Trajectories in Estimated Glomerular Filtration Rate in Youth-Onset Type 1 and Type 2 Diabetes: The SEARCH for Diabetes in Youth Study

Katherine D. Westreich[1], **Scott Isom**[2], **Jasmin Divers**[2], **Ralph D'Agostino**[2], **Jean M. Lawrence**[3], **Roopa Kanakatti Shankar**[4], **Lawrence M. Dolan**[5], **Giuseppina Imperatore**[6], **Dana Dabelea**[7], **Elizabeth J. Mayer-Davis**[8], **Amy K. Mottl**[1]

[1]University of North Carolina Kidney Center, UNC School of Medicine, Chapel Hill, NC;

[2]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, NC;

[3]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA;

[4]Division of Endocrinology, Children's National Medical Center, Washington DC;

[5]Division of Endocrinology, Cincinnati Children's Hospital, Cincinnati, OH;

[6]Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA;

[7]Department of Epidemiology, School of Public Health, University of Colorado Denver, Aurora, CO;

[8]Department of Nutrition, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC; Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC;

STRUCTURED ABSTRACT:

Aims: We sought to characterize the direction and associated factors of eGFR change following diagnosis of youth-onset type 1 and type 2 diabetes.

Methods: We assessed the direction of eGFR change at two visits (mean 6.6 years apart) in SEARCH, a longitudinal cohort study of youth-onset type 1 and type 2 diabetes. We used the CKiD$_{Cr-CysC}$ equation to estimate GFR and categorized 'rising' and 'declining' eGFR as an

Corresponding Author: Amy K. Mottl, MD MPH, 7024 Burnett Womack Bldg, CB 7155, Chapel Hill, NC, 27599-7155, (919) 445-2641 phone, (919) 966-4251 fax, amy_mottl@med.unc.edu.

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annual change of 3ml/min/1.73m^2 in either direction. Multivariable logistic regression evaluated factors associated with directional change in eGFR.

Results: Estimated GFR declined in 23.8% and rose in 2.8% of participants with type 1 diabetes (N=1225; baseline age 11.4 years), and declined in 18.1% and rose in 15.6% of participants with type 2 diabetes (N=160; baseline age 15.0 years). Factors associated with rising and declining eGFR (versus stable) in both type 1 and type 2 diabetes included sex, age at diagnosis, baseline eGFR and difference in fasting glucose between study visits. Additional factors in type 1 diabetes included time from baseline visit, HbA1c and body mass index.

Conclusions: Over the first decade of diabetes, eGFR decline is more common in type 1 diabetes whereas eGFR rise is more common in type 2 diabetes.

Keywords

Diabetes; eGFR; Kidney; Longitudinal; Youth; Trajectory

1.1   INTRODUCTION

Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in the United States and worldwide.[1, 2]. The economic burden of diabetes increases with progression from one CKD stage to the next, with the greatest cost incurred from diabetic ESKD, totaling more than 14 trillion U.S. dollars in 2014.[1, 3] Diabetic Kidney Disease (DKD) is responsible for much of the increased mortality risk in diabetes, mainly attributable to cardiovascular events, the risk of which, increases linearly with decreasing estimated glomerular filtration rate (eGFR).[4]

The rising prevalence of youth-onset diabetes (<20 years of age) is particularly worrisome from a public health viewpoint, as it increases population-level lifetime exposure to the diabetic milieu, thus increasing the opportunity for development of diabetic complications. From 2001 to 2009, the prevalence of youth onset type 1 diabetes increased by 21% and type 2 diabetes by 30%.[5] Kidney-related complications in youth onset type 2 diabetes take a particularly aggressive course. After only 5 years of diabetes, 17–42% of youth with type 2 diabetes exhibit microalbuminuria, as opposed to 11% in youth with type 1 diabetes.[6, 7]. Moreover, albuminuria is more likely to regress in type 1 diabetes and more likely to progress in type 2 diabetes.[8] The risk for ESKD and death after 20 years of diabetes is at least two-fold higher in youth-onset type 2 diabetes versus type 1 diabetes.[9, 10] Based on epidemiologic trends, we anticipate a substantial increase in the human and financial costs from DKD.

While current diabetes management strategies slow the progression of DKD, efforts have focused on reductions in albuminuria, yet the prevalence of decreased eGFR (<60ml/min/1.73m^2) has risen.[11] Decreased eGFR with normoalbuminuria occurs in a substantial proportion of people with diabetes and is more common in women and in type 2 diabetes. [12, 13] While historically albuminuria was considered the universal first step of progression to DKD, followed by GFR decline, recent evidence suggests that distinct pathophysiologic and molecular mechanisms are responsible for the two.[14] Biopsy studies show variability

in structural characteristics, some of which associate with the magnitude of albuminuria and others with measured GFR.[15, 16] Improved understanding of the early natural history of eGFR changes and associated clinical, structural and molecular factors is imperative for identifying novel biomarkers and therapeutic drug targets for DKD.

Numerous studies have documented the natural history of eGFR decline in DKD, mostly in diabetes of long duration, after GFR has dropped below $90ml/min/1.73m^2$. Studies of the earliest changes in eGFR are necessary to provide insight into DKD at a stage when interruption of the disease process is most feasible and may have the greatest impact. In early DKD, eGFR may rise toward hyperfiltration (>130ml/min) or fall toward subnormal (<90ml/min) levels. Both phenomena carry increased risk for progression to advanced kidney disease, but the precise time course and clinical factors associated with these changes have not been studied.[17–20]

We sought to: (1) characterize and compare the direction of eGFR changes over the initial years after diagnosis of youth-onset type 1 and type 2 diabetes; and (2) determine the sociodemographic and clinical factors associated with direction of eGFR change.

1.2 SUBJECTS, MATERIALS AND METHODS

1.2.1 Population

Youth with diabetes diagnosed at < 20 years of age were identified from a population-based incidence registry network at five U.S. sites (South Carolina, Ohio, Colorado, Washington, and California) by the SEARCH for Diabetes in Youth Registry Study [21]. Individuals with a new diagnosis of type 1 diabetes or type 2 diabetes in 2002–2006 or 2008 were invited for a baseline visit a mean of 9.4 ± 6.2 months after diagnosis, to measure risk factors for diabetes complications. In 2011–2015, those with 5 years of diabetes duration and a previously completed baseline visit were invited to participate in a follow-up visit, at which time diabetes risk factors and early diabetes-related complications were assessed (Figure 1). The follow-up visit was completed by 2,777 participants at a mean age of 17.9 + 4.8, and mean diabetes duration of 8.0 ± 2.0 years. A flow chart depicting exclusion criteria is shown in Figure 2. The distribution of demographic, metabolic, and socioeconomic characteristics of participants completing the follow-up visit were similar to that of the larger SEARCH registry.[22] The study was approved by Institutional Review Boards with jurisdiction, and the parent, participant or both provided consent or assent.

1.2.2 Data Collection and Laboratory Analyses

Race and ethnicity were self-identified using U.S. census methods [23]. Body mass index (BMI) was defined as weight (kilograms) divided by the square of the height ($meters^2$) and converted to a Z score [24]. Waist circumference was measured using the natural waist location. Three systolic and diastolic blood pressures measured with an aneroid manometer after 5 minutes of rest were averaged.

A blood draw occurred after an overnight fast, and was analyzed for hemoglobin A1c (HbA1c), glucose, lipids, creatinine (Jaffe), cystatin-C, and diabetes autoantibodies (GAD-65 antibodies (GAD_{65}) and insulinoma-associated-2 antibodies (IA-2A) at the

study's central laboratory (Northwest Lipid Metabolism and Diabetes Research, Seattle, WA)) [25]. Zinc-T8 autoantibody was analyzed at the Eisenbarth laboratory (University of Colorado, Aurora, CO) [26]. Urine albumin-to-creatinine ratio (UACR) was measured from a randomly collected urine sample. Cystatin C was measured using Siemens reagent on a BNII nephelometer (Siemens Healthcare Diagnostics). As noted in other studies, we identified an assay drift in cystatin C [27]. Calibration equations were utilized to make results traceable to the International Federation of Clinical Chemistry Standard.[28]

1.2.3   Assignment of Diabetes Type

Diabetes type was defined using an etiological classification [29, 30] based on one or more positive diabetes autoantibodies and estimated insulin sensitivity score (validated equation including waist circumference, A1c and triglyceride levels) at the baseline visit.[29] Type 1 diabetes was defined as at least one positive antibody or insulin sensitivity (score 8.15). Type 2 diabetes was defined as negative antibodies and insulin insensitivity (score <8.15).

1.2.4   Change in eGFR

We estimated GFR and its change using the Chronic Kidney Disease in Children ($CKiD_{Cr-CysC}$) equation, developed and validated in children with chronic kidney disease and used broadly in clinical and research settings.[31]

$$eGFR\,CKiD_{Cr-CysC} = 41.6 * (height\_cm/SCr\_mg/dl)^{0.5999} * (1.8/CysC\_mg/L)^{0.317}$$

As a sensitivity analysis, we estimated GFR and its change using the $Bouvet_{Cr-CysC}$ equation [32] due to the following features: inclusion of creatinine and cystatin c, which allows greater accuracy and precision in GFR estimation in both children and adults [31, 33]; validity up to 23 years of age [32]; and excellent performance at normal GFR and in hyperfiltration states (100% accuracy within 30% of measured GFRs between 90 and 200ml/min/1.73m2) [34].

$$eGFR\,Bouvet_{Cr-CysC} = 63.2 * [(SCr\_mg/dl * 88.4/96)^{-0.35}] * [(CysC\_mg/L/1.2)^{-0.56})] * [weight\_kg/45)^{0.30}] * [age\_yrs/14)^{0.4}] * 1.73/BSA$$

Annual change in eGFR was determined by the difference in eGFR between visits, divided by the number of years between visits. Studies have shown that measured GFR remains very stable throughout childhood and into early adulthood [35, 36]. The rate of decline of GFR among people with DKD is highly variable, but typically ranges 3–5ml/min/1.73m^2 per year. [37, 38] This led us to define *any* aberrant annual change in eGFR as   3mL/min/1.73m2 per year in either direction, as this is well beyond what would be expected for youth and young adults without diabetes, and is not out of range of what would be seen in people with DKD. Over the course of a minimum 5 year interval between the two visits, a change of > 3mL/min/1.73m2 per year translates to a conservative definition of aberrant GFR change (+/ − 15ml/min/1.73m2), even considering day-to-day variation and the error inherent in the estimating equations [39].

1.2.5 Statistical Analyses

We performed statistical analyses using SAS, version 9.4 (SAS Institute, Cary, NC).[40] Within each diabetes type, means and percentages of demographic and clinical characteristics were compared using chi square and t-tests. We selected the sample based on key information necessary for analyses (exposure/outcome variables) and assumed missing values in the selected sample were missing at random (Table 1). Transformations were done for continuous characteristics with skewed distributions. We used bivariate and multivariable linear analyses to determine whether baseline and time-varying characteristics (where appropriate) were predictive of the direction of eGFR change. There were 19 participants with type 1 diabetes who were missing one or more covariates and hence were excluded from multivariable analyses (N=1206). Multivariable logistic regression with a generalized logit link was used to evaluate the association between characteristics and categorical eGFR outcome variables (decline, stable, rise). Variables were selected based on existing data and clinical plausibility and included: age at diagnosis, sex (male/female), black race, time from baseline visit, baseline eGFR, glucose change from baseline to follow-up (to account for transient hyperfiltration due to acute hyperglycemia), and time varying HbA1c, BMI-Z score and (systolic blood pressure) SBP-Z score. The AUC variables are longitudinal cumulative exposure variables calculated as the weighted average of the measures of interest during the participant's time in the study (which varied between 2 and 5 visits) and weighted for the interval between each measurement. Statistical significance when comparing baseline demographics was set at an alpha of 0.0001 to account for multiple comparisons.

1.3 RESULTS

Participants meeting inclusion criteria were 1,225 youth and young adults with type 1 diabetes and 160 with type 2 diabetes. Stratifying by diabetes type, baseline sociodemographic and clinical characteristics of participants are shown in Table 1. With the exception of HbA1c, there were statistically significant differences between diabetes types in all demographic and clinical characteristics (see Table 1).

1.3.1 eGFR Trajectories

Using the $CKiD_{Cr-CysC}$ equation and *a priori* specified criteria to define change (decline versus stable versus rise), the majority of youth and young adults with type 1 and type 2 diabetes maintained a stable eGFR between the baseline and follow-up visit. Decline in eGFR occurred in 23.8% of participants with type 1 diabetes and 18.1% with type 2 diabetes. An increase in eGFR occurred in 2.8% of participants with type 1 diabetes and in 15.6% with type 2 diabetes. The classification of eGFR change as estimated by the $CKiD_{Cr-CysC}$ and $Bouvet_{Cr-CysC}$ equations were in agreement for 67% of the type 1 diabetes and 65% of the type 2 diabetes participants (Tables 2A and 2B), with the $Bouvet_{Cr-CysC}$ equation classifying more participants, as having a rise in eGFR, regardless of diabetes type.

1.3.2 Factors Associated with eGFR Trajectories

Results of multivariable logistic regression analyses for the outcome of direction of change in eGFR are depicted among those with type 1 diabetes in Table 3A. Characteristics associated with eGFR decline versus stable eGFR included male sex, younger age at

diagnosis, shorter time between study visits, higher baseline eGFR, lower glucose level at the follow up compared to baseline visit and lower time-averaged HbA1c. Associations comparing eGFR rise versus stable eGFR were essentially the opposite, with the exception of the time between study visits.

In multivariate analyses of the type 2 diabetes cohort (Table 3B), characteristics associated with decline in eGFR compared to stable eGFR included male sex, younger age at diagnosis, higher baseline eGFR and lower glucose level at the follow up compared to baseline. For rising versus stable eGFR, female sex, lower baseline eGFR, shorter duration between visits, higher glucose level at the follow-up compared to baseline visit and higher time-averaged HbA1c were significant. In sensitivity analysis, we found that our results were largely robust to choice of GFR estimating equation (Supplemental Tables 1A and 1B).

1.4   DISCUSSION

The rising incidence of type 1 and type 2 diabetes in youth [5] portends a surge in CKD and ESKD in the coming years. In contrast to the known stability of GFR over the course of childhood and early adulthood in the healthy state [35, 36], we have provided the first documentation that aberrant changes in eGFR ($3mL/min/1.73m^2$ per year) can occur early in the early years following diabetes diagnosis. Moreover, we have shown that the direction of change in eGFR differs by diabetes type, wherein, youth and young adults with type 1 diabetes have a greater risk for eGFR decline than rise, while those with type 2 diabetes are at greater risk of rise than decline.

1.4.1   Effect of Diabetes Type

The type 2 diabetes group has a much higher prevalence of obesity than those with type 1 diabetes, which may account for the greater proportion with rising eGFR, as obesity can result in a hyperfiltration state even in the absence of diabetes.[41] Additionally, there has been speculation that insulin resistance, rather than obesity, plays a causal role in the development of hyperfiltration in type 2 diabetes.[42] The opposing direction of eGFR change between the type 1 and type 2 diabetes groups could also be related to the older age of type 2 diabetes onset as opposed to type 1 diabetes. In support of this potential explanation is the finding that age of diabetes onset was older within the type 1 diabetes group with rising (13.6 yrs) versus declining (8.6 yrs) eGFR (data not shown). The pathophysiologic basis for this is unclear, as GFR is constant between ages 2 and about 35–40 in the healthy, physiologic state.[35, 43]

1.4.2   Effect of Baseline eGFR

Baseline eGFR was a highly significant predictor of direction of eGFR trajectory in both type 1 and type 2 diabetes, even after accounting for differences in acute glycemia at the time of eGFR measurement. It is possible that the observed changes may be partially due to regression to the mean [44], however, this seems unlikely given our conservative definition of eGFR change ($3mL/min/1.73m^2$ per year) and since adjustment for baseline eGFR did not entirely explain the differences between the three groups. The baseline visit occurred soon after diabetes diagnosis, and there was no statistical difference in diabetes duration at

the baseline visit between those with rising versus declining eGFR. It may be that some individuals are at higher risk of developing hyperfiltration within the first year of diagnosis, which predicts GFR decline over the ensuing several years. Our data suggests this may be the case in those who are younger at diagnosis, among females and particularly among youth and young adults with type 2 diabetes. Hyperfiltration has been shown to be a predictor of rapid (>3ml/min/1.73m^2/year) GFR decline among adults with type 1 diabetes.[18]

1.4.3 Effect of Glycemia

Both acute and chronic glycemic status influenced direction and magnitude of eGFR change. Physiology studies using 24-hour euglycemic clamps and measured GFR have demonstrated that an acute high glucose level over a number of hours reliably causes an increase in GFR. [45–47] We observed this pattern as well; within both diabetes types, those with eGFR rise had the highest gain in glucose between visits, and those with eGFR decline between visits had the least gain or a decline in glucose between visits (type 1 diabetes) or had a lower serum glucose level at follow up than at baseline (type 2 diabetes) (data not shown). To account for this effect, the change in fasting glucose between the two visits was included in the multivariate model. The reason for this physiologic effect may lie in the sodium-glucose cotransporter of the proximal tubule, which, under circumstances of hyperglycemia, will also reabsorb sodium, resulting in decreased sodium delivery to the macula densa and resultant vasodilatation of the afferent arteriole.[48, 49]

1.4.4 Study Limitations

This study has limitations, the most notable being lack of measured GFR. Choice of the appropriate GFR estimating equation proved quite difficult, given that obesity, hyperfiltration, hyperglycemia, and the transition from childhood to adulthood all affect accuracy and validity of GFR estimates. We utilized the CKiD$_{Cr-CysC}$ equation because it is widely used in clinical pediatrics and hence provides the most clinical relevance. One caveat to this is that it was derived and validated within a cohort of children with CKD and hence performs best within a much lower range of GFR than that seen in our study population. In contrast, the Bouvet$_{Cr-CysC}$ equation was derived in a cohort of children and young adults up to age 23 with normal or supranormal GFR, leading to excellent performance in this range of GFR [32]. The Bouvet$_{Cr-CysC}$ was therefore the most appropriate equation to verify our results and also provided the greatest test to their validity, given its strengths lie in opposition to those of the CKiD$_{Cr-CysC}$ equation. Notably, results of our analyses were mostly in agreement using the two equations, lending confidence to our findings.

The Bouvet equation could be considered problematic, particularly in our type 2 DM population because it includes weight, raising the question of whether observed eGFR changes could be due to change in weight rather than change in GFR. In order to address this, we performed post hoc analyses of changes in weight in both type 1 and type 2 diabetes. Weight change was much greater in those who had an eGFR decline than in those with rise in eGFR opposite of what would have been observed had weight been responsible for direction of eGFR change (data available upon request).

We also acknowledge that it is less than ideal to draw longitudinal conclusions from eGFR estimated at only two timepoints. Attempts to overcome these deficiencies included a broad definition of stable eGFR, defining change as much greater than observed physiologic change from year to year in this age group, and more than the error known to be inherent in GFR estimating equations. Over the mean follow up time of 6 years between visits, the defined threshold change of $3mL/min/1.73m^2$ would translate to a mean change of $18mL/min/1.73m^2$, which most nephrologists would deem clinically significant.

1.4.5   Study Strengths

Our study also has several strengths. The SEARCH for Diabetes in Youth Study is a large, multicenter longitudinal study with significant representation from ethnic minorities and includes youth with type 1 and type 2 diabetes. Its rigor is underscored by baseline data captured close to diabetes diagnosis. Very few studies have had the opportunity to document and contrast the early natural history of eGFR according to diabetes type, particularly without the added confounding of vast differences in age of onset between diabetes types.

1.4.6   Conclusion

We have identified distinct trajectories of eGFR over the early course of diabetes. Regardless of diabetes type, factors associated with the rising or declining trajectories (versus stable) included sex, age at diagnosis, baseline eGFR and baseline glucose levels. A greater preponderance of youth and young adults with type 2 diabetes had a rise in eGFR to hyperfiltration levels, and a greater proportion of individuals with type 1 diabetes had an early decline in eGFR. Whether these two phenotypes predict differing risks for progression to advanced kidney disease will be the focus of future study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Estimated glomerular filtration rate (eGFR) generally remains stable over the first 5–10 years of youth onset type 1 and type 2 diabetes.

- Approximately 20% of individuals with youth onset type 1 and type 2 diabetes will have a significant decline in eGFR, though still remaining within the normal range.

- Very few individuals with youth onset type 1 diabetes will have a rise in eGFR over the first 5–10 years, however, roughly 15% of youth onset type 2 diabetes experiences a significant rise in eGFR.

- Predictors of change in eGFR shared in youth onset type 1 and type 2 diabetes include age at diagnosis, sex, baseline eGFR and fasting glucose level.
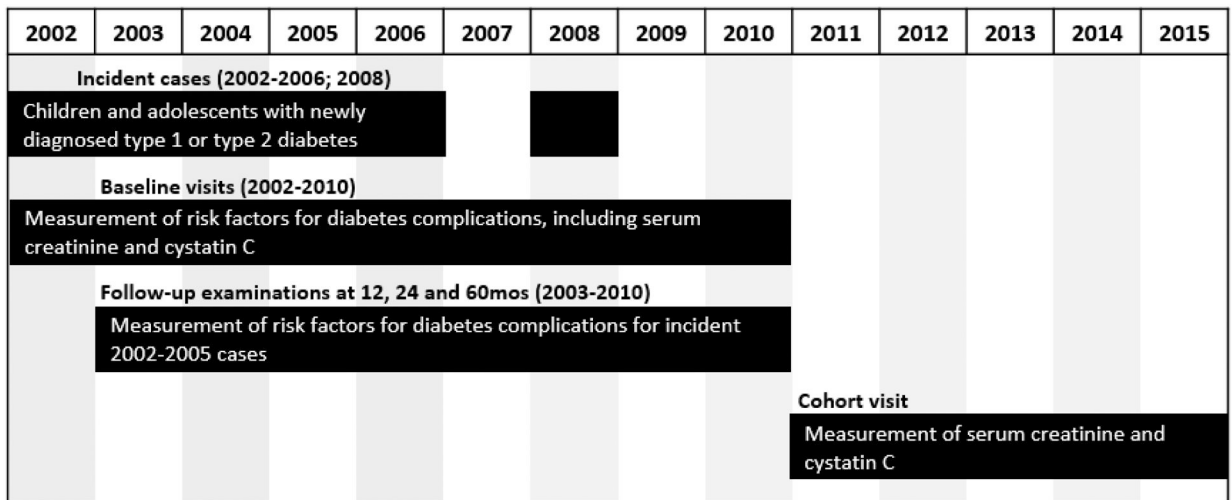
Figure 1:
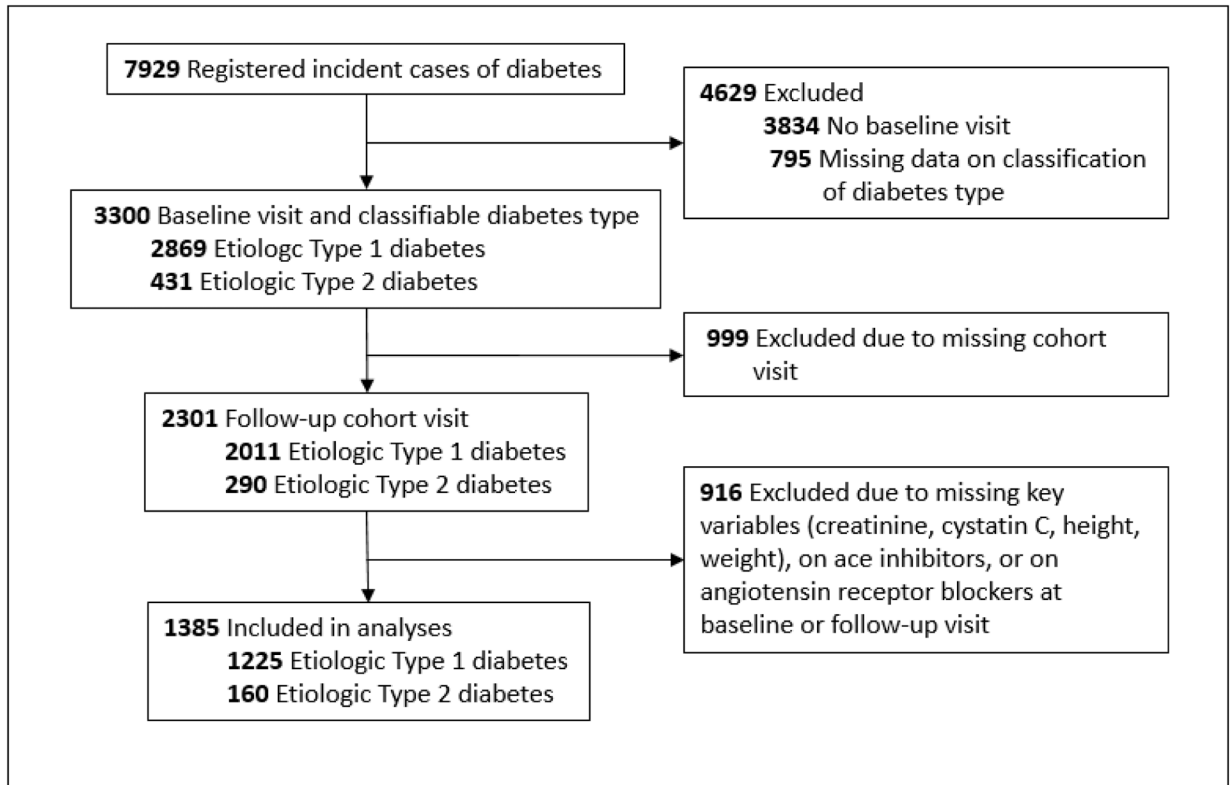Study design of the SEARCH for Diabetes in Youth Study.

Figure 2.
Flow chart of participants of the SEARCH for Diabetes in Youth Study included in the current analyses.

Table 1.

Baseline sociodemographic and clinical characteristics of 1,385 participants from the SEARCH for Diabetes in Youth Cohort Study.

Demographic and Clinical Characteristics	Type 1 DM		Type 2 DM		p-value
	missing	n=1225	missing	n=160	
Female sex, N (%)	0	598 (48.8)	0	104 (65.0)	0.0001
Race/Ethnicity, N (%)					
NH White		981 (80.1)		41 (25.6)	
NH Black	0	98 (8.0)	0	81 (50.6)	<0.0001
Hispanic		132 (10.8)		28 (17.5)	
Other race/missing		14 (1.1)		10 (6.3)	
Age at diagnosis, years, mean (SD)	0	10.6 (3.7)	0	14.0 (2.6)	<0.0001
Age at baseline visit, years, mean (SD)	0	11.4 (3.7)	0	15.0 (2.7)	<0.0001
Duration at baseline visit, months, mean (SD)	0	9.2 (6.2)	0	11.2 (6.3)	0.0002
Insulin Sensitivity Score (AUC)	11	8.4 (2.6)	0	3.9 (1.6)	<0.0001
HbA1c (AUC), %, mean (SD)	5	8.5 (1.3)	0	8.3 (2.3)	0.2
HbA1c (AUC), mmol/mol, mean (SD)	5	69 (15)	0	67(25)	0.2
BMI z-score (AUC)	0	0.6 (0.9)	0	1.9 (0.7)	<0.0001
SBP z-score (AUC)	9	−0.5 (0.9)	0	0.8 (1.1)	<0.0001
Total Cholesterol, mmol/L (AUC) *	42	4.2 (0.9)	8	4.2 (1.3)	0.03
Triglycerides, mmol/L (AUC) *	42	0.8 (0.4)	8	1.3 (2.0)	<0.0001
HDL, mmol/L (AUC)	43	1.4 (0.3)	8	1.1 (0.3)	<0.0001
eGFR at baseline, ml/min/1.73m^2	0	128.4 (22.0)	0	117.4 (22.7)	<0.0001
Albumin/creatinine ratio, mg/mmol (AUC) *	250	0.87 (0.92)	50	1.02 (2.55)	0.002

*
presented as median (IQR) with tests done on transformed variables due to skewed distributions

Table 2A.

Agreement between directional change of eGFR estimated by the CKiD$_{Cr-CysC}$ versus Bouvet$_{Cr-CysC}$ equations from baseline to follow-up visit occurring a mean of 6.6 years later among 1225 SEARCH Cohort Study participants with type 1 diabetes.

eGFR Bouvet$_{Cr-CysC}$	eGFR Bouvet$_{Cr-CysC}$			
	Decline	**Stable**	**Rise**	**Row totals, N (%)**
Decline	214	78	0	292 (23.8)
Stable	199	579	121	899 (73.4)
Rise	0	5	29	34 (2.8)
Column totals, N (%)	413 (33.7)	662 (54.0)	150 (12.2)	1225

Table 2B.

Agreement between directional change of eGFR estimated by the CKiD$_{Cr-CysC}$ versus Bouvet$_{Cr-CysC}$ equations from baseline to follow-up visit occurring a mean of 6.6 years later among 160 SEARCH Cohort Study participants with type 2 diabetes.

	eGFR Bouvet$_{Cr-CysC}$			
eGFR Bouvet$_{Cr-CysC}$	Decline	Stable	Rise	Row totals, N (%)
Decline	13	15	1	29 (18.1%)
Stable	2	66	38	106 (66.3%)
Rise	0	0	25	25 (15.6%)
Column totals, N (%)	15 (9.4)	81 (50.6)	64 (40)	160

Table 3A.

Multivariable logistic regression (with generalized logic link) analyses of factors associated with annual change in estimated glomerular filtration rate as calculated by the CKiD $_{Cr-CysC}$ equation with 'Stable' as the reference group (n=1206) among SEARCH participants with type 1 diabetes.

Type 1 DM	Overall p-value	Decline (vs Stable)			Rise (vs Stable)		
		OR	95%CI	p-value	OR	95%CI	p-value
Female sex	**<0.0001**	0.3	0.2, 0.4	<0.0001	5.5	2.0, 14.7	0.0007
NH Black race	0.7	1.0	0.6, 1.8	1.0	0.6	0.2, 2.1	0.4
Age at diagnosis (years)	**0.0001**	1.1	1.0, 1.1	0.003	1.2	1.1, 1.4	0.001
Time from baseline visit (years)	**<0.0001**	0.8	0.7, 0.8	<0.0001	0.5	0.3, 0.6	<0.0001
Baseline eGFR (ml/min/1.73m^2) (10 unit increase)	**<0.0001**	1.7	1.6, 1.9	<0.0001	0.9	0.8, 1.2	0.6
Glucose change from baseline (mg/dl) (50 unit increase)	**<0.0001**	0.8	0.8, 0.9	<0.0001	1.3	1.1, 1.5	0.002
HbA1c (%) (AUC)	**<0.0001**	0.7	0.6, 0.8	<0.0001	2.0	1.5, 2.7	<0.0001
Body mass index Z-score (AUC)	**<0.0001**	1.5	1.2, 1.8	<0.0001	1.0	0.6, 1.6	1.0
Systolic Blood pressure Z-score (AUC)	**0.002**	0.7	0.6, 0.8	0.0004	0.9	0.6, 1.5	0.7

*
Multivariable model also adjusts for geographic site

Table 3B.

Multivariable logistic regression (with generalized logic link) analyses of factors associated with annual change in estimated glomerular filtration rate as calculated by the CKiD $Cr-Cys_C$ equation with 'Stable' as the reference group (n=160) among SEARCH participants with type 2 diabetes.

Type 2 DM	Overall p-value	Decline (vs Stable)			Rise (vs Stable)		
		OR	95%CI	p-value	OR	95%CI	p-value
Female sex	**0.002**	0.2	0.1, 0.7	0.01	7.5	1.2, 46.1	0.03
NH Black race	0.9	0.9	0.3, 3.5	0.9	1.3	0.3, 5.9	0.8
Age at diagnosis (years)	**0.009**	0.7	0.5, 0.9	0.002	0.9	0.7, 1.2	0.5
Time from baseline visit (years)	0.08	0.7	0.5, 1.0	0.08	0.7	0.5, 1.1	0.1
Baseline eGFR (ml/min/1.73m^2) (10 unit increase)	**0.0004**	1.8	1.3, 2.4	0.0002	0.9	0.6, 1.3	0.5
Glucose change from baseline (mg/dl) (50 unit increase)	**<0.0001**	0.8	0.6, 1.1	0.1	2.4	1.6, 3.5	<0.0001
HbA1c (%) (AUC)	0.2	0.8	0.6, 1.1	0.1	1.1	0.8, 1.5	0.8
Body mass index Z-score (AUC)	0.5	1.5	0.6, 4.1	0.4	0.6	0.2, 2.5	0.5
Systolic Blood pressure Z-score (AUC)	0.3	1.6	0.9, 2.7	0.1	1.1	0.6, 2.2	0.8

*
Multivariable model also adjusts for geographic site