Pathophysiological Risk Factors of Type 2 Diabetes Subtypes: A Pooled Cohort Study in the United States

Jiali Guo[1,2], Jithin Sam Varghese[1,2]

[1]Emory Global Diabetes Research Center of Woodruff Health Sciences Center and Emory University, Atlanta, GA, USA
[2]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

INTRODUCTION

- Type 2 diabetes (T2D) has emerged as a major public health challenge in the United States, affecting over 34 million adults, representing 14.7% of the adult population.
- Current practice and guidelines largely rely on a one-size-fits-all approach that fails to account for substantial heterogeneity in disease progression and response to therapy.
- Critical gaps in translation of precision medicine research to clinical practice is the limited understanding of the natural history of these T2D subtypes during the period before diagnosis, especially among non-European origin populations.
- Using cohort studies of diverse populations from the United States, our objective was to study the associations of pathophysiological markers before T2D diagnosis and membership in data-driven T2D subtypes.

METHODS

Study Population

- The analysis included adult participants (≥18 years) from four longitudinal studies (CARDIA, DPP & DPPOS, JHS, MESA) who had no prior diagnosis of diabetes.
- We restricted our analysis to participants with HbA1c and BMI assessment at the last follow-up visit and one additional visit (**Index Visit**) with HbA1c and BMI prior to their diagnosis or last follow-up visit to minimize misclassification of T2D status.

Heterogeneity in metabolic trajectories

- Previously identified subtypes of newly diagnosed T2D: mild age-related diabetes (MARD), mild obesity-related diabetes (MOD), severe insulin-resistant diabetes (SIRD), and severe insulin-deficient diabetes (SIDD).
- Adjusted trajectories and 95% confidence intervals for each metabolic marker were estimated using linear mixed effects models with natural cubic splines to visualize flexible, non-linear trends.

Association of pathophysiological markers with subtypes

- The time-dependent relative hazards were estimated for the association between seven key pathophysiological markers and T2D subtypes using Time Dependent Cox Regression Models (TDCM) to account for time-varying values of biomarkers.

RESULTS

Cohort Construction

Adult participants from 4 cohorts without existing type 2 diabetes

	N	OBS
T2D	3,271	38,435
No T2D	12,908	93,097
Total	13,179	131,532

First and last visits when HbA1c and BMI were available

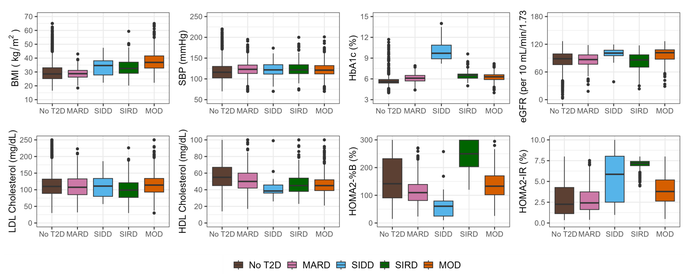
	N	OBS
T2D	1,562	16,517
No T2D	8,747	57,089
Total	10,309	73,606

Data were 73,606 observations from 10,309 participants (15.2% developed T2D) of four harmonized cohort studies (Coronary Artery Risk Development in Young Adults [CARDIA], Diabetes Prevention Program [DPP] and DPP Outcomes Study [DPPOS], Jackson Heart Study [JHS], and Multi-Ethnic Study of Atherosclerosis [MESA]) in the United States.

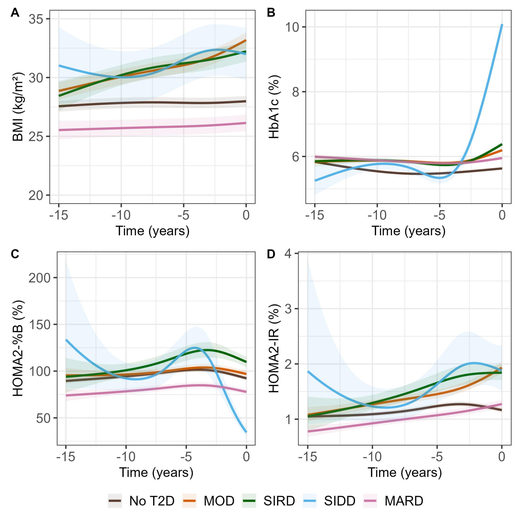
Descriptive Characteristics at Index Visit

	Overall	No T2D	MARD	MOD	SIDD	SIRD
N (%)	10,309	8,747 (84.8%)	455 (4.4%)	838 (8.1%)	28 (0.3%)	241 (2.3%)
Age at T2D diagnosis (years)	59.1 (10.6)	-	67.2 (8.1)	52.6 (7.0)	56.9 (11.5)	66.3 (9.7)
Female	6,145 (59.6%)	5,143 (58.8%)	247 (54.3%)	604 (72.1%)	11 (39.3%)	140 (58.1%)
Race & Ethnicity						
NH White	4,722 (45.8%)	4,078 (47.1%)	206 (43.2%)	354 (44.3%)	3 (12.5%)	81 (33.9%)
NH Black	3,868 (37.5%)	3,275 (37.8%)	156 (32.8%)	352 (44.0%)	16 (66.7%)	69 (28.9%)
Hispanic	1,160 (11.3%)	932 (10.8%)	52 (10.9%)	105 (13.1%)	8 (33.3%)	63 (26.4%)
Other	422 (4.1%)	464 (5.4%)	71 (14.9%)	27 (3.4%)	1 (4.2%)	28 (11.7%)
BMI (kg/m^2)	30.4 (6.8)	29.7 (6.4)	28.8 (3.6)	37.9 (6.9)	34.1 (7.3)	33.2 (6.1)
HbA1c (%)	5.7 (5.4, 6.0)	5.6 (5.4, 5.9)	6.1 (5.7, 6.5)	6.3 (5.9, 6.6)	9.7 (8.9, 10.9)	6.5 (6.1, 6.7)
HOMA2-%B (%)	139.7 (91.8, 224.1)	141.7 (90.6, 232.2)	109.6 (81.2, 139.1)	132.9 (102.0, 170.3)	60.5 (24.9, 79.4)	249.8 (203.2, 299.0)
HOMA2-IR (%)	2.5 (1.2, 4.5)	2.3 (1.1, 4.3)	2.4 (1.6, 3.7)	3.8 (2.6, 5.2)	5.9 (2.5, 8.0)	7.2 (6.9, 7.4)
Systolic BP (mmHg)	116.3 (23.1)	115.0 (23.7)	124.5 (18.3)	122.0 (17.3)	120.3 (23.9)	124.4 (18.6)
LDL cholesterol (mg/dL)	111.7 (32.6)	111.7 (32.4)	110.5 (33.8)	115.4 (34.0)	109.7 (35.0)	101.2 (33.7)
eGFR (mL/min/1.73 m²)	79.0 (20.5)	79.0 (20.4)	74.5 (20.1)	97.6 (20.5)	92.5 (27.3)	68.8 (16.5)

Notable differences in characteristics at the last follow-up: MARD (4.4%) featured older age, lower BMI, better lipid profiles, and reduced insulin resistance, while MOD (8.1%) involved younger age and higher BMI. SIDD (0.3%) showed severe β-cell dysfunction and poor glycemic and lipid profiles, whereas SIRD (2.3%) was marked by high insulin resistance and elevated β-cell function.

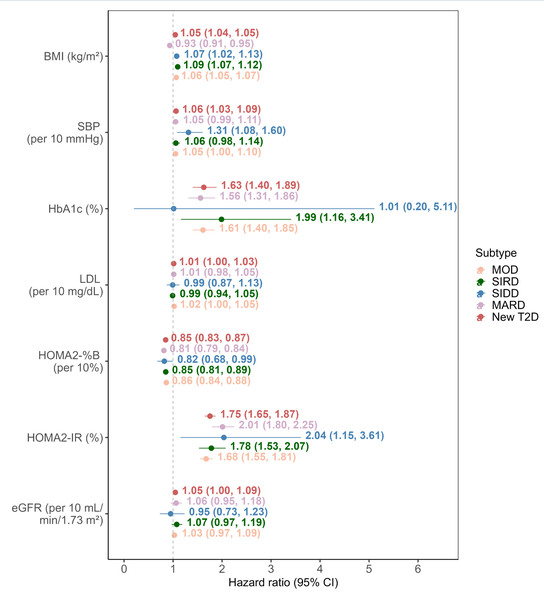


Heterogeneity in Metabolic Trajectories



In the 15-year interval preceding T2D diagnosis or the last follow-up, distinct and subtype-specific metabolic trajectories emerged after adjusting for study cohort, sex, race/ethnicity, censored age and the indicator variable for DPP intervention assignment.

Associations of Biomarkers with Subtypes



Hazard ratios and 95% confidence intervals from TDCM adjusted for socio-demographics, study cohort and DPP intervention assignment indicator.

IMPLICATIONS

- Known pathophysiological biomarkers are prognostically associated with onset of T2D.
- Characterizing the heterogeneity of T2D at diagnosis requires evaluating trajectories of risk factors, especially in the five years immediately before diagnosis.

DISCUSSIONS

- The non-linear trajectories suggest that using data from a single time-point may be insufficient for risk stratification of subtype membership among individuals with T2D.
- Limitations included heterogeneity in cohort inclusion criteria, follow-up schedules, and T2D definitions, potential measurement variability across biomarkers, high rates of non-monotone missingness despite imputation, and small sample size for SIDD.
- Our findings recommended a precision prevention framework focused on the three to five years before diagnosis, incorporating polygenic risk scores, deep phenotyping, and targeted interventions, tailored to subtype-specific metabolic trajectories and individual risk profiles.

Acknowledgements

We thank Zhongyu Li, Howard Chang, Shivani Patel, Mohammed K. Ali for their technical and clinical inputs.