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Interactive effect of diabetes mellitus and subclinical MRI markers of cerebrovascular disease on cognitive decline and incident dementia: a memory-clinic study

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Abstract

Background Cognitive impairment is an increasingly recognized comorbidity of diabetes, yet the mechanisms underlying this association remain poorly understood. This knowledge gap has contributed to conflicting findings regarding the impact of diabetes on long-term cognitive outcomes in older adults. The presence of cerebrovascular disease (CeVD) may potentially modify this relationship. However, interactive effect between diabetes and subclinical MRI markers of CeVD on cognitive trajectories and incident dementia remains unexplored.

Methods A total of 654 participants underwent brain MRI at baseline, from whom 614 with at least one follow-up were selected for longitudinal analysis. Cognitive tests were performed annually up to 5 years. CeVD markers of interest were lacunes, white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), cortical microinfarcts (CMIs), intracranial stenosis (ICS), and cortical infarcts. Blood-based Alzheimer biomarkers, including p-tau181 and p-tau181/Aβ42 ratio, were used as indicators of Alzheimer pathology.

Results At baseline, diabetes was associated with lower cognitive performance and higher burden of CeVD, but not p-tau181 or p-tau181/Aβ42 ratio. Longitudinally, we found an interactive effect of diabetes and WMHs, rather than an independent effect of diabetes, on cognitive decline and dementia risk. Subgroup analyses showed association of diabetes with cognitive outcomes was stronger in participants with high WMHs load but non-significant in those with low WMHs load. Moreover, these associations remained unchanged after adjusting for blood-based Alzheimer biomarkers.

Conclusions The effect of diabetes on cognitive decline is contingent upon the presence of WMHs and independent of Alzheimer's pathology. This finding raises the possibility of utilizing WMHs as an imaging biomarker to identify

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diabetic subgroup at greater risk of developing cognitive impairment. Furthermore, therapeutic interventions targeting WMHs may prevent cognitive deterioration in older adults with diabetes.

Keywords Diabetes, Magnetic resonance imaging, Cerebrovascular disease, Cognitive dysfunction

Background

The global prevalence of diabetes is on the rise, with an estimated 537 million adults aged 20 to 79 living with diabetes in 2021.This number is projected to reach 783 million by 2045 [1]. The surge in diabetes cases is paralleled by the increasingly recognized association of cognitive dysfunction as an important comorbidity of diabetes [2]. With increasing life expectancy and aging populations around the world, the concurrent rise in diabetes and dementia highlights the need for comprehensive strategies to address this public health challenge.

The Lancet Commission identified diabetes as a modifiable late-life risk factor for dementia [3]. However, the association of diabetes with cognitive decline in old age remains inconsistent [4]. Differences in follow-up duration and cognitive measurements may partially account for these discrepancies, but a key limitation within these studies may be not accounting for cerebrovascular disease (CeVD) [5–7].

CeVD, a common complication of diabetes and closely linked with cognitive impairment [8], may arise from poorly-controlled or long-duration diabetes [9]. Both of these factors are well-recognized contributors to accelerating cognitive decline and increasing the risk of dementia [10–12]. A prior autopsy study found that the effect of diabetes on cognition may be amplified by the presence of CeVD [13]. Moreover, a Swedish population-based cohort showed that diabetes is associated with higher risk of post-ischemic stroke dementia but not dementia without ischemic stroke [14]. However, no longitudinal studies to date have explored the interactive effect of diabetes and subclinical MRI markers of CeVD on cognitive outcomes. Additionally, the role of Alzheimer pathology in the association between diabetes and cognitive decline remains unclear.

Using data from a well-characterized prospective memory-clinic cohort, this study aims (1) to explore association of diabetes with cerebrovascular burden due to large-vessel disease (e.g., cortical infarcts, intracranial stenosis) and small-vessel disease (e.g., lacunes, white matter hyperintensities, cerebral microbleeds, cortical microinfarcts), (2) to examine interactive effect of diabetes and CeVD with cognitive outcomes, (3) to determine whether association between diabetes and cognitive decline persists after controlling for Alzheimer pathology.

Methods

Study design and participants

This study was undertaken within the framework of an ongoing prospective study based in memory clinics, with participants primarily recruited from the National University Hospital (NUH) and a limited number (n=21) from St Luke's Hospital, Singapore. Detailed study design and rationale have been previously described [15]. In brief, participants were considered eligible if they were ≥50 years old, possessed sufficient language skills for neuropsychological assessment, and met the diagnostic criteria specified below. Exclusion criteria included diagnoses of major psychiatric illness or substance abuse disorder, cognitive impairment due to traumatic brain injury, multiple sclerosis, tumor, epilepsy, or systemic disease, and significant visual or auditory abnormalities. Participants were assigned at research consensus meetings into one of the following diagnostic categories: (1) no cognitive impairment (NCI): Absence of objectively measurable cognitive impairment in a formal neuropsychological test, (2) cognitive impairment no dementia (CIND): presence of objective cognitive impairment in at least one cognitive domain, as determined by performance on a locally-validated neuropsychological test battery, without fulfilling the diagnostic criteria for dementia as outlined in Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) [16], and (3) dementia: diagnosed in accordance with DSM-IV criteria [16].

All participants were subjected to a thorough evaluation, including physical examinations and neuropsychological assessments, along with brain MRI scans. From the total of 700 participants recruited between August 2010 to August 2020, participants with either missing or suboptimal quality brain MRI scan (n=44), and those with incomplete baseline neuropsychological data (n=2) were excluded. In the main analysis, 654 participants (n=637 recruited from NUH) were included for the cross-sectional analysis, and 614 participants (n=600 from NUH) for the longitudinal analysis after excluding 40 participants without any follow-up. To investigate the potential role of Alzheimer pathology in the association of diabetes and cognitive decline, a subset of participants with available baseline p-tau181 (n=506) and p-tau181/Aβ42 ratios (n=478) were included. Of these Alzheimer biomarker subset groups, 476 with baseline p-tau181 and 448 with baseline p-tau181/Aβ42 ratios had at least one follow-up study visit and were therefore included for the longitudinal analyses.

Neuroimaging

At baseline, brain MRI scans were performed using 3T Siemens Magnetom Trio Tim scanner, with a 32-channel head coil at the Clinical Imaging Research Centre, National University of Singapore. The neuroimaging protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and susceptibility weighted images (SWI).

- WMHs were segmented by the lesion growth algorithm (LGA) implemented in the LST toolbox (version 3.0.0), which requires both T1-weighted and FLAIR sequences [17]. The total whole-brain WMHs volume was log-transformed to reduce skewness. Additionally, the Modified Fazekas scale was used to assess WMHs severity [18].
- Lacunes were characterized as round or ovoid lesions, typically ranging from 3 to 15 mm in size, localized in the subcortical regions, exhibiting low signal intensity on T1-weighted and FLAIR sequences, high signal intensity on T2-weighted images, and a hyperintense rim [19];
- CMBs were identified as focal, round hypointense lesions with blooming effect on SWI and were graded using the Brain Observer Microbleed Scale [20];
- CMIs were assessed using T1- and T2-weighted, as well as FLAIR images. They were characterized as hypointense lesions on T1-weighted images, with a diameter of less than 5 mm, confined to the cortex, and perpendicular to the cortical surface. The location of a hypointense cortical lesion identified on T1-weighted images was verified using FLAIR and T2-weighted images. The lesion was classified as a definite CMI if it exhibited hyperintensity or isointensity on FLAIR and T2-weighted images. Conversely, the lesion was excluded as a CMI if a hypointense signal was detected at the same location on FLAIR or T2-weighted images [21];
- Cortical infarcts were characterized as localized lesions affecting cortical gray matter, exhibiting signal intensity resembling cerebrospinal fluid, accompanied by a hyperintense rim on FLAIR imaging, and variable degrees of tissue loss, with prominent adjacent sulci and ipsilateral ventricular dilation [19];
- ICS was identified as a reduction in luminal diameter exceeding 50% in any of the assessed intracranial vessels, as evaluated through three-dimensional time-of-flight magnetic resonance angiography [22].

Based on MRI markers of small vessel disease (SVD) included in our study, we calculated the total SVD burden on an ordinal scale from 0 to 4, with 1 point added for each of the following: ≥ 1 lacunes, ≥ 1 CMBs, ≥ 1 CMIs, and the presence of WMHs with ≥2 Fazekas score. There were 486 participants with at least 1 follow-up CeVD data. We developed an incident CeVD score on an ordinal scale from 0 to 5, assigning 1 point if any incidence or progression observed in lacunes, CMBs, WMHs (as defined by the Modified Rotterdam Progression Scale), cortical infarcts, and ICS.

Neuropsychological assessment and ascertainment of incident dementia

All participants annually completed neuropsychological assessments that included Clinical Dementia Rating Sum-of-Boxes (CDR-SOB) and a locally validated neuropsychological battery [23]. This battery, aligned with the recommendation of the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network (60-minute NINDS-CSN) [24], evaluated six cognitive domains: Attention (Digit Span Forward and Backward), executive function (Verbal Fluency, Color Trail Test A&B), language (15-item modified Boston Naming Test), visuospatial function (Rey Complex Figure Test-copy), visuomotor speed (Symbol Digit Modalities Test), and memory (Rey Complex Figure Test-immediate/delayed recall and recognition, Hopkins Verbal Learning Test immediate/delayed recall and recognition). Composite z-scores of global and domain-specific cognition were computed as previously described [15]. Higher z-scores indicated better cognitive performance.

Dementia diagnoses for each participant were made at weekly consensus meetings attended by a panel comprising neurologists, psychologists, and researchers. Incident dementia was defined as the transition of participants from NCI or CIND to dementia, and the diagnosis of dementia was made according to DSM-IV criteria [16].

Plasma sampling and analysis

Non-fasting blood was collected from participants and subjected to plasma extraction before storage at −80°C until analysis. All biomarker measurements were performed by evaluators blinded to clinical data at the Sahlgrenska Academy, University of Gothenburg, Sweden, utilizing the Simoa HD-1 or HD-X platforms (Quanterix, Billerica, MA, USA). Detailed methodology has been described previously [25]. In brief, p-tau181 was quantified using the AT270 mouse monoclonal antibody (MN1050; Invitrogen, Waltham, MA, USA), specific for the threonine-181 phosphorylation site, through an ultrasensitive Simoa immunoassay. Aβ42 was determined using the Neurology 3-plex A assay kit (Quanterix, Billerica, MA, USA).

Diabetes assessment and covariates

Diabetes was defined by either self-reported history of diabetes or the use of glucose-lowering medication at each study visit. There were 48 participants with a self-reported history of diabetes who did not report using any glucose-lowering medication. A detailed questionnaire was administered to all participants to collect information on age (years), sex, education (years), current smoking (yes/no), and medical history, including hypertension, hyperlipidemia, stroke, atrial fibrillation, myocardial infarction, coronary angioplasty, pacemaker implantation, and congestive heart failure. All medical history was verified by medical records if available. Cardiovascular disease (CVD) was defined by presence of atrial fibrillation, myocardial infarction, coronary angioplasty, pacemaker implantation, or congestive heart failure. Apolipoprotein E (*APOE*) ε4 status was determined by the presence of at least one ε4 allele.

Statistical analysis

We compared baseline characteristics between diabetes and non-diabetes using Pearson's chi-squared test (for categorical variables), two-sample t test (for continuous normally distributed variables), or Mann-Whitney U test (for continuous non-normally distributed variables). Poisson regression was used to explore association of diabetes with lacunes, CMBs, CMIs, ICS, and cortical infarcts at baseline as count data, while linear regression was used to examine association of diabetes with log transformed WMHs. The models were adjusted for age, gender, and education (Model 1), and additionally for current smoking, hypertension, and hyperlipidemia (Model 2). When the outcome was small vessel disease, further adjustments were made for other MRI markers of small vessel disease (Model 3).

Next, generalized estimating equation (GEE) analysis was performed to investigate the independent effect of diabetes on cognitive decline by introducing 2-way interaction term (diabetes × time). Following this, we introduced 3-way interaction term (diabetes × CeVD marker × time) to examine the interactive effect of diabetes with each CeVD marker and total SVD burden on cognitive decline. Moreover, we used linear mixed-effects models as sensitivity analyses to account for random effects that could be induced by different study sites. In these analyses, log-transformed WMH volume was used as a continuous variable, while other CeVD markers were analyzed as count variables. Given the clinical relevance of the Fazekas scale in assessing WMH severity, an additional sensitivity analysis was conducted using a three-way interaction term (diabetes × Fazekas scale × time) to explore potential clinical implications. Statistical significance for 3-way interaction terms was established at $p<0.05$. To account for multiple comparisons across 6 MRI markers of CeVD, we applied the Bonferroni correction, which resulted in a more stringent significance threshold of $p<0.0083$ (0.05/6). If any significant interactive effects were found, incident CeVD score was adjusted to examine whether these interactive effects are independent of changes in CeVD markers. Binary CeVD markers were further used to better visualize these interactive effects. Specifically, WMHs were dichotomized into high versus low load, with high load WMHs defined as having a WMH volume ≥ 50th percentile of the study population in the main analysis and having Fazekas score ≥ 2 in the secondary analysis, whereas the remaining CeVD markers were dichotomized into presence versus absence. All models were firstly adjusted for age, gender, education, *APOE* genotype, study sites, hypertension, hyperlipidemia, current smoking, CVD, and baseline cognitive diagnosis. Considering the overlap between participants defined as diabetes and those who use glucose-lowering medication in our study, we adjusted for use of glucose-lowering medication in a separate model. Since existing evidence indicate that diabetes and stroke jointly lead to incident dementia, we repeated the same analyses for cognitive decline among stroke-free participants. If significant interactions between diabetes and CeVD were found, subgroup analyses were performed accordingly. Although $p<0.05$ was considered statistically significant for group comparisons, Bonferroni-corrected significance cutoffs, $p<0.0083$ (0.05/6), were used to address multiple tests across 6 cognitive subdomains when examining the association between diabetes and cognitive decline.

To explore whether Alzheimer pathology mediates any associations of diabetes with cognitive decline, we added blood-based Alzheimer biomarker and its interaction with time into the models where any subgroups demonstrated a significant effect of diabetes on cognitive decline. All models were adjusted for age, gender, education, *APOE* genotype, hypertension, hyperlipidemia, current smoking, CVD, and baseline cognitive diagnosis. We firstly utilized p-tau181 to maximize statistical power with a larger sample size ($n=476$). Additionally, we performed a sensitivity analysis using the p-tau181/Aβ42 ratio ($n=448$), as it has been shown to better reflect brain amyloid pathology in our previous study within this cohort [26].

Finally, we explored whether any significant interactive effect persisted among dementia-free participants with respect to global cognitive decline and incident dementia, using GEE models and Cox proportional hazards models, respectively. In the Cox proportional hazard model, we added 2-way interaction terms (diabetes × CeVD marker) to examine the interactive effect of diabetes and CeVD on incident dementia. All models were adjusted for age, gender, education, *APOE* genotype, hypertension,

hyperlipidemia, current smoking, and CVD. Missing data for covariates were imputed via multiple imputations, using chained equations through the package "mice". All *p* values presented were two-sided, and a value of $p<0.05$ was considered statistically significant. All statistical analyses were performed with R (version 4.2.1).

Results

Baseline participants characteristics

Baseline demographics, *APOE4* genotype, vascular risk factors, medical history, cognitive performance, p-tau181, p-tau181/Aβ42 ratio, and CeVD makers are presented in Table 1 for the overall sample and stratified by diabetes status. At baseline, there were 236 participants (36.1%) with diabetes. Those in the diabetic group exhibited a higher prevalence of hypertension, hyperlipidemia, stroke, and CVD. Additionally, the diabetic group showed a significantly higher prevalence of dementia, with significantly lower cognitive performance. Furthermore, diabetes was significantly associated with a higher prevalence of lacunes, high-load WMHs, CMIs, cortical infarcts and ICS. However, no difference in plasma p-tau181 or p-tau181/Aβ42 ratio was observed between diabetes and non-diabetes groups.

Table 2 showed the association of diabetes with MRI markers of CeVD. In an age, gender, and education-adjusted model, diabetes was positively associated with WMHs volume, lacunes count, and CMIs count, while

Table 1 Population characteristics at baseline

Characteristic	Overall, *N* = 654	No Diabetes, *N* = 418	Diabetes, *N* = 236	*p*-value[a]
Age (years), Mean (SD)	72.9 (8.0)	72.9 (8.2)	73.0 (7.7)	0.9
Gender, n (%)				0.8
Male	287 (44%)	182 (44%)	105 (44%)	
Female	367 (56%)	236 (56%)	131 (56%)	
Education (years), Mean (SD)	7.0 (5.1)	7.5 (5.1)	6.1 (4.8)	< 0.001
APOE4 genotype, n (%)				0.4
Non-carriers	467 (71%)	294 (70%)	173 (73%)	
Carriers	187 (29%)	124 (30%)	63 (27%)	
Hypertension, n (%)	474 (72%)	266 (64%)	208 (88%)	< 0.001
Hyperlipidemia, n (%)	481 (74%)	274 (66%)	207 (88%)	< 0.001
Current smoker, n (%)	46 (7.0%)	33 (7.9%)	13 (5.5%)	0.3
Stroke, n (%)	176 (27%)	102 (24%)	74 (31%)	0.038
CVD, n (%)	107 (16%)	55 (13%)	52 (22%)	0.003
CDR-SOB, Median (IQR)	1.0 (5.0)	1.0 (4.0)	2.5 (5.0)	< 0.001
Domain-specific cognition z-score, Mean (SD)				
Global cognition	-2.76 (2.62)	-2.43 (2.64)	-3.34 (2.48)	< 0.001
Attention	-0.83 (1.26)	-0.69 (1.26)	-1.09 (1.22)	< 0.001
Executive function	-2.73 (2.33)	-2.41 (2.46)	-3.31 (2.27)	< 0.001
Language	-2.59 (4.27)	-2.32 (4.28)	-3.07 (4.22)	0.030
Visuomotor speed	-1.49 (1.30)	-1.31 (1.35)	-1.79 (1.16)	< 0.001
Visuospatial function	-2.00 (2.21)	-1.73 (2.20)	-2.49 (2.16)	< 0.001
Memory	-2.04 (1.60)	-1.85 (1.64)	-2.37 (1.47)	< 0.001
Dementia, n (%)	242 (37%)	132 (32%)	110 (47%)	< 0.001
P-tau181[†], Median (IQR)	2.46 (2.01)	2.35 (1.90)	2.65 (2.31)	0.055
P-tau181/Aβ42[‡], Median (IQR)	0.25 (0.22)	0.26 (0.23)	0.24 (0.21)	0.54
MRI markers				
Lacunes, n (%)	183 (28.0%)	90 (21.5%)	93 (39.4%)	< 0.001
WMHV, Median (IQR)	5.04 (11.1)	4.3 (10.4)	7.4 (11.3)	< 0.001
High load WMHs, n (%)	327 (50.0%)	186 (44.5%)	141 (59.7%)	< 0.001
CMBs, n (%)	289 (44.2%)	177 (42.3%)	112 (47.5%)	0.24
CMIs, n (%)	136 (20.8%)	75 (17.9%)	61 (25.8%)	0.022
Cortical infarcts, n (%)	87 (13.3%)	46 (11.0%)	41 (17.4%)	0.029
ICS, n (%)	55 (8.4%)	25 (6.0%)	30 (12.7%)	0.005

Abbreviation: SD: standard deviation; CVD: cardiovascular disease; CDR-SOB: clinical dementia rating-sum of box; CeVD: cerebrovascular disease; WMHV: white matter hyperintensity volume; WMHs: white matter hyperintensities; CMBs: cerebral microbleeds; CMIs: cortical microinfarcts; ICS: intracranial stenosis;

p-value[a]: Pearson's chi-squared test for categorical variables, two-sample t test for continuous normally distributed variables, or Mann-Whitney U test for continuous non-normally distributed variables

[†]: 506 participants ($n=179$ with diabetes) with baseline p-tau 181

[‡]: 478 participants ($n=166$ with diabetes) with baseline p-tau 181/Aβ42

Table 2 Association of diabetes with MRI markers of CeVD at baseline

Small vessel disease					Large vessel disease		
	Log-transformed WMH volume	Lacune	CMBs	CMIs		Intracranial stenosis	Cortical infarct
	β (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)		RR (95% CI)	RR (95% CI)
Model 1	0.49 (0.26, 0.71), $p<0.001$	2.01 (1.65, 2.45), $p<0.001$	0.77 (0.70, 0.84), $p<0.001$	1.45 (1.21, 1.73), $p<0.001$	Model 1	1.30 (0.83, 2.03), $p=0.24$	1.50 (1.06, 2.12), $p=0.022$
Model 2	0.38 (0.15, 0.61), $p=0.001$	1.65 (1.34, 2.03), $p<0.001$	0.56 (0.51, 0.62), $p<0.001$	1.09 (0.91, 1.30), $p=0.37$	Model 2	0.95 (0.60, 1.49), $p=0.81$	1.06 (0.74, 1.51), $p=0.74$
Model 3	0.26 (0.04, 0.48), $p=0.019$	1.53 (1.24, 1.89), $p<0.001$	0.47 (0.43, 0.52), $p<0.001$	0.87 (0.73, 1.05), $p=0.15$			

RR: rate ratio

Model 1: adjusted for age, gender, and education

Model 2: Model 1 + current smoking, hypertension, and hyperlipidemia

Model 3: Model 2 + other MRI markers of small vessel disease

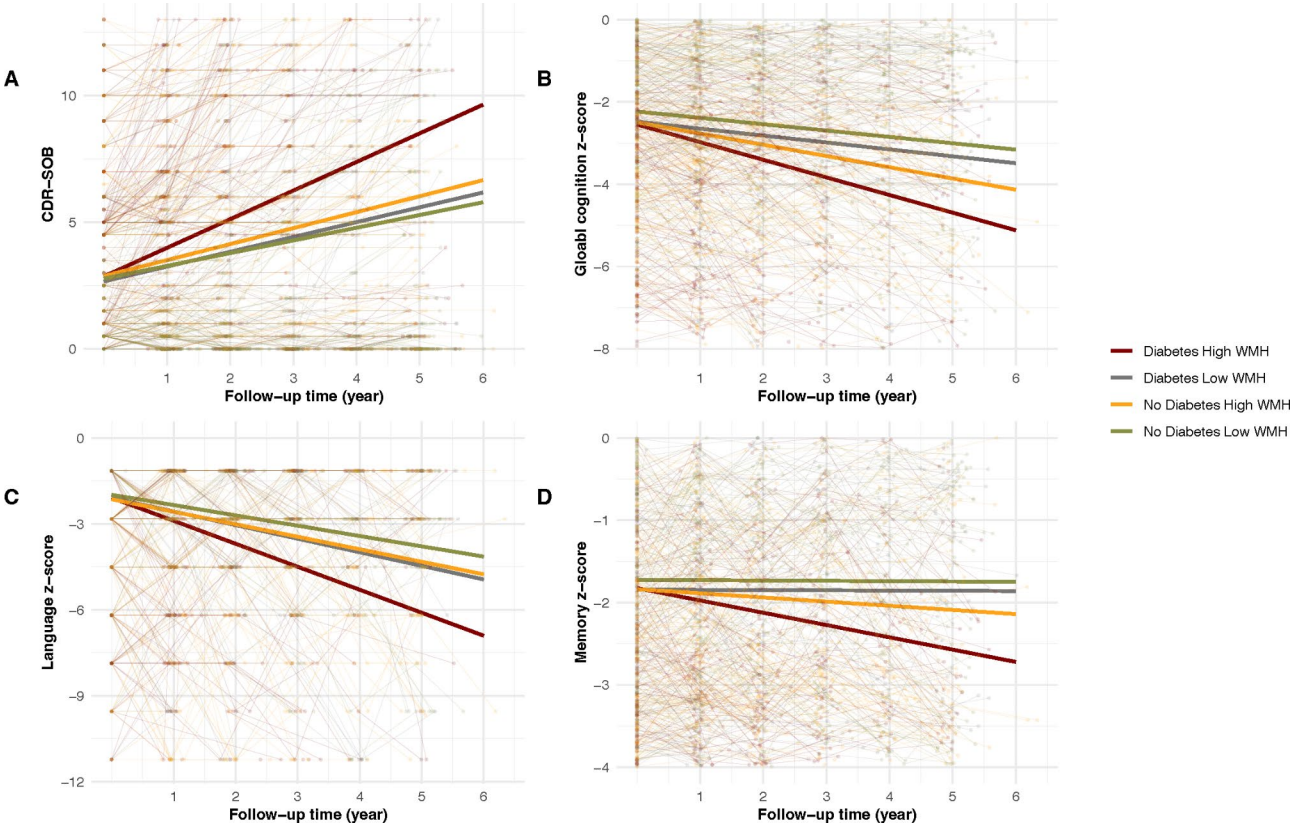

Fig. 1 Interactive effect of diabetes and WMH with cognitive decline of CDR-SOB (**A**), global cognition (**B**), language (**C**), and memory (**D**). Results were derived from GEE models adjusted for age, gender, education, *APOE* genotype, study sites, current smoking, hypertension, hyperlipidemia, CVD, and baseline cognitive diagnosis

negatively associated with CMBs count. Further adjustment for current smoking, hypertension, and hyperlipidemia attenuated the associations of diabetes with WMHs and lacunes, strengthened the association of diabetes with CMBs, and rendered the association with CMIs non-significant. Notably, diabetes remained positively associated with lacunes, and WMHs, while negatively associated with CMBs after controlling for other small vessel disease markers.

Interactive effect of diabetes and CeVD with cognitive decline

We examined potential moderation effects of CeVD over a mean (SD) follow-up of 3.9 (1.5) years. There was no independent effect of diabetes on cognitive decline in

any neuropsychological assessments (CDR-SOB: β=0.16; 95% CI -0.01 to 0.33; p=0.060, global cognition: β = -0.06; 95% CI -0.17 to 0.04; p=0.20, attention: β=0.02; 95% CI -0.03 to 0.07; p=0.51, executive function: β=0.01; 95% CI -0.06 to 0.08; p=0.80, language: β = -0.13; 95% CI -0.39 to 0.13; p=0.31, visuospatial function (β = -0.03; 95% CI -0.10 to 0.04; p=0.39), visuomotor speed (β=0.00; 95% CI -0.03 to 0.03; p=0.84), or memory (β = -0.03; 95% CI -0.08 to 0.01; p=0.16).

After introducing interaction terms between diabetes and each MRI marker of CeVD into the model, we observed interactive effects between diabetes and WMHs on CDR-SOB (p=0.009, Fig. 1A), global cognition (0.003, Fig. 1B), language (p=0.008, Fig. 1C), and memory (p=0.018, Fig. 1D). The interactive effects between diabetes and WMHs on global cognition and language remained significant after adjusting for multiple comparisons. Further adjusting for use of glucose-lowering medication did not significantly change these results (Table S1 in Additional file 1). Moreover, by replacing log-transformed WMH volume with Fazekas scale, similar results were observed (p=0.008 for CDR-SOB, p=0.024 for global cognition, p=0.036 for language, and p=0.011 for memory). An additional table S2 shows this in more detail (see Additional file 1). The sensitivity analysis using linear mixed-effects models showed similar results (Table S3 in Additional file 1). However, the interactive effects of diabetes with other CeVD markers and with total SVD burden on cognitive decline were not statistically significant. Among participants with at least 1 follow-up MRI scans (n=486), interactive effects between diabetes and WMHs persisted for global cognition (p=0.029), language (p=0.047) and memory (p=0.046), and these effects remained unchanged after adjusting for incident CeVD score.

Participants were stratified into four groups based on diabetes status (+/-) and WMH burden (high/low): DM-WMHs_low (n=225), DM-WMHs_high (n=171), DM+WMHs_low (n=91), and DM+WMHs_high (n=127). Compared to the DM-WMHs_low group, participants in the DM+WMHs_high group exhibited more rapid cognitive decline across multiple domains, including CDR-SOB, global cognition, executive function, language, visuospatial function, visuomotor speed, and memory. After correction for multiple comparisons, most of them remained significant, except those on language and visuomotor speed (Table 3). In a subgroup analysis excluding participants with a history of stroke, the interactive effects of diabetes and WMHs remained statistically significant for CDR-SOB, global cognition, language, and memory. Additionally, a significant interactive effect was observed for visuospatial function, although this association did not survive correction for multiple comparisons (Table 3).

Association of diabetes with cognitive decline stratified by WMHs and controlling for blood-based Alzheimer biomarker

Subgroup analyses based on WMHs status showed that diabetes was associated with cognitive decline solely among participants with high load WMHs, but not among those with low load (Table 4). Moreover, association of diabetes with cognitive decline in CDR-SOB, global cognition, language, and memory remained unchanged after controlling for p-tau181. Similar results were observed when replacing p-tau181 with p-tau181/Aβ42 ratio.

Interactive effect of diabetes and CeVD with global cognitive decline and incident dementia among dementia-free participants

A total of 398 participants who were dementia-free at baseline were included for this analysis (Diabetes, n=122; No diabetes, n=276; NCI, n=131; CIND=267). 29 participants of NCI (22.1%) and 121 participants of CIND (45.3%) were categorized as WMH_high. Over a mean (SD) follow-up of 3.74 (1.62) years, there were 67 incident cases of all-cause dementia, with most (n=64) previously diagnosed as CIND at baseline. Diabetes did not independently predict global cognitive decline or incident dementia. Instead, a significant interaction effect between diabetes and WMHs was observed (Global cognitive decline: p=0.014; Incident dementia: p<0.001; Table 5). To quantify this interaction, participants were divided into 4 groups: (1) DM-WMH_low (n=184), (2) DM-WMH_high (n=92), (3) DM+WMH_low (n=64), and (4) DM+WMH_high (n=58). Compared with those in the DM-WMH- group, only participants in the DM+WMH_high group were associated with greater cognitive decline (β = -0.24; 95% CI -0.41 to -0.06; p=0.009) and higher risk of dementia (HR=2.19; 95% CI 1.08 to 4.41; p=0.029). Subgroup analyses showed that diabetes is associated with cognitive decline (β = -0.17; 95% CI -0.34 to -0.01; p=0.043) and incident dementia (HR=2.50; 95% CI 1.13 to 5.54; p=0.024) among the high load WMH group, but not in the low load WMH group.

Discussion

In this memory clinic-based study, we found that older adults with diabetes had more lacunes and higher WMHs volume, but fewer CMBs, compared with those without diabetes. Rather than independently affecting cognition, a robust interaction between diabetes and WMHs was observed on longitudinal cognitive outcomes. Specifically, presence of high load WMHs modified association of diabetes with cognitive decline by affecting CDR-SOB, global cognition, language, memory, and risk of dementia. Our findings also suggest the effect of diabetes on cognitive decline is independent of Alzheimer pathology.

Table 3 Interactive effect of diabetes and WMHs with cognitive decline among all participants and stroke-free participants

	CDR-SOB		**Global cognition**	
	All sample	**Non-stroke**	**All sample**	**Non-stroke**
	β (SE), *p* value		**β (SE), *p* value**	
DM-WMHs_low	Reference		Reference	
DM-WMHs_high	0.09 (0.10), $p=0.35$	0.01 (0.11), $p=0.90$	-0.09 (0.06), $p=0.15$	-0.06 (0.06), $p=0.34$
DM+WMHs_low	0.03(0.10), $p=0.81$	-0.03 (0.12), $p=0.82$	0.07 (0.07), $p=0.29$	0.09 (0.07), $p=0.20$
DM+WMHs_high	0.44 (0.12), $p<0.001^{‡}$	0.37 (0.16), $p=0.017$	-0.22 (0.08), $p=0.004^{‡}$	-0.26 (0.09), $p=0.005^{‡}$
p for interaction	0.009	$0.005^{†}$	$0.003^{†}$	$0.002^{†}$
	Attention		Executive function	
	All sample	Non-stroke	All sample	Non-stroke
	β (SE), *p* value		β (SE), *p* value	
DM-WMHs_low	Reference		Reference	
DM-WMHs_high	-0.06 (0.04), $p=0.09$	-0.04 (0.04), $p=0.28$	-0.14 (0.04), $p<0.001^{‡}$	-0.12 (0.04), $p=0.006^{‡}$
DM+WMHs_low	0.04 (0.03), $p=0.22$	0.04 (0.03), $p=0.25$	0.08 (0.04), $p=0.07$	0.09 (0.05), $p=0.052$
DM+WMHs_high	-0.06 (0.04), $p=0.15$	-0.06 (0.05), $p=0.25$	-0.17 (0.05), $p<0.001^{‡}$	-0.18 (0.06), $p<0.001^{‡}$
p for interaction	0.61	0.40	0.096	0.17
	Language		Visuospatial function	
	All sample	Non-stroke	All sample	Non-stroke
	β (SE), *p* value		β (SE), *p* value	
DM-WMHs_low	Reference		Reference	
DM-WMHs_high	0.03 (0.14), $p=0.84$	0.01 (0.15), $p=0.95$	-0.13 (0.05), $p=0.005^{‡}$	-0.07 (0.04), $p=0.11$
DM+WMHs_low	0.05 (0.18), $p=0.47$	0.12 (0.19), $p=0.50$	0.04 (0.05), $p=0.44$	0.03 (0.05), $p=0.58$
DM+WMHs_high	0.42 (0.19), $p=0.035$	-0.50 (0.23), $p=0.031$	-0.18 (0.05), $p<0.001^{‡}$	-0.14 (0.06), $p=0.013$
p for interaction	$0.008^{†}$	$0.004^{†}$	0.066	0.026
	Visuomotor speed		Memory	
	All sample	Non-stroke	All sample	Non-stroke
	β (SE), *p* value		β (SE), *p* value	
DM-WMHs_low	Reference		Reference	
DM-WMHs_high	-0.03 (0.02), $p=0.077$	-0.01 (0.02), $p=0.44$	-0.04 (0.03), $p=0.16$	-0.03 (0.03), $p=0.37$
DM+WMHs_low	0.01 (0.02), $p=0.42$	0.02 (0.02), $p=0.41$	0.03 (0.03), $p=0.30$	0.05 (0.03), $p=0.14$
DM+WMHs_high	-0.05 (0.02), $p=0.035$	-0.02 (0.03), $p=0.40$	-0.13 (0.03), $p<0.001^{‡}$	-0.11 (0.04), $p=0.006^{‡}$
p for interaction	0.73	0.40	0.018	0.014

Abbreviations: SE: standard error; CDR-SOB: clinical dementia rating-sum of box; DM: diabetes mellitus; WMHs: white matter hyperintensities. 614 in total were included for longitudinal analysis (452 without stroke). Annual changes of cognitive decline were derived from GEE models adjusted for age, gender, education, *APOE* genotype, study sites, hypertension, hyperlipidemia, current smoking, CVD, and baseline cognitive diagnosis

†: Significant after adjustment for multiple comparisons for 3-way interaction terms ($p<0.0083$)

‡: Significant after adjustment for multiple comparisons for group difference regarding cognitive decline ($p<0.0083$)

Table 4 Effect of diabetes on cognitive decline stratified by WMHs and controlling for Alzheimer pathology

	CDR-SOB	**Global cognition**	**Language**	**Memory**
	β (95% CI), *p* value			
WMHs_low ($n=315$)				
Model 1	0.07 (-0.13, 0.26), $p=0.50$	0.05 (-0.10, 0.19), $p=0.52$	0.02 (-0.33, 0.37), $p=0.92$	0.01 (-0.04, 0.07), $p=0.63$
WMHs_high ($n=298$)				
Model 1	0.39 (0.13, 0.63), $p=0.003$	-0.17 (-0.30, -0.04), $p=0.008$	-0.49 (-0.83, -0.15), $p=0.005$	-0.08 (-0.13, -0.02), $p=0.009$
Model 1†	0.41 (0.10, 0.73), $p=0.009$	-0.23 (-0.40, -0.07), $p=0.005$	-0.53 (-0.96, -0.10), $p=0.016$	-0.10 (-0.18, -0.03), $p=0.006$
Model 2†	0.41 (0.11, 0.70), $p=0.007$	-0.21 (-0.37, -0.06), $p=0.006$	-0.50 (-0.92, -0.08), $p=0.020$	-0.09 (-0.17, -0.02), $p=0.012$
Model 1‡	0.43 (0.11, 0.74), $p=0.009$	-0.25 (-0.42, -0.09), $p=0.003$	-0.53 (-0.98, -0.09), $p=0.019$	-0.12 (-0.19, -0.04), $p=0.002$
Model 2‡	0.44 (0.14, 0.73), $p=0.004$	-0.26 (-0.41, -0.10), $p=0.001$	-0.55 (-0.97, -0.12), $p=0.011$	-0.12 (-0.19, -0.04), $p=0.007$

Model 1: adjusted for age, gender, education, APOE genotype, hypertension, hyperlipidemia, current smoking, CVD, and baseline cognitive diagnosis

Model 2†: Model 1 + blood-based Alzheimer biomarker × time

†: Using baseline p-tau 181 in the analysis, with 228 participants defined as WMH+

‡: Using baseline p-tau 181/Aβ42 in the analysis, with 218 participants defined as WMH+

Table 5 Interactive effect of diabetes and WMHs with global cognitive decline and incident dementia among dementia-free participants

	Global cognitive decline		Incident dementia	
	β (95% CI)	*p*-value	HR (95% CI)	*p*-value
All sample (*n* = 398)				
Diabetes vs. no diabetes	-0.04 (-0.15, 0.07)	0.51	1.26 (0.74, 2.14)	0.40
Stratified analysis				
DM-WMHs_low	Reference		Reference	
DM-WMHs_high	-0.08 (-0.17, 0.01)	0.084	0.86 (0.45, 1.65)	0.65
DM + WMHs_low	0.07 (-0.08, 0.22)	0.36	0.77 (0.36, 1.60)	0.48
DM + WMHs_high	-0.24 (-0.41, -0.06)	0.009	2.19 (1.08, 4.41)	0.029
P for interaction with WMHs	0.014		< 0.001	
Low WMH (*n* = 248)				
Diabetes vs. no diabetes	0.06 (-0.08, 0.19)	0.41	0.76 (0.36, 1.61)	0.47
High WMH (*n* = 150)				
Diabetes vs. no diabetes	-0.17 (-0.34, -0.01)	0.043	2.50 (1.13, 5.54)	0.024

Abbreviation: WMHs: white matter hyperintensities

All models were adjusted for age, gender, education, APOE genotype, hypertension, hyperlipidemia, current smoking, CVD, use of glucose-lowering medication

This study adds to the existing literature supporting the association between diabetes and CeVD involving both small vessel disease and large vessel disease. In line with previous research [13, 27–29], our results demonstrated the associations between diabetes and the presence of lacunes and ICS. Although we observed a direct association between diabetes and increased WMHs burden, it is important to acknowledge that previous studies have yielded inconclusive results on this relationship [30, 31]. Besides differences in methodology for measuring WMHs and population characteristics across studies, this discrepancy could also be ascribed to the premise that association of diabetes with WMHs might depend on the severity of diabetes [9] or vascular comorbidities [32]. In our study, participants with diabetes were more likely to have hypertension, hyperlipidemia, and CVD, possibly contributing to the significant finding. Moreover, the association of diabetes with infarcts remains unclear. The AGES-Reykjavik Study recently showed that infarcts in distinct brain regions correspond to different risk-factor profiles, associating diabetes specifically with subcortical infarcts instead of cortical infarcts [33]. Surprisingly, we found diabetes was associated with fewer CMBs. A similar observation was noted in the Northern Manhattan Study, where diabetic medication use was negatively associated the presence of CMBs [34]. In our clinic-based study, participants with diabetes were likely prescribed medication, and participants using diabetic medication were classified as having diabetes. One possible explanation is that diabetic medication may lower the risk of developing CMBs. Moreover, we found that CMIs were more likely to be observed in patients with diabetes compared with those without diabetes. However, further adjustment for other vascular risk factors rendered the association non-significant, which is consistent with earlier imaging and autopsy studies [13, 35].

Earlier longitudinal studies consistently showed a robust association between diabetes and cognitive health in late life among middle-aged individuals [36–38]. However, studies extending this association to elderly adults yielded inconclusive results [4]. Consistent with prior studies [5, 39], we found that individuals with diabetes were more likely to have poor cognitive performance and dementia at baseline. However, our study lacks robust evidence for diabetes being independently associated with cognitive decline. The disparity in the impact of midlife versus late-life diabetes on cognition could result from several factors. Firstly, diabetes may already affect cognition in earlier life stages through microvascular disease, as proposed by the ticking clock hypothesis [8]. And as individuals grow older, the influence of Alzheimer pathology or neurodegeneration likely becomes a primary factor affecting cognition. Secondly, studies using middle-aged population usually have a relatively long follow-up, enabling the observation of cumulative effects of diabetes, which could potentially contribute to cognitive decline since diabetes duration is a well-established risk factor for dementia [10]. This notion is further supported by the observation from the Doetinchem Cohort Study that incident diabetes cases during follow-up showed intermediate level of cognitive decline compared to prevalent diabetes cases and non-diabetic cases [38]. Furthermore, individuals with diabetes at late life may demonstrate varying durations, severities, and complications compared to those in their middle age, potentially leading to different susceptibilities to dementia. Hence, identifying diabetic patients at risk of dementia holds significant importance in old age.

Recent studies suggested that diabetes alone may not significantly affect cognitive health in elderly adults. And when diabetes is combined with cardiovascular comorbidities [10, 11], stroke [14], increased HbA_{1c} level [11], uncontrolled blood glucose [40], or early age at diabetes onset (enduring diabetes condition) [10], they would jointly lead to cognitive impairment. Our study further demonstrated that diabetes, in conjunction of high WMH load, would interactively accelerate cognitive decline and raise the risk of dementia. The Utrecht Diabetic Encephalopathy Study supported our findings, showing diabetic patients with accelerated cognitive decline had a larger WMH volume at baseline [41]. Moreover, an autopsy study from the SMART project found cross-sectional association of diabetes with cognition was modified by presence of infarcts, including large artery infarcts, lacunes, or microinfarcts [13]. Despite the SMART project and our study identifying different CeVD markers interacting with diabetes on cognition, these observations collectively suggested that the presence of CeVD could amplify the impact of diabetes on cognition. Overall, our findings may contribute to explaining the divergent results among previous studies that investigated the association between diabetes and cognitive decline in older adults.

The mechanisms by which diabetes and WMHs interact to affect cognitive decline are not fully understood. One likely explanation is that pronounced cognitive decline may only manifest in a subset of individuals with diabetes in old age, and presence of WMH indicates an advanced diabetes stage [9], thereby contributing to cognitive decline. Findings from CDOT study and ADNI cohort supported this hypothesis by showing the absence of a direct effect of diabetes on brain atrophy and cognitive decline among individuals with low CeVD burden [39, 42]. Additional longitudinal studies are needed to explore the potential interactive association between diabetes and CeVD, especially WMHs, on brain atrophy and cognitive decline. On the hand, association among diabetes, Alzheimer pathology, and cognitive decline remain unclear [13, 43, 44]. In the present study, we did not observe a significant difference in p-tau181 or p-tau181/Aβ42 between diabetes and non-diabetes groups. Additionally, there was no evidence suggesting that Alzheimer pathology mediated the relationship between diabetes and cognitive decline, which is consistent with findings from a previous memory clinic-based study [45].

Our study has several strengths. This is the first longitudinal study, to our knowledge, investigating the interaction of CeVD and diabetes on long-term cognitive outcomes. We evaluated a broad spectrum of CeVD markers, including both small vessel disease and large vessel disease. Moreover, our study is part of an ongoing well-characterized memory-clinic cohort that recruited individuals across various clinical stages, encompassing cognitively normal, mild cognitive impairment, and dementia. Detailed longitudinal cognitive assessment was used to capture global and domain-specific cognitive changes. Interactive effect of diabetes and WMHs on cognition persisted across different cognitive outcomes and in sensitive analyses performed exclusively among stroke-free participants. Some limitations should also be noted in our study. Firstly, diabetes is ascertained from self-report, without objective measures such as blood glucose or glycated hemoglobin. Additionally, we did not consider different classes of diabetic medications in our analysis. Furthermore, we were unable to distinguish type 1 and type 2 diabetes. However, it is noteworthy that older adults mostly have type 2 diabetes, since incidence of type 2 diabetes increases with age, and those with type 1 diabetes usually do not survive to old age [46]. Additionally, the follow-up period is relatively short, but this does not prevent us from observing the significant interactive effect between diabetes and WMHs. Studies with extended follow-up periods and larger sample size are needed to further validate our findings.

In summary, diabetes is associated with increased CeVD burden, and its impact on cognition in older adults depends on the presence of high load WMHs. Our findings highlight the considerable variability induced by WMHs in shaping the effect of diabetes on cognitive decline. Therefore, WMHs may emerge as a potential biomarker for identifying diabetes subgroups at risk of cognitive dysfunction, as well as a prospective therapeutic target to slow cognitive decline.

Abbreviations

CeVD	Cerebrovascular disease
WMHs	White matter hyperintensities
CMBs	Cerebral microbleeds
CMIs	Cortical microinfarcts
ICS	Intracranial stenosis
NCI	No cognitive impairment (NCI)
CIND	Cognitive impairment no dementia
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
FLAIR	Fluid-attenuated inversion recovery
SWI	Susceptibility weighted images
CVD	Cardiovascular disease (CVD)
APOE4	Apolipoprotein E ε4

Supplementary Information

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Additional file 1

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Author contributions
JC conceived the study idea, conducted data analyses, and wrote the first draft of the manuscript. JC, CR, CMT, ECJY, JRC, BYT, NV, MKPL, CC, and SH contributed to data acquisition for the work and reviewed the manuscript critically for important intellectual content. CC and SH supervised the work and made significant contributions to the interpretation of the results and editing of the manuscript. All authors read and approved the final version of the manuscript.

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Data availability
The datasets used in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participant
Ethics approval was obtained from the National Healthcare Group Review Board (reference 2010/00017; study protocol DEM4233), and the study was conducted in accordance with the Declaration of Helsinki. Prior to enrollment, written informed consent was obtained.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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