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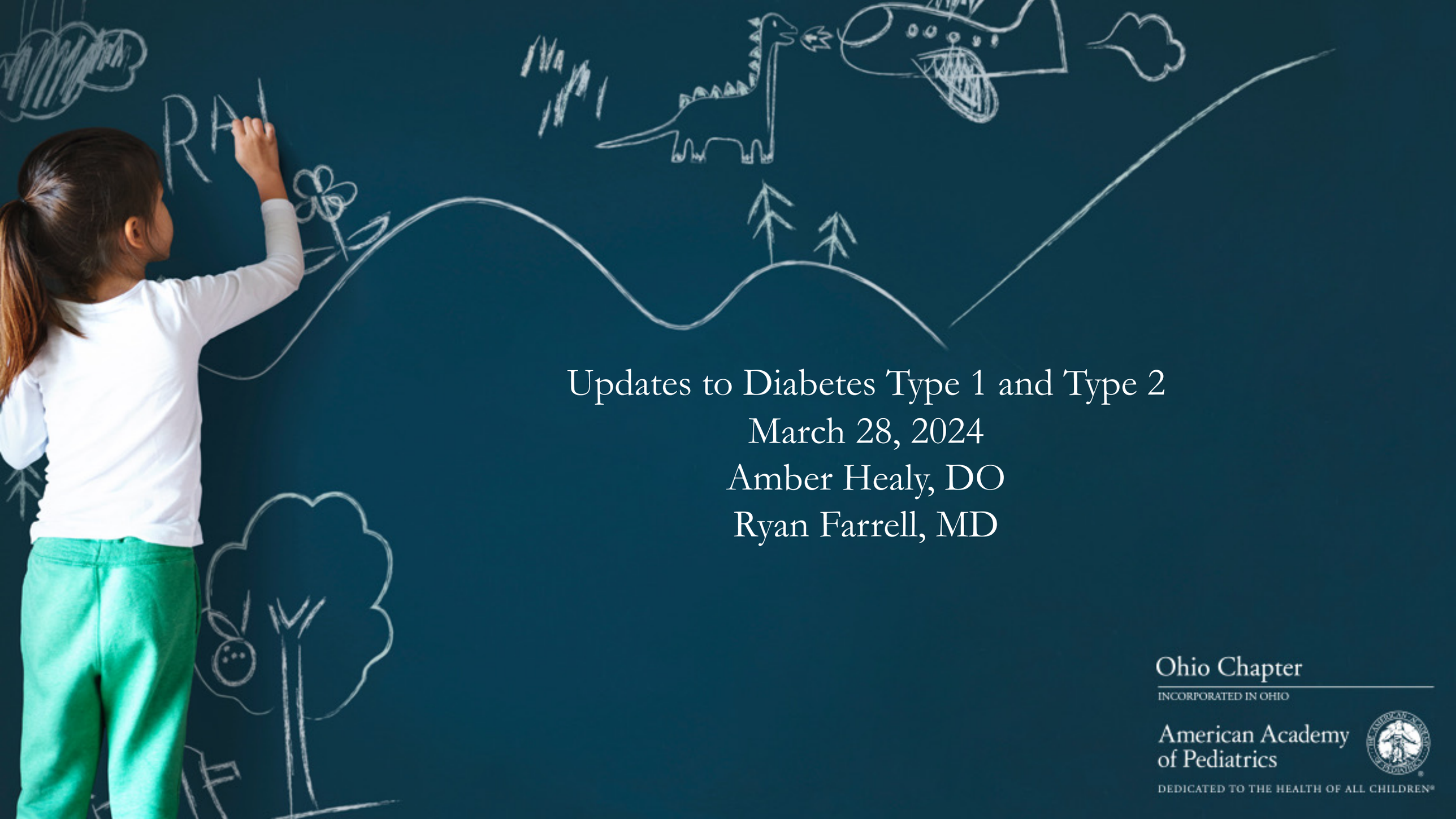

Updates to Diabetes Type 1 and Type 2

March 28, 2024

Amber Healy, DO
Ryan Farrell, MD

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DEI Disclosure

I have considered the Ohio AAP Diversity, Equity, and Inclusion standards in preparing this presentation. I invite your feedback in promoting equity within this learning space. If you have suggestions, please email me at bolling.cf@gmail.com

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CME Disclosure

Ryan Farrell, MD faculty of this educational activity, have no relevant financial relationship(s) with ineligible companies to disclose.

Amber Healy, D.O., faculty of this educational event, has the following relationship to disclose, served on advisory panel for Provention Bio.

All of the relevant financial relationships listed for these individuals have been mitigated

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Objectives

1) Describe when screening for Type 1 and Type 2 diabetes is indicated in practice.

2) List two actionable steps that can help prevent the progression of Type 2 diabetes.

3) Refer patients to endocrinology when screening suggests further evaluation and management is medically indicated.

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Type 1 Diabetes

- Brief Review:
  - Estimated to be 10% of people with diabetes
  - Relative or absolute insulin deficiency
  - Autoimmune mediated beta cell destruction
  - Some genetic component but most cases are de novo
  - Can occur at any age but has been more common in children
    - Ages 5-9 and 10-14 are where peak incidence occurs

Giwa AM et al. World J Diabetes. 2020.

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How to Screen for Type 1 Diabetes

- Checking auto-antibodies
- Guidelines recommend
  - Glutamic acid decarboxylase antibody 65 (GAD-65)
  - Zinc transporter8 antibody
  - Islet cell tyrosine phosphatase 2 autoantibody (IA-2, IA-2A)
- In clinical practice many people also check
  - Insulin autoantibody

Holt RG et al. Diabetalogia. 2021.

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How to Screen (cont.)

- Once 2 positive antibodies are identified consider yearly oral glucose tolerance tests to look for dysglycemia
- C-peptide can also be ordered part of lab work
  - Determines amount of insulin still being produced
- Antibodies presents in 80% of children by age 3

Sims et al. Sci Trans. 2021
Holt et al. Diabetologia. 2021

Staging of Type 1 Diabetes

Stage 1	Stage 2	Stage 3	Stage 4
• Normal BG • ≥ 2 autoantibodies • Presymptomatic • T1D risk 44% in 5 years	• Dysglycemia[1] • ≥ 2 autoantibodies • Presymptomatic • T1D risk 75% in 5 years	• Clinical Diagnosis • Hyperglycemia • Symptomatic	• Continued beta cell decrease • Overt T1D

1. Impaired glucose tolerance
2. Impaired fasting glucose

Sims et al. Sci Transl Med. 2021
El Sayed et al. Diabetes Care 2023

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When to Screen for Type 1 Diabetes

- Multiple studies support screening children who have relatives with type 1 diabetes
- There is also some evidence to support screening individuals with personal or family history of other autoimmune conditions or allergic diseases
- Universal screening is not widely recommended

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Why to Screen for Type 1 Diabetes

- To help families prepare
- To counsel patients and families on diabetes symptoms
- To prevent diagnosis occurring as DKA
- To consider new medication options for prevention

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Diagnostic Codes (ICD10)

- **E10.1-E10.9** Diagnosis for type 1 diabetes
- **Z13.1** Encounter for screening for diabetes mellitus
- **Z13.9** Encounter for screening unspecified
- **Z83.3** Family history of diabetes mellitus
- **Z83.49** Family history of other endocrine, nutritional, and metabolic disease
- **E34.9** Endocrine disorder unspecified

Adapted from Patient Education Material from Provention Bio

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Resources for Patients

- Trialnet.org
- Askhealth.org
- Cascadekids.org
- T1Detect: https://www.jdrf.org/t1d-resources/t1detect/
  - At Home Biosciences test kit
- Commercial Labs
  - LabCorp
  - Quest diagnostics

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Prevention Consideration

- Outside of prevention diagnosis as hospitalization and DKA
- Prevention of onset from stage 2 type 1 diabetes
- Teplizumab
  - Indicated for stage 2 type 1 diabetes
  - T cell modulation
  - Prevention of progression to stage 3 type 1 diabetes
    - Trial showed median of 2 years of preventing progression in treatment compared to control group
      - 24 months to diagnosis in control group compared to 48 months in treatment group
    - 43% in treatment group progressed to stage 3, while 72% in control group progressed to stage 3

Teplizumab

- Monoclonal antibody
- CD3 directed on T-cells
- Indicated for ages 8 and up
- 14- day infusion, 30 minutes per day
- Common side effects
  - Leukopenia
    - lymphopenia
  - Rash
  - Headache

Tzieldhcp.com. Retrieved March 1, 2024

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References

- Giwa AM, Ahmed R, Omidian Z, Majety N, Karakus KE, Omer SM, Donner T, Hamad ARA. Current understandings of the pathogenesis of type 1 diabetes: Genetics to environment. World J Diabetes. 2020 Jan 15;11(1):13-25. doi: 10.4239/wjd.v11.i1.13
- Holt, R.I.G., DeVries, J.H., Hess-Fischl, A. *et al.* The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* **64**, 2609–2652 (2021)
- Sims EK, Bundy BN, Stier K, Serti E, Lim N, Long SA, Geyer SM, Moran A, Greenbaum CJ, Evans-Molina C, Herold KC; Type 1 Diabetes TrialNet Study Group. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med. 2021 Mar 3;13(583):eabc8980. doi: 10.1126/scitranslmed.abc8980.
- American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S20–S42. https://doi.org/10.2337/dc24-S002
- Tzield. Provention Bio. https://www.tzieldhcp.com/?utm_source=google&utm_medium=cpc&utm_campaign=Tzield-DTC_GGL_BRND_Core_CNV_SEA_ALLM_US_EN+KW+-+EN+BR_ALL&utm_term=tzield&gad_source=1&gclid=EAIaIQobChMIh8qauqjYhAMVcmlHAR2gTw2sEAAYASABEgISt_D_BwE&gclsrc=aw.ds. Retrieved March 1, 2024.

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Youth-Onset Type 2 Diabetes (YT2D)

Controversies on Definitions, Screening, Prevention; a Call for More Data

Ryan Farrell, MD
Division of Pediatric Endocrinology
University Hospitals Rainbow Babies and Children's Hospital

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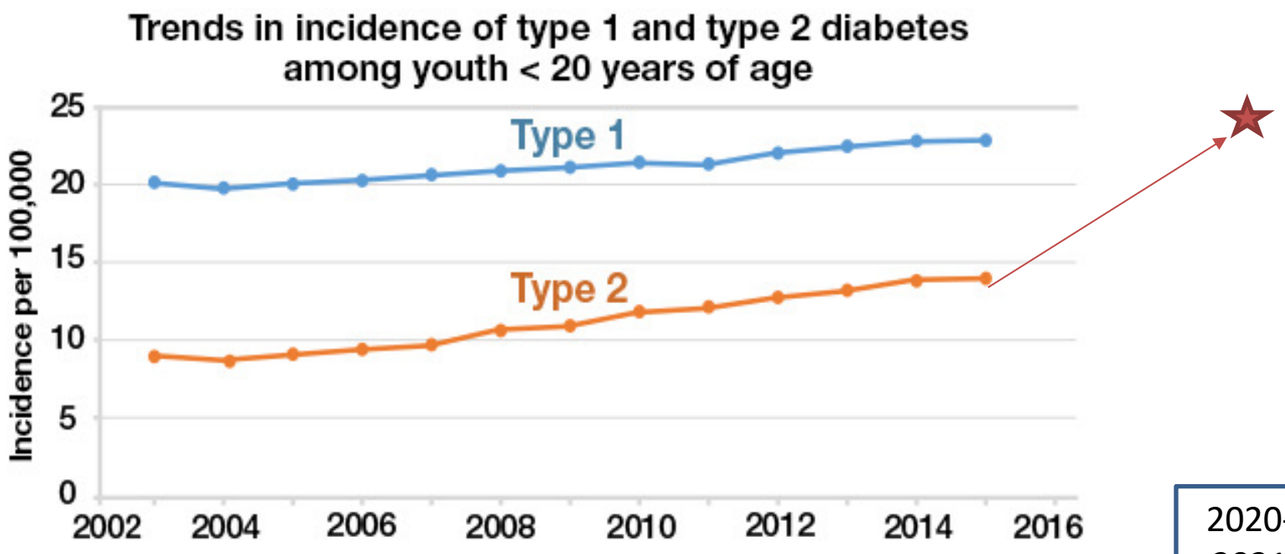
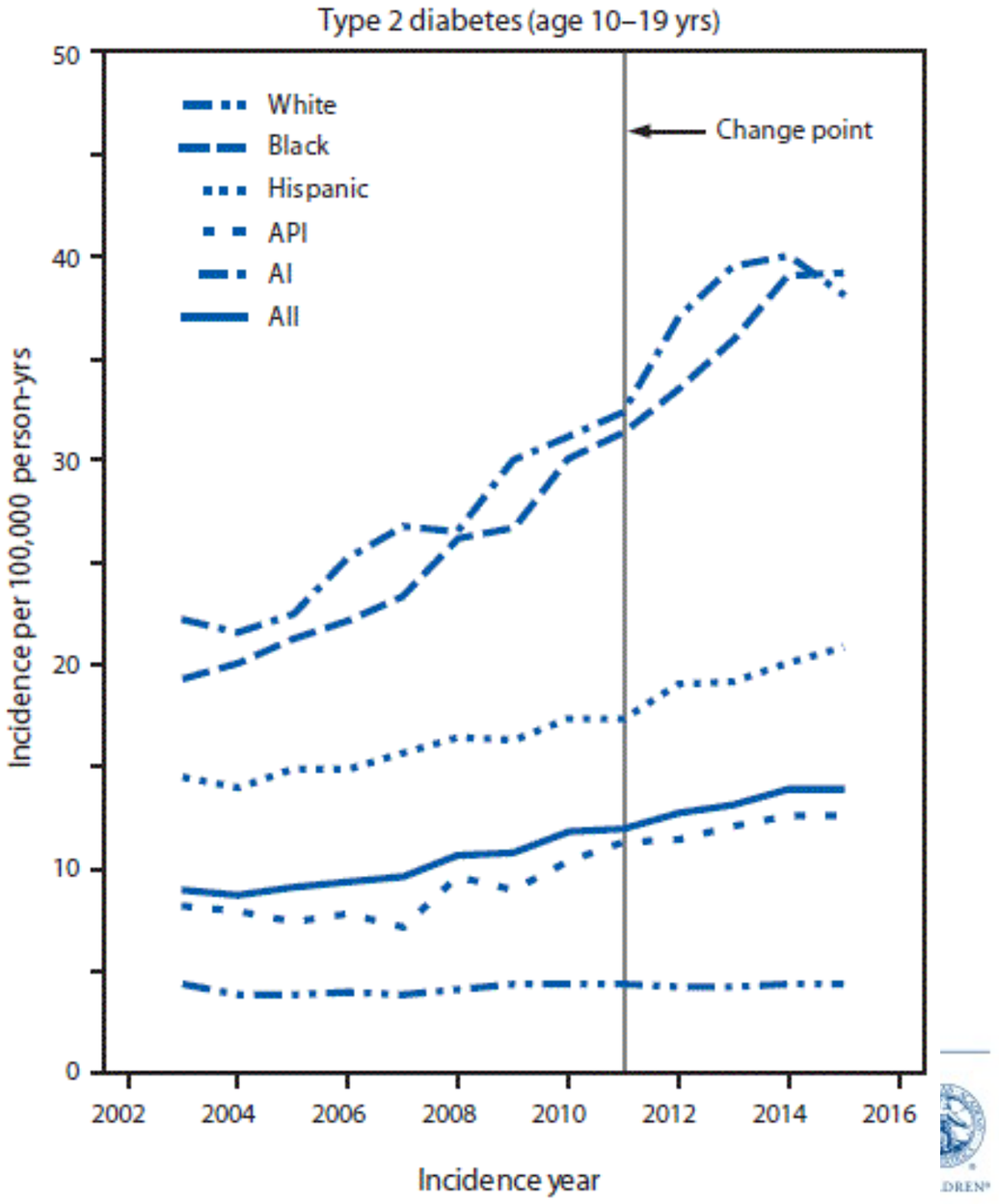
Youth-Onset Type 2 Diabetes Epidemiology

- The prevalence of YT2D has doubled between the years of 2001-2017, though it remains comparatively low (0.67 per 1000 people)
  - Rates have increased since 2020 (see ensuing slides)
- The increase in prevalence is not uniform and has more significantly impacted adolescents with a self-identified racial minority background
- Prepubertal children and/or children <10 years have substantially lower prevalence compared to older, pubertal adolescents
  - Seemingly no real increases in prevalence longitudinally



2020-2021

- 2002-2015: YT2D increased at 4.8% annually vs. 1.9% annually for T1D
  - Steepest rates of rise in minority populations
  - Non-Hispanic White adolescents stable over time
- 2020-2021: 62% increase from 2016-2019 (single health system data)



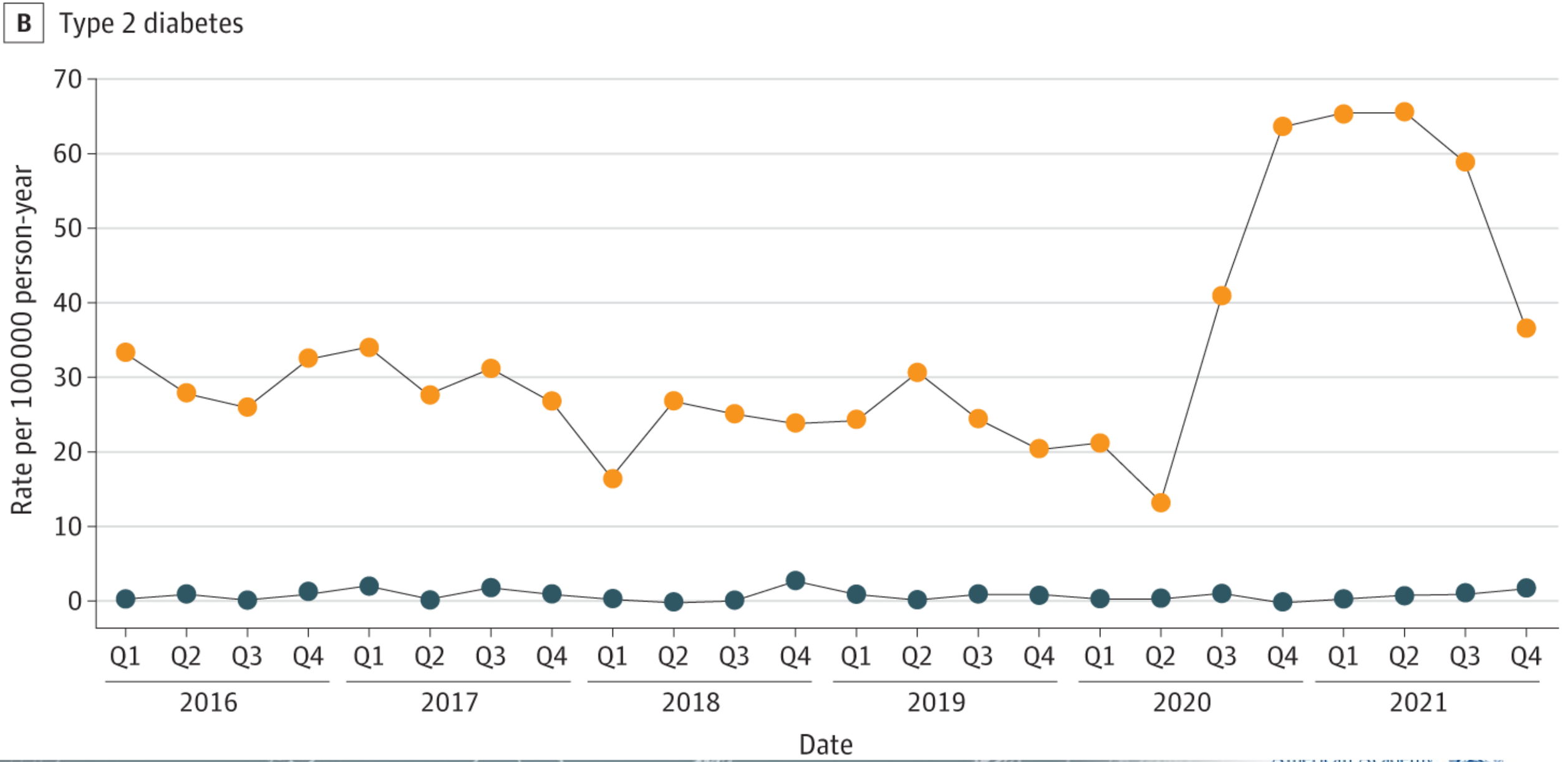


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Table 2. Adjusted IRRs and IRDs Comparing Diabetes Incidence in 2020-2021 to 2016-2019, by Diabetes Type, Age, Sex, and Race and Ethnicity

Characteristic	Rate per 100 000 PY		IRR (95% CI)	IRD (95% CI)
	2016-2019	2020-2021		
Type 1 diabetes				
Overall	18.09	21.13	1.17 (1.04 to 1.31)	3.03 (0.67 to 5.40)
Age group, y				
0-9	14.67	17.01	1.16 (0.96 to 1.40)	2.34 (−0.78 to 5.47)
10-19	20.93	24.47	1.17 (1.01 to 1.36)	3.54 (0.08 to 7.00)
Sex				
Female	17.67	20.29	1.15 (0.97 to 1.36)	2.61 (−0.70 to 5.93)
Male	18.51	21.84	1.18 (1.00 to 1.39)	3.33 (−0.04 to 6.69)
Race and ethnicity				
Asian and Pacific Islander, Non-Hispanic	8.00	12.82	1.60 (0.96 to 2.66)	4.82 (−0.75 to 10.39)
Black, Non-Hispanic	27.18	34.90	1.28 (0.91 to 1.80)	7.72 (−3.27 to 18.71)
Hispanic	15.39	18.55	1.21 (1.01 to 1.44)	3.17 (0.02 to 6.31)
White, Non-Hispanic	27.31	29.78	1.09 (0.90 to 1.33)	2.47 (−3.25 to 8.19)
Other[a]	8.83	9.93	1.13 (0.62 to 2.03)	1.10 (−4.53 to 6.74)
Type 2 diabetes				
Overall	14.56	23.53	1.62 (1.43 to 1.82)	8.96 (6.57 to 11.36)
Age group, y				
0-9	0.69	0.49	0.72 (0.26 to 2.03)	−0.19 (−0.77 to 0.39)
10-19	26.26	42.77	1.63 (1.44 to 1.84)	16.51 (12.12 to 20.89)
Sex				
Female	16.48	23.67	1.44 (1.22 to 1.69)	7.18 (3.71 to 10.66)
Male	12.73	23.26	1.83 (1.54 to 2.17)	10.53 (7.23 to 13.82)
Race and ethnicity				
Asian and Pacific Islander, Non-Hispanic	13.36	19.10	1.43 (0.95 to 2.15)	5.74 (−1.18 to 12.66)
Black, Non-Hispanic	24.02	46.79	1.95 (1.41 to 2.68)	22.77 (10.63 to 34.91)
Hispanic	19.31	31.08	1.61 (1.39 to 1.86)	11.77 (7.84 to 15.69)
White, Non-Hispanic	4.90	6.15	1.26 (0.81 to 1.95)	1.25 (−1.29 to 3.80)
Other[a]	5.36	15.89	2.96 (1.60 to 5.49)	10.52 (4.25 to 16.79)

- IRD: incidence rate difference;
- IRR: incidence rate ratio

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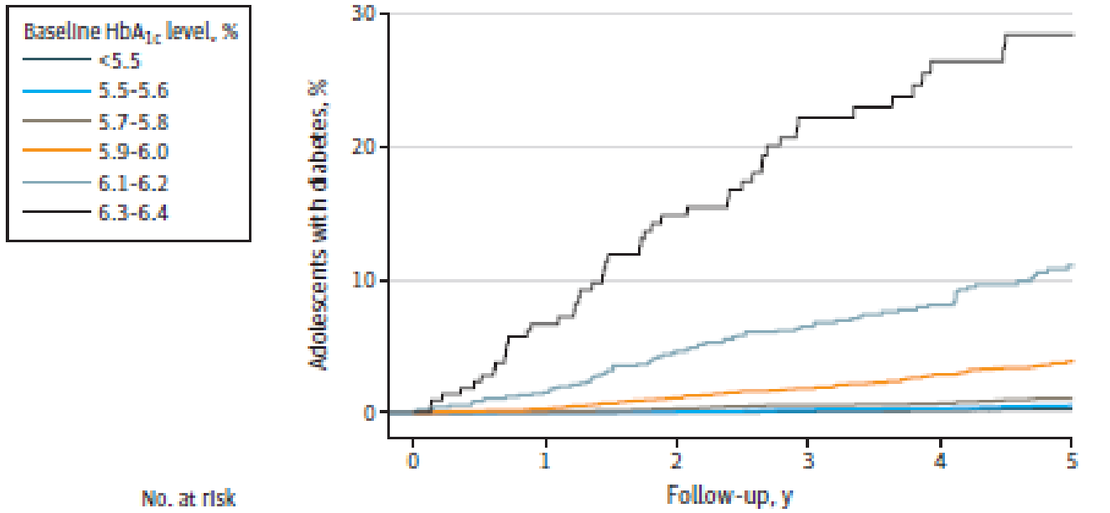
Prediabetes as a Risk Factor for YT2D

- Between 2005-2016, 1 in 5 teens had prediabetes
  - Rates of progression to YT2D are variable with surprisingly high rates of remission
- Screening children even at high risk is relatively low yield (<1% identification rate)
- Comparing prevalence of obesity vs. YT2D:
  - Obesity rates: ~20% of adolescents
  - YT2D 0.67 cases per 1000 adolescents
- Conversely, even among normal weight/BMI adolescents, upwards of 2.2% had elevated HbA1c as high as 6.2%

Increasing HbA1c levels in the prediabetes range are associated with YT2D

Figure. Cumulative Incidence of Type 2 Diabetes Over 5 Years of Follow-Up by Baseline Hemoglobin A_{1c} (HbA_{1c}) Level



No. at risk

Baseline HbA_{1c} level, %						
<5.5	36949	34193	24093	17879	13762	10866
5.5-5.6	20567	18998	15568	12691	9741	7297
5.7-5.8	11707	10876	9425	8009	6184	4626
5.9-6.0	4138	3804	3302	2848	2219	1607
6.1-6.2	970	878	750	641	487	360
6.3-6.4	221	189	138	104	80	59

Hoe FM, Darbinian JA, Greenspan LC, Lo JC. Hemoglobin A1c and Type 2 Diabetes Incidence Among Adolescents With Overweight and Obesity. *JAMA Netw Open*. 2024;7(1):e2351322. Published 2024 Jan 2. doi:10.1001/jamanetworkopen.2023.51322

2022 USPSTF Recommendations

- There is insufficient evidence to support screening asymptomatic children and adolescents for YT2D
  - Absence of data to demonstrate benefit or harm of screening
    - There are no studies that have demonstrated effective interventions to prevent the progression from prediabetes to YT2D
  - There is reason to question if adult reference ranges for diagnosis of prediabetes and diabetes can be applied to adolescents
    - Profoundly higher insulin resistance compared to adults, often mediated by puberty

Jonas DE, Vander Schaaf EB, Riley S, et al. Screening for prediabetes and type 2 diabetes in children and adolescents: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*.

American Diabetes Association (ADA) Screening Recommendations for YT2D

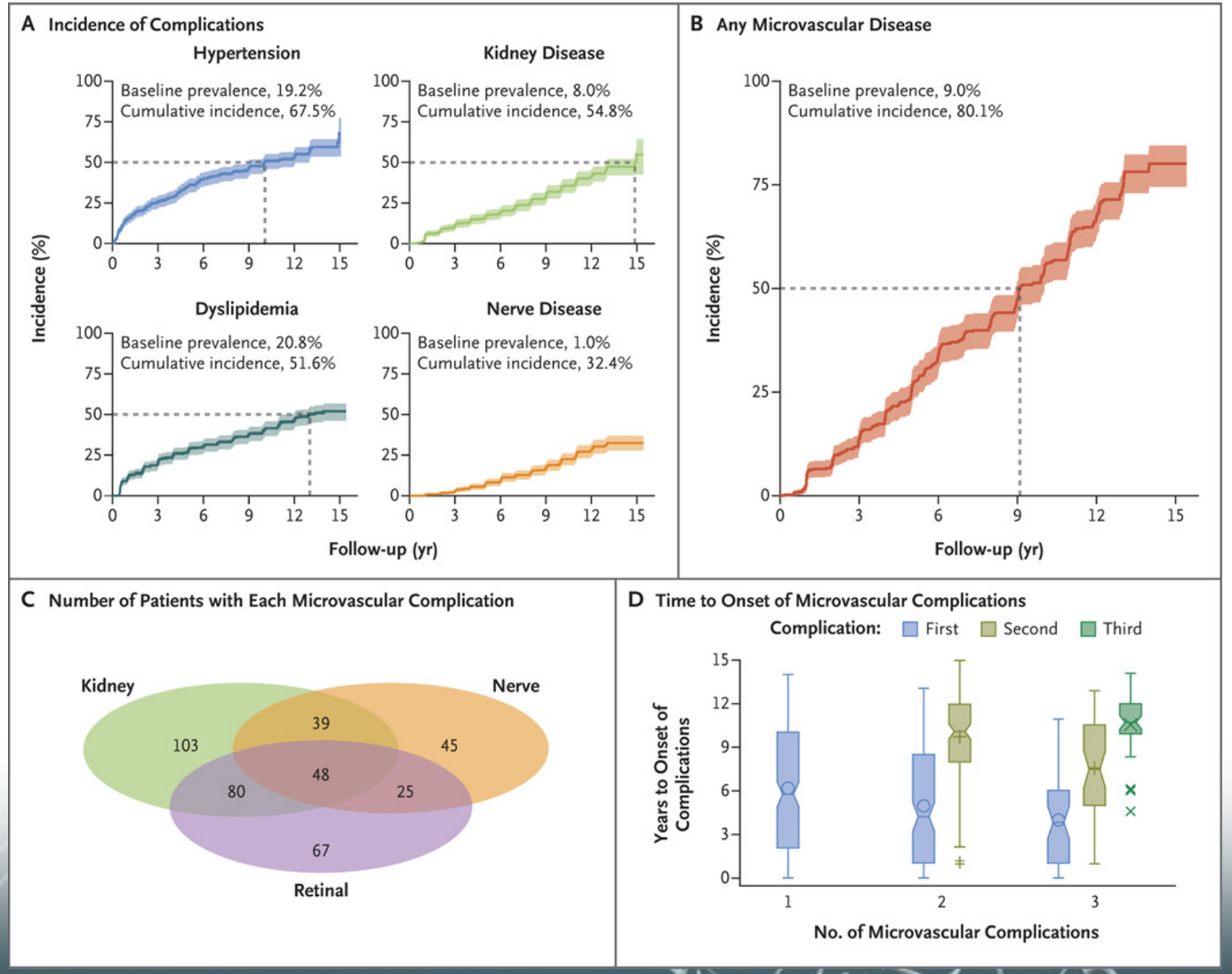
- Overweight or obese children (pubertal or at least age 10 years) with one additional risk factor:
  - Family history of T2D (first or second degree)
  - Minority race or ethnic group
  - Signs of insulin resistance
  - Small or large for gestational age
  - Maternal or gestational diabetes
- Repeat minimum every 3 years, sooner if BMI continues to rise
- Hemoglobin A1c vs. oral glucose tolerance test (1.75 g/kg max 75 g) vs. random glucose with symptoms

Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. *Diabetes Care*. 2018;41(12):2648-2668.

Importance of Screening

- Children with YT2D compared to adults:
  - More insulin resistant
  - Faster rates of beta cell failure (even with treatment with metformin and insulin)
  - Higher rates of diabetes complications
- Despite the more aggressive nature of YT2D, there are no prospective studies that have identified interventions that successfully prevent YT2D

YT2D is Associated with Rapid Progression of Diabetes Complications (TODAY Study)



TODAY Study Group, Bjornstad P, Drews KL, et al. Long-Term Complications in Youth-Onset Type 2 Diabetes. *N Engl J Med.* 2021;385(5):416-426. doi:10.1056/NEJMoa2100165

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Restoring Insulin Secretion (RISE) Consortium

- 91 children recruited:
  - Overweight/obese
  - Pubertal
  - 10-19 years old
  - Impaired glucose tolerance (60%) or YT2D <6 months
- Randomized to 2 treatment arms:
  - 12 months metformin
  - 3 months glargine + 9 months metformin
- Assessment of beta cell function (hyperglycemic clamp) at baseline, 12 months, and 15 months (3 months off treatment)

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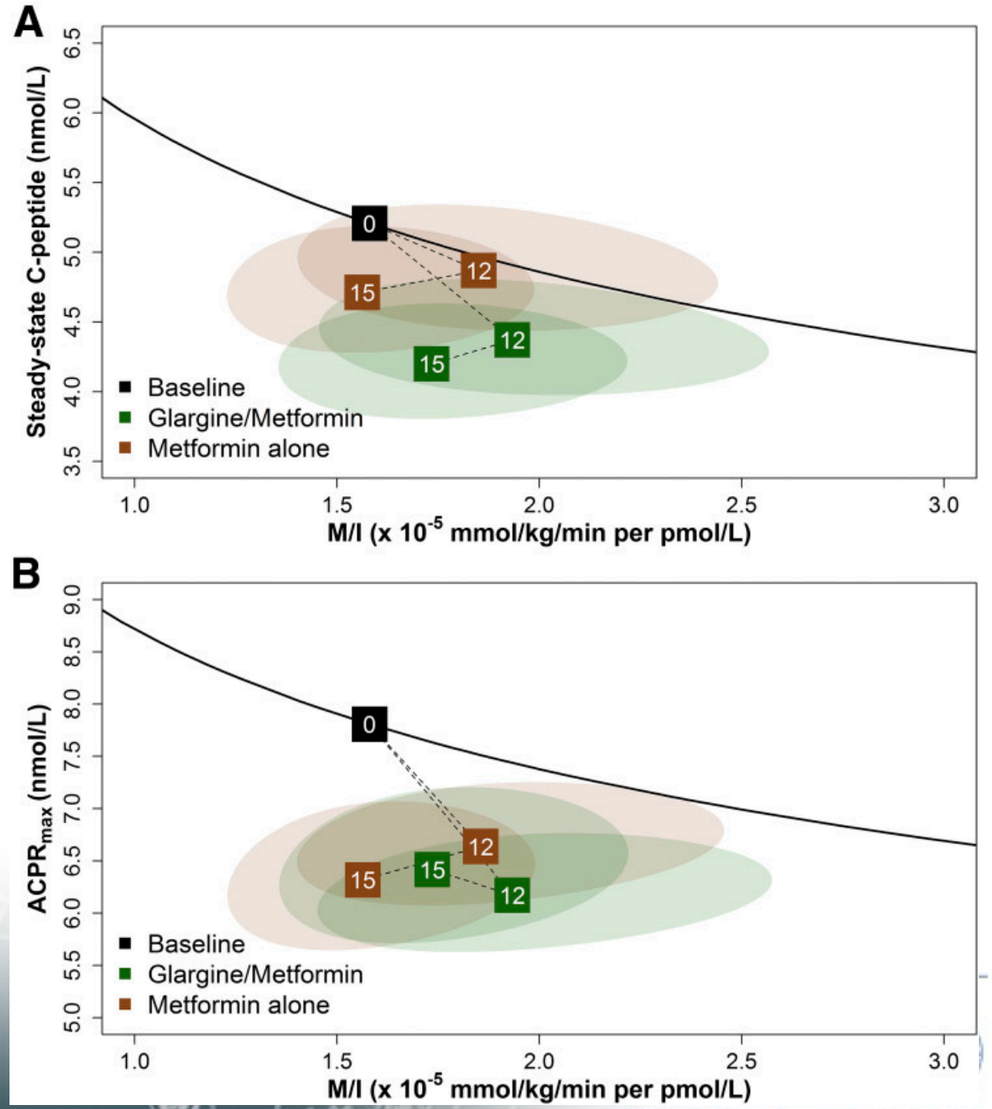
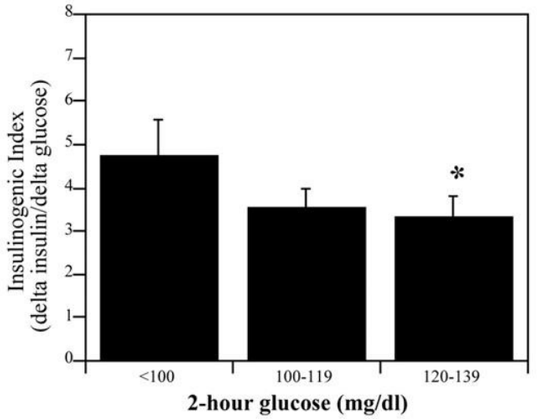
Restoring Insulin Secretion (RISE) Consortium

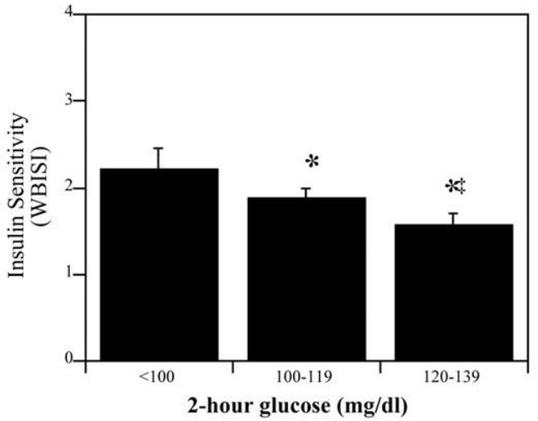
- Both treatment groups showed significantly lower markers of beta cell function at 12 and 15 months compared to baseline
- Youth in the study (compared to adults) had significantly lower insulin sensitivity
  - Beta cell demand is much higher in pubertal youth, which may explain the failure of recovery in beta cell function

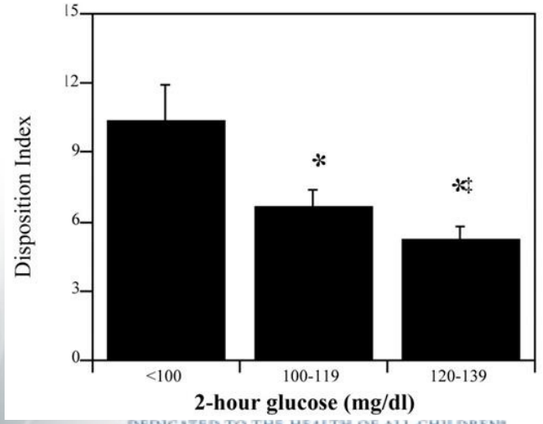


Defining Prediabetes and Intervention

- Obese youth with normal glucose tolerance on OGTT (2 hour glucose <140 mg/dl) have demonstrated impairments in beta cell function (disposition index) at 2h glucose levels of 120-139 > 100-120 mg/dl
  - Are adult OGTT reference ranges <u>appropriate</u> for children?
  - Should we be intervening with treatment in select pediatric populations even at levels of normoglycemia?







Catherine W. Yeckel, Sara E. Taksali, James Dziura, Ram Weiss, Tania S. Burgert, Robert S. Sherwin, William V. Tamborlane, Sonia Caprio, The Normal Glucose Tolerance Continuum in Obese Youth: Evidence for Impairment in β-Cell Function Independent of Insulin Resistance, *The Journal of Clinical Endocrinology & Metabolism*, Volume 90, Issue 2, 1 February 2005, Pages 747–754, https://doi.org/10.1210/jc.2004-1258

Importance of Screening and Early Intervention

- NIDDK has created a consortium to better clarify risk factors for YT2D, recruiting and following longitudinally
  - Goal for initiation of recruitment in 2024
- Since the completion of TODAY and RISE, new and effective therapies have been approved in pediatric age ranges to treat YT2D
  - Sodium-glucose cotransporter-2 (SGLT2) inhibitors (empagliflozin): approved down to age 10
  - Glucagon-like peptide 1 receptor agonists (GLP1a): approved down to age 10
    - Daily liraglutide
    - Weekly exenatide
    - Weekly dulaglutide
  - Metformin remains available with demonstrable benefits on glycemia, though 50% of those treated still require insulin within 3 years

June 14, 2012
N Engl J Med 2012; 366:2247-2256
DOI: 10.1056/NEJMoa1109333

Shah AS, Nadeau KJ, Kelsey MM. Broader Screening for Youth-Onset Type 2 Diabetes—We Just Are Not There Yet. *JAMA Netw Open.* 2022;5(9):e2220540. doi:10.1001/jamanetworkopen.2022.20540

Importance of Screening and Early Intervention

- These newer therapies have encouraging impacts on cardiovascular function and renal function in adults with type 2 diabetes
- Long-term impacts of these treatments on beta cell function and stress are not known in YT2D
- Addressing modifiable risk factors early (years before adolescence) are most likely to alter trajectory:
  - Excess energy intake, with specific emphasis on sugary drinks and highly processed carbohydrates
  - Low physical activity/sedentary lifestyle
  - Chronic stress, underlying mental health disorders
  - Sleep disorders
- Among those with YT2D, a 7% drop in weight was associated with improvements in A1c and other metabolic outcomes

Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. *Diabetes Care*. 2018;41(12):2648-2668.

Importance of Screening and Early Intervention

- The intensive nature of family-based lifestyle intervention programs is problematic for many families
- Informs recommendations by AAP to consider more aggressive use of anti-obesity medications (most of which are approved down to 12 years of age)
- Increasing consideration of adolescent metabolic bariatric surgery (MBS), with prospective data indicating that many outcomes are more durable and beneficial if performed before adulthood

Sarah E. Hampl, Sandra G. Hassink, Asheley C. Skinner, Sarah C. Armstrong, Sarah E. Barlow, Christopher F. Bolling, Kimberly C. Avila Edwards, Ihuoma Eneli, Robin Hamre, Madeline M. Joseph, Doug Lunsford, Eneida Mendonca, Marc P. Michalsky, Nazrat Mirza, Eduardo R. Ochoa, Mona Sharifi, Amanda E. Staiano, Ashley E. Weedn, Susan K. Flinn, Jeanne Lindros, Kymika Okechukwu; Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics* February 2023; 151 (2): e2022060640. 10.1542/peds.2022-060640

Inge TH, Courcoulas AP, Jenkins TM, et al; Teen–LABS Consortium. Five-year outcomes of gastric bypass in adolescents as compared with adults. *N Engl J Med.* 2019;380(22):2136-2145.

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Take Home Points

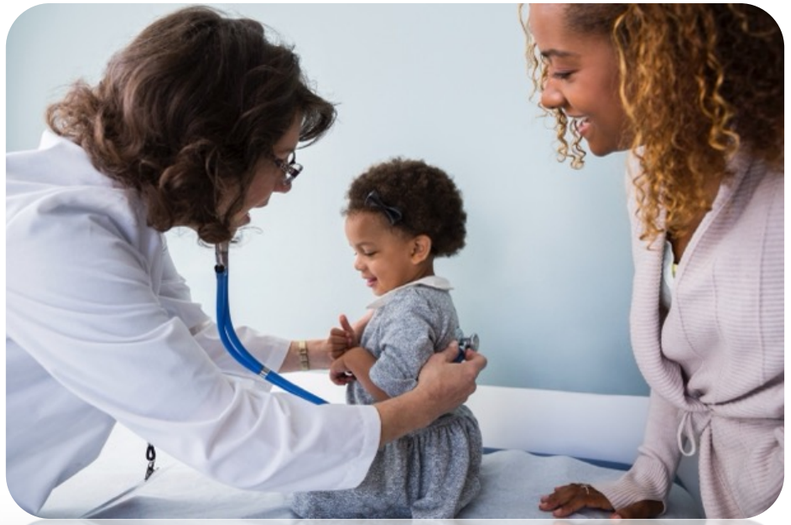
- To date, there are no studies that demonstrate effective therapies to prevent the progression from prediabetes in youth to YT2D
  - Newer therapies (GLP1a) have not been studied prospectively in children
    - Animal models have suggested increases in beta cell mass in response to GLP1a treatment
  - Screening of high risk groups in children continues to be low yield
- Defining prediabetes in youth and YT2D based on adult cutpoints may be problematic, and normoglycemia may need a more restrictive definition in children
- Puberty in the background of insulin resistance appears to result in beta cell stress, with insulin resistance exceeding that of what is seen in adults with T2D
  - YT2D is a considerably more aggressive disease with higher rates of complications compared to adults
- Interventions (lifestyle +/- pharmacotherapy) to address obesity and insulin resistance must begin in early years before adolescence, particularly in youth at risk for YT2D

Coming Soon!

Our final educational webinar for this series:

- **Anxiety in the "Tween" Aged Child (Thurs, May 15 @ Noon)**

Register Here:



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2024 Spring Meeting!

- Friday, April 19, 2024, at the Dublin Integrated Education Center

  (12:00 – 3:30)
- Topics Include:
  - Solutions for ADHD and Behavior Problems in the Young Child (4-6)
  - Helping You Make the Case: The Pediatricians Role in Lead Prevention, Working with Your System and Resources for Families

Register Here!

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PMP PARENTING at Mealtime & Playtime

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Next Training

Maximizing Micronutrients

Divya Denduluri, MS, RDN, LD, IBCLC and
Kylie Yike, MS, RDN, CSP, LD

April 24, 2024, from 12pm – 1pm

Learn about how to improve and
supplement a diet low in vitamin D,
iron, calcium, and more!

Lead Poisoning
PREVENTION RESOURCE

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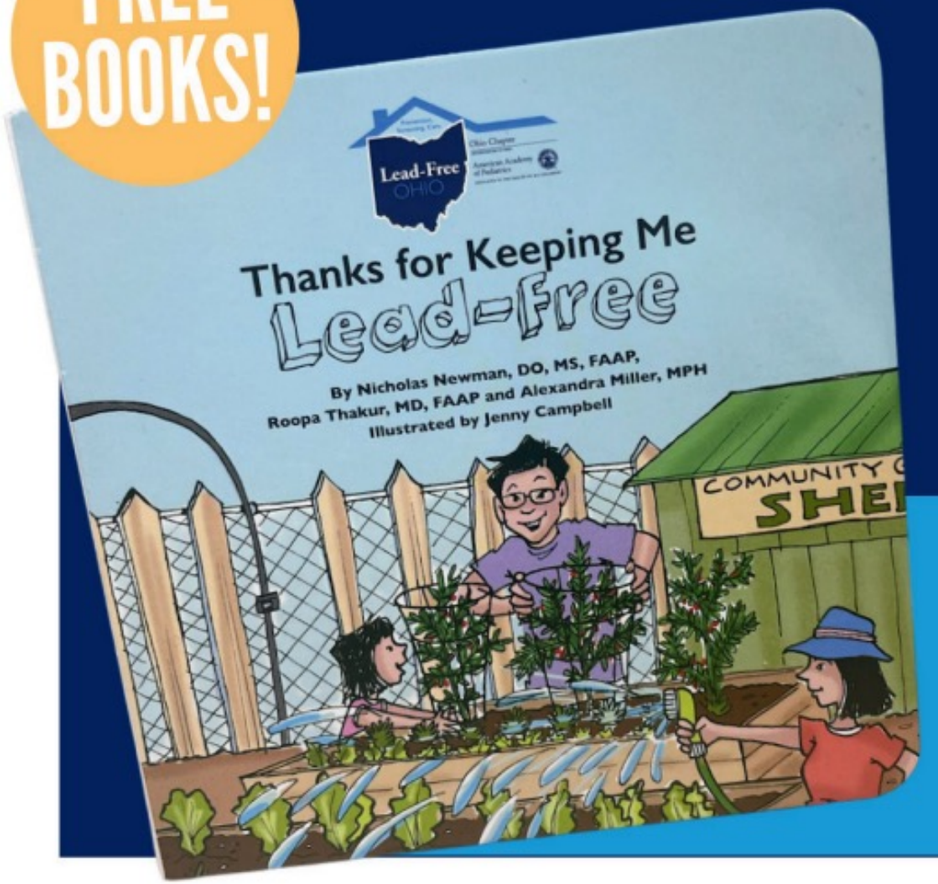

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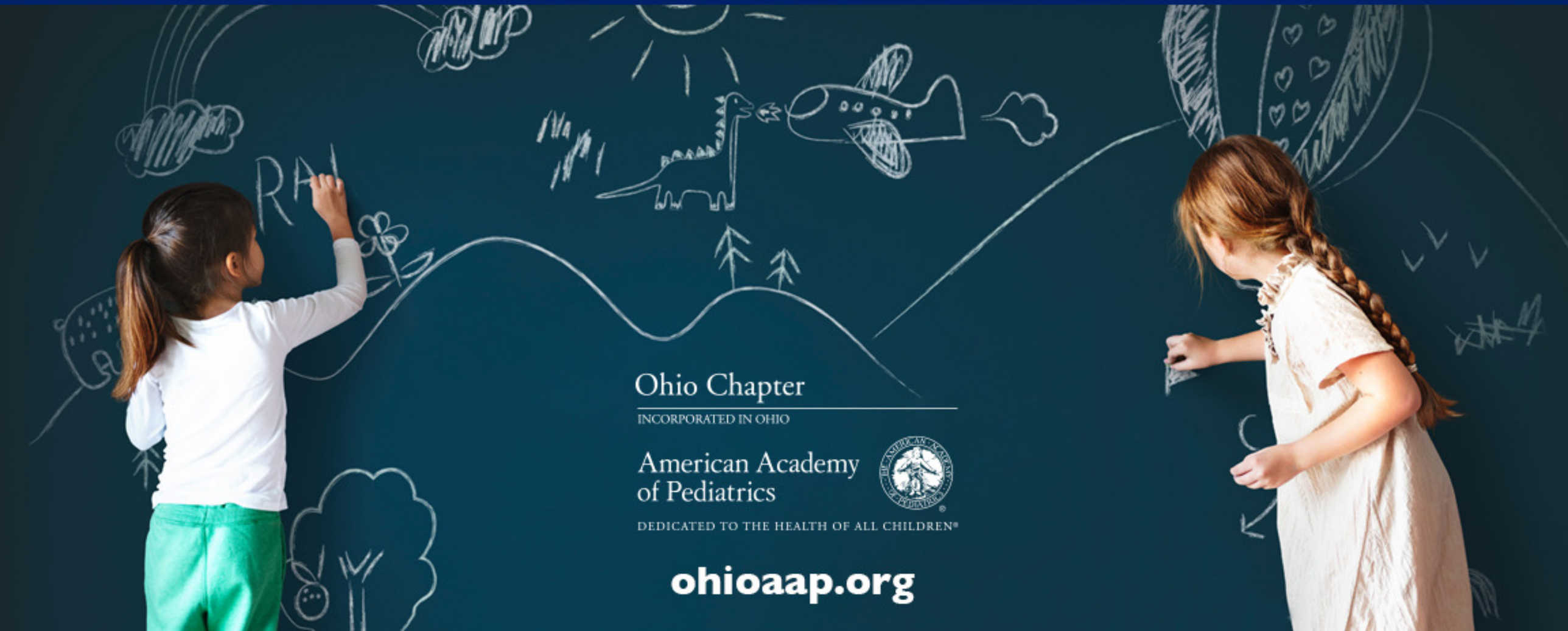
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