

Original Contribution

Earlier Age of Dementia Onset and Shorter Survival Times in Dementia Patients With Diabetes

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Diabetes is a risk factor for dementia, but relatively little is known about the epidemiology of the association. A retrospective population study using Western Australian hospital inpatient, mental health outpatient, and death records was used to compare the age at index dementia record (proxy for onset age) and survival outcomes in dementia patients with and without preexisting diabetes ($n = 25,006$; diabetes, 17.3%). Inpatient records from 1970 determined diabetes history in this study population with incident dementia in years 1990–2005. Dementia onset and death occurred an average 2.2 years and 2.6 years earlier, respectively, in diabetic compared with non-diabetic patients. Age-specific mortality rates were increased in patients with diabetes. In an adjusted proportional hazard model, the death rate was increased with long-duration diabetes, particularly with early age onset dementia. In dementia diagnosed before age 65 years, those with a ≥ 15 -year history of diabetes died almost twice as fast as those without diabetes (hazard ratio = 1.9, 95% confidence interval: 1.3, 2.9). These results suggest that, in patients with diabetes, dementia onset occurs on average 2 years early and survival outcomes are generally poorer. The effect of diabetes on onset, survival, and mortality is greatest when diabetes develops before middle age and after 15 years' diabetes duration. The impact of diabetes on dementia becomes progressively attenuated in older age groups.

Alzheimer disease; dementia; diabetes mellitus; mortality; proportional hazards models; retrospective studies; survival

Abbreviations: CI, confidence interval; HMDS, Hospital Morbidity Data System; ICD-8, *International Classification of Diseases, Eighth Revision*; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10-AM, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification*; MHIS, Mental Health Information System; SD, standard deviation.

Previous studies have demonstrated that diabetes is associated with an increased risk of dementia (1–6) and that the future global health burden from dementia is likely to be influenced by the worldwide increasing prevalence of diabetes (7, 8).

Diabetes has consistently been associated with vascular dementia (2, 9–15), but reports on the association between diabetes and Alzheimer's disease are less consistent. There are reports of a strong association between diabetes and risk of clinical Alzheimer's disease (2, 14, 16–18), reports that find no association (9, 11, 12, 15, 19), and reports of subsets of people with diabetes who are at greater risk of developing

Alzheimer's disease (10, 20, 21). Existing studies on the impact of diabetes on cognitive decline in people with established dementia are also controversial. Unchanged (22), faster (23, 24), and reduced (25, 26) rates of cognitive decline in individuals with diabetes have been reported with Alzheimer's disease, and a more rapid rate of cognitive decline was reported with vascular dementia (27). The mechanisms that drive these associations are likely to be related to variable combinations of ischemic brain injury (28, 29) and Alzheimer's disease-related neurodegeneration (30). In population models, relatively minor differences in incidence rates have been shown to have major impacts on future

dementia projections (31), but there are few such studies in relation to diabetes and dementia. A single study reported an early age of onset of vascular dementia in diabetes (27), and shorter survival times have been reported with the combination of Alzheimer's disease and diabetes (32).

The Western Australian Data Linkage System (WADLS) is an internationally renowned, population-based, validated, and ongoing data linkage system that creates links among a number of state health administrative data sets (33–35). In the present study, we used the Western Australian Data Linkage System to identify all people with Alzheimer's, vascular, and nonspecific dementia documented in hospital and mental health outpatient records between 1990 and 2005 with the aim of comparing age of dementia onset (using age at index dementia record as a proxy), age at death, and length of survival with dementia in those with and without a prior diagnosis of diabetes.

MATERIALS AND METHODS

Case ascertainment

The Western Australian Data Linkage System provided a de-identified extraction of linked data for years 1990–2005 from the Hospital Morbidity Data System (HMDS), Mental Health Information System (MHIS), and Mortality Data System for all persons with a dementia diagnosis in any of these data sets. The HMDS records all discharge summaries from all Western Australian acute hospitals (private and public) and day surgery clinics; the MHIS records all inpatient and outpatient contacts with public mental health services and all inpatient contacts with private mental health service providers. Study data were obtained in December 2006 following approval from the Curtin University Human Research Ethics Committee and the Western Australian Department of Health Confidentiality of Health Information Committee.

A case was defined as any person, aged 40 years or older, who had an index (first) record of dementia diagnosis in the HMDS or MHIS in the period from January 1, 1990, to December 31, 2005. The following *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* (ICD-10-AM), codes were used to identify cases: Alzheimer's dementia: 331.0, F00, G30; vascular dementia: 290.4, F01; and nonspecific dementia: 290.0, 290.1, 290.2, 290.3, 290.8, 290.9, 294.1, 294.8, 331.2, F02.8, F03, F05.1, G31.1, G31.8, and G31.9. Excluded from the study were 1) cases with any record of frontotemporal, Creutzfeldt-Jakob, Huntington's, or Parkinson's dementia; 2) cases without at least one inpatient hospital admission in the 5-year period prior to index record to reduce ascertainment bias related to hospitalization; 3) cases with any record of dementia prior to 1990; and 4) cases with first mention of diabetes recorded after their index dementia record. A hierarchy was used to assign dementia type to cases with more than one dementia code in their health records; Alzheimer's took precedence over vascular dementia that took precedence over the nonspecific dementia

diagnoses. Records from 1970 onward were used to identify cases with diabetes mellitus using *International Classification of Diseases, Eighth Revision* (ICD-8), code 250; *International Classification of Diseases, Ninth Revision* (ICD-9), codes 250.x; ICD-9-CM codes 250.x; and ICD-10-AM codes E10.x, E11.x, E13.x, and E14.x for years 1970–1978, 1979–1987, 1988–1999, and 2000–2005, respectively. No ICD-8 codes were available to distinguish between different types of diabetes mellitus. Therefore, the above ICD-9, ICD-9-CM, and ICD-10-AM codes included type 1, type 2, other specified, and unspecified diabetes mellitus. As the exact date of diabetes onset was not known, the duration of diabetes was defined as the number of years between the date of the index diabetes hospital record and the date of the index dementia record. Diabetes duration was then categorized as <6, 6–10, 11–15, and >15 years' duration.

Linked health records were also used to determine preexisting comorbidity using the Charlson Comorbidity Index (36). The comorbidity index consisted of groups of *International Classification of Diseases* codes weighted according to mortality risk (excluding dementia and diabetes); the total weighted index was divided into 3 discrete intervals. Any mention of each of the diagnostic categories on any hospital admission with a separation date within 5 years of index dementia record contributed to the comorbidity index (37). Comorbidities due to myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, hemi- or paraplegia, renal disease, tumors, lymphoma, leukemia, liver disease, and metastatic solid tumor were included in the comorbidity index.

Data and statistical analysis

Multivariate linear regression models were used to investigate factors associated with age at onset of dementia and age at death with dementia; the factors included diabetes duration, sex, dementia type, number of hospitalizations in the 5-year period prior to index dementia record, the source of the index record, comorbidity at year of index record, and year of index record. Sex and dementia type were included as they are known to be related to age of dementia onset. Numbers of hospitalizations were included because cases with more frequent hospital admissions prior to the index record were expected to appear younger at time of index dementia because of increased surveillance and recording of their health status. The source of index-record type was considered a potential confounder (e.g., mental health outpatient services are less likely to be provided to people from residential aged-care facilities). Year of index record was included to adjust for possible changes in hospital admission patterns over the 15 years of the study and changes in treatment and preventive practices. Box-Cox power transformations of the age variables were used to correct for the skewness of the residuals, and the appropriate back-transformation of model β coefficients was performed. The effect of diabetes duration on both age at index record and age at death was found to be modified by the type of dementia.

Survival analysis was used to estimate differences in mortality by diabetes duration. Because of both the relatively

low level of censoring (27.7%) that can increase bias if using time-on-study as the time scale and the presence of covariates strongly associated with age, age was used as the time scale with left truncation at age of index record (38). This allows control for the strong association of age with death and interpretation of the hazard rate as an age-specific mortality rate. The study censor date was December 31, 2005, or the date of last inpatient or outpatient visit if prior to the censor date. Patients who died during the index record admission or within 30 days of separation were excluded from the survival analysis. The average unadjusted age-specific mortality rates for the cohort were obtained from the weighted kernel smooth of the estimated hazard function. The relative rates of death by diabetes duration were estimated from covariate-adjusted regression using flexible parametric proportional hazards models constructed with restricted cubic splines (39). Multivariate model building started with inclusion of all significant univariate predictors, age group at index dementia record, diabetes duration, type of dementia, sex, comorbidity, and source of index record. The observed nonproportional hazards for comorbidity and source of index record were accounted for by including them in the final model as time-varying covariates with 1 df. All 2-factor interactions with diabetes duration, the primary risk factor of interest, were examined. Median survival time since time index record for each age group by diabetes duration was estimated by setting time since index record as analysis time. Data manipulation was performed by using SAS software (SAS Institute, Inc., Cary, North Carolina) and statistical analysis by using Stata, version 11, software (StataCorp LP, College Station, Texas).

RESULTS

Cohort characteristics and age at dementia onset

There were 32,768 patients with an index record of dementia between 1990 and 2005 (mean age: 81.5 (standard deviation (SD), 8.3) years; 38.8% male; 13.9% with diabetes). After exclusion of 6,663 dementia cases without a prior hospital admission in the 5-year period prior to index records (mean age: 81.1 (SD, 8.4) years; 33.7% male; 3.8% with diabetes) and 1,099 cases where diabetes was first recorded after date of index dementia (mean age: 79.7 (SD, 8.6) years; 39.2% male), there remained a study cohort of 25,006 dementia cases (mean age: 81.7 (SD, 8.2) years; 40.2% male; 17.3% with diabetes). Only 298 cases had type 1 diabetes (mean age: 76.9 (SD, 8.9) years; 49.0% male). The study cohort included 848 people (3.5%) aged 40–64 years, 3,168 (12.7%) aged 65–74 years, 11,049 (44.2%) aged 75–84 years, and 9,944 (39.8%) aged ≥85 years.

Of the cohort, 23,811 (95.2%) and 5,539 (22.2%) cases had at least 1 dementia diagnosis documented in inpatient hospital (including general and psychiatric hospitals) and mental health outpatient records respectively, with 4,344 (17.4%) having a dementia diagnosis in both inpatient and outpatient records. The index dementia record was located in the outpatient and inpatient records in 3,276 (13.1%) and 21,739 (86.9%) cases, respectively. A total of 1,195 (4.8%) cases had no dementia documented in inpatient hospital

records. For the 2,072 (8.2%) cases with their index record in the mental health outpatient records and a subsequent diagnosis in the inpatient hospital records, the mental health outpatient record ascertained the dementia diagnoses a median of 18 weeks earlier (interquartile range: 3–69). Of the 18,086 cases that died, dementia was also documented in 7,933 (43.9%) death records, and 9,187 (50.8%) had dementia documented in at least 2 data sets.

Diabetes was more commonly recorded in the younger age groups of the dementia cohort with 23.2% of those aged 40–64 years, 24.1% of those aged 65–74 years, 18.6% of those aged 75–84 years, and 13.1% of those aged ≥85 years having diabetes (Cochran-Armitage trend test: $P < 0.0001$). Diabetes was associated with an increased proportion of males, vascular dementia, comorbidity, more frequent hospitalizations (all χ^2 P values: $P < 0.001$), and being sourced from inpatient records ($P = 0.004$) when compared with non-diabetes. Overall, cases with diabetes were an average 2.2 (95% confidence interval (CI): 2.0, 2.5) (t -test $P < 0.001$) years younger at the time of index dementia record, and this trend of younger index age for diabetes was consistent when stratified by sex, dementia type, comorbidity, record source, and number of hospitalizations (Table 1). In a multivariate regression model of age at index record (age at dementia onset), diabetes remained a significant independent predictor of younger age at dementia onset after adjustment for all other variables (Table 2). There were differences in mean age at dementia onset by duration of diabetes and by dementia type. These differences were most marked with vascular dementia; for example, where diabetes had been present for 15 years or more, the age at index record was 5.7 years earlier than that for nondiabetic cases. The pattern with Alzheimer's disease and nonspecific dementia was similar but with less marked age difference (2.4 and 3.4 years, respectively, for longest duration diabetes).

Mortality and survival with dementia

By December 2005, 72.3% (18,083 cases) of the cohort had died. Of those who had died, the diabetic patients had dementia first recorded 2.3 (95% CI: 1.9, 2.6) years younger than those without diabetes (mean age: 80.6 (SD, 8.1) vs. 82.8 (SD, 7.6) years) ($P < 0.0001$), and the age at death occurred an average 2.6 (95% CI: 2.3, 2.9) years younger (mean age: 82.4 (SD, 8.0) vs. 85.0 (SD, 7.4) years) ($P < 0.0001$). A general trend of younger mean age at death was observed with increasing diabetes duration (Table 2), and this was quantified as dying on average 0.20 (95% CI: 0.17, 0.22) years younger with each increasing year of diabetes duration in an adjusted linear regression model with duration of diabetes included as a continuous variable in years.

After exclusion of 2,909 dementia cases who died during the index dementia hospital admission or within 30 days of index record, there remained 22,097 cases with follow-up time for survival analysis. Survival analysis was used to estimate age-specific mortality rates for the cohort by a history of diabetes (Figure 1). The mortality rate in dementia patients with diabetes was higher than that for those without diabetes, and this effect was stronger at a younger age.

Table 1. Characteristics of 25,006 Western Australian Dementia Patients by Diabetes Status at Time of Index Dementia Record, 1990–2005

	No Diabetes			Diabetes			Age Difference, Years	
	No.	%	Mean Age (SD), Years	No.	%	Mean Age (SD), Years	Mean	95% CI
Sex								
Male	8,169	39.5	80.3 (8.4)	1,887	43.7	78.5 (8.4)	1.8	1.4, 2.3
Female	12,521	60.5	83.3 (7.7)	2,429	56.3	81.0 (8.0)	2.3	1.9, 2.6
Dementia type								
Alzheimer	8,888	43.0	81.8 (7.4)	1,471	34.0	80.6 (7.4)	1.2	0.7, 1.6
Nonspecific	9,794	47.3	83.0 (8.5)	2,238	51.9	80.4 (8.5)	2.6	2.2, 3.0
Vascular	2,008	9.7	79.4 (8.5)	607	14.1	76.5 (8.5)	2.9	2.2, 3.7
Comorbidity ^a								
0	8,974	43.4	81.5 (8.6)	1,274	29.5	79.6 (8.4)	1.9	1.4, 2.4
1–2	7,356	35.6	82.7 (7.8)	1,617	37.5	80.4 (8.2)	2.2	1.8, 2.7
3–18	4,360	21.1	82.4 (7.6)	1,425	33.0	79.5 (8.2)	2.9	2.4, 3.3
Index record ^b								
Outpatient	2,756	13.3	78.9 (9.2)	511	11.8	77.3 (8.9)	1.7	0.8, 2.5
Inpatient	17,934	83.0	82.6 (7.8)	3,805	88.2	80.2 (8.0)	2.3	2.1, 2.6
Hospitalizations								
1–2	8,391	40.6	82.0 (8.1)	1,143	26.5	80.5 (7.8)	1.6	1.1, 2.1
3–4	5,152	24.9	82.5 (8.1)	1,002	23.3	80.6 (7.8)	1.9	1.3, 2.4
≥5	7,147	34.5	81.9 (8.2)	2,171	50.3	79.3 (8.7)	2.7	2.3, 3.1
Total	20,690	100.0	82.1 (8.1)	4,316	100.0	79.9 (8.3)	2.2	1.9, 2.5

Abbreviations: CI, confidence interval; SD, standard deviation.

^a Comorbidity, Charlson's weighted comorbidity index score.^b Outpatient (public mental health outpatient clinics); inpatient (private and public hospitals).

The association of mortality and diabetes remained after adjustment for covariates in a multivariate flexible parametric proportional hazards model and was found to be modified by age at index record and duration of diabetes (Figure 2). There was a significant trend of duration of diabetes on rate of death in all age groups except in those who had dementia diagnosed when aged over 85 years. The effect was most marked in those diagnosed with dementia at a young age. When dementia was diagnosed before age 65 years, those with longest duration diabetes (more than 15 years) died at almost twice the rate as those without diabetes (hazard ratio = 1.9, 95% CI: 1.3, 2.9). The death rates were also significantly greater with long-duration diabetes with the 65–74-year and 75–84-year age groups, although the effect was less marked with hazard ratios = 1.5 (95% CI: 1.1, 1.9) and 1.4 (95% CI: 1.2, 1.6), respectively. Median survival times from the date of index record for these age groups by length of diabetes duration are shown in Table 3, with longer duration of diabetes having a bigger impact on shortening median survival times in younger dementia cases compared with older dementia cases.

DISCUSSION

In the present study, we used administrative health data sets to explore the impact of preexisting diabetes on a surrogate

measure of age at dementia onset and subsequent survival in the Western Australian population. Over 17% of dementia cases had preexisting diabetes, but the prevalence was substantially greater, affecting almost 1 in 4 cases, in those with early onset dementia (<65 years). Dementia in those with preexisting diabetes developed an average 2.2 years earlier than in nondiabetic cases and was associated with an increased mortality rate and a shorter survival time after dementia onset. The magnitude of diabetes-related differences in survival and the mortality rate after onset were relatively modest overall. We conclude that, at the population level, the increased risk of dementia due to diabetes is explained predominantly by an early age of onset rather than by a major change in the natural history of diabetes-related dementia.

To our knowledge, this is the first epidemiologic study to include every identified dementia case from a large population database. Most previous large population studies have studied elderly populations only and, hence, missed any impact of diabetes on early onset dementia (1). The few studies that assessed midlife diabetes and then late-life dementia did not examine mortality rates and survival (2, 3). The public health significance of a 2.2-year age difference seems modest, yet it has been estimated that an intervention able to delay the onset of Alzheimer's disease by 2 years would reduce the projected quadrupling of Alzheimer's disease prevalence by year 2050 by over 20% (40). Diabetes

Table 2. Multivariate Linear Model Estimating Mean Differences in Age at Time of Index Dementia Record ($n = 25,006$) and Age at Death ($n = 18,083$) by Clinical and Demographic Variables, Western Australia, 1990–2005

Variable	Age at Index Dementia Record, Years ^a			Age at Death, Years ^a		
	Mean Difference	95% CI	P Value	Mean Difference	95% CI	P Value
Alzheimer's disease						
No diabetes history	0	Referent		0	Referent	
Diabetes history						
0–5 years	–1.1	–1.6, –0.6	<0.001	–0.8	–1.4, –0.2	0.006
6–10 years	–1.2	–2.0, –0.4	0.006	–1.1	–2.1, –0.2	0.022
11–15 years	–1.4	–2.5, –0.3	0.014	–2.1	–3.3, –0.9	0.001
>15 years	–2.4	–3.7, –1.1	<0.001	–3.8	–5.2, –2.3	<0.001
Vascular dementia						
No diabetes history	0	Referent		0	Referent	
Diabetes history						
0–5 years	–2.6	–3.6, –1.7	<0.001	–2.5	–3.5, –1.4	<0.001
6–10 years	–2.3	–3.7, –1.0	<0.001	–2.1	–3.6, –0.7	0.004
11–15 years	–3.3	–5.2, –1.4	<0.001	–2.8	–4.9, –0.7	0.010
>15 years	–5.7	–8.1, –3.4	<0.001	–6.9	–9.5, –4.4	<0.001
Nonspecific dementia						
No diabetes history	0	Referent		0	Referent	
Diabetes history						
0–5 years	–2.7	–3.1, –2.2	<0.001	–2.6	–3.1, –2.1	<0.001
6–10 years	–2.2	–2.0, –0.3	<0.001	–2.4	–3.2, –1.7	<0.001
11–15 years	–2.8	–3.7, –1.9	<0.001	–3.1	–4.1, –2.0	<0.001
>15 years	–3.4	–4.4, –2.4	<0.001	–3.8	–4.9, –2.6	<0.001
Sex						
Male	0	Referent		0	Referent	
Female	2.6	2.4, 2.8	<0.001	3.1	2.9, 3.3	<0.001
Index record						
Inpatient	0	Referent		0	Referent	
Outpatient	–2.8	–3.1, –2.5	<0.001	–1.6	–1.9, –1.3	<0.001
Index year						
1990–1994	0	Referent		0	Referent	
1995–1999	0.5	0.2, 0.7	<0.001	0.6	0.4, 0.9	<0.001
2000–2005	1.5	1.2, 1.7	<0.001	1.1	0.8, 1.3	<0.001
Comorbidity ^b						
0	0	Referent		0	Referent	
1–2	1.3	1.1, 1.5	<0.001	0.4	0.2, 0.7	0.001
3–18	1.3	1.1, 1.6	<0.001	–0.2	–0.5, –0.1	0.1
Hospitalizations	–0.4	–0.4, –0.3	<0.001	–0.4	–0.5, –0.3	<0.001

Abbreviation: CI, confidence interval.

^a Regression model adjusted for diabetes duration, sex, dementia type, number of hospitalizations in the 5-year period prior to index dementia record, the source of the index record, comorbidity at year of index record, and year of index record. Information on duration of diabetes and dementia type was entered in the model as an interaction term.

^b Comorbidity, Charlson's weighted comorbidity index score.

was previously estimated to account for 7%–13% of the population attributable risk for incident dementia (41), but this was based largely on studies of older populations. Given that the incidence and prevalence of type 2 diabetes are

increasing worldwide because of population aging and the global obesity problem (7, 8, 42), the impact of diabetes on dementia projections based on the present study is likely to be substantially greater than previously considered.

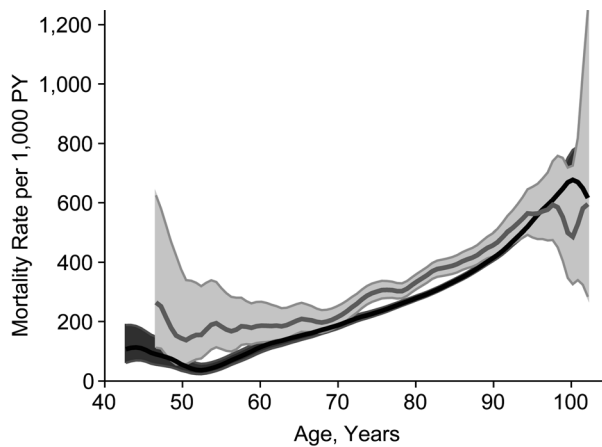


Figure 1. Age-specific mortality rate of the dementia cohort for those with a history of diabetes before index dementia record (gray line) and those without a history of diabetes (black line), Western Australia, 1990–2005. The dementia cohort includes 22,097 Western Australians with index dementia records who were alive for at least 30 days after index record. PY, person-years. Shading indicates 95% confidence intervals.

The population-based nature of this study meant that the diagnosis of dementia subtypes was documented by a range of medical staff of varying seniority and from various health-care settings and specialties. Although their diagnostic validity cannot be determined, we did find differences by

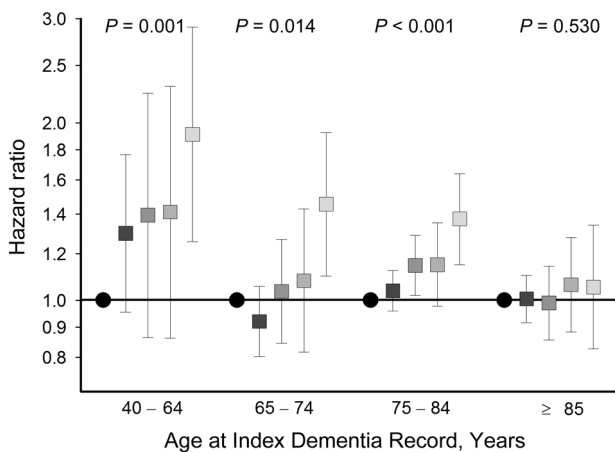


Figure 2. Relative rate of death (hazard ratio) for 22,097 Western Australian dementia cases with an increasing history of diabetes duration from 0–5 years (darkest square), 6–10 years (dark square), 11–15 years (pale square), and >15 years (palest square) compared with dementia cases with no history of diabetes (•) and similar age at index dementia record between 1990 and 2005 as estimated from a proportional hazards model. Model was also adjusted for type of dementia, comorbidity, sex, and source of record. Error bars indicate 95% confidence intervals, and values for P_{trend} tests of increasing history of diabetes duration are shown.

dementia subtypes consistent with the known literature (43). The effect was most marked in those who were diagnosed with vascular dementia that developed 3 years earlier although Alzheimer's disease developed a little over 1 year earlier in those with diabetes. The duration of diabetes was an important modifier of the relationship between diabetes and dementia onset and survival, with the greatest impact on younger cases with long diabetes duration. Again, this was most marked with vascular dementia, a condition known to occur with an earlier age of onset in diabetes (44), but was also seen with Alzheimer's disease and nonspecific dementia. Both microvascular complications and worsening macrovascular burden are strongly associated with long diabetes duration (45), suggesting that diabetes contributes in the pathophysiology and clinical expression of dementia by cerebral microvascular and/or macrovascular mechanisms. Vascular lesions may also augment the cerebral burden of Alzheimer's disease-related pathological changes and accelerate the clinical expression of Alzheimer's disease (46). Alternatively, it has been suggested that several of the metabolic abnormalities in type 2 diabetes, including insulin resistance, hyperglycemia, and chronic inflammation, promote Alzheimer's disease-related changes including β -amyloid accumulation (47, 48). Type 2 diabetes is a chronic progressive condition where escalating medical therapies including exogenous insulin and/or insulin secretagogues are required to control the worsening metabolic deficits (49). Cerebral β -amyloid deposition is a gradual, slow process that takes a decade or more to develop, in which case years of diabetes may be required to alter this pathway substantially.

The impact of diabetes duration on mortality was attenuated in older age and was absent in those aged ≥ 85 years. This may reflect a survivor effect; that is, only some people are able to survive the ravages of long-duration diabetes and live long enough to develop late-onset dementia. Extrapolating backwards from Figure 2, the excess risk of death with dementia due to diabetes is confined mainly to those diagnosed with diabetes before age 65 years who subsequently survive with diabetes for around 15 years. Although the present study cannot definitively distinguish whether increased mortality rates reflect faster rates of cognitive decline or are due to other diabetes-related comorbidity, the differences persisted after statistical adjustment for hospital admissions and comorbidities.

The strengths of our study include the large, population-based sample size; use of the Western Australian Data Linkage System that has been demonstrated to provide accurate hospital, mental health clinic, and death data within known limitations for case ascertainment; and the ability to control for a range of important modifiers and confounders including estimated duration of premorbid diabetes. The main limitations of the study are the use of health administrative data sets to obtain proxy measures of diabetes and dementia onset and the reliance on routine clinical diagnoses for diabetes and dementia subtypes. Although all cases in this study required a physician diagnosis of dementia, the specific diagnostic criteria used by each physician for dementia and all other medical conditions are not known, and the dementia diagnoses could not be verified. However, in a Danish study, 86% of dementia diagnoses and 81% of

Table 3. Median and 25th and 75th Percentile Survival Time From Time of Index Dementia Record by Age Group and Diabetes History ($n = 22,097$), Western Australia, 1990–2005

Age Group at Index Dementia Record, Years, by Diabetes Duration	No.	Survival Time, Years		
		25th Percentile	Median (50th Percentile)	75th Percentile
40–64 years				
No diabetes history	603	2.5	5.7	11.5
Diabetes history				
0–5 years	94	1.4	3.7	7.7
6–10 years	35	1.9	3.6	10.2
11–15 years	27	1.3	2.8	5.9
>15 years	31	0.5	2.7	5.7
65–74 years				
No diabetes history	2,219	1.6	3.5	6.4
Diabetes history				
0–5 years	380	1.0	3.3	6.6
6–10 years	152	1.0	2.7	5.7
11–15 years	75	1.0	2.5	6.7
>15 years	71	0.9	2.0	4.4
75–84 years				
No diabetes history	8,025	1.0	2.5	4.8
Diabetes history				
0–5 years	994	0.7	2.2	4.4
6–10 years	428	0.6	1.9	4.5
11–15 years	215	0.6	2.0	4.0
>15 years	176	0.6	1.2	3.6
≥85 years				
No diabetes history	7,473	0.7	1.8	3.4
Diabetes history				
0–5 years	602	0.6	1.6	3.1
6–10 years	258	0.6	1.6	3.1
11–15 years	149	0.5	1.4	2.9
>15 years	90	0.6	1.3	2.9
All cases ^a	22,097	0.8	2.3	4.4

^a Cases that died at time of index record or within 30 days of separation from index record from hospital inpatient records were excluded from survival analysis.

Alzheimer's disease diagnoses in hospital registers were correct (50). An Australian audit reported that the sensitivity, positive predictive value, and κ value for dementia diagnoses were 67%, 76%, and 0.71%, respectively, suggesting substantial agreement between medical charts and registry data (51). By including records from psychiatric outpatient contacts in addition to hospital inpatient records, we improved dementia case ascertainment by 5% and provided earlier estimates for dementia onset in a further 8% of cases. The greater likelihood of diabetes patients being hospitalized may have led to both increased and earlier detection of dementia cases with diabetes in the registers. To minimize this problem, we included only dementia cases who had at least 1 hospital admission in the 5-year period before the

index date and adjusted for number of hospitalizations within this period. As expected, cases with diabetes had more frequent hospital admissions, although the survival and age at onset differences persisted after adjustment for number of hospitalizations. The lower prevalence of diabetes among the excluded cases suggests that we excluded the more "healthy" dementia cases, so the differences between diabetic and nondiabetic cases observed in this study may be an underestimate of the true population estimate. Underdiagnosis of diabetes can also occur during hospitalization, and misclassification here would be expected to dilute the effects that we found. We were also unable to control for a range of potential confounders including low educational status, which is associated with both diabetes (52, 53) and dementia

(54) and could therefore contribute to our findings. There could also have been differences in degree of cognitive impairment at the time of index dementia record that could have skewed the results. Although we were also unable to adjust for other potentially important variables, such as diet, exercise, and glycemic control, we were able to adjust for diseases associated with these risk factors, incorporated into the Charlson Comorbidity Score.

In summary, diabetes was associated with an earlier age of onset of dementia and an earlier age of death through a reduced survival time compared with patients with dementia without diabetes. The increased risk of dementia due to diabetes that is seen in population studies is explained by an average 2-year earlier age at onset of disease rather than because of a prolonged disease course. These findings, amplified in early onset dementia and by long-duration diabetes, have major implications for estimating the future dementia disease burden due to diabetes as well as clinical implications for affected patients and their families.

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