Neurocognitive Outcomes in Young Adults With Early-Onset Type 1 Diabetes

A prospective follow-up study

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OBJECTIVE—The aim of this study was to reexamine the neurocognitive function of a cohort of young adults with early-onset type 1 diabetes and compare their cognitive function to a matched control group. We also examined whether cognitive function was related to prospectively obtained severe hypoglycemia history, long-term glycemic control, or severe diabetic ketoacidosis.

RESEARCH DESIGN AND METHODS—Testing included Wechsler Intelligence Scale for Children and Adults, Wechsler Memory Scale, Cattell Culture Fair Intelligence Test (CCFIT), Wisconsin Card Sorting Test (WCST), youth and adult self-report, and Beck Depression Inventory. We tested 34 control subjects (mean ± SE, age 19.5 ± 0.5 years) and 33 type 1 diabetic subjects (age 19.3 ± 0.5 years, age at type 1 diabetes onset 3.3 ± 0.3 years, A1C from diagnosis 8.7 ± 0.1%, and diabetes duration 16.0 ± 0.5 years).

RESULTS—There was no difference in full-scale IQ scores in type 1 diabetic and control subjects (100.7 ± 2.0 vs. 102.5 ± 1.4). There was no difference between groups in memory subtests or in reporting of emotional and behavioral difficulties. The type 1 diabetes group scored lower on the CCFIT for fluid intelligence compared with control subjects ($P = 0.028$) and also scored lower on WCST with more perseverative errors ($P = 0.002$) and fewer categories completed ($P = 0.022$).

CONCLUSIONS—These data suggest no difference in general intellectual ability, memory, and emotional difficulties in our cohort of young adults with early-onset type 1 diabetes compared with control subjects and no deterioration over time. There were, however, findings to suggest subtle changes leading to poorer performance on complex tasks of executive function.

Diabetes Care 34:2192–2197, 2011

The impact of type 1 diabetes on the developing brain remains controversial. Earlier age of diabetes onset has long been identified as one of the strongest risk factors associated with cognitive dysfunction, ranging from poorer performance on general intellectual testing (1,2) to specific deficits with visuospatial tasks, attention, and psychomotor efficiency. The effect of early-onset diabetes, however, is confounded by the impact of recurrent severe hypoglycemia. Repeated severe hypoglycemia has been reported to adversely affect various cognitive domains, in particular long-term memory, attention, and verbal IQ, although this has not been consistent across studies (3,4). Moreover, many of these studies are limited by their retrospective collection of hypoglycemia history.

We previously reported neurocognitive outcomes in 84 children with early-onset diagnosis of type 1 diabetes defined as type 1 diabetes onset before 6 years of age (4). In that initial study, we compared those subjects who had a history of early severe hypoglycemia with those who had a history of late severe hypoglycemia and also compared those who had experienced severe hypoglycemia with peers who had no history of seizures. Surprisingly, there were no group differences revealed on intellectual, memory, or behavioral measures. Furthermore, there was no evidence that episodes of seizure or coma, even those occurring in early childhood, resulted in broad cognitive dysfunction, nor was there evidence of specific memory difficulties at the time of testing.

In this study, we reevaluate the neurocognitive function of the cohort—with onset of type 1 diabetes before age 6 years—now that they are young adults. This early-onset type 1 diabetes cohort is unique in that all subjects were initially recruited from a population-based cohort and have been prospectively followed from diagnosis with documentation of hypoglycemia rates and other key clinical data, including A1C, at regular 3-month clinic visits.

Our aims were, first, to determine whether there had been any deterioration in neurocognitive function in this population-based cohort of young adults with early-onset type 1 diabetes over the 10 years since they were previously tested. Second, we sought for the first time to compare the neurocognitive outcomes of this cohort to a group of age- and sex-matched healthy young adults. Finally, we aimed to determine whether cognitive function in this cohort of patients with early-onset type 1 diabetes was related to their severe hypoglycemia history, long-term glycemic control, or history of severe diabetic ketoacidosis.

RESEARCH DESIGN AND METHODS

—Patients with early-onset type 1 diabetes, defined as onset of type 1 diabetes before age 6 years, attending Princess Margaret Hospital and who had been treated continuously at the center were eligible for the original study. Princess Margaret Hospital is the only pediatric diabetes referral center for the population of Western Australia, and almost all children

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Received 13 April 2011 and accepted 11 July 2011.
DOI: 10.2337/dc11-0697

diagnosed with type 1 diabetes in the state are registered and treated there. Previous studies have shown that this center has a case ascertainment close to 100%. All patients have had ongoing prospective documentation from diagnosis at 3-month intervals of hypoglycemic events, diabetic ketoacidosis, and glycemic control, measured by A1C. Severe hypoglycemia is defined as coma or seizure associated with hypoglycemia. Patient data were collected prospectively at routine clinic visits every 3 months using a specifically designed data collection form completed by a limited number of physicians. The details of data collection have been documented previously (5). In summary, both patients and parents were instructed on how to record details of the hypoglycemic event, including blood glucose levels and response to treatment. This information was subsequently reviewed by the clinician and if validated, recorded on the data collection form.

The original type 1 diabetes cohort consisted of 84 children with early-onset type 1 diabetes (4). This cohort included children with a history of early severe hypoglycemia, defined as severe hypoglycemia occurring before the age of 6 years; those with a history of late severe hypoglycemia, defined as severe hypoglycemia occurring after the age of 6 years; and those with early-onset diabetes with no history of severe hypoglycemia. Recruitment occurred between 1999 and 2000, and neurocognitive assessment was performed at the mean age of 10.0 years (range 6–15 years). Of these 84 subjects, 79 also went on to have neuroimaging with magnetic resonance imaging scans (6) and electroencephalograms.

Ten years later in 2009, we contacted 77 of these subjects (98%) for repeat neurocognitive assessment, neuroimaging, and electroencephalogram. Of those contacted, 33 (42%) subjects attended both neuroimaging and cognitive assessments. An additional eight participants attended neuroimaging only. A total of seven patients agreed to take part but did not attend three appointments arranged; three patients refused because of work or school commitments. An additional 17 patients refused, either with no reason given or because they did not wish to take part in research; and 9 patients had moved, either interstate or to a rural/remote area. In addition to the early-onset type 1 diabetes cohort, 34 age- and sex-matched siblings of patients with type 1 diabetes from the Western Australian type 1 diabetes database were recruited as control subjects. Control subjects reported no significant medical conditions and did not have type 1 diabetes.

Procedures

Subjects attended for 1 day of neurocognitive testing lasting ~8 h. Tests were administered by psychologists blind to the subjects' medical history. There were set breaks for rest and meals. Blood glucose levels were obtained on arrival and at 2-h intervals for the type 1 diabetes cohort. Levels were maintained between 4 and 15 mmol/L for the duration of neurocognitive testing.

Neurocognitive measures

Wechsler Intelligence Scale for Children and Wechsler Adult Intelligence Scale. General intellectual ability was measured using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (7) for subjects <16 years old and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (8) for subjects aged ≥16 years. Eight core subtests (block design, similarities, digit span, coding, vocabulary, letter-number sequencing, matrix peasoning, and symbol search) and two supplementary subtests (picture completion, and information) were administered. Full-scale IQ, verbal comprehension, perceptual reasoning, working memory, and processing speed index scores were computed by combining age-scaled subtest scores. While the WISC-IV and WAIS-IV are not entirely comparable, the correlation for full scale IQ scores between both tests is 0.91. This suggests that they are measuring highly similar constructs.

Wechsler Memory Scale. Memory was measured using the Wechsler Memory Scale, Fourth Edition (WMS-IV) (9). The WMS-IV is an individually administered battery that provides subtest and composite scores that are used to assess various memory abilities in individuals aged 16–90. The current study used three subtests (logical memory, verbal paired associates, and visual reproduction) administering both immediate and delayed-recall components. These subtests were used to compute three index scores (auditory memory, immediate memory, and delayed memory).

While the WMS-IV is designed to assess memory in individuals ≥16 years old, subjects aged 14 and 15 years in the current study were also assessed using this task. Previous research by Paniak et al. (10) assessed subjects aged 9–15 years on the Wechsler Memory Scale–Revised and found that this age-group had percentage recall scores for the logical memory and visual reproduction subtests similar to adult percentage recall scores. Typically, individuals aged ≤16 years are assessed using the Children's Memory Scale (CMS); however, there are difficulties in transferring scores from the CMS to the WMS-IV when calculating a group total. Correlations between indexes on the CMS and the WMS-IV differ greatly (range: r = 0.25–0.70). As a consequence, scaled scores for seven subjects younger than the age of 16 were computed using normative data for subjects aged 16 years.

Cattell Culture Fair Intelligence Test. Fluid intelligence was measured using the Cattell Culture Fair Intelligence Test (CCFIT). The CCFIT assesses novel problem-solving ability without relying on the use of knowledge that is specific to certain cultures. As a consequence, the CCFIT aims to measure intelligence independent of cultural experience, educational level, or verbal ability. This is aided by the task being largely nonverbal in nature, reducing the bias that is often found in more crystallized measures of fluid intelligence. The task consists of four timed subtests—series, classifications, matrices, and conditions—that test subjects' ability to perceive the relationship between figures and shapes. Raw scores for each of the subtests were converted into age-adjusted scaled scores (11), which were used to calculate a total score.

Wisconsin Card Sorting Test. The Wisconsin Card Sorting Test (WCST) (12) is a measure of executive function. The WCST assesses the execution of functions such as set-shifting, concept formation, and problem solving in response to tester feedback. The subjects were presented with four pictographic reference cards that were different in color, form, and number. Subjects were then presented with a deck of stimulus cards and asked to match each card to one of the four reference cards in whichever way they thought best. Without being informed, the participant was required to match cards using the rules of color, form, or number. Throughout the test, the administrator provided feedback to the subject, indicating to them whether they were correct or incorrect. Once the subject had achieved 10 correct matches in a row, the matching rule was changed without the subject's knowledge. Psychometric scores were generated from the WCST, the primary score being the number of perseverative errors made before the

subject realizes that the matching-criterion rule has changed.

Youth Self Report and Adult Self Report. Aspects of adaptive functioning and other behavioral problems were measured using the Achenbach Youth Self Report (YSR) (13) and Adult Self Report (ASR) (14). Subjects aged ≥18 years were administered the ASR, whereas the YSR was administered to subjects aged <18 years. Both questionnaires consist of eight indexes: anxious/depressed, attention problems, withdrawn, aggressive behavior, somatic complaints, rule-breaking behavior, thought problems, and intrusive behavior. Scores on the separate indexes form internalizing and externalizing scores that were used to calculate a total score.

Beck Depression Inventory. Symptoms of depression were evaluated using the Beck Depression Inventory, Second Edition (BDI-II) (15). The BDI-II is a 21-item self-report questionnaire that assesses the intensity of depression in both clinical and normal population groups.

State-Trait Anxiety Index and State-Trait Anxiety Index for Children. Anxiety was measured using the State-Trait Anxiety Index (STAI) for subjects aged >15 years and the State-Trait Anxiety Index for Children (STAI-C) for subjects aged ≤14 years (16,17). The STAI and the STAI-C are self-report instruments that measure and distinguish between both the temporary condition of state anxiety and the long-standing quality of trait anxiety.

Laboratory measurements

A1C was measured at each 3-month visit. A1C was assessed by an agglutination inhibition immunoassay (Ames DCA 2000; Bayer Ltd., Mishawaka, IN). The inter- and intra-assay coefficients of variation were 2.5 and 2.3%, respectively.

Statistical analysis

Clinical characteristics of the groups were compared using Student *t* test (mean ± SE) for variables normally distributed.

RESULTS

Clinical characteristics

The clinical characteristics of the early-onset type 1 diabetes cohort are shown in Table 1. Subjects with early-onset type 1 diabetes who attended for follow-up neurocognitive assessment did not differ from those who did not participate in the follow-up study with respect to age, duration of diabetes, mean A1C from diagnosis, or A1C at their last visit. The proportion of subjects with a history of early severe hypoglycemia, late severe hypoglycemia, and no history of severe hypoglycemia did not differ between those who attended and those who did not.

Table 1—*Clinical characteristics of early-onset type 1 diabetes cohort*

Clinical characteristic	Type 1 diabetes	Type 1 diabetes (did not participate in follow-up study)	*P*
Sample size (% of original cohort)	33 (42)	46 (58)	
Age (years)	19.3 ± 0.5	19.1 ± 0.4	0.758
Male (%)	15 (45)	21 (46)	0.986
Duration of diabetes (years)	16.0 ± 0.5	16.0 ± 0.5	0.950
Mean A1C from diagnosis (%)	8.7 ± 0.1	8.7 ± 0.1	0.841
A1C at last visit (%)	8.8 ± 0.3	8.8 ± 0.2	0.874
Severe hypoglycemia history—subjects in each group (%)			
Early severe hypoglycemia	6 (18)	13 (28)	0.301
Late severe hypoglycemia	14 (42)	20 (43)	0.926
Never had seizure/coma	13 (40)	13 (28)	0.299

Data are *n* (%) and mean ± SE.

Subjects who attended for follow-up testing performed similarly to those who did not attend on the Wechsler Intelligence Scale for Children, Third Edition (WISC-III); CMS; Achenbach child behavior checklist; and Children's Depression Index at baseline testing. Both groups were also similar in terms of gray and white matter volumes and left and right hippocampal volumes measured by magnetic resonance imaging. The proportion of subjects reported to have mesial temporal sclerosis was also similar in both groups ($P = 0.44$). The Index of Relative Socioeconomic Advantage and Disadvantage published by the Australia Bureau of Statistics (18) was used to determine the socioeconomic status of our cohort. Almost half (45%) of the type 1 diabetes group were classified as being in the highest quintile of least socioeconomic disadvantage, with 6% being in the lowest quintile or group of highest disadvantage. This is in keeping with our epidemiological studies showing that the incidence of type 1 diabetes was higher in higher socioeconomic groups (19). Our control population was similar to our type 1 diabetes cohort in terms of socioeconomic status. Our type 1 diabetes cohort was largely white with one subject of Indian descent. All of our control subjects were white.

Cognitive tests

Table 2 shows scores from the cognitive assessment for the early-onset type 1 diabetes cohort and control subjects. There were 33 type 1 diabetic subjects assessed at the mean age of 19.3 ± 0.5 years. There were 34 age- and sex-matched control subjects also assessed at the mean age of 19.5 ± 0.5 years. There was no difference in full-scale IQ scores in the type 1 diabetes cohort compared with control subjects (100.7 ± 2.0 vs. 102.5 ± 1.4; $P = 0.466$), nor were there any differences on the four index scores of verbal comprehension, perceptual reasoning, working memory, and processing speed ($P = 0.971$, $P = 0.504$, $P = 0.862$, and $P = 0.235$, respectively). There were no differences observed between the type 1 diabetes group and control subjects with WMS-IV subtests of auditory memory, immediate memory, and delayed memory ($P = 0.825$, $P = 0.757$, and $P = 0.368$, respectively).

The type 1 diabetes group scored lower on the CCFIT compared with control subjects (109.5 ± 2.3 vs. 117.8 ± 2.9; $P = 0.028$ with effect size of −0.53). With a conservative Bonferroni correction, this would just fail to reach the appropriate level of significance required. Nevertheless, the effect size for the CCFIT is approximately seven times the mean effect size for the null results. Moreover, the type 1 diabetes group also scored lower on the WCST with more perseverative errors and fewer completed categories than the control group ($P = 0.002$ and $P = 0.022$, respectively), usually taken to be indicators of processes related conceptually to fluid intelligence.

There were no differences between groups in reporting of emotional and behavioral difficulties assessed by both YSR and ASR ($P = 0.947$). There was also no difference in reporting of depressive

Table 2—*Results from neurocognitive tests*

	Type 1 diabetes	Control	*P*	Cohen *d* effect size
Sample size	33	34		
Age (years)	19.3 ± 0.5	19.5 ± 0.5	0.781	
WISC-IV and WAIS-IV				
Full-scale IQ	100.7 ± 2.0	102.5 ± 1.4	0.466	−0.18
Verbal comprehension index	100.6 ± 2.0	100.7 ± 1.7	0.971	−0.01
Perceptual reasoning index	100.3 ± 2.0	102.1 ± 1.6	0.504	−0.17
Working memory index	100.9 ± 2.4	101.4 ± 1.9	0.862	−0.04
Processing speed index	101.0 ± 2.2	104.8 ± 2.3	0.235	−0.29
WMS-IV				
Auditory memory index	102.6 ± 3.0	103.4 ± 2.1	0.825	−0.05
Immediate memory index	101.0 ± 3.0	102.2 ± 2.3	0.757	−0.08
Delayed memory index	99.9 ± 3.2	103.0 ± 2.5	0.368	−0.19
CCFIT				
CCFIT IQ	109.5 ± 2.3	117.8 ± 2.9	0.028*	−0.53
WCST				
Perseverative errors	19.2 ± 2.1	11.1 ± 1.3	0.002*	0.74
Completed categories	4.8 ± 0.3	5.6 ± 0.2	0.022*	−0.58
YSR and ASR				
Internalizing behaviors	53.3 ± 1.3	52.0 ± 1.6	0.534	0.15
Externalizing behaviors	48.8 ± 1.6	50.9 ± 1.7	0.389	−0.22
YSR/ASR total	50.4 ± 1.4	50.5 ± 1.4	0.947	−0.01
BDI-II				
BDI-II total	5.3 ± 1.0	5.8 ± 0.9	0.762	−0.09
STAI and STAI-C				
State total	33.6 ± 1.6	33.4 ± 1.3	0.909	0.02
Trait total	34.0 ± 1.4	34.8 ± 1.5	0.737	−0.10

Data are mean ± SE. *Significant results.

symptoms between groups assessed by BDI-II ($P = 0.762$). Scores for both state and trait anxiety were also similar for both groups ($P = 0.909$ and $P = 0.737$, respectively).

Severe hypoglycemia

Results of the cognitive tests by history of severe hypoglycemia are shown in Table 3. There was no difference between the early, late, and no history of severe hypoglycemia groups in full-scale IQ scores and indexes, memory subtests, and CCFIT scores. The early severe hypoglycemia subgroup did, however, complete fewer categories in the WCST compared with control subjects ($P = 0.028$).

A1C

The mean A1C from diagnosis for the type 1 diabetes group was 8.7% (range 7.2–10.2). There was no difference between full-scale IQ scores for subjects in the highest A1C quartile or lowest A1C quartile compared with control subjects ($P = 0.519$ and $P = 0.918$, respectively). In addition, there was no difference in full-scale IQ scores or other neurocognitive measures tested for subjects with a history of severe diabetic ketoacidosis versus those with no history of severe diabetic ketoacidosis.

Microvascular complications

Microvascular complications were assessed in the type 1 diabetes group according to standard clinical guidelines, including clinical examination, annual retinal examination by an ophthalmologist, and annual morning urine testing for microalbuminuria. At the last urinalysis, 3 of our 33 participants had evidence of microalbuminuria. None of the subjects had evidence of clinically significant diabetic retinopathy. The three subjects with microalbuminuria did not demonstrate poorer performance on the cognitive tests.

Comparison with previous WISC-III results

The mean full-scale IQ results for the original type 1 diabetes cohort ($n = 84$) was 104.3 ± 1.3 on the WISC-III. For the subset that attended for the follow-up study ($n = 33$), their follow-up full-scale IQ result was 100.7 ± 2.01 on either the WISC-IV or WAIS-IV compared with the previous mean full-scale IQ result of 106.2 ± 2.1 scored on the WISC-III 10 years earlier.

CONCLUSIONS—This study is the first to examine a population-based cohort of children diagnosed with diabetes before the age of 6 years and followed longitudinally for ~16 years from diagnosis and to have prospective documentation of severe hypoglycemia history collected in a rigorous and systematic manner. Many previous studies have relied on retrospective assessment. A1C was also recorded from diagnosis, allowing, for the first time, an assessment of the effect of glycemia during childhood on cognitive development. We found no differences in tests of general intellectual ability, memory, and emotional difficulties compared with age- and sex-matched healthy control subjects. A history of early seizure or coma associated with hypoglycemia occurring before the age of 6 years was not associated with lower full-scale IQ scores in young adults with early-onset type 1 diabetes. Overall, these are reassuring findings for families with young children with type 1 diabetes.

The type 1 diabetes group did, however, score lower on specific tests of fluid intelligence and complex tasks of executive function. Northam et al. (20) also found similar poorer performance on measures of executive function and processing speed. While processing speed has also been linked to fluid intelligence, the correspondence between deficits in the CCFIT and the WCST suggests that the link has more to do with executive functioning and, in particular, the processes associated with prefrontal cortex. Such cognitive processes include inhibition, set-shifting, goal maintenance, and other processes considered the foundations of fluid intelligence. Executive functions allow individuals to perform behaviors that are independent and self-serving. Such behaviors are needed in situations where habitual behaviors and responses are not appropriate, such as multitasking, deciding between two different alternatives, and mental planning. It is interesting to speculate on the impact that defects in executive function may have for diabetes self-care behaviors, particularly in view of the increasing demands on patients and the complexity of such care.

Executive function tasks appear to be more significantly affected in the early severe hypoglycemia subgroup, suggesting that there may be subtle developmental changes in the frontal cortex. Our numbers,

Table 3—*Results from neurocognitive tests by history of severe hypoglycemia*

	Type 1 diabetes			
	Early severe hypoglycemia (before 6 years)	Late severe hypoglycemia (after 6 years)	No history of severe hypoglycemia	Cohen *d* effect size (early severe hypoglycemia vs. control)
Sample size	6	14	13	
Age (years)	20.7 ± 1.5	19.3 ± 0.6	18.6 ± 0.6	
WISC-IV and WAIC-IV				
Full-scale IQ	95.2 ± 4.3	103.3 ± 2.6	100.5 ± 3.7	−0.74
Verbal comprehension index	93.5 ± 3.8	102.1 ± 2.3	102.2 ± 4.5	−0.65
Perceptual reasoning index	97.8 ± 4.8	103.9 ± 3.1	97.6 ± 3.0	−0.41
Working memory index	91.5 ± 5.1	102.9 ± 2.9	103.0 ± 4.4	−0.80
Processing speed index	103.0 ± 3.5	100.9 ± 3.2	100.2 ± 4.4	−0.14
WMS-IV				
Auditory memory index	101.7 ± 6.5	107.4 ± 3.9	97.8 ± 5.4	−0.11
Immediate memory index	100.7 ± 9.1	105.2 ± 4.6	96.5 ± 4.2	−0.09
Delayed memory index	97.0 ± 9.5	103.3 ± 3.7	97.5 ± 5.8	−0.40
CCFIT				
CCFIT IQ	107.5 ± 8.1	111.9 ± 4.9	107.9 ± 3.8	−0.66
WCST				
Perseverative error	24.8 ± 5.8	18.6 ± 2.8	17.15 ± 3.6	1.26
Completed categories	3.2 ± 0.8	5.0 ± 0.3	5.6 ± 0.2	−1.71

Data are mean ± SE.

however, are small in the early seizure subgroup. Rovet and Ehrlich (21) also demonstrated poorer performance on the WCST in the seizure group in their 7-year follow-up study of children with type 1 diabetes. These findings suggest that a history of early seizure may be associated with subtle developmental changes, leading to poorer performance on complex tasks of executive function.

Both acute hyperglycemia (22) and chronic hyperglycemia (23) have also been implicated in causing cognitive dysfunction in children with type 1 diabetes. In our group, we found no difference in full-scale IQ in our subjects with higher mean A1C or lower mean AIC compared with control subjects, suggesting that chronic hyperglycemia was not associated with poorer general intellectual ability in this cohort. This may be in part due to the reasonably tight range of A1C for this cohort. The possibility that there is an interaction between glycemic control and severe hypoglycemia cannot be discounted, but larger prospective studies would be required to explore this issue.

For the type 1 diabetes cohort, when comparing the full-scale IQ scores on WISC-IV and WAIS-IV to the previous results obtained from the WISC-III, there appears to be a drop of 5.5 IQ points on follow-up testing. This apparent decline should be treated with caution. New intelligence tests are restandardized so that the population mean is set at 100 as a result of the Flynn effect (24), a phenomenon where performance on intelligence tests is improving on average by ~3–4 IQ points per decade (25). In practice, this means that the same level of performance on a new version of a test will be scaled to a lower IQ score. Taking into account the Flynn effect, there is no significant deterioration in this cohort over the 10 years (current 104.7 ± 2.0 vs. previous 106.2 ± 2.1; $P = 0.150$). We conclude that there was no deterioration in full-scale IQ scores in our cohort after 10 years of childhood type 1 diabetes.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

T.T.L. contributed to study design, researched data, and wrote the manuscript. M.A. contributed to study design, researched data, and contributed to discussion. K.A.M. researched data and wrote the manuscript. E.A.D. contributed to discussion and reviewed and edited the manuscript. T.W.J. contributed to study design, researched data, and wrote the manuscript.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

The authors thank the participants and families of Princess Margaret Hospital Diabetes Clinic for participating in this study.

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