating a strong bias towards significant outcomes, for which *p*-values and effect sizes were more frequently reported.

Limitations

Limitations of the present review include the lack of a meta-analysis of the results of the included studies, which limits the generalizability of the results of the selected individual studies. The heterogeneity of the studies was also a factor that compromised the conduct of a meta-analysis. In addition, the selection of studies for this review was limited to electronic databases and peer-reviewed published articles in English and French. This excludes unpublished results and creates a bias in favor of studies reporting significant results. Therefore, the results of this systematic review should be interpreted with caution.

5. Conclusion

Our review highlights the current challenges in studying the association between cognitive decline and Aβ accumulation in cognitively healthy individuals and presents some of the factors that may influence this association. More studies are needed to provide a clearer picture of this relationship. From an early detection and prevention perspective, it remains essential to study the relationship between the clinical manifestation of the disease and its putative cause at an early stage of the disease, i.e., in cognitively healthy elderly individuals, and to follow its progression over several years. Future studies should consider methodological factors such as the longitudinal design and length of follow-up, as well as the sensitivity and variance of the tools and techniques used to measure cognition and Aβ. They should also consider the multiple confounding factors and the high heterogeneity of the disease progression.

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Authors' contributions

- Guarantors of integrity of entire study: all authors;
- Study concepts and design: all authors;
- Literature research: C.P. and L.S.R.
- Data acquisition and processing: C.P.
- Methods, analysis and interpretation: C.P. and D.P.
- Manuscript preparation: C.P. and D.P.
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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbas.2023.100074.

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