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Combined effects of diet, physical activity, obesity on continuous glucose monitoring-derived measures

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Thesis

COMBINED EFFECTS OF DIET, PHYSICAL ACTIVITY, OBESITY ON CONTINUOUS GLUCOSE MONITORING-DERIVED MEASURES

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DEDICATION

This work is dedicated to my family and my future self.

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COMBINED EFFECTS OF DIET, PHYSICAL ACTIVITY, OBESITY ON CONTINUOUS GLUCOSE MONITORING-DERIVED MEASURES

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ABSTRACT

Background: Diabetes is a prevalent disease that affects millions of people of all ages globally. The prevention of this disease is a crucial step in improving population health and longevity. While factors such as physical activity (PA), diet, and body mass index (BMI) are individually linked to traditional measures of diabetes status (including hemoglobin A1c and fasting blood glucose), their collective impact on more complex glycemic features that can be measured using continuous glucose monitoring (CGM) has not been fully elucidated. The primary objective of this study was to assess the joint association of diet, PA, and obesity with CGM-derived traits in individuals with prediabetes and normoglycemia.

Methods: The data utilized in this study were derived from participants in the Third Generation of the Framingham Heart Study, Omni 2 and New Offspring Spouse cohorts who wore a CGM and Fitbit monitor for a minimum of three complete days. Individuals with diabetes mellitus, those taking glucose-lowering medications, and those with less than two days of diet record completion were excluded from the study. The final sample size consisted 655 individuals, including 377 with normoglycemia and 278 with prediabetes. We used multivariable linear regression to examine the association of diet quality (AHEI – Alternative Healthy Eating Index), PA (average steps per day) and BMI with CGM-derived measures (mean glucose, coefficient of variation (CV), mean

difference between glucose values obtained at the same time of day (MODD), mean amplitude of glycemic excursions (MAGE), continuous overall net glycemic action (CONGA-1) and time spent >140 mg/dL). The models were adjusted for age, sex, CGM device lot number, CGM device location (arm vs. abdomen), alcohol and smoking status. We assessed models additionally including the other predictors (BMI, PA, and diet quality) in a stepwise fashion.

Results: Our cohort of 655 individuals demonstrated that those with prediabetes (N=278) had a higher BMI (29.2 vs. 26.5), and higher levels of CGM metrics compared to participants with normoglycemia (N=377). The study revealed significant associations between PA, diet, and BMI with glycemic control. The results showed that each additional 2,000 steps taken per day by the prediabetic cohort was associated with a reduction in mean glucose levels of approximately 1 mg/dL (Parameter Est. = -0.60, p=0.004). A similar reduction in mean glucose of 1 mg/dL was associated with a 5-6 point improvement in diet quality (Parameter Est. = -0.17, p=0.006), and a decrease in BMI of 3 kg/m² (Parameter Est. = 0.37, p=0.03). Notably, higher PA and better diet quality were linked to lower mean glucose levels and improved glucose variability, with these associations being more pronounced in normoglycemic individuals. In contrast, the prediabetic cohort exhibited fewer significant associations, with diet and PA showing moderate effects on mean glucose levels and J-index. Importantly, the interaction between PA and diet approached significance in the prediabetic group (p=0.05), indicating a potential combined effect on glycemic outcomes.

Conclusion: Overall, the findings of this study underscore the importance of integrating both PA and a high-quality diet to achieve optimal glycemic control. While PA alone was associated with improved glucose metrics, the combination of regular exercise and a healthy diet amplifies these associations, suggesting a synergistic effect. These results highlight the need for tailored lifestyle interventions that consider both PA and diet quality to effectively manage and prevent glucose dysregulation.

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LIST OF ABBREVIATIONS

AHEI-2010 ..... Alternative Healthy Eating Index-2010

AMPK ..... AMP-activated protein kinase

ASA24 ..... Automated Self-Administered 24-Hour Dietary Assessment Tool

BMI ..... Body Mass Index

CGM ..... Continuous Glucose Monitoring

CGMs ..... Continuous Glucose Monitors

CHD ..... Coronary Heart Disease

FHS ..... Framingham Heart Study

GBD ..... Global Burden of Disease

HbA1c ..... Hemoglobin A1C

IFG ..... Impaired fasting glycemia

IGT ..... Impaired glucose tolerance

MAGE ..... Mean Amplitude of Glycemic Excursions

MODD ..... Mean of Daily Differences

PreDM ..... Prediabetes

PUFA ..... Polyunsaturated Fatty Acid

T2DM ..... Type 2 Diabetes

INTRODUCTION

Diabetes is a widespread disease affecting 529 million people of all ages worldwide. [1] It is a non-infectious epidemic that, not only decreases life quality and requires perpetual therapy, but can also lead to death. According to the International Diabetes Federation Diabetes Atlas, it is responsible for an estimated 11.3% of deaths worldwide. [2] Pathophysiology of diabetes consists of insulin resistance and/or insulin deficiency, which both result in hyperglycemia. This in turn can lead to a variety of complications, including retinopathy, blindness, neuropathy, cardiovascular and cerebrovascular disease, nephropathy, and foot ulcers. The increasing number of people affected by this disease and its various complications are causing concern among medical professionals. Despite the availability of well-developed hormonal and non-hormonal therapies, diabetes remains a significant burden on the healthcare system, with an estimated cost of $412.9 billion in 2022. [3] Of this amount, about 70% represents direct healthcare expenditures attributable to diabetes, while almost 30% is accounted for by a decrease in labor productivity due to absenteeism, diminished effectiveness at both the work and home fronts, lack of a job resulting from prolonged and persistent disability, and an elevated risk of early death. However, managing diabetes is not only expensive but also extremely burdensome. The disease requires managing the patient's own care, including consistent medication adherence with daily insulin injections for some, monitoring blood glucose levels and making lifestyle changes involving daily decisions concerning diet and PA (PA). One recently developed tool that can help with some of these issues is continuous glucose monitoring (CGM).

Advances in diabetes management using continuous glucose monitoring

Continuous glucose monitors (CGMs) are devices that continuously monitor capillary blood glucose levels and provide real-time updates on glucose levels, as well as providing alarms for actual or predicted hypo- or hyperglycemia. CGMs are a small, comfortable, and user-friendly tool for people which allow them to monitor their glucose levels every few minutes without the need for hourly finger punctures required by traditional glucometers. CGMs have become increasingly popular and accurate over the years and are now considered a viable treatment option for diabetes. Since their commercial release in 2000, they have consistently improved in accuracy and convenience. [4] Real-time CGM has led to significant improvements for people with diabetes who, without it, may have experienced potentially life-threatening complications. Studies have shown that patients who used CGM to track their blood glucose levels demonstrated a significant decrease in their mean haemoglobin A1c (HbA1c) levels compared to patients who use self-monitoring. [5,6] This was observed in patients with both type 1 and type 2 diabetes mellitus who were taking prandial insulin and those who were not.

CGM applications for non-diabetics

In addition to aiding people with diabetes, CGM is also increasingly being used by people with pre-diabetes and by healthy individuals. It has been used in non-diabetic patients to help improve their overall health and to understand their personal glucose response curves and the triggers of their glucose spikes. [7,8] The use of CGM can be

helpful in informing future dietary and behavioural choices, as the regulation of blood glucose is highly variable, even in people who are not diabetic.

Individuals without diabetes have used CGM for health optimization in various ways. For instance, it can reveal the impact of exercise on blood sugar levels, allowing users to adjust the intensity and duration of exercise accordingly. Additionally, it can help endurance athletes track glucose levels while exercising and identify potential glucose-regulating problems. [9] CGM assists users in tracking their body's reactions to various foods and medications, enabling them to make informed choices regarding diet and treatment plans. Furthermore, CGM systems can be used to detect abnormal glucose regulation in healthy individuals, allowing for early intervention of diabetes. [10]

In addition to diabetes, diagnoses such as impaired glucose tolerance (IGT), impaired fasting glycemia (IFG) and insulin resistance leading to prediabetes are becoming more common. According to estimates, in 2021, approximately 97.6 million adults aged 18 years or older had prediabetes. [11] The monitoring of glucose curves using CGM may prove beneficial in the future for individuals at high risk of developing these conditions, such as those with obesity, a genetic disposition, advanced age, a family history of diabetes, physical inactivity, or certain medical diseases. This is because changes in insulin sensitivity lead to variations in glucose curves.

Current understanding of risk factors for diabetes.

The risk factors for diabetes are diverse and interconnected, encompassing a range of lifestyle and genetic elements. Being overweight or obese, a precursor condition like

prediabetes, and genetic predisposition significantly elevate the risk of developing diabetes. [12] Sedentary lifestyles, marked by physical inactivity, further compound this risk. Notably, certain racial and ethnic groups are more susceptible to diabetes, highlighting the potentially complex interplay of genetic and environmental determinants. Beyond these well-established factors, lifestyle elements such as diet, sleep, and physical activity (PA) exert profound influences on weight regulation and can potentially contribute to diabetes development. Evidence supports that impaired postprandial glucose, insulin, and lipid homeostasis are independent risk factors for obesity and noncommunicable diseases, including diabetes. [13,14]

There are numerous studies supporting the information above. An analysis of data collected from 64,227 middle-aged Chinese women demonstrated that higher energy intake was associated with a modestly increased risk of Type 2 Diabetes (T2DM), while PA was correlated with a decreased risk. [15] Furthermore, women who were less active with higher energy intake had a higher risk of T2DM compared to active participants with lower energy intake. Weight loss is a highly influential predictor in reducing the development of diabetes. According to a study conducted by Hamman et al., a 5-kg weight loss resulted in a 58% reduction in incidence of T2DM, with a 16% reduction in risk for every kilogram lost. [16]

It is well established that higher levels of PA are a fundamental aspect of a healthy lifestyle and well-being. The Centers for Disease Control and Prevention (CDC) have published the Physical Activity Guidelines for Americans, which recommend a minimum

of 150 minutes of moderate-intensity PA per week and at least two days/week of activities that strengthen muscles for adults. [20] A significant number of studies have observed a correlation between higher levels of moderate-to-vigorous PA and an increased risk of developing diabetes. A systematic review by Jeon et al., which included nearly 300,000 participants, has demonstrated that moderate-intensity PA can substantially reduce the risk of T2DM. [21]

A number of other studies aimed to observe the association between steps per day and diabetes or impaired fasting glucose and impaired glucose tolerance, using data from different populations in Northern countries, Australia, the United States, and Hispanic/Latino communities. [22-25] These studies found that individuals who accumulated more steps per day had a lower risk of developing diabetes or dysglycemia, with a 2-4% reduction in risk per 1000 steps per day. [22, 26]. While we are aware of a number of factors that contribute to higher glycemic variability, we lack an understanding of how these factors interact with one another. Some inverse associations were observed across a range of cohort characteristics, with the most notable associations observed among adults at high risk for diabetes, including those who were older, obese, or prediabetic. [26] Moreover, Cuthbertson, et al. sought to determine whether obesity, age, sex and prediabetes modify the association between step accumulation and diabetes incidence. Their findings indicated that adults with obesity exhibited a higher incidence of diabetes than adults without. A reduction in the risk of diabetes was observed amongst participants who were obese and who accumulated 10,000 steps per day, in comparison with those who were also obese, but who accumulated only 3,400 steps per day. This

reduction was found to be 19% (HR = 0.81, 95% CI 0.65, 1.01). In contrast, no association was observed among adults without obesity (HR = 1.01 [95% CI 0.81, 1.27]). So, it is now evident that the association between PA and diabetes is modified by body composition. Other characteristics also showed modifications, such as older adults achieving 10,000 steps/day had a 0.69 times lower risk of diabetes compared to those at 3400 steps/day; women at 10,000 steps/day had a 0.67 times lower risk, whereas men showed a weaker association; those with prediabetes achieving 10,000 steps/day had a 26% lower risk compared to 3400 steps/day, with no association among those without prediabetes.

The role of CGM in better understanding interactions among modifiable risk factors for diabetes.

Multiple studies have begun to utilize CGM devices to monitor participants' responses to meal composition, activity levels, and sleep patterns in individuals without diabetes. PREDICT (Personalized Responses to Dietary Composition Trial), one of the studies conducted in the UK by Berry, et al., [17] recruited 1002 twins and healthy adults and monitored their CMG-measures, PA, sleep, triglycerides, c-peptide, blood pressure, genetics, and gut microbiome providing nutritionally varied breakfasts and lunches for 13 days. Berry et all showed in their paper that meal composition is the most significant determinant of a postprandial glucose levels measured by CGM. However, the study was complicated by the fact that they advised participants to refrain from PA for three hours

after each test meal, which makes it challenging to draw definitive conclusions regarding this aspect of the results.

The utilisation of CGM devices in observational studies has facilitated a more nuanced comprehension of the interrelationship between dietary habits, PA, and glycemic variability in individuals at elevated risk for developing type 2 diabetes. [18] The study, conducted in 2022, sought to ascertain the impact of PA and self-reported dietary patterns on blood glucose level fluctuations in individuals at high risk for diabetes. The findings indicated a correlation between higher BMI, body fat, glucose, and insulin levels with elevated mean glucose levels. Conversely, a higher level of physical exertion and a greater PUFA were found to be associated with a reduction in glycemic variability and a longer duration of time spent in the target glucose range. Additionally, the consumption of higher levels of protein and reduced quantities of carbohydrates was associated with an increased proportion of time spent within the optimal range, highlighting the impact of diet composition and PA on glucose levels. However, the study had a small sample size of 28 participants and lasted only one week, which may explain the lack of statistical significance in many parameters. Expanding the sample size and duration could help confirm these findings.

Another study conducted in Israel utilized CGM devices, by Keshet, et al., to characterize CGM-derived measures and create a map for future research. [19] Additionally, the study aimed to investigate the relationship between CGM-derived measures and glucose effects on human health, including diabetes-related clinical parameters, such as associations of

mean blood glucose. In contrast to the PREDICT study, which sought to identify factors related to postprandial glucose, the Keshet study [19] is focused on factors associated with mean glucose and overall glucose variability. Investigators observed a strong positive association between MODD, CV and MAGE with higher percentage of carbohydrate consumption. Keshet et al. also showed that anthropometric and body composition measurements are linked to fluctuations in glycemic levels and average blood glucose concentrations. In contrast, markers of liver function and sleep characteristics appear to have a stronger association with glucose variability. [19] The study found significant associations between fractal dimensions, which describes blood vessel branching patterns in the retinal microvasculature, aiding in the detection of pathological changes, and measures of blood glucose variability, even in non-diabetic individuals. However, the study did not account for factors such as age and obesity, making it unclear how these variables may interact and contribute to higher glycemic outcomes. It is also possible that associations between variables may differ in individuals with prediabetes compared to those with normal glucose levels.

Most papers highlight the need for further studies to explore the associations between risk factors for type 2 diabetes and glucose levels, noting a lack of research on the effects of PA on glycemic variability in healthy individuals. Additionally, previous studies using CGM have not simultaneously accounted for multiple lifestyle behaviors, which is crucial for understanding their relative importance in glucose level variations. While it is known that factors such as diet, PA, and BMI are associated with CGM-measured parameters, there is a gap in the data regarding how these factors might modify each other and which

factors predominate when modelled together. Therefore, our study aims to evaluate the modification of diet, PA, and obesity with CGM-derived traits in non-diabetic individuals.

METHODS

Framingham Heart Study

In response to the notable surge in deaths attributed to coronary heart disease (CHD) in the United States during the initial decades of the 20th century, the US Public Health Service initiated a longitudinal, community-based study in Framingham in 1948.[28] The primary objective of the Framingham Heart Study (FHS) was to enhance comprehension of the natural progression of CHD and its underlying causes. The first generation of participants comprised 5,209 men and women aged 28–74 years, who underwent examinations every 2 years. The Framingham Offspring Study commenced in 1971, enrolling offspring of the original cohort and their spouses.[29] In 1995, the enrolment of a multi-ethnic cohort (Omni 1) aimed to enhance the representation of race and ethnicity in alignment with the town's demographics. In 2002, the FHS expanded its study population to include the grandchildren of the original participants, known as the GEN 3 cohort. The next year, a second Omni cohort (Omni 2) was introduced, along with the New Offspring Spouse (NOS) cohort, which included spouses of the Framingham Offspring cohort who had not been part of the study before.

Our analysis included participants from the GEN 3, Omni 2, and NOS cohorts who took part in the fourth examination of the FHS, conducted between September 2022 and August 2023. (Figure 1, n=1291). First, we excluded participants with missing CGM data and missing venous glucose or HbA1c (n=82). In addition, those who wore a CGM for less than three days (n=172), those who did not have any diet data, and those who

completed the diet record for less than two days (n=186 and n=68) were also eliminated. Exclusion criteria for diabetes mellitus were defined through self-report (current or historically), HbA1c >=6.7%, venous fasting glucose >=125 mg/dL and/or those who took glucose-lowering medications (n=82). Consequently, our sample of participants without diabetes was 701. Finally, we excluded those with missing information on important covariates; average steps (n=23) and missing CGM device location and lot number data (n=23). Our final sample size comprised 655 individuals including 377 with normoglycemia (defined as having 70-100 mg/dL fasting glucose levels and HbA1c levels below 5.7%) and 278 with pre-DM. Pre-DM was identified by fasting glucose levels of 100-126 mg/dL or HbA1c levels of 5.7-6.5%.

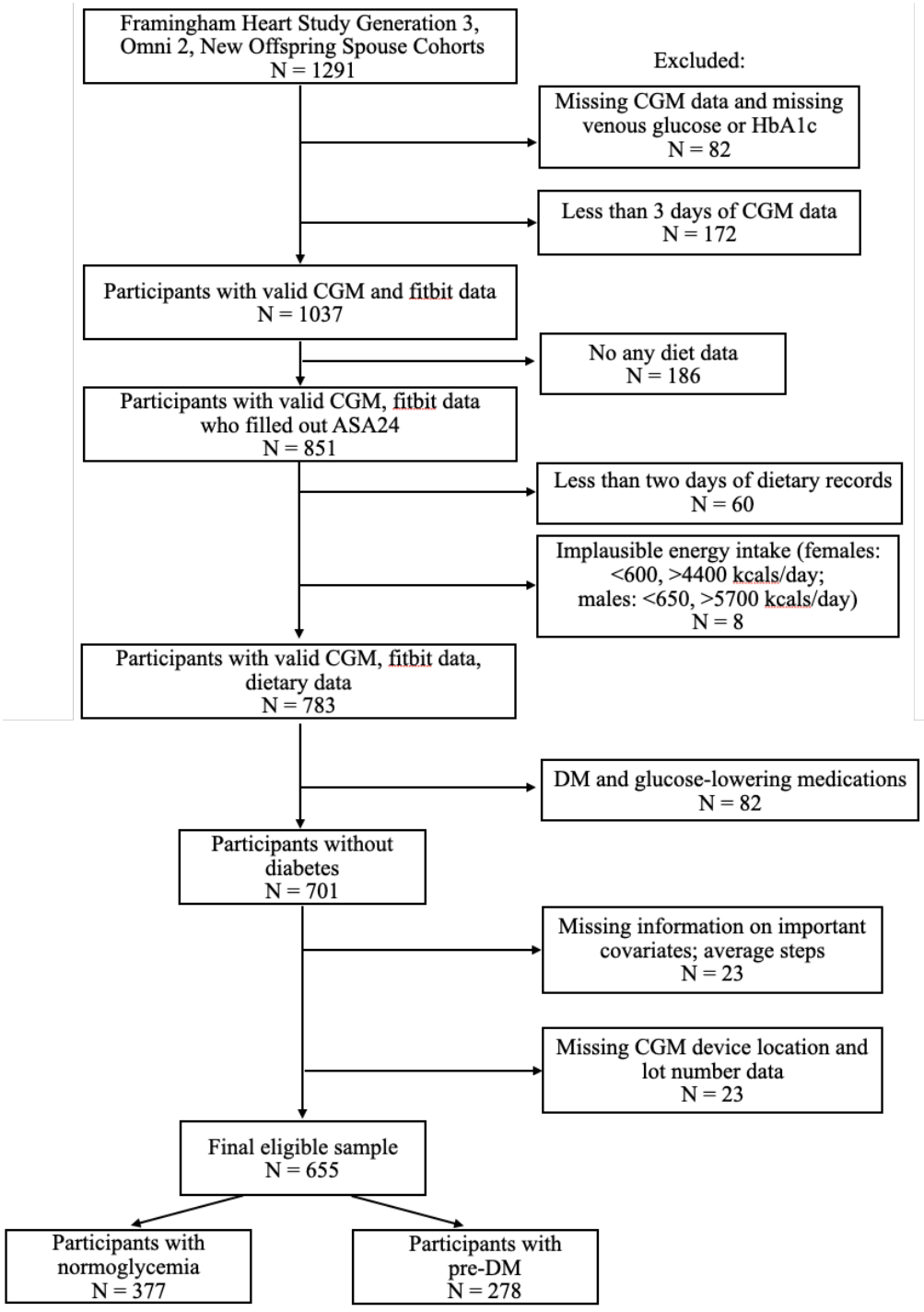

Fig.1: Figure chart for the primary analysis.

Continuous glucose monitor-derived measures

We asked participants to wear a Dexcom G6 Pro CGM for a minimum of three full days after the exam, with encouragement to extend usage up to ten days. A research assistant gave participants the choice of wearing the device on either the upper arm or abdomen. We excluded the initial and final partial days, along with days having fewer than 200 glucose values (equivalent to 70% of a potential 288 glucose values). We calculated mean glucose and time spent above 140mg/dL as measures of glycemic burden. Glucose variability measures were calculated separately by a statistical program cgm analysis through various CGM measures, including J_index, coefficient of variation (CV%), MODD, MAGE, and CONGA (as described in Table 1). [49]

Physical Activity

To monitor PA, participants were instructed to wear a Fitbit Inspire 2 heart rate device on their wrist continuously for seven days. Participants who had less than three days of wear were excluded from the study (Fig. 1). Fitbit data were downloaded using Fitabase. [50] PA was measured as average daily steps, using a proprietary algorithm. [34]

Dietary Assessment

Participants were instructed to utilize the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24) for a minimum of three days, including two weekdays and one weekend day [35]. Reports with calorie intakes of less than 600 kcal or greater than 5000 kcal were excluded from the analysis.

Table 1. CGM-derived measures.

Measure	Description	Reference
Mean glucose (mg/dL)	The mean glucose level during the entire device wear period	[4]
J_index	Represents the mean level and the variability of glycemia. Calculated using mean glucose levels and SD.	[30]
CV (%)	Coefficient of variation of all glucose values. Calculated as the ratio of SD to mean.	[31]
MODD	Mean difference between glucose values obtained at the same time of day (MODD). Parameter of between day glycemic variability. Takes into account the average of the absolute differences between glucose values measured at the same time, one day apart.	[32]
MAGE	Mean amplitude of glycemic excursions (MAGE). An index for within-day glycemic variability that takes into account significant changes in the blood glucose levels (more than one SD)	[32]
CONGA	Continuous Overall Net Glycemic Action (CONGA). Estimates within-day glycemic variability. It is calculated using standard deviation of differences in glucose measures taken 1 hour apart.	[33]
Time Above 140, %	The percentage of time when participants' blood glucose levels were above to 140 mg/dL	[38]

We calculated the Alternative Healthy Eating Index-2010 (AHEI-2010) and each of the AHEI components using a SAS program for each participant. The AHEI-2010 was originally created by the Harvard School of Public Health as measure of diet quality to identify future risk of diet-related chronic disease. [35] The AHEI-2010 is more strongly associated with coronary heart disease and diabetes and for both outcomes it is more strongly associated with the risk compared to the Healthy Eating Index - 2005. [36] The total AHEI-2010 score was obtained by summing the component scores. This score can

range from 0 (indicating non-adherence) to 110 (indicating perfect adherence) to the dietary guidelines. [37] The AHEI-2010 comprises of 11 components. Six of these are better consumed at higher intakes such as vegetables, fruits, whole grains, nuts and legumes, long-chain omega-3 fatty acids and polyunsaturated fatty acids (PUFA), one is better consumed at moderate intakes such as alcohol, and four should be limited or avoided such as sugar-sweetened beverages and fruit juices, red and processed meats, trans fats, and sodium.

Statistical Analysis

The results of the baseline characteristics table were stratified by glycemic status (normoglycemic and prediabetic) and presented as mean values and standard deviations. In order to investigate the relationship between CGM measures and PA, diet and BMI, regression models were utilised. To adjust for potential confounding, we included the following variables in our models: age, sex, CGM device lot number and device location, average alcohol intake, smoking status, average energy intake, BMI, diet (AHEI index) and PA (average steps per day). The beta-coefficients for PA were standardized to 1,000 steps. To address skewness, the variable Time Above 140 was cube root transformed. We determined that a statistical significance of $p < 0.05$ would be appropriate. To compare means of CGM-derived measures across different groups while controlling for the effects of our continuous covariates we used Analysis of Covariance.

RESULTS

Baseline Characteristics.

Table 2 represents general characteristics of 377 participants with normal glucose status (defined as having 70-100 mg/dL fasting glucose levels and HbA1c levels below 5.7%) and 278 participants with prediabetes. The mean age of the study participants ranged from 58.9 years among those with normal glucose tolerance to 61.7 years among those with prediabetes. There was a greater proportion of individuals with normoglycemia who were women compared to prediabetics, who had a higher proportion of men. BMI, energy intake, venous fasting glucose levels, and most CGM-derived parameters were higher among prediabetics. The exception was CGM-derived CV, which demonstrated no difference between the two groups (both 0.15 [0.03]). Normoglycemic participants also had a higher AHEI total score (53.6 vs. 52.1) and walked more (9761 vs. 9511 steps) compared to those who were prediabetic.

We first examined linear associations of PA, diet, and BMI with all CGM-derived measures in two cohorts of individuals with normal and elevated glucose status, adjusting for age, sex, lot number, device location, alcohol, and smoking status. (Table 3). Nearly all of the associations observed in the normoglycemic cohort were statistically significant for both diet and BMI. In contrast, the only associations that reached statistical significance in the prediabetic group were mean glucose, time above 140 and j-index. For those who walked more steps/day, time above 140 and J-index were lower for both normoglycemia and prediabetes.

Table 2. Baseline characteristics.

	Normoglycemia (N=377)	Prediabetes (N= 278)
Variable	Mean (SD)	Mean (SD)
Age, y	58.9 (8.7)	61.7 (7.8)
Sex, N (%) Male Female	 121 (32.10) 256 (67.90)	 144 (51.8) 134 (48.2)
BMI, kg/m2	26.5 (4.8)	29.2 (5.1)
CGM device lot number, N, % 5314664 5316321 5316322 5316325 5322147 5322149	 97 (25.73) 40 (10.61) 103 (27.32) 87 (23.08) 16 (4.24) 34 (9.02)	 59 (21.22) 39 (14.03) 72 (25.90) 73 (26.26) 12 (4.32) 23 (8.27)
Venous glucose, mg/dL	91.1 (5.3)	103.3 (7.4)
HbA1c, %	5.2 (0.3)	5.5 (0.3)
CGM-derived measures		
Mean Glucose, mg/dL	113.7 (11.2)	122.8 (13.7)
J_index	17.7 (3.5)	21.0 (5.0)
CV, %	0.15 (0.03)	0.15 (0.03)
MODD	16.6 (3.2)	18.9 (4.3)
MAGE	38.3 (9.5)	43.1 (11.0)
CONGA	20.5 (4.5)	22.3 (4.7)
Time Above 140, %	12 (10)	22 (18)
PA measures		
Fitbit days	7 (0.3)	7 (0.6)
Average steps	9761 (3898)	9511 (4202)
Diet measures		
Average energy intake, kcal	1863 (631)	2027 (679)
Energy from carbohydrate, %	42.2 (8.6)	41.5 (9.3)
Energy from protein, %	17.2 (4.3)	17.5 (4.5)
Energy from fat, %	37.9 (7.5)	38.5 (7.0)
Fiber	18.5 (9.4)	18.8 (9.4)

Total AHEI score	53.6 (13.0)	52.1 (13.3)
Vegetables	5.1 (2.8)	5.3 (2.8)
Fruit	2.2 (2.1)	2.2 (2.1)
Whole Grains	3.5 (3.0)	3.5 (3.1)
Nuts and Legumes	7.2 (3.8)	7.0 (3.9)
Long Chain Omega-3 fatty acids	3.7 (3.7)	3.7 (3.6)
PUFA	8.0 (2.2)	7.9 (2.1)
Alcohol	4.7 (3.5)	4.8 (3.5)
Sugar Sweetened Drinks and Fruit Juice	8.3 (3.5)	7.9 (3.4)
Red and Processed Meat	6.2 (3.5)	5.0 (3.6)
Sodium	5.0 (3.1)	5.1 (3.2)

**SD, standart deviation*

The association of PA with mean glucose was statistically significant for those with prediabetes, suggesting that each additional 2,000 steps taken per day by the prediabetic cohort was associated with a reduction in mean glucose levels of approximately 1.2 mg/dL (Parameter Est. = -0.60, p=0.004. Similarly, every additional 5.9 points higher diet quality was associated with around 1 mg/dL reduction in mean glucose (Parameter Est. = -0.17, p=0.006). With regard to BMI, every 2.7 kg/m² lower BMI was associated with the same reduction in mean glucose of approximately 1 mg/dL (Parameter Est. = 0.37, p = 0.03).

Table 3. The linear association of PA, diet and BMI with CGM-derived measures

Normoglycemic participants (N=377)						
CGM-derived measures	**PA**		**Diet**		**BMI**	
	Parameter Est.	P	Parameter Est.	P	Parameter Est.	P
Mean Glucose, mg/dL	-0.28	0.06	-0.12	0.01	0.40	0.0009
Time Above 140, %	-0.38	0.04	-0.22	0.0002	0.40	0.008
J_index	-0.10	0.03	-0.06	0.0002	0.10	0.01
CV, %	-0.0007	0.08	-0.0004	0.0009	-0.0007	0.02
MODD	-0.11	0.01	-0.06	<.0001	0.04	0.27
MAGE	-0.23	0.08	-0.15	0.0003	-0.21	0.05
CONGA_1	-0.05	0.39	-0.07	0.0007	-0.14	0.006
Prediabetic participants (N=278)						
CGM-derived measures	**PA**		**Diet**		**BMI**	
	Parameter Est.	P	Parameter Est.	P	Parameter Est.	P
Mean Glucose, mg/dL	-0.60	0.004	-0.17	0.006	0.37	0.03
Time Above 140, %	-0.66	0.006	-0.19	0.009	0.43	0.03
J_index	-0.20	0.009	-0.06	0.008	0.15	0.02
CV, %	0.0001	0.75	-0.00002	0.87	0.0002	0.55
MODD	-0.07	0.31	-0.02	0.22	0.08	0.14
MAGE	-0.18	0.27	-0.03	0.50	0.13	0.32
CONGA_1	0.02	0.81	-0.01	0.62	-0.02	0.75

**Model 1 adjusted for age, sex, lot number, device location, alcohol, smoking.*
Parameter Est. values for physical activity presented per 1000 steps taken.
Parameter Est. values for diet presented per 1 point of the AHEI.
Parameter Est. values for BMI presented per 1 point of BMI.

In individuals with normal glucose tolerance, the overall mean glucose level was lower, on average compared to prediabetics. It is therefore unsurprising that the effect size was lower for associations of PA and diet with mean glucose among those with

normoglycemia. (Parameter Est. = -0.28, P = 0.06, Parameter Est. = -0.12, P = 0.01, respectively). However, the BMI remains comparable with 0.40 parameter estimate and p = 0.0009. The J-index and time >140 exhibited a comparable trend to that of the mean glucose.

Table 4. The association of PA with CGM-derived measures in Normoglycemic participants (N=377)

CGM-derived measures	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P
Mean Glucose, mg/dL	-0.28 (0.15)	0.06	-0.18 (0.15)	0.23	-0.12 (0.16)	0.45	-0.06 (0.16)	0.71
Time Above 140, %	-0.38 (0.18)	0.04	-0.21 (0.19)	0.26	-0.23 (0.20)	0.24	-0.12 (0.20)	0.55
J_index	-0.10 (0.05)	0.03	-0.06 (0.05)	0.24	-0.06 (0.05)	0.20	-0.03 (0.05)	0.49
CV, %	-0.0007 (0.0004)	0.08	-0.0004 (0.0004)	0.30	-0.001 (0.0004)	0.005	-0.0009 (0.0004)	0.03
MODD	-0.11 (0.04)	0.01	-0.07 (0.04)	0.13	-0.11 (0.05)	0.02	-0.07 (0.05)	0.12
MAGE	-0.23 (0.13)	0.08	-0.13 (0.13)	0.34	-0.37 (0.14)	0.008	-0.28 (0.14)	0.04
CONGA_1	-0.05 (0.06)	0.39	-0.006 (0.06)	0.93	-0.13 (0.06)	0.04	-0.09 (0.06)	0.18

- *Model 1 adjusted for age, sex, lot number, device location, alcohol, smoking.*
- *Model 2: Model 1 + Diet*
- *Model 3: Model 1 + BMI*
- *Model 4: Model 1 + BMI + Diet*

Parameter Est. values presented per 1000 steps taken.

Multivariable analysis examining the role of physical activity in glucose homeostasis.

In normoglycemic participants, PA was associated with glucose variability measures such as CV, MODD, MAGE, and CONGA-1, after adjusting for BMI, but only MODD was statistically significant without BMI in the model. This adjustment reveals stronger correlations with glucose variability metrics, indicating the importance of considering BMI in the analysis. Conversely, the adjustment for BMI leads to a diminished effect for mean glucose, time above 140 variable and J_index indicating that the relationship between PA and these glucose parameters may be partially mediated by BMI in this population.

The association of PA with mean glucose and time above 140 in prediabetic participants in model 1is slightly attenuated, but remains statistically significant. (Table 5)

Multivariable analysis examining the role of diet in glucose homeostasis

As showed in Table 6, a higher diet quality is consistently associated with lower mean glucose levels and reduced glucose variability among normoglycemic individuals. Specifically, better diet quality is associated with a reduction in mean glucose levels only after adjusting for PA (Parameter Est. = -0.11, SE = 0.05, P = 0.03), but not after adjusting for BMI (Parameter Est. = -0.09, SE = 0.05, P = 0.07). The glucose variability parameters demonstrated statistical significance across all models, and the effect size remained similar when additional covariates were taken into account.

Table 5. The association of PA with CGM-derived measures in Prediabetic participants (N=278)

CGM-derived measures	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P
Mean Glucose, mg/dL	-0.60 (0.20)	0.004	-0.48 (0.21)	0.02	-0.51 (0.21)	0.02	-0.43 (0.22)	0.05
Time Above 140, %	-0.66 (0.24)	0.006	-0.53 (0.25)	0.03	-0.55 (0.25)	0.03	-0.46 (0.25)	0.07
J_index	-0.20 (0.07)	0.009	-0.15 (0.08)	0.04	-0.16 (0.08)	0.05	-0.13 (0.08)	0.10
CV, %	0.0001 (0.0004)	0.75	0.0001 (0.0004)	0.79	0.0002 (0.0004)	0.61	0.0002 (0.0005)	0.65
MODD	-0.07 (0.06)	0.31	-0.05 (0.07)	0.44	-0.04 (0.07)	0.55	-0.03 (0.07)	0.63
MAGE	-0.18 (0.16)	0.27	-0.17 (0.17)	0.33	-0.15 (0.17)	0.40	-0.14 (0.17)	0.43
CONGA_1	0.02 (0.07)	0.81	0.02 (0.07)	0.75	0.01 (0.07)	0.88	0.02 (0.07)	0.82

- *Model 1 adjusted for age, sex, lot number, device location, alcohol, smoking.*
- *Model 2: Model 1 + Diet*
- *Model 3: Model 1 + BMI*
- *Model 4: Model 1 + BMI + Diet*

Parameter Est. values presented per 1000 steps taken.

Table 6. The association of Diet with CGM-derived measures in Normoglycemic participants (N=377)

CGM-derived measures	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P
Mean Glucose, mg/dL	-0.12 (0.05)	0.01	-0.11 (0.05)	0.03	-0.09 (0.05)	0.07	-0.09 (0.05)	0.08
Time Above 140, %	-0.22 (0.06)	0.0002	-0.20 (0.06)	0.0009	-0.19 (0.06)	0.002	-0.18 (0.06)	0.003
J_index	-0.06 (0.01)	0.0002	-0.05 (0.02)	0.0008	-0.05 (0.02)	0.001	-0.05 (0.02)	0.002
CV, %	-0.0004 (0.0001)	0.0009	-0.0004 (0.0001)	0.003	-0.0005 (0.0001)	<.0001	-0.0005 (0.0001)	0.0002
MODD	-0.06 (0.01)	<.0001	-0.05 (0.01)	0.0002	-0.06 (0.01)	<.0001	-0.06 (0.01)	0.0002
MAGE	-0.15 (0.04)	0.0003	-0.14 (0.04)	0.001	-0.18 (0.04)	<.0001	-0.17 (0.04)	0.03
CONGA_1	-0.07 (0.02)	0.0007	-0.06 (0.02)	0.001	-0.09 (0.02)	<.0001	-0.08 (0.02)	<.0001

- *Model 1 adjusted for age, sex, lot number, device location, alcohol, smoking.*
- *Model 2: Model 1 + PA*
- *Model 3: Model 1 + BMI*
- *Model 4: Model 1 + PA + BMI*

Parameter Est. values presented per 1 point of the AHEI.

The findings in the prediabetic cohort (Table 7) indicate that better diet quality is associated with lower mean glucose levels, the percentage of time spent time above 140 mg/dL and J-index. The last mentioned two parameters shows a consistent, though slightly diminishing, effect with increased adjustment, losing statistical significance in the final model (p=0.07). This suggests that in prediabetic individuals, while diet quality

influences mean glucose levels and the time spent in hyperglycemic states, it does not appear to impact glucose variability measures significantly.

Table 7. The association of Diet with CGM-derived measures in Prediabetic participants (N=278)

CGM-derived measures	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P
Mean Glucose, mg/dL	-0.17 (0.06)	0.006	-0.14 (0.06)	0.03	-0.15 (0.07)	0.03	-0.13 (0.07)	0.05
Time Above 140, %	-0.19 (0.07)	0.009	-0.16 (0.08)	0.04	-0.16 (0.08)	0.04	-0.14 (0.08)	0.07
J_index	-0.06 (0.02)	0.008	-0.05 (0.02)	0.03	-0.05 (0.02)	0.04	-0.04 (0.02)	0.07
CV, %	-.00002 (0.0001)	0.87	-.00002 (0.0001)	0.87	-.000001 (0.0001)	0.99	-.000005 (0.0001)	0.97
MODD	-0.02 (0.02)	0.22	-0.02 (0.02)	0.32	-0.02 (0.02)	0.39	-0.02 (0.02)	0.45
MAGE	-0.03 (0.05)	0.50	-0.02 (0.05)	0.67	-0.02 (0.05)	0.68	-0.02 (0.05)	0.77
CONGA_1	-0.01 (0.02)	0.62	-0.01 (0.02)	0.60	-0.01 (0.02)	0.54	-0.01 (0.02)	0.54

- *Model 1 adjusted for age, sex, lot number, device location, alcohol, smoking.*
- *Model 2: Model 1 + PA*
- *Model 3: Model 1 + BMI*
- *Model 4: Model 1 + PA + BMI*

Parameter Est. values presented per 1 point of the AHEI.

Multivariable analysis examining the role of BMI in glucose homeostasis

Table 8 illustrates that higher BMI is significantly associated with higher mean glucose levels, with a consistent effect across all models. Time spent above 140 mg/dL also

shows a positive association with BMI, though the effect diminishes in later models, losing statistical significance in Model 3 and 4, after adjusting for diet. Interestingly, for measures of glucose variability, such as the CV and CONGA_1, higher BMI is associated with a reduction in variability, with highly significant results ($p < 0.0001$ in Model 4). Additionally, the MAGE index shows a significant inverse relationship with BMI, in all models. However, other measures like MODD do not show significant associations, suggesting that BMI's impact is more pronounced on mean glucose levels and certain variability measures rather than the difference in variability from day to day.

Table 8. The association of BMI with CGM-derived measures in Normoglycemic participants (N=377)

CGM-derived measures	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P
Mean Glucose, mg/dL	0.40 (0.12)	0.0009	0.36 (0.13)	0.005	0.33 (0.12)	0.007	0.32 (0.13)	0.01
Time Above 140, %	0.40 (0.15)	0.008	0.33 (0.16)	0.04	0.27 (0.15)	0.08	0.24 (0.16)	0.14
J_index	0.10 (0.04)	0.01	0.08 (0.04)	0.06	0.06 (0.04)	0.10	0.05 (0.04)	0.18
CV, %	-0.0007 (0.0003)	0.02	-0.001 (0.0003)	0.002	-0.001 (0.0003)	0.002	-0.001 (0.0003)	<.0001
MODD	0.04 (0.04)	0.27	0.008 (0.04)	0.84	0.003 (0.04)	0.94	-0.02 (0.04)	0.60
MAGE	-0.21 (0.11)	0.05	-0.32 (0.11)	0.005	-0.31 (0.11)	0.004	-0.4 (0.11)	0.0004

CONGA_1	-0.14 (0.05)	0.006	-0.18 (0.05)	0.0009	-0.19 (0.05)	0.0002	-0.22 (0.05)	<.0001

- *Model 1 adjusted for age, sex, lot number, device location, alcohol, smoking.*
- *Model 2: Model 1 + PA*
- *Model 3: Model 1 + Diet*
- *Model 4: Model 1 + PA + Diet*

Parameter Est. values presented per 1 point of BMI.

Unlike in normoglycemic participants, the associations in prediabetic individuals (Table 9) are weaker and lose statistical significance as adjustments for either diet or PA.

Table 9. The association of BMI with CGM-derived measures in Prediabetic participants (N=278)

CGM-derived measures	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P	Parameter Est. (SE)	P
Mean Glucose, mg/dL	0.37 (0.16)	0.03	0.25 (0.17)	0.15	0.26 (0.17)	0.12	0.18 (0.18)	0.31
Time Above 140, %	0.43 (0.19)	0.03	0.30 (0.20)	0.14	0.31 (0.20)	0.12	0.22 (0.21)	0.29
J_index	0.15 (0.06)	0.02	0.11 (0.06)	0.08	0.11 (0.06)	0.08	0.08 (0.06)	0.19
CV, %	0.0002 (0.0003)	0.55	0.0003 (0.0004)	0.47	0.0002 (0.0004)	0.49	0.0002 (0.0004)	0.56
MODD	0.08 (0.05)	0.14	0.07 (0.05)	0.21	0.07 (0.05)	0.21	0.05 (0.06)	0.33
MAGE	0.13 (0.13)	0.32	0.10 (0.14)	0.49	0.12 (0.14)	0.40	0.09 (0.14)	0.55
CONGA_1	-0.02 (0.06)	0.75	-0.01 (0.06)	0.80	-0.02 (0.06)	0.69	-0.03 (0.06)	0.65

- *Model 1 adjusted for age, sex, lot number, device location, alcohol, smoking.*
- *Model 2: Model 1 + PA*
- *Model 3: Model 1 + Diet*
- *Model 4: Model 1 + PA + Diet*

Parameter Est. values presented per 1 point of BMI.

Multivariable analysis examining potential effect modification

The analysis did not reveal significant interactions between PA, diet, and BMI with age or sex in either normoglycemic or prediabetic participants, as indicated by p-values greater than 0.05. Notably, the interaction between PA and diet approached significance in prediabetic group (p=0.05), suggesting a potential interaction of PA and diet on mean glucose levels that warrants further investigation.

Table 10. Testing for effect modification in the relation of PA, diet, BMI and mean glucose using interactions

	Normoglycemic (p-value) N=377	Prediabetic (p-value) N=278
PA*Age	0.7	0.2
Diet*Age	0.6	0.3
BMI*Age	0.3	0.9
PA*Sex	0.5	0.9
Diet*Sex	0.3	0.7
BMI*Sex	0.4	0.2
PA*BMI	0.3	0.9
PA*Diet	0.1	0.05
BMI*Diet	0.1	0.4

Model adjusted for age, sex, lot number, device location, alcohol, smoking.

Table 11 depicts the correlations between dietary quality, PA, and CGM-derived metrics across the entire participant cohort. Low PA was defined as an average of 7,500 or fewer steps per day, while high PA is defined as an average of 7,500 or more steps per day. A diet quality of less than 50 on the AHEI was classified as low, while a score of 50 or above was considered high.

Participants with both high PA and high diet quality had the best glycemic control. Specifically, this group had ~4 mg/dL lower mean glucose levels compared to the reference group (Low PA, Low Diet Quality, P = 0.006). Similarly, they experienced ~6% less time with glucose levels time above 140 mg/dL (Est. = -6.33, SE = 1.77, P = 0.0004), and the J_index (Est. = -1.54, SE = 0.50, P = 0.002). This group also demonstrated lower CV, MODD and MAGE.

Participants with low PA but high diet quality had slightly attenuated effect sizes in relation to mean glucose, time above 140 and j-index. Having high diet alone or high PA alone, but not both combined, was not associated with CV, MODD, MAGE, or CONGA_1.

Table 11. The association between diet quality, PA with CGM-derived measures in overall participants cohort divided into 4 groups

CGM-derived measures	Low PA, low diet quality (N=104)		High PA, low diet quality (N=169)		Low PA, high diet quality (N=104)		High PA, high diet quality (N=278)	
	Parameter Est.	P	Parameter Est.	P	Parameter Est.	P	Parameter Est.	P
Mean Glucose, mg/dL	ref.	ref.	-2.54 (1.58)	0.11	-3.44 (1.74)	0.05	-4.068 (1.46)	0.006
Time Above 140, %	ref.	ref.	-3.52 (1.92)	0.07	-5.07 (2.11)	0.02	-6.33 (1.77)	0.0004
J_index	ref.	ref.	-0.74 (0.54)	0.17	-1.32 (0.60)	0.03	-1.54 (0.50)	0.002
CV, %	ref.	ref.	-0.004 (0.004)	0.31	-0.004 (0.004)	0.26	-0.007 (0.003)	0.03
MODD	ref.	ref.	-0.66 (0.49)	0.18	-0.97 (0.53)	0.07	-1.26 (0.45)	0.005
MAGE	ref.	ref.	-1.93 (1.30)	0.14	-2.30 (1.42)	0.11	-3.18 (1.19)	0.008
CONGA_1	ref.	ref.	-0.05 (0.58)	0.94	-0.49 (0.64)	0.44	-0.57 (0.53)	0.29

Model adjusted for age, sex, lot number, device location, alcohol, smoking.

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DISCUSSION

Our findings emphasize the synergistic effect of high diet quality and high PA on glucose control. Participants who combined both high levels of PA and high diet quality exhibited more effective glucose control, suggesting that optimal glucose management benefits from an integrated approach involving both lifestyle factors. The differential impact observed between normoglycemic and prediabetic participants underscores the potential for targeted lifestyle interventions to mitigate the progression of hyperglycemia and associated complications. This analysis reveals that PA and diet were significantly associated with lower mean glucose levels and reduced time above 140 mg/dL in prediabetic individuals. These beneficial associations are robust across multiple models with varying covariate adjustments. These findings highlight the importance of PA and diet on glycemic control in prediabetic participants. In individuals with normal glucose tolerance, there was a significant negative correlation between PA, diet and BMI with measures of glycemic variability, including MODD and MAGE. It can be reasonably assumed that the control of PA, diet and BMI among individuals with normal glucose levels has a greater impact on glucose levels over the course of a day and on a day-to-day basis. In contrast, among individuals with prediabetes, these factors exert an influence on overall glucose parameters.

Moreover, the differential impact of these lifestyle factors between normoglycemic and prediabetic participants underscores the necessity for targeted interventions tailored to specific metabolic states. In prediabetic individuals, the data show a significant association between PA and diet with lower mean glucose levels, alongside a reduction in

the time spent above 140 mg/dL. This association remains robust across various statistical models with different covariate adjustments, suggesting that PA and diet play a pivotal role in the selective regulation of glycemic control in prediabetes. These findings are particularly relevant given the rising prevalence of prediabetes and the associated risk of progression to T2DM [54], which necessitates the development of effective preventive strategies. It is crucial to highlight that the lack of statistical significance in the associations between lifestyle factors and glycemic variability parameters in the prediabetic cohort may be attributed to the fact that individuals with elevated baseline glucose levels exhibit a narrower range of fluctuation.

We elected to concentrate our discussion on a single measure of glycemic burden and a single measure of glycemic excursions. In selecting a glycemic burden measure, we opted for mean glucose, as it is one of the most straightforward parameters to quantify and is widely used in this context. As for glucose variability, there are two important metrics - MAGE and MODD, both aim to capture fluctuations in blood glucose levels but focusing on different aspects of variability. [51] MAGE measures the average magnitude of significant glycemic fluctuations within a single day whereas MODD assesses day-to-day stability in glucose patterns by measuring the consistency of glucose values at the same time on consecutive days, reflecting the predictability of blood glucose levels over a longer period. [53] As our study lacks a long-term follow up, we decided to focus on MAGE, because it is commonly used to assess short-term glycemic variability and sensitive to short-term spikes. [52]

Physical Activity and Continuous Glucose Monitoring

In comparison to other works in the field, our results demonstrated notable similarities and some differences. Park and colleagues also analysed the association of PA with CGM-derived measures. [18]. Park demonstrated that there was no correlation between moderate-to-vigorous intensity PA and mean glucose levels in models that were adjusted for BMI and PA. Conversely, there was a statistically significant positive correlation with time-in-range%. PA was defined as hours per day using accelerometer in Park, et al. and as the number of steps per day in our study. A reduction in MODD and MAGE was observed in normoglycemic participants with higher levels of PA. A negative correlation between PA and mean glucose and % time above 140 mg/dL was observed in the prediabetic cohort. It is possible that differences between our works may have arisen due to the varying number of participants (28), the specific CGM device model employed, and the inclusion criteria utilized, such as HbA1c in range of 6.0–6.4%, a history of diabetes in first-degree family members, or a BMI of 25 to 30 kg/m^2 in the Park study. Additionally, other factors that may contribute to the observed discrepancies include ethnicity (the study population was predominantly Chinese, Indian, and Malay in Park's paper), age (the mean age was 46.0), and the use of different measures of PA (they reported hours per day).

In this study, we focused on assessing total PA through the average number of daily steps, without measuring the intensity of the exercise performed. While the total volume of PA provides valuable insights into general activity levels, incorporating both light and moderate-to-vigorous PA [42], it is important to acknowledge that exercise intensity may

offer additional, and potentially more informative data, regarding its impact on glycemic control and overall metabolic health. The American Heart Association recommendations focus on minutes of activity, rather than steps. [43] While step counts offer a straightforward and accessible measure of overall PA, they do not differentiate between light, moderate, or vigorous intensities, which may have distinct effects on metabolic health. Intensity, particularly in the form of moderate to vigorous PA, has been shown in previous research [18] to have a profound effect on glucose metabolism and insulin sensitivity. By not differentiating between light and more intense forms of activity, our analysis may have missed capturing the full extent of the benefits that could be achieved through higher-intensity exercise. This suggests that while total PA is valuable, integrating intensity measures may enhance the assessment of PA's effects on glycemic outcomes in populations at risk for metabolic disorders.

Diet and Continuous Glucose Monitoring

In regard to dietary composition, our findings revealed a robust negative correlation between diet quality and all CGM measures in participants with normal glucose levels. This was observed across all four models, including MODD and MAGE. However, when BMI adjustments were made, the strength of the association with mean glucose levels was reduced. In individuals with prediabetes, diet quality was found to have a strong negative correlation with only mean glucose, time above 140, and J-index. However, after adjusting for both PA and BMI, a strong correlation with mean glucose remained.

The research conducted by Keshet et al showed similar results: a statistically significant positive correlation was observed between median daily caloric intake and median daily carbohydrate caloric intake with MAGE and MODD. [19] Although no statistical significance was demonstrated between eA1C and median daily caloric intake, but a correlation was observed between median daily carbohydrate caloric intake and eA1C. The models used in the Keshet study were adjusted only for age and sex while our models included the following variables: age, sex, CGM device number and location, smoking status, alcohol consumption, PA, diet, BMI, and combinations of these factors.

In a further important study by Berry and colleagues, glucose 0h – 2h incremental area under the curve, a parameter similar to MAGE, was unsurprisingly associated with the composition of a specific meal, but not with diet quality. [17] They also showed that an increase in the consumption of fat, fiber, and protein resulted in a notable reduction in glucose levels, after adjusting for carbohydrate intake. In contrast to the aforementioned study, our research was not focused on the composition of a meal, but rather on the overall quality of the diet, measured by the AHEI.

We also highlight the possibility of a combined effect of PA and dietary habits on mean glucose levels in individuals with prediabetes. While Berry et al. monitored their participants' PA levels, they did not present any findings in this paper. [17] It is also important to note that Berry's research was more centred on intra-individual responses and variability, whereas our study focused on collecting general data from the population. The cohort under consideration in the before mentioned study comprised solely of

healthy individuals, with no adjustment made for glucose tolerance. It is important to note that the CGM employed by Berry and Keshet differs from that used in our own research. [17, 19]

Body Composition and Continuous Glucose Monitoring

A comparison of our work with other studies reveals that our results are in agreement with those of Park, et al., [18] and Noordam et al., [44] which indicate that higher BMI is associated with elevated mean glucose levels. Furthermore, a higher BMI was associated with less variation in glucose levels as measured by the CV% and more time-in-range% (Park, et al.). Noordam demonstrated that higher BMI was correlated with higher levels of the MODD, although no statistical significance was observed with regard to MAGE. [44] In contrast, we observed statistically significant reduction in MAGE, but not the MODD in normoglycemic cohort. Keshet et al. observed statistically significant correlation between BMI and lower CV and MAGE but higher MODD, j-index and eA1C (measure of mean glucose). [19] While our results showed significance among all the variables excluding MODD in normoglycemic individuals and only mean glucose, time above 140 and j-index were associated with BMI in prediabetic cohort. Additionally, a study conducted by Berry et al. demonstrated an association between BMI and elevated postprandial glycemic excursions. [17] In general, it can be stated that BMI is associated with higher glycemic burden, but lower glycemic variability. Due to explanation of why glucose variability in prediabetic cohort was not statistically significant, we can assume that if a person has higher glucose level (baseline), he has a smaller range to go up.

The discrepancies between the results may be attributed to the fact that Noordam's, Keshet's and Park's studies used different CGM device model. [44, 19, 18] Additionally, it is notable that the Noordam study cohort was comparable in size, yet the study design was an intervention study with strict exclusion criteria for individuals with an active lifestyle. The Keshet study included a larger number of individuals, had a lower mean BMI, and had a slightly younger demographic. It is also noteworthy that none of the investigators subdivided their participants by glucose status into normoglycemic and prediabetic groups.

Explaining potential mechanisms

It is widely proposed that diet and PA improve glucose parameters primarily through enhanced insulin sensitivity in both muscle and liver tissues. [45] PA activates AMP-activated protein kinase (AMPK) in skeletal muscle, which increases glucose uptake by promoting the translocation of GLUT-4 to the cell membrane, facilitating glucose entry into muscle cells. Over time, this increases mitochondrial efficiency and glycogen storage, leading to sustained improvements in insulin sensitivity. In the liver, the increase in glucose production resulting from exercise serves to compensate for the decrease in blood glucose levels associated with muscle exertion over the course of a short period. But it is important to note that the beneficial metabolic outcomes associated with exercise can be challenging to differentiate from the weight loss that occurs as a result of the PA itself. [46]

An additional factor that affects glucose metabolism is BMI. An increase in adipose tissue, particularly when its function is impaired, may lead to a decline in tissue sensitivity to insulin. [56] Individuals with overweight or obesity tend to have higher fasting glucose levels and elevated postprandial glycaemia compared to those with normal BMIs. Insulin-resistant adipose tissue displays impaired suppression of lipolysis, resulting in an excessive release of free fatty acids into the bloodstream. [56, 57] It has been demonstrated that elevated fatty acids promote insulin resistance in muscle and liver tissues by increasing diacylglycerol and triacylglycerol synthesis, and facilitating ectopic fat deposition in non-adipose organs. Furthermore, the enlargement of adipose tissue that occurs as a consequence of obesity leads to the recruitment of pro-inflammatory macrophages, which in turn drives chronic low-grade inflammation. This, in turn, impairs insulin signalling through the release of inflammatory cytokines and the accumulation of immune cells. [58] Dysfunctional adipocytes in obesity exhibit altered adipokine production, increased oxidative stress, and endoplasmic reticulum stress, all of which contribute to local and systemic insulin resistance. Furthermore, the disruption of pivotal insulin signalling pathways, including those involving the insulin receptor substrate proteins and PI3K/Akt signalling, serves to exacerbate insulin resistance. [60] The phenomenon of lipotoxicity, which is caused by the accumulation of excess free fatty acids in non-adipose tissues, and the dysregulation of adipokine secretion, which is marked by a reduction in the levels of insulin-sensitising adipokines, serve to amplify the extent of systemic insulin resistance. This sequence of events contributes to the development of metabolic disorders such as T2DM.

High quality diet, particularly one rich in polyunsaturated fats and fiber, enhances insulin sensitivity by reducing systemic inflammation and improving lipid profiles, likely via anti-inflammatory pathways. [47] Nutrients like omega-3 fatty acids help lower insulin resistance by affecting inflammatory mediators and improving metabolic function. [48] These mechanisms together—muscle and liver sensitization to insulin, reduced hepatic glucose output, and systemic anti-inflammatory effects offer a potential explanation for our findings on how lifestyle interventions improve glycemic control.

The Role of Continuous Glucose Monitoring in Enhancing Glucose Control

In recent years, CGM has emerged as a valuable tool for improving glucose management, offering a real-time, dynamic view of glucose levels. The potential of CGM to enhance glucose regulation extends beyond individuals with diabetes, as demonstrated by Zahedani et al [40]. Their study, involving 448 non-diabetic individuals and 192 individuals with diabetes, revealed a remarkable 51.4% improvement in time-in-range 70-180 mg/dL (TIR) over a ten-day period of CGM use. Notably, the average TIR improvement was 6.4% ($p < 0.001$), indicating a substantial reduction in hyperglycemia. Among non-diabetic participants who had poor TIR at baseline, 91.7% experienced significant improvements, with an average increase of 23.2% in TIR. These results underscore the efficacy of CGM in reducing hyperglycemia, even among non-insulin-dependent individuals and those in the early stages of glucose dysregulation.

The impact of CGM is further amplified by its ability to provide users with a visual representation of their glucose levels in response to various foods and activities. This

real-time feedback mechanism fosters more conscious decision-making regarding dietary and lifestyle choices, encouraging behaviors that support better glucose control. The influence of CGM on behavioral modification has broader implications, extending to weight management, BMI, and cholesterol levels. For instance, a study conducted by Chekima et al. [41] involving 40 overweight, non-diabetic young adults, demonstrated that the use of CGM, in conjunction with a low glycemic index and load diet, significantly improved dietary intake characterised by a reduction in total energy intake and carbohydrate intake, body composition, and metabolic parameters. These findings reveal the advantages of CGM technology as a comprehensive management tool, for overweight and obese individuals and as a potential primary prevention strategy for T2DM. However, there have been no longer-term studies showing that CGM can be a supportive technology used in interventions to prevent T2DM yet, though studies are ongoing. By providing real-time, personalized insights into physiological changes, CGM may empower individuals to make informed decisions that positively impact their long-term metabolic health.

Implications for Public Health and Future Research

The growing body of evidence supporting the potential effectiveness of lifestyle interventions and CGM in glucose regulation has significant public health implications. As the prevalence of metabolic disorders continues to rise globally, there is an urgent need to promote lifestyle modifications that encompass both PA and diet quality as central components of preventive healthcare strategies. Public health campaigns should emphasize the importance of maintaining a high level of PA and a nutritious diet to

achieve and sustain optimal glucose control. Furthermore, the integration of CGM into routine care for at-risk populations could serve as a catalyst for broader adoption of this technology, given its potential benefits in improving glucose parameters.

Future research should focus on exploring the long-term effects of combining high PA, diet quality, and CGM use on glucose regulation across diverse populations. Additionally, investigating the specific mechanisms through which these factors interact to influence glycemic control will be crucial in refining intervention strategies. Understanding the role of genetic and environmental factors in modulating these effects could also lead to more personalized approaches to managing glucose levels. Moreover, as CGM technology continues to evolve, studies should assess its cost-effectiveness and feasibility in various healthcare settings, particularly in low-resource environments where the burden of metabolic disorders is disproportionately high.

Our research offers a valuable foundation for exploring new interventions that incorporate CGM as an adjuvant therapy to enhance the effectiveness of diet and PA interventions. By leveraging CGM technology, healthcare providers and researchers can gain real-time insights into how individual dietary choices and exercise regimens directly influence glucose levels. This personalized feedback enables patients to make immediate adjustments, optimizing their lifestyle choices to maintain stable glucose levels and prevent long-term health complications.

One potential area for development is the creation of a tailored diet and exercise program, where CGM data is used to provide instant feedback on the body's response to different

types of foods and levels of PA. For example, patients can see how certain meals or exercises impact their glucose levels in real time, allowing for more informed decisions about portion sizes, meal timing, and the intensity of PA. This could lead to more sustainable behavior changes, as individuals would be empowered by the immediate data reflecting their body's metabolic responses.

Furthermore, integrating CGM with mobile health platforms or apps could allow patients and healthcare professionals to track glucose trends over time, enabling them to assess the long-term effectiveness of dietary and PA interventions. By analyzing patterns and outcomes, this approach could help in identifying which combinations of diet and PA yield the most positive results for maintaining optimal glucose levels. Ultimately, using CGM as an adjunct to lifestyle interventions not only enhances patient engagement but also provides a robust mechanism for tracking outcomes and fine-tuning personalized treatment strategies.

Additionally, different CGM-derived measures can be emphasized for each group to achieve better outcomes. In our research, not every measure showed a significant association in both normoglycemic and pre-diabetic cohorts. By focusing on the specific measures that correlate with outcomes in each group, we can refine our recommendations, ensuring that interventions are more effective and tailored to each patient's unique metabolic profile. By categorizing patients based on their glucose regulation status and focusing on the most relevant CGM-derived metrics for each group, we can develop more specific, data-driven recommendations. Through these targeted

interventions, we can offer precise, patient-centered care that aligns with their metabolic needs.

Strength and limitations of our study

Our study presents a number of strengths that contribute to the robustness and relevance of its findings. First, the use of variety of CGM-derived measures, such as mean glucose, time-in-range above 140 mg/dL, j-index and parameters of glucose variability. These diverse metrics offer a comprehensive view of glucose control, allowing us to capture nuanced patterns of glycemic fluctuations rather than relying on a single metric. In addition, our study accounts for confounding factors by adjusting for variables such as age, sex, CGM device lot number and location, alcohol, smoking status, BMI, diet and PA levels, which enhances the accuracy of our findings. By comparing different statistical models, we further strengthen the reliability of our conclusions, ensuring that our results are not overly dependent on a specific methodological approach. Another key strength is the division of participants into normoglycemic and pre-diabetic groups, which enables us to tailor our analysis to the specific needs and characteristics of each cohort. Our focus on both PA and a high-quality diet is also a major advantage, as it considers the combined effect of these factors rather than isolating them. This holistic approach acknowledges the importance of lifestyle synergy in achieving optimal glycemic outcomes.

However, our study is not without limitations. While the sample size is sufficient to yield meaningful insights, it is not large enough to generalize findings to the broader

population with absolute confidence. A larger cohort could enhance the statistical power and allow for more detailed subgroup analyses. Additionally, as with most nutrition studies, there is the issue of measurement error due to the reliance on self-reported dietary intake. Participants may misremember or underreport their food consumption, introducing potential biases that could affect the accuracy of our dietary data. Another limitation is the limited generalizability. Due to the cultural, genetic, and environmental diversity among populations, our findings, which are derived from a specific, homogenous cohort of individuals from mostly European ancestry, may not be applicable to all groups. Different populations may respond differently to the same interventions, so care must be taken in applying these recommendations more broadly. Lastly, while we have adjusted for many confounding factors, there remains the possibility of residual confounding—the influence of unmeasured or inadequately controlled factors that could still impact glycemic outcomes. This is an inherent challenge in observational research, where it is difficult to account for every variable that may influence the relationship between diet, PA, and glycemic control.

Conclusion and future directions

In conclusion, this analysis provides compelling evidence that an integrated approach to a healthy lifestyle—encompassing high PA, optimal diet quality, and appropriate BMI management—was associated with better glucose regulation.

By advancing our understanding of the multifaceted relationships between lifestyle factors and glucose regulation, we can develop more effective, personalized interventions

that address the root causes of hyperglycemia and its associated complications. Long-term studies are required to investigate whether CGM technology can be used as an adjuvant to improve the efficacy of lifestyle interventions. As we move forward, it is imperative that research, clinical practice, and public health policies converge to promote holistic, evidence-based strategies that empower individuals to take control of their metabolic health.

APPENDIX

We examined the association of PA, measured as average daily steps, with CGM-derived measures, stratified by their AHEI scores. (Table 12, Table 13) Participants were categorized into two groups: those with an AHEI score below 50 and those with an AHEI score of 50 or higher. Results showed no statistically significant associations with any of the CGM-derived measures in normoglycemic participants. (Table 12) These results suggest that PA does not significantly impact glucose metrics in normoglycemic individuals, regardless of their dietary quality.

Table 12. The association of PA with CGM-derived measures in Normoglycemic participants divided by two groups with low and high AHEI

CGM-derived measures	AHEI < 50 (N=223)		AHEI >= 50 (N=154)	
	Parameter Est. Average Steps (SE)	P	Parameter Est. Average steps (SE)	P
Mean Glucose, mg/dL	-0.23 (0.15)	0.14	-0.28 (0.34)	0.42
Time Above 140, %	-0.30 (0.21)	0.15	-0.29 (0.39)	0.45
J_index	-0.07 (0.05)	0.15	-0.11 (0.11)	0.31
CV, %	-0.0003 (0.0004)	0.53	-0.0013 (0.0008)	0.12
MODD	-0.06 (0.05)	0.17	-0.18 (0.10)	0.07
MAGE	-0.07 (0.15)	0.63	-0.54 (0.28)	0.06
CONGA_1	-0.002 (0.070)	0.98	-0.12 (0.13)	0.38

Model adjusted for age, sex, lot number, device location, alcohol, smoking.

Table 13 shows the same association in prediabetic cohort. In participants with an AHEI score of 50 or higher, the association between average daily steps and mean glucose

approached significance (Parameter Est. = -0.54, SE = 0.28, P = 0.05). However, other CGM-derived measures did not show significant associations.

Table 13. The association of PA with CGM-derived measures in Prediabetic participants divided by two groups with low and high AHEI

CGM-derived measures	AHEI < 50 (N=119)		AHEI >= 50 (N=159)	
	Parameter Est. Average Steps (SE)	P	Parameter Est. Average steps (SE)	P
Mean Glucose, mg/dL	-0.17 (0.35)	0.63	-0.54 (0.28)	0.05
Time Above 140, %	-0.30 (0.42)	0.47	-0.48 (0.32)	0.14
J_index	-0.08 (0.13)	0.53	-0.16 (0.10)	0.11
CV, %	-0.0005 (0.0009)	0.59	0.0005 (0.0005)	0.35
MODD	-0.14 (0.12)	0.24	0.04 (0.08)	0.66
MAGE	-0.25 (0.32)	0.44	-0.09 (0.20)	0.65
CONGA_1	0.05 (0.13)	0.70	0.02 (0.09)	0.80

Model adjusted for age, sex, lot number, device location, alcohol, smoking.

These findings imply that the beneficial effects of PA on glucose metabolism may be more pronounced in individuals adhering to healthier dietary patterns, as reflected by a higher AHEI score.

The relationships between dietary patterns and various CGM-derived glucose measures, differentiated by levels of PA are presented in Table 14 and Table 15. Participants were divided into two groups based on their daily PA levels. The first group included individuals with a daily step count of fewer than 7,500, comprising 117 individuals in the normoglycemic group and 91 in the prediabetic group. The second group consisted of

individuals with a daily step count of 7,500 or more, comprising 260 individuals in the normoglycemic group and 187 in the prediabetic group.

Table 14. The association of Diet with CGM-derived measures in Normoglycemic participants divided by two groups with low and high Average Steps

CGM-derived measures	PA < 7 500 (N=117)		PA >= 7500 (N=260)	
	Parameter Est.	P	Parameter Est.	P
Mean Glucose, mg/dL	-0.27 (0.08)	0.0008	-0.06 (0.06)	0.29
Time Above 140, %	-0.35 (0.10)	0.0007	-0.13 (0.07)	0.06
J_index	-0.10 (0.03)	0.0004	-0.04 (0.02)	0.04
CV, %	-0.0003 (0.0002)	0.18	-0.0003 (0.0001)	0.02
MODD	-0.07 (0.03)	0.01	-0.05 (0.02)	0.003
MAGE	-0.18 (0.08)	0.03	-0.10 (0.05)	0.03
CONGA_1	-0.06 (0.04)	0.10	-0.05 (0.02)	0.02

Model adjusted for age, sex, lot number, device location, alcohol, smoking.

Key observations from the table 14 highlight that in participants with lower PA levels (fewer than 7,500 steps per day), diet quality has a stronger and more consistent association with better glucose control across metrics, such as mean glucose levels and time spent above 140 mg/dL (Est. = -0.27, SE = 0.08, P = 0.0008 ,Est. = -0.35, SE = 0.10, P = 0.0007, respectively). The association between diet quality with MAGE and MODD are significant in both groups.

These results suggest that diet quality plays a particularly crucial role in glucose regulation among less physically active individuals, emphasizing the importance of dietary interventions in this population.

As for prediabetic participants, (Table 15) results showed that in more physically active group, diet quality has a significant and favorable impact on glucose control, as reflected in lower mean glucose levels, reduced time spent above 140 mg/dL, and improved J-index. In contrast, the less active group shows no significant associations between diet quality and glucose metrics.

Table 15. The association of Diet with CGM-derived measures in Prediabetic participants divided by two groups with low and high Average Steps

CGM-derived measures	PA < 7 500 (N=91)		PA >= 7500 (N=187)	
	Parameter Est.	P	Parameter Est.	P
Mean Glucose, mg/dL	-0.0001 (0.10)	0.9991	-0.23 (0.08)	0.004
Time Above 140, %	-0.04 (0.12)	0.75	-0.23 (0.09)	0.01
J_index	0.007 (0.03)	0.84	-0.077 (0.03)	0.008
CV, %	0.00003 (0.0002)	0.91	0.0001 (0.0002)	0.51
MODD	0.03 (0.03)	0.36	-0.03 (0.02)	0.30
MAGE	0.09 (0.08)	0.26	-0.03 (0.06)	0.60
CONGA_1	0.05 (0.04)	0.14	-0.01 (0.03)	0.59

Model adjusted for age, sex, lot number, device location, alcohol, smoking.

These results results suggest that the benefits of diet quality on glucose regulation are more pronounced in prediabetic individuals who maintain higher levels of PA, highlighting the importance of combining diet and exercise for optimal glucose management in this population.

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