

Diabetes mellitus and cognition

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Diabetes Mellitus and Cognition: A Pathway Analysis in the MEMENTO Cohort

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ABSTRACT

OBJECTIVE: To assess the role of biomarkers of Alzheimer's Disease (AD), neurodegeneration and small vessel disease (SVD) as mediators in the association between diabetes mellitus and cognition.

METHODS: The study sample was derived from MEMENTO, a cohort of French adults recruited in memory clinics and screened for either isolated subjective cognitive complaints or mild cognitive impairment. Diabetes was defined based on blood glucose assessment, use of antidiabetic agent or self-report. We used structural equation modelling to assess whether latent variables of AD pathology (PET mean amyloid uptake, $A\beta_{42}/A\beta_{40}$ ratio and CSF phosphorylated tau), SVD (white matter hyperintensities volume and visual grading), and neurodegeneration (mean cortical thickness, brain parenchymal fraction, hippocampal volume, and mean fluorodeoxyglucose uptake) mediate the association between diabetes and a latent variable of cognition (five neuropsychological tests), adjusting for potential confounders.

RESULTS: There were 254 (11.1%) participants with diabetes among 2,288 participants (median age 71.6 years; 61.8% women). The association between diabetes and lower cognition was significantly mediated by higher neurodegeneration (standardized indirect effect: -0.061, 95% confidence interval: -0.089; -0.032), but not mediated by SVD and AD markers. Results were similar when considering latent variables of memory or executive functioning.

CONCLUSION: In a large clinical cohort in the elderly, diabetes is associated with lower cognition through neurodegeneration, independently of SVD and AD biomarkers.

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INTRODUCTION

Type 2 diabetes (diabetes) is a risk factor for cognitive decline and dementia (1,2). Several underlying mechanisms could be involved, such as chronic hyperglycemia leading to advanced glycation end-products, atherosclerosis, and subsequent cerebrovascular lesions (3–5). Insulin dysregulation, including insulin resistance and insulin deficiency, may promote cerebral hypometabolism (6) and amyloid and tau pathologies, hallmarks of Alzheimer's disease (AD) (7). Diabetes has also been associated with brain structural modifications such as cerebral atrophy and cerebrovascular lesions (8–10). Moreover, while diabetes is associated with cerebral hypometabolism (11,12), results are conflicting regarding its association with amyloid and tau pathology, whether measured in the brain (PET) or in CSF (11,13,14).

Previous studies have suggested a mediating role of neurodegeneration and small vessel disease biomarkers on the association between diabetes and cognition (15–17). However, the mediating role of AD-specific lesions (amyloid plaques and neurofibrillary tangles), and the correlation between those different brain features have not been considered so far.

We thus estimated the mediating effect of biomarkers of AD, neurodegeneration and small vessel disease in the association between diabetes and cognition, in non-demented older adults recruited from French memory clinics.

METHODS

The MEMENTO Cohort

The MEMENTO cohort is a clinic-based study of patients presenting with a large variety of cognitive symptoms or subjective cognitive complaints, who were enrolled between April 2011 and June 2014, within the French national network of university hospital-based memory clinics (18). At inclusion, participants presented either 1) with mild cognitive impairment, when performing one standard deviation worse than the mean of the subject's own age, sex, and education-level group, in one or more cognitive domains, this deviation being identified for the first time through cognitive tests performed recently (less than 6 months preceding screening phase), or 2) with isolated cognitive complaints, if participants had subjective cognitive complaint (assessed through visual analogic scale), without any objective cognitive deficit as defined previously, while being 60 years and older. All participants had a Clinical

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Dementia Rating scale (19) score ≤0.5. Main exclusion criteria have been described elsewhere (22). All examinations (including neuropsychological battery administration, clinical examinations, brain MRI, CSF samples and fluorodeoxyglucose [FDG] and amyloid PET) followed standardized procedures (18).

Among the 2,323 participants included in the MEMENTO cohort, 2,288 participants from 26 study centers were included in this analysis after exclusion of participants with missing data on diabetes status (N = 35).

Standard protocol approvals, registrations, and patient consents

This study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The MEMENTO cohort protocol has been approved by the local ethics committee ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"; approval number 2010-A01394-35) and was registered in ClinicalTrials.gov (Identifier: NCT01926249).

Diabetes definition

Participants were classified as having diabetes at baseline visit either in presence of fasting blood glucose ≥ 7 mmol/L (≥126 mg/dL) or non-fasting blood glucose ≥ 11.1 mmol/L (≥200 mg/dL) or antidiabetic drug intake (Anatomical Therapeutic Chemical classification system: code A10A "insulins and analogues", and code A10B "blood glucose lowering drugs, excl. insulins") or self-reported history of diabetes.

Neuropsychological evaluation

A full neuropsychological test battery was administered to participants (18). Global cognition was assessed by Mini-Mental State Examination (MMSE) (20), long-term memory was assessed by Free and Cued Selective Reminding Test (FCSRT) (21), semantic verbal fluency via 'animal' words (22), visuo-spatial abilities by Rey-Osterrieth Complex Figure Test (23), and attention and executive functions by Trail Making Test (TMT) A and B (24).

Biomarkers assessment

MRI

As part of the inclusion criteria, participants had to agree to undergo brain MRI. Brain magnetic resonance images were acquired after a standardization of the imaging processes and coordinated by the CATI (http://cati-neuroimaging.com), a

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neuroimaging platform dedicated to multicentre studies (25). Full details are described elsewhere (18). Briefly, MRI machines of 1.5 and 3 Tesla were used across centers using harmonized protocols. All MRI scans acquired were then centralized, quality checked, and postprocessed to obtain standardized measurements for each participant. Whole-brain, gray matter, and white matter volumes were assessed with Statistical Parametric Mapping 8 (26), hippocampal volumes with the SACHA software (27), and mean cortical thickness of each hemisphere with FreeSurfer 5.3 averaged in the ROI of the Desikan-Killiany atlas (28). White matter lesions volumetry was performed using WHASA software (29) complemented by a centralized visual assessment by a trained rater using the Fazekas and Schmidt scale (30).

FDG-PET

18F-FDG-PET was offered to all participants but was not mandatory. PET images were acquired after a standardization of the acquisition and reconstruction imaging parameters, coordinated by the CATI (31). After a centralized quality check and postprocessing performed by the CATI, the following measures were obtained: mean FDG-PET uptake for the regions of interest (ROIs) of the Automated Anatomical Labeling atlas relative to the pons reference region (32), including partial volume correction, and mean FDG-PET uptake for a set of AD-specific ROIs inferred from the Alzheimer's Disease Neuroimaging Initiative database (33), expressed as standard uptake value ratios (SUVRs).

PET amyloid imaging

PET amyloid imaging was available for 643 participants of the analytical sample, using either 18F-florbetapir (Amyvid®, Eli Lilly) (N=437) or 18F-flutemetamol (Vizamyl®, GE Healthcare) (N=206) radioligands. Mean brain amyloid SUVR was computed, harmonized across the radioligands (34), and used for the current study.

CSF sampling

Lumbar puncture was offered to all participants but was not mandatory , and CSF centralized measurements of amyloid-β 42 peptide ($A\beta_{42}$), $A\beta_{40}$, total tau, and phosphorylated tau levels were performed using the standardised INNOTEST sandwich ELISA (Fujirebio, Ghent, Belgium).

Potential confounding factors

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Sociodemographic information recorded at baseline included age, sex and education (low education defined as no or primary school, intermediate education defined as secondary school or high school, and high education defined as university). Lifestyle factors included smoking status (never, former and current smoker) and current alcohol consumption (no, ≤ 1 drink/day, and >1 drink/day). Hypertension was defined as antihypertensive drug intake or mean of three blood pressure measurements either ≥ 140 mmHg for systolic blood pressure or ≥ 90 mmHg for diastolic blood pressure. Dyslipidemia was defined by plasma cholesterol > 6.24 mmol/L or use of any lipid-lowering drugs. Body mass index (BMI) was categorized as <20 kg/m², 20 to 25 kg/m², 25.1-29.9kg/m² and ≥30kg/m². History of cardiovascular disease was defined as a self-reported history of myocardial infarction, angina pectoris, coronary artery, or peripheral artery disease. History of stroke was self-reported. Depression was assessed with the Neuropsychiatric Inventory–Clinician (NPI-C) (35). APOE ε2, ε3, or ε4 alleles were determined for all participants by KBiosciences (Hoddesdon, UK; www.kbioscience.co.uk) as described elsewhere (18). APOE ε4 status was defined as presence of at least one ε4 allele versus absence.

Statistical analyses

Baseline characteristics were compared according to baseline diabetic status for the analytical sample. We used chi-square test (or Fisher exact test when appropriate) and Student t test (or non-parametric Mann-Whitney-Wilcoxon test when appropriate) for categorical and continuous variables comparisons, respectively.

Brain parenchymal fraction was computed as the sum of grey matter and white matter volumes divided by total intracranial volume. Total hippocampal volume was computed as the sum of left and right hippocampal volumes. WMH volume and hippocampal volume were adjusted for total intracranial volume using the residual approach (36). Mean FDG uptake across the brain was used.

Structural equation modeling (SEM) (37) was used to examine a potential mediating role of biomarkers respectively of AD, small vessel disease (SVD) and neurodegeneration in the association between diabetes and cognition. SEM was preferred over standard regression modeling for its ability to directly focus the mediation analysis on the dimensions of interest (here cognition, SVD, AD and neurodegeneration), and to define each dimension from several noisy observed indicators. The observed indicators of the four latent variables of interest, namely AD pathology, small vessel disease, neurodegeneration and cognition, are listed in

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Table 1. They were determined from the literature and validated in preliminary separated SEM analyses. Correlated residuals were assumed between left and right cortical thicknesses and between TMT A and TMT B scores to account for a potential common source of measurement error. Mean brain amyloid SUVR was normalized using a logarithmic transformation and then standardized (z-score) by radioligand. The relationships between diabetes, potential confounders, and latent variables of AD pathology, neurodegeneration, small vessel disease, and cognition were modelled in the structural linear regressions. For ease of interpretation, the four latent variables were standardized (mean 0, variance 1) so that one unit corresponds to the standard deviation of a given dimension. The indirect effects of diabetes on cognition through the latent dimensions were estimated with their 95% CI, using path analysis technique (37). All linear regressions of mediators and cognition were adjusted for the following potential confounding factors: age, sex, education (high education versus low and intermediate), smoking status (current smoker versus never or former smoker), alcohol consumption (>1 drink/day versus ≤1 drink/day), hypertension, dyslipidemia, obesity (≥30kg/m^2) and APOE genotype (ε4 carrier versus ε4 non-carrier). Missing values for observed indicators of latent variables and for confounding factors were handled using a full information maximum likelihood approach, assuming missingness at random. The multicentric nature of the data was accounted for and Huber-White robust standard errors were reported to correct for the potential intra-center correlation (38). The general goodness of fit was evaluated using robust Tucker-Lewis Index (TLI), robust Comparative Fit Index (CFI), robust Root Mean Square Error of Approximation (RMSEA) and its 90% confidence interval, p-value for test of close fit (null hypothesis RMSEA <0.05), and Standardized Root Mean Square Residual (SRMR) with cut-offs recommended in the literature (39).

Several sensitivity analyses were performed. First, we used a different definition of "diabetes" by excluding a self-reported history of diabetes. Second, additional baseline characteristics associated with availability of MRI, FDG-TEP, amyloid-PET and CSF data (living alone, Clinical Dementia Rating scale score, prevalent dementia, depression, stroke history, cardiovascular history, and physical activity expressed as metabolic equivalent of task minutes per week, **Table 2**) were used as auxiliary variables in the estimation process under FIML to strengthen the missing at random assumption. Third, as the mediation analysis framework makes the implicit assumption that mediators (i.e., AD pathology, small vessel disease and neurodegeneration) are anterior to the outcome (i.e., cognition), we tried to preserve this assumption by excluding biomarkers measurements performed more than 6

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months after cognitive assessments. Fourth, as CSF biomarkers are prone to variability whereas brain biomarkers are indicators of accumulated burden of lesions (40), we performed a sensitivity analysis using only brain amyloid load as indicator of the latent variable for AD pathology. Finally, we also compared the results with those obtained when considering interactions between diabetes and each mediator in the main adjusted model, as recommended for mediation analysis (41).

We also explored the mediating pathways in the association of diabetes with specific cognitive domains in separate models: a latent variable for memory (indicators: total free recall score and verbal fluency) and a latent variable for executive functioning (indicators: TMT A and TMT B scores).

Analyses were conducted using SAS v9.3 (SAS Institute Inc, Cary, NC, USA), and R version 3.5.1 (42) with the *lavaan* package for SEM analysis (38).

Data Availability

Anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with EU legislation on the general data protection regulation.

RESULTS

Baseline description

Compared to participants without diabetes at baseline, participants with diabetes (254, 11.1%) were more likely to be men, and to have lower education level. They were also more likely to have hypertension, dyslipidemia, obesity, and history of cardiovascular disease or stroke. Participants with diabetes had on average lower performances on executive functions and attention, memory and semantic verbal fluency (**Table 3**).

At baseline, 65.3% of participants with diabetes were taking antidiabetic medications (oral antidiabetic agents, 57.5%; insulin, 13.8%). Diabetes status was solely based on self-report in 60 (23.6%) of the diabetic participants. The median self-reported duration of diabetes was 10.0 years (interquartile range, 4.9-19.4 years).

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The model fit was adequate according to the recommended cutoffs: robust CFI = 0.951, robust TLI = 0.926, robust RMSEA = 0.040 (90% CI, 0.037; 0.042), p-value for test of close fit = 1.00, and SRMR = 0.038. Associations between diabetes, AD pathology, SVD, neurodegeneration and cognition are presented in **Figure 1**. Presence of diabetes was significantly associated with higher neurodegeneration but was not significantly associated with AD pathology and SVD. Higher levels of small vessel disease, neurodegeneration and AD pathology were independently associated with lower cognition. Once adjusted for neurodegeneration, AD pathology and SVD, there was no direct effect of diabetes on cognition (standardized β = 0.023, 95% CI: -0.030; 0.076, p = 0.40). Association between diabetes and lower cognition was mainly mediated by higher neurodegeneration (standardized β = -0.061, 95% CI: -0.089; -0.032, p < 0.001). The indirect effect of diabetes on cognition via SVD and AD pathology were non-statistically significant (standardized β = 0.000, 95% CI: -0.004; 0.004, p = 0.98 and standardized β = -0.013, 95% CI: -0.040; 0.015, p = 0.38, respectively).

In complementary analyses considering specific cognitive functions, associations between diabetes and lower memory or lower executive functioning were also mainly mediated by higher neurodegeneration (standardized β = -0.058, 95% CI: -0.088; -0.029, p<0.001 and standardized β = -0.034, 95% CI: -0.051; -0.016, p<0.001 respectively) (**Table 4**).

Sensitivity analyses

Results were similar when excluding self-reported history from the definition of diabetes, when adding auxiliary variables to the estimation process or when excluding delayed measures of biomarkers (**Table 5**). When using only brain amyloid load as indicator of the latent variable for AD pathology, the indirect pathway linking diabetes to lower cognition through higher neurodegeneration was of similar magnitude (standardized β = -0.066, 95% CI: -0.097; -0.034, p<0.001). Diabetes was significantly associated with higher AD pathology (standardized β = 0.107, 95% CI: 0.021; 0.193, p = 0.01), and higher AD pathology was significantly associated with lower cognition (standardized β = -0.144, 95% CI: -0.248; -0.039, p = 0.007). The indirect pathway linking diabetes to lower cognition through AD pathology remained non-statistically significant (standardized β = -0.015, 95% CI: -0.033; 0.002, p = 0.08) though. When considering interaction between diabetes and each intermediate latent variable, the indirect effects of diabetes on cognition via neurodegeneration (standardized β = -0.059, 95%CI: -0.089; -0.030, p < 0.001), AD pathology

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(standardized β = -0.011, 95%CI: -0.034; 0.012, p = 0.34) and SVD (standardized β = -0.001, 95%CI: -0.006; 0.003, p = 0.54) remained virtually the same.

DISCUSSION

In a cross-sectional analysis of a large clinical cohort of participants with either isolated cognitive complaints or mild cognitive impairment, we report that the deleterious effect of diabetes on cognitive performances is mainly mediated through markers of neurodegeneration whereas AD pathology (amyloid, p-Tau) or small vessel disease pathology do not seem to play a major role.

The association between diabetes and markers of neurodegeneration such as brain atrophy (8,12,13,43) and brain hypometabolism (11,12) has been consistently reported in cross-sectional studies. While diabetes is a risk factor for vascular disease and stroke, its association with subclinical cerebrovascular lesions (silent brain infarcts, WMH, cerebral microbleeds) is uncertain (44). In the present study, diabetes was not associated with small vessel disease, even though participants with diabetes had more frequent self-reported history of stroke.

The mediating role of neurodegeneration and small vessel disease in the association between diabetes and cognition has already been investigated in several studies. In a sample of 4,206 older adults of the Age, Gene/Environment Susceptibility–Reykjavik Study (mean age 76 years, 11% with diabetes), MRI markers of neurodegeneration (gray matter, normal white matter, and total brain tissue volumes) and small vessel disease (cortical infarcts, subcortical infarcts, WMLs, and CMBs) significantly mediated the cross-sectional association of diabetes with lower processing speed and executive function (15). In a longitudinal analysis on 817 participants from the Alzheimer's Disease Neuroimaging Initiative cohort (mean age 75 years, 15% with diabetes) the effect of diabetes on cognitive decline up to 60 months (mean follow-up time, 30 months) was significantly mediated by baseline cortical thickness (17). Similarly, in a sample of 448 older adults of the Swedish National Study on Aging and Care in Kungsholmen (mean age at baseline, 72 years), a higher cardiovascular burden, including diabetes as a component, was associated with a faster MMSE decline over 9 years; this effect being largely mediated by brain MRI markers of atrophy (volumes of total gray matter, ventricles, and hippocampus) and small vessel disease (volume of WMHs) (16). Nevertheless, none of those studies accounted for AD biomarkers, unlike the present study.

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Insulin resistance and associated insulin signaling impairment promote Aβ accumulation and tau phosphorylation (7). However, no association between diabetes and amyloid and tau biomarkers was reported in previous studies (11,13,45). In the present study, diabetes was associated with higher brain amyloid load measured on PET imaging, but diabetes was not associated with the latent variable of AD pathology, which included CSF biomarkers of amyloid and tau. This discrepancy between brain and CSF biomarkers can partly be explained by the variability of CSF biomarkers, whereas brain biomarkers are indicators of accumulated lesions.

Although it needs to be replicated in longitudinal studies, our finding that neurodegeneration mediates the association between diabetes and cognitive performances, independently of biomarkers of AD and small vessel disease supports the hypothesis of a direct role of diabetes-related insulin resistance in the development of cognitive impairment in older adults with diabetes. Indeed, insulin also plays an important role in neuronal synaptic plasticity and facilitates learning and memory in humans (4) and, therefore, impaired insulin signaling could directly contribute to neuronal dysfunction and degeneration. As impaired insulin signaling has also been linked to promotion of amyloid-β accumulation and tau hyperphosphorylation (7), brain insulin resistance could be a therapeutic target in AD and related dementias. Several exploratory clinical trials have reported a beneficial effect on cognition of intranasal insulin for healthy participants, participants with diabetes, mild cognitive impairment or AD (46), and longer-term trials are currently ongoing.

The MEMENTO study has several strengths to answer the current objectives. First, a wide range of biomarkers was acquired in a highly standardized setting on more than 2,000 participants allowing a multi-dimensional assessment of brain ageing and pathology biomarkers. Indeed, we were able to include simultaneously brain MRI, brain FDG-PET, amyloid-PET and CSF data in a mediation analysis of the diabetes-cognition association, offering a unique insight on underlying mechanisms. Second, we were able to model brain biomarkers as latent variables in a SEM framework, accounting for measurement error of the indicators, and we were able to estimate direct and indirect effects of diabetes on several domains of cognition. Third, results were robust to several sensitivity analyses. There are also some limitations. First, the temporal relationship between diabetes, biomarkers and cognition is not ensured by the cross-sectional design, and causality cannot be claimed. Nevertheless, we can

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hypothesize that diabetes preceded biomarkers measures in most participants with diabetes (duration was 4.9 years or more in 75% of participants with diabetes). We also modeled correlations between neurodegeneration, AD pathology and SVD instead of directed relationships because the causal interpretation of their interrelations requires longitudinal data. Second, no tau-PET data was available to assess tau pathology, and we had to use CSF phosphorylated tau as a proxy for cerebral tau accumulation, assuming a strong correlation between both, as suggested by existing evidence (40). Third, the analytical strategy relies on the assumption that data are missing at random. This assumption may be strong for CSF and PET-amyloid data, for which 70% to 80% of data were missing. However, we used a broad range of baseline characteristics associated with availability of CSF and PET-amyloid data as auxiliary variables in the estimation process, thus making the missing-at-random assumption more plausible. We must also acknowledge the unavailability of data regarding past and current glucose control that prevented us to explore whether diabetes control modified the explored relationships. Finally, the observed findings may not fully translate in the general older population, as participants in the MEMENTO study are adults with either isolated cognitive complaints or mild cognitive impairment who were seeking care in memory clinics.

The current results suggest that the detrimental effect of diabetes on cognition is mediated by neurodegeneration, independently of AD and small vessel disease pathologies, in a population of older adults at risk for dementia. Longitudinal studies are now needed to reinforce and confirm these findings.

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TABLES

Table 1. Observed indicators for latent dimensions variables

Latent variables	Observed indicators	Data available N (%)
Small vessel disease	White matter hyperintensities volume	1,884 (80.6%)
	Fazekas scale scores for paraventricular white matter hyperintensities	2,145 (93.8%)
	Fazekas scale scores for deep white matter hyperintensities	2,145 (93.8%)
Alzheimer's disease pathology	Mean brain amyloid uptake	643 (28.1%)
	CSF $A\beta_{42}/A\beta_{40}$ ratio	400 (17.5%)
	CSF Phosphorylated tau	408 (17.8%)
Neurodegeneration	Mean right cortical thickness	2,106 (92.0%)
	Mean left cortical thickness	2,106 (92.0%)
	Brain parenchymal fraction	2,103 (91.9%)
	Hippocampal volume	2,061 (90.1%)
	Mean brain FDG uptake	1,308 (57.2%)
Cognition	FCSRT total free recall score	2,269 (99.2%)
	TMT A (seconds/correct move)	2,265 (99.0%)
	TMT B (seconds/correct move)	2,192 (95.8%)
	Rey complex figure test, 3-minute copy score	2,125 (92.9%)
	Verbal fluency (number of animals produced)	2,245 (98.1%)

Abbreviations: FCSRT, Free and Cued Selective Reminding Test; TMT, Trail Making Test.

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Table 2. Baseline characteristics associated with the availability of MRI, FDG-PET, amyloid-PET and CSF data – MEMENTO Study, France (n = 2,288).

	Available data		P [a]
	No	Yes	
MRI, N	130	2,158	
Cardiovascular history	20 (15.4)	185 (8.6)	0.008
MMSE score	27.4 (2.2)	27.9 (1.9)	0.001
FCSRT total free recall score	24.3 (9.2)	26.1 (8.2)	0.01
FDG-PET, N	980	1,308	
Female sex	648 (66.1)	765 (58.5)	<0.001
Current alcohol consumption			0.006
No	352 (37.1)	399 (30.8)	
≤1d/day	412 (43.5)	604 (46.7)	
>1d/day	184 (19.4)	291 (22.5)	
Dyslipidemia	402 (55.0)	480 (46.3)	<0.001
MMSE score	27.8 (2.0)	28.0 (1.9)	0.009
TMT A (seconds/correct move)	2.1 (1.0)	2.0 (0.9)	0.005
TMT B (seconds/correct move)	5.2 (3.6)	4.9 (3.2)	0.02
Rey complex figure test, 3-minute copy score	14.5 (7.1)	15.6 (6.9)	<0.001
Verbal fluency, animals (number of words produced)	27.7 (8.7)	28.8 (8.7)	0.006
Amyloid-PET, N	1,645	643	
Current alcohol consumption			<0.001
No	584 (36.4)	167 (26.2)	
≤1d/day	713 (44.5)	303 (47.5)	
>1d/day	307 (19.1)	168 (26.3)	
Diabetes	201 (12.2)	53 (8.2)	0.007
Dyslipidemia	642 (52.8)	240 (43.6)	<0.001
Depression	677 (41.2)	212 (33.0)	<0.001
Clinical Dementia Rating scale			<0.001

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0	540 (33.0)	383 (59.8)	
0.5	1,096 (67.0)	258 (40.2)	
MMSE score	27.7 (2.1)	28.3 (1.5)	<0.001
FCSRT total free recall score	25.0 (8.6)	28.4 (6.9)	<0.001
TMT A (seconds/correct move)	2.1 (1.0)	1.9 (0.7)	<0.001
TMT B (seconds/correct move)	5.3 (3.6)	4.5 (2.7)	<0.001
Rey complex figure test, 3-minute copy score	14.7 (7.1)	16.4 (6.6)	<0.001
Verbal fluency, animals (number of words produced)	27.5 (8.8)	30.3 (8.2)	<0.001
CSF, N	1,877	411	
Age (years)	71.3 (8.6)	68.8 (8.8)	<0.001
Female sex	1197 (63.8)	216 (52.6)	<0.001
Living alone	602 (32.4)	101 (24.6)	0.002
Physical activity, MET-hour/week	52.2 (47.2)	59.7 (52.9)	0.01
Clinical Dementia Rating scale			0.02
0	777 (41.6)	146 (35.5)	
0.5	1089 (58.4)	265 (64.5)	
APOE ε4 carrier	501 (28.0)	155 (38.9)	<0.001
MMSE	27.9 (1.9)	27.7 (2.0)	0.001
FCSRT total free recall score	26.3 (8.2)	24.6 (8.8)	<0.001
Verbal fluency, animals (number of words produced)	28.4 (8.7)	27.9 (8.9)	0.04

Abbreviations: FCSRT, Free and Cued Selective Reminding Test; MET, metabolic equivalent of task; MMSE, Mini-Mental State Examination; TMT, Trail Making Test.
[a] P-values for comparison using t-tests for quantitative variables and chi-square test or Fisher test for qualitative variables. Comparisons for cognitive tests were adjusted for age, sex and education.

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Table 3. Baseline characteristics according to diabetes – MEMENTO Cohort, France (n = 2,288)

	Diabetes		
	No (n = 2,034)	Yes (n = 254)	P [a]
Age (years)	70.9 (8.8)	70.8 (7.9)	0.80
Female sex	1,302 (64.0)	111 (43.7)	<0.001
Education			0.02
Low	487 (23.9)	71 (28.0)	
Intermediate	722 (35.5)	103 (40.6)	
High	823 (40.5)	80 (31.5)	
Smoking status			0.05
Never	1,191 (59.0)	137 (54.8)	
Former	676 (33.5)	101 (40.4)	
Current	151 (7.5)	12 (4.8)	
Current alcohol consumption			0.17
No	658 (33.0)	93 (37.8)	
Up to 1 drink/day	918 (46.0)	98 (39.8)	
>1 drink/day	420 (21.0)	55 (22.4)	
Body mass index (kg/m²)			<0.001
<20	145 (7.3)	6 (2.4)	
20-25	910 (45.7)	68 (27.6)	
25.1-29.9	712 (35.8)	92 (37.4)	
≥30	223 (11.2)	80 (32.5)	
Hypertension	1,135 (59.8)	188 (77.4)	<0.001
Dyslipidemia	761 (48.9)	127 (60.5)	0.002
Self-reported cardiovascular history	156 (7.7)	49 (19.3)	<0.001
Self-reported stroke history	76 (3.7)	16 (6.3)	0.05
Depression	791 (38.9)	98 (38.6)	0.92
APOE ε4 carrier	596 (30.6)	60 (24.6)	0.05
Cognitive tests			
MMSE score	28.0 (1.9)	27.6 (2)	0.03 [b]
FCSRT total free recall score	26.2 (8.4)	24.2 (7.4)	0.03 [b]
TMT A (seconds/correct move)	2.05 (0.94)	2.16 (0.88)	0.02 [c]

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TMT B (seconds/correct move)	4.97 (3.39)	5.57 (3.41)	<0.001 [d]
Rey complex figure test, 3-minute copy score	15.1 (7.0)	15.5 (7.0)	0.89 [b]
Verbal fluency, (number of animals produced)	28.5 (8.7)	26.9 (8.7)	0.04 [b]

Missing data: education, 2; smoking status, 20; alcohol consumption, 46; body mass index, 52; hypertension, 148; dyslipidemia, 521; APOE genotype, 98; MMSE, 6; FCSRT, 19; TMT A, 23; TMT B, 96; Rey complex figure, 163; verbal fluency, 43.
Abbreviations: FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; TMT, Trail Making Test.
[a] P-values for comparison using t-tests for quantitative variables and chi-square test or Fisher test for qualitative variables, except when stated otherwise
[b] P-values for comparison using linear regression modeling adjusted on age, sex and education.
[c] P-value for comparison of log-transformed values of TMT A, adjusted on age, sex and education.
[d] P-value for comparison of log-transformed values of TMT B, adjusted on age, sex and education.

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Table 4. Association between diabetes, biomarkers of small vessel disease, neurodegeneration and Alzheimer's disease, and specific cognitive domains – Structural equation model

	Latent variable of memory		Latent variable of executive functioning	
	Standardized estimate (95% CI)	***P***	**Standardized estimate (95% CI)**	***P***
Direct effect of diabetes on				
SVD	0.001 (-0.035; 0.037)	0.95	0.001 (-0.034; 0.037)	0.94
AD pathology	0.047 (-0.059; 0.153)	0.38	0.053 (-0.049; 0.155)	0.31
Neurodegeneration	0.108 (0.071; 0.145)	<0.001	0.110 (0.074; 0.146)	<0.001
Direct effect of				
Diabetes on cognition	0.016 (-0.037; 0.069)	0.55	-0.017 (-0.070; 0.036)	0.53
SVD on cognition	-0.104 (-0.169; -0.040)	0.001	-0.094 (-0.163; -0.024)	0.008
Neurodegeneration on cognition	-0.542 (-0.737; -0.346)	<0.001	-0.306 (-0.441; -0.171)	<0.001
AD pathology on cognition	-0.282 (-0.421; -0.144)	<0.001	-0.169 (-0.269; -0.068)	0.001
Correlation between				
SVD and AD pathology	0.159 (0.064; 0.253)	<0.001	0.151 (0.057; 0.245)	0.001
SVD and neurodegeneration	0.038 (-0.056; 0.133)	0.42	0.023 (-0.077; 0.123)	0.65
AD and neurodegeneration	0.257 (0.116; 0.398)	<0.001	0.256 (0.128; 0.384)	<0.001
Indirect effect of diabetes on cognition				
Through SVD	0.000 (-0.004; 0.004)	0.95	0.000 (-0.003; 0.003)	0.94
Through AD pathology	-0.013 (-0.042; 0.015)	0.36	-0.009 (-0.027; 0.010)	0.34
Through neurodegeneration	-0.058 (-0.088; -0.029)	<0.001	-0.034 (-0.051; -0.016)	<0.001
Model fit indices				
Robust CFI	0.963		0.974	
Robust TLI	0.937		0.956	
Robust RSMEA (90% CI)	0.038 (0.035; 0.041)		0.032 (0.029; 0.035)	
p-value for test of close fit	1.00		1.00	
SRMR	0.035		0.035	

Abbreviations: AD, Alzheimer's disease; CFI, comparative fit index; RSMEA, root mean square error of approximation; SRMR, Standardized Root Mean Square Residual; SVD, small vessel disease; TLI, Tucker-Lewis Index.

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Table 5. Association between diabetes, biomarkers and global cognition - Sensitivity analyses

	Excluding self-reported history of diabetes		Adding auxiliary variables		Excluding delayed biomarker measurements (>6months)		Using only brain biomarkers as indicators	
	Standardized estimate (95% CI)	***P***	**Standardized estimate (95% CI)**	***P***	**Standardized estimate (95% CI)**	***P***	**Standardized estimate (95% CI)**	***P***
Direct effect of diabetes on								
SVD	-0.006 (-0.045; 0.033)	0.77	0.002 (-0.035; 0.038)	0.92	0.006 (-0.031; 0.043)	0.75	0.001 (-0.035; 0.036)	0.97
AD pathology	0.049 (-0.046; 0.143)	0.31	0.044 (-0.067; 0.155)	0.44	-0.007 (-0.172; 0.159)	0.94	0.107 (0.021; 0.193)	0.01
Neurodegeneration	0.084 (0.049; 0.121)	<0.001	0.109 (0.072; 0.146)	<0.001	0.106 (0.068; 0.144)	<0.001	0.108 (0.071; 0.144)	<0.001
Direct effect on cognition of								
Diabetes	0.030 (-0.017; 0.076)	0.21	0.023 (-0.030; 0.077)	0.39	0.012 (-0.047; 0.072)	0.69	0.030 (-0.020; 0.080)	0.23
SVD	-0.114 (-0.185; -0.044)	<0.001	-0.113 (-0.183; -0.043)	0.001	-0.108 (-0.187; -0.029)	0.007	-0.131 (-0.201; -0.061)	<0.001
Neurodegeneration	-0.576 (-0.743; -0.408)	0.001	-0.565 (-0.731; -0.399)	<0.001	-0.601 (-0.765; -0.436)	<0.001	-0.609 (-0.777; -0.442)	<0.001
AD pathology	-0.273 (-0.391; -0.154)	<0.001	-0.275 (-0.403; -0.147)	<0.001	-0.285 (-0.459; -0.111)	0.001	-0.144 (-0.248; -0.039)	0.007
Correlation between								
SVD and AD pathology	0.157 (0.060; 0.254)	0.002	0.163 (0.066; 0.260)	<0.001	0.161 (0.025; 0.298)	0.02	0.156 (0.054; 0.257)	0.003
SVD and neurodegeneration	0.040 (-0.053; 0.134)	0.39	0.038 (-0.133; 0.057)	0.43	0.039 (-0.056; 0.134)	0.42	0.039 (-0.056; 0.133)	0.42
AD and neurodegeneration	0.269 (0.130; 0.409)	<0.001	0.259 (0.127; 0.390)	<0.001	0.160 (0.004; 0.316)	0.04	0.236 (0.096; 0.376)	0.001
Indirect effect of diabetes on cognition								
Through SVD	0.001 (-0.004; 0.005)	0.77	0.000 (-0.004; 0.004)	0.92	-0.001 (-0.005; 0.003)	0.75	0.000 (-0.005; 0.005)	0.97
Through AD pathology	-0.013 (-0.037; 0.011)	0.28	-0.012 (-0.042; 0.018)	0.42	0.002 (-0.046; 0.049)	0.93	-0.015 (-0.033; 0.002)	0.08
Through neurodegeneration	-0.048 (-0.075; -0.021)	<0.001	-0.061 (-0.091; -0.032)	<0.001	-0.064 (-0.093; -0.035)	<0.001	-0.066 (-0.097; -0.034)	<0.001
Model fit indices								
Robust CFI	0.951		0.951		0.948		0.953	
Robust TLI	0.926		0.926		0.921		0.924	
Robust RSMEA (90% CI)	0.040 (0.037; 0.042)		0.040 (0.037 ; 0.042)		0.040 (0.038 ; 0.043)		0.043 (0.040 ; 0.046)	
p-value for test of close fit	1.00		1.00		1.00		1.00	
SRMR	0.038		0.032		0.042		0.033	

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Abbreviations: AD, Alzheimer's disease; CFI, comparative fit index; RSMEA, root mean square error of approximation; SRMR, Standardized Root Mean Square Residual; SVD, small vessel disease; TLI, Tucker-Lewis Index.

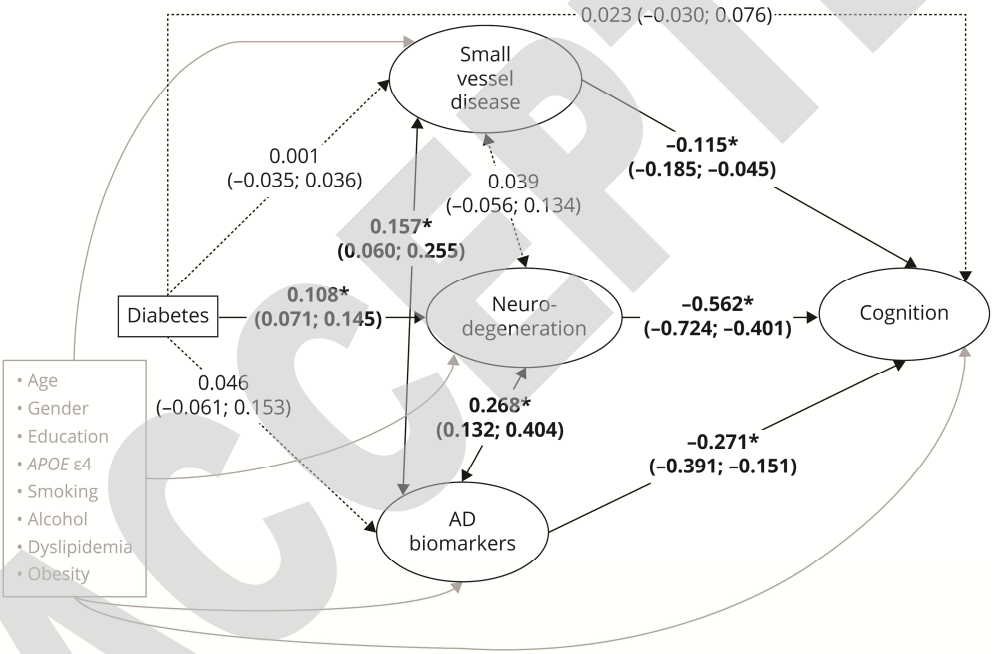
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FIGURE LEGEND

Figure 1. Structural equation model for the association between diabetes, small vessel disease, neurodegeneration, Alzheimer's disease biomarkers and cognition

Latent variables of interest are indicated in ovals and observed variables in rectangles. Directed arrows represent linear regressions. Bidirectional arrows represent correlations. Standardized regression coefficients estimates are presented with their 95% confidence interval. Solid lines indicate statistically significant associations and correlations at the 5% level. Dotted lines indicate non-statistically significant associations and correlations at the 5% level. Adjustment covariates and their directed arrows to small vessel disease, neurodegeneration, Alzheimer's disease biomarkers and cognition are represented in grey. For readiness, the observed indicators defining each latent variable (listed in Table 1) and residual variances for all variables were omitted. AD, Alzheimer's disease. * p<0.001



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