The accuracy of provider diagnosed diabetes type in youth compared to an etiologic criteria in the SEARCH for Diabetes in Youth Study

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Abstract

Background: Although surveillance for diabetes in youth relies on provider-assigned diabetes type from medical records, its accuracy compared to an etiologic definition is unknown.

Methods: Using the SEARCH for Diabetes in Youth Registry, we evaluated the validity and accuracy of provider-assigned diabetes type abstracted from medical records against etiologic criteria that included the presence of diabetes autoantibodies (DAA) and insulin sensitivity. Youth

who were incident for diabetes in 2002–06, 2008, or 2012 and had complete data on key analysis variables were included (n=4,001, 85% provider diagnosed type 1). The etiologic definition for type 1 diabetes was 1 positive DAA titer(s) or negative DAA titers in the presence of insulin sensitivity and for type 2 diabetes was negative DAA titers in the presence of insulin resistance.

Results: Provider diagnosed diabetes type correctly agreed with the etiologic definition of type for 89.9% of cases. Provider diagnosed type 1 diabetes was 96.9% sensitive, 82.8% specific, had a positive predictive value (PPV) of 97.0% and a negative predictive value (NPV) of 82.7%. Provider diagnosed type 2 diabetes was 82.8% sensitive, 96.9% specific, had a PPV and NPV of 82.7% and 97.0%, respectively.

Conclusion: Provider diagnosis of diabetes type agreed with etiologic criteria for 90% of the cases. While the sensitivity and PPV were high for youth with type 1 diabetes, the lower sensitivity and PPV for type 2 diabetes highlights the value of DAA testing and assessment of insulin sensitivity status to ensure estimates are not biased by misclassification.

Keywords

surveillance; diabetes autoantibodies; validity; type 1 diabetes; type 2 diabetes

INTRODUCTION

Classification of diabetes type in children and adolescents presents unique challenges. A pathophysiologic framework was developed by the American Diabetes Association (ADA) in 1997 and updated in 2010 to classify diabetes type into 3 broad categories: type 1 diabetes, evidence of beta cell destruction usually leading to absolute insulin deficiency; type 2 diabetes, a combination of insulin resistance and an inadequate compensatory insulin secretory response; and other specific types including genetic defects of beta-cell function or insulin action, diseases of the exocrine pancreas, endocrinopathies and drug, chemical or infection induced diabetes.(1) The SEARCH for Diabetes in Youth Study (SEARCH) operationalized the ADA framework into an etiologic definition of diabetes type for the pediatric population based on assessed autoimmunity status, as indicated by the presence of specific diabetes autoantibodies (DAA) and estimated insulin sensitivity.(2) Provider diagnosed diabetes type may not align with an etiologic definition for a variety of factors related to the changing clinical presentation of type 1 and type 2 diabetes in youth. The rising prevalence of obesity in the childhood population (3) minimizes the usefulness of body mass index (BMI) as a distinguishing feature between type 1 and type 2 diabetes. Insulin resistance, while usually present in type 2 diabetes, is also seen in many youth with type 1 diabetes who have a higher BMI or a family history of type 2 diabetes.(4) Diabetic ketoacidosis (DKA) at clinical presentation is common among youth with type 1 diabetes, however is increasingly present, at clinical presentation for youth with type 2 diabetes.(5) Given the move towards applying algorithms to the information in electronic health records (EHRs) to conduct population-level surveillance of low-prevalence conditions, such as type 1 and type 2 diabetes in youth, it is important to understand the validity and accuracy of provider diagnosed diabetes type in youth compared to etiologic criteria.(6–9) The rationale for this study was to provide a context for understanding potential sources of bias introduced into surveillance findings when relying solely upon information from EHR to classify

diabetes type in youth <20 years of age. The aim of the current study was to evaluate the validity and discriminatory ability of diabetes type as diagnosed by the patient's physician or other health care provider ("provider-diagnosed diabetes type", or "provider type") against an etiologic definition ("etiologic type") based on measurements of autoimmunity and insulin sensitivity. Findings will help to guide considerations for population-based surveillance systems of diabetes in youth.

METHODS

SEARCH is a multicenter study that conducts population-based ascertainment of incident diabetes in youth < 20 years of age in the U.S.(10) Youth were identified at five clinical centers in California, Colorado, Ohio, South Carolina, and Washington, as well as among selected American Indian populations.(11) Physician-assigned diabetes type was abstracted from diabetes treatment databases or medical records and was based on physician note fields up to 6 months after the initial diagnosis. We classified provider-assigned diabetes type as type 1 diabetes (combining type 1, type 1a and type 1b), type 2 diabetes, and other types (hybrid type, type unknown and type designated as other). Youth with gestational diabetes only were excluded. Youth whose diabetes was incident (newly-diagnosed) in years 2002–2006, 2008 and 2012, were invited to attend an in-person research visit. Written informed consent and assent, when appropriate, were obtained from all participants or from parents or legal guardians for participants who were too young to provide written consent, in accordance to guidelines established by local institutional review boards (10).

Measures

Participants had blood drawn after an 8-hour overnight fast. They were instructed to refrain from taking diabetes medications the morning of the visit and long-acting insulin was administered the evening before the SEARCH in-person visit. Date of birth and sex were collected by survey, and self-reported race and ethnicity data used the 2000 U.S. census questions.(11) Only one participant had missing data on race/ethnicity and was grouped in the "other" category. Race and ethnicity were considered solely as socio-cultural constructs. Fasting blood samples were obtained, processed locally and shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories). Samples were analyzed for the presence of three DAAs: glutamic acid decarboxylase 65 (GADA); insulinoma-associated 2 molecule (IA-2A) and zinc transporter 8 (ZnT8) using standardized assays and protocols.(12, 13) Hemoglobin A1c (HbA1c) was measured using a dedicated ion exchange high-performance liquid chromatography instrument (TOSOH Bioscience). Lipids including triglycerides were measured with a Hitachi 917 autoanalyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Waist circumference was measured using the National Health and Nutrition Examination Survey (NHANES) protocol.(14)

Participants

Figure 1 displays the study flow for the current analysis. A total of 9,374 SEARCH participants whose diabetes was diagnosed in 2002–2006, 2008 or 2012 were invited to attend a baseline study visit. Participants were excluded if they were not registered with the study within 30 months of the end of their diagnosis year (N=651), had a provider diagnosis

of diabetes type other than type 1 or type 2 (N=153) or did not complete a SEARCH in-person study visit (N=3,685). Of the 4,885 remaining youth that completed a SEARCH visit, 761 were excluded because they were missing data on DAA status. In addition, youth determined to have maturity onset diabetes in the young (MODY) based on etiologic criteria and youth who were DAA negative but missing insulin sensitivity index were excluded because they could not be classified with the etiologic definitions (n=123). This resulted in an analytic sample of 4,001 participants. Overall, a lower percentage of youth with a provider diagnosis of type 2 diabetes were in the final analytic sample (36.6% of those registered) compared to provider type 1 diabetes youth (49.1% of those registered), largely due to non-participation in an in-person visit, as previously reported.(15)

Supplemental Figure 1 compares the distribution of demographic information for all registered eligible youth in the SEARCH study to those who completed an in-person visit. The distributions of mean age at diagnosis, sex, and race/ethnicity groups closely mirror the distributions of all persons registered, suggesting that this analysis sample reflects reasonably well the overall characteristics of the SEARCH registered population, as shown previously.(16)

Etiologic diabetes type definitions

The etiologic approach for characterization of diabetes type among youth in the SEARCH study has been previously described.(2) DAA status was determined based on titers from the baseline visit. DAA positive was defined as positive titers for GADA, IA-2 or ZnT8 using the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria.(12) Insulin sensitivity was estimated using an equation previously developed and validated against direct measurements of the glucose disposal rate from euglycemic-hyperinsulinemic clamps (17): exp [4.64725 −0.02032*(waist [cm]) - 0.09779 * (HbA1c [%]) - 0.00235 * (Triglyceride [mg/dl]). Insulin resistance was defined as values < 8.15 and insulin sensitivity was defined as values ≥ 8.15. The threshold cut-point for insulin resistance was determined based on a score less than the 25th percentile of estimated insulin sensitivity among youth without diagnosed diabetes who participated in the 1999–2004 NHANES survey.(2) The etiologic definition for type 1 diabetes was presence of positive titers for one or more DAA regardless of insulin sensitivity status or, in the absence of a positive DAA titer, the presence of insulin sensitivity based on an insulin sensitivity score ≥ 8.15. The etiologic definition for type 2 diabetes was all negative DAA titers and insulin sensitivity score < 8.15. A sensitivity analysis was performed using an etiologic definition for type 1 diabetes defined as positive titers for at least 1 DAA, regardless of insulin sensitivity status.

Statistical analysis

Characteristics of participants were compared according to provider diagnosed diabetes type including age at diagnosis, race/ethnicity (non-Hispanic white, Hispanic (regardless of race), non-Hispanic black and other races or missing race/ethnicity). Provider diagnosed diabetes type was compared to the etiologic definition to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operator curve (ROC) and the kappa statistic (18) to quantify the level of agreement. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Of the 4001 youth in the analytic sample, 3,401 had provider diagnosed type 1 diabetes and 600 had provider diagnosed type 2 diabetes (Table 1).

Provider diagnosed Type 1 diabetes

The mean age at provider diagnosed type 1 diabetes was 10.3 (SD=4.1) years; 12.1% received their diagnosis at 0–4 years, 32.7% at 5–9 years, 41.5% at 10–14 years and 13.6% at 15–19 years of age. The majority (73.4%) were non-Hispanic white, 10.5% were non-Hispanic black, 13.0% were Hispanic and 3.1% were other or unknown races/non-Hispanic ethnicity. The majority (90.7%), had a positive titer for at least one DAA (60.5%, 72.2% and 63.3% were positive for GADA, IA-2A and ZnT8, respectively). Based on the insulin sensitivity score, 74.6% were insulin sensitive, 25.4% were insulin resistant and 7.4% of DAA negative youth had unknown insulin sensitivity due to missing values for at least one component of the score.

Provider diagnosed type 2 diabetes

The mean age of provider diagnosed type 2 diabetes was 14.4 (SD=2.6) years; 0.2% received their diagnosis at 0–4 years, 3.5% at 5–9 years, 53.0% at 10–14 years and 43.3% at 15–19 years of age. The analytic sample included 19.0% non-Hispanic white, 42.2% non-Hispanic black, 27.7% Hispanic and 11.2% youth of other race/non-Hispanic ethnicity. Positive titers for DAA were detected in 13.8% youth with provider diagnosed type 2 diabetes (8.2%, 7.5% and 6.5% were positive for GADA, IA-2A and ZnT8, respectively) and 94.8% were insulin resistant.

Comparison of provider diagnosed diabetes type to etiologic definition

Table 2 presents the comparison of provider diagnosed diabetes type to the etiologic definition. Overall (for type 1 diabetes and type 2 diabetes combined, based on the ROC curve), provider diagnosis of diabetes type correctly identified diabetes type 89.9% of the time compared to the etiologic criteria. Provider diagnosis of type 1 diabetes was 96.9% sensitive and 82.8% specific compared to the etiologic type, while the PPV and NPV were 97.0% and 82.7%, respectively. A provider diagnosis of type 2 diabetes in youth was 82.8% sensitive and 96.9% specific compared to the etiologic definition of DAA negative and insulin resistant. The PPV was 82.7% and the NPV was 97.0%.

In a sensitivity analysis presented in Supplemental Table 1, we evaluated an alternate definition of etiologic type 1 diabetes defined as DAA positive, regardless of insulin sensitivity status (i.e., omitting the group with DAA negative and insulin sensitivity, N=236). Provider diagnosis of type 1 diabetes correctly discriminated 79.6% (AUC) of the cases compared to the etiologic criteria with a lower kappa using this definition (0.66.)

We explored differences between concordant (true positive) and discordant (false positive) cases shown in Table 2 to identify potential reasons for the misclassification (Table 3). Compared with youth with a concordant type 1 diabetes diagnosis (N=3298), those with a physician type 2 diabetes diagnosis but a type 1 diabetes etiologic assessment (N=104) were

older at diagnosis, more likely to be of minority race/ethnicity, more likely to have obesity, less likely to present in DKA, and less likely to be treated with insulin. In contrast, compared with youth with a concordant type 2 diabetes diagnosis (N=496), those with a physician type 1 diabetes diagnosis but a type 2 diabetes etiologic assessment (N=103) were more likely to be non-Hispanic white, less likely to have obesity, more likely to present in DKA, and more likely to be treated with insulin.

DISCUSSION

Among a diverse cohort of 4,000 youth with newly diagnosed diabetes in the U.S., provider diagnosed type correctly discriminated between type 1 and type 2 diabetes 89.9% of the time compared to an etiologic definition that included DAA results and insulin sensitivity measurements. There were some differences by type of diabetes. When a provider diagnosed type 1 diabetes based on clinical judgement, this agreed with the etiologic definition in 97% of the cases (PPV). Youth with provider diagnosed type 1 diabetes who met the etiologic determination for type 2 (NPV=3%) were most likely to be 10 years of age, of white, non-Hispanic race/ethnicity, with a BMI 30 and experience DKA within a month of diagnosis. However, when a provider diagnosed type 2 diabetes based on clinical judgment alone, level of agreement with the etiologic definition was lower at 83% (PPV), with 17% of cases misclassified (NPV). Youth with provider diagnosed type 2 diabetes who met the etiologic determination for type 1 were more likely to be of race/ethnicity minority, with a BMI 30, and no DKA within 1 month of diagnosis. This finding underscores how the clinical presentations of type 1 and type 2 diabetes may overlap and determination of type based on traditional clinical and anthropometric features alone can result in misdiagnosis, especially among minority race/ethnicity subgroups. Importantly, our study suggests that surveillance systems that rely solely upon data from the EHR may mask important trends in incidence and prevalence according to diabetes type in youth, particularly amongst youth of Hispanic ethnicity or non-Caucasian racial subgroups.

The reasons why etiologic determination of diabetes type in youth would differ from provider-diagnosed type based on clinical judgement may relate to the changing demographic and clinical presentation of type 1 and type 2 diabetes in youth. Type 1 diabetes is no longer a rarity among youth of minority race/ethnicity in the U.S., with the steepest increase in incidence between 2002–2012 observed among Hispanic youth.(19) While the clinical presentation of type 1 diabetes in youth is frequently recognized by diabetic ketoacidosis (DKA), it can also be present (though at a lower frequency) in youth with type 2 diabetes, and has been found to be associated with younger age, minority race/ethnicity and male gender in SEARCH.(20) Insulin resistance, while usually present in type 2 diabetes, is also seen in many youth with type 1 diabetes who have a higher BMI or a family history of type 2 diabetes.(4) Further, youth of minority race/ethnicity have higher HbA1c levels compared to youth of white, non-Hispanic racial/ethnic populations in the U.S. youth population (21) and in the diabetic population.(22) Finally, the rising prevalence of obesity in childhood populations disproportionately impacts certain gender, racial and ethnic subpopulations (3) and may contribute to convergence of an insulin resistant phenotype of type 1 diabetes that could be misdiagnosed as type 2 diabetes based on clinical judgement alone.(23) Any or all of these factors may account for the lower agreement

between provider diagnosed diabetes type and etiologic diabetes type identified in the current study among youth with type 2 diabetes. DAA testing and assessment of insulin sensitivity status at clinical presentation could aide accurate diagnosis of diabetes type and ensure an optimal therapeutic approach to prevent diabetes-related complications.

Classifying and distinguishing diabetes type in children remains challenging and controversial.(24) The SEARCH etiologic classification was developed to operationalize the ADA framework for diagnosis of type 1 and type 2 diabetes (1) in a pediatric population based on presence of specific diabetes autoantibodies (DAA) and estimated insulin sensitivity.(2) The etiologic classification uses operational definitions of autoimmunity and insulin resistance that need validation in future studies. Our definition of autoimmunity assumes that the presence of any single DAA is evidence of autoimmunity. Further the cut-point to define insulin resistance is based on a quartile distribution in a healthy population. An additional limitation of the current study includes incomplete measurement of ZnT8 on the entire cohort. A total of 1,055 youth with provider diagnosed type 1 (31.0%) and 48 youth with provider diagnosed type 2 (8.0%) were missing results for ZnT8. GADA and IA-2A are the most frequent positive DAA at clinical onset of type 1 diabetes (25), however it is possible that some youth not tested for ZnT8 actually had DAA and the presence of insulin resistance and were misclassified by the etiologic classification.

Recently, there has been an increasing interest in conducting surveillance of youth-onset diabetes using EHR algorithms. The utility of different algorithms using administrative clinical data (inpatient and outpatient diagnosis codes, outpatient medications, and laboratory test results) has been explored previously in SEARCH, and utilized provider diagnosed diabetes type in the SEARCH study (based on chart review) as the "gold standard" (7–9) rather than an etiologic classification of type. Several researchers have explored identification of diabetes cases and classification of type from EHR and insurance claims data in large health systems. Using retrospective EHR data from a large multisite practice in Eastern Massachusetts, Klompas et al. (6) created and applied a surveillance algorithm to identify diabetes cases of all ages using diagnostic billing codes, laboratory and prescription data. Compared to a "gold standard" of chart review, their algorithm performed with 97% and 93% sensitivity to correctly identify cases with type 1 diabetes and type 2 diabetes, respectively. In the National Diabetes Surveillance System in Canada, algorithms that incorporated demographic data and drug utilization patterns demonstrated high sensitivity to identify type 1 diabetes (98.6%) but misclassified type 2 diabetes in youth >20% of the time.(26) A recent report from Kaiser Permanente Southern California using ICD-10 codes and chart review-based provider assessment of diabetes type as gold standard (27) indicated that assignment of type was improved over older studies using ICD-9.(6–9) The PPV for type 2 diabetes was 92.5% and accuracy (using AUC) was 0.98. The performance of algorithms to distinguish between diabetes type in youth using administrative clinical data has not yet been evaluated compared to an etiologic determination of type, and is warranted given findings from this analysis that suggest provider type based on chart review misclassifies 17% of the type 2 diabetes cases. Further, surveillance programs of diabetes in youth might consider periodic assessment of etiologic criteria to ensure prevalence or incidence estimates are not biased by misclassification.

This study has limitations and important strengths that should be considered when interpreting our results. This analysis was restricted to youth who had a baseline in-person visit with a physician diagnosis of type 1 diabetes or type 2 diabetes. Youth with unknown or missing provider type were excluded. Data were not available on etiologic diabetes type on 53% of all eligible ascertained and registered SEARCH cases who did not attend an in-person study visit or had missing data. However, the subset of participants with baseline in-person data were similar in the distribution of sociodemographic indicators to the larger population of all registered cases.(15) The etiologic definition of DAA does not consider autoantibodies we did not measure (e.g., insulin autoantibodies) and is based on DAA measurements at one time point only in a period up to 30 months after diagnosis. Provider diagnosed diabetes type was based on physician note fields up to 6 months after the initial diagnosis, thus changes to the clinical assessment of diabetes type later in the clinical course were not assessed. This may result in an underestimation of the discriminatory ability of provider diagnosed diabetes type later in the clinical disease course. The analytic sample for our study was limited to youth-onset diabetes cases ascertained by the SEARCH study; no data were available on cases not ascertained by the SEARCH study (true negatives and false negatives). Thus, NPV in our study is interpreted as the probability of being correctly classified as the other diabetes type by a provider, rather than the probability that a youth who does not receive a diabetes diagnosis by a provider, truly does not have disease. Strengths of this study include: a) the use of a registry that ascertains diabetes cases without regard to diabetes type in multiple sites across the U.S. with nearly complete case-ascertainment (28); b) the population of youth under surveillance collectively mirrors the distribution of race/ethnicity, age, parental educational attainment and median household income of the nation's pediatric population (28); c) the proportion of youth with provider diagnosed diabetes type who met etiologic criteria has been shown to be consistent over time (19); and d) to our knowledge, this is the only study among youth that has compared provider diagnosis of diabetes type to an etiologic definition based on clinical and biological measurements. As the public health community and researchers evaluate the opportunity to harness data from EHRs for sustainable surveillance of diabetes in youth, findings from this study provide validity assessment of provider diagnosis.

CONCLUSION

Provider diagnosis of diabetes type was in agreement with etiologic criteria for 90% of cases. While the sensitivity and PPV for provider-diagnosed diabetes type was high for youth with type 1 diabetes (which comprised the majority of the study population), the lower sensitivity and PPV for type 2 diabetes in youth suggests a need for periodic assessment of etiologic criteria to ensure prevalence or incidence estimates are not biased by misclassification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Abbreviations:

SEARCH	SEARCH for Diabetes in Youth Study
DAA	diabetes autoantibodies
PPV	positive predictive value
NPV	negative predictive value
ADA	American Diabetes Association
HER	electronic health record

GADA	glutamic acid decarboxylase 65
IA-2	insulinoma-associated 2 molecule
ZnT8	zinc transporter 8
HbA1c	hemoglobin A1c
NHANES	National Health and Nutrition Examination Survey
ROC	receiver operator curve

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Youth in the SEARCH study aged < 20 years at diagnosis and diagnosed in 2002-2006, 2008, or 2012 at one of five SEARCH sites
n=9,374 (provider diagnosed type 1=7,277; provider diagnosed type 2=1,919; other/unknown type=178)

Excluded for registration time > 30 months (n=651)

Registered into the SEARCH study within 30 months from the end of the diagnosis year
n=8,723 (type 1=6,931; type 2=1,639; other/unknown type=152)

Excluded for provider diagnosed diabetes type other than 1 or 2 (n=153)

Provider diagnosed type 1 or type 2 diabetes
n=8,570 (type 1=6,931; type 2=1,639)

Excluded for not attending an in-person study visit (n=3,685)

Completed an In-Person visit
n=4,885 (type 1=4,162; type 2=723)

Excluded for missing data on at least 1 DAA (n=761)

At least one diabetes autoantibody (DAA) result available
n=4,124 (type 1=3,476; type 2=648)

Excluded for missing data on insulin sensitivity index in conjunction with DAA negative or maturity onset diabetes in young (MODY) based on etiologic criteria (n=123)

Etiologic Type:
• Type 1 (+ titers for ≥ DAA or DAA negative and Insulin Sensitive) n=3,401
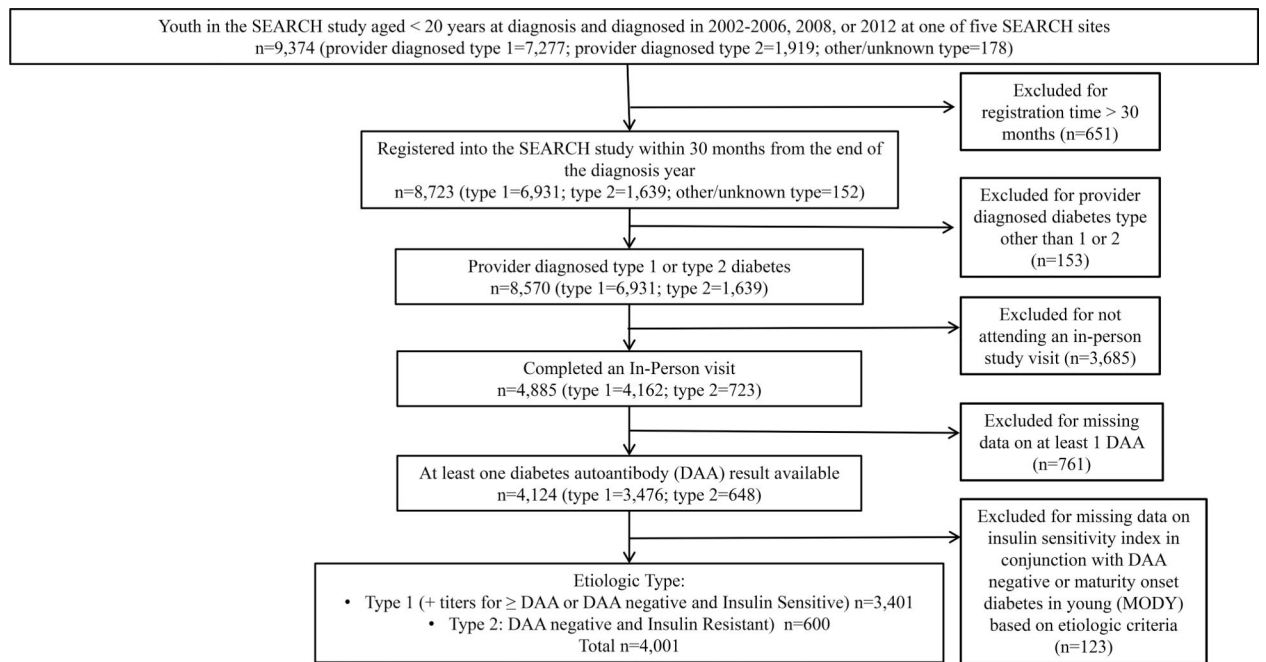• Type 2: DAA negative and Insulin Resistant) n=600
Total n=4,001

Figure 1:
Study Flow for Assessment of the Accuracy of Provider Diagnosed Diabetes Type Compared to an Etiologic Criteria in the SEARCH Study.

Diabetes autoantibody included glutamic acid decarboxylase 65 (GADA), insulinoma-associated 2 molecule (IA-2) and zinc transporter 8 (ZnT8)

Table 1.

Characteristics of participants with provider diagnosed type 1 diabetes and type 2 diabetes at <20 years in the SEARCH for Diabetes in Youth Study

	Provider Diagnosed Diabetes Type	
	Type 1 N=3401	Type 2 N=600
	N (%)	N (%)
Age at Diagnosis (mean years and standard deviation)	10.3 (4.1)	14.4 (2.6)
Age at Diagnosis (years)		
0–4	413 (12.1)	1 (0.2)
5–9	1,113 (32.7)	21 (3.5)
10–14	1,411 (41.5)	318 (53.0)
15–19	464 (13.6)	260 (43.3)
Race/Ethnicity		
White non-Hispanic	2,496 (73.4)	114 (19.0)
Black non-Hispanic	358 (10.5)	253 (42.2)
Hispanic	443 (13.0)	166 (27.7)
Others	104 (3.1)	67 (11.2)
Diabetes Autoantibodies (DAA)		
GADA positive [*]	2,056 (60.5)	49 (8.2)
IA-2A positive [†]	2,454 (72.2)	45 (7.5)
ZnT8 positive [‡]	1,485 (63.3)	36 (6.5)
Positive on any DAA (GADA, IA-2A or ZnT8)	3,083 (90.7)	83 (13.8)
Negative on all three DAA measured	277 (11.8)	485 (87.9)
Insulin Sensitivity Score [‖]		
Insulin sensitive [¶]	2,351 (74.6)	31 (5.2)
Insulin resistant [#]	800 (25.4)	562 (94.8)

diabetes autoantibodies=DAA; glutamic acid decarboxylase 65=GADA; insulinoma-associated 2 molecule=IA-2A; zinc transporter 8=ZnT8;

[*] 4 youth with provider diagnosed type 1 were missing results on GADA

[†] 4 youth with provider diagnosed type 1 were missing results on IA-2A

[‡] 1,055 youth with provider diagnosed type 1 and 48 youth with provider diagnosed type 2 were missing results for ZnT8

All three DAAs were measured on 2,894 youth (2347 with provider diagnosed type 1 and 552 with provider diagnosed type 2 diabetes)

[‖] Insulin sensitivity score = exp [4.64725 -0.02032*(waist [cm]) - 0.09779 * (HbA1c [%]) - 0.00235 * (Triglyceride [mg/dl]). Insulin sensitivity score was unknown for 250 youth with provider diagnosed type 1 and 7 youth with provider diagnosed type 2 diabetes.

[¶] Insulin sensitivity score ≥ 8.15

[#] Insulin sensitivity score < 8.15

Table 2:

Comparison of provider diagnosed diabetes type in youth <20 years of age to an etiologic definition in the SEARCH for Diabetes in Youth study

Type 1 Diabetes				
		Etiologic Type[*]		Total
		Yes	No	
Diabetes type from medical record	Yes	3,298	103	3,401
	No	104	496	600
Total		3,402	599	4,001
Sensitivity = 96.9% (95% CI: 96.3 – 97.5%), **Specificity** = 82.8% (79.6 – 85.6%)				
PPV = 97.0%, **NPV** = 82.7%				

Type 2 Diabetes				
		Etiologic Type[†]	Total	
		Yes	No	
Diabetes type from medical record	Yes	496	104	600
	No	103	3,298	3401
Total		599	3,402	4,001
Sensitivity = 82.8% (79.6 – 85.6%), **Specificity** = 97.0% (96.4 -97.6%)				
PPV = 82.7%, **NPV** = 97.0%				
Area under ROC curve = 89.9% (88.3 - 91.4%), Kappa = 0.80 (0.77 – 82.)				

Positive predictive value=PPV; negative predictive value=NPV; receiver operator curve=ROC.

[*] Etiologic definition in youth with type 1 diabetes was presence of at least 1 diabetes autoantibody (GADA, IA-2A and ZnT8 DA), regardless in insulin sensitivity or absence of autoantibodies in combination with insulin sensitivity based on an insulin sensitivity score 8.15.

[†] Etiologic definition in youth with T2D was absence of diabetes autoantibodies (GADA, IA-2A and ZnT8 DA) and insulin resistant based on an insulin sensitivity score < 8.15.

Table 3.

Comparison of demographic and clinical characteristics of cases who were concordant and discordant between provider diagnosed type of diabetes and etiologic type definition, by type of diabetes

	Etiologic Type 1			Etiologic Type 2		
	Provider Type Concordant	Provider Type Discordant		Provider Type Concordant	Provider Type Discordant	
	N (%)	N (%)	P	N (%)	N (%)	P
N	3298	104		496	103	
Age at Diagnosis (years)			<0.0001			0.0006
0–4	413 (12.5)	1 (1.0)		0 (0.0)	0 (0.0)	
5–9	1102 (33.4)	8 (7.7)		13 (2.6)	11 (10.7)	
10–14	1351 (41.0)	48 (46.2)		270 (54.4)	60 (58.3)	
15–19	432 (13.1)	47 (45.2)		213 (42.9)	32 (31.1)	
Race/Ethnicity			<0.0001			<0.0001
White non-Hispanic	2453 (74.4)	29 (27.9)		85 (17.1)	43 (41.7)	
Black non-Hispanic	330 (10.0)	36 (34.6)		217 (43.8)	28 (27.2)	
Hispanic	423 (12.8)	27 (26.0)		139 (28.0)	20 (19.4)	
Other	92 (2.8)	12 (11.5)		55 (11.1)	12 (11.7)	
Diabetes Autoantibodies (DAA)						
GADA positive	2056 (62.4)	49 (47.1)	0.002	0 (0.0)	0 (0.0)	NA
IA-2A positive	2454 (74.5)	45 (43.3)	<0.0001	0 (0.0)	0 (0.0)	NA
ZnT8 positive	1485 (66.0)	36 (42.4)	<0.0001	0 (0.0)	0 (0.0)	NA
Positive on any DAA	3083 (93.5)	83 (79.8)	<0.0001	0 (0.0)	0 (0.0)	NA
Negative on all three DAA measures	181 (8.1)	18 (21.2)	0.0002	467 (100.0)	96 (100.0)	NA
Insulin Sensitivity [*]			<0.0001			NA
Insulin sensitive [†]	2351 (71.3)	31 (29.8)		0 (0.0)	0 (0.0)	
Insulin resistant [‡]	697 (21.1)	66 (63.5)		496 (100.0)	103 (100.0)	
Unknown status	250 (7.6)	7 (6.7)		0 (0.0)	0 (0.0)	
BMI category			<0.0001			<0.0001
<85th percentile or BMI <25 (normal or under)	2209 (68.7)	22 (21.4)		8 (1.6)	26 (25.5)	
85th to <95th percentile or BMI 25 to <30 (overweight)	606 (18.8)	18 (17.5)		34 (6.9)	21 (20.6)	
95th percentile or BMI > 30 (obese)	402 (12.5)	63 (61.2)		451 (91.5)	55 (53.9)	
Unknown	81 (2.4)	1 (1.0)		3 (0.6)	1 (1.0)	
DKA within 1 month of diagnosis			0.0012			<0.0001
No	1729 (69.0)	73 (84.9)		366 (92.2)	56 (67.5)	
Yes	777 (31.0)	13 (15.1)		31 (7.8)	27 (32.5)	

	Etiologic Type 1			Etiologic Type 2		
	Provider Type Concordant	Provider Type Discordant		Provider Type Concordant	Provider Type Discordant	
	N (%)	N (%)	P	N (%)	N (%)	P
Unknown	792 (24.0)	18 (17.3)		99 (20.0)	20 (19.4)	
Medication(s) at time of visit			<0.0001			<0.0001
Metformin only	13 (0.4)	33 (32.0)		222 (44.8)	7 (6.9)	
Insulin only	3216 (97.7)	31 (30.1)		55 (11.1)	64 (62.7)	
Insulin + Anything else	34 (1.0)	24 (23.3)		125 (25.2)	27 (26.5)	
Other Oral	2 (0.1)	5 (4.9)		32 (6.5)	1 (1.0)	
None	26 (0.8)	10 (9.7)		62 (12.5)	3 (2.9)	
Unknown	7 (0.2)	1 (1.0)		0 (0.0)	1 (1.0)	

diabetes autoantibodies=DAA; glutamic acid decarboxylase 65=GADA; insulinoma-associated 2 molecule=IA-2A; zinc transporter 8=ZnT8; diabetic ketoacidosis=DKA

*
Insulin sensitivity score = exp [4.64725 -0.02032*(waist [cm]) - 0.09779 * (HbA1c [%]) - 0.00235 * (Triglyceride [mg/dl])

†
Insulin sensitivity score 8.15

‡
Insulin sensitivity score < 8.15