Accelerated Progression From Mild Cognitive Impairment to Dementia in People With Diabetes

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OBJECTIVE—The effect of diabetes on mild cognitive impairment (MCI) and its conversion to dementia remains controversial. We sought to examine whether diabetes and pre-diabetes are associated with MCI and accelerate the progression from MCI to dementia.

RESEARCH DESIGN AND METHODS—In the Kungsholmen Project, 963 cognitively intact participants and 302 subjects with MCI (120 with amnestic MCI [aMCI] and 182 with other cognitive impairment no dementia [oCIND]) age ≥75 years were identified at baseline. The two cohorts were followed for 9 years to detect the incident MCI and dementia following international criteria. Diabetes was ascertained based on a medical examination, hypoglycemic medication use, and random blood glucose level ≥11.0 mmol/l. Pre-diabetes was defined as random blood glucose level of 7.8–11.0 mmol/l in diabetes-free participants. Data were analyzed using standard and time-dependent Cox proportional-hazards models.

RESULTS—During the follow-up period, in the cognitively intact cohort, 182 people developed MCI (42 aMCI and 140 oCIND), and 212 developed dementia. In the MCI cohort, 155 subjects progressed to dementia, the multi-adjusted hazard ratio (95% CI) of dementia was 2.87 (1.30–6.34) for diabetes, and 4.96 (2.27–10.84) for pre-diabetes. In a Kaplan-Meier survival analysis, diabetes and pre-diabetes accelerated the progression from MCI to dementia by 3.18 years. Diabetes and pre-diabetes were neither cross-sectionally nor longitudinally associated with MCI.

CONCLUSIONS—Diabetes and pre-diabetes substantially accelerate the progression from MCI to dementia, and anticipate dementia occurrence by more than 3 years in people with MCI. The association of diabetes with the development of MCI is less evident in old people. ***Diabetes*** **59:2928–2935, 2010**

The impact of diabetes on cognitive function has been addressed in several studies showing that type 2 diabetes is associated with cognitive decline in aging (1). Furthermore, many large population-based longitudinal studies have demonstrated an increased risk of dementia in people with diabetes (2), but the association of diabetes with Alzheimer's disease is less evident in some studies (2,3). Overall, diabetes leads to a 20–70% greater decline in cognitive performance, and a 60% higher risk of dementia (4). Even pre-diabetes, the condition of impaired glucose regulation, has been related to cognitive decline and an increased risk of dementia (5,6), although a cross-sectional study found no association of impaired fasting blood glucose with cognitive function (7). In addition, three studies addressing the relation between diabetes and mild cognitive impairment (MCI) have also shown conflicting results (8–10).

MCI represents the usual transitional phase from normal cognitive function to dementia, although not all people with MCI will develop dementia (11). Different criteria and subdivisions of MCI have been proposed and modified over time (12). MCI has been subdivided into two major forms—amnestic MCI (aMCI) and other domain cognitive impairment no dementia (oCIND) (13–15). Progression to clinically diagnosable dementia occurs at a higher rate from MCI than from unimpaired cognition; the estimated rate of conversion is approximately 30% over 3 years (16). However, the extent to which diabetes accelerates this progression is unclear. Only two population-based studies have addressed this issue and both showed nonsignificant effect of diabetes on the conversion from MCI to dementia (10,17).

Most studies that have addressed the association of diabetes with dementia included people with MCI at baseline assessment as nondemented and people with pre-diabetes with a nondiabetic group. These studies may underestimate the risk of dementia associated with diabetes. We have demonstrated that diabetes and pre-diabetes increase the risk of dementia and its main subtypes (5,18–20). In the present study, we sought to investigate the association of diabetes and pre-diabetes with the risk of MCI and to verify the hypothesis that diabetes and pre-diabetes may accelerate the progression from MCI to dementia.

RESEARCH DESIGN AND METHODS

Study population. Data were derived from the Kungsholmen Project, which was a population-based prospective cohort study on aging and dementia, including all registered inhabitants who were age ≥75 years and living in the Kungsholmen district of central Stockholm, Sweden, in 1987 (21,22). By means of a two-phase survey, among the 1,700 participants at baseline (1987–1989), two cohorts (a cognitively intact cohort and an MCI cohort) were identified. The two cohorts were followed for 9 years (until 1997–1998) to detect incident dementia and MCI cases.

Cognitively intact cohort. The cognitively intact cohort consisted of 1,098 individuals after excluding 225 persons who were clinically diagnosed with prevalent dementia (using *Diagnostic and Statistical Manual of Mental Disorders*, *Revised Third Edition* [DSM-III-R] criteria) (23), 31 subjects with very low global cognitive status in the absence of a dementia diagnosis, and 9 with unknown educational level. An additional 337 subjects who were identified as having prevalent MCI (14,24) constituted the MCI cohort. Of the 1,098 cognitively intact individuals, 135 dropped out at the first follow-up examination resulting in 963 participants.

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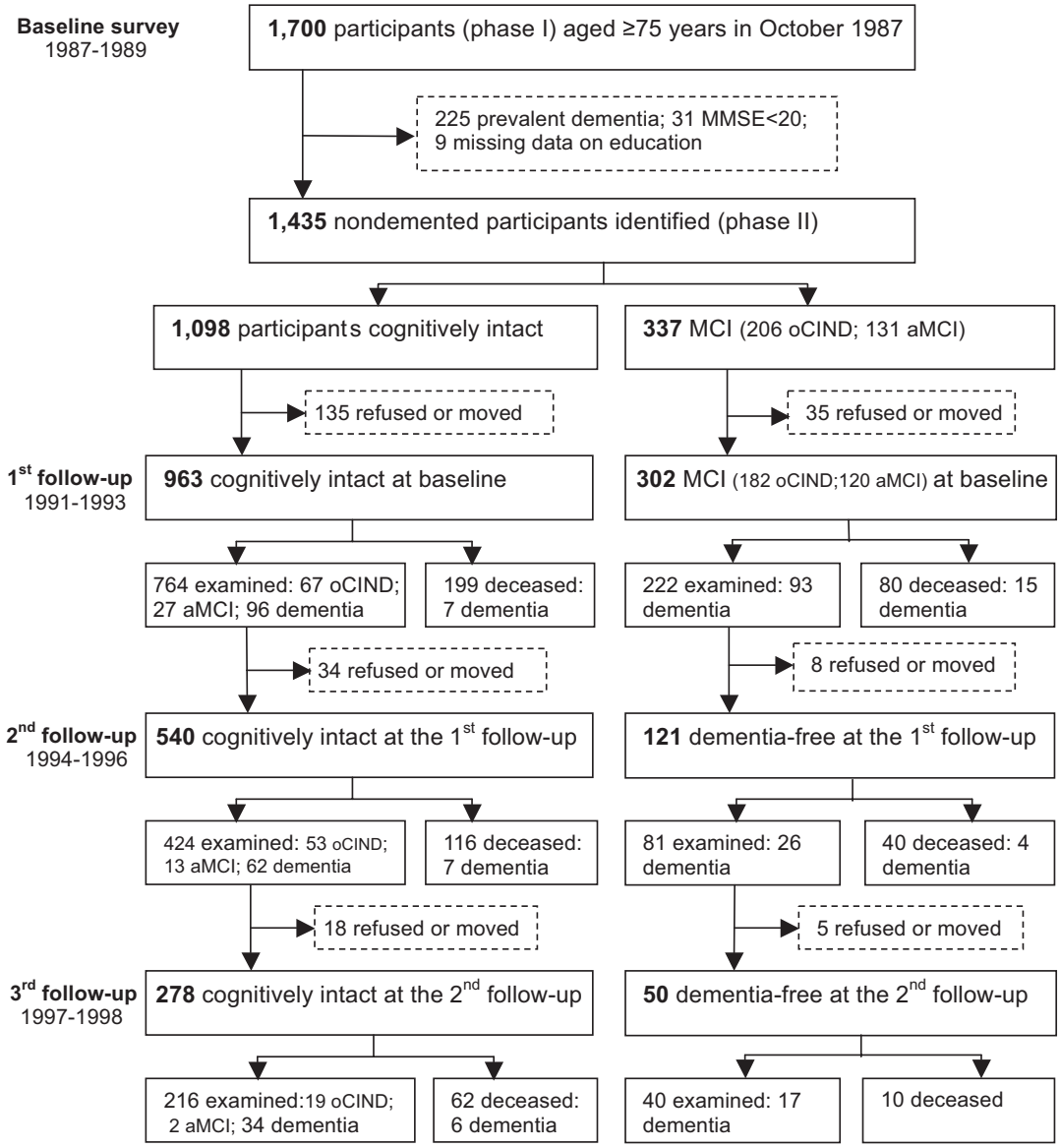

FIG. 1. Flowchart of the study population in the Kungsholmen Project.

MCI cohort. Of the 337 subjects with MCI, 35 refused to participate in the first follow-up examination or had moved, leaving 302 persons for the MCI cohort. This cohort included 120 aMCI subjects who had memory complaints and objective episodic memory impairment (14,24) and 182 oCIND subjects who had significant impairment in global cognitive performance, as defined in a previous report (15).

During the 9-year follow-up, three clinical examinations were carried out at an average interval of 3 years. Throughout the follow-up period, in the cognitively intact cohort, 357 people died and 52 dropped out. In the MCI cohort, 101 individuals died, and 13 were dropouts. Figure 1 shows the details of a flowchart of the study population from baseline to the third follow-up examination (1987–1989 to 1997–1998).

Medical records and death certificates were available for all participants who died during the follow-up. Informed consent was received from participants or from informants when the person was cognitively impaired. The Ethics Committee at Karolinska Institutet approved all phases of the Kungsholmen Project.

Data collection. Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE), and subjective memory problems were evaluated by questioning the subjects and close informants. Data on age, sex, and education were collected from subjects at baseline following standardized protocols (22,25). Education was measured as the maximum years of formal schooling, and was dichotomized (≥8 vs. <8 years) based on results from a previous study (26). Weight and height were measured with a standard scale in light clothing and with no shoes. BMI was calculated as weight (kg) divided by height (m) squared. Arterial blood pressure (i.e., systolic Korotkoff phase I and diastolic phase V) was measured on the right arm by nurses, with the subject placed in a sitting position after a 5-min rest. Information on medical history was taken for all participants from the inpatient registry system, which encompasses all hospitals in Stockholm from 1969 onward. The *International Classification of Disease*, 8th revision (ICD-8) and the ICD-9th revisions (ICD-9) were used in the registry system until 1997. Medical conditions derived from the inpatient register database included ischemic heart disease (ICD-8, ICD-9, codes 410–414), heart failure or left ventricular failure or other myocardial insufficiency (ICD-8. codes 427 and 428; ICD-9, code 428.x), atrial fibrillation (ICD-8 code 427.9; ICD-9 code 427), stroke (ICD-8, ICD-9, codes 430–438), hypertension (ICD-8 codes 400–404; ICD-9 codes 401–405), and diabetes (ICD-8, ICD-9. code 250). Information on medical drug use for the 2 weeks prior to the baseline interview was collected from the subjects. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) Classification System (27). Hypoglycemic drugs included hypoglycemic medications or insulin injection (ATC code A10). Blood pressure lowering drugs were defined as all medicines potentially used for lowering blood pressure (ATC codes C02, C03, and C07). Genomic DNA was prepared from peripheral blood samples that were taken at baseline, and APOE allelic status was determined following a standard procedure (28).

Assessment of diabetes and pre-diabetes. Blood samples were taken at baseline survey and at each follow-up examination. Random (nonfasting) blood glucose was measured using a glucose oxidase procedure at baseline and follow-ups. Diabetes was identified by clinical examination and through

the inpatient register system, use of hypoglycemic drugs, and random blood glucose level ≥11.0 mmol/l (19,29). Pre-diabetes was considered to be present if random blood glucose level was 7.8–11.0 mmol/l in diabetes-free participants (5,29).

Definition of mild cognitive impairment. People with MCI included all nondemented participants who fulfilled aMCI or oCIND criteria. Amnestic MCI is characterized by memory deficits, and was defined according to standard criteria (24,30) and operationalized as follows (15): *1*) absence of dementia; *2*) normal general cognitive function: absence of oCIND; *3*) memory complaints: self- or informant-reported memory problems; *4*) objective memory impairment: scoring 1.5 SD below age- and education-adjusted mean in a verbal episodic memory test (free recall of rapidly presented random words) (31); and *5*) normal activities of daily living (ADL): no impairment in the Katz ADL scale. A diagnosis of oCIND represents global cognitive impairment, and was defined as having no dementia and scoring 1 SD or more below age- and education-adjusted means on the MMSE derived from the dementia-free sample at baseline (15,32). A diagnosis of oCIND was applied to subjects who were considered neither as normal nor as aMCI nor as demented. In the present study, aMCI and oCIND were mutually exclusive.

Diagnosis of dementia. At baseline and follow-up, all participants underwent a comprehensive medical and cognitive assessment. Cognitive functions were tested by asking for facts of general knowledge and past personal information (semantic and episodic memory); by object naming and comprehension of commands and sentences (language); by problem solving and interpretation of proverbs (abstract thinking); by coping figures (visuospatial ability); and by calculation and solving mathematical problems (calculation). Dementia was diagnosed on the basis of clinical judgment following DSM-III-R criteria, in which a validated 3-step diagnostic procedure was used (22). Two examining physicians independently made a preliminary diagnosis, and in the case of disagreement, a third opinion was sought to reach a concordant diagnosis. The diagnosis of Alzheimer's disease (AD) required gradual onset, progressive deterioration, and lack of any other specific causes of dementia. The diagnosis of vascular dementia (VaD) required abrupt onset, stepwise deterioration, history of stroke, or focal deficits. The Hachinski scale was also used to support the differential diagnosis between AD and VaD (33). The diagnostic criteria for AD and VaD were equivalent to probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (34), and to the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (35). For deceased participants, the diagnosis of dementia and its subtypes was made by two physicians by reviewing the medical records and death certificates.

Statistical analysis. The baseline characteristics of people with diabetes and pre-diabetes and participants free from these conditions were compared using χ^2 tests for categorical variables and one-way ANOVAs for continuous variables. For the cross-sectional data at baseline, logistic regression analyses were used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) of MCI, aMCI, and oCIND separately in relation to diabetes and pre-diabetes in the dementia-free participants.

The incidence rates were calculated as the number of events occurring during the entire follow-up period divided by person-years of follow-up standardized by age, sex, and education. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs of dementia, AD, and MCI in relation to diabetes and pre-diabetes. Diabetes and pre-diabetes were modeled as separate and combined groups in the analyses. For nondemented subjects in the MCI cohort and non-MCI participants in the cognitively intact cohort, the follow-up time was calculated from the date of baseline interview to the date of the last follow-up examination or death. For the demented and MCI cases, the follow-up time was estimated as the full time during which the subjects were free of dementia or MCI plus half of the follow-up time during which dementia or MCI developed.

The proportional hazards assumption was confirmed by graphs and tests based on Schoenfeld residuals. Age, sex, education, baseline MMSE score, BMI, APOE genotype, and vascular disorders (i.e., heart disease, stroke, antihypertensive drug use, and blood pressure) were considered as potential confounders. As diabetes and pre-diabetes are related to elevated mortality, we also adjusted for survival status at follow-up (20). All dementia, AD, MCI, aMCI, oCIND, and death were used as separate outcomes in the Cox regression analyses. The Kaplan-Meier survival analysis was used to compare the cumulative probability of events among subjects in different groups. In secondary analyses, we modeled diabetes and pre-diabetes as time-dependent covariates. The statistical analyses were performed using Stata SE 10 for Windows (StataCorp, College Station, TX).

RESULTS

Cross-sectional relationship between diabetes and MCI. Among the 1,435 dementia-free participants at baseline, 337 were detected as MCI cases, including 131 aMCI and 206 oCIND. Compared with non-MCI subjects, people with MCI were older (OR 0.94, [95% CI 0.89–0.99, P = 0.015]), and had a lower level of education (<8 vs. ≥8 years, OR 2.13 [95% CI 1.35–3.38]) and MMSE score (OR 0.36 [95% CI 0.29–0.46]), and higher proportion of *APOE* ε4 carriers (OR 1.91 [95% CI 1.15–3.15]). The two groups showed no significant differences in terms of sex, stroke, heart disease, and blood pressure. Logistic regression analyses were performed to assess the cross-sectional relationship between diabetes and MCI based on the dementia-free subjects (n = 1,435). The multi-adjusted ORs related to diabetes or pre-diabetes were 1.32 (95% CI 0.82–1.31) for overall MCI, 1.12 (95% CI 0.67–1.20) for aMCI, and 1.03 (95% CI 0.57–1.23) for oCIND.

Nonparticipants of the follow-up. Of the 1,435 individuals who were initially identified as free of dementia at baseline, 170 subjects were lost to the first follow-up (Fig. 1). Compared with participants, dropouts were younger, but the two groups had no significant differences in other features. Multiple logistic regression analysis showed that being a dropout had ORs of 0.94 (95% CI 0.91–0.98) for old age, 1.26 (95% CI 0.84–1.87) for female sex, 1.24 (95% CI 0.89–1.73) for low education, 1.02 (95% CI 0.94–1.09) for a lower score on MMSE (<24 vs. ≥24), 0.35 (95% CI 0.28–1.06) for diabetes, 0.69 (95% CI 0.47–1.09) for heart disease, and 0.66 (95% CI 0.45–1.08) for stroke.

Characteristics of the two cohorts. Of the 1,265 nondemented participants, 963 were cognitively intact and 302 had MCI, which constituted the two cohorts for longitudinal analyses. In the cognitively intact cohort, 56 subjects (5.8%) had diabetes, and 30 (3.1%) had pre-diabetes (Table 1). In the MCI cohort, 18 (6.0%) subjects had diabetes, and 16 (5.3%) were ascertained as having pre-diabetes. Among the 34 MCI subjects with diabetes or pre-diabetes, 27 (79.4%) were classified as oCIND, and 7 (20.6%) had aMCI (Table 2).

Diabetes and MCI in the cognitively intact cohort. In the cognitively intact cohort, during the 9-year follow-up (4,656 person-years; mean per person = 4.8 years; maximum = 10.5 years), 182 participants developed MCI, including 42 aMCI and 140 oCIND. In addition, 212 were diagnosed with dementia, including 150 AD and 26 VaD. Table 3 shows the incidence rate standardized by age, sex, and education, and multi-adjusted HRs of MCI related to diabetes and pre-diabetes. We found no statistically significant association of either diabetes or pre-diabetes with incident MCI and its subgroups, whereas diabetes and pre-diabetes were significantly related to an increased risk of incident dementia. This association was present even when adjusting for several potential confounders, including *APOE* and vascular disorders. No interaction with *APOE* genotype or other variables was obtained.

Diabetes and dementia in the MCI cohort. In the MCI cohort, during the same period (1,092 person-years; mean per person = 3.6 years; maximum = 10.3 years), 155 subjects developed dementia, including 125 AD and 4 VaD. Using either standard or time-dependent Cox models, we found that diabetes and pre-diabetes were associated with an increased risk of developing dementia and AD in people with MCI after controlling for possible confounders, including *APOE* and vascular disorders (Table 4). Of the 125

TABLE 1
Cognitively intact cohort (n = 963): characteristics by diabetes status

Characteristics	Diabetes status at baseline			P value
	No	Diabetes	Pre-diabetes	
n	877	56	30	
Baseline				
Age (years)	81.1 ± 4.8	80.7 ± 5.0	81.5 ± 4.8	0.913
Female	656 (74.8)	38 (67.9)	22 (73.3)	0.510
Educational level ≥8 years	398 (45.4)	17 (30.4)	15 (50.0)	0.076
MMSE score	27.6 ± 1.3	27.2 ± 1.3	27.2 ± 1.4	0.678
SBP (mmHg)	156.0 ± 21.0	161.6 ± 26.7	152.9 ± 18.8	0.024
DBP (mmHg)	81.6 ± 11.0	75.0 ± 9.3	77.1 ± 10.1	0.339
Heart disease	128 (14.6)	25 (44.6)	3 (10.0)	<0.001
Stroke	48 (5.5)	5 (8.9)	0 (0.0)	0.223
Antihypertensive drug use	389 (44.4)	33 (58.9)	11 (36.7)	0.068
Random blood glucose (mmol/l)	5.1 ± 0.94	11.7 ± 4.6	8.8 ± 0.8	<0.001
Any *APOE* ϵ4 allele†	184 (21.0)	4 (10.0)	3 (7.1)	
BMI† (kg/m^2)	23.5 ± 3.48	24.3 ± 3.44	24.1 ± 3.28	0.204
During 9-year follow-up				
Incident dementia	192 (21.9)	13 (23.2)	7 (23.3)	0.274
Incident MCI	170 (20.9)	5 (8.9)	6 (21.2)	0.220

Data are n (%) or means ± SD. DBP, diastolic blood pressure; SBP, systolic blood pressure. †The number of subjects with missing values was 207 for *APOE* genotype and 94 for BMI.

AD subjects, 57 had aMCI and 68 had oCIND at baseline. We further performed stratified analysis according to MCI subgroups. Diabetes and pre-diabetes substantially increased the risk of progression from oCIND to dementia (HR 4.31 [95% CI 1.97–9.42]), but not from aMCI (HR 2.24 [95% CI 0.75–6.71]). However, the statistical power was limited for these stratified analyses because of the small number of people in each subgroup of MCI.

Kaplan-Meier survival analysis in people with MCI showed that the median time from baseline to dementia occurrence was 1.83 years (95% CI 2.44–4.24) in people with diabetes or pre-diabetes, and 5.01 years (95% CI 5.15–6.19) in people without such conditions. Thus, diabetes or pre-diabetes accelerated the progression from MCI to dementia by an average of 3.18 years (Fig. 2).

Supplementary analyses. Similar results were obtained when we used only the incident MCI cohort that was identified at the first follow-up examination (n = 94, of whom 36 developed dementia during the next 6-year follow-up), and when we repeated the analyses among participants who survived until the time when dementia status was determined (n = 170, 136 dementia and 115 AD). Further, we performed the analyses by leaving out the participants with missing values of *APOE* genotype or BMI, which produced results that were the same as those from the initial analysis. Finally, in the MCI cohort, among

TABLE 2
MCI cohort (n = 302): characteristics by diabetes status

Characteristics	Diabetes status at baseline			P value
	No	Diabetes	Pre-diabetes	
n	268	18	16	
Baseline				
MCI subtypes				
aMCI	113 (42.2)	2 (12.5)	5 (27.8)	
oCIND	155 (57.8)	14 (87.5)	13 (72.2)	0.035
Age (years)	82.1 ± 5.0	83.2 ± 5.3	82.6 ± 5.0	0.633
Female sex	203 (75.7)	14 (77.8)	14 (87.5)	0.555
Educational level ≥8 years	118 (44.0)	6 (33.3)	4 (25.0)	0.237
MMSE score	24.7 ± 1.7	24.1 ± 1.9	23.8 ± 1.8	0.028
SBP (mmHg)	154.0 ± 22.6	156.9 ± 27.7	150.9 ± 19.9	0.744
DBP (mmHg)	80.5 ± 10.6	80.0 ± 8.6	75.0 ± 9.3	0.127
Heart disease	47 (17.5)	6 (33.3)	2 (12.5)	0.202
Stroke	30 (11.2)	4 (22.2)	0 (0.0)	0.123
Antihypertensive drug use	109 (40.7)	12 (66.7)	8 (50.0)	0.081
Random blood glucose (mmol/l)	5.1 ± 1.0	12.2 ± 4.5	8.6 ± 0.8	<0.001
Any *APOE* ϵ4 allele†	78 (29.1)	5 (27.8)	2 (12.5)	0.296
BMI† (kg/m^2)	23.9 ± 3.8	24.2 ± 4.3	24.0 ± 2.9	0.380
During 9-year follow-up				
Incident dementia	137 (51.2)	11 (68.8)	7 (38.9)	0.221

Data are n (%) or means ± SD. DBP, diastolic blood pressure; SBP, systolic blood pressure. †The number of subjects with missing values was 90 for *APOE* genotype and 64 for BMI.

TABLE 3
Standardized incidence rates (per 1,000 person-years) and multi-adjusted HR and 95% CI of MCI and dementia related to diabetes and pre-diabetes in the cognitively intact cohort

	MCI (n = 182)		Dementia (n = 212)	
Exposure status	IR (95% CI)*	HR (95% CI)†	IR (95% CI)*	HR (95% CI)†
Baseline diabetes‡				
No	39.6 (34.0–46.1)	1.00 (Reference)	49.6 (43.7–56.3)	1.00 (Reference)
Yes (diabetes and pre-diabetes)	32.7 (18.1–59.0)	1.04 (0.52–2.07)	59.8 (39.7–90.0)	1.82 (1.07–3.10)
Pre-diabetes	40.9 (18.4 to 91.1)	1.07 (0.43–2.67)	52.6 (23.7–94.7)	1.64 (1.02–3.44)
Diabetes	26.3 (10.9–63.1)	1.01 (0.37–2.77)	69.6 (41.9–15.4)	2.10 (1.08–4.07)
Baseline and follow-up diabetes§				
Diabetes and pre-diabetes	34.6 (18.9–81.3)	1.06 (0.62–1.81)	72.6 (41.3–86.9)	1.81 (1.19–2.75)

IR, incidence rates. *Standardized by age, sex, and education. †Adjusted for age, sex, education, baseline MMSE score, BMI, heart disease, stroke, systolic blood pressure, diastolic blood pressure, follow-up survival status, and *APOE* genotype. ‡From standard Cox models. §From time-dependent Cox models.

the 34 people with either diabetes or pre-diabetes, 18 (52.9%) developed dementia and 16 (47.1%) died during the 9-year follow-up period. Diabetes and pre-diabetes were significantly associated with elevated mortality (HR 1.75 [95% CI 1.17–2.60]) after adjustment for age, sex, education, baseline MMSE score, BMI, *APOE* genotype, and vascular disorders.

DISCUSSION

The incidence of dementia is increased in patients with diabetes by 50–100% compared with people without diabetes, as shown by several reports, including those from our group (2). We are now able to extend these findings by showing that diabetes and pre-diabetes increase the risk of conversion from MCI to dementia. In this large longitudinal study of elderly adults, we found that *1*) diabetes and pre-diabetes substantially accelerate the progression from MCI to dementia; *2*) the risk effect of pre-diabetes on the progression from MCI to dementia appears stronger than diabetes; *3*) diabetes and pre-diabetes anticipate dementia occurrence by more than 3 years; and *4*) we confirm an increased risk of dementia, but not of MCI, in subjects with diabetes or pre-diabetes.

To date, Italian (10) and French (17) population-based longitudinal studies have examined the role of vascular risk factors, including diabetes, in the progression of MCI to dementia, and failed to find an association. There are several reasons for the discrepant findings. First, as pre-diabetes was not assessed in these two studies, subjects with this condition were included in the nondiabetes group, which might have diluted the effect of diabetes on dementia risk due to the strong influence of pre-diabetes on the progression from MCI to dementia, as shown in our report. Second, in the two studies, diabetes was identified based on fasting blood glucose ≥7.2 and ≥7.8 mmol/l, respectively, which are higher than the WHO criteria of 7.0 mmol/l (29). Finally, in both studies, the follow-up time was only 3.5 to 4 years, and the populations were younger than our cohort. As a result, the statistical power of the two studies may be limited because of the small number of incident dementia cases.

Findings from brain imaging and neuropathologic studies support the notion that the increased risk of cognitive decline and dementia in elderly people with diabetes reflects a dual pathologic process involving both cerebrovascular damage and neurodegenerative changes (36–38). In addition to vascular pathways, several possible pathophysiologic mechanisms, including hyperglyceamia, insulin resistance, oxidative stress, advanced glycation end products, and inflammatory cytokines, may explain the effect of glucose deregulation on dementia risk. Recent genetic studies have found that chromosome 10 contains the genes for both late-onset AD and type 2 diabetes (39). Interestingly, a clinicopathologic study suggested that there may be a shared predisposition for developing amyloid in both the pancreas and the brain (40). All these mechanisms may explain the accelerated progression from MCI to dementia observed in this study. In addition, in subjects with MCI, cognitive deficits may affect the ability to manage complex behaviors such as those required for diabetes self-care (41), which may lead to a vicious circle. Therefore, an additional increased risk of

TABLE 4
Standardized incidence rates (per 1,000 person-years) and multi-adjusted HR and 95% CI of dementia and Alzheimer disease related to diabetes and pre-diabetes in the mild cognitive impairment cohort

	All dementia (n = 155)		Alzheimer disease (n = 125)	
Exposure status	IR (95% CI)*	HR (95% CI)†	IR (95% CI)*	HR (95% CI)†
Baseline diabetes‡				
No	135.0 (114.2–159.6)	1.00 (Reference)	104.4 (86.0–126.8)	1.00 (Reference)
Yes (diabetes and pre-diabetes)	232.6 (146.6–369.2)	3.64 (2.05–6.45)	206.8 (126.7–337.5)	3.79 (2.02–7.11)
Pre-diabetes	281.3 (155.8–507.9)	4.96 (2.27–10.84)	225.7 (137.6–475.2)	5.73 (2.43–13.50)
Diabetes	182.9 (87.2–383.7)	2.87 (1.30–6.34)	156.7 (70.4–349.0)	2.83 (1.18–6.78)
Baseline and follow-up diabetes§				
Diabetes and pre-diabetes	275.4 (150.2–370.1)	3.89 (1.69–8.32)	239.4 (138.6–330.6)	4.22 (1.57– 9.01)

IR, incidence rates. *Standardized by age, sex, and education. †Adjusted for age, sex, education, baseline MMSE score, follow-up survival status, BMI, heart disease, stroke, systolic blood pressure, diastolic blood pressure, antihypertensive drug use, *APOE* genotype. ‡From standard Cox models. §From time-dependent Cox models.

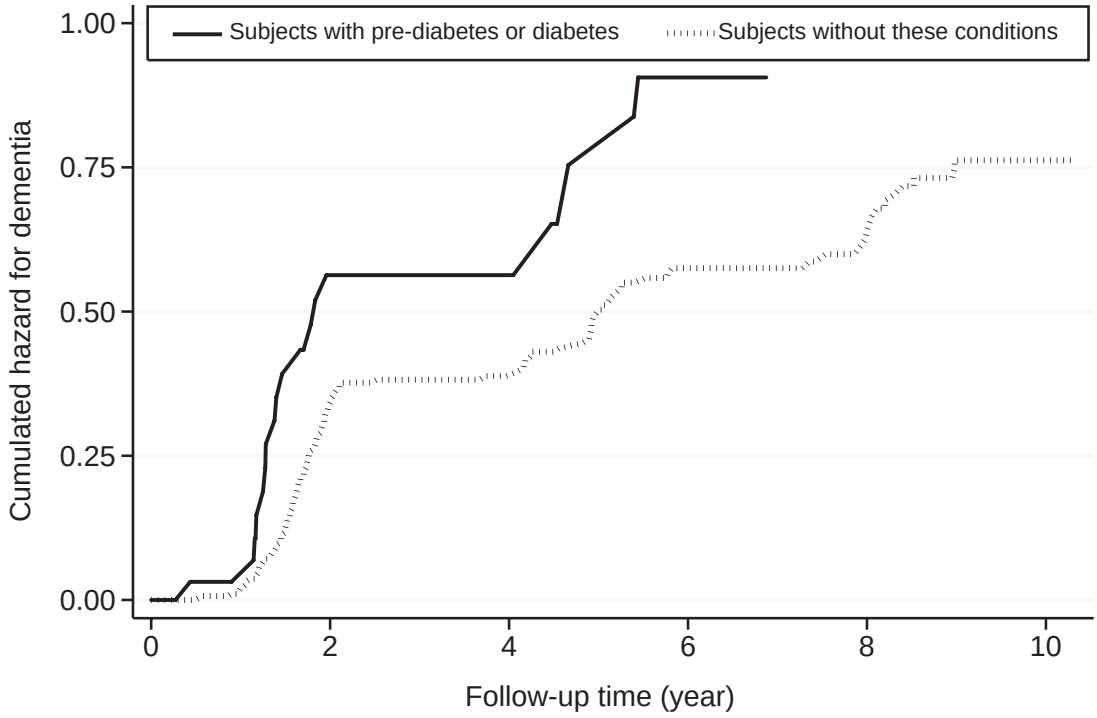

FIG. 2. Cumulative hazard for the progression from MCI to dementia by diabetes status in the MCI cohort (adjusted for age, sex, and education).

developing dementia resulting from diabetes can be expected in people with MCI.

The stronger effect of pre-diabetes than diabetes on the conversion from MCI to dementia may be caused by the high glycemic level in pre-diabetes that is a commonly ignored condition. In our study, about 30% of patients with diabetes had normal random blood glucose level by hypoglycemic treatment and dietary control; effective glycemic control may reduce the risk of dementia in people with diabetes (20). Further, insulin resistance (hyperinsulinemia without hyperglycemia) is stronger in people with pre-diabetes than those with frank diabetes (42).

A number of studies that evaluated the cognitive function in patients with diabetes or pre-diabetes have shown that poor glucose regulation is associated with global cognitive decline, with impaired verbal memory in particular, but the evidence for deficits in other cognitive domains is weak (43). However, a recent prospective study suggested that diabetes-related cognitive deficits and MCI may represent different entities that do not necessarily affect the same domains (44). Another longitudinal study reported that diabetes may be related to psychomotor slowing, but not to deficits in other cognitive domains typically involved in MCI (45). Results from our study showed that diabetes and pre-diabetes were associated with MCI and its subgroups, neither cross sectionally nor longitudinally. This is in agreement with an Italian longitudinal study (10) and a case-control study from the Mayo Clinic (8). However, the latter study found an association of MCI with a longer duration and greater severity of diabetes, and Luchsinger et al. (9) reported a higher risk of both aMCI and oCIND in diabetic patients in a population with very high prevalence of diabetes. These findings suggest that only severe and longstanding diabetes may be related to MCI. Unfortunately, our study sample was too small to verify this hypothesis. An alternative explanation suggested by van den Berg (46) is the old age of the study population involved, where the lower cognitive level at baseline may have masked any additional impact of diabetes. In other words, the standard MCI criteria may not be sensitive enough to identify those people with global cognitive deficits due to diabetes (16). Finally, another possibility is that in very old people, diabetes and pre-diabetes may accelerate the process of dementia so rapidly that a possible association between diabetes and MCI cannot be detected when follow-up examinations are carried out with intervals longer than 1 year.

The main strengths of our study are the population-based cohort study, the long-term prospective study design, and the assessment of diabetes at baseline and each follow-up examination. However, some limitations should be noted. First, we used random blood glucose to define diabetes and pre-diabetes, which might result in an attenuation of the associations. However, the prevalence of diabetes in our study population (8.9%) is comparable with those reported from an elderly Swedish population (47). Second, as there are no specific recommended tools to diagnose MCI, the operationalization of the criteria may differ slightly from those in other studies. In addition, prevalent MCI cases were included in the MCI cohort, which might contain persons with long-term cognitive impairment that remains stable over time. However, similar results were obtained when the incident MCI cohort identified at first follow-up examination was used. Third, as the Kungsholmen Project is based on an elderly population (the mean age was 82 years at baseline), the dropouts from the screening phase to the third follow-up were mainly because of death (48). Diabetes, MCI, and dementia are all associated with elevated mortality (20,49), which may lead to an underestimation of the strength of the diabetes-dementia or diabetes-MCI association due to selective survival. Thus, caution is needed when generalizing our findings to younger populations.

Finally, the diagnoses of dementia were made on a clinical basis. However, the clinical assessment for dementia was comprehensive and validated in a previous study (22). Although neuroimaging data may help detect vascular lesions in the brain, it is difficult to determine the significance of these lesions, as coexistence of AD-related pathologic changes and vascular lesions in the brain is very common in late life (50).

In summary, our results provide further support for the important role of diabetes and pre-diabetes in dementia, and highlight the need to control diabetes and detect pre-diabetes to prevent or postpone dementia in people with MCI. Our findings underline the importance of regularly monitoring cognitive function in people with diabetes and pre-diabetes. The lack of association between diabetes and the risk of MCI in our study suggests that diabetes may lead to dementia bypassing MCI or shortening the MCI phase in elderly people.

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W.X. initiated and designed the study, performed the analysis, and wrote the first draft. L.F. supervised the study, and contributed to the results interpretation and revision of the text. B.W. and L.B. contributed to the acquirement of the initial data and revised the text. B.C., H.-X.W., and C.Q. helped with the data interpretation and revised the report.

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