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Brief Report

Full title: Association between Prediabetes Diagnosis and Body Mass Index Trajectory of Overweight and Obese Adolescents

Short running title: Prediabetes Diagnosis and BMI Change in Youth

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Structured Abstract

Background: Prediabetes awareness in adults has been associated with improved weight management. Whether youth with prediabetes diagnosis experience similar improvements is unknown.

Objective: To investigate the association between prediabetes identification and body mass index trajectory in overweight and obese adolescents.

Subjects: Youth who were followed longitudinally in a large academic-affiliated primary care network and who were overweight/obese while 10-18 years old.

Methods: Retrospective cohort study. Subjects were categorized as "screened" if at least 1 hemoglobin A1c (HbA1c) result was available. Time series analysis was used to determine the difference in difference (DID) in body mass index Z-score (BMI-Z) slope before and after HbA1c between: 1) screened youth found to have prediabetes-range HbA1c (5.7-6.4%, 39-46 mmol/mol) versus normal HbA1c, and 2) screened versus age-matched unscreened obese youth.

Results: 4,184 (55.6% female) screened subjects (median follow-up 9.7 years) were included. 637 (15.2%) had prediabetes-range HbA1c. Prediabetes was associated with a greater decrease in BMI-Z slope than normal HbA1c (DID: -0.023/year [95% CI: -0.042 to -0.004]). When compared to age-matched unscreened subjects (n=2,087), screened subjects (n=2,815) experienced a greater decrease in BMI-Z slope after HbA1c than unscreened subjects at a matched age (DID: -0.031/y [95% CI -0.042 to -0.021]).

Conclusions: BMI-Z trajectory improved more among youth with prediabetes-range HbA1c but also stabilized in screened youth overall. Prospective studies are needed to identify provider- and patient-level drivers of this observation.

Introduction

Debate exists about the utility of screening for type 2 diabetes (T2D) in overweight or obese adolescents due to the low prevalence of undiagnosed T2D.[1,2] However, prediabetes, an intermediate state of glucose metabolism, occurs in approximately one-quarter of obese youth.[3] Although prediabetes in youth can be transient and related to insulin resistance of puberty,[4] it may also present an opportunity for T2D risk reduction. In adults, awareness of prediabetes status is associated with improvements in weight and glycemic status.[5,6] Therefore, we investigated whether prediabetes diagnosis by hemoglobin A1c (HbA1c) screening is associated with improved body mass index (BMI) trajectory in youth.

Methods

      This retrospective cohort study of data from the Children's Hospital of Philadelphia (CHOP) Primary Care Network (2000—2018) was approved by the CHOP Institutional Review Board. The cohort included non-diabetic (by International Classification of Disease-9/10 codes, *249.x, 250.x; E08.x-E.11x., E13.x*), youth who were overweight or obese (BMI Z-score (BMI-Z) ≥1.04) when 10-18 years old. "Screened" youth were those who underwent T2D screening via HbA1c between ages 10-18 years; if ≥ 1 HbA1c was available, only the first was considered. "Unscreened" youth were those without available HbA1c result while 10-18 years old. All screened subjects had ≥ 1 BMI before and after HbA1c. Unscreened obese youth were matched by age at start of follow up with screened youth and had ≥ 1 BMI before and after the matched age of the corresponding screened subject.

      To minimize confounding of the relationship between BMI and hyperglycemia, subjects were excluded if they were prescribed antipsychotics, frequent systemic glucocorticoids (>4 courses), or growth hormone, or had a transplant of any type or cystic fibrosis. Follow-up was from first to last BMI measurement or age 19 years. Among screened subjects, two groups were defined by HbA1c: prediabetes (5.7-6.4%, 39-46 mmol/mol) and normal (<5.7%, <39 mmol/mol). Subjects with HbA1c ≥6.5% (≥48

mmol/mol) were excluded to reduce confounding due to hyperglycemia-related weight loss.

Prior to analysis, anthropometric measurements identified as likely errors were excluded using an automated method.[7-9] The primary outcome was change in age- and sex-adjusted BMI Z-score[10] (BMI-Z) trajectory after HbA1c. To account for skewness, BMI-Z $\geq$1.96 were replaced with a modified standard deviation score.[11]

Time series analysis was used to determine the impact of: 1) HbA1c result (normal versus prediabetes among the screened group), and 2) the act of screening (screened versus unscreened) on BMI-Z trajectory. Plots of unadjusted mean BMI-Z per year were generated to depict trends by group. To account for intra-subject correlation, generalized estimating equations with autoregressive correlation structure and identity link were used, with BMI-Z as the dependent variable. Independent variables included time before or after HbA1c, indicator variable for pre/post-A1c, and HbA1c group (prediabetes versus normal) or screened versus unscreened. The outcome of interest, difference in difference (DID) in BMI-Z slope between groups before and after screening or matched age, was determined using an interaction term between time, pre/post-screening, and group.[12] The model adjusted for BMI-Z at HbA1c, age at HbA1c, sex, race (Caucasian, African American, Asian, multiple races, other), ethnicity (Hispanic, Non-Hispanic), and insurance type (private, public).

Two sensitivity analyses were conducted. First, BMI, BMI-Z without adjustment for extreme values, weight, and height (falsification test: height trajectory would not be modifiable) were used as dependent variables in separate models. Second, we repeated analyses using "normal" and "high" HbA1c of < or $\geq$ 6.0% (42 mmol/mol), based on clinical recommendations at our institution to consider referral to Endocrinology at that threshold, as well as the higher likelihood of persistent or progressive dysglycemia above that threshold in adolescents.[4]

Analyses were conducted using Stata 14 (Stata Corporation, TX). Descriptive analyses included means and standard deviations of continuous variables and distributions of categorical variables. Differences of means were assessed using Student's *t*-test. Group differences in categorical variables were assessed using Pearson's chi-squared test. Two-sided hypothesis tests were used; p<0.05 was considered statistically significant.

Results

After exclusion of 18 subjects with diabetes-range HbA1c, the screened cohort included 4,184 (n=2,327, 55.6% female) adolescents followed for a median of 9.7 years (IQR 8.0-10.7), contributing 38,694 BMIs, with a median follow-up of 2.3 (IQR 1.4-3.0) years after HbA1c measurement. 637 (15.2%) had prediabetes-range HbA1c (mean (SD) 5.9% (0.1%), 41 (1) mmol/mol). Mean age at testing was slightly higher among

those with normal HbA1c (13.2 [95% CI 13.1-13.3] versus 12.9 [95% CI 12.8-13.1] years). Weight, BMI, and BMI Z-score were higher among the prediabetes group at testing (all p<0.005). Gender distribution was not different (p=0.2). The prediabetes group had more African American youth (64% versus 42%, p<0.0001).

BMI-Z was similar at start of follow-up (p=0.5), gradually diverged, then plateaued (normal HbA1c) or decreased (prediabetes) after HbA1c (**Figure 1a**). In time series analysis, BMI-Z increase was significantly greater among the prediabetes group than the normal HbA1c group prior to screening (0.061/y [95% CI 0.049-0.073] versus 0.036/y [95% CI 0.030-0.042]). Post-HbA1c, both had significantly decreased slopes (prediabetes: 0.011/y [95% CI -0.006-0.029] versus normal: 0.009/y [95% CI 0.002-0.017]), but the improvement was greater in the prediabetes group: pre/post difference of -0.050/y (prediabetes) versus -0.027 (normal), DID = -0.023/y (95% CI: -0.042 to -0.004).

To assess the impact of screening regardless of result, 2,815 screened subjects were age-matched with 2,087 unscreened obese subjects. Screened subjects were more often female (55.3% versus 41.7%, p<0.001) and African American (46.3% versus 30.6%, p<0.001). Screened subjects had a plateau in BMI-Z after screening, while unscreened did not after matched age (**Figure 1b)**. Adjusting for BMI-Z at HbA1c (or matched age), sex, age, race, ethnicity, and insurance type, BMI-Z slope decreased more in the screened than the unscreened group (DID: -0.031/y [95% CI -0.042 to -0.021]).

Sensitivity analyses. Among the screened cohort, a greater improvement in slope in the prediabetes group was again found for BMI and unmodified BMI-Z, but not for weight or height (BMI DID: -0.13/y [95% CI -0.23 to -0.03]; unmodified BMI-Z DID: -0.013/y [95% CI -0.025 to -0.001]). The differential reduction in BMI-Z slope was even greater when a higher HbA1c threshold to define "abnormal" was used: DID = -0.049/y (95% CI -0.082 to -0.015).

Discussion

To our knowledge, this is the first study to report an improved BMI trajectory after prediabetes identification in overweight and obese youth. In addition, our demonstration of greater slowing of BMI-Z gain after screening versus no screening suggests that the act of screening may have value even if results are normal. Our study has several strengths, including the large, diverse cohort of adolescents screened by HbA1c, a median follow-up of nearly a decade, and use of a robust algorithm to identify implausible growth data.

One possible explanation for the greater improvement in BMI trajectory after prediabetes diagnosis is intrinsic motivation due to perceived risk.[13] Alternatively, differences in counseling by pediatricians may be operative. If elucidated, the factors responsible for this differential improvement could be harnessed to increase the utility of identifying prediabetes in adolescents. The differential improvement among screened

versus unscreened patients may reflect actions taken by pediatrician at the time of screening. This should be further explored to determine whether the act of ordering screening, beyond any associated counseling, is necessary to achieve the observed improvement in BMI trajectory.

We acknowledge limitations, including the inability to determine how prediabetes diagnosis was conveyed or patients counseled. We were unable to assess 1) patient-level factors influencing completion of ordered screening tests, or 2) provider-level factors related to screening some obese adolescents but not others, but we suspect additional risk factors, such as higher-risk race/ethnicity, informed some decision-making.[14] In addition, our findings are limited to prediabetes defined by HbA1c, which is 0.3-0.4% higher in African American compared to White non-diabetic adults even after adjustment for age and adiposity and does not have 100% concordance with fasting glucose and oral glucose tolerance tests.[15,16] Nonetheless, HbA1c is widely used for diabetes screening in pediatric practice.[17] Finally, the possible concurrent identification of other obesity- or family-related health risks was not investigated in this study. However, a previous study using data from the same primary care network found that routine lipid screening was not associated with altered BMI trajectory in overweight and obese youth.[18]

Whether results from T2D screening in overweight and obese adolescents can be leveraged to promote BMI improvement is unknown, but our findings suggest that HbA1c-based screening may be useful beyond its intended goal of T2D identification.

References

1. Wu EL, Kazzi NG, Lee JM. Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia. *JAMA Pediatr.* 2013;167(1):32-39.
2. Zeitler P, Arslanian S, Fu J, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth. *Pediatr Diabetes.* 2018;19 Suppl 27:28-46.
3. Andes LJ, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of Prediabetes Among Adolescents and Young Adults in the United States, 2005-2016. *JAMA Pediatr.* 2019:e194498.
4. Love-Osborne KA, Sheeder JL, Nadeau KJ, Zeitler P. Longitudinal follow up of dysglycemia in overweight and obese pediatric patients. *Pediatr Diabetes.* 2017.
5. Gopalan A, Lorincz IS, Wirtalla C, Marcus SC, Long JA. Awareness of Prediabetes and Engagement in Diabetes Risk-Reducing Behaviors. *Am J Prev Med.* 2015;49(4):512-519.

6. Owei I, Umekwe N, Ceesay F, Dagogo-Jack S. Awareness of Prediabetes Status and Subsequent Health Behavior, Body Weight, and Blood Glucose Levels. *J Am Board Fam Med.* 2019;32(1):20-27.

7. Gerber JS, Bryan M, Ross RK, et al. Antibiotic Exposure During the First 6 Months of Life and Weight Gain During Childhood. *JAMA.* 2016;315(12):1258-1265.

8. Daymont C, Neal A, Prosnitz A, Cohen MS. Growth in Children With Congenital Heart Disease. *Pediatrics.* 2012;131(1):e236-e242.

9. Daymont C, Ross ME, Russell Localio A, Fiks AG, Wasserman RC, Grundmeier RW. Automated identification of implausible values in growth data from pediatric electronic health records. *J Am Med Inform Assoc.* 2017;24(6):1080-1087.

10. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11.* 2002(246):1-190.

11. Prevention. NCfCDPaHP-CfDCa. Cut-Offs to Define Outliers in the 2000 CDC Growth Charts. 2014; http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/BIV-cutoffs.pdf. Accessed March 30, 2019.

12. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ.* 2015;350:h2750.

13. Rosenstock I, Stretcher V, Becker M. Social Learning Theory and the Health Belief Model. *Health Education Quarterly.* 1988;15(2):175-183.

14. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S13-S28.

15. Vajravelu ME, Lee JM. Identifying Prediabetes and Type 2 Diabetes in Asymptomatic Youth: Should HbA1c Be Used as a Diagnostic Approach? *Curr Diab Rep.* 2018;18(7):43.

16. Herman WH, Dungan KM, Wolffenbuttel BH, et al. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2009;94(5):1689-1694.

17. Lee JM, Eason A, Nelson C, Kazzi NG, Cowan AE, Tarini BA. Screening practices for identifying type 2 diabetes in adolescents. *J Adolesc Health.* 2014;54(2):139-143.

18. Gregory EF, Miller JM, Wasserman RC, Seshadri R, Rubin DM, Fiks AG. Routine Cholesterol Tests and Subsequent Change in BMI Among Overweight and Obese Children. *Acad Pediatr.* 2019;19(7):773-779.

Figure legend

Figure 1. Mean BMI Z-score by year before and after initial HbA1c. Vertical line at '0' indicates screening HbA1c. Line and grey bands represent linear regression line fit and associated 95% confidence intervals. **A)** Full screened cohort, **B)** Age-matched screened and unscreened cohort.

BMI–Z Pre/Post Screening, by A1c Result

BMI–Z Pre/Post Screening or Matched Date
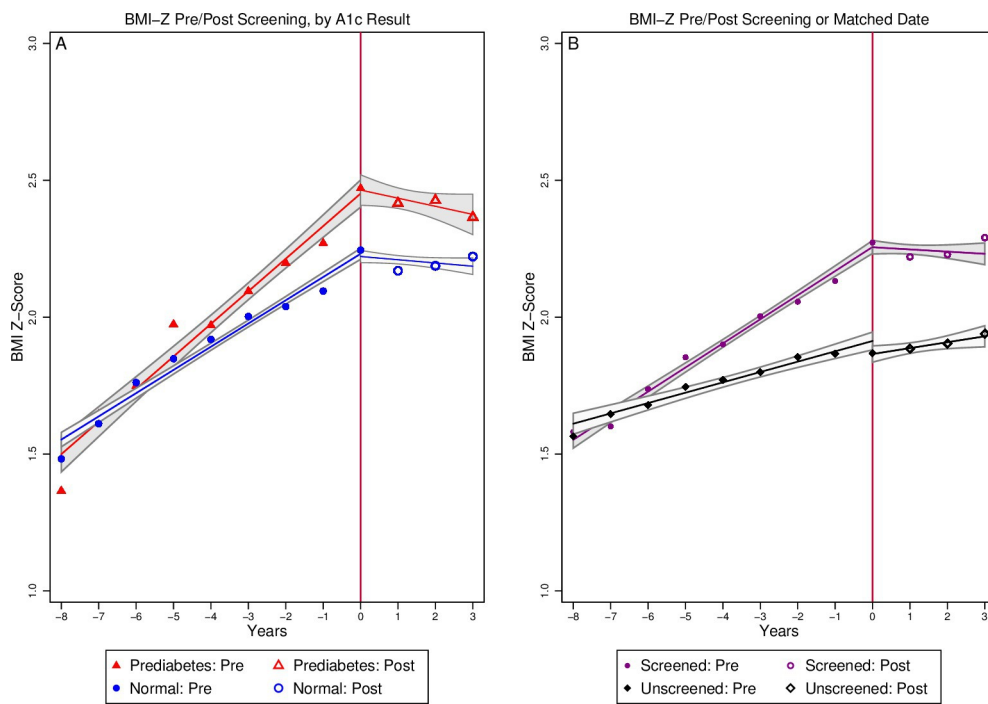
pedi_13028_figure1_a1c_screening.eps