Risk Factors for Decline in IQ in Youth With Type 1 Diabetes Over the 12 Years From Diagnosis/Illness Onset

Ashleigh Lin,[1] Elisabeth A. Northam,[2,3,4] George A. Werther,[3,4,5] and Fergus J. Cameron[3,4,5]

Diabetes Care 2015;38:236–242 | DOI: 10.2337/dc14-1385

OBJECTIVE

This study examined illness-related change in intelligence quotient (IQ) in a cohort of youth with type 1 diabetes studied prospectively from disease onset in childhood to follow-up 12 years later in late adolescence/early adulthood.

RESEARCH DESIGN AND METHODS

Participants included type 1 diabetes patients (*n* = 95; mean age at follow-up 21.3 years) and healthy control participants (HCs; *n* = 67; mean age at follow-up 21.0 years) from a cohort followed prospectively. Measures included Wechsler Preschool and Primary Scale of Intelligence-Revised, Wechsler Intelligence Scale for Children-Revised, and Wechsler Abbreviated Scale of Intelligence and prospective collection of data on metabolic control history.

RESULTS

Young people with type 1 diabetes showed greater decline in verbal IQ (VIQ) and full-scale IQ (FSIQ), but not performance IQ (PIQ), than HCs. Within the diabetes group, a younger age at diabetes onset was associated with a decline in PIQ and FSIQ ($P \leq 0.001$). A history of hypoglycemic seizures was associated with a decline in VIQ ($P = 0.002$). Long-term metabolic control was not associated with changes in IQ. Interaction terms were not significant, suggesting no moderating effect of one diabetes-related variable over another.

CONCLUSIONS

The presence of diabetes may negatively influence some aspects of IQ over time. Specific illness risk factors, such as an earlier age of disease onset and a history of hypoglycemic seizures, appear to put the young person at greater risk. Academic progress of children identified as at risk should be monitored and educational supports provided if necessary.

A constant supply of glucose is critical for normal cerebral metabolism (1,2). Thus the brain is one of the major organ systems affected in type 1 diabetes, as glucose homeostasis is frequently disrupted, even in well-controlled diabetes (3). Developing brains have high cerebral energy needs associated with brain growth and neural pruning and may be more sensitive than adults to glucose fluctuations (3). It is important to document specific illness-related risk factors for brain changes in young people with type 1 diabetes. Better understanding of the impact of childhood-onset disease on the central nervous system (CNS) will facilitate evidence-based pediatric management

[1]Telethon Kids Institute, University of Western Australia, Perth, Australia
[2]Department of Psychology, Royal Children's Hospital, Melbourne, Australia
[3]Department of Endocrinology and Diabetes, Royal Children's Hospital, Melbourne, Australia
[4]Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia
[5]Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia

Corresponding author: Ashleigh Lin, ashleigh.lin@telethonkids.org.au.

Received 3 June 2014 and accepted 5 November 2014.

A slide set summarizing this article is available online.

regimens and proactive interventions to minimize academic underachievement and functional impairment.

There is a growing literature documenting pathophysiological CNS changes (4–13) and neurocognitive deficits (14–23) in youth with type 1 diabetes. However, attempts to identify specific diabetes-related risk factors for CNS compromise have produced inconclusive findings. An association between cognitive deficits and an early age of disease onset is a robust finding (14), but associations between glycemic perturbations and CNS effects are less consistent. Given the alteration in conscious state that accompanies severe episodes, the focus traditionally has been on hypoglycemia as the explanation for cognitive deficits in children with type 1 diabetes. However, neuroimaging findings are inconsistent, with some studies finding no association between hypoglycemia history and structural brain changes (4,12) while others report positive correlations, but with little consistency between the brain regions affected (5,7,9–11). Meta-analytic cognitive studies also provide contrasting findings, with one reporting positive association between hypoglycemia history and cognitive deficit (23) and another finding no association (14).

There is now increasing concern that chronic exposure to hyperglycemia may impact on the developing brain, although research findings to date are inconsistent and probably reflect, in part, difficulty in obtaining accurate reports of lifetime metabolic control, particularly when measured retrospectively. Volumetric reductions in both gray and white matter and altered diffusion tensor imaging (DTI) parameters have been associated with greater exposure to hyperglycemia in several studies (4,6,10–13), but not in others (5,7–9). Similarly, an association between long-term poor metabolic control and cognitive deficits was found in some (5,16–18,20,22) but not other (9,14) studies. There is now compelling evidence that type 1 diabetes impacts upon the developing brain, but our understanding of the causal mechanisms that underlie CNS changes is limited. This makes it difficult to weigh the relative neurotoxicity of glycemic extremes and to tailor management regimens accordingly.

Controlled, longitudinal studies are particularly informative in documenting illness-related changes in cognitive function. The only study to date that has examined within-subject change in intelligence quotient (IQ) from childhood to follow-up in early adulthood (24) is limited by the fact that initial assessment of IQ occurred years after diabetes onset. Thus participants had already been exposed to a period of glycemic dysregulation before baseline assessment. Our group has previously reported that youth with type 1 diabetes had lower full-scale IQ (FSIQ) and verbal IQ (VIQ) scores than healthy community control participants (HCs) when assessed cross-sectionally 12 years after disease onset (9). In the current study, we used data from diabetes onset and from follow-up 12 years later to examine change in IQ scores in youth with type 1 diabetes and HCs. Within the diabetes group, we examined associations between changes in IQ and age of diabetes onset, history of serious hypoglycemia, and longer-term metabolic control.

RESEARCH DESIGN AND METHODS

Participants

Consecutive admissions to the Royal Children's Hospital, Melbourne, Australia, with newly diagnosed type 1 diabetes between 1990 and 1992 (n = 133), together with HCs (n = 126), stratified for age and sex, formed the original cohort. FSIQ $<$70 or history of CNS trauma or disease (e.g., epilepsy) were exclusions. Children with attention deficit hyperactivity disorder or learning difficulties were not excluded. Twelve years later, participants who could be located (125 youth with type 1 diabetes and 93 HCs, 94 and 74%, respectively) were invited for follow-up. A total of 106 participants with type 1 diabetes and 75 HCs consented (rates of 85 and 81%, respectively). Two participants with type 1 diabetes who developed a seizure disorder after diabetes onset were included in the current analyses.

This report is of participants who were assessed on the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; 34 with type 1 diabetes and 21 HCs) (25) or Wechsler Intelligence Scale for Children-Revised (WISC-R; 61 with type 1 diabetes and 49 HCs) (26) at study inception (baseline) and on the Wechsler Abbreviated Scale of Intelligence (WASI) (27) at follow-up 12 years later (95 with type 1 diabetes and 70 HCs). We did not included participants with type 1 diabetes onset before age 3 years who were assessed on the Bayley Scales of Infant Development (28) at baseline (n = 10) or HCs who were recruited later to match this younger cohort and had no baseline data (n = 10). Three HCs without socioeconomic status (SES) information at baseline were excluded from analyses. The sample reported in this article comprised 95 participants with type 1 diabetes and 67 HCs.

All assessments were conducted by psychology-trained research assistants. Blood glucose levels (BGLs) of type 1 diabetes participants were determined prior to assessment by capillary sample to ensure a reading between 4 and 18 mmol/L. There were no significant associations between BGL and IQ score at either time point. This study was approved by the Human Ethics Research Committee of the Victorian Government Department of Human Services.

Measures

SES was measured using the Daniel Scale of Occupational Prestige (29). This scale is based on parental occupation and rated on a six-point scale (1 = high, 6 = low SES). The WPPSI-R (25) and the WISC-R (26) are standardized measures of general intelligence used to assess children aged $<$7 years and 7–16 years, respectively. The WASI is a standardized, brief measure of intelligence for individuals aged 6 to 90 years. These measures provide FSIQ, VIQ, and performance IQ (PIQ) scores (mean = 100, SD = 15). The WPPSI-R, WISC-R, and WASI use similar tasks to assess comparable skills of general intelligence, and summary scale scores are highly correlated ($>$0.8) (27). The use of a longitudinally assessed HC group should control for variability related to the use of different test instruments at different time points.

Illness-Related Variables

The age of onset of diabetes was documented. Episodes of hypoglycemia associated with seizure/coma were recorded and corroborated through medical records. HbA_{1c} measurements from diagnosis were obtained for each patient (number of measurements, range = 9–55, median = 36) from hospital and clinic databases. HbA_{1c} levels prior to 1994 were measured using Bio-Rad (Hercules, CA) affinity column chromatography method and after 1994 using a Bayer

(Calabria, Barcelona, Spain) DCA 2000 latex immunoagglutination method. Equilibration between the two methods was achieved using the following: HbA_{1c} (measured by immunoagglutination) = 1.2 + 1.07 × HbA_{1c} (measured by column chromatography). This equation was derived after regression analyses were performed on 50 patients with paired samples using both measuring techniques. The percentage of total time from diagnosis that HbA_{1c} was ≥9.0% (74.9 mmol/mol) was calculated to estimate overall metabolic control. Previous episodes of diabetic ketoacidosis (DKA) were collected via self-report.

For the purpose of illustration and reporting mean change in IQ scores, each illness-related risk was dichotomized into two groups: diabetes onset <6 years (early-onset diabetes) and onset ≥6 years (late-onset diabetes); participants with one or more episode of hypoglycemia with seizure/coma (seizure history) versus no history of seizures/coma (no seizure); and participants with HbA_{1c} readings ≥9.0% (74.9 mmol/mol) for more than one-third of lifetime measurements (poor control) and those with HbA_{1c} ≥9.0% for less than one-third of lifetime measurements (good control).

Statistical Analyses

For each participant, a change in VIQ, PIQ, and FSIQ score from baseline to 12-year follow-up was calculated. Positive change scores indicated IQ increase over time; negative change scores indicated decline. ANCOVA was used to investigate the difference in changes in VIQ, PIQ, and FSIQ scores between participants with type 1 diabetes and HCs, covarying for IQ and SES at baseline and length of follow-up. Next, within the type 1 diabetes group, three linear regression analyses were conducted with change in VIQ, PIQ, and FSIQ scores, respectively, entered as the dependent variable. In the first block, age of diabetes onset (onset), number of hypoglycemic episodes (seizures), and percentage of time that HbA_{1c} was ≥9.0% (metabolic control) were entered as predictor variables. IQ and SES at baseline and length of follow-up were entered as covariates. In block two, interaction terms of the diabetes-related variables were entered (onset × metabolic control; onset × seizures; metabolic control × seizures). Here we interpret β-values.

Because participants with an earlier age of onset of diabetes <7 years were assessed by WPPSI-R at baseline and those ≥7 years were assessed by WISC-R, psychometric properties of the tests used may confound analyses. To overcome this, we tested whether change in IQ differed by baseline test (WPPSI-R vs. WISC-R) in HCs, any difference assumed to be a psychometric effect. HCs with WPPSI-R showed significantly greater loss in PIQ than HCs with WISC-R. To account for this, we created a test-standardized change in PIQ score for each participant with diabetes, which was the observed score minus the expected score. The observed score was the change in PIQ over the 12-year follow-up. The expected score was the mean decline in PIQ over time experienced by the HC group for WISC-R and WPPSI-R participants, respectively (essentially the psychometric effect). The test-standardized score for PIQ was used as the dependent variable in regression.

To test potential effects of fewer HbA_{1c} measurements, we selected ≥30 HbA_{1c} values over the follow-up period as a reasonable number of measurements (an average of 2.5 per year of diabetes). The sample with type 1 diabetes was dichotomized into those with ≥30 HbA_{1c} values and <30 values. Correlations were conducted between the percentage of time HbA_{1c} was ≥9.0% and change in IQ scores for each group separately. Next, regression analyses were repeated with those participants with ≥30 HbA_{1c} values only.

To test for effects of concurrent BGLs on cognitive performance, the mean BGL for each illness-related risk group (early or late onset, seizure history or no seizures, poor or good control) were compared using independent *t* tests. Additionally, regression analyses were repeated covarying for BGLs at baseline and 12-year follow-up assessment.

Episodes of DKA were indexed via self-report but were not verified on medical records. Thus analyses of the effect of DKA on change in IQ are exploratory, and results should be interpreted with caution. We conducted ANCOVAs to explore differences in change in IQ for participants reporting one or more

Table 1—Sample characteristics

	Type 1 diabetes (*n* = 95)	HC (*n* = 67)	Test statistic	95% CIs	*P* value
Baseline					
Age, years	8.55 (3.26)	9.07 (3.41)	$t = -0.98$	−1.56, 0.53	0.3
Female sex, *n* (%)	46 (48.4)	34 (50.7)	$\chi^2 = 0.09$		0.8
SES	4.41 (1.21)	4.41 (1.29)	$t = -0.02$	−0.40, 0.39	>0.9
VIQ	103.65 (14.00)	107.06 (12.27)	$t = -1.60$	−7.60, 0.79	0.1
PIQ	109.17 (14.22)	112.76 (11.81)	$t = -1.70$	−7.78, 0.59	0.09
FSIQ	107.05 (14.63)	110.76 (11.89)	$t = -1.71$	−7.98, 0.57	0.09
Follow-up					
Follow-up period, years	13.24 (1.05)	12.44 (1.20)	$t = 4.48$	0.44, 1.15	<0.001
Age, years	21.28 (3.80)	21.03 (3.81)	$t = 0.42$	−0.94, 1.45	0.7
SES	4.38 (1.15)	4.12 (1.10)	$t = 1.45$	−0.09, 0.62	0.2
VIQ	95.81 (12.54)	100.60 (14.15)	$t = -2.27$	−8.95, −0.62	0.02
PIQ	106.27 (13.54)	109.06 (12.71)	$t = -1.32$	−6.95, 1.37	0.2
FSIQ	100.94 (12.87)	105.18 (12.87)	$t = -2.07$	−8.30, −0.19	0.04
Number of hypoglycemic episodes	1.37 (2.35)				
Percentage of time HbA_{1c} ≥9%	43.32 (26.23)				

Data are mean (SD) unless otherwise indicated. Age at baseline is equivalent to age at diagnosis with diabetes. SES, 1 = high, 7 = low.

episode of DKA and those who did not, covaried for IQ and SES at baseline and length of follow-up.

RESULTS

Sample characteristics are presented in Table 1. At baseline, participants with type 1 diabetes did not differ significantly from HCs on age, sex, SES, or IQ scores. As previously reported (9), participants with type 1 diabetes had significantly lower VIQ and FSIQ scores than HCs at follow-up.

Type 1 Diabetes and HCs

Mean changes in IQ scores for participants with type 1 diabetes, HCs, and each risk group are presented in Table 2. Those with type 1 diabetes showed significantly greater decline in VIQ and FSIQ over time than HCs (change in VIQ, $F[1, 157] = 6.47$, $P = 0.01$; change in FSIQ, $F[1, 157] = 5.22$, $P = 0.02$). There was no significant group difference in change in PIQ ($F[1, 157] = 1.28$; $P = 0.3$).

Change in IQ Scores in Relation to Illness-Related Factors

Regression analyses within the type 1 diabetes group are presented in Table 3. For any given baseline score, these models predict the IQ score at 12-year follow-up as predicted by each of the illness-related variables and covariates.

For each regression model, the overall model was significant. Baseline IQ and SES were always significantly associated with change in IQ, and length of follow-up was never significantly associated with change in IQ. A younger age at diabetes onset was significantly associated with negative change in PIQ and FSIQ. Based on the model with change in PIQ as the dependent variable, for any given PIQ score at baseline, the predicted follow-up PIQ score would be reduced by 2.36 points for each year earlier that diabetes onset occurred. Similarly, based on the model for change in FSIQ, for any given baseline FSIQ score, the predicted follow-up FSIQ score would be reduced by 0.97 points for each year earlier that diabetes onset occurred. A greater number of hypoglycemic seizures was significantly associated with negative change in VIQ. Thus, according to the model with VIQ as the dependent variable, for any given baseline VIQ score, VIQ at follow-up would be reduced by 1.19 points for each

Table 2—Mean IQ scores at baseline and 12 years and change in IQ scores for HCs, participants with type 1 diabetes, and illness-related risk groups

	HC ($n = 67$)		Type 1 diabetes ($n = 95$)		Early-onset diabetes ($n = 29$)		Late-onset diabetes ($n = 66$)		Seizure history ($n = 41$)		No seizures ($n = 54$)		Poor control ($n = 60$)		Good control ($n = 35$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
IQ at baseline																
VIQ	107.06	12.27	103.65	14.00	105.41	15.16	102.88	13.51	103.00	15.50	104.15	12.88	102.97	12.93	104.83	15.80
PIQ	112.76	11.81	109.17	14.22	109.24	14.91	109.14	14.02	106.76	13.17	111.00	14.82	109.08	14.46	109.31	14.00
FSIQ	110.76	11.89	107.05	14.63	108.38	15.81	106.47	14.17	105.27	14.63	108.41	14.62	106.52	14.09	107.97	15.68
BGL	—	—	10.04	4.67	9.94	4.87	10.09	4.62	9.86	4.81	10.18	4.61	10.08	4.40	9.98	5.19
IQ at 12 years																
VIQ	100.60	14.15	95.81	12.54	94.90	13.50	96.21	12.18	91.98	12.25	98.72	12.06	95.67	13.37	96.06	11.13
PIQ	109.06	12.71	106.27	13.54	99.79	12.79	109.12	12.95	105.22	14.72	107.07	12.65	105.97	14.32	106.80	12.27
FSIQ	105.18	12.87	100.94	12.87	97.00	13.36	102.67	12.36	98.17	13.62	103.04	11.98	100.72	13.71	101.31	11.48
BGL	—	—	11.36	5.98	12.14	6.19	10.99	5.88	11.21	5.63	11.49	6.31	12.79	6.37	8.69	4.04
Change in IQ																
VIQ	−6.46	15.10	−7.84	10.58	−10.52	12.28	−6.67	9.60	−11.02	11.35	−5.43	9.35	−7.30	10.82	−8.77	10.23
PIQ	−3.70	11.02	−2.89	11.69	−9.45	11.18	−0.02	10.79	−1.54	11.12	−3.93	12.11	−3.12	11.95	−2.51	11.41
FSIQ	−5.58	11.92	−6.12	9.89	−11.38	10.03	−3.80	8.96	−7.10	9.98	−5.37	9.85	−5.80	9.68	−6.66	10.35

Change in IQ is calculated by subtracting baseline score from 12-year score. Thus a positive change indicates increase in IQ and a negative change indicates decrease in IQ. Ninety-one individuals with diabetes have BGL readings at baseline; 86 have readings at 12 years.

Table 3—Regression analyses within the group of participants with type 1 diabetes

	B	Beta	*t*-score	95% CI for B	*P* value
Change in VIQ (overall model: F = 10.239, $P < 0.001$)					
Onset	0.260	0.080	0.853	−0.346, 0.865	0.4
Seizure	−1.186	−0.264	−3.082	−1.951, −0.421	0.003
Metabolic control	0.025	0.061	0.740	−0.042, 0.091	0.5
Change in PIQ (overall model: F = 17.682, $P < 0.001$)					
Onset	2.359	0.564	6.876	1.677, 3.040	<0.001
Seizure	0.166	0.029	0.392	−0.677, 1.010	0.7
Metabolic control	−0.016	−0.031	−0.425	−0.091, 0.059	0.7
FSIQ (overall model: F = 11.877, $P < 0.001$)					
Onset	0.966	0.317	3.503	0.418, 1.515	0.001
Seizure	−0.559	−0.133	−1.627	−1.241, 0.124	0.1
Metabolic control	0.002	0.004	0.054	−0.058, 0.062	>0.9

The dependent variable used was the test-standardized score for change in PIQ. B, unstandardized β-coefficient; Beta, standardized β-coefficient.

additional seizure. Metabolic control did not significantly predict change in IQ score. None of the interaction terms were significant.

Examining the Effect of Reduced HbA_{1c} Measurements

Correlations between percentage of time HbA_{1c} was ≥9.0% and change in VIQ, PIQ, and FSIQ conducted separately for those participants with ≥30 HbA_{1c} values (n = 67; 70%) and those with <30 values were low for both groups ($r < 0.2$) and not statistically significant. All regression analyses were repeated including only participants with ≥30 HbA_{1c} values. Metabolic control still did not contribute significantly to change in VIQ, PIQ, and FSIQ ($P > 0.9$; $P = 0.2$; $P = 0.4$, respectively).

Potential Effect of BGL at the Time of Assessment

Mean BGL for participants with type 1 diabetes and each illness-related risk group (early or late onset, seizure history or no seizures, poor or good control) are reported in Table 2. The poor control group had significantly higher BGL prior to assessment at follow-up compared with the good control group (t[81.5] = 3.64; $P < 0.001$). There were no other significant group differences. Regression analyses were repeated covarying for BGL at baseline and then BGL at 12-year follow-up. Results were similar and are not reported here.

Exploration of Effect of DKA on Change in IQ

Thirty-one participants (32.6%) reported one or more episode of DKA (range 1–8; data missing on two participants). Means, SDs, and comparisons are presented in Table 4. Participants with one or more episode of DKA showed a greater loss in VIQ, PIQ, and FSIQ than participants without DKA episodes, but these were not statistically significant.

CONCLUSIONS

To our knowledge, this is the first study to document change in IQ from diagnosis with type 1 diabetes in childhood to follow-up in young adulthood. Some decline in IQ scores was evident in both type 1 diabetes and HC groups. This probably reflects, in part, the use of a more recently normed test at follow-up. However, the decline in VIQ and FSIQ was greater for participants with type 1 diabetes compared with HCs. PIQ did not appear to be negatively impacted by diagnosed diabetes. There was evidence of selective impact of specific illness risk factors on IQ. Early age of diabetes onset was associated with a decline in PIQ and FSIQ scores, while a history of hypoglycemic seizures was associated with a decline in VIQ. These findings are consistent with previous reports documenting adverse effects on cognition in those with diabetes onset very early in life (14,17,20) and in those who experience serious hypoglycemia (5,17,20,22,23). Thus the associations reported are not novel, but our access to IQ scores from diagnosis and follow-up provides particularly compelling evidence that the timing of diabetes onset and exposure to serious hypoglycemia are significant factors in the cognitive sequelae of type 1 diabetes.

To examine the effect of age of onset on change in PIQ, we used a test-standardized change in PIQ score to account for the psychometric effects of different baseline IQ tests. We feel confident that declines in PIQ and FSIQ are real effects of an earlier age of diabetes onset. We also note that the current findings are consistent with our cross-sectional findings at 12-year follow-up reported previously (9).

The early-onset effect identified in the meta-analysis conducted by Gaudieri et al. (14), and replicated by others (17,20), has traditionally been interpreted as a surrogate for the effect of hypoglycemia on an immature brain. Our findings do not support this hypothesis. Very few of our participants (n = 5) experienced hypoglycemic seizure early in life (30), and our regression analyses do not support an interaction between early-onset diabetes and known serious hypoglycemia, although we cannot rule out unrecognized event, particularly at night. While we demonstrated a very

Table 4—Change in IQ in relation to self-reported episodes of DKA

	Episodes of DKA (n = 31)		No history of DKA (n = 62)				
	Mean	SD	Mean	SD	F	df	*P* value
Change in VIQ	−9.41	8.09	−7.53	12.02	0.01	1,88	>0.9
Change in PIQ	−4.77	10.62	−1.90	12.30	0.19	1,88	0.7
Change in FSIQ	−8.19	8.89	−5.06	10.41	0.34	1,88	0.6

clear association between early-onset disease and deterioration in PIQ and FSIQ, as well as deficits in a range of specific cognitive deficits in a previous report (20), our neuroimaging findings provide a different picture. Contrary to our expectations, the early-onset subgroup of the cohort showed less evidence of brain changes than those with later-onset diabetes (31).

There are several possible explanations for these discrepant findings. Early exposure to glycemic perturbations may disrupt a later stage of neurodevelopment, a "sleeper" effect not yet evident in our younger participants. Alternatively, our neuroimaging techniques (volumetric measurement of white and gray matter) were insufficiently sensitive to detect subtle changes in brain architecture and connectivity in the early-onset subgroup. Recent studies using more sophisticated neuroimaging techniques such as DTI have shown altered diffusivity and anisotropy (a measure of the integrity of neural circuitry used in DTI) in young children with type 1 diabetes (4,6,12), suggesting compromised integrity of white matter structures critical for neural connectivity and efficient information processing.

In our sample, a history of hypoglycemic seizure/coma compromised VIQ, consistent with other data documenting an association between poorer language skills and positive seizure history (20,21,23,32). These findings suggest that clinical management regimens designed to avoid such events are warranted well into adolescence, despite the apparent resilience to hypoglycemic events shown by adults (33). We have previously suggested that the specific sensitivity of language skills to hypoglycemia may reflect a semantic memory deficit secondary to hypoglycemia-related hippocampal damage (30). However, our neuroimaging findings 12 years after disease onset (9) showed reduced volumes in the thalamus, a brain structure critical for arousal and vigilance, in those who had experienced a hypoglycemic seizure. Furthermore, the compromised white matter integrity demonstrated in recent DTI studies (4,6,12) is likely to degrade efficient processing of incoming information. Language development is highly sensitive to environmental input, particularly educational experience, thus subtle compromise of attention and information processing skills may lead to cumulative deficits in verbal knowledge stores over childhood.

We did not demonstrate an association between chronic poor metabolic control and changes in IQ. This null finding contrasts recent reports demonstrating the negative impact of poorly controlled diabetes on cognition (5,16–18,20,22), suggesting that it would be premature to discount the neurotoxic impact of hyperglycemia on the developing brain. It is possible that our measure of long-term metabolic control (percentage of time since diagnosis that HbA_{1c} was $\geq$9.0%) was insufficiently sensitive to discern changes in IQ. The number of available measurements of HbA_{1c} also varied widely across participants. Although our analyses suggested that people with fewer values were not driving the null findings, it would seem likely, intuitively, that those with missed clinic appointments and hence missing HbA_{1c} values, were more poorly controlled than regular attendees. Furthermore, participants with a known history of poor metabolic control were overrepresented in attrition from the sample at 12-year follow-up, undermining the power of our study to detect hyperglycemia-related changes in IQ.

There is now growing evidence on the potential effect of DKA on the developing brain, including cognitive ability (34). Self-reported DKA was not corroborated by scrutiny of medical records. Thus we lack complete confidence that every episode of DKA was reported. Exploratory analyses showed that although participants with and without DKA history did not differ significantly on change in IQ, those with a history of DKA showed greater mean IQ loss in absolute terms. This suggests a possible effect that should be studied in future research using more robust samples and more comprehensive DKA history.

It is necessary to interpret these findings in light of limitations of our study. We did not collect data on academic performance throughout the schooling of this cohort, although fewer participants with type 1 diabetes than HCs completed year 12, the preuniversity year of schooling in Australia (35), providing some external validation of our findings. Moreover, this study does not provide information on the timing or trajectory of changes in IQ, which limits the ability to implement specific interventions during the highest-risk periods.

A comprehensive understanding of the impact of type 1 diabetes on CNS structure and function remains an ongoing challenge. Our findings show that VIQ and FSIQ are negatively impacted over time in young people with type 1 diabetes. We demonstrated declines in IQ associated with the specific diabetes-related risks of early diabetes onset and history of hypoglycemic seizure, but not hyperglycemia. Recent in vitro and in vivo studies suggest that in addition to glycemic extremes, constantly fluctuating glycemic levels and disturbances in insulin homeostasis and counterregulatory hormone responses may exert toxic effects on the developing CNS (2,36). Laboratory studies that manipulate metabolic variables under experimentally controlled conditions may be needed to test explanatory models if we are to fully understand the impact of type 1 diabetes on the developing brain. More frequent assessment of youth with type 1 diabetes will help clarify the timing and trajectory of functional and structural brain changes to optimize intervention.

Acknowledgments. The authors thank the participants and their families for their commitment to this longitudinal study.

Funding. This research was supported by Juvenile Diabetes Research Foundation International (JDRF grant 1-2003-135). A.L. is funded by a National Health and Medical Research Council (Australia) Early Career Fellowship (1072593). E.A.N. is currently receiving research support from a JDRF Clinical Trial Network Pilot and Feasibility Study grant.

Duality of Interest. E.A.N. is currently receiving research support from Pfizer Australia (grant WI179088). G.A.W. reports receiving consulting fees from Ipsen and equity in Antisense Therapeutics Limited (Australia) and Neuren (Australia) and is currently receiving research support from Novo Nordisk and Sandoz. F.J.C. reports receiving lecture fees and/or consultancy fees from Novo Nordisk, Eli Lilly, and Medtronic as well as research grants from Eli Lilly and Medtronic. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.L. and E.A.N. were primarily responsible for data collection and analysis and the drafting of the manuscript. G.A.W. and F.J.C. contributed to the interpretation of the findings and the final editing of the manuscript. E.A.N. is the guarantor of this work and, as such, had full access to all the data in the

study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Tomlinson DR, Gardiner NJ. Glucose neurotoxicity. Nat Rev Neurosci 2008;9:36–45
2. Russo VC, Higgins S, Werther GA, Cameron FJ. Effects of fluctuating glucose levels on neuronal cells in vitro. Neurochem Res 2012;37:1768–1782
3. Arbelaez AM, Semenkovich K, Hershey T. Glycemic extremes in youth with T1DM: the structural and functional integrity of the developing brain. Pediatr Diabetes 2013;14:541–553
4. Antenor-Dorsey JA, Meyer E, Rutlin J, et al. White matter microstructural integrity in youth with type 1 diabetes. Diabetes 2013;62:581–589
5. Aye T, Reiss AL, Kesler S, et al. The feasibility of detecting neuropsychologic and neuroanatomic effects of type 1 diabetes in young children. Diabetes Care 2011;34:1458–1462
6. Aye T, Barnea-Goraly N, Ambler C, et al. White matter structural differences in young children with type 1 diabetes: a diffusion tensor imaging study. Diabetes Care 2012;35:2167–2173
7. Hershey T, Perantie DC, Wu J, Weaver PM, Black KJ, White NH. Hippocampal volumes in youth with type 1 diabetes. Diabetes 2010;59:236–241
8. Ho MS, Weller NJ, Ives FJ, et al. Prevalence of structural central nervous system abnormalities in early-onset type 1 diabetes mellitus. J Pediatr 2008;153:385–390
9. Northam EA, Rankins D, Lin A, et al. Central nervous system function in youth with type 1 diabetes 12 years after disease onset. Diabetes Care 2009;32:445–450
10. Perantie DC, Wu J, Koller JM, et al. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. Diabetes Care 2007;30:2331–2337
11. Perantie DC, Koller JM, Weaver PM, et al. Prospectively determined impact of type 1 diabetes on brain volume during development. Diabetes 2011;60:3006–3014
12. Barnea-Goraly N, Raman M, Mazaika P, et al.; Diabetes Research in Children Network (DirecNet). Alterations in white matter structure in young children with type 1 diabetes. Diabetes Care 2014;37:332–340
13. Marzelli MJ, Mazaika PK, Barnea-Goraly N, et al.; Diabetes Research in Children Network (DirecNet). Neuroanatomical correlates of dysglycemia in young children with type 1 diabetes. Diabetes 2014;63:343–353
14. Gaudieri PA, Chen R, Greer TF, Holmes CS. Cognitive function in children with type 1 diabetes: a meta-analysis. Diabetes Care 2008;31:1892–1897
15. Hershey T, Perantie DC, Warren SL, Zimmerman EC, Sadler M, White NH. Frequency and timing of severe hypoglycemia affects spatial memory in children with type 1 diabetes. Diabetes Care 2005;28:2372–2377
16. Kaufmann L, Pixner S, Starke M, et al. Neurocognition and brain structure in pediatric patients with type 1 diabetes. J Pediatr Neuroradiol 2012;1:25–35
17. Patiño-Fernández AM, Delamater AM, Applegate EB, et al. Neurocognitive functioning in preschool-age children with type 1 diabetes mellitus. Pediatr Diabetes 2010;11:424–430
18. Cato MA, Mauras N, Ambrosino J, et al.; Diabetes Research in Children Network (DirecNet). Cognitive functioning in young children with type 1 diabetes. J Int Neuropsychol Soc 2014;20:238–247
19. Ly TT, Anderson M, McNamara KA, Davis EA, Jones TW. Neurocognitive outcomes in young adults with early-onset type 1 diabetes: a prospective follow-up study. Diabetes Care 2011;34:2192–2197
20. Lin A, Northam EA, Rankins D, Werther GA, Cameron FJ. Neuropsychological profiles of young people with type 1 diabetes 12 yr after disease onset. Pediatr Diabetes 2010;11:235–243
21. Naguib JM, Kulinskaya E, Lomax CL, Garralda ME. Neuro-cognitive performance in children with type 1 diabetes—a meta-analysis. J Pediatr Psychol 2009;34:271–282
22. Perantie DC, Lim A, Wu J, et al. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. Pediatr Diabetes 2008;9:87–95
23. Blasetti A, Chiuri RM, Tocco AM, et al. The effect of recurrent severe hypoglycemia on cognitive performance in children with type 1 diabetes: a meta-analysis. J Child Neurol 2011;26:1383–1391
24. Asvold BO, Sand T, Hestad K, Bjørgaas MR. Cognitive function in type 1 diabetic adults with early exposure to severe hypoglycemia: a 16-year follow-up study. Diabetes Care 2010;33:1945–1947
25. Wechsler D. *Manual for the Wechsler Preschool and Primary Scale of Intelligence- Revised*. San Antonio, The Psychological Corporation, 1989
26. Wechsler D. *Manual for the Wechsler Intelligence Scale for Children-Revised*. New York, The Psychological Corporation, 1974
27. Wechsler D. *Wechsler Abbreviated Scale of Intelligence Manual*. San Antonio, The Psychological Corporation, 1993
28. Bayley N. *Manual for the Bayley Scales of Infant Development*. San Antonio, The Psychological Corporation, 1969
29. Daniel A. *Power, Privilege and Prestige: Occupations in Australia*. Melbourne, Longman-Cheshire, 1983
30. Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. Diabetes Care 2001;24:1541–1546
31. Pell GS, Lin A, Wellard RM, et al. Age-related loss of brain volume and T2 relaxation time in youth with type 1 diabetes. Diabetes Care 2012;35:513–519
32. Rovet JF, Ehrlich RM. The effect of hypoglycemic seizures on cognitive function in children with diabetes: a 7-year prospective study. J Pediatr 1999;134:503–506
33. Jacobson AM, Musen G, Ryan CM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007;356:1842–1852
34. Cameron FJ, Scratch SE, Nadebaum C, et al.; DKA Brain Injury Study Group. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. Diabetes Care 2014;37:1554–1562
35. Northam EA, Lin A, Finch S, Werther GA, Cameron FJ. Psychosocial well-being and functional outcomes in youth with type 1 diabetes 12 years after disease onset. Diabetes Care 2010;33:1430–1437
36. Northam EA, Cameron FJ. Understanding the diabetic brain: new technologies but old challenges. Diabetes 2013;62:341–342