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RISK FACTORS OF COGNITIVE DECLINE IN ELDERLY POPULATION

PhD Thesis

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Translational Medicine Program

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Budapest,

2025

„Az Emberért megyünk mi küzdelembe,

A fegyverünk: tudás és szeretet”

(We fight for Humanity, our weapons: knowledge and love)

Juhász Gyula

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1. LIST OF ABBREVIATIONS

A+	beta-amyloid positive
A-	beta-amyloid negative
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
Aβ	beta-amyloid
aHR	adjusted Hazard Ratio
BMI	Body Mass Index
CAIDE	Cardiovascular Risk Factors, Aging, and Incidence of Dementia
CDR	Clinical Dementia Rating
ChiSq	Chi-Square Test
CI	Confidence Interval
CSF	Cerebrospinal Fluid
CU	Cognitively Unimpaired
DEP+	depression-positive
DEP-	depression-negative
df	Degrees of Freedom
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
HR	Hazard Ratio
IQR	Interquartile Range
I^2	I-squared
MAPT	Multidomain Alzheimer Preventive Trial
MCI	Mild Cognitive Impairment
MH	Mantel-Haenszel Method
MMSE	Mini-Mental State Examination
n	number of participants
NIA-AA	National Institute on Aging – Alzheimer's Association
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory Questionnaire
OR	Odds Ratio
p	p-value
PET	Positron Emission Tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
p-tau	phosphorylated tau
QUIPS	Quality in Prognosis Studies
SD	Standard Deviation
SUVR	Standardized Uptake Value Ratio
T+	phosphorylated tau positive
T-	phosphorylated tau negative
Tau^2	Tau-squared

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

Our vision is that cognitive decline will be avoidable in the future with the help of widely used prevention tools. To achieve this, our mission is to develop prevention strategies by better-aligning dementia biomarkers and the known modifiable dementia risk factors. In light of all this, we have set two specific goals. Primarily, we aimed to evaluate the association between Alzheimer's disease-related proteins, pathological beta-amyloid and p-tau levels, and the rate of cognitive decline through a systematic review and meta-analysis. Secondly, we sought to estimate the role of modifiable dementia risk factors according to amyloid and p-tau status through a dataset analysis.

2.2. Scientometrics

Number of all publications:	5
Cumulative IF:	29.0
Av IF/publication:	5.8
Ranking (Sci Mago):	D1: 3, Q1: 2
Number of publications related to the subject of the thesis:	2
Cumulative IF:	15.2
Av IF/publication:	7.6
Ranking (Sci Mago):	D1: 2
Number of citations on Google Scholar:	51
Number of citations on MTMT (independent):	27
H-index:	4

2.3. Future plans

My future goals are to increase the use of current dementia prevention tools in patient care and to make this information widely available. I would also like to be involved in research to further develop dementia prevention, with a particular focus on late life depression and its therapeutic potential.

3. SUMMARY OF THE PhD

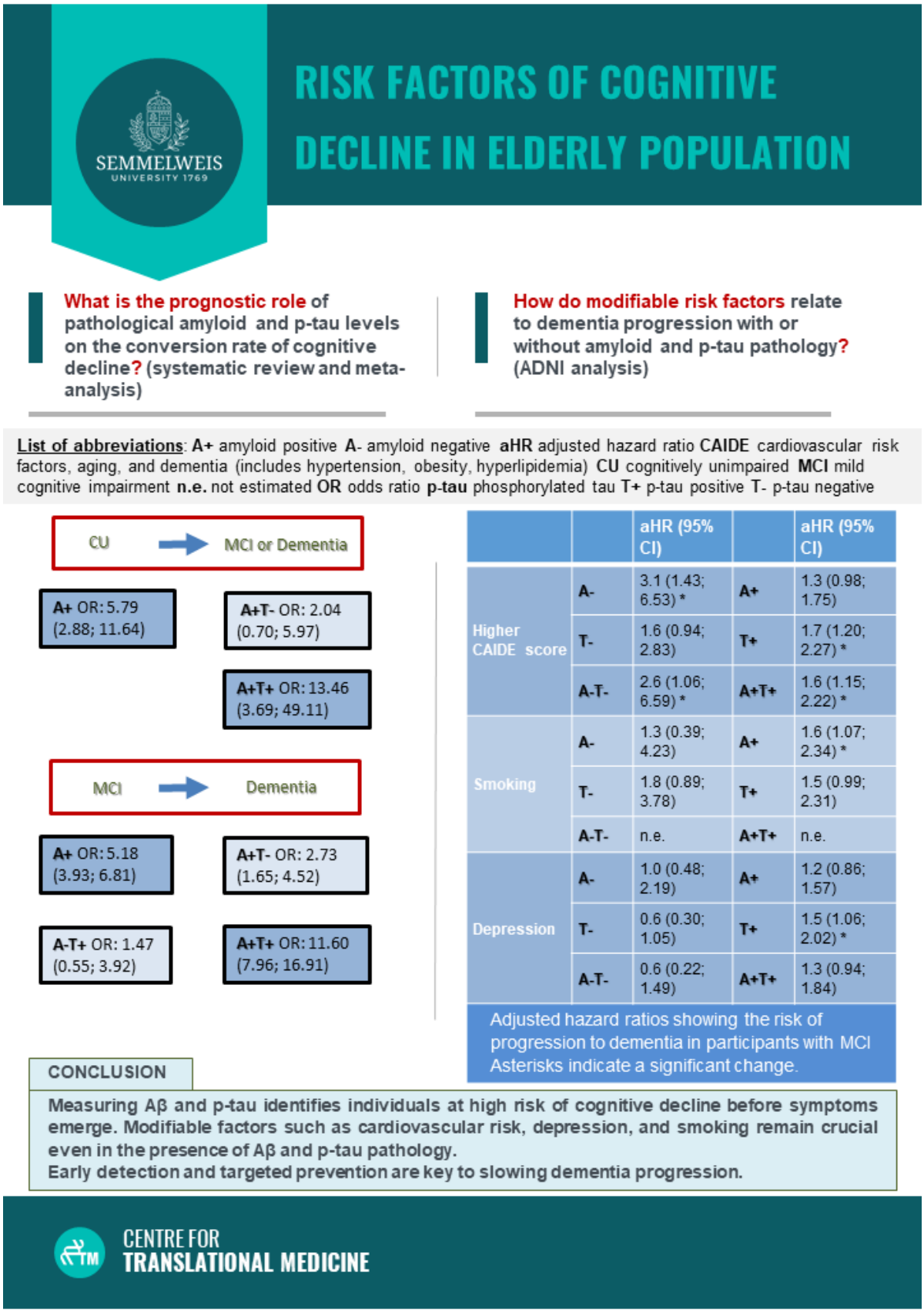
We aimed to investigate the role of Alzheimer's disease (AD) biomarkers and modifiable risk factors in the progression of cognitive decline. This was done by estimating the increased risk associated with AD pathological changes and by further developing existing prevention strategies. AD biomarkers, such as amyloid-beta (Aβ) and phosphorylated tau (p-tau) are considered to play a central role in the pathogenesis of AD and the are increasingly employed in diagnostic procedures. However, the extent to which these biomarkers predict cognitive decline in cognitively unimpaired (CU) individuals or those with mild cognitive impairment (MCI) remains unclear. In addition, the role of major modifiable risk factors such as hypertension, obesity, hyperlipidaemia, smoking and depression in relation to AD pathology requires further investigation.

A systematic review and meta-analysis was conducted to investigate the role of Aβ and p-tau biomarkers in the progression of cognitive deterioration. The findings indicate that Aβ positivity is a significant predictor of progression to MCI and dementia, and the presence of p-tau further elevates the risk of this progression.

Our second study examined the role of modifiable risk factors associated with Aβ and p-tau pathology. Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), data from 434 CU and 611 MCI participants were examined. The analysis showed that among MCI participants, the modifiable risk factors examined were associated with an increased risk of progression, even in the presence of AD pathology.

Our findings highlight the combined importance of AD biomarkers and modifiable risk factors in understanding disease progression. By incorporating these factors into risk assessment models, our research contributes to identifying high-risk individuals and underscores the potential for targeted interventions to delay or prevent the onset of dementia. Furthermore, it emphasises the necessity for further investigation of the population exhibiting AD pathology but cognitively unimpaired.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Our research aims to contribute to the understanding of early identification of individuals at risk of developing dementia. To this end, we are investigating the association between changes in Alzheimer's-related proteins (amyloid-beta (Aβ) and phosphorylated tau (p-tau))(1, 2) and dementia progression. It also examines known modifiable dementia risk factors(3, 4) (namely obesity, hypertension, hyperlipidaemia, smoking and depression) in relation to changes in Aβ and p-tau biomarkers.

5.1.2. What is the problem to solve?

Although Aβ and p-tau play a central role in the development of Alzheimer's disease (AD), and pathological Aβ changes are highly prevalent in all cases of dementia(5), the specificity of abnormal Aβ levels for AD and their central role in its pathomechanism have been questioned(6). Their use as a preventive screening target is still under debate(7). The extent to which the presence of these protein changes accelerates cognitive decline is still uncertain. In addition, the role of modifiable dementia risk factors in the context of these existing biomarker pathologies remains to be clarified.

5.1.3. What is the importance of the topic?

Dementia is a leading cause of years lived with disability and represents a significant long-term economic challenge to society(8). As the population ages, the consequences of dementia are anticipated to become even more severe(9). Given the current therapeutic limitations, early identification of at-risk individuals and the development of preventive strategies are crucial in dementia care.

5.1.4. What would be the impact of our research results?

By examining the correlation between Aβ and p-tau pathology and the rate of dementia progression, it may be possible to identify the population most susceptible to

developing dementia even before cognitive symptoms appear. Furthermore, if the role of modifiable dementia risk factors is estimated according to Aβ and p-tau status, the development of prevention strategies can be further advanced.

5.2. Overview of the field

5.2.1. Alzheimer's disease pathophysiology and diagnostic evolution

Dementia affects 55 million people worldwide, making it a leading cause of disability and a significant long-term economic burden(8). The most common cause of dementia is AD, which accounts for 60-80% of cases, followed by vascular dementia, Lewy body dementia, and frontotemporal dementia(8). AD is characterised by two primary proteinopathies: the extracellular deposition of Aβ as plaques and the intracellular accumulation of neurofibrillary tangles resulting from p-tau. These pathological aggregates disrupt neuronal signalling and axonal transport.(1, 2) While in the past specific pathology could only be confirmed post-mortem, in vivo tests are now available. With advances in biomarker technology, AD diagnostic criteria have evolved from solely clinical assessment and post-mortem confirmation to incorporating in vivo Aβ and p-tau biomarkers, emphasising preclinical stages(10-14). However, clinical practice still relies primarily on symptomatic presentation and radiological evidence of neurodegeneration to diagnose AD. In 2018, the U.S. National Institute on Aging–Alzheimer's Association (NIA-AA) introduced a framework for researchers(12) that defines AD purely in terms of specific biological changes, categorising cases according to Aβ (A) and p-tau (T) protein status: "Alzheimer's disease continuum" (A+), "Alzheimer's pathological changes" (A+T-), and "Alzheimer's disease" (A+T+), with A-T+ cases classified as "non-Alzheimer pathological changes". In contrast to the NIA-AA position statement, the International Working Group continues to emphasize that the diagnosis of AD should remain consistent with clinical symptoms(10). Their arguments include the low predictive accuracy of Aβ, the overshadowing of other important copathologies (e.g. α-synucleinopathy, TAR DNA-binding protein 43 pathology) and the resulting diagnostic confusion, as well as ethical and psychological considerations regarding the harmful effects of diagnosing cognitively unimpaired (CU) individuals with AD.

Regarding the NIA-AA recommendation, it is important to note that the latest update, published in 2024(11), introduced a significant change concerning p-tau. This involved further classification of various p-tau fragments (e.g. p-tau-217, -181, -231) and tau PET into two categories: Core 1 - T_1 (phosphorylated and secreted AD tau) and Core 2 - T_2 (AD tau proteinopathy). The two studies presented in this thesis were classified according to the recommendations of the 2018 NIA-AA framework since the conceptualisation of our research took place before 2024.

5.2.2. Modifiable dementia risk factors

While new anti-amyloid therapies are promising(15), current treatment options provide limited benefits. Consequently, addressing modifiable risk factors – such as smoking, depression, hypertension, hypercholesterinaemia, and obesity – through early lifestyle interventions has become a recommended approach for reducing dementia risk(16). Such modifiable risk factors are estimated to account for about 40% of dementia cases(3, 4) and are linked to both AD and cerebrovascular damage(17-27).

To estimate an individual's risk of developing dementia based on vascular factors, risk scores such as CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia)(28) have been developed. The CAIDE score is based on age, education, sex, blood pressure, body mass index, total cholesterol, and physical activity, and provides an accessible, single-score assessment. Obesity, hypertension, and hyperlipidemia, key components of CAIDE, are known to increase the risk of dementia by affecting cerebrovascular health and potentially contributing to AD pathology through mechanisms that promote Aβ accumulation(29, 30). Higher CAIDE scores have been associated with neurodegenerative markers, including cortical thinning, white matter lesions and CSF changes(31-35). In trials such as Finnish Geriatric Intervention study to prevent cognitive impairment and disability (FINGER)(36) and Multidomain Alzheimer's Preventive Trial (MAPT)(37), CAIDE helped identify at-risk individuals, with higher scores indicating cognitive benefits from lifestyle interventions. However, the relevance of CAIDE for dementia risk assessment in populations with specific cognitive and neuropathological profiles is less established.

The harmful effects of smoking on blood vessels, including cerebral vessels, are well-documented(38, 39), with smokers showing a higher risk of dementia than non-

smokers(24). Evidence suggests smoking may directly influence AD development(26, 40); older smokers exhibit reduced grey matter density in regions linked to early AD(41). In vitro and animal studies consistently show that cigarette smoke promotes amyloidogenic and tau abnormalities(26, 40). Smoking is also linked to cerebral oxidative stress, which accelerates tau hyperphosphorylation and enhances β-secretase cleavage of amyloid precursor protein, increasing Aβ oligomer production and extracellular Aβ aggregation(22).

Depression is a recognised risk factor for cognitive impairment, particularly in the context of vascular disease, as it adversely affects cerebrovascular health and increases the risk of stroke, and is also strongly associated with AD(17, 20, 42, 43). Some studies have reported that individuals with mild cognitive impairment (MCI) and pathological Aβ levels who exhibit depressive symptoms progress more rapidly to dementia than those without(44, 45).

6. OBJECTIVES

Prologue: We feel it is important to clarify that in this dissertation, the term “dementia” is used to refer to dementia syndromes of any cause, while the term “Alzheimer's disease”, or “AD” (including related terms such as “Alzheimer's continuum” and "Alzheimer's pathology") refers specifically to the protein alterations associated with AD, irrespective of the presence or absence of cognitive impairment. This nomenclature follows the recommendations outlined in the 2018 NIA-AA guideline(12) (consistent with the 2024 NIA-AA guideline)(11). Furthermore, we do not use the concept of “neurocognitive disorder” (major or mild) introduced in DSM-5(46), as it is currently not widely adopted either in clinical practice or in scientific literature.

6.1. Study I.

Pathological changes in Aβ and tau proteins associated with AD can emerge decades before cognitive symptoms(47), but the extent to which they accelerate cognitive decline remains unclear. Predictive estimates for individuals with abnormal protein levels who are otherwise cognitively unimpaired (CU) or have only mild cognitive impairment (MCI) vary widely between studies(48, 49). Systematically comparing progression rates in these populations is essential to clarify these associations. In the CU population over 50 years, the prevalence of being A+ ranges from 10 to 44%, while in MCI it ranges from 27 to 71%, depending on age(50). Considering this, we aim to investigate the effect of Aβ alone and in combination with p-tau on the progression to MCI and dementia through a systematic review and meta-analysis of the available literature. Understanding the prognostic impact of these biomarkers could underscore the clinical potential of the NIA-AA research framework, given that current therapies for MCI and dementia can only slow down the progression of the disease. Prevention starting at an early stage, or even before symptoms appear, provides the best opportunity to combat the disease effectively.

6.2. Study II.

There are strong evidence for lifestyle and healthcare-related risk factors for dementia(3, 4), and these modifiable risk factors may present opportunities for reducing dementia risk(36, 37). However, the association of such risk factors with clinical progression in biomarker-specific cognitive-neuropathological profiles is not well

understood. This study aims to focus on modifiable risk factors that are both well established in the literature and sufficiently represented in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort – namely, the CAIDE score (which incorporates hypertension, obesity, and hyperlipidaemia), depression, and smoking – and to examine their role in the progression to MCI or dementia among biomarker-homogeneous (in terms of Aβ and p-tau) CU and MCI subgroups. This was achieved through a comparative analysis of progression data between participants who were positive or negative for these modifiable risk factors within each subgroup, classified according to Aβ, p-tau, and both Aβ and p-tau pathology.

7. METHODS

7.1. Study I.

Our systematic review and meta-analysis was registered in the PROSPERO database (ID: CRD42021288100), with a pre-defined research plan and detailed objectives, is reported strictly in accordance with the recommendation of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guideline and was performed following the guidance of the Cochrane Handbook(51).

7.1.1. Search strategy, selection and data collection process

The present study included longitudinal prospective and retrospective studies using the NIA-AA 2018 recommended(12) measurement of Aβ and p-tau (for Aβ: amyloid PET, CSF Aβ42, or Aβ42/40 ratio; for p-tau: tau PET, or CSF p-tau), with the objective of examining the role of Aβ alone or in combination with p-tau in CU and MCI subjects in progression to MCI or dementia. Case reports and case series were excluded. Overlapping populations between different studies were taken into account during data extraction. The following search key was utilized: "(Amyloid or Aβ) AND (cerebrospinal fluid OR CSF OR PET OR positron emission tomography) AND (cognitive AND (impairment OR dysfunction OR decline))". The search was performed in Medline, Embase and Central databases on 31 October 2021 and the search was updated on 9 January 2024. After removing duplicates, we screened publications by title and abstract, and in the second round by full text. Two independent reviewers conducted the selection, and a third reviewer resolved disagreements. The degree of the agreement was quantified using Cohen's kappa statistics at each selection stage. Articles that only examined the ADNI database were excluded, as patient-level data were used instead.

ADNI is a publicly available (https://adni.loni.usc.edu/) follow-up study cohort at more than 60 clinical sites in the US and Canada that uses a variety of biomarkers, neuroimaging, and clinical assessments to study AD and dementia (see data management details in the original article(52)).

A standardized Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA) was used for data extraction. The following data were extracted: source of data used in the studies (clinical trial site or database name), baseline characteristics of the

population, type of exposure (Aβ, p-tau, and neurodegeneration), exposure measurement technique, and data on cognitive impairment separately for the different exposure groups).

7.1.2. Data synthesis

When multiple studies used the same population or cohort, data from the largest sample size were selected. Progression to AD with dementia and unspecified dementia were assessed together due to variations in the definition of AD related dementia and the reliance on neurocognitive testing for diagnosis. If both types of dementia were reported, the value for unspecified dementia was used. Populations with subjective cognitive symptoms were included in the CU group, as these could not be objectively distinguished.

Odds ratios (OR) and hazard ratios (HR) were calculated or used from the available data. Considering that studies report their results on different age groups, a meta-regression analysis was performed to investigate how age affects the likelihood of developing dementia based on Aβ levels.

Studies used different methods to determine Aβ positivity, with amyloid PET being preferred when multiple Aβ categories were involved. When cerebrospinal fluid (CSF) data were used, the Aβ42/40 ratio was preferred over Aβ42 because of its better concordance with amyloid PET(53). Subgroup analyses were performed to account for the confounding effects of the different Aβ measurement techniques. CSF p-tau181 levels or, when available, tau PET were used for p-tau assessment, although the ADNI database primarily provided CSF p-tau181 data for consistency.

Studies with different follow-up periods were pooled for the OR analysis, and meta-regression was used to assess the potential bias from different follow-up periods.

7.1.3. Statistical analysis

Statistical analyses were performed using the R programming environment (version 4.1.2) with the "meta" software package (version 5.2-0). Forest plots were used to visualize the synthesized data, showing ORs or HRs and corresponding confidence

intervals (CI) for individual studies and pooled effect sizes. For dichotomous outcomes, ORs and HRs with 95% CIs were calculated. ORs were derived by extracting the number of patients and events in each group from the studies. Raw data were pooled using a random-effects model with the Mantel-Haenszel method(54-56), assuming variation in true effect sizes due to demographic and clinical differences, such as age or cognitive impairment. Heterogeneity was assessed by calculating I^2, tau^2, and the prediction interval.

We performed outlier detection according to Viechtbauer et al (2010)(57). A study was identified as an outlier if its CI did not overlap with the pooled effect, and sensitivity analyses were performed by reanalyzing the data after excluding the outliers. This allowed a comparison of the pooled effects before and after exclusion, and thus an assessment of their influence on the overall result.

7.1.4. Risk of bias assessment

The risk of bias was assessed according to the recommendation of the Cochrane Collaboration; using the Quality in Prognosis Studies (QUIPS) tool (58). Two investigators independently evaluated study quality, with a third author resolving disagreements. Publication bias was assessed using Peter's regression test(59) and visual inspection of adjusted funnel plots.

7.2. Study II.

7.2.1. Study population

Follow-up data from 1045 (611 with MCI and 434 CU) participants in the ADNI were used(60). Classification into CU, MCI and all-cause dementia was based on the Clinical Dementia Rating (CDR) score (CDR=0 for CU, CDR=0.5 for MCI and >0.5 for dementia) and education level adjusted MMSE and Wechsler Logical Memory II subscale tests to aid in the diagnostic process. Participants were aged between 55 and 90 years and underwent a comprehensive medical examination. Individuals with severe neurological or psychiatric disorders and systemic diseases affecting cognition were excluded from the

study. Full details of the enrolment process are available at: https://adni.loni.usc.edu/help-faqs/adni-documentation/. The date of the ADNI database download was May 05, 2022, with data captured from 2005 onwards. CU and MCI were assessed using participant-level follow-up data (see the Supplementary to the original article for more details on data management). CU and MCI subgroups were classified according to Aβ, p-tau, or both Aβ and p-tau pathology. The median follow-up for both CU and MCI participants was four years.

7.2.2. Risk factors

We chose risk factors to examine that were well established in the literature and for which sufficient data were available in the ADNI. The risk factors, which included depression, smoking, hypertension, obesity and hyperlipidaemia, were treated as dichotomous variables. Hypertension, obesity and hyperlipidaemia were examined together using the CAIDE score, which is calculated on the basis of age, sex, education, hypertension (systolic blood pressure > 140 mm Hg), obesity (body mass index (BMI) > 30 kg/m^2) and hyperlipidaemia (total cholesterol >= 6.5 mmol/L)(28). Physical activity could not be included in the CAIDE calculation because data were unavailable in the ADNI database. Based on the median CAIDE score and the cut-off previously used in the FINGER study(36) we used six points as a cut-off for high dementia risk. Assignment to the smoking group was based on the participants' medical records. Similary, based on a history of depression documented in medical records, or baseline depressive symptoms, participants were divided into depression and no depression groups. Depressive symptoms were assessed using the Neuropsychiatric Inventory-Questionnaire (NPI-Q) in ADNI 1 or the Neuropsychiatric Inventory (NPI) in ADNI GO, ADNI 2, and ADNI 3(61-63). Following criteria established in previous studies for the CU and MCI populations, the cut-off point for categorizing depression was a severity score of ≥2 on the NPI-Q(64, 65) or a severity × frequency score of ≥4 on the NPI(66, 67).

7.2.3. Aβ and p-tau status

The default Aβ measurement was ^{18}F-Florbetapir (AV45) PET data, with SUVR calculated by averaging four cortical regions and using the cerebellum as a reference,

following the ADNI cut-off of 1.11(68). Florbetapir positivity using the same cut-off was shown to be correlated strongly with post-mortem findings(69). Where PET data were not available, Aβ1-42 CSF measurements (Roche Elecsys) were used with a cut-off of 977 pg/ml, given their high concordance with amyloid PET results (87% overall concordance)(70). Participants were classified as p-tau positive if CSF p-tau181 levels (INNO-BIA AlzBio3) exceeded 23 pg/ml, a cut-off that has shown high classification power in autopsy-based studies(71).

7.2.4. Statistical Analysis

The CU and MCI groups were divided into Aβ positive and negative (A+, A-), p-tau positive and negative (T+, T-) and Aβ and p-tau positive and negative (A+T+, A-T-) subgroups. Baseline characteristics of CU and MCI participants were compared between each biomarker positive and negative subgroup using t-test, Wilcoxon or Chi-square tests as appropriate. The associations of CAIDE score, depression, and smoking with progression to MCI and/or dementia were investigated in analyses stratified by cognitive and pathology status: CU A+/A-, CU T+/T-, CU A+T+/A-T-, MCI A+/A-, MCI T+/T-, MCI A+T+/A-T-. Where a subgroup included <20 participants, analysis was not performed due to a high risk of bias. Thus the methodology described was not applied to the CU and MCI A+T- and A-T+ subgroups because of the high risk of bias due to the small sample size (<20).

We calculated the adjusted Hazard Ratios (aHR) with their CI from a Cox Proportional Hazard Model (PROC PHREG in SAS 9.4). Progression to dementia in the MCI group or progression to dementia and MCI combined (in the CU group) were the dependent (predicted) variables in separate models, while Aβ and p-tau positivity served as predictor variables together with modifiable risk factors such as CAIDE score, smoking, and depression. Cox regression (Cox) analyses of smoking and depression included age, sex, education, baseline MMSE score, baseline hippocampal volume and ApoE4 carrier status as covariates. Cox regression analyses of CAIDE score included age, baseline MMSE score, and baseline hippocampal volume and ApoE4 carrier status as covariates (sex and education were already included in the CAIDE score). In order to test the proportional hazard assumption we repeated all Cox regressions by including the interaction of time and risk factors as covariates. Since the interaction of time and risk

factors were non-significant in all Cox regressions (all p values > 0.1) we can conclude that there is no evidence of the time dependency of the HR, i.e. the proportional hazard assumption were met in all cases. Death was included as a competing risk in the Cox regressions. All reported HR from Cox regressions are adjusted ones (aHR).

A sensitivity analysis was conducted to ensure the robustness of the results and minimise potential bias. As part of this, Kaplan-Meier survival analyses were performed for all subgroups, with survival plots provided alongside the adjusted Cox regression curves for comparison. The results section presents statistics from the Kaplan-Meier analyses, including log-rank tests and corresponding p-values. Furthermore, Cox regression was also performed with the CAIDE score as a continuous variable and with seven as an alternative cut-off. Finally, the effect of CAIDE as a risk factor in the MCI sample, regardless of biomarker status, was analysed.

8. RESULTS

8.1. Study I.

8.1.1. Search and selection, characteristics of the included studies

The systematic search of the three databases yielded 18,162 records, and after removing duplicates, 12,605 publications were screened. After the title-abstract, and full text selection, fifty-five studies were found to be eligible (**Figure 1**). As there were studies based on the same cohort, our analysis was finally performed by analysing the results of forty different publications. The Cohen's kappa was 0.91 for titles and abstracts and 0.86 for full-text selection.

The studies found expressed their results in different ways (in HR or presented the number of conversions for the different follow-up periods, which was converted to ORs). They also differed in terms of the exposure(s) studied, with some studies having data for Aβ alone and others in combination with p-tau. There was also a difference in the technique used to detect these proteins, which was based on PET-CT or on CSF measurement (Aβ 42 or 42/40 ratio). The trials were based on CU and MCI for the populations studied, and four trials studied these two groups together in a "mixed group". For CU, studies included cognitively healthy people and people with subjective cognitive complaints. To define the MCI, all studies used the Petersen criteria. The characteristics of the eligible trials are detailed in **Table 1 - 4**. Trials were excluded if they used a method that was not consistent with the 2018 NIA-AA recommendation.

The mixed studies (collective results for both MCI and CU groups) were all large studies (n>180), we decided that their joint analysis with MCI was more valuable as we could obtain results for a much larger sample size. To test this decision, we performed subgroup analyses of the Aβ-positive MCI and mixed population studies. Both the MCI (OR 5.83 [3.80; 8.93]) and mixed (OR 4.64 [95% CI 1.16; 18.61]) subgroups showed significantly different ORs compared with the unexposed group, with no significant difference between the two subgroups (p=0.55).

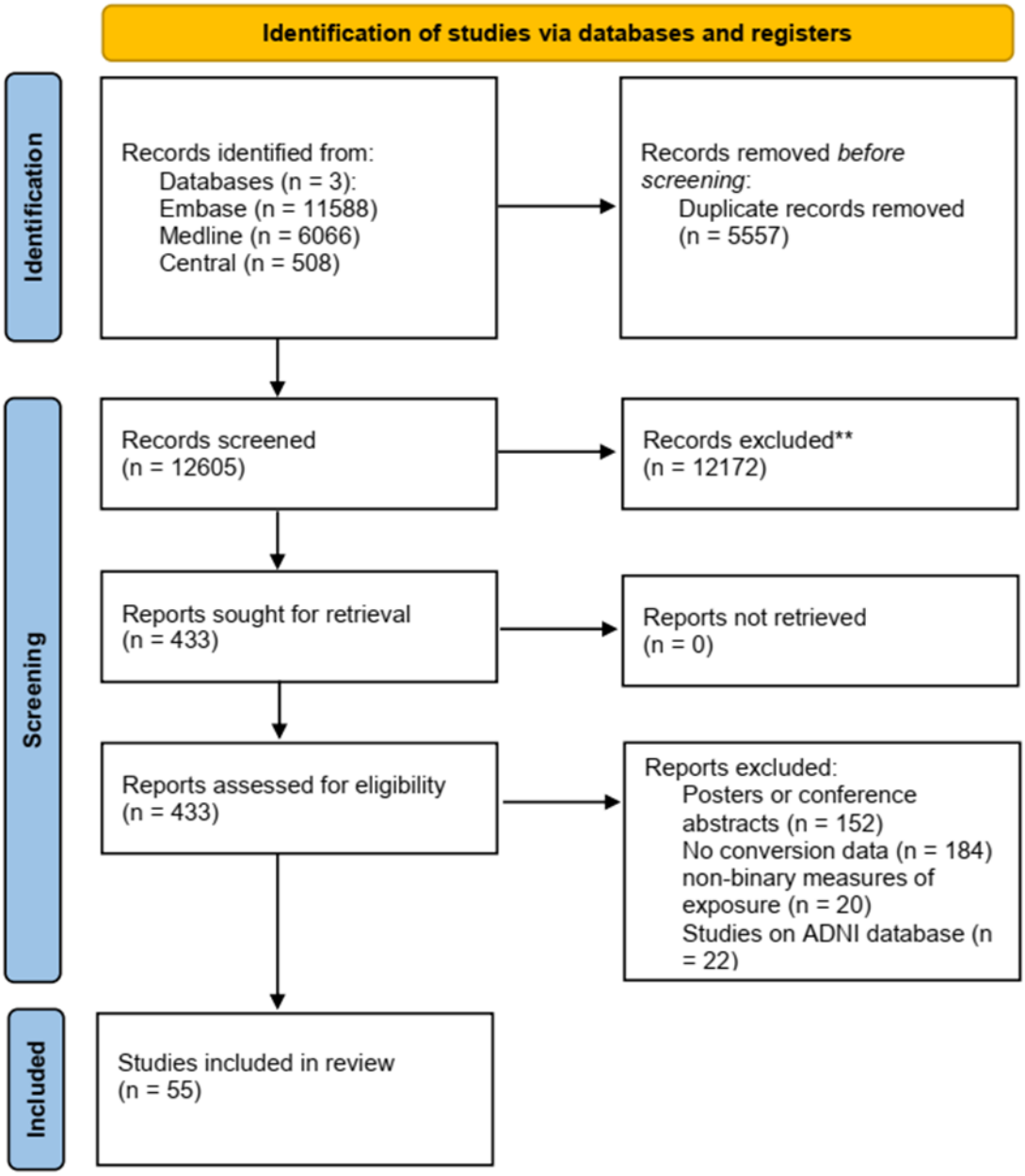


Figure 1 PRISMA 2020 Flow chart of selection

Figure template from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

8.1.2. Results for progression from CU to MCI or Dementia

8.1.2.1. Aβ Exposure – Odds Ratio

Based on meta-analysis of data from a total of 4,217 subjects, the OR for progression of Aβ-positive (A+) CU subjects to MCI or dementia compared with Aβ-negative (A-) subjects was 5.79 [95% CI 2.88; 11.64] (t(13) = 5.43; p = 0.0001), with high heterogeneity between studies (I2= 73% [55%; 84%]). Meta-regression analysis examining the relationship between mean age and OR values showed no significant association (R2 = 8.22%, beta = -0.05, SE = 0.05, [95% CI = -0.17 - 0.7], df = 11, p = 0.37) (**Table 1**, **Figure 2A**).

The correlation between the different follow-up times and the OR values was examined by meta-regression analysis and no relationship was found (R2 = 0.35%, beta = -0.014, SE = 0.024, [95% CI = -0.07 - 0.04], df = 8, p = 0.58).

To detect possible publication bias, a funnel plot was used, which showed that the studies with the large sample size were close to the centre line, confirming the validity of the pooled effect size. Peter's regression test did not confirm the asymmetry of the funnel plot (t = 0.9, df = 12, p = 0.31).

8.1.2.2. The Effect of Aβ Exposure in Terms of HR

By pooling four studies with data on 2,700 subjects, it was possible to perform a HR analysis of the progression of CU subjects to MCI or dementia as a function of Aβ status. It should be noted that ADNI accounted for 55.3% of the total population (weight: 78.5%). The HR based on this analysis was 2.33 [95% CI 1.88; 2.88] (p=0.001).

8.1.2.3. The Combined Effect of Aβ and p-tau Exposure in Terms of OR

The combined effect of Aβ and p-tau was examined using data from a total of 2,228 CU subjects. Compared with A-T- cases, the OR for the A+T+ group was 13.46 [95% CI 3.69; 49.11], whereas the OR for the A+T- group was 2.04 [95% CI 0.70; 5.97], showing a trend level increase in risk (t=2.1, P=0.12). For the A+T+ group, the subgroup analysis showed a significantly higher OR compared to the A+T- group (p <0.01) (**Table 2**, **Figure 2B**). Due to the small number of cases, the analysis for A-T+ was not performed.

Table 1 Articles used for Aβ OR analyses in the CU group

					follow-up (months)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
ADNI	ADNI	578	72.9 (6.3)	$_{amyloid}$PET	69 (48)	54
Arruda, 2023(72)	Florida Alzheimer's Disease Research Center	70	70.2 (6.5)	$_{amyloid}$PET	22.9 (7.1)	n.d.
Baldeiras, 2022(73)	Coimbra University Hospital; Hospital de Braga; Unidade Local de Saude de Matosinhos; Centro Hospi- ´ talar Baixo Vouga; Hospital Egas Moniz; Hospital de Faro, Portugal	24	63.6 (8.9)	CSF Aβ42/40	n.d.	n.d. (12-50)
Dang, 2018(74)	The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL)	599	70 (60 - 80)	$_{amyloid}$PET	66.9	88.5
Ebenau, 2020(75)	Amsterdam Dementia Cohort, SCIENCe! Subjective Cognitive Impairment Cohort (ADC)	342	60.0 (9.0)	$_{amyloid}$PET, CSF Aβ42	36 (24)	n.d.
Grontvedt, 2020(49)	Department of Neurology, Univ. Hosp. Trondheim, Norway	55	68 (53 - 79)	CSF Aβ42	n.d.	108 (72 - 120)
Hanseeuw, 2021(76)	Neurology Department, Saint-Luc University Hospital, Belgium	50	71.4 (7.5)	$_{amyloid}$PET	38.4 (15.6)	n.d.
Hatashita, 2019(77)	Department of Neurology, Shonan-Atsugi Hospital, Atsugi, Japan	32	71.0 (5.9)	$_{amyloid}$PET	72 (21.6)	n.d.
Lopez, 2018(78)	Ginkgo biloba memory study (GEM [Ginkgo Evaluation of Memory] Study, USA	148	84.2 (2.5)	$_{amyloid}$PET	68.4 (20.4)	n.d.

					follow-up (months)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
Ossenkoppele, 2022(79)	BioFINDER-1, -2	258	68.8 (10.1)	$_{amyloid}$PET	41.8 (18.9)	n.d.
Roberts, 2018(80)	Mayo Clinic Study of Aging (MCSA)	1377	70. 4 (8.8)	$_{amyloid}$PET	43.2 (24)	n.d.
Strikwerda-Brown, 2022(81)	Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease (Prevent AD), Harvard Aging Brain Study (HABS)	281	72.1 (6.0)	$_{amyloid}$PET	n.d.	32.7 (15.7 – 58.0)
Villemagne, 2011(82)	Austin Health Memory Disorders Clinic, USA	106	73.1 (7.5)	$_{amyloid}$PET	20	20
Vos, 2013(83)	Knight Alzheimer's Disease Research Center (KADRC) of the Washington University School of Medicine (WUSM)in St. Louis, USA	297	72.9 (6.0)	CSF Aβ42	n.d.	38.4 (12 - 156)

Aβ beta-amyloid, **AD** Alzheimer's Dementia, **ADNI** Alzheimer's Disease Neuroimaging Initiative, **CSF** Cerebrospinal Fluid, **CU** Cognitively Unimpaired, **MCI** Mild Cognitive Impairment, **n** number of participants, **n.d.** no data, **OR** Odds Ratio, **PET** Positron Emission Tomography, **SD** Standard Deviation, **SUVR** Standardized Uptake Value Ratio.

Table 2 Articles used for Aβ and p-tau OR analyses in the CU group

					follow-up time (months)	
study	**centre/cohort**	**measurement technique**	**subjects (n.)**	**age (mean (SD) / median (range))**	**mean (SD)**	**median (range)**
CU population A+T+ vs. A-T-						
ADNI	ADNI	$_{amyloid}$PET, CSF Aβ42, CSF p-tau181	334	72.9 (6.3)	69 (48)	54
Ebenau, 2020(75)	Amsterdam Dementia Cohort, SCIENCe! Subjective Cognitive Impairment Cohort (ADC)	$_{amyloid}$PET, CSF Aβ42; CSF p-tau181	216	60.0 (9.0)	36 (24)	n.d.
Ossenkoppele, 2022(79)	BioFINDER-1, BioFINDER-2, Harvard Aging Brain Study (HABS)	$_{amyloid}$PET; $_{tau}$PET	821	70.5 (9.8)	41.8 (18.9)	n.d.
Strikwerda-Brown, 2022(81)	The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), Knight Alzheimer's Disease Research Center (KADRC), Pre-	$_{amyloid}$PET; $_{tau}$PET	326	70.9 (5.6)	n.d.	39.8 (15.2 – 68.0)

					follow-up time (months)	
study	**centre/cohort**	**measurement technique**	**subjects (n.)**	**age (mean (SD) / median (range))**	**mean (SD)**	**median (range)**
	symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease (Prevent AD)					
CU population A+T- vs. A-T-						
ADNI	ADNI	$_{amyloid}$PET, CSF Aβ42, CSF p-tau181	364	72.9 (6.3)	69 (48)	54
Ebenau, 2020(75)	ADC	$_{amyloid}$PET, CSF Aβ42; CSF p-tau181	227	60.0 (9.0)	36 (24)	n.d.
Ossenkoppele, 2022(79)	BioFINDER-1, BioFINDER-2, HABS	$_{amyloid}$PET; $_{tau}$PET	1003	70.5 (9.8)	41.8 (18.9)	n.d.
Strikwerda-Brown, 2022(81)	AIBL, KADRC, Prevent AD	$_{amyloid}$PET; $_{tau}$PET	387	70.9 (5.6)	n.d.	39.8 (15.2 – 68.0)

A- beta-amyloid negative, **A+** beta-amyloid positive, **Aβ** beta-amyloid, **AD** Alzheimer's Dementia, **ADNI** Alzheimer's Disease Neuroimaging Initiative, **CSF** Cerebrospinal Fluid, **CU** Cognitively Unimpaired, **MCI** Mild Cognitive Impairment, **n** number of

participants, **OR** Odds Ratio, **PET** Positron Emission Tomography, **p-tau** Phosphorylated Tau, **SD** Standard Deviation, **SUVR** Standardized Uptake Value Ratio, **T-** phosphorylated tau negative, **T+** phosphorylated tau positive.

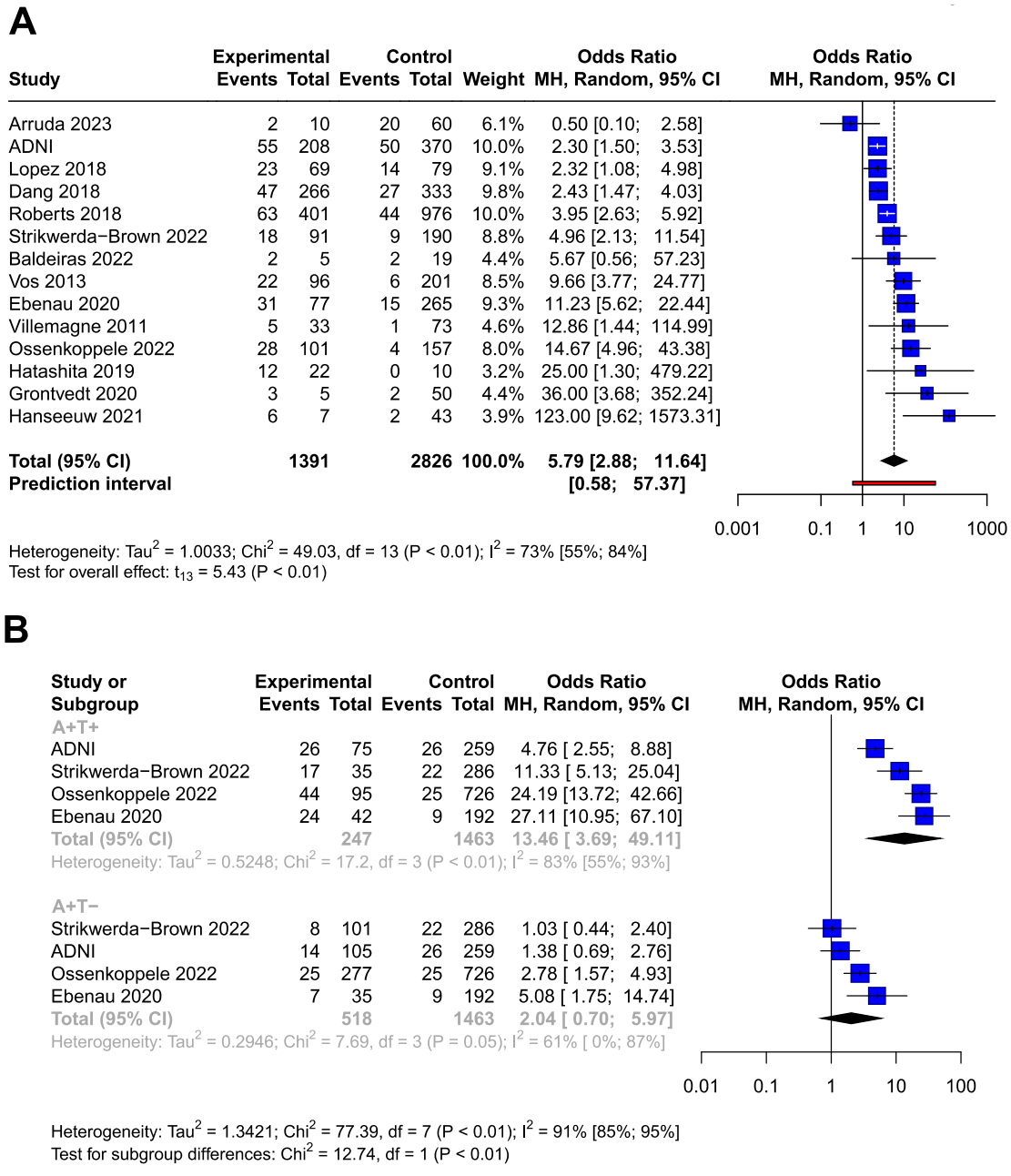


Figure 2 Progression of Aβ and p-tau exposed CU groups to MCI or dementia in OR

A: Aβ exposition in OR; **B:** Aβ and p-tau expositions in OR.

The squares and bars represent the mean values and 95% CIs of the effect sizes, and the squares' area reflects the weight of the studies. Diamonds represent the combined effects.

A- beta-amyloid negative, **A+** beta-amyloid positive, **Aβ** beta-amyloid, **ADNI** Alzheimer's Disease Neuroimaging Initiative, **Chi** Chi-Square Test, **CI** Confidence Interval, **CU** Cognitively Unimpaired, **df** Degrees of Freedom, **I²** I-squared, **MH** Mantel-Haenszel Method, **MCI** Mild Cognitive Impairment, **OR** Odds Ratio, **p-tau** phosphorylated tau, **Tau²** Tau-squared, **T-** phosphorylated tau negative, **T+** phosphorylated tau positive.

8.1.3. Results for progression from MCI to dementia

8.1.3.1. Aβ Exposure – Odds Ratio

The meta-analysis of studies with a total of 3,576 subjects found a significant association between amyloid positivity and progression to dementia. Compared with the

A- group, the OR for progression in the A+ group was 5.18 [95% CI 3.93; 6.81]; $t(21) = 12.47$; $p < 0.0001$. The heterogeneity was 44.8% (I^2 test) (**Table 3**, **Figure 3A**). Meta-regression analysis of the studies showed that the ORs decreased with increasing age of the study group ($R^2 = 59.05\%$, beta = -0.04, SE = 0.019, 95% CI = -0.03 to -0.083, df = 18, t = -2.27, p = 0.036) (**Figure 3B**).

A subgroup analysis comparing Aβ measurement techniques showed no significant difference between groups (p=0.88). The ORs were 5.87 [2.83; 12.19] for CSF Aβ42, 5.00 [3.31; 7.55] for CSF Aβ42/40 ratio and 5.32 [2.53; 11.18] for amyloid PET. Furthermore, meta-regression analysis showed no association between different follow-up times and OR values ($R^2 = 0\%$, beta = -0.002, SE = 0.07, 95% CI = -0.02 to 0.01, df = 11, p = 0.77). A funnel plot of the pooled studies showed no significant publication bias (Peter's regression test: t = 1.7, df = 20, p = 0.11).

8.1.3.2. Aβ Exposure – Hazard Ratio

Some studies reported their results as HR, which have the advantage of being independent of follow-up time. Based on the pooled results from these studies with a total of 1,888 subjects, the HR for progression to dementia was 3.16 [95% CI 2.07, 4.83], $p < 0.001$. To compare the differences between adjusted and unadjusted values, a subgroup analysis was performed, where unadjusted values were higher but did not reach

significance: unadjusted HR: 5.07 [95% CI 2.77; 9.26], adjusted HR: 2.86 [95% CI 1.70; 4.83], p = 0.055.

8..1.3.3. Combined Aβ and p-tau Exposure – Odds Ratio

The combined association of p-tau and Aβ with progression to dementia was examined for A+T+, A+T- and A-T+ exposures compared with the A-T- group by pooling data from 1,327 subjects. The OR for A+T+ was 11.60 [95% CI 7.96; 16.91], significantly higher ($p<0.001$) than for A+T- (2.73 [95% CI 1.65; 4.52]). There was no significant association with A-T+ exposure (OR: 1.47 [0.55; 3.92]), although in subgroup analysis the A+T- and A-T+ groups were not significantly different (p=0.15) (**Table 4**, **Figure 4**).

8.1.4. Risk of bias assessment

The risk of bias was assessed separately for each of the analyses discussed. Most studies had a low or moderate risk of bias, and three studies had a high risk of bias: two(84, 85) with attrition rates greater than 50% and one(86) because it included only monozygotic twins. These articles (n=197) were excluded from all analyses (see details of risk of bias assesment at the original article).

Table 3 Articles used for Aβ OR analyses in the MCI group

					follow-up (month)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
ADNI	ADNI	785	72.5 (7.5)	$_{amyloid}$PET	57 (40)	48
Arruda, 2023(72)	Florida Alzheimer's Disease Research Center	91	72.7 (8.7)	$_{amyloid}$PET	22.9 (7.1)	n.d.
Balassa, 2014(48)	Hospital Clinic Barcelona, Spain	51	57.9 (6)	CSF Aβ42	31 (15.8)	31.6 (8 - 82)
Baldeiras, 2022(73)	Coimbra University Hospital; Hospital de Braga; Unidade Local de Saude de Matosinhos; Centro Hospi-´talar Baixo Vouga; Hospital Egas Moniz; Hospital de Faro, Portugal	150	65.2 (8.7)	CSF Aβ42/40	n.d.	n.d. (12-50)

					follow-up (month)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
Bos, 2017(87)	Alzheimer Center Limburg, LeARN, DESCRIPA cohort	271	65.6 (7.7)	CSF Aβ42	30 (14.4)	n.d.
Cerami, 2015(88)	San Raffael Inst. Milan, Italy	34	69.8 (5.7)	CSF Aβ42	29 (8.5)	29 (15 - 60)
de Wilde, 2019(89)[a]	Alzheimer Center and Department of Neurology, VU University Medical Center Amsterdam, Netherland	110	65.5 (7.5)	$_{amyloid}$PET, CSF Aβ42	n.d.	22.8 (13.2 - 32.4)
Eckerstrom, 2021(90)	Goteborg MCI study	420	64.2 (7.3)	CSF Aβ42	31.6 (19)	n.d.
Frolich, 2017(91)	Dementia Competence Network (DCN), German multicenter cohort study	115	65.7 (9.3)	CSF Aβ42	25.5 (9.8)	n.d.

					follow-up (month)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
Grontvedt, 2020(49)	Department of Neurology, Univ. Hosp. Trondheim, Norway	57	64 (53 - 79)	CSF Aβ42	n.d.	108 (72 - 120)
Groot, 2022(92)	Malmö University Hospital, Sweden	147	72.1 (7.7)	CSF Aβ42/40	59.0 (25.1)	n.d.
Hanseeuw, 2021(76)	Neurology Department, Saint-Luc University Hospital, Belgium	46	71.4 (7.5)	$_{amyloid}$PET	38.4 (15.6)	n.d.
Herukka, 2005(93)	Neurologic Department at Kuopio University Hospital, Finland	66	70.4 (7.4)	CSF Aβ42	n.d.	36 (6-144)
Jimenez Bonilla, 2019(94)	Neurology, University Hospital 'Marqués de Valdecilla', University of Cantabria, Santander, Spain	14	67.1 (5.1)	$_{amyloid}$PET	60	60

					follow-up (month)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
Lopez, 2018(78)	Ginkgo biloba memory study (GEM [Ginkgo Evaluation of Memory] Study, USA	183	85.6 (2.9)	$_{amyloid}$PET	68.4 (20.4)	n.d.
Okello, 2009(95)	Imperial College Healthcare NHS Trust [London], The National Hospital for Neurology and Neurosurgery [London], St. Margaret's Hospital [Epping, and Victoria Hospital [Swindon], Turku Hosp., UK and Finland	31	69.4 (7.9)	$_{amyloid}$PET	36	36

					follow-up (month)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
Orellana, 2022(96)	ACE Alzheimer Center Barcelona, Spain	647	72.8 (7.8)	CSF Aβ42/40	21 (10.8)	n.d.
Ortega, 2019(97)	Hospital Santa Maria de Lleida, Spain	55	71.9 (6.7)	CSF Aβ42	n.d.	24 (no inf.)
Riemenschneider, 2002(98)	Department of Psychiatry, Pearth, Australia	28	69.2 (7.9)	CSF Aβ42	18	18
Rizzi, 2020(99)	Division of Geriatric Neurology, Neurology Service, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, Brazil	31	67.4 (60 - 78)	CSF Aβ42	60	60
Roberts, 2018(80)	Mayo Clinic Study of Aging (MCSA)	179	78.3 (7.4)	$_{\text{amyloid}}$PET	45.6 (24)	n.d.

					follow-up (month)	
study	**centre/cohort**	**subjects (n)**	**age (mean (SD), or median (range))**	**measurement technique**	**mean (SD)**	**median (range)**
Villemagne, 2011(82)	Austin Health Memory Disorders Clinic, USA	65	73.4 (8.5)	$_{amyloid}$PET	20 (3)	n.d.

Aβ beta-amyloid, **AD** Alzheimer's Dementia, **ADNI** Alzheimer's Disease Neuroimaging Initiative, **CSF** Cerebrospinal Fluid, **CU** Cognitively Unimpaired, **MCI** Mild Cognitive Impairment, **n** number of participants, **n.d.** no data, **OR** Odds Ratio, **PET** Positron Emission Tomography, **SD** Standard Deviation, **SUVR** Standardized Uptake Value Ratio.

[a]: See details of data extraction in the original article's Supplement, Appendix 3.

Table 4 Articles used for Aβ and p-tau OR analyses in the Mild Cognitive Impairment (MCI) group

					follow-up time (months)	
study	**centre/cohort**	**measurement techniques**	**subjects (n)**	**age (mean (SD) / median (range))**	**mean (SD)**	**median (range)**
MCI population A+T+ vs. A-T-						
ADNI	ADNI	$_{amyloid}$PET, CSF Aβ42; CSF p-tau181	535	72.5 (7.5)	53 (38)	42
Cerami, 2015(88)	San Raffael Inst. Milan, Italy	CSF Aβ42; CSF p-tau181	19	69.8 (5.7)	29 (8.5)	29 (15-60)
Eckerström, 2021(90)	Goteborg MCI study	CSF Aβ42; CSF p-tau181	262	64.2 (8.6)	34.74 (25)	n.d.
Grontvedt, 2020(49)	Department of Neurology, Univ. Hosp. Trondheim, Norway	CSF Aβ42; CSF p-tau181	40	64 (53 - 79)	n.d.	108 (72-120)
Hansson, 2006(100)	Malmö University Hospital, Sweden	CSF Aβ42; CSF p-tau181	99	71.8 (50 - 87)	n.d.	62.4 (48-81.6)
Herukka, 2005(93)	Neurologic Department at	CSF Aβ42; CSF p-tau181 (>70 pg/mL)	39	70.4 (8.2)	n.d.	36 (6-144)

					follow-up time (months)	
study	**centre/cohort**	**measurement techniques**	**subjects (n)**	**age (mean (SD) / median (range))**	**mean (SD)**	**median (range)**
	Kuopio University Hospital, Finland					
MCI population A+T- vs. A-T-						
ADNI	ADNI	$_{amyloid}$PET, CSF Aβ42; CSF p-tau181	323	72.5 (7.5)	53 (38)	42
Cerami, 2015(88)	San Raffael Inst. Milan, Italy	CSF Aβ42; CSF p-tau181	16	69.8 (5.7)	29 (8.5)	29 (15-60)
Eckerström, 2021(90)	Goteborg MCI study	CSF Aβ42; CSF p-tau181	198	62.6 (8.3)	31.6 (19)	n.d.
Grontvedt, 2020(49)	Department of Neurology, Univ. Hosp. Trondheim, Norway	CSF Aβ42; CSF p-tau181	26	64 (53 - 79)	n.d.	108 (72-120)
Hansson, 2006(100)	Malmö University Hospital, Sweden	CSF Aβ42; CSF p-tau181	44	71.8 (50 - 87)	n.d.	62.4 (48-81.6)
Herukka, 2005(93)	Neurologic Department at	CSF Aβ42; CSF p-tau181 (>70 pg/mL)	26	70.4 (8.2)	n.d.	36 (6-144)

					follow-up time (months)	
study	**centre/cohort**	**measurement techniques**	**subjects (n)**	**age (mean (SD) / median (range))**	**mean (SD)**	**median (range)**
	Kuopio University Hospital, Finland					
MCI population A-T+ vs. A-T-						
ADNI	ADNI	$_{amyloid}$PET, CSF Aβ42; CSF p-tau181	275	72.5 (7.5)	53 (38)	42
Cerami, 2015(88)	San Raffael Inst. Milan, Italy	CSF Aβ42; CSF p-tau181	15	69.8 (5.7)	29 (8.5)	29 (15-60)
Eckerström, 2021(90)	Goteborg MCI study	CSF Aβ42; CSF p-tau181	282	63.0 (7.6)	31.6 (19)	n.d.
Grontvedt, 2020(49)	Department of Neurology, Univ. Hosp. Trondheim, Norway	CSF Aβ42; CSF p-tau181	21	64 (53 - 79)	n.d.	108 (72-120)
Hansson, 2006(100)	Malmö University Hospital, Sweden	CSF Aβ42; CSF p-tau181	48	71.8 (50 - 87)	n.d.	62.4 (48-81.6)
Herukka, 2005(93)	Neurologic Department at	CSF Aβ42; CSF p-tau181 (>70 pg/mL)	37	70.4 (8.2)	n.d.	36 (6-144)

					follow-up time (months)	
study	**centre/cohort**	**measurement techniques**	**subjects (n)**	**age (mean (SD) / median (range))**	**mean (SD)**	**median (range)**
	Kuopio University Hospital, Finland					

A- beta-amyloid negative, **A+** beta-amyloid positive, **Aβ** beta-amyloid, **AD** Alzheimer's Dementia, **ADNI** Alzheimer's Disease Neuroimaging Initiative, **CSF** Cerebrospinal Fluid, **MCI** Mild Cognitive Impairment, **n** number of participants, **n.d.** no data, **OR** Odds Ratio, **PET** Positron Emission Tomography, **p-tau** Phosphorylated Tau, **SD** Standard Deviation, **SUVR** Standardized Uptake Value Ratio, **T-** phosphorylated tau negative, **T+** phosphorylated tau positive.

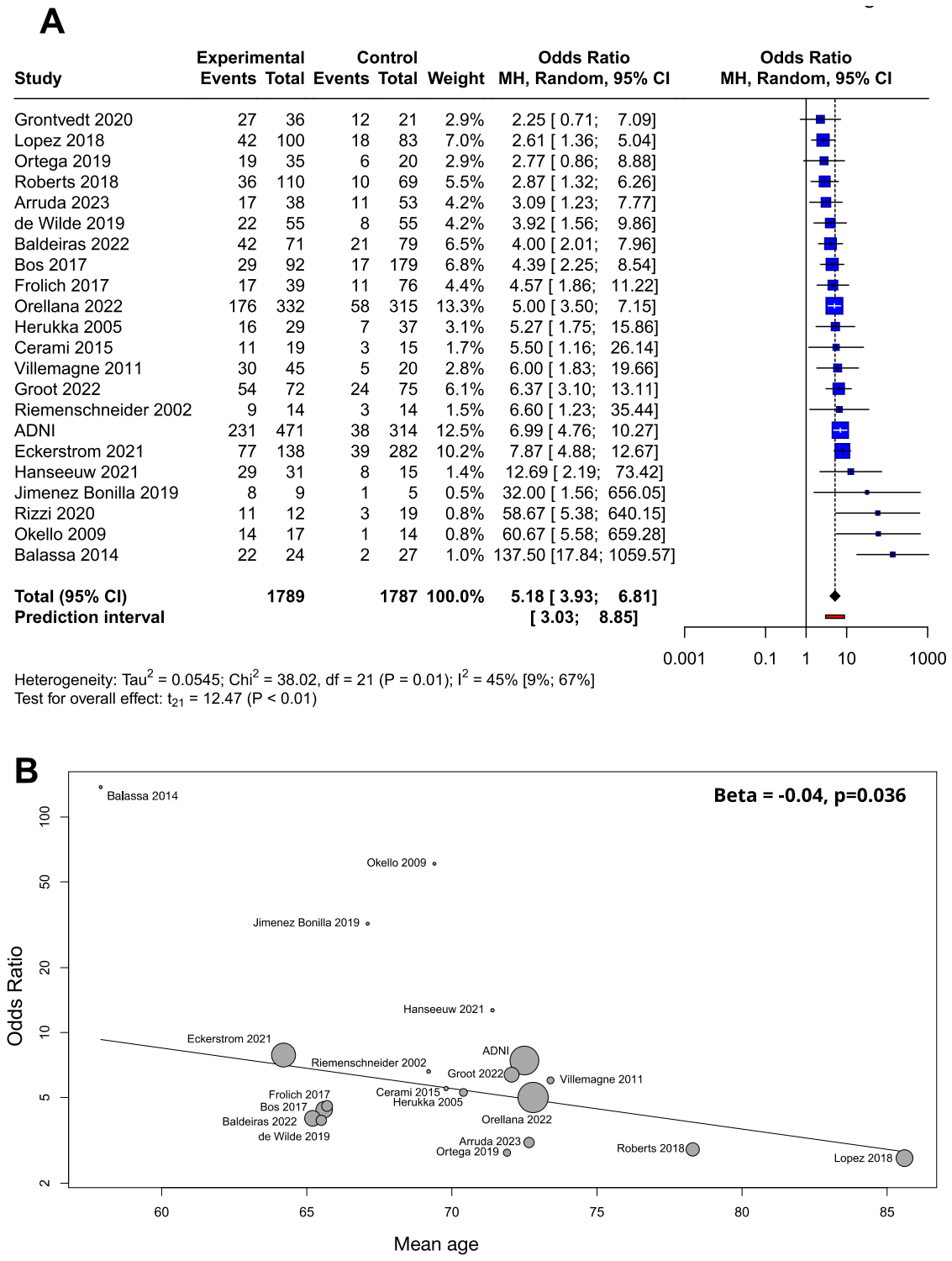


Figure 3 Progression of Aβ exposed MCI groups to dementia in OR

A: OR for Aβ exposition; **B:** meta-regression of age and ORs for progression regarding Aβ exposure.

The squares and bars represent the mean values and 95% CIs of the effect sizes, and the squares' area reflects the weight of the studies. Diamonds represent the combined effects. The size of the circle is proportional to the weight of each study in the meta-analysis. The line corresponds to meta-regression with age as covariate, and beta represents the slope of ORs by mean age.

Aβ beta-amyloid, **ADNI** Alzheimer's Disease Neuroimaging Initiative, **Chi** Chi-Square Test, **CI** Confidence Interval, **df** Degrees of Freedom **I^2** I-squared, **MH** Mantel-Haenszel Method, **MCI** Mild Cognitive Impairment **OR** Odds Ratio **p-tau** phosphorylated tau **Tau^2** Tau-squared.

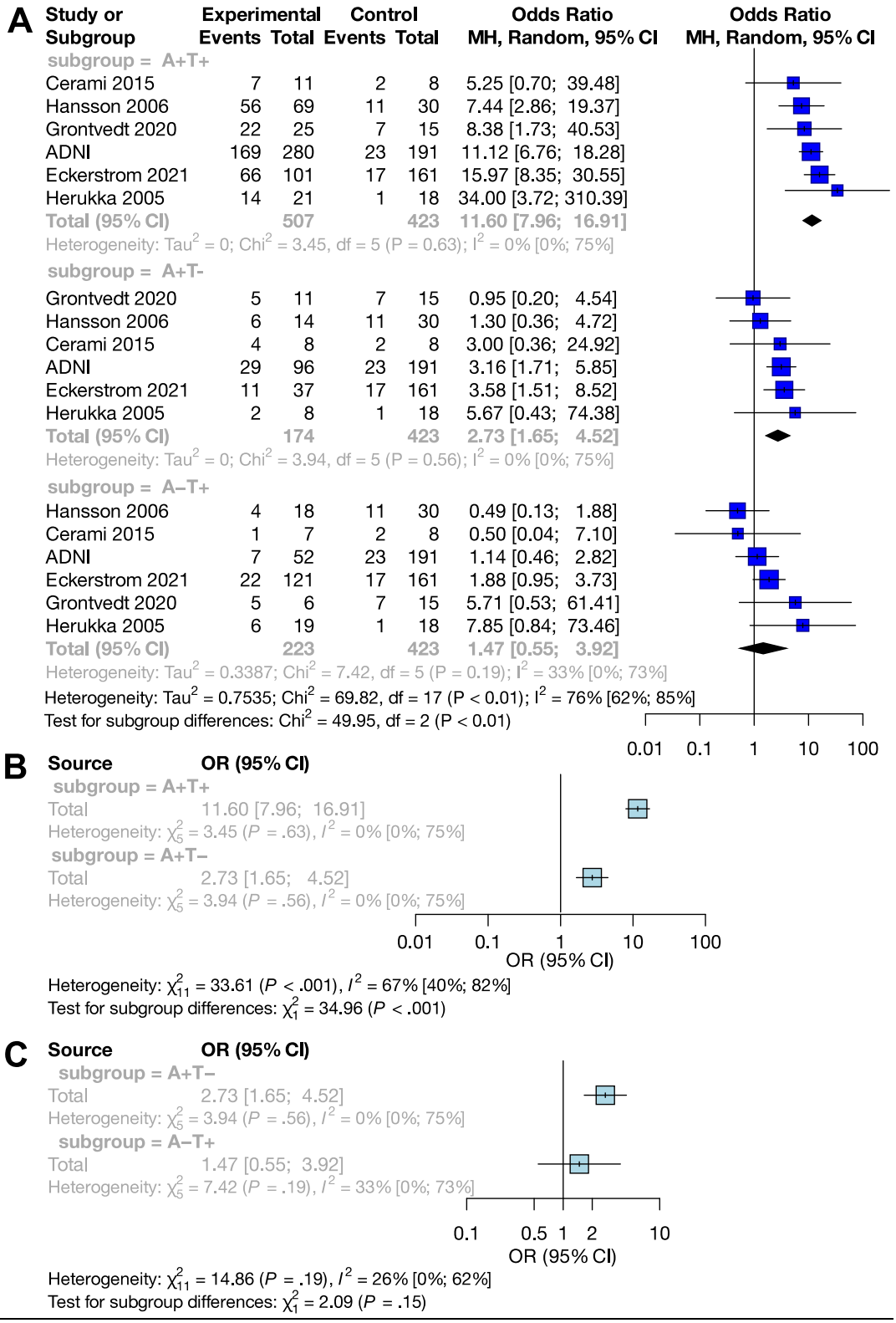


Figure 4 Progression of Aβ and p-tau exposed MCI groups to dementia in OR

A: Aβ and p-tau expositions in OR; **B**: subgroup analysis of comparisons between the A+T+ and A+T- groups; **C**: sub-group analysis of comparisons between the A+T- and A-T+ groups.

The squares and bars represent the mean values and 95% Cis of the effect sizes, and the squares' area reflects the weight of the studies. Diamonds represent the combined effects.

A- beta-amyloid negative, **A+** beta-amyloid positive, **Aβ** beta-amyloid, **ADNI** Alzheimer's Disease Neuroimaging Initiative, **Chi** Chi-Square Test, **CI** Confidence Interval, **df** Degrees of Freedom, **I²** I-squared, **MH** Mantel-Haenszel Method, **MCI** Mild Cognitive Impairment, **OR** Odds Ratio, **p-tau** phosphorylated tau, **Tau²** Tau-squared, **T-** phosphorylated tau negative, **T+** phosphorylated tau positive

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8.2. Study II.

8.2.1. Baseline characteristics

A total of 434 CU and 611 MCI subjects from the ADNI were analysed to investigate the association between the CAIDE score/smoking/depression and the pathological status of Aβ and p-tau with the progression to MCI or dementia. At baseline, the percentage of participants with high CAIDE scores, smoking and deprression did not differ significantly between the A+/A-, T+/T-, and A+T+/A-T-subgroups for either CU or MCI subjects. There were significant differences in mean age, ApoE4 carrier status, MMSE score, hippocampal volume and progression rate between the biomarker-negative and positive subgroups (see the table of baseline characteristics in the original article). For 103 CU and 60 MCI participants, p-tau data were missing, and only Aβ status was available for analysis. The number of CU participants in each biomarker subgroup was as follows: 277 (A-), 151 (A+), 217 (T-), 114 (T+), 157 (A-T-), and 59 (A+T+). Among MCI participants: 234 (A-), 377 (A+), 246 (T-), 305 (T+), 160 (A-T-), and 257 (A+T+).

8.2.2. Higher CAIDE score and dementia progression

In the CU population, the risk of progression to MCI or dementia was not significantly increased with a higher CAIDE score in either biomarker subgroups compared with a lower CAIDE score (**Table 5**). Similarly, the results of the KM analyses did not show a statistically significant difference between the high and low CAIDE score biomarker subgroups (all p-values > 0.1).

In the MCI population, participants with A-, T+, A-T-, and A+T+ had a significantly increased risk of progression to dementia if they had a higher CAIDE score

than if they had a low score. While in the A+ and T- subgroups, a similar statistical trend-level association was observed (**Table 5**, **Figure 5**). In detail: for A- Cox aHR=3.1 (95% CI 1.43-6.53; KM log-rank chi-square (ChiSq) = 8.1, p=0.004), for A+ Cox aHR=1.3 (95% CI 0.98-1.7; KM log-rank ChiSq = 0.16, p=0.7), for T- Cox aHR=1.6 (95% CI 0.94-2.83; KM log-rank ChiSq = 2.8, p=0.096), for T+ Cox aHR=1.7 (95% CI 1.20-2.27; KM log-rank ChiSq = 5.0, p=0.03), for A-T- Cox aHR=2.6 (95% CI 1.06-6.59; KM log-rank ChiSq = 4.7, p=0.03), and for A+T+ Cox aHR=1.6 (95% CI 1.15-2.22; KM log-rank ChiSq = 2.6, p=0.1).

A sensitivity analysis was performed to further explore the relationship between CAIDE score and risk of progression in the MCI group. The literature suggests that cut-offs above six are acceptable(101). In the sensitivity analysis, we used a cut-off of seven and the total CAIDE score as a continuous variable within the MCI group. Using seven as the cut-off, none of the aHRs remained statistically significant. However, when the CAIDE score was considered as a continuous variable, each one-point increase in the total score was associated with an increased risk of progression in the A- (Cox aHR=1.4, 95%CI 1.1-1.8), A-T- (Cox aHR=1.4, 95%CI 1.01-1.9), A+T+ (Cox aHR=1.1, 95%CI 1.01-1.3) and T+ (Cox aHR=1.1, 95%CI 1.01-1.3) subgroups. In the overall MCI cohort, regardless of biomarker status, higher CAIDE scores were associated with an increased risk of progression (Cox aHR=1.5, 95%CI 1.1-1.9).

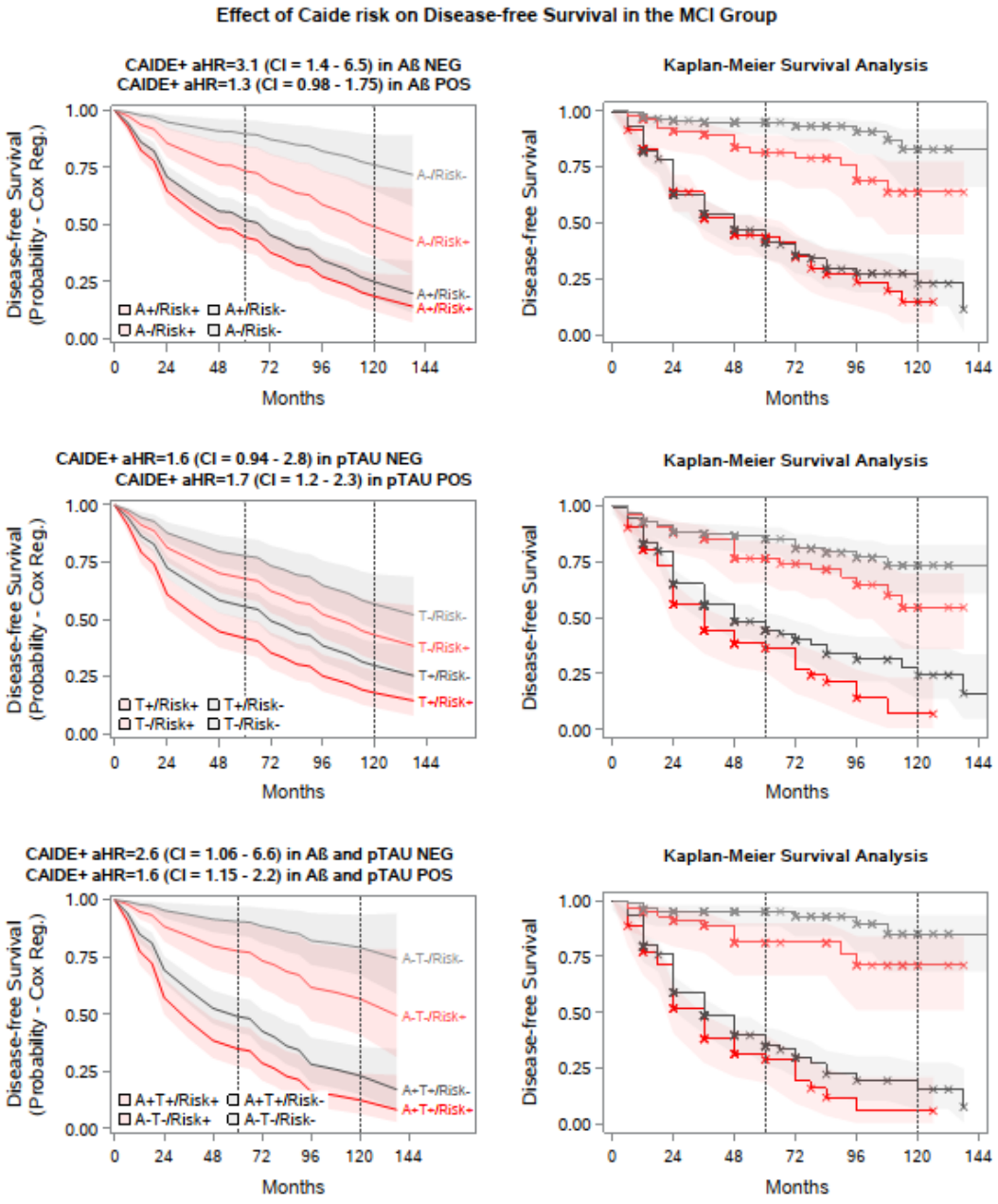

Figure 5 CAIDE Score and Dementia Progression in MCI by beta-amyloid/p-tau Status

CAIDE as a modifiable risk factor in MCI participants is presented in three separate panels: the top panel illustrates A-/A+ groups, the middle panel shows T-/T+ groups, and the bottom panel represents A-T-/A+T+ groups The pale lines in the figure represent the biomarker-negative group, the solid lines represent the biomarker-positive group, the red lines represent the modifiable risk factor-positive group, and the grey lines represent the modifiable risk factor-negative group. The shaded areas represent the confidence

intervals. Disease-free survival means no progression to dementia. **A-** beta-amyloid negative, **A+** beta-amyloid positive, **aHR** adjusted hazard ratio, **CI** confidence interval, **MCI** Mild Cognitive Impairment, **Risk+** CAIDE risk-positive, **Risk-** CAIDE risk-negative, **T-** phosphorylated tau negative, **T+** phosphorylated tau positive.

8.2.3. Smoking and dementia progression

In the MCI population, smokers had a significantly increased risk of progression to dementia compared with non-smokers in the A+ subgroup (Cox aHR=1.6, 95%CI 1.07-2.34, KM log-rank ChiSq = 11.5, p=0.0007), and a trend-level association was observed in the T+ subgroup (Cox aHR=1.5, 95%CI 0.99-2.31, KM log-rank ChiSq = 8.0, p=0.005). No association was observed in the A- and T- MCI subgroups (**Table 6**, **Figure 6**). The analysis was not conducted for the CU and A-T-, A+T+ MCI subgroups because there were only a small number of smokers in each subgroup, ranging from 6 to 16.

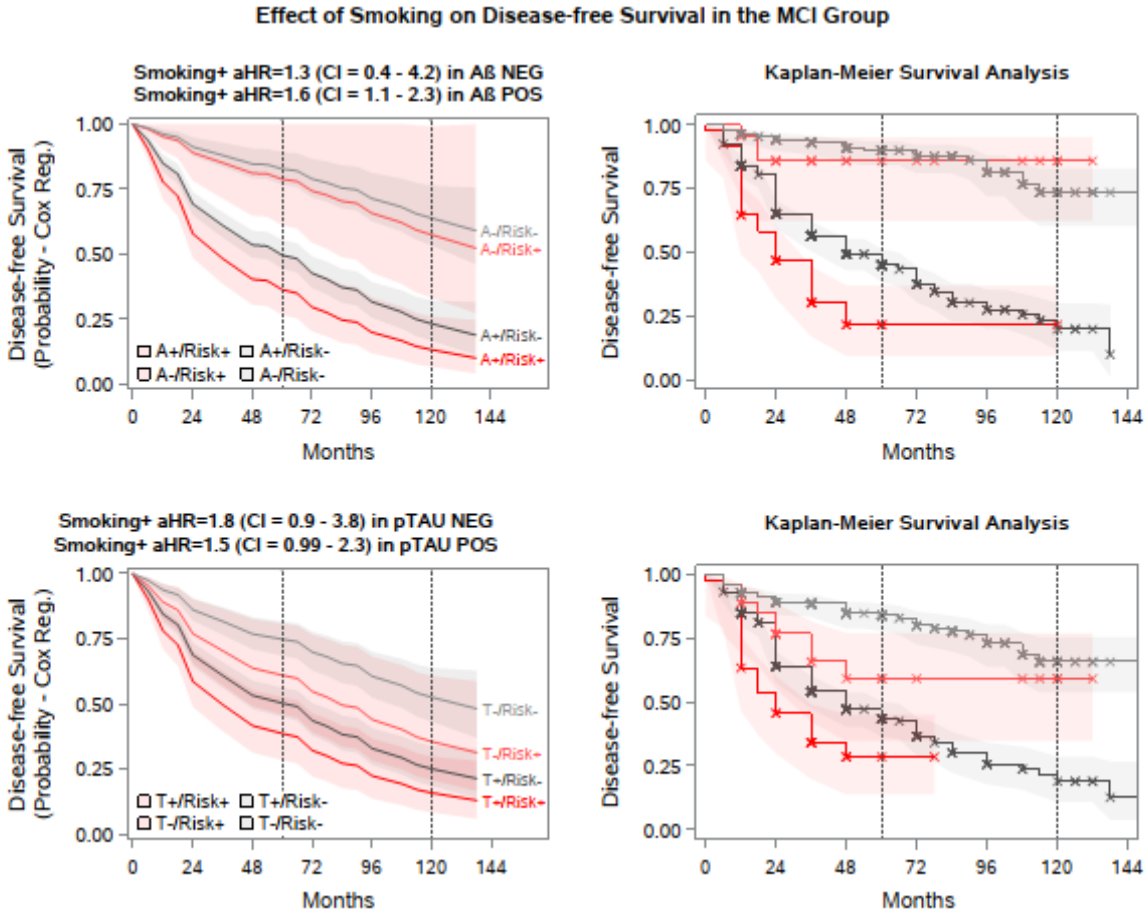

Figure 6 Smoking and Dementia Progression in MCI by beta-amyloid /p-tau Status

Smoking as a modifiable risk factor in MCI participants is presented in two separate panels: the top panel illustrates A-/A+ groups, and the bottom panel shows T-/T+ groups. The pale lines in the figure represent the biomarker-negative group, the solid lines represent the biomarker-positive group, the red lines represent the modifiable risk factor-positive group, and the grey lines represent the modifiable risk factor-negative group. The shaded areas represent the confidence intervals. Disease-free survival means no progression to dementia.
A- beta-amyloid negative **A+** beta-amyloid positive **aHR** adjusted hazard ratio **CI** confidence interval **MCI** Mild Cognitive Impairment **Risk+** smoking-positive **Risk-** smoking-negative **T-** phosphorylated tau negative **T+** phosphorylated tau positive.

8.2.4 Depression and dementia progression

No association was observed between depression and progression to MCI or dementia among CU individuals in the A-/A+ and T-/T+ subgroups compared with those without depression. Analysis by A-T-/A+T+ status was not performed due to the small number of individuals with A+T+ pathology and depression (n=12). The KM analyses also showed no statistically significant difference between the CU/depression risk groups (all p values > 0.1).

In the MCI group, a significant difference in the risk of progression to dementia was observed in the T+ subgroup (Cox aHR=1.5, 95%CI 1.06-2.02, KM log-rank ChiSq = 8.2, p=0.004), and a statistical association at trend level was observed in the A+T+ subgroup (Cox aHR=1.3, 95% CI 0.94-1.84; KM log-rank ChiSq = 3.9, p=0.049) (**Table 6**, **Figure 7**). No significant association was found between depression and progression to dementia in the A-, A+, T-, and A-T- subgroups.

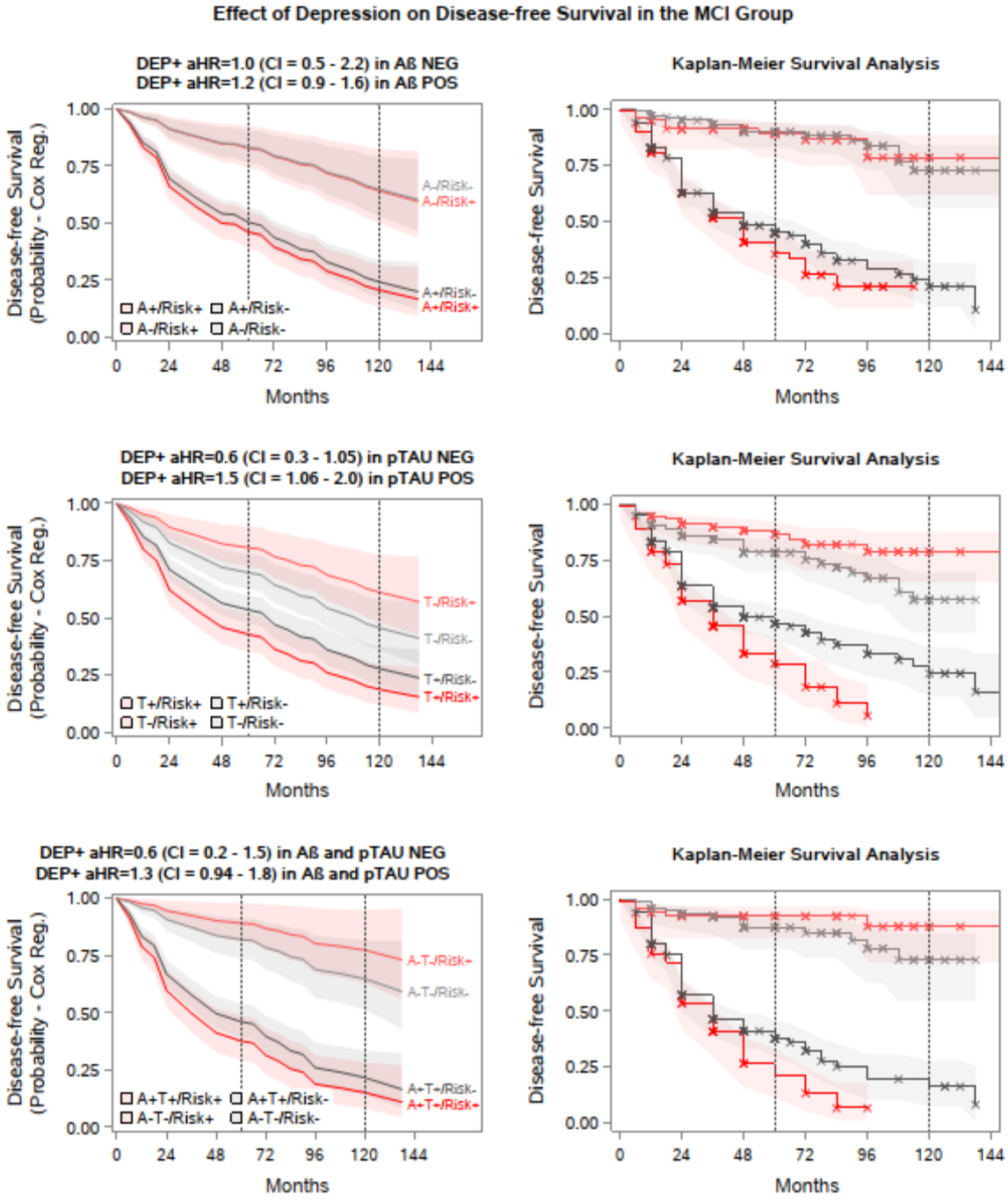

Figure 7 Depression and Dementia Progression in MCI by beta-amyloid /p-tau Status

Depression at baseline as a modifiable risk factor in MCI participants is presented in three separate panels: the top panel illustrates A-/A+ groups, the middle panel shows T-/T+ groups, and the bottom panel represents A-T-/A+T+ groups.The pale lines in the figure represent the biomarker-negative group, the solid lines represent the biomarker-positive

group, the red lines represent the modifiable risk factor-positive group, and the grey lines represent the modifiable risk factor-negative group. The shaded areas represent the confidence intervals. Disease-free survival means no progression to dementia.
A- beta-amyloid negative, **A+** beta-amyloid positive, **aHR** adjusted hazard ratio, **CI** confidence interval, **DEP+** depression-positive, **DEP-** depression-negative, **MCI** Mild Cognitive Impairment, **Risk+** depression-positive, **Risk-** depression-negative, **T-** phosphorylated tau negative, **T+** phosphorylated tau positive

Table 5 The effect of modifiable risk factors on progression to MCI and/or dementia

	CU				**MCI**			
		aHR (95% CI)		**aHR (95% CI)**		**aHR (95% CI)**		**aHR (95% CI)**
Higher CAIDE score	A-	1.6 (0.89; 2.93)	A+	1.0 (0.49; 1.92)	A-	**3.1 (1.43; 6.53)**	A+	1.3 (0.98; 1.75)
	T-	1.1 (0.54; 2.40)	T+	1.0 (0.55; 2.01)	T-	1.6 (0.94; 2.83)	T+	**1.7 (1.20; 2.27)**
	A-	1.9 (0.80; 4.25)	A+T	0.9 (0.39; 2.15)	A-T-	**2.6 (1.06; 6.59)**	A+T+	**1.6 (1.15; 2.22)**
Smoking	A-	n.e.	A+	n.e.	A-	1.3 (0.39; 4.23)	A+	**1.6 (1.07; 2.34)**
	T-	n.e.	T+	n.e.	T-	1.8 (0.89; 3.78)	T+	1.5 (0.99; 2.31)
	A-	n.e.	A+T	n.e.	A-T-	n.e.	A+T+	n.e.
Depression	A-	1.6 (0.81; 3.36)	A+	1.0 (0.42; 2.60)	A-	1.0 (0.48; 2.19)	A+	1.2 (0.86; 1.57)
	T-	1.2 (0.44; 3.19)	T+	1.1 (0.48; 2.45)	T-	0.6 (0.30; 1.05)	T+	**1.5 (1.06; 2.02)**
	A-	n.e.	A+T	n.e.	A-T-	0.6 (0.22; 1.49)	A+T+	1.3 (0.94; 1.84)

Bold numbers indicate a significant change
A- beta-amyloid negative, **A+** beta-amyloid positive, **aHR** adjusted Hazard Ratio, **CI** Confidence Interval, **CU** Cognitively Unimpaired, **MCI** Mild Cognitive Impairment, **n.e.** not estimated (due to small number of cases), **T-** phosphorylated tau negative, **T+** phosphorylated tau positive.

9. DISCUSSION

9.1. Summary of findings, international comparisons

This dissertation presents meta-analysis-level evidence from observational studies on the role of Aβ and p-tau in dementia progression. Furthermore, using the ADNI database examines the role of known modifiable dementia risk factors in dementia progression, such as obesity, hypertension, hyperlipidaemia (CAIDE elements), smoking and depression in relation to AD pathology.

Based on our results, pathological Aβ status is strongly associated with the risk of clinical progression, with ORs of 5.18 in the MCI population and 5.79 in the CU population. By additionally considering the p-tau status, the risk estimate can be further refined, as the ORs differ significantly between the A+T+ and A+T- groups compared to the A-T-. Moreover, analyses in our second study revealed that even in the presence of AD pathology, progression was significantly correlated with modifiable risk factors in numerous instances. While the adverse effects of the modifiable factors studied on AD pathology have been documented in the literature(18, 19, 21, 22, 24, 25, 29, 30), our study found no significant baseline differences in AD pathology between subgroups with and without these risk factors. Although the association of these factors with dementia risk is well established(3, 4, 16, 17, 25, 28, 40, 42), the novelty of our research lies in examining their role specifically in the context of the presence or absence of AD pathology.

A higher CAIDE score was linked to an increased risk of progression to dementia in MCI participants across the A-, T+, A-T-, and A+T+ subgroups, with a trend-level increase observed in the A+ and T- subgroups. The association between CAIDE score and risk of progression in almost all MCI biomarker subgroups, further supported by the unadjusted Kaplan-Meier survival analysis, suggests that addressing modifiable vascular and lifestyle factors is essential for reducing dementia risk, particularly in cases without AD pathology. Even in the presence of AD pathology, managing these factors may significantly lower dementia risk. The potential of lifestyle-based strategies, especially when combined with new anti-Aβ therapies, is underscored by recent multimodal prevention models such as the FINGER lifestyle intervention(102). Our findings emphasise the importance of managing hypertension, obesity, and hyperlipidaemia to prevent dementia in cognitively impaired individuals, many of whom may not be

candidates for anti-Aβ therapies(103). Notably, raising the CAIDE cut-off to seven reduced the effect, probably due to a smaller high-risk subgroup, as, the continuous CAIDE score still showed an increased risk of progression.

Smoking was significantly associated with dementia progression in the MCI A+ subgroup and showed a trend-level association in the MCI T+ subgroup, with no correlation in the A- or T- groups. This link may be due to smoking's direct effect on Aβ-associated degeneration(22, 25, 41, 104) and its adverse impact on vascular health(25, 38, 39, 41), as reduced oxygen supply is known to increase local Aβ deposition(105-107). Preclinical studies using AD-induced hypoxic models further support that smoking-related vascular reduction may raise dementia risk(105). Additionally, smokers often have other lifestyle risks, such as sedentary habits or poor diet, which may contribute to this association(108).

In our study, a history of depression and depressive symptoms was associated with an increased risk of cognitive decline in the T+ MCI subgroup, with a trend-level association in the A+T+ MCI group, but no significant association was found in A+ or biomarker-negative MCI groups. This association may be due to serotonin and cholinergic deficits caused by depression(71, 109-113), together with indirect effects of associated risk factors such as reduced physical activity, sleep disturbance, dietary changes and increased smoking(4, 114, 115). Both direct and indirect effects of depression are likely to contribute to dementia risk. However, it remains controversial whether depression in mid- and late-life is a prodrome of dementia or an independent risk factor(116, 117). Our findings highlight the importance of treating depressive symptoms, even in the presence of AD pathology, regardless of whether depression is a risk factor or a consequence of the disease.

It should be noted that in none of the CU biomarker subgroups was a significant association observed between progression and the risk factors tested (CAIDE score, depression). Given the well-documented impact of these risk factors on cognitive decline(3, 4), two possible explanations emerge: first, the relatively low progression rate in the CU group (19.1% vs. 36.2% in MCI) may have limited the statistical power to detect associations. Second, the median follow-up of four years in the CU group may be too short for the adverse effects of these risk factors to manifest in CU individuals.

The meta-regression result of our systematic review study shows that the OR decreases slightly with increasing mean age for the MCI population, suggesting that the effect of amyloid positivity on progression weakens with age. This may be due to the known association between ageing and higher dementia risk, as well as the prevalence of vascular and other neurodegenerative conditions in older adults. Combined with findings from Rodrigue et al.(118), these results suggest that while amyloid burden increases with age, its influence on progression rates gradually decreases. The statistical power of this analysis for CU subjects is limited due to the smaller number of studies and the narrow age range between them.

The appearance of Aβ is considered one of the earliest signs of AD(119, 120), and our meta-analysis supports this by showing that only the A+ (A+T- and A+T+) groups had an increased risk of progression compared to A-T-, while the A-T+ group did not. The specificity of abnormal Aβ levels for AD and its central role in its pathomechanism has been questioned(6); however, from a clinical point of view, measuring Aβ alone is effective in identifying at-risk populations. Meanwhile, p-tau alone is less predictive of progression. Our findings align with previous studies indicating a weaker association between cognitive decline and the A-T+ group compared to A+T- or A+T+ groups(121, 122). However, it's worth noting that T+ status is associated with neurodegeneration, and the A-T+ group may be linked to frontotemporal dementia(123). Further research is needed to clarify the role of the A-T+ group.

Finally, regarding our p-tau findings, it is important to note the significant update from the Alzheimer's Association Workgroup Recommendation 2024(11). In contrast to the 2018 NIA-AA recommendation(12), which allowed p-tau181 as a stand-alone indicator for the diagnosis of p-tau pathology, the 2024 recommendation introduces a more nuanced classification. This new framework differentiates between tau pathologies by categorising biomarkers into Core 1 (including p-tau181) and Core 2 (including tau PET). It specifies that CSF p-tau181 becomes abnormal earlier than tau PET, suggesting that secretion of these tau fragments may link Aβ pathology to early tau pathology. In ADNI and all meta-analysed studies except Strikwerda-Brown(81) and Ossenkoppele(79) (which used tau PET), p-tau classification was based on CSF p-tau181 levels. Our meta-analysis further emphasises the prognostic value of CSF p-tau181,

highlighting its potential role not only as a marker of p-tau pathology but also as a predictor of progression.

9.2. Strengths

9.2.1. Strengths of Study I.

Our systematic review and meta-analysis followed the PRISMA 2020 guidelines and the recommendations of the Cochrane Handbook(51). The analysis was strengthened by large sample sizes, particularly for Aβ (CU A+(n)= 1391, A-(n)=2826; MCI A+(n)= 1789, A-(n)= 1787), enhancing the reliability of the results. Subgroup analyses were perfomed to explore the potential influence of follow-up time, age, and different Aβ measurement techniques (amyloid PET vs. CSF Aβ42/40 vs. CSF Aβ42) on the ORs, providing a deeper understanding of the findings. HR analyses were conducted alongside the OR calculations for both the CU and MCI Aβ groups, and the results were consistent. Furthermore, outlier detection further confirmed the robustness of our conclusions.

9.2.2. Strengths of Study II.

In examining the relationship between modifiable risk factors and AD biomarkers, our study used a large, well-characterised sample from the ADNI, including 434 CU and 611 MCI individuals, with a median follow-up of four years. Cox proportional hazard models were adjusted for key covariates, including age, sex, education, baseline MMSE score, baseline hippocampal volume, and ApoE4 carrier status. Furthermore, Kaplan-Meier survival analyses were conducted for all subgroups, and the results were found to be consistent with those from the Cox models, thus providing additional evidence to support the reliability of the findings.

9.3. Limitations

Both studies have several limitations that should be considered when interpreting the results. Both studies used data from the ADNI, which is a well-characterised sample but not representative of the general population; the participants are educated and healthy

older adults. Except for one Brazilian(99), and one Japanese(77) study, all the studies and the ADNI used in the meta-analysis were from the "Western world". These may limit the generalisability of the results to more diverse populations.

Both our studies used both CSF and PET to determine Aβ pathology. Variability in biomarker cut-offs and measurement techniques across studies potentially influencing the accuracy of classification into biomarker positive and negative groups. While PET scens may exhibit slightly higher sensitivity than CSF techniques, the high concordance between these methods(124-126) suggests that methodological differences are likely to have a limited impact on heterogeneity. Our relevant subgroup analysis also points in this direction. Furthermore, the considerations on p-tau measurements (changes in the classification recommendations) made earlier in the discussion should be repeated here.

9.3.1. Limitations of Study I.

The CU populations in the pooled studies include people with no cognitive symptoms and those with subjective cognitive symptoms, resulting in varying distances from MCI or dementia. Also, the fact that studies have used different neuropsychological tests to define MCI, and that the definition of MCI itself has changed slightly over the years, may be due to the heterogeneity of the pooled sample. Neither CU nor MCI OR calculations could account for other potential risk factors (either modifiable or biologic) contributing to heterogeneity. Additionally, significant heterogeneity by mean age was observed, with our meta-regression analysis showing a decreasing effect of age on ORs in the MCI group.

Some studies with a large number of cases reported combined results for MCI and CU subjects; including these mixed populations in the MCI group, was a practical choice, as it allowed us to maximize the sample size. To assess potential bias, we conducted a subgroup analysis comparing mixed and MCI-only populations, which showed no significant differences. The OR for Aβ in the mixed group was 4.64 [95% CI 1.16; 18.61], compared with 5.83 [95% CI 3.80; 8.93] in the MCI-only studies, indicating that inclusion of the mixed population slightly reduced the overall OR in the main analysis (5.21 [95% CI 3.93; 6.90]).

In the OR analysis of Aβ in the CU group, the outlier value from the Arruda(72) study may be attributed to a statistical extreme due to the small number of A+ subjects compared to the much larger A- group. Similarly, in the Grontvedt(49) and Hanseeuw(76) studies, which report exceptionally high values, there is a similar uneven distribution between the A+ and A- groups. Outliers in the MCI Aβ OR analysis are also associated with small sample sizes. In the A+T+/A+T-/A-T+ analyses, no outliers were identified in either the MCI or CU groups.

Our OR analyses for Aβ were supported by HR calculations. However, due to the limited number of studies, we could not assess the effect of p-tau on HRs, limiting the completeness of the A/T analysis. Small sample sizes in some studies further contributed to variability, though their inclusion was important for a comprehensive analysis.

Follow-up times varied widely, from 20 months to over 10 years, and were reported as mean, median or maximum. While the odds of progression naturally increase with time, our meta-regression showed no significant effect of follow-up time on the ORs, with moderate heterogeneity supporting this finding. HRs independent of follow-up time yielded similar results to the OR analyses. It should be noted that pathological protein changes may precede symptoms by up to 20 years(12), making such long-term follow-up difficult, and none of the included studies extended beyond this period.

9.3.2. Limitations of Study II.

The CAIDE scoring system provides a comprehensive overview of cardiovascular and lifestyle risk factors. However, it was originally developed for middle-aged populations with 20 years of follow-up, whereas in our study it was applied to an older population with shorter follow-up. Since then, there have been examples of its use with shorter follow-ups and in older patients(16). Additionally, no uniform recommendation exists for the cut-off point separating high- and low-risk groups, meaning that cut-offs may differ across populations. Despite this, using the median to divide groups is appropriate for identifying risk due to CAIDE factors(36). The lack of data on physical activity may have slightly underestimated the association. Still, as physical activity only changes the CAIDE score by one point, its impact is less weighted than other modifiable factors, contributing two points each.

For depression, participants were classified based on medical history. Thus, we could not account for its severity and late or early onset. Symptoms of depression at baseline were assessed using a neuropsychiatric inventory, but no clinically structured interview was used to diagnose depressive disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). Smoking data were self-reported and we could not assess the severity of smoking, which is another limitation. In addition, the potential confounding effects of risk factors on each other were not taken into account in our calculations. We were unable to consider the effects of medications for depression, hyperlipidaemia, and hypertension in the analyses, as these conditions were only treated as categorical variables without considering whether they were treated or untreated. For CU participants, analyses for smoking were not performed due to the small number of cases, and analyses for depression were only partially completed. The smaller sample size for CAIDE and depression in the CU group reduced the statistical power compared with the MCI group.

We emphasise that our study aimed to investigate the role of modifiable risk factors in different biomarker subgroups, not to compare their effect between these different biomarker states. Due to statistical power limitations for interaction analyses, it remains unclear if the associations of CAIDE score, smoking and depression with clinical progression differ between the different biomarker subgroups.

10. CONCLUSION

The systematic review of the literature indicates that measuring Aβ and p-tau levels enables the identification of individuals at markedly increased risk of cognitive decline, even before the onset of clinical symptoms. Similarly, in mild cognitive impairment, abnormal levels of these proteins are strong predictors of further progression. In particular, Aβ is a key indicator of progression, although its predictive value appears to decline slightly with age. Importantly, this prognostic advantage of Aβ measurement is consistently observed across techniques, including amyloid PET, CSF Aβ42/40 ratio, and CSF Aβ42 measurement.

As in other diseases, both primary and secondary prevention are key priorities in dementia care. The impact of potentially modifiable risk factors on the development of dementia is well established; extending this evidence, our cohort analysis indicates that cardiovascular risk factors, depression, and smoking continue to play a significant role in disease progression even in the presence of abnormal Aβ and p-tau levels. Consequently, efforts should be directed towards reducing the harmful effects of these factors in at-risk populations.

11. IMPLEMENTATION FOR PRACTICE

Our findings highlight the potential for integrating biomarker-based risk stratification by Aβ and p-tau measurement with assessment of potentially modifiable risk factors in clinical practice. Identifying individuals according to their Aβ and p-tau status enables clinicians to recognise those at high risk of developing MCI and dementia at an early, asymptomatic stage. Combining this approach with an assessment of modifiable risk factors could allow for a more personalised preventive care plan. This combined assessment could inform early interventions, particularly those targeting modifiable factors, to potentially delay or reduce cognitive decline in at-risk populations(16, 37).

12. IMPLEMENTATION FOR RESEARCH

Our investigations demonstrate the need for further research into the interaction between AD biomarkers and modifiable risk factors to refine preventive strategies. The markedly disparate progression rates observed between biomarker-positive and biomarker-negative groups underscore the necessity of considering biomarker status in dementia research. Accordingly, future dementia risk prediction tools should be capable of incorporating amyloid and p-tau status alongside currently used risk factors in order to improve the accuracy of risk estimation.

Our study - probably due to statistical power limitations - did not find a statistically significant association between modifiable risk factors and AD pathology in the CU population. To uncover these associations, further studies with larger CU sample sizes and longer follow-up periods are needed to clarify these associations.

Future studies using longitudinal approaches are also necessary to establish the temporal relationship between risk factor management and dementia progression across a range of biomarker profiles. Expanding research to include diverse populations with varied baseline health statuses would additionally provide insights into generalisability and inform the development of tailored preventive strategies. Research into the specific mechanisms by which lifestyle factors influence biomarker changes and progression rates could also enhance understanding of the modifiable pathways associated with dementia.

13. IMPLEMENTATION FOR POLICYMAKERS

These findings suggest that prioritising early risk detection through biomarker screening and lifestyle assessment could have meaningful implications for public health. However, we cannot yet take a clear stance on routine biomarker screening for CU individuals; the development of anti-amyloid therapies is currently the relevant indicator in this regard. In the case of MCI individuals, routine biomarker screening already appears valuable. Policymakers could consider exploring initiatives to improve access to biomarker testing for those at risk and to promote preventive interventions targeting lifestyle factors such as vascular health, physical activity and mental well-being. Collaboration between healthcare systems, public health agencies and community organisations could also support comprehensive, community-based dementia prevention strategies. With a focus on improving quality of life and potentially reducing future healthcare burdens, these strategies could help meet the growing challenge of dementia in an ageing population.

14. FUTURE PERSPECTIVES

Future research should aim to expand and refine biomarker-guided strategies for dementia prevention and early intervention. Advances in anti-amyloid and tau-targeted therapies may make biomarker screening increasingly relevant. In addition, research exploring the synergistic effects of biomarker-targeted therapies with lifestyle interventions could provide a holistic approach to dementia prevention. Large-scale, longitudinal studies in diverse populations will be essential to understand the broader applicability of these strategies and to develop tailored interventions that consider individual risk profiles and health status. As dementia prevention becomes an increasing priority, the combination of biomarker-based risk assessment and actionable lifestyle interventions has the potential to significantly improve public health outcomes, reduce healthcare burden and improve quality of life for at-risk populations.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

Huszár Z, Engh MA, Pavlekovics M, Sato T, Steenkamp Y, Hanseeuw B, Terebessy T, Molnár Z, Hegyi P, Csukly G.
Risk of conversion to mild cognitive impairment or dementia among subjects with amyloid and tau pathology: a systematic review and meta-analysis
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Huszár Z, Solomon A, Engh MA, Koszovácz V, Terebessy T, Molnár Z, Hegyi P, Horváth A, Mangialasche F, Kivipelto M, Csukly G.
Association of modifiable risk factors with progression to dementia in relation to amyloid and tau pathology
Alzheimer's Research & Therapy 2024 Oct 26;16(1):238. doi: 10.1186/s13195-024-01602-9
D1, IF: 7.6

16.2. Publications not related to the thesis

Őri D, Szocsics P, Molnár T, Ralovich FV, **Huszár Z**, Bene Á, Rózsa S, Győrffy Z, Purebl G.
Stigma towards mental illness and help-seeking behaviors among adult and child psychiatrists in Hungary: A cross-sectional study
PLoS One 2022 Jun 10;17(6):e0269802. doi: 10.1371/journal.pone.0269802
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Domain-specific cognitive impairment in multiple sclerosis: A systematic review and meta-analysis

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Association of modifiable risk factors with progression to dementia in relation to amyloid and tau pathology

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Abstract

Background Dementia preventive interventions targeting multiple modifiable risk factors are a promising approach. However, the impact of modifiable risk factors in the presence of beta-amyloid or phosphorylated-tau (p-tau) pathology is unclear.

Methods The objective of the study was to examine the role of modifiable risk factors (vascular factors, depression, and smoking) in the progression to mild cognitive impairment (MCI) or dementia among 434 cognitively unimpaired (CU) and 611 individuals with MCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Vascular risk factors were summarized with the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) score, dichotomized into higher versus lower risk. Depression and smoking (yes/no) were categorised according to medical history or current symptoms. Analyses were stratified by beta-amyloid negative (A-) and positive (A +), p-tau negative (T-) and positive (T +), or beta-amyloid and p-tau negative (A-T-) and positive (A + T +) biomarker status. Cox proportional hazard models were adjusted for age, sex, education, baseline MMSE score, baseline hippocampal volume and ApoE4 carrier status.

Results Higher CAIDE score was associated with increased risk of progression to all-cause dementia in most MCI subgroups: adjusted hazard ratios (aHR) [95% CI] were 3.1 [1.43; 6.53] in the A- subgroup, 1.7 [1.20–2.27] in T +, 2.6 [1.06–6.59] in A-T-, and 1.6 [1.15–2.22] in the A + T + subgroup. Smoking (yes/no) was associated with increased dementia aHR in the A + MCI subgroup: 1.6 [1.07–2.34]. Depression increased dementia aHR in the T + MCI subgroup: 1.5 [1.06–2.02]. No significant associations were found in the CU biomarker subgroups.

Conclusion Addressing modifiable risk factors carries an important potential for reducing the risk of dementia even after the onset of Alzheimer's pathology. Knowledge of biomarker status can further optimize prevention strategies.

Keywords Modifiable risk factors, CAIDE, Depression, Smoking, Amyloid, Tau, MCI

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Background

Alzheimer's disease (AD) and other forms of dementia are major causes of years lived with disability and represent a substantial long-term economic challenge for society. As the population ages, the consequences of dementia are anticipated to become even more severe [1]. Although there have been recent advances in anti-amyloid agents [2], current pharmacological therapeutic options have limited benefits. Addressing modifiable risk factors e.g. via lifestyle-based intervention programs in early risk and/or disease stages has been recommended for dementia risk reduction [3]. Major risk factors including e.g. smoking, depression, high blood pressure, and obesity, were estimated to account for about 40% of dementia cases [4, 5]. These risk factors have been linked to both AD and cerebrovascular damage [6–16].

To estimate an individual's risk of developing dementia based on vascular factors, risk scores such as CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) have been developed [17]. The CAIDE score is based on age, education, sex, blood pressure, body mass index, total cholesterol, and physical activity. It provides a comprehensive and integrated assessment of an individual's risk profile, allowing a more accurate estimate of the overall dementia risk, simplifying complex information into a single score, and making it more accessible to individuals and health professionals. From the above risk factors, obesity, high blood pressure, and hyperlipidemia are well known to increase the risk of vascular disease and, thus, the likelihood of cerebrovascular damage. They may also play a role in the development of AD [18, 19]. In the context of obesity and hyperlipidemia, adipokines and cholesterol have been described to modulate amyloid precursor protein degradation and thus beta-amyloid (Aβ) accumulation. Hypertension may also impair Aβ clearance, and may thus directly contribute to AD [20, 21].

The CAIDE dementia risk score has been previously tested in observational studies in relation to various cerebrospinal fluid (CSF) and neuroimaging markers, and post-mortem brain pathology [22], and higher scores correlate with signs of neurodegeneration such as reduced cortical thickness, increased medial temporal atrophy, white matter lesions, reduced brain perfusion, increased neuroinflammation, and changes in CSF Aβ and total tau [23–27]. It was also used to identify older at-risk individuals from the general population in the Finnish Geriatric Intervention study to prevent cognitive impairment and disability (FINGER). The FINGER trial showed cognitive and other related health benefits for a 2-year multidomain lifestyle intervention versus regular health advice [28]. In the Multidomain Alzheimer's Preventive Trial (MAPT), cognitive benefits from the multidomain intervention were shown in participants with a higher CAIDE score [29]. While a higher CAIDE score may reflect the potential for lifestyle-based dementia risk reduction in individuals without substantial impairment, its associations with dementia risk are less clear in populations with specific cognitive and neuropathological profiles.

The harmful effects of smoking on blood vessels, including in the brain, are well known [30, 31]. Smokers have an increased risk of dementia compared to those who have never smoked [14]. Moreover, there is evidence suggesting direct impact on AD development. Older smokers have reduced grey matter density in brain regions associated with the early stages of AD [32]. In vitro and animal studies have shown that cigarette smoke exposure consistently promotes amyloidogenic and tau abnormalities [15, 16]. Smoking is associated with cerebral oxidative stress, which promotes hyperphosphorylation of tau proteins and increases β-secretase cleavage of amyloid precursor protein involved in the production of Aβ oligomers and extracellular fibrillar Aβ aggregation [11].

Depression has been indicated as a risk factor for cognitive impairment in the context of vascular conditions as it is associated with adverse cerebrovascular effects, including increased risk of stroke and vascular pathological changes, which contribute to cognitive decline, and are also strongly associated with AD [6, 9, 33, 34]. Some studies have also reported that individuals with mild cognitive impairment (MCI) and pathological Aβ levels who have depressive symptoms progress more quickly to dementia than those without depressive symptoms [35–37].

The typical pathological changes in Aβ and tau proteins associated with Alzheimer's disease appear decades before cognitive symptoms [38]. Detection of these protein changes in cognitively unimpaired (CU) or MCI individuals indicates a significant increase in the risk of cognitive decline [39–41]. While modifiable risk factors may provide room for dementia risk reduction, associations of the CAIDE risk score and additional risk factors such as depression and smoking with clinical progression in populations with more specific cognitive-neuropathological profiles is not fully clear. In the present study, we aimed to examine the role of defined modifiable risk factors, namely the CAIDE score, depression, and smoking, in the progression to MCI or all-cause dementia among biomarker-homogeneous (in terms of Aβ and p-tau) CU and MCI subgroups. This was accomplished by performing a comparative analysis of progression data between participants who were either positive or negative for these

modifiable risk factors within each subgroup, classified according to Aβ, p-tau, and both Aβ and p-tau pathology.

Methods

Study population

Data from 1045 (611 with MCI and 434 cognitively unimpaired) participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) were used. ADNI is a publicly available (https://adni.loni.usc.edu/) follow-up study cohort at more than 60 clinical sites in the US and Canada that uses a variety of biomarkers, neuroimaging, and clinical assessments to study Alzheimer's disease and dementia. Enrolled participants were categorised into CU, MCI and all-cause dementia groups using the Clinical Dementia Rating (CDR) score (CDR = 0 for CU, CDR = 0.5 for MCI and > 0.5 for dementia) and education level adjusted MMSE and Wechsler Logical Memory II subscale tests to aid in the diagnostic process. Participants were aged between 55 and 90 years and underwent a comprehensive medical examination. Individuals with severe neurological or psychiatric disorders and systemic diseases affecting cognition were excluded from the study. Full details of the enrolment process are available at https://adni.loni.usc.edu/help-faqs/adni-documentation/. The date of the ADNI database download was May 05, 2022, with data captured from 2005 onwards. CU and MCI were assessed using participant-level follow-up data (see Supplementary Appendix 1 for detailed ADNI data management) [42].

CU and MCI subgroups were classified according to Aβ, p-tau, or both Aβ and p-tau pathology. Analyses of the various dementia risk factors for the CU group were performed on data from 434 participants when considering Aβ pathology alone, 331 participants when considering p-tau pathology alone, and 219 participants when considering both Aβ and p-tau pathology. Analyses of the MCI group for Aβ pathology alone were based on data from 611 participants, for p-tau pathology alone on 551 participants, and on 417 participants when both pathologies were considered together. The median follow-up for both CU and MCI participants was four years. Detailed baseline data and progression to MCI or all-cause dementia during follow-up are shown in Tables 1 and 2.

Risk factors

The examined risk factors, such as depression, smoking, high blood pressure, obesity, and hyperlipidemia, were treated as dichotomous variables, and participants were categorised as having vs not having a risk factor according to their medical history. The CAIDE score was calculated based on age, sex, education, hypertension (Systolic Blood Pressure > 140 mm Hg), obesity (body mass index (BMI) > 30 kg/m^2) and hyperlipidemia (total cholesterol > = 6.5 mmol/L) as previously described in detail (Supplementary eTable 1) [17]. All risk factors were measured at baseline, which was the starting (zero) point of the survival analyses. Physical activity could not be included in the CAIDE calculation because data were unavailable in the ADNI database. Based on the median CAIDE score and the cut-off previously used in the FINGER study [28], we used six points as a cut-off for high dementia risk.

Assignment to the smoking group was based on the participants' medical records. Similary, based on a history of depression documented in medical records, or baseline depressive symptoms, participants were divided into depression and no depression groups. Depressive symptoms were assessed using the Neuropsychiatric Inventory-Questionnaire (NPI-Q) in ADNI 1 or the Neuropsychiatric Inventory (NPI) in ADNI GO, ADNI 2, and ADNI 3 [43–45]. Following criteria established in previous studies for the CU and MCI populations, the cut-off point for categorizing depression was a severity score of ≥ 2 on the NPI-Q [46, 47] or a severity × frequency score of ≥ 4 on the NPI [48, 49].

Aβ and p-tau status

We used the ^{18}F-Florbetapir (AV45) PET data as the default Aβ measurement where available. Florbetapir standardized uptake value ratio (SUVR) was created by averaging the four cortical regions and dividing them by the cerebellum as a reference. According to the ADNI recommendation, we applied the SUVR cut-off of 1.11 and used the whole cerebellum region as a reference [50]. In a previous study [51] Florbetapir positivity defined using the same cut-off was shown to be strongly correlated with post-mortem autopsy results. If PET data were unavailable, we used Aβ1-42 CSF measurements (Roche Elecsys) to maximize the analysis sample size. As previously indicated [52], we applied a cut-off of 977 pg/ml for Aβ1-42 measurements since this cut-off value showed the highest agreement with amyloid PET results (overall percent agreement 87%, 95% CI 84.2–89.5). Participants were defined as p-tau positive by CSF p-tau181 levels (INNO-BIA AlzBio3) above 23 pg/ml, a cut-off shown in a previous study on autopsy-based AD cases to have the best classification power [53].

The rationale for analyzing data on Aβ status separately was twofold. First, p-tau status was available for a smaller number of participants, thus focusing only on Aβ increased the statistical power. Second Aβ captures a broader risk group who may not (yet) have tau pathology. However, abnormal p-tau alongside Aβ indicates a more severe condition. Therefore, we studied A + T + /A-T- subgroups as well. We also analyzed groups subdivided

Table 1 Baseline information - Cognitively Unimpaired (CU)

Amyloid	*n*	**All** (*n* = 434)	**Amyloid positive** (*n* = 152)	**Amyloid negative** (*n* = 282)	**statistics**
Age: mean (SD) years	434	73.3 (6.2)	74.7 (5.9)	72.5 (6.2)	t = -4.3,df = 346.0,*p* = < .0001 *
Baseline MMSE	434	29.1 (1.2)	29.0 (1.1)	29.1 (1.2)	t = 0.1, df = 363.2, *p* = 0.9501
ApoE4 carrier status	434	124 (28.6%)	70 (46.1%)	54 (19.1%)	ChiSq = 35.0,df = 1.0,*p* = < .0001 *
Baseline Hippocampus Volume (mm3)	434	7483 (864)	7336 (860)	7562 (857)	t = 2.6, df = 307.7, *p* = 0.0089
Female gender: *n* (%)	434	240 (55.3%)	94 (61.8%)	146 (51.8%)	ChiSq = 4.1, df = 1.0, *p* = 0.0441
Higher CAIDE score: *n* (%)	428	131 (30.6%)	48 (31.8%)	83 (30.0%)	ChiSq = 0.2, df = 1.0, *p* = 0.6956
CAIDE Total Score	428	5.8 (1.5)	5.8 (1.5)	5.8 (1.4)	t = -0.3, df = 318.7, *p* = 0.7691
Depression as risk: *n* (%)	434	74 (17.1%)	28 (18.4%)	46 (16.3%)	ChiSq = 0.3, df = 1.0, *p* = 0.5773
Smokers: *n* (%)	356	40 (11.2%)	17 (13.6%)	23 (10.0%)	ChiSq = 1.1, df = 1.0, *p* = 0.2988
Follow-up time: median(IQR)	434	48 (24- 96)	48 (24- 90)	60 (24- 96)	ChiSq = 3.2, df = 1.0, *p* = 0.0724
Progression to MCI or dementia: *n* (%)	434	83 (19.1%)	38 (25.0%)	45 (16.0%)	ChiSq = 5.2, df = 1.0, *p* = 0.0223
p-tau181	***n***	**All (*n* = 331)**	**p-tau181 positive (*n* = 114)**	**p-tau181 negative (*n* = 217)**	**statistics**
Age: mean (SD) years	331	74.0 (5.8)	75.7 (6.1)	73.1 (5.4)	t = -3.9,df = 220.4,*p* = 0.0001 *
Baseline MMSE	331	29.0 (1.2)	29.0 (1.2)	29.0 (1.1)	t = 0.1, df = 227.2, *p* = 0.8962
ApoE4 carrier status	331	88 (26.6%)	39 (34.2%)	49 (22.6%)	ChiSq = 5.2, df = 1.0, *p* = 0.0229
Baseline Hippocampus Volume (mm3)	331	7452 (856)	7313 (881)	7525 (836)	t = 2.1, df = 219.4, *p* = 0.0354
Female gender: *n* (%)	331	171 (51.7%)	59 (51.8%)	112 (51.6%)	ChiSq = 0.0, df = 1.0, *p* = 0.9805
Higher CAIDE score: *n* (%)	327	105 (32.1%)	41 (36.6%)	64 (29.8%)	ChiSq = 1.6, df = 1.0, *p* = 0.2087
CAIDE Total Score	327	5.8 (1.5)	5.9 (1.5)	5.8 (1.5)	t = -0.7, df = 241.3, *p* = 0.5003
Depression as risk: *n* (%)	331	68 (20.5%)	23 (20.2%)	45 (20.7%)	ChiSq = 0.0, df = 1.0, *p* = 0.9043
Smokers: *n* (%)	331	37 (11.2%)	10 (8.8%)	27 (12.4%)	ChiSq = 1.0, df = 1.0, *p* = 0.3139
Follow-up time: median(IQR)	331	72 (36–102)	66 (36- 96)	72 (36–102)	ChiSq = 0.1, df = 1.0, *p* = 0.7322
Progression to MCI or dementia: *n* (%)	331	72 (21.8%)	39 (34.2%)	33 (15.2%)	ChiSq = 15.9,df = 1.0, *p* = < .0001 *
Amyloid and p-tau181	***n***	**All (*n* = 219)**	**Amyloid and p-tau181 positive (*n* = 60)**	**Amyloid and p-tau181 negative (*n* = 159)**	**statistics**
Age: mean (SD) years	219	73.7 (5.6)	76.4 (5.2)	72.6 (5.5)	t = -5.1,df = 119.5,*p* = < .0001 *
Baseline MMSE	219	29.1 (1.2)	29.1 (1.1)	29.1 (1.2)	t = -0.4, df = 122.3, *p* = 0.6813
ApoE4 carrier status	219	56 (25.6%)	28 (46.7%)	28 (17.6%)	ChiSq = 19.3,df = 1.0,*p* = < .0001 *
Baseline Hippocampus Volume (mm3)	219	7492 (800)	7245 (817)	7585 (776)	t = 2.8, df = 101.7, *p* = 0.0064
Female gender: *n* (%)	219	109 (49.8%)	33 (55.0%)	76 (47.8%)	ChiSq = 0.9, df = 1.0, *p* = 0.3418
Higher CAIDE score: *n* (%)	216	70 (32.4%)	23 (39.0%)	47 (29.9%)	ChiSq = 1.6, df = 1.0, *p* = 0.2056
CAIDE Total Score	216	5.8 (1.5)	5.9 (1.5)	5.8 (1.5)	t = -0.7, df = 108.2, *p* = 0.5080
Depression as risk: *n* (%)	219	42 (19.2%)	12 (20.0%)	30 (18.9%)	ChiSq = 0.0, df = 1.0, *p* = 0.8495
Smokers: *n* (%)	219	22 (10.0%)	6 (10.0%)	16 (10.1%)	ChiSq = 0.0, df = 1.0, *p* = 0.9890
Follow-up time: median(IQR)	219	72 (36- 96)	54 (36- 90)	72 (36–102)	ChiSq = 4.7, df = 1.0, *p* = 0.0305
Progression to MCI or dementia: *n*(%)	219	46 (21.0%)	23 (38.3%)	23 (14.5%)	ChiSq = 15.0,df = 1.0,*p* = 0.0001 *

CU Cognitively Unimpaired, *MCI* Mild Cognitive Impairment, *MMSE* Mini-Mental State Examination, *ApoE4* Apolipoprotein E epsilon 4 carriers, *CAIDE* Cardiovascular Risk Factors, Aging, and Dementia, *p-tau181* Phosphorylated tau 181, *CSF* Cerebrospinal Fluid, *n* Number of participants, *SD* Standard Deviation, *IQR* Interquartile Range, *ChiSq* Chi-Square Test, *df* Degrees of Freedom, *p* p-value

**p*-values indicate significant differences between biomarker positives and negatives (after correction for multiple comparisons $p < 0.05/11$, where 11 is the number of parameters compared), and are based on T-tests or Wilcoxon tests (follow-up time) in case of continuous variables and Chi-Square tests in case of categorical variables

Table 2 Baseline information - Mild Cognitive Impairment (MCI)

Amyloid	*n*	**All** (*n* = 611)	**Amyloid positive** (*n* = 377)	**Amyloid negative** (*n* = 234)	**statistics**
Age: mean (SD) years	610	72.5 (7.4)	73.5 (6.8)	70.9 (8.1)	t = -4.0,df = 481.4,*p* = < .0001 *
Baseline MMSE	611	27.8 (1.8)	27.4 (1.8)	28.4 (1.5)	t = 8.2,df = 630.7,*p* = < .0001 *
ApoE4 carrier status	611	300 (49.1%)	246 (65.3%)	54 (23.1%)	ChiSq = 102.8,df = 1.0,*p* = < .0001 *
Baseline Hippocampus Volume (mm3)	611	6865 (1133)	6631 (1064)	7242 (1142)	t = 6.6,df = 474.7,*p* = < .0001 *
Female gender: *n* (%)	611	255 (41.7%)	156 (41.4%)	99 (42.3%)	ChiSq = 0.1, df = 1.0, *p* = 0.8210
Higher CAIDE score: *n* (%)	606	223 (36.8%)	141 (37.8%)	82 (35.2%)	ChiSq = 0.4, df = 1.0, *p* = 0.5172
CAIDE Total Score	606	5.9 (1.4)	5.8 (1.4)	5.9 (1.5)	t = 0.8, df = 543.7, *p* = 0.4211
Depression as risk: *n* (%)	611	192 (31.4%)	110 (29.2%)	82 (35.0%)	ChiSq = 2.3, df = 1.0, *p* = 0.1290
Smokers: *n* (%)	576	70 (12.2%)	48 (13.5%)	22 (10.0%)	ChiSq = 1.5, df = 1.0, *p* = 0.2138
Follow-up time: median(IQR)	611	48 (30- 78)	48 (24- 60)	48 (36- 96)	ChiSq = 17.8,df = 1.0,*p* = < .0001 *
Progression to dementia: n(%)	611	221 (36.2%)	195 (51.7%)	26 (11.1%)	ChiSq = 103.2,df = 1.0,*p* = < .0001 *
p-tau181	***n***	**All (*n* = 551)**	**p-tau181 positive (*n* = 305)**	**p-tau181 negative (*n* = 246)**	**statistics**
Age: mean (SD) years	551	72.4 (7.5)	73.4 (7.4)	71.1 (7.4)	t = -3.4,df = 563.7,*p* = 0.0007 *
Baseline MMSE	551	27.7 (1.8)	27.4 (1.8)	28.1 (1.7)	t = 5.2,df = 578.7,*p* = < .0001 *
ApoE4 carrier status	551	273 (49.5%)	192 (63.0%)	81 (32.9%)	ChiSq = 49.1,df = 1.0,*p* = < .0001 *
Baseline Hippocampus Volume (mm3)	551	6820 (1150)	6582 (1077)	7116 (1171)	t = 5.5,df = 504.2,*p* = < .0001 *
Female gender: n (%)	551	230 (41.7%)	132 (43.3%)	98 (39.8%)	ChiSq = 0.7, df = 1.0, *p* = 0.4155
Higher CAIDE score: n (%)	548	196 (35.8%)	102 (33.7%)	94 (38.4%)	ChiSq = 1.3, df = 1.0, *p* = 0.2534
CAIDE Total Score	548	5.8 (1.4)	5.7 (1.3)	6.0 (1.5)	t = 2.2, df = 522.8, *p* = 0.0309
Depression as risk: n (%)	551	183 (33.2%)	90 (29.5%)	93 (37.8%)	ChiSq = 4.2, df = 1.0, *p* = 0.0398
Smokers: *n* (%)	551	68 (12.3%)	41 (13.4%)	27 (11.0%)	ChiSq = 0.8, df = 1.0, *p* = 0.3814
Follow-up time: median(IQR)	551	48 (36- 84)	48 (36- 66)	48 (36- 90)	ChiSq = 12.6,df = 1.0, *p* = 0.0004 *
Progression to dementia: *n* (%)	551	213 (38.7%)	163 (53.4%)	50 (20.3%)	ChiSq = 63.0,df = 1.0,*p* = < .0001 *
Amyloid and p-tau181	***n***	**All (*n* = 418)**	**Amyloid and p-tau181 positive (*n* = 257)**	**Amyloid and p-tau181 negative (*n* = 160)**	**statistics**
Age: mean (SD) years	417	72.1 (7.6)	73.4 (7.1)	69.9 (7.8)	t = -4.4,df = 343.3, *p* = < .0001 *
Baseline MMSE	417	27.7 (1.8)	27.3 (1.8)	28.4 (1.5)	t = 7.3,df = 419.3, *p* = < .0001 *
ApoE4 carrier status	417	213 (51.1%)	177 (68.9%)	36 (22.5%)	ChiSq = 84.9,df = 1.0, *p* = < .0001 *
Baseline Hippocampus Volume (mm3)	417	6763 (1142)	6477 (1026)	7221 (1174)	t = 6.6,df = 303.4, *p* = < .0001 *
Female gender: *n* (%)	417	184 (44.1%)	113 (44.0%)	71 (44.4%)	ChiSq = 0.0, df = 1.0, *p* = 0.9353
Higher CAIDE score: *n* (%)	414	144 (34.8%)	88 (34.5%)	56 (35.2%)	ChiSq = 0.0, df = 1.0, *p* = 0.8827
CAIDE Total Score	414	5.8 (1.4)	5.7 (1.3)	5.9 (1.6)	t = 1.3, df = 332.2, *p* = 0.2014
Depression as risk: *n* (%)	417	144 (34.5%)	78 (30.4%)	66 (41.3%)	ChiSq = 5.2, df = 1.0, *p* = 0.0228
Smokers: *n* (%)	417	45 (10.8%)	33 (12.8%)	12 (7.5%)	ChiSq = 2.9, df = 1.0, *p* = 0.0874
Follow-up time: median(IQR):	417	48 (36- 78)	48 (36- 60)	60 (36- 96)	ChiSq = 20.7,df = 1.0, *p* = < .0001 *
Progression to dementia: *n* (%)	417	178 (42.7%)	158 (61.5%)	20 (12.5%)	ChiSq = 96.7,df = 1.0, *p* = < .0001 *

CU Cognitively Unimpaired, *MCI* Mild Cognitive Impairment, *MMSE* Mini-Mental State Examination, *ApoE4* Apolipoprotein E epsilon 4 carriers, *CAIDE* Cardiovascular Risk Factors, Aging, and Dementia, *p-tau181* Phosphorylated tau 181, *CSF* Cerebrospinal Fluid, *n* Number of participants, *SD* Standard Deviation, *IQR* Interquartile Range, *ChiSq* Chi-Square Test, *df* Degrees of Freedom, *p* p-value

* *p*-values indicate significant differences between biomarker positives and negatives (after correction for multiple comparisons $p < 0.05/11$, where 11 is the number of parameters compared), and are based on T-tests or Wilcoxon tests (follow-up time) in case of continuous variables and Chi-Square tests in case of categorical variables

by CSF p-tau181 pathology alone (T + /T-), reflecting the 2024 classification [54], which indicates that *p*-tau181 becomes abnormal alongside amyloid PET, but before tau PET.

Statistical analysis

The CU and MCI groups were divided into Aβ positive and negative (A + , A-), p-tau positive and negative (T + , T-) and Aβ and p-tau positive and negative

(A + T +, A-T-) subgroups. Baseline characteristics of CU and MCI participants were compared between each biomarker positive and negative subgroup using t-test, Wilcoxon or Chi-square tests as appropriate. The associations of CAIDE score, depression, and smoking with progression to MCI and/or dementia were investigated in analyses stratified by cognitive and pathology status: CU A + /A-, CU T + /T-, CU A + T + /A-T-, MCI A + /A-, MCI T + /T-, MCI A + T + /A-T-.

We calculated the (adjusted) Hazard Ratios (HR) with their confidence interval (CI) from a Cox Proportional Hazard Model (PROC PHREG in SAS 9.4). Progression to dementia in the MCI group or progression to dementia and MCI combined (in the CU group) were the dependent (predicted) variables in separate models, while Aβ and p-tau positivity served as predictor variables together with modifiable risk factors such as CAIDE score, smoking, and depression. Cox regression (Cox) analyses of smoking and depression included age, sex, education, baseline MMSE score, baseline hippocampal volume and ApoE4 carrier status as covariates. Cox regression analyses of CAIDE score included age, baseline MMSE score, and baseline hippocampal volume and ApoE4 carrier status as covariates (sex and education were already included in the CAIDE score). In order to test the proportional hazard assumption we repeated all Cox regressions by including the interaction of time and risk factors as covariates. Since the interaction of time and risk factors were non-significant in all Cox regressions (all p values > 0.1) we can conclude that there is no evidence of the time dependency of the hazard ratios, i.e. the proportional hazard assumption were met in all cases. Death was included as a competing risk in the Cox regressions. All reported Hazard Ratios from Cox regressions are adjusted ones (aHR). Where a subgroup included < 20 participants, the survival analysis was not performed due to a high risk of bias.

The methodology described above was not applied to the CU and MCI A + T- and A-T + subgroups because of the high risk of bias due to the small sample size (< 20).

Sensitivity analyses

The Kaplan–Meier survival analyses were also performed for all biomarker groups and risk factors. The survival plots are included in the figures; therefore, the adjusted curves from the Cox regressions and the survival plots are easily comparable. In the results section, we also present the statistics (log-rank test and corresponding p values) from the Kaplan–Meier (KM) analyses.

Furthermore, we performed the Cox regression analysis with the CAIDE total score as a continuous variable and with seven as alternate cut-off value for the CAIDE score. Finally, we analyzed the effect of CAIDE as risk factor in the MCI sample regardless of biomarker status.

Results

Based on the analysis of 434 CU and 611 MCI participants, baseline characteristics did not differ significantly between the A-/A +, T-/T +, and A-T-/A + T + subgroups for either CU or MCI participants according to the percentage of participants with a higher CAIDE score, depression, and smoking. There were significant differences in age, ApoE4 carrier status, MMSE score, hippocampal volume and progression rate between the biomarker-negative and positive subgroups (Table 1 and 2).

A total of 103 CU and 60 MCI participants lacked p-tau data, with only data on their Aβ status available for analysis. The number of CU participants in each biomarker subgroup was 277 (A-), 151 (A +), 217 (T-), 114 (T +), 58 (A + T-), 53 (A-T +), 157 (A-T-), and 59 (A + T +). MCI participants included 234 (A-), 377 (A +), 246 (T-), 305 (T +), 86 (A + T-), 48 (A-T +), 160 (A-T-), and 257 (A + T +).

Higher CAIDE score and progression to MCI and/or dementia

Among CU participants with higher CAIDE scores, compared to those with lower scores, the risk of progression to MCI or dementia was not significantly increased in either the biomarker-negative or biomarker-positive subgroups (Table 3, Supplementary eFigure 1). The KM analyses did not show a statistically significant difference between any CU/CAIDE risk groups (all p values > 0.1).

In the MCI population (Table 3, Fig. 1), the risk of progression to dementia was significantly increased among A- MCI participants with higher compared to lower CAIDE scores (Cox aHR = 3.1, 95% CI 1.43–6.53, KM log-rank chi-square (ChiSq) = 8.1, $p = 0.004$), while in the A + MCI subgroup a statistical trend-level association was observed (Cox aHR = 1.3, 95% CI 0.98–1.7, KM log-rank ChiSq = 0.16, $p = 0.7$). In the T + subgroup, higher CAIDE score was related to higher dementia risk compared with lower CAIDE score (Cox aHR = 1.7 95%CI 1.20–2.27, KM log-rank ChiSq = 5.0, $p = 0.03$), with a similar trend in the T- subgroup (Cox aHR = 1.6, 95%CI 0.94–2.83, KM log-rank ChiSq = 2.8, $p = 0.096$). Higher CAIDE score was significantly associated with an increased progression risk among both the A-T- (Cox aHR = 2.6, 95%CI 1.06–6.59, KM log-rank ChiSq = 4.7, $p = 0.03$) and A + T + (Cox aHR = 1.6, 95%CI 1.15–2.22, KM log-rank ChiSq = 2.6, $p = 0.1$) MCI subgroups.

Table 3 The effect of modifiable risk factors on progression to MCI and/or dementia

Effect	CU				MCI			
	aHR (95% CI)		aHR (95% CI)		aHR (95% CI)		aHR (95% CI)	
Higher CAIDE score	A-	1.6 (0.89; 2.93)	A +	1.0 (0.49; 1.92)	A-	**3.1 (1.43; 6.53)**	A +	1.3 (0.98; 1.75)
	T-	1.1 (0.54; 2.40)	T +	1.0 (0.55; 2.01)	T-	1.6 (0.94; 2.83)	T +	**1.7 (1.20; 2.27)**
	A-T-	1.9 (0.80; 4.25)	A + T +	0.9 (0.39; 2.15)	A-T-	**2.6 (1.06; 6.59)**	A + T +	**1.6 (1.15; 2.22)**
Smoking	A-	n.e.	A +	n.e.	A-	1.3 (0.39; 4.23)	A +	**1.6 (1.07; 2.34)**
	T-	n.e.	T +	n.e.	T-	1.8 (0.89; 3.78)	T +	1.5 (0.99; 2.31)
	A-T-	n.e.	A + T +	n.e.	A-T-	n.e.	A + T +	n.e.
Depression	A-	1.6 (0.81; 3.36)	A +	1.0 (0.42; 2.60)	A-	1.0 (0.48; 2.19)	A +	1.2 (0.86; 1.57)
	T-	1.2 (0.44; 3.19)	T +	1.1 (0.48; 2.45)	T-	0.6 (0.30; 1.05)	T +	**1.5 (1.06; 2.02)**
	A-T-	n.e.	A + T +	n.e.	A-T-	0.6 (0.22; 1.49)	A + T +	1.3 (0.94; 1.84)

Bold numbers indicate a significant increase

CU Cognitively Unimpaired, *MCI* Mild Cognitive Impairment, *aHR* adjusted Hazard Ratio, *95% CI* 95% Confidence Interval, *A-* beta-amyloid negative, *A +* beta-amyloid positive, *T-* p-tau negative, *T +* p-tau positive, *n.e.* not estimated (due to small number of cases)

Sensitivity analysis for CAIDE score and risk for progression in the MCI group

According to the literature, cut-offs higher than six are acceptable [55]. We conducted the sensitivity analysis with the cut-off score of seven and also the CAIDE total score as a continuous variable in the MCI group. With seven as cutoff, none of the aHRs remained significant, while for CAIDE as a continuous variable, one point increase in the total score was associated with an increased risk in the A- (Cox aHR = 1.4, 95%CI 1.1–1.8), A-T- (Cox aHR = 1.4, 95%CI 1.01–1.9), A + T + (Cox aHR = 1.1, 95%CI 1.01–1.3), and T + groups (Cox aHR = 1.1, 95%CI 1.01–1.3). In the whole MCI sample, regardless of the biomarker status, higher CAIDE scores were associated with an increased risk of preogression (Cox aHR = 1.5, 95CI 1.1–1.9).

Smoking and progression to dementia

In the MCI population, the risk of progression to dementia was significantly increased in smokers compared to non-smokers in the A + (Cox aHR = 1.6, 95%CI 1.07–2.34, KM log-rank ChiSq = 11.5, $p = 0.0007$) subgroup, while a statistical trend-level association was observed in the T + subgroup (Cox aHR = 1.5, 95%CI 0.99–2.31, KM log-rank ChiSq = 8.0, $p = 0.005$). No association was observed in the A- and T- MCI subgroups (Table 3, Fig. 2). The analysis was not performed for MCI A-T- and A + T + subgroups, or any of the CU pathology subgroups due to the small number of smokers in each subgroup (ranging between 6 to 16, Table 2).

Depression and progression to MCI and/or dementia

A comparison between participants with and without depression in the CU group showed no significant association with progression to MCI or dementia across the A-/A + and T-/T + biomarker subgroups (Table 3, Supplementary eFigure2). Analysis stratified by A-T-/A + T + status was not performed due to the small number of individuals with A + T + pathology and depression ($n = 12$, Table 2). The KM analyses showed no statistically significant difference between CU/Depression risk groups (all p values > 0.1).

In the MCI group, a significant difference in the risk of progression to dementia was observed between participants with and without depression in the T + subgroup (Cox aHR = 1.5, 95%CI 1.06–2.02, KM log-rank ChiSq = 8.2, $p = 0.004$), and a statistical trend-level associacion was observed in the A + T + subgroup (Cox aHR = 1.3, 95%CI 0.94–1.84, KM log-rank ChiSq = 3.9, $p = 0.049$) (Table 3, Fig. 3). No significant relation was identified between depression and progression to dementia in the biomarker-negative subgroups.

Discussion

We investigated to what extent the CAIDE dementia risk score, smoking, and depression (history of depression, or current symptoms) as modifiable risk factors were related to clinical progression of cognitive impairment in the presence or absence of Aβ and p-tau pathology. Analyzing the CU and MCI individuals separately, we found that the association of these risk factors with progression varied depending on the presence or absence of AD pathological changes.

The adverse association of the currently studied modifiable risk factors with the occurrence of Aβ and p-tau pathology is well documented in the literature. However, in this study no significant baseline differences were found in the occurrence of AD pathology between the subgroups with and without risk factors such as higher CAIDE score, smoking, or depression. While the

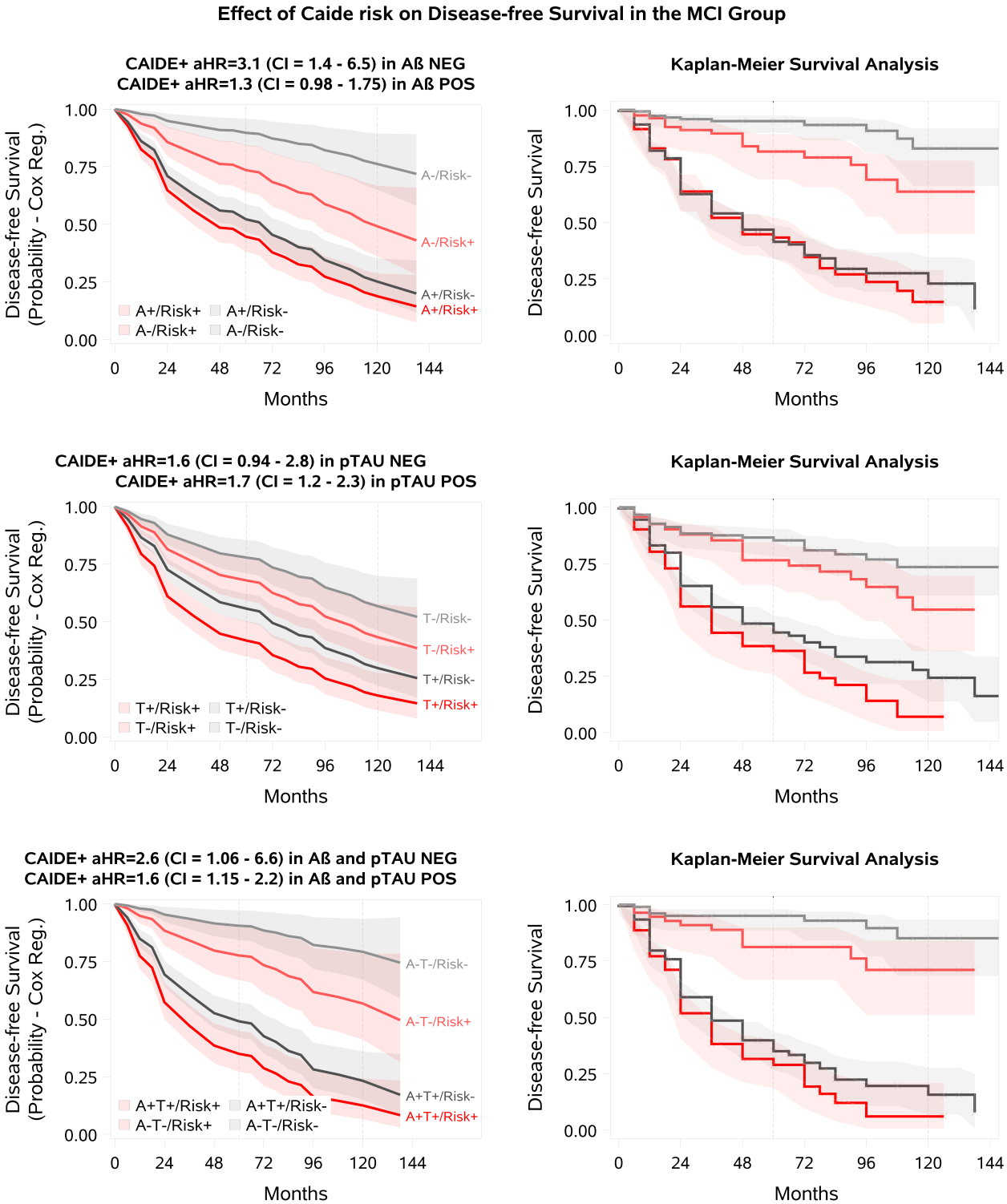

Fig. 1 CAIDE Score and Dementia Progression in MCI by beta-amyloid/p-tau Status. The pale lines in the figure represent the biomarker-negative group, the solid lines represent the biomarker-positive group, the red lines represent the modifiable risk factor-positive group, and the grey lines represent the modifiable risk factor-negative group. The shaded areas represent the confidence intervals. Disease-free survival means no progression to dementia. **A** CAIDE as a modifiable risk factor in MCI A-/A + participants. **B** CAIDE as a modifiable risk factor in MCI T-/T + participants. **C** CAIDE as a modifiable risk factor in MCI A-T-/A + T + participants

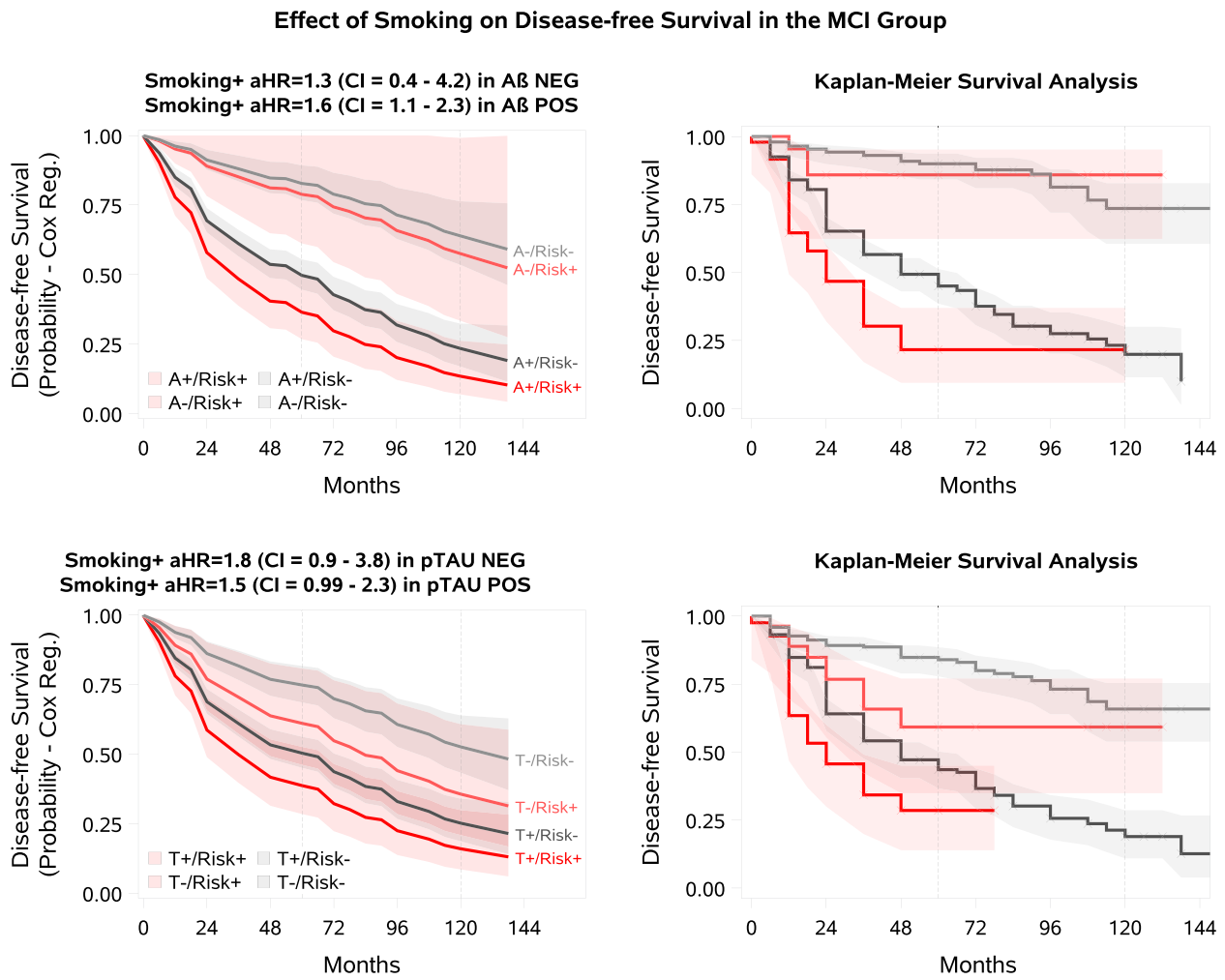

Fig. 2 Smoking and Dementia Progression in MCI by beta-amyloid /p-tau Status. The pale lines in the figure represent the biomarker-negative group, the solid lines represent the biomarker-positive group, the red lines represent the modifiable risk factor-positive group, and the grey lines represent the modifiable risk factor-negative group. The shaded areas represent the confidence intervals. Disease-free survival means no progression to dementia. **A** Smoking as a modifiable risk factor in MCI A-/A + participants. **B** Smoking as a modifiable risk factor in MCI T-/T + participants

influence of these modifiable factors on dementia risk is well established [3, 5, 6, 14, 17, 33, 34], the novelty of our research concerns their role specifically in the presence or absence of AD pathology.

A higher CAIDE score was associated with an increased risk of progression to dementia in MCI participants who were A-, T+, A-T-, and A+T+. Furthermore a statistical trend-level increase of risk was observed in the A+and T- subgroups. Associations were no longer significant when the CAIDE score cut-off was increased to seven, which may be due to smaller size of the higher risk group, since total CAIDE score as a continuous variable was related to an increased progression risk. Since higher CAIDE score was associated with higher progression risk in all almost MCI biomarker subgroups, and results were confirmed by a different unadjusted analytical approach (Kaplan–Meier survival analysis), these findings suggest that addressing modifiable vascular/lifestyle risk factors is critical to reducing the risk of progression due to non-AD pathology. Furthermore, even in the presence of AD pathology, managing these risk factors could significantly reduce the risk of dementia. Recent multimodal prevention models are combining e.g. FINGER lifestyle intervention with putative disease-modifying drugs [56]. The potential added benefit of lifestyle-based interventions would be particularly interesting to investigate in the context of new promising anti-Aβ therapies. Given

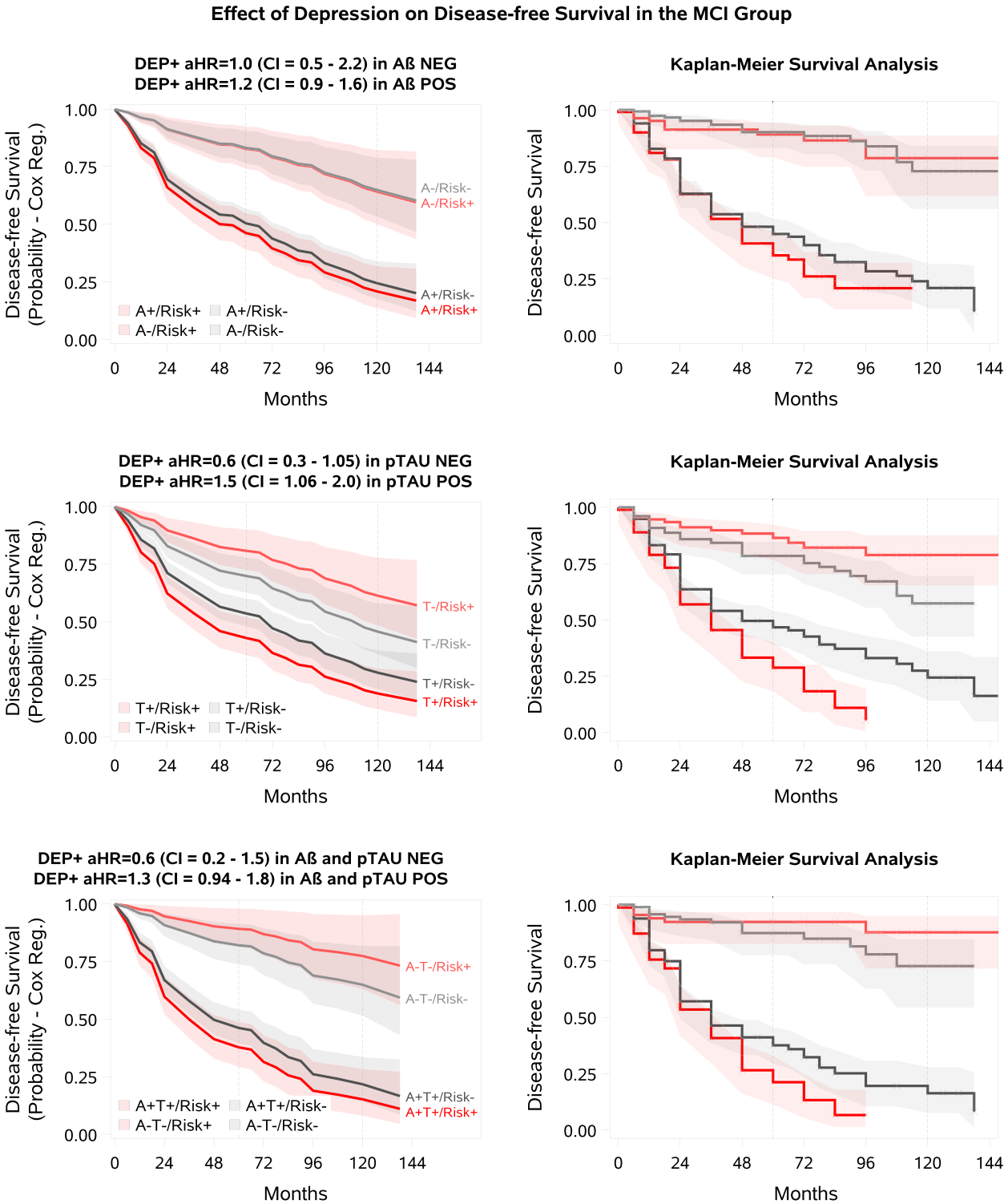

Fig. 3 Depression and Dementia Progression in MCI by beta-amyloid /p-tau Status. The pale lines in the figure represent the biomarker-negative group, the solid lines represent the biomarker-positive group, the red lines represent the modifiable risk factor-positive group, and the grey lines represent the modifiable risk factor-negative group. The shaded areas represent the confidence intervals. Disease-free survival means no progression to dementia. **A** Depression at baseline as a modifiable risk factor in MCI A-/A + participants. **B** Depression at baseline as a modifiable risk factor in MCI T-/ T + participants. **C** Depression at baseline as a modifiable risk factor in MCI A-T-/A + T + participants

the higher hazard ratios associated with higher CAIDE score in the non-AD MCI groups, our results further emphasize the importance of managing hypertension, obesity and hyperlipidaemia in dementia prevention, and highlight the potential for dementia risk reduction with vascular/lifestyle-based interventions in a significant group of cognitively impaired people who would most likely not be eligible for e.g. anti-Aβ therapies [57].

The detrimental relationship between depression and dementia is widely supported [6, 9, 33, 34]. Examining history of depression and depressive symptoms together, in the present study an increased risk of cognitive decline related to depression was found in the T + MCI subgroup, with a statistical trend-level association in the A + T + MCI subgroup. No statistically significant association with progression was observed in the A + and biomarker-negative MCI subgroups or in any CU subgroups studied (A + /A-,T + /T-). Notably, there was a significant difference in the prevalence of depression between the CU and MCI groups (17.1% vs 31.4%). One explanation for the link between depression and cognitive decline could be the serotonin and cholinergic deficits described as a consequence of depression [53, 58–62]. Depression is also associated with other risk factors for dementia, such as reduced physical activity, sleep disturbances, altered diet, and increased smoking [5, 63, 64]. Therefore, both direct and indirect effects of depression may increase the risk of dementia. An ongoing debate exists regarding whether mid- and late-life depression should be interpreted as a prodrome of dementia or as an independent risk factor [65, 66]. Our results highlight the importance of paying special attention to depressive symptoms, even in the presence of AD pathology, irrespective of whether depression is a risk factor or a consequence of the disease.

There is a well-established link between social activity and lower levels of depression [67, 68]. Social connections—including those facilitated by social media—have become increasingly important. Particularly for older adults who are at risk of isolation, social media platforms offer opportunities to maintain and enhance social interactions [69, 70]. Research suggests that certain types of social media use can have a positive impact on mental health, which may help to reduce certain dementia risk factors [71, 72]. Including social media use in lifestyle interventions may improve mental health and reduce the risk of dementia. Future research should explore the benefits of social media in vulnerable populations.

There was a significant association between smoking and progression to dementia in the MCI A + subgroup, and a trend-level association in the MCI T + subgroup, while the MCI A- and T- subgroups showed no correlation. Several mechanisms may explain the association between smoking and dementia [14, 30–32]. Some studies suggested that smoking may directly affect Aβ-associated degeneration [11, 14, 32, 73], accelerating its onset. In addition, smoking is known to have adverse effects on the vasculature [14, 30–32]. Other studies have shown that any factor that reduces oxygen supply leads to local Aβ deposition [74–76]. Preclinical research using AD-induced hypoxic models confirms that reduced brain vascularisation caused by smoking may contribute to an increased risk of dementia [74]. It should also be considered that smokers' lifestyles are often associated with other risk factors, such as a sedentary lifestyle or poor diet [77].

When interpreting our results for p-tau, it is important to note that the tau classification was based on CSF p-tau181, which is included in the Alzheimer's Association Workgroup Recommendation 2024 as a Core1 T_1 biomarker and is recommended to be used primarily in conjunction with CSF Aβ42, as it has greater diagnostic value in this context. In addition, CSF p-tau181 becomes abnormal at the same time as amyloid PET and before tau PET. It is thought that the secretion of these tau fragments may represent a physiological response to Aβ plaques and may link Aβ proteinopathy to early tau proteinopathy [54]. At the same time, it is worth highlighting the role of p-tau181 as a prognostic factor. In our previous meta-analysis based on several studies measuring CSF p-tau181, we found that individuals identified as A + T + (using CSF p-tau181) had significantly higher odds ratios for cognitive decline compared to the A + or A + T- groups [41].

Finally, it is important to note that no significant association was identified between progression and the risk factors tested (CAIDE score, depression) in any of the CU biomarker subgroups. Given the well-established deleterious role of these risk factors in cognitive decline, we have two possible explanations. Firstly, the relatively low progression rate in the CU group (19.1% compared with 36.2% in MCI) may have reduced the statistical power to detect significant associations. Secondly, the median follow-up of the healthy group was four years, which may be insufficient for the adverse effects of these risk factors to become apparent in individuals who are cognitively intact.

Strenghts and limitations

This study used a large, well-characterised sample from the ADNI, including 434 CU and 611 MCI individuals, with a median follow-up of four years. However, the present study has several limitations. Aβ status was determined based on PET scans in most participants, and on CSF in the rest. Although PET is known to be more sensitive, both methods are widely used in practice, the

concordance between the two methods is high, and CSF measurement is more widely available for financial reasons [38, 78].

The CAIDE scoring system provides a comprehensive and easy-to-use overview of cardiovascular and lifestyle risk factors. However, CAIDE was initially developed for a middle-aged population, and in the original study, it was used to predict the risk of dementia over 20 years. Since then, there have been examples of its use with shorter follow-ups and in older patients [3]. There is no uniform recommendation for the point value to separate the high- and low-risk groups so that this cut-off may differ in other populations. Nevertheless, utilizing the median for separating groups is appropriate for identifying the risk due to CAIDE factors. It should be noted that the lack of data on physical activity may lead to an underestimation of the association. However, the effect of physical activity is less weighted, changing the CAIDE score by only one point, compared with other modifiable risk factors, each of which contributes two points. Importantly, the accuracy and validity of cognitive tests and the CAIDE score may be influenced by cultural differences [79, 80]. To ensure that these assessments are globally applicable, future research should focus on validating and modifying them for a range of populations.

In the case of depression, it should be noted that the participants were classified based on their medical history. The severity of the depression or whether it was a late or early onset could not be considered. A more accurate classification method could further refine the results. Symptoms of depression at baseline were assessed by a detailed and comprehensive neuropsychiatric inventory developed for the detection of behavioral disturbances in dementia [43]. However, it has been utilised in preceding clinical trials with participants with MCI and CU and has been demonstrated to be a valid and reliable measure [46–48, 81]. Nevertheless, a clinically structured interview was not performed to diagnose depressive disorders according to the Diagnostic Diagnostic and Statistical Manual of Mental Disorders (DMS) [82]. In terms of smoking habits, only self-reported information was utilized, and a limitation of the study is the lack of consideration of the severity of smoking. Another limitation is that the potential confounding effect of these risk factors on each other is not included in our calculations. It also should be noted that the ADNI cohort is skewed towards white individuals and those with higher levels of education. This latter fact may restrict the generalisability of the findings to a more diverse population.

Another limitation is that the analyses could not take into account the effects of medications used for depression, hyperlipidaemia and hypertension. Therefore, these conditions were only included as categorical variables, as we could not take into account their treated or untreated status.

A limitation of the observations for CU participants is that analyses for smoking could not be performed due to the small number of cases, and analyses for depression were only partially performed. Additionally, the results for CAIDE scores and depression in the CU group are based on a moderately small sample size, resulting in lower statistical power compared to the MCI group.

We emphasise that our study aimed to investigate the role of modifiable risk factors in different biomarker subgroups, not to compare their effect between these different biomarker states. Due to statistical power limitations for interaction analyses, it remains unclear if the associations of CAIDE score, smoking and depression with clinical progression differ between the different biomarker subgroups.

Conclusion

Even after the onset of AD pathology, addressing modifiable risk factors remains critical to reducing the risk of dementia. As the effects of vascular/lifestyle-based interventions on dementia risk reduction are currently being investigated in randomized controlled trials, a key focus for future studies should be how the presence or absence of AD pathology may impact intervention effects, and potential added benefit of combining lifestyle-based and pharmacological therapies in populations who already have cognitive impairment and AD pathology.

Abbreviations

A-	Non-pathologic levels of beta-amyloid
A +	Pathologic levels of beta-amyloid
Aβ	Beta-amyloid
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
aHR	Adjusted Hazard Ratio
ChiSq	Chi-square
CI	Confidance interval
Cox	Cox regression analyses
CU	Cognitively unimpaired
CSF	Cerebrospinal fluid
HR	Hazard ratio
KM	Kaplan–Meier analyses
MCI	Mild cognitive impairment
PET	Positron emission tomography
p-tau	Phosphorylated tau
T-	Non-pathologic levels of phosphorylated tau
T +	Pathologic levels of phosphorylated tau

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01602-9.

Supplementary Material 1.

Authors' contributions
ZH: conceptualisation, methodology, formal analysis, writing—original draft; AS: conceptualisation, methodology, supervision, writing – review and editing; MAE: conceptualisation, writing – review and editing; VK: conceptualisation, writing – original draft; TT: supervision, writing – review and editing; ZM: supervision, writing – review and editing; PH: supervision, writing – review and editing; AH: conceptualisation, supervision, writing – review and editing; FM: conceptualisation, supervision, writing – review and editing; MK: conceptualisation, supervision, writing – review and editing; GC: conceptualisation, methodology, formal analysis, supervision, writing – review and editing, visualization.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
ADNI investigators obtained ethics approval from the local ethical committees of all involved sites. Access to all ADNI data was granted to us after registration to ADNI (https://adni.loni.usc.edu) and compliance with the data usage agreement. All work complied with ethical regulations for work with human participants. In accordance with the Declaration of Helsinki (consent for research), written informed consent was obtained from each participant or their designated representative. Ethics approval was obtained from the institutional review boards of each institution involved: Oregon Health and Science University; University of Southern California; University of California—San Diego; University of Michigan; Mayo Clinic, Rochester; Baylor College of Medicine; Columbia University Medical Center; Washington University, St. Louis; University of Alabama at Birmingham; Mount Sinai School of Medicine; Rush University Medical Center; Wien Center; Johns Hopkins University; New York University; Duke University Medical Center; University of Pennsylvania; University of Kentucky; University of Pittsburgh; University of Rochester Medical Center; University of California, Irvine; University of Texas Southwestern Medical School; Emory University; University of Kansas, Medical Center; University of California, Los Angeles; Mayo Clinic, Jacksonville; Indiana University; Yale University School of Medicine; McGill University, Montreal-Jewish General Hospital; Sunnybrook Health Sciences, Ontario; U.B.C. Clinic for AD & Related Disorders; Cognitive Neurology—St. Joseph's, Ontario; Cleveland Clinic Lou Ruvo Center for Brain Health; Northwestern University; Premiere Research Inst (Palm Beach Neurology); Georgetown University Medical Center; Brigham and Women's Hospital; Stanford University; Banner Sun Health Research Institute; Boston University; Howard University; Case Western Reserve University; University of California, Davis—Sacramento; Neurological Care of CNY; Parkwood Hospital; University of Wisconsin; University of California, Irvine—BIC; Banner Alzheimer's Institute; Dent Neurologic Institute; Ohio State University; Albany Medical College; Hartford Hospital, Olin Neuropsychiatry Research Center; Dartmouth-Hitchcock Medical Center; Wake Forest University Health Sciences; Rhode Island Hospital; Butler Hospital; UC San Francisco; Medical University South Carolina; St. Joseph's Health Care Nathan Kline Institute; University of Iowa College of Medicine; Cornell University and University of South Florida: USF Health Byrd Alzheimer's Institute (https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

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Competing interests
The authors declare no competing interests.

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Publisher's Note

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REVIEW

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Risk of conversion to mild cognitive impairment or dementia among subjects with amyloid and tau pathology: a systematic review and meta-analysis

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Abstract

Background Measurement of beta-amyloid (Aβ) and phosphorylated tau (p-tau) levels offers the potential for early detection of neurocognitive impairment. Still, the probability of developing a clinical syndrome in the presence of these protein changes (A+ and T+) remains unclear. By performing a systematic review and meta-analysis, we investigated the risk of mild cognitive impairment (MCI) or dementia in the non-demented population with A+ and A- alone and in combination with T+ and T- as confirmed by PET or cerebrospinal fluid examination.

Methods A systematic search of prospective and retrospective studies investigating the association of Aβ and p-tau with cognitive decline was performed in three databases (MEDLINE via PubMed, EMBASE, and CENTRAL) on January 9, 2024. The risk of bias was assessed using the Cochrane QUIPS tool. Odds ratios (OR) and Hazard Ratios (HR) were pooled using a random-effects model. The effect of neurodegeneration was not studied due to its non-specific nature.

Results A total of 18,162 records were found, and at the end of the selection process, data from 36 cohorts were pooled (*n*= 7,793). Compared to the unexposed group, the odds ratio (OR) for conversion to dementia in A+ MCI patients was 5.18 [95% CI 3.93; 6.81]. In A+ CU subjects, the OR for conversion to MCI or dementia was 5.79 [95% CI 2.88; 11.64]. Cerebrospinal fluid Aβ42 or Aβ42/40 analysis and amyloid PET imaging showed consistent results. The OR for conversion in A+T+ MCI subjects (11.60 [95% CI 7.96; 16.91]) was significantly higher than in A+T- subjects (2.73 [95% CI 1.65; 4.52]). The OR for A-T+ MCI subjects was non-significant (1.47 [95% CI 0.55; 3.92]). CU subjects with A+T+ status had a significantly higher OR for conversion (13.46 [95% CI 3.69; 49.11]) than A+T- subjects (2.04 [95% CI 0.70; 5.97]). Meta-regression showed that the ORs for Aβ exposure decreased with age in MCI. (beta = -0.04 [95% CI -0.03 to -0.083]).

Conclusions Identifying Aβ-positive individuals, irrespective of the measurement technique employed (CSF or PET), enables the detection of the most at-risk population before disease onset, or at least at a mild stage. The inclusion of tau status in addition to Aβ, especially in A+T+ cases, further refines the risk assessment. Notably, the higher odds ratio associated with Aβ decreases with age.

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Trial registration The study was registered in PROSPERO (ID: CRD42021288100).
Keywords Beta-amyloid, Phosphorylated tau, Dementia, Mild cognitive impairment, Alzheimer's disease

Background

Affecting 55 million people worldwide, dementia is one of the leading causes of years spent with disability and one of the costliest long-term illnesses in society. The most common cause of dementia is Alzheimer's disease (AD), responsible for 60-80% of cases [1, 2].

Two specific protein aggregates play a crucial role in the pathophysiology of AD. One is the amyloid plaque formation in the extracellular space, predominantly by Aβ aggregation. These plaques, among other pathological effects, inhibit the signaling function of neurons [3]. The other protein change is the appearance of neurofibrillary tangles within the neurons, which are formed by the phosphorylation of tau proteins (p-tau) and inhibit the axonal transport inside the cell [4]. Whereas the specific pathology could only be confirmed by autopsy in the past, in vivo tests are available today. Parallelly to this development, the diagnostic definitions of AD have evolved significantly over time, moving from purely clinical assessments and post-mortem examinations to the integration of in vivo amyloid and later p-tau biomarkers, emphasizing the role of preclinical stages [5–8]. Accordingly, researchers are increasingly trying to link the diagnosis of the disease to biological parameters. However, in general, the clinical practice only considers the quality of the symptoms of dementia and the fact of neurodegeneration confirmed by radiology when establishing an AD diagnosis.

The International Working Group (IWG) [5] emphasizes that diagnosis should align with clinical symptoms. However, for researchers in the field, the U.S. National Institute on Aging – Alzheimer's Association (NIA-AA) has issued a new framework recommendation [6]. This recommendation defines AD purely in terms of specific biological changes based on the Aβ (A) and p-tau (T) protein status, while neurodegeneration (N) is considered a non-specific marker that can be used for staging. In the recommendation, the category 'Alzheimer's disease continuum' is proposed for all A+ cases, 'Alzheimer's pathological changes' for A+T- cases, and 'Alzheimer's disease' for A+T+ cases. A-(TN)+ cases are classified as 'non-Alzheimer pathological changes'.

Aβ and p-tau proteins have long been known to be associated with AD development, and their accumulation can begin up to 15-20 years before the onset of cognitive symptoms [9]. Pathological amyloid changes are highly prevalent in dementia: 88% of those clinically diagnosed with AD and between 12 and 51% of those with non-AD are A+, according to a meta-analysis [10]. At the same time, the specificity of the abnormal beta-amyloid level for AD and its central role in its pathomechanism have been questioned [11]. Their use as a preventive screening target is a subject of ongoing discourse [12]. Yet it is still unclear to what extent their presence accelerates cognitive decline. What are the predictive prospects for an individual with abnormal protein levels who is otherwise cognitively healthy or with only mild cognitive impairment (MCI), meaning cases where there is a detectable decline in cognitive ability with maintained ability to perform most activities of daily living independently? [13] Research on non-demented populations shows substantial variation; for example, studies have shown OR values for conversion to dementia ranging from 2.25 [95% CI 0.71; 7.09] [14] to 137.5 [95% CI 17.8; 1059.6] [15]. Comparing conversion data systematically is necessary to provide a clearer picture.

In the CU population over 50 years, the prevalence of being A+ ranges from 10 to 44%, while in MCI it ranges from 27 to 71%, depending on age. Taking this into consideration [16], we aim to investigate the effect of Aβ alone and in combination with p-tau on the conversion to MCI and dementia, through a systematic review and meta-analysis of the available literature. Knowing the prognostic effect can highlight the clinical potential of this current research framework, given that, at present, the therapy of MCI or dementia can only slow down the decline. Prevention starting at an early stage or even before symptoms appear, provides the best chance against the disease.

Methods

Study registration

Our study was registered in the PROSPERO database (ID: CRD42021288100), with a pre-defined research plan and detailed objectives, is reported strictly in accordance with the recommendation of the PRISMA 2020 guideline and was performed following the guidance of the Cochrane Handbook [17].

We aimed to determine the change in odds of progression to MCI or dementia among non-demented subjects based on abnormal Aβ levels alone, or in combination with abnormal p-tau levels.

Search and selection

We included longitudinal prospective and retrospective studies that used the NIA-AA 2018 recommended

measurement of Aβ and p-tau (for Aβ: amyloid PET, CSF Aβ42, or Aβ42/40 ratio; for p-tau: tau PET, or CSF p-tau) and investigated the role of Aβ and +/- p-tau in CU and MCI subjects in progression to MCI or dementia. Case reports and case series were excluded. Overlapping populations were taken into account during the data extraction. Our search key was run in the Medline, Embase, and Central databases on 31 October 2021, and the search was updated on 9 January 2024 (see Supplementary Material, Appendix 1). After removing duplicates, we screened publications by title and abstract, and in the second round by full text. Two independent reviewers conducted the selection (ZH, MP), and a third reviewer (GC) resolved disagreements. The degree of the agreement was quantified using Cohen's kappa statistics at each selection stage.

As part of the selection process, articles that only examined the ADNI database [18] were excluded, as patient-level data were used instead (see Supplementary Material Appendix 2 for details of the patient-level data analysis of the ADNI).

A standardized Excel (Microsoft Corporation, Redmond, Washington, USA) document sheet was used for data extraction (for one special case of data extraction see Supplementary Material Appendix 3). Where data were available in graphical form only, we used an online software (Plot Digitizer) [19, 20]. The following data were extracted: source of data used in the studies (place of clinical trial or name of database), baseline characteristics of the population (age, gender, APOE status, and education level), type of exposure (Aβ, p-tau, and neurodegeneration), measurement technique of the exposure, data on cognitive impairment separately for the different exposure groups).

Data synthesis

Generally, where several studies used the same population sample or cohort, only data from the study with the largest sample size were used. Conversion to Alzheimer's dementia and to unspecified dementia was assessed together, as the definition of Alzheimer's dementia varied between the studies, and the diagnosis was based on neurocognitive tests. If conversion to both types of dementia was given, the value of the conversion to unspecified dementia was used. The population with subjective cognitive symptoms was scored jointly with the CU population, as these subpopulations could not be differentiated objectively.

Odds ratio and hazard ratio values were used or calculated based on the available information (for details on the methodology, see Supplementary Material Appendix 4). Considering that studies report their results on different age groups, a meta-regression analysis was performed to investigate how age affects the likelihood of developing dementia based on Aβ levels.

Studies applied different analysis methods to identify Aβ positivity. Where multiple amyloid categories were being considered, the preferred method was amyloid PET. When relying on CSF analysis, the Aβ42/40 ratio was given precedence over Aβ42 since the 42/40 ratio has a higher concordance with amyloid PET [21]. To estimate the confounding effect caused by different amyloid measurement techniques a subgroup analysis was performed. For the assessment of p-tau, studies measured p-tau181 levels from CSF samples, or employed tau PET. While there is also a limited number of tau PET measurements in the ADNI, in order to ensure consistency in the analyses, we used exclusively the CSF p-tau181 levels from the ADNI database.

For the OR analysis, studies with varying follow-up times were pooled. To estimate the resulting bias, a meta-regression analysis was performed to explore how follow-up time affected the results.

Statistical analysis

Statistical analyses were performed in the R programming environment (version 4.1.2) using the "meta" software package version 5.2-0. To visualize synthesized data, we used forest plots showing ORs or HRs and corresponding confidence intervals for each individual study and pooled effect sizes in terms of ORs and HRs. For dichotomous outcomes, odds ratios and hazard ratios with 95% confidence intervals (CI) were used as effect measures. To calculate odds ratios, the total number of patients in each study and the number of patients with the event of interest in each group were extracted from each study. Raw data from the selected studies were pooled using a random-effects model with the Mantel-Haenszel method [22–24]. The random-effects model was used as we assumed that the true effect would vary between studies due to differences in demographics and clinical measures, such as age or baseline cognitive impairment.

Heterogeneity was assessed by calculating I^2, tau^2, and the prediction interval. I^2 is defined as the percentage of variability in the effect size that is not caused by sampling error, whereas tau^2 is the square root of the standard deviation of the true effect size. As I^2 is heavily dependent on the precision of the studies and tau^2 is sometimes hard to interpret (as it is insensitive to the number of the studies and their precision), the prediction interval has also been calculated. The great advantage of the prediction interval is that this measure is easy to interpret: if the interval does not include zero, further studies are expected to show a similar result.

Sensitivity analysis

We performed outlier detection according to Viechtbauer et al. [25]. A study is considered an outlier if the confidence interval of the study does not overlap with the confidence interval of the pooled effect. The idea behind is to detect effect sizes that differ significantly from the overall effect. As a sensitivity analysis, we repeated the analyses after removing any outliers and then we compared the pooled effects before and after the exclusion, in order to detect if outliers would have a substiantial impact on the overall effect.

Risk of bias assement

The risk of bias was assessed according to the recommendation of the Cochrane Collaboration; using the QUIPS tool [26], two investigators (ZH and YS) independently assessed the quality of the studies, and a third author solved disagreements. Publication bias was examined using the Peter's regression test [27] and visual inspection of the adjusted Funnel-plots.

Results

Search results

During the systematic search (Fig. 1), 18,162 records were found, and finally, 46 eligible articles were obtained (Supplementary Material eTable 1); While some of the articles analyzed the same cohorts, we were able to pool data from 36 different cohorts or centres. The Cohens's kappa was 0.91 for the title and abstract, and 0.86 for the full-text selection. Given the amount of data found, we decided to examine the targeted outcomes separately and focus only on the conversion data in this report.

The investigated studies expressed their results in different ways. They calculated unadjusted or adjusted hazard ratios or presented the number of conversions for the different follow-up periods. In the latter case, we calculated odds ratios for the defined time periods. The measured exposures also differed: data were given only for Aβ or in combination with p-tau or neurodegeneration. There were also differences in the techniques used to measure exposure, with CSF sample being used in some cases and PET scan in others.

During data extraction, one [28] article was excluded because of inconsistently reported conversion data, and four [15, 29–31] were excluded from the A/T analysis because the definition of the pathologic Aβ and p-tau was based on Aβ/p-tau ratio, which did not comply with the NIA-AA 2018 recommendation.

Data synthesis

The eligible studies investigated three groups: CU, MCI, and mixed - in which the results were collectively expressed for both the MCI and CU groups. The CU group comprised either cognitively healthy subjects or individuals with only subjective cognitive complaints. To define the MCI group, all studies followed the Petersen criteria [32]. Four studies examined mixed groups. Since all of them studied large samples (n>180), it was considered more valuable to jointly analyze them with MCI, since the outcome was also the conversion to dementia. As a result of the joint analysis, our findings are based on a substantially larger sample. To support this decision, we performed a subgroup analysis comparing the Aβ positive MCI and mixed population studies. The OR differed significantly from the unexposed group in both the MCI (OR 5.83 [3.80; 8.93]) and the mixed (4.64 [95% CI 1.16; 18.61]) subgroups, and there was no significant difference between the two subgroups (p=0.55) (Supplementary Material eFigure 1).

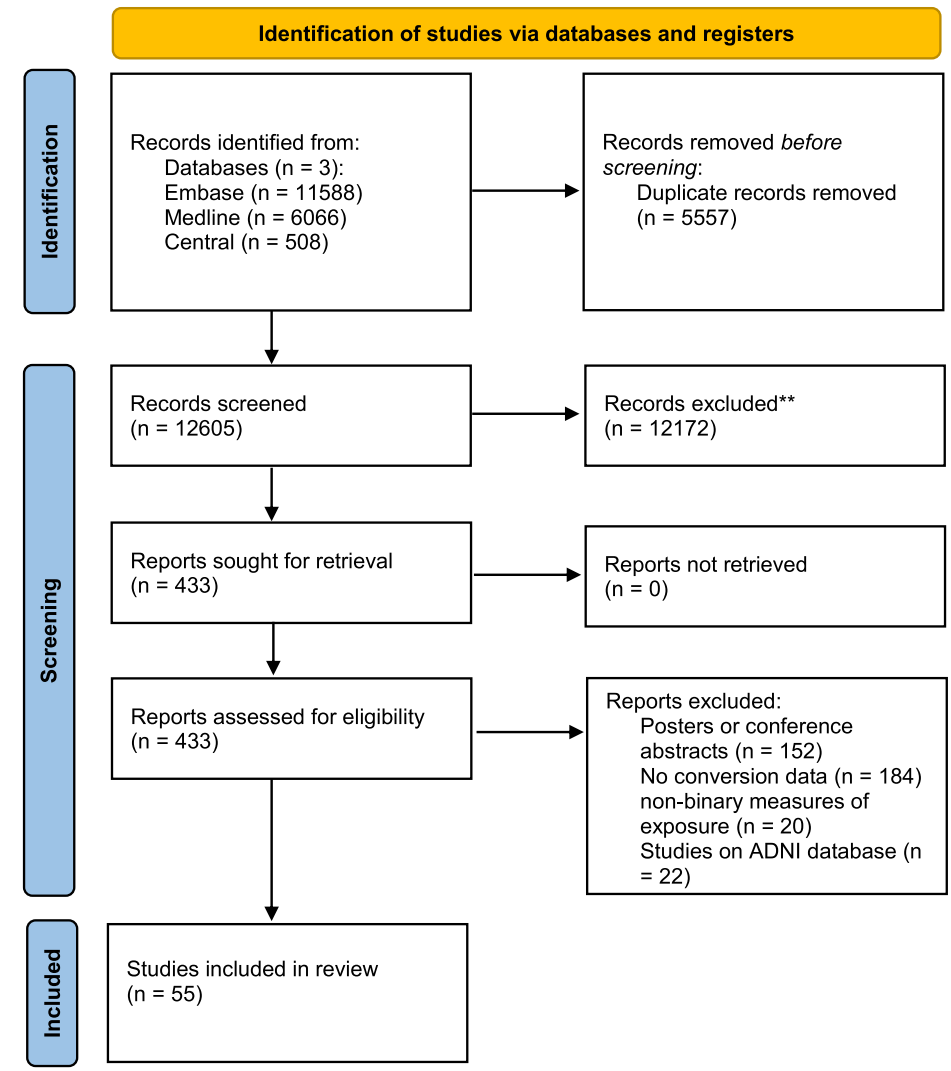
Conversion from MCI to dementia

Aβ exposition - in OR Based on a mixed model meta-analysis of 3,576 subjects (Table 1), we observed a significant association between Aβ positivity and higher conversion rates. Compared to the unexposed, the OR for conversion to dementia in the amyloid positives were 5.18 [95% CI 3.93; 6.81]; t(21)=12.47; (p<0.0001). The I^2- test for heterogeneity revealed that 44.8% of the variance across studies was due to heterogeneity (Fig. 2A). As a result of the outlier detection we excluded the Balassa study and found a very similar overall effect and a reduced heterogeneity (5.05 [95% CI 3.98; 6.40]; t(20) = 14.2; p < 0.0001; I^2 = 31.4%). Meta-regression analysis of mean age showed a statistically significant decrease in OR values with increasing age (R^2 = 59.05%, beta = -0.04, SE = 0.019, [95% CI = -0.03 to -0.083], df = 18, t = -2.27, p = 0.036) (Fig. 2B). The Hartunk-Knapp method was applied to adjust test statistics and confidence intervals to reduce the risk of false positives.

Beta-amyloid was determined by CSF Aβ42, CSF Aβ42/40 ratio or amyloid PET. When the three groups were compared in a subgroup analysis, the OR was 5.87 (2.83; 12.19) for CSF Aβ42, 5.00 (3.31; 7.55) for CSF Aβ42/40 ratio, and 5.32 (2.53; 11.18) for amyloid PET. The difference between the subgroups was not significant (p=0.88) (Supplementary Material eFigure 2).

The meta-regression analysis performed to examine the role of follow-up time showed no association with respect to the ORs (R^2 = 0%, beta = -0.002, SE = 0.07, [95% CI = -0.02 - 0.01], df = 11, p = 0.77) (Supplementary Material eFigure 3A).

We used a funnel plot to examine publication bias (Supplementary Material eFigure 4A). Most of the studies with large sample sizes lie close to the midline,



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Fig. 1 PRISMA flowchart of selection. Flowchart of the study screening process following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 statement

which confirms that the pooled effect size seems valid. However, the visual inspection of the plot raised the possibility of some publication bias in two ways: (1) Studies in the bottom right corner of the plot have significant results despite having large standard errors (2) The absence of studies in the bottom left corner (blank area in the figure) may indicate that studies with non-significant results were not published. In order to quantify funnel plot asymmetry, the Peter's regression test was applied. The test results were not significant ($t = 1.7$, df $= 20$, $p = 0.11$) so no asymmetry was proven in the funnel plot.

Table 1 Articles used for Aβ OR analyses in the Mild Cognitive Impairment (MCI) group

Study	Centre/cohort	Population	Subjects (*n*)	Age (mean (SD), or median (range))	Measurement technique (cut-offs)	Follow-up (month)		Conversion to
						Mean (SD)	Median (range)	
ADNI	ADNI	MCI	785	72.5 (7.5)	$_{amyloid}$PET (SUVR >1.11), CSF Aβ42 (<977 pg/mL)	57 (40)	48	unspecified dementia
Arruda, 2023 [33]	Florida Alzheimer's Disease Research Center	MCI	91	72.7 (8.7)	$_{amyloid}$PET (v.r.[a])	22.9 (7.1)	n.d.	unspecified dementia
Balassa, 2014 [15]	Hospital Clinic Barcelona, Spain	MCI	51	57.9 (6)	CSF Aβ42 (<500 pg/mL)	31 (15.8)	31.6 (8 - 82)	unspecified dementia
Baldeiras, 2022 [34]	Coimbra University Hospital; Hospital de Braga; Unidade Local de Saude de Matosinhos; Centro Hospi- ´talar Baixo Vouga; Hospital Egas Moniz; Hospital de Faro, Portugal	MCI	150	65.2 (8.7)	CSF Aβ42/40 ratio (<0.068)	n.d.[b]	n.d. (12-50)	unspecified dementia
Bos, 2017 [35]	Alzheimer Center Limburg, LeARN, DESCRIPA cohort	Mixed[d] (56.5% MCI)	271	65.6 (7.7)	CSF Aβ42 (≤ 550 pg/ml)	30 (14.4)	n.d.	unspecified dementia
Cerami, 2015 [36]	San Raffael Inst. Milan, Italy	MCI	34	69.8 (5.7)	CSF Aβ42 (<515 pg/m)	29 (8.5)	29 (15 - 60)	unspecified dementia
de Wilde, 2019 [37][c]	Alzheimer Center and Department of Neurology, VU University Medical Center Amsterdam, Netherland	MCI	110	65.5 (7.5)	$_{amyloid}$PET (v.r.), CSF Aβ42 (<813 pg/mL)	n.d.	22.8 (13.2 - 32.4)	unspecified dementia
Eckerstrom, 2021 [38]	Goteborg MCI study	Mixed[d] (58.1% MCI)	420	64.2 (7.3)	CSF Aβ42 (≤482 ng/L)	31.6 (19)	n.d.	unspecified dementia
Frolich, 2017 [39]	DCN (Dementia Competence Network, German multicenter cohort study)	MCI	115	65.7 (9.3)	CSF Aβ42 (<600 pg/ml)	25.5 (9.8)	n.d.	unspecified dementia
Grontvedt, 2020 [14]	Department of Neurology, Univ. Hosp. Trondheim, Norway	MCI	57	64 (53 - 79)	CSF Aβ42 (<630 pg/ml)	n.d.	108 (72 - 120)	unspecified dementia
Groot, 2022 [40]	Malmö University Hospital, Sweden	MCI	147	72.1 (7.7)	CSF Aβ42/40 ratio (<0.07)	59.0 (25.1)	n.d.	unspecified dementia
Hanseeuw, 2021 [41]	Neurology Department, Saint-Luc University Hospital, Belgium	MCI	46	71.4 (7.5)	$_{amyloid}$PET (v.r.)	38.4 (15.6)	n.d.	unspecified dementia
Herukka, 2005 [42]	Neurologic Department at Kuopio University Hospital, Finland	MCI	66	70.4 (7.4)	CSF Aβ42 (<452 pg/mL)	n.d.	36 (6-144)	unspecified dementia
Jimenez Bonilla, 2019 [43]	Neurology, University Hospital 'Marqués de Valdecilla', University of Cantabria, Santander, Spain	MCI	14	67.1 (5.1)	$_{amyloid}$PET (v.r.)	60	60	unspecified dementia
Lopez, 2018 [44]	Ginkgo biloba memory study (GEM [Ginkgo Evaluation of Memory] Study, USA	Mixed[d] (19.1% MCI)	183	85.6 (2.9)	$_{amyloid}$PET (SUVR >1.57)	68.4 (20.4)	n.d.	unspecified dementia

Table 1 (continued)

Study	Centre/cohort	Population	Subjects (*n*)	Age (mean (SD), or median (range))	Measurement technique (cut-offs)	Follow-up (month)		Conversion to
						Mean (SD)	Median (range)	
Okello, 2009 [45]	Imperial College Healthcare NHS Trust [London], The National Hospital for Neurology and Neurosurgery [London], St. Margaret's Hospital [Epping, and Victoria Hospital [Swindon], Turku Hosp., UK and Finland	MCI	31	69.4 (7.9)	$_{amyloid}$PET (v.r.)	36	36	unspecified dementia
Orellana, 2022 [46]	ACE Alzheimer Center Barcelona, Spain	MCI	647	72.8 (7.8)	CSF Aβ42/40 ratio (<0.069)	21 (10.8)	n.d.	unspecified dementia
Ortega, 2019 [47]	Hospital Santa Maria de Lleida, Spain	MCI	55	71.9 (6.7)	CSF Aβ42 (<450 pg/ml)	n.d.	24 (no inf.)	unspecified dementia
Riemenschneider, 2002 [48]	Department of Psychiatry, Pearth, Australia	MCI	28	69.2 (7.9)	CSF Aβ42 (<500 pg/mL)	18	18	unspecified dementia
Rizzi, 2020 [49]	Division of Geriatric Neurology, Neurology Service, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, Brazil	MCI	31	67.4 (60 - 78)	CSF Aβ42 (<618.5 pg/mL)	60	60	AD dementia[e]
Roberts, 2018 [50]	MCSA (Mayo Clinic Study of Aging)	MCI	179	78.3 (7.4)	$_{amyloid}$PET (SUVR >1.42)	45.6 (24)	n.d.	AD dementia[e]
Villemagne, 2011 [51]	Austin Health Memory Disorders Clinic, USA	MCI	65	73.4 (8.5)	$_{amyloid}$PET (SUVR >1.5)	20 (3)	n.d.	unspecified dementia

[a] visually read

[b] no data

[c] See details of data extraction in Supplement, Appendix 3

[d] A combined population of MCI and CU subjects

[e] Deffinition for AD in Rizzi 2020: McKhann et al. 2011 [8], in Roberts et al. 2018: DSM IV (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994), McKhann et al. 2011 [8], McKhann et al. 1984 [7]

The effect of Aβ exposition in terms of HR Several studies reported their results in HRs instead of or in addition to ORs (Supplementary Material eTable 2). The advantage of the HR value is that this measure is independent of the length of follow-up times of the studies. For these reasons, we also considered it important to analyze the results expressed in HR. Based on pooled data of patients studied (n=1,888), the HR for conversion to dementia was 3.16 [95% CI 2.07; 4.83], $p < 0.001$ (Fig. 3A).

To investigate the effect of adjustment, we conducted a subgroup analysis between the unadjusted and adjusted measurements. Although there was a trend for higher unadjusted HR values compared to the adjusted HRs, the difference did not reach statistical significance (unadjusted HR : 5.07 [95% CI 2.77 - 9.26], adjusted HR 2.86 [95% CI 1.70 - 4.83] p=0.055) (Fig. 3B). We could not analyze HR in the A+T-, A+T+, and A-T+ subgroups, due to the low number of available studies.

The effect of Aβ and p-tau exposition in terms of OR We examined the combined effect of p-tau and Aβ (Table 2), and compared A+T+, A+T-, and A-T+ exposures to A-T-. Based on pooled data for patients studied (n=1,327), the OR for conversion to dementia in A+T- was 2.73 [95% CI 1.65; 4.52], and the odds ratio was significantly higher in the presence of both exposures (A+T+) (p<0.001), with an OR of 11.60 [95% CI 7.96; 16.91]. The effect of A-T+ exposure on conversion was not significant (OR: 1.47 [0.55; 3.92]) (Fig. 4A).

Subgroup analyses showed that the A+T+ group had a significantly higher odds of conversion compared to the A+T- group (p <0.001), while the A+T- and A-T+ groups did not differ significantly (p=0.15) (Fig. 4B and C).

Conversion from CU to MCI or dementia

The effect of Aβ exposition in terms of OR Analyses on the CU population (n = 4,217) yielded very similar results to the MCI sample. The OR for conversion to MCI or dementia was 5.79 [95% CI 2.88; 11.64] (t(13) = 5.43; p = 0.0001), the results of the studies did however show a high degree of heterogeneity (I^2= 73% [55%; 84%]) (Table 3, Fig. 5A). As a result of the outlier detection we removed the Aruda study and found a very similar overall effect (6.33 [95% CI 3.42; 11.71]; t(12) = 6.54; $p < 0.0001$; $I^2 = 72.1\%$).

Meta-regression analysis of mean age did not show a significant association with OR. (R^2 = 8.22%, beta = -0.05, SE = 0.05, [95% CI = -0.17 – 0.7], df = 11, t =, p = 0.37).

Meta-regression analysis also showed no association between follow-up time and ORs (R^2 = 0.35%, beta = -0.014, SE = 0.024, [95% CI = -0.07 - 0.04], df = 8, p = 0.58) (Supplementary Material eFigure 3B).

We applied a funnel plot to examine publication bias (Supplementary Material eFigure 4B).Most of the studies with large sample sizes lie close to the midline, which reaffirms the pooled effect size's validity. In order to quantify funnel plot asymmetry, Peter's regression test was applied. The test results were not significant (t = 0.9, df = 12, p = 0.31) indicating that no asymmetry was demonstrated in the funnel plot.

The effect of Aβ exposition in terms of HR Four cohorts provided HRs for the CU population (n=2700) with one cohort (ADNI) representing the 55.3% of the total sample (weight: 78.5%) (Supplementary Material eTable 3). The pooled HR for conversion was 2.33 [95% CI 1.88; 2.88] (p=0.001) (Supplementary Material eFigure 5)

The combined effect of Aβ and p-tau exposition in terms of OR Using data from a total of 2228 subjects, we investigated the effect of p-tau in combination with Aβ (Table 4) in the CU population. The OR for conversion is 2.04 [95% CI 0.70; 5.97] for A+T-, and 13.46 [95% CI 3.69; 49.11] for the A+T+, compared to the A-T- group The OR shows a trend level increased risk (t=2.1, P=0.12) for the A+T- group compared to the A-T- group.

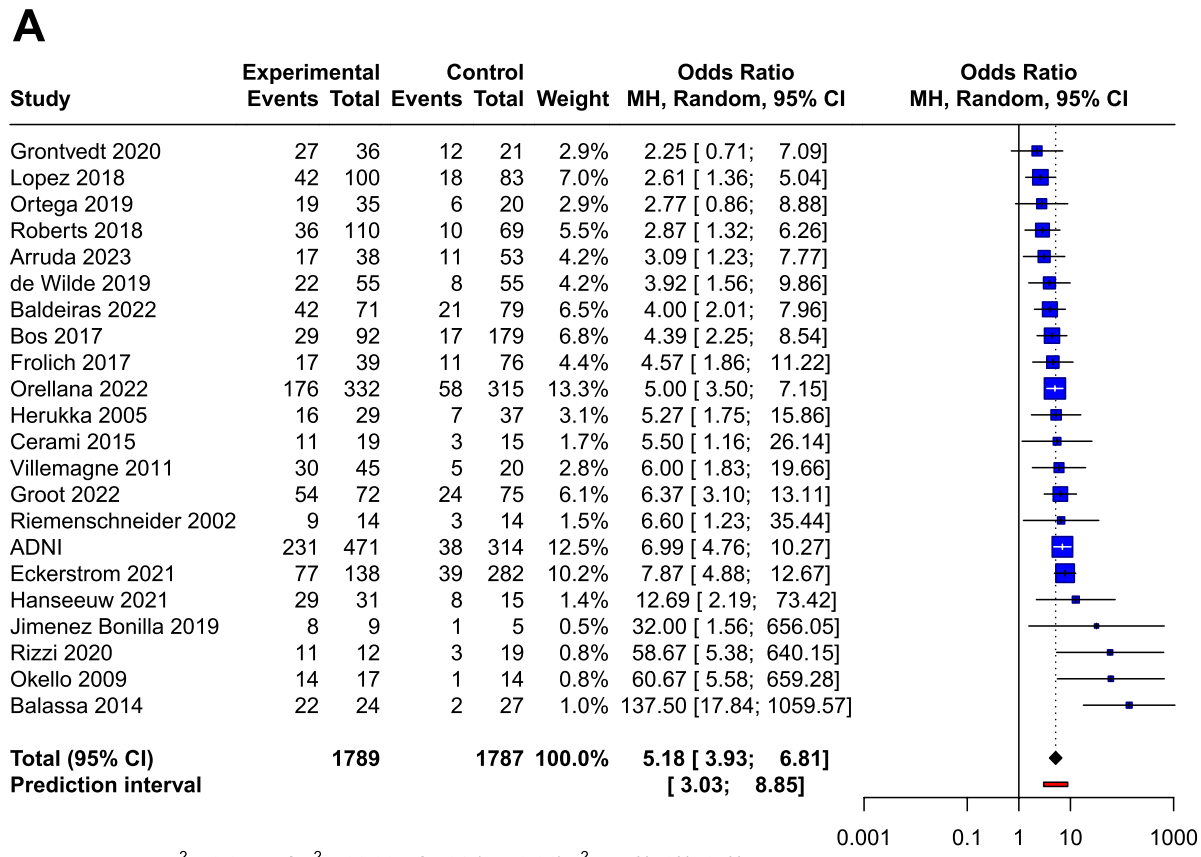
Similarly to the MCI population, subgroup analyses showed that the A+T+ group had significantly higher OR for conversion compared to the A+T- group (p <0.01). The analysis could not be performed for A-T+ due to the low number of these cases.

Risk of bias assessment

The risk of bias was assessed separately for the analyses discussed above. The overall risk of the studies ranged from low to moderate, except in three cases: twice we found a high risk of bias due to attrition of above 50%

(See figure on next page.)

Fig. 2 Conversion of Aβ exposed MCI groups to dementia in OR. The squares and bars represent the mean values and 95% CIs of the effect sizes, and the squares' area reflects the weight of the studies. Diamonds represent the combined effects, and the vertical dotted line represents the line of no association. **A** OR for Aβ exposition; **B** meta-regression of age and ORs for conversion regarding Aβ exposure. The size of the circle is proportional to the weight of each study in the meta-analysis. The line corresponds to meta-regression with age as covariate, and beta represents the slope of ORs by mean age



Heterogeneity: $Tau^2 = 0.0545$; $Chi^2 = 38.02$, df = 21 (P = 0.01); $I^2 = 45\%$ [9%; 67%]
Test for overall effect: $t_{21} = 12.47$ (P < 0.01)

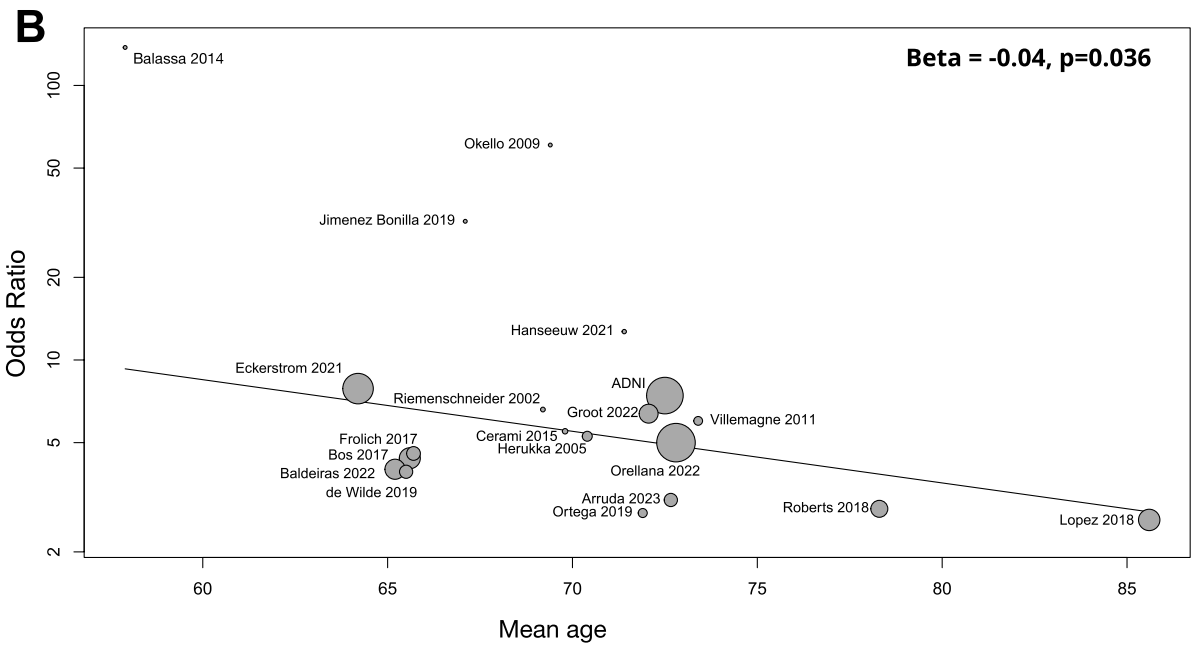


Fig. 2 (See legend on previous page.)

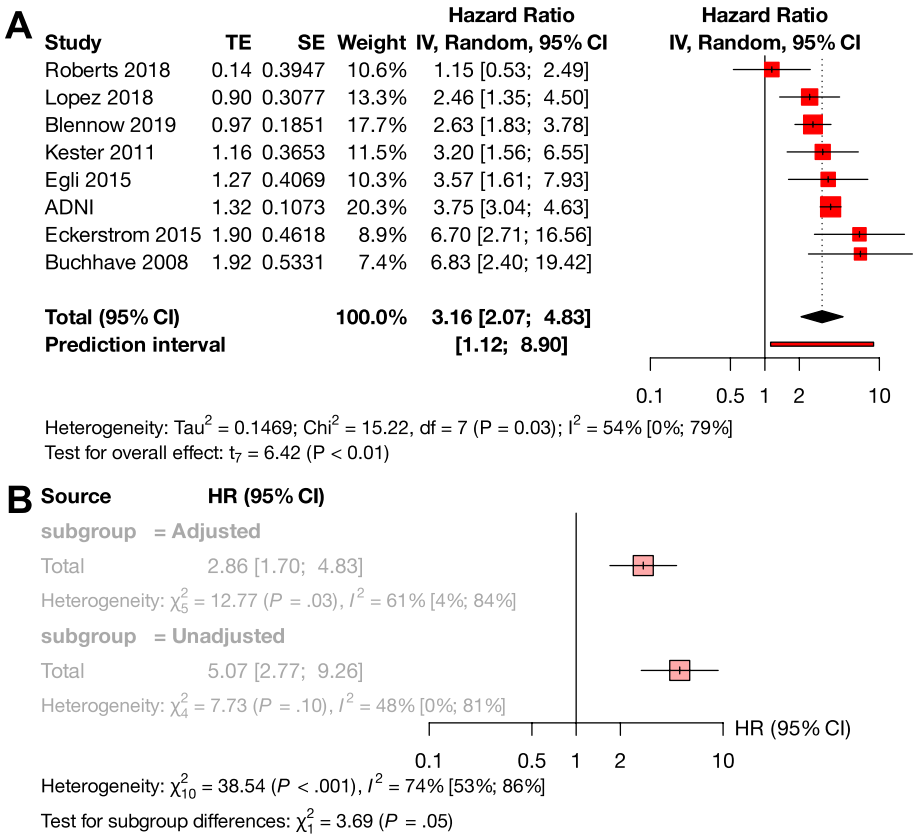


Fig. 3 Conversion of Aβ exposed MCI groups to dementia in HR. The squares and bars represent the mean values and 95% CIs of the effect sizes, and the squares' area reflects the weight of the studies. Diamonds represent the combined effects, and the vertical dotted line represents the line of no association. **A** HR for Aβ exposition; **B** sub-group analysis of studies with adjusted and unadjusted HR values

[59, 60], and once due to a focus on monozygotic twins [61] (Supplementary Material, eFigure 6). These articles (n=197) were excluded from all analyses.

Discussion

Summary and context

A pathological Aβ state are strongly correlated with the risk of clinical progression. The odds ratio for conversion is 5.18 in the MCI population and 5.79 in the CU population. Therefore, measuring Aβ levels alone can identify a population at high risk. The OR for conversion to dementia differs significantly between the A+T+ and A+T- groups in both the MCI and CU populations: while the OR is 2.73 [95% CI 1.65; 4.52] for MCI and 2.04 [95% CI 0.70; 5.97] for CU subjects in the A+T- group, it increases to 11.60 [95% CI 7.96; 16.91] for MCI and 14.67 [95% CI 3.69; 49.11] for CU in the A+T+ group. Note that in the case of A+T- at CU population, only a trend-level statistical correlation is visible.

The results of the meta-regression show a decrease in OR with mean age (Fig. 2B). Based on this result it seems that the impact of Amyloid positivity on conversion is decreasing with age. The fact that age is a risk factor for dementia and vascular and other neurodegenerative damage are more frequent in elderly age is a possible explanation to this finding. Our findings combined with the results of Rodrigue et al. [62] suggests that amyloid burden increases with age, while its impact on conversion rates slightly decreases with age.

The appearance of Aβ is assumed to be one of the earliest signs of AD [63, 64]. Our results fit into this picture by showing that only the A+T+ and A+T- groups showed an increased risk for conversion compared to A-T-, the A-T+ group did not. Thus, Aβ alone is suitable for detecting the population at risk, while p-tau alone is not as effective in the prediction conversion. Our result is in line with previous studies showing that the A-T+ group has a weaker association with cognitive decline compared to the A+T- or A+T+ groups [65, 66]. However, it is important to emphasize that previous results showing that T+ status is closely associated with neurodegeneration and the A-T+ group is related to frontotemporal dementia [67]. More research is needed to fully explain the significance of the A-T+ group.

Table 2 Articles used for Aβ and p-tau OR analyses in the Mild Cognitive Impairment (MCI) group

MCI population A+T+ vs. A-T-							
Study	**Centre/cohort**	**Population**	**Measurement techniques (cut-offs)**	**Subjects (*n.*)**	**Age (mean (SD) / median (range))**	**Follow-up time (months)**	
						Mean (SD)	**Median (range)**
ADNI	ADNI	MCI	$_{amyloid}$PET (SUVR >1.11), CSF Aβ42 (<977 pg/mL); CSF p-tau181 (>23 pg/mL)	535	72.5 (7.5)	53 (38)	42
Cerami, 2015 [36]	San Raffael Inst. Milan, Italy	MCI	CSF Aβ42 (<515 pg/m); CSF p-tau181 (> 52.5 pg/mL)	19	69.8 (5.7)	29 (8.5)	29 (15-60)
Eckerström, 2021 [38]	Goteborg MCI study	Mixed[a] (55.0 % MCI)	CSF Aβ42 (≤482 ng/L); CSF p-tau181 (≥52 ng/L)	262	64.2 (8.6)	34.74 (25)	n.d.[b]
Grontvedt, 2020 [14]	Department of Neurology, Univ. Hosp. Trondheim, Norway	MCI	CSF Aβ42 (<630 pg/ml); CSF p-tau181 (>66 pg/mL)	40	64 (53 - 79)	n.d.	108 (72-120)
Hansson, 2006 [52]	Malmö University Hospital, Sweden	MCI	CSF Aβ42 (<530 ng/L); CSF p-tau181 (≥60 ng/L)	99	71.8 (50 - 87)	n.d.	62.4 (48-81.6)
Herukka, 2005 [42]	Neurologic Department at Kuopio University Hospital, Finland	MCI	CSF Aβ42 (<452 pg/mL); CSF p-tau181 (>70 pg/mL)	39	70.4 (8.2)	n.d.	36 (6-144)
MCI population A+T- vs. A-T-							
ADNI	ADNI	MCI	$_{amyloid}$PET (SUVR >1.11), CSF Aβ42 (<977 pg/mL); CSF p-tau181 (>23 pg/mL)	323	72.5 (7.5)	53 (38)	42
Cerami, 2015 [36]	San Raffael Inst. Milan, Italy	MCI	CSF Aβ42 (<515 pg/m); CSF p-tau181 (> 52.5 pg/mL)	16	69.8 (5.7)	29 (8.5)	29 (15-60)
Eckerström, 2021 [38]	Goteborg MCI study	Mixed [a] (44.4 % MCI)	CSF Aβ42 (≤482 ng/L); CSF p-tau181 (≥52 ng/L)	198	62.6 (8.3)	31.6 (19)	n.d.
Grontvedt, 2020 [14]	Department of Neurology, Univ. Hosp. Trondheim, Norway	MCI	CSF Aβ42 (<630 pg/ml); CSF p-tau181 (>66 pg/mL)	26	64 (53 - 79)	n.d.	108 (72-120)
Hansson, 2006 [52]	Malmö University Hospital, Sweden	MCI	CSF Aβ42 (<530 ng/L); CSF p-tau181 (≥60 ng/L)	44	71.8 (50 - 87)	n.d.	62.4 (48-81.6)
Herukka, 2005 [42]	Neurologic Department at Kuopio University Hospital, Finland	MCI	CSF Aβ42 (<452 pg/mL); CSF p-tau181 (>70 pg/mL)	26	70.4 (8.2)	n.d.	36 (6-144)
MCI population A-T+ vs A-T-							
ADNI	ADNI	MCI	$_{amyloid}$PET (SUVR >1.11), CSF Aβ42 (<977 pg/mL); CSF p-tau181 (>23 pg/mL)	275	72.5 (7.5)	53 (38)	42
Cerami, 2015 [36]	San Raffael Inst. Milan, Italy	MCI	CSF Aβ42 (<515 pg/m); CSF p-tau181 (> 52.5 pg/mL)	15	69.8 (5.7)	29 (8.5)	29 (15-60)
Eckerström, 2021 [38]	Goteborg MCI study	Mixed [a] (46.1 % MCI)	CSF Aβ42 (≤482 ng/L); CSF p-tau181 (≥52 ng/L)	282	63.0 (7.6)	31.6 (19)	n.d.
Grontvedt, 2020 [14]	Department of Neurology, Univ. Hosp. Trondheim, Norway	MCI	CSF Aβ42 (<630 pg/ml); CSF p-tau181 (>66 pg/mL)	21	64 (53 - 79)	n.d.	108 (72-120)
Hansson, 2006 [52]	Malmö University Hospital, Sweden	MCI	CSF Aβ42 (<530 ng/L); CSF p-tau181 (≥60 ng/L)	48	71.8 (50 - 87)	n.d.	62.4 (48-81.6)
Herukka, 2005 [42]	Neurologic Department at Kuopio University Hospital, Finland	MCI	CSF Aβ42 (<452 pg/mL); CSF p-tau181 (>70 pg/mL)	37	70.4 (8.2)	n.d.	36 (6-144)

[a] A combined population of MCI and CU subjects

[b] no data

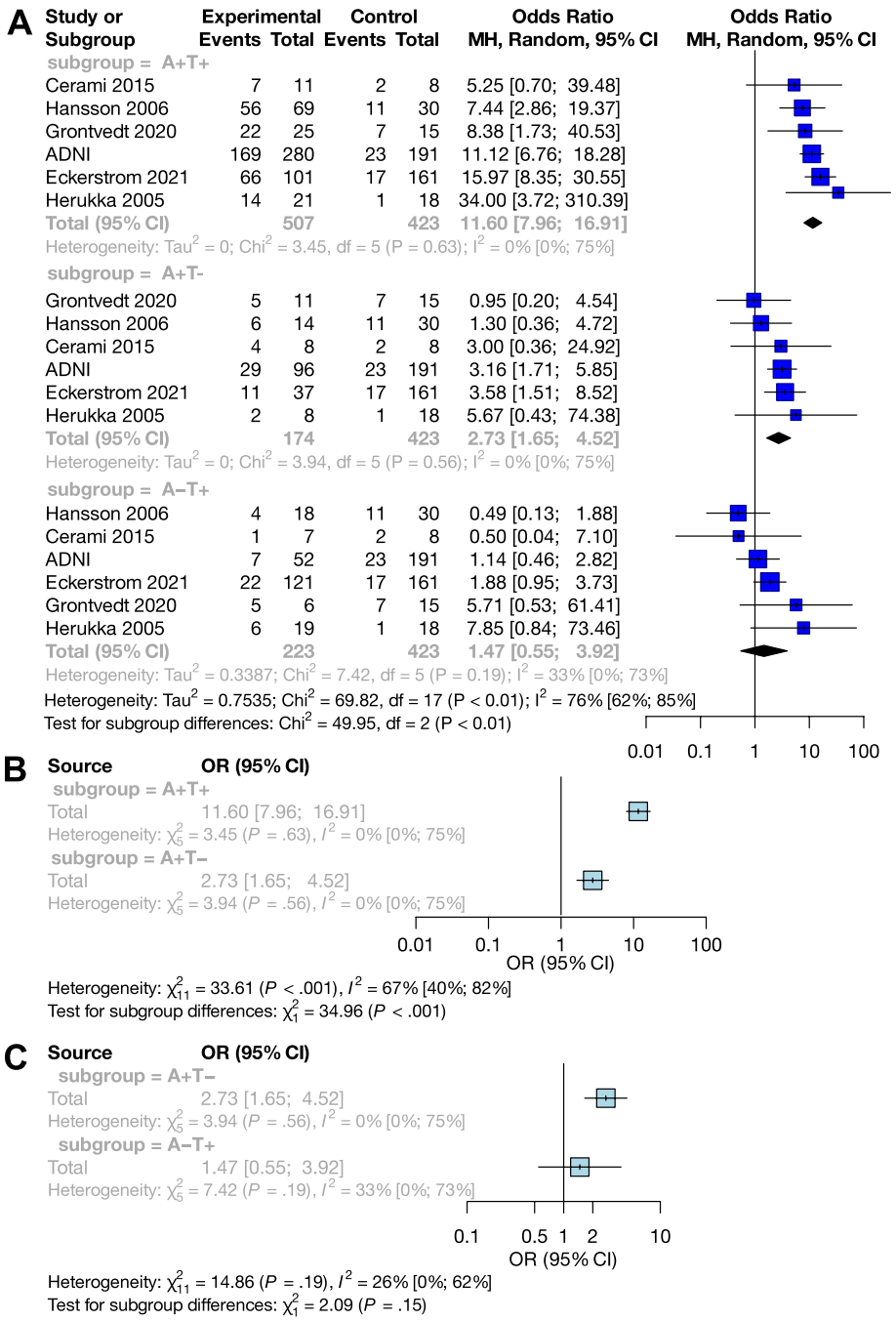


Fig. 4 Conversion of Aβ and p-tau exposed MCI groups to dementia in OR. The squares and bars represent the mean values and 95% CIs of the effect sizes, and the squares' area reflects the weight of the studies. Diamonds represent the combined effects, and the vertical dotted line represents the line of no association. **A** Aβ and p-tau expositions in OR; **B** sub-group analysis of comparisons between the A+T+ and A+T- groups; **C** sub-group analysis of comparisons between the A+T- and A-T+ groups

The PET scan is known to be a more sensitive tool for detecting Amyloid positivity compared to CSF sampling [68]. However, from a prognostic point of view, our results did not show a significant difference (p=0.73) between PET measurements (OR: 6.02) and the more cost-effective but invasive CSF Aβ42 measurements (OR: 5.11). It is important to note here that the present meta-analysis is underpowered for detecting prognostic

Table 3 Articles used for Aβ OR analyses in the Cognitively Unimpaired (CU) group

Study	Centre/cohort	Subjects (*n*)	Age (mean (SD), or median (range))	Measurement technique (cut-offs)	Follow-up (months)		Conversion to
					Mean (SD)	Median (range)	
ADNI	ADNI	578	72.9 (6.3)	$_{amyloid}$PET (SUVR >1.11), CSF Aβ42 (<977 pg/mL)	69 (48)	54	MCI or unspecified dementia
Arruda, 2023 [33]	Florida Alzheimer's Disease Research Center	70	70.2 (6.5)	$_{amyloid}$PET (v.r.)	22.9 (7.1)	n.d.	MCI or unspecified dementia
Baldeiras, 2022 [34]	Coimbra University Hospital; Hospital de Braga; Unidade Local de Saude de Matosinhos; Centro Hospi- ´ talar Baixo Vouga; Hospital Egas Moniz; Hospital de Faro, Portugal	24	63.6 (8.9)	CSF Aβ42/40 ratio (<0.068)	n.d.	n.d. (12-50)	MCI or unspecified dementia
Dang, 2018 [53]	AIBL (The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing)	599	70 (60 - 80)	$_{amyloid}$PET (SUVR >1.40)	66.9	88.5	MCI or unspecified dementia
Ebenau, 2020 [54]	ADC (Amsterdam Dementia Cohort, SCIENCe! Subjective Cognitive Impairment Cohort)	342	60.0 (9.0)	$_{amyloid}$PET (v.r.), CSF Aβ42 (<<813 pg/mL)	36 (24)	n.d.	MCI or unspecified dementia
Grontvedt, 2020 [14]	Department of Neurology, Univ. Hosp. Trondheim, Norway	55	68 (53 - 79)	CSF Aβ42	n.d.	108 (72 - 120)	unspecified dementia
Hanseeuw, 2021 [41]	Neurology Department, Saint-Luc University Hospital, Belgium	50	71.4 (7.5)	$_{amyloid}$PET (v.r.)	38.4 (15.6)	n.d.	unspecified dementia
Hatashita, 2019 [55]	Department of Neurology, Shonan-Atsugi Hospital, Atsugi, Japan	32	71.0 (5.9)	PET (SUVR >1.39)	72 (21.6)	n.d.	MCI or unspecified dementia
Lopez, 2018 [44]	Ginkgo biloba memory study (GEM [Ginkgo Evaluation of Memory] Study, USA	148	84.2 (2.5)	$_{amyloid}$PET (SUVR >1.57)	68.4 (20.4)	n.d.	MCI or unspecified dementia
Ossenkoppele, 2022 [56]	BioFINDER-1, -2	258	68.8 (10.1)	$_{amyloid}$PET (SUVR >1.03 in BioFINDER-1, -2)	41.8 (18.9)	n.d.	unspecified dementia
Roberts, 2018 [50]	MCSA (Mayo Clinic Study of Aging)	1377	70. 4 (8.8)	$_{amyloid}$PET (SUVR >1.42)	43.2 (24)	n.d.	MCI or AD dementia
Strikwerda-Brown, 2022 [57]	Prevent AD, HABS (Harvard Aging Brain Study)	281	72.1 (6.0)	$_{amyloid}$PET (24 Centiloids for global Aβ)	n.d.	32.7 (15.7 – 58.0)	MCI or unspecified dementia
Villemagne, 2011 [51]	Austin Health Memory Disorders Clinic, USA	106	73.1 (7.5)	$_{amyloid}$PET (SUVR >1.5)	20	20	MCI
Vos, 2013 [58]	Knight Alzheimer's Disease Research Center (KADRC) of the Washington University School of Medicine (WUSM)in St. Louis, USA	297	72.9 (6.0)	CSF Aβ42 (<459 pg/mL)	n.d.	38.4 (12 - 156)	MCI or unspecified dementia

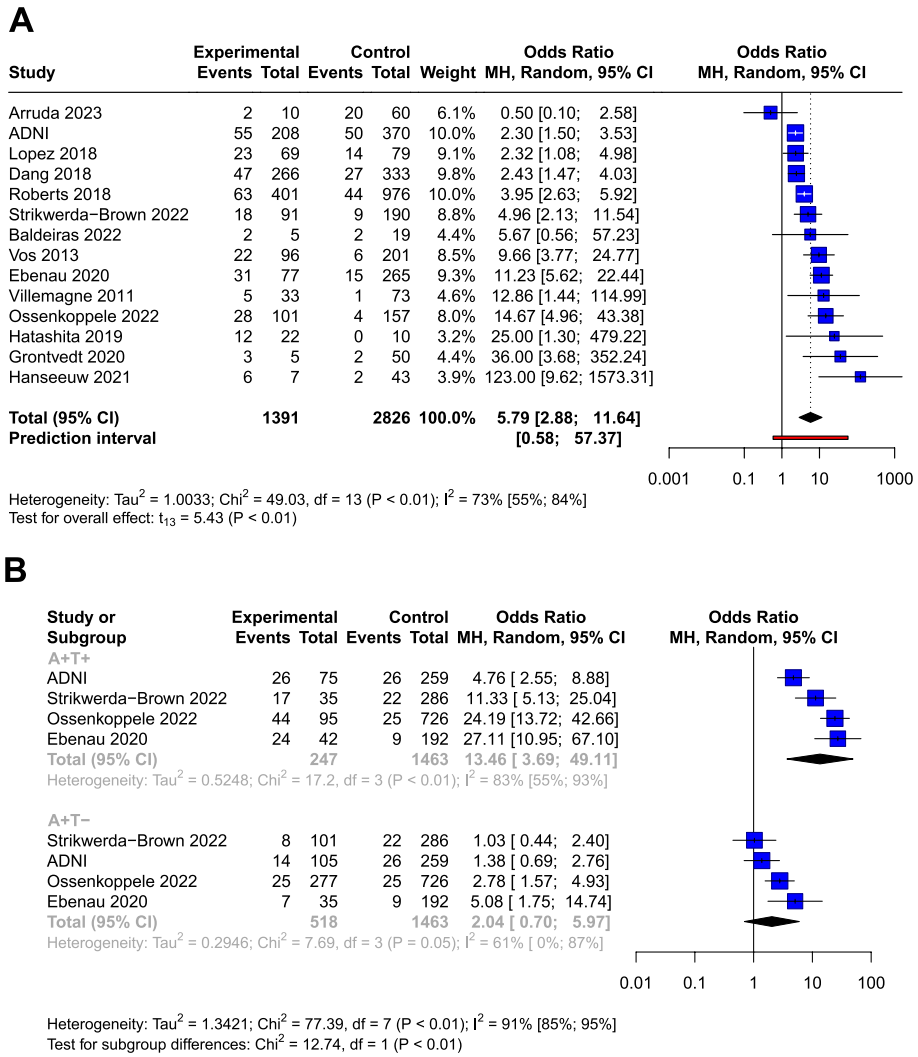


Fig. 5 Conversion of Aβ and p-tau exposed CU groups to MCI or dementia in OR. The squares and bars represent the mean values and 95% CIs of the effect sizes, and the squares' area reflects the weight of the studies. Diamonds represent the combined effects, and the vertical dotted line represents the line of no association. **A** Aβ exposition in OR. **B** Aβ and p-tau expositions in OR

differences between these methods. Due to the heterogeneity among studies, the impact of confounding factors, and standardised studies are required to evaluate the comparative prognostic value of these biomarkers accurately.

Our results based on ORs are further strengthened by the HR analyses giving similar results for Aβ exposure in the MCI (HR: 3.16) and CU (HR: 2.33) populations. It should be noted that in the HR analysis of the CU group, ADNI accounts for 78.5% of the weight, which is a limitation of this meta-analysis. This disproportionate representation may affect the overall result. Regarding the statistical trend-level association with a higher unadjusted HR, it should be noted that in the presence of a random distribution of other risk factors (e.g. baseline MMSE score or educational level), the unadjusted value may overestimate the HR. As in the case of a non-random distribution, the adjusted value underestimates the HR. With this in mind, we recommend reporting both values in the future.

Our analyses were performed on CU and MCI populations. Including mixed populations with the MCI population was a practical simplification, as several studies with a large number of cases gave their results combining MCI subjects with CU subjects, and we aimed to answer the set of questions based on the largest population. To investigate the potential bias of this method, we performed subgroup analysis comparing the mixed and MCI populations, and the result was not significant. The Aβ OR based on the mixed-only group is 4.64 [95%

Table 4 Articles used for Aβ and p-tau OR analyses in the Cognitively unimpaired (CU) group

CU population A+T+ vs. A-T-						
Study	**Centre/cohort**	**Measurement technique (cut-offs)**	**Subjects (*n.*)**	**Age (mean (SD) / median (range))**	**Follow-up time (months)**	
					Mean (SD)	**Median (range)**
ADNI	ADNI	$_{amyloid}$PET (SUVR >1.11), CSF Aβ42 (<977 pg/mL); CSF p-tau181 (>23 pg/mL)	334	72.9 (6.3)	69 (48)	54
Ebenau, 2020	ADC (Amsterdam Dementia Cohort, SCIENCe! Subjective Cognitive Impairment Cohort)	$_{amyloid}$PET (v.r.), CSF Aβ42 (<<813 pg/mL); CSF p-tau181 (>52 pg/mL)	216	60.0 (9.0)	36 (24)	n.d.[a]
Ossenkoppele, 2022	BioFINDER-1, BioFINDER-2, HABS	$_{amyloid}$PET (SUVR >1.03 in BioFINDER-1, -2, DVR >1.2 (>26 CL) in HABS); $_{tau}$PET (SUVR >1.26 in BioFINDER-1, SUVR >1.34 in BioFINDER-2, SUVR >1.36 in HABS)	821	70.5 (9.8)	41.8 (18.9)	n.d.
Strikwerda-Brown, 2022	AIBL, Knight ADRC, Prevent AD	$_{amyloid}$PET (24 Centiloids for global Aβ); $_{tau}$PET (SUVR >1.27 for tau meta-ROI)	326	70.9 (5.6)	n.d.	39.8 (15.2 – 68.0)
CU population A+T- vs. A-T-						
ADNI	ADNI	$_{amyloid}$PET (SUVR >1.11), CSF Aβ42 (<977 pg/mL); CSF p-tau181 (>23 pg/mL)	364	72.9 (6.3)	69 (48)	54
Ebenau, 2020	ADC (Amsterdam Dementia Cohort, SCIENCe! Subjective Cognitive Impairment Cohort)	$_{amyloid}$PET (v.r.), CSF Aβ42 (<<813 pg/mL); CSF p-tau181 (>52 pg/mL)	227	60.0 (9.0)	36 (24)	n.d.
Ossenkoppele, 2022	BioFINDER-1, BioFINDER-2, HABS	$_{amyloid}$PET (SUVR >1.03 in BioFINDER-1, -2, DVR >1.2 (>26 CL) in HABS); $_{tau}$PET (SUVR >1.26 in BioFINDER-1, SUVR >1.34 in BioFINDER-2, SUVR >1.36 in HABS)	1003	70.5 (9.8)	41.8 (18.9)	n.d.
Strikwerda-Brown, 2022	AIBL, Knight ADRC, Prevent AD	$_{amyloid}$PET (24 Centiloids for global Aβ); $_{tau}$PET (SUVR >1.27 for tau meta-ROI)	387	70.9 (5.6)	n.d.	39.8 (15.2 – 68.0)

[a] no data

CI 1.16; 18.61], and the OR calculated on the MCI-only studies is 5.83 [95% CI 3.80; 8.93]. Thus, the inclusion of the mixed population in the pool decreases the OR of the main analysis (5.21 [95% CI 3.93; 6.90]) slightly (Supplementary Material eFigure 1).

Strengths and limitations

There are several limitations to consider when interpreting our results. The study populations differ in several aspects; for cognitive status, the population ranges from those with no cognitive symptoms through those with subjective cognitive symptoms (these two groups were considered CU) to MCI groups. Therefore, the distance from the cognitive state corresponding to MCI or dementia also varies. Due to the different cut-offs used in the studies, subjects with grey area scores may oscillate between A- and A+ groups, increasing heterogeneity. Our study could not examine the role of other risk factors such as education, cardiovascular status, obesity, diabetes, depression, social and physical activity [69], or genetic status [70, 71], which may also contribute to heterogeneity. Furthermore, there is a considerable heterogeneity by mean age, and our meta-regression analysis of MCI group showed a significant decreasing effect of mean age on ORs.

In the OR analysis of Aβ in the CU group, in the context of the outlier value of the Arruda study, the possibility of a statistical extreme value can be assumed due to the small number of A+ subjects and the much larger A- group. Similarly, in the case of the Grontvedt [14] and Hanseeuw [41] studies, which show exceptionally high values, the A+ and A- groups show a similar uneven distribution. Similarly, the outliers in the MCI amyloid OR analysis are also associated with small sample sizes. For

the Aβ HR analysis in the CU group, the interpretability of the result is strongly influenced by one specific cohort (ADNI), which accounts for 78% of the overall weight. In the A+T+/A+T-/A-T+ analyses, no outliers were found in either the MCI or CU groups.

Furthermore, we note that although the Aβ OR analyses could be confirmed by also calculating the HRs, the inability to analyze the effect of p-tau on HR due to the low number of studies limits the completeness of the A/T analysis.

We pooled studies reporting AD-type dementia conversion and studies reporting conversion to unspecified dementia. This simplification was necessary because different studies defined Alzheimer's dementia differently, generally considering the amnestic clinical symptoms rather than biomarkers.

The fact that the studies used different neuropsychology tests to define MCI may contribute to the heterogeneity in the pooled sample. Another contributing factor would be the heterogeneity in the definition of MCI, however among the studies in our pool, only one, by Riemschneider et al. [48] (sample size = 28), precedes the 2003 'Key Symposium' [72] that transformed the MCI concept. All other studies were published subsequent to it. While MCI subgroups were deifned after the 2003 Symposium, the definition of MCI (objective cognitive impairment, essentially preserved general cognitive functioning, preserved independence in functional abilities) did not change afterwards. Furthermore, most of the studies pooled in the analyses were published after 2010.

Another source of heterogeneity is the relatively small sample size of some studies, leading to a higher variability of results. However, we thought that including studies with lower sample sizes was also important to get a complete picture.

It is essential to discuss the difference in the follow-up times between studies. The follow-up times ranged from 20 months to more than 10 years. Follow-up times were given in different ways, either as mean, median or up to a certain point. While naturally, the odds of conversion increase over time, our meta-regression analysis suggests that there is no significant difference in the odds ratios over (follow-up) time. The moderate heterogeneity of the studies also points in this direction. We also note here that hazard ratios independent of follow-up time showed similar results to OR analyses. Finally, yet importantly, we would like to point out that pathological protein changes can begin up to 20 years before the appearance of symptoms [6]. Such an extended follow-up is very difficult to carry out; therefore, all studies were shorter than that.

The results for Aβ are based on 7,793 individuals, and the combined analyses of Aβ and p-tau are based on data of over 3,500 individuals. Studies using CSF sampling or amyloid/tau PET to detect Aβ and p-tau were pooled together, despite using different kits and thresholds for positivity, contributing to the heterogeneity of results. This variation is acknowledged in Tables 1, 2, 3 and 4, where the cut-off values are provided. Previous large population studies have indicated that amyloid and tau PET scans exhibit slightly higher sensitivity compared to CSF sampling techniques [73, 74, 68]. Nonetheless, the concordance between these diagnostic methods remains substantial. Moreover, findings from prior research (Lee et al. [75], Toledo et al. [76], Palmqvist et al. [77]) demonstrating high concordance across different amyloid CSF and amyloid PET measurements suggest that the impact of methodological differences on heterogeneity may be limited, All techniques are recommended by the National Institute on Aging-Alzheimer's Association (NIA-AA) [6] for measurement.

Future directions

Conversion to Alzheimer's disease could not be analyzed specifically, as most of the articles examining conversion either did not define Alzheimer's disease or the definition was based on neuropsychological testing but not on biomarkers (i.e., Aβ and p-tau status were assessed only at baseline). According to the NIA-AA guideline [6] and our results, we recommend biomarker-based studies to assess conversion rates to Alzheimer's disease.

Conclusions

In view of the Aβ and p-tau status, the most endangered population can be identified before the appearance of cognitive symptoms or at least at a mild stage. While the significance of Aβ in conversion is clear, it appears that its ability to predict the onset decreases with age. If we consider the current therapeutic limitations and the importance of early prevention, we believe that the initiation of non-pharmacological and pharmacological treatments should be related to Aβ and p-tau status rather than cognitive status.

Identifying the most endangered population also makes research more effective. The efficacy of different dementia prevention approaches can be more accurately assessed by knowing the Aβ and p-tau status of the patient. As the population targeted by the interventions can be more homogeneous, the effectiveness can be measured more precisely by identifying the population most at risk of conversion.

Abbreviations

A-	Non-pathologic levels of beta-amyloid
A+	Pathologic levels of beta-amyloid
Aβ	Beta-amyloid
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative

CI	Confidance interval
CU	Cognitively unimpaired
CSF	Cerebrospinal fluid
HR	Hazard ratio
MCI	Mild cognitive impairment
N-	Absence of neurodegeneration
N+	Presence of neurodegeneration
NIA-AA:	National Institute on Aging Alzheimer's Association
OR	Odds ratio
PET	Positron emission tomography
p-tau	Phosphorylated tau
T-	Non-pathologic levels of phosphorylated tau
T+	Pathologic levels of phosphorylated tau

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
ZH: conceptualisation, project administration, methodology, formal analysis, writing – original draft; ME: conceptualisation, methodology, formal analysis, writing – review and editing; MP: conceptualisation, formal analysis, writing - review and editing; TS formal analysis, writing – review and editing; YS: formal analysis, writing – review and editing; BH: writing - review and editing; TT: conceptualisation, writing – review and editing; ZM: conceptualisation, supervision, writing - review and editing; PH: conceptualisation, supervision, writing - review and editing; GCs: conceptualization, methodology, formal analysis, supervision, writing – original draft, visualization. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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