OBJECTIVE — The purpose of this study was to determine longitudinal predictors of cognitive decline in older individuals with diabetes who did not have dementia.

RESEARCH DESIGN AND METHODS — Cognitive assessments were performed in 205 subjects with diabetes (mean age 75.3 years) and repeated a median 1.6 years later. The sample was drawn from an existing cohort study, and data on diabetes, cardiovascular risk factors, and complications were collected 7.6 ± 1.1 years before and at the time of the initial cognitive assessment. Cognitive status was defined using the Clinical Dementia Rating (CDR) scale, and cognitive decline was defined by change in CDR.

RESULTS — The sample included 164 subjects with normal cognition (CDR 0) and 41 with cognitive impairment without dementia (CDR 0.5). At follow-up, 33 (16.1%) had experienced cognitive decline (4 new cases of dementia and 29 cognitive impairment without dementia). Only educational attainment predicted cognitive decline from the data collected 7.6 years before cognitive assessment. Univariate predictors of cognitive decline at the time of the first cognitive assessment included age, education, urinary albumin-to-creatinine ratio (ACR), and treatment with either ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). With multiple logistic regression controlling for age and education, cognitive decline was predicted by natural logarithm ACR (odds ratio 1.37 [95% CI 1.05–1.78], P = 0.021), whereas treatment with either ACEIs or ARBs was protective (0.28 [0.12–0.65], P = 0.003).

CONCLUSIONS — In this sample of older patients with diabetes, microalbuminuria was a risk factor for cognitive decline, whereas drugs that inhibit the renin-angiotensin system were protective. These observations require confirmation because of their considerable potential clinical implications.

From the 1School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia; the 2School of Psychiatry and Neurosciences, University of Western Australia, Perth, Western Australia, Australia; and the 3Department of Community and Geriatric Medicine, Fremantle Hospital, Fremantle, Western Australia, Australia.

Corresponding author: Professor David Bruce, dbruce@cyllene.uwa.edu.au.

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Predictors of cognitive decline in diabetes

Clinical assessment
All subjects provided sociodemographic and clinical data at entry into the FDS. These were updated at the time of recruitment to the present study as part of a detailed review comprising cognitive assessment, clinical history (including medications taken), and physical examination. Fasting blood and urine samples were taken for automated biochemical tests including serum glucose, A1C, lipoproteins, creatinine, urinary albumin-to-creatinine ratio (ACR) (14), and apolipoprotein E genotype (APOE).

Complications were identified using standard definitions. Peripheral sensory neuropathy was defined as a score of >2 of 8 on the clinical portion of the Michigan Neuropathy Screening Instrument. Nephropathy was defined as a urinary ACR ≥3.0 mg/mmol in an early-morning urine sample (14). Creatinine clearance was assessed using the Cockcroft-Gault equation. Cerebrovascular disease was defined by self-reported stroke and transient ischemic attack supplemented by scrutiny of hospital records. Coronary heart disease was defined if there was a self-reported history of (or hospitalization for) myocardial infarction, angina, coronary artery bypass grafting, or angioplasty and/or definite myocardial infarction on a Minnesota coded electrocardiogram (14). The ankle-to-brachial index (ABI) was obtained from brachial and ankle systolic blood pressures using Doppler detection. Peripheral arterial disease was considered present when the ABI was ≤0.90 (worse side) or there had been a diabetes-related lower-extremity amputation (15). Depression was assessed using the Even Briefer Assessment Scale for Depression (16). A history of hypoglycemia was assessed by self-report at initial recruitment (frequency), and questions on severe hypoglycemia (hospitalization or unconsciousness, frequency, and timing) were included at the time of cognitive assessment.

Cognitive assessment
A two-step procedure was used for assessment of cognitive function, with initial screening followed by detailed assessment as described previously (10). The method is sensitive and detects early cognitive impairment (10). A positive screening test was defined by a Mini-Mental State Examination (MMSE) score <28/30 or a score ≥3.31 on the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) (17) or a positive response to a question on subjective memory loss. Screen-positive participants and an additional random sample of 34 screen-negative participants underwent 1) neurocognitive testing (global cognition, premorbid intelligence, memory, language, visuospatial, and executive functions; data not presented) and 2) a clinical assessment to exclude dementia by experienced clinicians (D.G.B., R.M.C., and O.P.A.) that included an informant whenever possible and scrutiny of hospital records for supplemental data.

RESULTS
Sample characteristics and prevalence of cognitive decline
At the time of the first cognitive assessment, the 205 study participants were aged 75.0 ± 4.1 years, 48.3% were male, all had type 2 diabetes, and one lived in residential care. They included 164 participants with normal cognition (77.4% with MMSE scores ≥28 and 16.6% with IQCODE scores ≥3.31) and 41 with cognitive impairment without dementia (51.2% with MMSE scores ≥28 and 68.3% with IQCODE scores ≥3.31). The eligible FDS subjects who did not participate were older (77.5 ± 4.9 years, \( P = 0.001 \)) and had more cognitive impairment without dementia (32.9% vs. 20.0%, \( P = 0.034 \)). After a median 1.6 (IQR 1.4–1.8) years follow-up, 33 (16.1%) had experienced cognitive decline, of whom 4 were new cases of dementia (2.0%) and 29 were new cases of cognitive impairment without dementia (14.1%). Of the four participants with new cases of dementia, one declined from normal to dementia whereas the other three had cognitive impairment without dementia at baseline.

Predictors of cognitive decline
Table 1 summarizes demographic and clinical variables that were assessed at the time of the first cognitive assessment classified by the presence or absence of subsequent cognitive decline. Compared with those with stable cognition, participants with cognitive decline were older, had achieved lower levels of schooling, had lower MMSE scores, were less likely to be receiving insulin therapy, had higher ACR and more clinical albuminuria, and were less likely to be taking antihypertensive medications. In particular, they were less likely to be taking either ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), with no between-group differences in other classes of antihypertensive medications. There were no differences in serum creatinine or calculated rates of creatinine clearance (data not shown).

Statistics
The computer package SPSS for Windows (version 11.5, SPSS, Chicago, IL) was used. Data are presented as proportions, means ± SD, geometric means (SD range), or (in the case of variables that did not conform to a normal or log-normal distribution) medians and interquartile range (IQR). Two-sample comparisons of proportions were performed by Fisher's exact test; for normally distributed variables, by Student's t test; and for nonnormally distributed variables, by the Mann-Whitney U test. Multiple logistic regression analysis using forward conditional modeling (\( P < 0.05 \) for entry and \( P > 0.10 \) for removal) was performed to determine independent predictors of cognitive decline. All clinically plausible variables with \( P < 0.20 \) in the respective bivariate analyses were considered for the models.
Table 1—Demographic and clinical variables at the time of first cognitive assessment in subjects who did or did not experience a subsequent decline in cognitive function after a median 1.6 years

| Variable                                      | No cognitive decline | Cognitive decline | P value* |
|-----------------------------------------------|----------------------|-------------------|----------|
| n                                             | 172                  | 33                |          |
| Age at assessment (years)                     | 74.7 ± 4.0           | 76.3 ± 4.4        | 0.037    |
| Sex (% male)                                  | 50.0                 | 39.4              | 0.34     |
| Education (% > primary schooling)             | 81.9                 | 51.5              | 0.001    |
| Cognitive impairment, no dementia (%)         | 22.0                 | 9.4               | 0.10     |
| Subjective memory complaints (%)              | 37.1                 | 37.5              | 1.00     |
| MMSE score                                    | 28 [27–29]           | 26 [25–28]        | 0.001    |
| IQCODE >3.31 (%)                              |                      |                   |          |
| Duration of diabetes (years)                  | 11.1 [8.3–16.1]      | 9.6 [7.9–15.1]    | 0.31     |
| Diabetic treatment, diet only (%)             | 15.7                 | 24.2              | 0.31     |
| Oral hypoglycemic agents (%)                  | 55.2                 | 63.6              | 0.45     |
| Insulin (± oral hypoglycemic therapy) (%)     | 29.1                 | 12.1              | 0.052    |
| Fasting glucose (mmol/l)                      | 7.9 [6.6–9.4]        | 8.2 [5.6–9.8]     | 0.73     |
| A1C (%)                                       | 7.0 [6.5–7.9]        | 7.5 [6.3–8.2]     | 0.64     |
| BMI (kg/m²)                                   | 28.9 ± 4.6           | 28.4 ± 4.2        | 0.61     |
| Overweight/obese waist-to-hip ratio (%)       | 76.0                 | 72.7              | 0.66     |
| History of severe hypoglycemia (%)            | 6.6                  | 9.1               | 0.71     |
| Systolic blood pressure (mmHg)                | 151 ± 24             | 151 ± 20          | 0.88     |
| Diastolic blood pressure (mmHg)               | 76 ± 17              | 78 ± 19           | 0.54     |
| Antihypertensive medication (%)               | 84.0                 | 68.8              | 0.049    |
| Treatment with ACEIs or ARBs (%)              | 64.0                 | 33.3              | 0.002    |
| Cholesterol (mmol/l)                          | 4.7 ± 0.8            | 4.8 ± 1.2         | 0.77     |
| HDL cholesterol (mmol/l)                      | 1.3 ± 0.4            | 1.2 ± 0.4         | 0.48     |
| Serum triglycerides (mmol/l)                  | 1.5 (0.9–2.5)        | 1.4 (0.8–2.3)     | 0.37     |
| Lipid-lowering medication (%)                 | 60.0                 | 50.0              | 0.33     |
| Albumin-to-creatinine ratio (mg/mmol)         | 2.7 (0–10.9)         | 6.0 (1.0–34.3)    | 0.020    |
| Nephropathy (%)                               | 42.9                 | 62.5              | 0.052    |
| Serum creatinine (µmol/l)                     | 91 (65–129)          | 86 (63–119)       | 0.40     |
| Peripheral neuropathy (%)                     | 27.1                 | 43.8              | 0.09     |
| Peripheral arterial disease (%)               | 35.7                 | 43.8              | 0.43     |
| Coronary heart disease (%)                    | 32.4                 | 30.3              | 1.00     |
| Cerebrovascular disease (%)                   | 20.1                 | 24.2              | 0.64     |
| Depression (%)                                | 13.5                 | 15.2              | 0.78     |
| APOE e4 carriers (%)                          | 21.8                 | 12.1              | 0.25     |

Data are mean ± SD, median [interquartile range], or geometric range (SD range). *Appropriate bivariate statistic.

Multiple logistic regression was used to investigate predictors of cognitive decline, and all clinically plausible variables with P < 0.2 in the univariate analyses were included in the model, i.e., age, education, presence of cognitive impairment without dementia, insulin treatment, taking antihypertensive medications, natural logarithm (ln) ACR, and neuropathy (MMSE was not included, given its strong association with cognitive impairment without dementia). In this model, the independent predictors of cognitive decline were lnACR (odds ratio 1.32 [95% CI 1.02–1.69], P = 0.033) and education beyond the primary school level (0.28 [0.12–0.65], P = 0.003), which was protective, and insulin treatment (0.31 [0.10–0.99], P = 0.049), also protective. In a second model with the binary variable being treatment/no treatment with ACEIs or ARBs substituted for antihypertensive treatment, significant predictors of cognitive decline were lnACR (1.37 [1.05–1.78], P = 0.021), with both higher education (0.32 [0.14–0.76], P = 0.009) and treatment with ACEIs/ARBs (0.28 [0.12–0.65], P = 0.003) being protective.

Subjects with normal cognition

In the subgroup of 164 participants with normal cognition, 29 experienced cognitive decline (28 to cognitive impairment without dementia [17.1%] and 1 case of dementia) after a median 1.6 [IQR 1.4–1.8] years (Table 2). The variables significantly associated with cognitive decline in univariate analyses were age, education, MMSE scores, treatment with any antihypertensive drugs, treatment with ACEIs or ARBs, and lnACR. In multiple logistic regression analyses, incorporating clinically plausible variables with univariate P values < 0.2 into the models, independent predictors of cognitive decline were lnACR (1.53 [1.14–2.06], P = 0.005), education beyond primary level (0.29 [0.11–0.73], P = 0.009), and taking antihypertensive medications (0.33 [0.11–0.97], P = 0.043). When treatment with ACEI or ARB drugs was substituted for antihypertensive medications, cognitive decline was predicted independently by lnACR (1.50 [1.10–2.04], P = 0.010), education beyond the primary level (0.22 [0.09–0.58], P = 0.002), and ACEI/ARBs (0.24 [0.09–0.62], P = 0.003), which were protective.

Predictors from FDS recruitment (1993–1996)

We performed the same analyses using variables obtained at entry into the FDS 7.6 ± 1.1 years before the first cognitive assessment. Compared with subjects who exhibited a subsequent cognitive decline, those without cognitive decline were younger (67.1 ± 4.0 vs. 68.9 ± 4.7 years, P = 0.024) and more likely to be educated beyond the primary level (81.9 vs. 51.5%, P < 0.001). Prevalence of micro- or macroalbuminuria (30.0 vs. 39.4%) and use of ACEIs (17.4 vs. 15.2%) were similar. Only educational attainment was independently associated with cognitive decline in the regression model (median 0.24 [IQR 0.11–0.52], P < 0.001). Virtually identical results were obtained when only subjects with normal cognition were analyzed separately (data not shown).

CONCLUSIONS—In the present study, almost 16% of a community-based sample of older patients with type 2 diabetes experienced a clinically relevant decrease in cognitive function after 1.6 years of follow-up. After controlling for age, education, and cognitive function, cognitive decline was predicted by urinary albumin excretion rates, whereas the use of either ACEIs or ARBs appeared to be protective. These findings were replicated in the subgroup of subjects who were cognitively normal. No clinical variables assessed an


### Predictors of cognitive decline in diabetes

| Demographic and clinical variables in cognitively normal subjects who did or not experience cognitive decline |
|---------------------------------------------------------------|
| **No cognitive decline** | **Cognitive decline** | **P value** |
| **n** | 134 | 30 |
| **Age at assessment (years)** | 74.4 ± 3.9 | 76.2 ± 4.5 | 0.025 |
| **Sex (% male)** | 45.5 | 36.7 | 0.42 |
| **Education (% > primary schooling)** | 84.2 | 50.0 | 0.001 |
| **MMSE score** | 28 [27–29] | 26 [25–28] | 0.001 |
| **IQCODE ≥3.31 (%)** | 14.3 | 20.0 | 0.41 |
| **Duration of diabetes (years)** | 10.5 [8.2–15.7] | 9.6 [8.0–14.5] | 0.64 |
| **Oral hypoglycemic agents (%)** | 54.5 | 63.3 | 0.42 |
| **Insulin (± oral hypoglycemic therapy) (%)** | 27.6 | 13.3 | 0.16 |
| **A1C (%)** | 7.0 [6.5–7.9] | 7.5 [6.5–8.2] | 0.35 |
| **BMI (kg/m²)** | 28.7 ± 4.8 | 28.2 ± 4.2 | 0.62 |
| **History of severe hypoglycemia (%)** | 4.6 | 6.7 | 0.65 |
| **Systolic blood pressure (mmHg)** | 150 ± 24 | 152 ± 20 | 0.75 |
| **Diastolic blood pressure (mmHg)** | 75 ± 17 | 78 ± 20 | 0.50 |
| **Antihypertensive medication (%)** | 84.8 | 69.0 | 0.060 |
| **Treatment with ACEIs or ARBs (%)** | 64.9 | 36.7 | 0.007 |
| **Albumin-to-creatinine ratio (mg/mmol)** | 2.8 (0.7–11.2) | 7.0 (1.3–37.9) | 0.003 |
| **Nephropathy (%)** | 45.1 | 65.5 | 0.063 |
| **Peripheral neuropathy (%)** | 26.5 | 41.4 | 0.12 |
| **Peripheral arterial disease (%)** | 34.6 | 44.8 | 0.39 |
| **Cerebrovascular disease (%)** | 15.2 | 23.3 | 0.29 |
| **Depression (%)** | 11.3 | 16.7 | 0.54 |
| **APOE e4 carriers (%)** | 22.0 | 10.0 | 0.20 |

Data are mean ± SD, %, median [interquartile range], or geometric range (SD range). *Appropriate bivariate statistic.

average of 7.6 years earlier predicted cognitive decline, possibly because the prevalence of microalbuminuria and the use of ACEIs or ARBs were relatively low.

Although microalbuminuria is common in the community, affecting 29% of individuals with diabetes, 16% of patients with hypertension, and 5% of healthy individuals (19), there are few data on its association with cognitive function. Two recent cross-sectional studies have reported findings consistent with the present study. In a study of subjects with type 2 diabetes, those with microalbuminuria had lower MMSE scores (11). In a population-based study, microalbuminuria inversely correlated with test scores of visuospatial function and motor speed in subjects with peripheral arterial disease (12). In contrast, a study conducted in the Rancho Bernardo cohort showed no association between microalbuminuria and cognitive decline (20).

Microalbuminuria is a risk factor for cardiovascular disease independently of renal function and conventional cardiovascular risk factors, and there is an increased risk even with low-grade albuminuria (19). In the present study, urinary albumin excretion assessed as a continuous variable was more strongly associated with cognitive decline than the presence of categorical microalbuminuria or albuminuria. There was no association with renal dysfunction as assessed from creatinine clearance. Microalbuminuria has been associated with stroke and cerebral small vessel ischemia (21); hence, a vascular mechanism may explain its effect on cognitive decline. Additional possibilities include endothelial dysfunction and chronic low-grade inflammation. Both are associated with microalbuminuria in type 2 diabetes (22) and may have a role in the pathogenesis of Alzheimer’s disease.

The protective effect of antihypertensive therapy was explained by the use of either ACEIs or ARBs. These two drug classes have nearly identical effects on the renin-angiotensin system and are known to reduce urinary albumin excretion and protect the kidney against diabetic nephropathy. Some of these beneficial effects may occur independently of blood pressure lowering, possibly by reducing inflammation in diabetic patients with microalbuminuria (23). Blood pressure lowering has been shown to be effective in preventing stroke-related dementia, but the data on Alzheimer’s disease are conflicting (24). The use of ACEIs was associated with reduced progression to dementia in patients with mild cognitive impairment (25) but not incident Alzheimer’s disease in a population-based study (26).

The strengths of the present study include its community-based sample, the large number of older diabetic subjects, the use of a clinically meaningful classification of cognitive decline, and the detailed nature of the clinical assessment, which allowed us to control for important modifiers, including education. The major limitations of the study are the relatively small sample size and the inherent features of cohort studies with potential biases at the recruitment phases and differential dropout rates. Attrition between FDS entry and recruitment to the present study was substantial. The FDS survivors who did not participate in the present cognitive study were older and more likely to have both cognitive impairment and chronic complications than those who were recruited. Because our sample was almost entirely community dwelling and relatively healthy and because the rate of decline from normal to CDR stage 0.5 found in our patients was similar to published annual conversion rates of 11.8–15.3% in aged populations (27), the true rate of decline in diabetes may be higher. Cognitive status was not assessed at FDS entry, which would have provided useful additional prospective data. The generalizability of the findings beyond those with diabetes is uncertain.

In summary, we found that clinical cognitive decline was a common occurrence in a sample of older diabetic individuals and was predicted by increased urinary albumin excretion, a potentially modifiable risk factor. The independent inverse association between ACEI or ARB therapy and cognitive decline suggests that these drug classes act through mechanisms distinct from those which act to reduce urinary protein excretion. These findings are of potential clinical importance and further confirmatory studies are needed in both diabetic and nondiabetic populations.

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