Acta Diabetologica (2019) 56:767–776
https://doi.org/10.1007/s00592-019-01322-9

ORIGINAL ARTICLE

Dementia complicating type 2 diabetes and the influence of premature mortality: the Fremantle Diabetes Study

David G. Bruce[1] · **Timothy M. E. Davis**[1] · **Wendy A. Davis**[1]

Received: 5 June 2018 / Accepted: 6 March 2019 / Published online: 3 April 2019

Abstract

Aims To investigate risk factors for, and the influence of premature mortality on, dementia complicating type 2 diabetes.

Methods Participants with type 2 diabetes in the community-based observational Fremantle Diabetes Study Phase 1 ($n = 1291$, mean age 64.0 years) were followed from 1993 to 1996 to end-June 2012. Incident dementia was identified from validated health databases. Dementia risk was assessed using Cox proportional hazards modelling supplemented by competing risk regression modelling in the total cohort and sub-groups defined by age of diabetes onset as mid-life (< 65 years) or late-life (≥ 65 years).

Results During mean ± SD follow-up of 12.7 ± 5.9 years, 717 participants (55.5%) died and 180 (13.9%) developed dementia. Overall, few risk factors predicted incident dementia and most predicted time to death. In mid-life diabetes, incident dementia was predicted by diabetes duration, cerebrovascular disease, schizophrenia, antipsychotic medication and the APOE ε4 allele. In late-life diabetes, risk factors were peripheral neuropathy, lack of exercise, lower fasting serum glucose, no antihypertensive therapy and the APOE ε4 allele. Competing risk analysis showed age to be a positive predictor compared with the inverse association in Cox models that suggested survivor bias in an older community-based cohort.

Conclusions Dementia in type 2 diabetes is multifactorial. An association with diabetes duration, independent of most possible confounders, suggests that one or more unmeasured processes specific to diabetes may be implicated in the pathogenesis. The risk factors for dementia were also associated with an increased risk of death. This suggests that recently reported improvements in mortality in type 2 diabetes may be accompanied by reductions in dementia incidence.

Keywords Type 2 diabetes · Dementia · Longitudinal study · Cohort study

Introduction

There is considerable evidence that type 2 diabetes increases the risk of dementia [1], an important association given the high global prevalence of type 2 diabetes and the potential for dementia prevention. Despite a substantial number of studies aimed at elucidating the underlying mechanisms, causal pathways remain unknown [1, 2] although both neurodegenerative and vascular pathways may be involved [1]. There are many potential dementia risk factors [1]. These include those shared with the general population such as the presence of APOE ε4 alleles [3] and depression [4], risk factors for diabetes itself, risk factors for cardiovascular disease associated with type 2 diabetes, and risk factors specific to diabetes such as hyperglycaemia and vascular complications [2]. There are also common co-morbidities including atrial fibrillation [5], cardiac failure [6], chronic lung disease [7] and schizophrenia [8] that have been associated with dementia.

In addition to this complexity, many variables in type 2 diabetes are inter-related leading to potential association by confounding. For example, there are strong associations between the duration of diabetes, levels of glycaemia, the need for intensified therapy and the risk of vascular complications [9]. In addition, long duration insulin therapy in type 2 diabetes increases the risk of hypoglycaemia [10]. Type

Managed by Massimo Federici.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00592-019-01322-9) contains supplementary material, which is available to authorized users.

✉ David G. Bruce
david.bruce@uwa.edu.au

[1] Medical School, Fremantle Hospital, University of Western Australia, P.O. Box 480, Fremantle, WA 6959, Australia

2 diabetes with onset in mid-life confers a greater risk of dementia than late-onset diabetes [11, 12] and the risk factor profiles differ by age at onset [12, 13]. Premature mortality is common in type 2 diabetes [14] and failure to account for competing risks from premature mortality can alter risk assessments for age-related conditions such as dementia [15, 16].

As a result of all these considerations, dementia studies in type 2 diabetes ideally need to include comprehensive clinical assessments and a long duration of follow-up. Phase I of the Fremantle Diabetes Study (FDS1) was a community-based, observational study that commenced in 1993 and comprised a comprehensive baseline assessment and follow-up for up to 20 years. The aim of the present study was to utilise the detailed longitudinal data available in FDS1 to investigate dementia risk factors in type 2 diabetes. We specifically explored the effect of age at onset of type 2 diabetes (whether this occurred in mid-life or late-life) on dementia risk as part of a full range of potential risk factors, and considered the possibility of competing risk given the high premature mortality rate in this cohort.

Materials and methods

Location and participants

The FDS1 cohort was recruited from a post code-defined urban community of 120,097 people in the state of Western Australia (WA). Descriptions of recruitment, sample characteristics including classification of diabetes type and details of non-recruited patients have been published [15, 17]. Of 2258 residents with diabetes identified between 1993 and 1996, 1426 (63%) were recruited to the FDS1 and 1296 were diagnosed with type 2 diabetes. Eligible residents who declined participation were a mean 1.4 years older than participants, but their sex distribution, proportions with type 2 diabetes and use of diabetes therapies were similar. Annual assessments continued until 2001 and collection of morbidity and mortality data continued through health service linkages using the WA Data Linkage System (WADLS) [18]. The FDS1 protocol was approved by the Human Research Ethics Committee at Fremantle Hospital and all subjects gave informed consent before participation. Data linkage was approved by the WA Department of Health Human Research Ethics Committee.

Clinical assessment

The FDS1 clinical assessment included a comprehensive questionnaire, a physical examination, 12-lead electrocardiograph (ECG) and biochemical testing of fasting blood and urine samples [17]. Details of medical conditions, medications, demographic, socioeconomic and lifestyle data were recorded. Biochemical testing used standard automated methods in a single laboratory. Baseline complications of diabetes were identified using standard definitions [17]. Neuropathy was defined using the clinical portion of the Michigan Neuropathy Screening Instrument. Albuminuria was assessed from early morning urine albumin:creatinine ratios and the estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine [19]. Retinopathy was detected using direct/indirect ophthalmoscopy and defined as one microaneurysm in either eye or worse and/or evidence of previous laser treatment and/or detailed ophthalmological data in patients assessed by ophthalmologists. Patients were classified as having ischaemic heart disease if there was a history of myocardial infarction, angina, coronary artery bypass grafting, or angioplasty, and as having cerebrovascular disease if there was a history of stroke and/or transient ischaemic attack. Peripheral arterial disease was defined as an ankle brachial index ≤ 0.90 or the presence of a diabetes-related amputation [20]. Atrial fibrillation was diagnosed from ECGs. Depressive symptomatology was assessed using data obtained from a quality of life questionnaire as previously described [21]. The age of diabetes onset was estimated from the reported dates of symptom onset or diagnosis, and we distinguished mid-life (onset age < 65 years) from late-life (onset age ≥ 65 years) diabetes [12].

In WA, all hospital admissions, contacts with mental health services and deaths are captured by the WADLS [18]. FDS1 was linked with the health datasets within the WADLS to confirm prevalent clinical data and to detect incident dementia and deaths. The Mental Health Information System commenced as a register of psychiatric inpatients in 1966, expanded in the 1970s to include hospitals and community mental health services and since 1980 has covered all outpatient, community-based and hospital-based mental health services. The Hospital Morbidity Data System, established in 1970, collects comprehensive data on all public and private hospital admissions in the state. We extracted a history of schizophrenia from the Mental Health and Hospital Morbidity Data databases given associations with both diabetes and dementia [8] and extracted a history of heart failure from 1982 from the Hospital Morbidity Data System.

Dementia case ascertainment

We have previously published evidence demonstrating that using WADLS improves dementia case identification [8, 22]. The WADLS was used to determine prevalent dementia status at study entry from 1982 and incident dementia to end-June 2012 from International Classification of Disease (ICD) coding as previously described [15]. Dementia cases included all patients diagnosed and registered in any of the

registers and was defined using the following ICD-9-CM and ICD-10-AM codes: Alzheimer's disease (331.0, F00, G30), vascular dementia (290.4, F01), unspecified dementia (290.0, 290.1, 290.2, 290.3, 294.2, 331.2, F03, G31.1), and other dementia (046.1, 291.2, 292.82, 294.1, 331.1, 331.11, 331.19, 331.82, 797, A81.0, F02, F05.1, F10.27, F10.97, G31.0, G31.10, G31.09. G31.83). A diagnostic dementia hierarchy allocated dementia type to the cases with more than one dementia code in their records [8]. If the code for unspecified dementia was reported in addition to a specific diagnosis, the latter was used. Dementia sub-diagnoses were documented by a wide range of treating physicians from specialist and general settings. Because the diagnostic accuracy may be low, we explored associations with all-cause dementia as the main end-point and investigated the three common subtypes, Alzheimer's disease, vascular dementia and unspecified dementia, for comparison purposes.

Data handling and statistical analysis

The computer packages IBM SPSS Statistics 22 (Armonk, NY: IBM Corp.) and STATA IC 13 (College Station, TX: StataCorp LP) were used for statistical analysis. Data are presented as proportions, mean ± SD, geometric mean (SD range), or, in the case of variables which did not conform to a normal or log-normal distribution, median and interquartile range [IQR]. For independent samples, two-way comparisons for proportions were by Fisher's exact test, for normally distributed variables by Student's *t* test, and for non-normally distributed variables by Mann–Whitney *U* test. Participants were followed from study entry to first record of any dementia, death or end-June 2012, whichever came first.

In aetiological research, regression models for cause-specific hazard functions are recommended because they directly measure the covariate effect on event rates among subjects at risk [16]. Since the relationship between the cause-specific hazard ratio (csHR) for incident dementia is a function of the hazard ratio (HR) for the competing event of death, the baseline cause-specific hazard for both dementia and death was assessed [23]. Cox proportional hazards models were used to generate csHRs for all-cause dementia and dementia subtypes and the HR for all-cause mortality. Although performing regression on the cumulative incidence function by assessing the subdistribution hazard is recommended for prognostic rather than aetiological research, presenting both csHRs and subdistribution hazard ratios (sdHRs) has been recommended as this provides a more complete understanding of competing risks data [24]. Fine–Gray competing risk models were used to generate sdHRs for all-cause dementia and dementia subtypes. Due to the presence of covariates strongly associated with age, age was used as the time scale with left truncation of age at study entry [25]. Plausible variables with $P \leq 0.20$ in bivariate statistics were considered for entry into the multivariate models. Unadjusted cause-specific cumulative incidence functions by age at diabetes diagnosis were derived and the differences between the functions were tested by the log-rank test. A two-tailed significance level of $P < 0.05$ was used throughout.

Results

Baseline characteristics, incident dementia and mortality

The study included 1291 FDS1 participants with type 2 diabetes after 5 (0.4%) with prevalent dementia at study entry were excluded. They were aged 64.0 ± 11.3 years, 48.6% were male and the median duration of diabetes was 4.0 [IQR 1.0–9.0] years. During 16,363 patient-years of follow-up to end-June 2012 (12.7 ± 5.9 years), 717 (55.5%) died and 180 (13.9%) were recorded with incident dementia before or at the time of death. The index dementia record was sourced from the Hospital Morbidity Data System in 76.5%, the Mental Health Information System in 14.0% and from death records in 9.5%, respectively. Unspecified dementia, Alzheimer's disease and vascular dementia were the commonest designated sub-diagnoses in 86 (47.8%), 57 (31.7%) and 20 (11.1%) cases, respectively. Of the 717 deaths, most (47.4%) were due to cardiovascular causes (cardiac, cerebrovascular, peripheral arterial diseases or sudden death), 4.6% were due to renal disease, 0.1% to hyperglycaemia, 19.0% to cancer, 26.1% to other known causes, 0.8% accidental, and 2.0% to unknown causes. After exclusion of two participants with no age of diabetes diagnosis recorded, mid-life diabetes occurred in 931 (72.8%) participants and late-life diabetes in 358 (27.2%) participants, respectively. During follow-up, 423 (45.4%) of those with mid-life diabetes died and 91 (9.8%) developed incident dementia. For late-life diabetes, the respective figures for deaths and dementia were 292 (81.6%) and 88 (24.6%).

Baseline predictors of dementia and death

The results of bivariate comparisons of baseline variables for incident dementia and all-cause death are summarised in the Online Resource Supplementary Table 1, the equivalent results by diabetes onset in the Online Resource Supplementary Table 2, and the results for death in the Online Resource Supplementary Tables 3 and 4. Compared to the participants without dementia, those with incident dementia were older at the time of recruitment and at diabetes onset, had longer diabetes duration, less education, lower body mass index, higher systolic blood pressure and were more likely

to have renal dysfunction, microalbuminuria, peripheral neuropathy and schizophrenia (Online Resource Supplementary Table 1). In mid-life diabetes, incident dementia was associated with the same variables as above plus there were differences in APOE genotypes and they were more likely to have cerebrovascular disease, retinopathy, to be treated with insulin and to have higher HbA_{1c} levels. In late-life diabetes, incident dementia was associated with older age and longer diabetes duration only (Online Resource Supplementary Table 2). Compared to those who survived, those who died were older at recruitment and at diabetes onset, were more likely to be male and to be an ex- or current smoker, had longer duration diabetes, were more likely to receive insulin therapy and had higher HbA_{1c} levels, a lower body mass index, higher blood pressures and more had atrial fibrillation, heart failure, ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, nephropathy, peripheral neuropathy, retinopathy and chronic lung disease (Online Resource Supplementary Table 3). The same associations were seen in those with mid-life diabetes, whereas those with late-life diabetes had mostly similar associations with death except that there was no sex difference and there were no differences in body mass index, treatment with insulin, cerebrovascular disease, retinopathy and chronic lung disease (Online Resource Supplementary Table 4). All plausible variables with $P \leq 0.20$ in bivariate statistics were considered for entry into multivariate models.

Table 1 summarises the results of modelling baseline associations with incident dementia and all-cause death in the combined cohort (csHRs for dementia, HRs for deaths from Cox models). The results from competing risk modelling that takes account of mortality (sdHRs from Fine–Gray model) are also presented. Age (negative association), diabetes duration, APOE ε4 alleles, physical exercise (negative association) and schizophrenia were associated with dementia in the Cox model. Two of these variables, diabetes duration and APOE ε4 alleles, also increased the risk of death in addition to a substantial number of diabetes-associated risk factors, complications and co-morbidities. Adjusting for the competing risk of death changed the inverse association between age and incident dementia to a positive one, and brought in marital status instead of diabetes duration and exercise history (which were also independent predictors of death). Schizophrenia and the presence of APOE ε4 alleles were significant variables in both Cox and Fine–Gray models.

The unadjusted cumulative incidence of all-cause dementia in late-life diabetes was greater than that in mid-life ($P < 0.001$; see Fig. 1). Table 2 summarises the modelling results in mid-life and late-life diabetes considered separately. In the Cox model of mid-life diabetes, dementia was predicted by age (inversely), diabetes duration, cerebrovascular disease, schizophrenia, antipsychotic medication use, while APOE ε4 alleles were deleterious and the APOE 2,3 genotype was protective. Age (inversely) as well as diabetes duration and cerebrovascular disease were risk factors shared with those for mortality. Adjusting for the competing risk of death changed the inverse association between age and incident dementia to a positive one in this age-group, while diabetes duration and cerebrovascular disease did not independently predict dementia. Schizophrenia, antipsychotic medication use, and the opposite effects of APOE ε4 alleles and the APOE 2,3 genotype, were also significant variables in the Fine–Gray model albeit with attenuated hazard ratios compared with those in the Cox model. In late-life diabetes, dementia was predicted by APOE ε4 alleles and peripheral neuropathy in the Cox model, while age, recent physical exercise, a higher fasting serum glucose and antihypertensive treatment were protective. Adjusting for the competing risk of death changed the inverse association between age and incident dementia to a positive one and there were no other predictors of dementia in the Fine–Gray model (see Table 2).

Dementia subtypes

The models for dementia subtypes were assessed for the entire cohort only (see Table 3). Alzheimer's disease was associated with APOE ε4 alleles and negatively associated with an eGFR in the 60–89 ml/min/1.73 m^2 range. Vascular dementia was associated with male sex, insulin treatment and schizophrenia. Unspecified dementia was associated with the APOE 2,4 genotype, lack of exercise, peripheral arterial disease and schizophrenia, whilst being married was protective.

Discussion

We investigated risk factors for incident dementia in a well-characterised, predominantly middle-aged, community-based cohort with type 2 diabetes. Mid-life and late-life diabetes were explored separately because the association with dementia is strongest in mid-life diabetes [11, 12], risk factor profiles differ by age [12, 13] and the cumulative incidence is also age-specific (see Fig. 1). Several broad conclusions can be drawn. First, only a few of the many variables that were assessed predicted dementia and even fewer were specific to diabetes. Second, diabetes duration was the only diabetes-specific dementia risk factor identified in mid-life diabetes. Third, most dementia risk factors also increased the risk of dying, a finding likely to have important implications for studies assessing the incidence of dementia in populations in which the competing risk of death is high.

In mid-life diabetes, incident dementia was predicted independently by the duration of diabetes, cerebrovascular

Table 1 Models of independent predictors of all-cause dementia and death in type 2 diabetes with age as the time scale

Baseline variable	Cox model, csHR[a] (95% CI)	*P* value	Fine–Gray model, sdHR[b] (95% CI)	*P* value
Dementia[e]				
Age (10 year increments)	0.45 (0.35–0.59)	< 0.001	2.03 (1.65–2.48)	< 0.001
Married/de facto relationship			0.73 (0.53–0.998)	0.049
Any exercise in past 2 weeks	0.62 (0.44–0.86)	0.005		
Diabetes duration (1 year increment)	1.02 (1.002–1.04)	0.032		
Schizophrenia	33.98 (10.46–110.42)	< 0.001	39.05 (12.49–122.1)	< 0.001
APOE 2,4 genotype	3.77 (1.64–8.65)	0.002	2.55 (1.16–5.64)	0.020
APOE 3,4 genotype	1.58 (1.07–2.32)	0.021	1.52 (1.05–2.22)	0.028
APOE 4,4 genotype	4.99 (2.16–11.55)	< 0.001	4.03 (1.37–11.91)	0.012
Death[f]				
Age (10 year increments)	0.32 (0.27–0.37)	< 0.001		
Male	1.56 (1.31–1.85)	< 0.001		
Aboriginal	2.32 (1.19–4.51)	0.013		
Current smoker	1.62 (1.28–2.05)	< 0.001		
Any exercise in past 2 weeks	0.82 (0.68–0.99)	0.042		
Diabetes duration (1 year increment)	1.02 (1.01–1.04)	< 0.001		
Fasting serum glucose (mmol/L)	0.96 (0.93–0.998)	0.039		
HbA_{1c} (increase of 1% or 11 mmol/mol)	1.11 (1.04–1.19)	0.001		
Ln(urinary ACR[c] (mg/mmol))[d]	1.18 (1.12–1.26)	< 0.001		
Atrial fibrillation	1.53 (1.10–2.13)	0.012		
Heart failure	1.80 (1.36–2.38)	< 0.001		
Coronary heart disease	1.24 (1.03–1.50)	0.023		
Peripheral arterial disease	1.56 (1.30–1.86)	< 0.001		
Peripheral sensory neuropathy	1.47 (1.23–1.76)	< 0.001		
Chronic pulmonary disease	1.44 (1.07–1.93)	0.016		
Depressive symptoms	1.26 (1.05–1.52)	0.013		
APOE 3,4 genotype	1.25 (1.01–1.56)	0.045		
APOE 4,4 genotype	2.71 (1.37–5.34)	0.004		

[a]Cause-specific hazard ratio

[b]Sub-distribution hazard ratio

[c]Albumin:creatinine ratio

[d]A 2.72-fold increase in urinary ACR corresponds to an increase of 1 in ln(ACR)

[e]Variables considered for entry into the dementia model: age, ethnic background, educational attainment, marital status, smoking status, exercise, diabetes duration, BMI, abdominal obesity, systolic and diastolic blood pressures, HDL-cholesterol, serum triglycerides, urinary ACR, eGFR, atrial fibrillation, heart failure, cerebrovascular disease, peripheral arterial disease, peripheral sensory neuropathy, Charlson's Comorbidity Index, chronic pulmonary disease, schizophrenia, APOE genotype

[f]Variables considered for entry into the death model: age, sex, ethnic background, educational attainment, marital status, smoking status, exercise, diabetes duration, diabetes treatment, fasting serum glucose, HbA_{1c}, history of hypoglycaemia, BMI, systolic and diastolic blood pressures, antihypertensive medication, lipid-modifying medication, aspirin use, urinary ACR, eGFR, atrial fibrillation, heart failure, coronary heart disease, cerebrovascular disease, peripheral arterial disease, peripheral sensory neuropathy, retinopathy, chronic pulmonary disease, depressive symptoms, antidepressant medication, APOE genotype

disease, APOE alleles, schizophrenia and the use of antipsychotic medications. The association with diabetes duration was independent of glycaemic control, blood glucose-lowering therapy and chronic complications, with each year of diabetes increasing the risk of dementia by approximately 4%. Diabetes duration may be acting as a surrogate for one or more unmeasured processes and previously suggested candidates include changes in neuronal insulin signalling, glycation of proteins, disruption of the blood brain barrier and/or neuroinflammation [26, 27]. Alternatively, the association between diabetes duration and dementia could reflect the single baseline assessment of glycaemic control and vascular complications in the present study, in that we were unable to accurately assess lifetime glycaemic exposure

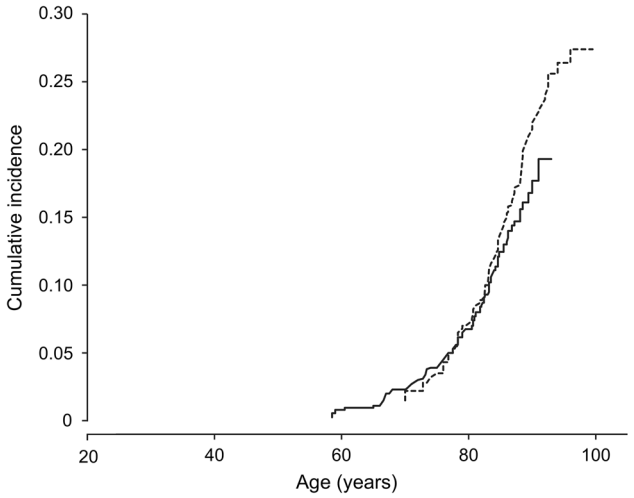

Fig. 1 Unadjusted cumulative incidence functions of all-cause dementia in mid-life (age at diagnosis < 65 years; continuous line) and late-life (age at diagnosis ≥ 65 years; dashed line) type 2 diabetes. The cumulative incidence functions are significantly different ($P < 0.001$)

and incident complications. The other mid-life dementia risk factors are likely to act via classic vascular and/or neurodegenerative pathways. The impact of APOE ε4 alleles on dementia risk was substantial, dose-dependent and consistent with previous studies in type 2 diabetes [3]. The finding of a protective effect from the APOE ε2/ε3 genotype has been reported in the general population [28] but may be novel in the context of type 2 diabetes. A history of cerebrovascular disease, schizophrenia and antipsychotic medications are each associated with recurrent stroke [8, 29, 30], increasing the risk of vascular dementia.

The presence of APOE ε4 alleles also independently increased dementia risk in late-life diabetes, but the risk profile was otherwise different. There were negative associations with exercise and antihypertensive therapy, consistent with some previous studies [1, 2], while neuropathy and fasting serum glucose were the only risk factors specific to diabetes. These latter associations have several possible explanations. Peripheral neuropathy is known to increase the risk of stroke in type 2 diabetes [31] or it could be acting as a marker for cerebral microvascular disease. Neuropathy was prevalent in this group despite an estimated duration of diabetes that was quite short (less than 4 years), suggesting that diabetes may have remained undiagnosed for many years. In a previous FDS1 study, both neuropathy and a lower fasting serum glucose increased the risk of severe hypoglycaemia [10] consistent with hypoglycaemia contributing to dementia in these participants [2].

Premature mortality, which is common in type 2 diabetes [14], has substantial implications if at-risk individuals do not survive sufficiently long to develop dementia, and most identified risk factors also increased the risk of dying in the present study. This could explain why some dementia risk factors found in general population samples were not predictive in diabetes. Atrial fibrillation, for example, has a markedly worse prognosis in type 2 diabetes [32]. There are also implications for future projections of dementia prevalence. The recent demonstration of improvements in rates of chronic complications and longevity in type 2 diabetes [33] could lead to more people surviving into old age and developing dementia. Alternatively the sharing of risk factors suggests that a parallel reduction in dementia risk could accompany improved survival, a phenomenon possibly occurring in some Western populations [34].

The competing risk models were performed to supplement the proportional hazards modelling, the latter being the preferred method for risk factor studies. However considering the results together can help with the interpretation of results and, in the present study, provides an explanation for the apparently contradictory impact of age [24]. The csHRs from Cox models implied that older age was paradoxically protective against dementia and dying whereas older age increased the dementia risk in the competing risk models. A likely explanation for such divergent results is related to selection bias at the time of recruitment to the study. Selection bias, a known limitation of observational studies, can reverse the direction of associations found in regression models [24]. For example, older participants who were in their seventies at the time of recruitment were already healthy survivors compared with younger recruits, many of whom might never reach the age when dementia incidence increases because of death due to cardiovascular and other diseases. The majority of existing studies of type 2 diabetes and dementia, especially those limited to older participants, are likely to be subject to similar sources of bias.

We emphasise caution when considering the results from the dementia subtypes given the source of diagnoses. Nevertheless, several findings are noteworthy. As expected, Alzheimer's disease was associated with the presence of APOE ε4 alleles but was also negatively associated with an eGFR within the low-normal range of 60–89 ml/min/1.73 m^2. This may be consistent with evidence linking renal disease and Alzheimer's disease [35] but also suggests that there may be a U-shaped relationship with eGFR in type 2 diabetes, similar to that recently reported between eGFR and mortality [36]. Vascular dementia was associated with male sex, insulin therapy and schizophrenia, consistent with an adverse cardiovascular risk. Unspecified dementia was associated with peripheral arterial disease, schizophrenia and the APOE ε2/ε4 genotype suggesting that both vascular and neurodegenerative pathways were involved.

The main limitation of the present study is the use of health administrative data for dementia case detection although the accuracy has been shown to be high in Danish

Table 2 Models of independent baseline predictors of dementia and deaths in type 2 diabetes stratified by age at diabetes diagnosis (< 65 and ≥ 65 years) with age as the time scale

Baseline variable	Cox model csHR[a] (95% CI)	*P* value	Fine–Gray model sdHR[b] (95% CI)	*P* value
Age at diabetes diagnosis < 65 years				
Dementia[e]				
Age (10 year increments)	0.33 (0.20–0.54)	< 0.001	2.00 (1.50–2.66)	< 0.001
Diabetes duration (1 year increment)	1.04 (1.01–1.08)	0.015		
Cerebrovascular disease	2.27 (1.18–4.37)	0.014		
Schizophrenia	19.52 (5.39–70.64)	< 0.001	7.95 (1.64–34.5)	0.010
Antipsychotic medications	4.59 (1.70-12.42)	0.003	3.20 (1.10–9.28)	0.033
APOE 2,3 genotype	0.19 (0.06–0.62)	0.006	0.26 (0.09–0.81)	0.020
APOE 2,4 genotype	3.06 (1.10–8.47)	0.032		
APOE 4,4 genotype	8.05 (2.72–23.83)	< 0.001	5.33 (1.31–21.8)	0.020
Deaths[f]				
Age (10 year increments)	0.32 (0.25–0.40)	< 0.001		
Male	1.71 (1.37–2.15)	< 0.001		
Aboriginal	3.68 (1.84–7.38)	< 0.001		
Current smoker	1.72 (1.30–2.27)	< 0.001		
Any exercise in past 2 weeks	0.79 (0.62–0.999)	0.049		
Diabetes duration (1 year increment)	1.03 (1.01–1.04)	0.002		
HbA_{1c} (increase of 1% or 11 mmol/mol)	1.11 (1.04–1.18)	0.001		
Ln(urinary ACR[c] (mg/mmol))[d]	1.17 (1.09–1.26)	< 0.001		
Atrial fibrillation	2.32 (1.41–3.83)	0.001		
Heart failure	1.89 (1.31–2.72)	< 0.001		
Coronary heart disease	1.39 (1.10–1.77)	0.006		
Cerebrovascular disease	1.64 (1.19–2.28)	0.003		
Peripheral arterial disease	1.39 (1.10–1.76)	0.006		
Peripheral sensory neuropathy	1.52 (1.21–1.90)	< 0.001		
Chronic pulmonary disease	1.52 (1.05–2.21)	0.029		
Age at diabetes diagnosis ≥ 65 years				
Dementia[g]				
Age (10 year increments)	0.33 (0.20–0.55)	< 0.001	2.21 (1.51–3.23)	< 0.001
Any exercise in past 2 weeks	0.37 (0.23–0.60)	< 0.001		
Fasting glucose (1 mmol/L increase)	0.86 (0.78–0.95)	0.003		
On antihypertensive medication	0.63 (0.40–0.99)	0.045		
Peripheral sensory neuropathy	2.26 (1.39–3.70)	0.001		
APOE 2,4 genotype	6.85 (1.57–29.81)	0.023		
APOE 4,4 genotype	7.03 (1.46–33.80)	0.015		
Deaths[h]				
Age (10 year increments)	0.33 (0.24–0.44)	< 0.001		
Male	1.50 (1.17–1.94)	0.002		
Asian	0.28 (0.09–0.89)	0.031		
Current smoker	1.87 (1.26–2.79)	0.002		
Ln(urinary ACR[a] (mg/mmol))[b]	1.14 (1.04–1.24)	0.006		
Heart failure	1.89 (1.33–2.68)	< 0.001		
Peripheral arterial disease	1.72 (1.32–2.22)	< 0.001		
Peripheral sensory neuropathy	1.46 (1.13–1.90)	0.004		
Depressive symptoms	1.72 (1.31–2.26)	< 0.001		
On antidepressants	1.79 (1.17–2.76)	0.008		

[a]Cause-specific hazard ratio

[b]Sub-distribution hazard ratio

[c]Albumin:creatinine ratio

Table 2 (continued)

[d]A 2.72-fold increase in urinary ACR corresponds to an increase of 1 in ln(ACR)

[e]Variables considered for entry into the dementia model for age at diabetes diagnosis < 65 years: age, ethnic background, English fluency, educational attainment, marital status, diabetes duration, diabetes treatment, HbA_{1c}, abdominal obesity, systolic blood pressure, urinary ACR, eGFR, heart failure, cerebrovascular disease, peripheral sensory neuropathy, schizophrenia, antipsychotic medication, APOE genotype

[f]Variables considered for entry into the death model for age at diabetes diagnosis < 65 years: age, sex, ethnic background, educational attainment, marital status, smoking status, exercise, diabetes duration, diabetes treatment, fasting serum glucose, HbA_{1c}, history of hypoglycaemia, BMI, systolic and diastolic blood pressures, antihypertensive medication, lipid-modifying medication, aspirin use, urinary ACR, eGFR, heart failure, coronary heart disease, cerebrovascular disease, peripheral arterial disease, peripheral sensory neuropathy, retinopathy, chronic pulmonary disease

[g]Variables considered for entry into the dementia model for age at diabetes diagnosis ≥ 65 years: age, exercise, age at diabetes diagnosis, fasting serum glucose, BMI, abdominal obesity, diastolic blood pressure, antihypertensive medication, total serum cholesterol, HDL-cholesterol, serum triglycerides, urinary ACR, eGFR, heart failure, coronary heart disease, cerebrovascular disease, peripheral sensory neuropathy, schizophrenia, antipsychotic medication, APOE genotype

[h]Variables considered for entry into the death model for age at diabetes diagnosis ≥ 65 years: age, sex, ethnic background, marital status, smoking status, exercise, diabetes duration, HbA_{1c}, systolic and diastolic blood pressures, lipid-modifying medication, aspirin use, urinary ACR, eGFR, atrial fibrillation, heart failure, coronary heart disease, cerebrovascular disease, peripheral arterial disease, peripheral sensory neuropathy, chronic pulmonary disease, depressive symptoms, antidepressant medication, APOE genotype

Table 3 Models of independent predictors of the dementia subtypes, Alzheimer's disease, vascular dementia and unspecified dementia in type 2 diabetes with age as the time scale

Baseline variable	Cox model csHR[a] (95% CI)	*P* value	Fine–Gray model sdHR[b] (95% CI)	*P* value
Alzheimer's disease[d]				
Age (10 year increments)	0.48 (0.31–0.74)	0.001	2.09 (1.48–2.95)	< 0.001
eGFR[c] 60–89 ml/min/1.73 m^2	0.51 (0.29-0. 88)	0.016		
APOE 3,4 genotype	2.17 (1.17–4.02)	0.014	1.98 (1.08–3.65)	0.028
APOE 4,4 genotype	8.46 (2.52–28.39)	0.001	6.38 (1.75–23.27)	0.005
Vascular dementia[e]				
Age (10 year increments)			1.86 (1.04–3.31)	0.035
Male	5.63 (1.85–17.15)	0.002	2.88 (1.18–7.04)	0.020
Ex-smoker			3.01 (1.25–7.24)	0.014
On insulin	4.14 (1.56–10.95)	0.004	3.32 (1.24–8.87)	0.017
Systolic blood pressure (increase of 10 mm Hg)			1.23 (1.06–1.42)	0.006
Schizophrenia	64.81 (7.81-537.74)	< 0.001	16.90 (1.77–161.59)	0.014
Unspecified dementia[f]				
Age (10 year increments)	0.36 (0.24–0.54)	< 0.001	1.95 (1.44–2.63)	< 0.001
Married/de facto relationship	0.60 (0.38–0.96)	0.031	0.55 (0.34–0.88)	0.012
Any exercise in past 2 weeks	0.58 (0.36–0.94)	0.028		
Peripheral arterial disease	1.74 (1.08–2.79)	0.023		
Schizophrenia	62.18 (13.71–281.94)	< 0.001	28.09 (6.43-122.83)	< 0.001
APOE 2,4 genotype	6.61 (2.32–18.82)	< 0.001	3.20 (1.19–8.63)	0.022

[a]Cause-specific hazard ratio

[b]Sub-distribution hazard ratio

[c]Estimated glomerular filtration rate

[d]Variables considered for entry into the Alzheimer's disease model: age, sex, age at diabetes diagnosis, fasting glucose, BMI, abdominal obesity, total serum cholesterol, HDL-cholesterol, eGFR, cerebrovascular disease, peripheral sensory neuropathy, APOE genotype

[e]Variables considered for entry into the vascular dementia model: age, sex, marital status, smoking status, alcohol consumption, age at diabetes diagnosis, diabetes treatment, history of hypoglycaemia, systolic and diastolic blood pressures, serum triglycerides, aspirin use, urinary ACR, cerebrovascular disease, retinopathy, schizophrenia, APOE genotype

[f]Variables considered for entry into the unspecified dementia model: age, sex, English fluency, educational attainment, marital status, exercise, age at diabetes diagnosis, fasting serum glucose, BMI, systolic blood pressure, HDL-cholesterol, eGFR, peripheral arterial disease, schizophrenia

and Australian hospital registers [37, 38] and combining health administrative datasets improves detection [22]. Other limitations include biases inherent in observational studies and the reliance on a single baseline assessment of glycaemic control and chronic complications. The study strengths include the involvement of a community-based cohort representative of the Australian urban diabetes community [17], the use of an established, well-developed data linkage system, and the ability to study a large range of relevant explanatory and confounding variables.

In conclusion, we identified few diabetes-specific risk factors for dementia in the present study, but the independent association with diabetes duration indicates the likelihood of other unmeasured variables in the pathogenesis of dementia complicating type 2 diabetes. Most dementia risk factors also increased the risk of death, suggesting that recently reported improvements in mortality may be accompanied by a reduction in dementia incidence in type 2 diabetes. The present findings may help guide the selection of explanatory variables for future studies and support further epidemiological studies of the relationship between type 2 diabetes and dementia.

Acknowledgements The authors thank the Fremantle Diabetes Study staff, investigators, and participants, and the staff at the Western Australian Data Linkage Branch.

Funding This work was supported by the Raine Foundation of the University of Western Australia and the Fremantle Hospital Medical Research Foundation. TMED was supported by a National Health and Medical Research Council of Australia Practitioner Fellowship (Grant number 1058260). The study sponsors had no role in the design, methods, recruitment of participants, data collection, analysis or preparation of the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed consent Informed consent was obtained from all patients for being included in the study.

References

1. Exalto LG, Whitmer RA, Kappele LJ et al (2012) An update on type 2 diabetes, vascular dementia and Alzheimer's disease. Exp Gerontol 47:858–864
2. Feinkohl I, Price JF, Strachan MW et al (2015) The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimer's Res Ther 7:46
3. Peila R, Rodriguez BL, Launer LJ et al (2002) Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. Diabetes 51:1256–1262
4. Sullivan MD, Katon WJ, Lovato LC et al (2013) Association of depression with accelerated cognitive decline among patients with type 2 diabetes in the ACCORD-MIND trial. JAMA Psychiatry 70:1041–1047
5. Jacobs V, Cutler MJ, Day JD et al (2015) Atrial fibrillation and dementia. Trends Cardiovasc Med 25:44–51
6. Qiu C, Winblad B, Marengoni A et al (2006) Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med 166:1003–1008
7. Rusanen M, Ngandu T, Laatikainen T et al (2013) Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. Curr Alzheimer Res 10:549–555
8. Zilkens RR, Bruce DG, Duke J et al Semmens JB (2014) Severe psychiatric disorders in mid-life and risk of dementia in late- life (age 65–84 years): a population based case-control study. Curr Alzheimer Res 11:681–693
9. Turner RC, Cull CA, Frighi V et al (1999) Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 281:2005–2012
10. Davis TME, Brown SGA, Jacobs IG et al (2010) Determinants of severe hypoglycemia complicating type 2 diabetes: the fremantle diabetes study. J Clin Endocrinol Metab 95:2240
11. Zilkens RR, Davis WA, Spilsbury K et al (2013) Earlier age of dementia onset and shorter survival times in dementia patients with diabetes. Am J Epidemiol 177:1246–1254
12. Xu W, Qiu C, Gatz M et al (2009) Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. Diabetes 58:71–77
13. Bruce DG, Davis WA, Starkstein SE et al (2014) Mid-life predictors of cognitive impairment and dementia in type 2 diabetes mellitus: the Fremantle Diabetes Study. J Alzheimers Dis 42(Suppl 3):S63–S70
14. Emerging Risk Factors C, Seshasai SR, Kaptoge S et al (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 364:829–841
15. Davis WA, Zilkens RR, Starkstein SE et al (2017) Dementia onset, incidence and risk in type 2 diabetes: a matched cohort study with the Fremantle Diabetes Study Phase I. Diabetologia 60:89–97
16. Koller MT, Raatz H, Steyerberg EW et al (2012) Competing risks and the clinical community: irrelevance or ignorance? Stat Med 31:1089–1097
17. Davis TM, Bruce DG, Davis WA (2013) Cohort profile: the Fremantle Diabetes Study. Int J Epidemiol 42:412–421
18. Holman CD, Bass AJ, Rouse IL et al (1999) Population-based linkage of health records in Western Australia: development of a health services research linked database. Aust N Z J Public Health 23:453–459
19. Levey AS, Stevens LA, Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
20. Norman PE, Davis WA, Bruce DG et al (2006) Peripheral arterial disease and risk of cardiac death in type 2 diabetes. Diabetes Care 29:575
21. Bruce D, Davis W, Starkstein S et al (2005) A prospective study of depression and mortality in patients with type 2 diabetes: the Fremantle Diabetes Study. Diabetologia 48:2532–2539
22. Zilkens RR, Spilsbury K, Bruce DG et al (2009) Linkage of hospital and death records increased identification of dementia cases and death rate estimates. Neuroepidemiology 32:61–69
23. Lau B, Cole SR, Gange SJ (2009) Competing risk regression models for epidemiologic data. Am J Epidemiol 170:244–256

24. Latouche A, Allignol A, Beyersmann J et al (2013) A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. J Clin Epidemiol 66:648–653
25. Thiebaut AC, Benichou J (2004) Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med 23:3803–3820
26. Zlokovic BV (2011) Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 12:723–738
27. De Felice FG, Ferreira ST (2014) Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 63:2262–2272
28. Serrano-Pozo A, Qian J, Monsell SE et al (2015) APOEepsilon2 is associated with milder clinical and pathological Alzheimer disease. Ann Neurol 77:917–929
29. Luitse MJ, Biessels GJ, Rutten GE et al (2012) Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 11:261–271
30. Douglas IJ, Smeeth L (2008) Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ 337:a1227
31. Brownrigg JR, Hughes CO, Burleigh D et al (2016) Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study. Lancet Diabetes Endocrinol 4:588–597
32. Du X, Ninomiya T, de Galan B et al (2009) Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. Eur Heart J 30:1128–1135
33. Gregg EW, Li Y, Wang J et al (2014) Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med 370:1514–1523
34. Wu YT, Fratiglioni L, Matthews FE et al (2015) Dementia in western Europe: epidemiological evidence and implications for policy making. Lancet Neurol 15:116–124
35. Bugnicourt JM, Godefroy O, Chillon JM et al (2013) Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc of Nephrol JASN 24:353–363
36. Davis TM, Chubb SA, Davis WA (2016) The relationship between estimated glomerular filtration rate trajectory and all-cause mortality in type 2 diabetes: the Fremantle Diabetes Study. Eur J Endocrinol 175:273–285
37. Phung TK, Andersen BB, Hogh P et al (2007) Validity of dementia diagnoses in the Danish hospital registers. Dement Geriatr Cogn Disord 24:220–228
38. Henderson T, Shepheard J, Sundararajan V (2006) Quality of diagnosis and procedure coding in ICD-10 administrative data. Med Care 44:1011–1019