Effects of the presence of diabetes on the progression of Alzheimer's disease measured through biomarkers: retrospective cohort study

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This modest achievement is dedicated to them.

Eun Woo Kim

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ABSTRACT

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Background: The shared comorbidities such as insulin resistance, promotion of inflammatory responses, and increased oxidative stress between diabetes mellitus (DM) and Alzheimer's Disease (AD) pathology would indicate a relationship between them. Specifically, changes in biomarkers (amyloid, tau) and alterations in brain structure precede cognitive decline. If DM exacerbated AD pathology, this would be deeply concerning for the cognitive well-being of DM individuals. However, such relationship has not been well-established in existing research. Moreover, this association has not been concurrently confirmed across aspects such as biomarkers, brain structure, and neuropsychological assessments. Therefore, it is crucial to investigate the acceleration of AD pathology in DM patients from various perspectives.

Objective: Based on existing research suggesting that DM impacts AD onset, the hypothesis of this study posits that DM will contribute to cognitive deterioration. To achieve this, I comprehensively evaluated the impact of DM on cognitive decline, incorporating clinical assessments based on amyloid–tau–neurodegeneration (ATN) framework, as well as neuropsychological tests. Particularly, observing DM-related changes at mild cognitive impairment (MCI), which precedes dementia, can be significant for maintaining quality of life through early intervention. Therefore, the study examined the impact of DM on cognition in individuals with mild cognitive impairment.

Methods: In this study, participants were classified as 637 cognitively normal (CN) (81 with DM, 556 without DM) and 943 MCI (132 with DM, 811 without DM). Linear mixed-effects models were used to predict the longitudinal cognitive changes associated with DM. Additionally, to investigate the influence of DM on ATN framework, moderation analyses were performed. Finally, to determine if DM exacerbates cognitive impairment, a survival analysis was conducted to compare the time to conversion to cognitive diagnosis.

Results: Regarding the longitudinal prediction of cognitive decline due to DM, both CN and MCI demonstrated worsening in clinical dementia rating (CDR-SB), with a significant decline in cognitive function scores observed particularly in the MCI. There were decreases in the volume of the middle temporal cortex in CN and the entorhinal cortex, hippocampus, right parahippocampal cortex in MCI. The interaction between DM and biomarkers was associated with increased cerebrospinal fluid tau levels in CN and decreased tau PET levels in entorhinal and parahippocampal cortices. According to the moderation analysis, DM significantly influenced positive relationship between the levels of Aβ and tau in the hippocampus in CN, but not in MCI. The conversion time from CN to MCI and from MCI to AD was shorter with DM.

Conclusion: The present findings suggest that the presence of DM exacerbates cognitive impairment, as evidenced by volumetric reductions in brain regions associated with cognition, memory, and information processing, along with cognitive decline and AD biomarker pathology. Accordingly, DM could be a reliable indicator for predicting ATN pathology. Particularly, cognitive decline was more rapid at early stages of AD, such as MCI. Therefore, considering the DM status in early cognitive decline is valuable for improving the effectiveness of early treatment and prognosis.

Key words: diabetes mellitus, mild cognitive impairment, biomarker, neurodegeneration, cognitive function

I. INTRODUCTION

The United Nations categorizes societies as “aging” when > 7% of the population is ≥ 65 years old, “aged” and “super-aged” for a proportion > 14% or > 20%, respectively. Countries such as Korea, the United States, England, and Japan, along with other organization for economic co-operation and development (OECD) nations, have either already reached or are to reach super-aged status within a few years.[1]

As societies progress toward super-aging, there is an increase in the number of people affected by metabolic and degenerative brain disorders. Among these, diabetes mellitus (DM) and Alzheimer’s disease (AD) are relevant examples.[2,3] Specifically, individuals with type 2 DM are at a 1.5 times greater risk of developing AD and a 2.5 times higher risk of vascular dementia.[4]

Given the link between DM and dementia, it becomes imperative to meticulously manage DM to mitigate the risk of dementia.[5,6] Moreover, as enhancing insulin resistance shows promise in alleviating AD pathology, AD is sometimes referred to as type 3 DM.[7,8]

Thus, insulin resistance in brain cells appears to be deeply associated with dementia. Moreover, if DM exacerbated AD pathology, this would be deeply concerning for the cognitive well-being of DM individuals.

1.1. Diabetes Mellitus

1.1.1. Onset and types of DM

DM is a chronic condition characterized by sustained high levels of glucose in the blood, which can arise from various factors. The main types of DM are type 1 and type 2.[9]

1.1.1.1. Factors contributing to DM onset

DM can arise from genetic, environmental, and lifestyle factors as well as their interactions. The factors contributing to onset can be broadly categorized into genetic and non-genetic factors.[9]

For type 1 DM, the influence of genetic factors is more pronounced, and having a family history increases the risk of onset.

Non-genetic factors include obesity, lifestyle, smoking, and stress. Obesity is one of the most important factors increasing the risk of DM onset. Obesity can increase insulin resistance and impair blood glucose regulation mechanisms, leading to DM.[10,11] Unhealthy eating habits and lack of exercise can also increase the risk of DM.[12] Smoking can increase insulin resistance and the risk of vascular diseases, which are complications of DM.[13] Lastly, stress can increase the risk of DM by affecting blood glucose regulation mechanisms. Cortisol, a stress hormone, can increase blood glucose levels, and chronic stress can worsen insulin resistance. Finally, these factors can interact to increase the risk of DM onset.[10]

1.1.1.2. Types of DM

Type 1 DM is characterized by a lack of insulin secretion due to the autoimmune destruction of the beta cells that produce insulin. It typically occurs in young adults or children and requires an external insulin supply through insulin injections or pumps.[9] On the other hand, type 2 DM arises from insulin resistance and inadequate insulin secretion, often promoted by factors such as obesity, unhealthy eating habits, and physical inactivity. It usually occurs in adults and can be initially treated with oral glucose-lowering agents and lifestyle changes.[12]

1.1.2. Mechanisms of DM

1.1.2.1. Insulin resistance and insulin secretion deficiency

The main mechanisms of DM involve insulin resistance and insulin secretion deficiency.[12] Insulin

is an important hormone for regulating blood glucose levels and transporting glucose into cells. Insulin resistance refers to a state where cells do not properly respond to insulin signals, leading to increased blood glucose levels. Also, beta cells of the pancreas fail to produce sufficient insulin, blood glucose levels rise.

1.1.2.2. Abnormalities in blood glucose regulation and metabolic pathways

Insulin binds to receptors on the cell surface, triggering signaling cascades within cells. This primarily induces glucose uptake via glucose transporter type 4 (GLUT4) in insulin-sensitive tissues such as skeletal muscle, adipose tissue, and the liver. The glucose absorbed via GLUT4 can be utilized for energy production or stored as glycogen. However, in DM, glucose production is deregulated, leading to fasting hyperglycemia. Insulin usually inhibits glucose production and glycogen breakdown in the liver, but insulin resistance leads to increased glucose release from the liver.[14,15]

DM often accompanies dyslipidemia, where triglyceride and low-density lipoproteins cholesterol levels increase while high-density lipoprotein cholesterol levels decrease. Additionally, insulin resistance promotes fat breakdown in adipose tissue, releasing free fatty acids (FFAs) into the bloodstream. Excessive FFAs impair insulin signaling in peripheral tissues, worsening insulin resistance.[16]

Recent research suggests that mitochondrial dysfunction and oxidative stress can contribute to the pathogenesis of DM.[17] In fact, mitochondrial dysfunction in insulin-sensitive tissues reduces adenosine triphosphate (ATP) production and promotes insulin resistance. Furthermore, oxidative damage interferes with insulin signaling pathways, exacerbating metabolic abnormalities.

1.1.3. Therapeutic options for DM

Therapeutic options for DM include oral glucose-lowering agents, insulin injections, vascular

protectants, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Oral glucose-lowering agents regulate blood glucose levels by lowering postprandial blood glucose or suppressing glucose production in the liver. They mainly stimulate insulin secretion or increase cellular glucose uptake. Examples include sulfonylureas, metformin, and thiazolidinediones.

Insulin injections can regulate blood glucose levels in DM patients who cannot achieve adequate blood glucose control with oral glucose-lowering agents.

DM can damage blood vessels and increase the risk of cardiovascular disease. Therefore, vascular protectants, such as angiotensin-converting enzyme inhibitors or statins, are prescribed to maintain vascular health and prevent complications from DM.[18,19]

GLP-1 receptor agonists, like liraglutide lixisenatide and semaglutide, promote insulin secretion to lower blood glucose levels and reduce glucagon secretion.

Finally, SGLT2 inhibitors, which are also called gliflozins, are a class of drugs that lower blood glucose levels by preventing kidneys from reabsorbing glucose that is created by body and the extra glucose leaves through in urine.

1.2. Alzheimer's disease

AD is the most common type of dementia, characterized by cognitive and functional decline resulting from neurodegenerative processes. Pathologically, it manifests through cognitive dysfunction and brain alterations such as the presence of amyloid-beta (Aβ) plaques and hyperphosphorylated tau neurofibrillary tangles (NFTs).[20,21]

There are two types of AD: early-onset (EOAD) and late-onset AD (LOAD). Particularly, LOAD typically occurs after 65 years old, representing approximately 90% of all AD cases, with frequent

involvement of hippocampal impairment.[22]

Apolipoprotein E (APOE) allele mutations are the most significant genetic risk factors for AD.[23,24] One APOE ε4 allele increases the risk of AD by 2-3 times, while two APOE ε4 alleles increase the risk by “15” to “17” times.[25] In fact, carriers of the APOE ε4 allele tend to develop AD approximately a decade earlier than non-carriers.[26]

Sex is another a risk factor for AD, with different incidence rates between males and females.[27] Women have a higher incidence of AD, and their cognitive decline tends to be more severe.[28]

Additionally, factors such as aging, DM, obesity, educational level, and environmental exposure can increase the risk of developing AD.

1.2.1. Biomarker changes

Biomarkers are measurable indicators associated with the pathology of AD. As a result of the development of neuroimaging and neurochemical biomarkers capable of estimating AD pathology, the National Institute on Aging and Alzheimer’s Association Research Framework proposed as a classification system for AD, namely, the ATN classification system which determines the presence of amyloidosis (A), taupathy (T), and neurodegeneration (N) for AD research purposes. Each classification is based on biomarkers indicative of the characteristic pathology of AD. 'A' is evaluated by a decrease in cerebrospinal fluid (CSF) Aβ and Aβ positron emission tomography (PET) ligand binding, reflecting Aβ deposition in the brain parenchyma and vessel walls. 'T' is assessed by an increase in phosphorylated tau in the CSF and tau PET ligand binding in the brain cortex. 'N' based on the brain atrophy observed on magnetic resonance imaging or metabolic decline in the brain.

Changes in specific biomarkers such as Aβ plaques and tau presence in the brain and CSF can occur before clinical symptoms, making them useful for early diagnosis and AD progression monitoring.[29]

1.2.1.1. Amyloid beta

Aβ is generated through cleavage of amyloid precursor protein (APP) and exists in two forms: Aβ40 and Aβ42. Aβ40 consists of 40 amino acids and is the most found in the brain, including in AD. Aβ42, consisting of 42 amino acids, is considered a crucial form associated with AD, particularly due to its excessive accumulation in the brain, which may be related to AD the onset and progression.

Aβ monomers are secreted into the extracellular space and self-assembled into various forms. Soluble Aβ oligomers are highly neurotoxic and implicated in synaptic dysfunction and cognitive impairment in AD. Binding of Aβ oligomers to receptors induces oxidative stress, mitochondrial dysfunction, inflammatory responses, and excessive tau phosphorylation.[30]

1.2.1.2. Tau

The primary function of tau in neurons is to stabilize microtubules, allowing for axonal transport within nerve cells. The balance between repetitive tau phosphorylation and dephosphorylation during axonal transport is crucial. Its disruption leads to formation of hyperphosphorylated tau protein aggregates known as NFTs.[30] Mutations in tau genes can cause neurodegenerative diseases, such as frontotemporal dementia.[31] Additionally, amyloid plaques promote tau hyperphosphorylation via adenosine monophosphate-activated protein kinase (AMPK).[32]

1.2.2. Brain atrophy

AD is associated with damage to critical regions responsible for memory and cognitive function, including the hippocampus, entorhinal cortex, parahippocampal cortex and middle temporal cortex.[33-41]

The hippocampus, situated bilaterally within the medial temporal lobe, plays a pivotal role in

memory consolidation.[37] The entorhinal cortex, located in the medial aspect of the temporal cortex, contributes to functions such as spatial memory, temporal perception, and learning from new experiences. Additionally, it is closely linked with the hippocampus, exerting a significant influence on memory formation and long-term memory.[38] The parahippocampal cortex, surrounding the hippocampus, participates in functions related to memory, learning, and spatial cognition.[33] The corpus callosum, a bundle of nerve fibers between the cerebral hemispheres, facilitates communication among brain regions involved in visual information processing, cognitive reasoning, and decision-making.[39] The middle temporal cortex, part of the cerebral cortex, is associated with functions such as language comprehension, semantic memory process, integration of information from different senses.[40] Moreover, neuronal loss has been observed in this region in AD.[37,41]

With disease progression, there is a volumetric reduction in these brain regions, accompanied by neuronal connectivity impairments.

1.2.3. Cognitive decline

Cognitive decline is a hallmark feature of AD, encompassing cognitive domains such as memory, language, executive function, and visuospatial skills. As a result, individuals with AD experience difficulties in recalling recent events or learning new information.

1.3. DM and AD

Evidence suggests a relationship between DM and the onset and progression of AD.[42-44]

First, DM is associated with metabolic abnormalities related to insulin resistance, leading to reduced effectiveness of insulin and elevated blood glucose levels. These metabolic abnormalities can increase insulin resistance in the brain, promoting Aβ the generation and tau aggregation.[42]

Second, DM increases the risk of vascular diseases, which can affect brain vasculature. Vascular diseases impair cerebral blood circulation and can damage brain tissue, which is associated with the onset of AD.[18]

Third, DM can promote inflammatory responses. Inflammation can cause damage to brain tissue and may contribute to AD onset and progression. Neuroimaging in elderly individuals with DM evidenced some risk factors for AD, including hippocampal lesions and nodules within the brain.[45]

Finally, some studies suggest that drugs used to treat DM may hinder the onset or delay the progression of AD.[44-54]

In summary, type 2 DM and AD share common etiological factors such as increased oxidative stress, elevated inflammation, and cognitive impairment.[55,56]

However, the existence of a direct correlation between type 2 DM and AD is debatable.[57] While DM increases the risk of AD and dementia, the effects of various risk factors were considered independent of a link between DM and AD.[58] Additionally, there is no correlation between DM and increased Aβ, suggesting that DM may not be sufficient for the onset of AD.[5] Similarly, another study reported that a strong correlation between DM and lower bilateral frontal and parietal cortical thickness and an increase in CSF phosphorylated tau (p-tau). However, neither brain Aβ load nor CSF Aβ levels were related to DM.[59] Also, previous finding indicated that cerebral cortical Aβ was considerably lower in people with DM than nDM.[60] Approximately 30% of those clinically diagnosed with AD among the DM participants were tau positive.[61]

While high blood glucose levels can exacerbate dementia-related neuropathology, it remains uncertain whether they can lead to cognitive decline or increase the risk of dementia.[62]

1.4. Aim of study

The shared comorbidities such as insulin resistance, promotion of inflammatory responses, and

increased oxidative stress between DM and AD pathology would indicate a relationship between them. However, the notion that DM can exacerbate AD pathology has not been well-established in existing research. Moreover, this association has not been concurrently confirmed across aspects such as biomarkers, brain structure, clinical evaluation and neuropsychological assessments. Unlike vascular dementia, AD is mainly driven by Aβ and tau protein tangles, and it exhibits a gradual cognitive decline. This necessitates long-term studies, including biomarker analysis. additionally, if the moderating effects of diabetes on beta-amyloid, tau, and the progression of neurodegeneration are confirmed, it would validate the acceleration of AD pathology in DM patients from various perspectives.

Based on existing research suggesting that DM impacts AD onset, the hypothesis of this study posits that DM will contribute to cognitive deterioration. Hence, this study aimed to clarify how DM influences cognitive function, particularly in individuals experiencing mild cognitive impairment (MCI), which precedes dementia. As MCI often follows predictable pathways leading to AD, observing possible DM-related changes at earlier stages of cognitive impairment than in full-blown AD may inform a proactive treatment at the onset of MCI.

To achieve this, I comprehensively evaluated the impact of DM on cognitive decline, incorporating clinical assessments based on ATN pathology, as well as neuropsychological tests (Figure 1). This study used a large-scale AD cohort, the Alzheimer's disease neuroimaging initiative (ADNI), which comprises standardized measurements of imaging, genetics, CSF biomarkers, and clinical databases.[63]

This research would help gain a better understanding of the complex relationship between DM and AD further contributing to the development of more effective dementia management and prevention strategies for DM patients.

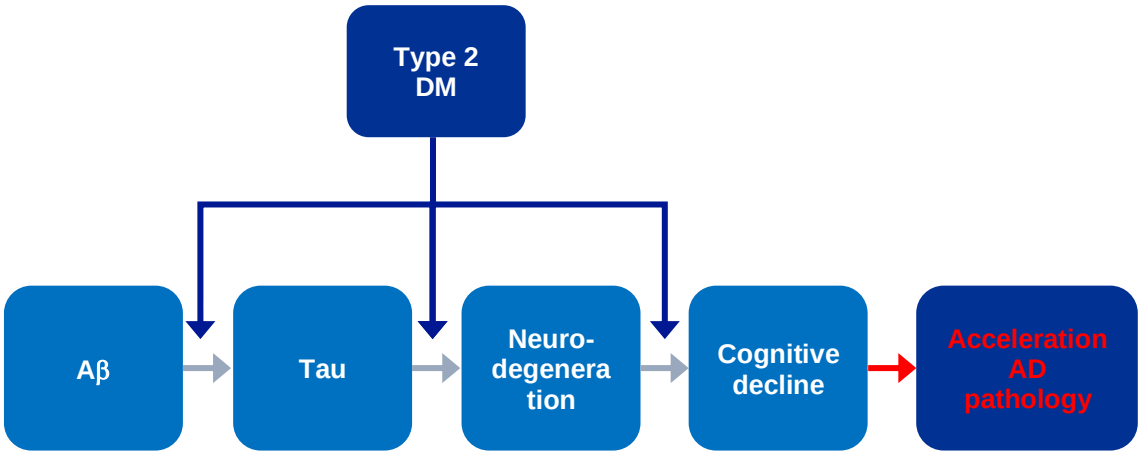


Figure 1. Hypothesis scheme of the study.
Abbreviations: DM, diabetes mellitus; AD, alzheimer's disease; Aβ, amyloid beta.

2. MATERIALS AND METHODS

2.1. Data collection

The data in this study were obtained from the ADNI database (http://adni.loni.usc.edu). ADNI is a multi-site longitudinal study conducted in the United States and Canada and launched in 2003 as a public-private partnership. ADNI aims to measure progression from pre-dementia stages to early AD using neuroimaging and biomarkers. This study was approved by the Institutional Review Board at each participating site, and written informed consent was obtained from participants or authorized representatives.

Demographic, diagnostic, and cognitive assessment data were collected from the following files: “ADNIMERGE.csv”, “LABDATA.csv”, “APOERES.csv”, “RECMHIST.csv”, “VITALS.csv”.

The ADNI project recruited participants across four phases: ADNI 1, ADNI GO, ADNI 2, and ADNI 3, with participants ranging in age from 55 to 90 years. Participants had visited over a period of 12 to 192 months, with repeated measurements taken every 12 or 24 months.

2.2. Participants

Detailed characteristics of participants including the inclusion and exclusion criteria were previously described.[64] Participants with type 1 DM were excluded due to the predominant genetic and autoimmune influences. The classification criteria were as follows[65]:

Participants were categorized as cognitively normal (CN, n = 637) or MCI (n = 943) at baseline. For the CN group, the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score was 0, and the Mini-Mental State Examination (MMSE) score ranged from 24 to 30. The memory criterion, based

on delayed recall of a paragraph from the Logical Memory II subscale of the Wechsler Memory Scale-Revised, had cutoff scores adjusted for education level: ≥ 9 for 16 yr of education, ≥ 5 for 8-15 yr and ≥ 3 for 0-7 yr. For the MCI group, the CDR-SB score was ≥ 0.5, with a mandatory memory box score of at least 0.5. MMSE scores also ranged from 24 to 30, with memory cutoffs at ≤ 8, ≤ 4 and ≤ 2, respectively, for these education levels.

At baseline, participants were classified into non-DM (nDM, n = 1367) and DM (n = 213) groups based on the presence of DM. DM was diagnosed using American Diabetes Association guidelines.[66] Diagnostic criteria for DM included at least one of the following: fasting blood glucose ≥ 126 mg/dL, a documented DM diagnosis, or current DM medication use. Data were retrieved from study files ("ADSXLIST.csv", "RECCMEDS.csv", and "RECMHIST.csv").

2.3. Biomarker measurements

Biological markers and neuroimaging data were obtained from the ADNI files: "UCBERKELEY_AMY_6MM.csv", "UCBERKELEY_TAU_6MM.csv".

Amyloid deposition was quantified using standardized uptake value ratios (SUVRs) of [^{18}F] florbetapir PET. The regional uptake of florbetapir was normalized using the whole cerebellum as a reference. Tau deposition was measured with [^{18}F] flortaucipir PET and quantified using SUVR, with uptake normalized to the inferior cerebellar gray matter.

2.4. Brain structure analysis

Each participant underwent an MRI scan every 12 months. Brain volume data were extracted from the "UCBERKELEY_AMY_6MM.csv" file in the ADNI database. MRI data were processed using Freesurfer version 7.1.1 to segment and parcellate brain regions. Baseline and follow-up MRI

scans were coregistered with PET scans taken closest in time.

Regions of interest (ROIs) were defined for key areas of cognitive and AD pathology, including the hippocampus, entorhinal cortex, parahippocampal cortex, middle temporal cortex, corpus callosum, cerebral white matter, subcortical white matter, and brainstem.[33-36,67,68]

2.5. Cognitive function assessment

The CDR-SB was used to evaluate the severity and functional impairment of dementia, as it is a widely adopted primary outcome measure in recent dementia studies.[69]

The MMSE were used as well.[64] The MMSE, designed to measure various cognitive functions, is the most widely used screening tool for detecting early AD symptoms in patients with memory decline, with proven reliability and validity. The examination consists of tasks assessing orientation in time and place, memory registration, attention and calculation, recall, language, and visuospatial construction, with a total score of 30.

Both assessments were measured at baseline and repeated every 6-12 months to evaluate the trajectory of cognitive decline.

2.6. Other clinical variables

The presence of hypertension is associated with both DM and AD; thus, it was determined by one of the following: (i) taking antihypertensive medication, (ii) systolic blood pressure ≥ 140 mmHg, or (iii) diastolic blood pressure ≥ 90 mmHg. These were considered as covariates in the analysis.

2.7. Statistical analysis

2.7.1. Comparison between groups

To compare baseline demographic and clinical characteristics between groups with and without DM in CN and MCI, independent t-tests were used for continuous variables and chi-square tests for categorical variables.

2.7.2. Relationship between DM and outcome variables

Multiple regression analyses were conducted to identify relationships between DM and cognitive and brain variables, as well as volumes of ROIs at baseline. Covariates included age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.

2.7.3. Longitudinal impact of DM on AD biomarkers, volumes of ROIs and cognitive function

Linear mixed-effects models were used to predict the longitudinal cognitive changes associated with DM. Dependent variables included AD biomarkers, volumes of ROIs and cognitive function. The fixed effects comprised DM status, time after baseline, and the interaction between DM status and time after baseline. Random effects included intercepts and slopes. Covariates included age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.

To test whether the relationship between baseline DM status and longitudinal cognition differed by sex or APOE ε4 allele, linear mixed-effects models with interactions of DM status × time after baseline × sex or APOE ε4 allele were conducted.

2.7.4. Moderation effect of DM

In previous research, cognitive decline follows this sequence: changes in Aβ and Tau, alterations in brain structure, and decline in cognitive function.[70] Therefore, it is important to examine the influence of DM, considering that changes in biomarkers and brain volume precede cognitive impairment. To investigate whether DM influences the relationship between biomarkers (Aβ, tau) and between the biomarker (tau) and volumes of ROIs, moderation analyses were performed using Hayes' method (Figure 2).[71] DM presence was used as moderating variable. Age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke were adjusted for.

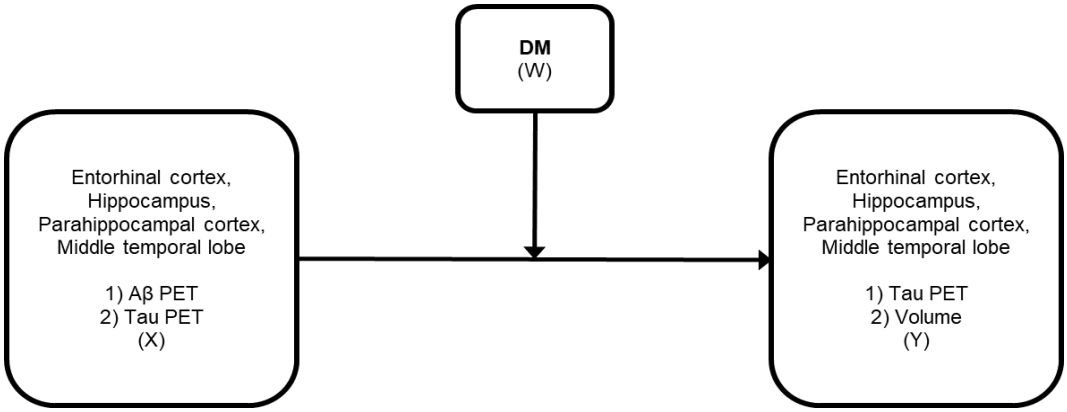


Figure 2. Schematic model of the moderation analysis. The regions of interest Aβ PET, and Tau PET were the independent variable(X) and the presence of DM was the moderator(W). The regions of interest Tau PET, volumes were the dependent variables(Y).
Abbreviations: DM, DM mellitus; Aβ, amyloid beta; PET, positron emission tomography.

2.7.5. Impact of DM on other variables

At baseline, multiple regression analyses were conducted to examine whether the duration of DM influences cognitive function, volumes of ROIs, and AD biomarker levels. Based on previous findings showing changes in cognitive function around the early 4-6 years of DM duration,[72,73] the

duration of DM was categorized into ≤ 5 years and > 5 years for analysis.

Mann-Whitney U tests, a non-parametric test, were performed to investigate whether DM medication (metformin) affects cognitive function and volumes of ROIs.

Finally, to determine if DM exacerbates cognitive impairment, a survival analysis using Kaplan-Meier survival curves and log-rank tests was conducted to compare the time to conversion to cognitive diagnosis.

2.7.6. Software computing statistics

All analyses were performed using SPSS version 27.0 (IBM SPSS, IBM Corp, Armonk, NY, USA). The false discovery rate (FDR) was used for statistical correction of multiple comparisons by Hochberg and Benjamini to control for multiple hypothesis testing.[74] Statistical significance was defined as an FDR-corrected $P < .05$. Moderation analyses were performed using PROCESS macro version 4.2.

3. RESULTS

3.1. Participants characteristics

Table 1 summarizes the clinical and demographic characteristics of the study participants. There was a tendency for participants diagnosed as CN with DM to have a shorter follow-up than those without DM ($p < 0.001$). Among participants diagnosed with MCI, those with DM tended to have lower educational levels ($p = 0.029$), a history of hypertension ($p = 0.001$), and a shorter follow-up period ($p = 0.009$) than those without.

Table 1. Demographic and clinical characteristics of the study groups

	CN			MCI		
	DM	non-DM	p -value	DM	non-DM	p -value
	n=81	n=556		n=132	n=811	
Age (years)	73.23 (6.21)	73.19 (6.23)	0.958	73.00 (7.85)	72.72 (7.63)	0.695
Sex			0.127			0.584
Male	43 (53.1%)	245 (44.1%)		80 (60.6%)	471 (58.1%)	
Female	38 (46.9%)	311 (55.9%)		52 (39.4%)	340 (41.9%)	
Education (years)	16.40 (2.76)	16.56 (2.51)	0.592	15.45 (2.83)	16.03 (2.80)	**0.029**
Glucose level	143.81 (27.25)	83.19 (20.46)	**<0.001**	148.79 (40.65)	91.16 (15.81)	**<0.001**
History of hypertension			0.091			**0.001**
No	39 (48.1%)	323 (58.1%)		50 (37.9%)	436 (53.8%)	
Yes	42 (51.9%)	233 (41.9%)		82 (62.1%)	375 (46.2%)	
History of stroke			0.128			0.789
No	79 (97.5%)	552 (99.3%)		130 (98.5%)	801 (98.8%)	
Yes	2 (2.5%)	4 (0.7%)		2 (1.5%)	10 (1.2%)	
Number of APOE ε4 allele			0.884			0.425
0	58 (71.6%)	388 (69.8%)		72 (54.5%)	401 (49.4%)	
1	21 (25.9%)	149 (26.8%)		49 (37.1%)	317 (39.1%)	
2	2 (2.5%)	19 (3.4%)		11 (8.3%)	93 (11.5%)	
Follow-up period (months)	35.78 (36.17)	41.86 (41.03)	**<0.001**	30.29 (29.41)	32.84 (33.70)	**0.009**
DM duration (year)	7.20(5.73) (n=30)			9.55(9.24) (n=64)		
DM drug (monotherapy)						
Insulin	5 (13.9%)			4 (10.5%)		
Metformin	26			28		

	(72.2%)	(73.7%)
SU	5 (13.9%)	6 (15.8%)

Data are presented as mean (standard deviation) for continuous variables and n (%) for categorical variables. Bold signals represent statistical significance ($p < 0.05$).
Abbreviations: APOE, apolipoprotein E; CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; SU, sulfonylurea.

3.2. Cognitive function, volumes of ROIs and AD biomarkers

Table 2 presents the cognitive function, ROI volume, and AD biomarkers at baseline. Among CN individuals, those with DM had smaller volumes in the middle temporal cortex ($p = 0.047$) and corpus callosum (anterior, $p = 0.047$; posterior, $p = 0.047$). Among participants with MCI, those with DM had smaller volumes in the whole brain ($p = 0.044$), left entorhinal cortex ($p = 0.046$), right parahippocampal cortex ($p = 0.046$), cerebral white matter (total, $p = 0.045$; right, $p = 0.042$), brainstem ($p = 0.003$).

At baseline, there were no significant differences in cognitive function scores and AD biomarkers (CSF Aβ, CSF tau, CSF p-tau, Aβ PET, tau PET) between participants with and without DM, both in the CN and MCI groups.

Table 2. Cognitive and brain variables of the study groups

	CN			MCI		
	DM	non-DM	p-value	DM	non-DM	p -value
Cognitive variables	n=81	n=556		n=132	n=811	
CDR-SB	0.02 (0.10)	0.03 (0.13)	0.219	1.58 (0.91)	1.50 (0.89)	0.394
MMSE	29.06 (0.97)	29.12 (1.13)	0.629	27.50 (1.81)	27.64 (1.85)	0.427
Brain variables						
Brain volume (ml)	n=77	n=528		n=128	n=788	
Ventricles	33.71 (18.02)	33.76 (18.54)	0.984	39.46 (19.70)	40.35 (22.93)	0.679
Whole Brain	1020.22 (110.35)	1042.41 (107.54)	0.090	1018.24 (116.22)	1036.59 (110.68)	**0.044**
ICV	1484.24 (173.30)	1498.61 (160.59)	0.460	1529.85(167.90)	1539.93 (163.42)	0.516
	n=54	n=406		n=75	n=485	
Entorhinal cortex	3.85 (0.78)	3.73 (0.67)	0.214	3.46 (0.86)	3.62 (0.84)	0.121
Entorhinal cortex, left	2.01 (0.47)	1.91 (0.38)	0.138	1.75 (0.45)	1.85 (0.47)	**0.046**
Entorhinal cortex, right	1.84 (0.39)	1.82 (0.38)	0.682	1.71 (0.50)	1.77 (0.44)	0.287
Hippocampus	8.01 (0.98)	7.93 (0.94)	0.544	7.42 (1.07)	7.56 (1.07)	0.309
Hippocampus, left	3.96 (0.46)	3.92 (0.47)	0.536	3.65 (0.52)	3.74 (0.53)	0.182
Hippocampus, right	4.05 (0.55)	4.01 (0.50)	0.580	3.78 (0.60)	3.82 (0.57)	0.511
Parahippocampal cortex	3.95 (0.51)	3.90 (0.54)	0.506	3.70 (0.55)	3.81 (0.62)	0.176
Parahippocampal cortex, left	2.08 (0.34)	2.31 (0.32)	0.284	1.95 (0.33)	1.98 (0.37)	0.431
Parahippocampal cortex, right	1.87 (0.26)	1.87 (0.28)	0.965	1.76 (0.29)	1.83 (0.31)	**0.046**
Middle temporal cortex	20.06 (2.76)	20.80 (2.81)	**0.047**	19.66 (2.93)	20.15 (2.98)	0.186
CC, anterior	0.86 (0.15)	0.92 (0.16)	**0.016**	0.91 (0.17)	0.93 (0.16)	0.368
CC, central	0.48 (0.10)	0.50 (0.11)	0.122	0.73 (0.08)	0.49 (0.10)	0.114
CC, posterior	1.02 (0.17)	1.08 (0.17)	**0.015**	1.06 (0.18)	1.09 (0.19)	0.126

Cerebral WM	419.82 (55.87)	425.78 (56.00)	0.463	422.93 (56.59)	436.31 (58.55)	**0.045**
Cerebral WM, left	210.14 (27.86)	213.17 (28.07)	0.456	211.51 (28.43)	218.04 (30.40)	0.081
Cerebral WM, right	209.69 (28.13)	212.61 (28.05)	0.472	211.43 (28.29)	218.27 (29.02)	**0.042**
Subcortical WM	160.23 (33.67)	164.15 (34.64)	0.434	16.90 (37.30)	169.20 (37.14)	0.114
Brainstem	20.50 (2.63)	20.91 (2.53)	0.263	20.14 (2.14)	20.96 (2.51)	**0.003**
Biomarker	n=40	n=253		n=86	n=518	
CSF Aβ	1283.75 (435.55)	1186.31 (450.04)	0.197	968.04 (425.16)	965.21 (441.95)	0.956
CSF tau	238.97 (97.58)	232.57 (84.06)	0.664	301.36 (141.93)	281.63 (125.37)	0.186
CSF p-tau	21.36 (8.92)	21.48 (8.84)	0.938	29.64 (17.19)	27.24 (14.01)	0.156
Aβ PET	n=141	n=319		n=75	n=485	
Entorhinal cortex	0.89 (0.07)	0.90 (0.09)	0.556	0.94 (0.13)	0.92 (0.12)	0.192
Entorhinal cortex, left	0.90 (0.07)	0.90 (0.10)	0.935	0.95 (0.14)	0.92 (0.13)	0.145
Entorhinal cortex, right	0.89 (0.08)	0.91 (0.10)	0.337	0.93 (0.13)	0.92 (0.13)	0.320
Hippocampus	1.09 (0.07)	1.07 (0.09)	0.186	1.07 (0.12)	1.06 (0.11)	0.249
Hippocampus, left	1.08 (0.07)	1.07 (0.09)	0.261	1.06 (0.12)	1.05 (0.11)	0.457
Hippocampus, right	1.09 (0.08)	1.08 (0.09)	0.160	1.08 (0.12)	1.06 (0.11)	0.134
Parahippocampal cortex	0.97 (0.11)	0.99 (0.13)	0.422	1.05 (0.15)	1.03 (0.16)	0.320
Parahippocampal cortex, left	0.96 (0.11)	0.97 (0.13)	0.412	1.03 (0.16)	1.02 (0.16)	0.561
Parahippocampal cortex, right	0.98 (0.12)	1.00 (0.13)	0.468	1.07 (0.16)	1.04 (0.16)	0.179
Middle temporal cortex	1.02 (0.16)	1.06 (0.19)	0.194	1.18 (0.26)	1.17 (0.26)	0.888
CC, anterior	1.50 (0.16)	1.48 (0.20)	0.565	1.49 (0.19)	1.45 (0.21)	0.110
CC, central	1.37 (0.16)	1.39 (0.18)	0.526	1.38 (0.17)	1.37 (0.18)	0.732
CC, posterior	1.71 (0.21)	1.70 (0.20)	0.742	1.65 (0.22)	1.64 (0.22)	0.657
Cerebral WM	1.62 (0.11)	1.63 (0.16)	0.379	1.69 (0.19)	1.66 (0.18)	0.328

Cerebral WM, left	1.61 (0.11)	1.63 (0.16)	0.301	1.68 (0.19)	1.66 (0.18)	0.310
Cerebral WM, right	1.62 (0.11)	1.64 (0.16)	0.481	1.69 (0.19)	1.67 (0.18)	0.325
Subcortical WM	1.93 (0.13)	1.92 (0.19)	0.629	1.92 (0.21)	1.90 (0.18)	0.371
Brainstem	1.51 (0.08)	1.51 (0.11)	0.720	1.47 (0.13)	1.47 (0.12)	0.709
Tau PET	n=38	n=307		n=29	n=182	
Entorhinal cortex	1.17 (0.18)	1.17 (0.15)	0.859	1.34 (0.40)	1.33 (0.32)	0.831
Entorhinal cortex, left	1.17 (0.20)	1.17 (0.16)	0.950	1.29 (0.38)	1.33 (0.33)	0.561
Entorhinal cortex, right	1.19 (0.19)	1.17 (0.16)	0.535	1.31 (0.41)	1.35 (0.34)	0.597
Hippocampus	1.22 (0.15)	1.24 (0.14)	0.328	1.25 (0.24)	1.33 (0.22)	0.114
Hippocampus, left	1.22 (0.15)	1.24 (0.15)	0.335	1.25 (0.25)	1.33 (0.22)	0.102
Hippocampus, right	1.21 (0.15)	1.24 (0.15)	0.332	1.26 (0.24)	1.33 (0.23)	0.137
Parahippocampal cortex	1.11 (0.10)	1.12 (0.12)	0.780	1.20 (0.30)	1.24 (0.28)	0.461
Parahippocampal cortex, left	1.12 (0.11)	1.12 (0.13)	0.757	1.19 (0.29)	1.25 (0.27)	0.349
Parahippocampal cortex, right	1.11 (0.10)	1.11 (0.12)	0.825	1.21 (0.32)	1.24 (0.29)	0.615
Middle temporal cortex	1.18 (0.10)	1.20 (0.15)	0.523	1.26 (0.24)	1.35 (0.39)	0.214
CC, anterior	0.88 (0.13)	0.90 (0.12)	0.338	0.88 (0.16)	0.89 (0.13)	0.789
CC, central	0.83 (0.13)	0.83 (0.11)	0.736	0.85 (0.14)	0.85 (0.13)	0.845
CC, posterior	0.94 (0.12)	0.95 (0.12)	0.495	0.97 (0.19)	0.97 (0.16)	0.914
Cerebral WM	1.17 (0.10)	1.18 (0.10)	0.326	1.20 (0.19)	1.24 (0.18)	0.188
Cerebral WM, left	1.16 (0.10)	1.18 (0.10)	0.331	1.19 (0.17)	1.24 (0.18)	0.174
Cerebral WM, right	1.17 (0.10)	1.18 (0.10)	0.334	1.20 (0.20)	1.25 (0.18)	0.219
Subcortical WM	1.14 (0.10)	1.14 (0.11)	0.824	1.18 (0.18)	1.19 (0.14)	0.806
Brainstem	0.98 (0.09)	1.00 (0.08)	0.137	0.97 (0.11)	1.00 (0.08)	0.102

Data are presented as mean (standard deviation).
The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke. Bold signals represent statistical significance ($p < 0.05$).
Abbreviations: Aβ, amyloid beta; CC, corpus callosum; CDR-SB, clinical dementia rating-sum of boxes; CN, cognitively normal; CSF, cerebrospinal fluid; DM, diabetes mellitus; ICV, intracranial volume; MCI, mild cognitive impairment; MMSE, mini-mental status examination; PET, positron emission tomography; p-tau; phosphorylated tau; WM, white matter.

3.3. Association between DM and cognitive function, volumes of ROIs and AD biomarkers

The results of multiple linear regression models to assess the relationship between DM and cognitive function and ATN pathology at baseline are shown in Table 3. No significant associations were observed between DM and CDR-SB and MMSE scores in both CN and MCI. However, in CN, the volume of the whole brain (FDR-adjusted p = 0.007) and middle temporal cortex (FDR-adjusted p = 0.042) showed significant negative associations with DM. However, there were no significant associations between DM and AT levels.

In analyses of MCI at baseline, the volume of the brainstem (FDR-adjusted p = 0.018) showed a significant negative association with DM. Additionally, CSF tau levels (FDR-adjusted p = 0.050) showed a positive association with DM, but no significant association with Aβ and tau PET levels.

Table 3. Association between DM and cognitive function, volumes of ROIs, AD biomarkers at baseline

	CN			MCI		
Outcome	Standardized beta	p-value	Adjusted p-value	Standardized beta	p-value	Adjusted p-value
Cognitive variables						
CDR-SB	-0.036	0.362	0.724	0.025	0.442	0.885
MMSE	0.000	0.997	0.997	-0.018	0.571	0.571
Brain variables						
Brain volume						
Ventricles	-0.019	0.616	0.616	-0.021	0.485	0.485
Whole Brain	-0.103	**0.002**	**0.007**	-0.060	**0.024**	0.072
ICV	-0.067	**0.042**	0.063	-0.023	0.390	0.585
Entorhinal cortex	0.036	0.417	0.674	-0.076	**0.046**	0.104
Entorhinal cortex, left	0.064	0.153	0.268	-0.083	**0.043**	0.111
Entorhinal cortex, right	-0.001	0.983	0.994	-0.055	0.179	0.215
Hippocampus	0.000	0.994	0.994	-0.061	0.104	0.144
Hippocampus, left	0.002	0.961	0.994	-0.071	**0.048**	0.096
Hippocampus, right	-0.003	0.951	0.994	-0.047	0.207	0.233
Parahippocampal cortex	0.012	0.796	0.983	-0.066	0.113	0.145
Parahippocampal cortex, left	0.034	0.456	0.684	-0.043	0.310	0.310
Parahippocampal cortex, right	-0.017	0.708	0.929	-0.081	**0.049**	0.088
Middle temporal cortex	-0.113	**0.006**	**0.042**	-0.078	**0.041**	0.123
CC, anterior	-0.129	**0.005**	0.084	-0.048	0.254	0.269
CC, central	-0.087	**0.048**	0.216	-0.081	**0.050**	0.082
CC, posterior	-0.122	**0.008**	0.052	-0.072	0.084	0.126
Cerebral WM	-0.065	0.103	0.264	-0.090	**0.010**	0.060
Cerebral WM, left	-0.066	0.100	0.299	-0.085	**0.017**	0.077
Cerebral WM, right	-0.065	0.108	0.242	-0.093	**0.008**	0.072
Subcortical WM	-0.066	0.120	0.239	-0.075	**0.040**	0.144
Brainstem	-0.078	0.061	0.221	-0.122	**0.001**	**0.018**

Biomarker						
CSF Aβ	0.086	0.119	0.357	-0.009	0.803	0.803
CSF tau	0.040	0.475	0.712	0.073	**0.047**	**0.050**
CSF p-tau	0.007	0.903	0.903	0.076	**0.045**	0.135
Aβ PET						
Entorhinal cortex	-0.015	0.745	0.838	0.068	0.092	0.370
Entorhinal cortex, left	0.006	0.898	0.898	0.074	**0.048**	0.486
Entorhinal cortex, right	-0.032	0.488	0.838	0.054	0.182	0.370
Hippocampus	0.058	0.206	0.838	0.056	0.181	0.370
Hippocampus, left	0.049	0.287	0.838	0.039	0.351	0.486
Hippocampus, right	0.062	0.177	0.838	0.070	0.095	0.370
Parahippocampal cortex	-0.029	0.525	0.838	0.055	0.166	0.565
Parahippocampal cortex, left	-0.030	0.513	0.838	0.038	0.334	0.370
Parahippocampal cortex, right	-0.025	0.572	0.838	0.068	0.088	0.682
Middle temporal cortex	-0.045	0.300	0.838	0.027	0.475	0.644
CC, anterior	0.020	0.664	0.838	0.065	0.117	0.490
CC, central	-0.028	0.543	0.838	0.017	0.682	0.370
CC, posterior	0.017	0.707	0.838	0.022	0.608	0.370
Cerebral WM	-0.024	0.607	0.838	0.051	0.219	0.370
Cerebral WM, left	-0.029	0.530	0.838	0.054	0.192	0.565
Cerebral WM, right	-0.018	0.694	0.838	0.050	0.226	0.370
Subcortical WM	0.024	0.606	0.838	0.038	0.381	0.370
Brainstem	-0.012	0.798	0.845	-0.028	0.502	0.370
Tau PET						
Entorhinal cortex	0.025	0.637	0.919	0.064	0.284	0.977
Entorhinal cortex, left	0.009	0.870	0.919	0.025	0.696	0.977
Entorhinal cortex, right	0.047	0.396	0.792	0.026	0.688	0.977
Hippocampus	-0.050	0.374	0.792	-0.048	0.455	0.977
Hippocampus, left	-0.049	0.383	0.792	-0.053	0.410	0.977
Hippocampus, right	-0.049	0.375	0.792	-0.042	0.515	0.977
Parahippocampal cortex	-0.007	0.902	0.919	0.007	0.911	0.977

Parahippocampal cortex, left	-0.008	0.892	0.919	-0.006	0.923	0.977
Parahippocampal cortex, right	-0.006	0.919	0.919	0.022	0.744	0.977
Middle temporal cortex	-0.026	0.646	0.919	-0.032	0.635	0.977
CC, anterior	-0.058	0.267	0.792	-0.017	0.800	0.977
CC, central	-0.011	0.838	0.919	-0.001	0.988	0.988
CC, posterior	-0.030	0.571	0.919	0.031	0.646	0.977
Cerebral WM	-0.062	0.263	0.792	-0.047	0.487	0.977
Cerebral WM, left	-0.060	0.280	0.792	-0.052	0.441	0.977
Cerebral WM, right	-0.062	0.259	0.792	-0.040	0.555	0.977
Subcortical WM	-0.018	0.736	0.919	0.012	0.854	0.977
Brainstem	-0.089	0.100	0.792	-0.143	0.057	0.977

Reference group is nDM. Multivariate linear regression was constructed with DM mellitus as a predictor, adjusting for age, sex, years of education, number of APOE ε4 alleles, hypertension and stroke. Bold signals represent statistical significance ($p < 0.05$).
p values were adjusted for FDR using Benjamini-Hochberg procedure.
Abbreviations: Aβ, amyloid beta; CC, corpus callosum; CDR-SB, clinical dementia rating-sum of boxes; CN, cognitively normal; CSF, cerebrospinal fluid; DM, diabetes mellitus; ICV, intracranial volume; MCI, mild cognitive impairment; MMSE, mini-mental status examination; PET, positron emission tomography; p-tau; phosphorylated tau; WM, white matter.

3.4. Predictive value of DM on cognitive function, volumes of ROIs and AD biomarkers

Linear mixed-effects models were used to predict cognitive decline over a follow-up period of up to 204 months at baseline. In subsequent analyses, the brain regions with significant differences in biomarkers and brain structure according to DM and with regions involved in memory formation and cognition were designated as ROIs: entorhinal cortex, hippocampus, parahippocampal cortex, and middle temporal cortex. In both CN and MCI groups, the interaction between DM and time showed a tendency toward increasing CDR-SB scores (CN, FDR-adjusted $p = 0.009$; MCI, FDR-adjusted $p < 0.001$, Figure 3A, 3B), and decreasing MMSE scores (FDR-adjusted $p = 0.031$, Figure 3D).

The interaction between DM and time for the brain volume showed a significant decrease in middle temporal cortex (FDR-adjusted $p < 0.001$, Figure 4G) in the CN. In MCI participants, there was a significant decrease in the volume of the entorhinal cortex (FDR-adjusted $p = 0.045$, Figure 4B), hippocampus (FDR-adjusted $p = 0.050$, Figure 4D), right parahippocampal cortex (FDR-adjusted $p = 0.047$, Figure 4F).

The interaction between DM and time for biomarkers showed a significant effect on increasing CSF tau levels (FDR-adjusted $p = 0.047$) in the CN. In addition, there were significant effects on decreasing entorhinal cortex tau PET (total; left; right all FDR-adjusted $p < 0.001$) and parahippocampal cortex tau PET (total; right all FDR-adjusted $p < 0.001$) levels. However, CSF Aβ, tau, and Aβ, tau PET levels had no significant effects in MCI (Table 4).

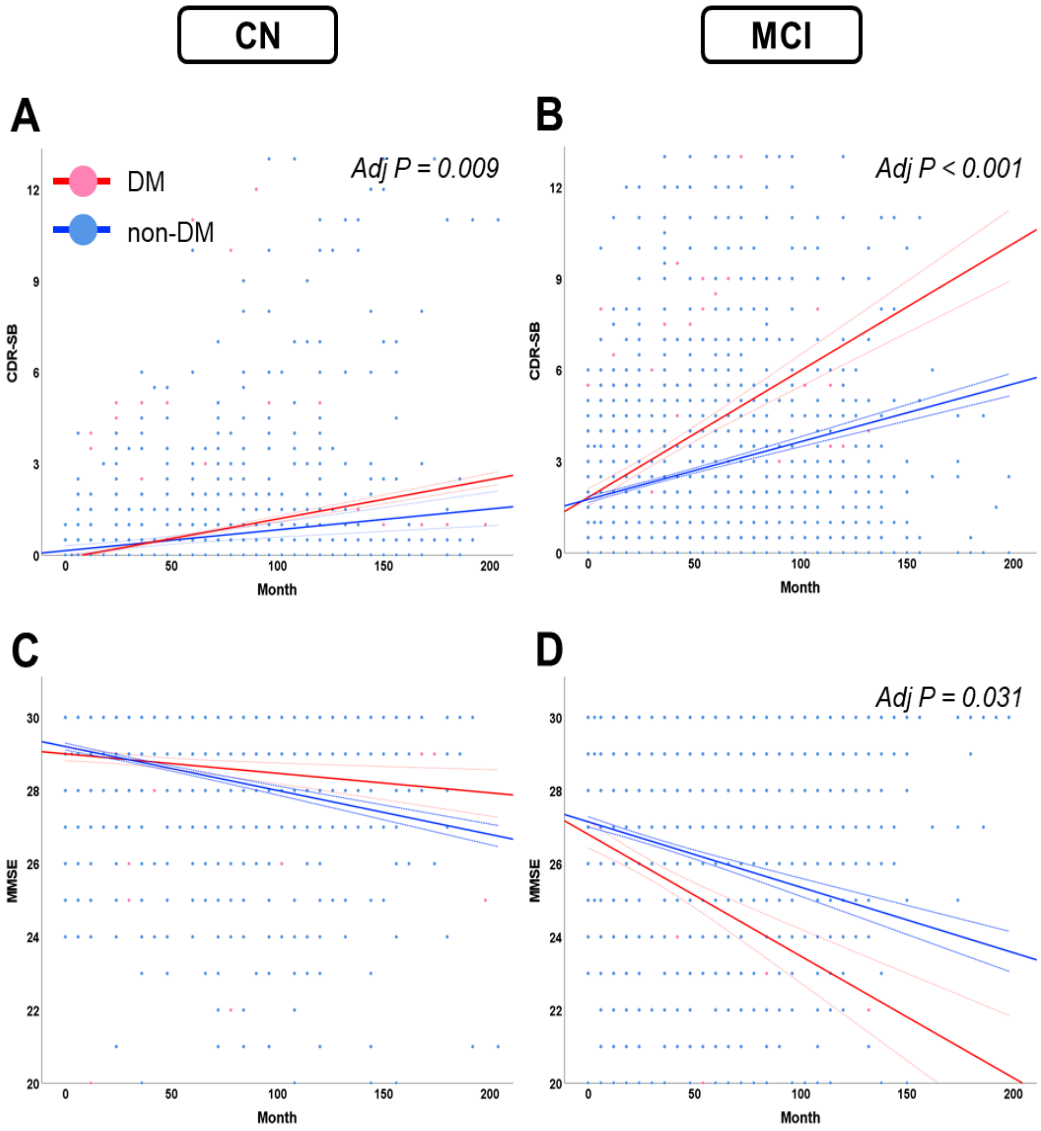
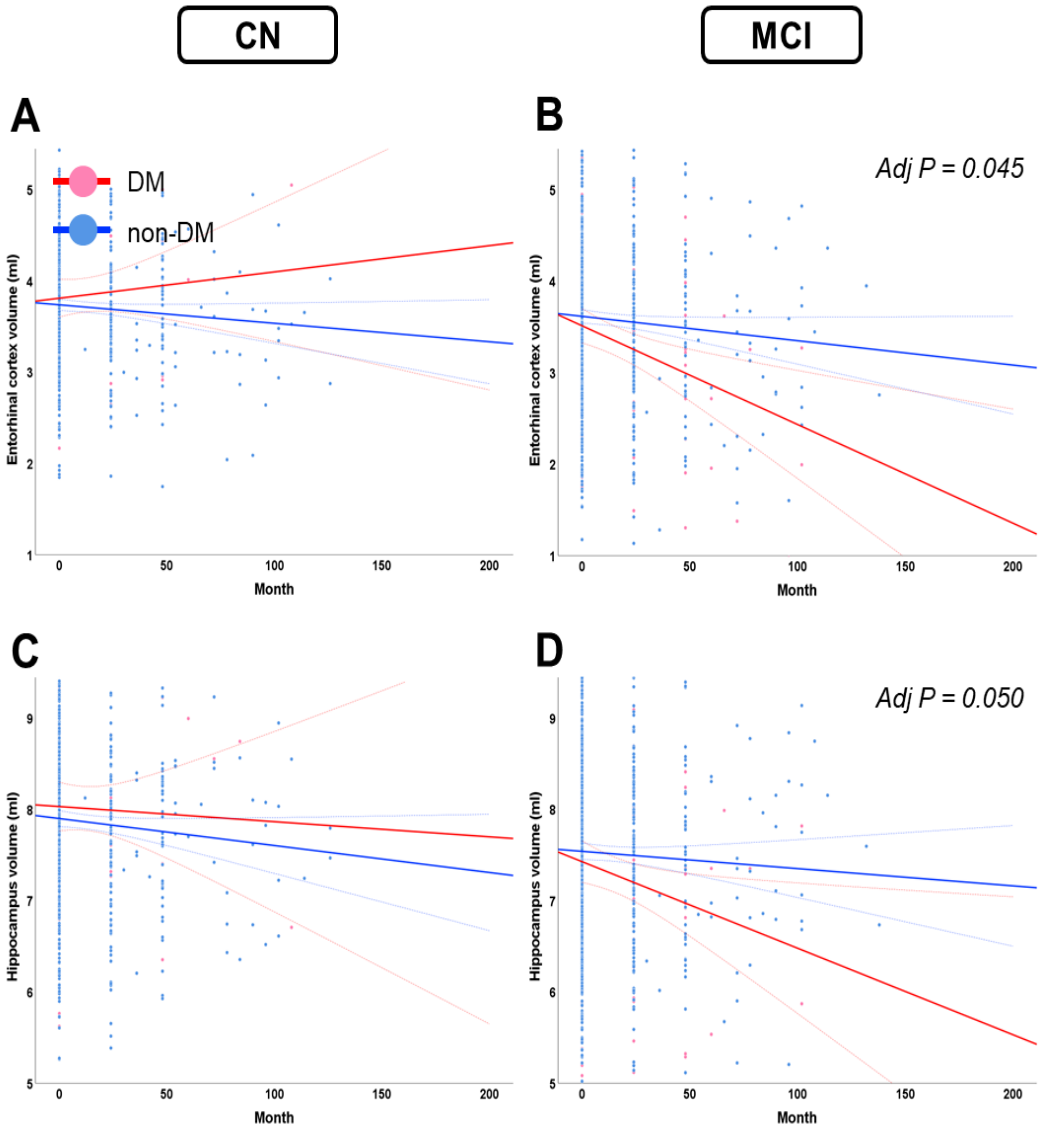


Figure 3. Predictive effect of DM on cognitive function between baseline and time since baseline. The linear mixed-effects model was applied to evaluate the predictive ability of longitudinal cognitive changes in DM. The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
p values were adjusted for FDR using Benjamini-Hochberg procedure.
Abbreviations: CDR-SB, clinical dementia rating-sum of boxes; CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; MMSE, mini-mental status examination.



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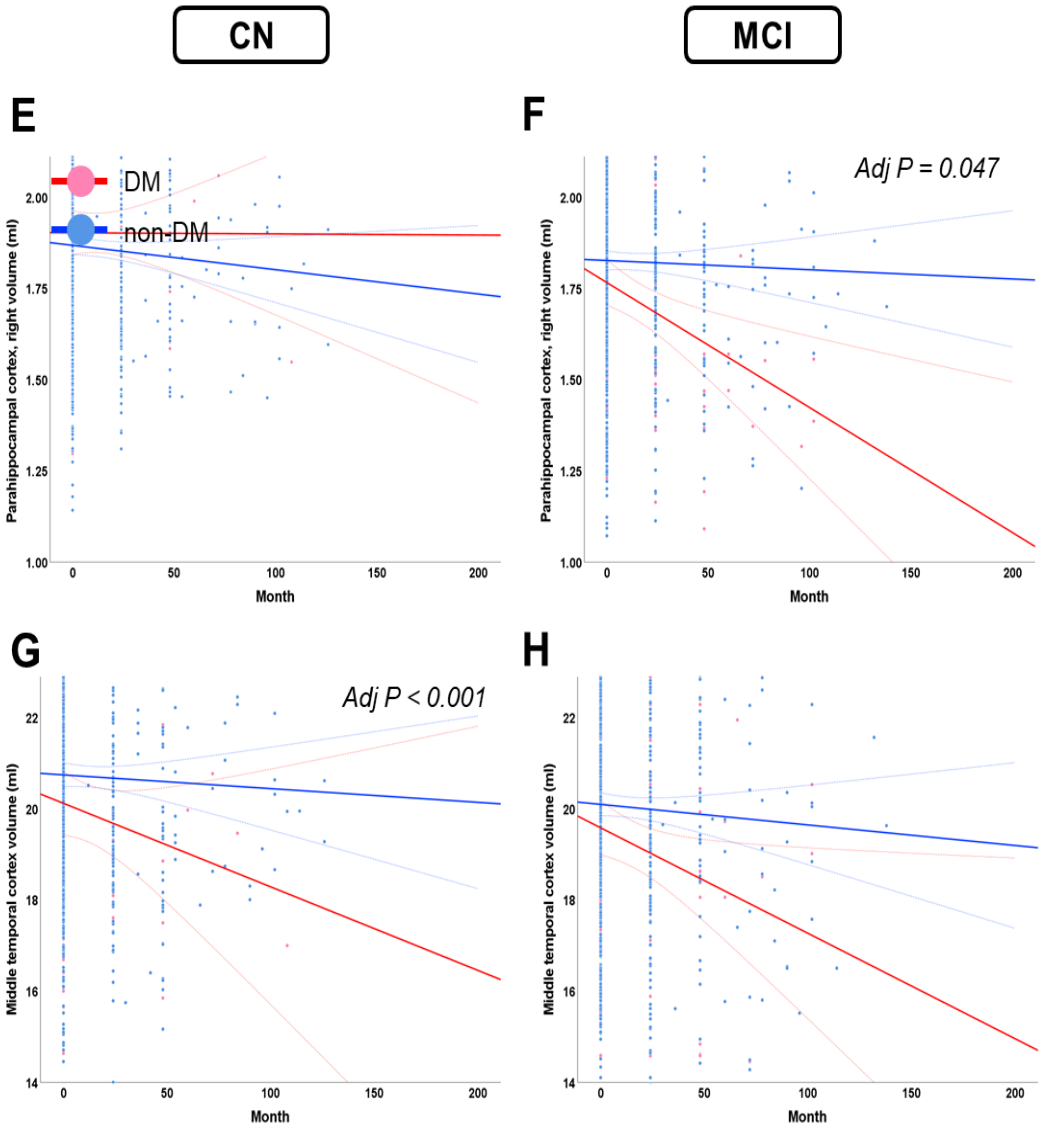

Figure 4. Predictive effect of DM on brain volume between baseline and time since baseline.
The linear mixed-effects model was applied to evaluate the predictive ability of longitudinal brain volume changes in DM. The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
p values were adjusted for FDR using Benjamini-Hochberg procedure.
Abbreviations: CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment.

Table 4. Predictive effect of DM on biomarkers between baseline and time since baseline

	CN					MCI				
	DM×time interaction					DM×time interaction				
Outcome	Unstandardized beta	SE	t	p-value	Adjusted p-value	Unstandardized beta	SE	t	p-value	Adjusted p-value
Biomarker	n=40					n=86				
CSF Aβ	2.137	3.440	0.621	0.537	0.537	0.144	1.908	0.075	0.940	0.975
CSF tau	1.785	0.588	3.038	**0.016**	**0.047**	0.017	0.543	0.031	0.975	0.975
CSF p-tau	0.089	0.070	1.269	0.219	0.329	0.011	0.059	0.195	0.845	0.975
Aβ PET	n=141					n=75				
Entorhinal cortex	0.001	0.000	1.955	0.084	0.253	-0.001	0.000	-2.018	0.053	0.265
Entorhinal cortex, left	0.000	0.000	1.030	0.321	0.723	-0.001	0.000	-2.923	**0.010**	0.100
Entorhinal cortex, right	0.001	0.000	3.370	**0.032**	0.143	0.000	0.000	-1.274	0.209	0.523
Hippocampus	0.000	0.000	3.510	1.000	1.000	0.000	0.000	-0.966	0.357	0.510
Hippocampus, left	0.000	0.000	-0.668	0.520	0.780	0.000	0.000	-0.942	0.356	0.593
Hippocampus, right	0.001	6.775E-05	3.032	**0.020**	0.183	0.000	0.000	-0.586	0.563	0.626
Parahippocampal cortex	6.487E-05	0.000	0.148	0.886	0.997	-0.001	0.000	-1.317	0.194	0.647
Parahippocampal cortex, left	0.000	0.000	-0.230	0.824	0.997	0.000	0.000	-0.901	0.479	0.599
Parahippocampal cortex, right	N.A.	N.A.	N.A.	N.A.	N.A.	0.000	0.000	-1.047	0.302	0.604

Middle temporal cortex	0.000	0.001	0.876	0.421	0.757	0.000	0.000	0.508	0.613	0.613
Tau PET	n=38					n=29				
Entorhinal cortex	-0.003	0.000	-7.586	**<0.001**	**<0.001**	0.005	0.004	1.232	0.218	0.727
Entorhinal cortex, left	-0.002	0.000	-6.274	**<0.001**	**<0.001**	0.005	0.005	0.989	0.341	0.568
Entorhinal cortex, right	-0.003	0.000	-8.303	**<0.001**	**<0.001**	0.005	0.005	0.962	0.355	0.394
Hippocampus	-0.004	0.002	-1.726	0.114	0.146	0.003	0.004	0.979	0.348	0.497
Hippocampus, left	-0.004	0.002	-1.646	0.159	0.159	0.004	0.004	1.082	0.299	0.748
Hippocampus, right	-0.004	0.002	-1.800	0.101	0.146	0.003	0.003	0.975	0.350	0.438
Parahippocampal cortex	-0.001	0.000	-4.924	**<0.001**	**<0.001**	0.005	0.004	1.380	0.192	0.960
Parahippocampal cortex, left	-0.001	0.001	-1.873	0.117	0.147	0.006	0.004	1.759	0.099	0.990
Parahippocampal cortex, right	-0.001	0.000	-3.865	**<0.001**	**<0.001**	0.004	0.003	1.041	0.319	0.638
Middle temporal cortex	-0.001	0.000	-1.570	0.137	0.152	0.001	0.004	0.134	0.992	0.992

The linear mixed-effects model was applied to evaluate the predictive ability of longitudinal biomarker changes in DM.
The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
Bold signals represent statistical significance ($p < 0.05$).
p values were adjusted for FDR using Benjamini-Hochberg procedure.
Abbreviations: Aβ, amyloid beta; CN, cognitively normal; CSF, cerebrospinal fluid; DM, diabetes mellitus; MCI, mild cognitive impairment; PET, positron emission tomography; p-tau; phosphorylated tau.

3.5. Impact of DM on the relationship between biomarkers and volume of ROI: moderation analysis

Table 3 identified differences in cognitive function, brain structure, and biomarkers depending on DM status. To assess the influence of DM on the ATN pathology process, a moderation analysis was conducted (Figure 2). DM significantly influenced biomarker levels in the hippocampus (Table 5). In CN with DM, there was a more increase in tau levels with increasing Aβ levels in the hippocampus (Figure 5A, 5C).

However, DM did not have a significant impact on the relationship between tau PET and brain volume (Table 6).

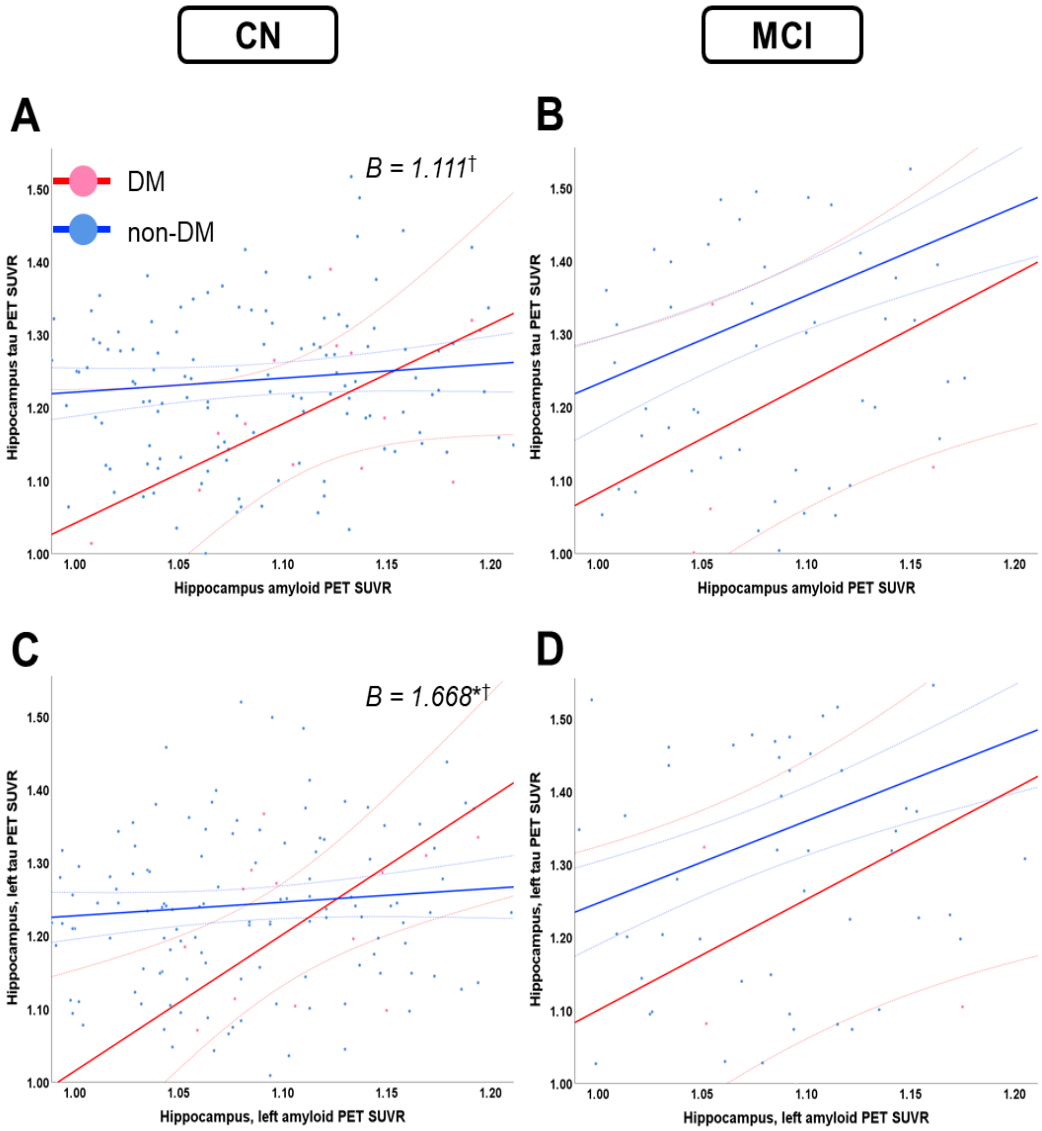

Figure 5. Conditional effect of DM on the relationship between Aβ and Tau of ROIs: moderation analysis. The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke. Presented numbers are unstandardized beta.
*P values were adjusted for FDR using Benjamini-Hochberg procedure.
†p value or adjusted p value <0.05
Abbreviations: CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; PET, positron emission tomography.

Table 5. Impact of DM on the relationship between Aβ and Tau of ROIs: moderation analysis

	CN					MCI				
Outcome	Unstandardized beta	SE	t	p-value for Aβ×DM	Adjusted p-value	Unstandardized beta	SE	t	p-value for Aβ× DM	Adjusted p-value
Tau PET										
Entorhinal cortex	-0.045	0.426	-0.106	0.916	0.950	0.772	0.668	1.155	0.252	0.535
Entorhinal cortex, left	-0.099	0.434	-0.227	0.821	0.950	0.962	0.678	1.420	0.160	0.535
Entorhinal cortex, right	-0.034	0.381	-0.088	0.930	0.950	0.782	0.771	1.013	0.314	0.535
Hippocampus	1.111	0.614	1.808	**0.050**	0.250	0.238	0.585	0.407	0.685	0.841
Hippocampus, left	1.668	0.582	2.867	**0.005**	**0.005**	0.353	0.552	0.639	0.525	0.750
Hippocampus, right	0.283	0.583	0.485	0.628	0.950	0.197	0.632	0.311	0.757	0.535
Parahippocampal cortex	0.087	0.241	0.359	0.720	0.950	0.460	0.425	1.082	0.283	0.841
Parahippocampal cortex, left	0.018	0.287	0.063	0.950	0.950	0.399	0.399	0.999	0.321	0.535
Parahippocampal cortex, right	0.120	0.209	0.572	0.568	0.950	0.512	0.477	1.072	0.287	0.535
Middle temporal cortex	-0.024	0.212	-0.115	0.909	0.950	-0.065	0.329	-0.197	0.844	0.844

The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke. Bold signals represent statistical significance ($p < 0.05$).

p values were adjusted for FDR using Benjamini-Hochberg procedure.

Abbreviations: CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; PET, positron emission tomography.

Table 6. Impact of DM on the relationship between Tau and volume of ROIs: moderation analysis

	CN					MCI				
Outcome	Unstandardized beta	SE	t	p-value for Tau× DM	Adjusted p-value	Unstandardized beta	SE	t	p-value for Tau×DM	Adjusted p-value
Brain volume										
Entorhinal cortex	0.530	1.519	0.349	0.728	0.910	-0.587	0.821	-0.715	0.477	0.955
Entorhinal cortex, left	-0.120	0.819	-0.146	0.884	0.947	-0.438	0.438	-1.000	0.321	0.955
Entorhinal cortex, right	1.154	0.847	1.363	0.175	0.710	-0.144	0.457	-0.315	0.754	0.955
Hippocampus	1.139	1.229	0.927	0.355	0.710	0.231	1.251	0.185	0.854	0.955
Hippocampus, left	0.583	0.621	0.939	0.349	0.710	0.123	0.576	0.213	0.832	0.955
Hippocampus, right	0.626	0.660	0.948	0.345	0.710	0.085	0.728	0.116	0.908	0.955
Parahippocampal cortex	-0.519	1.294	-0.401	0.689	0.910	-0.043	0.750	-0.057	0.955	0.955
Parahippocampal cortex, left	-0.054	0.810	-0.066	0.947	0.947	-0.145	0.419	-0.346	0.730	0.955
Parahippocampal cortex, right	-0.432	0.652	-0.663	0.509	0.848	0.076	0.409	0.185	0.854	0.955
Middle temporal cortex	-6.471	6.147	-1.053	0.294	0.710	-1.439	3.692	-0.390	0.698	0.955

The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke. Bold signals represent statistical significance ($p < 0.05$).

p values were adjusted for FDR using Benjamini-Hochberg procedure.

Abbreviations: CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment.

3.6. Predictive value of DM on cognitive function, volumes of ROIs according to sex

In both CN and MCI groups, the triple interaction between DM, sex, and time in the linear mixed-effects models did not show significant effects on cognitive tests and brain volume (Table 7). This indicates that the changes in cognitive function and brain volume related to DM are not associated with sex.

Table 7. Predictive effect of DM between baseline and time since baseline by sex

	CN					MCI				
	DM×Sex×time interaction					DM×Sex×time interaction				
Outcome	Unstandardized beta	SE	t	p-value	Adjusted p-value	Unstandardized beta	SE	t	p-value	Adjusted p-value
Cognitive variables	n=38					n=52				
CDR-SB	0.003	0.003	1.107	0.269	0.538	0.009	0.008	1.123	0.261	0.261
MMSE	0.002	0.006	0.293	0.770	0.77	-0.015	0.011	-1.340	0.180	0.261
Brain variables (brain vol.)										
Entorhinal cortex	-0.001	0.008	-0.163	0.871	0.91	0.007	0.007	0.952	0.346	0.895
Hippocampus	0.003	0.012	0.229	0.819	0.91	0.002	0.009	0.247	0.806	0.895
Parahippocampal cortex	0.004	0.007	0.628	0.533	0.91	-0.001	0.004	-0.133	0.895	0.895
Middle temporal cortex	-0.004	0.034	-0.113	0.910	0.91	0.013	0.019	0.668	0.511	0.895

Reference group is male.
The linear mixed-effects model was applied to evaluate the predictive ability of longitudinal biomarkers and brain volume changes in DM.
The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
p values were adjusted for FDR using Benjamini-Hochberg procedure.
Abbreviations: CDR-SB, clinical dementia rating-sum of boxes; CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; MMSE, mini-mental status examination.

3.7. Predictive value of DM on cognitive function, volumes of ROIs by number of APOE ε4 alleles

In CN, the triple interaction between DM, APOE ε4, and time in the linear mixed-effects models did not show any significant effects on cognitive tests and brain volume (Table 8). This suggests that the changes in cognitive function and brain volume related to DM are not associated with the number of APOE ε4 alleles.

Table 8. Predictive effect of DM between baseline and time since baseline by APOE ε4

	CN					MCI				
	DM×APOE ε4×time interaction					DM×APOE ε4×time interaction				
Outcome	Unstandardized beta	SE	t	p-value	Adjusted p-value	Unstandardized beta	SE	t	p-value	Adjusted p-value
Cognitive variables	n=23					n=60				
CDR-SB	-0.002	0.003	-0.816	0.415	0.415	0.012	0.007	1.740	0.082	0.164
MMSE	0.005	0.006	0.820	0.412	0.415	-0.010	0.010	-0.990	0.322	0.322
Brain variables (brain vol.)										
Entorhinal cortex	-0.002	0.007	-0.304	0.767	0.846	0.004	0.008	0.437	0.663	0.663
Hippocampus	0.022	0.008	2.753	0.060	0.240	0.008	0.009	0.891	0.376	0.589
Parahippocampal cortex	0.001	0.006	0.197	0.846	0.846	0.011	0.004	3.168	0.201	0.589
Middle temporal cortex	0.021	0.020	1.053	0.317	0.634	0.018	0.023	0.776	0.442	0.589

Reference group is APOE ε4 0copy.
The linear mixed-effects model was applied to evaluate the predictive ability of longitudinal biomarker and brain volume changes in DM.
The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
p values were adjusted for FDR using Benjamini-Hochberg procedure.
Abbreviations: APOE, apolipoprotein E; CDR-SB, clinical dementia rating-sum of boxes; CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; MMSE, mini-mental status examination.

3.8. Association between DM duration and cognitive function, volumes of ROIs

To investigate the relationship between DM duration and cognitive function and brain volume, multiple linear regression models were conducted at baseline.

In both CN and MCI groups, cognitive function and brain volume did not show significant associations with DM duration (Table 9).

Table 9. Results of the multiple regression analysis for the association between DM duration and cognitive function, brain volume at baseline

	CN			MCI		
Outcome	Standardized beta	p-value	Adjusted p-value	Standardized beta	p-value	Adjusted p-value
Cognitive variables	n=15			n=35		
CDR-SB	0.075	0.651	0.710	0.197	0.129	0.258
MMSE	0.065	0.710	0.710	0.032	0.799	0.799
Brain variables (brain vol.)						
Entorhinal cortex	-0.374	0.110	0.147	0.207	0.203	0.406
Hippocampus	-0.369	**0.047**	0.094	0.295	0.056	0.224
Parahippocampal cortex	-0.460	**0.045**	0.094	0.104	0.535	0.678
Middle temporal cortex	-0.006	0.983	0.983	0.067	0.678	0.678

Reference group is a duration of DM of 5 years or less.
Multivariate linear regression was constructed with DM mellitus as a predictor, adjusting for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
Bold signals represent statistical significance ($p < 0.05$).
p values were adjusted for FDR using Benjamini-Hochberg procedure.
Abbreviations: CDR-SB, clinical dementia rating-sum of boxes; CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; MMSE, mini-mental status examination.

3.9. Association between DM drug(metformin) and cognitive function, volumes of ROIs

Analyses were conducted to determine if the use of the DM drug (metformin) differed in cognitive function and brain volume among DM by cognitive status.

In MCI, the use of metformin significantly reduced the volume of the entorhinal cortex compared to the DM group not taking the drug ($p = 0.045$, Table 10).

Table 10. Results of association between DM drug (metformin) and cognitive function, brain volume at baseline

	CN			MCI		
Outcome	Metformin	no drug	p-value	Metformin	no drug	p-value
Cognitive variables	n=26	n=174		n=28	n=321	
CDR-SB	0.00(0.00)	0.04(0.13)	0.150	1.62(1.00)	1.54(0.87)	0.833
MMSE	29.00(1.06)	28.95(1.26)	0.876	28.07(1.62)	27.59(1.83)	0.194
Brain variables (Brain vol.)	n=23	n=109		n=21	n=174	
Entorhinal cortex	3.91(0.83)	3.81(0.67)	0.787	3.41(0.83)	3.71(0.88)	**0.045**
Hippocampus	8.19(0.80)	7.84(0.99)	0.081	7.51(1.21)	7.62(1.00)	0.545
Parahippocampal cortex	4.01(0.58)	3.86(0.55)	0.134	3.74(0.44)	3.84(0.60)	0.345
Middle temporal cortex	20.24(2.72)	20.31(2.73)	0.919	19.78(3.44)	20.23(2.90)	0.507

Mann Whitney U non-parametric test was constructed adjusting for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
Bold signals represent statistical significance ($p < 0.05$).
Abbreviations: CDR-SB, clinical dementia rating-sum of boxes; CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment; MMSE, mini-mental status examination.

3.10. Differences in conversion time between the CN and MCI according to DM status

The conversion time from CN to MCI and from MCI to AD due to DM was compared using survival analysis. Using the Kaplan-Meier method, the conversion time from CN to MCI (DM, month = 140.46; non-DM, month = 170.42, p = 0.003, Figure 6A) and from MCI to AD (DM, month = 71.38; non-DM, month = 93.86, p = 0.013, Figure 6B) was shorter in individuals with DM. Additionally, the time from MCI to AD conversion was shorter than from CN to MCI.

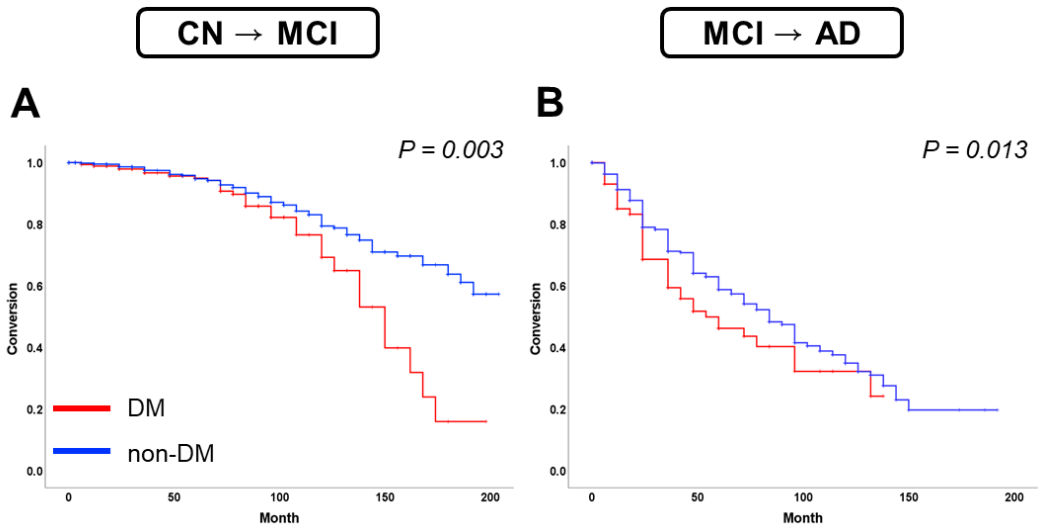

Figure 6. Differences in conversion time between the CN and MCI by DM, as determined using the Kaplan-Meier method. The analysis was adjusted for age, sex, years of education, number of APOE ε4 alleles, hypertension, and stroke.
Abbreviations: CN, cognitively normal; DM, diabetes mellitus; MCI, mild cognitive impairment.

4. DISCUSSION

This study aimed to clarify the relationship between DM and ATN pathology. Specifically, the prediction of cognitive decline by DM was assessed in CN and MCI. The following results were obtained:

1) At baseline, in both CN and MCI groups, DM showed negative associations with the volume of brain regions related to memory and cognitive function. Additionally, in MCI, DM showed a positive association with CSF tau levels.

2) Regarding the longitudinal prediction of cognitive decline, the interaction between DM and time showed cognitive impairment in both CN and MCI. In CN, there was a significant decrease in the volume of the middle temporal cortex. In MCI, significant decreases were observed in the volume of the entorhinal cortex, hippocampus, and right parahippocampal cortex. The interaction between DM and biomarkers showed a significant increase in CSF tau levels in CN but a decrease in tau PET levels in entorhinal and parahippocampal cortices.

3) According to the moderation analysis, DM significantly influenced positive relationship between the levels of Aβ and tau in the left hippocampus in CN.

4) Metformin significantly reduced the volume of the entorhinal cortex in MCI compared to DM patients not taking the drug.

5) The conversion time from CN to MCI and from MCI to AD was shorter with DM. Additionally, the conversion time from MCI to AD was shorter than that from CN to MCI conversion.

4.1. Impact of DM on ATN pathology

4.1.1. Biomarkers (Aβ, tau)

At baseline, there was no association between DM and biomarkers in CN, but the interaction between DM and time showed an increase in CSF tau levels. However, there were no changes in CSF Aβ or Aβ PET levels. Previous studies reported an increase in total tau and p-tau levels in the CSF of dementia patients.[29] Thus, the increase in CSF tau levels and the absence of changes in Aβ levels observed in this study aligns with previous findings reporting an increase in CSF tau and no association to CSF Aβ levels in patients with dementia.[75,76] However, the lack of changes in CSF Aβ levels with DM may be due to measurement limitations of CSF Aβ levels. The maximum measured Aβ value in the CSF was 1700 pg/mL, and the ceiling effect may have prevented identifying significant associations.

Previous studies on tau PET levels yielded conflicting results regarding the relationship between DM and elevated tau levels in the CSF and the brain.[60] Some studies reported that DM is associated with decreased NFT in the cerebral cortex and hippocampus[77] and that DM increases tau levels in the brain independent of Aβ.[59,78] However, the decrease in brain tau levels could also be influenced by the effects of DM medication.[76,79]

In this study, DM increased CSF tau levels and decreased tau PET levels in entorhinal and parahippocampal cortices in CN participants, consistent with previous findings.[59,77,78] Moreover, this result does not exclude the possibility of reduced tau in the brain due to DM medication.

In MCI, an increase in CSF tau levels was observed at baseline, but no significant changes in CSF or brain Aβ and tau levels over time depending on DM. The absence of significant changes in MCI may be because Aβ and tau levels are already increased regardless of DM status. Further research is needed to clarify the relationship between DM and tau pathology in MCI.

In the moderation analysis, DM at baseline had a significant effect on the positive relationship

between Aβ and Tau in the hippocampus in CN. Especially in DM, there was a notable pattern where tau levels increased steeply as Aβ levels increased, compared to non-DM. This finding is consistent with previous studies showing that the cortical Aβ levels in DM were significantly lower than in those without DM, and that individuals diagnosed with AD in DM exhibited positive tau pathology. This suggests that DM influences the biological changes evident in the early stages of cognitive decline, especially the impact on tau levels. And it might suggest that DM is associated with biomarkers of tau and dementia through a different pathway than Aβ.

4.1.2. Neurodegeneration and cognitive function

At baseline, DM showed a negative association with the volume of the whole brain and middle temporal cortex in CN, and with that of the brainstem in MCI. Additionally, in CN and MCI, the interaction between DM and time showed higher decreases in the volume of brain regions related to cognition, memory, and information processing.

This aligns with previous studies reporting associations between DM and volumetric changes in the cerebral cortex and middle temporal cortex,[80,81] contrast to studies showing greater brain atrophy in DM but no association with hippocampal atrophy.[82]

The present results indicate that the rate of volumetric changes in the brain regions depends on DM, becoming more pronounced with poorer cognition. This suggests that DM is a reliable indicator for predicting brain volume reduction. While DM showed no association with cognitive function in both CN and MCI participants at baseline, cognitive function decreased in both groups over time under DM.

Thus, beyond explaining the impact of DM on AD pathology, the results of this study suggest that DM may help predict cognitive decline.

4.2. Other DM factors affecting cognitive function

Metformin, one of the representative DM drugs that improve insulin resistance and regulate blood glucose levels, significantly reduced the volume of the entorhinal cortex in MCI. This suggests that its effect on cognition may be negative in cognitively impaired participants with DM, consistent with previous research.[83,84]

The conversion time from CN to MCI and from MCI to AD was shorter with DM than without. Additionally, the time from MCI to AD conversion was shorter than from CN to MCI. This suggests a rapid cognitive decline due to DM, with a more pronounced effect with worsening cognition.

Sex and APOE ε4 genotype did not predict cognitive decline. The first may require further investigation into metabolic mechanisms given reports of higher AD risk in females and higher DM risk and insulin resistance in males.[85]

Additionally, the relationship between DM and cognitive function or brain volume did not vary by APOE ε4 status, suggesting no interaction between DM and APOE ε4 affecting cognition. In previous studies, DM has been reported to have an inverse relationship with cognitive decline in individuals with the APOE ε4 allele,[86] to inhibit cognitive decline[87] or to show no association.[88] However, other studies demonstrated an association between APOE ε4 and cognitive impairment with peripheral insulin resistance.[89] While APOE ε4 is an important factor in AD pathology,[88] considering previous studies and the present results, the impact of DM on cognition in relation to APOE ε4 remains unclear.

Although cognitive decline was expected to increase with longer duration of DM,[72,73] there was no significant association between cognitive function and brain volume and DM duration > 5 years in CN and MCI. The lack of significance may be due to the small sample size with information on DM duration at baseline. Additionally, if longitudinal changes in the outcome variables according to the duration of DM are observed, it is expected that the relationship will be confirmed.

4.3. Strengths and limitations of the study

The strengths of this study include the comprehensive analysis of the relationship between DM and cognitive decline in both CN individuals and patients with MCI. Particularly, while most studies have assessed CSF tau,[90] the significance lies in the observation of an association between DM and tau on PET.

Changes in ATN pathology attributed to DM in the early stages of AD, such as MCI, can be meaningful for maintaining quality of life through early intervention. Additionally, brain regions related to cognition were analyzed in detail for volume and biomarker changes.

The study confirmed the effects of DM through long-term follow-up further demonstrating cognitive decline due to DM over cognitive conversion periods. To date, there are no longitudinal studies focusing on the predictive power of DM for cognitive decline, including ATN pathology. The present study analyzed results covering a mean follow-up of 35.2 months, with analysis results based on up to 204 months of follow-up.

However, this study has some limitations. First, the data used for analysis were retrospectively collected from the ADNI database, which may introduce bias. Second, due to strict inclusion criteria, the number of participants with DM was relatively small compared to participants without DM, which may obscure the relationship between DM and AD biomarkers.

Therefore, future research should overcome these limitations by using additional data for analysis. Analysis using alternative more easily accessible methods than CSF, is required in the future. For example, recent developments in diagnostic methods utilizing bodily fluids such as blood, saliva, urine, etc., suggest their potential for future studies. Particularly, metabolomics revealed decreases in the levels of 10 phospholipids in the serum of older adults in the pre-dementia stages with 90% accuracy. This finding holds promise for future clinical diagnosis and analysis.

Based on the findings suggesting that DM adversely affects cognition, DM medications could also influence cognition in CN and at pre-dementia stages. Therefore, future studies on DM

medications are warranted to provide insights into how DM treatment can prevent or improve cognitive decline.

Finally, the ADNI data used in this study were obtained from participants residing in the United States and Canada, which may limit generalization to other ethnical groups.

5. CONCLUSION

In conclusion, the present findings suggest that the presence of DM exacerbates cognitive impairment, as evidenced by volumetric reductions in brain regions associated with cognition, memory, and information processing, along with cognitive decline and AD biomarker pathology.

Accordingly, DM could be a reliable indicator for predicting ATN pathology. Particularly, cognitive decline was more rapid at early stages of AD, such as MCI. Therefore, DM monitoring and management in MCI patients are crucial in clinical practice. Furthermore, it is important to consider DM status in older adults showing early cognitive decline. This is valuable for improving the effectiveness of early treatment and prognosis of patients with DM.

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Abstract in Korean

바이오 마커로 측정한 알츠하이머병 진행에 대한 당뇨병의 영향: 후향적 코호트 연구

연구배경: 당뇨는 알츠하이머 병리와 인슐린 저항성, 염증반응 촉진, 산화 스트레스 증가 등의 여러 공통 병인을 공유한다는 측면에서 연관이 있을 것으로 예상된다. 특히, 인지기능 저하가 발생하기 전 생체표지자(아밀로이드, 타우)의 변화 및 뇌 구조의 변화가 선행된다. 당뇨의 존재가 이러한 알츠하이머 병리의 악화에 영향을 미친다면, 이는 당뇨환자의 인지건강에 매우 심각한 문제가 될 것이다. 그러나 기존의 연구들에서 당뇨의 존재와 알츠하이머 병리 가속화와의 관련성은 잘 확립되지 않았다. 또한 이러한 관련성은 바이오마커 분석과 뇌 구조, 신경심리검사 등의 측면들에서 영향이 동시에 확인되지 않았다. 따라서 당뇨의 알츠하이머 병리의 가속화를 다양한 측면에서 확인하는 것이 중요할 것이다.

연구목적: 당뇨가 알츠하이머병 유발에 영향을 미친다는 기존의 연구결과에 기반하여, 당뇨가 인지기능 악화를 초래할 것이라고 예측하였다. 이에 본 연구는 당뇨가 인지기능에 미치는 영향을 규명하고자 하였다. 이를 위하여 당뇨와 알츠하이머병의 임상적 판단의 기준이 되는 ATN(아밀로이드, 타우, 신경퇴행) 병리 및 신경심리검사분석을 포괄하여 인지기능 악화에 대한 당뇨의 영향을 평가하였다. 특히, 치매 초기단계인 경도인지장애에서 당뇨에 의한 변화의 관찰은 인지저하가 더 진행된 알츠하이머병 단계보다 이른 치료의 개입으로 삶의 질 유지에 의미있다고 볼 수 있으므로 경도인지장애에서 당뇨의 영향을 보았다.

연구방법: 본 연구는 기준 시점에서 인지상태 및 당뇨 존재 유무에 따라 참가자를 분류하였다(정상인지 당뇨 81명, 정상인지 비당뇨 556명, 경도인지장애 당뇨 132명, 경도인지장애 비당뇨 811명). 인지장애 군별로 당뇨 및 비당뇨 참가자를 분류한

상태에서 선형 혼합효과 모델을 적용하여 당뇨의 종단적 인지기능 변화를 예측하는 능력을 평가하였다. 또한 ATN병리에서 당뇨의 영향을 조사하기 위해 조절 분석을 수행하였다. 추가적으로 당뇨로 인하여 인지기능 저하가 더 악화되는지를 생존분석을 통하여 인지진단이 전환되는 기간을 비교하였다.

결과: 당뇨의 종단적 인지저하 예측에 대하여 정상인지 군과 경도인지장애 군에서 임상적 치매등급(CDR-SB)의 악화를 보였으며, 특히 경도인지장애 군에서는 인지기능점수의 저하를 보였다. 또한, 정상인지 군에서 중측두피질(middle temporal cortex), 경도인지장애 군에서 내후각피질(entorhinal cortex), 해마(hippocampus), 오른쪽 해마주위피질(right parahippocampal cortex)의 용적이 유의하게 감소하였다. 바이오마커에 대하여 당뇨는 정상인지 군에서 뇌척수액 타우 수준 증가 및 내후각피질 타우(entorhinal cortex tau PET), 해마주위피질 타우(parahippocampal cortex tau PET)수준 감소에 영향을 주었다. 조절 분석 결과, 당뇨의 존재는 정상인지 군에서 해마의 아밀로이드와 타우간 양의 관계에 영향을 주었으나, 경도인지장애 군에서는 유의한 영향을 보이지 않았다. 정상인지 군에서 경도인지장애 군으로, 경도인지장애 군에서 알츠하이머 군으로의 전환기간은 당뇨에서 더 짧았다.

결론: 본 연구의 결과는 당뇨의 존재가 인지와 기억, 정보처리와 관련된 뇌 부위의 용적 감소 및 인지기능 저하, 알츠하이머 바이오마커 병리와 연관되어 인지능력을 악화하는 것으로 나타났다. 이는 당뇨가 ATN병리를 예측하는데 신뢰할 만한 지표로 작용한다는 것을 시사한다. 특히, 이러한 인지 기능 악화는 치매전구기 시기인 경도인지장애 군에서 더 빠른 악화를 보였다. 따라서 초기 인지저하를 보이는 인구를 대상으로 당뇨상태를 고려한다면, 조기치료의 효과와 예후를 개선하는데 유용할 것이다.

핵심되는 말: 당뇨, 경도인지장애, 바이오마커, 신경퇴행, 인지기능