



Twenty -year glycemia trajectories and risk for cognitive impairment in adults with pre-diabetes or type 2 diabetes: The Diabetes Prevention Program Outcomes Study

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INTRODUCTION

Type 2 diabetes (T2D) in adulthood is a significant risk factor for development of cognitive impairment (CI) later in life.^{1,2}

Dysregulation of blood glucose levels, or dysglycemia, is the most well-studied metabolic factor in T2D as it relates to CI.³

Work to date has included only cross-sectional measures of glycemia or cumulative glycemic burden with short-duration T2D (<10 years).

OBJECTIVE

Examine longitudinal glycemia trajectories from mid- to late-life in relation to prevalence of CI among adults living with pre-diabetes or T2D.

METHODS

Glycemia was defined as **HbA1c** and measured annually over 22 years of follow-up in DPP/DPPOS.

N = 1,483 participants were included who were enrolled in DPP and who had ≥ 3 HbA1c measures during follow-up in DPP/DPPOS and completed cognitive assessments in 2023-2025, 25 years after DPP enrollment.

- HbA1c exposure over time** was estimated using two methods:
- Linear Mixed Effects (LME)** model output participant-level intercept (mean HbA1c) and linear slope (rate of change per 5 years) as continuous exposure variables for modeling.
 - K-means trajectory clusters with LME parameters** output 2 derived clusters of glycemia trajectories as a 2-level categorical exposure variable for modeling.

Cognitive impairment (CI) was assessed via the National Alzheimer's Coordinating Center Uniform Data Set (v3; NACC-UDS3).

- The primary CI outcome was defined as a 3-level categorical variable based on the Clinical Dementia Rating (CDR): **dementia** (CDR ≥ 1 ; n=48), mild cognitive impairment (**MCI**; CDR=0.5; n=462), and **normal cognition** (CDR=0; n=973).

Multinomial logistic regression models were run to test the association between trajectories of HbA1c exposure (LME and k-means derived variables) and prevalence of CI, adjusted sequentially for demographic characteristics, cardiometabolic factors, and finally, APOE-4 status.

DESCRIPTIVE RESULTS

Participant Characteristics

Over **one-third (34%)** of participants were determined to have **cognitive impairment** (31% MCI, 3% dementia).

Age at enrollment, income, race and ethnicity, and APOE-4 status differed significantly by CI group (p<0.05; **Table 1**).

- Participants with **dementia** were older, male, with higher prevalence of ≥ 1 APOE-4 allele, and predominantly non-Hispanic (NH) White, relative to the other CI groups.
- Participants with **MCI** were predominantly female, and similar income and race and ethnicity distribution to the dementia group, but lower prevalence of ≥ 1 APOE-4 allele.
- Mean systolic blood pressure (SBP) and mean body mass index (BMI)** differed significantly by CI group (p<0.05; **Table 2**).

Table 1 Descriptive characteristics of analytic sample (N=1,483) by CI category.			
	Normal (n=973)	MCI (n=462)	Dementia (n=48)
Age at DPP enrollment (yrs), median (IQR)	47 (41,52)	50 (45,55)	57 (51,65)
Sex, n (%)			
Female	763 (78)	302 (65)	26 (54)
Male	210 (22)	160 (35)	22 (46)
Education (yrs), median (IQR)	16 (13,17)	15 (12,18)	14 (12,16)
Income, n (%)			
< \$35,000	233 (24)	144 (31)	15 (31)
\$35,000 - < \$50,000	187 (19)	100 (22)	10 (21)
\$50,000 - < \$75,000	227 (23)	99 (21)	9 (19)
> \$75,000	270 (28)	88 (19)	7 (15)
Refused	55 (6)	31 (7)	7 (15)
Race and ethnicity, n (%) ¹			
NH White	554 (57)	176 (38)	21 (44)
NH Black	163 (17)	138 (30)	12 (25)
Hispanic	149 (15)	90 (19)	8 (17)
AI/AN	63 (7)	31 (7)	1 (2)
Asian, NH/PI	44 (4)	27 (6)	6 (13)
APOE-4 status, n (%)			
≥ 1 APOE-4 alleles	173 (18)	102 (22)	22 (46)
0 APOE-4 alleles	647 (66)	289 (63)	19 (40)
Unknown	147 (16)	71 (15)	7 (14)
SBP, median (IQR) ^{2,3}	119 (114,125)	121 (115,128)	122 (117,128)
LDL, median (IQR) ^{2,3}	109 (95,124)	108 (92,123)	110 (97,123)
HDL, median (IQR) ^{2,3}	49 (43,57)	49 (41,57)	49 (43,55)
Triglycerides, median (IQR) ²	131 (101,169)	126 (97,169)	137 (91,177)
BMI (kg/m ²), median (IQR) ^{2,3}	33 (29,37)	32 (28,37)	29 (26,36)

1: NH = non-Hispanic, AI/AN = American Indian or Alaska Native, NH/PI = Native Hawaiian or Pacific Islander.
2: Mean values calculated using all repeated measures across 22 years of follow-up in DPP/DPPOS.
3: SBP=systolic blood pressure; LDL=low-density lipoprotein; HDL=high-density lipoprotein; BMI=body mass index.

MODEL RESULTS

K-means Cluster Model

- Too few dementia cases to report result; only MCI vs. normal shown.
- A sustained increasing HbA1c trajectory was associated with a 39% higher odds of CI, compared to a stable HbA1c (OR=1.39, 95% CI: 0.97,1.99; p=0.07) (**Figure 1**).
- When fully adjusted for cardiometabolic factors and APOE-4, this association was strengthened and marginally significant (**Table 3**).
- Older age at enrollment, male sex, NH black race, Hispanic ethnicity, higher mean SBP, and APOE-4 positive status were significantly associated with higher odds of MCI.

Table 3 Fully adjusted K-means model with 3-category CI outcome (dementia not shown).		
Cluster	MCI OR (95% CI) ¹	p-value
C1: Stable	Ref.	---
C2: Increasing	1.48 (1.00 to 2.18)	0.05

1: reference category is normal.

LME Model

- A larger HbA1c intercept (higher average HbA1c) was associated with a 31% greater likelihood of MCI (OR=1.31, 95% CI: 1.01,1.70; p=0.04).
- When fully adjusted this association was weakened and attenuated to non-significance.
- No LME parameters were associated with dementia.
- Older age at enrollment, male sex, NH black race, Hispanic ethnicity, higher mean SBP, and having ≥ 1 APOE-4 allele were significantly associated with higher odds of dementia and of MCI (p<0.05, not shown).

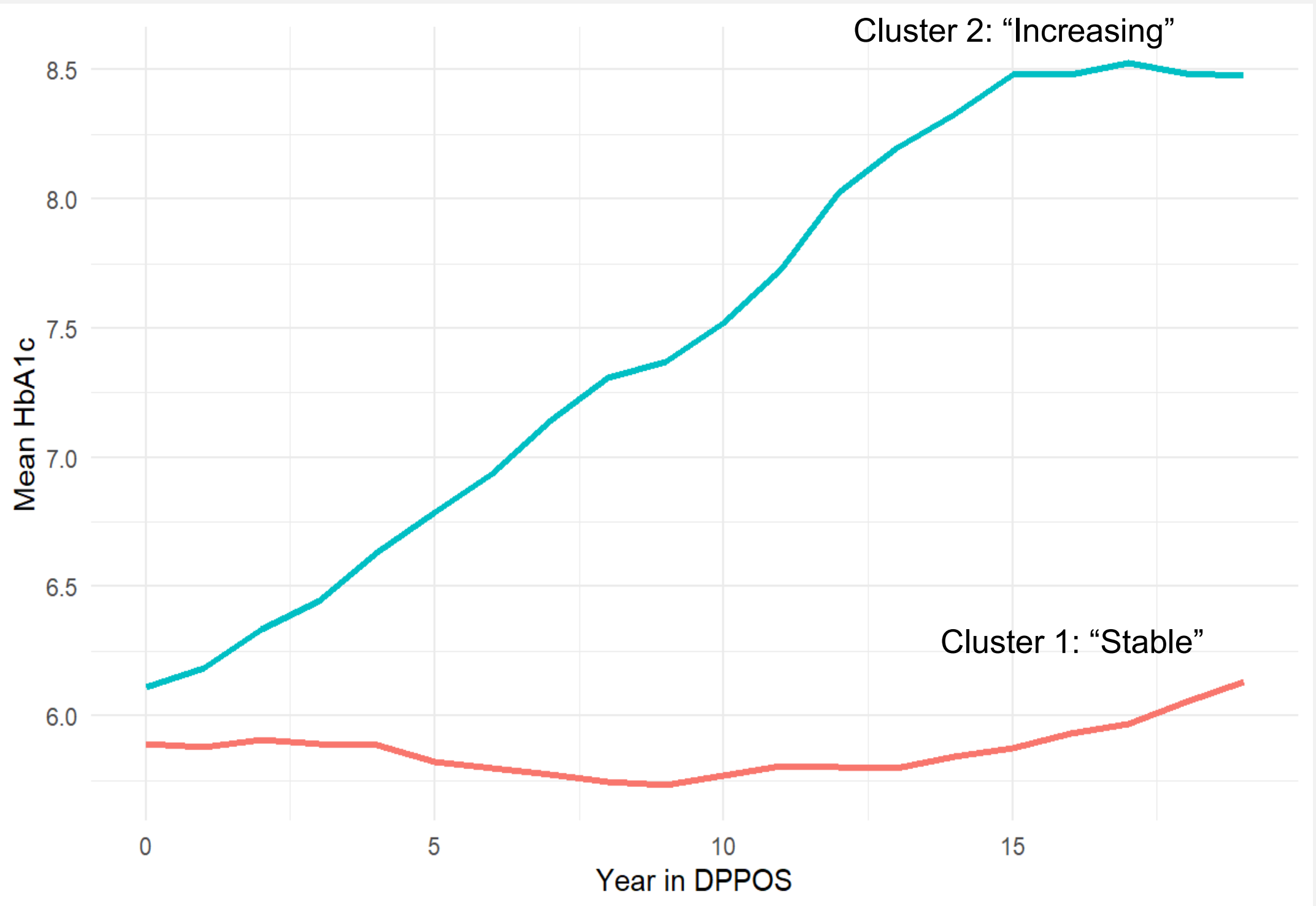


Figure 1 HbA1c cluster trajectories identified in k-means analysis; Cluster 1, N=1,473, MCI, n=393, dementia=45; Cluster 2, N=209, MCI n=69, dementia n=3).

CONCLUSIONS

In adults, cumulative glycemia exposure and glycemia trajectory from mid-life to late life are risk factors for cognitive impairment. The relationship is attenuated when accounting for cardiometabolic and genetic risk factors.

LIMITATIONS

- The small number of dementia cases prevented examining the 3-level CI variable as an outcome with cluster trajectories.
- Continued data collection with capture of new dementia cases will allow for robust testing of glycemia effects on incident dementia risk.

FUTURE DIRECTIONS

- Examination of glycemia exposure with specific CI neuropathology (e.g., vascular vs. Alzheimer's Disease) is needed.
- Future work should examine cumulative burden and trajectories of glycemia within defined life stages, delineating the effects of HbA1c in mid-life from the effects in late life.
- Downstream pathophysiology of hyperglycemia, such as advanced glycation end products should be examined as more proximal risk factors for cognitive impairment in people with T2D.

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