Higher Prevalence of Elevated Albumin Excretion in Youth with Type 2 than Type 1 Diabetes: The SEARCH for Diabetes in Youth Study

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Running title: Elevated Albuminuria in Youth with Type 1 and Type 2 Diabetes

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Abstract

Objective: To estimate the prevalence of an elevated albumin-to-creatinine ratio (ACR (≥30 μg/mg)) among youth with type 1 or type 2 diabetes mellitus, and to identify factors associated with elevated ACR and their effect on the relationship between elevated ACR and type of diabetes.

Research Design and Methods: Cross-sectional data were analyzed from 3259 participants with onset of diabetes at <20 years of age in SEARCH for Diabetes in Youth, a multicenter, observational study of diabetes in youth. Multiple logistic regression was used to explore determinants of elevated ACR and factors accounting for differences in this prevalence between type 2 and type 1 diabetes.

Results: The prevalence of elevated ACR was 9.2% in type 1 and 22.2% in type 2 (prevalence ratio, 2.4; 95% confidence interval, 1.9-3.0; P<0.0001). In multiple logistic regression analysis, female sex, HbA1c and triglyceride values, hypertension, and type of diabetes (2 vs. 1) were significantly associated with elevated ACR. Adjustment for variables related to insulin resistance (obesity, hypertension, dyslipidemia, and inflammation) attenuated, but did not completely explain, the association of diabetes type with elevated ACR.

Conclusions: Youth with type 2 diabetes have a higher prevalence of elevated ACR than youth with type 1 diabetes, in an association that apparently does not completely depend on age, duration of diabetes, race/ethnicity, sex, level of glycemic control, or features of insulin resistance.
Reports of type 1 and type 2 diabetes mellitus are becoming more common in youth (1,2), but little is known about whether the burden and risk factors for diabetes-related complications differ by type of diabetes in youth. An abnormal concentration of albumin in the urine is one of the earliest forms of clinical evidence of nephropathy, and microalbuminuria predicts progression to diabetic nephropathy (3) and cardiovascular disease (4). Current recommendations of the American Diabetes Association (ADA) are to screen for microalbuminuria once a child is 10 years old and has had type 1 diabetes for 5 years, and to screen children with type 2 diabetes at diagnosis and annually thereafter. Two of three values must be abnormal before the clinical diagnosis can be made, due to variability in albumin excretion rates (5). A spot urine early in the morning measuring the albumin-to-creatinine ratio (ACR) is one such screening method (5), and repeated abnormalities are required to clinically diagnose albuminuria.

While an extensive literature exists on microalbuminuria and elevated ACR in children and adolescents with type 1 diabetes (6 – 15), and diabetic nephropathy is well described in adults with type 2 diabetes (16), little data exist in youth with type 2 diabetes (17 – 20). Recently, clinical features of insulin resistance were found to be predictive of incident microalbuminuria among youth with type 1 diabetes (21). In adults, microalbuminuria is a component of the World Health Organization’s (WHO’s) definition of the metabolic syndrome (22) and is associated with insulin resistance measured with the clamp technique (23, 24).

The SEARCH for Diabetes in Youth Study is a multicenter, population-based study of youth with diabetes mellitus (25) (list of SEARCH Investigators included in the online appendix available at http://care.diabetesjournals.org). The aim of this report on 3259 youth participating in the SEARCH study is to identify factors associated with elevated ACR in youth with diabetes and study their effect on the relationship between elevated ACR and type of diabetes.

**RESEARCH DESIGN AND METHODS**

A detailed description of the study methods in SEARCH has been published (25). In brief, SEARCH is an ongoing study that began in 2001 to conduct population-based ascertainment of cases of diabetes in youth <20 years. Cases were identified: a) in geographically defined populations in Ohio, Washington, South Carolina and Colorado; b) among health plan enrollees in Hawaii (Hawaii Medical Service Association, Med-Quest, Kaiser Permanente Hawaii) and in southern California; (Kaiser Permanente); and c) among young people listed on rolls of health service beneficiaries in 3 American Indian populations in Arizona and New Mexico, and among participants in the National Institute of Diabetes and Digestive and Kidney Diseases Pima Indian study in Arizona (26). The study was reviewed and approved by the local institutional review boards (IRBs) that had jurisdiction over the local study populations.

During the study visit, survey information was collected, and blood was drawn for measurement of HbA1c, fasting glucose, c-peptide, lipids, fibrinogen, high-sensitivity C-reactive protein (CRP), and diabetes autoantibodies, and an examination was performed to measure systolic and diastolic blood pressure, height, weight, and waist circumference, as previously described (27). The average of 2 weight (electronic scale) and 2 height measurements (stadiometer) was used to calculate body mass index (BMI) (kg/m²). Overweight was defined as a BMI ≥95th
percentile for age and sex, based on the 2000 CDC Growth Charts. Waist circumference was measured using the National Health and Nutrition Examination Survey protocol (28). High blood pressure was defined as a) antihypertensive medication use (although it is possible that alternately these medications could have been started for albuminuria or ‘renal prophylaxis’); or b) systolic or diastolic blood pressure >95th percentile for age, sex, and height in participants ≤17 years; or c) systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg in participants aged 18 years or older (29).

Blood samples were obtained fasting, under conditions of metabolic stability, in the absence of fever and acute infections. Specimens were processed locally and shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle). A spot urine sample was collected in the morning after an overnight rest. Urine was not collected in girls who were menstruating. Urinary creatinine was measured by the Jaffe method using Roche Diagnostics reagent on the Hitachi 917 autoanalyzer. Two quality control samples were analyzed in each run, and the inter-assay coefficient of variation was consistently <2%. Urine creatinine is present at high concentration, and therefore the sensitivity of the assay (0.2 mg/dL) is not a factor. Urine albumin was measured immunochemically using Dade-Behring reagent on the BNII nephelometer. The sensitivity of that assay is also 0.2 mg/dL. The inter-assay coefficient of variation is <5% for the high-level quality control sample and <6.5% for the low-level.

ACRs were categorized according to ADA guidelines (4): normal: <30 µg/mg, microalbuminuria: 30-299 µg/mg, macroalbuminuria: ≥300 µg/mg. Given the small number of participants with macroalbuminuria, (n=51/3259, 1.6%), micro- and macroalbuminuria were combined to define elevated ACR (≥30µg/mg).

The clinical diabetes type was categorized as: type 1 (reported type 1a, type 1, type 1b) and type 2.

Race/ethnicity was based on self-report and included data collected using the format for the 2000 census questionnaire. Five specific categories were created [Hispanic, American-Indian only, African-American only, Asian/Pacific Islander only, non-Hispanic White only], and a sixth category of multiple/other/unknown race. Because of limitations in the size of samples, for most analyses all racial/ethnic groups other than non-Hispanic white were combined into a single category. This analysis includes participants from the 2001-2003 SEARCH study cohorts.

Statistical Methods
The prevalence of elevated ACR (≥30 µg/mg) was calculated and stratified according to diabetes type and age, sex, diabetes duration, race/ethnicity, and BMI category. Multiple logistic regression analysis was used to examine the adjusted odds ratios (ORs) of having an elevated ACR (≥30µg/mg vs. <30 µg/mg) in patients with type 2 vs. type 1 diabetes. The covariates entered in sequential models were as follows: model 1) type of diabetes, demographic factors, and duration of disease; model 2) model 1 covariates plus factors related to insulin resistance with different distributions by type of diabetes; model 4) all of the covariates from models 1 through 3; and model 5) in a subset of 2561 participants with measurements of fibrinogen and CRP available, these markers of inflammation were added to model 4 covariates. In these models we examined whether the hypothesized association between
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type of diabetes (2 vs. 1) and elevated ACR was explained by the addition of a particular (set of) metabolic risk factors. In addition, in model 4 we examined which of the above variables were independently associated with elevated ACR. We considered several 2-way interactions that were not significant (diabetes type x sex, and type x duration) as well as an interaction between diabetes type and BMI, which was found to be significant. P values ≤0.05 were considered significant. Statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, NC) and S-PLUS software version 6.0 (Insightful Corp., Seattle, Wash.).

RESULTS
Of 8768 patients with diabetes identified by SEARCH in 2001-2003, 3950 (45%) had a study visit. Of this group, 3259 contributed data to the analysis, as patients without an ACR measurement and patients with a diabetes type coded as Other/Unknown/MODY were excluded. Of the final group, 2885 had type 1 and 374 type 2 diabetes.

Participants with type 1 diabetes had a mean age at registration of 11.9 years (interquartile range, IQR=8.7-15.4), a disease duration of 3.7 years (IQR=0.5-5.7), and included 49% females and 76% non-Hispanic white individuals. Participants with type 2 diabetes were, on average, 16.2 years old (IQR=14.0-18.6), had a disease duration of 1.9 years (IQR=0.4-3.2), and included 63% females and 19% non-Hispanic whites. The prevalence of elevated ACR was 2.3 times as high in youth with type 2 diabetes (22.2% [95% CI, 18.3-26.7%]) as in those with type 1 (9.2% [8.2-10.3%]), and it was slightly higher in females (12.8% [10.7–15.0%]) than in males (10.6% [8.3–12.9%]). Table 1 shows that among subjects with type 1 diabetes, the prevalence of elevated ACR was higher in adolescents than in younger children (P<0.0001), and in females than in males (P=0.0005). Neither was statistically significantly different in type 2. The prevalence tended to increase with duration of diabetes, especially if longer than 60 months (overall P=0.004 for type 1; P=0.0004 for type 2). For youth with type 1 diabetes, the percent having an elevated ACR did not vary substantially with race/ethnicity (P=0.55, non-Hispanic white vs. other than non-Hispanic white). In contrast, for youth with type 2 diabetes, the percent having an elevated ACR was higher among the group made up of minorities than it was in non-Hispanic whites (P=0.032). Patterns of elevated ACR by BMI differed by type of diabetes; in youth with type 2 there were no significant differences between BMI categories, but in youth with type 1 the prevalence was highest in the leanest children (P=0.007).

The variables that “explained” the effect of diabetes type (1 vs. 2) on the prevalence of elevated ACR are presented in Figure 1. In model 1, adjustment for age, sex, race/ethnicity, and duration of diabetes explained little of the excess in elevated ACR in patients with type 2 [OR=2.08 (95% CI, 1.47–2.95)]. In model 2, addition of HbA1c actually increased the OR for the association between diabetes type and elevated ACR [OR=2.42 (1.68–3.49)]. In model 3, features related to insulin resistance were added to model 1 (presence of hypertension, BMI, waist circumference, LDL-c, HDL-c, triglyceride concentrations), and the OR dropped to 1.68 (1.05–2.67). Thus, the variables added in model 3 explained 19% of the increased prevalence of elevated ACR in type 2 versus type 1 patients. The OR of 1.68 indicates that even after accounting for all of these factors, patients with type 2 diabetes were still 68% more likely to have an elevated ACR than were those with type 1. Simultaneous adjustment for age, sex, duration of diabetes, race/ethnicity,
HbA1c, hypertension status, HDL-c and LDL-c, log triglyceride, waist circumference, and BMI (model 4) did not reduce further the difference by type of diabetes; indeed, it became marginally higher [OR=1.79 (1.11–2.88)]. In a subset of 2561 patients (model 5) with all of the model 4 covariates available plus measurements of fibrinogen and CRP available, this addition of inflammatory markers reduced the difference by type of diabetes slightly [OR=1.68 (1.00–2.81)] from that seen in model 4, again suggesting that features related to insulin resistance (obesity, hypertension, dyslipidemia, inflammation) mediate a portion of the increased prevalence of elevated ACR in youth with type 2 diabetes versus type 1.

The adjusted ORs (and 95% CI) for the association between elevated ACR and each covariate included in model 4 are shown in Table 2. Further analysis found a significant interaction between diabetes type (2 vs. 1) and BMI on the prevalence of ACR was noted (P< 0.0002), suggesting that the difference in elevated ACR by type of diabetes increases with increasing BMI. Female sex, higher HbA1c, hypertension, and increased triglyceride concentrations were independently associated with elevated ACR, regardless of age, race/ethnicity, waist circumference, LDL-c, and HDL-c. (Hypertension is no longer significant if subjects on anti-hypertensive medications with normalized blood pressure are excluded.) Additional adjustment for self-reported habitual physical activity, current smoking status, and the presence of diabetes autoantibodies (either GAD65 or IA-2) did not change the results above. Elevated ACR is more prevalent as DM duration increases (Table 1), but once the other risk factors are controlled for (Table 2) then the relationship of duration to elevated ACR changes suggesting that these other risk factors account for the increasing prevalence of elevated ACR with duration.

**DISCUSSION**

This study finds a high prevalence of elevated ACR (22.2%) in youth with type 2 diabetes, well over twice the percentage for participants with type 1 (9.2%). Variables related to insulin resistance and inflammation explain part, but not all, of the increased prevalence in youth with type 2 diabetes. Major strengths of this study are the large sample, the geographically and ethnically diverse population, and the extensive demographic, anthropometric, biochemical, and behavioral data collected in these children.

That 22.2% of youth with type 2 diabetes could already have an elevated ACR at a mean age of 16.2 years and a mean duration of diabetes of 1.9 years suggests the possibility of a relatively more rapid progression to diabetes-related vascular complications in this population, since elevated ACR was shown to predict progression to diabetic nephropathy (3) and cardiovascular disease (4). This may result in increased morbidity and mortality in the future, in part due to the younger age at onset of type 2 diabetes, as previously reported in the Pima Indian population (30). Previous data on microalbuminuria in youth with type 2 diabetes are limited and based on much smaller samples, but with similar estimates of 22% (19), 22.7% (20), and 40% (17). While longitudinal data are needed to better understand the determinants of type 2 diabetes–related complications in youth, our data suggest that efforts to prevent or delay type 2 diabetes in children could have a dramatic public health impact in terms of future burden of related vascular complications.

Our finding of an elevated ACR in 9.2% of youth with type 1 diabetes is comparable to published estimates of microalbuminuria in type 1 youth (6,7,10 – 15). As expected, older
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age, female sex, and duration of diabetes over 5 years were associated with higher estimates (Table 1). These data also support the current recommendation for screening (for microalbuminuria) in youth with type 1 diabetes.

In adults, a diagnosis of microalbuminuria can precede type 2 diabetes and is a component of WHO’s definition of the metabolic syndrome (22). Accordingly, microalbuminuria might be an early marker of type 2 diabetes, as well as diabetic nephropathy. Previously, focal segmental glomerulosclerosis has been reported in obese children (31), and the possibility of ‘fatty kidney disease’ analogous to nonalcoholic fatty liver disease and of whether obese youth without diabetes should be screened for microalbuminuria deserve further study. In our study, the higher prevalence of elevated ACR in youth with type 2 diabetes remained significant after controlling for potential risk factors with differential distribution between type 2 and type 1 cases (Figure 1). Adjustment for variables related to insulin resistance, however, explained more of the difference in elevated ACR by type of diabetes than did the other pathways considered. This result suggests that elevated ACR in youth with type 2 diabetes may primarily be a marker of underlying obesity-associated insulin resistance. The fact that the difference in elevated ACR by type of diabetes increased with increasing BMI (P< 0.0002 for the interaction between diabetes type and BMI) supports this notion. However, even after accounting for all potential contributors to an elevated ACR measured as part of the SEARCH study, the difference in prevalence between youth with type 2 and type 1 diabetes remained largely unexplained. Other unmeasured factors reflecting obesity, insulin resistance, inflammation, or genetics could be explanatory. In addition, Burgert and colleagues have discussed the ‘oxidative stress theory’ as a possible hypothesis linking recurrent postprandial hyperglycemia to vascular oxidative stress and subsequent endothelial dysfunction and microalbuminuria in obese youth without diabetes (32). The situation may be different in type 1 youth, among whom being leaner was associated with a higher prevalence of an elevated ACR (Table 1). The less overweight individuals with T1DM may exhibit weight loss associated with chronic poor glucose metabolism, in turn related to elevated ACR.

We found that high blood pressure, hyperglycemia, and high triglyceride concentrations are associated with elevated ACR, independent of type of diabetes (Table 2). In a retrospective clinic population with type 1 diabetes over 6 years of follow-up, Gorman found that persistence or progression of albuminuria occurred in two-thirds of type 1 children, with HbA1c and initial ACR as independent predictors (33). Although studies in adults report variable rates of progression (3,34), generally type 1 patients with microalbuminuria have a significantly higher risk of progression to clinical proteinuria and death from a cardiovascular cause (35). Detection of increases in excretion of urinary albumin is clinically important, as safe and effective treatment with angiotensin-converting enzyme inhibitors have been demonstrated (36 – 39). In our study, however, only 12% of youth with elevated ACR were treated with antihypertensives.

Certain limitations of our data set must be discussed. A single spot urine specimen for the ACR was obtained. Due to the variability in albumin excretion rates, repeated abnormal ACR measurements are required to diagnose albuminuria (5) and, therefore, a single elevated value cannot be used to establish the clinical diagnosis. As SEARCH is a large epidemiologic study conducted in an outpatient
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In a single ACR measurement was used to define “elevated ACR”. The ACR using a spot morning urine has high sensitivity and specificity when compared with 24-hour urine collections (40) and ACR is highly correlated to the 24-hour AER in healthy 4-16 year-olds (41) and type 1 children (42,43). Our estimates of the greater frequency of elevated ACR in type 2 diabetes (vs. type 1) are very similar to that of microalbuminuria by Eppens (19), in which 3 timed overnight urine samples were obtained (22% vs. 6% reported by Eppens and 22.2% vs. 9.2% reported in SEARCH). Importantly, physical activity, which can falsely elevate the ACR, was not a significant predictor of elevated ACR in multiple logistic regression analysis (data not shown).

Another concern is that the youth included in this report represent a sample of all youth ascertained by SEARCH. To evaluate potential bias due to incomplete research visit participation, the prevalence of elevated ACR was also estimated using a re-weighting, semi-parametric efficient estimator developed for 2-stage study designs (44). Estimates were calculated using data on study site, age, sex, race/ethnicity, diabetes type, and duration and were combined by inversely weighting based on standard errors. The crude and re-weighted estimates of prevalence were similar suggesting that any possible selection bias is unlikely to influence our estimates.

Finally, our cross-sectional design limits assessment of causality in the interpretation of independent associations of elevated ACR. The design also limits our ability to definitively identify which factors and pathways account for the increased ACR in youth with type 2 diabetes relative to those with type 1. Residual confounding resulting from incomplete adjustment for differences in age, duration of diabetes and body size between youth with type 1 and type 2 diabetes may also be an issue. The availability of better markers of insulin resistance and visceral adiposity, difficult to obtain in large epidemiologic studies like SEARCH, may have provided more conclusive answers.

In conclusion, we report that 9.2% of youth with type 1 diabetes and 22.2% of youth with type 2 had an elevated ACR. Variables related to insulin resistance and inflammation explain part of the increased prevalence in youth with type 2 diabetes. For either type, hyperglycemia, high blood pressure, and hypertriglyceridemia are significant determinants of elevated albumin excretion. Longitudinal data on the natural evolution, screening, and treatment of microalbuminuria in youth with diabetes are needed, as both type 1 and type 2 disease are increasing (1,2) and diabetic vascular complications in general and nephropathy in particular could have overwhelming consequences.

ACKNOWLEDGEMENTS
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References


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### Table 1. Prevalence of Elevated ACR among SEARCH Participants with Type 1 and Type 2 Diabetes, by Age, Sex, DM duration, Race/Ethnicity, BMI and HbA1c Category*

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>P value**</th>
<th>T2DM</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>265/2885 (9.2%)</td>
<td></td>
<td>83/374 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;12</td>
<td>89/1291 (6.9%)</td>
<td>&lt;0.0001</td>
<td>2/19 (10.5%)</td>
<td>0.27</td>
</tr>
<tr>
<td>≥12</td>
<td>176/1593 (11.1%)</td>
<td></td>
<td>81/355 (22.8%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>109/1480 (7.4%)</td>
<td>0.0005</td>
<td>29/140 (20.7%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Female</td>
<td>156/1405 (11.1%)</td>
<td></td>
<td>54/234 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>DM duration in months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0 to &lt;12</td>
<td>51/515 (9.9%)</td>
<td>0.0041</td>
<td>15/92 (16.3%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>12 to &lt; 60</td>
<td>94/1291 (7.3%)</td>
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<td>44/225 (19.6%)</td>
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<tr>
<td>≥ 60</td>
<td>120/1074 (11.2%)</td>
<td></td>
<td>24/57 (42%)</td>
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<td>Race/Ethnicity</td>
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</tr>
<tr>
<td>NHW</td>
<td>198/2199 (9.0%)</td>
<td>Ref</td>
<td>9/71 (12.7)</td>
<td>Ref</td>
</tr>
<tr>
<td>AA</td>
<td>19/197 (9.6%)</td>
<td>0.76</td>
<td>18/110 (16.4%)</td>
<td>0.50</td>
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<tr>
<td>H</td>
<td>32/310 (10.3%)</td>
<td>0.45</td>
<td>15/64 (23.4%)</td>
<td>0.10</td>
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<tr>
<td>API</td>
<td>6/53 (11.3%)</td>
<td>0.47</td>
<td>6/25 (24.0%)</td>
<td>0.21</td>
</tr>
<tr>
<td>AI</td>
<td>2/19 (10.5%)</td>
<td>0.69</td>
<td>33/92 (35.9%)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Multiple/Other</td>
<td>8/107 (7.5%)</td>
<td>0.59</td>
<td>2/11 (18.2%)</td>
<td>0.64</td>
</tr>
<tr>
<td>BMI</td>
<td>191/1867 (10.2%)</td>
<td>0.0069</td>
<td>12/49 (24.5%)</td>
<td>0.82</td>
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<tr>
<td>&lt;85%</td>
<td>49/620 (7.9%)</td>
<td></td>
<td>13/53 (24.5%)</td>
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</tr>
<tr>
<td>85 to &lt; 95%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c %</td>
<td>NHW</td>
<td>AA</td>
<td>*</td>
<td>AI</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
<td>---</td>
</tr>
<tr>
<td>≥95%</td>
<td>18/341 (5.3%)</td>
<td>57/266 (21.4%)</td>
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<td></td>
</tr>
<tr>
<td>HbA1c %&lt;7.6</td>
<td>60/866 (6.9%)</td>
<td>&lt;0.0001</td>
<td>19/190 (10.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7.6 to &lt;8.7%</td>
<td>71/963 (7.4%)</td>
<td>10/35 (28.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8.7%</td>
<td>128/945 (13.5%)</td>
<td>53/139 (38.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NHW=non Hispanic White only; AA=African-American only; H=Hispanic; API=Asian/Pacific Islander only; AI=American Indian only; DM=diabetes mellitus; BMI=body mass index.

* Different sample sizes reflect completeness of data: age, 3,258; sex, 3,259; DM duration, 3,254; Race/Ethnicity, 3,258; BMI, 3,196; HbA1c, 3,138.

** P-values are for association with elevated ACR.
<table>
<thead>
<tr>
<th><strong>Table 2. Adjusted Odds Ratios of an Elevated Albumin-to-Creatinine Ratio in SEARCH Participants</strong></th>
<th><strong>Odds Ratio (95% CI)</strong></th>
<th><strong>P</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age per 1 y</strong></td>
<td>1.03 (0.98-1.08)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Sex (females vs. males)</strong></td>
<td>1.40 (1.09-1.81)</td>
<td>0.0090</td>
</tr>
<tr>
<td><strong>Race/ethnicity (all others vs. non-Hispanic whites)</strong></td>
<td>1.01 (0.75-1.36)</td>
<td>0.95</td>
</tr>
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<td><strong>Type 2 vs. Type 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 95th percentile</td>
<td>2.10 (0.83 – 5.32)</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI &lt; 95th percentile</td>
<td>1.48 (0.79 – 2.77)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Diabetes duration, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 to &lt;60 vs. &lt;12</td>
<td>0.62 (0.43-0.89)</td>
<td>0.027</td>
</tr>
<tr>
<td>≥60 vs. 0 to &lt;12</td>
<td>0.78 (0.52-1.16)</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c per 1 %</strong></td>
<td>1.22 (1.13-1.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hypertension (present vs. absent)</strong></td>
<td>2.11 (1.49-3.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Waist circumference per 1 cm</strong></td>
<td>1.00 (0.98-1.01)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>LDL cholesterol per 1 mg/dl</strong></td>
<td>1.00 (1.00-1.01)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>HDL cholesterol per 1 mg/dl</strong></td>
<td>1.00 (1.00-1.01)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Triglycerides per 1 log mg/dl</strong></td>
<td>1.49 (1.17-1.88)</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

*P* values are for overall effects on elevation of the albumin-to-creatinine (ACR) ratio from the multiple logistic regression model.

Diabetes type*BMI interaction *P* =0.0002 (model with BMI continuous).
**Figure 1.** Adjusted Odd Ratios and 95% Confidence Intervals for the Association between DM type (T2DM vs T1DM) and elevated ACR

Model 1=adjusted for age, sex, race, duration; OR for diabetes type (2 vs. 1) =2.08 (1.47-2.95), \( P<0.0001 \).
Model 2=Model 1+ HbA1c; OR for diabetes type (2 vs. 1) =2.42 (1.68-3.49), \( P<0.0001 \).
Model 3=Model 1+ hypertension, BMI, waist, HDL-c, LDL-c, triglycerides; OR for diabetes type (2 vs. 1) =1.68 (1.05-2.67), \( P=0.030 \).
Model 4=All; OR for diabetes type (2 vs. 1) =1.79 (1.11-2.88), \( P=0.017 \).
Model 5 (subset of 2561 participants with measurements of fibrinogen and CRP)=Model 4+ fibrinogen, CRP; OR for DM type (type 2 vs. 1) T1DM) =1.68 (1.00-2.81), \( P=0.048 \).