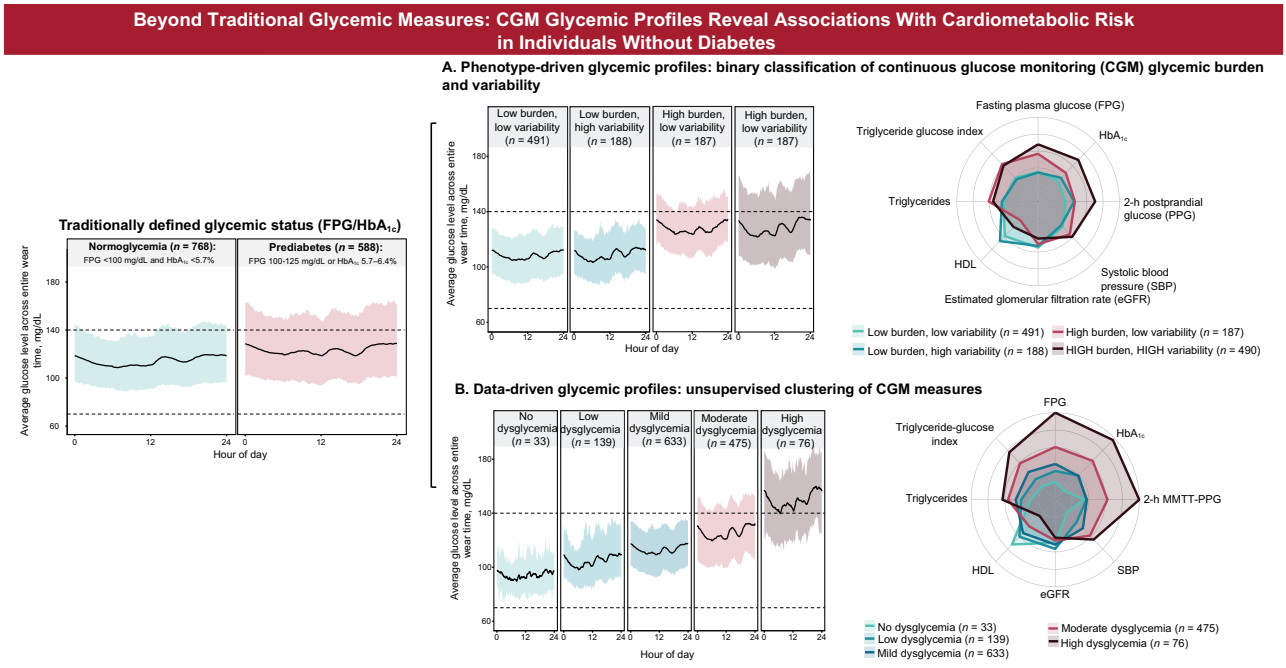
Diabetes Care
American Diabetes Association

Beyond Traditional Glycemic Measures: CGM Glycemic Profiles Reveal Associations With Cardiometabolic Risk in Individuals Without Diabetes

Bahar Bakhshi, Honghuang Lin, Naznin Sultana, Elizabeth Healey, Havelah Queen, Ge Gao, Sophie E. Claudel, Erika T. Minetti, Gary F. Mitchell, Joanne M. Murabito, Donald M. Lloyd-Jones, Michael C. Cheney, Devin W. Steenkamp, Matthew Nayor, Vanessa Xanthakis, Maura E. Walker, and Nicole L. Spartano

Diabetes Care 2026;49(11):2040–2049 | https://doi.org/10.2337/dc26-1197



Time-series glucose profiles generated by averaging glucose levels across the entire CGM wear time among 1,356 Framingham Heart Study participants, with the shaded areas representing the 5th–95th percentile interval.
2-h MMTT-PPG, 2-h postprandial glucose following a mixed-meal tolerance test.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Fasting plasma glucose and HbA_{1c} may not fully capture the heterogeneity underlying dysglycemia or its associations with cardiometabolic risk factors (CMRFs).

- **What is the specific question(s) we wanted to answer?**
  Are continuous glucose monitoring (CGM) measures cross-sectionally associated with CMRFs and clinical risk prediction equations for CVD risk among individuals without diabetes, and can CGM glycemic profiles reveal discordance with traditionally defined glycemic status and exhibit varying risks in clinical risk prediction equations for CVD risk?

- **What did we find?**
  CGM measures and glycemic profiles, especially those representing glycemic burden, were positively associated with CMRFs and 10-year CVD risk estimates.

- **What are the implications of our findings?**
  CGM phenotyping may improve diabetes prevention and further enhance risk stratification in individuals without diabetes.

ORIGINAL ARTICLE

Beyond Traditional Glycemic Measures: CGM Glycemic Profiles Reveal Associations With Cardiometabolic Risk in Individuals Without Diabetes

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OBJECTIVE

Fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c}) may not fully capture the heterogeneity underlying dysglycemia or its associations with cardiometabolic risk factors (CMRFs). We cross-sectionally investigated whether continuous glucose monitoring (CGM) measures and glycemic profiles could reveal 10-year cardiovascular disease (CVD) risk and individual CMRFs among individuals without diabetes.

RESEARCH DESIGN AND METHODS

We included 1,356 participants without prevalent diabetes or CVD from the Framingham Heart Study, who wore a blinded Dexcom G6 Pro CGM for up to 10 days. CGM glycemic profiles were characterized using *1*) binary classification of glycemic burden and variability and *2*) unsupervised clustering of CGM measures. We performed multivariable-adjusted linear and logistic regression models to examine associations of CGM measures and profiles with 10-year CVD risk estimates (PREVENT equations) and individual CMRFs.

RESULTS

Participants' mean was age 59.3 years; 55.8% were women, and 92.6% were non-Hispanic White. CGM measures were positively associated with 10-year CVD risk estimates and CMRFs. For example, 1 SD higher % time >140 mg/dL (15.4%) was associated with 2% higher 10-year CVD risk estimates and 21–26% higher odds of hypertension and dyslipidemia, even after adjusting for FPG. Glycemic profiles representing higher CGM dysglycemia revealed discordance with traditionally defined glycemic status (FPG and HbA_{1c}). Although 48.1–84.2% of individuals with traditionally defined prediabetes were included in CGM profiles representing higher dysglycemia, such profiles were associated with 6–7% higher 10-year CVD risk estimates, in addition to worse CMRFs.

CONCLUSIONS

Glycemic measures reflective of continuous glucose dynamics may provide additional insights into cardiometabolic risk beyond traditional measures.

Dysglycemia is a phenotypically heterogeneous risk factor for cardiometabolic disease, currently characterized by static glucose thresholds (1). Even without progression to type 2 diabetes (T2D), impaired glycemic traits (e.g., fasting plasma glucose

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Received 20 May 2026 and accepted 15 August 2026

This article contains supplementary material online at https://doi.org/10.2337/figshare.33273822.

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[FPG] and hemoglobin A_{1c} [HbA_{1c}]) are associated with adverse cardiometabolic outcomes, including atherosclerotic cardiovascular disease (CVD), heart failure, chronic kidney disease, and all-cause mortality (2,3). However, the existing T2D diagnostic framework oversimplifies the pathobiology underlying dysglycemia and its dynamic nature (4). Impaired glycemic traits do not occur in isolation but instead are broader manifestations of perturbations in glucose homeostasis and cardiometabolic regulation that may not be fully captured by static measures (5–7). Understanding temporal glucose patterns may be pivotal in uncovering early or intermittent dysglycemia and its downstream cardiometabolic risks (7,8).

Continuous glucose monitoring (CGM) may aid in characterizing the heterogeneity underlying dysglycemia by enabling dynamic phenotyping of individuals across the dysglycemia continuum (7). Emerging evidence suggests that CGM summary measures (e.g., % time >140 mg/dL) are cross-sectionally correlated with cardiometabolic risk factors (CMRFs) (9–11) and longitudinally associated with the development of cardiometabolic disease (12). Leveraging the rich analytic framework of CGM, recent studies have also characterized subtypes indicative of distinct differences in glycemic burden or variability (8,13–15). Such glycemic profiles may reflect latent metabolic dysfunction, providing a foundation for investigations into precision preventive strategies for cardiometabolic diseases, such as T2D (6). Although a majority of glycemic profiling efforts have focused on individuals with T2D (8,13), additional studies are required to replicate and extend prior findings, particularly in those without T2D (14,15).

In a sample of individuals without T2D or CVD from the Framingham Heart Study (FHS), we cross-sectionally related CGM summary measures and 2-h postprandial plasma glucose (PPG) after a standardized mixed meal to clinical risk prediction equations for CVD risk and individual CMRFs. We next derived CGM glycemic profiles, evaluated phenotypic divergence between traditionally defined glycemic status (FPG/HbA_{1c}) and CGM glycemic profiles, and additionally characterized their associations with clinical risk prediction equations for CVD risk and individual CMRFs. Our findings provide complementary insights into associations between CGM and CMRFs, with important clinical implications for uncovering the heterogeneity in dysglycemia and cardiometabolic risk that are otherwise not captured by traditional measures.

RESEARCH DESIGN AND METHODS

Study Sample

Participants from the FHS Third Generation, New Offspring Spouse, and Omni 2 cohorts attending their fourth examination cycle (2022–2025) were invited to undergo an oral mixed-meal tolerance test (MMTT) and wear a Dexcom G6 Pro CGM for up to 10 days (n = 2,718) (16). Of those, we included participants who completed both pre- and post-MMTT blood draws and had ≥3 valid days of CGM data after their visit. Details of exclusion criteria are shown in Supplementary Fig. 1, including self-reported T2D (n = 5), prevalent T2D defined as HbA_{1c} ≥6.5% or FPG ≥126 mg/dL or taking glucose-lowering medication (n = 228), prevalent CVD (i.e., centrally adjudicated coronary heart disease, congestive heart failure, stroke, or peripheral arterial disease up to 2022 [17,18]; n = 94), and missing important covariates (n = 206), resulting in a final sample size of 1,356.

All FHS study protocols and procedures were conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board for human research at Boston University Medical Campus. All participants provided written consent before participation in the study.

Glycemic Traits

Participants were asked to wear a blinded Dexcom G6 Pro monitor on their arm or abdomen for up to 10 days. Interstitial glucose values were measured every 5 min (maximum 288 readings/day) for the entire wear time (average wear time 8.2 days). The mean absolute relative deviation for Dexcom G6 Pro has been reported to be ∼9% (19).

CGM Summary Measures

CGM data preprocessing was conducted according to the steps detailed in Supplementary Fig. 1 to define valid days of CGM wear. We used the standardized, open-source R package iglu to calculate CGM summary measures (Supplementary Fig. 2) (20). We included 10 CGM summary measures, chosen based on previous literature (9), which can be broadly categorized into measures of overall glycemic burden (mean glucose and % time >140 mg/dL), measures of glycemic variability (coefficient of variation [CV], mean amplitude of glycemic excursions [MAGE], continuous overall net glycemic action over 1 h [CONGA 1-h], and mean of daily differences [MODD]), and composite scores reflecting the quality of glycemic control and management (J-index and Glycemic Risk Assessment Diabetes Equation [GRADE]) or indices of hyper- and hypoglycemia (low blood glucose index [LBGI] and high blood glucose index [HBGI]), as listed in Supplementary Table 1 (9,21).

2-h MMTT-PPG

Before wearing a CGM and after a 10-h overnight fast, participants were asked to consume a liquid meal containing a total of 600 kcal, including 75 g carbohydrates, 21 g fat, and 29 g protein within 5 min. Plasma samples were collected before and 2 h after the challenge to measure FPG and 2-h MMTT-PPG.

Individual CMRFs

Two seated systolic blood pressure (BP) and diastolic BP measurements were taken after a 5-min rest period, and the averages were used for analysis. Hypertension was defined as systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg or use of antihypertensive medication. Fasting blood samples (≥10 h) were used to measure plasma total cholesterol, triglycerides, and HDL using standard clinical assays. Dyslipidemia was defined as high triglycerides (≥150 mg/dL or use of lipid-lowering medication) or low HDL (<40 mg/dL for men and <50 mg/dL for women or use of lipid-lowering medication). Estimated glomerular filtration rate (eGFR) was evaluated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based eGFR equation (22). Reduced kidney function was defined as eGFR <90 mL/min/1.73 m^2.

10-Year Predicted CVD Risk Estimates

The 10-year predicted CVD risk estimates were evaluated using the Predicting Risk of Cardiovascular Disease Events (PREVENT) equations developed by the American Heart Association. PREVENT-CVD equations allow for sex-specific race-free risk calculation for U.S. adults aged 30–79 years and have been previously described in detail (23). We used the base equations estimating the total 10-year

CVD risk, incorporating traditional CMRFs within predetermined ranges, such as age, sex, smoking status, systolic BP (90–200 mmHg), total cholesterol (130–320 mg/dL), HDL (20–100 mg/dL), antihypertensive medication use, statin use, diabetes status, and eGFR.

Statistical Analysis

Participant characteristics according to the 10-year CVD risk estimate categories are reported as mean (SD) for continuous variables and *n* (%) for categorical variables. Traditionally defined glycemic status was characterized as normoglycemia (FPG <100 mg/dL and HbA_{1c} <5.7%) or prediabetes (FPG 100–126 mg/dL or HbA_{1c} 5.7–6.4%).

Glycemic Traits, 10-Year Predicted CVD Risk Estimates, and Individual CMRFs

Primary Analyses

We investigated the associations of glycemic traits (2-h MMTT-PPG and CGM measures) with 10-year predicted CVD risk estimates by performing multivariable linear regression on standardized glycemic traits (mean [SD] 0 [1]) and log-transformed PREVENT risk estimates. The models were adjusted for age, sex, smoking status, and use of antihypertensive or lipid-lowering medication (model 1), with additional adjustments for FPG (model 2) and BMI (model 3). We next categorized PREVENT risk estimates as <5.0%, 5.0% to <7.5%, and ≥7.5% and performed multinomial regression on standardized glycemic traits (mean [SD] 0 [1]) and PREVENT risk categories, with <5.0% as reference and adjustment for covariates in models 1–3.

Secondary Analyses

Despite providing a clinically relevant composite CVD risk estimate, PREVENT equations do not reveal the heterogeneity along the path to CVD. We therefore performed multivariable linear regression on standardized glycemic traits to determine their associations with standardized CMRFs, including BP, lipid profile, triglyceride-glucose index, and eGFR. All linear models were adjusted for age, sex, smoking, BP treatment, and lipid-lowering medication use (model 1), with additional adjustments for FPG (model 2) and BMI (model 3). We additionally applied multivariable logistic regression on standardized glycemic traits and binary cardiometabolic states: hypertension, dyslipidemia (high triglycerides or low HDL), and reduced kidney function. Given that BP treatment and lipid-lowering medication use were included in the definitions of individual CMRFs, we adjusted the logistic models for age, sex, and smoking, with additional adjustments for FPG and BMI, to avoid overadjustment and subsequent bias toward null (24). All analyses were corrected for multiple testing (false discovery rate–corrected *q* value of <0.05 was considered statistically significant).

CGM Glycemic Profiles and 10-Year Predicted CVD Risk Estimates

Glycemic dynamics consist of inherently interrelated, multidimensional components, including burden and variability. We therefore defined glycemic profiles based on two different analytic approaches.

Phenotype-Driven Glycemic Profiles

Phenotype-driven glycemic profiles were defined according to population-based medians of glycemic burden (i.e., % time >140 mg/dL) and variability (i.e., MAGE), hypothesizing that higher CGM burden and variability may synergistically be associated with higher 10-year predicted CVD risk estimates and adverse CMRFs. Additionally, their corresponding age- and sex-adjusted partial correlations were moderate (r = 0.47), indicating that % time >140 mg/dL and MAGE capture distinct aspects of glycemia (Supplementary Figs. 2 and 3). Participants were cross-classified into four mutually exclusive groups based on placement below or above the median value of % time >140 mg/dL and MAGE: *1*) low burden, low variability; *2*) low burden, high variability; *3*) high burden, low variability; and *4*) high burden, high variability.

Data-Driven Glycemic Profiles

Data-driven glycemic profiles were defined using unsupervised clustering of CGM measures derived from the iglu package, details of which are described in the Supplementary Methods. To minimize selection bias and preserve cluster stability, we performed iterative robust sparse k-means clustering in a larger analytic data set of individuals without T2D with ≥3 days of valid CGM data (n = 1,761) (Supplementary Fig. 1) and subsequently merged the cluster assignments with the final analytic data set for downstream analyses (n = 1,356).

To investigate the associations of glycemic profiles with PREVENT risk estimates, we performed separate multivariable linear regression models for phenotype- and data-driven glycemic profiles with log-transformed 10-year predicted CVD risk estimates, adjusting for covariates in models 1–3, and applied corrections for multiple testing (FDR-corrected *q* value of <0.05 was considered statistically significant).

Sensitivity Analyses

We stratified our linear regression analysis on glycemic traits and 10-year predicted CVD risk estimates by *1*) traditionally defined glycemic status (i.e., normoglycemia and prediabetes) and *2*) age categories (i.e., <50, 50–64, and ≥65 years). Because age, sex, and use of antihypertensive or lipid-lowering medication are all components of PREVENT equations and may result in overadjustment, we conducted sensitivity analyses evaluating the associations of glycemic traits and profiles with 10-year predicted CVD risk estimates using a crude model and models adjusted only for FPG and BMI. We additionally performed analyses excluding individuals with <7 days of CGM data (n = 173), resulting in a sample of 1,183 individuals, and repeated our regression analysis of glycemic traits and CGM profiles with 10-year CVD risk. All analysis were performed in R, version 4.5.2.

RESULTS

Of the 1,356 participants (Supplementary Table 2), 55.8% were female and 56.6% had traditionally defined normoglycemia. Mean (SD) age was 59.3 (8.4) years, and mean (SD) BMI was 27.9 (4.4) kg/m^2. Compared with those in the 5–7.5% (n = 269) and <5% (n = 701) PREVENT categories, individuals in the ≥7.5% PREVENT category (n = 386) were older and had higher BMI, in addition to having higher traditional glycemic measures, higher CGM summary measures, and less favorable cardiometabolic profiles.

Glycemic Traits and 10-Year Predicted CVD Risk Estimates

Primary Analyses

Higher 2-h MMTT-PPG, CGM measures of glycemic burden (e.g., mean glucose and % time >140 mg/dL), and CGM composite indices of glycemic control (e.g., J-index and GRADE) were associated with

higher 10-year predicted CVD risk estimates, with associations persisting after further adjustment for FPG and BMI (Fig. 1*A* and Supplementary Table 3). For example, 1 SD higher % time >140 mg/dL, GRADE, and 2-h MMTT-PPG were associated with 3–4% higher 10-year predicted CVD risk estimates, after adjusting for FPG (ratios obtained after back-transforming β values reported in Supplementary Table 3). However, CGM measures of glycemic variability (e.g., CV and MAGE) were not associated with 10-year predicted CVD risk estimates.

Results from the multinomial regression indicated that higher glycemic traits, including 2-h MMTT-PPG, CGM measures of glycemic burden, and CGM composite scores (except for LBGI), were associated with higher odds of having ≥7.5% PREVENT risk estimates, compared with <5% as reference (Fig. 1*B* and Supplementary Table 4). For example, after adjusting for FPG, a 1 SD higher CGM mean glucose was associated with 53% higher odds of having ≥7.5% PREVENT risk estimates (95% CI 1.11–2.11), compared with <5% as reference. However, none of the glycemic traits were associated with the odds of being in the 5.0% to <7.5% 10-year predicted CVD risk category, compared with <5% as reference (Supplementary Table 5).

Glycemic Traits and Individual CMRFs

Secondary Analyses

We observed several associations between glycemic traits and individual CMRFs. In linear models, higher 2-h MMTT-PPG, CGM measures of glycemic burden, and CGM composite scores (except for LBGI) were associated with higher levels of fasting triglycerides, HDL, and triglyceride-glucose index, a surrogate measure of insulin resistance (Supplementary Fig. 4). In logistic models, higher 2-h MMTT-PPG, CGM measures of glycemic burden, and CGM composite scores (except for LBGI) were associated with higher odds of having hypertension and dyslipidemia (high triglycerides or low HDL) (Fig. 2 and Supplementary Table 6). For instance, 1 SD (15.4%) % time >140 mg/dL was associated with 21–26% higher odds of hypertension and dyslipidemia, independent of FPG. Similar to associations with 10-year predicted CVD risk estimates, CGM measures of glycemic variability were not associated with CMRFs, except for MODD, which showed positive associations with fasting triglycerides and HDL, triglyceride-glucose index, and higher odds of dyslipidemia.

Glycemic Profiles and 10-Year Predicted CVD Risk Estimates

As described in RESEARCH DESIGN AND METHODS, we defined glycemic profiles according to a binary classification of CGM % time >140 mg/dL and MAGE to evaluate a simple, scalable approach for understanding the heterogeneity in dysglycemia. Across phenotype-driven glycemic profiles, we observed distinct CGM signatures characterized by progression of glycemic traits from low burden, low variability to high burden, high variability (Fig. 3*A* and Supplementary Table 7). Notably, our

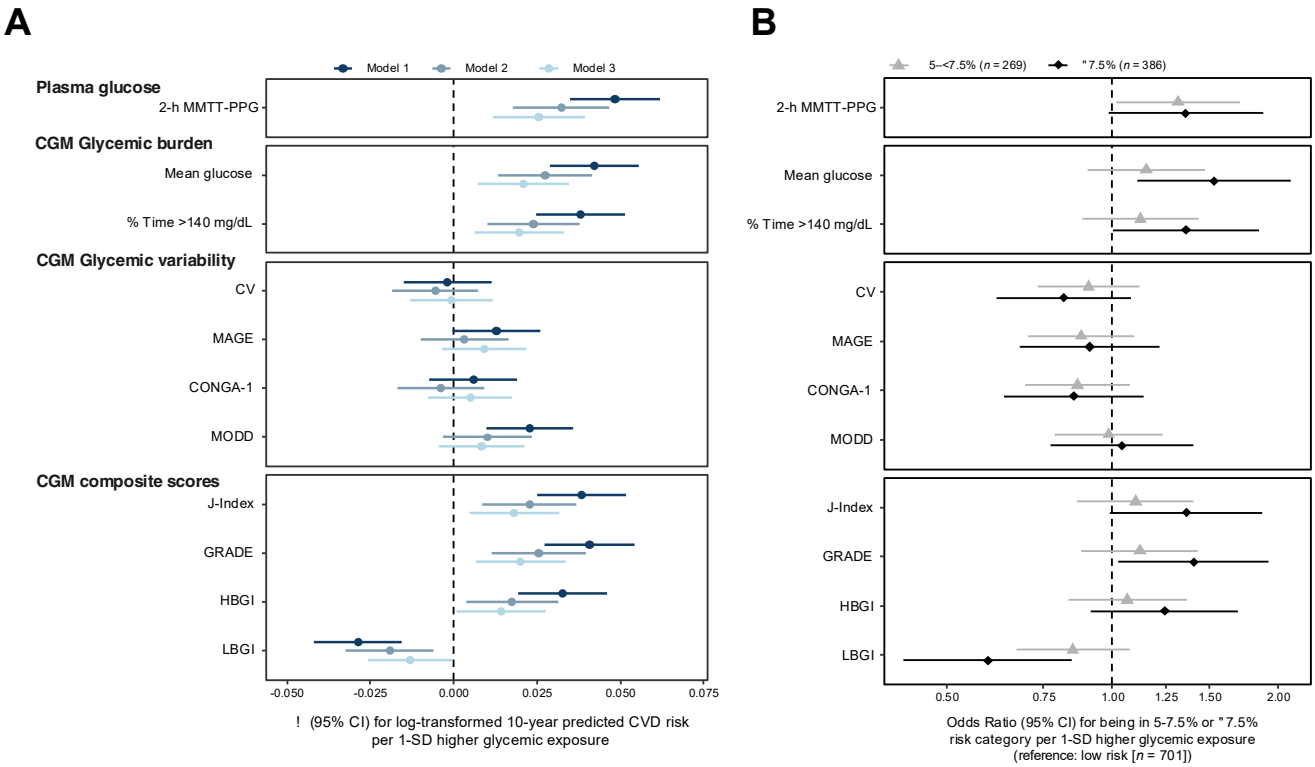


Figure 1—*A*: Associations of glycemic traits with 10-year predicted CVD risk estimates in individuals without T2D (*n* = 1,356). Multivariable-adjusted linear regression models were performed on standardized 2-h MMTT-PPG, CGM summary measures, and PREVENT scores. β (95% CI) values are shown. Model 1 was adjusted for age, sex, smoking status, antihypertensive medication use, and lipid-lowering medication use. Model 2 was additionally adjusted for FPG and model 3 for BMI. *B*: Associations of glycemic traits with odds of being in 5% to <7.5% (*n* = 269) and ≥7.5% PREVENT risk categories (*n* = 386), compared with <5% category (*n* = 701) as reference. Multinomial regression models were performed on standardized 2-h MMTT-PPG and CGM summary measures and PREVENT scores, adjusting for age, sex, smoking, antihypertensive medication use, lipid-lowering medication use, and FPG (model 2).

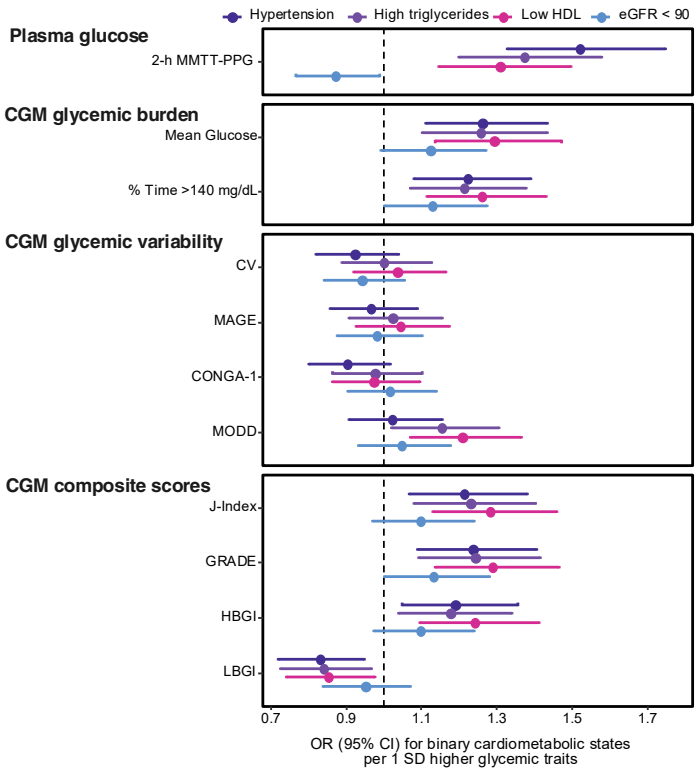


Figure 2—Associations of glycemic traits with binary cardiometabolic states in the overall population (n = 1,356). Hypertension was defined as systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg or antihypertensive medication use (n = 488). High triglyceride level was defined as triglycerides ≥150 mg/dL or lipid-lowering medication use (n = 479). Low HDL was defined as HDL <40 mg/dL for men and HDL <50 mg/dL for women or lipid-lowering medication use (n = 485). Loss of kidney function was defined as eGFR <90 mL/min/1.73 m^2 (n = 25). Logistic regression models were performed on standardized 2-h MMTT-PPG and CGM summary measures with cardiometabolic states, adjusting for age, sex, smoking, and FPG. OR, odds ratio.

phenotype-driven glycemic profiles revealed phenotypic divergence within traditionally defined glycemic status (Fig. 3*B*). Although a majority of individuals within the low burden, low variability CGM phenotype had normoglycemia, the proportion of individuals with traditionally defined prediabetes increased within the low burden, low variability to high burden, high variability phenotypes (29.1% vs. 59.8%, respectively). Additionally, cardiometabolic risk profiles seemed to worsen in those with high burden, high variability (Fig. 3*C*), and median 10-year predicted CVD risk estimates were greater with more severe phenotype-driven glycemic profiles (P for trend <0.001) (Supplementary Table 8). Lastly, glycemic profiles with high burden (including both high burden, low variability [n = 187], and high burden, high variability [n = 490]) were associated with 6–7% higher 10-year predicted CVD risk estimates, after adjusting for relevant confounders (ratios obtained from back-transforming β values reported in Fig. 3*D* and Supplementary Table 8).

For the data-driven glycemic profiling, we selected five glycemic profiles via unsupervised robust sparse k-means clustering clustering (k:5), choosing the highest weighted silhouette score (0.23), with the profiles exhibiting excellent stability across resampling analyses, as reflected by high adjusted Rand index (ARI) and coclustering agreement scores (mean [SD] ARI 0.85 [0.14] and mean [SD] coclustering agreement 0.93 [0.06], across 50 resampling runs of 80% sample size) (25). Data-driven glycemic profiles demonstrated a gradual worsening of CGM dysglycemia (Fig. 4*A*). Three profiles exhibited more favorable glycemic control (no [n = 33], low [n = 139], and mild dysglycemia [n = 633]), with an intermediate profile of moderate dysglycemia (n = 475) and a group with high dysglycemia (n = 76) (Supplementary Table 9). Data-driven glycemic profiles additionally depicted phenotypic divergence from traditionally defined glycemic status (similar to phenotype-driven glycemic profiles), with individuals with normoglycemia exhibiting varying degrees of CGM dysglycemia (Fig. 4*B*). Furthermore, glycemic profiles with moderate and high dysglycemia had worsened cardiometabolic profiles (Fig. 4*C*) and higher median 10-year predicted CVD risk estimates (P for trend <0.001) (Supplementary Table 10). To investigate whether data-driven glycemic profiles were significantly associated with 10-year predicted CVD risk estimates, we combined clusters of no (n = 33) and mild dysglycemia (n = 139), setting them as reference (n = 172). Moderate and high dysglycemia were associated with greater 10-year predicted CVD risk estimates, after adjusting for relevant confounders (Fig. 4*D* and Supplementary Table 10). However, the association between high dysglycemia and 10-year predicted CVD risk estimates attenuated toward null after further adjustment for FPG, likely because of small sample size or because the association may partly be explained by FPG.

When comparing the two approaches (Supplementary Fig. 5), individuals classified as having high glycemic burden and variability largely overlapped with the moderate and high dysglycemia clusters, whereas individuals with low burden and low variability were predominantly distributed across the no, low, or mild dysglycemia clusters. The overall concordance between the two approaches highlights the utility of using only two CGM measures of burden and variability (i.e., % time >140 mg/dL and MAGE) to classify individuals' glycemic profiles, although both CGM subtyping methods have the potential for providing additional insights into glycemic heterogeneity.

Sensitivity Analyses

When stratified by traditionally defined glycemic status, linear associations of glycemic traits with 10-year predicted CVD risk estimates were similar in terms of magnitude among individuals with normoglycemia and prediabetes (Supplementary Fig. 6 and Supplementary Table 11). When stratified by age category (Supplementary Fig. 7), we observed weaker associations among CGM summary measures (except for MAGE) with 10-year predicted CVD risk estimates among those aged <50 years.

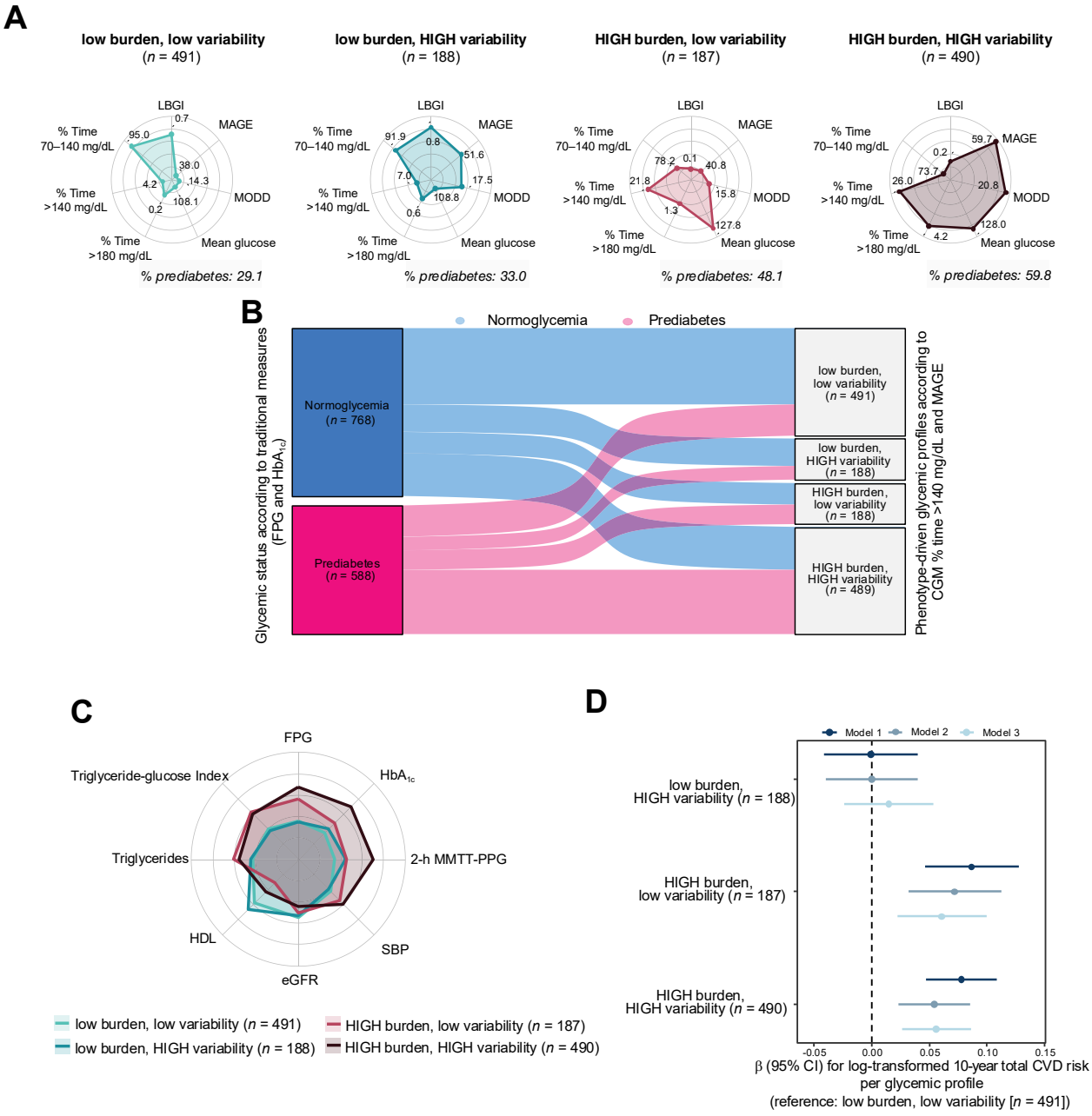


Figure 3—*A*: CGM signatures of phenotype-driven glycemic profiles defined according to placement below or above median value of % time >140 mg/dL and MAGE: low burden, low variability (n = 491); low burden, high variability (n = 188); high burden, low variability (n = 187); and high burden, high variability (n = 490). Radar plots illustrate the average multivariable CGM signatures for glycemic profiles, with each CGM variable presented on a standardized scale (mean ±1 SD). *B*: Transitions between glycemic status defined according to traditional measures (FPG/HbA_{1c}) and phenotype-driven glycemic profiles. *C*: Cardiometabolic risk factors of phenotype-driven glycemic profiles. Radar plots illustrate the average value of cardiometabolic risk factors for glycemic profiles (z score scale; ±1 SD from mean) *D*: Associations of phenotype-driven glycemic profiles and 10-year predicted CVD risk estimates, compared with low burden, low variability (n = 491), as reference. Model 1 was adjusted for age, sex, smoking status, antihypertensive medication use, and lipid-lowering medication use. Model 2 was additionally adjusted for FPG, and model 3 for BMI. SBP, systolic BP.

The small sample size of those aged <50 years (n = 184) limited our ability to interpret these findings.

Adjusting for age, sex, and antihypertensive or lipid-lowering medication use significantly attenuated the associations between glycemic traits and 10-year predicted CVD risk estimates (Supplementary Tables 3–6). Notably, CGM measures of glycemic variability (e.g., CV, MAGE, and CONGA-1 were significantly associated with 10-year predicted CVD risk estimates in the crude model, in addition to models adjusted for FPG and BMI. However, as discussed above, after further adjustment for covariates, the associations attenuated toward null (Supplementary Table 3). After excluding individuals with <7 days of CGM data, the magnitude of associations between glycemic traits, profiles, and 10-year predicted CVD risk estimates did not change substantially (Supplementary Figs. 10–12).

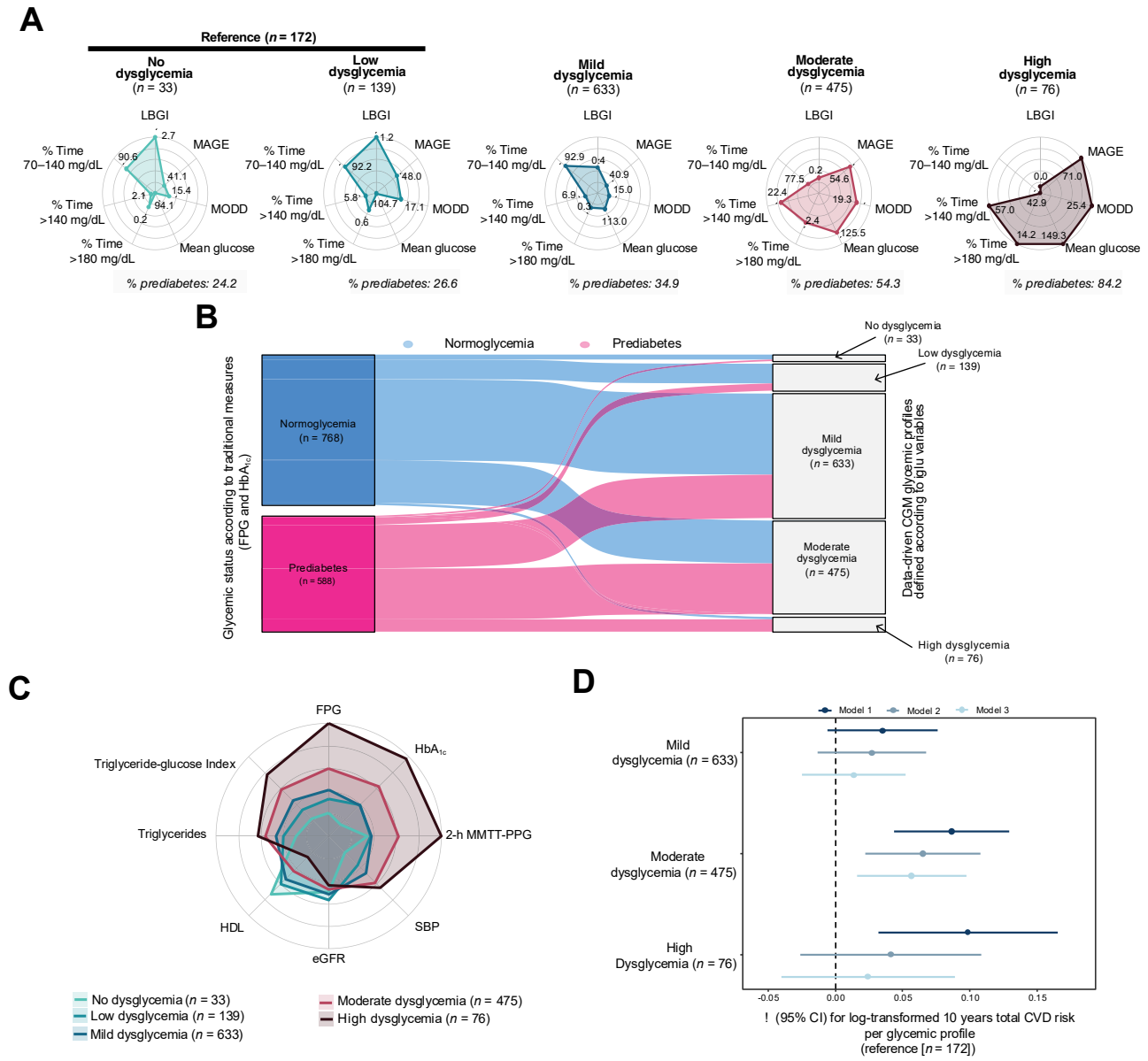


Figure 4—*A*: CGM signatures of data-driven glycemic profiles among individual without T2D: favorable glycemic control (no [*n* = 33] or low dysglycemia [*n* = 139]) and mild (*n* = 633), moderate (*n* = 475), and high dysglycemia (*n* = 76). Radar plots illustrate the average multivariable CGM signatures for glycemic profiles, with each CGM variable presented on a standardized scale (mean ±1 SD). *B*: Transitions between glycemic status defined according to traditional measures (FPG/HbA_{1c}) and data-driven glycemic profiles. *C*: Cardiometabolic risk factors of data-driven glycemic profiles. Radar plots illustrate the average value of cardiometabolic risk factors for glycemic profiles (*z* score scale; ±1 SD from mean). *D*: Associations of data-driven glycemic profiles and 10-year predicted CVD risk estimates, compared with clusters with favorable glycemic control (*n* = 172) as reference. Model 1 was adjusted for age, sex, smoking status, antihypertensive medication use, and lipid-lowering medication use. Model 2 was additionally adjusted for FPG and model 3 for BMI. SBP, systolic BP.

CONCLUSIONS

Among individuals without T2D, we showed that 2-h PPG assessed after a standardized mixed meal, as well as glycemic measures derived from continuous glucose dynamics assessed over a more extended monitoring period, was cross-sectionally associated with higher 10-year predicted CVD risk estimates and adverse CMRFs. When examining the CGM summary measures consistently associated with cardiometabolic risk, our analyses specifically pointed to measures of glycemic burden, such as mean glucose and % time >140 mg/dL. For instance, a 15% longer time spent at glucose levels >140 mg/dL (equivalent to 1 SD) was associated with 2% higher 10-year predicted CVD risk estimates, as well as 21–26% higher odds of hypertension or dyslipidemia, independent of FPG and BMI. Furthermore, our CGM glycemic profiling captured multidimensional aspects of glycemia, including burden and variability, and subsequently revealed the heterogeneity in glycemic status that may be missed by traditional measures, with the dysglycemic profiles linked to higher 10-year predicted CVD risk estimates and worse CMRFs.

Our findings align with a small but growing body of literature characterizing the cross-sectional associations of CGM measures and health outcomes (9–11). Emerging studies have also reported that higher % time >140 mg/dL is longitudinally associated with the development of

cardiometabolic outcomes, including T2D, among individuals without T2D (12,26). In addition, CGM glycemic patterns from a multimodal transformer model better predicted T2D development compared with HbA_{1c} alone, suggesting that CGM glycemic patterns may aid in T2D risk stratification (27). Taken together, our results, in addition to prior literature, underscore the untapped clinical potential of using CGM to characterize dynamic glycemic traits and identify early metabolic dysfunction before T2D onset.

Although glycemia encompasses several distinct but interrelated dimensions, including overall burden and variability, the associations of our phenotype-driven glycemic profiles with 10-year predicted CVD risk estimates were primarily driven by glycemic burden, not variability. Considering that the existing variability measures were predominantly developed among individuals with diabetes, in whom glucose excursions are often more pronounced (28), it is plausible that these measures may be limited in terms of capturing biologically meaningful variations in glucose levels among individuals without T2D. Nonetheless, postprandial hyperglycemia, a short-term clinical measure of glycemic variability, has been previously linked to micro- and macrovascular complications among individuals with T2D (29,30). We therefore should not discount the potential role of glycemic variability in the development of long-term cardiometabolic outcomes, including progression to T2D, which has not been explored to our knowledge. Subsequent longitudinal studies are warranted to evaluate whether CGM glycemic variability and other novel CGM phenotypes could be informative in predicting cardiometabolic outcomes (6).

CGM glycemic profiling is a rapidly evolving field with an overarching goal of identifying subtypes indicative of distinct degrees of glycemic dysregulation (7). Most studies to date have focused on individuals with T2D (8,13,31), whereas efforts to characterize glycemic profiles in individuals without T2D remain limited (14,15). A prior smaller-scale study using CGM time-series clustering identified glycemic profiles representing low, medium, and high variability, among which the high variability group was positively correlated with CMRFs, such as insulin resistance (14). However, this analytic approach did not yield distinct glycemic subtypes when replicated in a larger independent study, highlighting the substantial knowledge gaps in establishing scalable methods to define clinically meaningful glycemic profiles in individuals without T2D (15). As evidence linking CGM measures, glycemic profiles, and cardiometabolic risk continues to accumulate, curating clinical guidelines specifically tailored to at-risk individuals becomes increasingly important. In our prior work, we found limited overall consensus among diabetologists and endocrinologists with CGM expertise in interpreting CGM profiles and potentially providing subsequent follow-up recommendations to FHS participants without T2D (32). Given that CGM devices are now available for over-the-counter purchase (33) and are targeted toward a broader population irrespective of T2D status, additional studies are required to establish reference ranges, define at-risk CGM glycemic profiles, and provide clinical guidance to health care providers.

Future studies should additionally identify complementary multimodal phenotyping (e.g., lifestyle assessments or standard metabolic challenges) that may be required to fully leverage the potential clinical utility of CGM for characterizing glycemic heterogeneity and informing cardiometabolic risk. Results from our current investigation showed that higher 2-h PPG after consumption of a standardized mixed meal was related to 3% higher 10-year predicted CVD risk estimates and 25–30% higher odds of having hypertension or dyslipidemia. In this context, emerging studies have also demonstrated the utility of CGM glucose curves after a standardized carbohydrate challenge (oral glucose tolerance test) for predicting the physiology underlying dysglycemia (6,34). However, a mixed-meal challenge may offer a more real-life, physiologically relevant representation of postprandial metabolism, in comparison with the oral glucose tolerance test (35). Therefore, additional studies are needed to investigate CGM responses to a standardized mixed meal and whether the CGM glucose curves may aid in uncovering glycemic heterogeneity among individuals without T2D. Work from our group and others has further shown that lower carbohydrate quality, as well as overall lower diet quality, is associated with higher CGM measures among individuals without T2D (21). However, further research is needed to investigate the added value of integrating CGM glycemic profiles that reflect underlying metabolic dysfunction to enhance targeted lifestyle interventions and alleviate cardiometabolic risk among at-risk individuals (9,21).

Strengths and Limitations

Our findings should be interpreted considering some limitations. Although we included a large sample size, the FHS sample predominantly consists of White participants of European ancestry, which may limit the generalizability of our results. Additionally, we used PREVENT equations to estimate CVD risk, providing several methodologic and clinical advantages, such as *1*) incorporating race-free, sex-specific CVD risk estimation and improved risk prediction compared with previously established equations (e.g., pooled cohort equations) (23) and *2*) capturing a broader spectrum of cardiovascular–kidney–metabolic risk that may aid in identifying early metabolic dysfunction (36). However, we did not measure the ratio of urine albumin to creatinine (uACR) in our samples and therefore could not use PREVENT equations that additionally incorporate the uACR, HbA_{1c}, and social deprivation index to capture the entire cardiovascular–kidney–metabolic spectrum. Our analysis investigating the associations between glycemic traits and individual CMRFs were aimed at identifying the PREVENT components driving the associations between glycemic traits and 10-year predicted CVD risk estimates. Therefore, the associations between CGM and CMRFs should be interpreted as a decomposition of the 10-year predicted CVD risk estimates. Although our CGM data were only recently collected, we cannot yet investigate the longitudinal associations of CGM measures with long-term cardiometabolic outcomes among our participants. Lastly, glycemic profiles identified through both phenotype- and data-driven approaches in this study need to be externally validated.

Conclusion

CGM measures and glycemic profiles provide new insights into associations between dysglycemia and cardiometabolic risk among those without T2D. Although the medical community has already begun capitalizing on CGM for diabetes management, future work is warranted to determine whether CGM has the potential to

inform current clinical practices on T2D screening and prevention in addition to CVD risk stratification in individuals without diabetes.

Acknowledgments. The authors thank FHS participants for their continued support of the study.
Funding. This investigation was supported by FHS contracts with the National Heart, Lung and Blood Institute (NHLBI) (N01-HC25195, HHSN2682015000001I, and 75N92019D00031), with additional support from the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK129305) (N.L.S.) and NHLBI (R01HL156975) (M.N.). B.B. is supported by a predoctoral fellowship from the American Heart Association (26PRE1564902). E.H. is supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (T32HD040128) and has recieved research funding from Dexcom, Inc. Dexcom, Inc., provided CGM devices at a discounted rate.
Duality of Interest. G.F.M. is the owner of Cardiovascular Engineering, Inc. (a company that designs and manufactures devices measuring vascular stiffness; the company uses these devices in clinical trials evaluating effects of diseases and interventions on vascular stiffness); serves as a consultant to and receives grants and honoraria from Novartis, Merck, Bayer, Servier, Philips, and deCODE genetics; and is an inventor on pending patent applications (disclosing methods for predicting various measures of biologic age using pressure waveforms). D.W.S. and N.L.S. are consultants for Abbott and have received investigator-initiated grant funding from Novo Nordisk. D.W.S. is a clinical trial investigator for Abbott Diabetes Care. E.H. has received sponsored research funding from Dexcom, Inc. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. B.B. analyzed data and wrote the manuscript. All authors designed research, contributed to discussion, and reviewed and edited the manuscript. B.B., M.E.W., and N.L.S. conducted research and supervised all analyses and writing. N.L.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation. Parts of this study were presented in abstract form at the 86th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 5–8 June 2026.
Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Elizabeth Selvin and Justin B. Echouffo-Tcheugui.

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