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Sex-Based Differences in Screening and Recognition of Prediabetes and Type 2 Diabetes in Pediatric Primary Care

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Abstract

Background: Risk-based screening for type 2 diabetes (T2D) in youth with overweight/obesity is recommended, but rates remain low in practice. Identification of factors impacting provider ordering and patient completion of testing may guide strategies to improve screening.

Objective: To evaluate predictors of hemoglobin A1c (A1c)-based T2D screening in pediatric primary care.

Methods: This retrospective cohort study included 10-18 year-old patients with overweight/obesity (body mass index Z-score ≥1.04) followed in a large academic-affiliated pediatric primary care network, 2009—2018. Percentages of patients with ordered and completed A1c were determined, and multivariable Cox proportional hazards regression was used to evaluate independent predictors of screening.

Results: 34,927 (48.0% female; 52.5% with BMI Z- score ≥1.64) youth followed for a median of 3.0 years were included. 21% (7,457) of patients had screening ordered and 14% (4,966) completed screening during follow-up. In multivariable regression, after controlling for race/ethnicity, body mass index, family history of diabetes, and age,

males were significantly less likely to have ordered screening, but were equally or more likely to complete screening if ordered.

Conclusions: Male adolescents were less likely to undergo A1c-based T2D screening due to differential ordering practices. The source of this differential practice should be pursued to avoid under-recognition of cardiometabolic risk in at-risk male youth.

Introduction

Youth-onset type 2 diabetes (T2D) has been rising by 5% annually in the United States[1] and is associated with cardiometabolic complications.[2] Since 2000, the American Diabetes Association (ADA) has recommended screening in youth age ≥10 years who have overweight/obesity (body mass index (BMI) ≥85th percentile for age/sex) with ≥2 additional risk factors (family history; Native American, African American, Latino, Asian, Pacific Islander race/ethnicity; signs/conditions associated with insulin resistance: acanthosis nigricans, polycystic ovary syndrome (PCOS), dyslipidemia, hypertension, small-for-gestational-age).[3] T2D is more common in female than male adolescents,[1,4,5] but guidelines have not recommended sex-based screening.

Although early treatment is associated with durable metabolic control,[6] more than half of at-risk adolescents are not screened.[7,8] Previous work demonstrated that T2D screening is appropriately completed more often in youth with T2D family history and

those with higher BMI percentile, but also more often among females.[9] The origin of these differences, whether due to provider ordering practice or to patient follow-through, has not been explored. To inform screening implementation, we investigated factors associated with ordered and completed T2D screening in youth who had overweight or obesity across a large, diverse pediatric primary care network.

Methods

Study Population

This retrospective cohort study included youth ages 10 – 18 years without known diabetes mellitus (*International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) (249.x, 250.x); *ICD-10-CM* (E08.x-E.11x., E13.x)) who had ≥1 visit in the Children's Hospital of Philadelphia (CHOP) Primary Care Network January 2009—August 2018. Only visits at which a patient had overweight/obesity (BMI ≥85th percentile, or BMI Z-score ≥1.04 based on sex-/age-specific United States Centers for Disease Control references[10,11]) were included. The CHOP Institutional Review Board approved the study.

Statistical Analysis

Although T2D may also be diagnosed using plasma glucose,[12] only A1c (commonly used by pediatricians[9] before endorsement in 2010[13]) was investigated to

ensure testing was for diabetes identification. The percent of patients in whom A1c was *ordered* or *completed*, and the percent found to have prediabetes-range (5.7-6.4% [39-46 mmol/mol]) or diabetes-range (≥ 6.5% [48 mmol/mol]) A1c were reported by sex and weight category (overweight: BMI Z-score 1.04-1.63 versus obese: BMI Z-score ≥ 1.64).[14] Continuous data, all right-skewed, were summarized using median and interquartile range (IQR). Pairwise comparisons were made using non-parametric Kruskal-Wallis test by ranks with Dunn test and Bonferroni adjustment for multiple comparisons. Categorical variables were summarized using proportions and distributions compared using chi^2.

Predictors of *ordered* and *completed* tests were identified using multivariable multiple failure Cox proportional hazards regression with the Andersen-Gill formulation. Patients were censored after one diabetes-range A1c or at end of follow-up (age 19, or last visit). Covariates included BMI-Z, sex, age, year, race/ethnicity (Non-Hispanic White [NHW], Non-Hispanic Black [NHB], Hispanic, Asian/Native Hawaiian/Pacific Islander/American Indian/Alaskan Native [A/NH/PI/AI/AN], and "other" including unreported), and whether a phlebotomy laboratory was present onsite (*completion* models). The proportional hazards assumption was assessed graphically. In sensitivity analysis, patients with PCOS (*ICD-9-CM* 256.4, *ICD-10-CM* E28.2), which only impacts females and could contribute to sex-based discrepancies in screening, were excluded.

Two-sided *P*-values < 0.05 were considered statistically significant. Analyses were performed using Stata 14 (StataCorp LP, College Station, TX).

Results

Cohort characteristics

The cohort consisted of 34,927 (48% female) patients who had overweight/obesity (**Table 1**) followed for a median (IQR) of 3.0 (1.1-4.9) years. Patients with obesity were younger at baseline, with longer follow-up and more visits, had higher proportion of documented diabetes family history, and were more often non-NHW (p<0.0001 for each). Follow-up was slightly longer for females. Diabetes family history was more commonly recorded for females than males with obesity (10.4% versus 7.8%, p<0.0001).

Screening and Identification of Prediabetes or Type 2 Diabetes

Overall, 21% (7,457) of patients had screening ordered and 14% (4,966) completed screening. Screening differed by sex, with females undergoing ordered and completed screening 30% (youth with obesity) to 70% (youth with overweight) more often than males (p<0.0001 for each; **Figure 1**). No sex difference was found in prediabetes identification among patients with overweight who completed screening or among the cohort overall (*completed*: 7.0% of females versus 11.4% of males, p=0.1;

overall: 0.3% of females versus 0.2% of males, p=0.4). Among patients with obesity, no sex difference in prediabetes prevalence was found among those who completed screening (females: 19.3% versus males: 20.2%, p = 0.5), but prediabetes was identified in more females than males with obesity overall (5.6% versus 4.1%, p<0.0001). T2D prevalence did not differ by sex among those who completed testing (females: 1.2% versus males: 1.1%, p=0.7) or overall among patients with obesity (females: 0.35% versus males: 0.22%, p=0.09).

Predictors of Ordering and Completion of Ordered Screening

Ordered screening

Among patients with overweight status, ordered screening was more likely in NHB (HR 1.5, 95% CI 1.3-1.8) and Hispanic (HR 1.7, 95% CI 1.3-1.8) youth, higher BMI-Z (per 1.0 increase, HR 50.1, 95% CI 33.6-74.8), documented diabetes family history (HR 1.7, 95% CI 1.3-2.3), and more recent years (HR 1.2, 95% CI 1.1-1.2). Ordered screening was less likely among males (HR 0.6, 95% CI 0.5-0.7) but did not differ by age.

Among patients with obesity, ordered screening was again more likely among non-NHW youth (NHB HR 1.2, 95% CI 1.1-1.2; Hispanic HR 1.2, 95% CI 1.1-1.4; A/NH/PI/AI/AN HR 1.3, 95% CI 1.2-1.6; “other” HR 1.1, 95% CI 1.0-1.3) and higher BMI-Z (HR 4.7, 95% CI 4.4-4.9). Again, males (HR 0.7, 95% CI 0.6-0.7) were less likely to

have ordered screening. Older patients (HR 0.51, 95% CI 0.49-0.53) were less likely to have screening ordered. Family history and year were not significant. Exclusion of patients with PCOS did not significantly alter hazard ratio estimates or significance.

Completed screening

Among patients with overweight status who had screening ordered, completion was more likely among youth with higher BMI-Z (HR 2.2, 95% CI 1.2-4.0) and those attending practices with onsite phlebotomy (HR 5.4, 95% CI 4.1-7.0) and less likely among older youth (HR 0.94, 95% CI 0.91-0.98) and in more recent years (HR 0.93, 95% CI 0.89-0.98). Sex, race/ethnicity, and family history did not predict completion.

In patients with obesity, completion was more likely among males (HR 1.05, 95% CI 1.00-1.11), Hispanic youth (HR 1.2, 95% CI 1.1-1.3), and youth attending practices with onsite phlebotomy (HR 2.8, 95% CI 2.6-2.9). Completion was less likely with increasing age (HR 0.87, 95% CI 0.86-0.89), increasing BMI-Z (HR 0.88, 95% CI 0.82-0.95), and in more recent years (HR 0.94, 95% CI 0.93-0.95). Family history was not significant. Exclusion of patients with PCOS did not significantly alter hazard ratio estimates or significance.

Discussion

Although T2D is more common in female than male adolescents,[1,4,5] the reverse sex pattern is recognized for prediabetes, a condition also associated with cardiometabolic risk.[15] Additionally, T2D is more common among adult men than women.[16] Despite the absence of sex-based screening recommendations, a previous study found that completion of T2D screening was greater among female than male adolescents.[9] Our findings confirmed this observation and identified its origin: provider-level differences in screen-ordering, even after adjustment for T2D risk factors.

Due to the asymptomatic nature of prediabetes and early T2D, screening is necessary to identify at-risk patients. The impact of surveillance is evident when our cohort's identified A1c-defined prediabetes prevalence (obese: 4.8%, overweight: 0.2%) is compared to that from a study by Andes et al using data from the National Health and Nutrition Examination Study, in which the entire cohort underwent screening (obese: 8%, overweight: 4.2%).[15] As T2D disproportionately impacts racial- and ethnic-minority youth[17] and our proportion of NHB and Hispanic youth was nearly identical to that of Andes et al (37% versus 34%),[15] our lower identified prevalence was likely due to under-recognition. Furthermore, assuming males truly have a higher prediabetes risk,[15] our finding of equal or lower prediabetes prevalence in males raises the possibility that male youth at highest risk were missed.

The identified sex-based differences in ordering were not explained by documented PCOS. Differential ordering may be related to provider knowledge of

higher T2D prevalence in females; however, screening guidelines do not include sex as a criterion. Providers may also order more obesity-related screening in girls in an effort to garner more lifestyle change buy-in, which may be more challenging for families of females given greater parental underestimation of overweight in girls than boys.[18] Qualitative studies are needed to explore this possibility.

Limitations related to the retrospective nature of our study should be considered. We assessed only A1c-based screening and were unable to determine the overall screening rate. Due to differential follow-up, screening rates for patients with overweight versus obesity cannot be directly compared. Family history may have been ascertained differently depending on the provider's level of concern for diabetes. Finally, differences in exam findings that may prompt screening, such as acanthosis nigricans, were not possible to assess due to limitations in the automated electronic medical record extraction required due to the large cohort.

In conclusion, despite no sex-based risk stratification in pediatric T2D screening guidelines, male youth were less likely to have A1c-based diabetes screening ordered and ultimately had lower screening rates. The source of this differential practice should be pursued to avoid under-recognition of cardiometabolic risk in at-risk male youth.

Conflict of interest: The study sponsor had no role in the study design, collection, analysis, interpretation of the data, writing of the report, or decision to submit the manuscript for publication. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

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Author contributions: Dr. Vajravelu conceived of and designed the study, completed data analysis, and wrote the first draft of the manuscript. Dr. Lee provided critical review for the manuscript. Drs. Amaral and Kelly contributed to study design and analysis and provided critical review for the manuscript. All authors had final approval of the submitted manuscript.

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Tables

Table 1. Cohort Characteristics, by Weight Status and Sex	Overweight*			Obese*			p (across all groups)
	Females	Males	p (F v M)	Females	Males	p (F v M)	
n (% of cohort)	8294 23.7%	8289 23.7%		8453 24.2%	9891 28.3%		
BMI-Z During Follow-up (median, IQR)	1.23 (1.14-1.35)	1.25 (1.15-1.37)	0.04	1.85 (1.64-2.15)	1.86 (1.64-2.16)	0.2	< 0.001
Age (Years) at Start of Follow-Up (median, IQR)	11.9 (10.7-13.7)	11.6 (10.6-13.6)	0.003	10.9 (10.4-11.7)	10.9 (10.4-11.8)	0.2	< 0.001
Family History of Diabetes, n (%)	383 (4.6%)	303 (3.7%)	0.08	881 (10.4%)	776 (7.8%)	< 0.001	< 0.001
Number of visits (median, IQR)	2 (1-3)	2 (1-3)	< 0.001	4 (3-5)	4 (3-5)	0.3	< 0.001
Years of follow-up (median, IQR)	1.44 (0.00-3.39)	1.21 (0.00-3.10)	< 0.001	4.16 (2.55-5.79)	4.05 (2.44-5.66)	< 0.001	< 0.001
PCOS, n (% of females)	37 (0.4%)			154 (1.8%)			< 0.001
Race/ethnicity, n (%)							
NHW	4,754 57.3%	5,039 60.8%	0.2	3,570 42.2%	5,063 51.2%	0.05	< 0.001
NHB	2,247 27.1%	2,008 24.2%		3,662 43.3%	3,246 32.8%		
Hispanic	405 4.9%	327 3.9%		518 6.1%	593 6.0%		
Asian/Native Hawaiian/Pacific Islander/American Indian/Alaskan Native	192 2.3%	216 2.6%		143 1.7%	220 2.2%		
Other	696 8.4%	699 8.4%		560 6.6%	769 7.8%		

*Overweight: BMI-Z 1.04-1.63 at all visits during follow-up; obese: BMI-Z ≥1.64 at least once during follow-up, otherwise 1.04-1.63

p-values determined by Kruskal-Wallis test by ranks with Dunn test and Bonferroni correction for multiple comparisons

Figure Legends

Figure 1. Percent of cohort with ordered A1c, completed A1c, prediabetes-range A1c (5.7-6.4% [39-46 mmol/mol]), and diabetes-range A1c (≥ 6.5% [48 mmol/mol]) during follow-up. Within each weight group, females were more likely to have ordered and completed screening than males ($p<0.0001$ for each). Prediabetes was identified in more females than males among patients with obesity ($p<0.0001$) but not overweight ($p=0.4$). Percent of patients with identified T2D did not differ by sex in either weight group ($p>0.05$ for each comparison).

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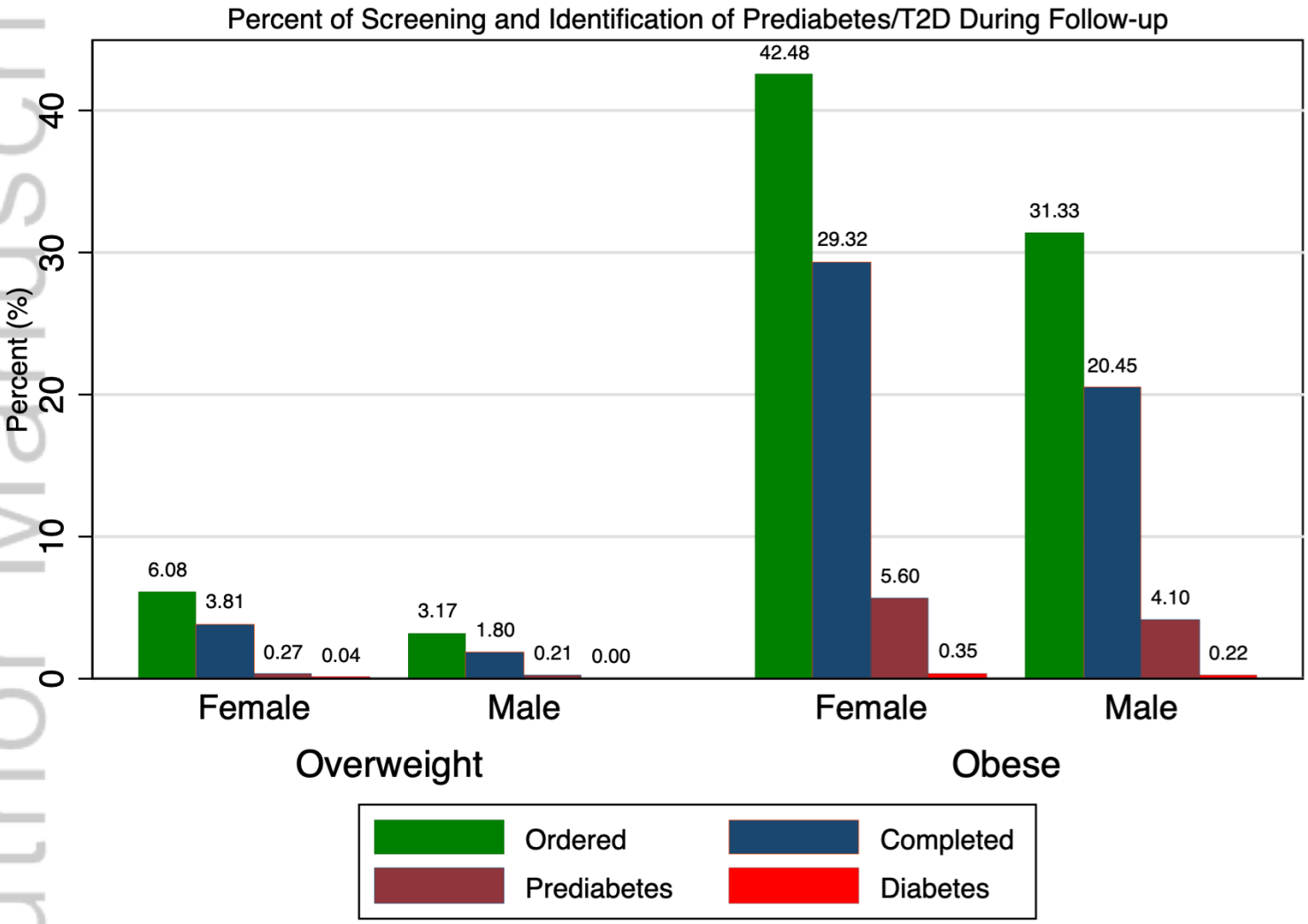

IJPO_12699_Figure 1 - screening and dysglycemia by gender and weight group.tiff

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