# *Type 2 Diabetes as Clinical Endpoint in Pediatric NASH*

## Liver Forum 10
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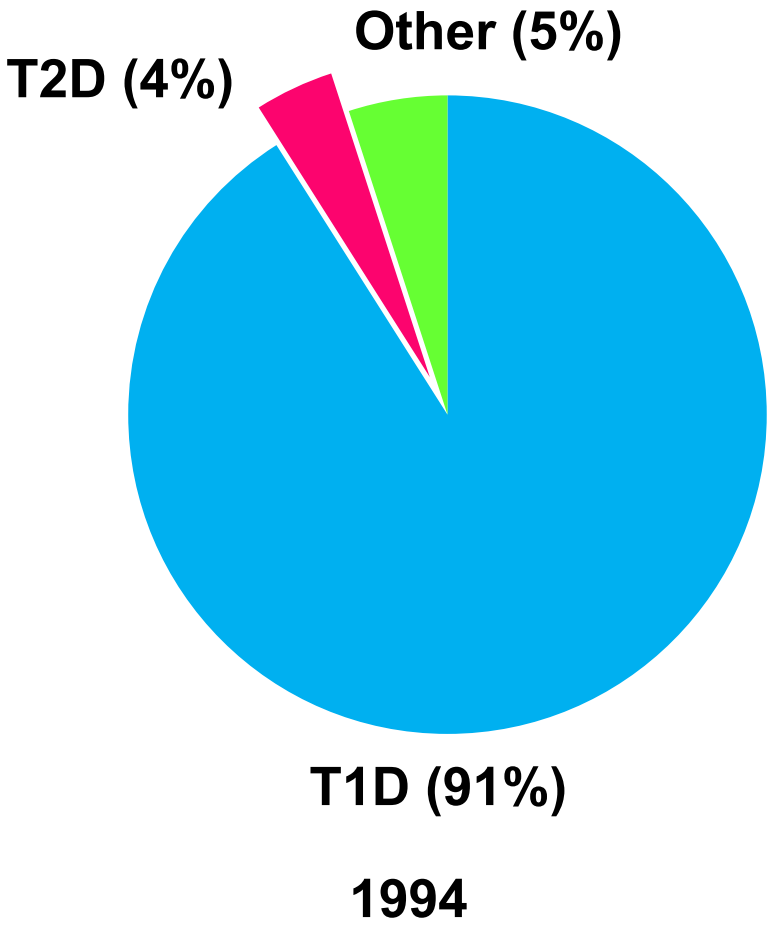
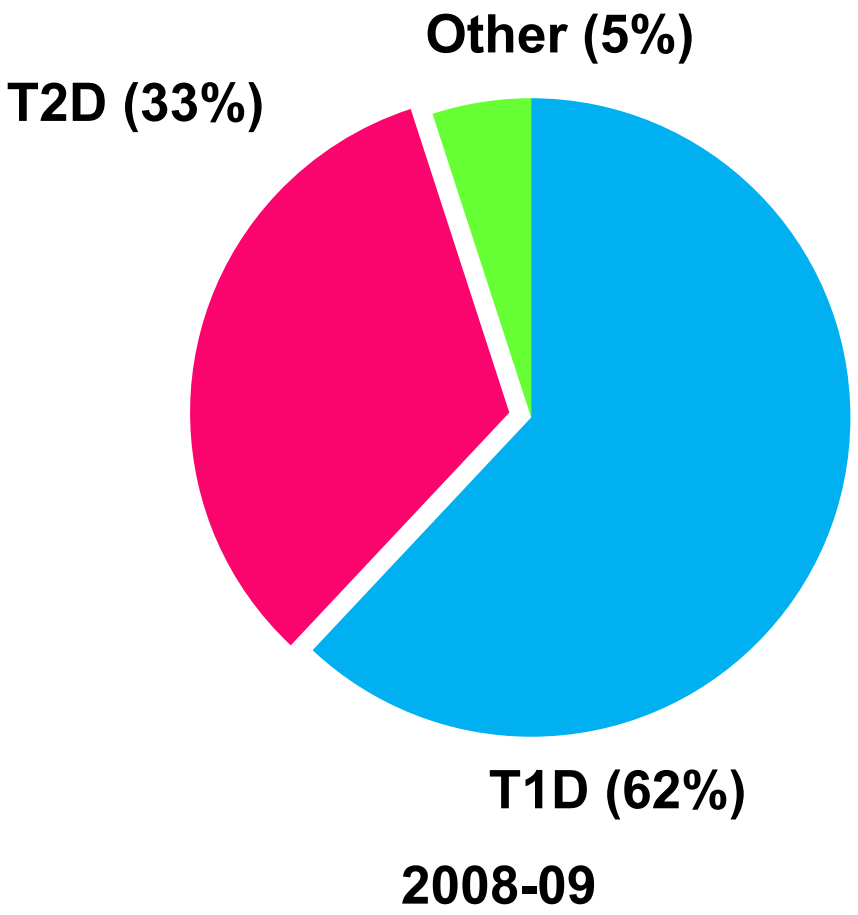
# *Objectives/Outline*

1. Overlap between T2D and NAFLD in youth
2. Differences between youth vs. adult-onset T2D
3. Relevance to pediatric clinical trials in NASH and T2DM
4. Considerations/Recommendations

# Type 2 Diabetes (T2D) in Adolescents

## *A growing proportion of diabetes in youth*




Modified from CDC.gov

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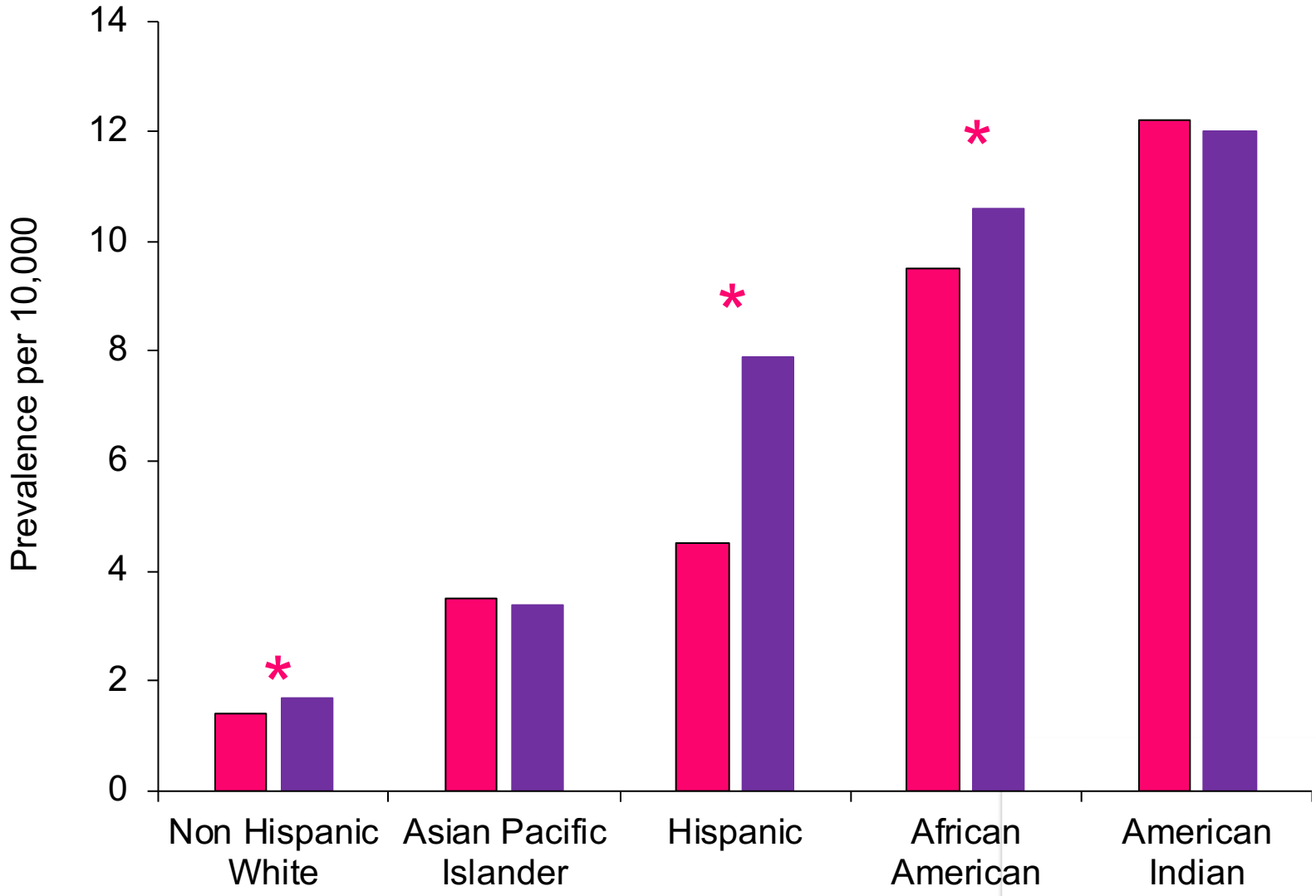
# Youth Onset T2D Prevalence rose 30%

## *2001 vs 2009*

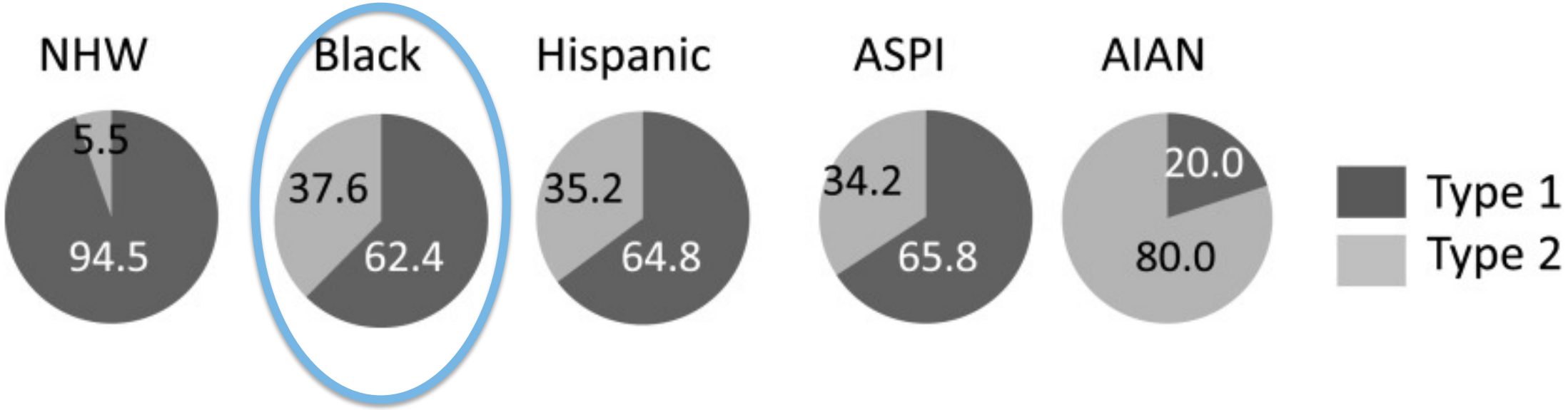
p<0.05 from 2001 to 2009 in

- Both sexes
- All ages 10-19
- Hispanic
- Non-Hispanic white
- Black youth




Dabelea. JAMA. 2014 May 7;311(17):1778-86

# Racial differences in Type 2DM




**African-American Youth:**

**High risk of Type 2 Diabetes, but low risk of NAFLD**

Diabetes Care 2014;37:402

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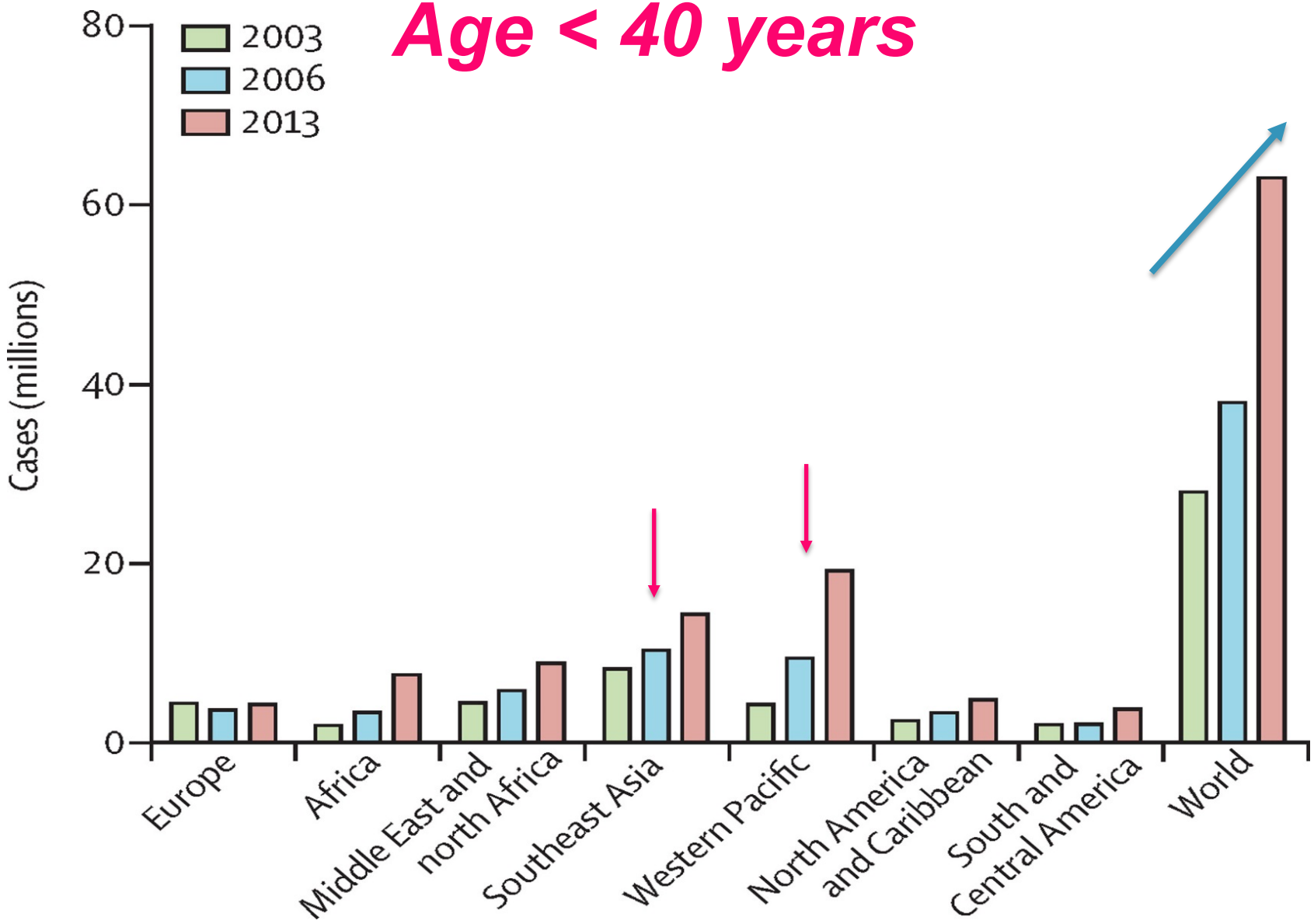
# Global increase in T2D

## *Age < 40 years*




IDF Atlas 2013. Figure from Lascar. Lancet Diabetes Endocrinol. 2018 Jan;6(1):69-80.

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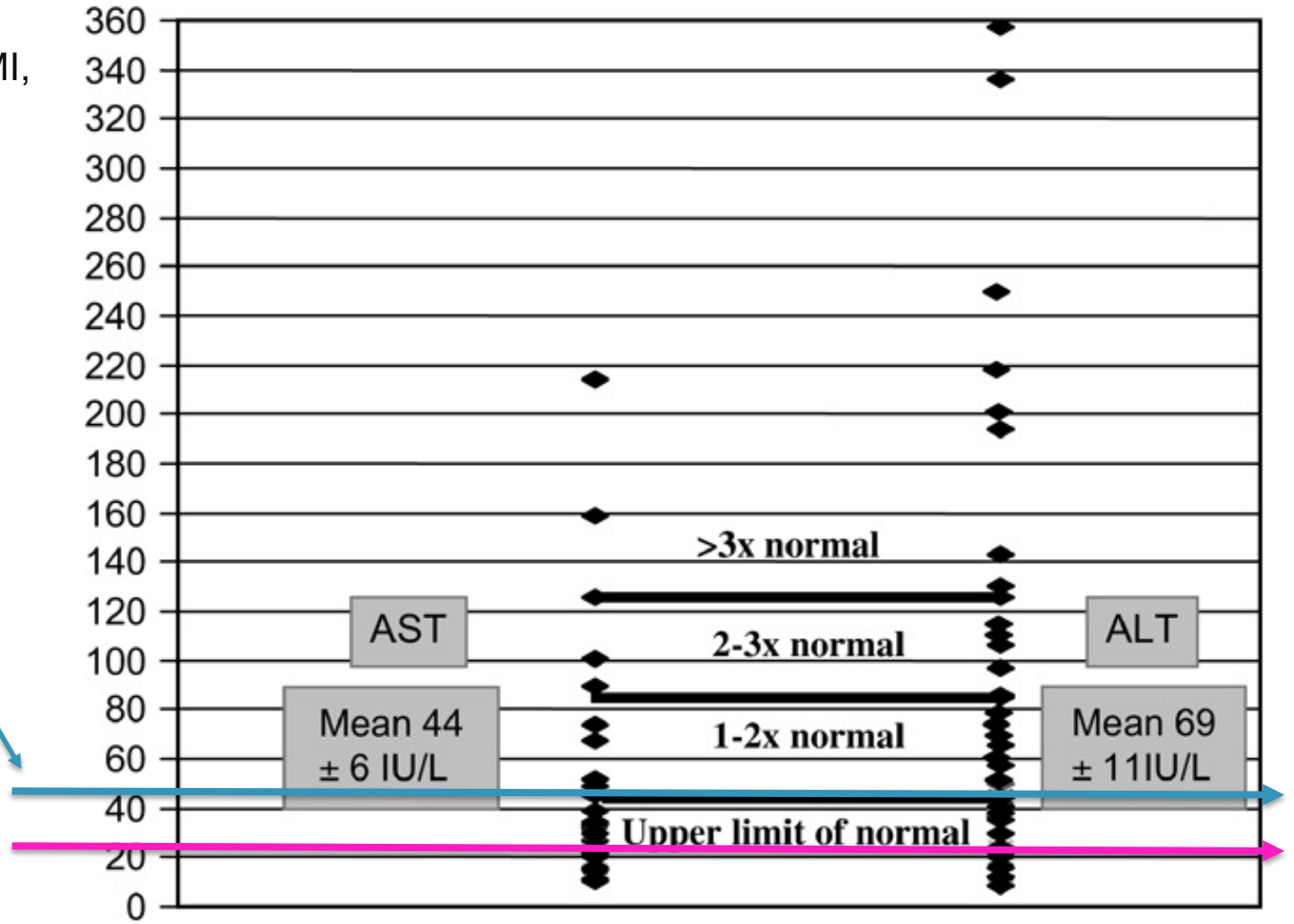
# Among children with Type 2 Diabetes, Nonalcoholic Fatty Liver Disease is Common

- N=115 children with T2DM
- 42% had liver enzymes (Similar age, sex, BMI, A1C)

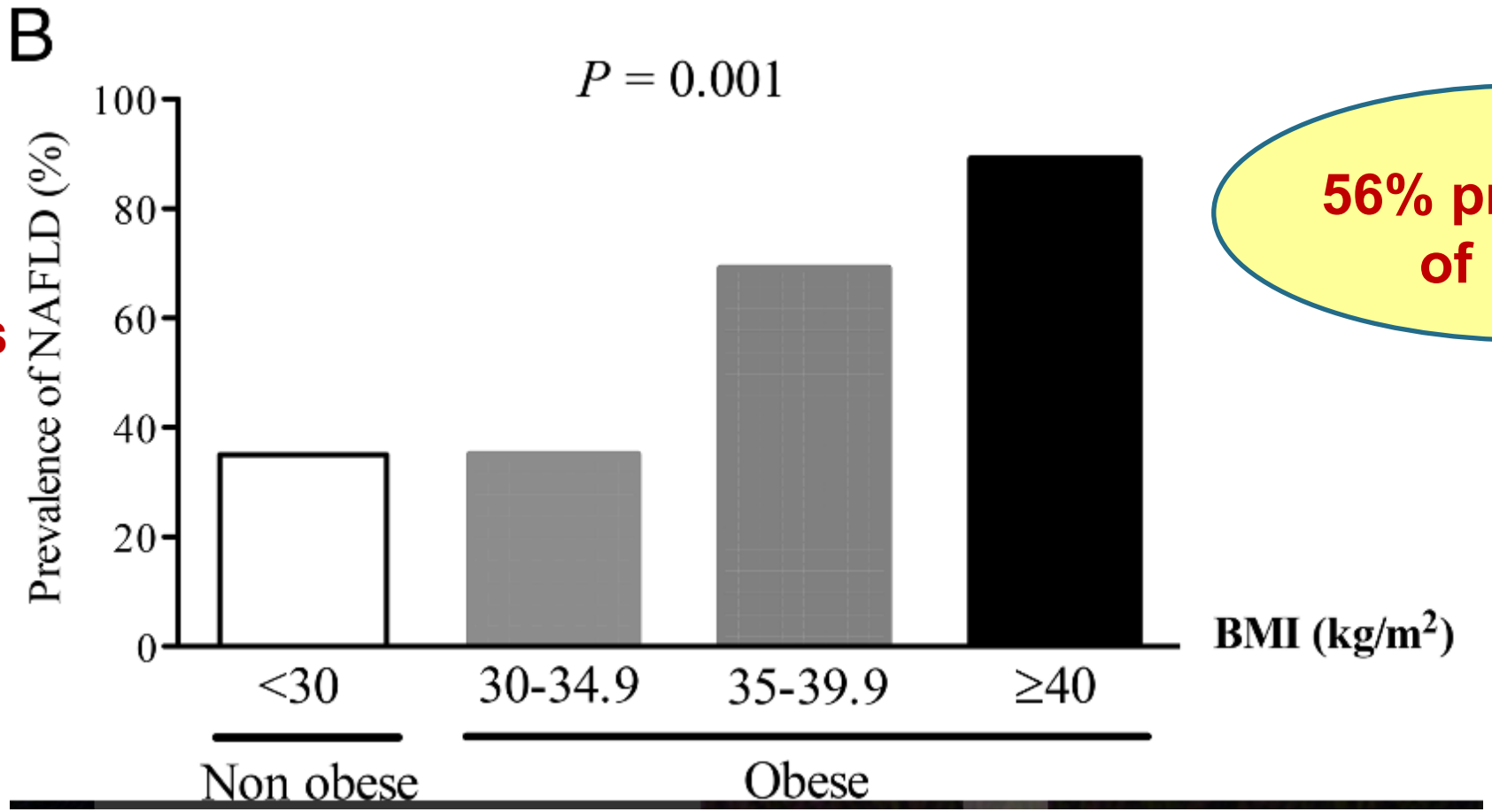
48% had ALT ≥ ULN for lab ref range (approximately 40 IU/L)

Majority > biologically normal ALT threshold (<26 IU/L males, <22 IU/L for females)




Nadeau KP. JPGN 2005;41:94-98

# Normal ALT does not exclude NAFLD or NASH
## 50% prevalence in 103 adults with T2DM & normal ALT




MRS

56% prevalence of NASH

ALT 23 (17-23)

ALT 23 (20-30)

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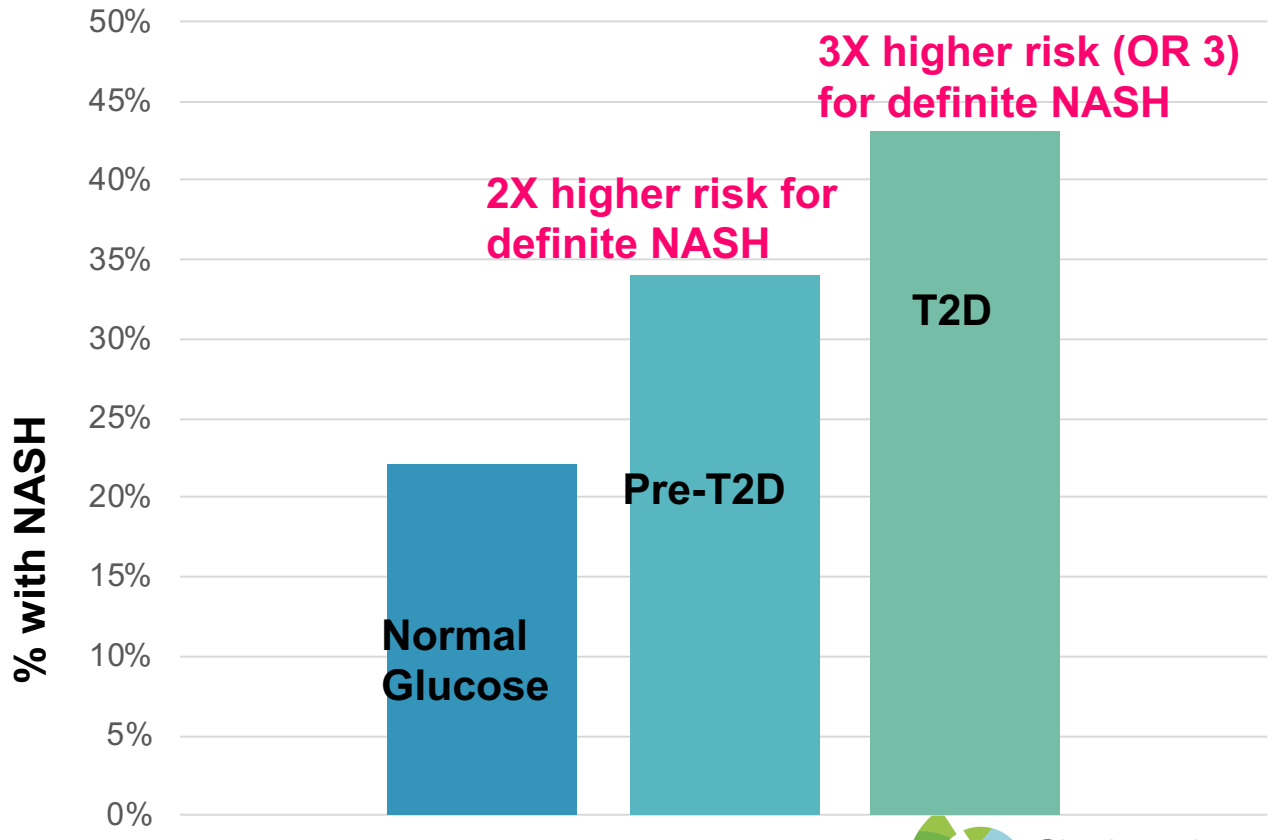
*Portillo-Sanchez. JCEM 2015; 100(6):2231*

# Among children with NAFLD, T2DM carries increased risk of NASH

- 675 children with biopsy-confirmed NAFLD, mean age 12.6, mean BMI 32.5
  - 23.4% had prediabetes
  - 6.5% had diabetes




Newton KP et al. JAMA Pediatrics

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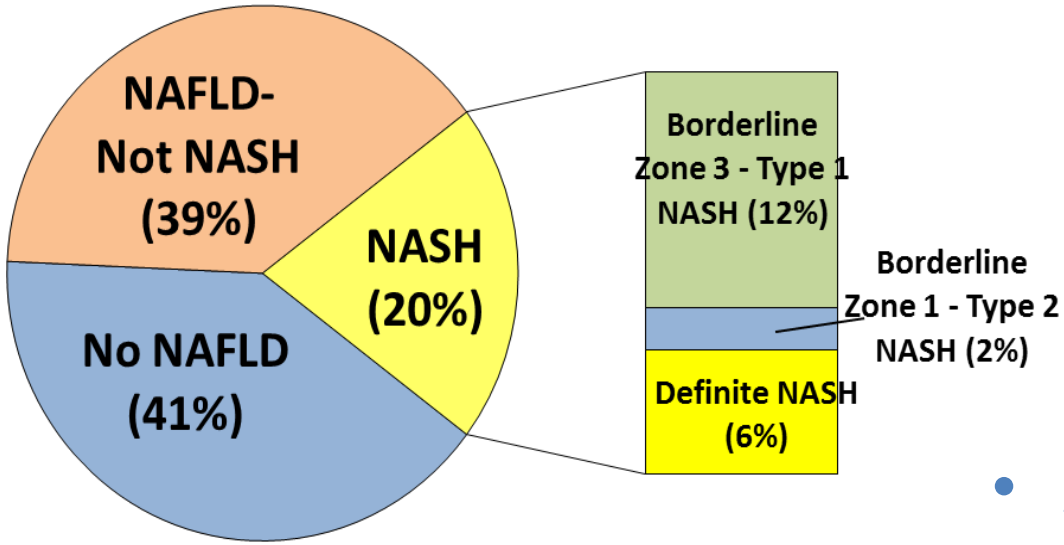
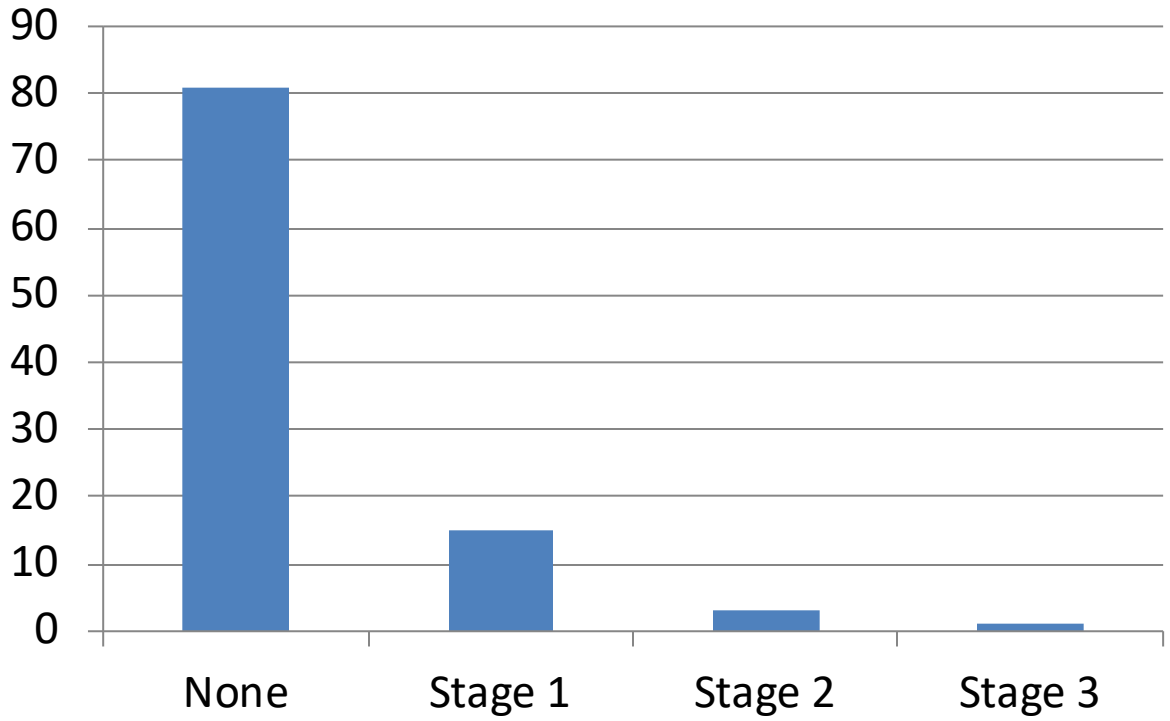
# Diabetes risk factor for NASH in adolescents undergoing bariatric surgery




- **ALT elevation**
  - Mild (22-39 females, 26-39 males) OR 3.41
  - High (>40 U/L) OR 6.66
- **Fasting glucose elevation**
  - 100-125 mg/dL OR 1.48
  - ≥126 mg/dL OR 8.10

*Xanthakos et al.. Gastroenterology 2015*

# Diabetes and ALT only significant predictors of fibrosis in bariatric cohort




- **Diabetes** **OR 2.56 (1.10, 5.96) p=0.03**
- **ALT>40 U/L** **OR 2.41 (0.84, 6.98) p=0.08**

***Xanthakos et al.. Gastroenterology 2015***

# T2DM risk factor for NASH progression?

- In 122 (88%) of children receiving standard lifestyle counseling and placebo over 1 or 2 years in the NASH CRN,
  - Half showed improvement in NASH or fibrosis
  - **But over 1/3 experienced worsening in NASH or fibrosis,**
- Disease progression related to worsening **HbA1C**
  - **Progression to NASH (RO 3.4)**
  - **Progression to fibrosis (RO 2.3)**

# Does NAFLD increase risk of T2DM?

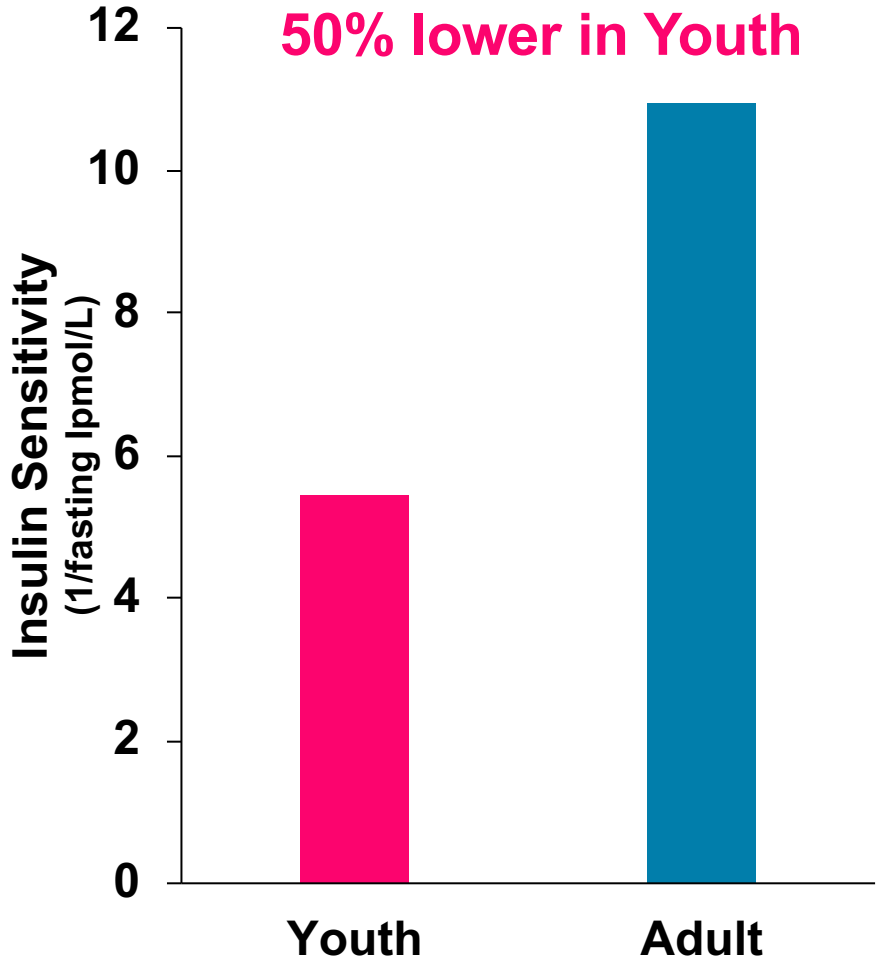
- **Type 2 diabetes mellitus developed in 8%** over period of observation
  - Doubling from baseline (6% to 13%) over 1-2 years
- Incidence rate of **44.3/1000 person years**
- **>300 fold the estimated population incidence rate** of 0.12/1000 person years in adolescents[1]

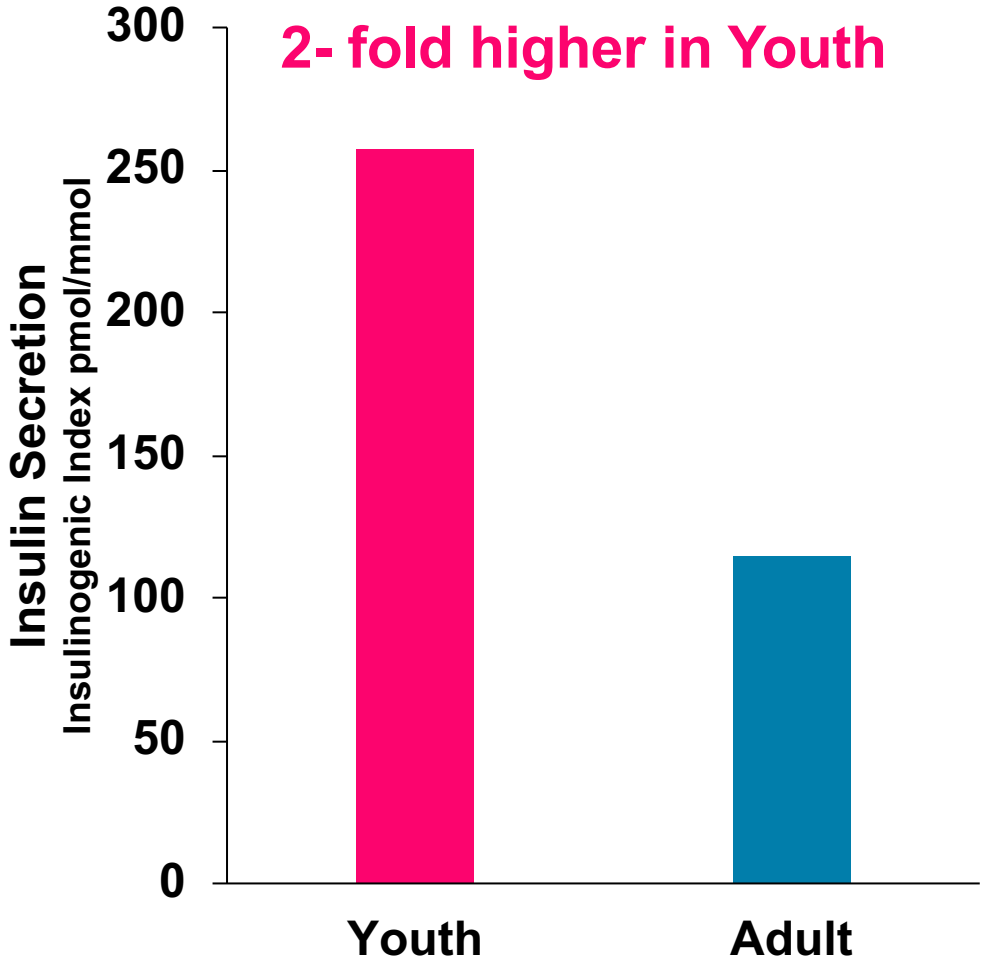
Presented at AASLD 2017

[1]JAMA. 2007;297:2716-2724

# T2DM in youth differs from adults

# Adolescent vs. Adult T2D




RISE Consortium. Diabetes Care 2018.

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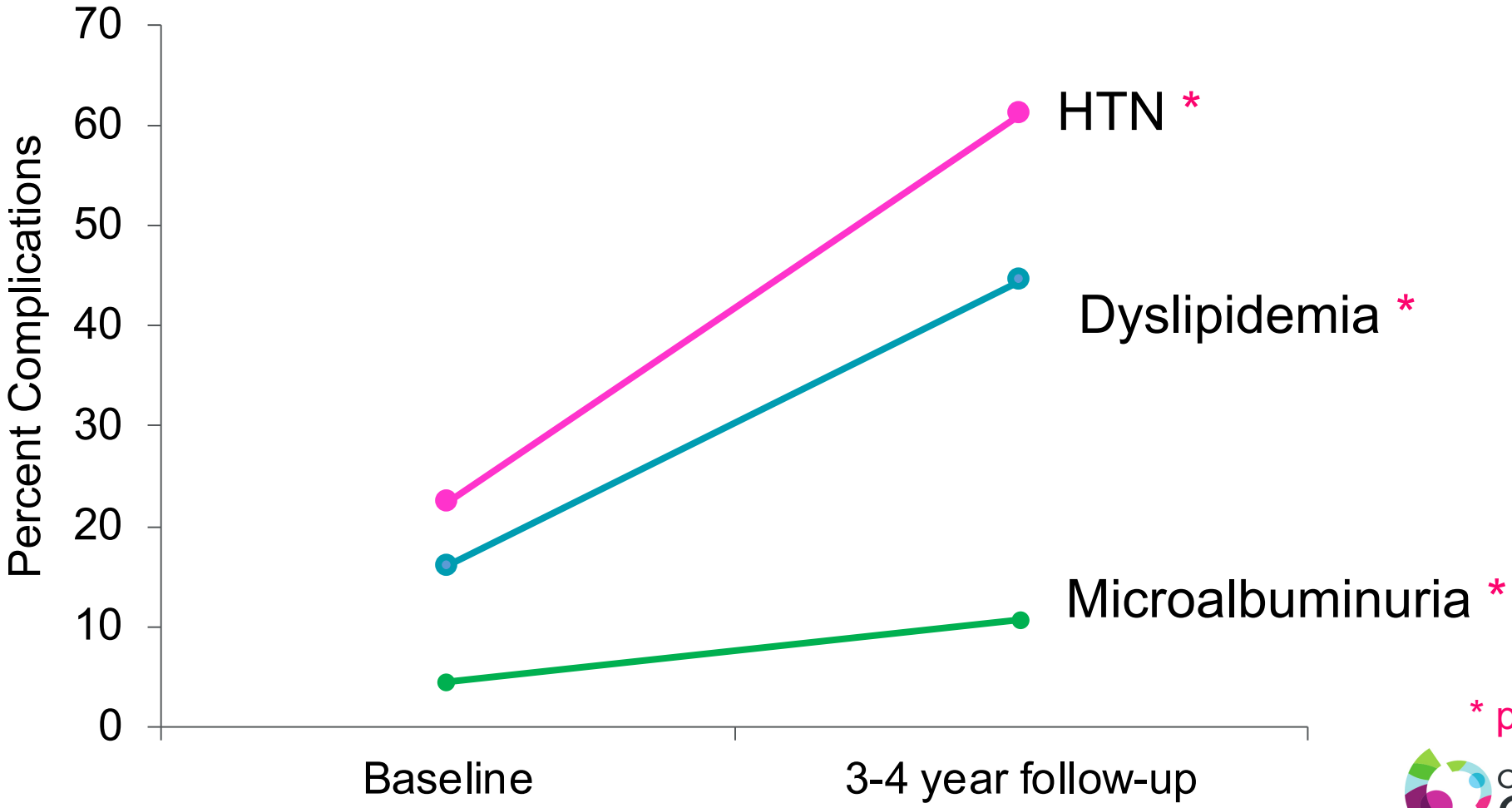
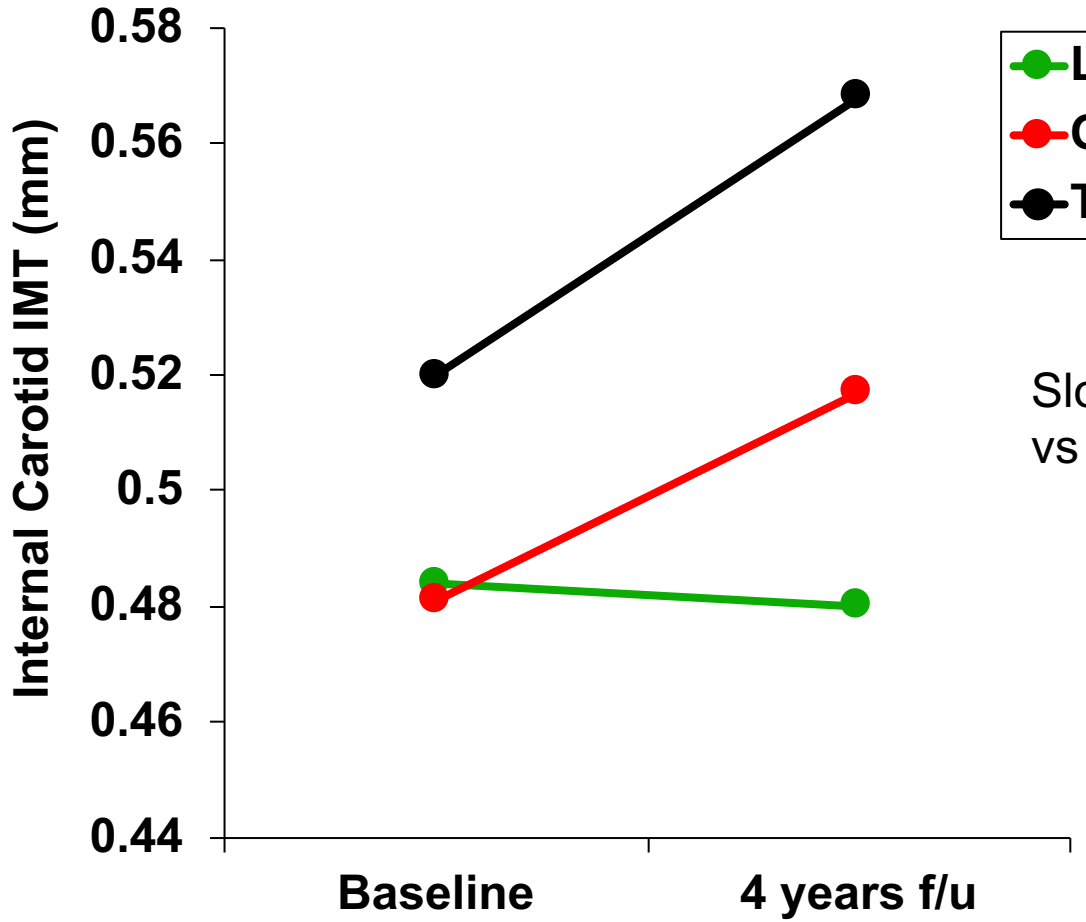
# CV risk factor profile
## *worsens rapidly over time in youth*




* p<0.05

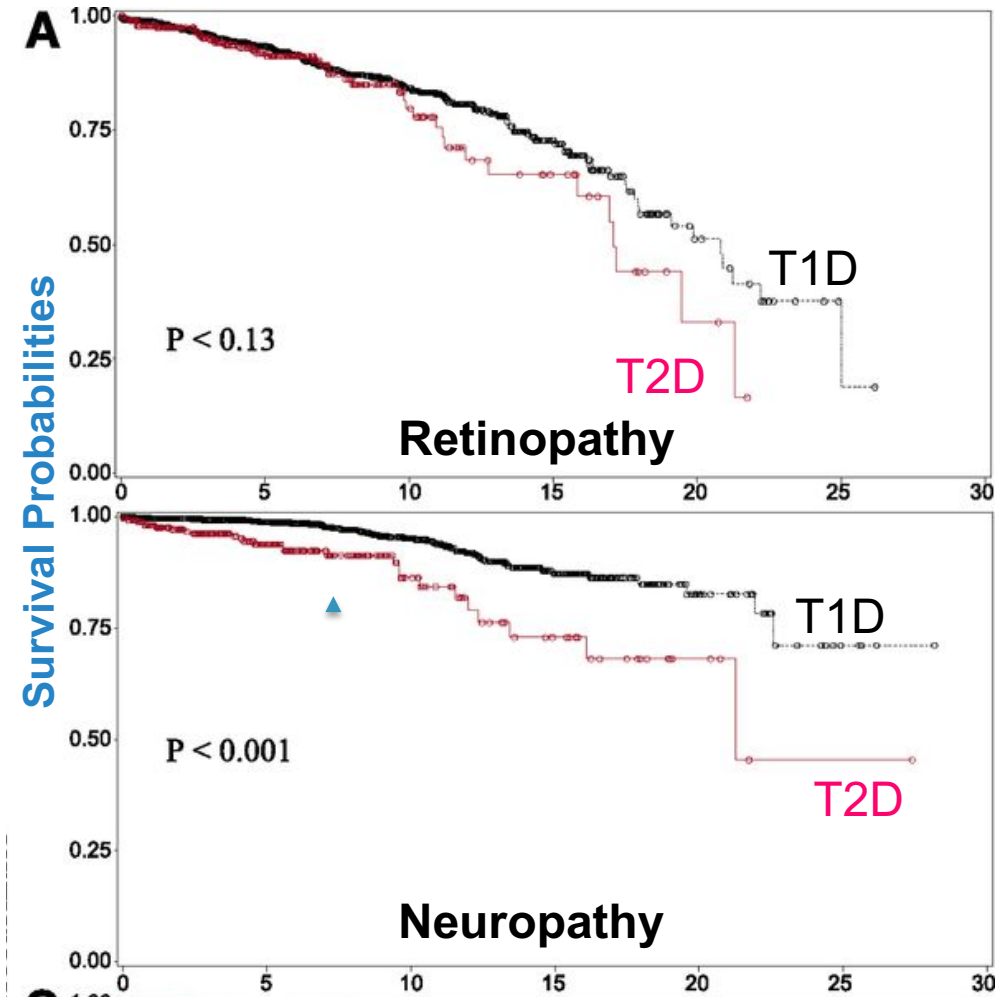
# Carotid Thickness Overtime in *T2D vs. Obese & Lean Youth*

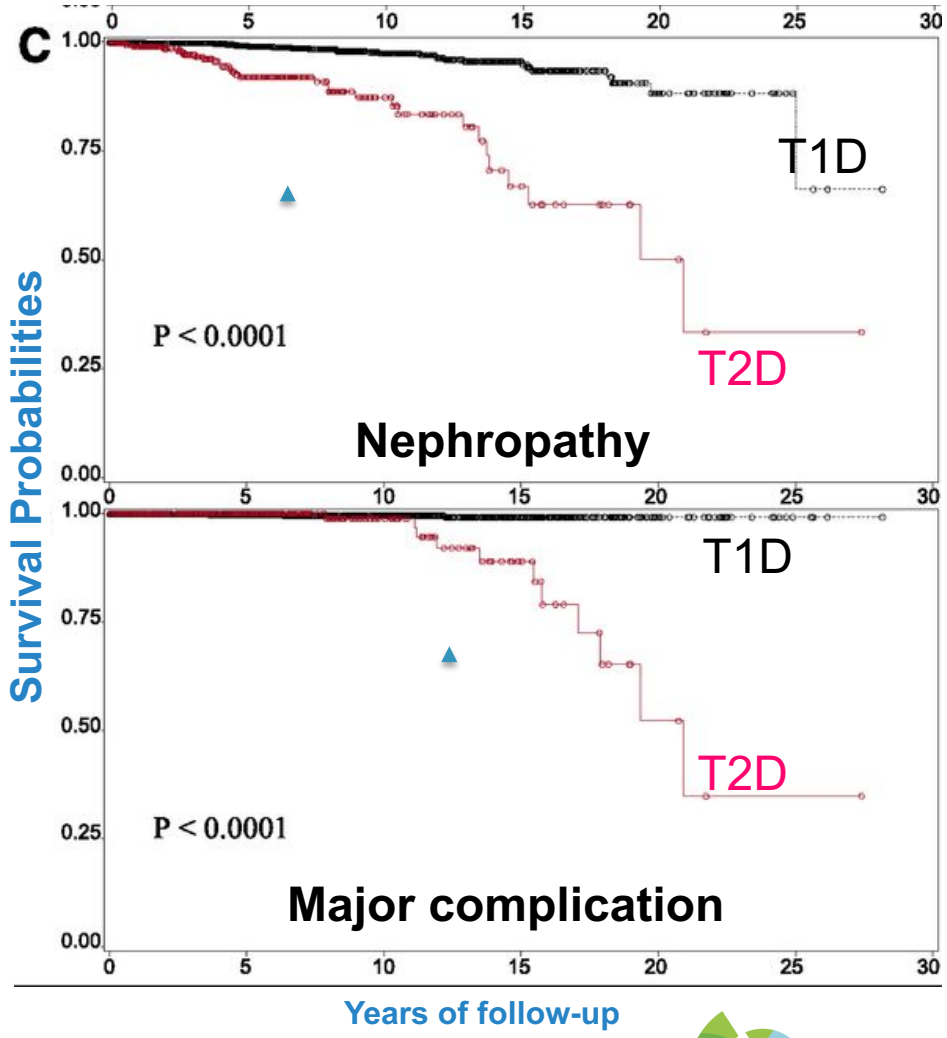



Slope for obese and T2D vs lean ($p<0.05$), n=226

Urbina, unpublished data

# Complications in T1D vs T2D Youth-Onset Diabetes




n=342 T2D youth, n= 1011 T1D youth

Allison B. Dart et al. Dia Care 2014;37:436-443

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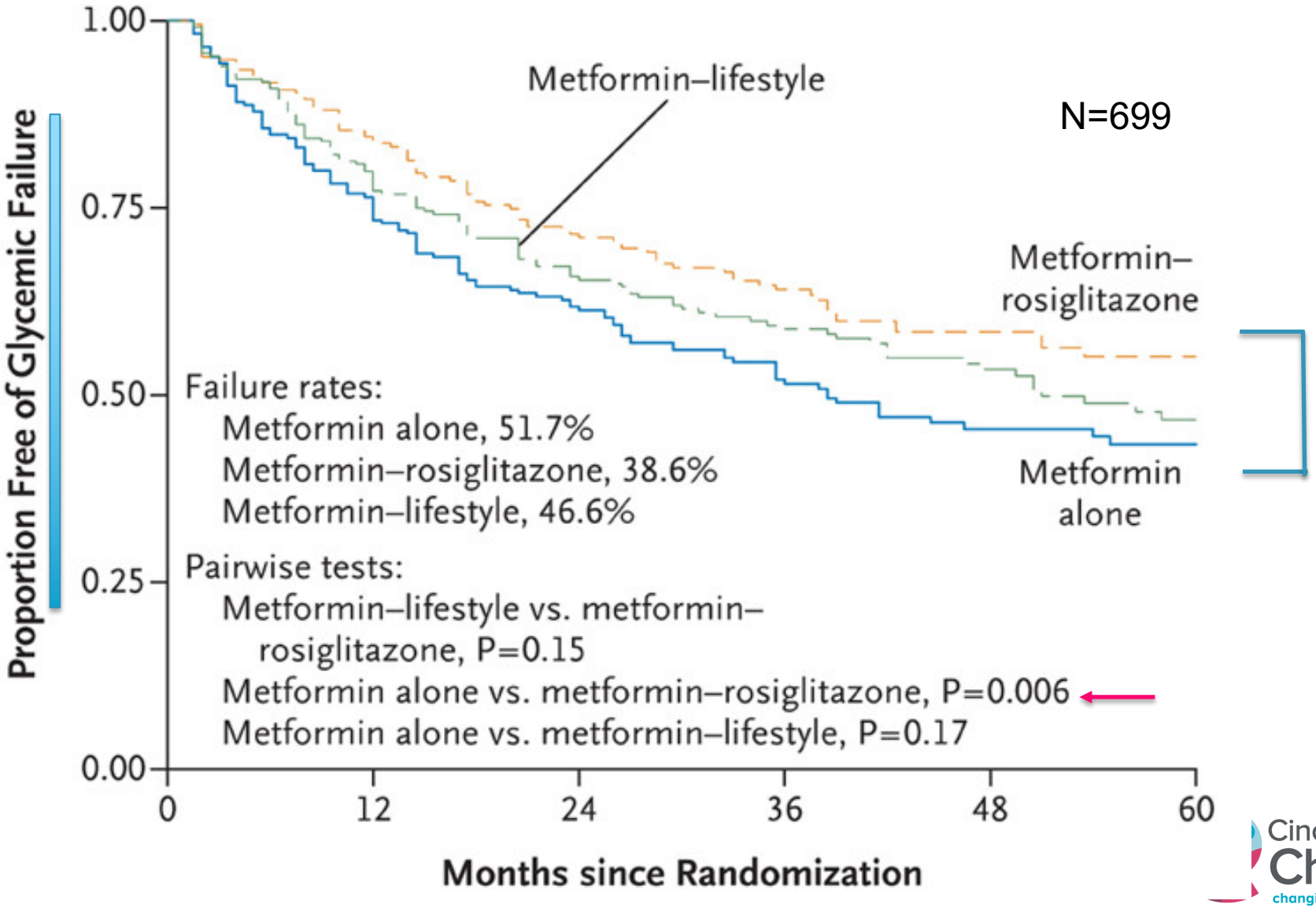
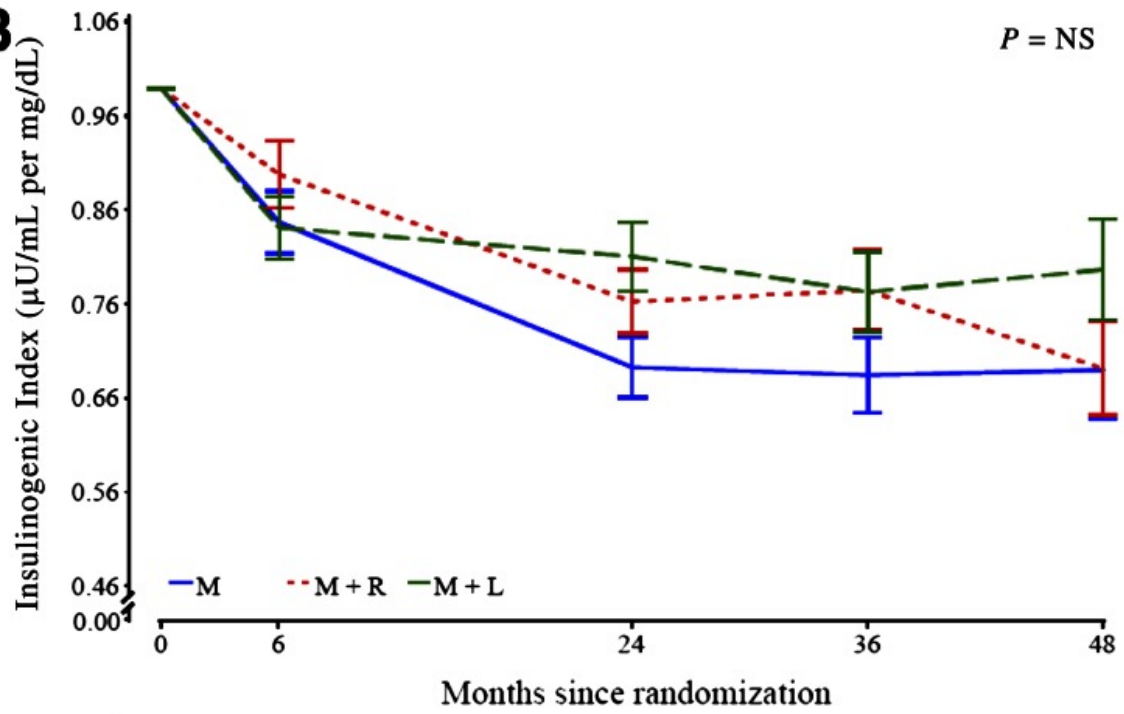
# Medical Treatment in Youth with T2D



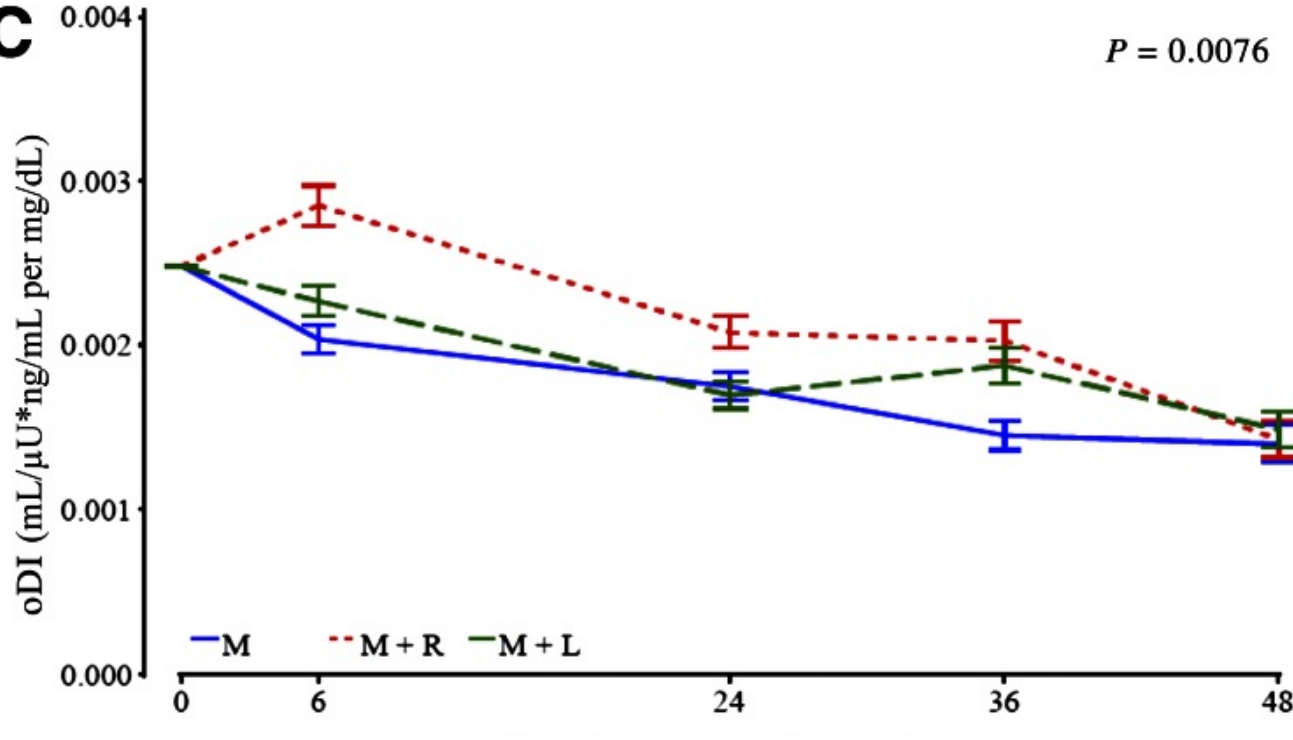

TODAY Study Group. N Engl J Med 2012;366:2247-2256.

# Rapid decline overtime *despite treatment*

*Insulin secretion*




*Beta cell function*




TODAY Study Group. Diabetes Care. 2013 Jun; 36(6): 1749–1757.

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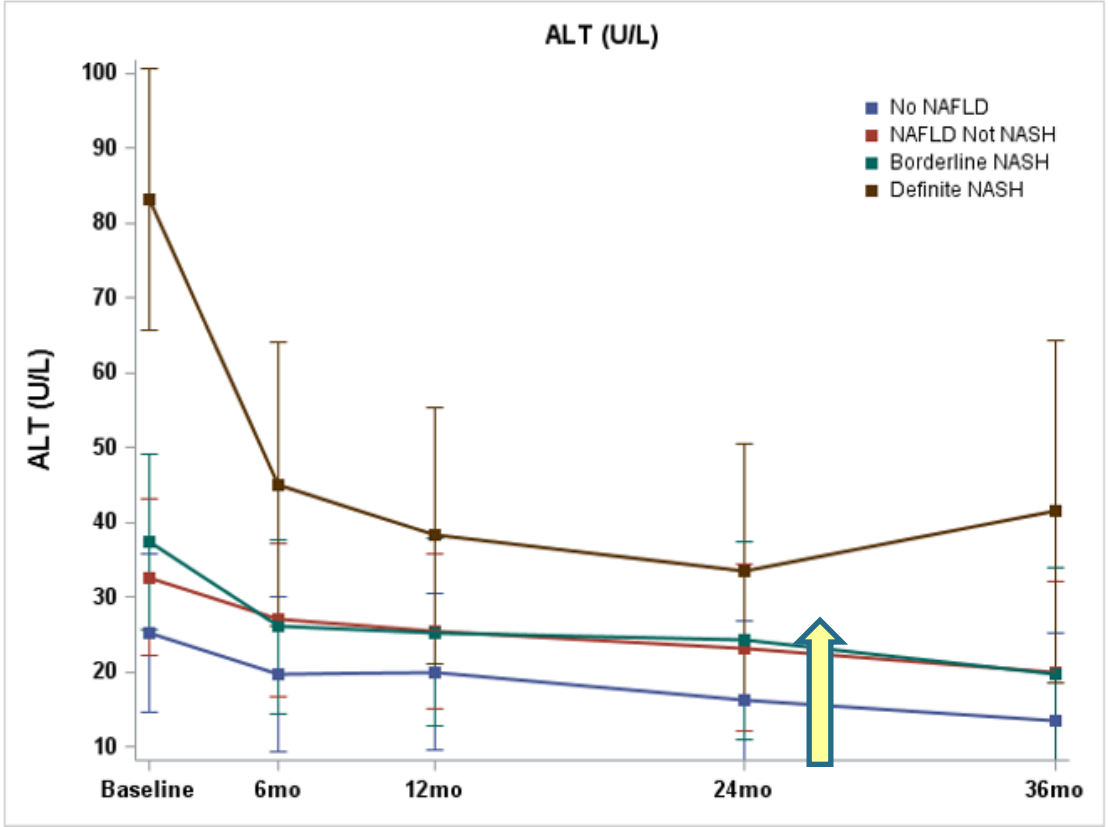
# Relevance to pediatric trials for youth with NASH and/or T2DM

- How will having both youth-onset NASH + T2DM affect responses to treatments?
- Unclear as not well phenotyped or represented in prior trials…
  - For most T2DM trials, ALT > 2.5 to 3x ULN is an exclusion, lack of liver imaging
  - For earlier NASH trials, diabetes was an exclusion and/or poorly controlled T2DM an exclusion (A1C >9%)

# ALT response after bariatric surgery by liver phenotype

- **Most studies short term to date**
  - **1-3 years in adults,**
  - **1-2 years in teens**
  - **Remission vs. Cure?**




*Bacha F...Xanthakos S. ADA mtg 2018*

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# *Summary*

- Strong overlap between T2D and NAFLD in youth
  - Exception: Sub-Saharan African heritage
- T2D in youth more rapidly progressive than Adult T2D
- Will youth with T2DM + NASH have worse outcomes and responses to treatment?
- Finding mutually beneficial treatments important
- Recommendations
  - Important subgroup for NASH and Diabetes clinical trials
  - Correct classification of T2DM at trial entry and follow-up
  - Capture duration of T2DM at trial entry
  - More cross-talk needed in pediatric NASH and T2DM trials

# Diagnosis of incident T2D

- **Any** of the following + **Negative islet cell antibodies**
  - Fasting glucose ≥126mg/dL
  - Random glucose >200mg/dL + symptoms
  - **Hemoglobin A1c > 6.5%**
  - 2 hr OGTT blood glucose >200mg/dL

Arslanian. Evaluation and Management of Youth-Onset Type 2 Diabetes: A Position Statement by the American Diabetes Association. 2018

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# Caveat: Taking metformin can cloud the picture

- **If participant has HbA1C < 6.5% could be:**
  - **Well controlled T2DM**
  - **PCOS**
  - **Prediabetes**
  - **Antipsychotic medication**

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# The Type 2 Diabetes Team!

Email: type2clinic@cchmc.org

## Diabetes Providers

Amy Shah, MD MS
Pediatric Endocrinologist

Nancy Morwessel, CNP
Diabetes Nurse Practitioner

Nancy Crimmins, MD MS
Pediatric Endocrinologist

## Subspecialists

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Gastroenterologist

Sarita Hunsaker, PhD
Psychologist

## Diabetes Education Team

Amy Poetker, RD
Diabetes Registered Dietician

Brigitte Shular, MSW
Diabetes Social Worker

Jana Norvell
Diabetes Nurse Educator

## Bariatrics Team

Michael Helmrath, MD
Bariatric Surgeon

Linda Kollar, CNP
Bariatric Nurse Practitioner

Susan Sewell, RD
Bariatric Dietician

Kaitlyn Wessels
Bariatric Social Worker

## Program Coordinators

Kelsey Frenck
T2D Clinic Coordinator

Penni Taylor
Bariatric Coordinator

Cassandra McDaniel
Bariatric Coordinator

# Diabetes Auto-antibodies?

| | |
|---|---|
| Glutamic Acid Decarboxylase (GAD) | Enzyme in the pancreatic beta cells that produces insulin. |
| Insulin Autoantibodies (IAA) | Antibodies targeting insulin itself |
| Insulinoma-Associated-2 Autoantibodies (IA-2) | Enzyme in the pancreatic beta cells that produces insulin. |
| Zinc Transporter 8 (ZnT8) | Beta cell specific enzyme |

- TODAY study screened n=1,206 youth clinically diagnosed with type 2 diabetes

- 118 (9.8%) were antibody positive
- Antibody + youth tended to be
  - Less obese
  - Fewer features of the metabolic syndrome
  - More likely male
  - More likely Non-hispanic White
- Antibody + youth are “obese type 1”
  - At risk for faster progression to insulin dependence
  - Diabetic ketoacidosis
  - Autoimmune conditions

Klingensmith GJ. TODAY Study Group. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. Diabetes Care 2010;33:1970–1975