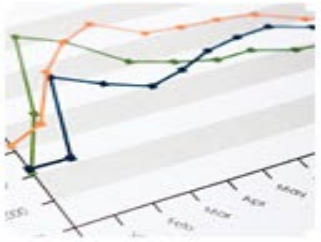
# HRSA Outreach Program

## *Western Oklahoma Wellness*

## *July 19, 2022*



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# Agenda

- Housekeeping Items
- HRSA Outreach Program – Western Oklahoma Wellness
  - Saundra Burchill – OFMQ
- Youth Onset Type 2 Diabetes
  - Jeanie B. Tryggestad, MD
    - Associate Professor, Pediatric Diabetes/Endocrinology
    - Paul and Ruth Jonas Chair, Children's Hospital Foundation
- Questions & Closing

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    - respects and attends to any special needs of the learners;
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# About WOW

- Western Oklahoma Wellness is a program to advance rural healthcare through increased access to care, education, and opportunities to reduce the onset of diabetes and other chronic conditions.

- Counties We Work In:
  - Beckham, Greer, Kiowa, Washita, Roger Mills

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# Funded Through HRSA

- We Work With:
  - **ONIE Project**: The Oklahoma Nutrition Information and Education (ONIE) Project promotes healthy living through innovative and creative strategies for communities, families and individuals.
  - **SWOSU Rural Health Center**: The RHC develops programs for community-based healthcare services collaborating with local pharmacies and hospitals for the advancement of the health and well-being of the medically underserved population in Oklahoma.
  - **Community Partners**: County-Specific Health Departments, State Health Department, OSU Extension, Town of Granite, Mangum Regional Hospital, Elkview General Hospital, Cordell Memorial Hospital, Roger Mills Hospital, City of Elk City
- WOW is funded through the HRSA Rural Health Care Outreach Services Program, Grant No. D04RH40277

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# Jeanie B. Tryggestad, MD

- Dr. Jeanie B. Tryggestad is an associate professor of pediatrics in the section of diabetes/endocrinology at the University of Oklahoma Health Sciences Center and holds the Paul and Ruth Jonas Chair in Diabetes/Endocrinology. A Native of Southwest Oklahoma, she received her Bachelor of Science in Biology from Oklahoma Christian University. She completed her medical school education at the University of Oklahoma Health Sciences Center graduating with distinction. Dr. Tryggestad completed her residency in pediatrics and fellowship in pediatric endocrinology at the University of Oklahoma Health Sciences Center as well. She is board certified in pediatrics as well as pediatric endocrinology.
- Dr. Tryggestad's clinical research interests are on the impact of youth onset type 2 diabetes on complications. She is a Co-Principle Investigator for the NIH funded TODAY trial in Oklahoma and served on the Comorbidity Assessment Committee.
- Dr. Tryggestad's other research interest focus on the impact of maternal diabetes on the future cardiometabolic health of the offspring and the impact of obesity and diabetes on vascular function. She has been awarded grant through the NIH to understand the impact of maternal diabetes on miRNA expression and protein regulation in infants.
- Dr. Tryggestad serves as the co-director of the type 2 diabetes comprehensive clinic in youth at OU Children's. Her clinical interests are focused on type 1 and type 2 diabetes with special focus on Native American populations. She also serves as the director of the Turner Syndrome Clinic.

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# Relevant Disclosures

Under the Oklahoma State Medical Association CME guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 24 months.

Jeanie B. Tryggestad, MD has no financial relationships or affiliations to disclose.

# Youth Onset Type 2 Diabetes: Treatments, Complications, and the Path to Improved Outcomes

Jeanie B. Tryggestad, MD
Associate Professor, Pediatric Diabetes/Endocrinology
Paul and Ruth Jonas Chair, Children's Hospital Foundation

July 19, 2022

# Learning Objectives

- To examine the trends in youth onset diabetes prevalence over the past 20 years.
- To describe the progression of youth onset T2DM.
- To recognize the complications that arise in youth onset T2DM
- To identify the available treatment modalities available for youth onset T2DM

# Practice Gaps

- Practitioners fail to intensify treatment early in youth onset type 2 diabetes.
- Practitioners may not know the rates of complications in youth onset type 2 diabetes.
- Practitioners fail to begin screening for diabetes related complications at diagnosis in youth with type 2 diabetes.

# Case 1

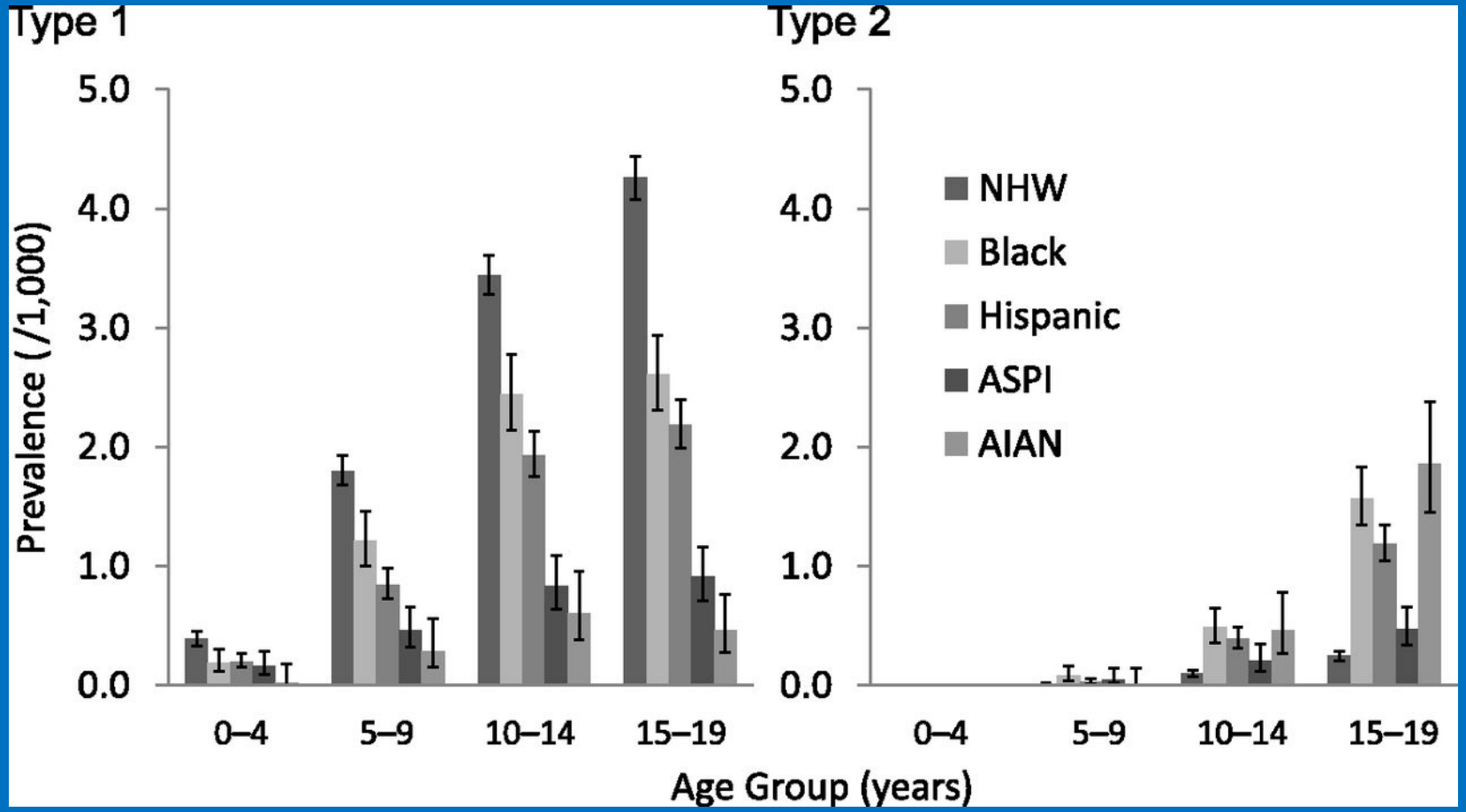
- 16yo Hispanic male presented to ED with polyuria and polydipsia and 60lb weight loss in 2 months (weight now at 91%)
- FSBS 487mg/dL, pH 7.29, Bicarb 15mEq/L
- ? Mild acanthosis on his neck

# Case 2

- 16yo Hispanic female, obese, acanthosis on neck, family history of type 2 diabetes (T2DM) presents with polyuria and polydipsia
- Serum glucose 371mg/dL, A1C 9.5% at PCP so referred for diabetes

# Prevalence of Diabetes in Youth

# Youth Onset Diabetes

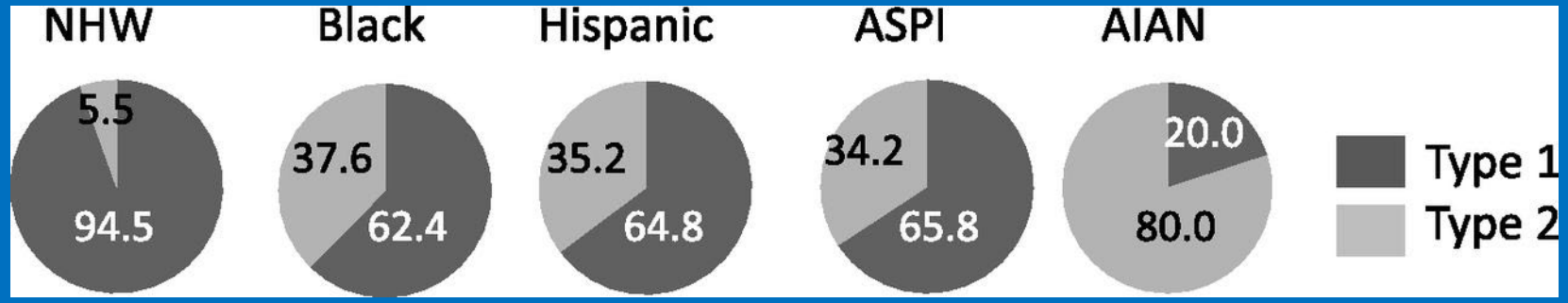





David J. Pettitt et al. Dia Care 2014;37:402-408

American Diabetes Association.

# Proportion of type 1 and type 2 diabetes among 15–19 year olds in SEARCH by race/ethnicity.

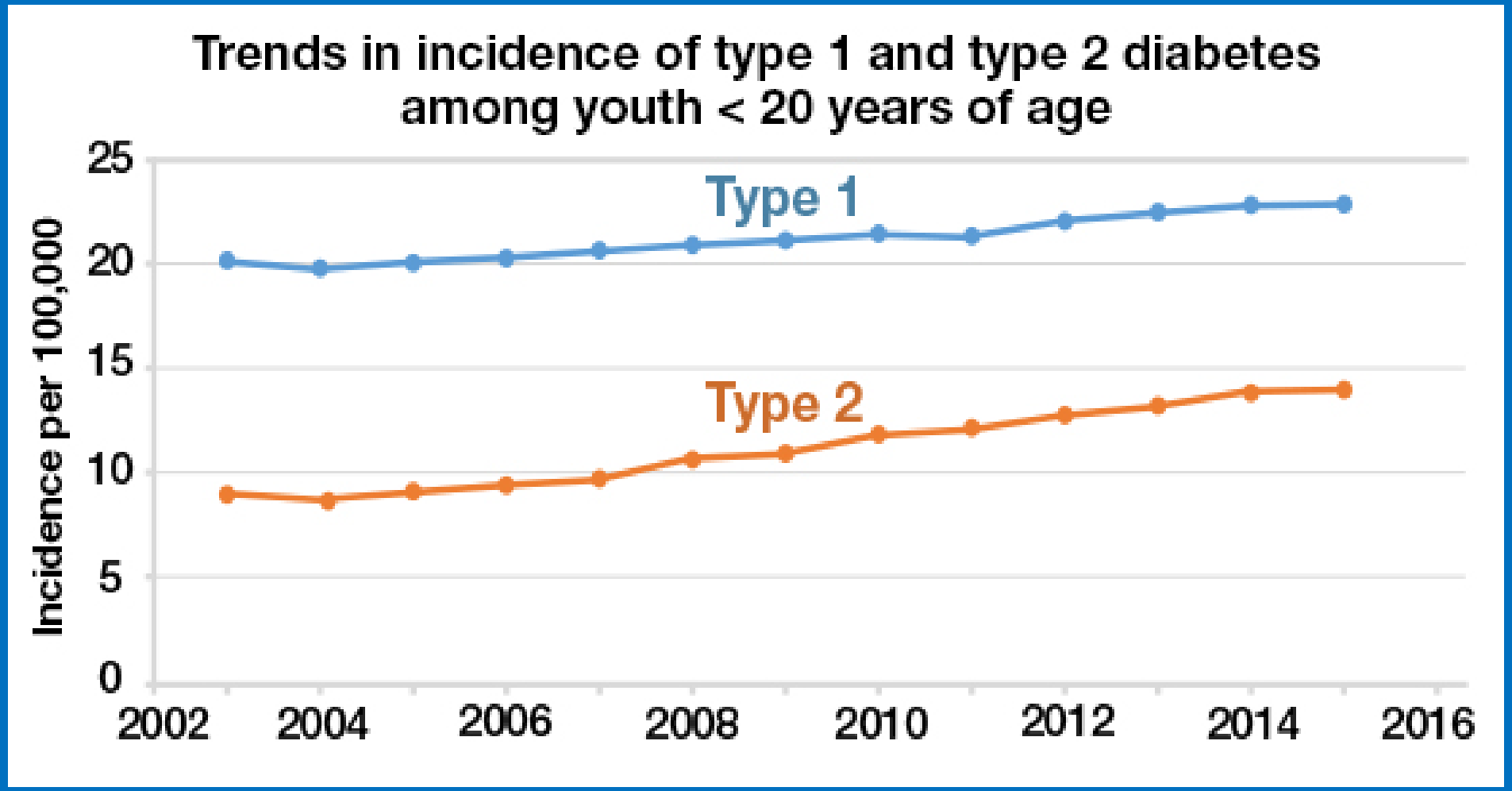





David J. Pettitt et al. Dia Care 2014;37:402-408

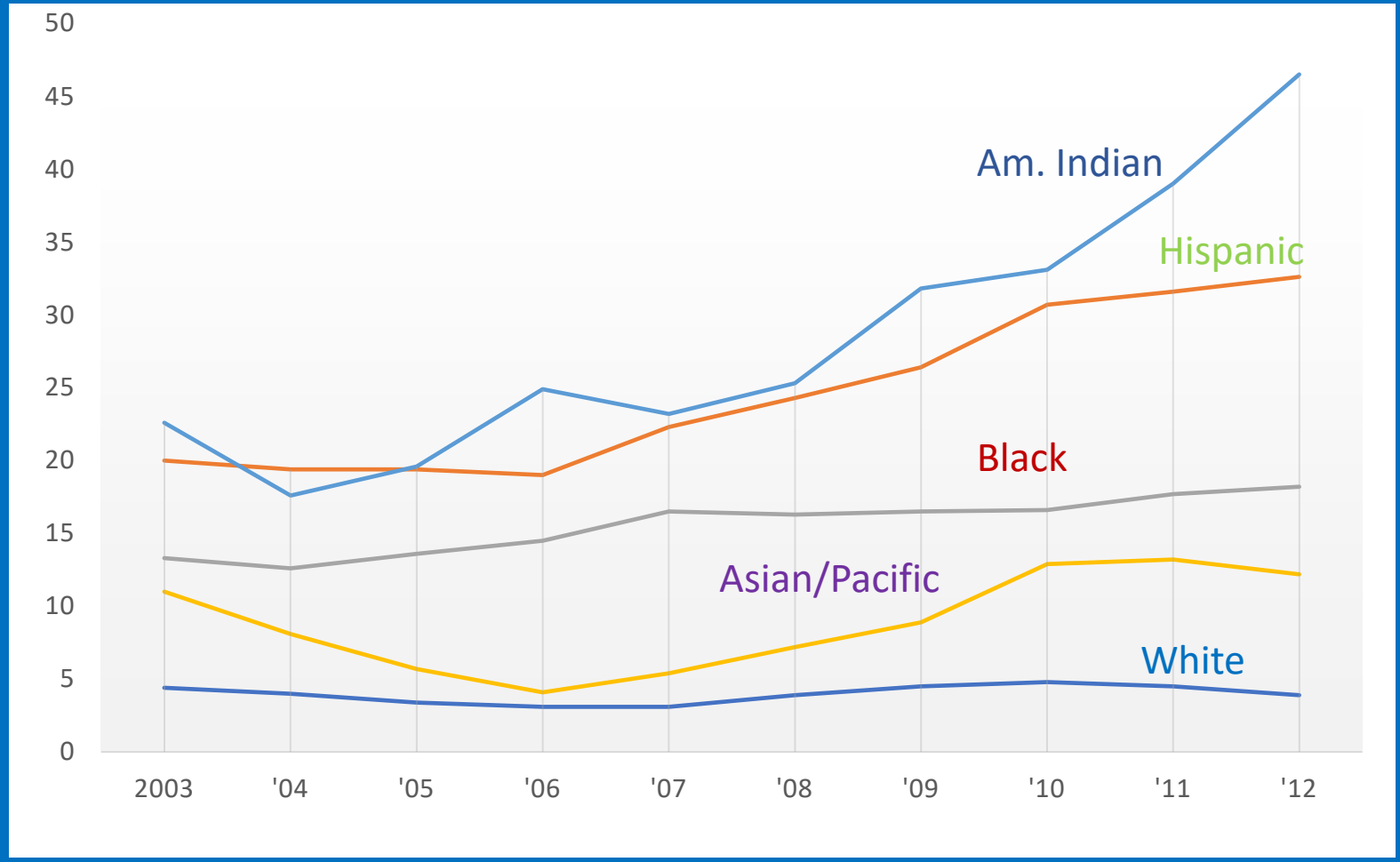
American Diabetes Association.

# SEARCH for Diabetes in Youth Study (2002-2016)




Divers j, et al. Trends in Incidence of Type 1 Type 2 Diabetes Among Youths- Selected Counties and Indian Reservations MMWR Mor Mortal Wkly Rep 2020:69:161-165.

# Youth Onset T2DM




Mayer-Davis, *JAMA* 376:1419, 2017

# OKLAHOMA

- In our OU Children's Clinic, approximately 1 in 3 new-onset patients with diabetes is DM2
- Among OK Medicaid patients, >50% of children with diabetes are DM2
- In American Indian communities, >50% of children with diabetes are DM2, and
  ~75% of new-onsets are DM2

# Studies of T2DM Progression in Youth

# Treatment Options for Type 2 Diabetes in Adolescents and Youth


FUNDED BY
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
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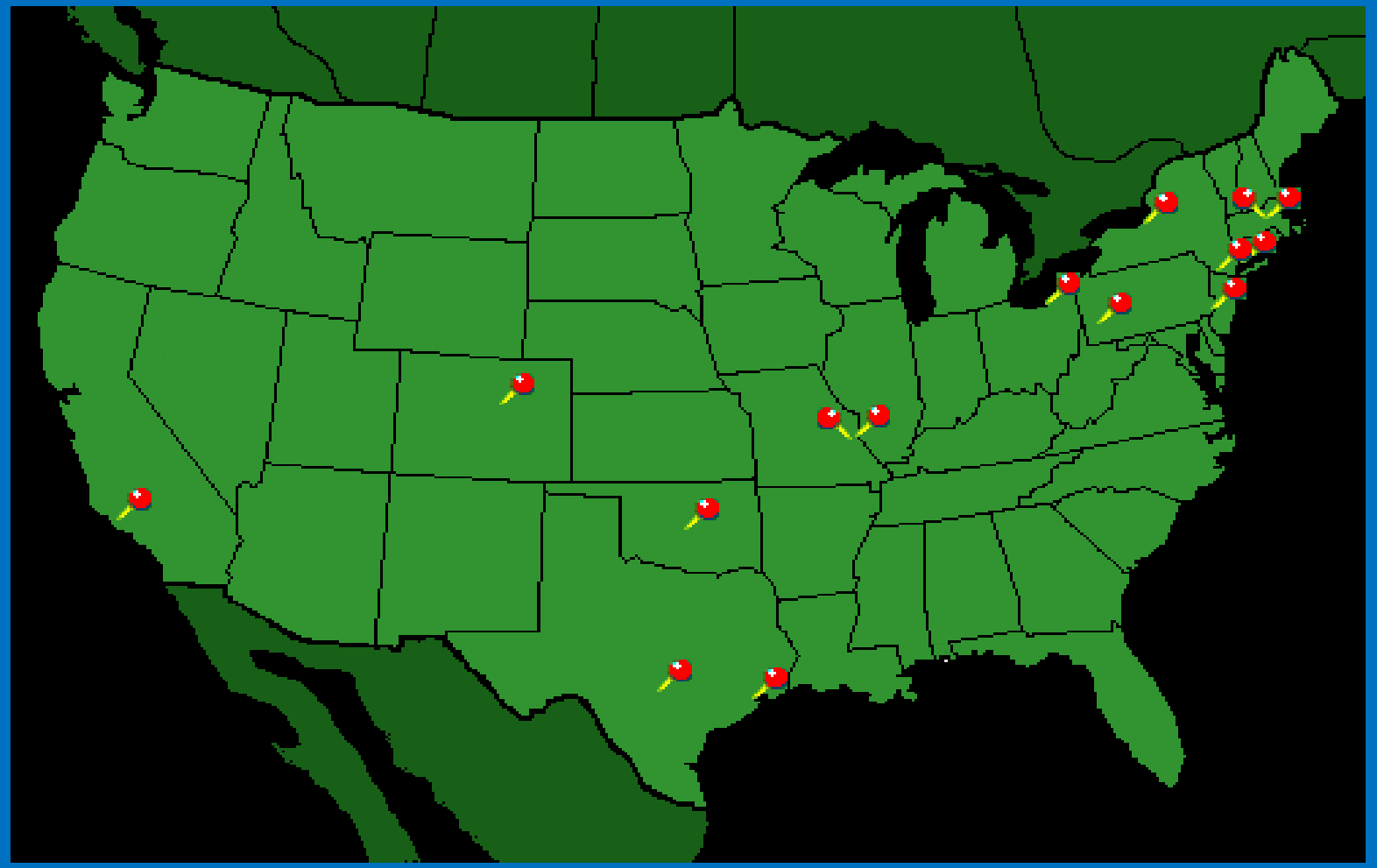
# Rationale for TODAY

Given

- Epidemic increase of T2D.
- Increase in risk factors (e.g., obesity).
- Lack of large-scale studies on treatment of T2D in youth.

Need for a systematic national study to assess treatment options for T2D in youth.

# The 15 TODAY Clinical Centers



TODAY
Treatment Options for type 2 Diabetes in Adolescents & Youth

THE UNIVERSITY OF OKLAHOMA
CIVI ET REIPUBLICAE
1890

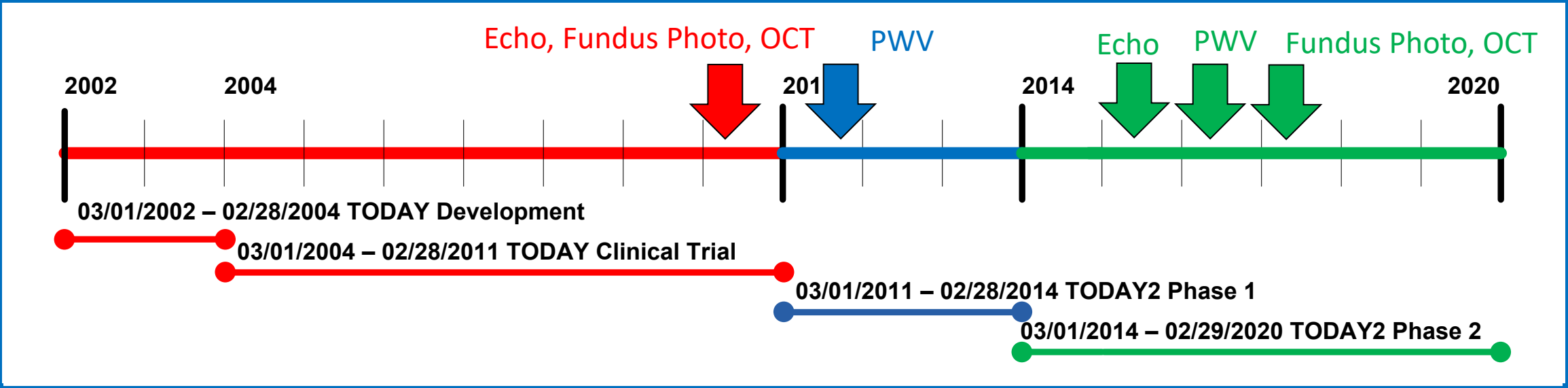
THE UNIVERSITY OF OKLAHOMA
College of Medicine

ABSENTEE SHAWNEE TRIBE
OF OKLAHOMA


the Chickasaw Nation


Chadwick JQ, Copeland KC, Daniel MR, Erb-Alvarez JA, Felton BA, Khan SI, Saunkeah BR, Wharton DF, Payan ML. *American Journal of Epidemiol* 2014 Dec 15 180(12):1202-7. doi: 10.1093/aje/kwu246. Epub 2014 Nov 11.

# TODAY Through TODAY2




## TODAY

- All Visits: Height, Weight, BP, HbA1c, Diabetes Care/ Management, Medical History
- Annually: Neuropathy Measures, Lipids, Kidney Function Labs

## T2P1

- All Visits: Height, Weight, BP, HbA1c, Diabetes Care/ Management, Medical History
- Annually: Neuropathy Measures, Lipids, Kidney Function Labs

## T2P2

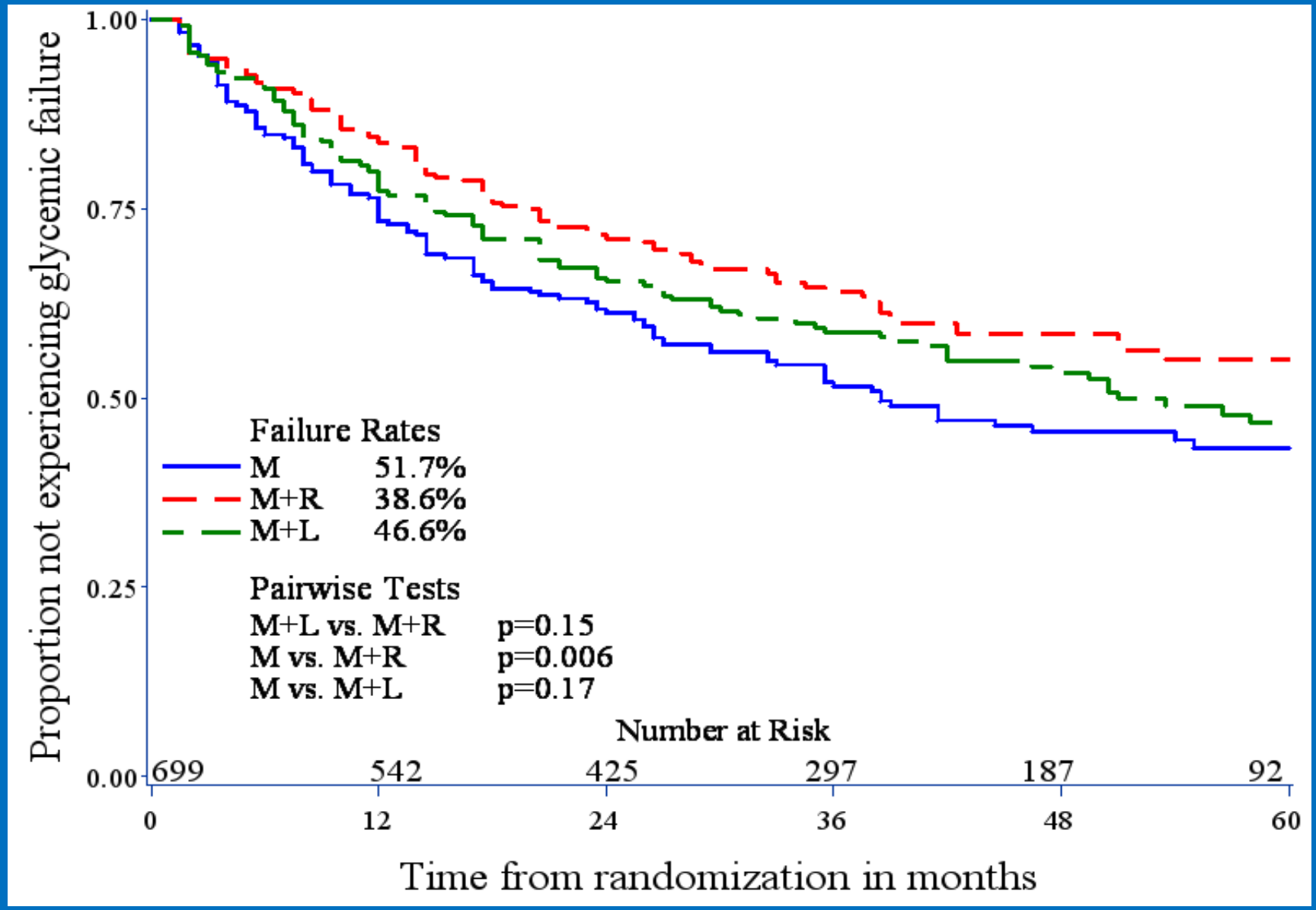
- All Visits: Height, Weight, BP, HbA1c, Medical History
- Annually: Neuropathy Measures, Lipids, Kidney Function Labs

# TODAY Cohort Baseline Characteristics

| | |
|---|---|
| Age (years) | 14.0 ± 2.0 |
| Duration of T2D (months) | 7.8 ± 0.44 |
| BMI | 34.9 ± 7.6 |
| BMI Z-score | 2.23 ± 0.47 |
| Tanner 4-5 | 84% |
| Female | 65% |
| Ethnicity | |
| White | 20% |
| Hispanic | 41% |
| Black | 32% |
| American Indian | 6% |
| GDM | 33% |
| Acanthosis | 86% |

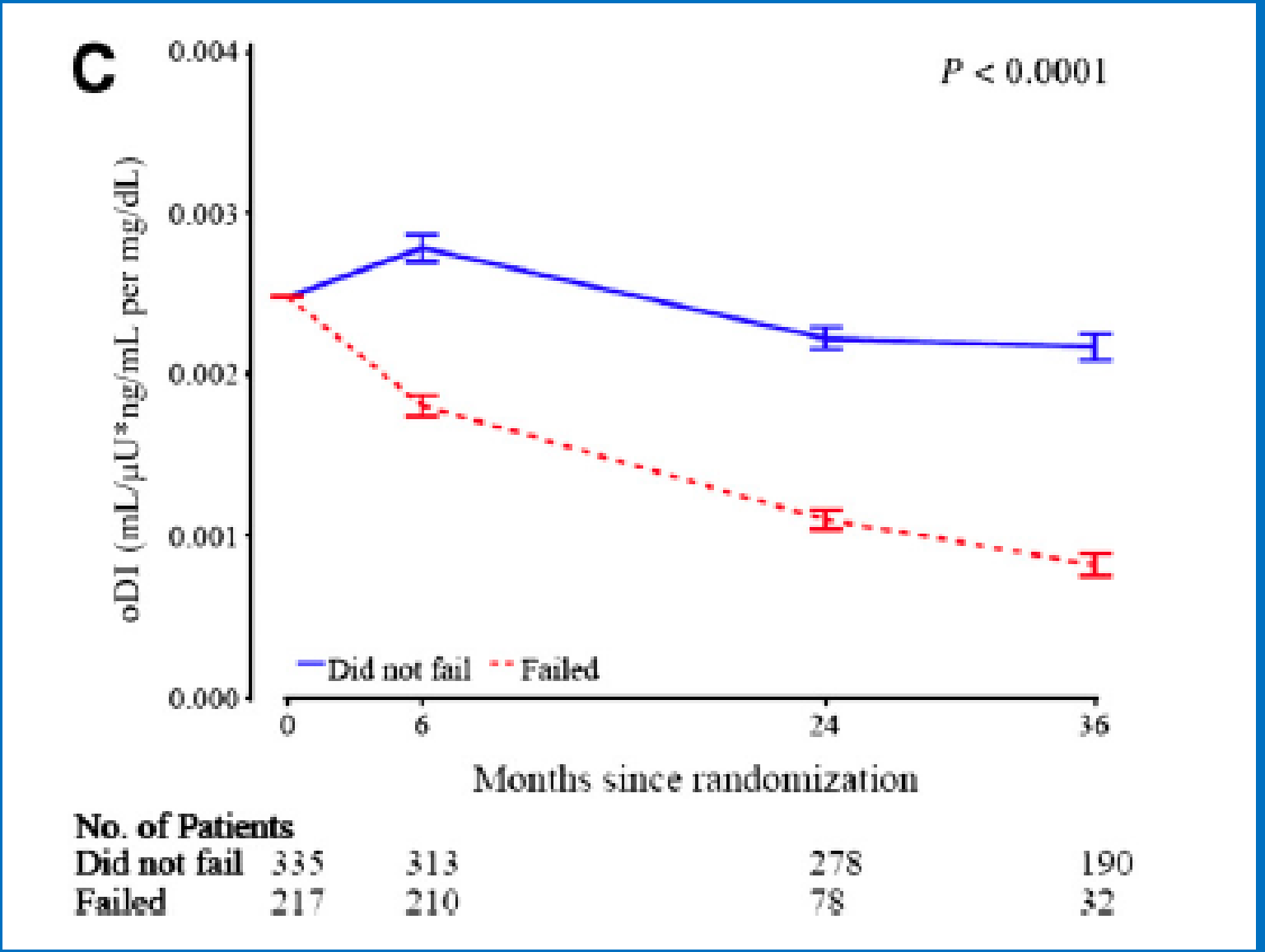
# Time-to-Event Analysis

319 of 699 = 45.6% experienced primary outcome over a maximum 72 months of follow-up




NEJM 2012; 366:2247-2256

# Beta Cell Failure in TODAY

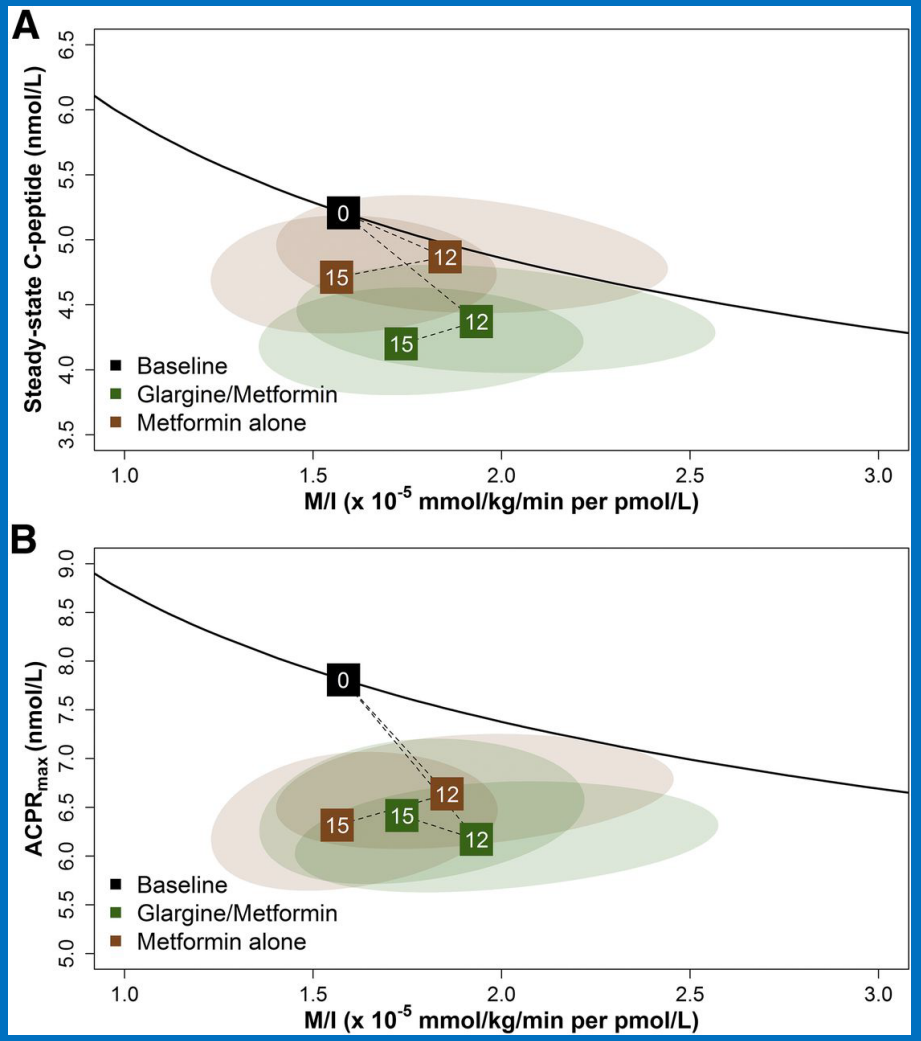



TODAY Study Group. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and β-cell function in TODAY. Diabetes Care. 2013 Jun;36(6):1749-57

# RISE: Restoring Insulin Secretion Pediatric Medication Study

- Participants
  - Obese youth with impaired glucose tolerance
  - Youth with recently diagnosed T2DM
- Intervention
  - Metformin 12 months
  - Glargine 3 months, then metformin
- Outcome
  - Decline in beta-cell function at the end of therapy

# Relationship of the two coprimary outcomes: hyperglycemic clamp-derived β-cell responses (steady-state C-peptide and ACPRmax) paired with M/I.






The RISE Consortium Dia Care 2018;41:1717-1725

# Youth Onset T2DM Complications

# Macrovascular Disease

- Leading cause of morbidity and mortality in diabetes
- Cardiovascular disease is the leading cause of death in patients with diabetes
- 2/3 of deaths in people with T2DM is related to cardiovascular disease
- Risk factors
  - Hypertension
  - Dyslipidemia
  - Arterial stiffness

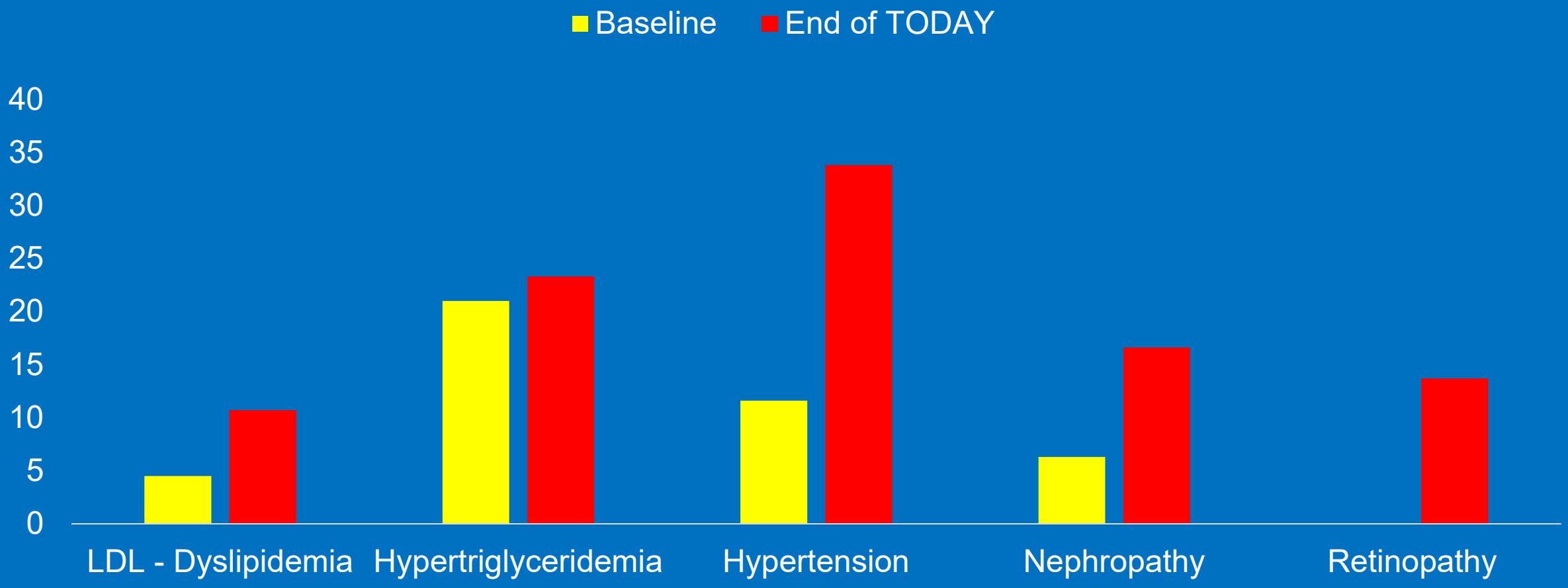
ADA Standards of Care - 2021

# Microvascular Disease

- Nephropathy
  - Occurs in 20-40% of patients with Diabetes
  - May be present in persons with T2DM at diagnosis
  - Is the leading cause of End Stage Renal Disease (ESRD) in US
  - Increases cardiovascular risk
- Retinopathy
  - The leading cause of blindness in 20-74 year old
  - Strongly associated with diabetes duration and glycemic control
- Neuropathy
  - Heterogenous group including peripheral, autonomic, and GI neuropathies
  - Glycemic control is key to stopping progression

ADA Standards of Care - 2021

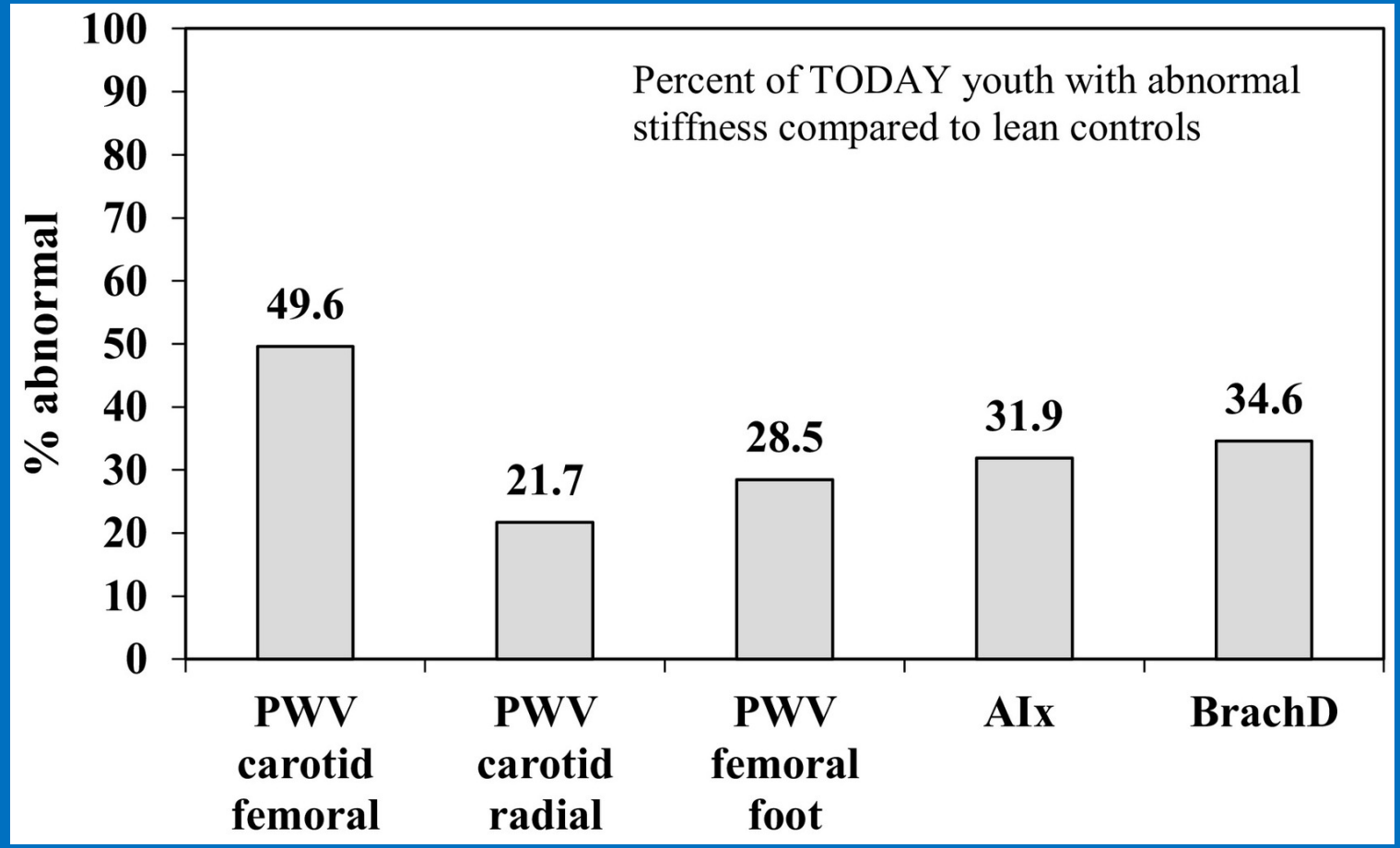
# Complications and Comorbidities In Youth Onset T2DM - TODAY




Percentage of TODAY study participants experiencing complications and comorbidities at baseline and end of study.

Tryggestad JB, Willi SM. *J Diabetes Complications*. 2015;29(2):307-312. doi:10.1016/j.jdiacomp.2014.10.009

# Arterial Stiffness in Youth Onset T2DM




Shah AS, El Ghormli L, Gidding SS, Bacha F, Nadeau KJ, Levitt Katz LE, Tryggestad JB, Leibel N, Hale DE, Urbina EM. J Diabetes Complications. 2018 Aug;32(8):740-745. doi: 10.1016/j.jdiacomp.2018.05.013. Epub 2018 May 25. PMID: 29936086; PMCID: PMC6444355.

# Heart Rate Variability in Youth Onset T2DM

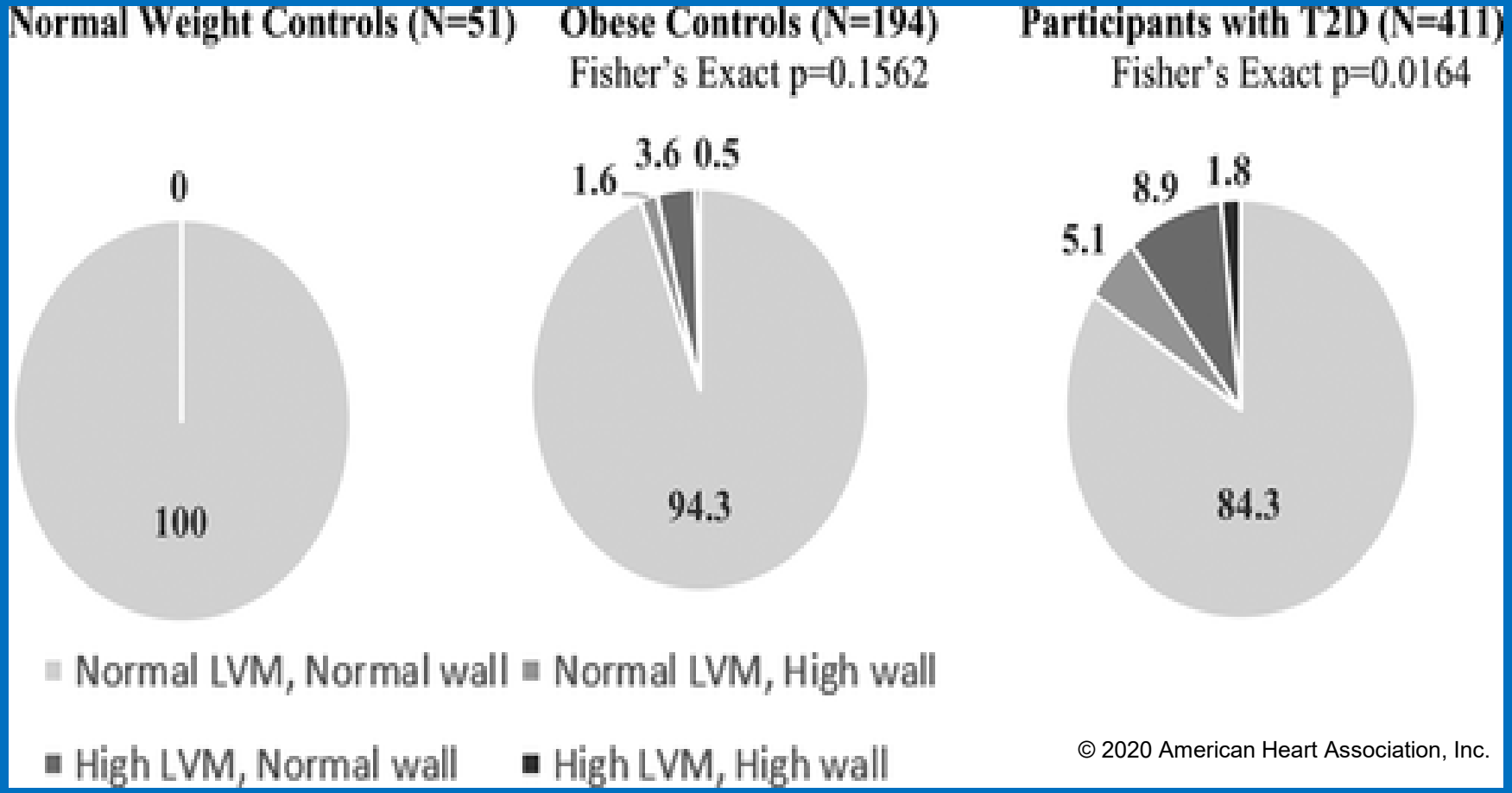
| Variable | TODAY, *n* = 397 | Obese control subjects, *n* = 133 | *P* value | |
|---|---|---|---|---|
| | | | Unadjusted | Adjusted |
| SDNN (ms)* | 58.1 ± 29.6 | 67.1 ± 25.4 | <0.0001 | <0.0001 |
| RMSSD (ms)* | 53.2 ± 36.7 | 67.9 ± 35.2 | <0.0001 | <0.0001 |
| PNN50 (%)* | 26.3 ± 23.7 | 39.7 ± 23.0 | <0.0001 | <0.0001 |
| LF Power (n.u.)† | 47.3 ± 20.0 | 39.5 ± 19.7 | 0.0001 | <0.0001 |
| HF Power (n.u.)* | 52.7 ± 20.0 | 60.5 ± 19.7 | 0.0001 | <0.0001 |
| LF:HF ratio† | 1.4 ± 1.7 | 1.0 ± 1.1 | <0.0001 | <0.0001 |

HRV indices in TODAY participants versus obese control subjects

- Unadjusted means ± SD are shown in the table. Total power for TODAY participants was 2,576 ± 2,919. *P* value from general linear model comparing mean of the obese control subjects to the TODAY participants. SDNN, RMSSD, and LF:HF ratio were log transformed prior to testing because of skewed distribution. A nonparametric rank-based test was used to compare the PNN50 values. Unadjusted and adjusted *P* values for age, sex, race-ethnicity, smoking, and BMI are given for the cardiac autonomic function measures. n.u., normalized units.
- * Lower = worse.
- † Higher = worse.

Shah AS, El Ghormli L, Vajravelu ME, et al. *Diabetes Care*. 2019;42(11):2143-2150. doi:10.2337/dc19-0993

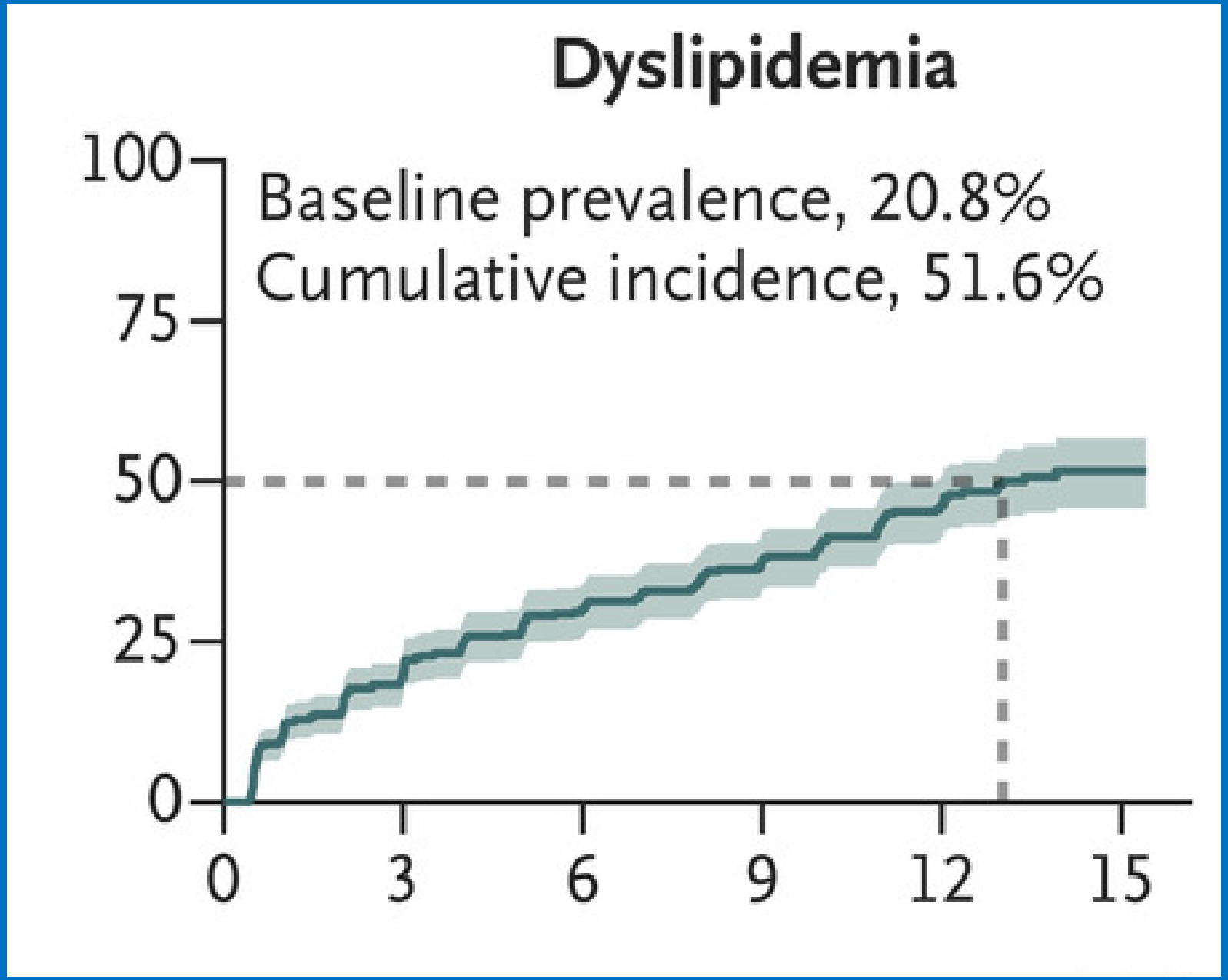
# Cardiac Changes in Youth Onset T2DM





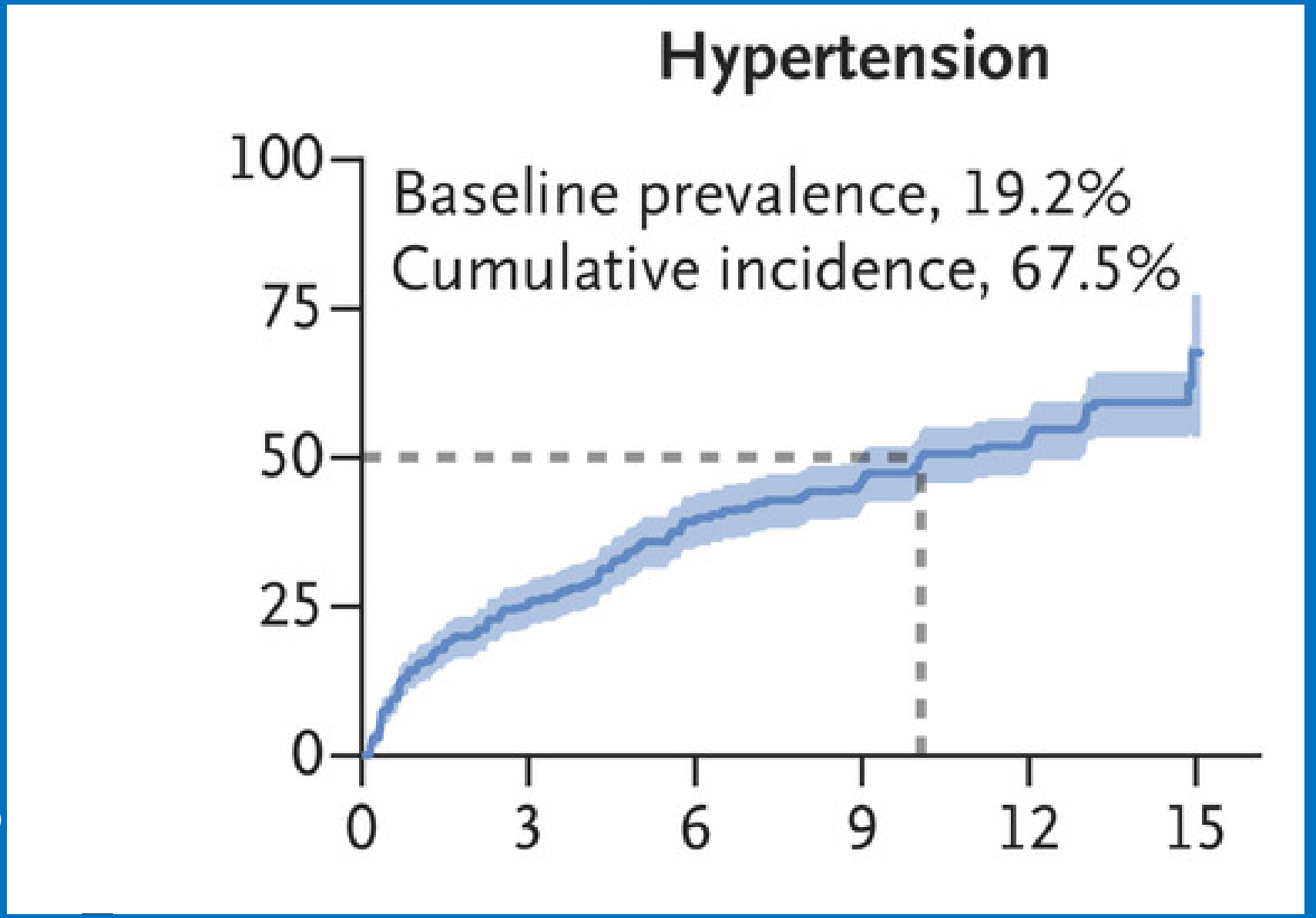

TODAY Study Group. Longitudinal Changes in Cardiac Structure and Function From Adolescence to Young Adulthood in Participants With Type 2 Diabetes Mellitus: The TODAY Follow-Up Study. Circ Heart Fail. 2020 Jun;13(6):e006685. doi: 10.1161/CIRCHEARTFAILURE.119.006685. Epub 2020 Jun 5. PMID: 32498621.

# Cardio-Metabolic Risk in Youth Onset T2DM




TODAY Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggestad J, White NH, Zeitler P. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021 Jul 29;385(5):416-426. doi: 10.1056/NEJMoa2100165. PMID: 34320286.

# Cardio-Metabolic Risk in Youth Onset T2DM

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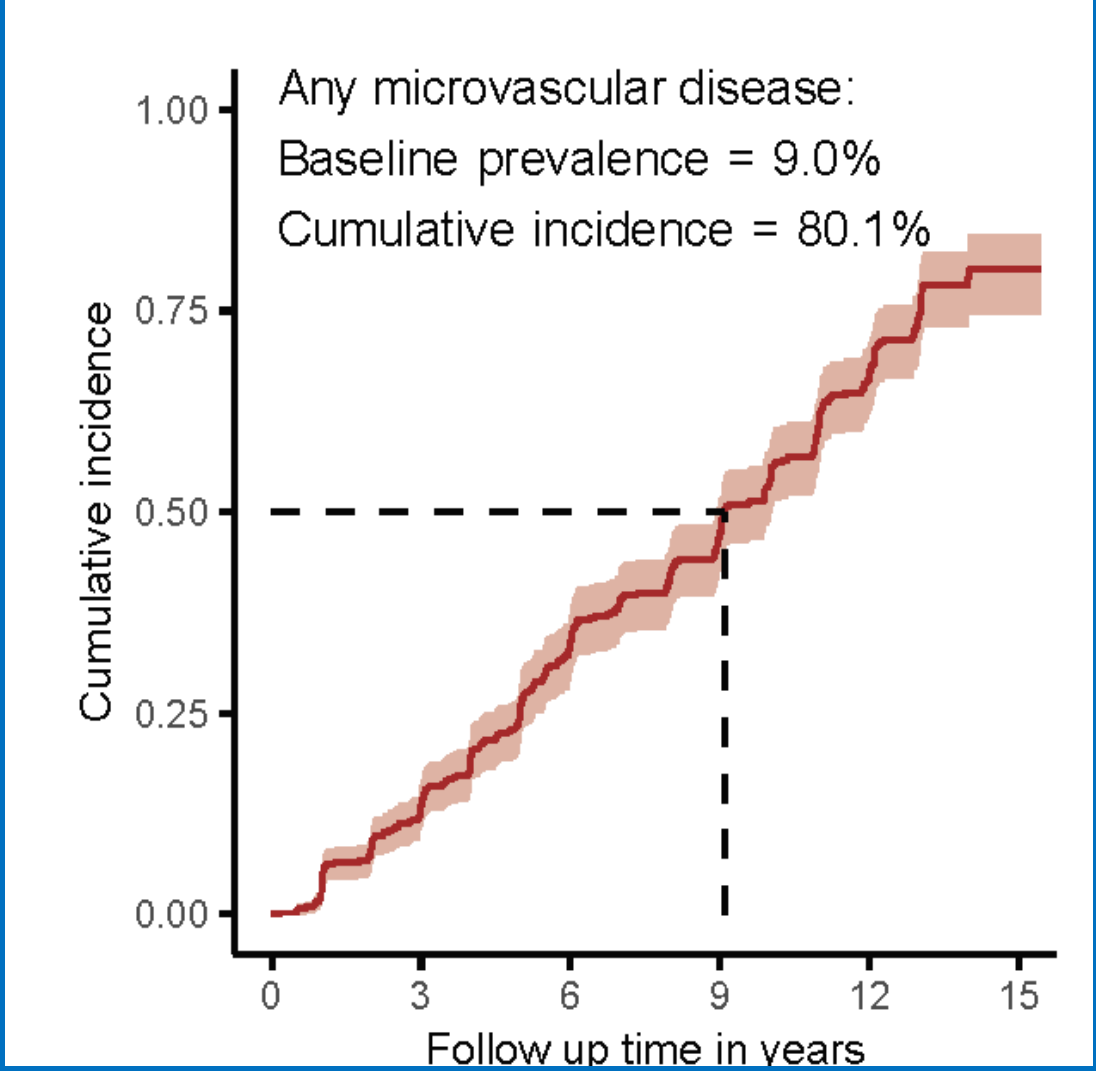
# Cumulative Incidence of Microvascular Complications




| | Hazard Ratio (95% CI) |
|---|---|
| Race/Ethnicity | |
| H vs NHW | **1.50 (1.13, 2.00)** |
| H vs NHB | 1.02 (0.82, 1.28) |
| NWB vs NHW | **1.46 (1.09, 1.16)** |
| Adjusted Models (sex, race, age, duration) | |
| HbA1c (per 1% or 11 mmol/mol) | **1.18 (1.14, 1.23)** |
| BMI (per 5 kg/m$^2$) | **1.08 (1.01, 1.15)** |
| Insulin sensitivity (per 1 SD) | **0.81 (0.73, 0.90)** |
| Hypertension | **1.39 (1.12, 1.72)** |
| Dyslipidemia | **1.28 (1.03, 1.59)** |

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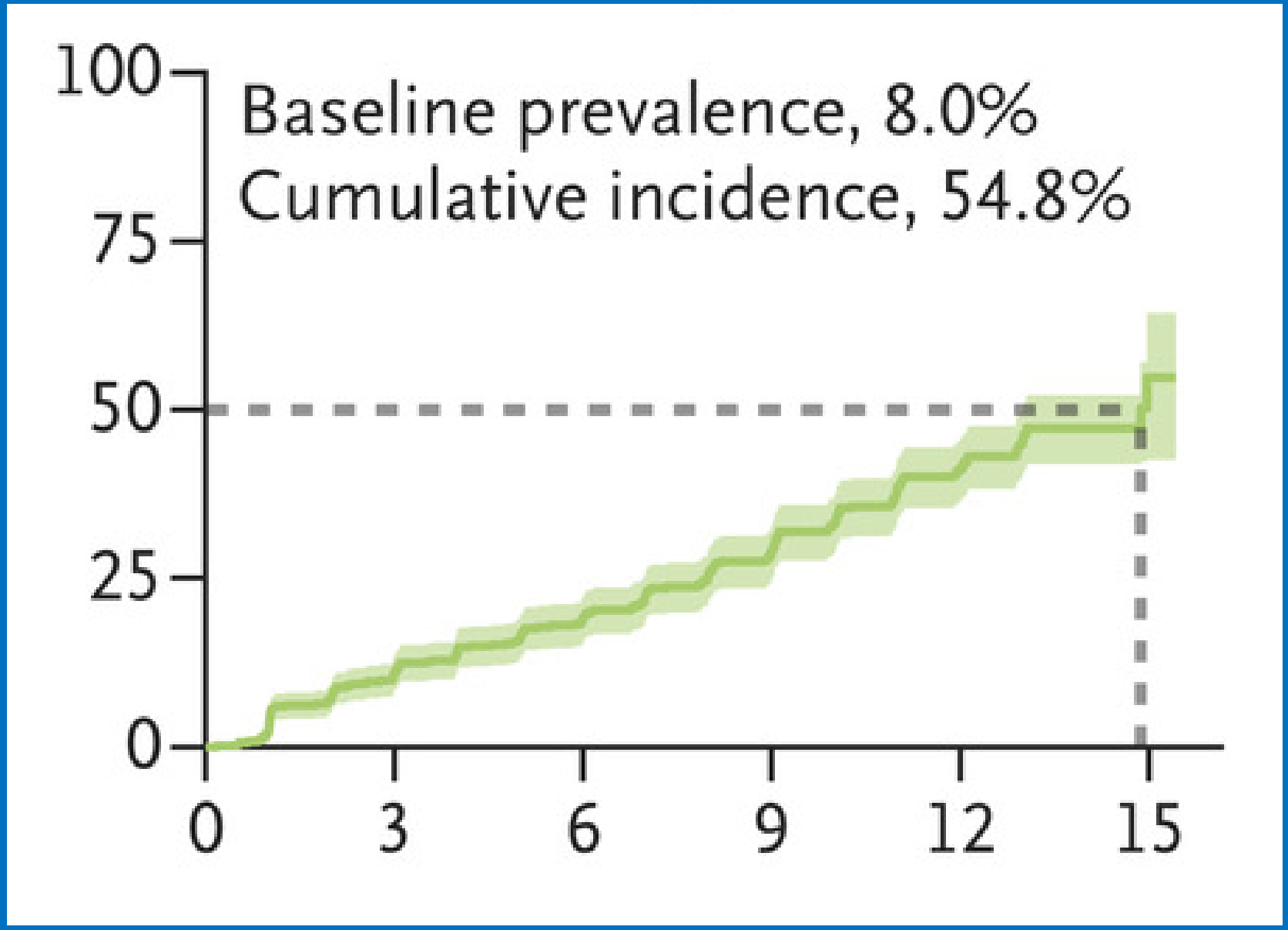
# Nephropathy in Youth Onset T2DM

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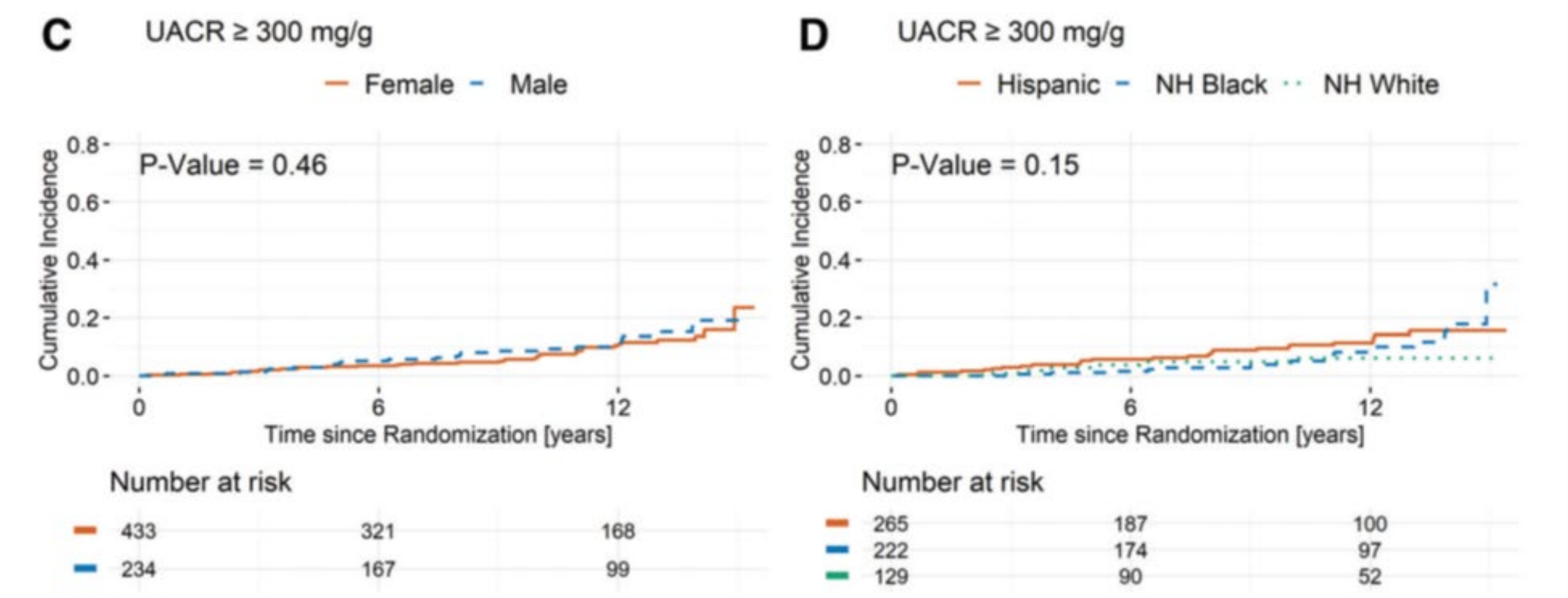
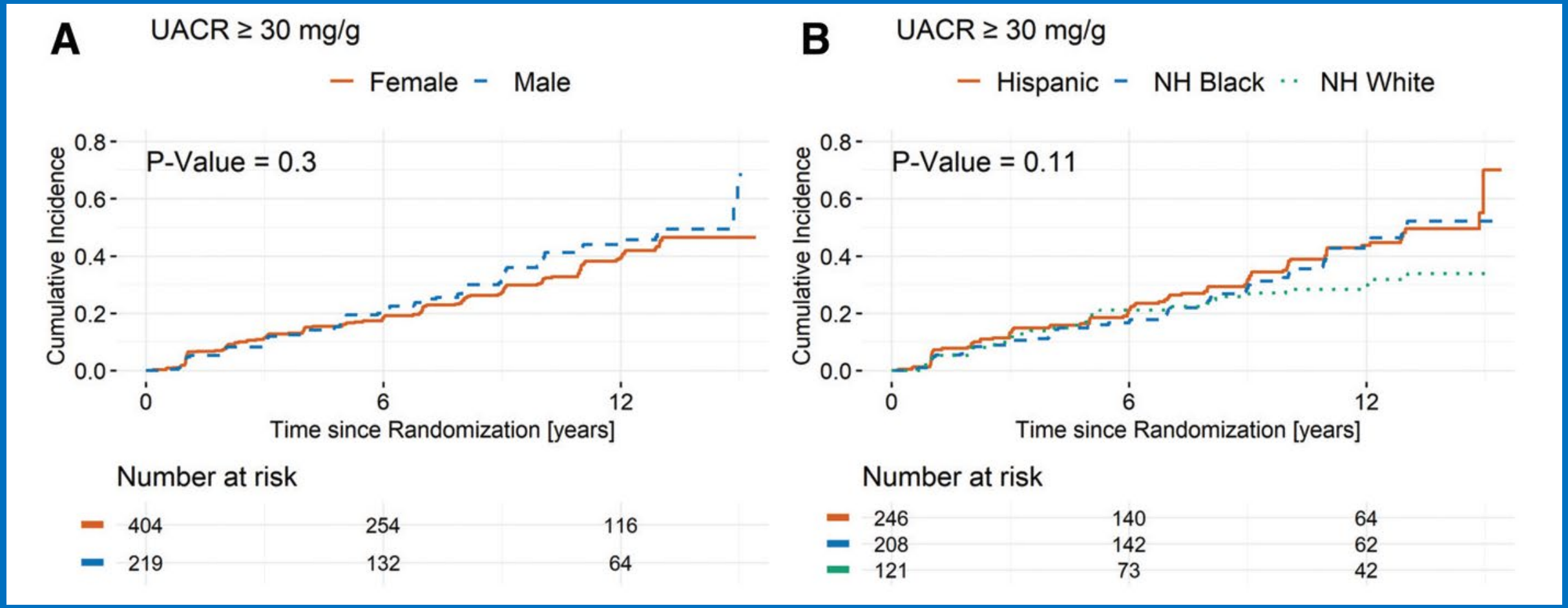
# Nephropathy in T2DM




The TODAY Study. Diabetes Care. 2021

# Nephropathy in T2DM




The TODAY Study. Diabetes Care. 2021

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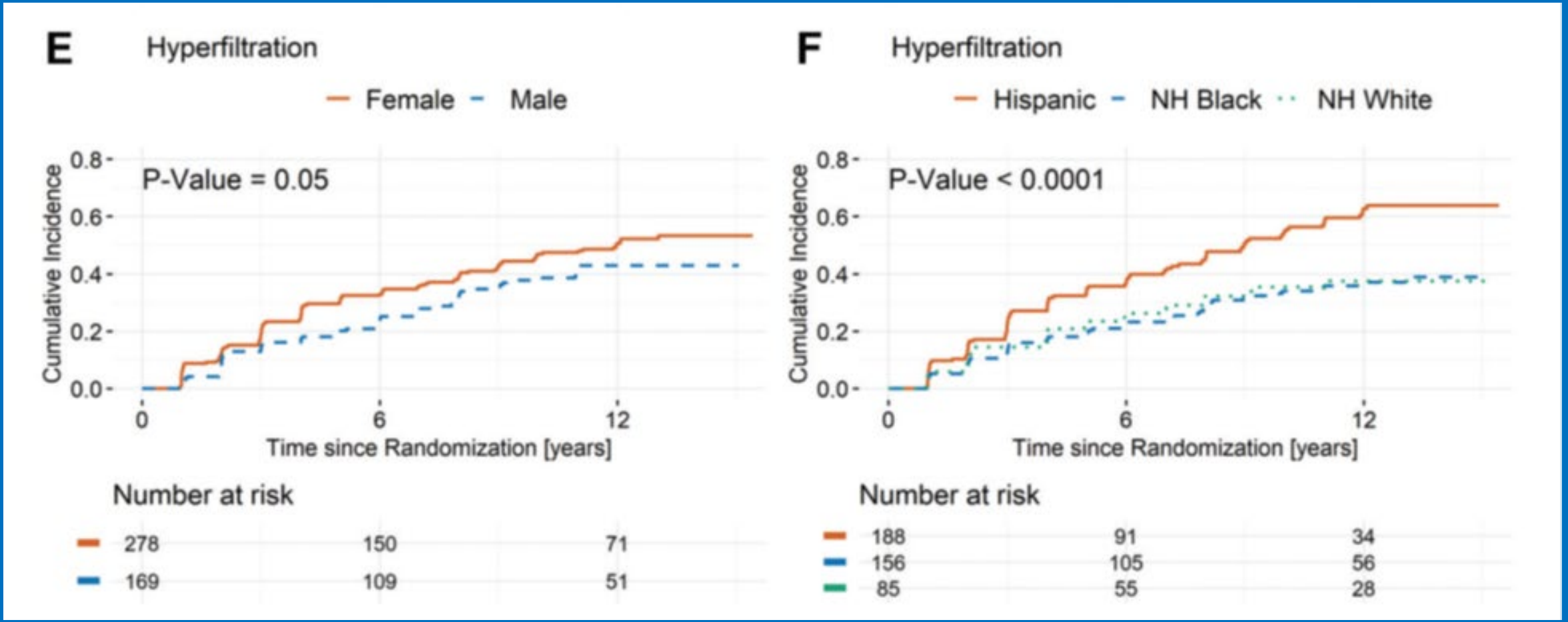
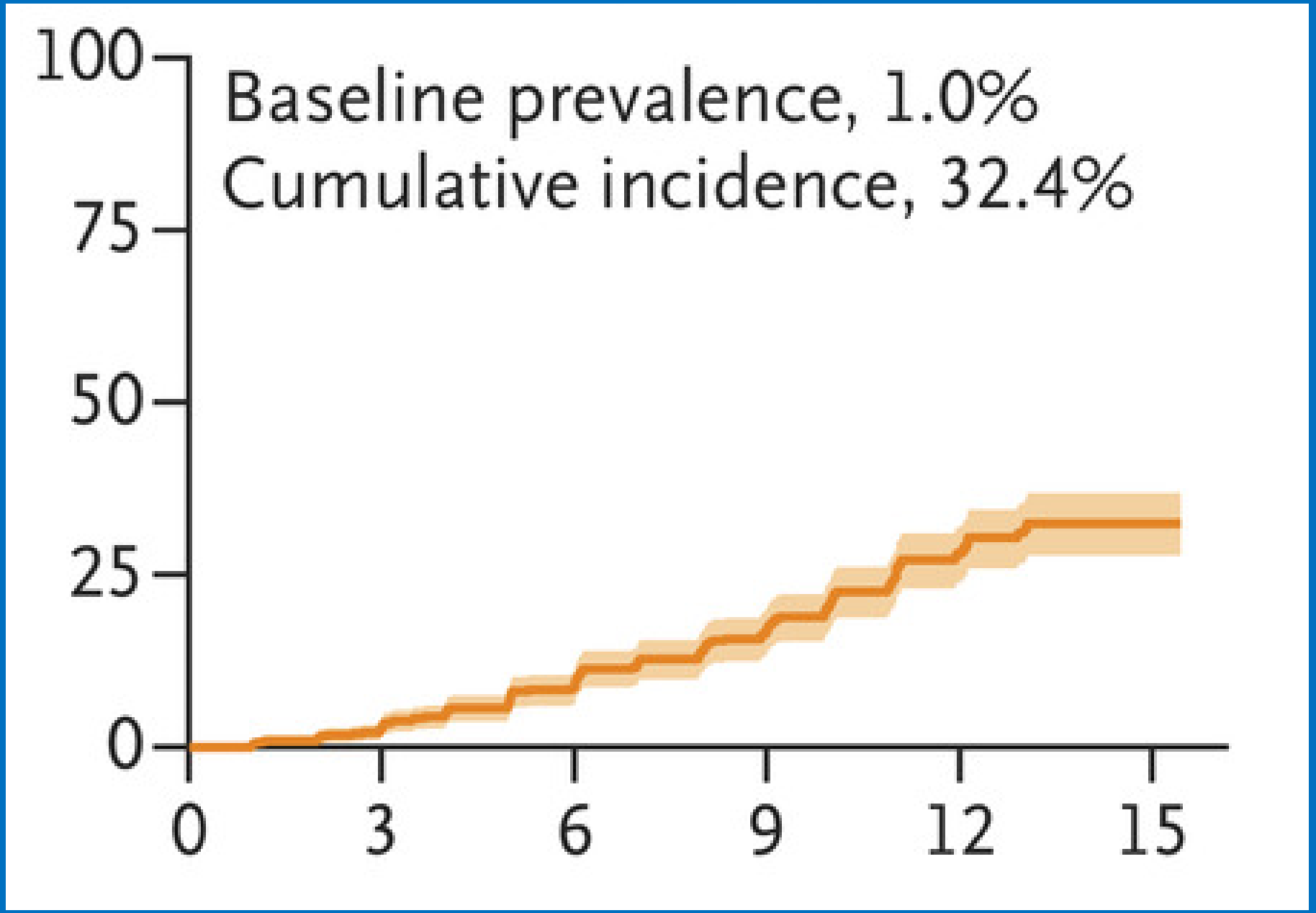



The TODAY Study. Diabetes Care. 2021

# Neuropathy in Youth Onset T2DM

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# Retinopathy and Clinically Significant Macular Edema – Progression Over Time

| | TODAY (N=496) | TODAY2 (N=404) |
|---|---|---|
| Diabetic retinopathy (DR) | | |
| No definitive DR | 86.3% | 50.0% |
| Very mild non-proliferative DR (NPDR) | 13.7% | 22.8% |
| Mild NPDR | 0.0% | 16.3% |
| Moderate NPDR | 0.0% | 3.7% |
| Moderately severe NPDR | 0.0% | 0.7% |
| Severe NPDR | 0.0% | 1.2% |
| Early or stable, treated PDR | 0.0% | 2.2% |
| High risk PDR | 0.0% | 1.0% |
| Macular edema | 0.0% | 3.5% |

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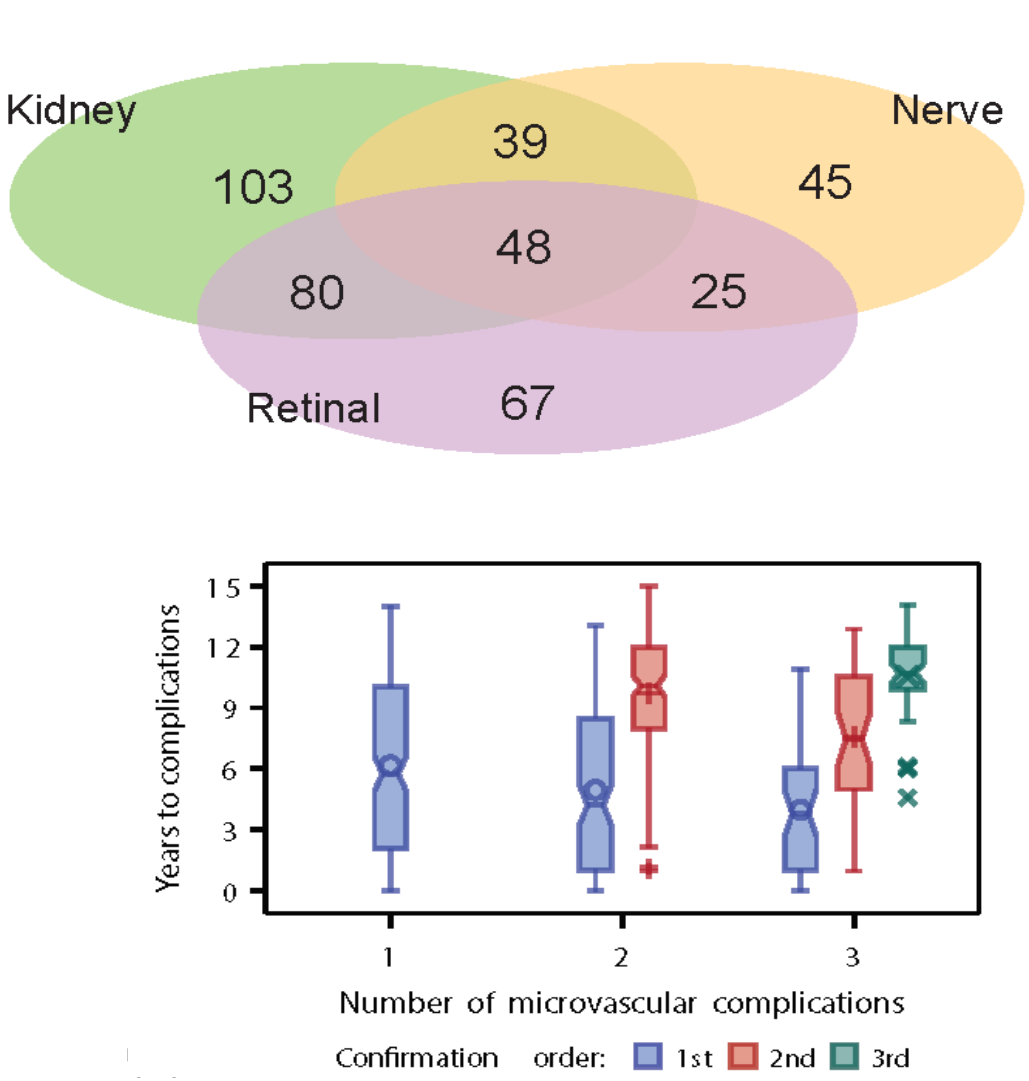
# Clustering of Microvascular Complications




| | Hazard Ratio (95% CI) |
|---|---|
| Race/Ethnicity (vs. NHW) | |
| H | **1.57 (1.06, 2.33)** |
| NHB | **1.80 (1.20, 2.68)** |
| Adjusted models (sex, race/ethnicity, age, duration) | |
| HbA1c (per 1% or 11 mmol/mol) | **1.78 (1.64, 1.93)** |
| Insulin sensitivity (per 1 SD) | **0.65 (0.56, 0.74)** |
| Hypertension | **3.09 (2.31, 4.15)** |
| Dyslipidemia | **2.43 (1.83, 3.22)** |

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| | # Events | # Patients | Event Rate (per 1000 PYr) |
|---|---|---|---|
| **Heart, Vascular, and Cerebrovascular Events** | | | |
| Arrhythmia | 11 | 9 | 1.61 |
| Coronary artery disease | 3 | 3 | 0.42 |
| Congestive heart failure | 6 | 6 | 0.88 |
| Left ventricular systolic dysfunction | 5 | 5 | 0.71 |
| Myocardial infarction | 4 | 3 | 0.58 |
| Deep vein thrombosis | 6 | 6 | 0.88 |
| Vascular Insufficiency | 1 | 1 | 0.15 |
| Stroke | 4 | 3 | 0.58 |
| Transient ischemic attack | 1 | 1 | 0.15 |

TODAY Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggestad J, White NH, Zeitler P. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021 Jul 29;385(5):416-426. doi: 10.1056/NEJMoa2100165. PMID: 34320286.

# Deaths

- Myocardial infarction
- Kidney failure
- Sepsis complication end-stage kidney disease
- Post-operative sepsis with multi-organ failure
- Drug overdose

# Treatment and Screening Recommendations for T2DM in Youth

# Recommendations

- Glycemic Control
  - Start metformin at onset
  - If A1c is above 8.5% insulin therapy with a long acting analogue is needed
  - Consider GLP-1 analogues to optimize glucose control

- Screening/Treatment
  - Screen for dyslipidemia, hypertension, nephropathy and retinopathy at diagnosis and annually thereafter
  - Start antihypertensive if BP>95% for height or over 135mmHg systolic
  - Start ACEI for urine albumin/Cr ratio >30mg/g

# Metformin

- Mechanism of action
  - Decrease hepatic glucose production
  - Decrease intestinal absorption of glucose
  - Improve insulin sensitivity
- Studies in youth
  - Decrease A1c
  - Decrease weight
  - Improve lipid profile

# Limitations of Metformin Therapy

- TODAY study
  - 50% of youth with T2DM failed initial therapy with metformin within 4 years
- SEARCH
  - 2 years after diagnosis, 50% has A1c >8% and 50% required insulin therapy

Pinto, CA Pediatric Diabetes 2018

# GLP-1 Agonist

- Mechanism of action
  - Glucagon like peptide-1 (GLP-1) agonist
  - Glucose dependent stimulation of insulin
  - Delayed gastric emptying
  - Appetite suppression
- Studies in Youth
  - Mean A1c decreased by 0.4-0.64%
  - Lower fasting glucose
- Preparations
  - Liraglutide – daily injection
  - Exenatide – weekly injection

Tamborlane NEJM 2019

# Long Acting Insulins

- Detemir (Levemir®)
- Glargine (Lantus®, Basaglar®, Toujeo®U-300)
- Degludec (Tresiba®)

# Rapid acting insulins

- Lispro (Admelog®, Humalog®)
- Aspart (NovoLog®)
- Glulisine (Apidra®)

# Cases

- Case 1 - 16yo Hispanic male presented to ED with polyuria and polydipsia and 60lb weight loss in 2 months (weight now at 91%)
  - Type 1 DM with positive antibodies

- Case 2 - 16yo Hispanic female, obese, acanthosis on neck, family history of type 2 diabetes (T2DM) presents with polyuria and polydipsia
  - Type 2 DM

# Conclusion and Pearls

- Type 2 diabetes in youth is much more aggressive that adult onset T2DM
  - Complications are happening earlier
  - Deaths in the TODAY trial (6 total)
- With increase in failure of beta cell function with time, new meds are needed to preserve the beta cell function in youth
- Novel interventions are also needed to prevent diabetes even as early as pre-pregnancy interventions

# Questions?

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# Upcoming Events!

- *Webinar Series*: Chronic Kidney Disease
  - Meri Hicks, SWOSU
  - Tuesday, August 16th (12-1pm)

- **WOW Consortium Meeting**
  - Tuesday, September 20th (2-3pm)
  - Microsoft Teams

- *Webinar Series*: Inpatient Glycemic Control
  - Mary Shreffler, OU Health
  - Tuesday, September 27th (TBD)

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**For more information on WOW and to join our consortium:**

**Email jnoble@ofmq.com**

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