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Diet quality and continuous glucose monitor-derived glycemic traits in non-diabetics

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Thesis

DIET QUALITY AND CONTINUOUS GLUCOSE MONITOR-DERIVED GLYCEMIC TRAITS IN NON-DIABETICS

by

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ABSTRACT

Background

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, which is often preceded by poor diet quality, physical inactivity, and weight gain. Evidence shows that lifestyle changes, including increasing diet quality and physical activity can prevent development and improve management of T2DM. It is unknown how diet quality affects specific glycemic traits.

Objective

The overall goal of the current study was to evaluate the association between diet quality and continuous glucose monitor (CGM)-derived glycemic traits in non-diabetic individuals.

Methods

Using data from the Framingham Heart Study, we included participants in the Generation (Gen) 3, New Offspring Spouse, and Omni 2 cohorts without diabetes, who attended the fourth examination and who wore a continuous glucose monitor for ≥3 days from September 2022 to April 2023 (n=569). We further excluded data from 122 participants who did not complete ≥2-day diet records or wear a fit bit physical activity monitor for ≥3 days. We used linear

regression models to assess the association of diet quality (macronutrient composition, the Healthy Eating Index [HEI], and HEI components) with CGM-derived mean glucose and glycemic variability, measured using the CGM coefficient of variation (CV) and continuous overall net glycemic action (CONGA1), adjusting for age, sex, CGM device lot number, body mass index (BMI), and physical activity (average Fit bit steps/day).

Results

Of our sample of 447 non-diabetics, we observed 194 (43.4%) with prediabetes, defined as venous fasting glucose ≥126mg/dL, hemoglobin A1c ≥6.5%, or taking glucose lowering medication. We reported that participants with prediabetes had a higher BMI (29 vs. 26 kg/m^2), higher mean CGM glucose (123 vs. 113 mg/dL) higher CONGA1 (22.23 vs. 16.5%), similar CV (both 0.2%), and ~3 point lower HEI total score compared to participants with normoglycemia. Among both normoglycemic and prediabetics we observed associations with lower percent energy intake (EI) from total fat and saturated fat, higher percent EI from carbohydrate, and higher refined grains with higher glycemic variability, measured using CONGA1. Many other dietary factors (including total energy, sodium, dairy products, vegetables, fiber, and protein intake) were associated with one of the CGM measures (CONGA1, CV, or mean glucose), but only in normoglycemic or pre-DM participants.   No other CGM results consistent among participants from both glycemic status groups.

Conclusion

Overall, the daily consumption of more refined grains and total carbohydrates and less fat and protein-containing foods was associated with higher glycemic variability in our non-DM participants. We also observed associations with individual dietary components with some, but not all, glucose metrics, warranting further investigation in larger cohorts.

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LIST OF ABBREVIATIONS

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

BU .... Boston University

BMI .... Body Mass Index

CVD .... Cardiovascular Disease

CGM .... Continuous Glucose Monitor

DASH .... Dietary Approaches to Stop Hypertension

DPP .... Diabetes Prevention Program

DM .... Diabetes Mellitus

DGA .... Dietary Guidelines for Americans

FFQ .... Food Frequency Questionnaires

FHS .... Framingham Health Study

GDM .... Gestational Diabetes Mellitus

GV .... Glycemic Variability

HBA1C .... Hemoglobin A1c

HEI .... Healthy Eating Index

IR .... Insulin Resistance

MNT .... Medical Nutrition Therapy

OGTT .... Oral Glucose Tolerance Test

PREDM .... Pre-Diabetes

RD .... Registered Dietitian

SE..Standard Error

T2DM..Type 2 Diabetes Mellitus

INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease that affects 37.3 million people in America and is the eighth leading cause of mortality.[1] The majority of people with DM have type 2 (T2) DM, which begins with insulin resistance, but can also result in reduced insulin secretion. Complications from T2DM can lead to heart disease, vision loss, nerve damage, kidney disease, and even death if T2DM is not properly managed.[2] DM risk can be modified by lifestyle choices, but, there are other contributing non-modifiable factors, such as older age and genetical predisposition, as well as environmental risk, .[3] It is clear that heredity also plays an important role in the development of DM.[4] A study of the occurrence of DM across generations was observed in the Framingham Offspring study, whereby the offspring who had a single parent with DM had 2-3 times the risk of developing DM, however, when both parents had DM, offspring had 6 times the risk of DM.[4]

Individuals from certain race and ethnic backgrounds also have a higher risk for DM. However, the role of race and ethnicity is likely much more complex than genetics, and instead may include differences in environmental, socioeconomic, lifestyle, and socio-cultural factors. Hispanic, Asian-American and African American individuals, have a higher incidence of developing DM.[3] A meta-analysis that included 495 different studies on Hispanic and non-Hispanics found that hemoglobin (Hb)A1c was 0.5% higher in patients with Hispanic background compared to non-Hispanics.[5] There are many potential factors contributing to these differences, but it is apparent that there is a lack of DM awareness combined with a gap in medical care in some Hispanic communities that may further complicate our understanding of the different rates of DM development among different communities.[5]

Nutrition and Diabetes

DM is an alarming disease that can be managed with a combination of therapies. DM treatment is focused on therapies that promote a healthy diet, exercise, prescribed drugs, glucose monitoring devices, surgical procedures etc.[6] Medical Nutrition Therapy (MNT) is a key factor for improving glycemic targets, achieving weight management and improving cardiovascular risk factors. MNT is a personalized diet plan provided to people living with diabetes by a registered dietitian.[3] This nutrition therapy has been associated with lowering HbA1c levels by 1.0-1.9% in T1DM and 0.3-2% in those with T2DM.[7] In MNT, there is not a recommended macronutrient composition for DM patients, instead, diets such as the Mediterranean Diet, vegetarian diets and Dietary Approaches to Stop Hypertension (DASH) are recommended because they have shown positive results in the management of DM.[3]

The American Diabetes Association has strongly reinforced the need for healthy eating patterns that include a variety of nutrient-dense foods. These will help improve overall health through the improvement of glycemic control, weight management, and dyslipidemia, which are all risk factors for cardiovascular disease (CVD) risks in DM patients.[8]

Following a healthy diet and being physically active not only improves DM management but is also the most effective tool in preventing the development of DM, as demonstrated by the very successful Diabetes Prevention Program (DPP).[9] DPP is a randomized controlled trial conducted in high-risk individuals with elevated fasting plasma glucose and impaired glucose tolerance. DPP tested strategies to prevent or delay T2DM with a pharmaceutical intervention (metformin), placebo, or an intensive lifestyle intervention, for which the major goals were to reduce weight to at least 7% of initial body weight and be physically active for at least 150/week. Individuals at high risk that changed their lifestyle behaviors with a focus on diet and exercise, reduced the incidence of T2DM by 58% compared to the metformin group.[10]

There is extended evidence that lifestyle changes, such as diet, play a key role in T2DM prevention. In the Nurses' Health study, researchers examined the relationship between whole grain consumption and risk of developing T2D in healthy women who were free of DM, cancer, and CVD. Findings from this study found that an increase in consumption of whole grains by two-servings-per-day was associated with a 21% decrease in risk of developing T2DM[11] Foods are defined as whole grains only if all the components of the kernel, i.e., the bran, the germ and the starchy endosperm are present in the same proportions as their natural composition. Whole grains offer health benefits in glucose metabolism by slowing and lowering postprandial blood sugar and insulin. In the refining process, the germ and bran are removed, and the observed health benefits are lost [11] due to the lower fiber and loss of nutrients.

Sugary drinks have a high glycemic load. Glycemic load refers to how fast quick a specific carbohydrate elevates blood sugar levels. [11] Excess energy intake from sugar-sweetened beverages (SSB) contribute to weight gain and increase the risk of T2DM due to the large amounts of added sugars. HFCS is composed of 55% glucose and 45% fructose.[48] This causes rapid spikes in blood sugar, which contributes to insulin resistance. A prospective cohort study among women in the Nurses' Health Study (NHS) II indicated that higher consumption of SSBs was associated with weight gain and increased risk of T2DM.[12]

The quality of the dietary fat consumed may also play a role in the development of T2D. Fatty acids are known to influence glucose metabolism and insulin signaling.[13] Substituting energy intake from saturated fats and trans fatty acids with unsaturated (polyunsaturated and/or monounsaturated fats) has been associated with reducing the risk of T2DM and insulin sensitivity.[13]

A meta-analysis of data from 440,000 individuals provided evidence that eating red and processed meat led to an increased the risk of DM [14]. They found that eating 3-ounce servings of red meat daily was linked to a20% higher risk of developing DM compared to those who rarely ate meat.[14].

Diabetes technology for diabetes prevention

One measure that can be used to assess a DM patient's long-term glucose management is HbA1c. HbA1c gives an estimate of an individual's glycemic control over the past three months and is a good predictor of DM-related complications.[15] However, there are some limitations because HbA1c is not a direct measure of glycemia, and it does not measure short term swings in blood glucose levels.[15]

Oral glucose tolerance tests (OGTT) are another way to measure glycemic control. For this test a measure of blood sugar is collected at baseline, after which the study participant drinks a concentrated sugar mixture composed of 75g of glucose diluted with 250 to 300 ml of water, followed by another blood draw to measure glucose levels.[16]

Although OGTT is a reliable and low-costly glucose measure, it doesn't provide any information on changes in your blood sugar values throughout the day.[16]

Continuous glucose monitoring (CGM) is a new measure that became accessible in the year 2000, but with substantial measurement inaccuracy.[17] Today, CGM inaccuracy has been reduced to within 10% of capillary (finger stick) glucose.[18] Over the past years, CGM has been a very helpful tool that enabled clinicians and people with DM to get rapid glucose results and overcome the limitations of HbA1c.[19] Glucose patterns observed via CGM data can aid patients in understanding whether specific interventions are working for them, to better glycemic control or prevention hypoglycemia at specific times of the day.[20] Relevant studies have shown the advantages of using CGM. For example, a randomized clinical trial (RCT) in adults with T1DM showed that there was a more substantial decrease in HBA1c levels with adults using CGM compared with self-monitored blood glucose management (using finger stick).[21] There has been a significant advancement in CGM technology since 2000, and in 2016, the FDA had approved CGM to replace fingerstick glucose tests for people living with DM [22]. By 2022, CGMS were approved to be worn continuously for 180 days to help practitioners make better decisions for treating DM. [23]

Using CGM has allowed a more thorough evaluation of the fluctuations in blood glucose concentrations, including time, number, and proportions of those fluctuations. Numerous factors like sleep [24], activity levels, sedentary lifestyle, and diet [25] may affect plasma glucose concentrations in people with DM. While HbA1c provides glycemic control information over the past three months, CGM prescribers have access to glucose patterns and are provided with more detailed information compared with only HbA1c. CGM devices report interstitial fluid glucose readings every few minutes, typically 5-15 minutes, depending on the device.[26] People living with DM now have access to real-time data that will help keep track of their glucose changes thanks to CGM devices.[26]

Glycemic status in non-diabetics

While the technology for managing DM has improved greatly in recent years, screening for DM remains relatively constant. In individuals without DM, there are a few different clinical tools that are used for screening for DM, typically HbA1c≥6.5% or fasting blood glucose level ≥126mg/dL indicate a DM diagnosis. Occasionally a 75g OGTT can also be used to identify potentially impaired postprandial glucose if post two-hour glucose levels are 140 to 199mg/dL.[27]

Acute hyperglycemia, most of the time, displays no symptoms and does not produce overt permanent damage, but it is unclear whether acute glycemic excursions can be harmful.[28] On the other hand, chronic hyperglycemia is clearly associated with severe complications such as damaged kidney, neurological conditions, diseases of the heart or blood vessels.[28] Most treatments aim to keep blood glucose levels in a range of

70-180 mg/dL, which can occasionally even be accomplished in individuals with DM by consuming a healthy diet and implementing physical activity in addition to medications.[28]

However, preliminary (unpublished) evidence from our research group suggests that acute hyperglycemia may be more common among individuals with no other elevated standard glycemic measures.

Low blood glucose, or hypoglycemia, is rarely seen in individuals who are healthy and do not have DM, but it can develop in children and older adults at any period.[29] This can happen because of overproduction of insulin, hereditary metabolism, lack of food over a long period of time, among other health-related conditions.[29]

Glycemic status is influenced by the food we eat, social standing, one’s ability to physically perform and mental health conditions.[30] Over time, there has been a major focus on evaluating the effect of diet quality components such as glycemic index (GI) on glycemic response.[31] GI is used to estimate how much specific foods increase our blood sugar levels.[31] Previous studies have shown that managing a diet with moderate GI foods helps the glycemic response in patients with DM.[32]

Foods with high GI, for example, simple carbohydrates, are digested and metabolized faster meaning they are released quicker into our blood, causing an acute rise in blood glucose.[31] In contrast, foods with low GI, tend to take longer to digest/metabolize and release glucose into the blood. Although carbohydrates have been known to significantly act on postprandial glycemia, evidence suggests that fat and protein also play a big role in the glycemic response.[32] Fats can act to delay the absorption of glucose and slow down the hyperglycemic peak.[32] On the other hand, proteins promote the release of insulin resulting in glucose facilitation.[32]

Although diet is an essential factor that determines blood glucose levels, there is mounting evidence that different people have different glycemic reactions to the same diet.[33] These glycemic responses differ with physiological, genetic, and microbial factors.[34]

Healthy Eating Index and Diabetes

In the past few decades, the use of dietary patterns in research and for public health messages has accelerated dramatically.[35] These trends can be observed by comparing the number of publications each year when using the near term, "dietary pattern." The general purpose of designing dietary pattern indices is to integrate large amounts of information into a single useful measure or summative score by integrating diet quality indices (DQIs) based on specific dietary patterns or guidelines. [35] More importantly, scoring methods focus on both protective dietary patterns and unfavorable food intakes. [36] A higher DQI reflects a healthier diet quality.[36] The original DQIs designed for the Dietary Guidelines for Americans in 2003[40] are the Healthy Eating Index (HEI), Diet Quality Index and the Diet Quality Index-Revised. Many other dietary patterns have been explored for their associations with health outcomes, including, the Mediterranean Diet score, Dietary Approaches to Stop Hypertension (DASH), and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet.[21]

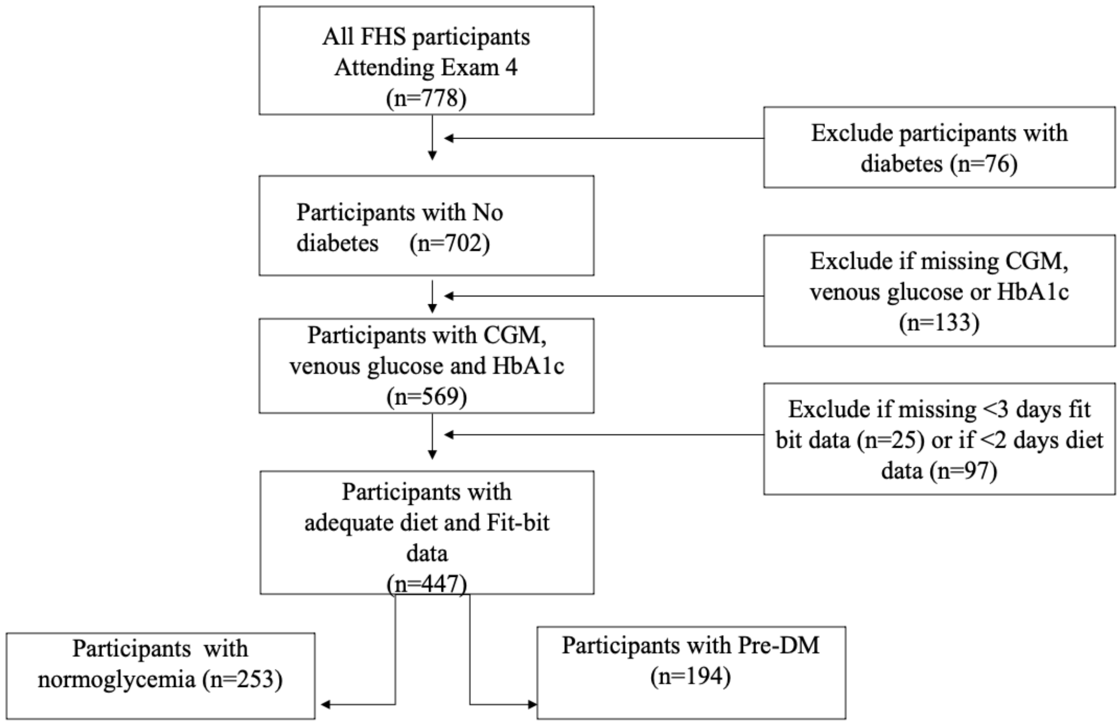
In the present investigation we propose to use CGM to determine the role of dietary patterns on glycemic traits in participants without DM. We chose to use the HEI and its components to explore the role of diet in this investigation. Our results will provide further evidence linking dietary habits with potential future risk for DM.

METHODS

The Framingham Heart Study (FHS) has been ongoing since 1948. Originating as a cohort of 5,209 men and women ages 30 to 62 years, [37] it was initiated by the US public health service to study the epidemiology and risk factors for CVD. Framingham is a town located in the west of Boston, Massachusetts, it was selected due to its success on previous studies of tuberculosis. [38] The initial cohort was followed up biennially to learn about the differences by which those who have CVD compared to those who remain disease free. The initial plans were to follow up the original cohort for 20 years, but after FHS continued to receive federal funding, they expanded the study.[38] In 1971, the second generation of the original cohort was enrolled, known as the Framingham Offspring Study, which included the children of those in the original cohort and the spouses of these children (n=5124). [38] In 1995, a multi-ethnic cohort was enrolled (Omni 1, n=506) to better reflect the race and ethnicity representation of town. In 2002, the FHS enrolled the grandchildren of the original cohort (GEN 3 n=4,095). The next year, FHS investigators enrolled a second Omni cohort (Omni 2, n=410) and spouses of the Framingham Offspring cohort who were not already enrolled (New Offspring Spouse [NOS] cohort, n=103).

In our main analyses, we included participants in the GEN 3, Omni 2, and NOS cohorts who attended the fourth examination of the FHS (n=778) from September 2022 until the end of April 2023 (Figure 1).

Figure 1: Flow chart for the primary analysis



Participants with DM (defined through self-report, HbA1c >=6.7%, or venous fasting glucose >=125 mg/dL) or taking glucose-lowering medication were excluded (n=76). We further excluded those who did not agree to wear the CGM, those who did not wear the monitor for at least 3 full days, and those missing venous glucose or HbA1c (n=133). Finally, we excluded those who did not wear a Fit-bit monitor for at least 3 days (n=25), and those who did not complete the diet record for at least 2 days (n=97). We were left with a sample size of 253 for normoglycemic and 194 for pre-DM.

Continuous Glucose Monitor Assessment

Participants were instructed to wear a Dexcom G6 Pro CGM after the exam for no less than four days but were encouraged to wear it for ten days. Participants were given the option to wear the device on their upper arm or abdomen. We excluded the first and last partial days. We also excluded days with less than 200 glucose values (70% of a potential 288 glucose values). Glucose variability was identified by using several CGM measures such as mean glucose, coefficient of variation (CV%), CONGA1 (described in Table 3).[47]

Table 1: Baseline Characteristics		
Measure	**Normoglycemic (n=253)**	**Pre-DM (n=194)**
	Mean (S.D)	**Mean (S.D)**
CGM device lot number, N (%)		
5314664	19 (11.05)	17(11.8)
5316321	17 (9.8)	12(9.0)
5316322	48 (27.9)	35(24.3)
5316325	88 (51.1)	88(51.2)
5316326	0(0)	1(0.7)
Age, y	59.1 (8.6)	62.1 (7.8)
Sex, N (%)		
Male	80 (31.6)	108 (55.7)
Female	173 (68.4)	86 (44.3)
BMI, kg/m2	26.1 (4.5)	29.4 (5.0)
Venous plasma glucose, mg/dL	90.6 (5.5)	103.0 (7.4)
CGM Coefficient of variation, %	0.2 (0)	0.2 (0)
CGM Mean glucose, mg/dL	113.5 (11.6)	123.1 (14.3)
CGM CONGA1	16.5 (3.1)	22.3 (4.9)
Average steps	9555 (4083)	9279 (4259)
Days of diet data	2.9 (0.5)	2.9 (0.4)

Energy (kcal) per day	1886.2 (619.2)	1995.0 (669.8)
% Energy from carbohydrate	42.6 (8.7)	41.5 (9.2)
% Energy from protein	17.0 (4.2)	17.8 (4.5)
% Energy from fat	38.1 (7.7)	38.9 (7.6)
Fiber residual	0.8 (8.7)	-1.0 (7.8)
Total HEI score	62.0 (13.7)	58.9 (13.4)
Vegetables & Legumes (cups/d)	1.9 (1.1)	1.9 (1.1)
Dark Green Vegetables & Legumes (cups/d)	0.4 (0.5)	0.4 (0.4)
Total intact fruits (cup eq) per day	1.0 (0.9)	0.9 (0.9)
Whole fruit (cup eq.) per day	0.9 (0.8)	0.7(0.7)
Whole grains (oz eq.) per day	1.1 (1.2)	1.1 (1.1)
Total milk, yogurt, cheese & whey (cup. eq) per day	1.4 (1.1)	1.6 (1.2)
Animal & plant protein (oz)	6.9 (3.7)	7.6 (4.0)
Fish & plant protein (oz)	3.0 (3.1)	2.6(2.6)
Fatty acids (G)	47.5 (21.1)	49.9 (21.4)
Saturated Fats (g)	25.7 (12.4)	28.6 (12.8)
Sodium (mg)	2985.1 (1040.4)	3288.0 (1164.6)
Refined grains (oz eq.) per day	4.2 (2.4)	4.4 (2.5)
Added Sugars (tsp. eq) per day	10.2 (7.8)	10.8 (8.1)

Diet Assessment

Participants were instructed to use a diet record tool (Automated Self-Administered 24-Hour Dietary Assessment Tool, ASA24) for at least three days including two days in the week and one weekend day. [39] We excluded days on which participants recorded <600 kcal or >5000 kcal. We calculated the (HEI)-2015 and each of the HEI components using a SAS program for each participant (using the "By Person" methods) made available by the National Cancer Institute.[40] The read me file demonstrates how to calculate the HEI components and scoring in SAS program, using data from ASA24. SAS calculates HEI using simple methods and doesn't not account for measurement error. [40]

The HEI was developed to assess the quality of diet independently of energy intake. The HEI-2015-2020 uses a score from 0-100, the higher the score the better adherence to the ideal diet according to the Dietary Guidelines for Americans (DGA).[40] The HEI-2015 is composed of 13 components including total vegetables, greens and beans, total fruit, whole fruit, whole grain, dairy, total protein foods, seafood and plant protein, fatty acids, saturated fats, sodium, refined grains and added sugars.[41]

We created new variables for each of the 13 HEI components, each of these were the original HEI component divided by the number of data days to get the average intake for each component (see Table 2). We additionally calculated fiber using a residuals method (centered at the mean fiber intake for sample) and assessed average macronutrient (carbohydrates, protein, fat) intake as a percent of kilocalories consumed.

Table 2: Healthy Eating Index-2015 components, point values, and standards for scoring				
Healthy Eating Index (HEI)Components	**Description (each variable represents the average over all recorded days)**	**Maximum points**	**Standard for minimum score**	**Standard for minimum score of zero**
Vegetables & legumes (cups)	Total vegetables and legumes	5	≥1.1 cup equiv. per 1,000 kcal	No Dark Green Vegetables or Legumes
Dark Green vegetables & Legumes (cups)	Dark green vegetables and legumes	5	≥0.2 cup equiv. per 1,000 kcal	No Vegetables
Total intact fruits (cup eq.)	Total intact fruits (whole or cut) and fruit juices	5	≥0.8 cup equiv. per 1,000 kcal	No Fruits
Whole fruit (cup eq.)	Citrus, Melons, Berries, and other Fruits to calculate Whole Fruit (i.e., non-juice) consumption	5	≥0.4 cup equiv. per 1,000 kcal	No Whole Fruits
Whole grains (oz eq.)	Grains defined as whole grains and contained the entire grain kernel the bran, germ, and endosperm	10	≥ 1.5 oz equiv. per 1,000 kcal	No Whole Grains
Total milk, yogurt, cheese & whey (cup. eq)	Total milk, yogurt, cheese, whey. For some foods, the total dairy values could be higher than sum of milk, yogurt, and cheese (because dairy component composed of whey which is not included in the US department of agriculture database as a separate variable)	10	≥1.3 cup equiv. per 1,000 kcal	No Dairy
Animal & plant protein (oz)	All animal and plant proteins, including meat, poultry, fish, eggs, nuts, seeds, soy, and legumes	5	≥2.5 oz equiv. per 1,000 kcal	No Protein Foods
Fish & plant protein (oz)	All fish and plant proteins, including fish, nuts, seeds, soy, and legumes	5	≥0.8 oz equiv. per 1,000 kcal	No Seafood or Plant Proteins
Fatty acids (g)	Monounsaturated and polyunsaturated fatty acids	10	≤ 2.5	≤1.2

Saturated fats (g)	Total saturated fatty acids	10	≤8% of energy	≥16% of energy
Sodium (mg)	Sodium	10	≤ 1.1 grams per 1,000 kcal	≥2.0 grams per 1,000 kcal
Refined grains (oz eq.)	Refined grains that do not contain all the components of the entire grain kernel	10	≤1.8 oz equiv. per 1,000 kcal	≥4.3 oz equiv. per 1,000 kcal
Added sugars (tsp.eq)	Foods defined as added sugars	10	≤6.5% of energy	≥26% of energy

Reference: Developing the Healthy Eating Index (HEI) | EGRP/DCCPS/NCI/NIH. (n.d.).

Physical Activity Assessment

Participants were instructed to wear a Fitbit Inspire 2-Heart Rate monitor on their wrist for seven days.[42] We used the average amount of steps/day as our measure of physical activity. We excluded days that participants did not reach 1000 steps because these days may have had less wear time.

Covariates

In this examination, we explored covariates sex (dichotomous), age (years), body mass index (BMI) (a continuous measure of weight in kg divided by height in meters, squared), physical activity (continuous) and CGM lot number and energy intake.

Statistical Analysis

Means with standard deviations (SD) for baseline characteristics were calculated for descriptive purposes. Regression models were used to study the relationship between CGM measures and the HEI. We adjusted for confounders such as age, sex, total energy intake, CGM device lot number BMI and physical activity. Statistical significance was set at $p<0.05$. We did not perform corrections for multiple testing due to the exploratory nature of these analyses. Results will need to be replicated in the larger sample size upon completion of data collection.

Results

The baseline characteristics of 447 non-DM participants, with an average age of 60 years during the fourth examination, are presented in Table 1. Pre-DM participants had higher mean BMI (29 kg/m^2) compared to those who were normoglycemic (BMI=26 kg/m^2). Participants with pre-DM also had higher mean glucose (123.1 vs. 113.5 mg/dL), higher CONGA1 (22.3 vs. 16.5%), but CV% was similar (both 0.2%). Normoglycemic participants had higher HEI total score, fiber, fruit, seafood, and plant protein, while pre-DM had higher intakes of dairy, total animal and plant protein, saturated fat, sodium refined grains, and added sugar. Vegetable and whole grain intake was similar across these groups with different glycemic status.

Table 3: CGM Variables

CGM Variables	Description
Mean glucose mg/dL	Average of all CGM glucose values
Coefficient of Variation (CV)	Standard deviation for all CGM values/mean CGM glucose

Associations of Diet and CGM outcomes:

We first examined the association between HEI and its components and macronutrients with venous glucose in normoglycemic and pre-DM participants, the only associations that reached statistical significance was higher sodium intake as a component of HEI with higher venous glucose in both pre-DM and normoglycemic (Table 4).

Table 4: The association of diet quality with VENOUS GLUCOSE

			Normoglycemic n=253		Pre-DM n=194	
		Model	B Estimate. (SE)	P Value	B Estimate. (SE)	P Value
Macros	Total energy intake (per 1000 kcal)	1	0.1 (0.1)	0.23	0 (0.1)	0.7
		2	0.1 (0.1)	0.4	-0.1(0)	0.65
	Percent energy from carbohydrate	1	-0.04 (0.05)	0.39	-0.04 (0.07)	0.53
		2	-0.01 (0.05)	0.83	-0.04 (0.07)	0.6
	Percent energy from protein	1	0.04 (0.1)	0.68	0.12 (0.15)	0.43
		2	0.02 (0.09)	0.78	0.17 (0.15)	0.28
	Percent energy from fat	1	-0.05 (0.05)	0.36	0.005 (0.08)	0.95
		2	-0.04 (0.05)	0.52	0.001 (0.08)	0.99
	Fiber residual	1	-0.09 (0.05)	0.07	-0.07 (0.09)	0.43
		2	-0.07 (0.06)	0.26	-0.04 (0.09)	0.65
	HEI total score	1	-0.06 (0.03)	0.06	-0.04 (0.05)	0.36
		2	-0.05 (0.03)	0.11	-0.03 (0.05)	0.52
High Carbs	Refined grains (oz eq.)	1	0.24 (0.21)	0.25	0.26 (0.30)	0.39
		2	0.30 (0.21)	0.16	0.20 (0.30)	0.5
	Added sugars (tsp.)	1	-0.06 (0.07)	0.35	-0.08 (0.09)	0.38
		2	-0.05 (0.07)	0.47	-0.09 (0.01)	0.35
	Whole grains (oz eq.)	1	-0.67 (0.41)	0.1	-0.19 (0.68)	0.16
		2	-0.50 (0.42)	0.24	0.12 (0.67)	0.87
F+V	Vegetables & legumes (cups)	1	-0.13 (0.41)	0.74	0.50 (0.64)	0.44
		2	-0.05 (0.41)	0.91	0.44 (0.63)	0.49
	Dark Green vegetables & Legumes (cups)	1	-0.63 (0.89)	0.48	0.21 (1.54)	0.89
		2	-0.34 (0.91)	0.71	0.40 (1.56)	0.8
	Whole fruit (cup eq.)	1	-0.75 (0.49)	0.13	-1.63 (0.90)	0.07
		2	-0.57 (0.50)	0.26	-1.36 (0.90)	0.13
	Total intact fruits (cup eq.)	1	-0.65 (0.45)	0.15	-1.34 (0.77)	0.08
		2	-0.50 (0.47)	0.29	-1.10 (0.78)	0.29
	Seafood & plant protein (oz)	1	-0.18 (0.18)	0.32	-0.15 (0.26)	0.58
		2	-0.11 (0.18)	0.55	-0.09 (0.27)	0.73

High protein	Animal & plant protein (oz)	1	-0.04 (0.16)	0.81	0.04 (0.19)	0.82
		2	-0.04 (0.16)	0.79	0.11 (0.19)	0.57
	Total milk,yogurt,cheese & whey (cup. eq)	1	-0.02 (0.46)	0.97	0.04 (0.61)	0.96
		2	-0.03 (0.47)	0.94	0.02 (0.61)	0.97
High Fats	Fatty acids (G)	1	-0.04 (0.04)	0.33	-0.01 (0.05)	0.83
		2	-0.02 (0.04)	0.61	-0.009 (0.05)	0.87
	Saturated fats (g)	1	0.02 (0.06)	0.79	0.04 (0.07)	0.58
		2	0.02 (0.06)	0.72	0.04 (0.08)	0.64
	Sodium (g)	1	0.1 (0.1)	0.05	0.2 (0.1)	0.03
		2	0.1 (0.1)	0.05	0.002 (0.1)	0.04

*Model 1 adjusted for age, sex, kcal and lot number. Model 2 adjusted for (Model 1+ BMI +Physical activity).

Among both normoglycemic and pre-DM, we observed statistically significant associations with lower percent energy from fat (p=0.03) (and saturated fat (p=0.02)), higher percent energy from carbohydrates (p=0.01), and higher refined grains (p=0.03) with higher CONGA1, in the full model adjusting for age, sex, kcal, lot number, BMI and physical activity (Table 7). There were additional dietary factors associated with CONGA1 in either normoglycemic or pre-DM, but not both. When assessing which dietary factors relate to mean glucose, we also observed different results among the two glycemic status groups. Higher percent energy from carbohydrates and refined grains (p=0.03) were associated with mean glucose (like CONGA1), but only among normoglycemic, whereas HEI protein components; seafood and animal (both with a p=0.03) and fiber intake (p=0.03) were associated with mean glucose in those with pre-DM (Table 6). Only in normoglycemic were dietary factors associated with CV (total energy (p=0.03) and vegetable/legume intake (p=0.05)).

For normoglycemic participants there was an association with higher intake of refined grains ($p=0.03$) (Table 6), and lower total vegetables legumes ($p=0.0007$) (Table 5) associated with higher mean glucose, higher CV and higher CONGA1 (Table 7), $p\leq0.05$, which was not observed in pre-DM after adjusting for age, sex, kcal, lot number BMI and physical activity. Among pre-DM, we observed dietary factors significantly associated with lower mean glucose (Table 6): animal, fish and plant proteins, and fiber intake ($p=0.03$) in model 1 adjusting for age, sex, total energy intake and lot number and ($p=0.06$) when further adjusting for BMI and physical activity.

Among both normoglycemic and pre-DM, we observed statistically significant associations with higher percent energy from carbohydrates ($p=0.01$ & $p=0,002$), lower percent energy from fat ($p=0.03$ & $p=0.01$), and higher refined grains ($p=0.03$ & $p=0.02$) with higher CONGA1 (Table 7). In normoglycemic only, we observed associations of lower intake of total milk, yogurt, cheese, and whey ($p=0.05$), fish and plant protein ($p=0.02$), and saturated fats ($p=0.02$) with higher CONGA1 (Table 7). Among pre-DM, we observed associations of lower fatty acid intake higher sodium intake and higher intake of animal and plant protein with lower CGM measure CONGA1 (Table 7, all with a $p=0.02$).

It is important to note that most statistical significance would be lost if correcting for multiple testing. A priori, we decided not to make these adjustments due to the exploratory nature of our analysis, but replication is required for confirmation of our results.

Table 5. The association of diet quality with CGM-derived Coefficient of Variation

		Normoglycemic n=253		Prediabetic n=194	
	Model	**B Estimate (SE)**	**P Value**	**B Estimate (SE)**	**P Value**
Macros					
Total energy intake (per 1000 kcal)	1	0.1 (0)	0.05	0. 9 (0.1)	0.15
	2	0. 1 (0)	0.03	0. 3 (0. 6)	0.69
Percent energy from carbohydrate	1	0.0003 (0.0003)	0.26	0.0008 (0.0004)	0.36
	2	0.0003 (0.0003)	0.33	0.0008 (0.0004)	0.06
Percent energy from protein	1	-0.0001 (0.0005)	0.76	-0.0006 (0.0001)	0.5
	2	-0.0001 (0.0005)	0.82	-0.0009 (0.0001)	0.37
	2	-0.0003(0.0003)	0.29	-0.0005 (0.0005)	0.32
Fiber residual	1	-0.0001 (0.0003)	0.71	0.0001 (0.0006)	0.84
	2	-0.0004 (0.0003)	0.19	0.0003 (0.0006)	0.65
HEI total score	1	-0.0002 (0.0002)	0.23	-0.00002(0.0003)	0.96
	2	-0.0003 (0.0002)	0.12	-0.0001 (0.0003)	0.67
High Carbs					
Refined grains (oz eq.)	1	0.002 (0.001)	0.15	0.002 (0.002)	0.18
	2	0.001 (0.001)	0.1	0.003 (0.002)	0.13
Added sugars (tsp. eq)	1	0.0002 (0.0003)	0.59	-0.0005 (0.0006)	0.43
	2	0.0003 (0.0003)	0.43	0.00003 (0.0006)	0.96
Whole grains (oz eq.)	1	-0.002 (0.002)	0.45	-0.0003 (0.004)	0.94
	2	-0.001 (0.002)	0.37	0.0006 (0.004)	0.89
F+V					
Vegetables & legumes (cups)	1	-0.002 (0.002)	0.26	-0.0007 (0.004)	0.85
	2	-0.004 (0.002)	0.05	-0.0004 (0.003)	0.92
Dark Green vegetables & Legumes (cups)	1	-0.005 (0.005)	0.31	-0.0006 (0.001)	0.95
	2	-0.007 (0.005)	0.09	-0.001 (0.001)	0.88
Whole fruit (cup eq.)	1	-0.004 (0.003)	0.16	-0.0002 (0.006)	0.97
	2	-0.005 (0.003)	0.08	0.001 (0.006)	0.84
Total intact fruits (cup eq.)	1	-0.003 (0.002)	0.14	-0.001 (0.005)	0.74
	2	-0.004 (0.002)	0.11	-0.002 (0.005)	0.73
	1	-0.001(0.0009)	0.16	0.0006 (0.002)	0.7

High protein	Seafood & plant protein (oz)	2	-0.002 (0.0009)	0.08	-0.0002 (0.002)	0.9
	Animal & plant protein (oz)	1	0.00002 (0.0008)	0.1	-0.001 (0.001)	0.88
		2	-0.0001 (0.0008)	0.9	-0.001 (0.001)	0.25
	Total milk,yogurt,cheese & whey (cup. eq)	1	-0.004 (0.002)	0.09	0.002 (0.004)	0.45
		2	-0.004 (0.002)	0.1	0.004 (0.004)	0.27
High Fat	Fatty acids (G)	1	0.0002 (0.0002)	0.26	-0.0005 (0.0003)	0.1
		2	0.0001 (0.0001)	0.5	-0.0004 (0.0003)	0.22
	Saturated fats (g)	1	-0.0004 (0.0003)	0.18	-0.0006 (0.0005)	0.19
		2	-0.0005(0.0004)	0.08	-0.0003 (0.0005)	0.55
	Sodium (g)	1	0. 3 (0.1)	0.39	0. 1 (0)	0.14
		2	0.3 (0. 3)	0.35	0.01 (0. 1)	0.11

Model 1 adjusted for age, sex, kcal and lot number. Model 2 adjusted for (Model 1+ BMI+Physical activity).

Table 6: The association of diet quality with CGM-derived: MEAN GLUCOSE

			Normoglycemic n=253		Pre-DM n=194	
		Model	B Estimate (SE)	P Value	B Estimate (SE)	P Value
Macros	Total energy intake (per 1000 kcal)	1	0.1 (0.2)	0.94	-0.1 (0.2)	0.5
		2	0.1 (0.2)	0.98	0.9 (0.2)	0.66
	Percent energy from carbohydrate	1	0.16 (0.1)	0.12	0.11 (0.12)	0.34
		2	0.28 (0.12)	0.02	0.06 (0.12)	0.62
	Percent energy from protein	1	-0.27 (0.22)	0.22	-0.47 (0.28)	0.1
		2	-0.35 (0.22)	0.11	-0.35 (0.28)	0.22
	Percent energy from fat	1	-0.17 (0.12)	0.17	0.015 (0.15)	0.92
		2	-0.21 (0.13)	0.11	-0.03 (0.15)	0.81
		1	-0.18 (0.12)	0.15	-0.35 (0.17)	0.03

	Fiber residual	2	-0.12 (0.13)	0.38	-0.31 (0.16)	0.06
	HEI total score	1	-0.07 (0.07)	0.33	-0.17 (0.09)	0.05
		2	-0.05 (0.07)	0.51	-0.11 (0.09)	0.2
High Carbs	**Refined grains (oz eq.)**	1	0.90 (0.47)	0.05	0.87 (0.54)	0.11
		2	1.02 (0.47)	0.03	0.53 (0.55)	0.33
	Added sugars (tsp. eq)	1	0.16 (0.1)	0.3	0.14 (0.17)	0.4
		2	0.19 (0.15)	0.22	0.04 (0.18)	0.82
	Whole grains (oz eq.)	1	-0.22 (0.93)	0.81	-0.09 (1.25)	0.94
		2	0.36 (0.96)	0.71	0.28 (1.24)	0.82
F+V	**Vegetables & legumes (cups)**	1	-1.18(0.92)	0.2	-0.10 (1.18)	0.93
		2	-1.23 (0.92)	0.19	0.13 (1.17)	0.91
	Dark Green vegetables & Legumes (cups)	1	-1.33 (2.03)	0.51	-3.92 (2.84)	0.17
		2	-2.27 (2.86)	0.43	-0.95 (2.04)	0.64
	Whole fruit (cup eq.)	1	-0.42 (1.12)	0.71	-1.82 (1.67)	0.28
		2	-0.05 (1.14)	0.97	-1.38 (1.66)	0.41
	Total intact fruits (cup eq.)	1	0.70 (1.04)	0.5	-0.88 (1.44)	0.54
		2	-0.48 (1.05)	0.65	-0.50(1.43)	0.73
High Protein	**Seafood & plant protein (oz)**	1	-0.44 (0.40)	0.27	-1.40 (0.47)	0.003
		2	-0.27 (0.41)	0.51	-1.05 (0.49)	0.03
	Animal & plant protein (oz)	1	-0.56 (0.36)	0.12	-0.95 (0.33)	0.007
		2	-0.57 (0.35)	0.11	-0.74 (0.35)	0.03
	Total milk, yogurt,cheese & whey (cup. eq)	1	-0.44 (1.04)	0.68	0.34 (1.13)	0.76
		2	-0.79 (1.06)	0.46	0.44 (1.22)	0.7
High Fat	**Fatty acids (G)**	1	-0.11 (0.08)	0.169	-0.03 (0.10)	0.76
		2	-0.10 (0.09)	0.24	-0.008 (0.10)	0.93
	Saturated fats (g)	1	-0.08 (0.13)	0.53	0.10 (0.14)	0.44
		2	-0.17 (0.14)	0.23	0.03 (0.14)	0.83
	Sodium (g)	1	0 (0.2)	0.98	0.2 (0.2)	0.16
		2	-0.3 (0.1)	0.84	0.2 (0.2)	0.12

	Table 7: The association of diet quality with CGM-derived CONGA1					
			Normoglycemic n=253		Pre-DM n=194	
		Model	B Estimate SE	P Value	B Estimate SE	P Value
Macros	Total energy intake (per 1000 kcal)	1	0. 1 (0.6)	0.11	0. 4 (0.6)	0.58
		2	0. 1 (0 6)	0.05	0.7 (0.7)	0.29
	Percent energy from carbohydrate	1	0.10 (0.04)	0.01	0.12 (0.039)	0.002
		2	0.11 (0.04)	0.01	0.122 (0.04)	0.003
	Percent energy from protein	1	-0.07 (0.08)	0.36	-0.13 (0.09)	0.17
		2	-0.07 (0.08)	0.41	-0.13 (0.09)	0.19
	Percent energy from fat	1	-0.07 (0.05)	0.13	-0.12 (0.05)	0.02
		2	-0.11 (0.05)	0.031	-0.14 (0.05)	0.01
	Fiber residual	1	-0.01 (0.05)	0.8	0.04 (0.06)	0.43
		2	-0.07(0.05)	0.18	0.05 (0.06)	0.43
	HEI total score	1	-0.03 (0.03)	0.37	-0.008 (0.03)	0.79
		2	-0.04 (0.03)	0.19	-0.002 (0.03)	0.96
High Carbs	Refined grains (oz eq.)	1	0.34 (0.18)	0.05	0.43 (0.18)	0.02
		2	0.38 (0.17)	0.03	0.42 (0.18)	0.02
	Added sugars (tsp.eq)	1	0.07 (0.06)	0.21	0.02 (0.06)	0.78
		2	0.092 (0.06)	0.11	-0.001 (0.06)	0.99
	Whole grains (oz eq.)	1	0.14 (0.35)	0.7	0.36 (0.41)	0.38
		2	0.09 (0.35)	0.79	0.33 (0.42)	0.42
F+V	Vegetables & legumes (cups)	1	-0.54 (0.35)	0.12	0.16 (0.39)	0.67
		2	-0.83 (0.33)	0.01	0.23 (0.40)	0.55
	Dark green vegetables & legumes (cups)	1	-0.64 (0.77)	0.41	-0.56 (0.94)	0.54
		2	-1.20 (0.74)	0.11	-0.34 (0.97)	0.72
	Whole fruit (cup eq.)	1	-0.46 (0.43)	0.23	-0.42 (0.55)	0.45
		2	-0.63 (0.42)	0.13	-0.45 (0.56)	0.42
	Total intact fruits (cup eq.)	1	-0.47 (0.40)	0.24	-0.21 (0.47)	0.66
		2	-0.59 (0.39)	0.13	-0.24 (0.48)	0.62
		1	-0.27 (0.15)	0.07	-0.16 (0.16)	0.33

	Seafood & plant protein (oz)					
		2	-0.34 (0.15)	0.02	-0.11 (0.17)	0.49
High Protein	**Animal & plant protein (oz)**	1	-0.11 (0.14)	0.42	-0.29 (0.11)	0.01
		2	-0.13 (0.13)	0.31	-0.29 (0.12)	0.02
	Total milk,yogurt,cheese & whey (cup. eq)	1	-0.81 (0.39)	0.04	0.46 (0.37)	0.22
		2	-0.77 (0.39)	0.05	0.49 (0.38)	0.19
High Fats	**Fatty acids (G)**	1	0.001 (0.03)	0.97	-0.07 (0.03)	0.02
		2	-0.02 (0.03)	0.57	-0.08 (0.03)	0.02
	Saturated fats (g)	1	-0.01 (0.05)	0.05	-0.06 (0.04)	0.17
		2	-0.12 (0.05)	0.02	-0.08 (0.05)	0.01
	Sodium (g)	1	0.3 (0.6)	0.59	0.1 (0.5)	0.02
		2	0.0004 (0.6)	0.52	0.001 (0.5)	0.02

Model 1 adjusted for age, sex, kcal and lot number. Model 2 adjusted for (Model 1+ BMI +Physical activity).

DISCUSSION

Our study examined the associations of diet quality and CGM measures in participants without DM. In our investigation in individuals who had normoglycemia and pre-DM, we observed that lower intake of carbohydrates, higher fat, and many favorable components of the HEI (but not the total HEI score itself) were associated with lower CONGA1, a CGM-derived measure of glycemic variability. Some of these HEI components were more strongly associated with CONGA1 in normoglycemia, while others were more strongly associated with CONGA1 in pre-DM. Few dietary factors were associated with higher CGM-derived CV, only lower vegetable and legume consumption and higher total energy intake (after adjusting for BMI and other covariates), only in individuals with normoglycemia. There were also some associations of dietary factors with CGM-derived mean glucose, for which in those with normoglycemia, higher carbohydrate and refined grain intake was more strongly associated with higher mean glucose. In contrast, among pre-DM, specific higher protein foods (meat, fish, nuts, seeds, soy, and legumes) and higher fiber intake were associated with lower mean glucose.

Our results are somewhat consistent with a large study of non-DM conducted in Israel (n=7578) by Keshet, et al., reporting that individuals who consume diets with a higher total energy have higher CGM-derived CV, using a different CGM device called the Freestyle Libre. Like our study, which used the Dexcom G6 pro device, total carbohydrate intake was also associated with higher mean glucose and glycemic variability (CONGA1 in our study, which was not measured in their study). In Keshet, et al., they used unadjusted correlation analysis to observe consistent relationships among macronutrient intake and many different CGM measures. We did not consistently observe these associations, which may be because we adjusted for covariates including BMI, age, sex, CGM lot number and physical activity. [44] Instead, many of our significant associations with glycemic variables were observed with specific HEI components.

Another study conducted in Bulgaria (n=94) also observed the impact of nutrition on CGM (using the Freestyle Libre CGM device) measures such as CV, CONGA1, lability index, j-index, low glucose index, high glucose index, glycemic risk assessment in diabetes equation, mean absolute glucose, M-value, and mean amplitude of glycemic excursions in impaired glucose tolerance subjects.[43]

They reported that CGM measures such as CV worsened in those who consumed more carbohydrates and refined grains. Those who had a higher consumption of whole grains showed an improvement in CV. [43] Comparatively, in our study, we also observed significant associations between individuals who consumed more carbohydrates and refined grains with high glycemic variability, but when measured by CONGA1, not CV. It is possible that different CGM-derived features may differ by device and among different populations, but it is also important to note a lower reliability of results from a smaller study.

The ZOE Predict study is another study that explored associations between CGM-derived traits and metabolic and cardiometabolic health traits in individuals living with DM. [48] This was study the first intervention study conducted in the United Kingdom (UK) aiming to create algorithms that predict an individual's postprandial responses to certain foods. [48] In this study, they explored similar CGM measures as we used in the current study, such as coefficient of variation (CV) and mean glucose. They observed that individuals who had lower glycemic variability were those who consumed less carbohydrates. [48] This study also saw associations across time in range, glucose variability, diet, and lifestyle as being potential points to ameliorate glycemic traits from CGM. [48] Compared to our study we didn't assess for these as they weren't the focus of our investigation.

Carbohydrate quality and diabetes risk

Over the past decades the prevalence of obesity has been increasing in adults, which is associated with higher risk of T2DM and metabolic disease. [49] A person's lifestyle behaviors, such as consuming an unhealthy diet and being physically inactive are key factors that contribute to obesity. [49] There is numerous evidence that explores lifestyle changes, especially diet, which plays a significant role in T2DM prevention. For example, elevated carbohydrates and poor carbohydrate quality have been studied as a major contributor of metabolic diseases and weight gain. A study that examined the prospective relationship of carbohydrate quality index with changes in waist circumference. The carbohydrate quality index includes four elements of the quality of a carbohydrate: fiber, glycemic index, the ratio of whole grain to total grain, and the ratio of a solid to total carbohydrate. Basically, a diet with a higher carbohydrate quality index, the better carbohydrate quality one is consuming. [50]

This study reported that better carbohydrate quality may help reduce abdominal adiposity over time. [50]

There is evidence suggesting that some types of carbohydrates may be beneficial to metabolic health, while others are detrimental. In the Nurses' Health study, among women who were free of DM, cancer, and CVD, they found that increasing whole grains by two-servings-per-day was significantly associated with 21% decrease of developing T2DM [11] As mentioned in this study, whole grains slow down and lower postprandial blood sugar and insulin. [11] There have been other studies examining sugar-sweetened beverages (SSB) having a high glycemic load. A prospective cohort study done in the Nurses' Health Study II found that he higher consumption of SSBs was associated with weight gain and increase development of T2DM. [12] Although we did not measure carbohydrate quality or SSB specifically, we did observe associations between higher refined and total carbohydrate intake with higher CGM-derived trait, CONGA1 and lower intake of fiber with higher mean glucose.

Another essential part of diet is the carbohydrate type that individuals consume. The results of our study confirm that higher intake of refined grains was associated with higher mean glucose and CONGA1. Whereas higher intake of fiber was associated with lower mean glucose. This result is also consistent with a previous study that showed that fiber rich foods are successful in improving glycemic variability in patients with T2DM. [59]

Nutrition is an important preventative care measure for DM, but the effect of macronutrients on glucose variability is in individuals with DM is also being explored. A recent study demonstrated that a low carbohydrate diet improved the range of glucose variability and diminished required insulin doses and HbA1c levels in subjects with DM. [45]

Dietary patterns and diabetes risk

Given that the evidence suggests that DM risk is associated with carbohydrate quality, dietary fiber and sugary drinks, there may be other dietary patterns that are important to explore in relation to CGM traits such as the alternative HEI (AHEI), Mediterranean diet and DASH diet.

Alternative Healthy Index (AHEI) is very similar the original HEI and was created for the prevention of noncommunicable diseases. Although these two scoring systems are very similar, the difference is in the scoring. AHEI includes trans-fat and the ratio of polyunsaturated fatty acid to saturated fatty acid. It also includes the ratio of red to white meat and soy in the protein component. [51] A study that examined the role of diet in prevention and controlling DM in observational and intervention studies found that adherence to a healthy diet assessed by the AHEI was strongly associated with lowering diabetes risk. [52]

Given the limited differences between HEI and AHEI, it may not be very informative to investigate AHEI, but the association between adherence to DASH or Mediterranean diet and CGM-derived traits may be more interesting.

They also found that adherence to the Dietary Approaches to stop Hypertension (DASH) diet that is rich in greens fruits, low-fat dietary product was associated with decreasing DM risk. [53] The DASH diet is a healthy meal plan that has the purpose to prevent or manage high blood pressure. In this study they showed how the following this diet can significantly decrease fasting plasma insulin.

Another diet that could be explored in future studies is the Mediterranean diet, this diet is distinguished by a high vegetable intake, variety of whole grain breads, fruit, olive oil, nuts and seeds and a small number of fish and poultry and red meat intake. Additionally, a discrete amount of wine paired up with a meal. [55] Adherence to the Mediterranean diet can play a role in the mechanisms of T2D for example, anti-inflammatory action, glucagon peptide compounds and significant positive changes in the gut microbiota. [55]

The potential role of continuous glucose monitoring in prevention of diabetes

In addition to using CGM to measure glycemic traits, CGM may also be used in an intervention setting to help patients achieve dietary goals. A study conducted at the University of Virginia, explored if CGM's and activity monitors would improve metabolic control and reliance in diabetes medication. During the research study, they developed and alternative lifestyle option known as glycemic excursion minimization. Glycemic excursion minimization focuses on reducing post nutrient glucose excursions instead of decreasing body weight. [54] In this study they found that glycemic excursion minimization together with information from CGM may be a beneficial intervention for adults who are newly diagnosed with T2DM [54]. Participants significantly reduced their HbA1c levels ($p<.001$), they also significantly reduced their intake of carbohydrate. Participants in the study expressed that CGM was the most significant piece of the study [54].

CGM displays automated text messages with the purpose to improve metabolic control, these text messages allow a person to be aware of when their glucose spikes up or drops. This allows people to see which dietary factors affect their glucose excursions more than others.[54]

Strengths and Limitations

The strengths of our study include the large sample size which has a larger power to detect statistically significant results than previous studies [43]. Participants also had direct assessment of glucose variability through CGM measures constantly throughout the study period (up to 10 days), which is a novel measure in populations without DM. However, we had some limitations in our study. First, although diet records are a strong diet assessment tool, consumption was still self-reported through ASA24 which can be inconvenient and inaccurate because not all the foods are included. As a results subject random measurement may occur which may attenuate true associations.

It can be hard to use for some individuals and they might not be able to respond correctly. Second, there was no adjustments for other covariates that may influence glucose measures such as - smoking status, medications, or alcohol intake, due to the preliminary nature of the data that is still in the process of being collected. In addition, we cannot rule out residual confounding. These could be potential confounders that we were unable to explore. Third, the cohort was not diverse, with a mostly white cohort, these results may not be generalizable to the larger population. Finally, the cross-sectional design limits our ability to infer causality.

Conclusion:

The primary outcome results showed that HEI total score components and BMI are predictors of CGM measures in non-diabetic individuals. Overall, the daily consumption of refined grains and higher total energy was associated with higher CGM measures, whereas daily meat, fish, plant protein and fiber intake were associated with lower mean glucose in individuals with pre-DM. It is evident that diet plays a crucial role in the develop of DM. We have identified food groups that may be associated with better glucose control in populations without DM. It is not clear from our results whether consumption of these specific foods could prevent DM. From a public health standpoint, it is important to conduct additional research that confirm our results and follow our participants longitudinally to determine whether they predict DM development.

REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed [Aug 28 2023]

2. Menke A., Casagrande S., Geiss L., Cowie C.C. Prevalence of and Trends in Diabetes among Adults in the United States, 1988–2012. *JAMA.* 2015;314:1021–1029. doi: 10.1001/jama.2015.10029.

3. American Diabetes Association; 5. Lifestyle Management: Standards of Medical Care in Diabetes—2019. *Diabetes Care* 1 January 2019; 42 (Supplement_1): S46–S60. https://doi.org/10.2337/dc19-S005

4. J B Meigs, L A Cupples, P W Wilson; Parental transmission of type 2 diabetes: The Framingham Offspring Study. *Diabetes* 1 December 2000; 49 (12): 2201–2207. https://doi.org/10.2337/diabetes.49.12.2201

5. Julienne K. Kirk, Leah V. Passmore, Ronny A. Bell, K.M. Venkat Narayan, Ralph B. D'Agostino, Thomas A. Arcury, Sara A. Quandt; Disparities in Hemoglobin A1C Levels Between Hispanic and Non-Hispanic White Adults With Diabetes: A meta-analysis. *Diabetes Care* 1 February 2008; 31 (2): 240–246. https://doi.org/10.2337/dc07-0382

6. Modzelewski R, Stefanowicz-Rutkowska MM, Matuszewski W, Bandurska-Stankiewicz EM. Gestational Diabetes Mellitus-Recent Literature Review. *Journal Clinical Medicine* 2022 Sep 28;11(19):5736. doi: 10.3390/jcm11195736. PMID: 36233604; PMCID: PMC9572242.

7. Franz, M. J., MacLeod, J., Evert, A., Brown, C., Gradwell, E., Handu, D., ... & Robinson, M. (2017). Academy of Nutrition and Dietetics nutrition practice guideline for type 1 and type 2 diabetes in adults: Systematic review of evidence for medical nutrition therapy effectiveness and recommendations for integration into the nutrition care process. *Journal of the Academy of Nutrition and Dietetics*, 117(10), 1659-1679.

8. Evert A.B., Dennison M., Gardner C.D., Garvey W.T., Lau K.H.K., MacLeod J., Mitri J., Pereira R.F., Rawlings K., Robinson S., et al.

Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. *Diabetes Care.* 2019;42:731–754. doi: 10.2337/dci19-0014.

9. The Diabetes Prevention Program Research Group. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care.* 1999 Apr;22(4):623-34. doi: 10.2337/diacare.22.4.623. Erratum in: Diabetes Care 1999 Aug;22(8):1389. PMID: 10189543; PMCID: PMC1351026.

10. Centers for Disease Control and Prevention. (2023, August 1). *National Diabetes Prevention Program*. Centers for Disease Control and Prevention.

11. Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. *PLoS Medicine.* 2007 Aug 28;4(8):e261.

12. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-Sweetened Beverages, Weight Gain, and Incidence of Type 2 Diabetes in Young and Middle-Aged Women. *JAMA.* 2004;292(8):927–934. doi:10.1001/jama.292.8.927

13. Risérus U, Willett WC, Hu FB. Dietary fats and prevention of type 2 diabetes. *Progress in Lipid Research.* 2009 Jan 1;48(1):44-51.

14. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Willett WC, Hu FB. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *The American Journal of Clinical Nutrition.* 2011 Aug 10;94(4):1088-96.

15. Chehregosha H, Khamseh ME, Malek M, Hosseinpanah F, Ismail-Beigi F. A View Beyond HbA1c: Role of Continuous Glucose Monitoring. *Diabetes Therapy.* 2019 Jun;10(3):853-863. doi: 10.1007/s13300-019-0619-1. Epub 2019 Apr 29. PMID: 31037553; PMCID: PMC6531520.

16. Cologne, Germany: Institute for Quality and Efficiency in Health Care *IQWiG* 2006-. Glucose tolerance tests: What exactly do they involve?

[Updated 2020 Oct 22]. Available from:
https://www.ncbi.nlm.nih.gov/books/NBK279331

17. DeVries, JH, Bailey, TS, Bhargava, A, et al. Day-to-day fasting self-monitored blood glucose variability is associated with risk of hypoglycemia in insulin-treated patients with type 1 and type 2 diabetes: A post hoc analysis of the SWITCH Trials. *Diabetes, Obesity & Metabolism*. 2019; 21: 622–630. https://doi.org/10.1111/dom.13565

18. Gross, T. M., Bode, B. W., Einhorn, D., Kayne, D. M., Reed, J. H., White, N. H., & Mastrototaro, J. J. (2000). Performance evaluation of the MiniMed® continuous glucose monitoring system during patient home use. *Diabetes Technology & Therapeutics*, *2*(1), 49-56.

19. Chehregosha, H., Khamseh, M.E., Malek, M. *et al.* A View Beyond HbA1c: Role of Continuous Glucose Monitoring. *Diabetes Therapy* 10, 853–863 (2019).

20. Miller EM. Using Continuous Glucose Monitoring in Clinical Practice. *Clinical Diabetes.* 2020 Dec;38(5):429-438. doi: 10.2337/cd20-0043. PMID: 33384468; PMCID: PMC7755046.

21. Food and Drug Administration. FDA expands indication for continuous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decisions. Dec 20, 2016.

22. Food and Drug Administration. Eversense E3 Continuous Glucose Monitoring System – P160048/S016. March 2, 2022.

23. Reddy, N. (2023, July 8). Monitoring technologies- Continuous Glucose Monitoring, mobile technology, biomarkers of glycemic control. *Endotext* - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK279046/

24. Toi N, Inaba M, Kurajoh M, Morioka T, Hayashi N, Hirota T, Miyaoka D, Emoto M, Yamada S. Improvement of glycemic control by treatment for insomnia with suvorexant in type 2 diabetes mellitus. *Journal of Clinical Translational Endocrinology.* 2018 Dec 18;15:37-44. doi:

10.1016/j.jcte.2018.12.006. Erratum in: *Journal of Clinical Translational Endocrinology*. 2020 Dec 17;23:100246. PMID: 30619717; PMCID: PMC6306692.

25. Good to Know: Factors Affecting Blood Glucose. *Clinical Diabetes.* 2018 Apr;36(2):202. doi: 10.2337/cd18-0012. PMID: 29686462; PMCID: PMC5898168.

26. Laffel LM, Kanapka LG, Beck RW, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial. *JAMA.* 2020;323(23):2388–2396. doi:10.1001/jama.2020.6940

27. Eyth E, Basit H, Swift CJ. Glucose Tolerance Test. [Updated 2023 Apr 23]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532915/

28. Cook A, Burkitt D, Mcdonald L, Sublett L. Evaluation of glycemic control using neutral protamine Hagedorn (NPH) insulin sliding scale versus insulin aspart sliding scale in continuously tube-fed patients. *Nutrition Clinical Practice*. (2009) 24:718–22. doi: 10.1177/0884533609351531

29. Tubiana-Rufi N, Moret L, Chwalow J, Czernichow Public Health and factors associated with Glycaemic control in 165 children with insulin-dependent diabetes, aged 7-23 year. *Archives of Pediatrics*. 1994;1(11):982-90.

30. Khodarahmi M, Siri G, Mohammadi M, Farhangi MA, Aleseidi S. The Role of Dietary Glycemic Index and Glycemic Load in Mediating Genetic Susceptibility via MC4R s17782313 Genotypes to Affect Cardiometabolic Risk Factors among Apparently Healthy Obese Individuals. *Biomed Research International.* 2022 Nov 16;2022:3044545. doi: 10.1155/2022/3044545. PMID: 36440355; PMCID: PMC9683967.

31. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. Impact of different dietary approaches on glycemic control and cardiovascular risk factors in patients with type 2 diabetes: A protocol for a systematic review and network meta-analysis. *Systemic Review.* (2017) 6:1–7.

32. Alami F, Mohseni GK, Ahmadzadeh M, Vahid F, Gholamalizadeh M, Masoumvand M, Shekari S, Alizadeh A, Shafaei H and Doaei S (2022) The Association Between Fasting Blood Sugar and Index of Nutritional Quality in Adult Women. *Frontiers in Nutrition.* 9:883672.

33. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, Ben-Yacov O, Lador D, Avnit-Sagi T, Lotan-Pompan M, Suez J, Mahdi JA, Matot E, Malka G, Kosower N, Rein M, Zilberman-Schapira G, Dohnalová L, Pevsner-Fischer M, Bikovsky R, Halpern Z, Elinav E, Segal E. Personalized Nutrition by Prediction of Glycemic Responses. *Cell* 2015 Nov 19; 163(5):1079-1094. doi: 10.1016/j.cell.2015.11.001. PMID: 26590418.

34. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al.. Richness of human gut microbiome correlates with metabolic markers. *Nature* (2013) 500:541–6. 10.1038/nature12506

35. Arvaniti F., Panagiotakos D.B. Healthy indexes in public health practice and research: A review. *Critical Reviews in Food Science and Nutrition.* 2008;48:317–327. doi: 10.1080/10408390701326268.

36. Wirt, A., & Collins, C. (2009). Diet quality – What is it and does it matter? *Public Health Nutrition, 12*(12), 2473-2492. doi:10.1017/S136898000900531X

37. Kannel WB, Levy D. Commentary: Medical aspects of the Framingham Community Health and Tuberculosis Demonstration, *International Journal of Epidemiology*, 2005, vol. 34 (pg. 1187-8)

38. Andersson C;Johnson AD;Benjamin EJ;Levy D;Vasan RS;, charlotte. (2019, November 16). 70-year legacy of the Framingham Heart Study. *Nature Reviews. Cardiology.* https://pubmed.ncbi.nlm.nih.gov/31065045/

39. National Cancer Institute. The Healthy Eating Index – Simple HEI Scoring Algorithm - Per Person. https://epi.grants.cancer.gov/hei/sas-code.html Updated Dec

40 . U.S. Department of Health and Human Services and U.S. Department of Agriculture . *2015–2020 Dietary Guidelines for Americans.* 8th ed. U.S. Department of Agriculture; Washington, DC, USA: 2015.

41. Zhou, J.; Lou, L.; Jin, K.; Ye, J. Association between Healthy Eating Index-2015 and Age-Related Cataract in American Adults: A Cross-Sectional Study of National Health and Nutrition Examination Survey National Health and Nutrition Examination Survey NHANES 2005–2008. *Nutrients* 2023, *15*, 98. https://doi.org/10.3390/nu15010098

42. St Fleur RG, St George SM, Leite R, Kobayashi M, Agosto Y, Jake-Schoffman DE. Use of Fitbit Devices in Physical Activity Intervention Studies Across the Life Course: Narrative Review. *JMIR mHealth and uHealth.* 2021 May 28;9(5):e23411. doi: 10.2196/23411. PMID: 34047705; PMCID: PMC8196365.

43. Dimova R, Chakarova N, Del Prato S, Tankova T. The Relationship Between Dietary Patterns and Glycemic Variability in People with Impaired Glucose Tolerance. *Journal of Nutrition.* 2023 May;153(5):1427-1438. doi: 10.1016/j.tjnut.2023.03.007. Epub 2023 Mar 10. PMID: 36906149; PMCID: PMC1019661

44. Keshet A, Shilo S, Godneva A, Talmor-Barkan Y, Aviv Y, Segal E, Rossman H. CGMap: Characterizing continuous glucose monitor data in thousands of non-diabetic individuals. *Cell Metabolism.* 2023 May 2;35(5):758-769.e3. doi: 10.1016/j.cmet.2023.04.002. Epub 2023 Apr 19. PMID: 37080199.

45. Ting Mao, Fansu Huang, Xuping Zhu, Dong Wei, Lianmeng Chen, Effects of dietary fiber on glycemic control and insulin sensitivity in patients with type 2 diabetes: A systematic review and meta-analysis, *Journal of Functional Foods.* 2021;82:104500. https://doi.org/10.1016/j.jff.2021.104500

46. Developing the Healthy Eating Index (HEI) | EGRP/DCCPS/NCI/NIH. (n.d.). https://epi.grants.cancer.gov/hei/developing.html#2015c

47. Vigers T, Chan CL, Snell-Bergeon J, Bjornstad P, Zeitler PS, Forlenza G, Pyle L. cgmanalysis: An R package for descriptive analysis of

continuous glucose monitor data. *PLoS One.* 2019 Oct 11;14(10):e0216851. doi: 10.1371/journal.pone.0216851. PMID: 31603912; PMCID: PMC6788735.

48. Bermingham KM, Smith HA, Gonzalez JT, Duncan EL, Valdes AM, Franks PW, Delahanty L, Dashti HS, Davies R, Hadjigeorgiou G, Wolf J, Chan AT, Spector TD, Berry SE. Glycaemic variability, assessed with continuous glucose monitors, is associated with diet, lifestyle and health in people without diabetes. *Research Square* [Preprint]. 2023 Oct 30:rs.3.rs-3469475. doi: 10.21203/rs.3.rs-3469475/v1. PMID: 37961419; PMCID: PMC10635370.

49. Casanueva, F.F., Moreno, B., Rodríguez-Azeredo, R., Massien, C., Conthe, P., Formiguera, X., Barrios, V. and Balkau, B. (2010), Relationship of abdominal obesity with cardiovascular disease, diabetes and hyperlipidaemia in Spain. *Clinical Endocrinology,* 73: 35-40]

50. Sawicki CM, Lichtenstein AH, Rogers GT, Jacques PF, Ma J, Saltzman E, McKeown NM. Comparison of Indices of Carbohydrate Quality and Food Sources of Dietary Fiber on Longitudinal Changes in Waist Circumference in the Framingham Offspring Cohort. *Nutrients*. 2021 Mar 19;13(3):997. doi: 10.3390/nu13030997. PMID: 33808767; PMCID: PMC8003409.

51. Kennedy T.E., Ohls J., Carlson S., Fleming K. The Healthy Eating Index: Design and applications. *Journal of the American Dietetic Association.* 1995;95:1103–1108. doi: 10.1016/S0002-8223(95)00300-2.

52. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. *Journal of Nutrition.* 2012;142(6): 1009–1018.

53. Esposito K, Maiorino MI, Ceriello A, Giugliano D. Prevention, and control of type 2 diabetes by Mediterranean diet: a systematic review. *Diabetes Research and Clinical Practice* 2010;89(2):97–102.

54. Oser, TK, Cucuzella M, Stasinopoulus M, Moncrief M, McCall A, Cox DJ, An Innovative, Paradigm-Shifting Lifestly Intervention to reduce Glucose Excursions With the Use of Continouse Glucose Monitoring to Educate, Motivate and Activate Adults with Newly Diagnosed Type 2 Diabetes: Pilot Feasibility Study 2022 Feb 23;7 *JMIR Diabetes*. 2022 Feb 23;7(1):e34465. doi: 10.2196/34465. PMID: 35050857; PMCID: PMC8908197.

55. Martín-Peláez S, Fito M, Castaner O. Mediterranean Diet Effects on Type 2 Diabetes Prevention, Disease Progression, and Related Mechanisms. A Review. *Nutrients*. 2020 Jul 27;12(8):2236. doi: 10.3390/nu12082236. PMID: 32726990; PMCID: PMC7468821.

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