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RESEARCH ARTICLE

The association of diabetes with Alzheimer's disease biomarkers and vascular burden across European aging and memory clinic cohorts

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Abstract

INTRODUCTION: It remains unclear whether diabetes mellitus (DM) is associated with Alzheimer's disease (AD) pathology and associated vascular burden.

METHODS: We included cognitively normal (CN), mild cognitive impairment (MCI), and dementia individuals. We assessed associations between DM and AD biomarkers (amyloid beta [Aβ], phosphorylated tau-181 [p-tau181], total tau [t-tau], and medial temporal atrophy [MTA]) and vascular burden (white matter hyperintensities, microbleeds) by logistic regression. Secondary analyses assessed associations between DM and profiles of Aβ combined with p-tau181/t-tau/MTA/white matter hyperintensity/microbleeds.

RESULTS: We included 5550 participants (65.8+-8.7 years, 8.7% DM). DM was associated with lower odds of abnormal AD biomarkers: Aβ in MCI (odds ratio [OR] = 0.70, 95% confidence interval [CI]: 0.51–0.95, $p = 0.02$) and dementia (OR = 0.44, 0.26–0.78, $p = 0.003$), and p-tau181 in dementia (OR = 0.64, 0.41–1.00, $p = 0.045$). Secondary analyses indicated associations of DM with abnormal t-tau (OR = 1.57, 1.00–2.46, $p = 0.048$) and MTA (OR = 1.96, 1.05–3.68, $p = 0.04$) only in CN individuals with normal Aβ.

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DISCUSSION: In cognitively impaired individuals, DM was associated with lower odds of Aβ pathology, whereas DM was associated with neurodegeneration markers in CN individuals without Aβ pathology.

KEYWORDS
diabetes mellitus, medial temporal atrophy (MTA), microbleeds, tau, amyloid beta, cerebrospinal fluid (CSF), elderly persons, magnetic resonance imaging (MRI), positron emission tomography (PET), white matter hyperintensity (WMH)

Highlights

- Diabetes mellitus (DM) was associated with lower odds of amyloid beta (Aβ) and phosphorylated tau (p-tau) pathology across clinical populations.
- DM was associated with total tau and medial temporal atrophy in cognitively normal individuals without Aβ pathology.
- DM may be associated with dementia through neurodegenerative pathways other than Alzheimer's disease.

1 | BACKGROUND

Alzheimer's disease (AD) constitutes the majority of dementia cases and increases steadily in prevalence across Europe.[1] AD often co-occurs with cardiovascular and metabolic diseases, such as diabetes mellitus (DM). Many studies have indicated associations of DM, hyperglycemia, and insulin resistance with worse cognitive performance and cognitive decline,[2,3] and increased risk of developing AD dementia.[4] Moreover, it has been suggested that AD and DM share similar mechanisms of insulin resistance, and patterns of vascular burden and atrophy, in the brain.[5–7] Nevertheless, the relationship between DM and AD pathology and associated vascular burden remains unclear. This knowledge is particularly important for understanding the etiology underlying AD.

AD is typically characterized by amyloid beta (Aβ) and tau pathology, which can be measured through biomarkers.[8] Commonly used biomarkers include Aβ42 in cerebrospinal fluid (CSF) or global Aβ on positron emission tomography (PET), and phosphorylated tau (p-tau) in CSF. Neurodegeneration markers less specific to AD include CSF total tau (t-tau) and medial temporal atrophy (MTA). Commonly observed vascular co-pathologies with AD are white matter hyperintensities (WMHs) and microbleeds, which are detectable with magnetic resonance imaging (MRI).

Few studies have assessed the relationship between DM and specific AD biomarkers, and results have been inconclusive.[6,9,10] These inconsistencies may be due to differences in study populations, cognitive status, and definitions of DM. Associations of DM with brain atrophy and vascular burden, such as WMHs, have been shown repeatedly in population studies.[6,11,12] However, it remains unclear if these changes are also observed in aging and memory clinic settings and whether these pathologies reflect changes related to AD.

Our study aimed to assess whether DM is associated with (1) AD-related biomarkers (i.e., Aβ, p-tau181, t-tau, and MTA), and (2) markers of vascular burden on MRI (i.e., WMHs and microbleeds) in memory clinic and aging cohorts, including participants across the AD clinical spectrum, that is, cognitively normal (CN), mild cognitive impairment (MCI), and dementia. As secondary analysis, we explored the association of DM with biomarker profiles based on Aβ abnormality in combination with the presence of tau, MTA, or vascular burden to assess whether DM is differently associated with pathologies across stages of AD based on amyloid status.

2 | METHODS

2.1 | Participants

We performed this study as part of the Prevention and Remediation of Insulin Multimorbidity in Europe (PRIME) project, exploring the role of insulin signaling in brain disorders. We included 5550 participants from 10 existing aging and memory clinic cohorts in Europe: Amsterdam Dementia Cohort (ADC, $n = 2{,}286$),[13] BioBank Alzheimer Center Limburg (BB-ACL, $n = 156$),[14] European Medical Information Framework (EMIF) PreclinAD ($n = 199$)[15] and EMIF 90+ ($n = 100$)[16] in The Netherlands, Czech Brain Aging Study (CBAS, $n = 227$) in the Czech Republic,[17] Gipuzkoa Alzheimer Project (GAP, $n = 192$) in Spain,[18] CLEMENS ($n = 185$) in Switzerland,[19] Metabolic Syndrome in Men (METSIM, $n = 58$) in Finland,[20] and the European multicohort studies European Medical Information Framework (EMIF) Multimodal Biomarker Discovery Study (MBD, $n = 381$)[21] and European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS, $n = 1766$).[22] Overlapping participants across cohorts were

RESEARCH IN CONTEXT

1. **Systematic review**: Many studies have demonstrated an association between diabetes mellitus (DM) and a clinical diagnosis of Alzheimer's disease (AD) dementia. To date, it remains largely unclear whether DM is also associated with underlying AD biomarkers.
2. **Interpretation**: Our study showed that DM is consistently associated with lower odds of amyloid-β in individuals with dementia, whereas DM was associated with neurodegeneration markers in cognitively normal individuals with normal amyloid-β. These findings suggest that DM may be associated with cognitive decline through processes of neurodegeneration different from amyloid-β pathways.
3. **Future directions**: For improving diagnostic and prognostic procedures, further research exploring the underlying mechanisms behind the associations between DM, neurodegeneration, and cognitive decline is necessary.

excluded. Further details on inclusion and definitions across cohorts are provided in Table S1.

Participants were included if data were available on DM diagnosis or use of antidiabetics from which a DM diagnosis could be inferred. In addition, at least one AD biomarker measure of Aβ or tau had to be available, that is, CSF Aβ42, amyloid-PET, CSF p-tau181, or t-tau. No additional inclusion or exclusion criteria were considered.

All cohort studies were approved by the local ethics committees and conducted according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants gave written informed consent at their respective sites. As only existing data were used, this study was not subject to approval by the medical ethical committee (METC) at the Maastricht University Medical Center (MUMC+), declaration number 2020-2481. The research project was approved by the MUMC+ Board of Directors.

2.2 | Clinical assessment

All participants were assessed through standard protocol procedures at each site, including neurological and psychiatric assessment, medical history, and neuropsychological examination. The presence of DM was indicated by medical history or self-report (n = 5524), or by DM medication use (i.e., insulin or oral glucose lowering drugs; n = 5086). The used definitions for each cohort are described in S1. Although we could not differentiate for diabetes type (i.e., type 1 or 2), the sample primarily reflects type 2 DM, as this constitutes the majority of cases, especially at an older age.[23] The presence of cardiometabolic comorbidities (i.e., obesity, hypertension, hypercholesterolemia) was based on medical history.

Cognitive status was established in each cohort according to standard study protocols. Definitions per cohort are described in Table S1. Overall, individuals were classified as MCI if showing impairment on neuropsychological tests[24–26] and/or the Clinical Dementia Rating scale (CDR = 0.5).[27] In each cohort, a clinical diagnosis of dementia was defined by either the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRA),[28] European Federation of Neurological Societies-Eurpean Neurological Society (EFNS-ENS),[29] or Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria diagnosed by a professional. Across all cohorts, most or all dementia cases concerned AD dementia. Individuals with neuropsychological scores within the normal range, and thus not classified as MCI or dementia, were classified as CN.

2.3 | Assessment of AD biomarkers and vascular burden

2.3.1 | CSF measures

Nine cohorts (all except EMIF 90+) determined Aβ42 (n = 5205), p-tau181 (n = 5204), and t-tau (n = 5191) levels from CSF using lumbar puncture. For Innotest enzyme-linked immunosorbent assays (ELISAs), we used cutoffs calculated by Gaussian mixture modeling to define Aβ abnormality, as these cutoffs are shown to better capture abnormal levels of Aβ over time.[30,31] For other Aβ assays, cutoffs were locally defined per cohort.[30,32] We used predefined and local p-tau181 and t-tau cutoffs for all cohorts. Data availability for biomarkers per cohort are reported in Table S2. Biomarker modality, cutoffs, and assays are further specified in Table S3.

2.3.2 | PET measures

Three cohorts measured Aβ by both PET scans and CSF (ADC, CBAS, and EMIF PreclinAD). One cohort (EMIF 90+) measured Aβ on PET only. Aβ abnormality was assessed through visual assessment according to local study protocols. We used PET measures if CSF measures were unavailable or unreliable (n = 342). The modality and tracers are specified in Table S3.

2.3.3 | MRI measures

MRI measures were available in eight cohorts (ADC, BB-ACL, CBAS, GAP, EMIF MBD, EMIF Preclin-AD, EMIF 90+, and EPAD). We used 1.5T or 3T MRI scanners and validated semi-qualitative visual rating scales to assess MTA and WMHs in all eight cohorts. The Scheltens scale was used to define MTA severity, with a score ranging from 0–4[33] and is based on three brain structures: the choroid fissure, temporal horn of the lateral ventricle, and hippocampus. The Fazekas scale was used to measure severity of WMHs, with a score

ranging from 0–3.[34] The total count of microbleeds was determined in seven cohorts (abovementioned minus GAP, $n = 4127$). The presence of MTA and WMHs was defined by scores ≥2.[35,36] The presence of microbleeds was defined by having at least 1 (≥1) microbleed. Details on the availability of MRI measures per cohort are described in Table S2.

2.4 | *APOE ε4* carriership

For nine cohorts (all except CLEMENS), data on apolipoprotein E ε4 (*APOE ε4*) carriership was available for most participants ($n = 5150$). *APOE ε4* carriership was defined by carrying at least one e4 allele (yes/no). Details on the availability of *APOE ε4* carriership per cohort are described in S2.

2.5 | Profiles of Aβ with other AD and vascular burden markers

For secondary analyses, we classified participants into different biomarker profiles based on Aβ abnormality in combination with abnormality of one other AD biomarker (p-tau181, t-tau, or MTA) or vascular burden marker (WMHs or microbleeds), with a plus (+) indicating abnormal biomarker levels, and a minus (–) indicating normal biomarker levels.

2.6 | Statistical analyses

Pearson chi-square test and one-way analysis of variance (ANOVA) were used to compare baseline characteristics between cognitive status groups (i.e., CN, MCI, and dementia). As main analyses, separate logistic regression models were used to assess the associations between DM as predictor and dichotomized (normal/abnormal) AD biomarkers (Aβ, p-tau181, t-tau, and MTA) or vascular burden (WMHs and microbleeds) as outcome measures. Analyses were stratified for cognitive status, and all models were adjusted for age, sex, and cohort. In additional models, we added *APOE ε4* carriership and common vascular comorbidities (obesity, hypertension, and hypercholesterolemia) as covariates. For secondary analyses, we used multinomial regression to explore the association of DM with profiles of Aβ combined with p-tau181, t-tau, MTA, WMHs, or microbleeds, to explore whether DM was differently associated with other AD or vascular biomarkers in the absence or presence of Aβ (indicating a more advanced AD stage). Reference categories were defined by normal Aβ (A) as well as by normal levels of the other AD or vascular biomarkers. Differences between the other subgroups were also tested.

In sensitivity analyses, we repeated the Aβ analyses in cohorts with only CSF measures (excluding EMIF 90+ with only PET measures) and assessed the effect of DM medication use through stratifying for medication use. In addition, we repeated all main analyses with DM x cohort interactions to explore differences in associations per cohort. All analyses were performed using R, version 4.3.2 (2023), with significance levels set at $p < 0.05$. *p*-values after false discovery rate (FDR) corrections for multiple testing are additionally reported for all analyses.

3 | RESULTS

3.1 | Demographics

We included 5550 participants (49% women) with a mean age of 65.8 (SD = 8.7) years. Overall, 2686 individuals (48%) were classified as CN, 1524 (27%) individuals as MCI, and 1340 (24%) individuals were diagnosed with dementia. Participant characteristics stratified for cognitive status are described in Table 1. *APOE ε4* carriership and AD biomarker abnormality differed between all cognitive groups (CN < MCI < dementia; all *p*'s < 0.001). Vascular burden was more prevalent in MCI as compared to CN (WMH: $p < 0.001$, microbleeds: $p = 0.004$). In total, 541 participants (8.7%) were diagnosed with DM, with the highest prevalence in the MCI group (13%) as compared to the CN (7.8%) and dementia (10%) groups. Notably, individuals with dementia had cardiometabolic comorbidities less often than the MCI group (obesity: $p = 0.02$, hypertension: $p < 0.001$, hypercholesterolemia: $p < 0.001$). Patient characteristics stratified by DM status are described in Table S4 and characteristics stratified by cohort are listed in Table S5.

Among CN individuals, 61% had both normal amyloid and p-tau markers, 19% had only abnormal amyloid, 12% had only abnormal p-tau, and 8% had both abnormal amyloid and p-tau. In the MCI group, 30% had both normal amyloid and p-tau markers, 25% had only abnormal amyloid, 12% had only abnormal p-tau, and 33% had both abnormal amyloid and p-tau. In the dementia group, 4% had both normal amyloid and p-tau markers, 17% had only abnormal amyloid, 3% had only abnormal p-tau, and 76% had both abnormal amyloid and p-tau. Overall, p-tau and t-tau were overlapping in 92% of the cases (55% with normal p-tau and t-tau, 37% with abnormal p-tau and t-tau).

3.2 | Associations of DM with AD biomarkers and vascular burden

Results on the associations of DM with AD biomarkers and MRI vascular burden are shown in Table 2 and Figure 1. In the CN group, no associations between DM and AD biomarkers or vascular burden markers were found. In the MCI and dementia groups, we found that individuals with DM had lower odds of abnormal Aβ as compared to normal Aβ (odds ratio [OR] = 0.70, $p = 0.02$ and OR = 0.44, $p = 0.003$, respectively). In the dementia group, individuals with DM also had lower odds of abnormal p-tau181 as compared to normal levels of p-tau181 (OR = 0.64, $p = 0.045$). No associations were found between DM and t-tau, MTA, WMHs, or microbleeds in the MCI and dementia groups. The odds distributions for each association are visualized in Figure S1.

TABLE 1 Participant characteristics stratified by cognitive status.

Variables	*N*	CN *N* = 2686	MCI *N* = 1524	Dementia *N* = 1340
Age, years, mean (SD)	5550	64.3 (8.9)[b,c]	67.8 (8.2)[a,c]	66.5 (8.3)[a,b]
Education, years, mean (SD)	5512	13.9 (3.9)[b,c]	12.5 (3.8)[a,c]	11.1 (3.5)[a,b]
Female, *n* (%)	5550	1,361 (51%)[b]	677 (44%)[a,c]	709 (53%)[b]
MMSE score, mean (SD)	5467	28.6 (1.5)[b,c]	26.7 (2.6)[a,c]	20.6 (5.1)[a,b]
APOE ε4 carrier, *n* (%)	5150	934 (36%)[b,c]	651 (50%)[a,c]	805 (65%)[a,b]
Abnormal CSF/PET Aβ, *n* (%)	5547	724 (27%)[b,c]	869 (57%)[a,c]	1,237 (92%)[a,b]
Abnormal CSF p-tau, *n* (%)	5204	490 (20%)[b,c]	657 (45%)[a,c]	1,006 (79%)[a,b]
Abnormal CSF t-tau, n (%	5191	403 (16%)[b,c]	680 (47%)[a,c]	1,029 (81%)[a,b]
Abnormal MTA, *n* (%)	4368	258 (11%)[b,c]	299 (27%)[a,c]	402 (47%)[a,b]
Abnormal WMH, *n* (%)	4,484	381 (16%)[b,c]	318 (27%)[a]	226 (25%)[a]
Microbleeds, *n* (%)	4,127	361 (16%)[b,c]	225 (21%)[a]	182 (22%)[a]
DM, *n* (%)	5,550	209 (7.8%)[b,c]	195 (13%)[a,c]	137 (10%)[a,b]
Diabetes medication, *n* (%)	5086	161 (6.9%)[b]	170 (12%)[a,c]	110 (8.3%)[b]
Obesity, *n* (%)	5186	430 (17%)[b,c]	161 (12%)[a,c]	116 (9.2%)[a,b]
Hypertension, *n* (%)	5502	766 (29%)[b]	539 (36%)[a,c]	366 (28%)[b]
Hypercholesterolemia, *n* (%)	5457	653 (25%)[c]	406 (27%)[c]	187 (14%)[a,b]

Note: Abnormal Aβ was defined by either CSF or PET, depending on each cohort.
Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; CN, cognitively normal; CSF, cerebrospinal fluid; DM, diabetes mellitus; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MTA, medial temporal atrophy; p-tau, phosphorylated tau; PET, positron emission tomography; t-tau, total tau; WMH, white matter hyperintensity.
ANOVA indicated that CN, MCI, and dementia groups differed significantly on all variables (all *p*'s < 0.001). Post hoc analysis assessed group differences:
[a]Significantly different from CN.
[b]Significantly different from MCI.
[c]Significantly different from dementia.

TABLE 2 Associations of DM with AD biomarkers and vascular burden.

	CN			MCI			Dementia		
AD	***OR* (CI)**	***p***	***p FDR***	***OR* (CI)**	***p***	***p FDR***	***OR* (CI)**	***p***	***p FDR***
Aβ	0.77 0.54 – 1.08	0.135	0.248	0.70 0.51 – 0.95	**0.023**	0.138	0.44 0.26 – 0.78	**0.003**	**0.018**
p-tau	1.27 0.87 – 1.84	0.207	0.248	0.80 0.58 – 1.12	0.194	0.388	0.64 0.41 – 1.00	**0.045**	**0.135**
t-tau	1.36 0.92 – 2.00	0.116	0.248	0.73 0.53 – 1.02	0.063	0.189	0.72 0.46 – 1.14	0.154	0.308
MTA	1.48 0.84 – 2.52	0.165	0.248	1.24 0.81 – 1.90	0.315	0.450	0.78 0.46 – 1.30	0.342	0.410
Vascular									
WMHs	0.78 0.48 – 1.24	0.314	0.314	1.03 0.68 – 1.54	0.896	0.896	0.71 0.38 – 1.27	0.260	0.390
Microbleeds	0.68 0.41 – 1.07	0.109	0.248	0.81 0.49 – 1.28	0.375	0.450	0.91 0.48 – 1.65	0.776	0.776

Note: In bold associations that are statistically significant. All analyses were adjusted for age, sex, and cohort.
Abbreviations: Aβ, Amyloid-beta, CN, cognitively normal; CI, confidence interval; FDR, false discovery rate, MCI, mild cognitive impairment; MTA, medial temporal atrophy as defined by Scheltens score, OR, odds ratio; p-tau, phosphorylated tau; t-tau, total tau; WMH, white matter hyperintensity as defined by Fazekas score.

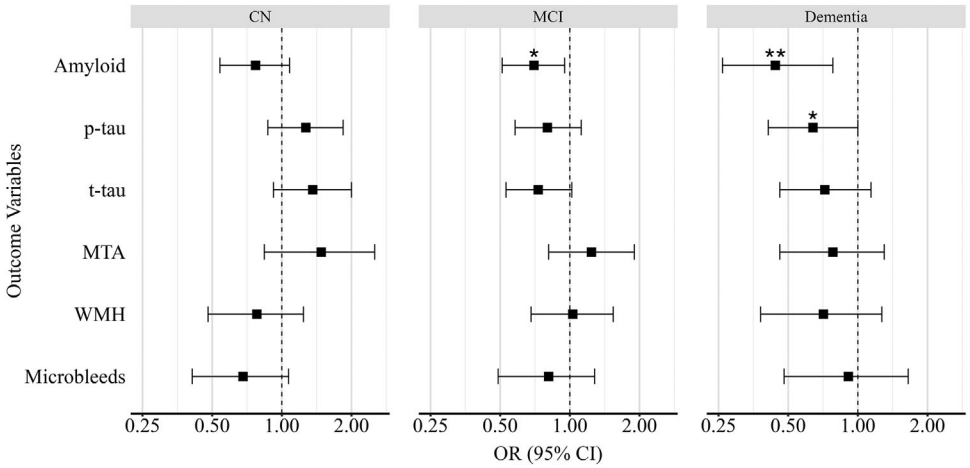

FIGURE 1 Associations of DM with AD and vascular biomarkers. Shown are the ORs from the logistic regression analyses assessing the association of DM with AD biomarkers (abnormal Aβ, p-tau181, t-tau, or MTA) and vascular burden (WMH or microbleeds). All analyses were adjusted for age, sex, and cohort. Aβ, amyloid beta; AD, Alzheimer's disease; CN cognitively normal, DM, diabetes mellitus; MCI, mild cognitive impairment; MTA, medial temporal hypertrophy; OR, odds ratio; p-tau, phosphorylated tau; t-tau, total tau; WMH, white matter hyperintensity. $^{**}p < 0.01$, $^{*}p < 0.05$. Unadjusted for multiple comparisons.

After adjusting for *APOE* ε4 carriership and cardiometabolic comorbidities (obesity, hypertension, and hypercholesterolemia), or FDR correction for multiple comparisons, only the association between DM and lower odds of abnormal Aβ in the dementia group remained significant. Results of the adjusted models are shown in Table 2 (FDR correction) and Table S6 (adjusted models). Table S7 shows ORs of all covariates included in the last model.

3.3 | Associations of DM with profiles of Aβ in combination with tau, MTA, and vascular burden markers

Secondary analyses assessed associations of DM with different profiles of Aβ in combination with one other biomarker being p-tau181, t-tau, MTA, WMHs, or microbleeds, as shown in Table 3. Of interest, in CN individuals with normal Aβ, DM was associated with higher odds of abnormal t-tau (OR = 1.57, 95% CI: 1.00–2.47, $p = 0.048$) or MTA (OR = 1.96, 95% CI: 1.05–3.68, $p = 0.04$), as compared to individuals with normal levels of both Aβ and the other biomarker. These associations were not found in CN individuals with abnormal Aβ. No associations of DM with profiles of Aβ in combination with p-tau181, WMHs, or microbleeds were found.

In MCI, DM was associated with a lower odds of having abnormal Aβ and p-tau181 (OR = 0.60, 95% CI: 0.39–0.91, $p = 0.02$) or abnormal Aβ and t-tau (OR = 0.56, 95% CI: 0.37–0.84, $p = 0.01$) as compared to persons with normal levels of both Aβ and p-tau181/t-tau. DM was also not associated with having only abnormal Aβ, p-tau181, or t-tau. We did not find associations of DM with profiles of Aβ in combination with MTA, WMHs, or microbleeds.

In individuals with dementia, DM was associated with a lower odds of having abnormal Aβ regardless of p-tau181, t-tau, or WMH status, as compared to persons with both normal Aβ and normal p-tau181/t-tau/WMHs (see Table 3; A+ p-tau+ vs A− p-tau-: OR = 0.29, $p < 0.001$, A+ p-tau- vs A− p-tau-: OR = 0.38, $p = 0.01$, A+ t-tau+ vs A− t-tau-: OR = 0.32, $p = 0.003$, A+ t-tau- vs A− t-tau-: OR = 0.37, $p = 0.02$, A+ WMH+ vs A− WMH-: OR = 0.32, $p = 0.02$, and A+ WMH- vs A− WMH-: OR = 0.44, $p = 0.048$). Most associations were attenuated after adjustment or FDR correction for multiple comparisons, as presented in Table 3.

Other significant differences between the profile groups are listed in Table S8. Generally, these associations similarly showed that DM was associated with a lower odds of having abnormal Aβ as compared to groups with normal Aβ. In addition, in CN individuals, DM was associated with a higher odds of only abnormal p-tau181, t-tau, or MTA, as compared to only abnormal Aβ.

3.4 | Sensitivity analyses

When the main analyses in cohorts using only CSF measures of Aβ were repeated (i.e., excluding 342 individuals with PET measures), the association between DM and Aβ remained similar in the MCI group (OR = 0.66, 95% CI: 0.48–0.91, $p = 0.011$) and dementia group (OR = 0.41, 95% CI: 0.24–0.71, $p = 0.001$).

We additionally explored whether DM medication use (i.e., insulin or oral glucose–lowering drugs) changed the association of DM with AD biomarkers and vascular burden. Results did not differ between individuals using DM medication ($n = 441$) as compared to those not using DM medication ($n = 85$).

Logistic regression analyses including interactions with each cohort showed variability across cohorts in the strength of the identified associations of DM with AD biomarkers and vascular burden. The comparison of odds of individuals with versus without DM between cohorts is shown in Figure S2.

TABLE 3 Associations of DM with different profiles of AD and vascular biomarkers.

	CN			MCI			Dementia		
	N	*OR* (CI)	*p*	*N*	*OR* (CI)	*p*	*N*	*OR* (CI)	*p*
A– p-tau- vs	1508	1.27	0.292	441	1.12	0.636	51	0.56	0.269
A– p-tau+	295	0.82 – 1.96	0.106	177	0.69 – 1.82	0.381	44	0.20 – 1.56	**0.011**[b,c]
A+ p-tau–	480	0.70	0.911	357	0.82	**0.016**[b]	211	0.38	**<0.001**[a,b,c]
A+ p-tau+	195	0.45 – 1.08		480	0.53 – 1.27		962	0.18 – 0.80	
		1.03			0.60			0.29	
		0.59 – 1.82			0.39 – 0.91			0.14 – 0.58	
A– t-tau- vs	1,567	1.57	**0.048**[c]	444	0.88	0.614	46	0.70	0.486
A– t-tau+	237	1.00 – 2.47	**0.292**	174	0.53 – 1.45	**0.180**	49	0.26 – 1.89	**0.022**[b,c]
A+ t-tau–	499	0.80	0.744	330	0.74	**0.006**[a,b]	191	0.37	**0.003**[a,b,c]
A+ t-tau+	166	0.52 – 1.21		506	0.48 – 1.15		980	0.16 – 0.87	
		0.90			0.56			0.32	
		0.48 – 1.70			0.37 – 0.84			0.15 – 0.67	
A– MTA– vs	1,584	1.96	**0.035**[c]	400	1.29	0.391	28	1.02	0.980
A– MTA+	161	1.05 – 3.68	0.784	116	0.72 – 2.32	0.089	29	0.19 – 5.59	0.734
A+ MTA–	547	0.95	0.687	415	0.68	0.504	433	0.80	0.451
A+MTA+	97	0.65 – 1.39		183	0.44 – 1.06		373	0.22 – 2.94	
		0.83			0.82			0.60	
		0.34 – 2.02			0.46 – 1.46			0.16 – 2.26	
A– WMH–	1,527	0.65	0.155	405	1.35	0.295	50	0.68	0.646
vs	246	0.35 – 1.18	0.175	124	0.77 – 2.36	0.489	17	0.13 – 3.51	**0.048**
A– WMH+	513	0.76	0.667	441	0.86	0.194	621	0.44	**0.018**[b]
A+ WMH–	135	0.50 – 1.13		194	0.56 – 1.32		209	0.19 – 0.99	
A+ WMH+		0.86			0.68			0.32	
		0.44 – 1.70			0.38 – 1.22			0.12 – 0.82	
A– V^{MB}– vs	1,341	0.59	0.084	426	0.69	0.312	47	0.66	0.724
A– MB+	242	0.32 – 1.07	0.430	82	0.33 – 1.43	0.063	11	0.07 – 6.45	0.262
A+ MB–	495	0.85	0.480	443	0.67	0.167	605	0.59	0.279
A+ MB+	119	0.57 – 1.27		143	0.45 – 1.02		171	0.23 – 1.49	
		0.77			0.65			0.56	
		0.37 – 1.59			0.35 – 1.20			0.20 – 1.60	

Note: Persons without any AD or vascular burden biomarkers present were used as reference group. + indicates abnormality of markers, whereas – indicates normal biomarkers. All analyses were adjusted for age, sex, and cohort. Bold text indicates associations that are statistically significant.

Abbreviations: A, amyloid; AD, Alzheimer's disease; *APOE*, apolipoprotein E; CN, cognitively normal; CI, confidence interval; FDR, false discovery rate; MB, microbleed; MCI, mild cognitive impairment; MTA, medial temporal atrophy; OR, odds ratio; p-tau, phosphorylated tau; t-tau, total tau; WMH, white matter hyperintensity.

[a]Remains significant after FDR correction.

[b]Remains significant after adjustment for *APOE* ε4 carriership.

[c]Remains significant after adjustment for cardiometabolic comorbidities (obesity, hypertension, and hypercholesterolemia).

4 | DISCUSSION

In this study, we demonstrated that DM status is associated with a lower odds of Aβ and p-tau181 abnormality in individuals with dementia, and, to a lesser extent, with a lower odds of Aβ abnormality in MCI. Moreover, in CN individuals with normal levels of Aβ, DM was associated with a higher odds of neurodegeneration (abnormal t-tau and MTA). DM was not associated with MRI markers of vascular burden. These results suggest that DM is not associated with Aβ pathology but may be associated with other neurodegenerative pathways involving t-tau and MTA.

We found that DM was consistently associated with a lower odds of Aβ abnormality in individuals with dementia, independent from other AD and vascular biomarkers. This finding is in line with our recent meta-analysis demonstrating an association of DM and impaired glucose metabolism with decreased Aβ pathology.[37] This reversed association was observed only for memory clinic studies, and more strongly in study samples with a higher prevalence of dementia and lower cognition scores. This reversed association could be explained by an association of DM with non-AD dementia but not AD dementia. What seems an inverse association might reflect persons in the dementia group with other diabetes-related or vascular pathologies rather than Aβ. The fact that we did not find associations of DM with vascular pathologies might be explained by co-occurring vascular burden patterns in persons with DM and persons without DM but abnormal amyloid. Recent cohort and polygenic risk score studies similarly suggest that type 2 DM is not associated with AD dementia but rather with other types of dementia such as vascular dementia.[38,39] Another systematic reviews similarly indicates that DM is not associated with post-mortem AD pathology.[40] It is important to note is that even

though DM might not be linked to AD, it might influence the cumulative clinical progression to (AD) dementia.

Moreover, we found that DM status was associated with markers of neurodegeneration, t-tau and MTA, but only in CN individuals with normal Aβ biomarkers. The subtle association between DM and neurodegeneration was diluted in clinical populations. To our knowledge, this is the first study to emphasize that neurodegeneration in DM takes place at a relatively early stage and is not induced through pathways involving Aβ pathology. This is in line with our previous work, where we found associations between DM and tau (CSF p-tau, t-tau, and PET temporal tau) but not Aβ pathology.[37,41] Associations with p-tau and t-tau were more often found in population studies as compared to memory clinic studies, corresponding to our current findings for individuals with normal cognition. These findings underscore the importance of assessing associations in different settings and across different ages. Longitudinal studies might help exploring trajectories of vascular versus AD biomarker changes. Similarly, vascular risk in general, as measured by the Framingham general cardiovascular risk score, has been shown previously to be associated with p-tau and t-tau but not Aβ pathology.[42] Although similar patterns of brain insulin resistance are observed in DM and AD,[5,7] it has been suggested that insulin resistance in AD drives neurodegeneration through pathways other than Aβ pathology.[43] Different pathways could involve inflammation, brain glucose metabolism, brain insulin resistance, oxidative stress, or mitochondrial dysfunction.[44]

Although clear associations have been shown in previous studies,[6,11,12] we did not observe associations of DM with vascular burden and only found associations with neurodegeneration for Aβ-normal individuals. This could be explained by the lower prevalence of DM and vascular disease in our study sample, as mostly memory clinic populations with a focus on AD were included. The dementia group most likely included a high frequency of AD patients, possibly inducing selection bias regarding vascular contributions. In ADC, the largest cohort in our study, similar results were found.[45] Generally, studies have predominantly indicated clear associations of type 2 DM with lacunae and infarcts,[6] which were not measured in our study. In addition, previous studies typically involved healthy mid-life participants, whereas our study participants were on average older and mostly included clinical populations. This underscores the importance of exploring differences across settings and age.

The role of DM medication use should be further explored in future studies. Assessing the effects of DM medication use is usually complicated by the fact that almost all individuals diagnosed with DM use medication. Earlier studies have shown, however, that insulin or metformin use may slow the progression to AD dementia,[46,47] and that only untreated DM is associated with increased Aβ pathology.[48]

4.1 | Strengths and limitations

Through the unique collaboration between multiple memory clinic and aging cohorts we were able to assess the association of DM with AD biomarkers and vascular burden on a large scale and across different cognitive groups. Although data pooling brings many advantages such as larger sample sizes and power, it also comes with limitations. We could not consider type of dementia, as not all cohorts provided this information. We assume, however, that most individuals were diagnosed with AD, as most cohorts focused on the AD continuum and this is the most common type of dementia. For the same reason, DM type, duration, and severity could not be considered. In addition, the Aβ42/40 ratio might have slightly lower diagnostic accuracy than Aβ42 alone. Another limitation is that not all cohorts used the same inclusion criteria, definitions for cognitive status and DM, and biomarker measurement methods (as shown in Tables S1 and S3), which could explain differences in associations between the cohorts as shown in the sensitivity analysis. However, our analyses partly corrected for this by including demographics and cohort as covariates. Although sample sizes differed across the different sub-analyses due to differences in data availability per cohort, the results of this study remained mostly consistent throughout our secondary analyses. Associations of DM with non-AD neurodegeneration and vascular burden markers may be underestimated. Vascular contributions may be relatively low, as our study sample focused largely on individuals within the AD continuum. The prevalence of DM was relatively low as compared to the general elderly population in Europe, estimated at above 15% in persons 50 years of age or older.[49] In addition, we used only MRI visual rating scales. Although these are used in routine clinical practice, visual rating scales may be less sensitive as compared to volumetric MRI measures. In addition, localization of vascular burden, especially microbleeds, would provide much more information. Vascular measures such as lacunae and infarcts would probably also help capturing vascular consequences of DM.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Our study showed that DM is consistently associated with lower odds of Aβ in individuals with dementia, whereas DM was associated with neurodegeneration markers of t-tau and MTA in CN individuals with normal Aβ. These findings suggest that DM may be associated with cognitive decline through processes of neurodegeneration different from Aβ pathways. This supports the hypothesis that DM is associated mainly with causes of dementia other than AD. This knowledge is particularly relevant for improving diagnostic procedures as well as prevention strategies in the future.

Future studies should explore associations of metabolic markers (i.e., plasma glucose, hemoglobin A1c [HbA1c], and insulin resistance) with DM, as well as possible mediating effects of vascular risk factors (such as body mass index, blood pressure, and cholesterol level) on the association between DM and neurodegenerative markers. This could provide relevant insights in the mechanisms underlying the association between DM and dementia. As heterogeneous results are found across studies, future studies should explore possible differences between populations (e.g., diagnostic groups, age groups, but also multi-ethnic and variable socioeconomic populations) and changes of biomarkers

and vascular burden over time. Moreover, future prognostic procedures could be improved through examining whether DM and AD biomarkers contribute independently or synergistically to cognitive decline and dementia.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants provided written informed consent at their respective study sites.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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