Severe Hypoglycemia and Cognitive Decline in Older People With Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study

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OBJECTIVE

People with type 2 diabetes are at increased risk of age-related cognitive decline and dementia. Hypoglycemia is a candidate risk factor, but the direction of association between episodes of severe hypoglycemia and cognitive decline in type 2 diabetes remains uncertain.

RESEARCH DESIGN AND METHODS

In the Edinburgh Type 2 Diabetes Study, cognitive function was assessed in 831 adults with type 2 diabetes (aged 60–75 years) at baseline and after 4 years. Scores on seven neuropsychological tests were combined into a standardized general ability factor *g*. Self-reported history of severe hypoglycemia at baseline (history of hypoglycemia) and at follow-up (incident hypoglycemia) was recorded.

RESULTS

A history of hypoglycemia was reported by 9.3% of subjects, and 10.2% reported incident hypoglycemia. Incident hypoglycemia was associated with poorer cognitive ability at baseline (age- and sex-adjusted odds ratio for lowest tertile of *g* 2.04 [95% CI 1.25–3.31], *P* = 0.004). Both history of hypoglycemia and incident hypoglycemia were also associated with greater cognitive decline during follow-up (mean follow-up *g* adjusted for age, sex, and baseline *g* −0.25 vs. 0.03 [*P* = 0.02] and −0.28 vs. 0.04 [*P* = 0.01], respectively), including after addition of vascular risk factors and cardiovascular and microvascular disease to the models (−0.23 vs. 0.03 [*P* = 0.04] and −0.21 vs. 0.05 [*P* = 0.03], respectively).

CONCLUSIONS

The relationship between cognitive impairment and hypoglycemia appeared complex, with severe hypoglycemia associated with both poorer initial cognitive ability and accelerated cognitive decline.

Diabetes Care 2014;37:507–515 | DOI: 10.2337/dc13-1384

Type 2 diabetes is associated with an increased risk of cognitive impairment, age-related cognitive decline, and dementia (1). Given the increasing numbers of elderly people with type 2 diabetes in the general population, the identification of potentially modifiable risk factors and the prevention of cognitive decline during older age in this group are of major importance to public health. Although the

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Received 11 June 2013 and accepted 3 October 2013.

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mechanisms underlying progressive cognitive impairment are likely to be multifactorial (2), cerebral insults associated with diabetes-associated episodes of severe hypoglycemia (those in which a patient requires external assistance to aid recovery) are possible contributors. In studies of individuals with type 1 diabetes, in whom relatively frequent episodes of severe hypoglycemia are well-recognized, severe hypoglycemia has been associated with lower cognitive ability and implicated in provoking cognitive decline in children (3) but not in adults (4). However, severe hypoglycemia is also relatively common in adults with insulin-treated type 2 diabetes and to a lesser extent in individuals treated with sulfonylureas (5). Because type 2 diabetes is predominant in the older population, the investigation of the relationship between hypoglycemia and age-related cognitive decline in this group, which has received limited attention, is particularly pressing.

Retrospective analyses of hospital records have suggested that exposure to one or more episodes of severe hypoglycemia is associated with an increase in the subsequent risk of dementia in people with type 2 diabetes (6–9). These findings may be inflated by the higher incidence of hypoglycemia in hospital inpatients than in patients in community settings (10) but are supported by observations of cross-sectional links between a history of severe hypoglycemia and impaired cognitive function short of frank dementia (11,12). However, the extent to which these associations are explained by hypoglycemia occurring as a consequence of poor cognitive ability leading to suboptimal glycemic control (13) as opposed to hypoglycemia preceding and possibly causing decrements in cognitive ability is unknown. The very few prospective analyses performed to date (which might help to resolve this question) have not implicated severe hypoglycemia as a risk factor for negative cognitive outcome (14–16). However, these studies either have neglected relatively mild cognitive decline (14) or have been part of randomized controlled trials in which the nature of the intervention itself potentially affected the relationship between severe hypoglycemia and cognitive ability (15,16). The principal aim of the current study was to determine the association of both prevalent and incident severe hypoglycemia with cognitive decline measured prospectively through a range of age-sensitive cognitive tests in a representative sample of older adults with type 2 diabetes living independently in the general population and participating in a well-established observational epidemiological study (the Edinburgh Type 2 Diabetes Study [ET2DS]).

RESEARCH DESIGN AND METHODS

Study Population

Recruitment and examination procedures for the prospective ET2DS have been reported previously (17). In brief, in 2006/2007, a sample of 1,066 men and women with type 2 diabetes (aged 60–75 years), largely representative of all individuals invited at random from a population-based diabetes register (18), attended a baseline clinic. In 2010/2011, 831 participants (attenders) returned for a 4-year follow-up; nonattenders were followed up through postal questionnaires, linkage to hospital records, death certificate data, and review of hospital notes. All participants gave written informed consent.

Clinical Examination

At the baseline clinic and year-4 follow-up, HDL cholesterol, total cholesterol, and plasma HbA_{1c} concentrations were measured in fasting blood samples; systolic and diastolic brachial blood pressures were measured; and smoking history (current, never, and former) was self-reported. Diabetic retinopathy was assessed at baseline as absent, mild, or moderate/severe on the basis of seven-field retinal photographs. History of myocardial infarction (MI), angina, stroke, and transient ischemic attack (TIA) was determined at baseline through self-report of a physician diagnosis, World Health Organization chest pain questionnaire, 12-lead electrocardiogram, and linkage to hospital discharge records, as detailed previously (18). The same sources of data and criteria were used to ascertain incident MI, angina, stroke, and TIA events between baseline and year 4. Scores on the self-administered depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) (19) (score range 0–21) measured symptoms of depression at baseline and at year 4. Scores <24 of 30 on the Mini-Mental State Examination (20) were used together with additional criteria (21) to identify participants with dementia by year 4 follow-up.

Measurement of Hypoglycemia

Reporting of severe hypoglycemia in the ET2DS is summarized in Fig. 1. At baseline, a questionnaire determined participants' history of severe hypoglycemia (history of hypoglycemia), which was defined as an episode of hypoglycemia requiring the assistance of another person to effect recovery. Participants were asked about the number of episodes they had experienced over their lifetime and within the past year. A similar questionnaire at the year 4 examination determined severe hypoglycemia since baseline (incident hypoglycemia), including the number of episodes experienced in total, and in the year preceding the examination. Data from participants who expressed uncertainty were not used.

Additionally, 898 consenting participants were enrolled in a detailed 6-month survey of severe hypoglycemia, commencing ~1 year after baseline. Once every 2 months for a total of 6 months, participants returned self-completed questionnaires based on the Edinburgh Hypoglycemia scale (22) that comprised items on symptoms, date and time of any hypoglycemic episode, loss of consciousness, help from another person, treatment, and blood glucose values, if measured. For those who reported severe hypoglycemia or who failed to return a questionnaire, data were obtained and verified by telephone.

Cognitive Assessment at Baseline and Year 4

With the aim to minimize effects of measurement error on the baseline and year 4 cognitive test data (a prerequisite for the validity of analyses of cognitive

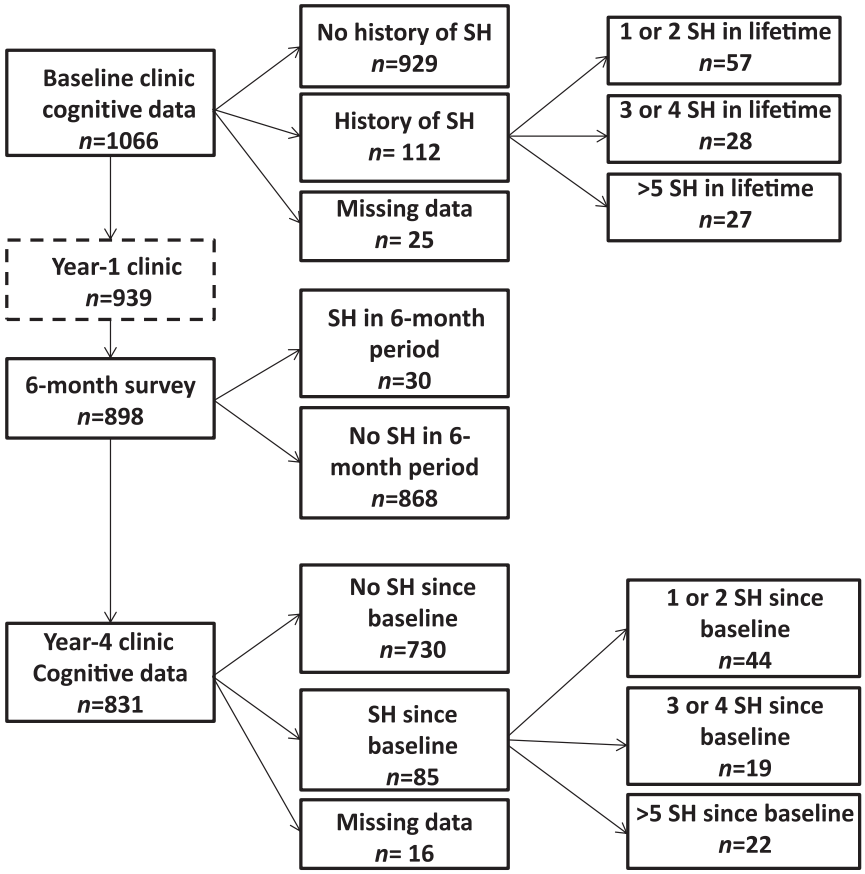

Figure 1—Reporting of severe hypoglycemia (SH) in the ET2DS.

change), conditions for cognitive testing were kept the same at the two time points as much as possible. At both times, the absence of current hypoglycemia was confirmed by measuring blood glucose before commencing each testing session, which was only undertaken if values were ≥4.0 mmol/L. Participants were also reminded by letter to bring their glasses or hearing aids as required and were prompted to use these at the clinic. Data from participants with severe sensory impairment were not used. The Logical Memory (LM) and Faces subtests of the Wechsler Memory Scale—Third Edition (U.K.) assessed verbal and nonverbal memory, respectively (23). Executive function was measured with the Borkowski Verbal Fluency Test (BVFT) and the Trail Making Test B (TMT-B). The Digit Symbol—Coding (DSC), Letter-Number Sequencing (LNS), and Matrix Reasoning (MR) subtests of the Wechsler Adult Intelligence Scale—Third Edition (U.K.) assessed speed of processing, working memory, and nonverbal reasoning, respectively (24). Peak premorbid ability was estimated by the junior and senior Mill Hill Vocabulary Scale (MHVS) (25), a valid measure of crystallized intelligence relatively immune to age-related decline (26).

Statistical Analysis

TMT-B, HADS-D, and duration of diabetes were transformed to their natural logarithms because of skewed distributions. Data were missing on the seven age-sensitive cognitive tests (LM, Faces, MR, DSC, TMT-B, LNS, BVFT) for between 0.6% (BVFT) and 1.7% (LNS) of participants at baseline and for between 0.8% (MR) and 4.7% (LNS) at year 4 follow-up. Multiple imputation accounting for age and sex was carried out for participants with missing data on one, two, or three cognitive tests. Different cognitive tests tending to load on a single factor of global cognitive ability, which has been termed *g* (27), is commonly observed. With the aim to extract *g*, components with eigenvalues >1 were extracted from a principal components analysis of scores on the seven cognitive tests after their imputation. All seven cognitive tests loaded on a single component with an eigenvalue >1; inspection of the scree plot also suggested a strong general cognitive ability factor. The use of the standardized factor *g* derived from this method is advantageous because in contrast to scores on individual cognitive tests, it partly offsets test-specific measurement error. In the ET2DS, *g* has been found to capture participants' overall performance at baseline and year 4 follow-up, as described previously (21).

All analyses were adjusted for age and sex. Initially, ANCOVA was used to compare mean baseline *g* between individuals with incident hypoglycemia and the remaining sample. This method does not entirely eliminate the influence from potential confounders to allow their dismissal, especially in observational studies, but reduces

covariate-associated noise in the data (28); therefore, it was used to address the issue of confounding in the current study. Additionally, odds ratios (ORs) for incident hypoglycemia were calculated in participants with low baseline *g* (i.e., who scored in the lowest tertile of *g*) in logistic regression models. Analyses were repeated with restriction to incidence of first-ever incident hypoglycemia.

Further logistic regression analyses ascertained the OR for reduced follow-up *g* and accelerated decline in *g* (both scoring in the lowest tertiles of distribution) according to history of previous hypoglycemia at baseline and of subsequent incident hypoglycemia between baseline and year 4. Additionally, ANCOVA was used to determine hypoglycemia associations with follow-up cognitive test performance and cognitive change. Cognitive change between baseline and year 4 was represented by inclusion of baseline cognitive test scores in the models of follow-up scores. This method was chosen over the alternative of raw change scores because its parameter estimates are more straightforward and no assumptions are made regarding the group difference in cognitive function at baseline (29).

Cognitive change between estimated peak premorbid ability and year 4 ability was represented by inclusion of baseline MHVS in models of year 4 cognitive test scores. For all outcomes, vascular risk factors (HDL and total cholesterol, systolic and diastolic blood pressure, smoking), HbA_{1c}, cerebrovascular disease (stroke, TIA), coronary heart disease (angina, MI), and diabetic retinopathy as a measure of microvascular disease (vascular covariates) were then added to the models. Treatment modality, duration of diabetes, and HADS-D were also included in analyses performed post hoc and presented in the text. Baseline covariates were used for analyses of a baseline history of hypoglycemia, and year 4 covariates were used in analyses of incident hypoglycemia. An exception to this was smoking status, which was found to be relatively stable over the course of the study, and retinopathy, which was measured only at baseline. Analyses were performed with SPSS version 19.0 (IBM Corporation, Armonk, NY) statistical software.

RESULTS

Characteristics of Follow-up Study Population

Characteristics of attenders of the year 4 follow-up are presented in Table 1. Attenders were largely similar to nonattenders in terms of baseline clinical characteristics but had higher baseline cognitive function (21). In addition, nonattendance was significantly associated with a baseline history of hypoglycemia (31.3 and 20.5% of participants with and without a history of hypoglycemia at baseline, respectively, were nonattenders; P = 0.01).

History of Hypoglycemia

In the total study population attending follow-up (n = 831), 77 (9.3%) participants reported a history of hypoglycemia at baseline and 85 (10.2%) experienced incident hypoglycemia. Of the latter, 27 (31.8%) also had a baseline history of hypoglycemia ($P < 0.001$ for risk of recurrent severe hypoglycemia). Of 898 participants enrolled in the 6-month hypoglycemia survey, 30 reported a total of 45 episodes of severe hypoglycemia. For 18 of the 45 episodes in which blood glucose readings were self-reported, all but 1 of 14 measurements made before treatment were <3.0 mmol/L, suggesting that participants were reasonably accurate at identifying hypoglycemia. Of the 30 participants reporting hypoglycemia in the 6-month survey, 25 recovered after treatment with a glucose drink or ingesting food, 1 required injection with glucagon, and 3 required intravenous glucose (information was missing for 1 participant). Twenty-three of the 30 participants attended the year 4 follow-up; most (74%) reported incident hypoglycemia in the 4 years since baseline, demonstrating a reasonable level of recall of hypoglycemia at follow-up.

Association of Baseline Cognitive Function With Incident Hypoglycemia

Baseline global cognitive function was lower in participants with incident hypoglycemia than in those remaining free of incident hypoglycemia (age- and sex-adjusted mean g −0.08 [95% CI −0.27 to 0.12] vs. 0.17 [0.10–0.24], P = 0.019). Participants scoring in the lowest tertile of *g* were at a twofold higher risk of experiencing incident hypoglycemia compared with higher-scoring participants (age- and sex adjusted OR 2.04 [95% CI 1.25–3.31], P = 0.004). Results were largely unchanged when restricted to participants who experienced their first-ever severe hypoglycemic episode during the follow-up period (age- and sex-adjusted OR 2.45 [1.37–4.39], P = 0.002; adjusted mean g −0.08 [−0.33 to 0.16] vs. 0.18 [0.12–0.25], P = 0.038). The presence of dementia in four participants was not significantly associated with incident hypoglycemia ($P > 0.05$). Because their exclusion did not alter P values and effect sizes (data not shown), results are reported for the entire sample.

Baseline History of Hypoglycemia, Cognitive Function, and Cognitive Change

Participants with a history of hypoglycemia had lower performance on MR, DSC, TMT-B, and *g* at year 4 (Table 2) and were marginally more likely to score in the lowest tertile of *g* (age- and sex-adjusted OR 1.65 [0.99–2.76], P = 0.055) compared with the remaining population. All associations persisted when MHVS (which estimates premorbid ability) was included in the model (all $P < 0.05$) (data not shown). All except DSC (P = 0.145) survived further addition of baseline vascular covariates, baseline HADS-D, duration of diabetes, and baseline treatment modality into the model (all $P < 0.05$) (data not shown).

A history of hypoglycemia was also associated with a steeper decline between baseline and year 4 on MR, TMT-B, and *g* (Table 2), although the OR for cognitive decline (lowest tertile of standardized residuals signifying a 4-year decline in *g*) was not statistically significant (1.36 [0.82–2.24], P = 0.230). Inclusion of baseline vascular covariates marginally attenuated the associations with MR and *g* (Table 2). For MR ($P <$ 0.05) but not *g* (P = 0.083), the association remained statistically significant when baseline HADS-D,

Table 1—Characteristics of year 4 attenders according to incident hypoglycemia reported at follow-up

	All attenders (maximum *n* = 831)	Incident hypoglycemia (maximum *n* = 85)	No incident hypoglycemia (maximum *n* = 730)	*P* value for difference or trend*
Age (years)	67.69 ± 4.16	66.69 ± 4.05	67.79 ± 4.17	0.022
Male sex	430 (51.7)	32 (37.6)	939 (53.8)	0.005
Duration of diabetes (years)	6.00 (3.00–11.00)	9.50 (5.25–15.00)	6.00 (300–10.00)	<0.001
Baseline treatment				<0.001
Insulin ± tablets	139 (16.7)	31 (36.5)	103 (14.1)	
Sulfonylureas ± other tablets	210 (25.3)	28 (32.9)	179 (24.6)	
Other tablets	316 (38.0)	19 (22.4)	292 (40.1)	
Diet alone	165 (19.9)	7 (8.2)	155 (21.3)	
Year 4 treatment				<0.001
Insulin ± tablets	178 (21.4)	40 (47.1)	133 (18.2)	
Sulfonylureas ± other tablets	255 (30.7)	25 (29.4)	228 (31.2)	
Other tablets	283 (34.1)	16 (18.8)	261 (35.8)	
Diet alone	115 (13.8)	4 (4.7)	108 (14.8)	
Plasma HbA_{1c} (%)	7.39 ± 1.13	7.86 ± 1.22	7.32 ± 1.06	<0.001
Plasma HbA_{1c} (mmol/mol)	57 ± 12.4	62 ± 13.3	56 ± 11.6	<0.001
Systolic BP (mmHg)	133 ± 16	130 ± 15	132 ± 16	0.086
Diastolic BP (mmHg)	69 ± 9	67 ± 6	69 ± 9	0.002
Vascular disease				
MI	111 (13.4)	12 (14.1)	98 (13.4)	0.860
Angina	222 (26.7)	22 (25.9)	197 (27.0)	0.828
Stroke	44 (5.3)	2 (2.4)	42 (5.8)	0.189
TIA	27 (3.2)	7 (8.2)	19 (2.6)	0.005
Retinopathy	266 (32.0)	33 (39.3)	227 (31.5)	0.150
Total cholesterol (mmol/L)	4.34 ± 0.90	4.34 ± 0.81	4.32 ± 0.90	0.890
HDL cholesterol (mmol/L)	1.29 ± 0.36	1.26 ± 0.35	1.29 ± 0.36	0.351
Smoking status				
Current smoker	108 (13.0)	18 (21.2)	88 (12.1)	0.018
Ex-smoker	390 (46.9)	37 (43.5)	349 (47.8)	0.455
Never smoked	333 (40.1)	30 (35.3)	293 (40.1)	0.388
HADS-D	3 (1–6)	5 (2–7)	3 (1–5)	<0.001
MMSE	28.47 ± 1.64	28.59 ± 1.48	28.51 ± 1.57	0.647
Dementia	4 (0.5)	0 (0.0)	2 (0.3)	0.629
MHVS	31.45 ± 5.07	30.80 ± 4.84	31.63 ± 5.07	0.151

Data are mean ± SD, median (interquartile range), or *n* (%). Data are from baseline unless otherwise indicated. BP, blood pressure; MMSE, Mini-Mental State Examination. *Comparing the incident hypoglycemia with the no incident hypoglycemia group.

baseline treatment, and disease duration were added to the model (data not shown).

Incident Hypoglycemia, Cognitive Function, and Cognitive Change

Incident hypoglycemia was associated with lower *g*, MR, LNS, TMT-B, DSC, and Faces performance at year 4 (Table 3). The risk of reduced cognitive function at follow-up (scoring in the lowest tertile *g*) was increased threefold for the incident hypoglycemia group (age- and sex-adjusted OR 2.97 [1.82–4.86], $P < 0.001$). All associations remained statistically significant when MHVS was added to the respective models, suggesting that participants with incident hypoglycemia experienced a steeper estimated lifetime decline between their peak premorbid and late-life ability than did the group free of incident hypoglycemia (Table 3). All associations except for DSC further survived the inclusion of year 4 vascular covariates (Table 3) and the inclusion of HADS-D at year 4, treatment at year 4, and disease duration in the respective models (all $P < 0.05$) (data not shown).

Participants with incident hypoglycemia also experienced a steeper decline between baseline and year 4 in MR, TMT-B, DSC, Faces, and *g* (Table 3). Those with the highest rate of decline (scoring in the lowest tertile of standardized residuals signifying a decline in *g*) were marginally more likely to have experienced incident hypoglycemia than the remaining population (age- and sex-adjusted OR 1.53 [0.95–2.47], $P = 0.084$). The associations with decline in MR, TMT-B, Faces, and *g* survived inclusion of year 4 vascular covariates (Table 3). The association with decline in Faces and MR further survived addition of HADS-D at year 4, treatment at year 4, and disease duration to the model (both $P < 0.05$); for TMT-B and *g*, the findings were just short of statistical significance ($P = 0.064$ and 0.072, respectively) (data not shown).

CONCLUSIONS

Lower cognitive ability at baseline was associated with a twofold higher incidence of severe hypoglycemia over 4 years. In addition, severe hypoglycemia was associated with a steeper decline in cognitive function. The latter was observed when cognitive change was

Table 2—Association of baseline history of hypoglycemia with cognitive function at year 4 follow-up and 4-year cognitive decline

	No baseline history (n = 739)	Baseline history (n = 77)	P value for group difference	Effect size of group difference (partial η^2)
Model 1: age, sex				
MR	11.76 (11.39 to 12.13)	10.14 (8.97 to 11.31)	0.009	0.008
LNS	8.96 (8.75 to 9.16)	8.33 (7.67 to 8.99)	0.076	0.004
BVFT	37.19 (36.27 to 38.11)	34.63 (31.72 to 37.54)	0.100	0.003
DSC	50.51 (49.53 to 51.49)	46.31 (43.19 to 49.44)	0.012	0.012
ln(TMT-B)	109.84 (106.70 to 113.07)	129.02 (117.68 to 141.60)	0.001	0.013
Faces	69.37 (68.78 to 69.96)	68.70 (66.85 to 70.56)	0.500	0.001
LM	27.28 (26.69 to 27.84)	27.71 (25.86 to 29.56)	0.661	<0.001
g	0.04 (−0.03 to 0.11)	−0.26 (−0.49 to −0.04)	0.009	0.008
Model 2: age, sex, baseline score				
MR	11.75 (11.47 to 12.03)	10.22 (9.34 to 11.11)	0.001	0.013
LNS	8.92 (8.74 to 9.09)	866 (8.10 to 9.22)	0.394	0.001
BVFT	37.04 (36.50 to 37.59)	36.17 (34.45 to 37.89)	0.340	0.001
DSC	50.31 (49.63 to 50.99)	48.31 (46.14 to 50.49)	0.086	0.004
ln(TMT-B)	110.72 (108.20 to 113.18)	119.94 (111.72 to 128.90)	0.036	0.005
Faces	69.40 (68.92 to 69.87)	68.49 (66.98 to 70.00)	0.260	0.002
LM	27.31 (26.85 to 27.77)	27.34 (25.89 to 28.80)	0.966	<0.001
g	0.03 (−0.04 to 0.10)	−0.25 (−0.48 to −0.02)	0.020	0.007
Model 3*				
MR	11.82 (11.53 to 12.11)	10.35 (9.41 to 11.29)	0.004	0.011
LNS	8.95 (8.77 to 9.13)	8.70 (8.12 to 9.29)	0.423	0.001
BVFT	37.33 (36.77 to 37.89)	36.47 (34.65 to 38.30)	0.381	0.001
DSC	50.38 (49.79 to 51.08)	48.73 (46.46 to 51.01)	0.176	0.002
ln(TMT-B)	109.95 (107.45 to 112.51)	117.57 (109.07 to 126.72)	0.097	0.004
Faces	69.52 (69.03 to 70.01)	68.81 (67.21 to 70.41)	0.409	0.001
LM	27.45 (26.98 to 27.91)	27.93 (26.42 to 29.45)	0.549	<0.001
g	0.03 (−0.04 to 0.11)	−0.23 (−0.47 to 0.01)	0.040	0.006

Data are adjusted mean (95% CI). n = 808–811 for model 1; n = 807–810 for model 2; n = 768–770 for model 3. Means for ln(TMT-B) are geometric means. *Adjusted for age, sex, baseline score, and baseline data on HDL cholesterol, total cholesterol, systolic blood pressure, diastolic blood pressure, smoking, HbA_{1c}, stroke, TIA, angina, MI, and retinopathy.

measured subsequently to the hypoglycemic events and, even more strongly, when the two were occurring simultaneously during the 4-year follow-up period. Thus, the results suggest that the experience of severe hypoglycemia may be associated with lesser prior cognitive ability and is a risk factor for accelerated cognitive decline. In addition to global cognitive ability measured by g, associations with cognitive outcome were most consistently observed for processing speed, nonverbal memory, executive function, and reasoning.

Previous cross-sectional studies demonstrated a relationship between hypoglycemia and poorer cognitive function in people with type 2 diabetes (11,12,14). However, uncertainty remains about the reasons for this association and the direction of any possible causal relationship between hypoglycemia and cognitive decrements. Evidence supports that people with poorer cognitive ability may be more susceptible to hypoglycemia. Lower baseline scores on a screening instrument for dementia predicted 5-year incident severe hypoglycemia in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (15). Clinically diagnosed dementia has been shown to predict a two- to threefold increased risk of hospital admission or emergency treatment for hypoglycemia in the Fremantle Diabetes Study (14) and in the Health, Aging and Body Composition Study (9). In the Memory in Diabetes study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD-MIND) trial, lower baseline cognitive test scores also predicted an increased risk of a first-ever hypoglycemic episode over 3.5 years of follow-up (11). These findings are consistent with the current study in which baseline g predicted subsequent severe hypoglycemia. It is possible that people with lower or declining cognitive ability are less able to recognize hypoglycemia, to treat it appropriately when it occurs, or to prevent it through modification of diabetes therapy.

Less epidemiological evidence supports the hypothesis that hypoglycemia may have a direct or indirect effect on the brain, resulting in cognitive decrements. In type 1 diabetes, the balance of evidence suggests that hypoglycemia may not affect cognitive function in this way (30). Incidence of severe hypoglycemia over 18 years was not associated with concurrent cognitive decline in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort (4), and in a smaller study, 10-year incidence of severe hypoglycemia failed to predict

Table 3—Association of incident hypoglycemia with cognitive function at year 4 follow-up and with 4-year and estimated lifetime cognitive decline

	No incident hypoglycemia (n = 730)	Incident hypoglycemia (n = 85)	P value for group difference	Effect size of group difference (partial η^2)
Cognitive ability at year 4				
Model 1: age, sex				
MR	11.82 (11.45 to 12.19)	10.02 (8.92 to 11.12)	0.003	0.011
LNS	9.02 (8.82 to 9.23)	8.00 (7.38 to 8.61)	0.002	0.012
BVFT	37.20 (36.27 to 38.12)	35.34 (32.60 to 38.09)	0.211	0.002
DSC	50.69 (49.70 to 51.67)	46.63 (43.69 to 49.57)	0.011	0.008
ln(TMT-B)	109.29 (106.16 to 112.51)	126.85 (116.28 to 138.52)	0.001	0.013
Faces	69.63 (69.05 to 70.22)	67.08 (65.33 to 68.83)	0.007	0.009
LM	27.42 (26.83 to 28.01)	26.77 (25.00 to 28.54)	0.493	0.001
g	0.07 (0.00 to 0.13)	−0.33 (−0.53 to −0.12)	<0.001	0.015
Four-year cognitive decline				
Model 2*				
MR	11.75 (11.47 to 12.04)	10.57 (9.72 to 11.41)	0.009	0.008
LNS	8.97 (8.79 to 9.14)	8.42 (7.89 to 8.94)	0.052	0.005
BVFT	37.15 (36.61 to 37.70)	35.77 (34.14 to 37.40)	0.116	0.003
DSC	50.51 (49.82 to 51.19)	48.21 (46.16 to 50.26)	0.038	0.005
ln(TMT-B)	109.95 (107.55 to 112.51)	119.82 (112.06 to 128.25)	0.019	0.007
Faces	69.59 (69.11 to 70.07)	67.53 (66.11 to 68.96)	0.008	0.009
LM	27.36 (26.90 to 27.83)	27.27 (25.87 to 28.66)	0.900	<0.001
g	0.04 (−0.03 to 0.12)	−0.28 (−0.49 to −0.06)	0.006	0.009
Model 3†				
MR	11.78 (11.49 to 12.07)	10.65 (9.77 to 11.53)	0.017	0.007
LNS	8.98 (8.80 to 9.16)	8.54 (7.99 to 9.09)	0.140	0.003
BVFT	37.32 (36.76 to 37.88)	36.16 (34.46 to 37.86)	0.205	0.002
DSC	50.56 (49.86 to 51.26)	48.79 (46.66 to 50.92)	0.122	0.003
ln(TMT-B)	109.73 (107.23 to 112.28)	119.10 (111.05 to 127.74)	0.029	0.006
Faces	69.69 (69.20 to 70.18)	67.64 (66.15 to 69.12)	0.010	0.009
LM	27.46 (26.99 to 27.94)	27.33 (25.88 to 28.77)	0.860	<0.001
g	0.05 (−0.02 to 0.13)	−0.21 (−0.43 to 0.01)	0.028	0.006
Estimated lifetime cognitive decline				
Model 4‡				
MR	11.78 (11.45 to 12.11)	10.30 (9.24 to 11.22)	0.004	0.011
LNS	9.02 (8.83 to 9.21)	8.16 (7.60 to 8.73)	0.006	0.010
BVFT	37.11 (36.26 to 37.96)	35.95 (33.41 to 38.49)	0.394	0.001
DSC	50.61 (49.69 to 51.53)	47.22 (44.46 to 49.98)	0.023	0.007
ln(TMT-B)	109.29 (106.38 to 112.28)	124.71 (114.89 to 135.23)	0.003	0.011
Faces	69.60 (69.03 to 70.17)	67.24 (65.55 to 68.93)	0.010	0.008
LM	27.37 (26.84 to 27.90)	27.36 (25.77 to 28.95)	0.990	<0.001
g	0.06 (0.00 to 0.12)	−0.26 (−0.43 to −0.09)	0.001	0.015
Model 5§				
MR	11.81 (11.47 to 12.15)	10.28 (9.24 to 11.32)	0.007	0.010
LNS	9.03 (8.84 to 9.23)	8.24 (7.64 to 8.83)	0.013	0.008
BVFT	37.26 (36.94 to 38.13)	36.53 (33.89 to 39.17)	0.608	<0.001
DSC	50.61 (49.68 to 51.55)	48.22 (45.38 to 51.08)	0.121	0.003
ln(TMT-B)	109.18 (106.17 to 112.28)	122.73 (112.73 to 133.49)	0.010	0.009
Faces	69.70 (69.13 to 70.28)	67.32 (65.56 to 69.08)	0.012	0.008
LM	27.47 (26.93 to 28.01)	27.51 (25.86 to 29.15)	0.963	<0.001
g	0.07 (0.01 to 0.13)	−0.22 (−0.39 to −0.04)	0.003	0.012

Data are adjusted mean (95% CI). n = 807–810 for model 1; n = 806–809 for model 2; n = 775–777 for model 3; n = 798–801 for model 4; n = 767–769 for model 5. Means for ln(TMT-B) are geometric means. *Adjusted for age, sex, and baseline score. †Model 2 + baseline smoking, retinopathy, and year 4 data on HDL cholesterol, total cholesterol, systolic blood pressure, diastolic blood pressure, HbA_{1c}, stroke, TIA, angina, and MI. ‡Adjusted for age, sex, and baseline MHVS. §Model 4 + baseline smoking, retinopathy, and year 4 data on HDL cholesterol, total cholesterol, systolic blood pressure, diastolic blood pressure, HbA_{1c}, stroke, TIA, angina, and MI.

subsequent levels of cognitive function (31). However, people with type 1 diabetes typically are younger and have a lower prevalence of comorbidities than those with type 2 diabetes (32). In addition, the Diabetes Interventions and Complications Trial cohort was atypical in that the participants had been selected for having high compliance with treatment and a low risk of hypoglycemia such that these findings may have been affected by low prevalence of both the risk factor (hypoglycemia) and the outcome (age-related cognitive decline). In type 2

diabetes, one relatively small study established no links between a baseline history of severe hypoglycemia and conversion among normal cognition, impairment, and frank dementia over 18 months (14). Conversely, some evidence suggests that the experience of hypoglycemia may be a risk factor for future dementia developing in type 2 diabetes (6,7,9). Dementia lies at an end point of the continuum of age-related cognitive impairment, and to our knowledge, the current study has supplemented the current literature by providing the most robust evidence to date that exposure to severe hypoglycemia either preceding or concurrent with change in cognition during aging is associated with an increase in the rate of age-related cognitive decline in older people with type 2 diabetes without frank dementia. The finding of a relationship between hypoglycemia and the memory domain in particular is consistent with published evidence for associations of hypoglycemia with dementia, which commonly is preceded by memory impairment (33).

The findings contrast those of the ACCORD-MIND and ADVANCE trials in which patients in intensive treatment groups (with higher incidence of hypoglycemia) experienced cognitive decline at similar rates over 40 months and 5 years of follow-up, respectively, compared with the respective standard treatment groups (15,16). However, both studies were randomized controlled trials involving strict glycemic control and with cognitive function as a secondary end point. Because improving glycemic control may improve cognitive dysfunction when glycemic control is suboptimal (34), detrimental effects of hypoglycemia were potentially counteracted by the specific therapeutic interventions. The ADVANCE trial also assessed cognitive decline with a screening instrument for dementia, which is likely to be insensitive to subtle cognitive changes (35), and annual incidence of hypoglycemic episodes (defined on the basis of criteria comparable to severe hypoglycemia in the current study) was low compared with the ET2DS and ACCORD-MIND trials because none of its participants were receiving insulin treatment.

In addition to its prospective nature, the strengths of the current study lie in the relatively large size and in the population being representative of the full spectrum of people with type 2 diabetes living in the community, with treatment modalities ranging from diet to insulin, and with the inclusion of the age range at which cognitive decline often becomes apparent. A detailed battery of validated cognitive tests covered the major cognitive domains, and a reasonably comprehensive list of potential confounders was considered in the analyses, although, of course, residual confounding by any unmeasured variable cannot be ruled out. Despite potential weakness in the self-reporting of severe hypoglycemia given that not all severe episodes generate symptoms, particularly in people who have impaired awareness of hypoglycemia (36), a short prospective survey embedded into the main study demonstrated that the participants appeared to be identifying most, if not all, episodes at least of symptomatic severe hypoglycemia and that their recall (even over a number of years) was reasonably accurate. Although self-reported episodes of severe hypoglycemia may not represent all episodes of hypoglycemia, including milder episodes or symptom-free severe episodes, the measure appears to be a useful marker of a more generalized risk of exposure to hypoglycemia. One limitation of the study, which is inherent to all observational studies, is the inability to evaluate the potential for causality in the reported associations. Nonetheless, such observational studies make important contributions to the understanding of associations and inform the design of future studies aimed specifically at investigating the issue of causality. The mechanism by which hypoglycemia could potentially disrupt cognitive function is unclear. Although reports of permanent brain damage or chronic severe cognitive deficit are rare (37,38), glucose deprivation has been directly linked to neuronal death in vitro, and some evidence in type 1 diabetes suggests structural differences in the brain between patients who have and those who have not been exposed to hypoglycemia (3).

In the current study, we show that low cognitive ability is associated with an increase in the risk of subsequent episodes of severe hypoglycemia. Moreover, severe hypoglycemia at baseline and during follow-up was associated with an increased risk of subsequent and/or concurrent cognitive decline. If the latter association is found to be causal in nature, it will be necessary to address the effect of strict glycemic control on cognitive function in the clinical management of older people with type 2 diabetes. In the meantime, change in cognitive function should be considered as a clinical end point in the design of all future randomized trials of novel antidiabetes agents that have the potential to induce or augment the frequency of hypoglycemia.

Funding. The sponsor for the ET2DS was the University of Edinburgh. The study was funded by the Medical Research Council (U.K.) and the Chief Scientist Office of the Scottish Executive. I.J.D., B.M.F., and J.F.P. are members of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative (which has funding from the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and Medical Research Council, G0700704/84698).

Duality of Interest. This study has received funding from Pfizer plc. M.W.J.S. has received fees for speaking from Novo Nordisk, Eli Lilly, Pfizer, and Bristol-Myers Squibb and has received support for travel and accommodations at a scientific meeting from Sanofi. No other potential conflicts of interest relevant to this article were reported.

The funder had no other role in the design, analysis, or preparation of this article.

Author Contributions. I.F. performed the literature search and statistical analysis, contributed to the data collection, created the figure, and drafted the manuscript with supervision from I.J.D., M.W.J.S., and J.F.P. P.P.A., M.K., C.M.R., J.R.M., and S.M. contributed to the data collection, interpretation of findings, and preparation of the final manuscript. I.J.D. and B.M.F. contributed to the interpretation of findings and preparation of the final manuscript. M.W.J.S. and J.F.P. contributed to the interpretation of findings and preparation of the final manuscript, conceived and designed the ET2DS, and oversaw the data acquisition and

analysis. I.F. and J.F.P. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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