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The association of glucose metabolism measures and diabetes status with Alzheimer's disease biomarkers of amyloid and tau: A systematic review and meta-analysis

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ABSTRACT

Conflicting evidence exists on the relationship between diabetes mellitus (DM) and Alzheimer's disease (AD) biomarkers. Therefore, we conducted a random-effects meta-analysis to evaluate the correlation of glucose metabolism measures (glycated hemoglobin, fasting blood glucose, insulin resistance indices) and DM status with AD biomarkers of amyloid-β and tau measured by positron emission tomography or cerebrospinal fluid. We selected 37 studies from PubMed and Embase, including 11,694 individuals. More impaired glucose metabolism and DM status were associated with higher tau biomarkers (r=0.11[0.03–0.18], p=0.008; I2=68%), but were not associated with amyloid-β biomarkers (r=-0.06[-0.13–0.01], p=0.08; I^2=81%). Meta-regression revealed that glucose metabolism and DM were specifically associated with tau biomarkers in population settings (p=0.001). Furthermore, more impaired glucose metabolism and DM status were associated with lower amyloid-β biomarkers in memory clinic settings (p=0.004), and in studies with a higher prevalence of dementia (p<0.001) or lower cognitive scores (p=0.04). These findings indicate that DM is associated with biomarkers of tau but not with amyloid-β. This knowledge is valuable for improving dementia and DM diagnostics and treatment.

1. Introduction

Alzheimer's disease (AD) has been increasing in prevalence over the last decade, exacerbating its considerable burden on society and healthcare systems (Gustavsson et al., 2023). Emerging evidence suggest that diabetes mellitus (DM) and its associated phenotypes, such as hyperglycemia and insulin resistance, may play an important role in the development of AD dementia (Griffith et al., 2018; Shieh et al., 2020; Pal

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et al., 2018) and lead to an increased risk of cognitive decline (Fanelli et al., 2022; Gómez-Martínez et al., 2021). Hypoglycemic drugs have also been shown to reduce cognitive decline in mild cognitive impairment (MCI) and AD (Wang et al., 2022). Moreover, patients with DM often show similar patterns of brain atrophy and vascular damage (e.g., white matter hyperintensities) as patients with AD (Biessels et al., 2020; Zhang et al., 2022a). However, to date, the link of DM with underlying AD pathophysiology remains unclear while this is important for diagnostics in DM and AD.

The use of AD biomarkers allows to investigate the association between DM and AD in greater detail. AD is typically characterized by the aggregation of amyloid-β plaques and tau tangles in the brain before the onset of clinical symptoms. Biomarkers of amyloid-β and tau can be measured by positron emission tomography (PET) scans or in cerebrospinal fluid (CSF) and have been shown to be specific to AD (Scheltens et al., 2016). On PET, tracer uptake is typically measured globally for amyloid and in medial temporal areas or entorhinal cortex for tau. In CSF, amyloid-β-42 and p-tau181 measures are commonly used. Studies exploring the association of DM with amyloid-β and tau biomarkers by CSF or PET yield inconsistent results, as some studies are showing positive associations but others negative or no associations. Previous smaller reviews summarizing the literature suggest that no association between DM and amyloid exists but are inconclusive on the association with tau biomarkers (Biessels et al., 2020; Piri et al., 2019; Lu et al., 2018). Studies have however been insufficient to perform reliable meta-analyses in the past. Inconsistent findings across studies could be explained by differences in demographics, study settings (i.e., population or memory clinics), sample characteristics (i.e., inclusion of cognitively healthy or impaired individuals), measures of DM (DM status, hyperglycemia, or insulin resistance), DM prevalence, AD biomarker modalities (i.e., CSF or PET), and statistical methodologies. Yet, knowledge on which factors impact the association between DM and AD biomarkers is still lacking.

Therefore, we aim to perform a comprehensive systematic review and meta-analysis of existing studies to evaluate whether glucose metabolism measures – including fasting blood glucose, glycated hemoglobin (HbA1c), and insulin resistance indices – and DM status, are associated with amyloid-β and tau biomarkers as assessed by PET or CSF. In addition, we will investigate whether demographics, study setting, cognitive impairment status, and statistical methods may influence these associations by using meta-regression.

2. Methods

2.1. Study design and search strategy

This systematic review and meta-analysis was performed at the Alzheimer Center Limburg, Maastricht University, The Netherlands, in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020 (Page et al., 2021). A systematic search of the literature was performed in the Embase and PubMed databases for studies published up to end of May 2023. The search query included relevant keywords derived from four categories: (1) predictor: glucose metabolism measure, i.e., fasting blood glucose, HbA1c, or an insulin resistance index, or DM status, (2) outcome: AD biomarkers as defined by amyloid-β or tau, (3) AD biomarker measurement method: CSF or PET, and (4) population: older adults or memory clinic cohort. See Appendix A for the complete search term. This study was registered on PROSPERO with ID CRD42023474768.

2.2. Study selection and eligibility criteria

Studies were included when reporting complete cross-sectional results that could be converted to a correlation coefficient. Studies were also included when glucose metabolism or DM status were measured a certain time interval before the AD biomarker measure (but were analysed separately). Studies focusing on type 2 diabetes (T2DM) or DM of mixed types were included. Mixed DM primarily refers to T2DM as this constitutes the majority of cases (Xu et al., 2018). Studies focusing on DM type 1 were excluded, as well as studies on neurological or neurodegenerative diseases other than dementia. We additionally excluded studies with a combined measure of amyloid-β and tau, as well as case reports, abstract conferences, book chapters, letters, editorials, commentaries, reviews, clinical trials, animal studies, and studies reported in a different language than English. After duplicate removal, title and abstract screening and subsequent full-text screening were performed by two independent reviewers (VG and JC). Any disagreement was solved after consultation and open discussion with two senior researchers (SV and WJ). When studies used the same research cohort (overlapping participant samples), we selected the study with the largest sample size. Corresponding authors were contacted by email in case their study did not provide sufficient data for meta-analysis.

2.3. Data extraction and selection

All test statistics reporting cross-sectional associations between glucose metabolism measures or DM status and AD biomarkers of interest were extracted and synthesized for the selected studies. In addition, the following data were extracted: cohort/country, design, setting, number of participants, diagnosis, inclusion- and exclusion criteria of each study, mean age, sex, mean education years, cognition score on the Mini-Mental State Examination (MMSE), type of glucose metabolism measure (fasting blood glucose, HbA1c, or IR) or DM status type (T2DM or DM), prevalence of DM, AD biomarker (amyloid or tau) and its assessment modality (PET or CSF), PET tracers or CSF assays, prevalence of dementia, APOEe4 gene carriership, details on statistical methods, covariates used in model, and interval in years between the glucose metabolism measure or DM status and AD biomarker measure. Data extraction was performed by two researchers independently (MR and JC) and reviewed by a third researcher (VG) in case of inconsistencies.

2.3.1. Predictors: glucose metabolism measures and DM status

Glucose metabolism measures included HbA1c, fasting blood glucose levels, or an insulin resistance index score (HOMA-IR, Matsuda or QUICKI index). DM status could include either mixed DM or only T2DM. When results for both glucose metabolism and DM status or for multiple glucose metabolism measures were reported, we selected the measure or analysis that used the largest sample size. If the sample size was the same, we prioritized studies based on the most direct measures of DM in the following order: (1) HbA1c, (2) fasting blood glucose, (3) insulin resistance index, (4) DM status.

2.3.2. Outcome measures: AD biomarkers

AD biomarkers entailed amyloid-β and tau. PET is a commonly used method to measure protein binding to a tracer, for which various reliable amyloid (e.g. 11 C-PiB, 18 F-flutemetamol, 18 F-florbetapir, 18 F-florbetaben) and tau tracers (e.g. AV-1451, 18 F-MK-6240) have been developed to detect AD. We selected composite summary scores for amyloid-β if they were reported. If no composite score was available, a mean correlation was calculated from all studied regions. For tau PET, we prioritized entorhinal cortex followed by temporal cortex measures.

For CSF studies, we extracted data from analyses using amyloid-β42 as amyloid-β measure and phosphorylated tau181 (p-tau181) as tau measure for all included studies. These measures are commonly used and reliable biomarkers for amyloid and tau in AD. If t-tau was available, it was additionally extracted for sensitivity analyses. Total tau (t-tau) is a less specific AD marker indicating general neurodegeneration. For CSF amyloid-β, reported associations were multiplied by −1 so that a positive effect size represented a positive association of glucose metabolism measures or DM status with more abnormal amyloid-β. In this way, we were able to directly compare CSF amyloid-β with amyloid-β PET outcomes.

2.3.3. Selection of statistical analysis

The included studies used variable statistical methodologies with both continuous and dichotomous predictors and outcome measures. We extracted the available results that were reported, which could include correlation coefficients, linear regression betas with SE or SD, logistic regression odds ratios with CI (only when a dichotomous predictor was used), means and SD or median and ranges per group (t-test), 2×2 tables, or structural equation modeling (SEM) coefficients. For analyses based on groups, we included groups based on DM status or a glucose metabolism measure cutoff, or groups based on amyloid-β or tau positivity. When multiple statistical methods were used within the same study, we prioritized the analyses that used the lowest number of covariates but were at least adjusted for age. If none or all models were adjusted for age, we prioritized correlations and linear regression analyses, followed by group comparisons (t-test or ANOVA), and then logistic regression and chi-squared tests. We prioritized statistical methods as such because calculation of effect sizes is considered more accurate (i.e. more direct) for continuous variables (Rousson, 2014).

2.4. Quality assessment

The observational study quality evaluation (OSQE) checklist (Drukker et al., 2021) was used to rate all included studies. We used the cross-sectional checklist (with 6 items, excluding item 4 and the optional items), and where appropriate the case control checklist (with 11 items, excluding items 4, 8, 11, and the optional items). Low quality studies were defined by a total score of ≤50% (Grinstead and Yoon, 2022). Quality assessment was performed by two independent reviewers (JC and MR) and discussed with a third reviewer (VG) in case of disagreement or uncertainty.

2.5. Statistical analyses

To assess the cross-sectional association of glucose metabolism and DM status with AD biomarkers, we performed a random effects meta-analysis for amyloid-β and tau separately, using the DerSimonian & Laird and Knapp-Hartung method to better account heterogeneity. For each study, we converted results to correlation coefficients as effect size. Analyses were stratified for glucose metabolism measures versus DM status or for modality (PET versus CSF). We ran a separate analysis for studies with a time interval between the assessment of glucose metabolism or DM status and the AD biomarker measure.

Depending on the statistical methods used in each study, results of each study were converted to a correlation coefficient to be able to compare effect sizes. Pearson and Spearman correlations were used directly (Bonett and Wright, 2000), whereas linear regression coefficients were converted to partial correlation coefficients (Aloe and Becker, 2012). Structural equation modeling (SEM) coefficients of direct effects (Frison et al., 2021; Koncz et al., 2022) were also handled as regression coefficients with the same approach. Data from 2×2 tables or odds ratios were converted to tetrachoric correlation coefficients (Sánchez-Meca et al., 2003). Reported means and standard deviations for groups were converted to a biserial correlation coefficient (Jacobs and Viechtbauer, 2017). When needed, group comparison medians and ranges were converted to means (Luo et al., 2018) and standard deviations (Wan et al., 2014). When results were reported for more than two subgroups, we calculated means and standard deviations for the combined groups.

Meta-regression was used to test potential moderating effects of age, sex, education years, setting (memory clinic or population), prevalence of dementia, type of glucose metabolism measure (blood glucose/HbA1c vs IR), DM status type (T2DM vs DM), DM prevalence, correlation type (regular, partial, biserial, or tetrachoric), MMSE score, whether studies adjusted for age (yes/no), and APOEe4 carriership (yes/no). All moderators were tested in separate models. Heterogeneity was assessed by the I2 statistic and prediction intervals, where I2 ≥ 50% and P < 0.10 was considered evidence of substantial heterogeneity. We assessed whether publication bias is likely to affect our results by using Egger's test and funnel plots (Egger et al., 1997).

As sensitivity analyses, we repeated the meta-analyses without low-quality studies and outliers. We also performed a separate analysis for CSF t-tau as outcome measure and compared the outcomes of amyloid-β and tau when only meta-analysing studies that used both outcomes within the same sample. We used the *metafor* package (Viechtbauer, 2010) in R (version 4.2.2, 2022) for all analyses.

3. Results

After full-text screening, we included a total of 37 studies in our meta-analysis, of which 33 cross-sectional studies and 6 studies where the glucose metabolism measure or DM status was measured a certain time interval before the AD biomarker measure. An overview of the study selection is shown in a PRISMA flowchart in Fig. 1. Study characteristics are described separately for PET studies (Table 1) and CSF studies (Table 2).

We excluded 12 studies that used overlapping participant samples (Kemppainen et al., 2018; Laws et al., 2017; Li et al., 2018; Moran et al., 2015; Morris et al., 2014; Nettiksimmons et al., 2013; Ou et al., 2020; Palta et al., 2021; Thomas et al., 2020; Willette et al., 2015; Zhang et al., 2022b; Toppala et al., 2019). One study was only included in the tau analyses due to overlapping cohorts for amyloid-β (Vemuri et al., 2017a). We only included the "external validation cohort" from Kang et al. (2021a), as the "training cohort" included an overlapping cohort (Kang et al., 2021b). Two studies with a combined measure of amyloid-β and tau were additionally excluded (Sundermann et al., 2021; Besga et al., 2012). We included the study of Palix et al. (2022) in two parts, as results were provided for the cognitively normal and mild cognitive impairment/dementia groups separately. In the study of Pagano et al. (2018), we did not include groups with Parkinson patients. In one study where no composite score for amyloid-β was available on PET, we calculated the mean correlation for the frontal cortex and posterior cingulate cortex (Walters et al., 2018). Some authors provided additional details on results after contacting them (Palix et al., 2022; Bos et al., 2017; Kučikienė et al., 2022). Two studies reported associations of glucose metabolism and DM certain years before and at the same timepoint of the PET measure and were thus included in the cross-sectional and time interval meta-analyses (Ekblad et al., 2018; Gottesman et al., 2017).

3.1. Quality assessment

The included 37 studies showed an average OSQE score of 76.7% (SD=15.9%) on all relevant items. OSQE scores are attached in Supplementary table 1. Three studies were rated as low quality and were excluded in a sensitivity analysis (Chiang et al., 2017; Lau et al., 2021; Takenoshita et al., 2019).

3.2. Association of glucose metabolism measures and DM status with amyloid-β

In total, 32 studies reported data for a total of 11,694 participants. 16 studies used a glucose metabolism measure (5 fasting blood glucose, 4 HbA1c, and 7 insulin resistance index) and 17 studies used DM status (7 T2DM and 10 mixed DM types) as predictor. Most of the included studies measured amyloid-β by PET scans (19 out of 32).

Meta-analysis results on the association of DM with amyloid-β are depicted in a forest plot in Fig. 2. Higher levels of glucose metabolism measures or DM status were not associated with biomarkers of amyloid-β (r= −0.06[-0.13 – 0.01], p=0.08, k=33). Heterogeneity was high between studies (I^2 =81.0%, Q= 168.4, p<0.0001, prediction interval= −0.37 – 0.26). When stratifying for glucose metabolism measures versus DM status, no difference in associations was found (glucose metabolism:

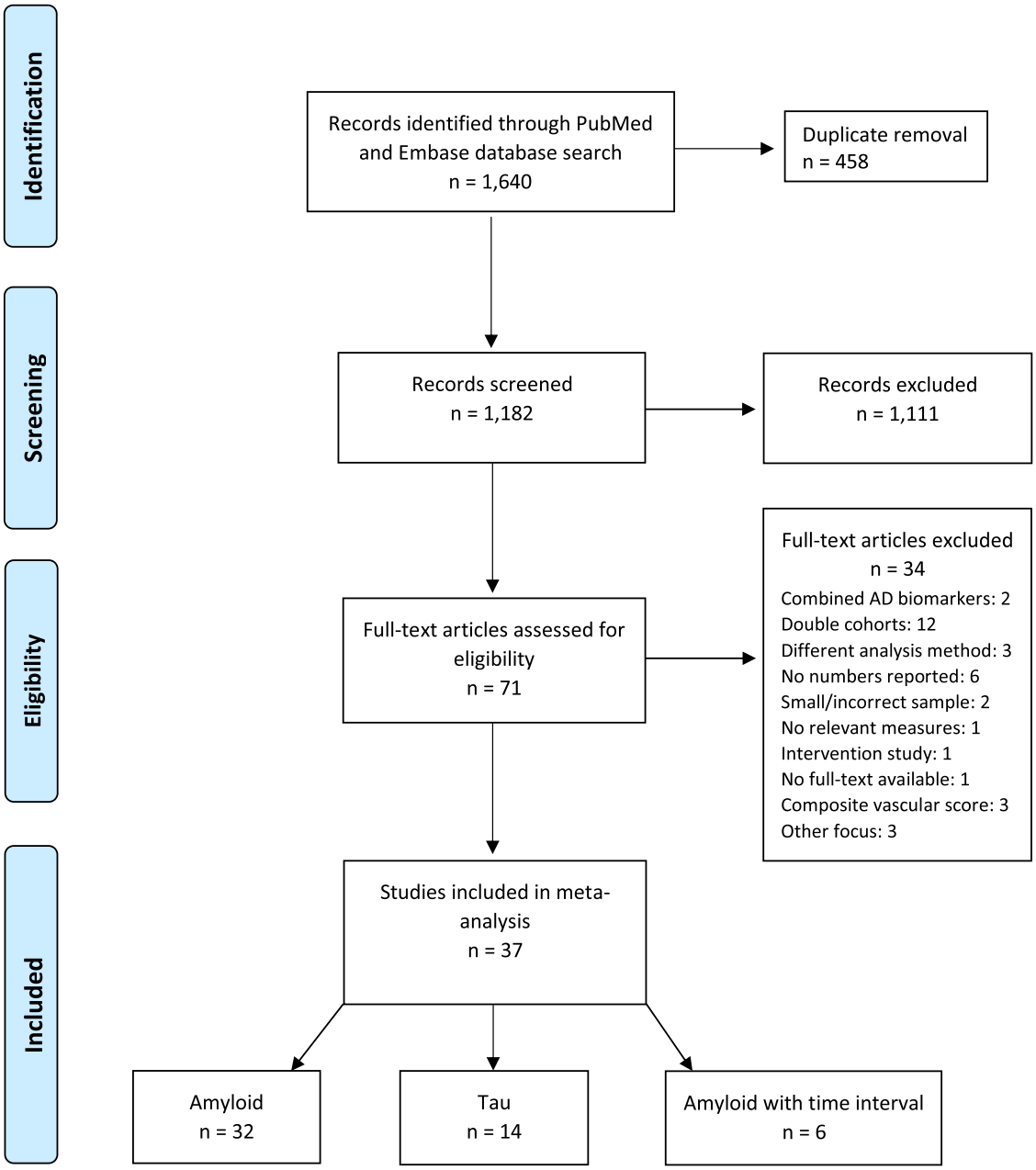

Fig. 1. PRISMA flowchart of study inclusion.

r=-0.06[-0.18–0.06], p=0.30, k=16, DM: r=-0.06[-0.14–0.02], p=0.14, k=17, difference: QM=0.001, p=0.97). Likewise, no differences in associations were found for PET versus CSF biomarker modalities (PET: r=-0.04[-0.13–0.04], p=0.34, k=20, CSF: r=-0.09[-0.20–0.03], p=0.13, k=13, difference: QM=0.43, p=0.51). Egger's regression test showed no significant asymmetry of the funnel plot (t= 0.18, p=0.86), indicating a low likelihood of publication bias in this analysis (Supplementary fig. 1a).

To explore factors underlying the large heterogeneity, we performed meta-regression. Meta-regression showed an association of higher glucose metabolism measures or having DM with lower amyloid-β biomarkers in memory clinic studies (r= −0.18[-0.29 – −0.08], p=0.001, k=10) but not in population studies (r=0.001[-0.07 – 0.07], p=0.99, k=23). Similarly, the association of higher glucose metabolism measures or DM with lower amyloid-β biomarkers was stronger with an increasing dementia prevalence (slope decrease per % more dementia= −0.005, p<0.001, k=33) or decreasing MMSE score (slope increase per MMSE point= 0.05, p=0.01, k=16), as depicted in Fig. 3. When biserial correlation was used, a stronger association was found between higher glucose metabolism measures or DM and lower amyloid-β biomarkers (r=-0.13[-0.24 – −0.02], p=0.03) as compared to other correlation types. When DM prevalence was higher, stronger associations were found between higher glucose metabolism measures or DM status and lower amyloid-β biomarkers (r=-0.005 [-0.008 – −0.002], p=0.005), but this result did not remain significant when removing one study that included DM patients only (Takenoshita et al., 2019) (p=0.76, k=30). No moderating effects were found for age, sex, education years, type of glucose metabolism measure (blood glucose/HbA1c vs IR), DM status type (T2DM vs DM), study adjustment for age, or APOEe4 carriership.

3.3. Association of glucose metabolism measures and DM status with tau

Data on tau was reported in 14 studies including a total of 6230 participants. Of these studies, 13 were also included in the amyloid-β

Table 1

Study characteristics of cross-sectional studies on associations between glucose metabolism measures or DM status amyloid and tau measures on PET. *AD* Alzheimer's disease, *BMI* Body Mass Index, *CDR* clinical dementia rating, *CN* cognitively normal, *Dem* dementia, *DM* diabetes mellitus – mixed types, *Edu* education, *ERC* entorhinal cortex, *FBG* fasting blood glucose, *FBB* florbetaben, *FBP* florbetapir, *Fem* female, *FMM* flutemetamol, *HbA1c* glycated hemoglobin, *HOMA-IR* Homeostatic model assessment for insulin resistance, *HT* hypertension, *MCI* mild cognitive impairment, *MMSE* mini-mental state examination, *MTL* medial temporal lobe, *PET* positron emission tomography, *PiB* Pittsburgh compound B, *PCC* posterior cingulate cortex, *SCD* subjective cognitive decline, *T2DM* type 2 diabetes mellitus, *QUICKI* Quantitative insulin sensitivity check index. *Global PET regions usually consisted of (pre)frontal, (lateral) parietal, posterior and anterior cingulate/precuneus and lateral temporal cortex, sometimes with occipital or striatum, with cerebellum as reference region. #A subsample (N=114) was used for the tau analyses; demographics of amyloid sample are given. **This study also analyzed CSF data (N=135) but was included in PET sample due to larger sample size.

Author	Cohort/ hospital	N	Setting	Diagnosis groups	Dem %	Inclusion criteria	Age Mean	Fem %	Edu years	DM %	Apo E4%	MMSE Mean	Predictor	PET tracer	Regions	Amyloid /Tau	Statistical analysis	Covariates
Byeon et al. (2021)	KBASE	430	Both	CN, MCI	0	55–90	70.6	56	11.2	17		25.5	DM	PiB, Tau: AV-1451	Global*, Tau: MTL SUVR	Both	Linear regression	Age, sex, education, homocysteine, vascular risk, B12, folate, creatinine, diagnosis
Chiang et al. (2017)	New York	33	Population	CN	0	55–75	62.5	40	15.7	49	22		T2DM	PiB	Global* SUVR	Amyloid	Linear regression	Age, APOEe4
Ekblad et al. (2018)	Health 2000	60	Population	Mostly CN, no dementia	0	Enriched APOEe4, matching, 1934–1949	55.4	55	12.1	8	50		HOMA-IR	PiB	Global* SUVR	Amyloid	Linear regression	Age, sex, education
Ekblad et al. (2023)	ASIC-E4	60	Population	CN	0	No DM	67.7	63		0	67		HOMA-IR	PiB	Global* SUVR	Amyloid	Spearman correlation	None
Ennis er al. (2023)	WRAP/WI-ADRC	394	Population	Mostly CN, few MCI & dementia	2	Enriched AD risk	68	66	16.1	9	40		T2DM	PiB, Tau: FMK-6240	Global* DVR, Tau: ERC SUVR	Both	T-test	None
Friso et al. (2021)	MEMENTO	643	Memory clinic	SCD, MCI	0	≥60, CDR ≤0.5	70.9	62		8	30	28.3	DM	FBP, FMM	Global* SUVR	Amyloid	SEM	Age, gender, education, APOEe4, smoking, alcohol, dyslipidemia, obesity
Gottesman et al. (2017)	ARIC	322	Population	CN, MCI	0	Cognitive decline (vs midlife)	75.8	58		40	31		DM	FBP	Global* SUVR	Amyloid	Logistic regression	Age, sex, race, educational level, APOEe4, BMI, smoking, HT, cholesterol
Kang et al. (2021a)	Kyung Hee & Dong-A	187	Memory clinic	MCI	0	Amnestic MCI	68	61	10	23	37		DM	FBB, FMM	Global* visual read	Amyloid	Chi-squared	None
Kang et al. (2021b)	Samsung MC Seoul	1047	Memory clinic	SCD, MCI, dementia	49		71.1	61	11	20	37	23	DM	FBB, FMM	Global* visual read	Amyloid	Logistic regression	Age, sex, education, dyslipidemia, APOEe4, diagnosis, hypertension, WMH
Lau et al. (2021)	90+	166	Population	CN, MCI, dem	4	>90, residents Orange County	93	61		11			DM	FBP	PCC/ precuneus SUVR	Amyloid	T-test	None
Luchsinger et al. (2020)	CUIMC	350	Population	Mostly CN, no dementia	0	55–69	64.2	72	10.5	32	35		HbA1c	FBB	Global* SUVR	Amyloid	Linear regression	Age, sex, APOEe4

(*continued on next page*)

Table 1 (*continued*)

Author	Cohort/ hospital	N	Setting	Diagnosis groups	Dem %	Inclusion criteria	Age Mean	Fem %	Edu years	DM %	Apo E4%	MMSE Mean	Predictor	PET tracer	Regions	Amyloid /Tau	Statistical analysis	Covariates
Morris et al. (2016)	Kansas MC	73	Population	CN	0	≥65, sedentary, CDR = 0	72.8	62	16.2	16	33		FBG	FBP	Global* SUVR	Amyloid	ANOVA	None
Palix et al. (2022) (1) CN	IMAP+	105	Population	CN	0	≥60, No DM	49.2	48	13	0	32		FBG	FBP	Global* SUVR	Amyloid	Linear regression	Age, sex, education, BMI,
Palix et al. (2022) (2) CI		45	Memory clinic	MCI, dementia	40		70.8	33	11.6	0	62							APOEe4, platelets, MPV
Pekkala et al. (2020)	FINGER-PET	41	Population	CN	0	Elevated dementia risk (by CAIDE)	71.1	51		15	29		HbA1c	PiB	Global* visual read	Amyloid	Mann-Whitney U	None
Roberts et al. (2014)	MCSA	749	Population	CN, MCI	0	Residents Olmsted County	79.2	44	13.8	26	27		T2DM	PiB	Global* SUVR	Amyloid	Logistic regression	Age, sex
Takenoshita et al. (2019)	Tokyo MC	64	Memory clinic	AD	100	AD + DM	79.8	49	12.5	100		22.8	HbA1c	PiB	Global*	Amyloid	ANOVA	None
Taylor et al. (2017)	APEX	128	Population	CN	0	Sedentary, from physical intervention trial	71.3	66	16.5	13		29	T2DM	FBP	Global* visual read	Amyloid	Chi-squared	None
Vemuri et al. (2017a)	MCSA	430	Population	CN, MCI, dementia	1	>60	74.7	44	14.7	40	28		HbA1c	Tau: AV-1451	Tau: ERC SUVR	Tau	ANCOVA	Age
Walters et al. (2018)	NYU & WCMC	70	Population	CN	0	30–60, education >12 y, CDR = 0	49	69	16	0	39	29	QUICKI IR	PiB	Frontal, PCC/ precuneus	Amyloid	Linear regression	Age, gender, APOEe4
Woodfield et al. (2022)	AIBL	295	Population	CN	0	≥60, exclusion A-T+	78.5	56		7	32		HOMA-IR	PiB, FBP, FMM	Global* SUVR	Amyloid	Linear regression	Age, sex, APOEe4

Table 2
Study characteristics of cross-sectional studies on associations of glucose metabolism measures or DM status and amyloid and tau in CSF. *AD* Alzheimer's disease, *BMI* Body Mass Index, *CN* cognitively normal, *dem* dementia, *DM* diabetes mellitus – mixed types, *Edu* education, *ELISA* enzyme-linked immunosorbent assay, *FBG* fasting blood glucose, *Fem* female, *HbA1c* glycated hemoglobin, *HOMA-IR* Homeostatic model assessment for insulin resistance, *MCI* mild cognitive impairment, *MMSE* mini-mental state examination, *SCD* subjective cognitive decline, *T2DM* type 2 diabetes mellitus, *VCI* vascular cognitive impairment. *Antwerp, Barcelona, Brescia, Coimbra, DCN, DESCRIPA, EDAR, EADC-PET, Gothenburg, Liege, Lisbon.

Author	Cohort/ hospital	N	Setting	Diagnosis groups	Dem %	Inclusion criteria	Age Mean	Fem %	Edu years	DM %	Apo E4%	MMSE Mean	Predictor	CSF assay	Amyloid/ Tau	Analysis	Covariates
Bos et al. (2017)	Multiple*	495	Memory clinic	MCI	0		68.9	47	10.9	11	23	26.6	DM	Multiple (Per cohort)	Amyloid	Logistic regression	None
Dumurgier et al. (2011)	Paris Nord	94	Memory clinic	AD	100	No DM	72.5	63		0	50	20	FGB	Innotest ELISA	Both	AB: linear regressiontau: spearman	Amyloid: age, gender, Tau: none
Exalto et al. (2010)	VUMC Amsterdam	245	Memory clinic	SCD, MCI, dementia	38	≥45	66.0	59		9		27	HbA1c	Innotest ELISA	Both	Linear regression	Age, sex, diagnosis
Gregory et al. (2022)	EPAD LCS	1230	Both	CN	0	≥50	66.3	58	14.6	7	40		DM	Roche Elecsys	Both	T-test	None
Groeneveld et al. (2019)	TRACE-VCI	533	Memory clinic	SCD, MCI, dementia	53	Vascular injury/VCI	67.7	46		15		25.2	T2DM	Innotest ELISA	Both	Mann-Whitney U	None
Hoscheidt et al. (2016)	IMPACT	70	Population	CN	0	No DM	57.7	79	15.9	0	47		HOMA-IR	MSD Multiplex Soluble APP	Amyloid	Linear regression	Age, sex, BMI
Janelidze et al. (2016)	Bio-FINDER	710	Both	CN, SCD, MCI, dementia	8	≥60	71.9	54		10		27.8	DM	Euroimmun immunoassay	Amyloid	T-test	Age, gender, diagnosis
Kučikienė et al. (2022)	RWTH Aachen & BB-ACL	824	Memory clinic	SCD, MCI, dementia	36	≥45	68.7	47	11.6	16		24.9	DM	Innotest ELISA	Both	T-test	None
McIntosh and Nation (2019)	ADNI	901	Population	CN, MCI	0	55–90	73.5	44	16.0	13	42	28.1	T2DM	Roche Elecsys	Both	T-test	None
Pagano et al. (2018)	PPMI	28	Population	CN	0	DM: duration > 2 years	62.6	18	16.4	50		28.3	T2DM	INNOBIA AlzBio3	Both	Mann-Whitney U	None
Wang et al. (2023)	Hebei Medical University	138	Population	CN	0	≥65, hip fracture, hospital	81.2	60	5.1	18			HOMA-IR	Innotest ELISA	Both	Linear regression	None
Westwood et al. (2017)	METSIM - IRS	58	Population	CN	0	Only men, No DM	62.7	0		0	40	29.0	Matsuda IR	Innotest ELISA	Both	T-test	None
Zhao et al. (2022)	CABLE	1106	Population	CN	0	40–90	62.3	40	9.7		14	27.9	FBG	Innotest ELISA	Both	Linear regression	Age, sex, education, APOEe4

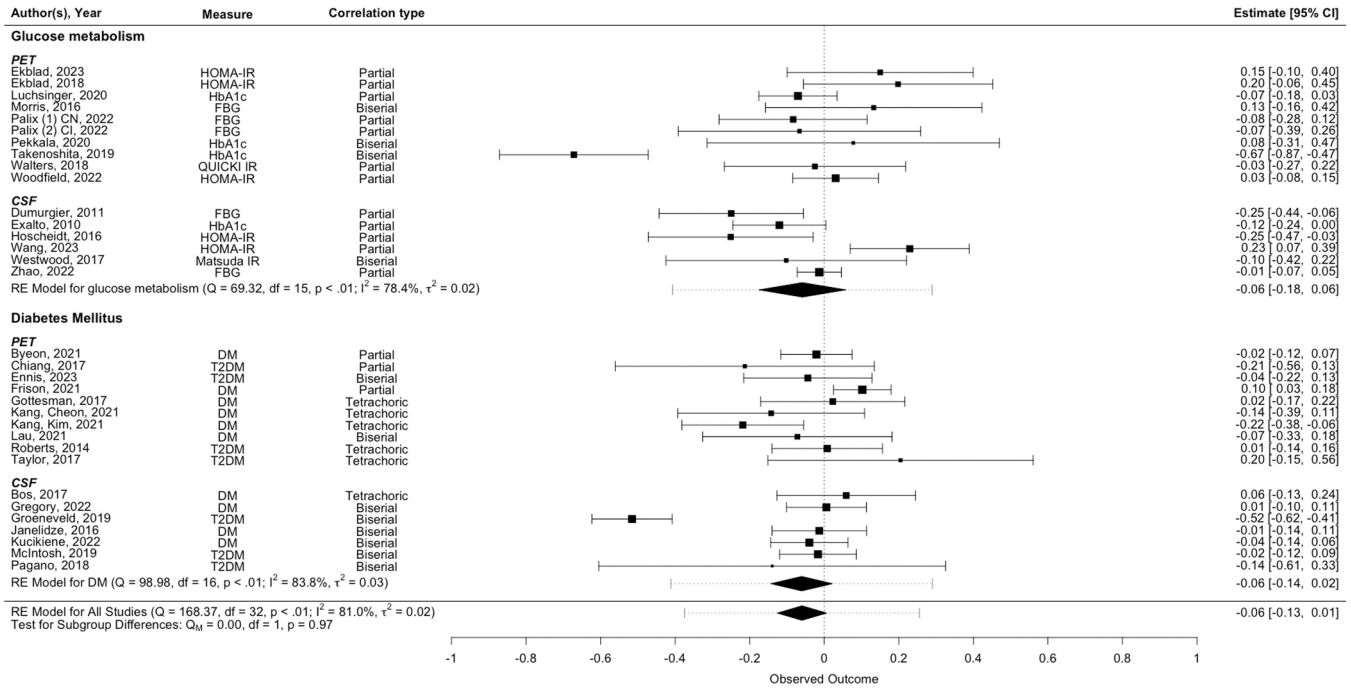

Fig. 2. Forest plot of meta-analysis on the association of glucose metabolism and DM status with amyloid-β (k=32). Stratified results are shown for glucose metabolism measures versus DM status. Results are grouped by biomarker modality (PET and CSF). Bars show correlation estimates with confidence intervals per study. Size of squares represents study weight (based on variance). The diamond represents the summary effect size with the dotted line representing the prediction interval. Columns show further details on which measure was used as predictor and which type of correlation was used as effect size. *DM* diabetes mellitus – mixed types, *FBG* fasting blood glucose, HbA1c glycated hemoglobin, *HOMA-IR* Homeostatic model assessment for insulin resistance, *T2DM* type 2 diabetes mellitus, *QUICKI* Quantitative insulin sensitivity check index.

analysis. Glucose metabolism measures were used in 6 studies (2 fasting blood glucose, 1 HbA1c, 3 insulin resistance index), while DM status was used in 8 studies (4 T2DM and 4 mixed DM types). Only 3 out of 14 studies used PET.

Meta-analysis showed that higher glucose metabolism measures and DM status were associated with higher tau biomarkers (r= 0.11[0.03 – 0.18], p= 0.008, k=14). Results are presented in a forest plot in Fig. 4. Substantial heterogeneity between studies was shown (I^2 =68%, Q=41, p<0.001, prediction interval= −0.10 – 0.31). Similar findings were shown for glucose metabolism measures and DM status (glucose metabolism: r=0.15[-0.01–0.30], p=0.06, k=6, DM: r=0.08[-0.01–0.18], p=0.08, k=8, difference: QM=0.82, p=0.37). Likewise, no difference was found when stratifying for PET and CSF modalities (PET: r=0.05 [-0.13–0.22], p=0.37, k=3, CSF: r=0.13[0.04–0.22], p=0.009, k=11, difference: QM=1.41, p= 0.23). Egger's regression test showed no significant asymmetry of the funnel plot (t= 0.80, p=0.44), indicating a low likelihood of publication bias in this analysis (Supplementary figure 1b).

Meta-regression showed that the association of higher measures of glucose metabolism and DM status with higher tau biomarkers only existed in population studies (r=0.15[0.07 – 0.23], p=0.001, k=9), but not in memory clinic studies (r= 0.02[-0.09 – 0.12], p=0.74, k=5). In addition, the association between higher measures of glucose metabolism and higher tau biomarkers was predominantly present in studies using IR measures (r=0.30[0.16 – 0.43], p=0.003, k=3) as compared to blood glucose or HbA1c measures (r=0.06[-0.001 – 0.13], p=0.053, k=3). No moderating effects were shown for age, sex, education years, dementia prevalence, DM status type (T2DM vs DM), DM prevalence, correlation type, MMSE score, study adjustment for age, or APOEe4 carriership.

3.4. Associations with a time interval between the glucose metabolism measures or DM status and amyloid-β

Six studies reported associations with a time interval between the glucose metabolism measure or DM status and amyloid-β PET, for a total of 2226 participants with a time interval ranging from 2 to 28 years. No CSF or tau studies reported results with a time interval. Study characteristics are described in Supplementary Table 2 (Koncz et al., 2022; Thambisetty et al., 2013; van Arendonk et al., 2023; Vemuri et al., 2017b).

Meta-analysis did not show an association of glucose metabolism or DM status with amyloid-β on PET after a time interval (r= 0.01[-0.14 – 0.17], p= 0.86, k=6), as shown in Supplementary Fig 2. Substantial heterogeneity between studies was shown (I^2 =72%, Q=18, p=0.003, prediction interval= −0.30 – 0.32). No differences in associations were found when comparing glucose metabolism measures versus DM status (Qm=0.19, p=0.66). Egger's regression test did not show asymmetry of the funnel plot (t= 0.64, p=0.56), indicating a low likelihood of publication bias.

The number of years that glucose metabolism or DM was measured before PET assessment did not modify the association (slope increase per year of interval= 0.002, CI= −0.01 – 0.02, p= 0.80). Studies with a larger prevalence of females showed a greater association of higher glucose metabolism measures or DM with higher amyloid-β biomarkers on PET later in time (slope increase per % more females= 0.02, CI= 0.004 – 0.04, p= 0.03). Age, dementia prevalence, type of glucose metabolism measure (blood glucose/HbA1c vs IR), DM status type (T2DM vs DM), DM prevalence, correlation type, MMSE scores, whether studies adjusted for age, or APOEe4 carriership did not modify the association. Studies with a higher dementia prevalence however tended to show an association of higher glucose metabolism measures and DM status with lower amyloid-β biomarkers later in time (slope decrease per % more dementia= −0.01[-0.02 – 0.002], p=0.08).

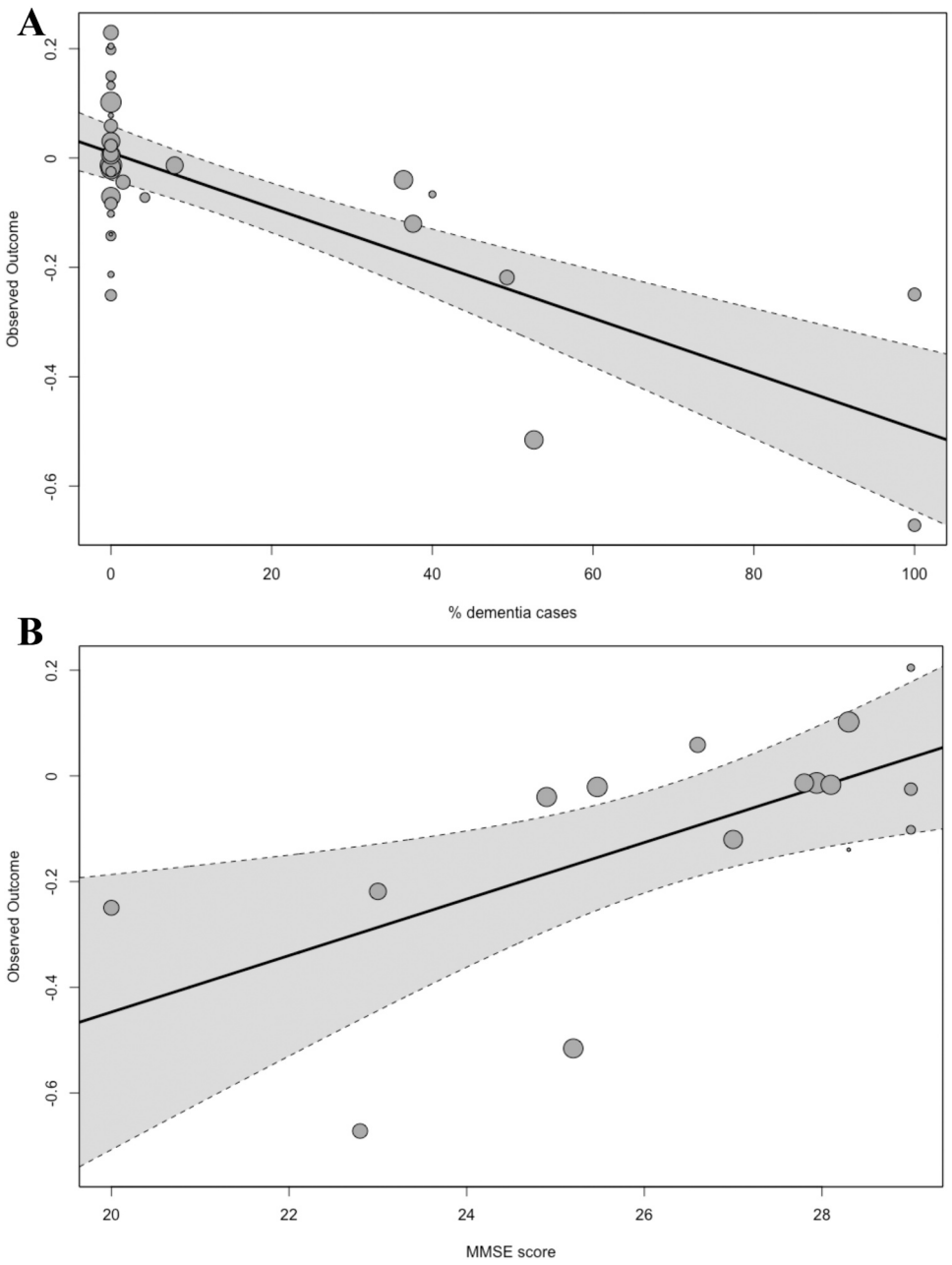

Fig. 3. Bubble plots showing changes in the association of glucose metabolism measures and DM status and amyloid-β for (A) dementia prevalence and (B) MMSE score (higher score means better performance). Size of circles represent weight of the studies. All studies reported dementia prevalence and 16 studies reported mean MMSE.

3.5. Sensitivity analyses

Excluding low quality studies resulted in excluding three amyloid studies. By excluding these studies, similarly no association of glucose metabolism measures and DM status with amyloid-β was found (r= −0.04, CI= −0.10 – 0.02, p= 0.20, k=30). Yet, meta-regression results on setting, prevalence of dementia, and MMSE score remained significant, while the effect of biserial correlation studies and DM prevalence on the association turned non-significant. No studies were excluded for the tau or time interval analyses. When considering CSF t-tau, we also found an association of higher glucose metabolism measures and DM status with higher levels of CSF t-tau biomarkers (r=0.13[0.03 – 0.24], p=0.02, k=10).

Two extreme outliers were indicated by the funnel plot in Supplementary figure 1a (of which one was also rated as low quality). These outlying findings could be explained by the different types of population used in these studies, including persons with vascular cognitive impairment (Groeneveld et al., 2019) or persons with AD dementia (Takenoshita et al., 2019). When excluding these outliers, we did not find an association of glucose metabolism and DM status with amyloid-β (p=0.37). In addition, the association with lower amyloid-β biomarkers in memory clinic studies (p=0.12) and studies using biserial correlation (p=0.60) turned non-significant. The moderating effects of dementia prevalence and MMSE scores remained significant. When excluding the PET study that only measured amyloid based on frontal cortex and posterior cingulate cortex (47), main results did not change (r=-0.06, CI [-0.13 – 0.01], p=0.08, k=32). Results also remained similar when only looking at glucose metabolism measures (r=-0.06, CI[-0.19 – 0.06], p=0.32, k=15) or PET studies (r=-0.04, CI[-0.14 – 0.05], p=0.36, k=19).

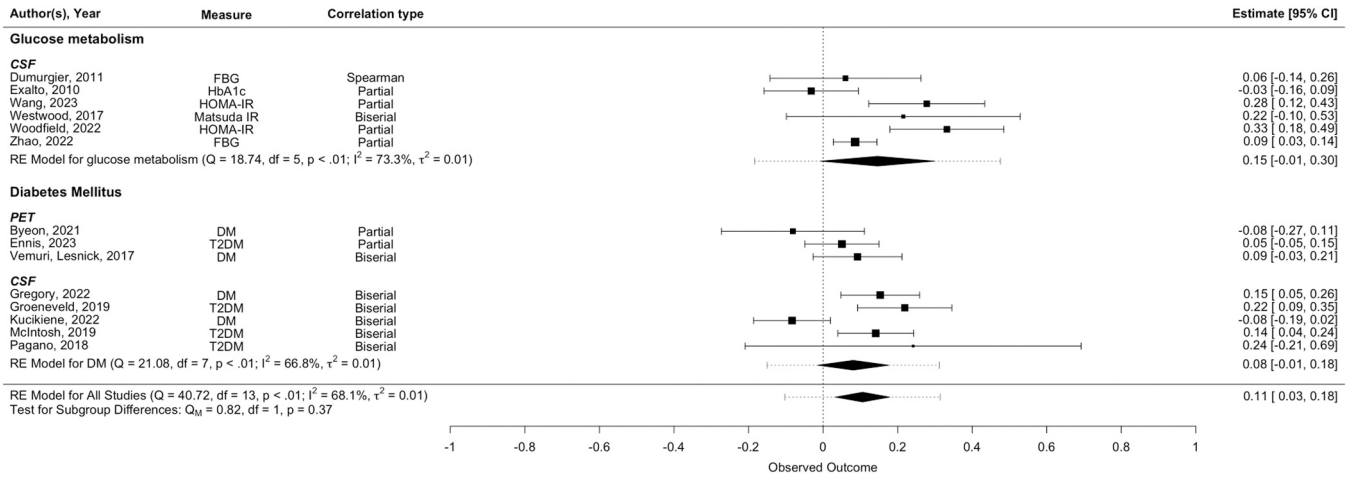

Fig. 4. Forest plot of meta-analysis on the association of glucose metabolism and DM status with tau (k=14). Stratified results are shown for glucose metabolism measures versus DM status. Results are grouped by biomarker modality (PET and CSF). Bars show correlation estimates with confidence intervals per study. Size of squares represents study weight (based on variance). The diamond represents the summary effect size with the dotted line representing the prediction interval. Columns show further details on which measure was used as predictor and which type of correlation was used as effect size. *DM* diabetes mellitus – mixed types, *FBG* fasting blood glucose, HbA1c glycated hemoglobin, *HOMA-IR* Homeostatic model assessment for insulin resistance, *T2DM* type 2 diabetes mellitus.

We repeated the meta-analysis in a subset of studies measuring both amyloid-β and tau within the same sample. Supplementary Fig. 3 shows the comparison of amyloid-β versus tau biomarkers. Results remained similar, showing an association of glucose metabolism measures and DM with higher tau but not amyloid-β biomarkers. This may suggest that the association with tau is independent from amyloid-β.

4. Discussion

Our meta-analysis showed that more impaired glucose metabolism and a diagnosis of DM were associated with higher tau biomarkers, while they were not clearly associated with amyloid-β biomarkers. Yet, in memory clinic studies or studies with higher dementia prevalence or lower global cognition scores, an association of more impaired glucose metabolism and DM with lower amyloid-β biomarkers was shown. The association between impaired glucose metabolism and DM with tau was specifically present in population studies. Together, these findings might suggest that impaired glucose metabolism and DM are associated with biomarkers of tau independent from amyloid-β.

We found that more impaired glucose metabolism and DM were associated with lower amyloid-β biomarkers in memory clinic studies or studies with a higher prevalence of dementia or lower global cognition. Earlier reviews mostly reported no association with amyloid-β measures assessed by PET or CSF (Biessels et al., 2020; Piri et al., 2019; Lu et al., 2018). Previous post-mortem studies similarly reported an association of DM with less AD pathology (Braak and CERAD stages) or no association between DM and AD pathology (Hadley et al., 2022). This suggests that DM is related to dementia and cognitive impairment through a different pathway than amyloid-β.

An explanation could be that DM, and especially the elevated levels of insulin in DM patients, might protect against amyloid-β. Earlier studies have shown that higher blood insulin levels are associated with less amyloid-β (Byun et al., 2017; Pekkala et al., 2020; O'Bryant et al., 2022), and that insulin administration slows AD progression (Kellar et al., 2021; de la Monte, 2017). Similar patterns are also found for studies assessing the link between BMI and AD biomarkers, where higher BMI has been associated with less amyloid-β (Hsu et al., 2016; Thirunavu et al., 2019). This could partly explain our findings, as type 2 DM often co-exists with increased BMI.

In contrast to our findings for amyloid-β, we found that more impaired glucose metabolism and DM were associated with higher tau biomarkers. Most studies measured p-tau in CSF, a biomarker specific to AD which usually goes paired with an increase in amyloid (Hampel et al., 2004). A possible explanation for this may be that impaired glucose metabolism and DM exacerbate tau accumulation in amyloid positive persons only (Ennis et al., 2023; Albrecht et al., 2020). It can however be argued whether the increase in tau constitutes AD pathology or might be DM-related tau independent from AD. All studies finding an association with p-tau, also found an association with less AD-specific t-tau. Some researchers suggest diabetes-related dementia as a separate entity, with normal amyloid-β but abnormal tau (Takenoshita et al., 2019). In line with this, a large cohort study using polygenic risk scores recently demonstrated that DM is not related to AD, but mainly to vascular dementia (Dybjer et al., 2023). This would suggest that, despite that DM and AD are often comorbid, they constitute independent disease processes. Animal cell studies have also suggested that insulin resistance and insulin-like growth factors drive neurodegeneration through other pathways than key AD pathology (Lane et al., 2017). Other suggested pathways are vascular brain injury, brain glucose metabolism, inflammation, oxidative stress, mitochondrial dysfunction, and glycation end products (Biessels et al., 2020; Verdile et al., 2015).

Our meta-analysis indicates an association of more impaired glucose metabolism and DM with higher tau biomarkers in population settings specifically. When tau accumulation in DM would represent non-AD pathology, the small effects at population level might disappear in memory clinic settings with the development of larger amounts of AD-related tau accumulation. Moreover, the association with tau was stronger in studies using an IR measure compared to other glucose metabolism measures. However, all three studies using IR were also population studies. Thus far, most studies have assessed tau in CSF, and therefore more research is necessary to assess whether there is a link between DM and tau on PET.

It is important to note that substantial heterogeneity between studies was observed. We can partly explain the heterogeneity by the different associations across different settings and cognitive impairment levels (dementia prevalence and global cognition). Future studies should further investigate whether other moderating factors, such as prediabetes stages, medication usage, DM duration and severity, whether DM is controlled or uncontrolled, blood glucose variability, and other vascular comorbidities may play a role. Previous studies demonstrated associations of prediabetes (but not DM) and untreated diabetes with amyloid-β accumulation (Luchsinger et al., 2020; McIntosh and Nation, 2019; de Bruijn and Ikram, 2014). Moreover, most studies only include white participants while metabolic markers and AD biomarkers are

possibly stronger in non-white ethnic groups (O'Bryant et al., 2022; Luchsinger et al., 2020).

4.1. Strengths and limitations

In this study, we were able to compile and summarize many studies and a large sample of participants on the relationship between glucose metabolism measures or DM status and key AD biomarkers. This however also brings some limitations, given potential differences in the sample selection (recruitment strategy and inclusion criteria), study design, and methodology used between the pooled studies. However, our analyses did not show differences between associations found for glucose metabolism versus DM status, or for the different modalities and methodologies used. The stronger association when using biserial correlation coefficients was driven by two outliers (Takenoshita et al., 2019; Groeneveld et al., 2019), both using biserial correlation, and disappeared when they were excluded. Another limitation could be that we included studies with mixed types of DM, rather than only T2DM. We however assume that our conclusions can only be generalized for T2DM, as this is the most common type of DM studied (Xu et al., 2018). Furthermore, we had to exclude several studies where non-effects were reported without the necessary metrics (Byun et al., 2017; Gomez et al., 2018; Honea et al., 2022; Rahman et al., 2020; Reed et al., 2012; Starks et al., 2015; Toledo et al., 2012; Haapalinna et al., 2018). This could have resulted in publication bias. Yet, Egger's test and funnel plots did not indicate high likelihood of publication bias in our analyses. As a relatively small number of studies reported findings regarding tau on PET and with a time interval between the glucose metabolism or DM status and amyloid-β, these results should be interpreted with caution. Future research should further explore whether glucose metabolism or DM status at mid-life might be associated with AD biomarker development at older age.

4.2. Conclusion and future directions

Our systematic review and meta-analysis findings suggest that DM and related measures are associated with higher tau biomarkers, but not with amyloid-β biomarkers. This suggests that DM is associated with biomarkers of tau and dementia through a different pathway than amyloid-β. While DM and AD are common comorbidities, they might thus reflect independent patterns of neuropathology. This is valuable for improving future diagnostics, prognostics, and potential treatment of patients with DM and AD.

Future studies assessing the association between glucose metabolism or DM status and tau, especially on PET, are needed to confirm our findings regarding tau. The link with newly developed AD blood biomarkers would additionally be an interesting target for future studies. Furthermore, as most current studies are cross-sectional, future prospective studies are warranted to assess how mid-life glucose metabolism and DM can impact late-life neuropathology. As a substantial heterogeneity was found between studies, it should also be explored how associations might change in certain subpopulations, such as different ethnic groups. Moreover, further research should explore potential differences in associations for prediabetes, and explore how factors as DM medication, its duration and severity, as well as related comorbidities, might affect the development of AD pathophysiology.

Author contributions

VG performed the systematic search, the meta-analysis, drafted the manuscript, and contributed to decisions on data extraction and quality rating. MR and JC contributed equally by being first and second reviewers for the systematic search, data extraction and quality rating. WV supported in statistical analysis. The project was executed under supervision of PJV, WJ, and SV. All co-authors critically reviewed and approved the manuscript.

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Appendix A. Search terms in PubMed and Embase with MeSh terms

PubMed

(insulin[mh] OR insulin*[tiab] OR ((blood[tiab] OR serum[tiab] OR plasma[tiab] OR fast*[tiab] OR level*[tiab] OR peripher*[tiab] OR tolerance[tiab] OR intolerance[tiab]) AND glucose[tiab]) OR blood glucose[mh] OR glycemi*[tiab] OR hyperglycemi*[tiab] OR hypoglycemi*[tiab] OR glycated hemoglobin A[mh] OR HbA1c[tiab] OR (glyc*[tiab] AND hemoglobin*[tiab]) OR glucose metabolism disorders [mh] OR diabetes mellitus[mh] OR diabet*[tiab] OR prediabet*[tiab]) AND (amyloid[mh] OR amyloid*[tiab] OR a-beta[tiab] OR abeta[tiab] OR plaque*[tiab] OR tau proteins[mh] OR tau[tiab] OR neurofibrillary tangle*[tiab]) AND (PET[tiab] OR positron-emission tomography[mh] OR positron emission tomography[tiab] OR CSF[tiab] OR cerebrospinal fluid[mh] OR cerebrospinal fluid[tiab]) AND (alzheimer disease[mh] OR alzheimer*[tiab] OR MCI[tiab] OR mild cognitive impairment[tiab] OR cognitive dysfunction[mh] OR SCD[tiab] OR cognitive decline[tiab] OR SCI[tiab] OR cognitive impairment*[tiab] OR subjective complain*[tiab] OR cognitive complain*[tiab] OR dementia[mh:noexp] OR dementia[tiab] OR aging[mh] OR elder*[tiab] OR cognitively healthy [tiab] OR cognitively normal[tiab] OR cognitive performance*[tiab] OR cognitive function*[tiab] OR cognitive assessment[tiab] OR normal cognition[tiab]) NOT (animals[mh] NOT humans[mh])

Embase

(exp insulin/ OR insulin*.ti,ab,kw. OR ((blood.ti,ab,kw. OR serum.ti,ab,kw. OR plasma.ti,ab,kw. OR fast*.ti,ab,kw. OR level*.ti,ab,kw. OR peripher*.ti,ab,kw. OR tolerance.ti,ab,kw. OR intolerance.ti,ab,kw.) AND glucose.ti,ab,kw.) OR exp glucose blood level/ OR glycemi*.ti,ab,kw. OR hyperglycemi*.ti,ab,kw. OR hypoglycemi*.ti,ab,kw. OR exp hemoglobin A1c/ OR HbA1c.ti,ab,kw. OR (glyc*.ti,ab,kw. AND hemoglobin*.ti,ab,kw.) OR exp disorders of carbohydrate metabolism/ OR exp diabetes/ OR diabet*.ti,ab,kw. OR prediabet*.ti,ab,kw.) AND (exp amyloid/ OR exp amyloid plaque/ OR exp amyloid beta protein/ OR amyloid*.ti,ab,kw. OR abeta.ti,ab,kw. OR a-beta.ti,ab,kw. OR plaque*.ti,ab,kw. OR exp tau protein/ OR tau.ti,ab,kw. OR neurofibrillary tangle*.ti,ab,kw. OR biomarker*.ti,ab,kw.) AND (PET.ti,ab,kw. OR exp positron emission tomography/ OR positron emission tomography.ti,ab,kw. OR CSF.ti,ab,kw. OR exp cerebrospinal fluid/ OR cerebrospinal fluid.ti,ab,kw.) AND (exp alzheimer disease/ OR alzheimer*.ti,ab,kw. OR MCI.ti,ab,kw. OR mild cognitive impairment.ti,ab,kw. OR exp mild cognitive impairment/ OR exp "cognitive defect"/ or exp "intellectual impairment"/ OR SCD.ti,ab,kw. OR cognitive decline.ti,ab,kw. OR SCI.

ti,ab,kw. OR cognitive impairment*.ti,ab,kw. OR subjective complain*.ti,ab,kw. OR cognitive complain*.ti,ab,kw. OR dementia/ OR dementia.ti,ab,kw. OR exp aging/ OR elder*.ti,ab,kw. OR cognitively healthy.ti,ab,kw. OR cognitively normal.ti,ab,kw. OR cognitive performance*.ti,ab,kw. OR cognitive function*.ti,ab,kw. OR cognitive assessment.ti,ab,kw. OR normal cognition.ti,ab,kw.) NOT ((exp animal/ or exp invertebrate/ or nonhuman/ or animal experiment/ or animal tissue/ or animal model/ or exp plant/ or exp fungus/) NOT (exp human/ or human tissue/))

Limit to conference abstracts

1 not 2

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105604.

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