Supplemental Materials

Neurocognitive Assessment

Digit Span. This task requires participants to recall increasingly longer strings of numbers. In the forward digit task, participants are asked to repeat two digits in the order they were uttered by the researcher. If they can do so successfully, the experimenter increases the length of the span, until participants fail to do so or a 9-digit length is reached. In the backward task, participants are asked to repeat the digit list in backward order, starting from the last digit and proceeding in order to the first digit uttered by the researcher. The forward digit span assesses short-term memory, on the capacity to maintain information on line, and the backward digit task assesses working memory, or the ability to mentally manipulate and transform information on line.

Long-Term Memory Measures. In the *Color-Task*, 80 black-ink object drawings on a white square background are presented on a computer screen with either a green, red, yellow, or blue border (20 of each color in a random order), and participants are instructed to try to remember both the item and the color of the border that went with that item. Each drawing is shown for 1 second, followed by a 1-second interval in which a fixation point is presented. Then, participants are given a self-paced recognition test including 80 studied drawings and 80 new drawings presented in random order. No color border is presented. Participants first determine whether or not they had seen the drawing before. When a drawing is recognized, participants select the color of the border with which they think the drawing had been previously presented. The *Spatial-Position task* is identical to the color task, except that the drawings do not vary in colored border, but in the spatial position in which they appear (i.e., one of the 4 quadrants of the computer screen; 20 items in each quadrant in a random order). Thus, participants are instructed to remember and then are tested on their memory for the association between drawing and spatial position. Each memory task takes approximately 25 minutes, and a 30 minute break is given between them. Drawings for each task are chosen from a set of 320 unambiguous line drawings; We used these materials in our previous research. Use of these

drawings in the Color versus Spatial-Position and task order were counterbalanced across participants.

Each memory task provides two indices of memory performance. One is the item-context association rate (rate of correct item-color and item-spatial positions associations recollected over the total of previously viewed items correctly recognized). This index is the primary measure of interest for this report because it is thought to reflect the kind of memory process that is hypothesized to be the most affected by DKA. The other index, *d′* is a well-established measure which corresponds to the normalized difference between hit rates (correct identification of an item that was seen previously) and false-alarm rates (incorrect identification of an item as being seen previously when it was not). This measure reflects the ability to discriminate between old and new items, and varies from 0 (no ability to discriminate) to 4 (nearly perfect ability to discriminate).

IQ. The Wechsler Abbreviated Scale of Intelligence (WASI) is a measure of IQ designed for individuals aged 6 to 89. The WASI includes four subtests; the Block Design and Matrix Reasoning tests measure Performance IQ, and the Vocabulary and Similarities tests measure Verbal IQ. Full scale IQ is also computed, which we used in the current report. This test takes about 35 minutes to administer.

Supplemental Table 1. Summary of imputation. The number and percent of patients with imputed data are shown for outcomes, predictors, and covariates used in mixed regression models.

	Overall	Non-DKA	Mild DKA	Moderate/Severe DKA
All Patients	1134	376	328	430
Memory Item space rate*	91 (8.0%)	25 (6.6%)	28 (8.5%)	38 (8.8%)
Memory Item color rate*	83 (7.3%)	19 (5.1%)	29 (8.8%)	35 (8.1%)
Full Scale IQ*	29 (2.6%)	3 (0.8%)	11 (3.4%)	15 (3.5%)
Digit Span Recall: Forward*	5 (0.4%)	2 (0.5%)	1 (0.3%)	2 (0.5%)
Digit Span Recall: Backward*	5 (0.4%)	2 (0.5%)	1 (0.3%)	2 (0.5%)
Maternal Parental Education†	83 (7.3%)	32 (8.5%)	15 (4.6%)	36 (8.4%)
Hypoglycemic episodes	8 (0.7%)	1 (0.3%)	3 (0.9%)	4 (0.9%)
New Onset Patients	591	199	198	194
Memory Item space rate*	43 (7.3%)	13 (6.5%)	14 (7.1%)	16 (8.2%)
Memory Item color rate*	43 (7.3%)	8 (4.0%)	16 (8.1%)	19 (9.8%)
Full Scale IQ*	12 (2.0%)	1 (0.5%)	5 (2.5%)	6 (3.1%)
Digit Span Recall: Forward*	2 (0.3%)	1 (0.5%)	1 (0.5%)	0 (0.0%)
Digit Span Recall: Backward*	2 (0.3%)	1 (0.5%)	1 (0.5%)	0 (0.0%)
Maternal Parental Education†	39 (6.6%)	21 (10.6%)	8 (4.0%)	10 (5.2%)
Hypoglycemic episodes	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Baseline pH	16 (2.7%)	0 (0.0%)	8 (4.0%)	8 (4.1%)
Previously Diagnosed Patients	543	177	130	236
Memory Item space rate*	48 (8.8%)	12 (6.8%)	14 (10.8%)	22 (9.3%)
Memory Item color rate*	40 (7.4%)	11 (6.2%)	13 (10.0%)	16 (6.8%)
Full Scale IQ*	17 (3.1%)	2 (1.1%)	6 (4.6%)	9 (3.8%)
Digit Span Recall: Forward*	3 (0.6%)	1 (0.6%)	0 (0.0%)	2 (0.8%)
Digit Span Recall: Backward*	3 (0.6%)	1 (0.6%)	0 (0.0%)	2 (0.8%)
Maternal Parental Education†	44 (8.1%)	11 (6.2%)	7 (5.4%)	26 (11.0%)
Hypoglycemic episodes	7 (1.3%)	1 (0.6%)	3 (2.3%)	3 (1.3%)
Baseline pH	18 (3.3%)	0 (0.0%)	6 (4.6%)	12 (5.1%)
12 month average HbA1c	13 (2.4%)	1 (0.6%)	2 (1.5%)	10 (4.2%)
Previous DKA episodes	2 (0.4%)	0 (0.0%)	1 (0.8%)	1 (0.4%)

*Primary and secondary outcomes; included in multiple imputation models; imputed values were deleted prior to inclusion in statistical models; †Used as Socioeconomic status

Supplemental Table 2. Characteristics of participants who experienced DKA who were eligible for follow-up in the PECARN FLUID trial as a function of whether they completed the neurocognitive visit or were lost to follow-up.

	2-6 Month Follow-up Neurocognitive Visit		
	Lost to Follow-up (N = 317)	Follow-up Visit Completed (N = 841)	P-value
Age at screening (years): Mean (SD)	13.1 (3.10)	12.4 (2.98)	<.001[1]
Previously diagnosed with diabetes: N (%)	224 (70.7%)	437 (52.0%)	<.001[2]
New onset diabetes: N(%)	93 (29.3%)	404 (48.0%)	
Male: N(%)	159 (50.2%)	383 (45.5%)	0.16[2]
Female: N(%)	158 (49.8%)	458 (54.5%)	
Maternal Parental Education: N(%)[3]			0.05[2]
No education	1 (0.4%)	2 (0.3%)	
Some high school or less	21 (7.4%)	67 (8.6%)	
High school graduate or GED	84 (29.6%)	180 (23.0%)	
Vocational school or some college	94 (33.1%)	244 (31.2%)	
College degree	68 (23.9%)	203 (26.0%)	
Master's or doctoral degree	16 (5.6%)	86 (11.0%)	
12-month weighted mean HbA1c (%): Mean (SD)[3]	11.0 (2.07)	10.5 (1.83)	0.006[1]
Moderate/Severe DKA: N(%)	194 (61.2%)	480 (57.1%)	0.21[2]
Previously Diagnosed: Moderate/Severe DKA: N (%)	145/224 (64.7%)	278/437 (63.6%)	0.78[2]
New Onset: Moderate/Severe DKA: N (%)	49/93 (52.7%)	202/404 (50.0%)	0.64[2]

Including patients enrolled in the DKA study aged 6 years or older and otherwise eligible for follow-up: English speaking/reading, non-withdrawal, alive and not re-enrolled during follow-up window.

[1] Two-sided Wilcoxon rank-sum with normal approximation and continuity correction.

[2] Chi-squared test of no association.

[3] Missing data about maternal parental education for 92 enrollments and HbA1c for 519 enrollments due to not being routinely collected for new onset patients.

Supplemental Table 3. **Regression models applied to all patients.** (A) Standardized Regression Coefficients and 95% Confidence Intervals*†; and (B) Adjusted Means*† and Raw means as a function of DKA Status

	Spatial Task		Digit Span Recall: Backward	
A. Regression Coefficients	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
DKA Status‡	0.02 (-0.04, 0.08)	0.50	0.01 (-0.04, 0.07)	0.68
Male	-0.12 (-0.18, -0.06)	<0.001	-0.06 (-0.11, -0.01)	0.03
Age	0.27 (0.21, 0.33)	<0.001	0.45 (0.39, 0.50)	<0.001
Previously Diagnosed	-0.03 (-0.10, 0.03)	0.29	-0.02 (-0.07, 0.04)	0.56
Socioeconomic Status§	0.08 (0.02, 0.14)	0.01	0.12 (0.06, 0.17)	<0.001
Previous Severe Hypoglycemia	-0.07 (-0.13, -0.00)	0.04	-0.02 (-0.08, 0.03)	0.43
B. DKA Status	Adjusted Mean (SE)	Mean (SD)	Adjusted Mean (SE)	Mean (SD)
No DKA	0.67 (0.013)	0.69 (0.194)	6.8 (0.12)	6.9 (2.04)
Mild DKA	0.67 (0.010)	0.69 (0.172)	6.8 (0.09)	6.9 (2.02)
Moderate/Severe DKA	0.68 (0.012)	0.71 (0.184)	6.8 (0.11)	7.1 (1.91)

*Regression coefficients are standardized and represent the mean change in outcome associated with a 1 SD change in a continuous factor or the change associated with that level (Male, Previously Diagnosed, Previous Severe Hypoglycemia) for binary variables. Note that the estimated change for the reference value (Female, New Onset, No Hypoglycemia) are -1 times the coefficient. Adjusted means average over sex, previous diagnosis and previous severe hypoglycemia, and assume age=12, socioeconomic status=1.

†Random effect of site included in each model

‡ DKA Status is on a numeric scale: 0=no DKA, 1=mild DKA, 2=moderate/severe DKA

Socioeconomic status is indicated by maternal education and is on a numeric scale: 0=high school/GED or less, 1=some college/vocational school, 2=college degree or more; when missing, income and paternal education were used to impute socioeconomic status

Supplemental Table 4. Regression model applied to previously diagnosed patients, including an interaction between Socioeconomic Status and DKA Status. Standardized Regression Coefficients and 95% Confidence Intervals.*†

	IQ	
	Sample Mean	S.D.
	101.90	13.37
Regression Factor	Coefficient (95% CI)	P-value
DKA Status‡	0.08 (-0.07, 0.23)	0.31
Male	-0.00 (-0.08, 0.08)	0.99
Age	Not Estimated	
Socioeconomic Status§	0.42 (0.28, 0.56)	<0.001
Previous Severe Hypoglycemia	0.03 (-0.04, 0.10)	0.39
Mean HbA1c	-0.09 (-0.16, -0.03)	0.005
Duration	-0.03 (-0.12, 0.05)	0.43
Previous DKA Episodes	-0.10 (-0.18, -0.02)	0.010
Interaction between DKA Status and Socioeconomic Status	-0.23 (-0.39, -0.07)	0.006

*Regression coefficients are standardized and represent the mean change in outcome associated with a 1 SD change in a continuous factor or the change associated with that level (Male, Previous Severe Hypoglycemia) for binary variables. Note that the estimated change for the reference value (Female, No Hypoglycemia) are -1 times the coefficient.

†Random effect of site included in each model

‡ DKA Status is on a numeric scale: 0=no DKA, 1=mild DKA, 2=moderate/severe DKA

§ Socioeconomic status reflects maternal education and is on a numeric scale: 0=high school/GED or less, 1=some college/vocational school, 2=college degree or more; when missing, income and paternal education was used to impute socioeconomic status

Supplemental Table 5. Regression model applied separately to previously diagnosed patients and including an interaction between age-at-onset and DKA status. Regression Coefficients* and 95% Confidence Intervals, adjusted means and raw means as a function of age-at-onset and DKA Status.

	Color Task	
Regression Coefficients	Coefficient (95% CI)	P-value
DKA Status‡	-0.34 (-0.60, -0.08)	0.010
Male	-0.04 (-0.12, 0.04)	0.32
Age	0.49 (0.40, 0.58)	<0.001
Socioeconomic Status§	0.06 (-0.03, 0.14)	0.17
Previous Severe Hypoglycemia	0.03 (-0.06, 0.11)	0.53
Mean HbA1c	-0.12 (-0.23, -0.02)	0.02
Age at onset of diabetes 4 to <7 years old^	-0.26 (-0.50, -0.02)	0.10
Age at onset of diabetes 7 years old or more^	-0.20 (-0.45, 0.05)	
Interaction 1 (age at onset 4 to 7 years old x DKA)	0.28 (0.05, 0.51)	0.05
Interaction 2 (age at onset 7 years old or more x DKA)	0.26 (-0.02, 0.55)	
DKA Status and Age at Onset	Adjusted Mean (SE)	Mean (SD)
Age at onset of diabetes <4 years old		
No DKA	0.57 (0.046)	0.53 (0.168)
DKA	0.44 (0.022)	0.45 (0.183)
Age at onset of diabetes 4-<7 years old		
No DKA	0.46 (0.028)	0.45 (0.145)
DKA	0.47 (0.021)	0.48 (0.180)
Age at onset of diabetes 7 years old or more		
No DKA	0.49 (0.021)	0.53 (0.196)
DKA	0.46 (0.017)	0.52 (0.164)

*Regression coefficients are standardized and represent the mean change in outcome associated with a 1 SD change in a continuous factor or the change associated with that level for binary variables. Note that the estimated change for the reference value are -1 times the coefficient. Adjusted means average over sex, and previous severe hypoglycemia, and assume age=12, socioeconomic status=1 and mean HbA1c=9.6. A random effect of site is included in the model.

^ Age at onset reflects 3 groups of children: those whose diabetes onset was between zero and 3.99 years of age, those whose onset was between 4 and 6.99 years of age; and those whose onset was at 7 years of age or later.

‡ DKA Status is binary in this analysis (i.e., DKA exposure versus No DKA exposure) where no DKA is the reference value. The use of this variable (instead of the DKA Status variable used in previous analyses capturing levels of DKA severity) is motivated by the small number of observations across each age of onset and severity of DKA.

§ Socioeconomic status is indicated by maternal education and is on a numeric scale: 0=high school/GED or less, 1=some college/vocational school, 2=college degree or more; when missing, income and paternal education were used to impute socioeconomic status

Supplemental Figure 1. Study Flowchart