# The interactive effects of type 2 diabetes mellitus and schizophrenia on all-cause mortality: The Fremantle Diabetes Study

W. A. Davis[1], S. E. Starkstein[2], D. G. Bruce[1], T. M. E. Davis[1]

[1]School of Medicine and Pharmacology, the University of Western Australia, Fremantle Hospital, Western Australia

[2]School of Psychiatry and Clinical Neurosciences, the University of Western Australia, Fremantle Hospital, Western Australia

**Correspondence:** W.A. Davis, telephone: +61 89431 2276; fax: +61 89431 2977; email: wendy.davis@uwa.edu.au

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**Summary**

In a study of the effects of type 2 diabetes and schizophrenia on mortality in 1,296 community-based diabetic patients followed for a mean±SD 12.9±6.1 years and in 5,159 matched non-diabetic residents, 0.4% of each group had schizophrenia. Patients with both conditions had a six-fold adjusted increased risk of death.

**Key words:** type 2 diabetes mellitus, schizophrenia, mortality, interaction, premature death

## Introduction

Strong evidence links diabetes with mental disorders (1). Type 2 diabetes (T2DM) and schizophrenia both cause premature death, mostly from cardiorespiratory disease or cancer (2). Since the combined effect of T2DM and schizophrenia on mortality is unknown and potentially substantial, we assessed this interaction in a large Australian community.

## Materials and methods

Longitudinal data from 1,296 T2DM participants recruited from an urban population of 120,097 to the Fremantle Diabetes Study Phase I (FDS1) between 1993 and 1996 were analysed. Of these, 1,291 were matched 1:4 on age, sex, and postcode with 5,159 non-diabetic residents from the electoral roll. All hospitalizations, deaths, and community-based mental health service attendances in Western Australia (WA) are recorded in the WA Data Linkage System (WADLS) (3) and were available for both cohorts (n=6,455) to end-2012. In addition, FDS1 T2DM participants underwent detailed annual assessments (4) including identification of complications (5). The Fremantle Hospital Human Rights Committee approved FDS1 and subjects gave witnessed informed consent. WADLS access was approved by the Human Research Ethics Committee of the WA Health Department.

Baseline schizophrenia status from International Classification of Diseases 9-CM codes (6) for the pooled cohort from 1982 until FDS1 entry or equivalent date for non-diabetic residents was ascertained from the WADLS (2) which has a low coding error rate (7) and high sensitivity/specificity for schizophrenia (8). Each subject's Charlson Comorbidity Index (CCI) (9), excluding diabetes and its complications, was calculated from WADLS data for the five-year period before FDS1 entry.

Kaplan-Meier analysis compared survival by schizophrenia status in FDS1 patients and by T2DM/schizophrenia status in the combined cohort. Cox proportional hazards modelling identified independent risk factors for all-cause mortality in FDS1 participants. Due to covariates strongly associated with age, age was used as the time-scale with left truncation at entry (10). After adjusting for the most parsimonious model, schizophrenia was entered. For pooled FDS1/matched non-diabetic data, age- (as time-scale), sex-and CCI-adjusted survival was compared by T2DM/schizophrenia status.

**Results**

Five (0.4%) FDS1 T2DM participants had schizophrenia at entry. Compared with non-schizophrenic T2DM participants, they had a similar age, age at diabetes diagnosis, sex, BMI and $HbA_{1c}$ ($P \geq 0.55$). During a mean±SD 12.9±6.1 years' follow-up, 738 (56.9%) FDS1 T2DM participants died, including all with schizophrenia (Table 1). Only 1.4% took antipsychotic medications at entry (4 (80.0%) with schizophrenia versus 14 (1.1%) without, $P<0.001$), but this did not predict mortality ($P=0.23$). In Kaplan-Meier analysis, schizophrenia status predicted reduced survival (log-rank test, $P=0.047$). After adjusting for other risk factors for death and with age as time-scale, schizophrenia added significantly to the model with a hazard ratio of 3.46 (Table 2).

The baseline prevalence of schizophrenia in FDS1 T2DM participants and in matched non-diabetic residents (21 of 5,159) was 0.4% ($P \geq 0.99$). During 92,391 patient-years of follow-up, 2,907 (45.1%) persons in the combined cohort died. In Kaplan-Meier analysis, T2DM/schizophrenia status predicted survival (log-rank test, $P<0.001$). Compared to residents without schizophrenia or T2DM, those with T2DM and schizophrenia had the worst age- (as time-scale), sex- and CCI-adjusted mortality, with a 5.86-fold increased risk versus

3.51-fold for schizophrenia alone and 1.58-fold for T2DM alone ($P<0.001$; Table 3). The age at death of the 2,165 people without T2DM/schizophrenia was 80.8±8.8 years versus 71.9±9.1 years for the five with schizophrenia and T2DM ($P=0.025$).

**Discussion**

In representative, community-based patients with T2DM, schizophrenia independently increased the risk of death more than three-fold. From pooled analysis, those with both T2DM and schizophrenia were six times more likely to die and they died at a significantly younger age.

In a large UK primary care database, people with schizophrenia and diabetes had a 52% increased risk of death compared to those with diabetes alone after adjusting for age, sex, socioeconomic status, obesity, smoking and statin use (11). Further adjustment for antipsychotic treatment attenuated this increase to 38%, but other potential confounders were not included and diabetes type was not stipulated. The Cox modelling used time-in-study rather than age (as in our study) as time-scale, the latter being more meaningful and less restrictive (12), while the time of ascertainment of variables such as smoking status and obesity was heterogeneous. The higher schizophrenia prevalence and lower associated mortality than in our study may reflect differences in populations, healthcare, diabetes type and/or statistical analysis. Consistent with our data, a UK regional study of in-hospital mortality showed that T2DM doubled the risk of death in schizophrenia (13), while 25-year follow-up of an English community-based cohort recruited in 1981–1982 (14) showed that schizophrenia increased the risk of death 2-3 times that in the general population.

The limitations of the present study included the small number of schizophrenic participants.

Although key variables (age, sex, race/ethnicity and diabetes type/treatment) were similar in FDS1 patients and eligible people who were not recruited (4), healthier residents, especially those without mental illness, may have participated. However, the prevalence of schizophrenia in FDS1 T2DM patients (0.4%) was the same as in the matched non-diabetic residents at a time when government-subsidized second generation antipsychotic agents (SGAs, which increase diabetes risk) were not available. In addition, a systematic review reported median point and lifetime prevalences of schizophrenia of 0.46% and 0.4%, respectively (15), in accord with our data. The strengths of our study are the comprehensive FDS1 assessments in a large community-based, representative sample, the well-validated WADLS including data from matched non-diabetic residents.

**Conclusions**

Schizophrenia is associated with premature mortality in T2DM, and the combination of schizophrenia and T2DM increases the risk of death six-fold compared to that in people with neither condition. With the expanding use of SGAs and associated obesity, diabetes may increasingly complicate schizophrenia at a relatively young age, with potential for worse outcomes than in FDS1. These patients will require intensive management for chronic co-morbid conditions such as diabetes.

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**Table 1.** Characteristics of the type 2 diabetes cohort at study entry by survival to the end of 2012

| | Deceased | Alive | *P*-value |
|---|---|---|---|
| Number (%) | 738 (56.9) | 558 (43.1) | |
| Age at FDS entry (years) | 69.3±8.9 | 56.9±10.1 | <0.001 |
| Sex (% male) | 52.8 | 43.0 | <0.001 |
| Ethnic background (%): | | | <0.001 |
| Anglo-Celt | 65.2 | 56.5 | |
| Southern European | 17.1 | 18.6 | |
| Other European | 8.9 | 7.9 | |
| Asian | 1.8 | 5.6 | |
| Indigenous Australian | 1.6 | 1.3 | |
| Mixed/other | 5.4 | 10.2 | |
| Not fluent in English (%) | 16.0 | 14.3 | 0.44 |
| Education beyond primary level (%) | 70.9 | 78.1 | 0.004 |
| Currently married/de facto (%) | 60.5 | 72.4 | <0.001 |
| Alcohol (standard drinks/day) | 0 [0-0.8] | 0 [0-0.7] | 0.58 |
| Smoking status (% never/ex/current) | 40.8/42.8/16.4 | 49.8/36.8/13.4 | 0.005 |
| Any exercise in past 2 weeks (%) | 67.4 | 77.8 | <0.001 |
| Age at diagnosis (years) | 69.4±8.9 | 56.9±10.1 | <0.001 |
| Duration of diabetes (years) | 5.0 [1.9-11.0] | 2.4 [0.5-6.0] | <0.001 |
| Diabetes treatment (%): | | | <0.001 |
| Diet | 27.0 | 38.5 | |
| Oral agents | 57.7 | 53.7 | |
| Insulin ± oral agents | 15.3 | 7.8 | |
| Fasting glucose (mmol/L) | 8.5 [6.9-10.80] | 8.3 [6.8-10.7] | 0.29 |
| $HbA_{1c}$ (%) | 7.6 [6.6-9.0] | 7.2 [6.2-8.6] | <0.001 |
| BMI ($kg/m^2$) | 29.0±5.1 | 30.3±5.7 | <0.001 |
| Obesity (% by waist circumference) | 63.9 | 65.5 | 0.56 |
| SBP (mm Hg) | 157±264 | 143±21 | <0.001 |
| DBP (mm Hg) | 81±12 | 80±10 | 0.023 |
| BP-lowering medication (%) | 59.8 | 39.2 | <0.001 |
| Total cholesterol (mmol/L) | 5.4±1.1 | 5.5±1.1 | 0.10 |
| HDL-cholesterol (mmol/L) | 1.07±0.34 | 1.05±0.30 | 0.23 |
| Serum triglycerides (mmol/L) | 1.9 (1.1-3.3) | 1.9 (1.1-3.3) | 0.34 |
| Lipid-modifying medication (%) | 9.4 | 12.0 | 0.14 |
| Aspirin use (%) | 26.7 | 15.3 | <0.001 |
| Urinary albumin:creatinine (mg/mmol) | 4.8 (1.0-22.5) | 1.7 (0.6-5.4) | <0.001 |
| eGFR (CKD-EPI) categories (%): | | | <0.001 |
| ≥90 ml/min/1.73$m^2$ | 13.4 | 34.4 | |
| 60-89 ml/min/1.73$m^2$ | 52.1 | 54.9 | |
| 45-59 ml/min/1.73$m^2$ | 21.8 | 9.8 | |
| 30-44 ml/min/1.73$m^2$ | 9.6 | 0.7 | |
| <30 ml/min/1.73$m^2$ | 3.1 | 0.2 | |
| Ischemic heart disease (%) | 39.2 | 16.8 | <0.001 |
| Cerebrovascular disease (%) | 14.6 | 3.8 | <0.001 |

| | | | |
|---|---|---|---|
| Peripheral arterial disease (%) | 40.1 | 15.5 | <0.001 |
| Peripheral sensory neuropathy (%) | 41.7 | 16.9 | <0.001 |
| Retinopathy (%) | 21.1 | 10.4 | <0.001 |
| Charlson Comorbidity Index: | | | <0.001 |
| 0 | 60.4 | 86.2 | |
| 1-2 | 29.7 | 12.0 | |
| 3+ | 9.9 | 1.8 | |
| Schizophrenia (%) | 0.7 | 0 | 0.07 |
| Antipsychotic medication use (%) | 1.8 | 0.9 | 0.23 |

**Table 2.** Cox proportional hazards model of independent predictors of death with age as the time-scale for the type 2 diabetic cohort.

| | Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| Male | 1.52 (1.29-1.78) | <0.001 |
| Aboriginal | 3.11 (1.64-5.91) | 0.001 |
| Current smoker | 1.98 (1.59-2.47) | <0.001 |
| BMI (increase of 1 $kg/m^2$) | 1.03 (1.01-1.04) | 0.004 |
| SBP (increase of 10 mm Hg) | 0.92 (0.88-0.96) | <0.001 |
| DBP (increase of 5 mm Hg) | 1.07 (1.03-1.12) | 0.002 |
| $Log_e$(urinary albumin:creatinine ratio (mg/mmol)) | 1.19 (1.13-1.26) | <0.001 |
| eGFR (CKD-EPI) category: | | <0.001 |
| ≥90 ml/min/1.73$m^2$ | 2.01 (1.52-2.66) | <0.001 |
| 60-89 ml/min/1.73$m^2$ | 1.12 (0.92-1.37) | 0.30 |
| 45-59 ml/min/1.73$m^2$ | 1.00 (reference) | |
| 30-44 ml/min/1.73$m^2$ | 1.18 (0.87-1.61) | 0.58 |
| <30 ml/min/1.73$m^2$ | 1.60 (0.97-2.62) | 0.09 |
| Retinopathy | 1.43 (1.17-1.75) | 0.001 |
| Ischemic heart disease | 1.33 (1.11-1.58) | 0.002 |
| Peripheral arterial disease | 1.33 (1.12-1.57) | 0.001 |
| Charlson Comorbidity Index: | | <0.001 |
| 0 | 1.00 (reference) | |
| 1-2 | 1.30 (1.08-1.57) | 0.006 |
| 3+ | 2.36 (1.76-3.16) | <0.001 |
| Schizophrenia | 3.46 (1.27-9.43) | 0.015 |

**Table 3.** Cox proportional hazards model of independent predictors of death with age as the time-scale for the combined type 2 diabetic and non-diabetic cohorts.

| | Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| Male | 1.64 (1.52-1.76) | <0.001 |
| Charlson Comorbidity Index: | | <0.001 |
| 0 | 1.00 (reference) | |
| 1-2 | 1.58 (1.45-1.73) | <0.001 |
| 3+ | 2.36 (2.05-2.71) | <0.001 |
| Schizophrenia/type 2 diabetes status: | | <0.001 |
| No schizophrenia and no diabetes | 1.00 (reference) | |
| No schizophrenia but type 2 diabetes | 1.58 (1.45-1.72) | <0.001 |
| Schizophrenia but no diabetes | 3.51 (1.75-7.04) | <0.001 |
| Schizophrenia and type 2 diabetes | 5.86 (2.44-14.11) | <0.001 |