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Featured Article

Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: A population-based cohort study

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Abstract

Introduction: The impact of prediabetes and diabetes on cognitive decline and the potential underlying mechanisms remain unclear. We investigated whether prediabetes and diabetes accelerate cognitive decline and brain aging, and the initial pathological changes linked to microvascular processes.

Methods: Nine-year longitudinal data from the Swedish National Study on Aging and Care-Kungsholmen (n = 2746, age ≥60 years) and the magnetic resonance imaging subsample (n = 455) were used. Cognitive function was assessed with Mini-Mental State Examination. Brain magnetic resonance imaging markers included total brain tissue, white matter, gray matter, white matter hyperintensities, and hippocampal volumes.

Results: Compared with diabetes-free status, prediabetes and diabetes were independently associated with accelerated cognitive decline. Prediabetes was cross-sectionally associated with smaller total brain tissue volume ($P < .01$), particularly smaller white matter volume. Diabetes was associated with larger white matter hyperintensities volume. Longitudinally, diabetes was associated with faster white matter hyperintensities accumulation. No associations between prediabetes or diabetes and hippocampal volume were found.

Discussion: Diabetes and prediabetes accelerate cognitive decline and might predict microvascular lesions among dementia-free older adults.

Keywords: Type 2 diabetes; Prediabetes; Cognitive decline; Cerebral microvascular lesions; Magnetic resonance imaging; White matter hyperintensities; Longitudinal study; Aging

1. Introduction

Rapid population aging combined with sedentary habits has led to the current epidemic of prediabetes and diabetes. At present, 415 million people live with diabetes, and 318 million have prediabetes worldwide [1]. Prediabetes and type 2 diabetes (hereafter, diabetes), which account for about 90% of all diabetic cases, can damage small and large blood vessels, resulting in disabling complications such as retinopathy, nephropathy, neuropathy, cardiovascular diseases, and cerebrovascular diseases [1,2]. Meanwhile, over 47 million people live with dementia, and this number is expected to triple by 2050 [3]. Findings from many population-based studies consistently show an increased risk of dementia in people with diabetes or prediabetes [4,5]. Before dementia, diabetes has been related to deficits in different cognitive domains [4] and to accelerate cognitive decline, especially

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in psychomotor speed and executive function [6,7]. However, other prospective studies have failed to confirm such associations [8,9]. Only a few studies have investigated the association between prediabetes and cognitive decline, showing mixed evidence [6,10–12].

Cerebral small vessel disease (SVD)—including white matter hyperintensities (WMH) and brain atrophy—are major contributors to vascular dementia [13], whereas atrophy of the medial temporal lobe (containing the hippocampus) is a marker of neurodegeneration in Alzheimer's disease (AD) [14]. Although the association between diabetes and dementia is well established, whether cognitive decline in prediabetes or diabetes is linked to vascular or AD-related neurodegenerative mechanisms remains unclear. Previous cross-sectional magnetic resonance imaging (MRI) studies have consistently reported associations between diabetes and lower global brain volume [15–18]. On the other hand, associations between diabetes and microvascular lesions (e.g., WMH) or AD-related neurodegenerative markers (e.g., cortical gray matter and hippocampal atrophy) have been found in some studies [16,17,19,20], but not in others [19,21]. The few longitudinal studies on the progression of cerebral microvascular lesions or AD-neurodegenerative markers in diabetes have revealed inconsistent findings [22–24]. So far, no population-based MRI study has shown the impact of prediabetes on the development of microvascular lesions and neurodegenerative markers. To date, the challenge to unravel further the etiology of the diabetes-related cognitive decline is to integrate findings on structural MRI and cognitive functioning [15].

In this study, we hypothesized that prediabetes and diabetes accelerate cognitive decline and brain aging, with the initial pathological changes possibly being linked to microvascular processes. Therefore, we specifically aimed to examine the degree of cognitive decline according to prediabetes and diabetes and assess the impact of prediabetes and diabetes on cerebral microvascular lesions and neurodegenerative markers among dementia-free older adults, using data from a longitudinal population-based cohort of Swedish older adults.

2. Methods

2.1. Study population

The study population cohort was derived from the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), a population-based study targeting people aged ≥60 years living at home or in institutions in central Stockholm [25]. The sampling was stratified by age cohorts; the younger age cohorts (60, 66, and 72 years) were followed up every sixth year and the older age cohorts (78, 81, 84, 87, 97, 93, 96, and 99+ years) every third year because of more rapid changes in health and a higher attrition rate in older age groups.

In total, 3363 individuals agreed to participate in the baseline (March 2001–June 2004). After excluding participants with baseline dementia (n = 319), missing Mini-Mental State Examination score (MMSE; n = 153), missing glycated hemoglobin (HbA1c) if without diabetes (n = 89), with neuropsychiatric (e.g., Parkinson's disease or schizophrenia) or developmental disorders (n = 35), and with type 1 diabetes (n = 21), 2746 dementia-free participants were retained for the present study and followed up until 9 years (mean follow-up = 6.4 ± 1.7 years; range = 2.1–10.3 years). During follow-up, 651 (23.7%) died and 453 (16.5%) refused to participate (Fig. 1).

During baseline (September 2001–October 2003), noninstitutionalized, nondisabled, and nondemented participants in SNAC-K were invited to undertake structural brain MRI, and 555 individuals were scanned. People with suboptimal MRI quality (n = 53), neurological conditions (including brain infarcts, tumors, aneurysms, or stroke; n = 34), neuropsychiatric disorders (n = 6), and missing HbA1c (n = 5) were excluded. Thus, 455 participants at baseline in the MRI subsample were rescanned at the third and/or sixth year of follow-up. During follow-up, 39 (8.6%) people died and 35 (7.7%) dropped out (Supplementary Fig. 1).

SNAC-K and SNAC-K MRI were approved by the Karolinska Institutet Ethical Committee and the Regional Ethical Review Board in Stockholm, Sweden. Written informed consent was collected from all participants or a proxy.

2.2. Data collection

Data on demographics (i.e., age, sex, and education), lifestyle factors (i.e., smoking, alcohol consumption, and physical exercise), medical history, and current medication use were collected through structured interviews and clinical examination. Cognitive functioning was examined by trained psychologists (protocol available at http://www.snac.org). Peripheral blood samples were collected from all participants.

Education level was trichotomized into elementary, high school, or university. Smoking status was dichotomized as never/former versus current. Socioeconomic status (SES), derived by the longest-held occupation, was categorized into white-collar versus blue-collar workers [26]. Alcohol consumption was categorized into never/occasional versus current (which included light-to-heavy drinking). Physical activity was categorized into inactive, moderate, and vigorous, based on the intensity and frequency of the physical exercise [27]. Body weight and height were measured without shoes and heavy clothes. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m^2) and classified as underweight (<20.0), normal weight (20–25), overweight (>25–30), or obese (≥30). Arterial blood pressure was measured twice at a 5-min interval on the left arm in a sitting position; hypertension was identified (blood pressure ≥ 140/90 mm Hg). Chronic medical conditions were ascertained based on physicians' examination, medical history, medication use, laboratory tests, and linkage with the Swedish National Patient

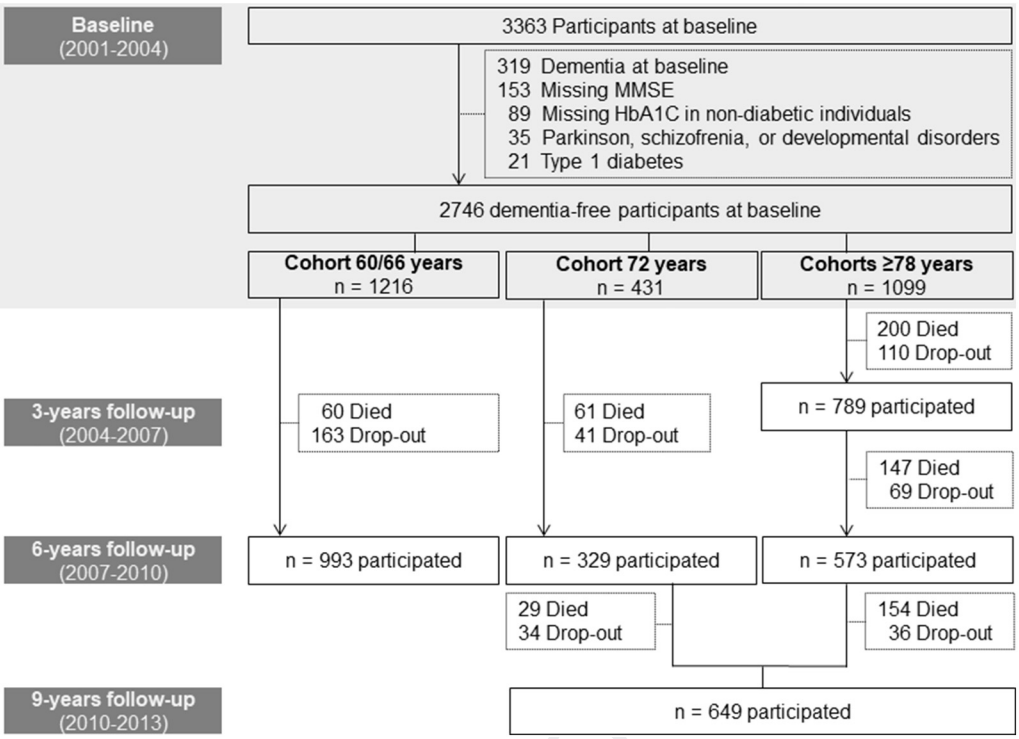

Fig. 1. Flowchart of the SNAC-K cohort. Abbreviations: MMSE, Mini-Mental State Examination; HbA1c, glycated hemoglobin; SNAC-K, Study on Aging and Care-Kungsholmen. Drop-out included refusal (from participant or proxy), language difficulties, canceled testing, and no contact or moved.

Register, which covers all inpatient care in Sweden since 1987 and also outpatient care since 2001. Codes from the International Classification of Disease, tenth revision (International Classification of Disease 10; described in Appendix A), were used to identify the chronic medical conditions, such as heart diseases (atrial fibrillation, bradycardias and conduction diseases, ischemic heart disease, cardiac valve diseases, and heart failure) and cerebrovascular diseases [28]. The apolipoprotein E (*APOE*) genotypes were detected using a microsequencing method (AffiGen APOE, Sangtec Medical) based on a polymerase chain reaction with biotinylated primers. *APOE* allelic status was dichotomized into any ε4 versus non-ε4 carriers.

2.3. Assessment of diabetes, prediabetes, and hyperglycemia

HbA1c (%) was measured with the Swedish Mono-S filament High Performance Liquid Chromatography, and 1.1% was added to equate the measured HbA1c values with international values [27]. Diabetes was ascertained based on self-reported medical history, medication use, medical records from the registry (International Classification of Disease 10 code E11), or HbA1c $\geq$ 6.5% [29]. Prediabetes was identified in nondiabetic participants with HbA1c levels of 5.7%–6.5% [29]. Based on the distribution, HbA1c was divided into quintiles (Q1 to Q5), ranging from normoglycemia (lower quintiles) to hyperglycemia (higher quintiles). For ease of interpretation, glycemic levels were then categorized into three groups according to the quintiles significantly associated with a faster cognitive decline: (1) Q1 (HbA1c 4.3%–5.3%); (2) Q2–Q3 (HbA1c $\geq$ 5.4%–5.7%); and (3) Q4–Q5 (HbA1c $\geq$ 5.8%), which corresponded to hyperglycemia.

2.4. Assessment of cognitive decline and dementia

At each wave, global cognitive function was assessed with MMSE. Dementia was diagnosed by examining physicians according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, using a validated three-step procedure, which has been previously described [27].

2.5. Brain markers on MRI

The MRI protocol is described in Appendix B. Volumetric measurements of gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid volume were derived after segmentation of the T1-weighted images in SPM12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Center for Neuroimaging, FIL, London, UK), implemented in Matlab 10 (The Mathworks Inc., MA), using the improved unified segmentation algorithm that uses an extended set of tissue-probability maps [30]. The "light cleanup" option was used to further remove odd voxels from the images. GMV and WMV were summed up to obtain total brain tissue volume (TBTV). Total intracranial volume was calculated by adding the GMV, WMV, and cerebrospinal fluid volume. All segmentations were inspected by

a neuroimaging expert (G.K.). Hippocampal volume (HV) was computed with automated segmentation of the T1-weighted images performed with the Freesurfer 5.1 image-analysis suite (http://surfer.nmr.mgh.harvard.edu/) [31,32]. White matter hyperintensities volume (WMHV) were manually drawn on FLAIR images by G.K. and further interpolated on the corresponding T1 images to compensate for the gap between slices in FLAIR (the intrarater reliability was high [>0.987]) [33]. All MRI measurements were adjusted by total intracranial volume and age [34], and the adjusted volumes were used in data analyses.

2.6. Statistical analysis

Baseline characteristics of participants by diabetes status (diabetes free, prediabetes, or diabetes) or by participation in MRI scanning were compared using chi-square or one-way ANOVA, followed by pairwise comparisons with Bonferroni correction.

Linear mixed-effect models (equation described in Appendix C) with unstructured variance-covariance matrices were used to determine the associations between diabetes status and annual cognitive changes in MMSE and the progression of the MRI markers, using follow-up time (years) as time scale. The fixed effect included baseline diabetes status (diabetes-free vs. prediabetes or diabetes), linear annual follow-up time, and their interaction (diabetes status × time). The random effect included random intercept and slope for time, allowing individual differences at baseline and across time. Age, sex, education, SES, BMI, smoking, alcohol consumption, physical activity, hypertension, heart diseases, cerebrovascular diseases, and *APOE* ε4 were considered as potential confounders and adjusted for in data analyses. In addition, the relationship between hyperglycemia and cognitive decline was examined with mixed-effect models including baseline glycemic levels as predictors.

In supplementary analyses, multiple imputation by chained equations was conducted to address potential bias by missing data. Five imputed datasets were created, and Rubin's rule was used for pooling estimates and obtaining valid statistical inferences; all available covariates and outcomes were used in the imputation models. Potential reverse causality was addressed by excluding incident dementia or censoring the outcomes at the time of dementia diagnosis. Prediabetes was modeled as time-varying variable. The WMV-WMHV relationship was also assessed (Appendix D).

Data were analyzed with Stata SE, version 14.0 (StataCorp LP., College Station, TX).

3. Results

3.1. Characteristics of the baseline study population

In the SNAC-K cohort, the mean age of the 2746 participants was 71.7 years (standard deviation = 10.2), and 1723 (62.8%) were women. Of all participants, 947 (34.5%) had prediabetes, and 242 (8.8%) had diabetes. Participants with prediabetes or diabetes were more likely to be older, male, less physically active, consume less alcohol, have fewer years of formal education, have higher BMI, have cardiovascular and cerebrovascular diseases, and/or have lower MMSE scores than diabetes-free participants (Table 1).

In the MRI subsample, the prevalence of prediabetes and diabetes was 29.9% and 7.0%, respectively. Participants with prediabetes or diabetes were older and more likely to have heart diseases; smaller TBTV, GMV, and WMV; and larger WMHV than diabetes-free people (Supplemental Table 1).

3.2. Prediabetes and diabetes in relation to cognitive decline

Table 2 provides the mixed-effect models' β-coefficients (95% CIs) of the association between baseline diabetes status and annual MMSE changes in the SNAC-K cohort. Compared with diabetes-free status, prediabetes and

Table 1
Baseline characteristics of the SNAC-K participants (n = 2746)

Characteristics	Diabetes free n = 1557	Prediabetes n = 947	Diabetes n = 242	*P*
Age, years	71.3 ± 10.0	74.6 ± 10.4*	74.1 ± 9.5*	<.001
Female	987 (63.4)	621 (65.6)	115 (47.5)	<.001
Education				
Elementary	183 (11.8)	162 (17.1)	47 (19.4)	<.001
High school	754 (48.5)	482 (51.0)	130 (53.7)	
University	618 (39.7)	302 (31.9)	65 (26.9)	
Socioeconomic status				
Blue-collar	302 (19.6)	217 (23.1)	57 (23.7)	.069
White-collar	1242 (80.4)	723 (76.9)	184 (76.4)	
Current smoking	816 (52.7)	534 (56.7)	139 (58.2)	.075
Alcohol consumption	1141 (73.6)	582 (61.8)	130 (54.2)	<.001
Physical activity				
Inactive	366 (23.5)	285 (30.1)	90 (37.2)	<.001
Moderate	810 (52.0)	464 (49.0)	113 (46.7)	
Vigorous	381 (24.5)	198 (20.9)	39 (16.1)	
BMI, kg/m^2	25.2 ± 3.7	25.8 ± 4.0*	27.5 ± 4.9*	<.001
Underweight (<20)	91 (5.8)	50 (5.3)	8 (3.3)	<.001
Normal (20–25)	713 (45.8)	384 (40.6)	68 (28.1)	
Overweight (25–30)	608 (39.1)	379 (40.0)	99 (40.9)	
Obese (≥30)	145 (9.3)	134 (14.2)	67 (27.7)	
Hypertension	1060 (68.1)	677 (71.5)	193 (79.8)	.001
Heart diseases	265 (17.0)	252 (26.6)	113 (46.7)	<.001
Cerebrovascular diseases	77 (5.0)	64 (6.8)	20 (8.3)	.043
HbA1c, %	5.3 ± 0.2	5.9 ± 0.2*	7.1 ± 1.3*	<.001
Any *APOE* ε4	437 (29.8)	261 (29.5)	52 (23.5)	.155
MMSE	28.9 ± 1.3	28.7 ± 1.5*	28.5 ± 1.6*	<.001

Abbreviations: SNAC-K, Study on Aging and Care-Kungsholmen; BMI, body mass index; *APOE* ε4, apolipoprotein ε4 allele; MMSE, Mini-Mental State Examination; HbA1c, glycated hemoglobin.

NOTE. Data are presented as means ± standard deviations or numbers (proportions).

NOTE. Missing data: 3 for education, 21 for socioeconomic status, 16 for smoking, 13 for alcohol consumption, and 173 for *APOE* ε4.

*Pairwise mean comparisons using Bonferroni correction: $P < .05$ (reference group was diabetes-free participants).

Table 2
Mixed-effect models' β-coefficients and 95% confidence intervals (95% CIs) of the associations between diabetes status and baseline performance (intercept), and annual changes over 9 years (diabetes status × time), in Mini-Mental State Examination (MMSE) Q7

	n	Model 1 β (95% CI)*	Model 2 β (95% CI)†	Model 3 β (95% CI)‡
Diabetes status (intercept)				
Diabetes free	1557	Reference	Reference	Reference
Prediabetes	947	0.08 (−0.03 to 0.20)	0.08 (−0.03 to 0.20)	0.05 (−0.07 to 0.17)
Diabetes	242	−0.17 (−0.36 to 0.03)	−0.08 (−0.28 to 0.12)	−0.10 (−0.31 to 0.10)
Time, years¶		−0.20 (−0.22 to −0.17)§	−0.20 (−0.22 to −0.18)§	−0.20 (−0.23 to −0.18)§
Diabetes status × time (years)¶				
Diabetes-free × time		Reference	Reference	Reference
Prediabetes × time		−0.06 (−0.10 to −0.02)§	−0.06 (−0.10 to −0.02)§	−0.05 (−0.09 to −0.01)#
Diabetes × time		−0.10 (−0.17 to −0.03)§	−0.11 (−0.18 to −0.04)§	−0.11 (−0.18 to −0.04)§

Abbreviations: BMI, body mass index; *APOE* ε4, apolipoprotein ε4 allele.
*Adjusted for baseline age, sex, and education.
†Adjusted for model 1 + socioeconomic status, BMI, smoking, alcohol consumption, physical activity, hypertension, heart diseases, and cerebrovascular diseases.
‡Adjusted for model 2 + *APOE* ε4.
¶Time (years) represents the annual change in MMSE (slope) for the reference group, whereas diabetes status × time represents the additional annual change in MMSE for prediabetes or diabetes.
§*P* values < .01.
#*P* values < .05.

diabetes were associated with faster cognitive decline over 9 years (model 1). The results remained significant after further adjusting for SES, vascular risk factors and disorders (model 2), and *APOE* ε4 (model 3). Supplementary Fig. 2 shows the trajectories of MMSE decline by diabetes status over time. Participants with prediabetes or diabetes lost up to 3 points on the MMSE with a predicted mean MMSE score below 27 or 26, respectively.

We further assessed the association between HbA1c and MMSE changes. Higher HbA1c level (continuous variable) was dose-dependently associated with even faster cognitive decline. Specifically, a 1-point increment in HbA1c level was associated with a 0.04-point faster annual decline in MMSE score (β −0.04 [95% CI, −0.07 to −0.01]). In multi-adjusted mixed-effect models, compared with lower glucose level (Q1 [HbA1c 4.3%–5.4%]), hyperglycemia (Q4–Q5 [(HbA1c ≥ 5.8%)]) was significantly associated with a steeper cognitive decline (Supplementary Table 2; model 3: β_{slope} −0.08 [95% CI, −0.13 to −0.03], *P* = .001). The difference in cognitive decline between Q2–Q3 (HbA1c ≥ 5.4%–5.7%) and Q1 (reference) was not statistically significant. Fig. 2 shows the estimated trajectories of MMSE decline over 9 years in SNAC-K participants with hyperglycemia, in comparison to those with a lower glycemic level.

3.3. Prediabetes, diabetes, and brain MRI markers

In the multiadjusted (by sex, education, SES, BMI, hypertension, and heart disease) mixed-effect models, compared with diabetes-free status, prediabetes was associated with smaller TBTV, particularly in the WMV, and diabetes was associated with larger WMHV at baseline. HV was not associated with prediabetes or diabetes (Table 3: intercept). Longitudinally, diabetes was independently associated with a faster increase in WMHV (β, 0.57 [95% CI, 0.08–1.07], *P* = .023) (Table 3: diabetes status × time; Fig. 3). Participants with diabetes showed a tendency toward greater WMV loss than diabetes-free individuals, but the difference did not approach conventional significance (*P* > .05; Table 3).

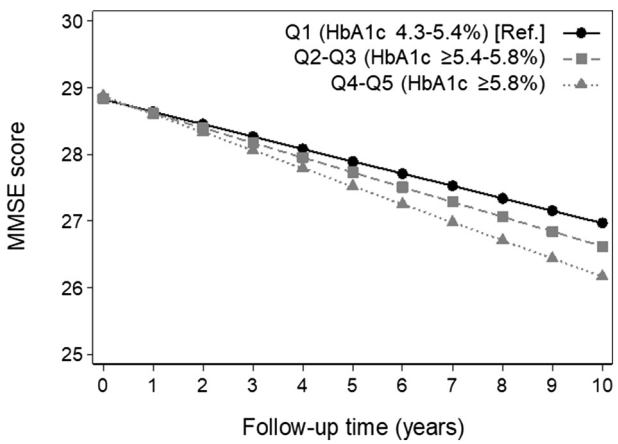

Fig. 2. Estimated trajectories of MMSE over 9 years by quintiles of glycated hemoglobin. Participants with lower glycemic level (Q1 [HbA1c 4.3%–5.3%; reference], black circle), intermediate glycemic level (Q2–Q3 [HbA1c ≥ 5.4%–5.8%], gray square), and hyperglycemia (Q4–Q5 [HbA1c ≥ 5.8%], gray triangle) are included. Mixed model was adjusted for baseline age, sex, education, BMI, smoking, alcohol consumption, physical activity, hypertension, cardiovascular diseases, and cerebrovascular diseases. Trajectories were plotted based on the mean values of the covariates. Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; HbA1c, glycated hemoglobin.

Table 3
β-coefficients and 95% confidence intervals (95% CI) for the associations of diabetes status with baseline brain volumes (intercept) and annual brain volume changes over 6 years (diabetes status × time), from multivariable mixed-effect models

		TBTV*	GMV*	HV*	WMV*	WMHV*
	n	β (95% CI)†	β (95% CI)†	β (95% CI)†	β (95% CI)†	β (95% CI)†
Diabetes status (intercept)						
Diabetes free	287	Reference	Reference	Reference	Reference	Reference
Prediabetes	136	−19.1 (−34.0 to −4.19)‡	−9.07 (−19.5 to 1.33)	−0.06 (−0.22 to 0.11)	−9.92 (−19.4 to −0.46)§	1.74 (−0.15 to 3.64)
Diabetes	32	−20.4 (−47.4 to 6.66)	−7.73 (−26.6 to 11.1)	−0.12 (−0.43 to 0.19)	−12.6 (−29.8 to 4.53)	3.63 (0.18 to 7.08)§
Time, years¶		−7.72 (−8.34 to −7.10)‡	−3.57 (−4.05 to −3.09)‡	−0.07 (−0.09 to −0.06)‡	−4.13 (−4.60 to −3.65)‡	0.36 (0.23 to 0.50)‡
Diabetes status × time (years)						
Diabetes free × time		Reference	Reference	Reference	Reference	Reference
Prediabetes × time		−0.46 (−1.67 to 0.75)	−0.48 (−1.41 to 0.46)	−0.003 (−0.02 to 0.02)	−0.06 (−1.00 to 0.87)	0.11 (−0.15 to 0.38)
Diabetes × time		−1.59 (−3.90 to 0.71)	−0.48 (−2.26 to 1.30)	−0.03 (−0.07 to 0.01)	−0.95 (−2.74 to 0.84)	0.57 (0.08 to 1.07)§

Abbreviations: GMV, gray matter volume; HV, hippocampal volume; WMV, white matter volume; WMHV, white matter hyperintensities volume; TBTV, total brain tissue volume; BMI, body mass index.

*Brain volumes (mL) were adjusted for intracranial volume and age.

†Mixed models were adjusted for sex, education, socioeconomic status, BMI, hypertension, and heart diseases.

‡P values < 0.01.

§P values < 0.05.

¶Time (years) represents the annual change in brain volumes (slope) for the reference group, whereas diabetes status × time represents the additional annual brain volume change for prediabetes or diabetes.

In separate multiadjusted mixed-effect models, hyperglycemia was associated with smaller TBTV (β, −24.2 [95% CI, −41.5 to −6.87], P = .006) and WMV (β, −12.6 [95% CI, −23.6 to −1.60], P = .025), as well as larger WMHV (β, 3.32 [95% CI, 1.04–5.60], P = .004) at baseline in a dose-dependent fashion.

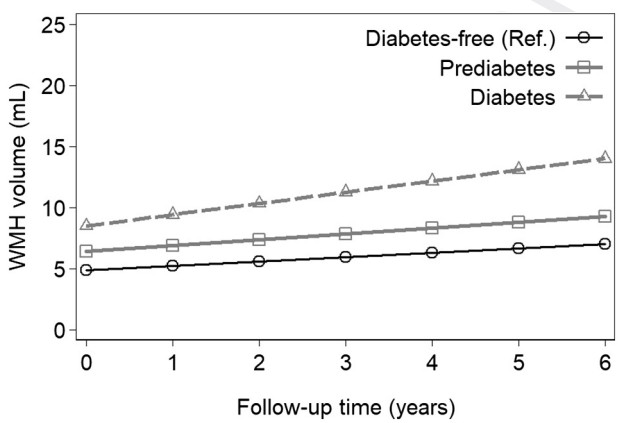

Fig. 3. Trajectories of WMH changes by baseline diabetes status. The figure shows the annual trajectories of brain-volume changes in WMH in diabetes-free older adults (reference group; black white circle) versus prediabetes (gray white square) and diabetes (gray white triangle) from mixed-effect model, adjusted for sex, education, socioeconomic status, BMI, hypertension, and heart diseases. The trajectories were plotted based on the mean values of the covariates in the mixed-effect model. Abbreviations: BMI, body mass index; WMH, white matter hyperintensities.

4. Discussion

In this population-based prospective cohort study, we found that prediabetes and diabetes were independently associated with accelerated cognitive decline and prediabetes was related to smaller global brain volume, especially lower white matter volume, whereas diabetes increased the accumulation of WMH. The association between prediabetes or diabetes and HV was not evident. These findings suggest that microvascular lesions might be the initial pathological changes underlying cognitive decline and subsequent dementing disorders in diabetes.

Although diabetes is a recognized risk factor for dementia, studies examining the association between prediabetes and cognitive decline are limited, and most have reported no association [6,10−12]. In our study, we observed accelerated cognitive decline in older adults with prediabetes, providing evidence for the potentially harmful effect of prediabetes on cognitive function. Indeed, older adults with prediabetes and diabetes had a clinically relevant MMSE decline by losing up to three points in the MMSE score over time. Our findings also demonstrate accelerated cognitive decline among older adults with diabetes. Glucose regulation has been proposed to play a role in the onset and progression of neural and cognitive complications of diabetes. However, the few previous longitudinal studies examining the role of glycemic control in diabetes-related cognitive decline have yielded mixed results [11,35,36]. Increased HbA1c levels have been associated with faster decline in memory and reasoning in middle-aged individuals with diabetes [12],

but other cohort studies did not find such associations [35,36]. These studies partly lack longer follow-ups and assessments of prediabetes or glycemic control that may account for the discrepant findings.

Considering the intricate relationship between brain and behavior, brain alterations (i.e., vascular and neurodegenerative markers) can help in the understanding of the etiology of cognitive decline related to prediabetes and diabetes. However, data on the association between prediabetes and structural brain alterations are limited. To our knowledge, this association has been investigated in four previous cross-sectional [17,20,21] and two longitudinal studies [23,24], with inconsistent results. Of these studies, Weinstein et al. [17] observed smaller occipital gray matter volume and reduced white matter integrity in middle-aged adults with prediabetes, and Shawn et al. [24] reported increased cortical thickness over 12 years in nondiabetic older adults with increased blood glucose levels, although other studies found no differences in brain volumes between people with prediabetes and who are diabetes free. In the present study, prediabetes was associated with smaller brain volumes, mostly reflecting smaller white matter volume. This suggests that vascular brain alterations may already exist and can be detected at the prediabetes stage. In addition, compared with normoglycemia, prediabetes seems to have faster progression of brain atrophy and vascular brain lesions, albeit to a lesser extent than diabetes. However, differences were not statistically significant. Therefore, this result needs to be interpreted with caution, and further studies with longer follow-ups are required to confirm the presence of vascular brain alterations already at the prediabetes stage.

WMH are part of SVD and reflect microvascular lesions in the cerebral white matter, likely due to demyelination and axonal loss [13]. Thus, increased WMH would result in white matter tissue loss and, over time, in brain atrophy and subsequent cognitive decline. Many cross-sectional studies have addressed the role of WMH in diabetes-related cognitive decline and dementia, but results remain controversial. Some studies observed greater WMHV in diabetes [17,20], whereas others did not [16,19]. Also, few longitudinal studies have examined the progression of WMHV, generally showing no exacerbated changes in WMHV in relation to diabetes [23,37]. Our findings highlight that diabetes may increase markedly the accumulation of WMH over time. The discrepancy between our findings and those of previous longitudinal studies may reflect differences in study design, especially the combination of shorter follow-up periods and younger ages at study entry, as well as selected samples from clinical settings rather than from the population at large. In line with previous research [18,19,23], our findings further showed that neither prediabetes nor diabetes were associated with HV, a classic marker of AD-related neurodegeneration. In addition, we also found an inverse correlation between WMHV and WMV. Together, these data point toward the existence of a vasculopathic process, especially in the microvasculature, underlying the onset and progression of prediabetes- and diabetes-related cognitive decline rather than an AD neurodegenerative process [15,38]. However, our results do not exclude that AD-related degeneration may play a role in diabetes-related cognitive decline. Indeed, the simple brain measure of HV may not be as specific and sensitive for AD as other more complex brain MRI measures based on high-dimensional pattern classification methods, such as the Spatial Pattern of Abnormality for Recognition of Early AD index, which may provide a better representation of the underlying neurodegenerative process [39].

Diabetes and prediabetes can affect the brain through different pathways, primarily originating from chronic hyperglycemia, which triggers a complex interplay between systemic (i.e., inflammation, oxidative stress) and biochemical (i.e., advanced glycation end products) factors, leading to accelerated cognitive decline [15,40]. Hyperglycemia can induce neuroinflammation and oxidative stress, causing loss of pericytes, which are vascular cells that together with endothelial cells, glial cells, and neurons form the neurovascular unit, directly involved in maintaining the integrity of the blood-brain barrier and brain homeostasis [41]. In turn, dysfunction of blood-brain barrier permeability may lead to changes in the brain microvasculature and, over time, to white matter abnormalities [40,42]. In our study, hyperglycemia is linked to smaller TBTV and WMV, as well as increased WMHV and cognitive decline, supporting the crucial role of hyperglycemia in the etiopathogenesis of pre/diabetes-related brain abnormalities and cognitive decline.

Our study has several strengths including the longitudinal design with a large cohort of older adults with repeated measurements of cognitive functioning and brain imaging. The comprehensive assessment of diabetes status based on integration of different data sources allowed for identifying participants with prediabetes and undiagnosed diabetes and to separate type 1 from type 2 diabetes. Other advantages are the inclusion of potential diabetes- and dementia-related confounders and the integration of brain-based, clinical, and cognitive data. However, some potential limitations need to be acknowledged. Selection bias might have led to a younger, relatively healthier MRI sample with better cognitive function at baseline. Hence, this may have resulted in underestimation of the magnitude of the associations among prediabetes/diabetes, brain alterations, and cognitive changes. Selective loss at follow-up (dropouts and deaths) might have introduced a second source of bias, which also could have underestimated the strength of the observed associations. However, this should have a relatively small impact on our results. Indeed, the number of persons who dropped out or died was small in both SNAC-K and MRI cohorts. The probability of participation was independent of the diabetes or prediabetes status, and analyses using multiple imputation yielded estimates with similar magnitude and direction as the initial analyses. Furthermore, intrinsic limitations in the MMSE (e.g., ceiling effects, suboptimal test-retest reliability, poor sensitivity to subtle changes in highly educated healthy individuals, lack of items assessing

processing speed and executive function) might have led to an underestimation of the diabetes status–cognitive decline association. Future prospective studies using composite scores of global cognition derived by cognitive tests battery in conjunction with advanced statistical methods (i.e., Item Response Theory; Appendix D) are needed. Finally, potential confounding due to unmeasured factors (e.g., stress, environmental factors) cannot be completely ruled out. These limitations, together with potential selection effects and small sample sizes, may also account for the lack of association between diabetes status and cognitive decline in the MRI subsample. Consequently, whether brain markers (i.e., TBT and WMH) mediated the association between diabetes status and accelerated cognitive decline could not be addressed directly. However, the patterns of cognitive decline in the MRI subsample mirrored those observed in the SNAC-K cohort, and it is known that brain changes occur years before clinically evident cognitive decline [43]. Therefore, it is likely that the brain abnormalities observed in our study underlie the diabetes-related cognitive decline that has not yet become detectable in the smaller MRI subsample. Our findings can be generalized to western populations with similar characteristics as the SNAC-K participants.

In summary, our findings provide evidence of an accelerated cognitive decline related to prediabetes and diabetes, showing that the harmful effect of high blood sugar levels on cognition starts already at the prediabetic stage. Microvascular lesions may underlie the cognitive decline related to diabetes. Future larger prospective neuroimaging studies are needed to address directly whether brain vascular lesions mediate the diabetes-related accelerated cognitive decline. In addition, the extent to which the synergetic action of WMH together with other markers of SVD (i.e., microbleeds), systemic processes (i.e., inflammation, oxidative stress), and biological markers of glycemia (i.e., insulin resistance) can predict future cognitive decline and dementing disorders in prediabetes/diabetes should be elucidated.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.06.3060.

RESEARCH IN CONTEXT

1. Systematic review: PubMed and Web of Science databases were searched, and titles and abstracts were screened. Few studies have addressed the relation of prediabetes and cognitive decline, whereas several studies have examined the association between diabetes and cognitive decline, but results are mixed. In addition, the cerebral mechanisms underlying prediabetes/diabetes-related cognitive decline have not been well investigated in population-based cohorts.
2. Interpretation: This longitudinal population-based study suggests that harmful effect of high blood sugar levels on cognition may start already at the prediabetic stage. Furthermore, these findings contribute to clarifying the pathophysiology of prediabetes/diabetes-related cognitive decline in the initial stage, pointing toward the existence of cerebral microvascular processes, primarily stemming from chronic hyperglycemia.
3. Future directions: Future research should elucidate the extent to which the synergistic effects of markers of small vessel disease, systemic processes (i.e., inflammation), and markers of glucose metabolism can predict cognitive decline in prediabetes/diabetes.

References

[1] IDF Diabetes Atlas 7th ed. 2015 Brussels, Belgium: International Diabetes Federation, 2015. Available at: http://www.diabetesatlas.org. Accessed January 21, 2018.
[2] Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. Lancet Diabetes Endocrinol 2016;4:537–47.
[3] World Alzheimer Report 2015: The Global Impact of Dementia [Report Online] 2015 Available at: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf. Accessed January 21, 2018.
[4] Biessels GJ, Strachan MWJ, Visseren FLJ, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic

stages: towards targeted interventions. Lancet Diabetes Endocrinol 2014;2:246–55.
[5] Xu W, Qiu C, Winblad B, Fratiglioni L. The effect of borderline diabetes on the risk of dementia and Alzheimer's disease. Diabetes 2007;56:211–6.
[6] Marseglia A, Dahl Aslan AK, Fratiglioni L, Santoni G, Pedersen NL, Xu W. Cognitive trajectories in prediabetes and diabetes: a population-based cohort study. J Gerontol A Biol Sci Med Sci 2018;73:400–6.
[7] Spauwen PJ, Kohler S, Verhey FR, Stehouwer CD, van Boxtel MP. Effects of type 2 diabetes on 12-year cognitive change: results from the Maastricht Aging Study. Diabetes care 2013;36:1554–61.
[8] Fischer AL, De Frias CM, Yeung SE, Dixon RA. Short-term longitudinal trends in cognitive performance in older adults with type 2 diabetes. J Clin Exp Neuropsychol 2009;31:809–22.
[9] van den Berg E, Reijmer YD, de Bresser J, Kessels RP, Kappelle LJ, Biessels GJ. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia 2010;53:58–65.
[10] Samaras K, Lutgers HL, Kochan NA, Crawford JD, Campbell LV, Wen W, et al. The impact of glucose disorders on cognition and brain volumes in the elderly: the Sydney Memory and Ageing Study. Age (Dordr) 2014;36:977–93.
[11] Tuligenga RH, Dugravot A, Tabák AG, Elbaz A, Brunner EJ, Kivimäki M, et al. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: a post-hoc analysis of the Whitehall II cohort study. Lancet Diabetes Endocrino 2014;2:228–35.
[12] Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004;63:658–63.
[13] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–38.
[14] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger–Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9:1118–27.
[15] Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? Diabetes 2014;63:2244–52.
[16] Roberts RO, Knopman DS, Przybelski SA, Mielke MM, Kantarci K, Preboske GM, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. Neurology 2014;82:1132–41.
[17] Weinstein G, Maillard P, Himali JJ, Beiser AS, Au R, Wolf PA, et al. Glucose indices are associated with cognitive and structural brain measures in young adults. Neurology 2015;84:2329–37.
[18] Wisse LE, de Bresser J, Geerlings MI, Reijmer YD, Portegies ML, Brundel M, et al. Global brain atrophy but not hippocampal atrophy is related to type 2 diabetes. J Neurol Sci 2014;344:32–6.
[19] Moran C, Beare R, Phan TG, Bruce DG, Callisaya ML, Srikanth V, et al. Type 2 diabetes mellitus and biomarkers of neurodegeneration. Neurology 2015;85:1123–30.
[20] Schneider ALC, Selvin E, Sharrett AR, Griswold M, Coresh J, Jack CR Jr, et al. Diabetes, prediabetes, and brain volumes and subclinical cerebrovascular disease on MRI: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Diabetes care 2017;40:1514–21.
[21] Bamberg F, Hetterich H, Rospleszcz S, Lorbeer R, Auweter SD, Schlett CL, et al. Subclinical disease burden as assessed by whole–body MRI in subjects with prediabetes, subjects with diabetes, and normal control subjects from the general population: the KORA-MRI Study. Diabetes 2017;66:158–69.
[22] Espeland MA, Bryan RN, Goveas JS, Robinson JG, Siddiqui MS, Liu S, et al. Influence of type 2 diabetes on brain volumes and changes in brain volumes: results from the Women's Health Initiative Magnetic Resonance Imaging studies. Diabetes care 2013;36:90–7.
[23] Reitz C, Guzman VA, Narkhede A, DeCarli C, Brickman AM, Luchsinger JA. Relation of dysglycemia to structural brain changes in a multiethnic elderly cohort. J Am Geriatr Soc 2017;65:277–85.
[24] Shaw ME, Nettersheim J, Sachdev PS, Anstey KJ, Cherbuin N. Higher fasting plasma glucose is associated with increased cortical thinning over 12 years: The PATH through life study. Brain Topogr 2017;30:408–16.
[25] Lagergren M, Fratiglioni L, Hallberg I, Berglund J, Elmståhl S, Hagberg B, et al. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). Aging Clin Exp Res 2004;16:158–68.
[26] Rydwik E, Welmer AK, Angleman S, Fratiglioni L, Wang HX. Is midlife occupational physical activity related to disability in old age? The SNAC-Kungsholmen study. PLoS One 2013;8:e70471.
[27] Marseglia A, Fratiglioni L, Laukka EJ, Santoni G, Pedersen NL, Backman L, et al. Early cognitive deficits in type 2 diabetes: a population-based study. J Alzheimers Dis 2016;53:1069–78.
[28] Calderon-Larranaga A, Vetrano DL, Onder G, Gimeno-Feliu LA, Coscollar-Santaliestra C, Carfi A, et al. Assessing and measuring chronic multimorbidity in the older population: a proposal for its operationalization. J Gerontol A Biol Sci Med Sci 2017;72:1417–23.
[29] American Diabetes Association. Standards of medical care in diabetes–2013. Diabetes care 2013;36(Suppl 1):S11–66.
[30] Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005; 26:839–51.
[31] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341–55.
[32] Gerritsen L, Kalpouzos G, Westman E, Simmons A, Wahlund LO, Backman L, et al. The influence of negative life events on hippocampal and amygdala volumes in old age: a life-course perspective. Psychol Med 2015;45:1219–28.
[33] Kohncke Y, Laukka EJ, Brehmer Y, Kalpouzos G, Li TQ, Fratiglioni L, et al. Three-year changes in leisure activities are associated with concurrent changes in white matter microstructure and perceptual speed in individuals aged 80 years and older. Neurobiol Aging 2016;41:173–86.
[34] Jack CR Jr, Twomey CK, Zinsmeister AR, Sharbrough FW, Petersen RC, Cascino GD. Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. Radiology 1989;172:549–54.
[35] Christman AL, Matsushita K, Gottesman RF, Mosley T, Alonso A, Coresh J, et al. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia 2011;54:1645–52.
[36] Yaffe K, Falvey CM, Hamilton N, Harris TB, Simonsick EM, Strotmeyer ES, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Intern Med 2013;173:1300–6.
[37] de Bresser J, Tiehuis AM, van den Berg E, Reijmer YD, Jongen C, Kappelle LJ, et al. Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes. Diabetes care 2010;33:1309–14.
[38] Abner EL, Nelson PT, Kryscio RJ, Schmitt FA, Fardo DW, Woltjer RL, et al. Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. Alzheimers Dement 2016;12:882–9.
[39] Davatzikos C, Xu F, An Y, Fan Y, Resnick SM. Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: the SPARE-AD index. Brain 2009;132:2026–35.
[40] Salameh TS, Shah GN, Price TO, Hayden MR, Banks WA. Blood-Brain barrier disruption and neurovascular unit dysfunction in diabetic mice: protection with the mitochondrial carbonic anhydrase inhibitor topiramate. J Pharmacol Exp Ther 2016;359:452–9.
[41] Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 2011; 12:723–38.
[42] Love S, Miners JS. Small vessel disease, neurovascular regulation and cognitive impairment: post-mortem studies reveal a complex relationship, still poorly understood. Clin Sci (Lond) 2017;131:1579–89.
[43] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.