Factors Associated With Microalbuminuria in 7,549 Children and Adolescents With Type 1 Diabetes in the T1D Exchange Clinic Registry

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OBJECTIVE—To examine factors associated with clinical microalbuminuria (MA) diagnosis in children and adolescents in the T1D Exchange clinic registry.

RESEARCH DESIGN AND METHODS—T1D Exchange participants <20 years of age with type 1 diabetes ≥1 year and urinary albumin-to-creatinine ratio (ACR) measured within the prior 2 years were included in the analysis. MA diagnosis required all of the following: *1*) a clinical diagnosis of sustained MA or macroalbuminuria, *2*) confirmation of MA diagnosis by either the most recent ACR being ≥30 mg/g or current treatment with an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB), and *3*) no known cause for nephropathy other than diabetes. Logistic regression was used to assess factors associated with MA.

RESULTS—MA was present in 329 of 7,549 (4.4%) participants, with a higher frequency associated with longer diabetes duration, higher mean glycosylated hemoglobin (HbA_{1c}) level, older age, female sex, higher diastolic blood pressure (BP), and lower BMI ($P \leq 0.01$ for each in multivariate analysis). Older age was most strongly associated with MA among participants with HbA_{1c} ≥9.5% (≥80 mmol/mol). MA was uncommon (<2%) among participants with HbA_{1c} <7.5% (<58 mmol/mol). Of those with MA, only 36% were receiving ACEI/ARB treatment.

CONCLUSIONS—Our results emphasize the importance of good glycemic and BP control, particularly as diabetes duration increases, in order to reduce the risk of nephropathy. Since age and diabetes duration are important nonmodifiable factors associated with MA, the importance of routine screening is underscored to ensure early diagnosis and timely treatment of MA.

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Elevated urinary albumin excretion is an early sign of diabetic kidney disease (DKD). The American Diabetes Association (ADA) recommends screening for microalbuminuria (MA) annually in people with type 1 diabetes after 10 years of age and 5 years of diabetes duration, with a diagnosis of MA requiring two of three tests to be abnormal (1). Early diagnosis of MA is important because effective treatments exist to limit the progression of DKD (1). However, although reduced rates of MA have been reported over the past few decades in some (2–4) but not all (5,6) studies, it has been suggested that the development of proteinuria has not been prevented but, rather, has been delayed by ~10 years and that further improvements in care are needed (7).

Limited data exist on the frequency of a clinical diagnosis of MA in the pediatric population with type 1 diabetes in the U.S. Our aim was to use the data from the T1D Exchange clinic registry to assess factors associated with MA in 7,549 children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The T1D Exchange Clinic Network includes 67 U.S.-based pediatric and adult endocrinology practices. A registry of individuals with type 1 diabetes commenced enrollment in September 2010 (8). To be enrolled in the clinic registry, an individual must have a clinical diagnosis of presumed autoimmune type 1 diabetes and islet cell antibodies present or, if antibodies were negative or unknown, then insulin must have been started at or shortly after diagnosis and used continually thereafter (except in the case of a pancreas or islet cell transplant) (8). Each clinic received approval from an institutional review board. Informed consent was obtained according to institutional review board requirements from adult participants and parents/guardians of minors; assent from minors was obtained as required. Data were collected for the registry's central database from the participant's medical record and by having the participant or parent complete a comprehensive questionnaire, as previously described (8).

As of 1 August 2012, the registry included 13,314 participants <20 years of age with type 1 diabetes for at least 1 year, enrolled at all of the 67 clinics. Eligibility criteria for inclusion in the analyses included age <20 years, diabetes duration ≥1 year, the availability of a current clinical assessment of renal status, and a urinary albumin-to-creatinine ratio (ACR) result within the prior 2 years, all based on data collected for the registry at enrollment. Current renal status and most

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recent ACR were collected from the participant's medical chart. The majority of eligible ACR measurements were spot collection (97%). The remaining collection types were 24 h (<1%), overnight (<1%), and other (2%). A diagnosis of MA required all of the following: *1*) a clinical diagnosis of sustained MA or macroalbuminuria (not based on a single urinalysis result), *2*) confirmation of MA diagnosis by either the most recent ACR ≥30 mg/g or current treatment with an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB), and *3*) no known cause for nephropathy other than diabetes. A diagnosis of no MA required the following: *1*) a clinical assessment that MA was not currently or previously present and *2*) the most recent ACR <30 mg/g.

Based on these definitions, 329 participants were classified as having MA (n = 319) or macroalbuminuria (sustained ACR ≥300 mg/g, n = 10), hereafter combined and referred to as MA; 7,220 were

Table 1—*Factors associated with MA*

	Total *n*	Frequency of MA	Unadjusted OR (99% CI)	Univariate *P* value	Full model§ OR (99% CI)	Full model§ *P* value	Reduced model∈ OR (99% CI)	Reduced model∈ *P* value
Sex∑				<0.001		<0.001		<0.001
Male	3,880	3.1%	1.0		1.0		1.0	
Female	3,663	5.6%	1.8 (1.4–2.5)		1.8 (1.3–2.4)		1.8 (1.3–2.4)	
Race/ethnicity△				0.002		0.88		–
White, non-Hispanic	5,919	4.0%	1.0		1.0		–	
Black, non-Hispanic	467	7.7%	2.0 (1.3–3.7)		1.3 (0.8–2.2)		–	
Hispanic or Latino	733	5.0%	1.3 (0.8–2.1)		1.1 (0.6–1.7)		–	
Other	402	5.0%	1.3 (0.7–2.3)		1.2 (0.6–2.3)		–	
Age, years#				<0.001		<0.001		<0.001
<10	920	1.4%	1.0		1.0		1.0	
10 to <13	1,648	2.4%	1.7 (0.7–3.9)		1.6 (0.7–3.8)		1.6 (0.7–3.8)	
13 to <16	2,292	5.0%	3.7 (1.7–7.8)		2.8 (1.2–6.2)		2.8 (1.2–6.2)	
16 to <18	1,456	5.8%	4.3 (2.0–9.3)		3.0 (1.3–7.0)		3.0 (1.3–6.9)	
18 to <20	1,233	6.4%	4.8 (2.2–10.4)		3.3 (1.4–7.8)		3.3 (1.4–7.7)	
Age of diagnosis, years#				0.18		–		–
<13	6,918	4.3%	1.0		–		–	
≥13	631	5.4%	1.3 (0.8–2.1)		–		–	
Duration, years#				<0.001		0.008		0.008
<5	2,608	3.5%	1.0		1.0		1.0	
5 to <10	3,298	3.8%	1.1 (0.8–1.6)		0.9 (0.6–1.3)		0.9 (0.6–1.3)	
≥10	1,643	6.9%	2.1 (1.4–3.0)		1.4 (0.9–2.2)		1.4 (0.9–2.1)	
Average HbA_{1c}, % (mmol/mol)#,∏				<0.001		<0.001		<0.001
<6.5 (<48)α	165	1.8%	–		–		–	
6.5 to <7.5 (48 to <58)	1,265	1.8%	1.0		1.0		1.0	
7.5 to <8.5 (58 to <69)	2,971	3.5%	1.9 (1.1–3.5)		1.8 (1.0–3.4)		1.8 (1.0–3.4)	
8.5 to <9.5 (69 to <80)	1,906	3.4%	1.9 (1.0–3.6)		1.7 (0.9–3.4)		1.8 (0.9–3.4)	
≥9.5 (≥80)	1,217	11%	6.6 (3.7–12.0)		4.9 (2.6–9.2)		5.2 (2.8–9.6)	
BMI#,¥				0.02		<0.001		<0.001
Obese	1,026	3.3%	1.0		1.0		1.0	
Overweight	1,704	4.2%	1.3 (0.7–2.2)		1.2 (0.7–2.2)		1.2 (0.7–2.1)	
Normal	4,613	4.6%	1.4 (0.9–2.3)		1.7 (1.0–2.9)		1.7 (1.0–2.8)	
Underweight	55	11%	3.6 (1.1–11.9)		4.5 (1.3–15.8)		4.3 (1.2–15.0)	
Systolic BP#,‡				0.004		0.84		–
Systolic BP <90th %	5,865	4.1%	1.0		1.0		–	
Systolic BP ≥90th %	1,366	5.4%	1.3 (0.9–1.9)		1.0 (0.7–1.5)		–	
Diastolic BP#,‡				<0.001		0.002		<0.001
Diastolic BP <90th %	6,722	3.9%	1.0		1.0		1.0	
Diastolic BP ≥90th %	509	10%	2.9 (1.9–4.3)		2.2 (1.4–3.5)		2.2 (1.4–3.3)	

§Full model includes all variables that were significant in univariate analysis, at the 0.10 significance level. ∈Reduced model contains variables that remained after backward selection, at a stay significance level of 0.01. ∑There were a total of six transgender individuals in this cohort. △Twenty-eight participants are missing race/ethnicity data. #Tests of significance were obtained by treating as a continuous variable. ∏Twenty-five participants are missing average HbA_{1c} data. αDue to a very small count of MA cases in the <6.5% HbA_{1c} group, the 6.5 to <7.5% group was considered the reference group for the odds ratio (OR) calculations. ¥Underweight was defined as <5th percentile, normal defined as 5th to <85th percentile, overweight defined as 85th to <95th percentile, and obese defined as ≥95th percentile. There were 151 participants that were missing BMI data, mainly due to a missing height measurement from the most recent visit. BMI z score was used in logistic regression models. ‡There were 318 participants that were missing the BP z score, mainly due to a missing height measurement from the most recent visit. BP z scores were used in logistic regression models.

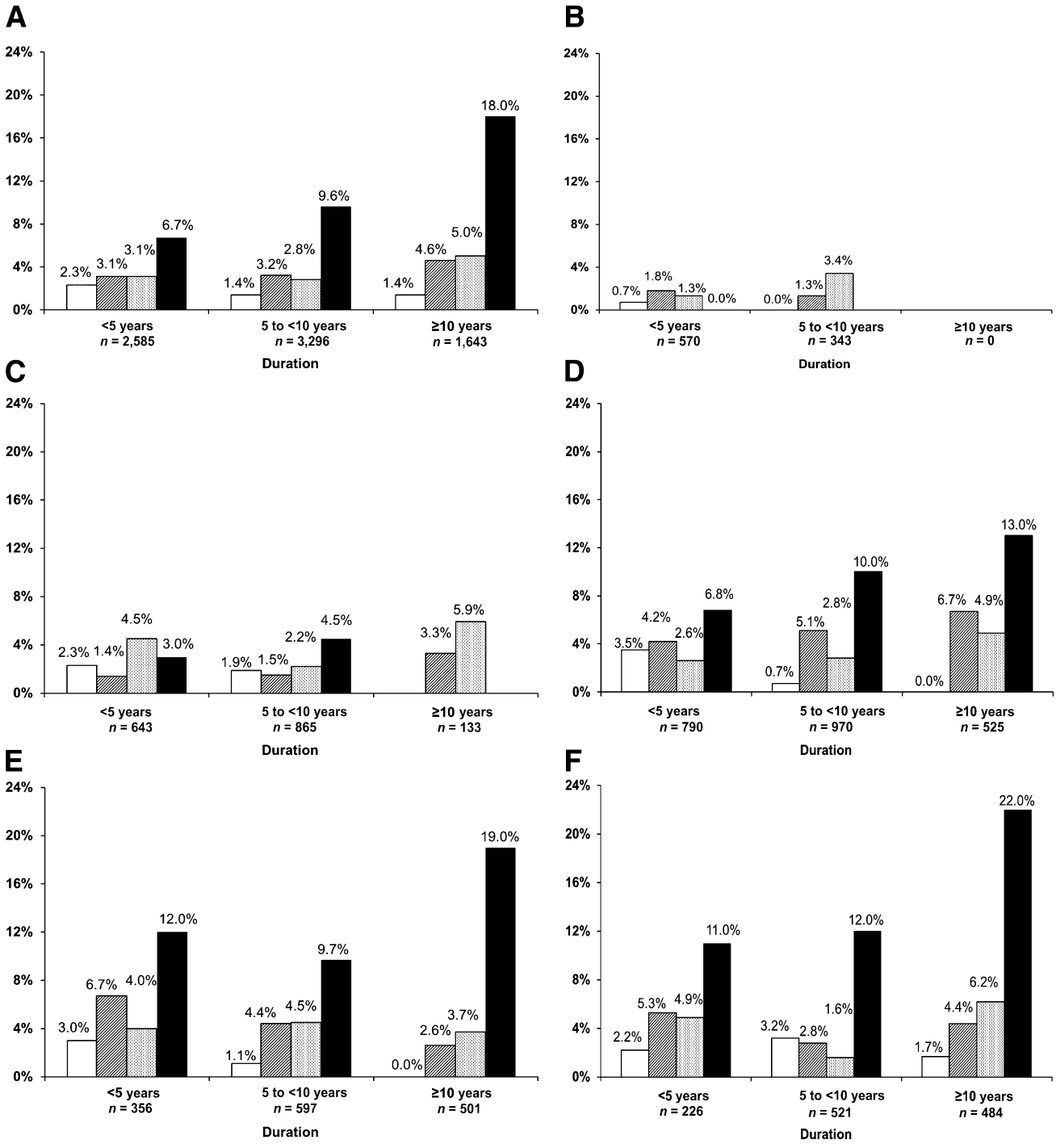

Figure 1—A: *MA by diabetes duration and average HbA_{1c} for all ages.* B: *MA by diabetes duration and average HbA_{1c} for age <10 years.* C: *MA by diabetes duration and average HbA_{1c} for age 10 to <13 years.* D: *MA by diabetes duration and average HbA_{1c} for age 13 to <16 years.* E: *MA by diabetes duration and average HbA_{1c} for age 16 to <18 years.* F: *MA by diabetes duration and average HbA_{1c} for age 18 to <20 years. Solid white bars, HbA_{1c} <7.5% (<58 mmol/mol); white bars with diagonal black lines, HbA_{1c} = 7.5 to <8.5% (58 to <69 mmol/mol); white bars with vertical black dashes, HbA_{1c} = 8.5 to <9.5% (69 to <80 mmol/mol); solid black bars, HbA_{1c} ≥9.5% (≥80 mmol/mol). The duration and HbA_{1c} of groups with* n *<30 are not included in the figure. Diabetes duration ranged from 1 to 19 years.*

classified as having no MA. Excluded from the analyses were 12 participants who had nephropathy due to a cause other than diabetes, 3 participants who had renal failure (either receiving dialysis or had kidney transplant), 5,201 participants who did not have an ACR determination within the prior 2 years, and 549 participants who had an ACR within the prior 2 years but did not meet the definitions of either MA or no MA (197 of the 549 had previous but not current MA, 26 had a clinical diagnosis of MA but the ACR was <30 mg/g and they were not on current treatment with an ACEI or

ARB, 301 had a clinical diagnosis of no MA but the ACR was ≥30 mg/g, and 25 had renal status reported as unknown by the clinic). The 5,765 excluded cases were similar to those included in the analyses in sex (48 vs. 49% female), race/ethnicity (76 vs. 78% non-Hispanic white), and average glycosylated hemoglobin (HbA_{1c}; both 8.4%). As would be anticipated in view of screening guidelines, there were more young participants and more with shorter diabetes duration among those excluded than included (35% of those excluded were <10 years of age vs. 12% of those included; 63 vs. 35%, respectively, had diabetes duration <5 years).

HbA_{1c} was collected from the medical chart for up to the past 13 years. A weighted average HbA_{1c} level was computed for each participant from all available values, excluding any HbA_{1c} values that were obtained within 1 year after diagnosis. Of the included HbA_{1c} values, 68% were obtained from DCA point of care, 2% were obtained from other point of care, 27% were obtained from laboratory assay, and 3% were unknown. To calculate average HbA_{1c}, the area under the curve was calculated using the trapezoid rule and then scaled by time to reflect overall average HbA_{1c}. Data for systolic and diastolic blood pressure (BP), height, and weight were obtained from the most recent clinic visit. Age-, sex-, and height-adjusted BP *z* scores were calculated; age- and sex-adjusted BMI percentiles and *z* scores were calculated from height and weight measurements. BMI categories were defined by percentiles; underweight was defined as <5th percentile, normal was defined as 5th to <85th percentile, overweight was defined as 85th to <95th percentile, and obese was defined as ≥95th percentile. LDL, HDL, and triglyceride (TG) levels were the most recent values available in the chart. LDL values were included only if obtained with fasting status or from direct LDL (1,848 of 7,549 with available results), and TG values were included only if obtained with fasting status (1,444 of 7,549 with available results). The majority of the cohort (79%) had available HDL results, as fasting status was not required.

Statistical methods

The proportion of participants with MA was calculated according to demographic and clinical factors. Univariate logistic regression was used to assess the relationship between each factor and the presence of MA. Factors with a *P* value <0.10 from univariate models were included in an initial multivariate model (full model), and then a backward elimination procedure was used to remove variables with a *P* value >0.01 (reduced model). A forward selection process resulted in a similar model. Lipids were assessed in univariate models but not included in the full or reduced multivariate model due to a large number of participants without recent or fasting lipid results. Instead, the factors found to be significant in the main multivariate reduced model were added to each of these individual lipid models to adjust for confounding, among those with available lipid data. Interactions among age, diabetes duration, and HbA_{1c} were evaluated in the regression model, and no interaction terms were found to be statistically significant (all *P* values >0.01). Tests of significance were reported from models using continuous variables when possible. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). All *P* values are two-sided. In view of the large sample size and multiple comparisons, only *P* values ≤0.01 were considered statistically significant, and 99% CIs are presented.

RESULTS—The analysis cohort included 7,549 participants, with mean age of 13.8 ± 3.5 years (range 2 to 19), mean age at type 1 diabetes onset of 6.9 ± 3.9 years, and mean diabetes duration of 6.5 ± 3.7 years; 49% were female. The racial/ethnic distribution was 78% non-Hispanic white, 6% non-Hispanic black, 10% Hispanic, and 5% other. The average of all HbA_{1c} levels (for up to the past 13 years) was 8.4 ± 1.3% (69 ± 13.7 mmol/mol) (Table 1).

Among the 329 participants with MA, 117 (36%) were using an ACEI or ARB and 212 (64%) were not. Among the 117 with MA receiving an ACEI or ARB, 97 had an ACR ≥30 mg/g, whereas 20 had an ACR <30 mg/g. Other than the 20 who were on ACEI or ARB and had an ACR <30 mg/g, the remaining 309 (94% of those with MA) had a most recent ACR of ≥30 mg/g. Five percent of those with MA were on medication for dyslipidemia compared with 2% of those with no MA. Two percent of those with no MA were on an ACEI or ARB. When participants with no MA who were on an ACEI or ARB were excluded from the analysis, the results did not change (data not shown).

The frequency of MA was strongly associated with diabetes duration and with HbA_{1c} ($P < 0.001$ for each) (Table 1), with the frequency being the highest when both longer duration and higher HbA_{1c} levels were present (Fig. 1). Few participants with an average HbA_{1c} of <7.5% (<58 mmol/mol) had MA (<2%), and only 3 out of 165 participants with an average HbA_{1c} of <6.5% (<48 mmol/mol) had MA. Other factors associated with an increased frequency of MA in univariate models ($P \leq 0.01$) included female sex, non-Hispanic black race, older age, and above-normal systolic and diastolic BP (Table 1). In a multivariate model, only female sex, older age, and elevated diastolic BP remained significant, and BMI *z* score was statistically significant as well (Table 1).

The effect of age on frequency of MA when controlling for duration and HbA_{1c} levels was explored in Fig. 2. It can be seen that increasing age is mainly associated with an increase in the frequency of MA when HbA_{1c} was ≥9.5% (≥80 mmol/mol). The higher MA frequency in females was seen across the age range (Supplementary Table 1). Elevated TG and LDL, but not HDL, levels were associated with an increased frequency of MA in a univariate analysis ($P < 0.001$ for TG and $P = 0.002$ for LDL), but none were significant when participants with lipid results were entered into a multivariate model adjusting for the other significant associated factors found previously. To further explore the data, the frequency of MA by the potential predictors was stratified by race/ethnicity (Supplementary Table 2).

CONCLUSIONS—In this study, we used the large T1D Exchange database to determine the frequency of clinically diagnosed MA and to identify factors associated with MA in children and adolescents with type 1 diabetes. We found that MA was associated with longer diabetes duration, higher mean HbA_{1c} level, older age, female sex, higher diastolic BP, and lower BMI. MA frequency was particularly high, exceeding 15%, with duration ≥10 years and average HbA_{1c} ≥9.5% (≥80 mmol/mol). In contrast, MA was infrequent when average HbA_{1c} was <7.5% (<58 mmol/mol), irrespective of age and duration.

The associations of MA with age, duration of diabetes, HbA_{1c}, and diastolic BP have been shown in other pediatric type 1 diabetes studies (6,9–20). Of these

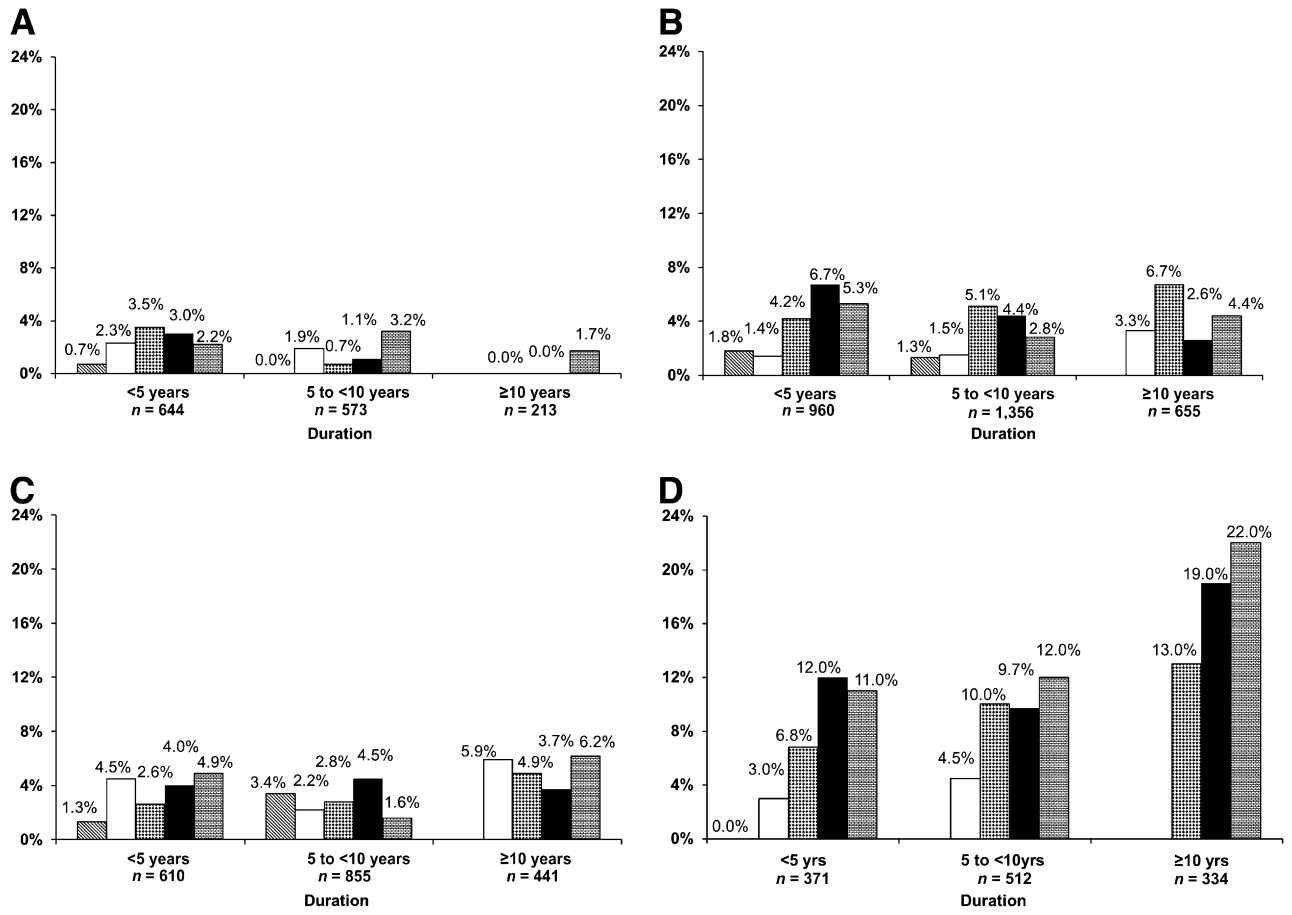

Figure 2—A: *MA by diabetes duration and age for HbA_{1c} <7.5% (<58 mmol/mol).* B: *MA by diabetes duration and age for HbA_{1c} = 7.5 to <8.5% (58 to <69 mmol/mol).* C: *MA by diabetes duration and age for HbA_{1c} = 8.5 to <9.5% (69 to <80 mmol/mol).* D: *MA by diabetes duration and age for HbA_{1c} ≥9.5% (≥80 mmol/mol). White bars with diagonal black lines, <10 years of age; solid white bars, 10 to <13 years of age; white bars with black diamonds, 13 to <16 years of age; solid black bars, 16 to <18 years of age; bars with horizontal brick pattern, 18 to <20 years of age. Duration and age-groups with* n *<30 are not included in the figure. Diabetes duration ranged from 1 to 19 years.*

risk factors, both glucose and BP control are modifiable and are the basis for the prevention of DKD. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive diabetes management reduced development of MA by 39% and macroalbuminuria by 54% in the full cohort (21), with development of MA being reduced by 55% in participants 13–18 years of age at enrollment (22). Additionally, BP control with ACEI/ARBs has been shown to reduce progression of MA to proteinuria (23). The finding of a lower frequency of MA in overweight and obese participants compared with those with normal or low BMI contrasts with adult type 1 diabetes studies (24,25) but is similar to the SEARCH study in which a one-time elevated ACR was inversely associated with BMI categories (15). Although further exploration into total daily insulin per kilogram of body weight and HbA_{1c} of these BMI groups did not provide a biologically plausible explanation for this, this finding will certainly benefit from longitudinal follow-up. It will be important to determine the progression, or lack thereof, to further kidney disease in this underweight group. The higher frequency of MA in girls and young women is also similar to previous reports (15). When the relationship between potential predictors and MA stratified by race/ethnicity was considered, no obvious interactions were found that could be explained by biological plausibility. Rather, any differences were likely due to confounding by HbA_{1c}.

The T1D Exchange clinic registry by its nature has some limitations. Among the 67 participating clinics, there is inherent variation in diabetes management, compliance with ADA screening guidelines, type and timing of urine sample obtained, and use of interventions (e.g., ACEI or ARB) once MA has been diagnosed. Because of this lack of a standard testing approach followed by all clinics, we cannot use our data to determine the optimal screening strategy for MA. On that same note, a degree of caution is needed in interpreting the data with respect to MA prevalence. Nevertheless, the 4.4% frequency of MA in our study is similar to that reported by the large Diabetes Patienten Verlaufsdokumenation (DPV) study (4.3%) in Germany and Austria, which also queried clinical databases (26). In contrast, the MA frequency we report is less than that reported by the SEARCH study (9.2%), but SEARCH prevalence was based on a one-time ACR elevation (15) rather than sustained MA, which was required in our study. Although this lack of standardization of MA testing might affect interpretation of MA prevalence, it is not likely to have an important effect on the interpretation of factors associated with the frequency of MA. Finally, in interpreting the absolute

MA frequency, it is important to note that a small proportion of nondiabetic children will have MA (27,28). One study found that 5.1% of nondiabetic individuals (also without hypertension, cardiovascular disease, or elevated serum creatinine) had MA. This could account for the MA diagnosis in at least some of the cohort, particularly in those with a short duration of type 1 diabetes (28).

Another potential limitation of the data is that we cannot identify the exact timing of the clinical diagnosis of MA from the database and thus cannot assess whether the diagnosis of MA influenced subsequent HbA_{1c} levels. Thus, it is possible that the association between HbA_{1c} levels and MA could be even stronger than what we found if the diagnosis of MA led some patients to improve their glycemic control.

Our results provide strong support for prior literature in emphasizing the importance of good glycemic and BP control, particularly as diabetes duration increases, in order to reduce the risk of DKD. Longitudinal follow-up of this cohort will provide important information with respect to the predictive value of MA for the subsequent development of impaired renal function. Since age and diabetes duration are important nonmodifiable factors associated with MA, the importance of routine screening is underscored to ensure early diagnosis and timely treatment of MA.

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M.D., R.W.B., and W.V.T. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. S.N.D. performed statistical analysis, researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. D.M.M. contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. L.A.F., R.G.-K., L.M.L., K.M.M., H.S., and M.J.T. researched data, contributed to discussion, and reviewed and edited the manuscript. R.W.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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