



National Institute of
Diabetes and Digestive
and Kidney Diseases

Gestational and Type 2 Diabetes in Women and Girls: Challenges, Progress, and Paths Forward

Griffin P. Rodgers, M.D., M.A.C.P.

Director, National Institute of Diabetes and Digestive and Kidney
Diseases

National Institutes of Health

October 23, 2018

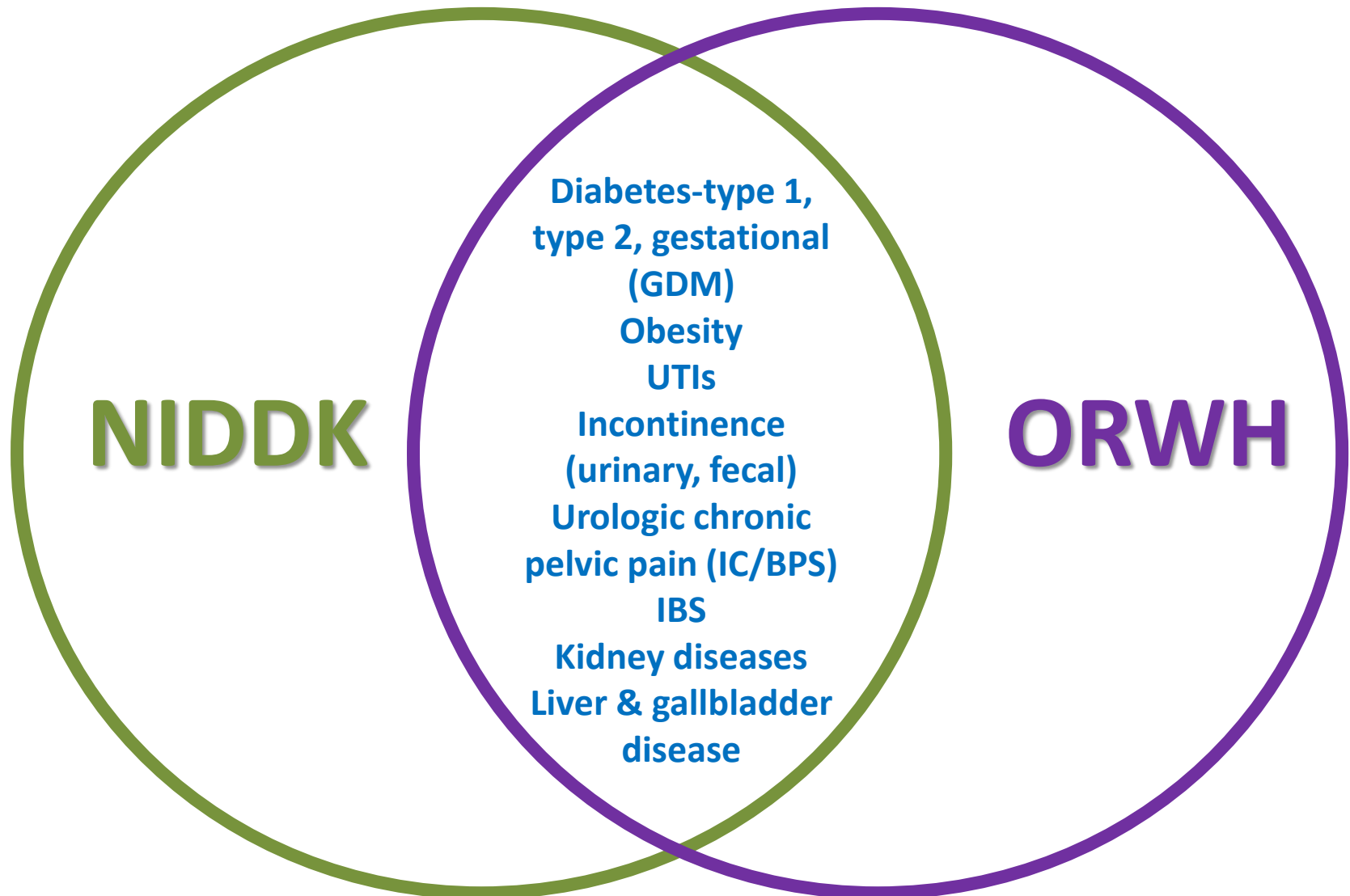
Advisory Committee for Research on Women's Health

Twitter: @NIDDKgov



NIH National Institute of
Diabetes and Digestive
and Kidney Diseases

NIDDK and ORWH Research Areas of Common Interest—Examples



Working Together to Support Research on the Health of Women and SABV

Urinary Incontinence Treatment Network (UITN)



Specialized Centers of Research on Women's Health (IBS, UTIs, UI)



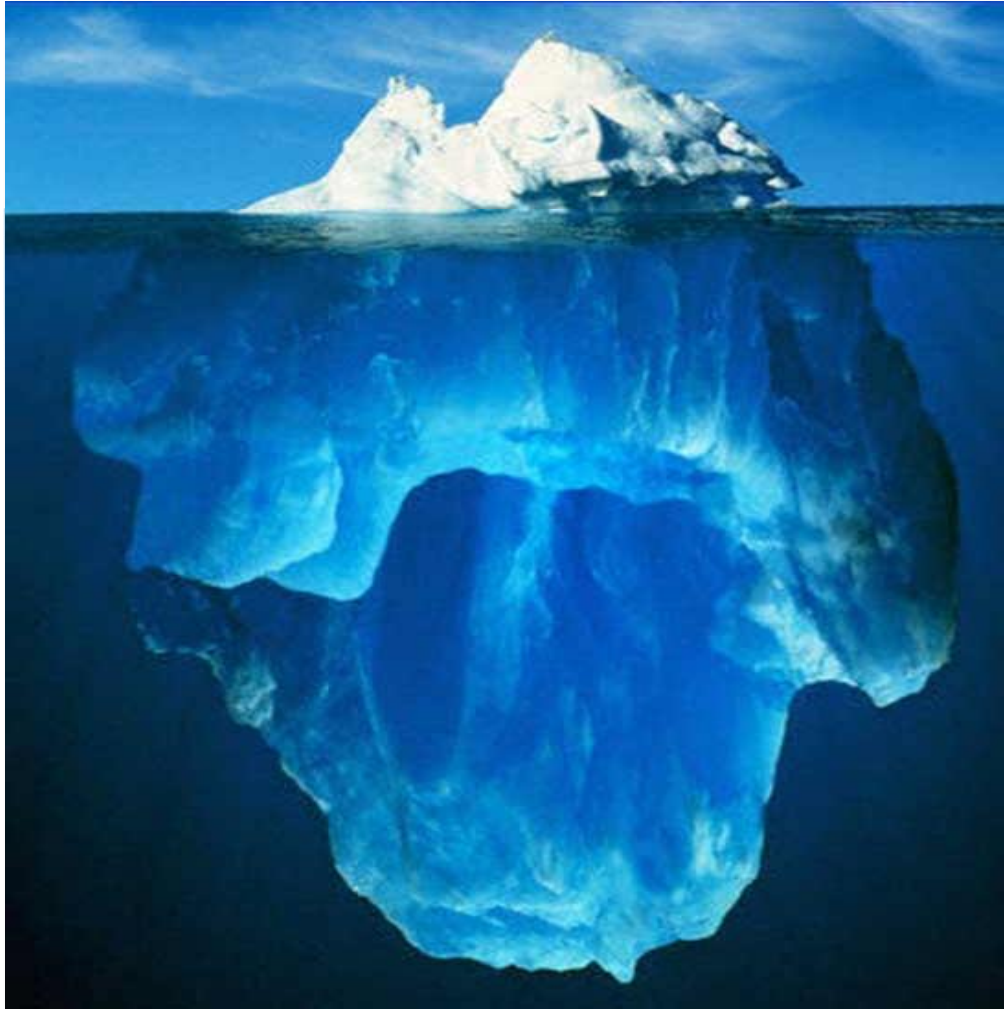
Program to Reduce Incontinence by Diet and Exercise (PRIDE) study



Challenges



Diabetes: The Tip of the Iceberg



U.S. Diabetes

30.3 million*

23.1 million diagnosed;
7.2 million undiagnosed

U.S. Prediabetes

84.1 million†

9.8 million aware of their prediabetes
74.3 million unaware

*All ages, 2015

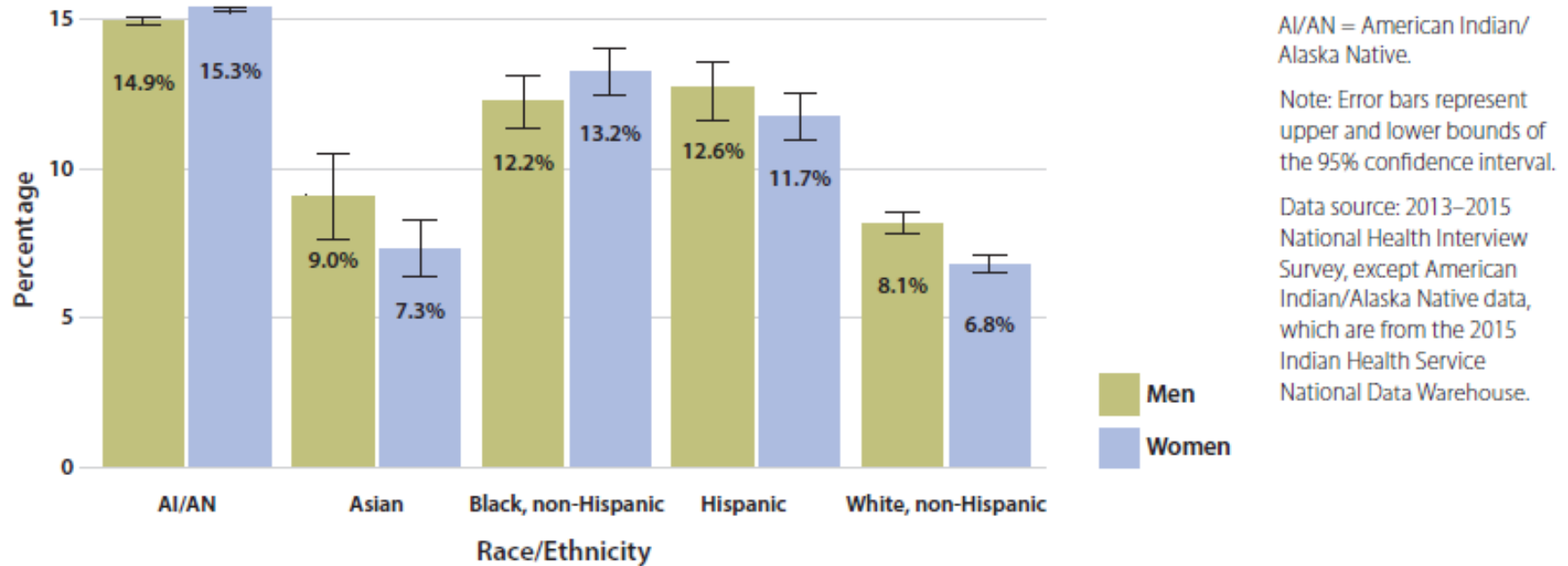
† Age 18 and older with IFG +/-or A1c between 5.7 and 6.4 (2015)



NIH National Institute of
Diabetes and Digestive
and Kidney Diseases

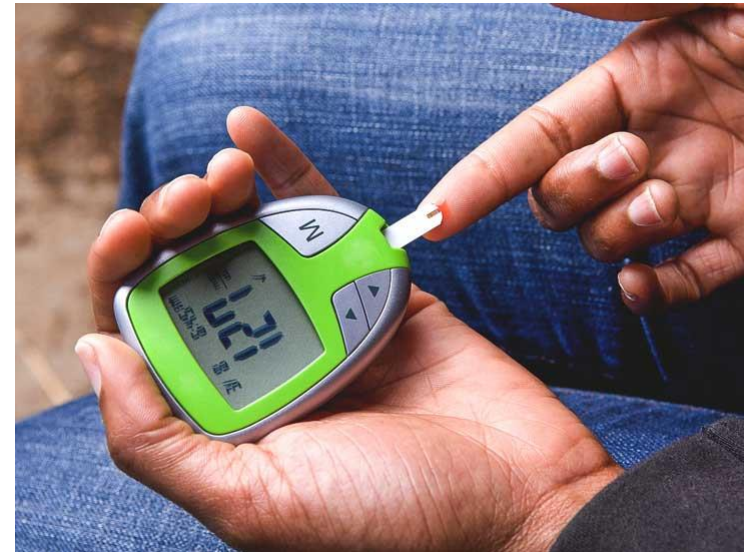
Burden of Diagnosed Diabetes in the United States by Gender and Race/Ethnicity

Figure 1. Estimated age-adjusted prevalence of diagnosed diabetes by race/ethnicity and sex among adults aged ≥ 18 years, United States, 2013–2015



Major Forms of Diabetes

- **Type 1 diabetes**
 - Misguided autoimmune attack destroys the insulin-producing beta cells in the pancreas of those who are genetically susceptible
 - 5% of diabetes cases
 - Usually strikes in childhood or youth
- **Type 2 diabetes**
 - Body does not make or use insulin well
 - 95% of diabetes cases
 - Associated with obesity, older age, certain racial and ethnic groups in the United States.
- **Gestational diabetes mellitus (*see next slide*)**

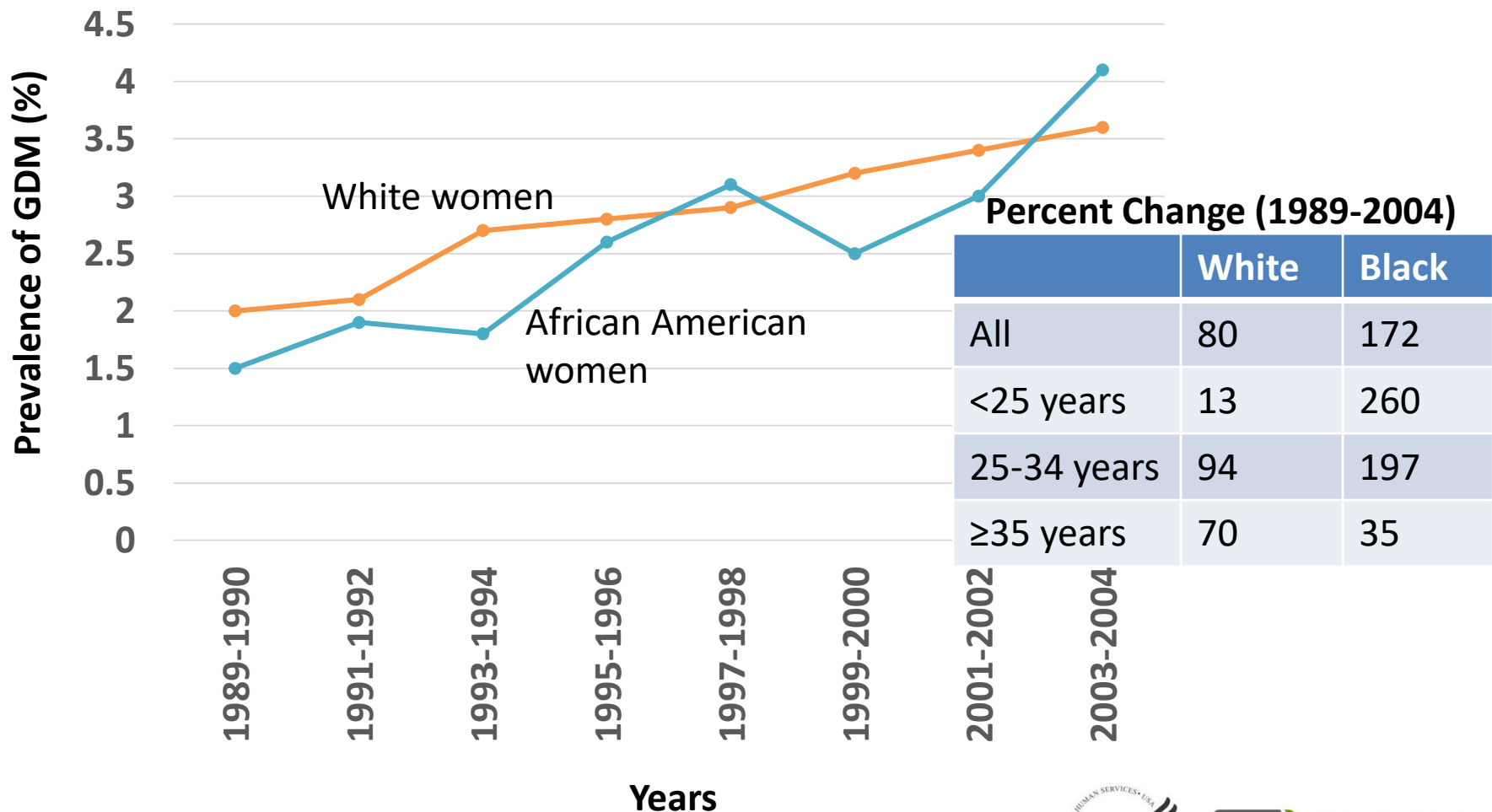


Gestational Diabetes Mellitus (GDM)

- Diagnosed during pregnancy
- Complicates ~7 percent of pregnancies in the U.S. each year
- If uncontrolled, may lead to high blood pressure
- Increases risk of subsequent type 2 diabetes in mothers and obesity and type 2 diabetes in offspring
- Risk factors include
 - Close relative with diabetes
 - African American, American Indian, Asian American, Hispanic/Latino, or Pacific Islander
 - 25 years old or older
 - Overweight
 - Previous GDM or previous baby weighing more than 9 pounds



Prevalence of GDM Is Increasing...



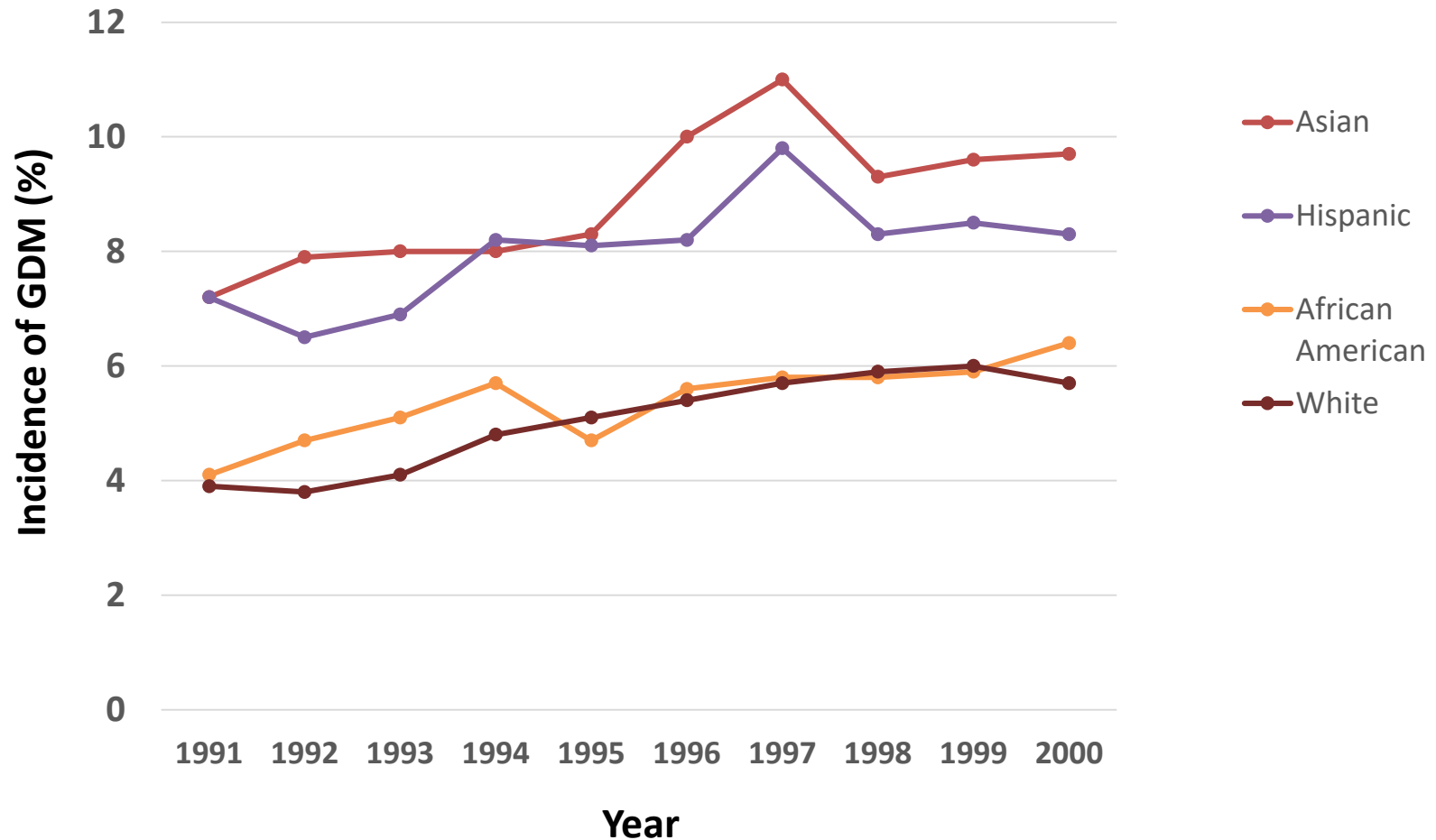
Source: *Diabetes in America, 3rd Edition, Table 4.2.*

Data from Getahun D, et al. *Am J Obstet Gynecol* 198: 525.e1–525.e5, 2008.



...And So Is GDM Incidence

Age-adjusted incidence in women age 15-49 years, Kaiser Permanente Northern California
Gestational Diabetes Registry



Source: *Diabetes in America, 3rd Edition, Table 4.4.*

Data from Ferrara A, et al. *Obstet Gynecol* 103:526–533, 2004.

Gestational Diabetes and Type 2 Diabetes— Distinct But Related in Girls and Women

Obesity, race/ethnicity,
age, genetics (type 2,
GDM)
“Black box” (GDM)

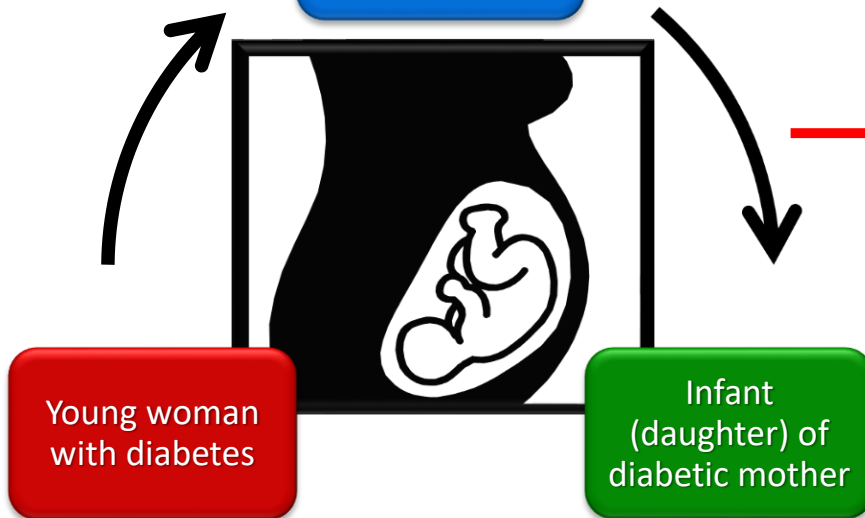
Type 2 diabetes
GDM

Pregnant
woman with
diabetes

GDM

Higher risk for
type 2 diabetes
and its
complications

Negative
pregnancy
outcomes



Young woman
with diabetes

Infant
(daughter) of
diabetic mother

Early diagnosis of type 2
diabetes in girls and boys=

- Harder to control
- Longer time to develop devastating complications, disease more aggressive than in adults

Increased risk of obesity, type 2 diabetes
(girls and boys)

Progress and Paths Forward



NIDDK Clinical Studies Addressing Type 2 Diabetes and Diabetes/Hyperglycemia During Pregnancy

HAPO/
Hyperglycemia & Adverse Pregnancy Outcome
HAPO
FOLLOW-UP STUDY



RISE



Normal \rightleftharpoons Pre-diabetes \rightleftharpoons Type 2 Diabetes \rightarrow Complications

Preclinical state Clinical disease Complications



NIH National Institute of Diabetes and Digestive and Kidney Diseases



Diabetes Prevention Program

- 3234 participants (45% minority, 68% female) with IGT who were overweight or obese
- Compared 3 approaches to diabetes prevention for 3 years:

■ Placebo

■ Metformin

■ Lifestyle





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Diabetes and
Digestive and Kidney Diseases
Bethesda, Maryland 20892

July 7, 2000

TO: Vivian Pinn, M.D.
Associate Director for Research on Women's Health

FROM: Director, NIDDK

SUBJECT: Continued Support of Diabetes Prevention Program (DPP)

The ORWH has provided \$200,000 annually to co-sponsor the Diabetes Prevention Program (DPP) since its inception in 1994. The NIDDK is very appreciative of this support, which has been used to facilitate the recruitment and retention of women, including women with a history of gestational diabetes (GDM), into the DPP. I am now

Page 2 – Vivian Pinn, M.D.

The ORWH support has been instrumental to the success of this study in meeting its recruitment and retention goals, and we look forward to continued partnership as the study is completed.

A handwritten signature in black ink, appearing to read "Allen Spiegel".

Allen M. Spiegel, M.D.

Lifestyle Intervention

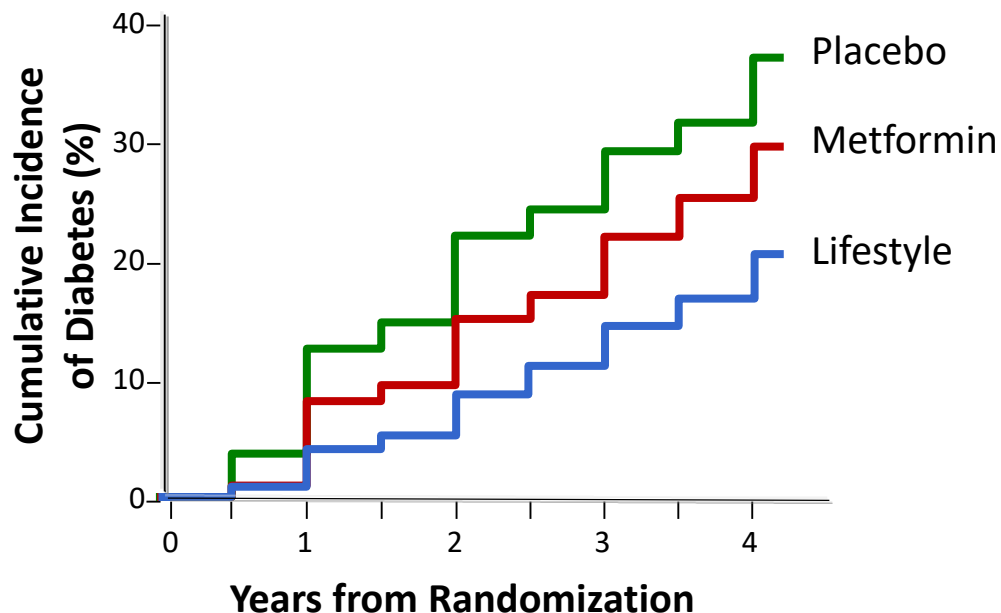
- Intensive behavioral modification program with the following goals
 - 7% weight loss
 - 150 minutes/week physical activity
- Intervention delivery
 - 16 session core curriculum delivered one-on-one over 24 weeks
 - Monthly visits post core





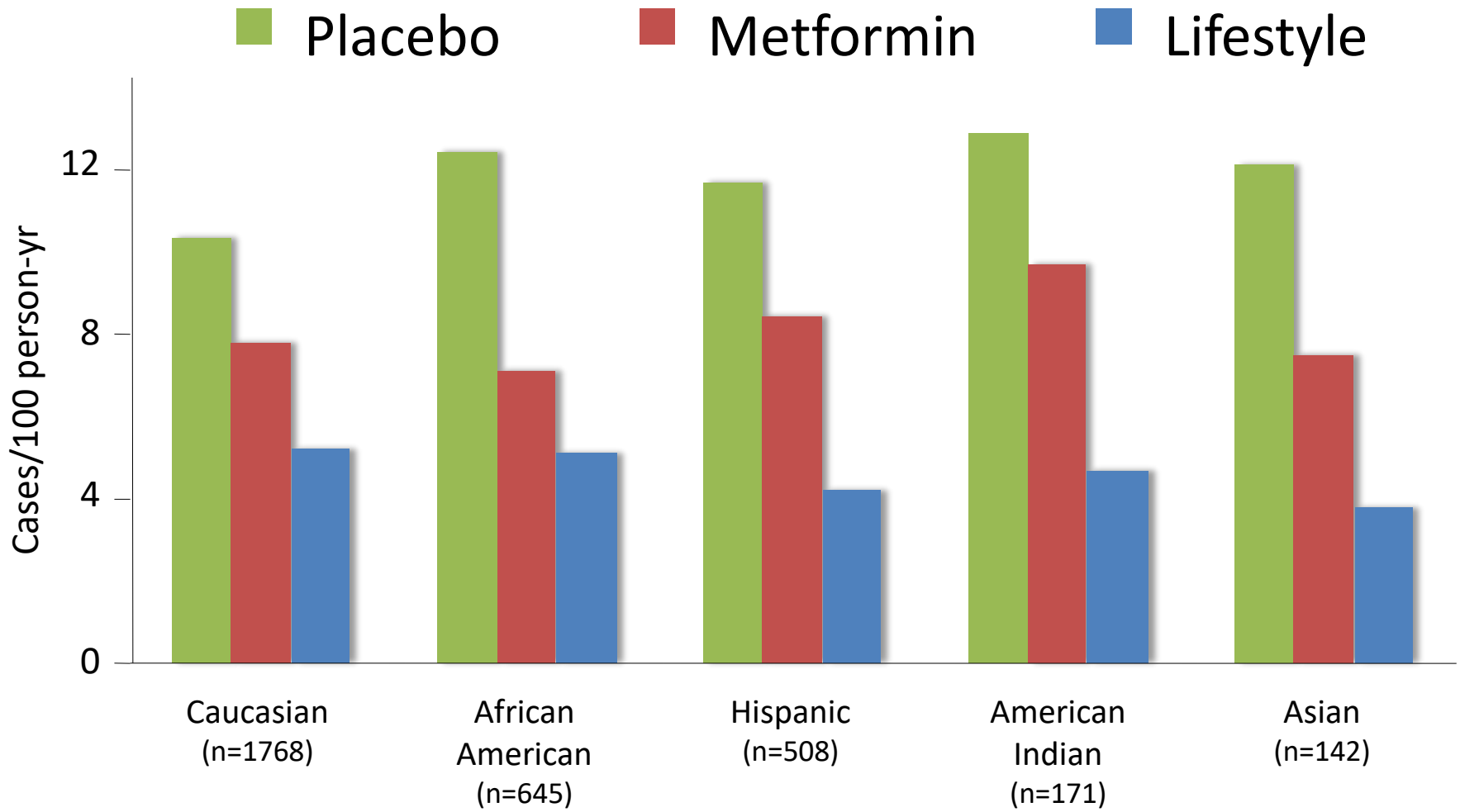
The Diabetes Prevention Program: Results

Percent Reduction in Diabetes Incidence Compared to Placebo



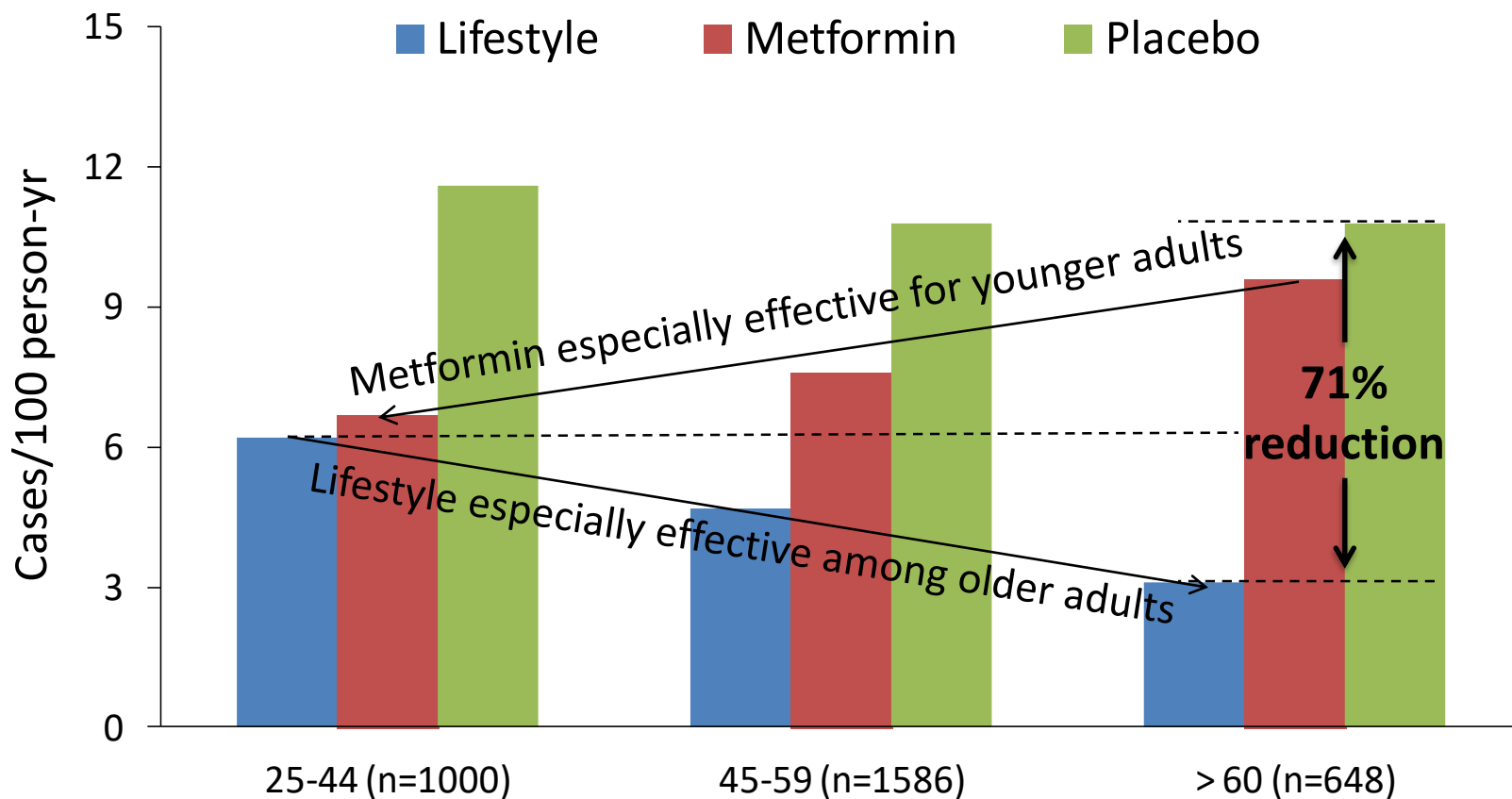
- Lifestyle modification lowered risk by **58%** (modest weight loss, from exercise and reduced fat and caloric intake)
- Metformin medication lowered risk by **31%**

DPP Results by Race



DPP Interventions by Age Group

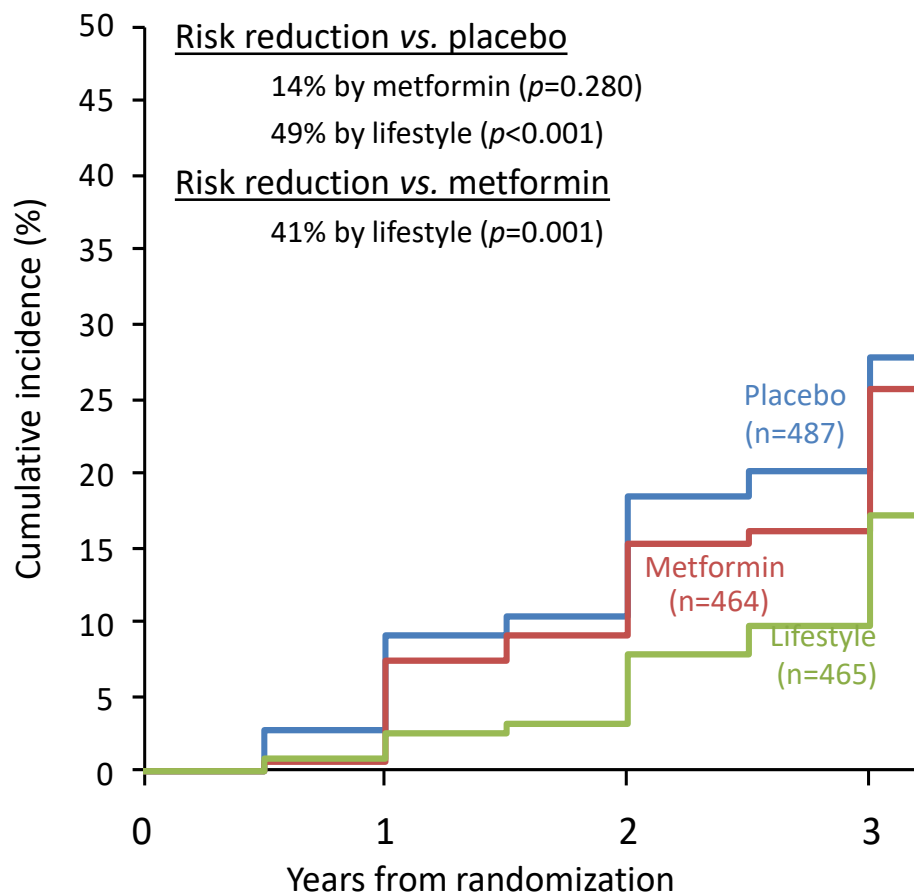
Effect of Age on Intervention Response



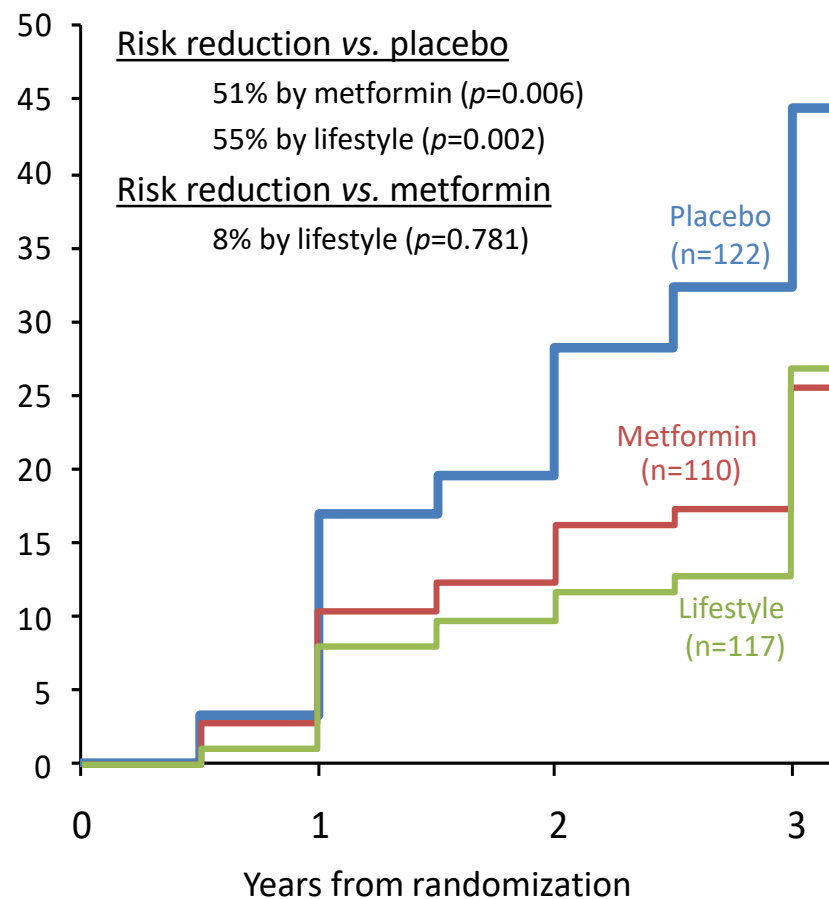


Cumulative Incidence of Diabetes in DPP Parous Women without and with a History of GDM

without GDM



with GDM



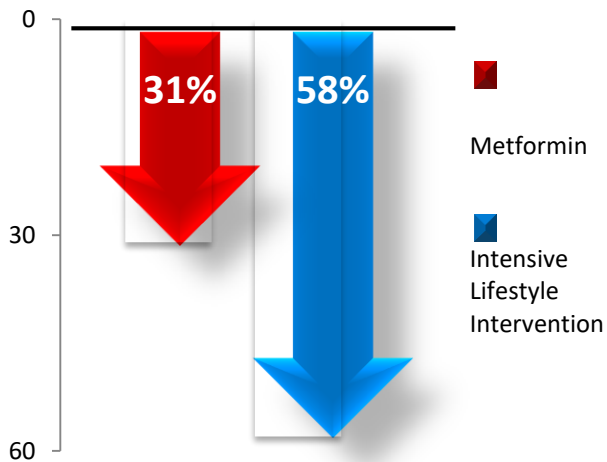
Adjusted for age

Data from Ratner RE, et al, *Clin Endocrinol Metab* 93: 4774–4779, 2008



The Diabetes Prevention Program: Collaborative and Transformative

Percent Reduction in Diabetes Incidence Compared to Placebo



Follow-up Research



- Metformin cost-saving

Diabetes Prevention Program (DPP)

3,234 individuals at risk for type 2 diabetes

- Lifestyle modification lowered risk by **58%** (modest weight loss, from exercise and reduced fat and caloric intake)
- Metformin medication lowered risk by **31%**

DPPOS Phase 3:

- Metformin for prevention of CVD and cancer
- Partnership with NHLBI, NCI, NIA, with support from ORWH

NIDDK Clinical Studies Addressing Type 2 Diabetes and Diabetes/Hyperglycemia During Pregnancy



Normal ↔ Pre-diabetes ↔ Type 2 Diabetes → Complications

Preclinical state Clinical disease Complications



NIH National Institute of Diabetes and Digestive and Kidney Diseases

GDM: Pregnancy and Birth Complications

Risks for the mother

- High blood pressure/preeclampsia
- Difficult or dangerous delivery
- Cesarean section



Risks for the baby

- Being born very large and with extra fat
- Low blood glucose right after birth
- Breathing problems
- Injury during birth (shoulder dystocia)

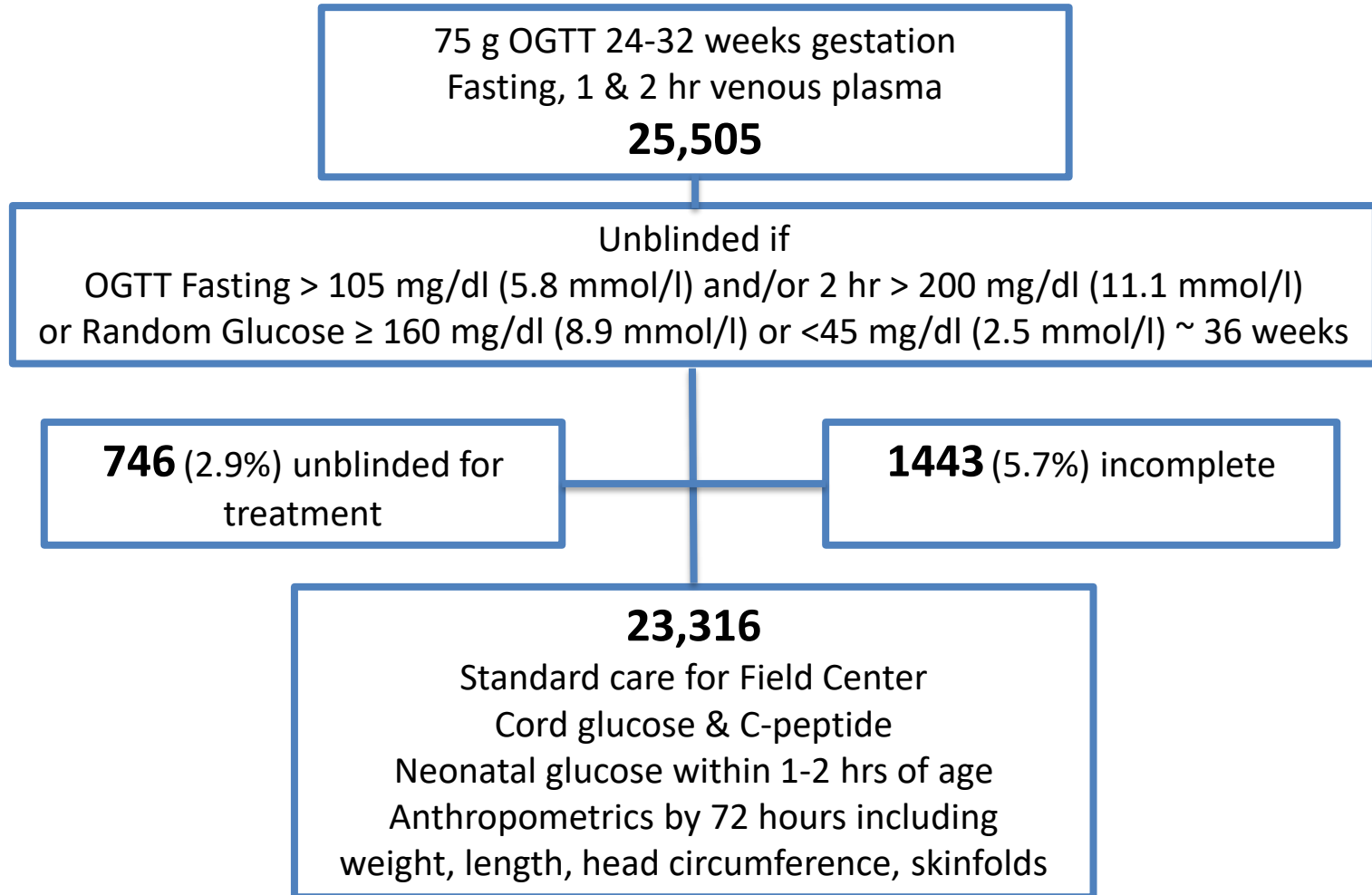


Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO)

- **Known:** GDM is associated with adverse perinatal outcomes and increased risk of subsequent type 2 diabetes in mothers.
- **HAPO:** Determine if there are adverse perinatal outcomes associated with maternal glucose intolerance less severe than overt diabetes
- International study at 15 sites
- Recruitment 2000-2006
- Funded by NICHD with co-funding from NIDDK

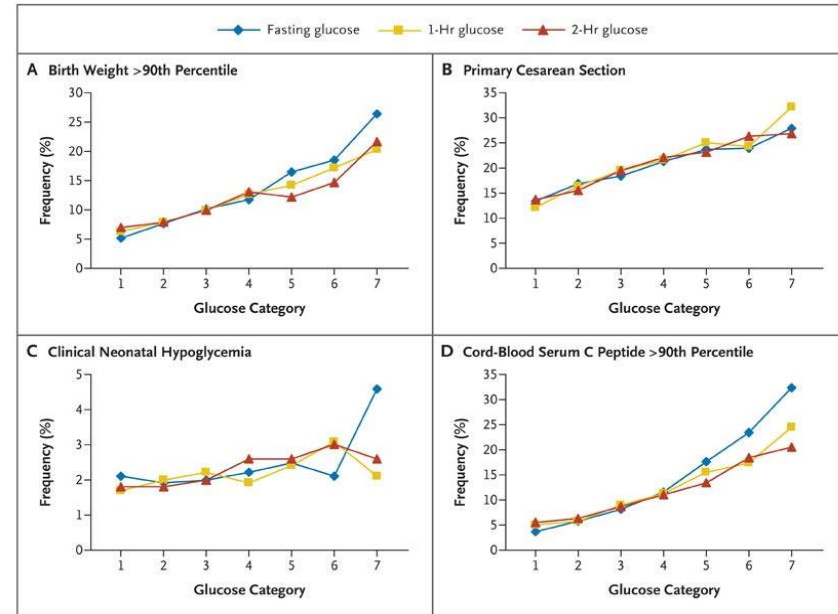


HAPO Protocol



HAPO Results

- Strong, continuous independent associations of maternal glucose below levels of overt diabetes with increased birth weight, cord-blood c-peptide, neonatal hypoglycemia and primary C-section, after controlling for possible confounders.
- Secondary outcomes, including neonatal adiposity, also showed continuous linear associations.
- The associations were observed across all centers and thus are generalizable.
- International Association of Diabetes and Pregnancy Study Groups (IADPSG) and WHO in 2013 adopted new criteria for diagnosing GDM based on HAPO data.



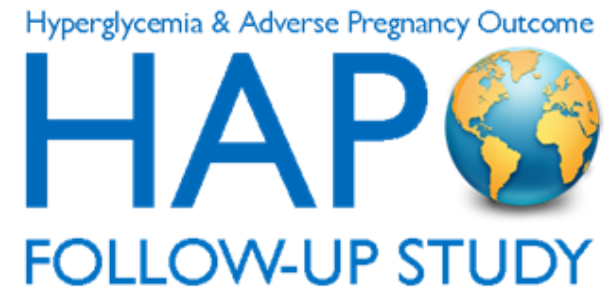
The HAPO Study Cooperative Research Group. *New England Journal of Medicine* (2008)



HAPO Follow Up Study

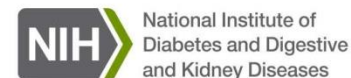
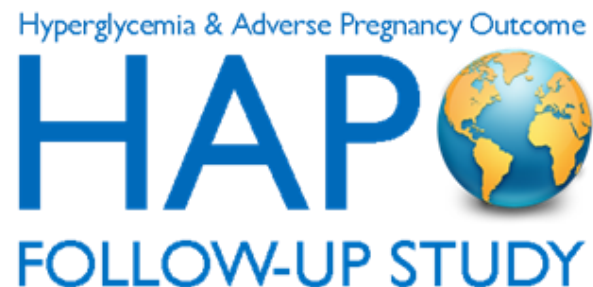
HAPO follow-up study (HAPO FUS) examined long-term sequelae 8 to 12 years after delivery. Primary goals:

- To determine associations of maternal glucose levels during pregnancy with adiposity in offspring at ages 8 to 12
- To determine associations of maternal glucose levels during pregnancy and maternal diabetes or prediabetes 8 to 12 years later



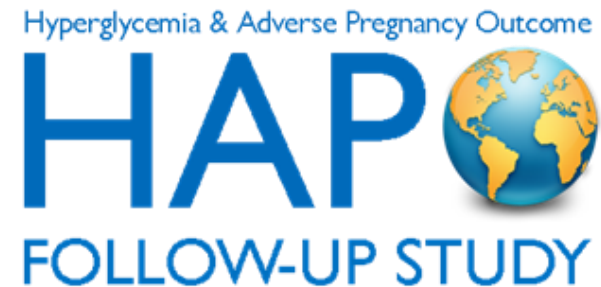
HAPO FUS Secondary Aims

- To determine associations of maternal glucose levels during pregnancy with metabolic disorders in offspring at ages 8 to 12 (glycemia, insulin sensitivity and secretion, lipids, blood pressure and inflammation)
- To determine associations of maternal glucose levels during pregnancy with measures of cardiovascular (CV) risk in mothers 8 to 12 years later
- To determine associations of measures of neonatal adiposity and hyperinsulinemia with measures of obesity/adiposity, as well as metabolic disorders (glycemia, insulin sensitivity and secretion, lipids, blood pressure and inflammation), in offspring at ages 8 to 12



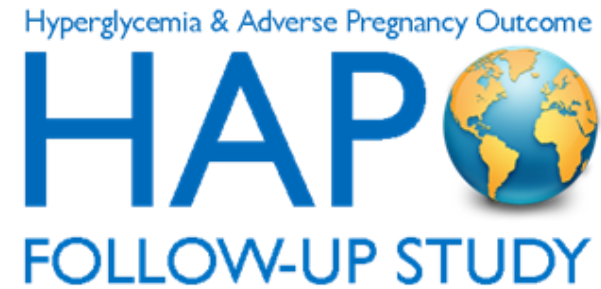
HAPO FUS Key Results

- HAPO FUS ultimately followed up at 10 to 14 years postpartum, avg 11.4 years
- “New” GDM confers future type 2 diabetes risk to mom
 - 52.2% developed type 2 diabetes or prediabetes compared with 20.1% of mothers without “new” GDM
 - Over five-fold increase in likelihood of developing type 2 diabetes during follow up period in mothers with “new” GDM (adjusted for type 2 diabetes risk factors)
- Results in offspring mixed:
 - Relationship between “new” GDM and overweight and obesity (combined outcome) in offspring, adjusted for mom’s BMI, not significant.
 - However, “new” GDM confers 1.58-fold increase in childhood obesity risk to offspring (adjusted for mom’s BMI).
- Bottom line: strong relationship between “new” GDM and subsequent type 2 diabetes in the mothers and obesity in the offspring.
- → Analysis of dysglycemia in offspring is ongoing



HAPO FUS: Unique Characteristics

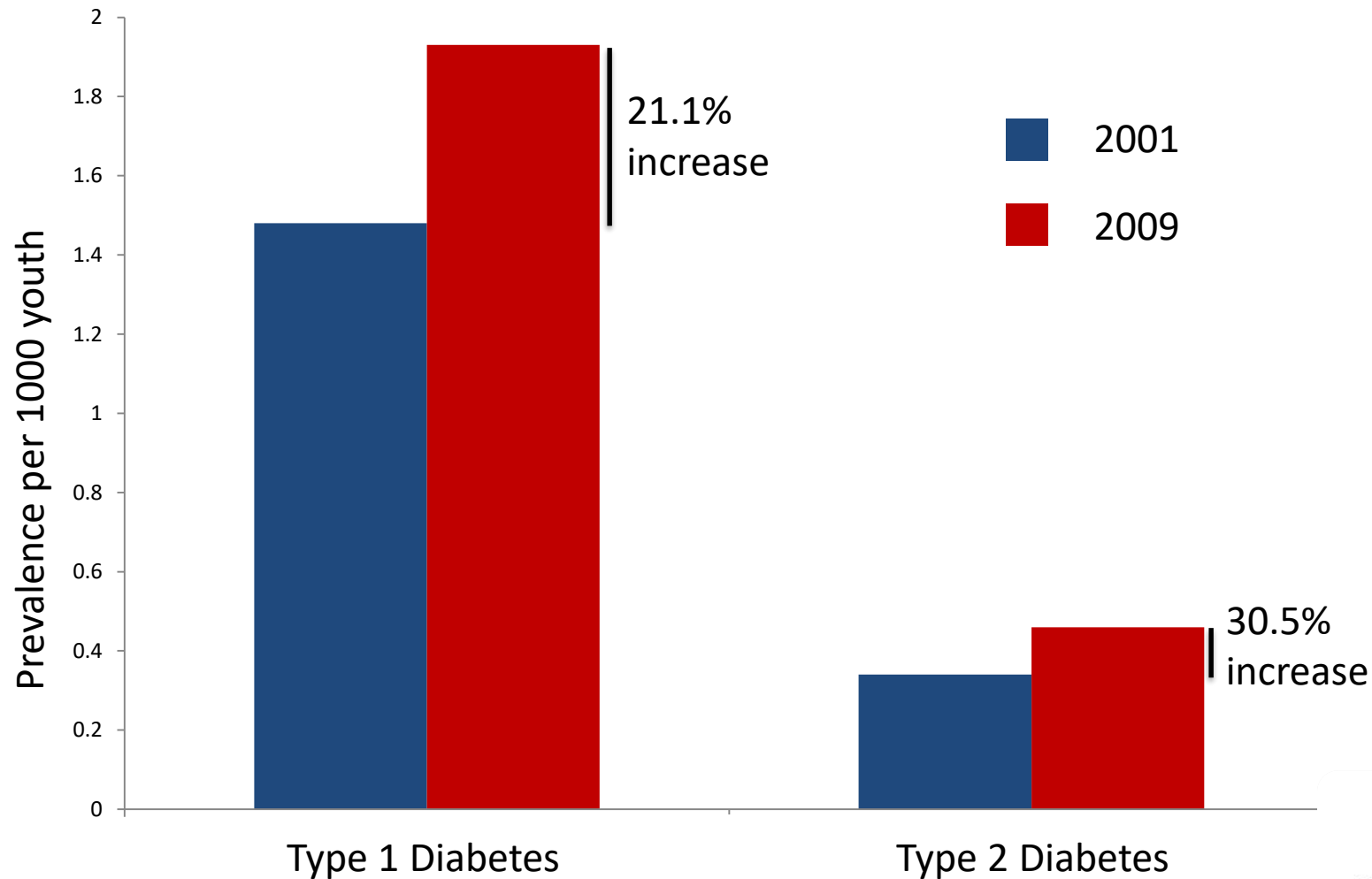
- Large, diverse, multi-center cohort
- Well standardized procedures followed during pregnancy and at follow-up
- Multiple potential antepartum predictors of long-term outcomes
- A major strength of HAPO is that it was a blinded cohort with no intervention for GDM as then defined (“new” GDM)



SEARCH for Diabetes in Youth



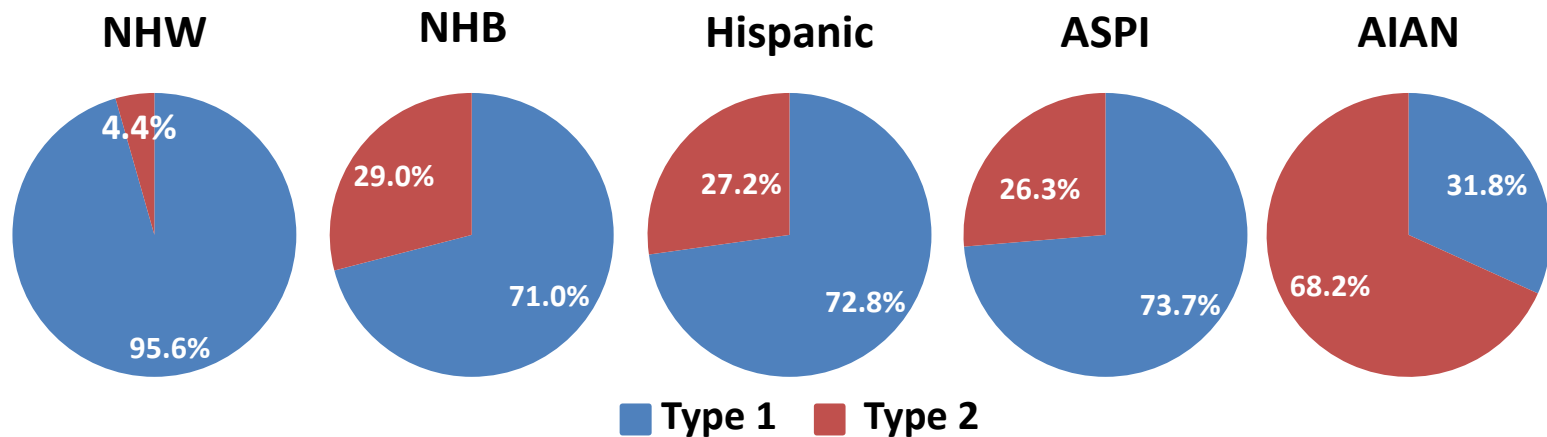
Rates of Childhood Diabetes Rising



Dabelea *et al.*, *JAMA* **311**:1778-1786, 2014.



Proportion of Type 1 and Type 2 Diabetes by Race/Ethnicity in Youth aged 10 to 19 Years



NHW: non-Hispanic white; NHB: non-Hispanic black; API: Asian or Pacific Islander; AIAN: American Indian or Alaska Native

Hamman et al. ADA 2012



NIDDK Clinical Studies Addressing Type 2 Diabetes and Diabetes/Hyperglycemia During Pregnancy



Normal ↔ Pre-diabetes ↔ Type 2 Diabetes → Complications

Preclinical state Clinical disease Complications



Treatment Options for type 2 Diabetes in Adolescents and Youth

Rationale:

- Increased youth T2D
- Adult drugs not tested/approved in youth
- Adolescent effects on glycemia/metabolism



Cohort:

- Age 10-17 years (avg 14)
- BMI >85th p'tile (avg 35.7)
- T2D <2 yr (avg 8 months)
- 35% male
- 20% White
- 32% NHB
- 41% Hispanic
- 6% AI

Treatment groups:

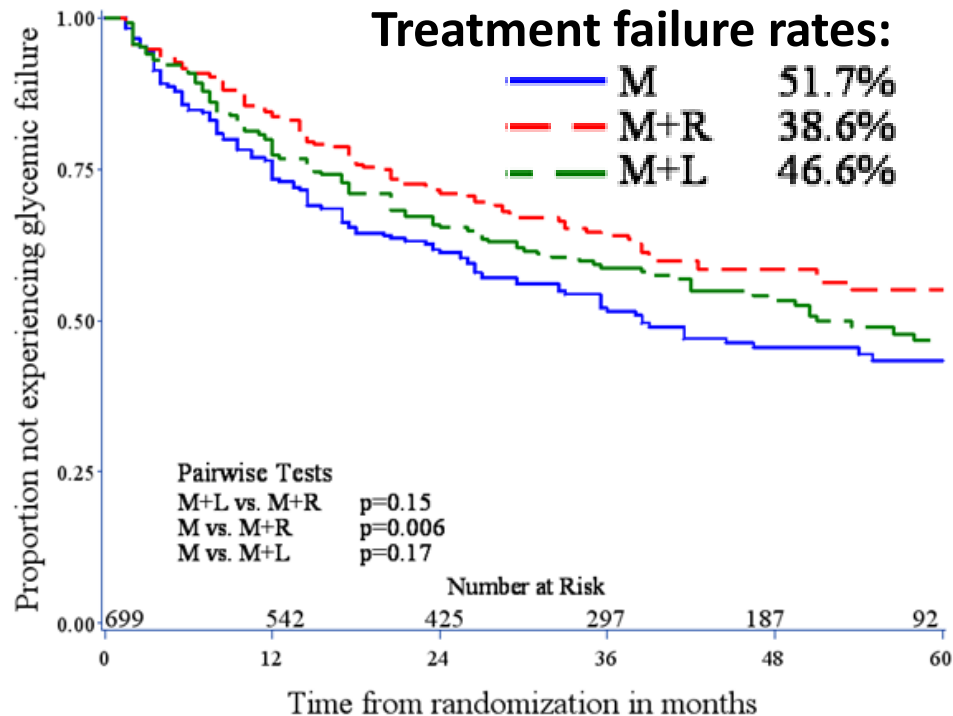
- Metformin
- Metformin + rosiglitazone*
- Metformin + intensive lifestyle

*Use of rosiglitazone was investigational under FDA IND

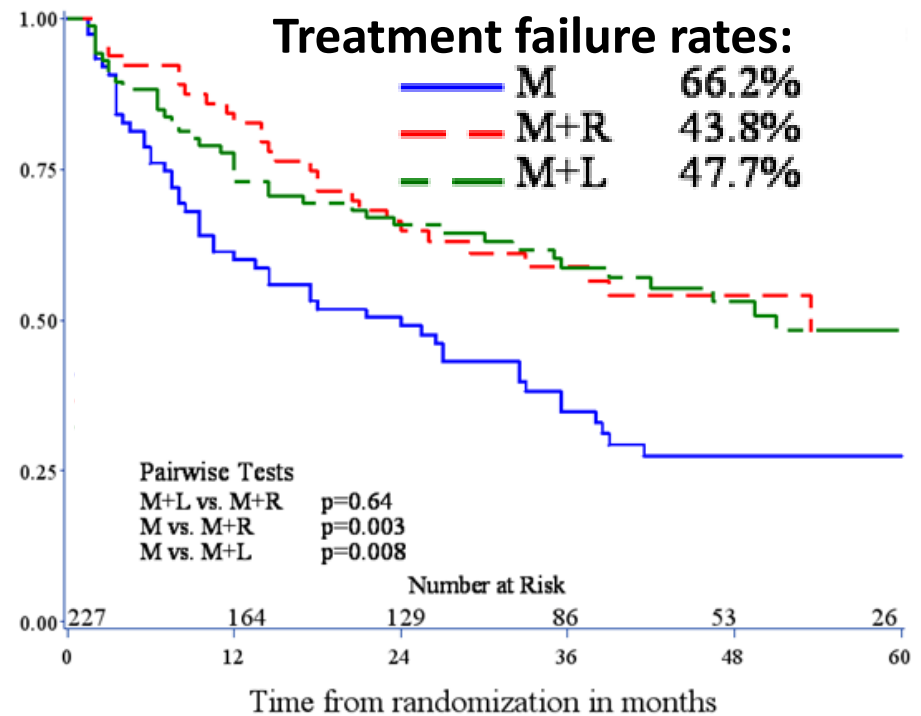




Time-to-outcome Analyses



Cohort Overall



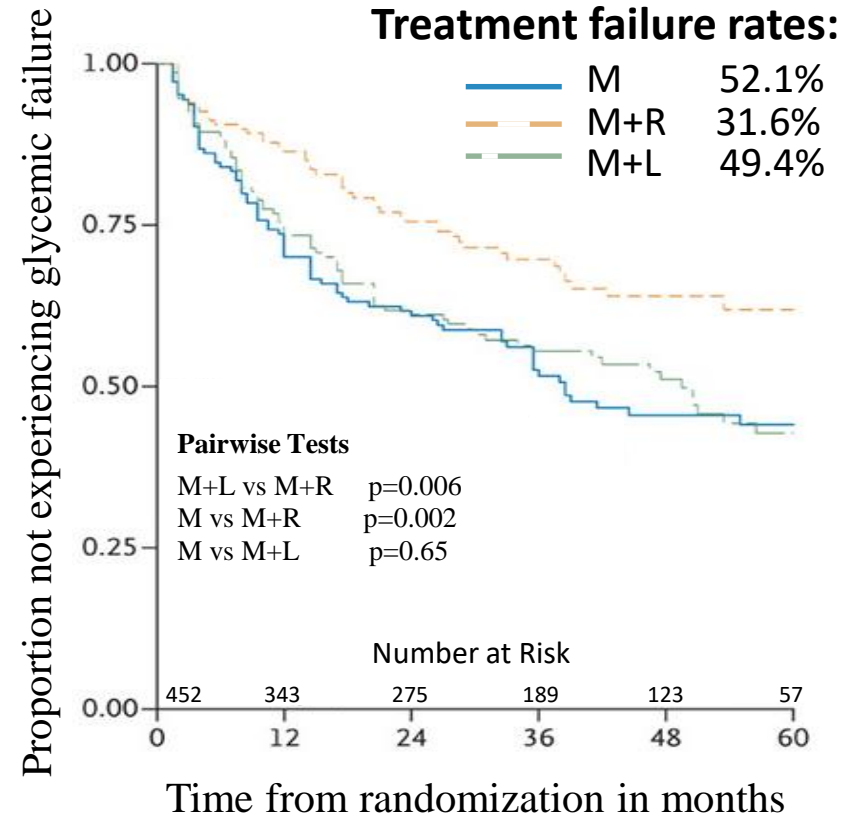
NH Black

Data source: TODAY Study Group. *NEJM* 366:2247-2256, 2012.

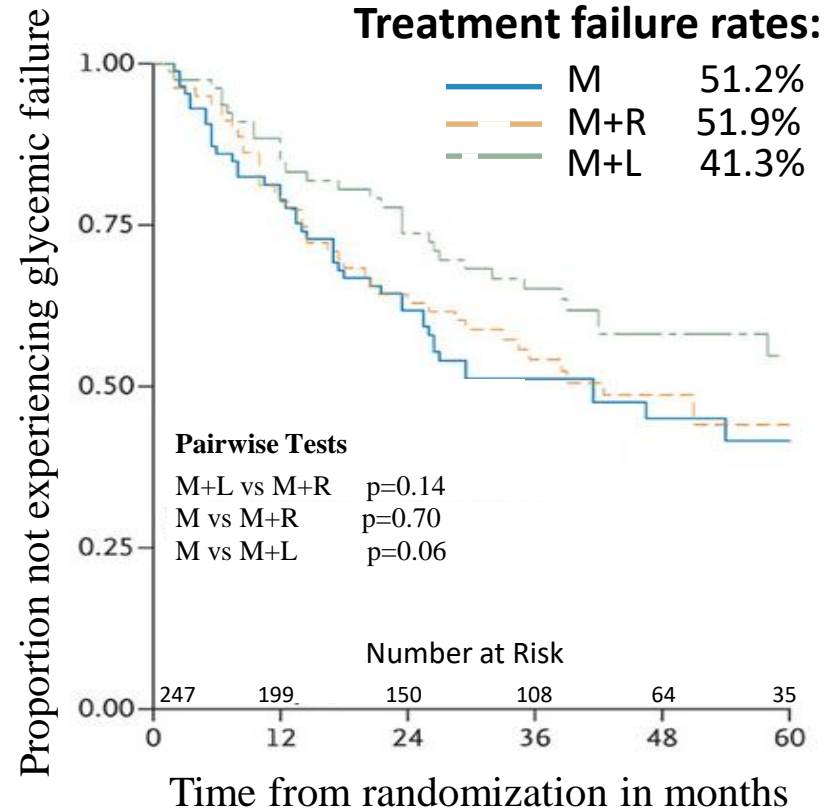




Time-to-outcome Analyses According to Gender



GIRLS



BOYS



Summary

- Type 2 diabetes can be prevented or delayed in people at high risk, including women with a history of GDM
- Women with a history of GDM respond differently to interventions to prevent/delay onset of type 2 diabetes
- Our understanding of what constitutes GDM and its short- and long-term impacts on mothers and offspring is evolving, with many questions still to be answered
- Prevention of type 2 diabetes in youth is a high priority due to its highly aggressive nature and challenges in finding effective treatments; treatment efficacy may differ by gender
- Girls with type 2 diabetes may experience even greater adverse pregnancy outcomes than adults with the disease



New Initiative: Understanding Natural History of GDM to Lay Groundwork for Future Intervention

“Understanding the Glycemic Profile of Pregnancy” (RFA-DK-18-018, RFA-DK-18-019)

- Goal: Establish a clinical research consortium that can recruit pregnant women in their first trimester to examine maternal blood glucose levels across the span of pregnancy and detect and characterize the development of abnormal glucose levels during that time
- Builds on research gaps identified during August 2017 expert workshop on gestational diabetes treatment convened by NIDDK and ORWH; an area of particular focus was lack of knowledge on when in pregnancy abnormal blood glucose levels first manifest.



November is National Diabetes Month

National Diabetes Month Promoting Health After Gestational Diabetes



National Radio Media Tour

- 17 interviews on radio networks and stations in states with the highest rates of diabetes
- Upcoming interviews on National Diabetes Month's theme
 - Tom Joyner Morning Show
 - Erica Campbell Morning Show

National Diabetes Month

NIH National Institute of Diabetes and Digestive and Kidney Diseases

Did you have gestational diabetes when you were pregnant?

November is National Diabetes Month. If you developed diabetes when you were pregnant (called gestational diabetes), you have a greater chance of getting diabetes later in life. Your child may also have a greater chance of being obese and developing type 2 diabetes.

If you've had gestational diabetes—

- 1** 
Understand your risk.
An estimated half of all women who had gestational diabetes will go on to develop type 2 diabetes later in life.
- 2** 
Find out if you have type 2 diabetes.
Get tested within 12 weeks after your baby is born. If the test is normal, get tested every 3 years.
- 3** 
Tell your child's doctor you had gestational diabetes.
Your child's doctor may monitor their growth charts more closely.
- 4** 
Take charge of your health.
Make healthy food choices and stay active as a family to prevent or delay type 2 diabetes.

Search Online for “NIDDK National Diabetes Month”





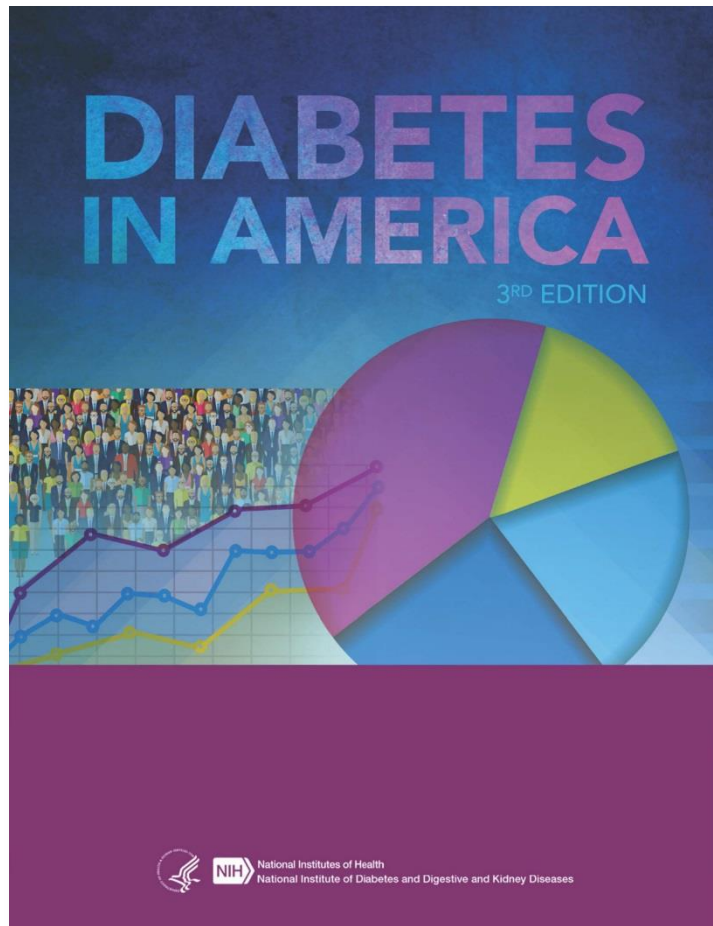
- **Healthy Moments** radio program reaches over 60 million listeners and provides reliable, science-based, healthy lifestyle tips, actionable suggestions, and other important health information.
- Airs weekly in
 - [WMMJ Majic 102.3 FM](#) Washington, DC
 - [WWIN Magic 95.9 FM](#) Baltimore, MD
 - [KMJQ Majic 102.1 FM](#) Houston, TX
 - [WAMJ Majic 107.5 FM](#) Atlanta, GA
 - [WHHL Hot 104.1 FM](#) St. Louis, MO
 - [WENZ Z 107.9 FM](#) Cleveland, OH
 - [Get Up! Mornings with Erica Campbell](#) Network (38 stations)



Topics:

- Diabetes and the Heart Health Connection
- Women and Heart Health Risk Factors
- What Can we Do About It?
- Women Getting Involved in Clinical Trials

Diabetes in America, 3rd ed.



- Compilation and assessment of epidemiologic, public health, clinical, and clinical trial data on diabetes and its complications in the United States
- 42 chapters written by NIDDK researchers and leading experts from around the world; includes chapters on both GDM and on preexisting diabetes and pregnancy
- First edition in more than 20 years; completed August 2018

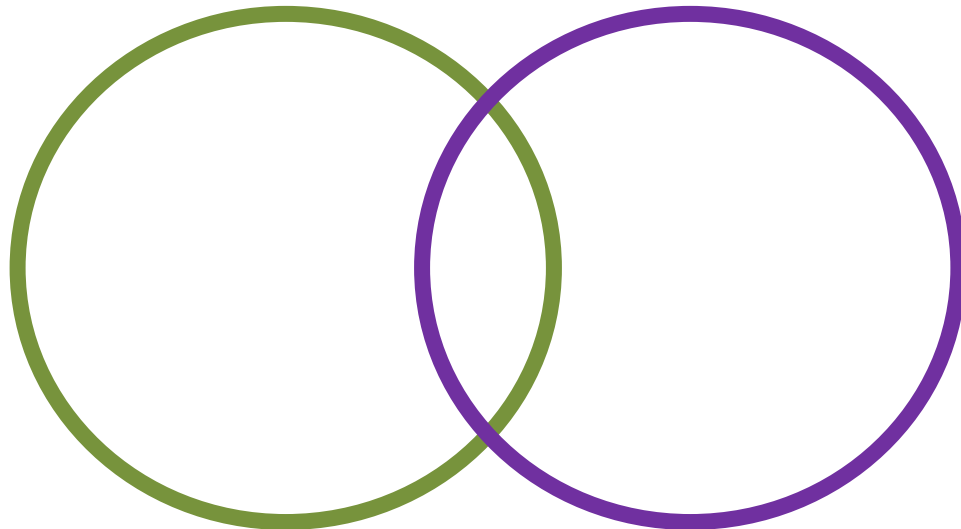
Available in chapter PDFs on NIDDK website



NIDDK Alignment with New Strategic Plan for Women's Health Research

NIDDK Core Values

- Maintain a Vigorous Investigator-Initiated Research Portfolio
- Support Pivotal Clinical Studies and Trials
- Preserve a Stable Pool of Talented New Investigators
- Foster Exceptional Research Training and Mentoring Opportunities
- Ensure Knowledge Dissemination Through Outreach and Communications





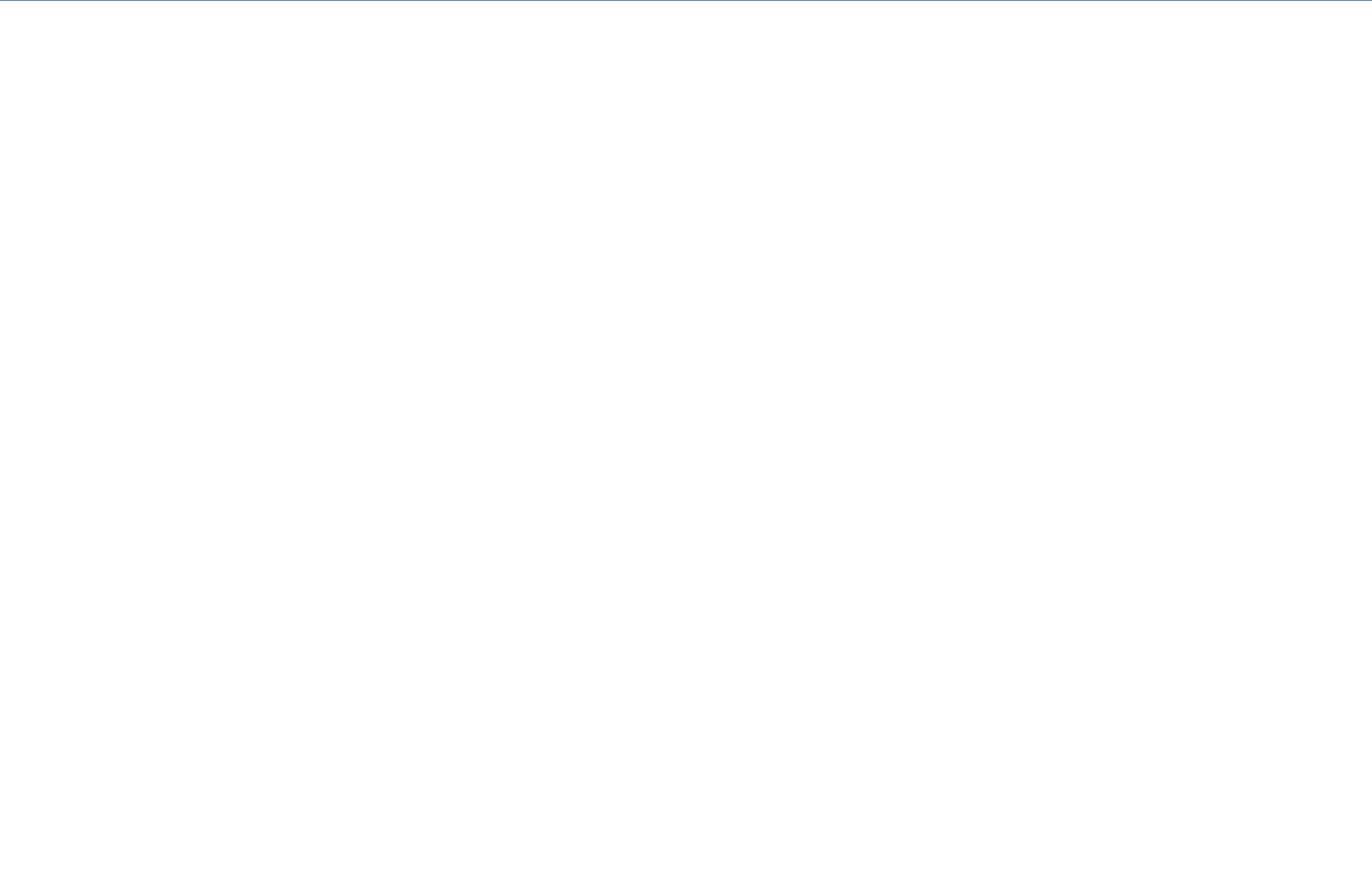
National Institute of
Diabetes and Digestive
and Kidney Diseases

*National Institute of
Diabetes and Digestive
and Kidney Diseases*

www.niddk.nih.gov

Twitter: @NIDDKgov

Facebook: @NIDDKgov



TODAY Study—Pregnancy

- Despite counseling, of the 452 enrolled female participants, 46 (10.2%) had 63 pregnancies. The mean age at first pregnancy was 18.4 years; the mean diabetes duration was 3.17 years.
- Seven pregnancies were electively terminated; three pregnancies had no data reported.
- Of the remaining 53 pregnancies, 5 (9.4%) resulted in early pregnancy loss, and 7 (13%) resulted in loss with inadequate pregnancy duration data.
- Two pregnancies ended in stillbirth, at 27 and 37 weeks, and 39 ended with a live-born infant.
- Of the live-born infants:
 - six (15.4%) were preterm
 - eight (20.5%) had a major congenital anomaly; **reported rate in adult women with type 2 diabetes is approximately 5%**
- Pregnancy was associated with household income and structure but not with other demographic factors, race/ethnicity, or treatment group/outcome



RISE: Baseline Data and Results from Youth Study

RISE Baseline Data: Youth versus Adults (IGT or T2D, diabetes drug naïve; 66 youth, 355 adults)

- Youth had more insulin resistance and other signs of disease progression than their adult counterparts at the same stage in the disease
- The pediatric group at baseline responded to the severe insulin resistance with a greater insulin response than adults--potentially a reason for the youth's more rapid loss of beta cell function

The RISE Consortium, Diab Care 2018, 41: 1696-1706, 2018; The RISE Consortium, Diab Care 2018, 41: 1707-1716, 2018

RISE Pediatric Medication Study

Cohort:

- 91 youth ages 10-19 (25 White, 23 Black, 34 Hispanic, 9 Other; 65 female)
- impaired glucose tolerance or recent-onset type 2 diabetes

Design:

- Participants at four study sites randomly assigned to one of two treatment groups:
 - Group 1: 3 months of long-acting insulin (glargine) followed by 9 months of metformin
 - Group 2: 12 months of metformin only
- Participants then monitored for three more months after treatment ended.

Results:

Neither treatment approach preserved the participants' ability to make insulin

The RISE Consortium, Diab Care 2018, 41: 1717-1725, 2018

HAPO FUS Measurements

- Mothers & Children
 - BP, height, weight, waist
 - Percent body fat using the BOD POD (air displacement plethysmography)
- Children
 - Arm circumference
 - Triceps, subscapular, supra-iliac skinfolds
 - Pubertal assessment by Tanner stage
- Mothers and children not self-reporting diabetes on treatment underwent a 2-hour OGTT after an overnight fast (HbA1c, glucose, insulin, lipids)



HAPO FUS Questionnaires

- Socio-demographics -- Marital status, education
- Family medical history -- Diabetes, hypertension
- Lifestyle variables
 - Smoking status, alcohol consumption, physical activity, sleep for mothers
 - Smoking status, physical activity, sleep for children
- Mother's pregnancy and breastfeeding history
- Medical history and medication use for mother, HAPO child and HAPO child's father



CVD Risk Factor Prevalence (TODAY EOS)

