Published in final edited form as:
Pediatr Diabetes. 2013 September ; 14(6): 447–454. doi:10.1111/pedi.12030.

Severe Hypoglycemia and Diabetic Ketoacidosis among Youth with Type 1 Diabetes in the T1D Exchange Clinic Registry

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Abstract

Objective—Severe hypoglycemia (SH) and diabetic ketoacidosis (DKA) are common serious acute complications of type 1 diabetes (T1D). The aim of this study was to determine the frequency of SH and DKA and identify factors related to their occurrence in the T1D Exchange pediatric and young adult cohort.

Research Design and Methods—The analysis included 13,487 participants in the T1D Exchange clinic registry aged 2-<26 years with T1D ≥2 years. Separate logistic regression models were used to evaluate the association of baseline demographic and clinical factors with the occurrence of SH or DKA in the prior 12 months.

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Financial Disclosures

E.C., D.X., J.C.W., J.I.W., A.R., S.S., S.W., D.S., and K.M. have nothing to declare; R.B.'s nonprofit employer has received consultant payments on his behalf from Sanofi and Animas and a research grant from NovoNordisk with no personal compensation to R.W.B. M.H. received consultant payments from NovoNordisk, Daiichi Sankyo, Bristol Meyer-Squibb, and Xeris Pharm. B.T. received consultant payments from Medtronic and Animas.

Results—Non-White race, no private health insurance and lower household income were associated with higher frequencies of both SH and DKA ($p<0.001$). SH frequency was highest in children <6 years old ($p=0.005$), but across the age range, SH was not associated with HbA1c levels after controlling for other factors ($p=0.72$). DKA frequency was highest in adolescents ($p<0.001$) and associated with higher HbA1c ($p<0.001$).

Conclusions—Our data show that poor glycemic control increases the risk of DKA but does not protect against severe hypoglycemia in youth and young adults with type 1 diabetes. The high frequencies of SH and DKA observed in disadvantaged minorities with T1D highlight the need for targeted interventions and new treatment paradigms for patients in these high risk groups.

Keywords

Pediatric Diabetes; Type 1; hypoglycemia; diabetic ketoacidosis; Childhood Type 1

Introduction

Severe hypoglycemia (SH) and diabetic ketoacidosis (DKA) are common acute complications of type 1 diabetes (T1D) causing significant morbidity and, occasionally, mortality (1-3). Many factors collectively make patients with type 1 diabetes vulnerable to severe hypoglycemic events, including early loss of the plasma glucagon responses to hypoglycemia, blunted epinephrine responses during sleep, impaired glucose counter regulation resulting from recurrent episodes of mild hypoglycemia especially during the night, progressive loss of the modulating effects of residual endogenous insulin secretion (4-6), and the immediate and delayed glucose-lowering effects of aerobic exercise (7). Since publication of the results of the landmark Diabetes Control and Complications Trial (DCCT), the aim of treatment of T1D has been to achieve target glycemic control to minimize vascular complications while attempting to avoid hypoglycemia (1, 8). Recent randomized clinical trials of new diabetes technologies have shown that the rates of SH in youth with T1D have decreased substantially as compared with that observed in DCCT (9, 10). However, the current risk of SH in children, adolescents and young adults with T1D, and associated risk factors, in clinical practice settings in the United States have not been established. Similarly, current data are limited on the risk of DKA in clinical practice settings.

The T1D Exchange Clinic Network established a registry of more than 25,000 individuals with T1D at 67 diabetes centers in the U.S., spanning all ages, durations of T1D, and racial/ethnic and socio-economic groups. The registry databases provided an opportunity to assess the current frequencies of SH and DKA in clinical practice, and identify factors related to the occurrence of these two major complications in children, adolescents, and young adults with T1D.

Research Design and Methods

The T1D Exchange clinic registry commenced enrollment in September 2010 (11). Each participating clinic received approval from an institutional review board (IRB). Informed consent was obtained from adult participants and parents/guardians of minors, and assent

was obtained from minors according to IRB requirements. Data were collected from the participant's medical record and by the participant or parent completing a comprehensive questionnaire, as previously described (11). This report includes data on 13,487 participants enrolled through August 1, 2012, who met the following criteria: less than 26 years old with T1D for at least 2 years. Young adults were included in this cohort since our HbA1c data indicated that this age group was more similar to adolescents than older adults (11).

Information on the occurrence of SH events and episodes of DKA in the prior 12 months was obtained from a questionnaire completed by participants ≥18 years old, the parent or guardian of participants <13 years old, and by either the participant or parent/guardian for participants 13 to <18 years old. SH was defined as an episode of documented or presumed low blood glucose that resulted in seizure or loss of consciousness. Participants were asked how many times they were hospitalized for DKA in the prior 12 months. Data for SH were available for only 9,930 participants (74%, not present for the other 3,557 who were enrolled prior to this question being modified on the participant questionnaire) and for DKA for 13,005 (96%) participants. Information on the occurrence of DKA and SH also was collected from the clinics' medical records. The frequency of ≥1 DKA or SH events ascertained from the patients' medical records was consistently lower across age groups compared with what the participants reported, likely due to failure of clinicians to routinely obtain and document this information in the medical record; therefore, only participant reported events were used in all analyses.

Statistical Methods

Separate logistic regression models were used to evaluate the association of baseline demographic and clinical factors with the occurrence of a participant-reported SH or DKA event in the prior 12 months. Factors with a p-value <0.10 from individual factor models adjusted for age were included in an initial multivariate model and then a backward elimination procedure was used to remove variables with a p-value ≥0.01. A forward selection process resulted in a similar model. Tests of significance were reported from models using continuous or ordinal variables and odds ratios were reported from models using the categorical variables. Interactions among age, diabetes duration, gender, and HbA1c were evaluated and no interaction term was significant at a significance level of 0.01. Because parent education level was missing in participants aged ≥18 years old and this variable was correlated with level of household income and health insurance status, parental education level was only evaluated in a univariate model, and not in the multivariate models.

Data analyses were performed using SAS software, Version 9.3 (2011 SAS Institute Inc., Cary, NC). All p-values are two-sided.

Results

The cohort included 13,487 participants ranging in age from 2.4 to 25.9 years: 377 (3%) 2-< 6 years, 4,405 (33%) 6-<13 years, 5,081 (38%) 13-<18 years, and 3,624 (27%) 18-<26 years (Table 1). Forty-nine percent were female and 79% were non-Hispanic white. Mean HbA1c (±SD) was 8.6% ±1.5%. Median (interquartile range) diabetes duration was 6.0 (4.0 to 10.0) years. Characteristics of the cohort overall and stratified by age groups are shown in Table 1.

Severe Hypoglycemia

One or more SH events within 12 months occurred in 6.2% of the 9,930 participants with available data. SH was more common in participants 2-<6 years old than in the older age groups (9.6% in 2-<6 years, 5.2% in 6-<13 years, 6.3% in 13 -<18 years and 6.9% in 18-<26 years, p=0.005, Table 2). After adjusting for age, SH was more common in participants who were non-Hispanic black (p<0.001), from families with lower annual household income (p<0.001), without private health insurance (p<0.001), had longer duration of diabetes (p<0.001), higher HbA1c (p=0.001) and used multiple daily injections (MDI) for insulin delivery (compared with pump users, p<0.001) (Table 2). In a multivariate analysis, associations were similar, except there was not a significant association of SH with either the average HbA1c in the prior 12 months (p=0.72) or method of insulin delivery (p=0.09). Results were similar in each age group (supplemental Table 1).

DKA

At least one DKA event within 12 months occurred in 9.9% of the 13,005 participants: 9.4% in participants <6 years old, 7.6% in 6-<13 year olds, 11.4% in 13 -<18 year olds, and 10.5% in 18-<26 year olds (Table 3). The frequency of DKA was significantly higher in participants 13-<18 years old compared with the other age groups (p<0.001). After adjusting for age, a higher frequency of DKA was associated with female gender (p<0.001), non-white race (p<0.001), lower income (p<0.001), no private insurance (p<0.001), higher HbA1c (p<0.001), and MDI insulin method (compared with pump use, p<0.001, Table 3). In a multivariate analysis, female gender, higher HbA1c, non-white race, lower income, and lack of private insurance continued to be significantly associated with a higher frequency of DKA (Table 3). Results were similar for each age group (supplemental Table 2).

The frequencies of occurrence of SH and DKA reported by clinics from medical record extraction were lower as compared with participant self-report (2.5% vs. 6.2% for SH and 7.2% vs. 9.9% for DKA).

Discussion

Despite advances in the management of T1D, the T1D Exchange clinic registry data indicate that SH and DKA events continue to be common occurrences in children, adolescents, and young adults with T1D who are receiving treatment at leading diabetes treatment centers in the United States. Consistent with other studies, the frequencies of both SH and DKA were higher in those with lower socioeconomic status, particularly in non-Hispanic black participants. In evaluating the data generated from this large registry, it is important to recognize that the cohort is not population-based. Although this could affect the representativeness of the cohort, we cannot surmise whether the observed SH and DKA frequencies would be more likely to be over- or underestimates of the true values. A lack of representativeness, even if present, is not likely to affect the interpretation of the analyses of factors associated with SH or DKA.

Accurate collection of SH and DKA data is difficult outside of a well-controlled clinical trial with frequent patient contact and prospective recording of events, although because of the

study effects, clinical trial data may not represent what occurs in usual clinical practice. We collected SH and DKA information both directly from the patient participant and from data extraction from the medical record. We believe that the discrepancies between the two sources more likely reflect under reporting in the medical records than over reporting by the participants, particularly for SH for which hospitalization generally does not occur. For DKA, hospitalization at an institution closer to the patient's home and not affiliated with the clinic is possible. In comparing our results with those of other studies, it is important to recognize that our SH definition required the occurrence of seizure or loss of consciousness and not just an event that required the assistance of someone. This more extreme definition was used because of the concern after our initial data collection that a 'requiring assistance' definition was leading to variable interpretation and reporting by participants and parents. For DKA events, we required overnight hospitalization to be more certain of the diagnosis. For both SH and DKA, we only report the frequency of participants with one or more events in the prior 12 months believing that this is more reliable than self-reported number of events.

Our finding of an overall 12-month frequency of 6.2% of one or more SH events with seizure or loss of consciousness is difficult to compare to most previous studies. This is mostly due to (a) SH definition-- many other studies have reported SH as a hypoglycemic event requiring the assistance of another person without reporting data on seizure/loss of consciousness and (b) how the data were reported-- many other studies have reported either the SH rate as number of events per 100 person-years or report prevalence of one more events over a time period, usually variable, that is more than one year. For example, in 13-17 year-olds in the DCCT, the overall prevalence of one or more episodes of SH with seizure or coma was 43.1%, over 9 years of follow-up (12). In a cohort of children with T1D younger than 20 years old in Denver, prevalence of one or more SH events leading to loss of consciousness or seizure was 27% over a 4-year period (13), and 27.8% over 1992-2002 and 22.6% over 2000-2009 in the Australian cohorts younger than 19 years old (14, 15). The percent of subjects with at least one event of hypoglycemia related seizure or loss of consciousness in our study was similar to the percent reported in the six-month control period (6%) for the 15-24 year old group in the Juvenile Diabetes Research Foundation (JDRF) continuous glucose monitoring study (16).

As has also been shown in previous studies, children <6 years of age in our population had a higher frequency of SH compared with older age groups. The failure to observe a substantial increase in the frequency of SH in patients with HbA1c levels <7.5%, as seen in the DCCT, is a testament to the improvements in intensive treatment regimens over the past 20 years. It is also notable that at the other end of the HbA1c spectrum, the high frequency of SH in poorly controlled patients show that elevated HbA1c levels, per se, do not protect against SH.

The frequency of having at least one DKA event within 12 months was 9.9% overall. As with SH, the results are difficult to compare with those of most other studies; reported DKA frequencies of 1 or more events include 19.5% over 7.4 years in the DCCT, 15.7% over 4 years in the Denver cohorts, and 5.9% over 13.5 years in a German and Austrian registry of children younger than 20 years old (2, 12, 13). It is possible that a difference in health care

insurance systems among countries explains some of the differences in frequency of DKA. Consistent with other studies (2, 13) a higher frequency of DKA was strongly associated with higher HbA1c levels. DKA was more common in adolescents and young adults but this was related to poorer glycemic control and after adjusting for HbA1c, age was no longer associated with DKA frequency. DKA frequency was higher in female subjects. Incidence rates of DKA also have been shown to be higher in females and in immigrant groups in Germany and Austria (2), but not in the Hvidoere study group (17). Of note, we did not find an increase in the frequency of DKA in pump users compared with injection users which is reassuring given the possibility of loss of insulin delivery in pump users due to infusion site failure. This is consistent with the data published by the German and Austrian registry (2).

In summary, both SH and DKA remain common acute complications of T1D in children, adolescents, and young adults. DKA should be largely preventable. However, SH is not totally avoidable with current therapy of T1D in which it is not possible to precisely match insulin delivery to changing insulin needs. Unfortunately rates of DKA and SH may be difficult to lower until there is either a closed loop system that functions independent of patient behavior or widespread availability of islet or pancreas transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

E.C. initiated idea, wrote manuscript, contributed to discussion, and reviewed/edited the manuscript. D.X. performed statistical analysis, researched data, wrote manuscript, and reviewed/edited the manuscript. J.C.W. wrote manuscript, researched references, contributed to discussion, and reviewed/edited the manuscript. J. I. W, contributed to discussion and reviewed/edited the manuscript. M.H. contributed to discussion and reviewed/edited the manuscript. A.R. contributed to discussion and reviewed/edited the manuscript. S.S. contributed to discussion and reviewed/edited the manuscript. W.T. contributed to discussion and reviewed/edited the manuscript. S.W. contributed to discussion and reviewed/edited the manuscript. D.S. contributed to discussion and reviewed/edited the manuscript. K.M. performed statistical analysis, researched data, contributed to discussion, and reviewed/edited the manuscript. R.W.B. researched data, wrote manuscript, contributed to discussion, and reviewed/edited the manuscript.

Funding was provided by the Leona M. and Harry B. Helmsley Charitable Trust.

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Table 1

Participant Characteristics

	All N=13487	<6 Years Old N=377	Age Group 6-<13 Years Old N=4405	13-<18 Years Old N=5081	18-<26 Years Old N=3624
Genders[*]: Female	49%	43%	49%	50%	49%
Race/Ethnicity					
White Non-Hispanic	79%	82%	78%	78%	82%
Black Non-Hispanic	6%	4%	6%	6%	5%
Hispanic or Latino	10%	8%	10%	11%	10%
Other Race/Ethnicity	5%	6%	6%	5%	4%
Household Annual Income[a]					
<$35,000	22%	23%	19%	19%	30%
$35,000 - <$75,000	28%	33%	28%	27%	27%
≥$75,000	51%	44%	53%	54%	43%
Parent Education[a,//]					
≤ High school diploma\GED	45%	32%	32%	34%	NA
Associate degree or Bachelor degree	36%	41%	42%	40%	NA
Master degree, Professional or Doctorate degree	19%	27%	25%	25%	NA
Insurance Status[a]					
Private	74%	72%	73%	74%	74%
Other	26%	27%	26%	26%	24%
No insurance	<1%	<1%	<1%	<1%	2%
Body Mass Index (BMI)[a,¥]					
Normal/underweight	61%	61%	67%	60%	56%
Overweight	24%	21%	20%	25%	29%
Obese	14%	18%	13%	15%	15%
Duration of T1D *(years)*					
Median (25^{th}, 75^{th} percentiles)	6.0 (4.0, 10.0)	2.0 (2.0, 3.0)	4.0 (3.0, 6.0)	7.0 (4.0, 10.0)	10.0 (6.0, 14.0)
2-<5 years	35%	>99%	50%	31%	15%
5-<10 years	40%	<1%	46%	42%	34%
≥10 years	26%	NA	4%	27%	52%
Mean HbA1c in Past Year[a,β]					
mean±SD (%)	8.6±1.5	8.1±1.0	8.3±1.1	8.8±1.6	8.6±1.7
<6.5%	3%	3%	2%	2%	5%
6.5-<7.0%	6%	7%	6%	4%	9%
7.0-7.5%	12%	13%	13%	11%	13%
7.5-<8.0%	18%	23%	22%	16%	15%
8.0-<9.0%	31%	32%	37%	30%	26%
9.0-<10.0%	16%	18%	14%	18%	14%

	All N=13487	<6 Years Old N=377	Age Group 6-<13 Years Old N=4405	13-<18 Years Old N=5081	18-<26 Years Old N=3624
≥10.0%	14%	3%	7%	19%	18%
Insulin Method Past Year[a]					
Pump at least 1 yr	46%	33%	46%	47%	45%
Injections	42%	40%	38%	43%	47%
Pump<1year	12%	27%	16%	10%	9%
Insulin Units kg/day[a]					
mean±SD	0.9±0.4	0.8±0.4	0.9±0.4	0.9±0.4	0.8±0.4
<0.57 units/kg	17%	26%	15%	16%	22%
0.57-<0.82 units/k	32%	44%	37%	24%	36%
0.82-<1.08 units /k	30%	22%	31%	33%	25%
≥1.08 units/kg	21%	8%	18%	28%	17%
Family History of T1D [a,§]	14%	17%	14%	14%	13%

[*] Total of 6 transgenders in cohort.

[a] 4,251 participants are missing household income; 1,042 are missing education level; 1,961 are missing insurance status; 558 are missing BMI data; 97 participants do not have A1c data in past year; 59 are missing insulin method data; 856 are missing total daily insulin data; and 458 are missing family history of T1D.

[//] For participants less than 18 years of age, education reported is highest parent education. For participants older than 18 years of age, parent education level was not collected. The education level of participants themselves are 78%, 21% and 1% with ≤high school diploma, associate/ bachelor degree, and master degree or above, respectively.

[¥] For participants less than 20 years of age, BMI <5th percentile is considered underweight; 5th-<85th percentile normal weight; 85th-<95th percentile is overweight; and ≥95th percentile is obese. For participants older than 20 years of age, BMI <18.5 is considered underweight; 18.5-<25 normal weight; 25-<30 overweight; and ≥30 obese.

[β] Mean HbA1c in 12 months prior to enrollment.

[§] Indicates those with a first- degree family member with T1D including parent, sibling, half-sibling, or child.

Table 2

Factors Associated with ≥1 Severe Hypoglycemic Event in Past 12 Months

	N	% with ≥ 1 SH event	P-value[§] unadjusted/adjusted by age	Multivariate Model 1[*]		Multivariate Model 2[†]	
				OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
Total	9930	6.2%					
Age group [#]			0.005/NA		0.006		0.006
<6 Years	272	9.6%		1.00		1.00	
6-<13 Years	3208	5.2%		0.45 (0.28, 0.71)		0.44 (0.28, 0.69)	
13-<18 Years	3719	6.3%		0.48 (0.30, 0.76)		0.47 (0.30, 0.74)	
18-<26 Years	2731	6.9%		0.46 (0.28, 0.74)		0.46 (0.29, 0.74)	
Gender			0.94/0.96				
Female	4891	6.1%					
Male	5034	6.3%					
Race/Ethnicity			<0.001/<0.001		<0.001		<0.001
White Non-Hispanic	7781	5.7%		1.00		1.0	
Black Non-Hispanic	578	13.5%		2.09 (1.58, 2.76)		2.24 (1.71, 2.93)	
Hispanic or Latino	1038	5.5%		0.81 (0.60, 1.08)		0.86 (0.64, 1.15)	
Other Race/Ethnicity	533	7.1%		1.16 (0.82, 1.65)		1.20 (0.85, 1.70)	
Household Income [‡]			<0.001/<0.001		0.03		
≥ $75,000	3476	4.9%		1.0			
$35,000 - <$75,000	1942	6.1%		1.09 (0.85, 1.40)			
Less than $35,000	1540	9.4%		1.38 (1.05, 1.81)			
Parent Education [‡&]			0.09/0.09	NA			
≤ High school diploma\GED	2338	6.9%					
Associate degree or Bachelor degree	2772	4.9%					
Master, Professional or Doctorate degree	1726	5.9%					
Insurance Status			<0.001/<0.001		<0.001		<0.001
Private	6384	5.0%		1.00		1.0	
No insurance/non-private ins.	2354	8.9%		1.46 (1.18, 1.80)		1.69 (1.39, 2.04)	
Body Mass Index (BMI) [‡]			0.97/0.94				

Pediatr Diabetes. Author manuscript; available in PMC 2014 September 01.

	N	% with ≥ 1 SH event	P-value[§] unadjusted/adjusted by age	Multivariate Model 1[*]		Multivariate Model 2[†]	
				OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
Normal/underweight	5855	5.8%					
Overweight	2294	6.0%					
Obese	1354	6.5%					
Duration of T1D[‡] *(years)*			<0.001/<0.001		<0.001		<0.001
2-<5 years	3399	5.0%		1.0		1.0	
5-<10 years	3962	6.0%		1.33 (1.07, 1.65)		1.30 (1.05, 1.61)	
≥10 years	2569	8.1%		1.87 (1.46, 2.40)		1.80 (1.41, 2.30)	
Mean HbA1c in Past Year [‡]			<0.001/0.001		0.72		
<6.5%	259	5.8%		1.0			
6.5-<7.0%	601	5.5%		0.92 (0.49, 1.73)			
7.0-<7.5%	1175	5.7%		0.95 (0.53, 1.70)			
7.5-<8.0%	1774	4.2%		0.66 (0.37, 1.18)			
8.0-<9.0%	3060	6.3%		0.95 (0.55, 1.65)			
9.0-<10.0%	1557	7.8%		1.03 (0.59, 1.81)			
≥10.0%	1424	7.4%		0.80 (0.45, 1.42)			
Insulin Method Past Year			<0.001/<0.001		0.09		
Pump at least 1 yr	4637	5.3%		1.0			
Injections	4192	7.4%		1.23 (1.02, 1.48)			
Pump<1year	1053	5.4%		1.03 (0.76, 1.40)			
Insulin Units kg/day [‡]			0.41/0.52				
<0.57 units/kg	1632	7.0%					
0.57-<0.82 units/k	2968	6.1%					
0.82- <1.08 units /k	2806	5.5%					
≥1.08 units/kg	2011	6.3%					
Family History of T1D			>0.99/0.99				
No	8511	6.2%					
Yes	1416	6.2%					

[§]P values are unadjusted/adjusted for age group.

[*] The multivariate logistic regression model includes variables having age-adjusted P -value < 0.10. Missing values were imputed for covariates and an indicator for missing values was added to the regression model.

[†] The multivariate logistic regression model was concluded by using backward selection keeping those variables with P- value < 0.01.

[#] age was analyzed as categorical variable.

[‡] P-value obtained by treating as continuous variable. BMI Z score was analyzed. Education level and income category analyzed as ordinal variables.

[&] Univariate analysis on education level was limited to participants<18years old. Education was excluded from multivariate analysis due to missing data for participants older than 18 years.

Table 3

Factors Associated with ≥1 DKA Event in the Past 12 Months

	N	% with ≥ 1 DKA event	P-value[§] unadjusted/adjusted by age	Multivariate Model 1[*]		Multivariate Model 2[†]	
				OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
Total	13005	9.9%					
Age group [#]			<0.001/NA		0.28		
<6 Years	361	9.4%		1.00			
6-<13 Years	4246	7.6%		0.71 (0.48, 1.06)			
13-<18 Years	4911	11.4%		0.83 (0.56, 1.23)			
18-<26 Years	3487	10.5%		0.80 (0.54, 1.19)			
Gender			<0.001/<0.001		0.008		0.009
Female	6404	10.9%		1.00		1.0	
Male	6595	8.8%		0.85 (0.75, 0.96)		0.85 (0.75, 0.96)	
Race/Ethnicity			<0.001/<0.001		<0.001		<0.001
White Non-Hispanic	10304	8.1%		1.00		1.00	
Black Non-Hispanic	720	24.9%		1.65 (1.34, 2.04)		1.64 (1.34, 2.01)	
Hispanic or Latino	1306	13.2%		1.13 (0.93, 1.38)		1.15 (0.95, 1.38)	
Other Race/Ethnicity	675	13.5%		1.23 (0.95, 1.59)		1.28 (1.01, 1.64)	
Household Income [‡]			<0.001/<0.001		<0.001		<0.001
≥ $75,000	4673	5.5%		1.0		1.0	
$35,000 - <$75,000	2541	9.5%		1.26 (1.04, 1.54)		1.27 (1.05, 1.54)	
Less than $35,000	1996	18.4%		1.73 (1.40, 2.13)		1.78 (1.46, 2.17)	
Parent Education [&‡]			<0.001/<0.001	NA			
≤ High school diploma\GED	3029	15.1%					
Associate degree or Bachelor degree	3725	8.1%					
Master, Professional or Doctorate degree	2310	3.9%					
Insurance Status			<0.001/<0.001		<0.001		<0.001
Private	8475	6.6%		1.00		1.00	
No insurance/non-private ins.	3042	16.8%		1.47 (1.25, 1.72)		1.48 (1.26, 1.72)	
Body Mass Index (BMI) [‡]			0.78/0.84				

	N	% with ≥ 1 DKA event	P-value[§] unadjusted/adjusted by age	Multivariate Model 1[*]		Multivariate Model 2[†]	
				OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
Normal/underweight	7676	9.5%					
Overweight	3014	9.8%					
Obese	1780	11.3%					
Duration of T1D[‡] *(years)*			0.14/0.56				
2-<5 years	5836	9.3%					
5-<10 years	3843	10.2%					
≥10 years	3326	10.4%					
Mean HbA1c in Past Year [‡β]			<0.001/<0.001		<0.001		<0.001
<6.5%	364	0.8%		0.30 (0.09, 0.97)		0.27 (0.08, 0.86)	
6.5-<7.0%	793	1.8%		0.62 (0.33, 1.15)		0.58 (0.32, 1.05)	
7.0-<7.5%	1612	3.0%		1.00		1.00	
7.5-<8.0%	2303	4.8%		1.65 (1.15, 2.37)		1.54 (1.09, 2.17)	
8.0-<9.0%	4017	7.6%		2.52 (1.82, 3.50)		2.35 (1.73, 3.20)	
9.0-<10.0%	2004	13.3%		4.11 (2.94, 5.75)		3.94 (2.87, 5.39)	
≥10.0%	1825	28.9%		9.37 (6.74, 13.03)		9.23 (6.79, 12.55)	
Insulin Method Past Year			<0.001/<0.001		0.10		
Pump at least 1 yr	6114	6.9%		1.00			
Injections	5431	13.3%		1.12 (0.96, 1.29)			
Pump<1year	1404	9.2%		1.28 (1.02, 1.61)			
Insulin Units kg/day [‡]			0.01/0.03		0.38		
<0.57 units/kg	2143	11.3%		1.00			
0.57-<0.82 units/k	3940	8.0%		0.91 (0.75, 1.10)			
0.82-<1.08 units /k	3679	7.9%		0.82 (0.68, 1.00)			
≥1.08 units/kg	2643	12.6%		1.05 (0.87, 1.28)			
Family History of T1D			0.61/0.62				
No	11201	9.9%					
Yes	1797	9.5%					

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[*] The multivariate logistic regression model includes variables having age-adjusted P -value <0.10. Missing values were imputed for covariates and an indicator for missing values was added to the regression model.

[†] The multivariate logistic regression model was concluded by using backward selection keeping those variables with P- value <0.01.

[#] age was analyzed as categorical variable.

[‡] P-value obtained by treating as continuous variable. BMI Z score was analyzed. Education level and income category analyzed as ordinal variables.

[&] Univariate analysis on education level was limited to participants <18years old. Education was excluded from multivariate analysis due to missing data for participants older than 18 years.

[β] mean HbA1c in 12 months prior to enrollment.

Pediatr Diabetes. Author manuscript; available in PMC 2014 September 01.