Racial and Ethnic Disparities in Comorbidities in Youth With Type 2 Diabetes in the Pediatric Diabetes Consortium (PDC)

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OBJECTIVE

Type 2 diabetes in the U.S. is more prevalent in youth of minority racial-ethnic background, but disparities in health outcomes have not been examined in this population.

RESEARCH DESIGN AND METHODS

We examined racial-ethnic differences in the initial presentation and subsequent comorbidities in 1,217 youth with type 2 diabetes (63% girls) enrolled in the Pediatric Diabetes Consortium (PDC) Registry from February 2012 to June 2018. Demographic and clinical data were collected from medical records and participant self-report.

RESULTS

Overall, the mean age at presentation was 13.4 ± 2.4 years, and BMI was 35.0 ± 9.4 kg/m^2. HbA_{1c} was higher and C-peptide was lower in non-Hispanic Black (NHB) and Hispanic (H) youth compared with non-Hispanic White (NHW) youth. NHB were three times as likely to present in diabetic ketoacidosis (19%) versus NHW (6.3%) and H (7.5%), and NHB and H both had a worse HbA_{1c} trajectory compared with NHW peers. Microalbuminuria was documented in 11%, hypertension in 34%, and dyslipidemia in 42% of Registry participants, with no significant difference among racial-ethnic groups. Nonalcoholic fatty liver disease (NAFLD) was diagnosed in 9% and 11% of H and NHW, respectively, versus 2% in NHB.

CONCLUSIONS

NHB and H youth with type 2 diabetes presented with worse metabolic control and had persistently worse HbA_{1c} trajectories compared with NHW. Comorbidities exist in a large percentage of these youth independent of race-ethnicity, except for NAFLD being less prevalent in NHB. Greater efforts are needed to mitigate racial-ethnic disparities at diagnosis and in the management of youth with type 2 diabetes.

Non-Hispanic Black (NHB) and Hispanic (H) adults have a prevalence rate for type 2 diabetes nearly double that of non-Hispanic White (NHW) individuals (1). Health disparities exist among adults with type 2 diabetes of different race-ethnicity, with individuals from minority racial-ethnic groups having worse long-term diabetes

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outcomes than NHW adults (2). A similar or greater prevalence of type 2 diabetes in NHB and H youth compared with NHW youth has been reported by the epidemiology study, SEARCH for Diabetes in Youth (SEARCH) study, designed to define the epidemiology of diabetes, especially type 2 diabetes, in U.S. youth (3). SEARCH also compared the prevalence and incidence rates of type 2 diabetes in U.S. youth from 2002 through 2012 and showed that in 2012 there was an increase in incidence of 4.8% per year overall, which was significantly higher in NHB (6%) and in H (6.5%) youth compared with NHW (0.6%) peers (3,4). SEARCH is a Centers for Disease Control and Prevention (CDC)-funded, National Institutes of Health-supported study designed to define the epidemiology of diabetes, especially type 2 diabetes, in U.S. youth. The study population in SEARCH was selected to represent, or overrepresent, H and NHB youth, as well as Asian, Pacific Islanders, and American Indian youth, to ensure adequate representation of these populations thought to be at greatest risk for youth-onset type 2 diabetes (3).

Racial-ethnic disparities in glycemic outcomes and in diabetes treatment options have been described in type 1 diabetes in SEARCH and then in the Type 1 Diabetes (T1D) Clinic Exchange Registry, a large U.S. registry reporting patient data obtained directly from patients and confirmed from their medical records (5–7). These reports show higher HbA_{1c} values in NHB and H children, youth, and young adults compared with their NHW peers. Of greater concern, these reports also document less intensive treatment (i.e., lower use of insulin pumps and continuous glucose monitors) in NHB and H youth and young adults versus NHW similarly aged patients, even when adjusted for family income (5–7). Likewise, disparities in glycemic outcomes have been shown in youth with T2D in SEARCH.

Both SEARCH and Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY), a large National Institutes of Health-funded trial of three different treatment options in adolescents with type 2 diabetes, and others, have shown high rates of risk for complications and early presence of complications and comorbidities in youth and young adults with type 2 diabetes (8–10). However, little is documented about racial-ethnic differences in diabetes care or racial-ethnic differences in nonglycemic outcomes in youth with type 2 diabetes in the U.S. Determining whether there are racial-ethnic differences in care and outcomes is especially important in youth-onset type 2 diabetes because it disproportionately affects Black and Brown youth and youth from disadvantaged backgrounds (3,4,11).

From 2012 to 2018, the Pediatric Diabetes Consortium (PDC) enrolled a large cohort (N = 1,217) of children and adolescents with type 2 diabetes at 18 pediatric diabetes centers in the U.S. The PDC racial-ethnic and social demographics for NHB, H, and NHW youth included in this report are similar to those in SEARCH, which is recognized to be representative the U.S. type 2 diabetes youth population. Therefore, we think the PDC type 2 diabetes population is relatively representative of the NHB, H, and NHW youth-onset pediatric type 2 diabetes population in the U.S. (11,12). The aims of these analyses are to evaluate racial-ethnic differences in glycemic control at presentation and over time in this large cohort as well as race-ethnicity–related differences in the prevalence of diabetes comorbidities in youth with type 2 diabetes enrolled in the PDC.

RESEARCH DESIGN AND METHODS

PDC Type 2 Diabetes Registry

The PDC Registry protocol was approved by the Institutional Review Boards at each of the 18 participating centers, and 1,217 participants were enrolled in the registry between February 2012 and June 2018, and followed annually until December 2018. PDC Registry sites (see Supplementary Material) are located across the U.S. and are geographically diverse, serving fboth urban and rural populations. To be included in the registry, participants with type 2 diabetes had to be $<$21 years of age, diagnosed with diabetes using the criteria of the American Diabetes Association (13), overweight or obese at the time of diagnosis (BMI $\geq$85% for age and sex), and negative for type 1 diabetes-associated autoantibodies. If diabetes autoantibodies were unavailable at diagnosis, an elevated C-peptide (above the normal fasting level for the laboratory) and/or absence of insulin requirement at 6 months postdiagnosis were used to verify the clinical diagnosis of type 2 diabetes. Patients with other forms of diabetes were excluded.

Data Collection

Demographic, clinical, and laboratory data at enrollment and at the initial diagnosis of diabetes were collected from the electronic health records and from interviews with the participants and/or parents, as previously described (11). Data were also collected regarding participant race-ethnicity, family history of diabetes in parents, siblings, half-siblings, maternal and paternal grandparents, age at onset of diabetes, and type of diabetes. Race-ethnicity determination was collected as reported in each site's electronic health record. This was universally recorded as the family's self-reported race-ethnicity, generally using the U.S. Census categories. All available physical examination, HbA_{1c} and clinical data at or after diabetes diagnosis were collected. BMI was computed from height and weight measured by a health care provider $\leq$28 days of enrollment and diagnosis dates, respectively. BMI percentile and SD scores adjusted for age and sex were calculated using the 2000 CDC population growth chart data (14). Blood pressure (BP) percentiles adjusted for age, sex, and height were calculated from data from the National High Blood Pressure Education Program Working Group in Children and Adolescents (15). Hypertension was defined as a medical problem noted in the medical record as not resolved, or systolic or diastolic BP measurement $\geq$95th percentile for those aged $<$18 years and systolic BP $\geq$140 or diastolic BP $\geq$90 for those aged $\geq$18 years. Dyslipidemia was defined as any of the following criteria noted in the medical record: unresolved hypertriglyceridemia, elevated LDL cholesterol, decreased HDL cholesterol, or a non-HDL cholesterol $\geq$145 mg/dL ($\geq$3.76 mmol/L). Microalbuminuria and nonalcoholic fatty liver disease (NAFLD) were defined as the patient having either disease as an ongoing medical condition at any time data were captured after enrollment. Diabetic ketoacidosis (DKA) was defined by the Diabetes Control and Complications Trial criteria of pH $<$7.3 or HCO_3 $<$15

mEq/L with hyperglycemia and treatment in a health care facility.

Methods

HbA_{1c} levels were measured by the DCA 2000 (Siemens Health Care) point-of-service method at all of the centers. Random C-peptide concentration was obtained ≤28 days of diagnosis and was available in a subset of the study population (n = 631), some of whom had participated in an ancillary study of the PDC Registry (16). That study measured C-peptide by a two-site immunoenzymatic assay using a Tosoh 2000 auto-analyzer (TOSOH, Biosciences, South San Francisco, CA) at the Northwest Lipid Research Laboratory (University of Washington, Seattle, WA). Otherwise, C-peptide levels were obtained from the local site databases.

Statistical Analysis

Characteristics for participants of each race-ethnicity group at diabetes diagnosis are described using percentages, mean and SD, or median and interquartile range. For HbA_{1c}, BMI, and C-peptide, values obtained ≤28 days of diagnosis were used for the analyses. To assess the racial-ethnic differences in participants' characteristics at diagnosis, logistic regression models were used to compare binary variables, and linear regression models were used to compare continuous and ordinal variables among H, NHW, and NHB participants. A multinomial regression model was used to compare seasonality at diagnosis among racial-ethnic groups. We adjusted for age, sex, and clinical center in the models comparing clinical characteristics at diagnosis (BMI Z-score, HbA_{1c}, C-peptide, and DKA) as well as comorbidities reported during the study.

Post diabetes diagnosis, HbA_{1c} and BMI values from the same participants were captured at 6, 12, 24 and 36 months based on prespecified visit windows. Distribution of HbA_{1c} levels and BMI Z-scores at diagnosis, 6, 12, 24, and 36 months in each group are illustrated by box plots. Repeated-measures linear regression models with spatial power covariance structure were conducted to assess the differences of HbA_{1c} and BMI among racial-ethnic groups longitudinally, adjusting for age, sex, and clinical center. This type of model can handle missing data (related mainly to different length of follow-up in the registry) by assuming missing at random. Missingness assumption was assessed by comparing the participants' characteristics at diabetes diagnosis between those with and without missing data for HbA_{1c} or BMI Z-score at 36 months. There was no significant difference in participants' characteristics at diagnosis between participants with versus without missing data, except for age and sex, which were adjusted for in the model.

As a result of multiple comparisons, the false discovery rate (FDR) was controlled using the adaptive Benjamini-Hochberg procedure, and FDR-adjusted P values are reported. All reported P values are two-sided. All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Subject Characteristics

At diagnosis, 92% participants were obese (≥95th age and sex adjusted percentile). The mean ± SD BMI among study participants was 35.0 ± 9.4 kg/m^2, and mean ± SD age was 13.4 ± 2.4 years. There were no significant differences in age or BMI Z-score among the three racial-ethnic groups (Table 1). Of note, 7% of the youth were <10 years of age at diagnosis of type 2 diabetes. There were differences in sex distribution, with a greater proportion of girls in the NHB (69%) compared with the H (60%) group and the NHW (55%) group, with no significant difference in sex distribution between the H and NHW groups. NHB and H youth were more likely to have nonprivate health insurance and to belong to families with lower socioeconomic status compared with the NHW group. More than 90% of participants had a family history of type 2 diabetes, with no significant difference by race-ethnicity.

Metabolic Differences Among the Three Race-Ethnicity Groups

At diagnosis, mean HbA_{1c} was significantly higher in NHB (10.2% [88 mmol/mol]) and H (9.9% [85 mmol/mol]) youth compared with NHW (9.0% [75 mmol/mol]) peers (both $P < 0.001$) (Table 1 and Fig. 1). NHB youth had significantly lower C-peptide at diagnosis compared with NHW and H youth, with no significant differences in C-peptide between H and NHW youth (Table 1). In addition to a lower C-peptide at diagnosis, NHB youth were more likely to present in DKA (19%) compared with the other two groups (8% in H and 6% in NHW, both $P < 0.001$) (Table 1). After diagnosis, HbA_{1c} continued to be significantly higher in the NHB and H compared with NHW youth during the first 3 years, after adjusting for age, sex, and clinical center (Fig. 1). There was no significant difference in the BMI Z-score over time among the three groups (Supplementary Fig. 1).

Comorbidities by Race-Ethnicity

Comorbidities of diabetes during the initial 3 years of type 2 diabetes were highly prevalent in the PDC participants after adjusting for age, sex, and clinical center (Fig. 2). Microalbuminuria was present in 11%, hypertension in 34%, and dyslipidemia in 42% of youth, with no significant differences among the three racial-ethnic groups. However, NAFLD was diagnosed in 9% of H and 11% of NHW versus only 2% of NHB ($P < 0.001$ vs. the other 2 groups).

CONCLUSIONS

This study from a large number of youth enrolled in the PDC Registry revealed important race-ethnicity differences in the severity of presentation and clinical course of youth with type 2 diabetes. NHB and H youth presented with worse metabolic control at diagnosis of type 2 diabetes compared with NHW. In particular, NHB youth had three-times higher rates of DKA at presentation compared with other race-ethnicities. NHB and H youth continued to have a worse HbA_{1c} trajectory than NHW over time. Youth with type 2 diabetes also had a high prevalence of cardiovascular comorbidities independent of race-ethnicity. This study adds to the limited data regarding the racial disparities in health-related outcomes in the high-risk group of youth with early-onset type 2 diabetes.

Our findings of a higher HbA_{1c} at presentation of type 2 diabetes in youth of a minority background suggests greater severity of the disease process at presentation. It is also particularly noteworthy that NHB youth were three times more likely to present with DKA. This is

Table 1—Participants' characteristics at diagnosis of type 2 diabetes by race-ethnicity (*N* = 1,217)

	NHW (*n* = 145)*	H (*n* = 629)*	NHB (*n* = 443)*	Adjusted *P* value†		
				H vs. NHW	NHB vs. NHW	H vs. NHB
Age (years)	13.5 ± 2.2	13.5 ± 2.3	13.2 ± 2.4	0.93	0.18	0.06
<10	10 (7)	41 (7)	31 (7)			
10–<13	50 (34)	232 (37)	183 (41)			
13–<15	46 (32)	176 (28)	119 (27)			
≥15	39 (27)	180 (29)	110 (25)			
Female sex	80 (55)	380 (60)	306 (69)	0.25	0.004	0.005
Health insurance				<0.001	0.005	<0.001
Private	61 (42)	100 (16)	128 (29)			
CHIP or other government plan	75 (52)	489 (78)	299 (67)			
Military	4 (3)	4 (<1)	2 (<1)			
None	5 (3)	36 (6)	14 (3)			
Family income				<0.001	<0.001	<0.001
<$25,000	41 (35)	226 (54)	133 (42)			
$25,000–$49,999	22 (19)	130 (31)	108 (34)			
$50,000–$74,999	33 (28)	45 (11)	45 (14)			
$75,000–$99,999	12 (10)	9 (2)	15 (5)			
≥$100,000	10 (8)	9 (2)	14 (4)			
BMI Z-score‡	2.40 ± 0.35	2.24 ± 0.47	2.34 ± 0.43	0.11§	0.49§	0.57§
HbA_{1c} (%)	9.0 ± 2.7	9.9 ± 2.6	10.2 ± 2.8	<0.001§	<0.001§	0.13§
HbA_{1c} (mmol/mol)	75 ± 29	85 ± 28	88 ± 31			
<7.0% (<53 mmol/mol)	39 (30)	98 (17)	71 (17)			
7.0–<9.0% (53–<75 mmol/mol)	35 (27)	124 (22)	95 (23)			
9.0–<11.0% (75–97 mmol/mol)	29 (22)	137 (24)	69 (17)			
≥11.0% (≥97 mmol/mol)	29 (22)	212 (37)	183 (44)			
C-peptide (ng/dL)	4.6 (3.0–7.4)	3.6 (2.3–5.8)	2.6 (1.6–4.1)	0.06§	<0.001§	<0.001§
C-peptide (nmol/L)	1.5 (0.99–2.5)	1.2 (0.8–1.9)	0.86 (0.5–1.4)			
DKA	8 (6)	43 (8)	73 (19)	0.49§	<0.001§	<0.001§
Family history of diabetes	130 (94)	569 (92)	407 (94)	0.52	0.63	0.10
Seasonality				0.92	0.81	0.62
Winter	38 (26)	164 (26)	122 (28)			
Spring	31 (21)	137 (22)	107 (24)			
Summer	40 (28)	187 (30)	118 (27)			
Fall	36 (25)	141 (22)	96 (22)			

Data are presented as mean ± SD, median (interquartile range), or *n* (%). *Number of participants with missing or "unknown" data (NHW/H/NHB): family income (27/210/128), BMI Z-score (27/130/85), HbA_{1c} (13/58/25), C-peptide ≤28 days of diagnosis (79/297/210), DKA (17/57/50), and family history of diabetes (6/8/12). †FDR-adjusted *P* values. ‡BMI percentile adjusted for age and sex based on 2000 CDC growth charts. §*P* value adjusted for age, sex, and clinical center. CHIP, Children's Health Insurance Program.

consistent with observations from the SEARCH study, where DKA at presentation of type 2 diabetes was related to minority race-ethnicity (*P* = 0.013), younger age at diagnosis (*P* = 0.001), and male sex (*P* = 0.001) (17). NHB youth had significantly lower C-peptide concentrations at diagnosis compared with the two other groups, which may have played a role in the increased frequency of DKA at diagnosis.

Some race-ethnicity differences in insulin sensitivity and secretion have been reported in adults and children in studies where race-ethnicity was defined based on ancestry or self-identification of race-ethnicity, suggesting potential biologic differences in the risk for diabetes (18–23). NHB youth were found to have lower insulin sensitivity compared with H (24) and NHW peers of similar adiposity (24,25), as well as a higher acute insulin response to glucose (25,26). This has been attributed to greater insulin secretion for the degree of insulin resistance and reduced hepatic insulin extraction (27). We previously reported increased insulin secretion for the degree of insulin resistance in NHB children compared with NHW children without diabetes and in early-onset type 2 diabetes (18). Whether this higher initial insulin production may eventually result in a rapid loss of β-cell function is not clear but may explain, at least in part, the more rapid β-cell failure in type 2 diabetes in NHB youth and, more generally, in all youth with type 2 diabetes compared with adults (28).

While these factors may play a role in β-cell failure, it is highly plausible that the presentation with higher rates of DKA and thus more advanced disease in NHB compared with H and NHW children may arise from factors related to social determinants of health (e.g., access to care, lower socioeconomic status). While the majority of youth with type 2 diabetes are disproportionally from families

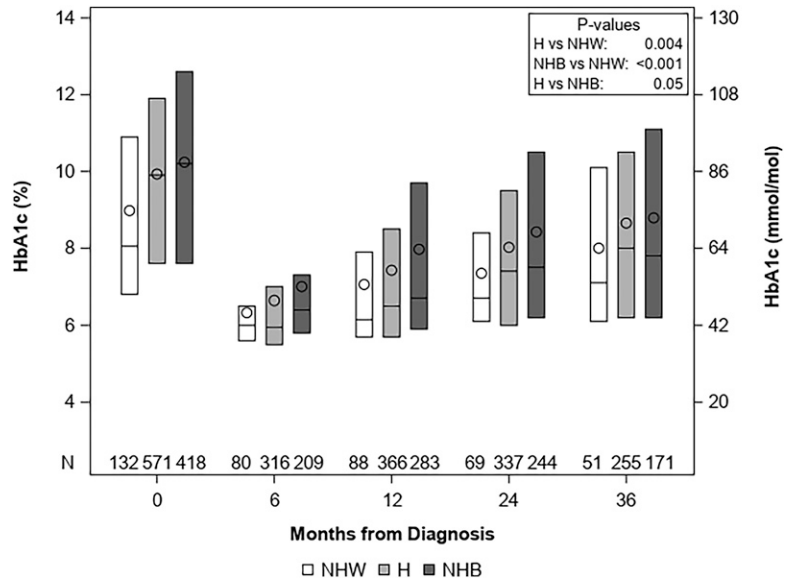

Figure 1—HbA_{1c} trajectory by race-ethnicity. The bottom and top of each box denote the 25th and 75th percentiles, the line inside the box denotes the median, and the circle is the mean. Reported *P* values are FDR-adjusted *P* values from longitudinal analyses (mixed-effects linear regression model excluding diagnosis), adjusted for age, sex, and clinical center. The numbers on the *x*-axis refer to the number of observations at each time point. Missing data were mainly related to different lengths of follow-up in the registry. There was no significant difference in participants' characteristics at diagnosis, except for age and sex, which were adjusted for in the model. There was no significant difference in sociodemographic factors between participants with vs. without missing data during follow-up.

with a lower socioeconomic status, NHB and H youth come from more financially disadvantaged families and are less likely to have private health insurance. Therefore, they may have greater barriers to accessing health care and delay in seeking health care for an apparent non-emergent health concern than their NHW peers, leading to greater metabolic instability at diagnosis of youth-onset type 2 diabetes. In addition, we previously reported a high percentage of loss of follow-up (55%) after a median duration of 1.3 years from enrollment in the PDC, although this was mostly related to increasing age, with no differences by race-ethnicity (29).

The advanced disease at presentation is quite concerning given that our previous studies identified HbA_{1c} at diagnosis to be a good predictor of longer-term diabetes control in youth with type 2 diabetes, independent of age at diagnosis, BMI, or race-ethnicity (30). Similarly, β-cell function was found to be the main determinant of HbA_{1c} at diagnosis and over time in the TODAY study (31,32). While longitudinal data on the relationship between DKA at presentation and long-term control in type 2 diabetes are not available, youth with DKA at presentation with type 1 diabetes have a worse HbA_{1c} trajectory overtime independent of demographic-, socioeconomic-, and treatment-related factors and baseline fasting C-peptide (33,34). This suggests that higher rates of DKA at diagnosis in NHB youth with type 2 diabetes portends increased risk for long-term worse diabetes control and thus risk for diabetes complications. Indeed, our data show persistently higher HbA_{1c} in NHB youth compared with NHW and in H compared with NHW over 36 months post diagnosis of diabetes.

	Hypertension	Dyslipidemia	Microalbuminuria	Non-Alcoholic Fatty Liver Disease
Adjusted P-value[a] Hispanic vs Non-Hispanic White	0.77	0.77	0.93	0.92
Adjusted P-value[a] Non-Hispanic Black vs Non-Hispanic White	0.68	0.93	0.68	<0.001
Adjusted P-value[a] Hispanic vs Non-Hispanic Black	0.93	0.17	0.28	<0.001

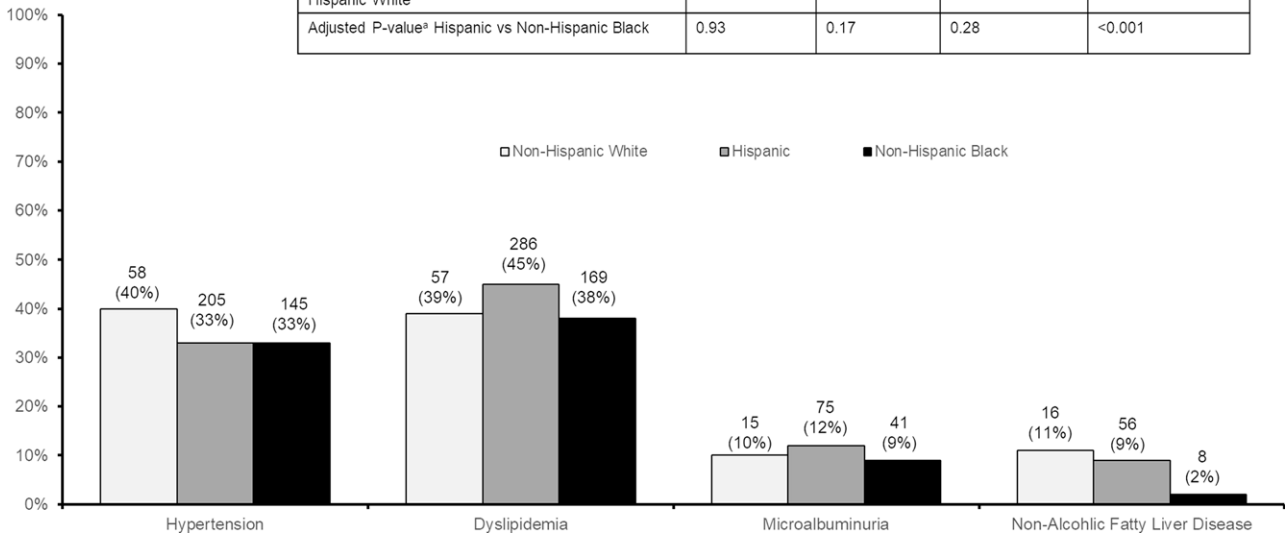

Figure 2—Comorbidities of type 2 diabetes by race-ethnicity. [a]FDR-adjusted *P* values, and models adjusted for age, sex, and clinical center.

A study comparing the PDC Registry to the European DPV (Diabetes Patienten Verlaufsdokumentation) registry found that 70% of DPV versus only 34% of PDC youth were diagnosed by targeted diabetes testing (35). PDC youth also had a higher HbA_{1c}, 9.9% (85 mmol/mol) vs. 7.1% (54 mmol/mol) ($P < 0.001$) and were more likely to present in DKA (7.5% vs. 1.3%; $P < 0.001$). These data suggest that earlier targeted screening of at-risk youth with obesity may be a helpful way to improve health at diagnosis and lead to improved outcomes especially in H and NHB youth.

Beginning in 2018, the American Diabetes Association consensus guidelines for identification of youth with type 2 diabetes have recommended targeted screening of overweight and obese youth, especially minority youth (28). Hopefully, these recommendations will result in earlier diagnosis of type 2 diabetes in all youth, better preservation of C-peptide, and improved long-term outcomes. However, if the current disparities in the social determinants of health are not addressed, minority youth may still experience a greater delay in diagnosis of type 2 diabetes, and disparities in severity of β-cell loss at diagnosis may not be adequately improved.

Another important finding from our current analysis is that comorbidities exist in a large percentage of youth with type 2 diabetes independent of race-ethnicity. More than a third of our youth with type 2 diabetes had diagnoses of hypertension, a third had dyslipidemia, and ∼10% had microalbuminuria over the 36 months following the diagnosis of diabetes. NAFLD was noted in ∼10% of H and NHW but was less prevalent in NHB youth (2%). The high prevalence of these comorbidities is consistent with reports from the TODAY and SEARCH studies (36,37). The underlying risk factors for comorbidities were investigated in an earlier report from the PDC on a smaller group of participants. In that analysis, we found that hypertension was associated with higher BMI ($P < .001$), dyslipidemia with higher HbA_{1c} ($P < 0.001$), and microalbuminuria with longer diabetes duration ($P = 0.001$) (38). With respect to liver disease, NHB children and adults have been reported to have lower prevalence of NAFLD compared with Hs and NHWs (39,40).

Limitations of this study stem from the data being derived from a clinical registry with variable clinical practices across sites. Comorbidities were evaluated at different times during participation in the registry, and the date of diagnosis of the comorbidity was not captured. As such, we could not produce a time-based analysis to assess the etiologic factors contributing to comorbidities such as glycemic control, diabetes duration or other factors. We are also not able to ascertain adherence with prescribed medical therapy to treat diabetes and comorbidities or to assess health care use. These are important areas to explore in future studies. We did not have measures of insulin sensitivity and stimulated C-peptide concentrations. Nevertheless, in the absence of differences in BMI among racial groups, it is unlikely that higher insulin resistance contributed to the more severe presentation or worse HbA_{1c} trajectory in NHB youth. An additional limitation is the lack of adequate numbers of Asian, Pacific Islanders, or American Indians in our PDC cohort to include these populations in our analysis.

In conclusion, race-ethnicity differences in type 2 diabetes severity are evident at diagnosis and persist over time in NHB and H youth compared with NHW peers. Greater efforts need to be dedicated to understanding the underlying causes for these racial-ethnic disparities to inform intervention efforts. More targeted screening of at-risk children (i.e., those overweight or obese, with a close relative with type 2 diabetes, or from a high-risk racial-ethnic group) may help to diagnose type 2 diabetes in children at an earlier stage. In addition, improvement in glycemic control in youth with type 2 diabetes is necessary to improve comorbidities that are highly prevalent in these youth independent of race-ethnicity. Novel models of health care delivery should take into account race-ethnicity factors and support the use of adjunct therapies for diabetes and comorbidities and monitoring the response to these therapies.

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