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

A Latent Class Trajectory Approach

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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

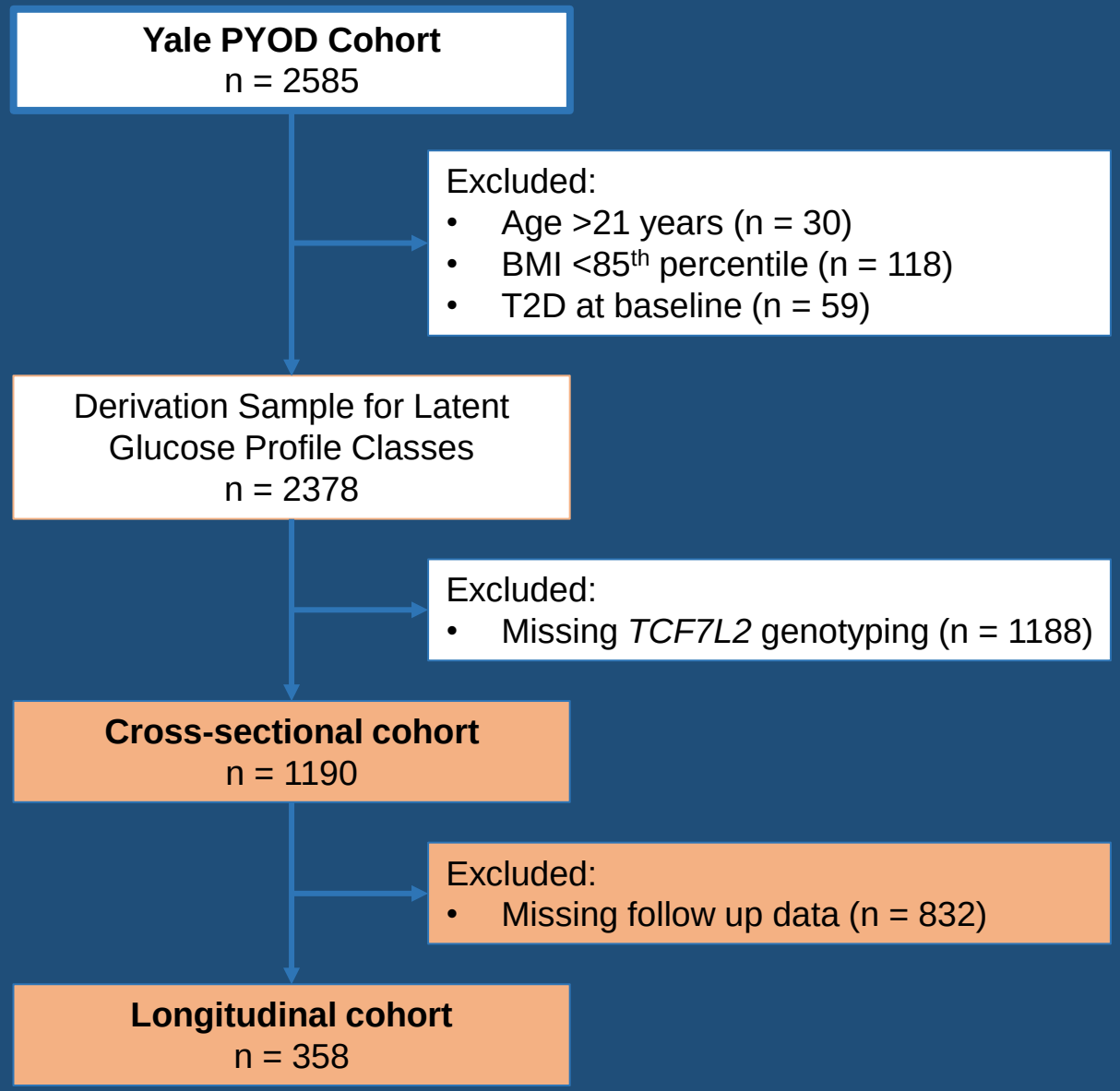
Objectives

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

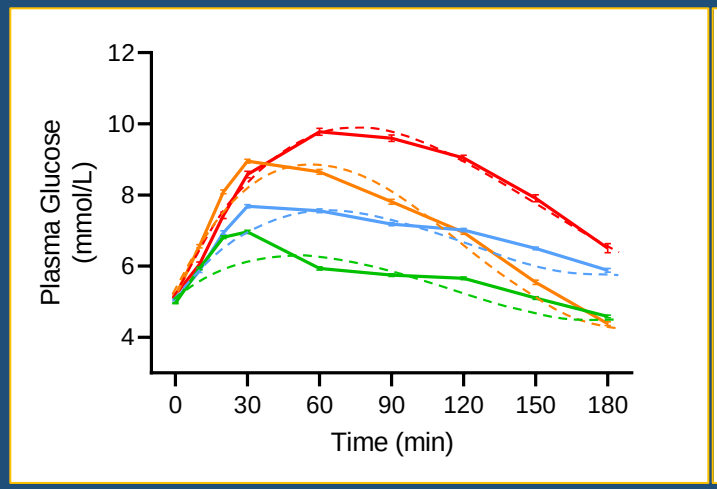
Veronica Shabanova, PhD

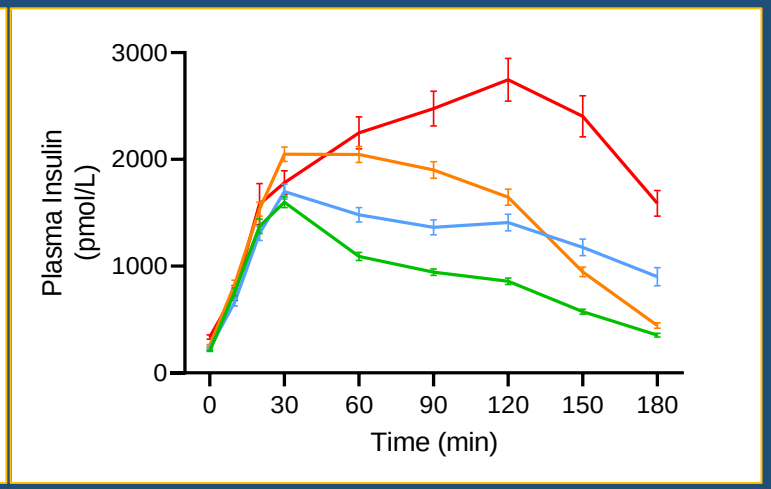
Latent classes of glucose trajectories were modeled from the baseline OGTTs in the derivation sample using growth mixture modeling, with a random intercept for each child and an orthogonal polynomial (third degree) for the fixed effect of time (minutes of OGTT).

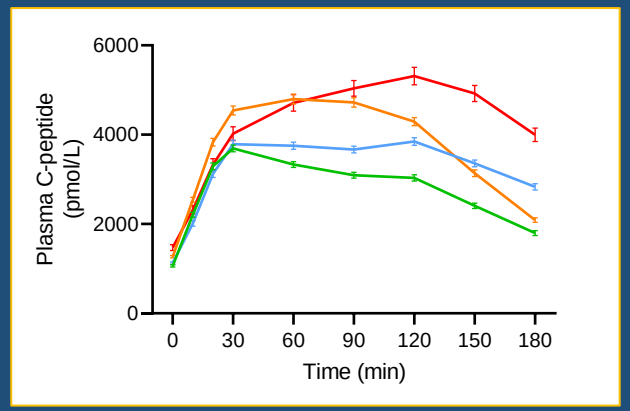
A detailed description of data analysis is reported in :

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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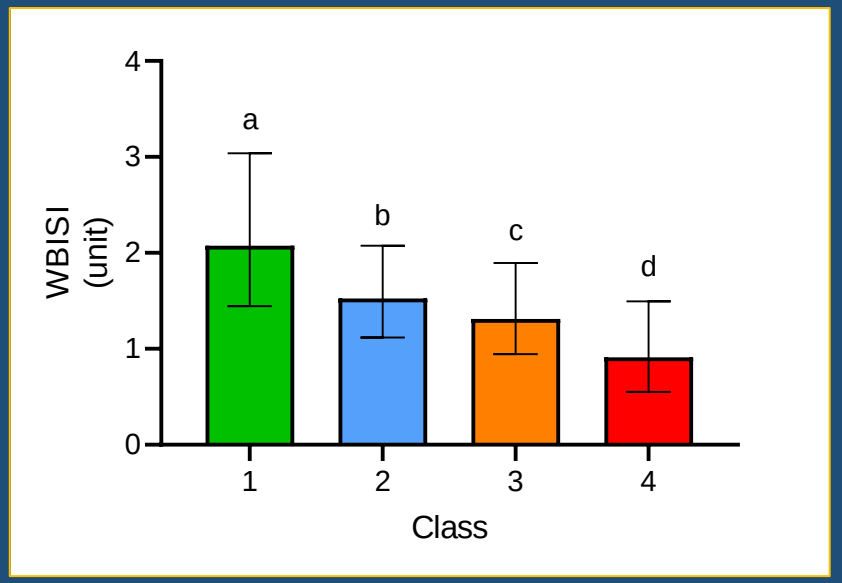
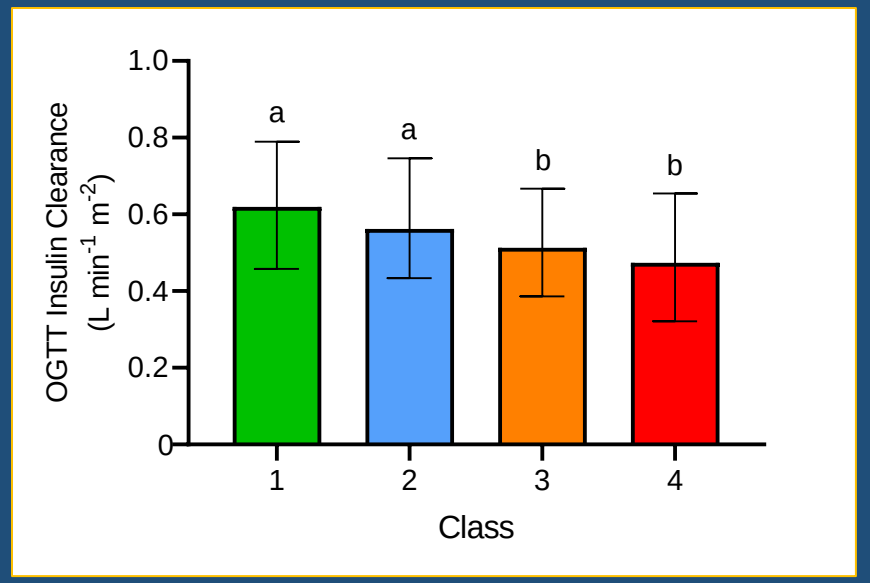
Model-Based Parameters of Insulin Sensitivity and Clearance

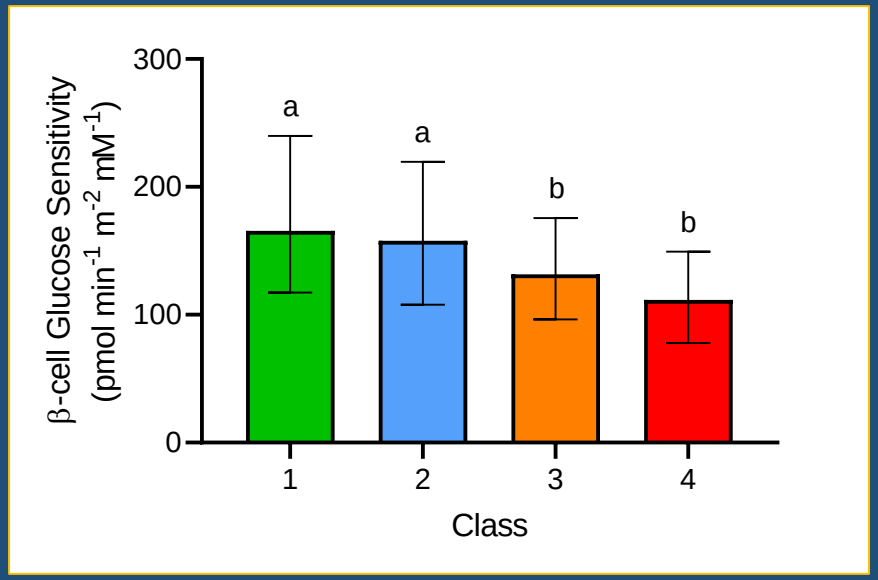


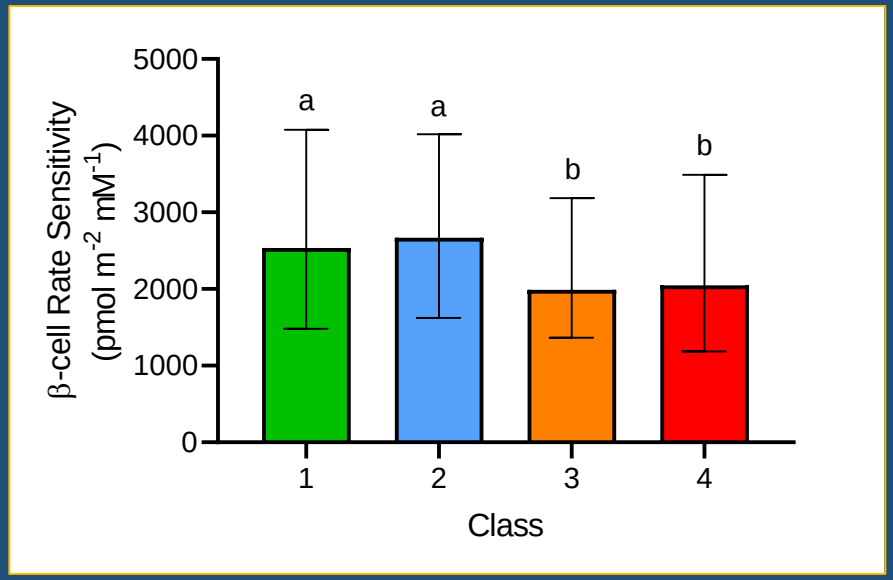


Mari A and Ferrannini E
Beta-cell function assessment from modelling of oral tests: an effective approach
Diabetes Obes Metab
2008

Trico D et al , Diabetes Care 2022

Model-Based Parameters of Beta-cell function





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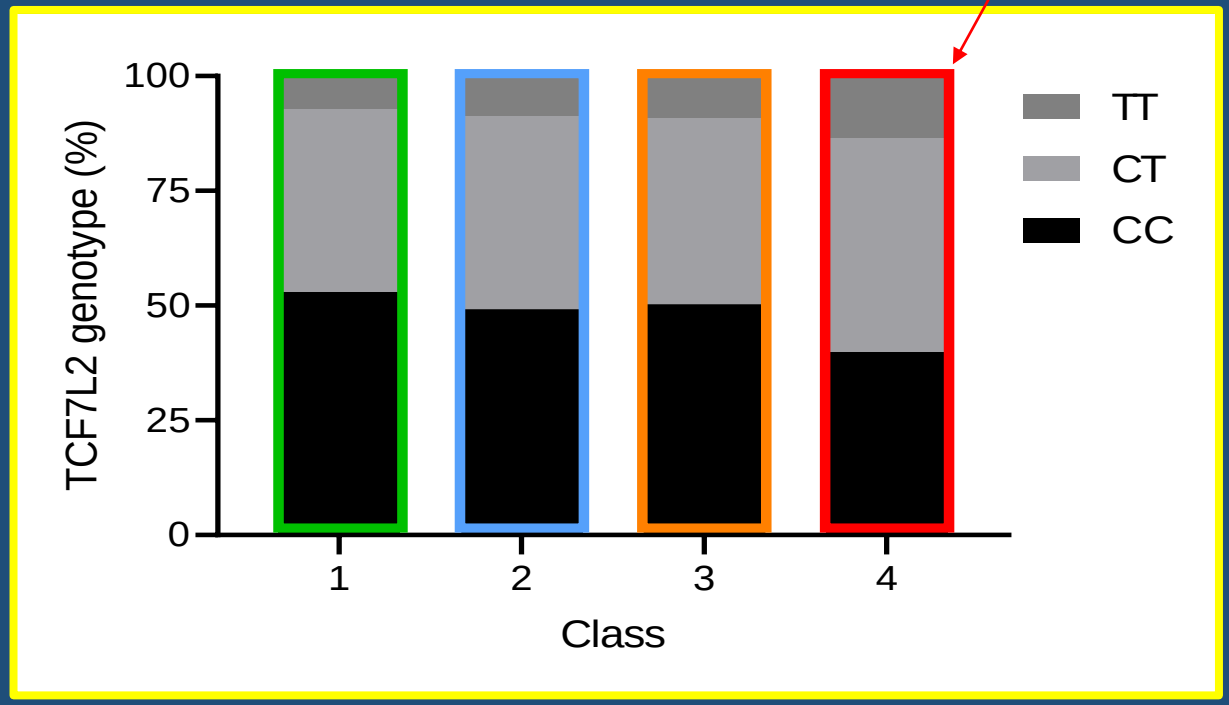
Higher prevalence of the T risk allele for the common *TCF7L2* variant rs7903146 in the class four of glucose response pattern



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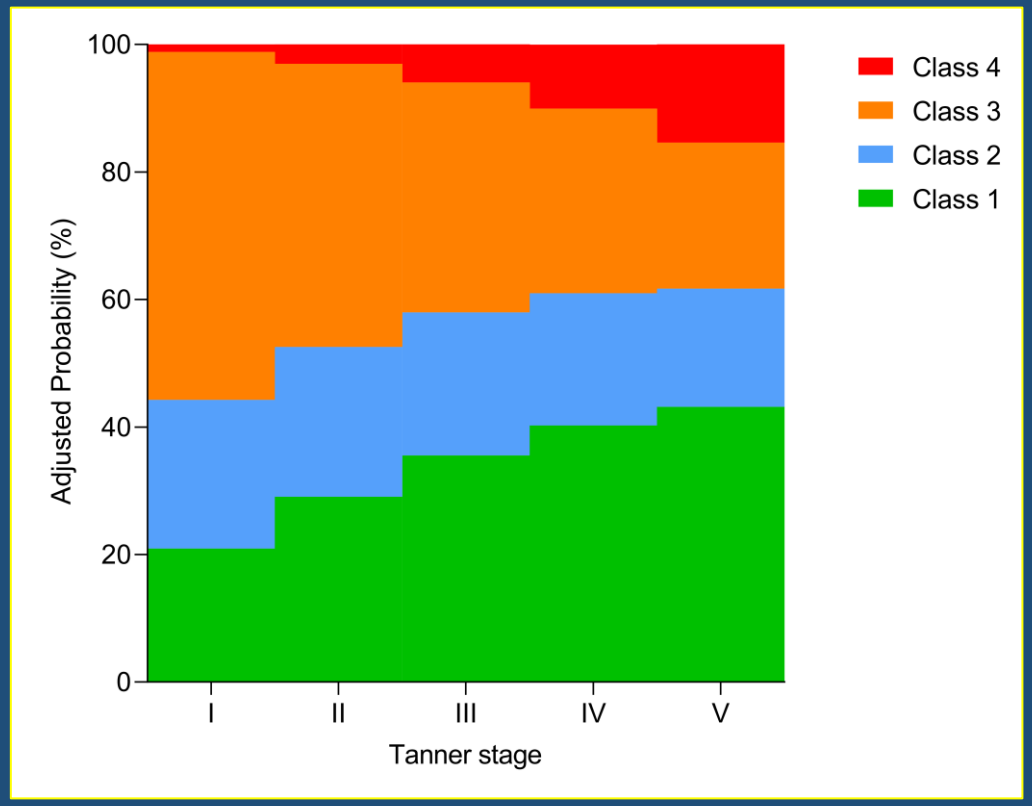
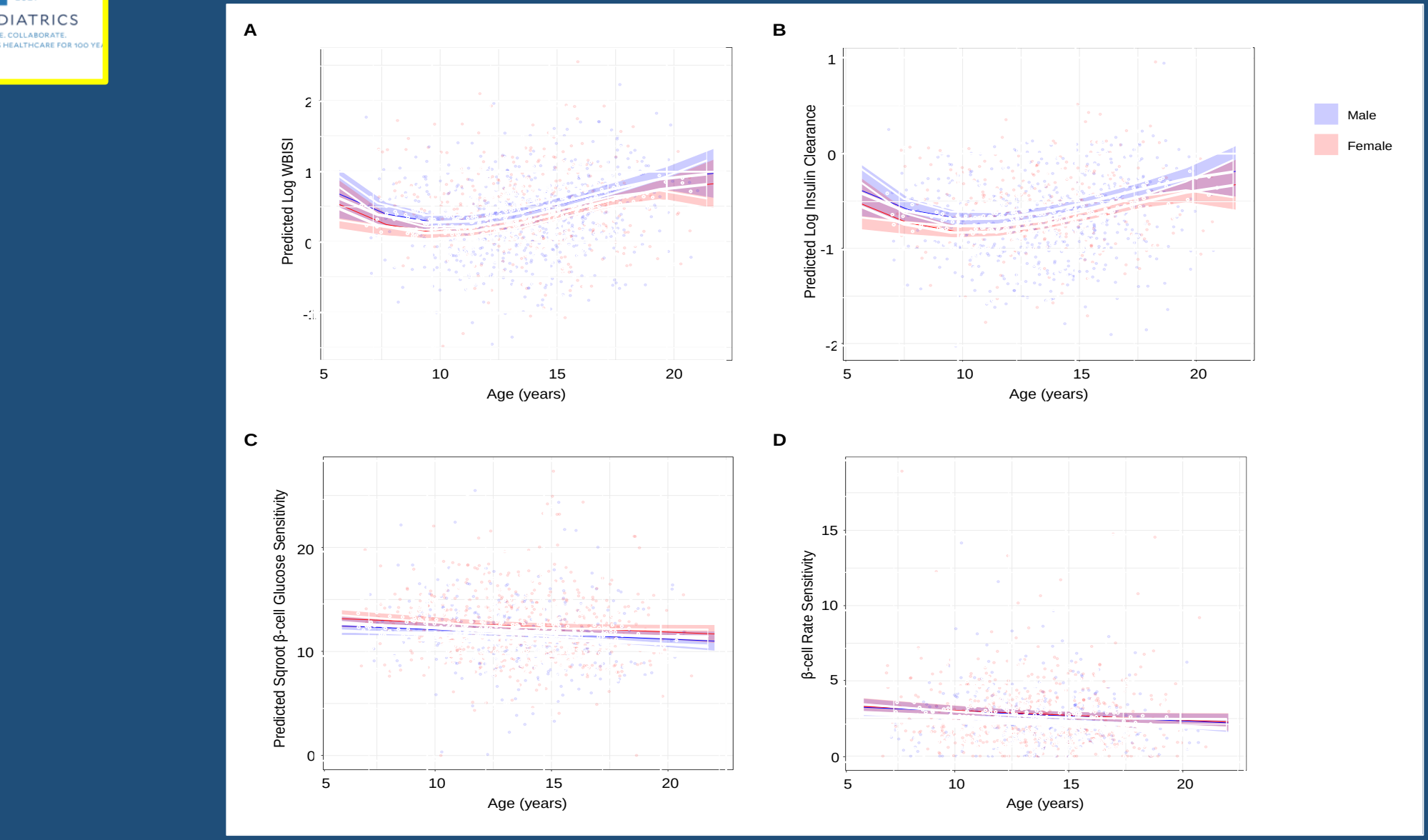
Longitudinal follow-up of the Cohort (n=358 (multiple OGTT over 5 years)



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 .

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Thank You for Your Attention