TITLE

Earlier age of dementia onset and shorter survival times in dementia patients with diabetes.

RUNNING HEAD

Dementia onset age and survival in diabetes

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ABBREVIATIONS

AD Alzheimer's disease

CI confidence interval

HR hazard ratio

HMDS Hospital Morbidity Data System

ICD International Classification of Disease

MHIS Mental Health Information System

SD standard deviation

ABSTRACT

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 pre-existing diabetes (n=25,006; diabetes, 17.3%). Inpatient records from 1970 determined diabetes history in this study population with incident dementia between years 1990-2005. Dementia onset and death occurred an average 2.2 years and 2.6 years earlier, respectively, in diabetic compared to non-diabetic patients. Age-specific mortality rates were increased in patients with diabetes. In an adjusted proportional hazard model the rate of dying 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 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.

KEYWORDS Alzheimer disease, dementia, diabetes mellitus, epidemiology, mortality, proportional hazards models, retrospective studies, survival

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 AD are less consistent. There are reports of a strong association between diabetes and risk of clinical AD [2, 14, 16-18], reports which find no association [9, 11, 12, 15, 19], and reports of subsets of people with diabetes who are at greater risk of developing AD[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 AD 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 AD-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 AD 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, vascular and non-specific 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.

METHODS

Case ascertainment

The Western Australian Data Linkage System provided a de-identified extraction of linked data for years 1990 to 2005 from the Hospital Morbidity Data System (HMDS), Mental Health Information Services (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 1 January 1990 to 31 December 2005. The following International Classification of Disease-9-CM (ICD) and ICD-10-AM codes were used to identify cases. Alzheimer's Dementia: 331.0, F00, G30; Vascular Dementia: 290.4, F01; Non-Specific 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 (i) cases with any record of fronto-temporal, Creutzfeldt-Jakob, Huntington's or Parkinson's dementia, (ii) cases without at least one inpatient hospital admission in the five

year period prior to index record to reduce ascertainment bias related to hospitalization, (iii) cases with any record of dementia prior to 1990, and (iv) 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 which took precedence over the non-specific dementia diagnoses. Records from 1970 onwards were used to identify cases with diabetes mellitus using ICD-8 code 250, ICD-9 codes 250.x, ICD-9-CM codes 250.x and ICD-10-AM codes E10.x, E11.x, E13.x, E14.x for years 1970-1978, 1979-1987, 1988-1999, 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 type1, 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 less than 6 years, 6-10 years, 11-15 years and greater than 15 years duration.

Linked health records were also used to determine pre-existing comorbidity using the Charlson Comorbidity Index [36]. The comorbidity index consisted of groups of ICD codes weighted according to mortality risk (excluding dementia and diabetes); the total weighted index was divided into three discrete intervals. Any mention of each of the diagnostic categories on any hospital admission with a separation date within five 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 five 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 beta coefficients were 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. Due to both the relatively low level of censoring (27.7%) which 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. Study censor date was 31 December 2005 or date of last inpatient or outpatient

visit if prior to censor date. Patients who died during the index record admission or within 30 days of separation were excluded from the survival analysis. The average un-adjusted 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 non-proportional hazards for comorbidity and source of index record were accounted for by including them in the final model as time-varying covariates with one degree of freedom. All two-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 using SAS and statistical analysis using Stata 11 (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 (SD), age 81.5 (8.3) years, 38.8% male, 13.9% with diabetes). After excluding 6,663 dementia cases without a prior hospital admission in the five year period prior to index records (age 81.1 (8.4) years, 33.7% male, 3.8% with diabetes) and 1,099 cases where diabetes was first recorded after date of index dementia (age 79.7 (8.6) years, 39.2% male) there remained a study cohort of 25,006 dementia cases (age 81.7 (8.2) years, 40.2% male, 17.3% with diabetes). Only 298 cases had Type 1 Diabetes (age 76.9 (8.9) years, 49.0%

male. The study cohort included 848 people (3.5%) aged 40-64years, 3168 (12.7%) aged 65-74 years, 11049 (44.2%) aged 75-84 years and 9944 (39.8%) aged 85+ years.

Of the cohort, 23,811(95.2%) and 5539 (22.2%) cases had at least one dementia diagnosis documented in inpatient hospital (including general and psychiatric hospitals) and mental health outpatient records respectively, with 4344 (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 3276 (13.1%) and 21,739 (86.9%) cases respectively. A total of 1195(4.8%) cases had no dementia documented in inpatient hospital records. For the 2072 (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 7933(43.9%) death records and 9187 (50.8%) had dementia documented in at least two data sets.

Diabetes was more commonly recorded in the younger age groups of the dementia cohort with 23.2% of 40-64 year olds, 24.1% of 65-74 year olds, 18.6% of 75-84 year olds and 13.1% of those 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

adjusting 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 non-diabetic cases. The pattern with AD and non-specific 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 (SD), age 80.6 (8.1) vs 82.8 (7.6) years, $P < 0.0001$) and the age at death occurred an average 2.6 (95% CI 2.3, 2.9) years younger (82.4 (8.0) vs 85.0 (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 excluding 2909 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 those without diabetes and this effect was stronger at a younger age.

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 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 (HR) 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 (HR 1.5, (95%CI 1.1, 1.9) and 1.4 (95%CI 1.2, 1.6), respectively). Median survival times from 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 to older dementia cases.

DISCUSSION

In the present study we used administrative health datasets to explore the impact of pre-existing diabetes on a surrogate measure of age at dementia onset and subsequent survival in the Western Australian population. Over 17% of dementia cases had pre-existing 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 pre-existing diabetes developed an average 2.2 years earlier than in non-diabetic 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 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 epidemiological study to include every identified dementia case from a large population database. Most previous large population studies have studied elderly populations only, hence missed any impact of diabetes on early-onset dementia [1]. The few studies that assessed mid-life diabetes 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 AD by 2 years would reduce the projected quadrupling of AD prevalence by 2050 by over 20% [40]. Diabetes was previously estimated to account for 7-13% of the population attributable risk for incident dementia [41] but this was largely based on studies of older populations. Given that the incidence and prevalence of type 2 diabetes are increasing worldwide because of population ageing 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.

The population-based nature of this study meant that the diagnosis of dementia sub-types were documented by a range of medical staff of varying seniority and from various health care settings and specialties. Whilst their diagnostic validity cannot be determined, we did find differences by dementia sub-types consistent with the known literature [43]. The effect was most marked in those who were diagnosed with vascular dementia which developed three years earlier whilst AD developed a little over one 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 AD and non-specific 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 AD-related pathological changes and accelerate the clinical expression of AD [46]. Alternatively, it has been suggested that several of the metabolic abnormalities in type 2 diabetes, including insulin resistance, hyperglycaemia and chronic inflammation, promote AD-related changes including beta-amyloid accumulation [47, 48]. Type 2 diabetes is a chronic progressive condition where escalating medical therapies including exogenous insulin and/or insulin secretogogues are required to control the worsening metabolic deficits [49]. Cerebral beta-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, i.e. 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 mainly confined to those diagnosed with diabetes before age 65 years who subsequently survive with diabetes for around 15 years. Whilst the present study cannot definitively distinguish whether increased mortality rates reflect faster rates of cognitive decline or is 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, the 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 pre-morbid diabetes. The main limitations of the study are the use of health administrative datasets to obtain proxy measures of diabetes and dementia onset and the reliance on routine clinical diagnoses for diabetes and dementia sub-types. While 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 AD diagnoses in hospital registers were correct [50]. An Australian audit reported that the sensitivity, positive predictive value and kappa 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 one hospital admission in the five-year period before 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 non-diabetic cases observed in this study may be an underestimate of the true population estimate. Under-diagnosis 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. While 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.

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.	**%**	**Age(SD) Years**	**No.**	**%**	**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
Non-specific	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								
0	8974	43.4	81.5 (8.6)	1,274	29.5	79.6 (8.4)	1.9	1.4-2.4
1-2	7356	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

SD, standard deviation. CI, confidence interval. [a]Comorbidity, Charlson's weighted comorbidity index score. [b]Outpatient, public mental health outpatient clinics; Inpatient, private and public hospitals.

Table 2: Multivariate Linear Model Estimating Mean Differences in Age at Time of Index Dementia Record (n= 25006) and Age at Death (n=18083) by Clinical and Demographic Variables, Western Australia, 1990-2005.

	Age at Index Dementia Record[a]			Age at Death[a]		
Variable	**Δ mean**	**95% CI**	***P*-value**	**Δ mean**	**95% CI**	***P*-value**
Alzheimer's Disease						
No diabetes history	0 (referent)			0		
Diabetes 0-5 years	-1.1	-1.6, -0.6	<0.001	-0.8	-1.4, -0.2	0.006
Diabetes 6-10 years	-1.2	-2.0, -0.4	0.006	-1.1	-2.1, -0.2	0.022
Diabetes 11-15 years	-1.4	-2.5, -0.3	0.014	-2.1	-3.3, -0.9	0.001
Diabetes > 15 years	-2.4	-3.7, -1.1	<0.001	-3.8	-5.2, -2.3	<0.001
Vascular Dementia						
No diabetes history	0			0		
Diabetes 0-5 years	-2.6	-3.6, -1.7	<0.001	-2.5	-3.5, -1.4	<0.001
Diabetes 6-10 years	-2.3	-3.7, -1.0	<0.001	-2.1	-3.6, -0.7	0.004
Diabetes 11-15 years	-3.3	-5.2, -1.4	<0.001	-2.8	-4.9, -0.7	0.010
Diabetes > 15 years	-5.7	-8.1, -3.4	<0.001	-6.9	-9.5, -4.4	<0.001
Non-specific Dementia						
No diabetes history	0			0		
Diabetes 0-5 years	-2.7	-3.1,-2.2	<0.001	-2.6	-3.1, -2.1	<0.001
Diabetes 6-10 years	-2.2	-2.0, -0.3	<0.001	-2.4	-3.2, -1.7	<0.001
Diabetes 11-15 years	-2.8	-3.7, -1.9	<0.001	-3.1	-4.1, -2.0	<0.001
Diabetes > 15 years	-3.4	-4.4, -2.4	<0.001	-3.8	-4.9, -2.6	<0.001
Sex						
Male	0			0		
Female	2.6	2.4, 2.8	<0.001	3.1	2.9, 3.3	<0.001
Index Record						
Inpatient	0			0		
Outpatient	-2.8	-3.1, -2.5	<0.001	-1.6	-1.9, -1.3	<0.001
Index Year						
1990-94	0			0		
1995-99	0.5	0.2, 0.7	<0.001	0.6	0.4, 0.9	<0.001
2000-05	1.5	1.2, 1.7	<0.001	1.1	0.8, 1.3	<0.001
Comorbidity						

		Age at Index Dementia Record[a]			Age at Death[a]	
	0	0		0		
	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

Abbreviations: Δ mean, mean difference; CI, confidence interval; Comorbidity , Charlson's weighted comorbidity index score.

[a] Regression model adjusted for diabetes duration, sex, dementia type, number of hospitalizations in the five year period prior to index dementia record, the source of the index record, comorbidity at year of index record and year of index record. Duration of diabetes and dementia type was entered in the model as an interaction term.

Table 3: Median, 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 at Index Dementia Record	Diabetes Duration	N	Survival Time (years)		
			25%	Median (50%)	75%
40-64 years	No diabetes	603	2.5	5.7	11.5
	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	2219	1.6	3.5	6.4
	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	8025	1.0	2.5	4.8
	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
	No diabetes	7473	0.7	1.8	3.4
	0-5 years	602	0.6	1.6	3.1
85+ years	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]		22097	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.

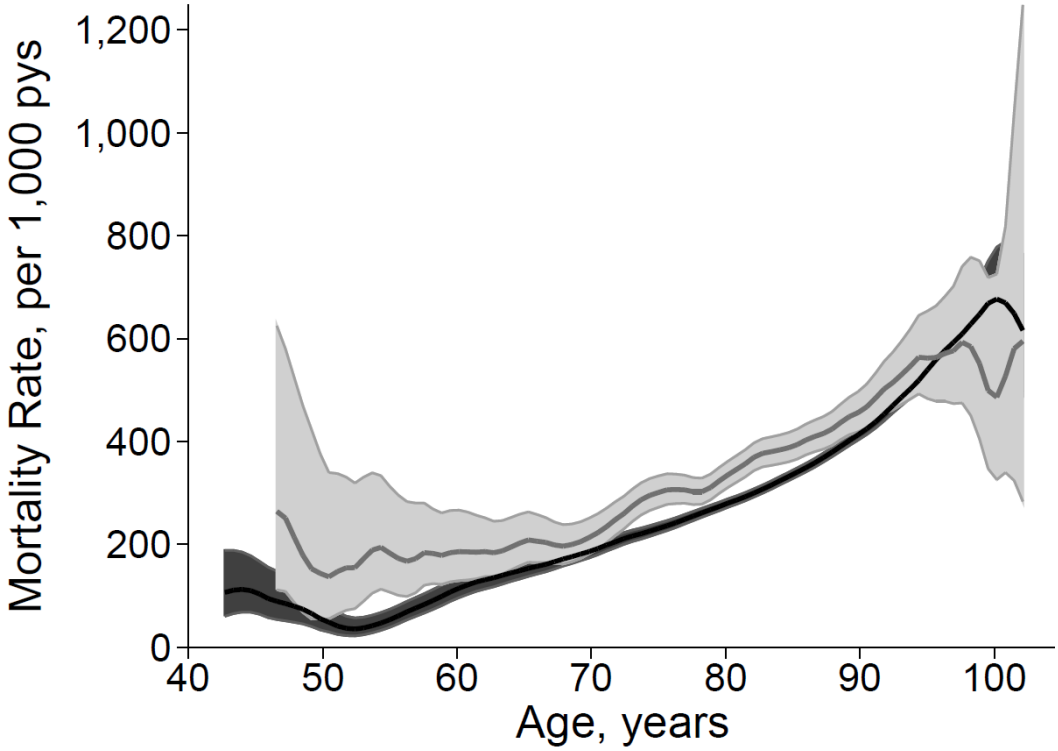

Figure 1 Legend: Age-specific mortality rate of the dementia cohort for those with a history of diabetes before index dementia record (grey line) and those without a history of diabetes (black line). pys, person years. 95% confidence intervals are indicated by shading. Dementia cohort includes 22097 Western Australians with index dementia records between 1990 and 2005 and alive for at least 30 days after index record.

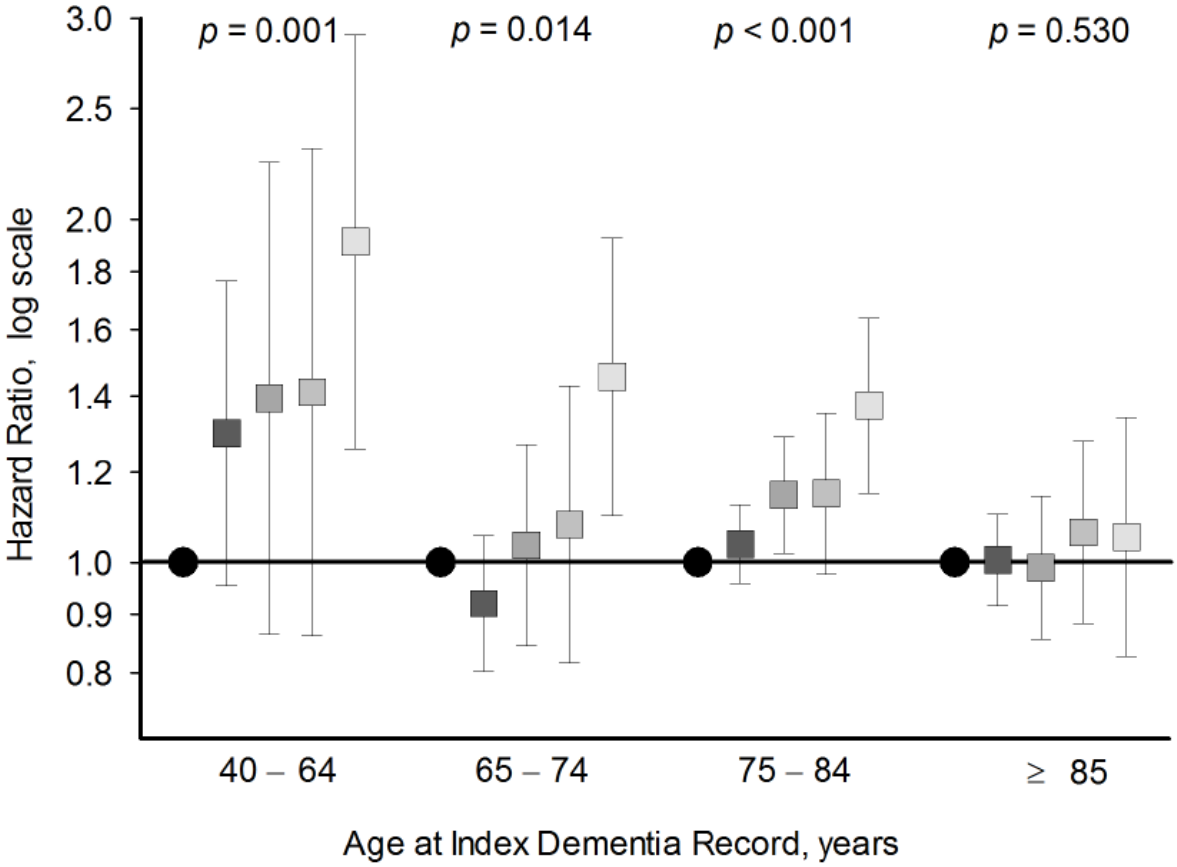

Figure 2 Legend: Relative rate of death (hazard ratio) for dementia cases with an increasing history of diabetes duration from 0-5 years (darkest square), 6-10 years (dark square), 11-15 years (pale square) and more than 15 years (palest square) compared to dementia cases with no history of diabetes (●) and similar age at index dementia record estimated from a proportional hazards model. Model was also adjusted for type of dementia, comorbidity, sex and source of record. 95% confidence intervals indicated by error bars and p-value for trend test of increasing history of diabetes duration. (n=22,097 Western Australians with index dementia record between 1990 and 2005).

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