

Mid- and Late-Life Diabetes in Relation to the Risk of Dementia

A Population-Based Twin Study

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OBJECTIVE—We aimed to verify the association between diabetes and the risk of dementia, Alzheimer's disease, and vascular dementia in twins and to explore whether genetic and early-life environmental factors could contribute to this association.

RESEARCH DESIGN AND METHODS—This study included 13,693 twin individuals aged ≥ 65 years. Dementia was diagnosed according to DSM-IV (*Diagnostic Manual of Mental Disorders*, 4th ed.) criteria. Information on diabetes was collected from the inpatient registry and self- or informant-reported history of diabetes. Data were analyzed following two strategies: 1) unmatched case-control analysis for all participants using generalized estimating equation (GEE) models and 2) cotwin matched case-control analysis for dementia-discordant twin pairs using conditional logistic regression.

RESULTS—Of all participants, 467 were diagnosed with dementia, including 292 with Alzheimer's disease and 105 with vascular dementia, and an additional 170 were diagnosed with questionable dementia. Diabetes was present in 1,396 subjects. In GEE models, diabetes was associated with adjusted odds ratios (ORs) (95% CI) of 1.89 (1.51–2.38) for dementia, 1.69 (1.16–2.36) for Alzheimer's disease, and 2.17 (1.36–3.47) for vascular dementia. Compared with late-life diabetes (onset age ≥ 65 years), the risk effect of mid-life diabetes (onset age < 65 years) on dementia was stronger. Conditional logistic analysis of 210 dementia-discordant twin pairs led to ORs of 2.41 (1.05–5.51) and 0.68 (0.30–1.53) for dementia related to mid- and late-life diabetes, respectively.

CONCLUSIONS—Diabetes increases the risk of Alzheimer disease and vascular dementia. The risk is stronger when diabetes occurs at mid-life than in late life. Genetic and early-life environmental factors might contribute to the late-life diabetes–dementia association but could not account for the mid-life diabetes–dementia association. *Diabetes* 58:71–77, 2009

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Population-based longitudinal studies (1–12) have shown that the risk of dementia in general is increased in people with diabetes. Even pre-diabetes has been associated with an increased risk of dementia and Alzheimer disease (13). Although diabetes may be linked to dementia through several biologically plausible pathways (14), our understanding of the mechanisms for such an association is still limited. Both dementia and diabetes are complex age- and lifestyle-related disorders. In addition to strong influence of environmental elements, genetic components also play a part in both Alzheimer's disease and diabetes (15,16). Epidemiological and clinical studies (11,17–19) have reported that environmental factors acting in early life, such as birth weight and childhood socioeconomic situation, are also involved in the development of diabetes as well as dementia. Evidence from genetic and epidemiological studies (20,21) has indicated that genetic and environmental factors may interact to affect the association between diabetes and dementia during the life course.

The recent upsurge of interest in applying a life-course approach to chronic disease epidemiology and the hypothesis of "developmental origins of adult disease" prompt renewed attention to twin studies. Twins provide naturally matched pairs, in which confounding effects of a large number of potentially causal factors (e.g., genetics and childhood environment) may be removed when comparisons are made between twins. Because twins are generally reared together, they share their early-life environment. Twin studies involving a life-course approach may help to identify genetic influences and timing of environmental influences on the relationship between age-related disorders. In the current study, we sought to 1) verify the association between diabetes and risk of dementia and its main subtypes in twins, 2) examine whether the effect of diabetes on dementia risk varies according to age of diabetes onset, and 3) explore whether genetic and early-life familial environmental factors could explain this association using data from the population-based Swedish twin cohort.

RESEARCH DESIGN AND METHODS

Participants were members of the nationwide Swedish Twin Registry (22). In 1998–2001, all living twins in the registry who were born in 1935 and earlier (aged ≥ 65 years) were invited to participate in a study concerning dementia known as HARMONY (23). In brief, a total of 20,206 individuals in the Swedish Twin Registry were eligible for screening. Of these, 5,771 were not reached by a telephone, 712 could be reached but were not able to undertake the interview, and 30 failed to complete the cognitive screening test, leading to 13,693 subjects with complete cognitive test data. Of these, a total of 1,939

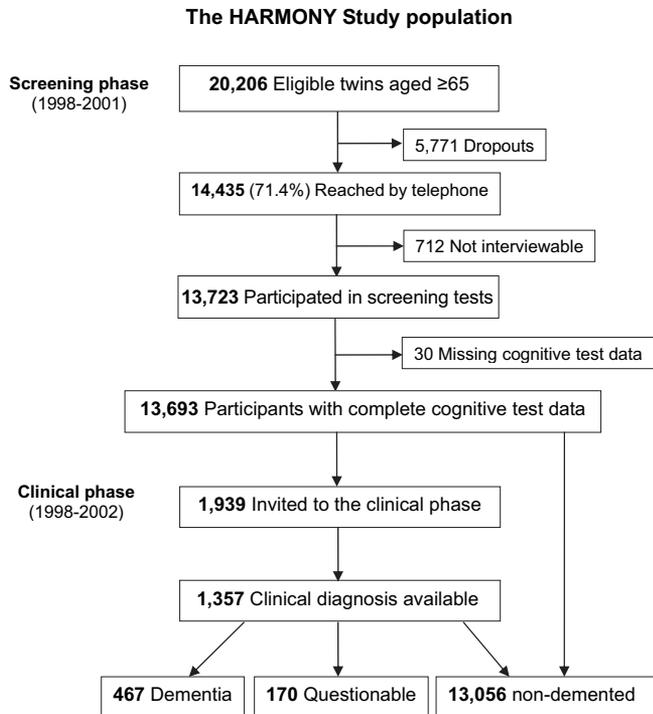


FIG. 1. Flowchart of the study population in the HARMONY study.

individuals were invited to the clinical phase, including participants who were screened as positive for cognitive dysfunction, subjects who were with suspected dementia, or demented twin's partner and normal control subjects. Clinical diagnoses were available for 1,357 individuals. The participation rates were 71.4% for the screening phase and 70.0% for the clinical phase (Fig. 1).

Informed consent was required from all participants during the telephone interview and again in the clinical phase. The data collection procedures were reviewed and approved by the Swedish Data Inspection Board, Stockholm, Sweden; the Regional Ethics Committee at Karolinska Institutet, Stockholm; and the institutional review board of the University of Southern California.

Diagnosis of dementia and its major subtypes. A two-step procedure was used in the diagnosis of dementia. The first step was cognitive screening through a telephone interview using the validated TELE questionnaire for the twins (24,25) and the Blessed Dementia Rating Scale for the informants (26). The TELE and Blessed Dementia Rating Scale were combined into an ordinal scale with scores ranging from 0 (cognitive intact) to 3 (cognitive dysfunction) (24). The second step was a full clinical workup that entailed a visit by an assessment team composed of a nurse and a physician. The assessment team made an initial diagnosis based on a protocol that followed the Consortium to Establish a Registry for Alzheimer's Disease and included physical and neurological examination, a review of medical history, informant interview, and a neuropsychological assessment. The neuropsychological battery included the Mini-Mental State Examination; the Consortium to Establish a Registry for Alzheimer's Disease word list immediate and delayed recall, verbal fluency, block design, figure copying, judgment, information, symbol-digit, and prospective memory; as well as the Memory in Reality test. These preliminary diagnoses were reviewed by a diagnostic board consisting of a neurologist and a neuropsychologist. Clinical diagnoses of dementia followed DSM-IV criteria (27). The case subjects completely fulfilling the DSM-IV criteria were diagnosed as having "dementia," in contrast with a category of "questionable dementia," which was used for individuals who did not fulfill one of the first three DSM-IV diagnostic criteria but did exhibit either cognitive impairment or functional disability. Participants were first classified as demented, questionable, or nondemented and then given a differential diagnosis for dementia subtype for demented subjects (23). Differential diagnoses were made according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease (28) and the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for vascular dementia (29). More details of the clinical examination and diagnostic procedure have been reported previously (24). The age of dementia onset was estimated by the assessment team based on information that was obtained from a detailed informant interview. Age at onset was defined as the age when definite and enduring symptoms of dementia first appeared (30).

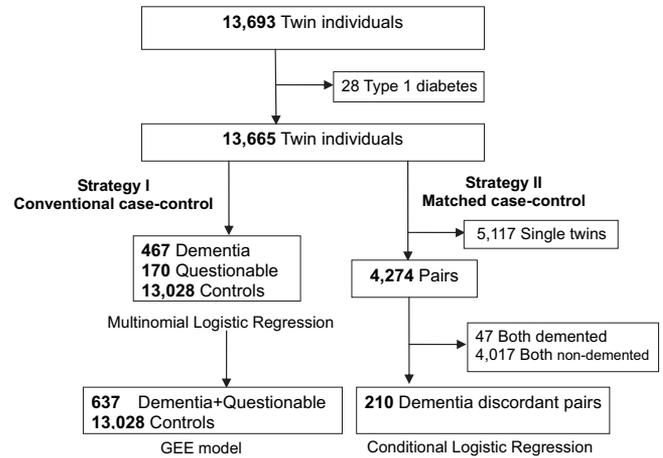


FIG. 2. Two analytical strategies for the HARMONY study.

Covariates and identification of diabetes. For 13,693 individuals who participated in the screening phase, information concerning demographic factors, education, health status and behavior, common diseases, use of medications, height, and weight was obtained during the telephone interview. For twins who had completed surveys by the Swedish Twin Registry in 1961, 1963, and 1967 for the older cohort and in 1973 for the younger cohort, information on height and weight is available. Information on history of vascular disorders (hypertension, heart disease, and stroke) was derived from the inpatient registry system. Each record in the system included up to eight discharge diagnoses according to the ICD-7 through 1968. ICD-8 was used by the register system until 1986; since 1987 the ICD-9 has been used. Medical conditions derived from the inpatient register database included hypertension (ICD-7 codes 444–447, ICD-8 codes 400–404, and ICD-9 codes 401–405), ischemic heart disease (ICD-7 codes 420–421, ICD-8 and -9 codes 410–414), cardiac dysrhythmia, heart failure or other myocardial insufficiency (ICD-7 codes 433 and 434, ICD-8 and -9 codes 427 and 428), and stroke (ICD-7 codes 330–334, ICD-8 and -9 codes 430–438). Vascular diseases including hypertension, heart disease (ischemic heart disease, cardiac heart disease, cardiac dysrhythmia, and heart failure), and stroke were ascertained based on the information from self- or informant-report and the inpatient registry. Survival status from screening phase to October 2004 was obtained from the Cause of Death Register.

Diabetes was detected by integrating information from inpatient registry (ICD-7 codes 260, ICD-8 and -9 codes 250) and self- and informant-reported history of diabetes. The age of diabetes onset was estimated according to the earliest recorded date of diabetes either in the inpatient registry or the date of diabetes onset reported by probands or informants. To address the potential modifying role of age at the time of exposure on dementia risk, we distinguished mid-life (aged <65 years) and late life (aged ≥65 years) diabetes (31). Information on the age of diabetes onset was missing in 71 (5.1%) patients. The date of telephone interview was used as approximate onset date for these patients in the analyses, although it may lead to underestimation of the association of diabetes duration with dementia risk.

Statistical analysis. The characteristics of participants with dementia, questionable dementia, and nondementia were compared using χ^2 tests for categorical variables, one-way ANOVA for continuous variables with normal distribution, and Mann-Whitney test for continuous variables with nonnormal distribution. To verify whether the association between diabetes and dementia differed depending on diagnostic certainty, multinomial logistic regression was used to estimate the odds ratios (ORs) and 95% CIs of dementia and questionable dementia separately in relation to diabetes.

Two analytical strategies were applied: 1) unmatched case-control analyses using generalized estimating equation (GEE) models, which are conceptually equivalent to logistic regression for the analysis of classical case-control design but control for the clustering of twins within a pair; and 2) dementia-discordant cotwin matched case-control analyses using conditional logistic regression models (Fig. 2). The latter strategy is more informative than using unrelated case-control samples, and it allows matching for unmeasured familial factors, which could be related to genetic background or early life environment. Case and control subjects are comparable with respect to genetic and early-life environmental history (such as childhood socioeconomic status) (32). If the association found in GEE analyses becomes attenuated in cotwin matched case-control analyses, genetic factors or familial environments or both are likely to play a role in the association. If strength of the association further decreases when only monozygotic twin

TABLE 1
Characteristics of the study participants ($n = 13,693$) by dementia diagnosis

	No dementia	Questionable dementia	Dementia	<i>P</i> value
<i>n</i>	13,056	170	467	
Age (years)	73.1 ± 6.4	79.8 ± 6.8	81.5 ± 6.6	<0.001
Female sex	7,281 (55.8)	84 (49.4)	302 (64.5)	<0.001
Education (years)*	8.6 ± 3.0	7.9 ± 2.8	7.4 ± 2.4	<0.001
Zygotic status				
Monozygotic	3,070 (23.5)	47 (27.7)	138 (29.5)	
Same sex dizygotic	5,404 (41.4)	72 (42.4)	209 (44.8)	
Opposite sex dizygotic	4,351 (33.3)	49 (28.8)	104 (22.3)	
Indeterminate	231 (1.8)	2 (1.2)	16 (3.4)	<0.001
Type 2 diabetes	1,257 (9.6)	32 (18.8)	107 (22.9)	<0.001
Type 1 diabetes	28 (0.2)	—	—	—
Stroke	937 (7.2)	52 (30.6)	142 (30.4)	<0.001
Heart disease	1,540 (11.8)	72 (42.4)	326 (69.8)	<0.001
Hypertension	4,334 (33.2)	57 (33.5)	166 (35.6)	>0.05
BMI (kg/m ²)	25.1 ± 3.7	24.4 ± 3.6	23.9 ± 4.7	<0.001
<25	6,024 (46.1)	257 (55.0)	97 (57.1)	
25–29.99	4,531 (34.7)	114 (24.4)	55 (32.4)	
≥30	958 (7.3)	34 (7.3)	9 (5.3)	
Missing	1,543 (11.8)	62 (13.3)	9 (5.3)	<0.001

Data are *n* (%) or means ± SD. *A total of 155 subjects had missing value of education.

pairs are analyzed, genetic confounding can be suspected. In contrast, if a significant association remains when using cotwin matched pairs, the influences of genetic or early environmental factors on the association are likely to be marginal (22). We hypothesized that diabetes would be a significant risk factor for dementia in a classical case-control analysis, whereas in the matched-pair analysis, by controlling for genetic, maternal (maternal nutrition status and disease) (17,18), and environmental factors shared by twins, we would find an attenuated association between diabetes and dementia. Logistic regression was used to test the difference in ORs from the GEE model and conditional logistic regression by examining the difference of diabetes among unmatched versus cotwin control subjects (23).

Age, sex, education, zygotic status, vascular factors (i.e., heart disease including ischemic heart disease, cardiac dysrhythmia and heart failure, stroke, and hypertension), and BMI were considered as potential confounders in all models. Education was missing in 155 subjects. The expectation maximization imputation method was used to replace the missing information based on Little's test for missing completely at random. The statistical analyses were performed using SAS statistical software version 9.1 (SAS institute, Cary, NC) and SPSS 15.0 (SPSS, Chicago, IL).

RESULTS

Among 13,693 participants, 467 (3.4%) received a diagnosis of dementia including 292 with Alzheimer's disease and 105 with vascular dementia, and an additional 170 (1.4%) were diagnosed with questionable dementia. The prevalence of dementia was 3.9% in female and 2.7% in male subjects ($\chi^2 = 17.5$, $P < 0.001$). The prevalence of dementia in this Swedish twin cohort was comparable with several major epidemiological studies of dementia prevalence in Europe and the U.S. (23). The estimated mean age of dementia onset was 76.8 years.

Of 13,693 participants, 1,288 were self-reported and 99 were informant-reported as having diabetes at the screening phase, which covered 276 (88.2%) of 313 subjects recorded as having diabetes in the inpatient registry. In total, diabetes was identified in 1,424 subjects (10.4%), including 28 type 1 diabetic patients (1.9% of all diabetic patients). The prevalence of type 2 diabetes (1,396) was 9.8% in female and 11.2% in male subjects ($\chi^2 = 6.83$, $P = 0.009$). The mean age of type 2 diabetes onset was 63.8 years.

Table 1 shows the characteristics of the study participants by dementia status. Compared with nondemented

participants, subjects with dementia or questionable dementia were older, had a lower level of education and BMI at the time of assessment (using categorical variable as covariate in following analyses), had a higher proportion of monozygotic and same-sex dizygotic zygosity, and were more likely to have type 2 diabetes, stroke, and heart disease. Data on current BMI were missing in 1,614 twins. The prevalence of dementia and questionable dementia was 4.7% in participants with BMI available and 4.4% in participants with missing BMI ($\chi^2 = 0.26$, $P = 0.601$). In the subsequent analyses, 28 patients with type 1 diabetes were excluded.

Characteristics of the 1,396 patients with type 2 diabetes are reported in Table 2. Compared with people with late-life diabetes, participants with mid-life diabetes had

TABLE 2
Clinical characteristics of patients with type 2 diabetes by onset age of diabetes ($n = 1,396$)

	All patients	Onset age <65 years	Onset age ≥65 years	<i>P</i>
<i>n</i>	1,396	643	753	
Age (years)	74.4 ± 6.6	71.5 ± 5.4	77.0 ± 6.5	0.001
Female	751 (52.6)	307 (41.9)	426 (58.1)	0.001
Onset age	64.2 ± 12.2	54.6 ± 10.2	72.4 ± 6.2	<0.001
Duration (years) (median)	8.0	14.0	3.0	<0.001
Modality of treatment				
Oral drugs	582 (41.7)	264 (41.4)	318 (42.2)	
Insulin	100 (7.3)	61 (9.5)	39 (5.2)	
Oral drugs and insulin	291 (21.3)	201 (31.3)	90 (12.0)	
Diet	272 (19.1)	93 (14.0)	179 (23.6)	
Missing	151 (10.8)	24 (3.7)	127 (16.9)	<0.001
Hypertension	748 (53.6)	362 (56.3)	386 (51.3)	0.060
Heart disease	341 (24.2)	92 (14.3)	246 (32.7)	<0.001
Stroke	233 (16.7)	86 (13.4)	147 (19.5)	0.002

Data are *n* (%) or means ± SD, unless otherwise indicated.

TABLE 3

Adjusted OR (95% CI) of dementia and questionable dementia related to diabetes: results from multinomial logistic regression

Dementia status	Subjects (<i>n</i>)	Diabetic case subjects (<i>n</i>)	Basic-adjusted OR (95% CI)*	Multiadjusted OR (95% CI)†
No dementia	13,028	1,257	1.00 (reference)	1.00 (reference)
Questionable	170	32	2.56 (2.02–1.34)	1.99 (1.58–2.64)
Dementia	467	107	2.00 (1.34–2.96)	1.76 (1.17–2.65)

*Adjusted for age, sex, and education. †Adjusted for age, sex, education, zygosity status, stroke, heart disease, hypertension, and BMI.

longer duration of diabetes and higher proportion of treatment with insulin. In the multinomial logistic analysis including the whole study population, diabetes was significantly associated with an increased risk of both dementia and questionable dementia. As the diabetes-related ORs were similar for dementia and questionable dementia, these two categories were combined as outcome of dementia in subsequent analyses (Table 3).

Table 4 shows the basic- and multiadjusted ORs and 95% CIs of dementia, Alzheimer's disease, and vascular dementia in association with diabetes derived from the GEE models. Diabetes was significantly related to increased risk of dementia, Alzheimer's disease, and vascular dementia. The risk tended to be higher for vascular dementia than for Alzheimer's disease. We also examined the effect of mid-life and late-life diabetes on dementia risk. Compared with patients with late-life diabetes, patients with mid-life diabetes appeared to be at a higher risk for dementia. The effect of mid-life diabetes on dementia risk remained statistically significant even after additional adjustment for diabetes duration (OR 2.07 [95% CI 1.12–3.68]).

All participants included 4,274 twin pairs and 5,117 single twins. Of 4,274 twin pairs, 4,071 were pairs in which both were nondemented and 47 were pairs in which both were demented, leaving 210 pairs discordant for dementia status. In the cotwin matched case-control analyses including both monozygotic and dizygotic pairs, the association between mid-life diabetes and dementia risk remained significant after adjustment for sex, education, stroke, heart disease, hypertension, and BMI at age <65 years, but the association with late-life diabetes largely diminished (Table 5). Of 210 dementia-discordant pairs, 46 pairs were monozygotic and 161 pairs were dizygotic. The multiadjusted ORs of dementia related to diabetes were 1.06 (95% CI 0.48–2.34) in dizygotic pairs and 1.87 (0.30–11.79) in monozygotic pairs.

In GEE models, mid- and late-life diabetes were significantly associated with 176% (OR 2.76 [95% CI 1.97–3.87]) and 63% (1.63 [1.23–2.16]) increased risk for dementia, respectively (Table 4). In the conditional logistic regression analyses, the point estimate of ORs for dementia related to mid-life diabetes dropped only slightly and was still significant (2.41 [1.05–5.51]), but the OR related to late-life diabetes was largely attenuated and no longer statistically significant (0.68 [0.30–1.53]) (Table 5). The attenuation of the regressing coefficients between unpaired and paired analyses in twins suggests that factors that are common to twins in a pair contribute to the observed association in whole cohort. The ORs from GEE models based on all participants and those from conditional logistic models based on dementia-discordant pairs for the association of dementia with late-life diabetes were statistically significantly different (1.76 [1.08–2.88]; $P = 0.02$), but no difference was detected for the mid-life diabetes–dementia association (1.04 [0.55–1.99]; $P = 0.89$). The comparison of the results from the whole cohort and matched pairs indicated that the influences of genetic or family environmental factors on the association between mid-life diabetes and dementia might be small, but they play a role in the late-life diabetes–dementia association.

Among 13,693 participants, 2,633 died between the screening phase and 2004. In the GEE model, type 2 diabetes was related to an elevated risk of death with a multiadjusted OR of 2.15 (95% CI 1.87–2.47). We repeated the analysis using mean age of diabetes onset for 71 diabetic patients with missing age at diabetes onset, which produced the results that were much the same as those from the initial analysis. Further, combination of subjects with questionable dementia and nondemented subjects as control subjects did not alter the initial results. Finally, the analyses were repeated in 8,534 participants with mid-life BMI available, for which information on weight and height during the age of 40–65 years was taken from the Swedish

TABLE 4

Adjusted OR (95% CI) of dementia, Alzheimer's disease, and vascular dementia related to diabetes and separately to diabetes with onset before and after age 65 years: results from GEE models

	Subjects (<i>n</i>)	All dementia	Alzheimer's disease	Vascular dementia
Diabetes status				
No	12,296	498; 1.00 (reference); 1.00 (reference)	236; 1.00 (reference); 1.00 (reference)	74; 1.00 (reference); 1.00 (reference)
Yes	1,396	139; 2.45 (1.97–3.03)*; 1.89 (1.51–2.38)†	56; 2.03 (1.47–2.80)*; 1.69 (1.16–2.36)†	31; 3.60 (2.33–5.57)*; 2.17 (1.36–3.47)†
Age of diabetes onset				
<65 years	643	48; 2.95 (2.14–4.08)*; 2.76 (1.97–3.87)†	16; 2.32 (1.37–3.94)*; 2.25 (1.29–3.92)†	12; 4.94 (2.61–9.35)*; 3.94 (1.90–8.15)†
≥65 years	753	91; 2.12 (1.64–2.75)*; 1.63 (1.23–2.16)†	40; 1.88 (1.29–2.74)*; 1.56 (1.05–2.32)†	19; 2.90 (1.70–4.94)*; 1.62 (0.92–2.80)†

Data are *n*; OR (95% CI) or OR (95% CI). *Adjusted for age, sex, and education. †Adjusted for age, sex, education, stroke, heart disease, hypertension, and BMI.

TABLE 5

Cotwin matched case-control analyses on the association of diabetes with dementia by age of diabetes onset: results from conditional logistic regression models

	All twin pairs (<i>n</i> = 210)	Diabetes onset at midlife (<i>n</i> = 100)	Diabetes onset in latelife (<i>n</i> = 110)
	Demented twin (no diabetes; diabetes)	Demented twin (no diabetes; diabetes)	Demented twin (no diabetes; diabetes)
Nondemented cotwin			
No diabetes	139; 37	63; 22	76; 15
Diabetes	23; 11	9; 6	14; 5
Basic-adjusted OR (95% CI)*	1.67 (0.96–2.92)	2.51 (1.10–5.72)	1.32 (0.66–2.65)
Multiadjusted OR (95% CI)†	1.15 (0.55–2.38)	2.41 (1.05–5.51)	0.68 (0.30–1.53)

*Adjusted for sex and education. †Adjusted for sex, education, stroke, heart disease, hypertension, and BMI.

Twin Registry, and the similar results were obtained when adjusting for mid-life BMI (data not shown).

DISCUSSION

In this large-scale population-based twin study, diabetes is independently associated with an increased risk of dementia, Alzheimer's disease, and vascular dementia. The risk effect is stronger in people with mid-life diabetes than in those with late-life diabetes. Findings from cotwin matched case-control analyses suggest that unmeasured familial factors (genetic factors and early life environments) might contribute to the association between late-life diabetes and dementia but could not account for the association of mid-life diabetes with dementia.

Diabetes is a risk factor for cognitive impairment and dementia, as reported in numerous population-based studies, but it remains in debate whether this concerns only vascular dementia or also Alzheimer's disease. Some prospective studies did find an association between diabetes and increased risk of Alzheimer's disease (1,2,5,9,11,12, 33), while others did not (3,4,6,10). We found that diabetes is associated with moderately increased risk of dementia, Alzheimer's disease, and vascular dementia in Swedish twins. The risk tends to be stronger for vascular dementia. These results are in agreement with findings from the Honolulu-Asia Aging Study (5), which reported an association between diabetes and increased risk of dementia, Alzheimer's disease, and vascular dementia. We also found that patients with mid-life diabetes had greater dementia risk than those with late-life diabetes. Recent reports (34) showed that long-term diabetes has a stronger risk effect for the development of cognitive impairment and dementia. However, in our study the association between mid-life diabetes and dementia was still significant after adjustment for diabetes duration, suggesting that age at exposure to diabetes may also be relevant for the development of dementia.

Neuroimaging studies have recently demonstrated that people with type 2 diabetes had moderately elevated risk for lacunes, hippocampal atrophy, and deep white matter lesions, which support the notion that the increased risk of cognitive decline and dementia in people with diabetes is probably due to dual pathological processes involving both cerebrovascular damage and neurodegenerative changes (35). In addition to microvascular and macrovascular disease, there are other pathophysiological mechanisms through which diabetes could increase the risk of dementia, including glycemia, insulin resistance, oxidative stress, advanced glycation end products, and inflammatory cytokines (20,36). Hyperinsulinemia is suggested to ex-

plain the increased risk of Alzheimer's disease in diabetic patients, as the effect of high levels of insulin on dementia risk is independent of diabetes and blood glucose (37). These pathways may act separately or interactively, but which of these mechanisms are clinically relevant is unclear. In addition, the different mechanisms may interact during the long prodromal phases of both diabetes and dementia (38).

In cotwin control analyses, the risk effect of mid-life diabetes on dementia remained significant, but the association between late-life diabetes and dementia risk was largely diminished. Thus, the association between late-life diabetes and dementia may be attributed to genetic and early environmental factors (such as maternal nutrition status and childhood socioeconomic situation), although similar exposures at mid-life and late life could also have occurred. These findings suggest that the association observed in the unmatched case-control analysis between late-life diabetes and dementia is more likely to be endogenous. Our findings support recent evidence that the molecular defects associated with the development of diabetes also contribute to an increased risk of all types of dementia (39). Genome-wide association studies have shown that the insulin-degrading enzyme (*IDE*) gene links to both late-onset Alzheimer's disease and type 2 diabetes (40). *IDE* has been demonstrated to degrade insulin and β -amyloid and to inhibit islet amyloid polypeptide (a protein coexpressed and secreted with insulin by β -cells) oligomer formation and cytotoxicity (41). There may be shared predisposition for developing islet amyloid in patients with diabetes and brain amyloid in those with Alzheimer's disease. A population-based clinicopathological study (42) has shown the possible link between neurodegenerative processes that lead to loss of cortical brain cells in Alzheimer's disease and the loss of β -cells in type 2 diabetes. Furthermore, there is now abundant evidence that early-life growth and development has an effect on risk of disease in adult life (43). Several studies have observed the relationship between low birth weight and increased risk of diabetes (44). In addition, childhood low socioeconomic status may also contribute to the risk of both diabetes (19) and dementia (45). Thus, the link between diabetes and dementia is probably determined by the complex interplay of genetic and environmental exposures throughout the life course.

In contrast to late-life diabetes, mid-life diabetes was associated with an increased risk of dementia even when controlling for genetic and familial factors, suggesting that mid-life diabetes–dementia association might be exogenous and is more likely attributable to adulthood environ-

ments (e.g., occupation and lifestyle such as exercise, diet, smoking, and social activities as well as glycemic control in patients with diabetes) (21). Our results indicate that genetic and unmeasured early-life environmental factors are likely to play a role in the association of late-life diabetes with dementia but could not explain mid-life diabetes in association with dementia, which implicated the involvement of adulthood environments in the development of mid-life diabetes–dementia association and highlighted the need to maintain a healthy lifestyle during adulthood in order to reduce the risk of dementia late in life.

Obesity is related to inflammation and insulin resistance, and the lifespan-dependent relation of obesity with dementia has been reported (46). In our study, information on weight and height were based on self- or informant report, and BMI as a covariate in the analyses may lead to residual confounding. However, all our analyses showed that BMI did not substantially affect the diabetes-dementia association, suggesting that the confounding due to BMI on the diabetes-dementia association, if it exists, is likely to be minimal.

Some limitations of the study should be mentioned. First, the use of prevalent dementia cases may have introduced some confounding effect due to differential survival among case subjects. In this study, the mean age of diabetes onset was much younger than the mean age of dementia onset. The temporality of the given association is clear. In addition, diabetes is associated with an elevated mortality in our study as reported previously (47), which would probably lead to an underestimation of the strength of association between diabetes and dementia risk. Second, we identified patients with diabetes based on self- and informant-reported information and on inpatient medical history. Information on blood glucose concentration was not available. Because diabetes is commonly (~30%) undiagnosed in elderly people (48), in this study a substantial proportion of the subjects with diabetes might have been erroneously assigned to the nondiabetic group, which would also lead to an underestimation of the risk attributable to diabetes. Third, both sets of influences are anonymous; thus, we are unable to infer which genes might be involved or which environmental factors might be important. Fourth, information from informants was used for participants who could not provide information about history of diseases due to impaired cognition (7.0%). However, the bias of using reports from an informant has been previously found to be minimal (49). Finally, both diabetes and dementia (especially Alzheimer's disease) are genetically influenced disorders with substantial concordance in twins (15,50). Thus, the matched pairs could be regarded as "overmatched," as twin pairs are similar on many aspects, such as genetic susceptibility and lifestyle. Nevertheless, the comparison of the results from the cohort as a whole with the matched pairs provides important information about the potential role of genetic and familial influences in the associations from the cohort analyses. Furthermore, as the discordant pairs included both monozygotic and dizygotic twins, genetic effects were not perfectly controlled for.

In conclusion, our results show that diabetes increases the risk of Alzheimer's disease and vascular dementia in the Swedish twins. The risk effect is stronger when diabetes occurs at mid-life than in late life. These findings add to the growing evidence of a link between diabetes, vascular damage, and neurodegenerative changes in the brain.

Genetic and early-life environmental factors might contribute to the association between late-life diabetes and dementia, but adulthood environments might be responsible for mid-life diabetes–dementia association. These findings suggest that diabetes-dementia association may develop across a lifespan. Further studies are required to reveal which early life and adulthood environmental factors as well as genes might be involved for the diabetes-dementia association.

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