# Mechanistic Insights Into the Heterogeneity of Glucose Response in Youth with Obesity :

*A Latent Class Trajectory Approach*

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No Disclosure related to the work presented at this Conference.

# Background

Recently, Hulman et al. using a latent class mixed model framework, showed that the glucose trajectories of healthy adults following a 120 min OGTT may be classified into 4 distinct groups of individuals with abnormalities in insulin secretion and insulin sensitivity.

In the current study, to gain insights into the pathophysiology of glucose dysregulation in youth, we used the *latent class analysis* to examine the heterogeneity in glucose response curves during frequently sampled 180min -OGTTs , in a large multiethnic cohort of adolescents with obesity.
A subgroup of these adolescents were followed longitudinally and had multiple repeated OGTT over 5 years to assess the effect of age on the stability or transition among classes.

***Hulman et all Diabetes Care 2018***
***Trico D et all Diabetes Care 2022***

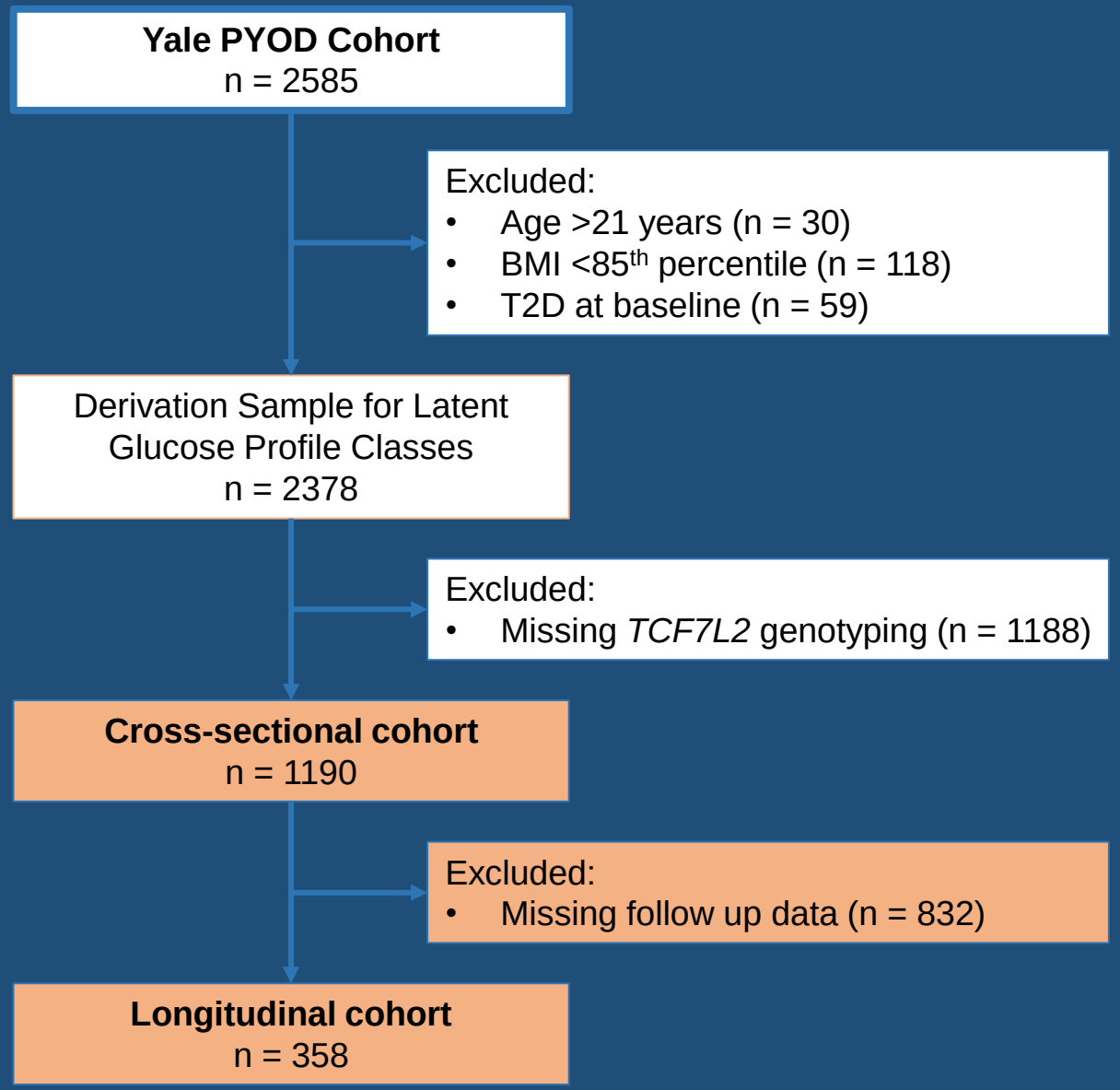
# Objectives

*1- To determine the prevalence of various glucose response classes in youths with obesity;*

*2- To assess the main pathogenic determinants of the different glucose patterns, and*

*3 - Explore the association of the TCF7L2 risk allele, the single strongest known genetic risk factor for youth-onset T2D with the various glucose response classes.*

# The Pathophysiology of Youth Onset T2D (PYOD) Study Consort Diagram



# Statistical Analysis

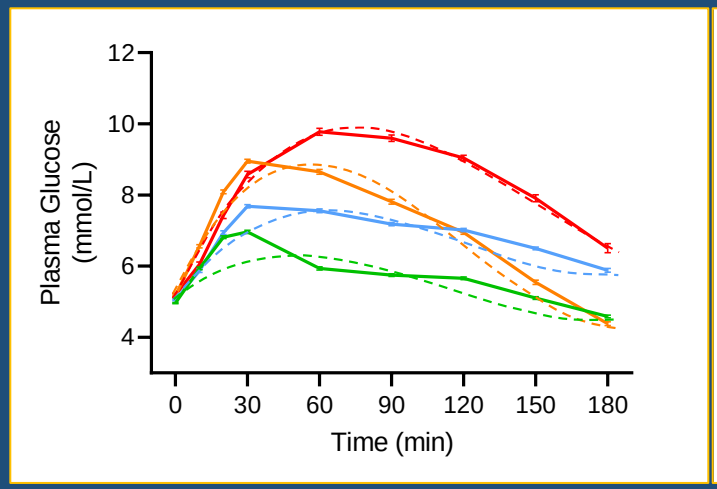
Veronica Shabanova, PhD

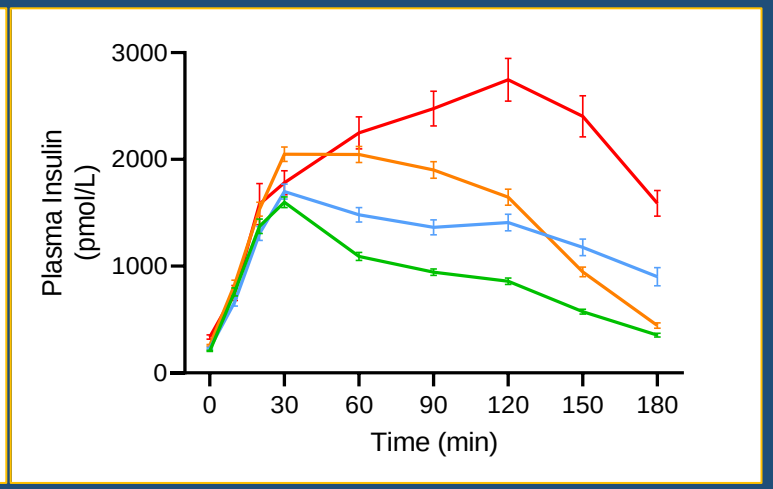
Latent classes of glucose trajectories were modeled from the baseline OGTTs in the derivation sample using growth mixture modeling, with a random intercept for each child and an orthogonal polynomial (third degree) for the fixed effect of time (minutes of OGTT).

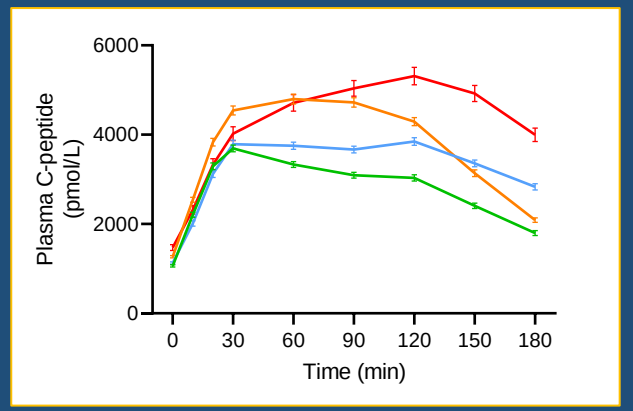
A detailed description of data analysis is reported in :

*Trico D and V. Shabanova , Mechanistic Insights Into the Heterogeneity of Glucose Response Classes in Youths With Obesity: A Latent Class Trajectory Approach*
*Diabetes Care, 2022*

# Post–load Glucose, Insulin, and C-Peptide Trajectories differed greatly across Class




Class 1 Class 2 Class 3 Class 4

**Domenico Trico, MD PhD**

*Trico D et al , Diabetes Care 2022*

# Demographics and Clinical Characteristics by Latent Classes of Postload Glucose Profiles

- The number of participants included in each class decreased progressively from class 1 to 4, with class 1 having the greatest percentage of subjects (35%) and class 4 the lowest (11%)

- Class 4 had the highest number of youth in Tanner 4 stages, as did family history of T2D.

- Non-Hispanic White and African American participants were more represented in classes 3 and 4 while the proportion of Hispanic participants was similar across classes.

- Notably, Glucose Tolerance status varied greatly by class, with
class 1 having 99% NGT,
class 2 having 82% NGT,
class 3 having 75% NGT,
and
class 4 having only 7% NGT.

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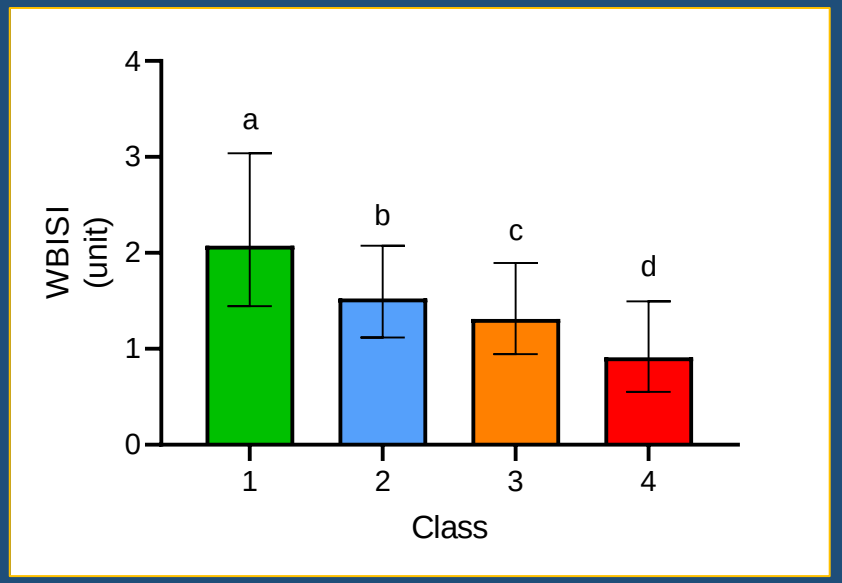
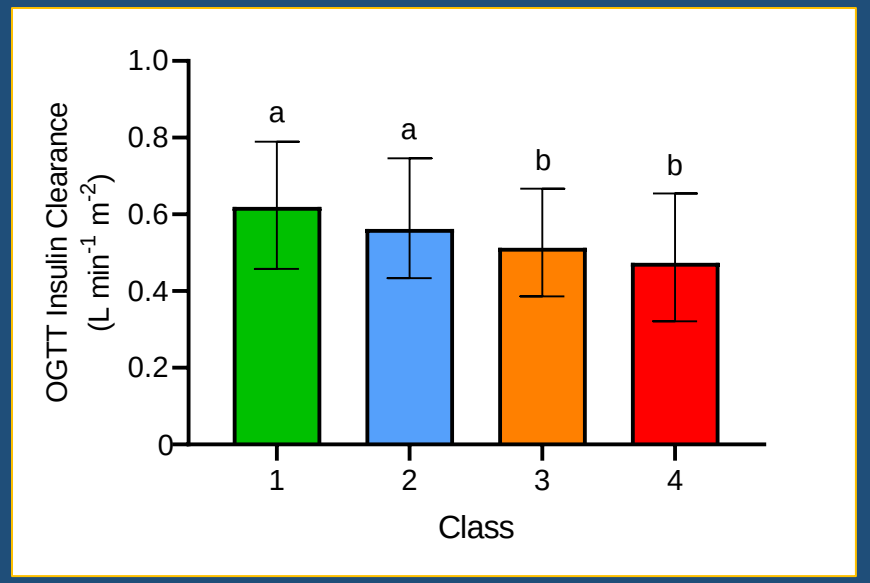
# Model-Based Parameters of Insulin Sensitivity and Clearance

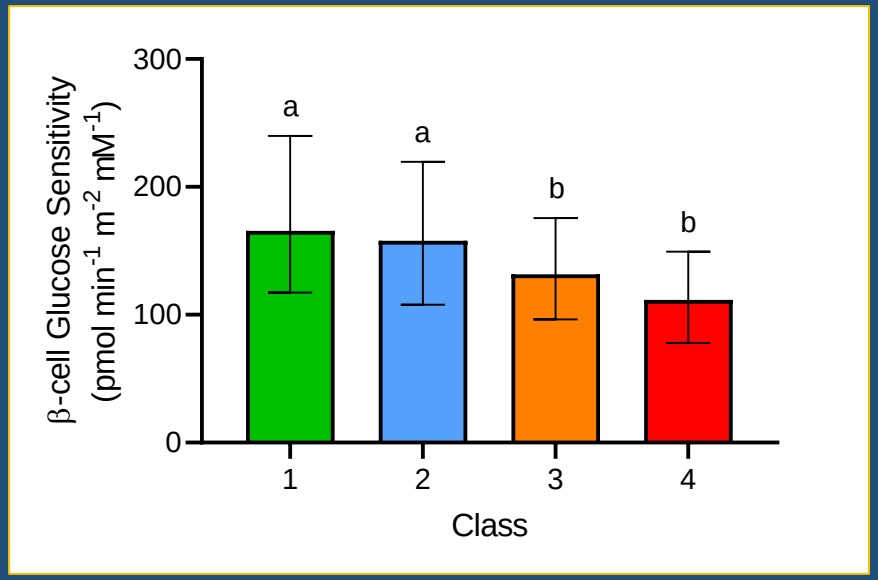


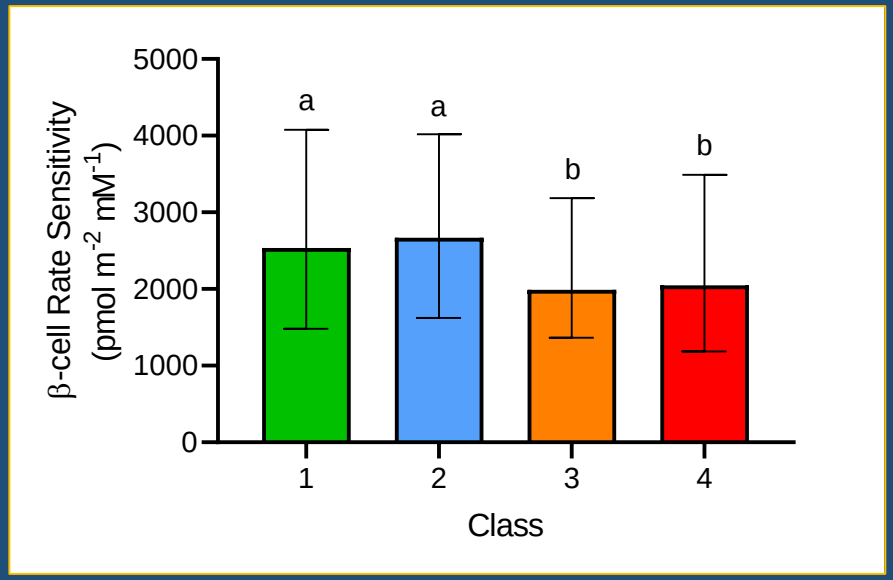




Mari A and Ferrannini E
Beta-cell function assessment from modelling of oral tests: an effective approach
*Diabetes Obes Metab*
2008

*Trico D et al , Diabetes Care 2022*

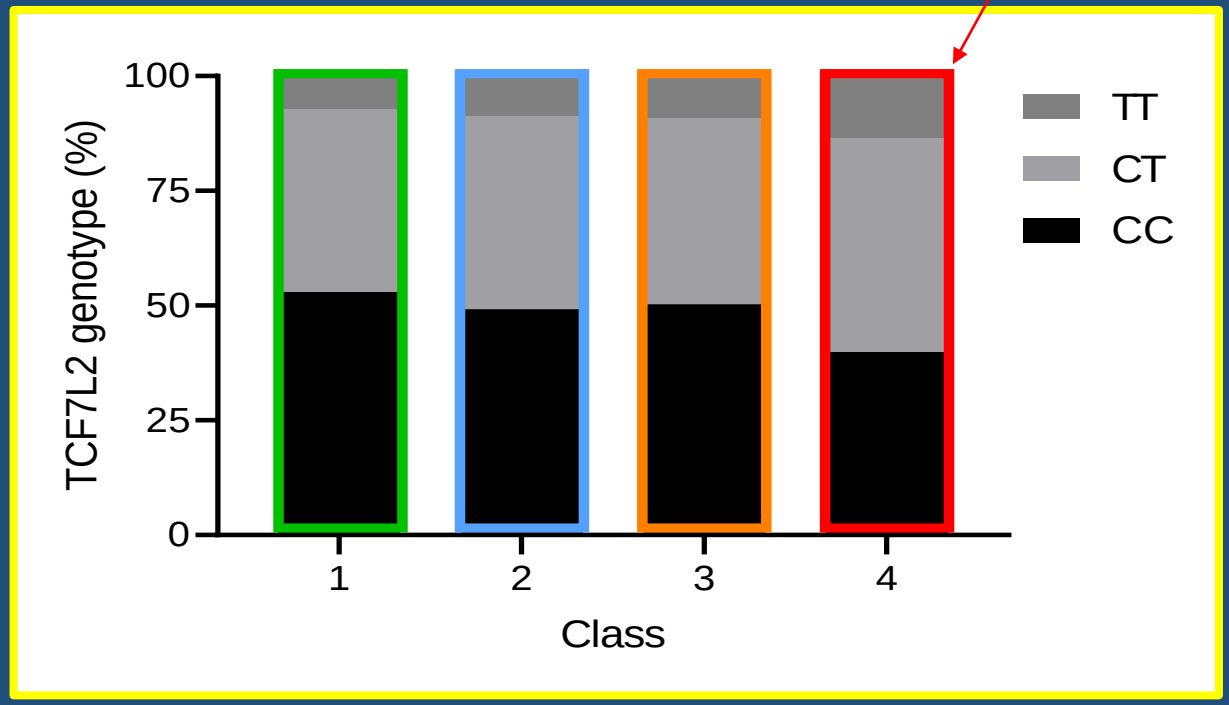
# Model-Based Parameters of Beta-cell function



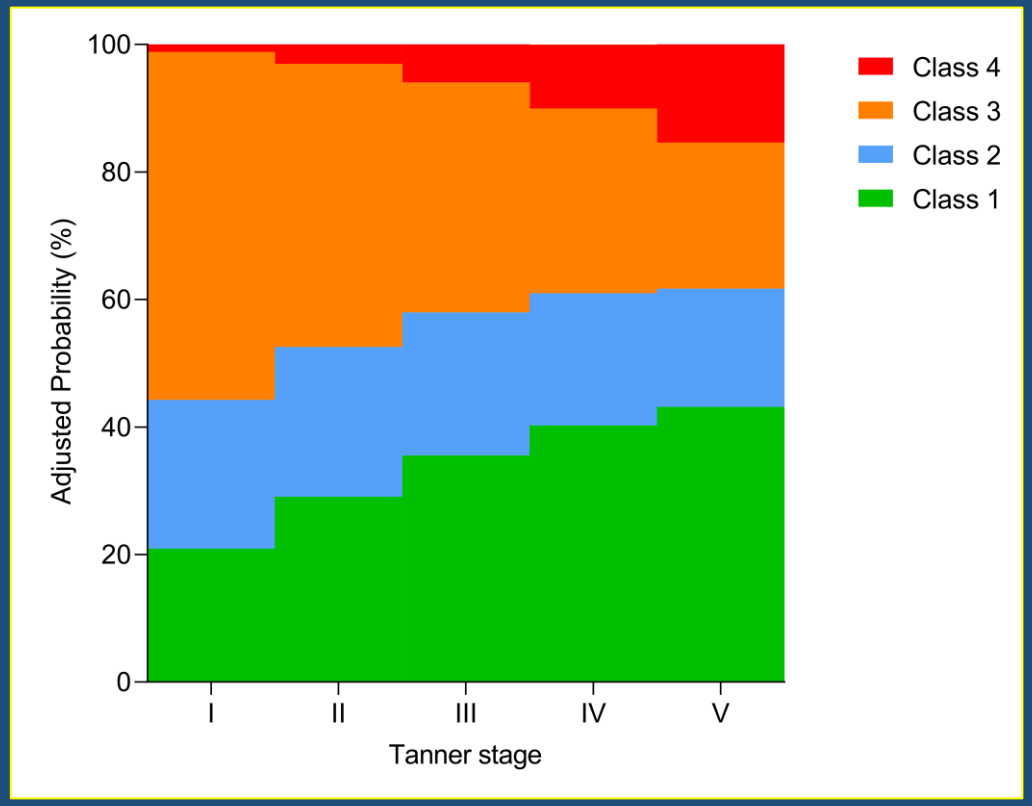

*Trico D et al , Diabetes Care 2022*

# Higher prevalence of the T risk allele for the common *TCF7L2* variant rs7903146 in the class four of glucose response pattern




*Trico D et al , Diabetes Care 2022*

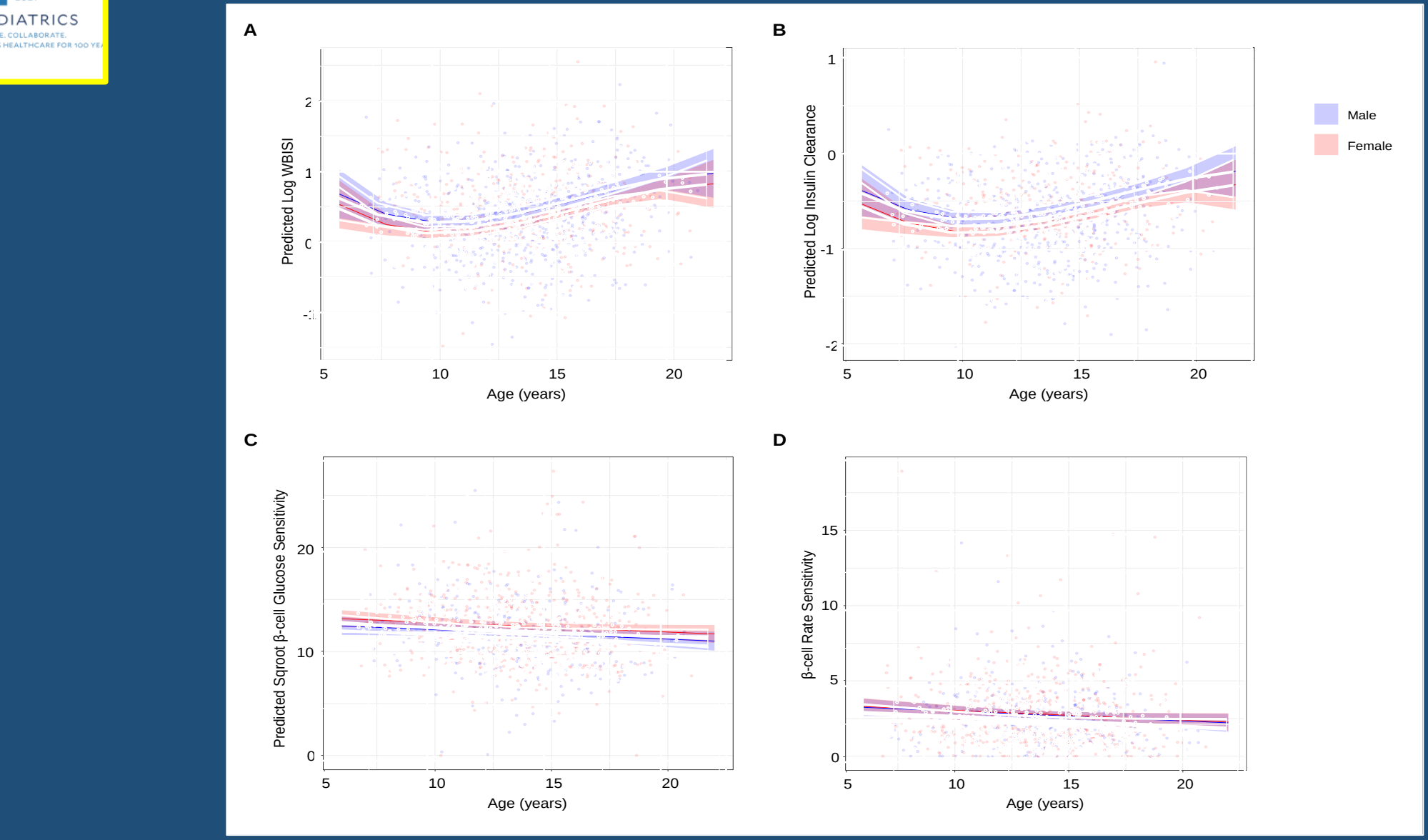
# Longitudinal follow-up of the Cohort (n=358 ( multiple OGTT over 5 years )




Model-predicted probability to be classified as class 1 and 4 increased steadily with age, while probability to be classified as class 2 and 3 declined, after adjustment for sex and race/ethnicity (

*Trico D et al , Diabetes Care 2022*

# Longitudinal changes in Insulin Sensitivity, Clearance , β-cell glucose sensitivity and rate sensitivity



# Key findings

- Four latent classes (1 to 4) were identified. Participants in class 3 and 4 had the worst metabolic and genetic risk profiles, featuring impaired insulin sensitivity, clearance, and β-cell function.

- Insulin sensitivity was the strongest determinant of class assignment at enrollment and of the longitudinal change from class 1 and 2 to higher classes. Transitions between classes 3 and 4 were explained only by changes in β-cell glucose sensitivity.

- Of note, although participants in class 4 featured all the essential metabolic defects for T2D development at enrollment ,some changed class at follow-up to class 3, 2, or even class 1.

- This dynamic movement across glucose classes may be specific to youth, given that, in adults, a high stability of classes over time has been described .

# "The Yale Pediatric Childhood Obesity / T2D Research Team "

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American Diabetes Association.
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# Thank You for Your Attention