

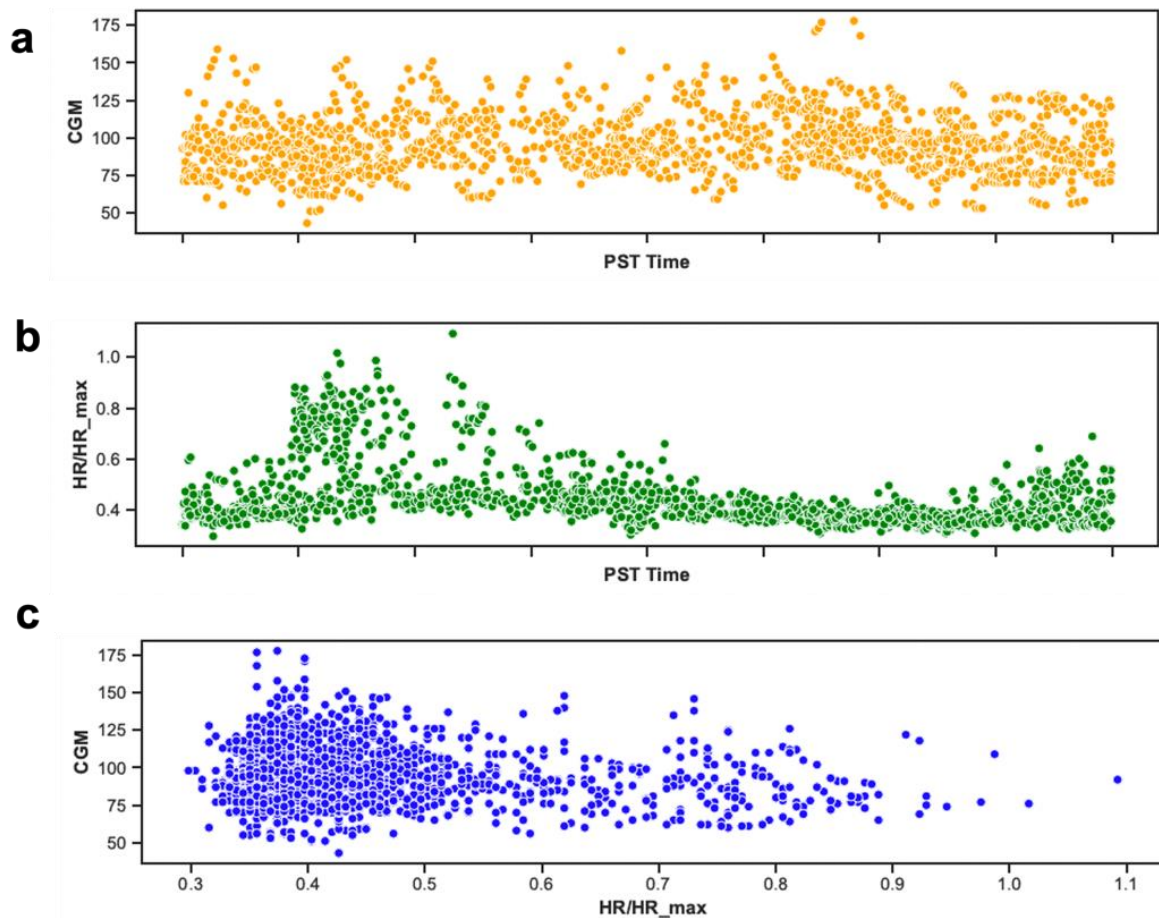
Supplementary Figure Legends

Supplementary Figure 1. Time series correlation analysis between heart rate and CGM

a, CGM time series for ID 43883-065 on 02-06-2020. This scatter plot showcases the temporal changes in CGM levels over a 24-hour period in Pacific Standard Time (PST).

b, HR/HRmax time series for ID 43883-065 on 02-06-2020. This scatter plot highlights the temporal changes in HR/HRmax over a 24-hour period in Pacific Standard Time (PST).

c, Correlation between HR/HRmax and CGM for ID 43883-065 on 02-06-2020. This scatter plot illustrates the correlation between HR/HRmax and CGM levels, revealing intriguing patterns.

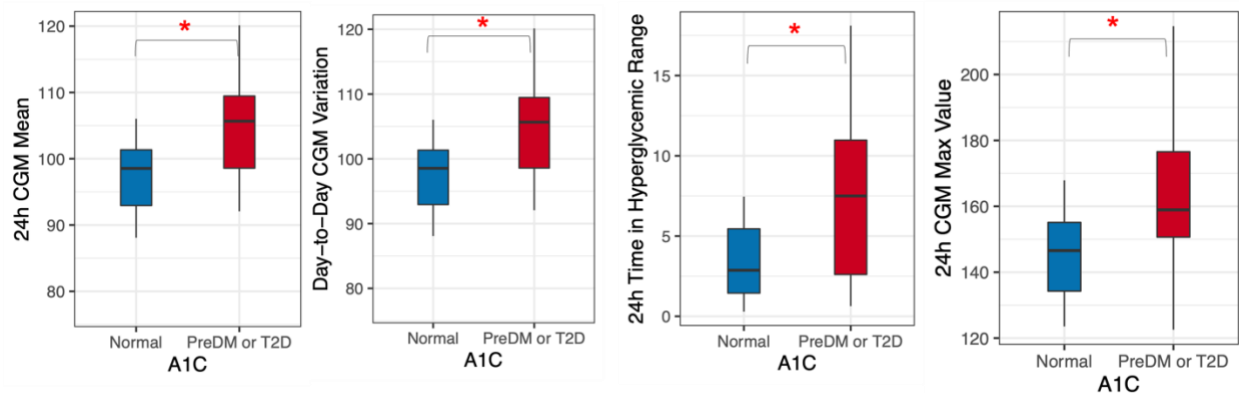


Supplementary Figure 2. CGM results of the study participants.

Box plots showing a difference in **a**, 24-hour CGM mean levels by glycemic status. **b**, day-to-day CGM variation by glycemic status. **c**, time spent in hyperglycemic range for 24 hours by glycemic status. **d**, 24-hour CGM max values by glycemic status.

Glycemic status was determined by HbA1c (normoglycemia when $\text{HbA1c} < 5.7\%$ ($\text{HbA1c} < 39$ mmol/mol), prediabetes when $5.7\% \leq \text{HbA1c} < 6.5\%$ ($39 \text{ mmol/mol} \leq \text{HbA1c} < 48 \text{ mmol/mol}$), and type 2 diabetes when $\text{HbA1c} \geq 6.5\%$ ($\text{HbA1c} \geq 48 \text{ mmol/mol}$). Glycemic status was denoted as normoglycemia (blue) and prediabetes or type 2 diabetes (red) groups. The central line inside the boxes represents the median, and the error bars indicate 1.5 times the IQR from the lower and upper quartiles. Hyperglycemic range for 24h was defined as >140 mg/dL and the time in target range for 24h was defined as 70-140 mg/dL. A two-sided Kruskal-Wallis test was used for differential analysis. One asterisk indicates $P < 0.05$.

A1C, HbA1c; CGM, continuous glucose monitoring; PreDM, prediabetes; type 2 diabetes, type 2 diabetes



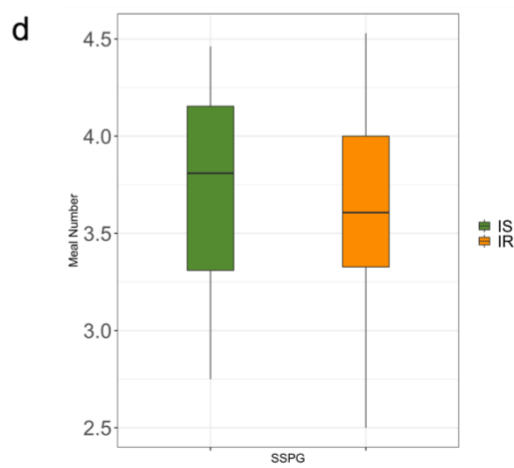
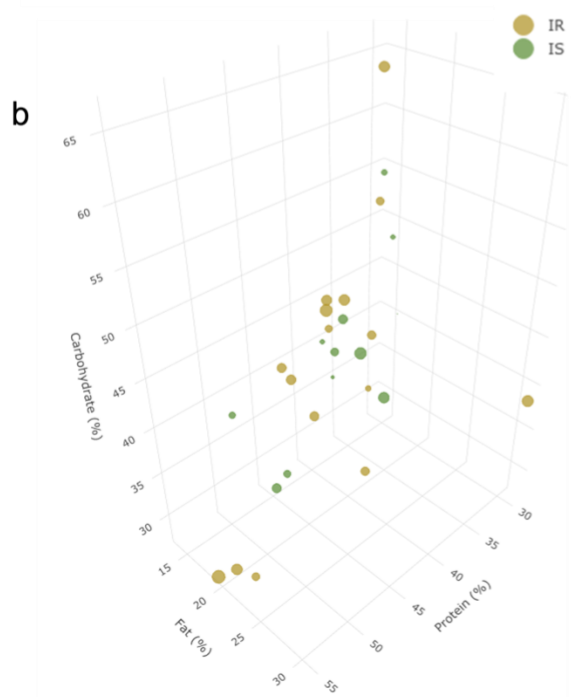
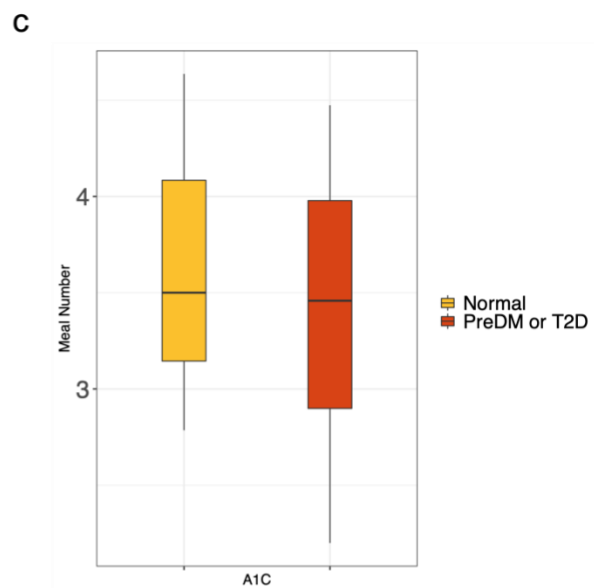
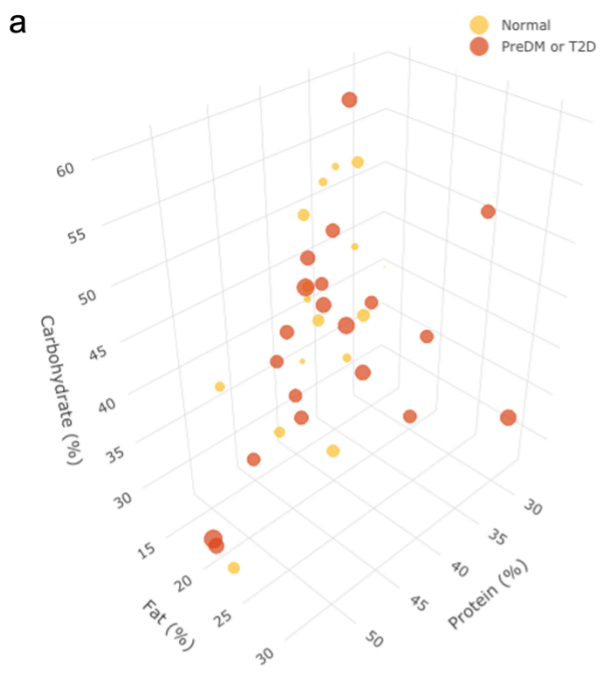
Supplementary Figure 3. Daily macronutrient composition and total daily meal numbers.

a, 3D scatter plot showing the distribution of each participant's macronutrient consumption: carbohydrate %, protein %, and fat % of the total daily caloric intake. A circle-shaped point indicates each participant. The color represents one's glycemic status: normoglycemia (yellow) or prediabetes/type 2 diabetes (red). Glycemic status was determined by HbA1c (normoglycemia when $\text{HbA1c} < 5.7\%$ ($\text{HbA1c} < 39 \text{ mmol/mol}$), prediabetes when $5.7\% \leq \text{HbA1c} < 6.5\%$ ($39 \text{ mmol/mol} \leq \text{HbA1c} < 48 \text{ mmol/mol}$), and type 2 diabetes when $\text{HbA1c} \geq 6.5\%$ ($\text{HbA1c} \geq 48 \text{ mmol/mol}$)).

b, 3D scatter plot showing the distribution of each participant's macronutrient consumption: carbohydrate %, protein %, and fat % of the total daily caloric intake. A circle-shaped point indicates each participant. The color represents muscle insulin sensitivity status (green for IS and orange for IR). Muscle insulin sensitivity was determined by SSPG levels (IS when SSPG $< 120 \text{ mg/dL}$, IR when SSPG $> 120 \text{ mg/dL}$).

c, Box plots showing differences in total daily meal numbers between normal and prediabetes/type 2 diabetes groups ($n = 36$ participants).

d, Box plots showing differences in total daily meal numbers between muscle insulin-sensitive and resistant groups ($n = 28$ participants).

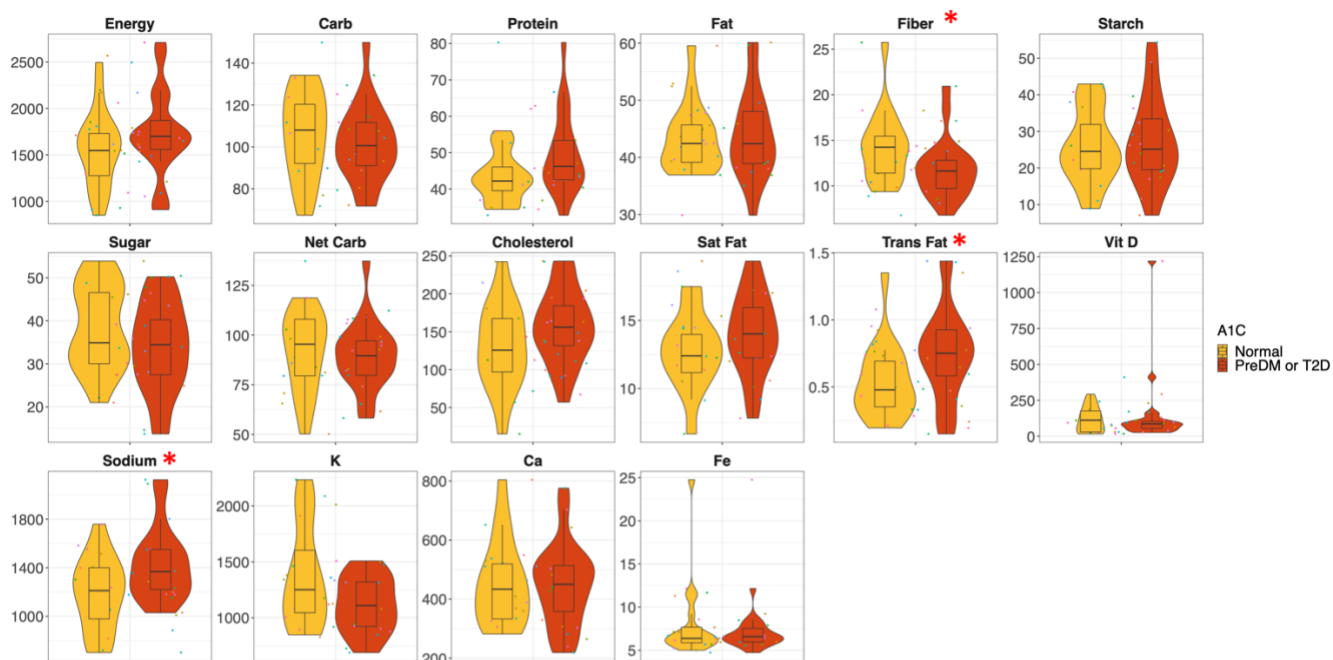


Supplementary Figure 4. Nutrient intake profiles of the study participants.

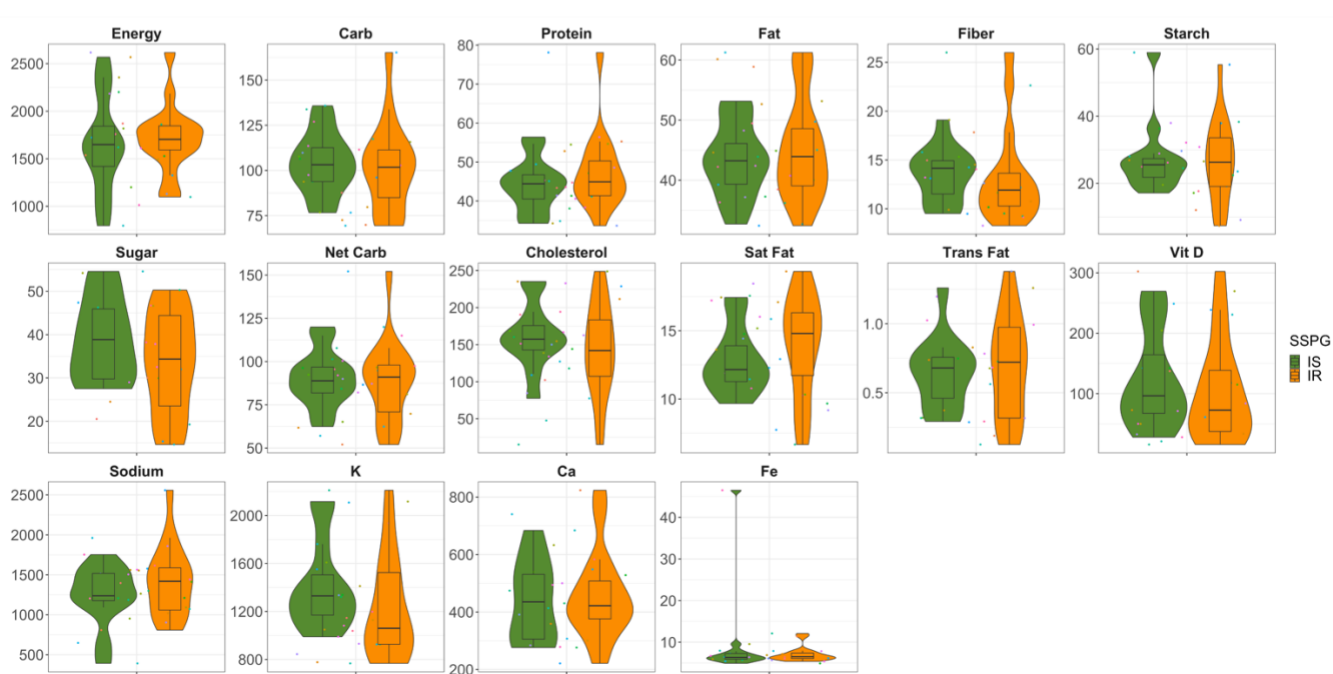
a, Violin plots showing nutrient features by glycemic status (normoglycemia yellow and prediabetes/type 2 diabetes red). The violin plots illustrate kernel probability density of the data at different values and the horizontal bar depicts the median of the distribution. A two-sided Kruskal-Wallis test was used for differential analysis. One asterisk indicates $P < 0.05$. Carb, carbohydrate; sugar, total sugar including added sugar; Sat Fat, saturated fat; K, potassium; Ca, calcium; Fe, iron intakes.

b, Violin plots showing nutrient features by muscle insulin sensitive status (IS green and IR orange). The violin plots illustrate kernel probability density of the data at different values and the horizontal bar depicts the median of the distribution. A two-sided Kruskal-Wallis test was used for differential analysis. No significant difference in nutrient intakes were detected between IS and IR groups. Carb, carbohydrate; sugar, total sugar including added sugar; Sat Fat, saturated fat; K, potassium; Ca, calcium; Fe, iron intakes.

a



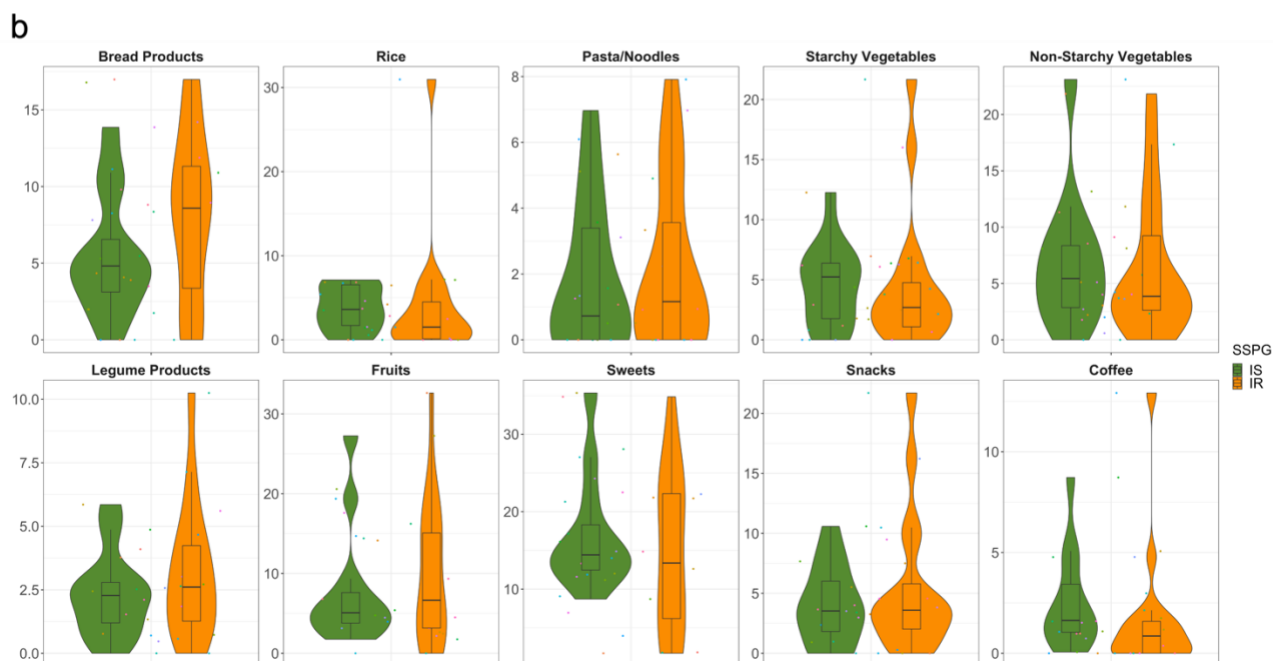
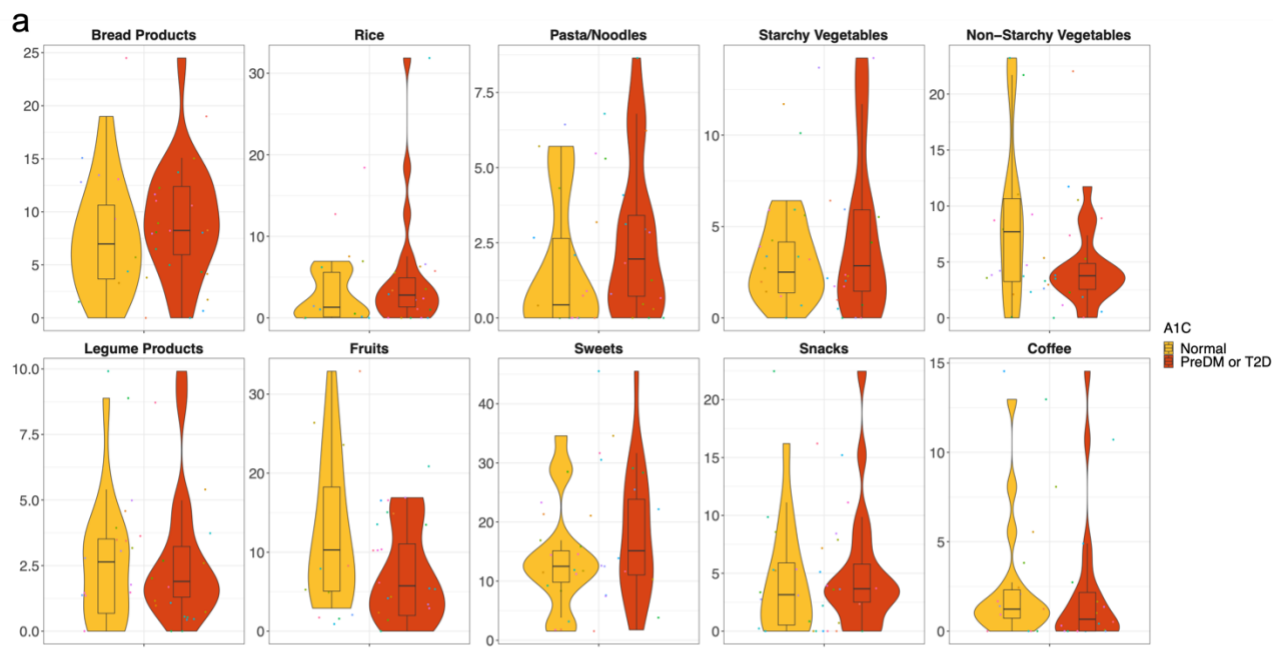
b



Supplementary Figure 5. Carbohydrate source food group intake profiles of the study participants.

a, Violin plots showing food group features by glycemic status (normoglycemia yellow and prediabetes/type 2 diabetes red). The violin plots illustrate kernel probability density of the data at different values and the horizontal bar depicts the median of the distribution. The proportion of daily carbohydrate intake of each food group out of the total daily carbohydrate intake from all food groups was calculated. A two-sided Kruskal-Wallis test was used for differential analysis. No significant difference in food group intakes were detected between normoglycemia and prediabetes/type 2 diabetes groups.

b, Violin plots showing food group features by muscle insulin sensitive status (IS green and IR orange). The violin plots illustrate kernel probability density of the data at different values and the horizontal bar depicts the median of the distribution. A two-sided Kruskal-Wallis test was used for differential analysis. No significant difference in food group intakes were detected between IS and IR groups.



Supplementary Figure 6. PCA based on nutrient features by metabolic characteristics.

a, PCA plot by nutrient features. A circle-shaped point indicates each participant. The color gradation represents one's HbA1c level ranging from low (yellow) to high (red). No clear separation of the cohort exists.

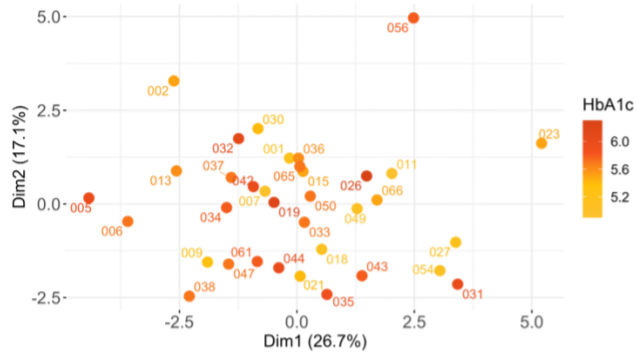
b, PCA plot by nutrient features. A point indicates each participant, and the different shapes and colors of the points represent muscle insulin sensitivity status (green circle for IS and orange triangle for IR). Muscle insulin sensitivity was determined by SSPG levels. No clear separation of the cohort exists.

c, PCA plot by nutrient features. A circle-shaped point indicates each participant. The color represents one's incretin effects ranging from low (yellow) to high (dark green). No clear separation of the cohort exists.

d, PCA plot by nutrient features. A point indicates each participant, and the different shapes and colors of the points represent beta cell function status (green triangle for normal, red circle for dysfunction). Beta cell function was determined by disposition index values (Method section for the detailed definition). No clear separation of the cohort exists.

e, Integrated lifestyle prediction model of metabolic subphenotypes (normoglycemia vs. PreDM/type 2 diabetes; full model with all coefficients).

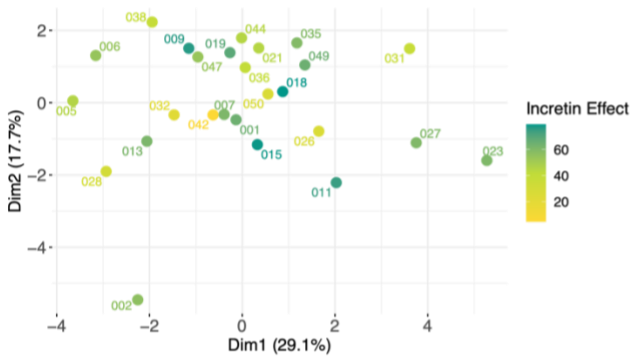
a PCA based on nutrient features colored by A1C



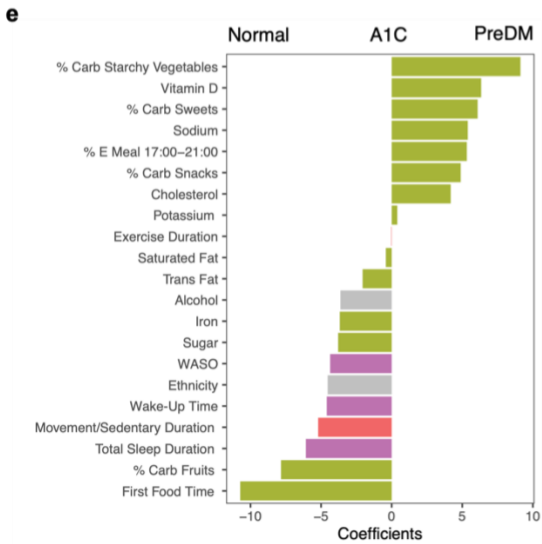
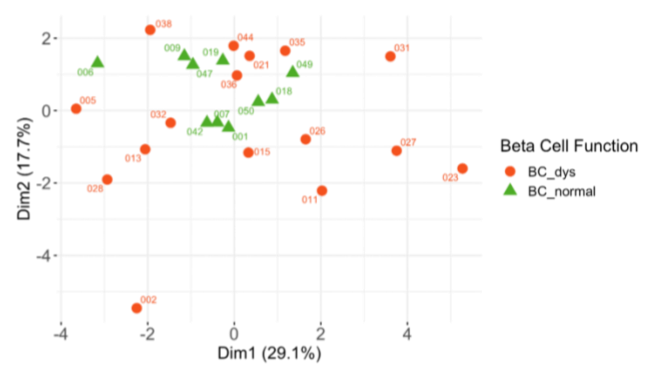
b PCA based on nutrient features colored by muscle IR



c PCA based on nutrient features colored by IE%



d PCA based on nutrient features colored by disposition index

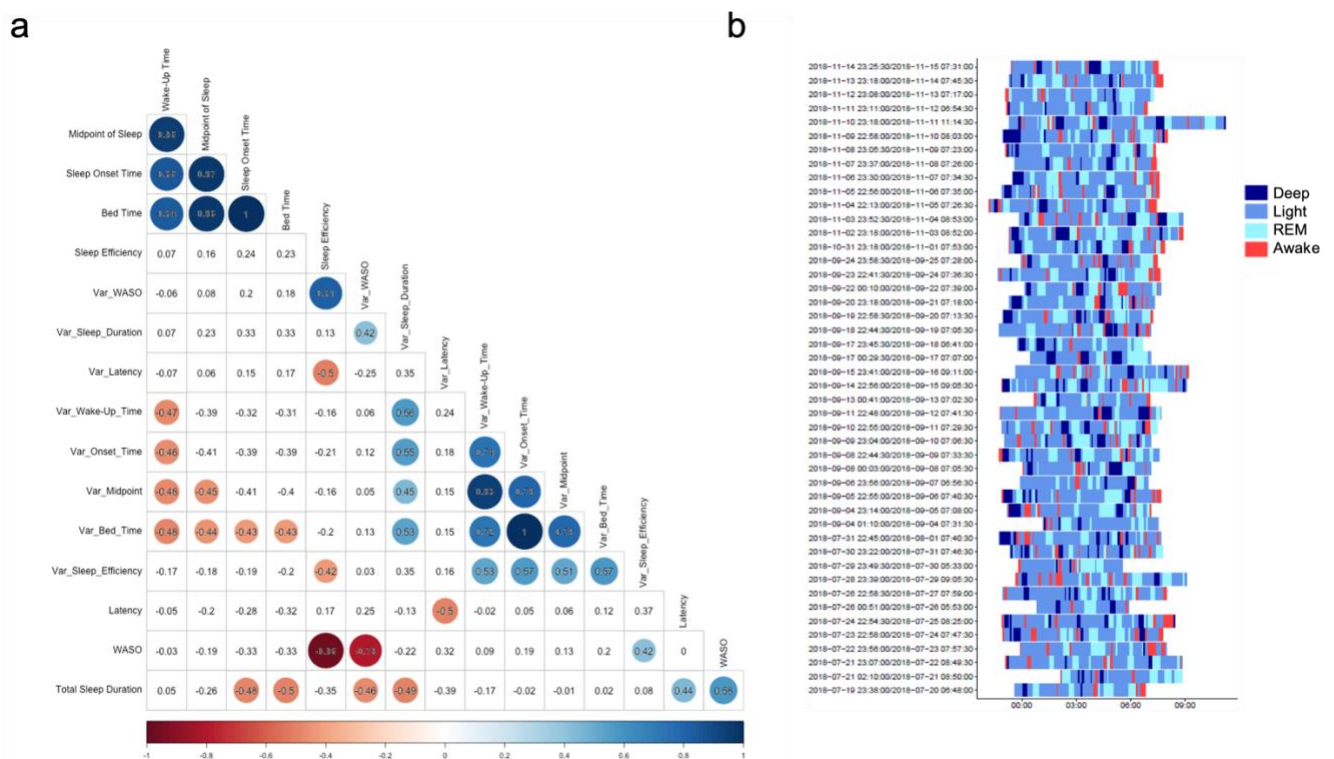


Supplementary Figure 7. Personal profiling of sleep habits

a, Correlation matrix of sleep features by Spearman correlation analysis. A cross mark in the box indicates non-significant, otherwise significant ($P < 0.05$). The color gradation represents correlation coefficients ranging from -1.0 (negative correlation) to 1.0 (positive correlation).

Sedentary duration is the duration of “0” step count per day (minutes), and movement duration is the duration of non-zero step count per day (minutes). Active duration is the hours per day for which step count > 250 .

b, Day-to-day sleep variations of an individual. Each row indicates different nights of wearable sleep records. Boxes with different colors indicate different sleep stages: Deep blue for deep stage, medium blue for light stage, light blue for REM stage, and red for awake. The length of each box corresponds to the amount of time spent in each stage of sleep.

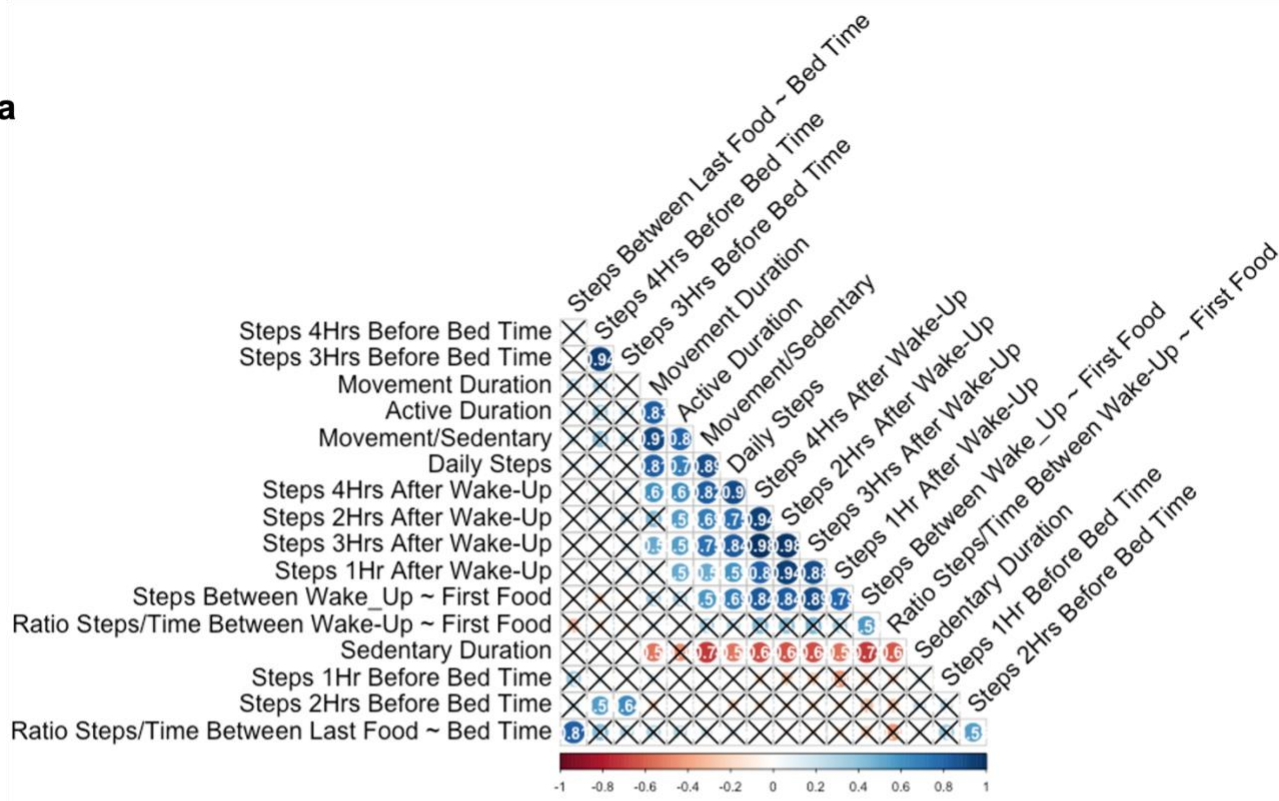


Supplementary Figure 8. Personal profiling of physical activity habits

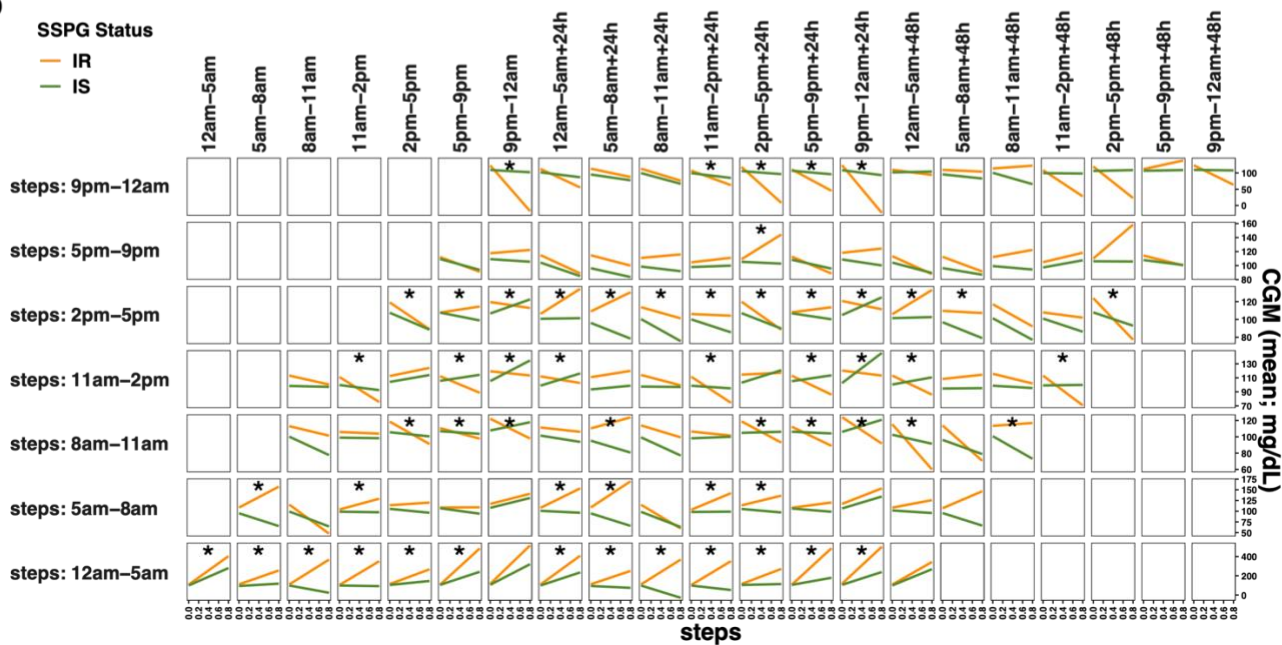
a, Correlation matrix of physical activity features by Spearman correlation analysis. A cross mark in the box indicates non-significant, otherwise significant ($P < 0.05$). The color gradation represents correlation coefficients ranging from -1.0 (negative correlation) to 1.0 (positive correlation). Sedentary duration is defined as the duration of “0” step count per day (minutes), and movement duration is defined as the duration of non-zero step count per day (minutes). Active duration is defined as hours per day for which step count > 250 .

b, Interaction effects plot for step counts and SSPG status on CGM. Effects of step count and SSPG status on mean sensor-glucose values were assessed through linear models at each time window, permuted as in the Pearson correlation analysis. We split the time-series of step counts into 7-time windows of the day. The X-axis indicates the standardized step counts of a specific time window, and the Y-axis represents the corresponding sensor-glucose values up to the next 48 hours. The orange line represents IR, and the green line IS, where interaction effects were considered significant (asterisk) if multiple testing-adjusted q-value < 0.01 .

a



b

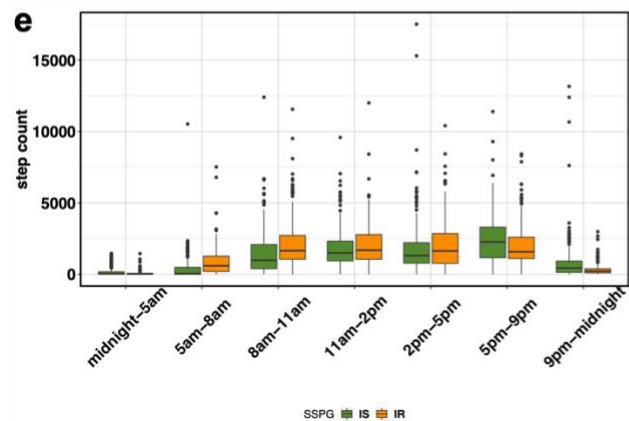
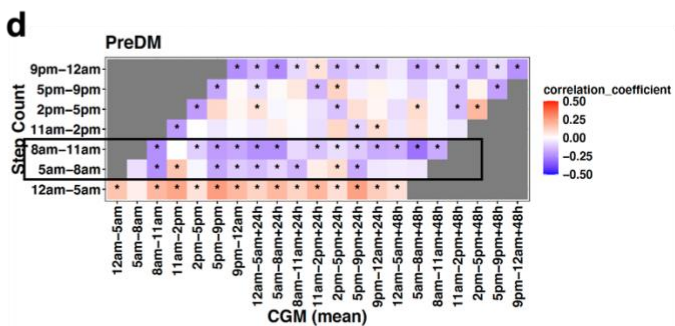
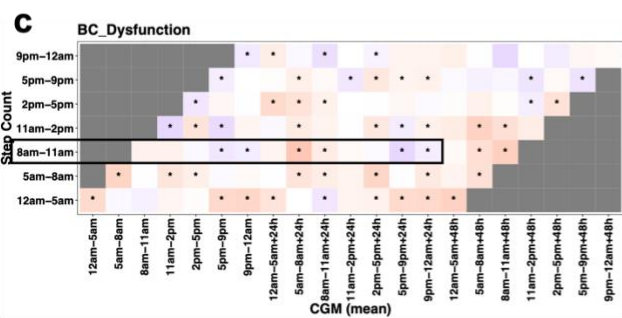
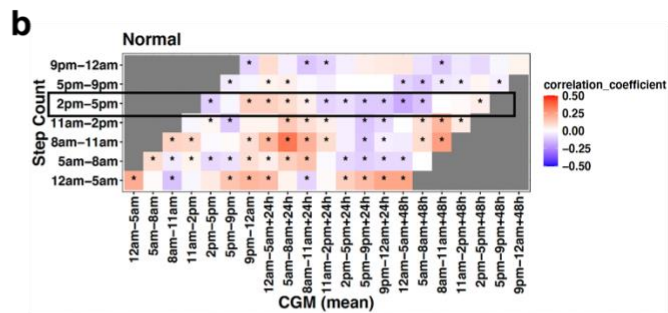
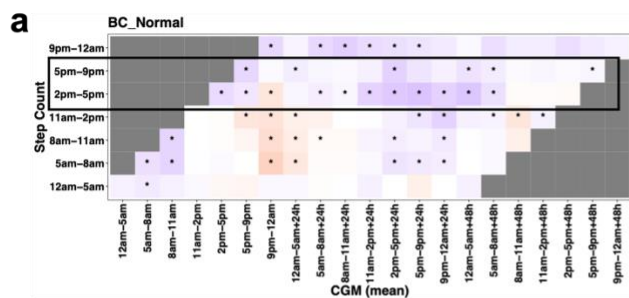


Supplementary Figure 9. Time series correlation analysis between step counts and CGM by metabolic characteristics

a, c, and e, Shifted correlation analysis plot between step count and CGM in different time windows of the day for beta cell normal (a), and dysfunction (c). We split the time-series of step counts into 7-time windows of the day, and correlations with CGM up to 48 hours were then calculated using Pearson correlation with permutation and considered significant (asterisk) if $q < 0.01$. The color gradation represents correlation coefficients ranging from -0.5 (negative correlation) to 0.5 (positive correlation). CGM, continuous glucose monitoring; BC, beta-cell.

b and d, Shifted correlation analysis plot between step count and CGM in different time windows of the day for normoglycemia (b) and prediabetes (d). We split the time-series of step counts into 7-time windows of the day, and correlations with CGM up to 48 hours were then calculated using Pearson correlation with permutation and considered significant (asterisk) if $q < 0.01$. The color gradation represents correlation coefficients ranging from -0.5 (negative correlation) to 0.5 (positive correlation). CGM, continuous glucose monitoring; PreDM, prediabetes.

e, Distribution of step counts for muscle insulin sensitive (IS) and insulin resistant (IR) subgroups in 7 time-windows of the day.



Supplementary Table 1. Baseline demographics and clinical lab results of the Validation cohort

	Main cohort (n = 36)	Validation Cohort (n = 10)	P-value
Demographics			
Age, y	56.2 ± 11.4	51.9 ± 11.0	0.544
Sex, n (M / F)	17 / 19	4 / 6	1.00
BMI, kg/m ²	26.0 ± 3.38	23.9 ± 4.33	0.196
Ethnicity, n (Caucasian / Asian)			
	23 / 10	9 / 1	1.00
Medication Statin Use, n (Yes / No)			
	2 / 34	3 / 7	0.264
Smoking, n (Yes / No)			
	2 / 25	2 / 8	0.560
Exercise, min	159.2 ± 114	218 ± 138	1.00
Systolic Blood Pressure, mmHg	116 ± 10.6	119.8 ± 13.9	0.179
Diastolic Blood Pressure, mmHg	72.3 ± 8.39	72.0 ± 8.19	0.460
Clinical Labs			
HbA1c, %	5.64 ± 0.376	5.46 ± 0.435	0.203
Fasting Plasma Glucose, mg/dL	97.9 ± 12.9	89.9 ± 9.53	0.916
Triglyceride, mg/dL	93.2 ± 41.0	60.2 ± 21.8	0.225

Total Cholesterol, mg/dL	188 ± 35.8	166 ± 35.1	0.120
HDL, mg/dL	61.5 ± 19.5	63.8 ± 20.8	0.732
LDL, mg/dL	108 ± 28.7	90.2 ± 23.2	0.206
Non-HDL, mg/dL	126 ± 34.0	102 ± 21.4	0.187
Fasting Insulin, mmol/L	9.54 ± 6.93	6.08 ± 2.58	0.812
Creatinine, mg/dL	116 ± 69.6	106 ± 47.0	0.813
hs-CRP, mg/L	1.19 ± 1.62	1.80 ± 2.24	0.340
ALT/SGPT, U/L	27.3 ± 11.6	27.5 ± 17.7	0.711
Metabolic Test Results			
OGTT at 2 hours, mg/dL	132 ± 33.7	114 ± 35.7	0.815
SSPG, mg/dL	139 ± 74.6	73.4 ± 28.5	0.767
Disposition Index	1.56 ± 0.839	2.71 ± 1.59	0.473
Incretin Effects, %	51.7 ± 18.9	48.8 ± 22.3	0.102

Supplementary Table 2. Lifestyle Definition

Diet Parameters	Definition	
Energy	Energy	
Carb	Carbohydrate	
Pro	Protein	
Fat	Fat	
Fib	Fiber	
Sugar	Sugar	
Starch	Starch	
Net Carb	Net Carbohydrate	
Chol	Cholesterol	
Sat Fat	Saturated Fat	
Trans Fat	Trans Fat	
Sodium	Sodium	
MUFA	MUFA	
PUFA	PUFA	
W3	Omega-3 Fatty Acids	
W6	Omega-6 Fatty Acids	
Water	Water	
Caffeine	Caffeine	
Alcohol	Alcohol	
B1	Vitamin B1	
B2	Vitamin B2	
B3	Vitamin B3	
B5	Vitamin B5	
B6	Vitamin B6	
B12	Vitamin B12	
Folate	Folate	
Vit A	Vitamin A	
Vit C	Vitamin C	
Vit D	Vitamin D	
Vit E	Vitamin E	
Vit K	Vitamin K	
Ca	Calcium	
Cu	Copper	
Fe	Iron	
Mg	Magnesium	
Mn	Manganese	
Phos	Phosphorus	
K	Potassium	
Se	Selenium	
Zn	Zinc	
Cystine	Cystine	
Histidine	Histidine	
Isoleucine	Isoleucine	
Leucine	Leucine	
Lysine	Lysine	
Methionine	Methionine	
Phenylalanine	Phenylalanine	
Threonine	Threonine	
Tryptophan	Tryptophan	
Tyrosine	Tyrosine	
Valine	Valine	
Meal Num	Daily Total Meal Numbers	
%E Meal 5:00-8:00	(Energy from Meal 5:00-8:00/Daily Total Energy)*100	
%E Meal 8:00-11:00	(Energy from Meal 8:00-11:00/Daily Total Energy)*100	
%E Meal 11:00-14:00	(Energy from Meal 11:00-14:00/Daily Total Energy)*100	
%E Meal 14:00-17:00	(Energy from Meal 14:00-17:00/Daily Total Energy)*100	
%E Meal 17:00-21:00	(Energy from Meal 17:00-21:00/Daily Total Energy)*100	
%E Meal 21:00-5:00	(Energy from Meal 21:00-5:00/Daily Total Energy)*100	
% Carb Fruits	(Daily Carbohydrate from Fruits/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Rice	(Daily Carbohydrate from Rice/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Starchy Vegetables	(Daily Carbohydrate from Starchy Vegetables/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Pasta Noodles	(Daily Carbohydrate from Pasta and Noodles/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Non-Starchy Vegetables	(Daily Carbohydrate from Non-Starchy Vegetables/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Bread Products	(Daily Carbohydrate from Bread Products/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Coffee	(Daily Carbohydrate from Coffee/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Legume Products	(Daily Carbohydrate from Legume Products/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Sweets	(Daily Carbohydrate from Sweets/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted
% Carb Snacks	(Daily Carbohydrate from Snacks/Daily Total Carbohydrate from All Food Groups)*100	* Carbohydrate Amount is Energy-Adjusted

First Food Time	First Food Eating Time after Wake-Up
Last Food Time	Last Food Eating Time before Bed-Time
Daily Eating Window	Daily Eating Span
Fasting Window	Overnight Fasting Period
Last Food ~ Bed Time	Duration between Last Food Eating and Bed Time (Time from Last Food Eating to Bed Time)
Wake-Up Time ~ First Food	Duration between Wake-Up and First Food Eating Time (Time from Wake-Up to First Food Eating)

Physical Activity Parameters	Definition
Daily Step Numbers	Total Step Numbers per Day
Steps 1 Hr before Bed Time	Steps 1 hour before Bed Time
Steps 2 Hrs before Bed Time	Steps 2 hours before Bed Time
Steps 3 Hrs before Bed Time	Steps 3 hours before Bed Time
Steps 4 Hrs before Bed Time	Steps 4 hours before Bed Time
Steps 1 Hr after Wake-Up Time	Steps 1 hour after Wake-Up
Steps 2 Hrs after Wake-Up Time	Steps 2 hours after Wake-Up
Steps 3 Hrs after Wake-Up Time	Steps 3 hours after Wake-Up
Steps 4 Hrs after Wake-Up Time	Steps 4 hours after Wake-Up
Steps Last Food ~ Bed Time	Steps between Last Food Eating and Bed Time
Steps Wake-Up Time ~ First Food	Steps between Wake-Up and First Food Eating
Movement Duration	Duration of Non-Zero Step Count per Day (minutes)
Sedentary Duration	Duration of "0" Step Count per Day (minutes)
Active Duration	Hours per Day for Which Step Count is > 250
Steps between 5 AM – 8 AM	Steps between 5 AM – 8 AM
Steps between 8 AM – 11 AM	Steps between 8 AM – 11 AM
Steps between 11 AM – 2 PM	Steps between 11 AM – 2 PM
Steps between 2 PM – 5 PM	Steps between 2 PM – 5 PM
Steps between 5 PM – 9 PM	Steps between 5 PM – 9 PM
Steps between 9 PM – 12 AM	Steps between 9 PM – 12 AM
Steps between 12 AM – 5 AM	Steps between 12 AM – 5 AM
Steps/Duration Last Food~Bed Time	Ratio of Steps to Duration between Last Food Eating and Bed Time
Steps/Duration Wake-Up ~ First Food	Ratio of Steps to Duration between Wake-up and First Food Eating

Sleep Parameters	Definition
Latency	Time Spent to Accomplish the Transition from Full Wakefulness to Sleep
Total Sleep Duration	Actual Time Spent Asleep
WASO	Wake Up After Sleep Onset
Sleep Efficiency	(WASO/Total Sleep Duration)*100
Bed Time	Bed Time
Wake Time	Wake-Up Time
Onset Time	Sleep Onset Time
Midpoint of Sleep	Clock Time between Sleep Onset and Wake-Up Time

Supplementary Table 3. LASSO (Diet)

Metabolic Outcome	Diet Parameter	LASSO Coefficient	P Value
HbA1c	% Carb Starchy Vegetables	0.027	0.023
	% Carb Snacks	0.003	0.050
Fasting Plasma Glucose	% E Meal 14:00 - 17:00	-0.001	0.033
	% Carb Starchy Vegetables	0.087	0.005
	Midpoint of Eating Window	-0.002	0.031
OGTT at 2 Hours	Daily Eating Window	0.010	0.011
SSPG	% Carb Fruits	0.014	0.063
	% Carb Bread Products	0.029	0.048
Disposition Index	% E Meal 21:00 - 05:00	0.029	0.049
Incretin Effect	% E Meal 21:00 - 05:00	0.035	0.032
	Midpoint of Eating Window	0.010	0.049
Hepatic IR Index	Fiber	-0.034	0.110
	Starch	-0.372	0.049
	Iron	0.432	0.026
	% Carb Fruits	0.080	0.110
	% Carb Coffee	-0.010	0.174
	% Carb Bread Products	0.004	0.178
	% Carb Sweets	-0.281	0.027
	% Carb Snacks	-0.023	0.111
	Daily Eating Window	-0.172	0.054
	Last Food ~ Bed Time	-0.028	0.116
Adipose IR	% Fat	-0.011	0.065
	Meal Numbers	-0.201	0.032
	% E Meal 17:00 - 21:00	0.751	0.009
	% Carb Rice	0.031	0.034
	% Carb Coffee	-0.054	0.064
	% Carb Sweets	-0.122	0.023

CGM Outcome	Diet Parameter	LASSO Coefficient	P Value
24h Mean Glucose	% Carb Fruits	-0.013	0.027
	% Carb Starchy Vegetables	0.009	0.032
	% Carb Coffee	-0.011	0.033
	% Carb Snacks	0.008	0.034
24h Max Glucose	Cholesterol	-0.020	0.022
24h Time in Target Range	Energy	0.021	0.076
	Fiber	-0.007	0.107
	% Carb Rice	0.632	0.012
	% Carb Coffee	-0.394	0.002
	% Carb Bread Products	0.020	0.079
24h Time in Hyperglycemic Range	% Carb Snacks	0.016	0.005
24h Time in Hypoglycemic Range	% Carb Coffee	0.113	0.000
24h Glycemic Variability	Energy	-0.052	0.043
	Starch	0.071	0.047
	Vitamin D	0.004	0.122
	% Carb Rice	-0.688	0.003
Night-Time Mean Glucose	% E Meal 17:00 - 21:00	0.020	0.088
	% Carb Coffee	-0.041	0.070
	% Carb Snacks	0.314	0.009

Night-Time Max Glucose	Cholesterol	-0.022	0.071
	% Carb Sweets	-0.004	0.112
	% Carb Snacks	0.017	0.078
Night-Time Time in Target Range	Starch	0.304	0.032
	% E Meal 05:00 - 08:00	0.074	0.064
	% E Meal 17:00 - 21:00	-0.267	0.005
	% Carb Pasta Noodles	-0.242	0.046
	% Carb Non-Starchy Vegetables	0.084	0.121
	% Carb Sweets	0.122	0.059
	% Carb Snacks	-0.516	0.008
Night-Time Time in Hyperglycemic Range	% E Meal 17:00 - 21:00	0.290	0.011
	% Carb Snacks	0.430	0.003
	% Carb Coffee	0.011	0.001
Night-Time Time in Hypoglycemic Range	% Carb Coffee	0.011	0.001
Night-Time Glycemic Variability	% Carb Pasta Noodles	0.015	0.037
	% Carb Sweets	-0.003	0.065
Next Day Mean Glucose	Energy	-0.135	0.314
	Fiber	0.157	0.271
	% Fat	-0.007	0.076
	Calcium	-0.119	0.113
	% E Meal 05:00 - 08:00	-0.156	0.313
	% E Meal 17:00 - 21:00	0.232	0.078
	% Carb Non-Starchy Vegetables	-0.081	0.075
	% Carb Coffee	-0.387	0.014
	% Carb Legume Products	0.005	1.000
	% Carb Sweets	-0.189	0.170
	% Carb Snacks	0.470	0.012
	Last Food ~ Bed Time	-0.400	0.146
	Wake-Up Time ~ First Food	0.325	0.141
Next Day Max Glucose	Energy	-0.011	1.000
	% Carb	0.061	0.257
	% Fat	-0.317	0.082
	Vitamin D	0.137	0.128
	Calcium	-0.508	0.059
	Iron	-0.325	0.296
	% E Meal 8:00 - 11:00	-0.161	0.135
	% E Meal 17:00 - 21:00	0.280	0.080
	% Carb Rice	0.023	0.273
	% Carb Coffee	-0.057	0.129
	% Carb Snacks	0.586	0.082
	Daily Eating Window	0.038	0.175
	Wake-Up Time ~ First Food	0.229	0.128
Next Day Time in Target Range	% Carb Coffee	-0.008	0.022
Next Day Time in Hyperglycemic Range	% Carb Snacks	0.098	0.003
Next Day Time in Hypoglycemic Range	% Carb Coffee	0.220	0.000
Next Day Glycemic Variability	% Fat	-0.024	0.069

Supplementary Table 4. LASSO (Sleep)

Metabolic Outcome	Sleep Parameter	LASSO Coefficient	P Value
HbA1c	Wake Up Time	-0.021	0.050
Fasting Plasma Glucose	Wake Up Time	-0.194	0.046
OGTT at 2 Hours	Variability in WASO	0.025	0.128
SSPG	Wake Up Time	-0.033	0.077
Disposition Index	Wake Up Time	0.017	0.263
Incretin Effect	Wake Up Time	0.187	0.047
	Variability in Sleep Efficiency	-0.006	0.213
Hepatic IR Index	Latency	1.055	0.163
	Sleep Efficiency	0.161	0.433
	Bed Time	0.355	0.578
	Wake Up Time	0.652	0.641
	Variability in Latency	-1.100	0.619
	Variability in Sleep Efficiency	-1.065	0.333
	Variability in Bed Time	0.353	0.699
	Variability in Wake Up Time	0.187	0.571
Adipose IR	Latency	-0.030	0.115

CGM Outcome	Sleep Parameter	LASSO Coefficient	P Value
Night-Time Mean Glucose	Sleep Efficiency	-0.011	0.151
	Variability in Latency	0.702	0.022
	Variability in Sleep Efficiency	0.138	0.081
	Variability in Bed Time	0.053	0.116
Night-Time Max Glucose	Latency	0.314	0.277
	Sleep Efficiency	-0.074	0.177
	Bed Time	-0.150	0.266
	Wake Up Time	-0.077	0.602
	Variability in Latency	1.623	0.037
	Variability in WASO	-0.046	0.648
	Variability in Bed Time	0.134	0.107
	Variability in Wake Up Time	-0.256	0.377
Night-Time Time in Target Range	Variability in Latency	-0.054	0.124
Night-Time Time in Hyperglycemic Range	Variability in Latency	0.422	0.060
	Variability in Sleep Efficiency	0.085	0.120
Night-Time Time in Hypoglycemic Range	Variability in Bed Time	-0.053	0.012
Night-Time Glycemic Variability	Bed Time	-0.011	0.252
Next Day Mean Glucose	Variability in Sleep Efficiency	0.002	0.078
	Variability in Bed Time	0.002	0.081
Next Day Max Glucose	Variability in Bed Time	0.031	0.019
Next Day Time in Target Range	Latency	-0.004	0.132
	Variability in WASO	-0.016	0.079
Next Day Time in Hyperglycemic Range	Variability in Sleep Efficiency	0.033	0.042

Next Day Time in Hypoglycemic Range	Sleep Efficiency	0.032	0.083
	Variability in Bed Time	-0.015	0.098
Next Day Glycemic Variability	Latency	0.010	0.030

Supplementary Table 5. LASSO (Physical Activity)

Metabolic Outcome	Activity Parameter	LASSO Coefficient	P Value
HbA1c	Steps 2 Hours Before Bed Time	-0.203	0.025
	Steps/Duration Between Last Food and Bed Time	-0.338	0.024
	Movement Duration	0.068	0.216
Fasting Plasma Glucose	Steps/Duration Between Last Food and Bed Time	-0.018	0.104
OGTT at 2 Hours	Steps 2 Hours Before Bed Time	-0.280	0.055
	Steps/Duration Between Last Food and Bed Time	-0.287	0.069
SSPG	Steps/Duration Between Last Food and Bed Time	-0.042	0.136
Disposition Index	Steps 1 Hour Before Bed Time	-0.246	0.314
	Steps 2 Hours Before Bed Time	0.719	0.301
	Steps/Duration Between Last Food and Bed Time	-0.800	0.298
	Steps/Duration Between Wake-Up and First Food	0.011	0.497
	Steps 1 Hour After Wake-Up	0.076	0.472
	Sedentary Duration	-0.023	0.570
	Movement Duration	-0.544	0.102
Incretin Effect	Steps/Duration Between Wake-Up and First Food	0.016	0.322
Hepatic IR Index	Sedentary Duration	-0.009	0.082
Adipose IR	Steps/Duration Between Wake-Up and First Food	-0.023	0.386

CGM Outcome	Activity Parameter	LASSO Coefficient	P Value
24h Mean Glucose	Steps 1 Hour Before Bed Time	0.033	0.292
	Steps 2 Hours Before Bed Time	0.005	0.332
	Steps/Duration Between Wake-Up and First Food	0.044	0.301
24h Max Glucose	Steps 1 Hour After Wake-Up	-0.003	0.264
24h Time in Target Range	Steps/Duration Between Last Food and Bed Time	0.029	0.226
	Steps/Duration Between Wake-Up and First Food	0.038	0.220
24h Time in Hyperglycemic Range	Steps 2 Hours Before Bed Time	0.418	0.218
	Steps/Duration Between Last Food and Bed Time	-0.546	0.437
	Steps/Duration Between Wake-Up and First Food	0.652	0.749
	Steps 1 Hour After Wake-Up	-0.769	0.057
	Sedentary Duration	-0.030	0.783
	Movement Duration	0.126	0.627
24h Time in Hypoglycemic Range	Steps/Duration Between Last Food and Bed Time	-0.025	0.221
24h Glycemic Variability	Steps 1 Hour Before Bed Time	-0.863	0.802
	Steps 2 Hours Before Bed Time	0.723	0.291
	Steps/Duration Between Last Food and Bed Time	-1.033	0.489
	Steps/Duration Between Wake-Up and First Food	2.441	0.756
	Steps 1 Hour After Wake-Up	-2.240	0.143
	Sedentary Duration	-0.108	0.796
	Movement Duration	-0.341	0.121
Night-Time Mean Glucose	Steps 2 Hours Before Bed Time	0.007	0.251
Night-Time Max Glucose	Steps/Duration Between Last Food and Bed Time	-0.006	0.134
	Sedentary Duration	0.029	0.100
Night-Time Time in Target Range	Steps 1 Hour Before Bed Time	-0.040	0.685
	Steps 2 Hours Before Bed Time	-0.676	0.202
	Steps/Duration Between Last Food and Bed Time	1.384	0.010
	Steps/Duration Between Wake-Up and First Food	0.739	0.311
	Steps 1 Hour After Wake-Up	-0.218	0.763
	Sedentary Duration	-0.079	0.734
	Movement Duration	-0.475	0.522

Night-Time Time in Hyperglycemic Range	Steps 1 Hour Before Bed Time	0.063	0.409
	Steps 2 Hours Before Bed Time	0.395	0.229
	Steps/Duration Between Last Food and Bed Time	-0.646	0.127
Night-Time Time in Hypoglycemic Range	Steps 1 Hour Before Bed Time	-0.040	0.097
Night-Time Glycemic Variability	Steps 1 Hour Before Bed Time	-0.061	0.238
	Steps 2 Hours Before Bed Time	-0.011	0.354
	Steps/Duration Between Last Food and Bed Time	-0.300	0.109
	Sedentary Duration	0.315	0.085
Next Day Mean Glucose	Steps/Duration Between Last Food and Bed Time	-0.013	0.350
Next Day Max Glucose	Sedentary Duration	0.032	0.129
Next Day Time in Target Range	Steps 1 Hour Before Bed Time	-0.026	0.240
	Sedentary Duration	-0.217	0.037
Next Day Time in Hyperglycemic Range	Steps 1 Hour Before Bed Time	0.252	0.145
	Sedentary Duration	0.136	0.208
Next Day Time in Hypoglycemic Range	Sedentary Duration	0.031	0.147
Next Day Glycemic Variability	Sedentary Duration	0.072	0.094

Supplementary Table 6. Differences of Step Count Distribution between 7 Time Windows of the Day by Wilcoxon Test

IR	5 AM - 8 AM	8 AM - 11 AM	11 AM - 2 PM	2 PM - 5 PM	5 PM - 9 PM	9 PM - 12 AM
12 AM - 5 AM	1.12E-34	5.82E-56	3.12E-51	9.70E-48	6.22E-49	9.27E-29
5 AM - 8 AM		2.55E-20	1.55E-18	6.24E-14	2.83E-17	1.07E-09
8 AM - 11 AM			0.988	0.314	0.727	1.47E-44
11 AM - 2 PM				0.422	0.667	1.97E-39
2 PM - 5 PM					0.659	3.95E-33
5 PM - 9 PM						9.94E-38

IS	5 AM - 8 AM	8 AM - 11 AM	11 AM - 2 PM	2 PM - 5 PM	5 PM - 9 PM	9 PM - 12 AM
12 AM - 5 AM	0.234	8.3E-54	5.1E-79	9.6E-76	7.5E-77	1.9E-39
5 AM - 8 AM		1.7E-36	6.8E-58	1.5E-53	3.0E-63	1.0E-20
8 AM - 11 AM			4.6E-07	1.9E-04	1.6E-15	1.8E-11
11 AM - 2 PM				0.105	2.7E-06	2.4E-37
2 PM - 5 PM					1.5E-08	2.4E-31
5 PM - 9 PM						4.1E-43

Supplementary Table 7. Prediction Model Performance of Main and Validation Cohorts

Metabolic Classes	Lambda	Number of Selected Features	Main Cohort LASSO MSE	Main Cohort Baseline MSE	Validation Cohort LASSO MSE	Validation Cohort Baseline MSE
HbA1c (Normal/PreDM or T2D)	0.0091	21	0.19	0.44	0.40	0.50
Muscle Insulin Resistance (IS/IR)	0.1754	3	0.21	0.43	0.50	0.10
Beta-Cell Function (Normal/Dysfunction)	0.1308	5	0.23	0.38	0.20	0.00
Incretin Function (Normal/Dysfunction)	0.0954	8	0.15	0.42	0.20	0.50
Adipose Insulin Resistance (IS/IR)	0.0444	9	0.00	0.50	NaN	NaN
Hepatic Insulin Resistance (IS/IR)	0.0262	10	0.08	0.50	NaN	NaN

Misclassification Error, MSE
Least Absolute Shrinkage and Selection Operator, LASSO

Supplementary Table 8

Figures	Data Analysis and Key Findings	Interpretation
2b, 2d, 2f	- PCA analysis based on six meal timing features - Individuals with high A1C (red) vs. low A1C (yellow), normal incretin function (dark green) vs. dysfunction (yellow), and muscle insulin sensitivity (green) vs. muscle insulin resistance (orange) exhibit distinct clustering patterns.	- The PCA plot shows that individuals with lower A1C levels tend to cluster at the top left, while those with higher A1C levels are positioned at the bottom right, suggesting that eating timing behaviors differ systematically between these groups. - This visual distinction supports the idea that metabolic characteristics are associated with specific meal timing patterns.
2c, 2e, 2g	- Multiple linear regression analysis to quantify effect sizes while adjusting for potential covariates, including age, sex, BMI, and ethnicity - This analysis identified specific time intervals where differences in energy intake were significantly associated with metabolic susceptibility, including A1C levels, incretin function, and muscle insulin resistance.	- The MLR analysis highlights distinct associations between meal timing and metabolic characteristics. - Higher energy intake between 14:00-17:00 was associated with lower A1C levels in individuals with prediabetes compared to those with normal glucose levels. - In contrast, higher energy intake between 17:00-21:00 was associated with higher A1C levels in prediabetes. - These associations remained significant after adjusting for confounding factors, which reinforces the robustness of these findings from PCA.

Fig 3b	- Diet features only: Least absolute shrinkage and selection operator (LASSO) to select the most relevant dietary features associated with glucose outcomes (metabolic test metrics & CGM metrics). - Selected dietary features were then analyzed using multiple linear regression models, adjusting for covariates including age, sex, BMI, and ethnicity. - To account for multiple hypothesis testing across glucose outcomes, Benjamini-Hochberg (BH) adjusted p-values were used, with $P_{BH} < 0.1$ considered statistically significant.	- The LASSO + MLR analysis revealed significant associations between diet (both component and timing) and glucose outcomes (both metabolic test metrics and CGM metrics). - Higher energy intake from 14:00-17:00 was associated with lower fasting blood glucose levels, even after adjusting for covariates. - Higher energy intake from 17:00-21:00 was associated with more time spent in the night-time hyperglycemic range (>100 mg/dL). - The forest plot presents a concise summary of multiple regression models, where each horizontal panel corresponds to a specific glucose outcome. The plot displays point estimates (beta coefficients) along with confidence intervals, highlighting significant associations between dietary parameters and glucose outcomes.
Fig 4b	- Sleep features only: LASSO to select the most relevant sleep features associated with glucose outcomes (metabolic test metrics & CGM metrics). - Selected sleep features were then analyzed using multiple linear regression models, adjusting for covariates. - Significant sleep features ($P_{BH} < 0.1$) are presented in the Figure.	- The LASSO + MLR analysis revealed significant associations between sleep and glucose outcomes (both metabolic test metrics and CGM metrics). - Greater day-to-day variability in sleep efficiency was associated with higher nighttime mean glucose levels, more time spent in the nighttime hyperglycemic range (>100 mg/dL), and higher next-day mean glucose values. - The overall findings suggest that sleep stability may be an important factor in glucose regulation.
Fig 4c	- Physical activity features only: LASSO to select the most relevant activity features associated with glucose outcomes (metabolic test metrics & CGM metrics). - Selected activity features were then analyzed using multiple linear regression models, adjusting for covariates. - Significant activity features ($P_{BH} < 0.1$) are presented in the	- The LASSO + MLR analysis revealed significant associations between physical activity and CGM outcomes. - More steps 1- 2 hours before bed and prolonged sedentary time during the day were associated with increased hyperglycemia. In contrast, greater step density after the last meal was linked to reduced time in the nighttime hyperglycemic range.

	Figure.	
Fig 5a	- Interaction plots of step counts and SSPG status on CGM (steps and CGM features included) - Steps and CGM data were aggregated within multiple time-of-day windows, and then the impact of steps and SSPG status (IR vs IS) on glucose was measured via linear regression models at each time window. - Significant interactions (where multiple testing-adjusted q-value < 0.01) are shown in the Figure.	-The relationship between step counts and CGM values differ depending on time of day and SSPG status. -Significant interactions effects occurred predominantly in the windows where steps were aggregated between 2-5pm, 11am-2pm, 8am-11am, and 12am-5am .
Fig 5b	-Permuted Pearson correlations were used to assess the association between step count and mean CGM at different time windows. -These correlations were performed in the overall cohort (Figure 5d), and separated within the IS (Figure 5b) and IR (Figure 5c) groups, displayed with a heatmap denoting the correlation coefficient. -These shifted correlations were considered significant when multiple testing-adjusted q-value < 0.01, denoted by an asterisk in the Figure.	-In the IS group (but not the IR group), step counts from 2-5pm were primarily negatively associated with glucose levels within the next 48-hour window. -In the IR group (but not the IS group), step counts from 8-11am were primarily associated with lower glucose values the next day. -Activity timing is an important factor to consider for glucose regulation, with many effects depending on IR/IS status.
Fig 6a	- Permuted network analysis - To identify intercorrelations among the three lifestyles, we used Spearman correlation with permutation. All correlation analyses were adjusted for multiple testing (q value < 0.2). - All three lifestyle factors were	- Food groups: Higher rice intake was linked to lower sleep efficiency and longer sleep latency, while greater consumption of legumes and fruits was associated with longer total sleep duration and shorter latency. - Nutrients: Higher intakes of fiber and potassium correlated with longer sleep duration; saturated fat was linked to longer sedentary time, and vitamin D intake was associated with more active time.

	time-matched. - The color gradation represents correlation coefficients ranging from -1.0 to 1.0. Lifestyle features: light green (diet); purple (sleep); red (activity); dark green (combined features from diet and sleep); blue (combined features from diet, sleep, and activity).	- Meal timing: More energy consumed between 8-11 a.m. was linked to longer sleep duration, while delayed first meals and longer time from waking to eating were related to lower sleep efficiency and longer latency. - Overall, the data indicate a complex interplay among lifestyle behaviors, suggesting that even subtle variations in daily routines can meaningfully shape individual metabolic profiles.
Fig 6b, c, d, e, f, g, h	- Classification models were built combining demographic, diet, sleep, and activity features by Elastic Net with cross validation. - Important features, the hyperparameter lambda, and the models were selected through leave-one-out and misclassification errors. The plots show top 10 selected features for the models. - Different colors indicate different types of lifestyle features. light green (diet); purple (sleep); red (activity); dark green (combined features from diet and sleep) - Prediction accuracies were evaluated with the independent set. Comparison of accuracy for predicting incretin function in training main cohort and validation cohorts. The Y axis indicates classification accuracy (%).	- Integrated lifestyle prediction model of metabolic subphenotypes - The classifications are for Fig 6b. Normoglycemia vs. PreDM/type 2 diabetes; Fig 6c. Incretin Normal vs. Dysfunction; Fig 6d. beta-cell Normal vs. Dysfunction; Fig 6e. Muscle IR vs. IS; Fig 6f. Adipose IS vs IR; and Fig 6g. Hepatic IR vs. IS. - Prediction accuracies confirm that the selected features through our prediction models effectively captured the relevant links between lifestyle factors and metabolic subphenotypes, and were not simply a result of overfitting. - Overall, different combinations of lifestyle features are associated with distinct metabolic subphenotypes, highlighting a need for personalized strategies to prevent T2D development.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (Page 2) (b) Provide in the abstract an informative and balanced summary of what was done and what was found (Page 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 3)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 4)
Methods		
Study design	4	Present key elements of study design early in the paper (Pages 4, 5, 16, 17)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Pages 4, 5, 16, 17)
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Pages 4, 16) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (N/A) <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (N/A) (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed (N/A) <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case (N/A)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Pages 17-22)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Pages 20-22)
Bias	9	Describe any efforts to address potential sources of bias (Pages 20-22)
Study size	10	Explain how the study size was arrived at (Page 17)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Pages 17-22)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (Pages 20-21) (b) Describe any methods used to examine subgroups and interactions (Pages 22) (c) Explain how missing data were addressed (Page 21) (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed (N/A) <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed (N/A) <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (N/A) (e) Describe any sensitivity analyses (N/A)

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Pages 4, 5, 16, 17) (b) Give reasons for non-participation at each stage (N/A) (c) Consider use of a flow diagram (N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Pages 4, 16) (b) Indicate number of participants with missing data for each variable of interest (Pages 21) (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) (Page 16-18)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time (Pages 17-22) <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure (N/A) <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures (N/A)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Pages 4-11) (b) Report category boundaries when continuous variables were categorized (Pages 6-9) (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Pages 4-11)
Discussion		
Key results	18	Summarise key results with reference to study objectives (Pages 12)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Pages 15,16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Pages 12-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page 16)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 23)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Title : Precision Diets for Diabetes Prevention
Approval Period: 11/30/2023 - 10/09/2024

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Title : Precision Diets for Diabetes Prevention

Approval Period: 11/30/2023 - 10/09/2024

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Title : Precision Diets for Diabetes Prevention

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Title : Precision Diets for Diabetes Prevention

Approval Period: 11/30/2023 - 10/09/2024

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CITI Training current				Y
Name Mahasish Shome		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc. Post-Doc
Department Genetics	5120	Phone		E-mail mshome@stanford.edu
CITI Training current				Y

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Name Nicole Turk		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc. Assistant Clinical Research Coordinator
Department Medicine - Med/Endocrinology	5103	Phone		E-mail nturk@stanford.edu
CITI Training current				Y

Name Gurmenjit Kaur Bahia		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc. Undergraduate
Department Biology	7260	Phone		E-mail gurmenb@stanford.edu
CITI Training current				Y

Name Yingzhou Lu		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc. Post-Doc
Department Pathology	5324	Phone		E-mail lyz66@stanford.edu
CITI Training current				Y

Participant Population(s) Checklist**Yes/No**

- Children (under 18) N
 - Pregnant Women and Fetuses N
 - Neonates (0 - 28 days) N
 - Abortuses N
 - Prisoners N
 - International Participants N
- Please enter the countries separated by comma
-
- Impaired Decision Making Capacity N
 - Cancer Subjects N
 - Laboratory Personnel N
 - Healthy Volunteers N
 - Students N
 - Employees N
 - Other (i.e., any population that is not specified above) Y

Study Location(s) Checklist**Yes/No**

- Stanford University Y

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- | | |
|---|---|
| • Clinical & Translational Research Unit (CTRU) | Y |
| • Stanford Medicine Health Care
Tri-Valley | Y |
| • Stanford Medicine Children's Health | |
| • VAPAHCS (Specify PI at VA) | |
| • Other (Click ADD to specify details) | |

General Checklist

1. Multi-site

Yes/No

- | | |
|--|---|
| • Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial) | N |
|--|---|

2. Collaborating Institution(s)

Yes/No

- | | |
|---|---|
| • Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions. | N |
|---|---|

3. Cancer Institute

Yes/No

- | | |
|---|---|
| • Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids with a scientific hypothesis stated in the protocol). | N |
|---|---|

4. Clinical Trials

Yes/No

- | | |
|--|---|
| • Investigational drugs, biologics, reagents, or chemicals? | N |
| • Commercially available drugs, reagents, or other chemicals administered to subjects that are being studied? | Y |
| • Investigational Medical Device / Commercial Medical Device used off-label or if being studied? | N |
| • IDE Exempt Device (Commercial Medical Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Medical Devices) | N |
| • Will this study be registered on clinicaltrials.gov? (See Stanford decision tree) | N |
| • Who will register for ClinicalTrials.gov?
NCT# | |

5. Tissues and Specimens

Yes/No

- | | |
|--|---|
| • Human blood, cells, tissues, or body fluids (tissues)? | Y |
|--|---|

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- Tissues to be stored for future research projects? Y
- Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see Material Transfer Agreements N

6. Biosafety (APB)

Yes/No

- Are you submitting a Human Gene Transfer investigation using a biological agent or recombinant DNA vector? If yes, please complete the Gene Transfer Protocol Application Supplemental Questions and upload in Attachments section. N
- Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies. N
- Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies. N

7. Human Embryos or Stem Cells

Yes/No

- Human Embryos or Gametes? N
- Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells) N

8. Veterans Affairs (VA)

Yes/No

- The research recruits participants at the Veterans Affairs Palo Alto Health Care System(VAPAHCS). N
- The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes. N
- The research is sponsored (i.e., funded) by VAPAHCS. N
- The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) in connection with her/his VAPAHCS responsibilities. N
- The research is conducted using any property or facility of VAPAHCS. N

9. Equipment

Yes/No

- Use of Patient related equipment? If Yes, equipment must meet the standards established by Biomedical Engineering (BME) (650-725-5000) N
- Medical equipment used for human patients/subjects also used on animals? N
- Radioisotopes/radiation-producing machines, even if standard of care? ; More Info N

10. Payment

Yes/No

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- Subjects will be paid/reimbursed for participation? See payment considerations. N

11. Funding**Yes/No**

- Training Grant? N
- Program Project Grant? N
- Federally Sponsored Project? N
- Industry Sponsored Clinical Trial? N

Funding

Funding - Grants/Contracts			
Funding Administered By :	STANFORD	SPO # (if available) :	112285
Grant # (if available) :	5RM1HG00773509	Funded By (include pending) :	National Institutes of Health
Principal Investigator :	Howard Chang		
Grant/Contract Title if different from Protocol Title :			
For Federal projects, are contents of this protocol consistent with the Federal proposal?			
Is this a Multiple Project Protocol (MPP)?			
Is this protocol under a MPP?			

Funding - Fellowships**Gift Funding****Dept. Funding****Department Name :** Genetics**Other Funding****Other Fund Name :** PHIND- Precision Health and Integrated Diagnostics Center**Other Fund Name :** Spectrum Pilot Grants**Resources :****a) Qualified staff.****Please state and justify the number and qualifications of your study staff.**

All participants of this study have extensive experience in Human Subject Research with expertise in integrated Personal Omics Profiling (iPOP).

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Dr. Michael Snyder, Principal Investigator, will coordinate the activities of group members and oversee the entire project. He has extensive experience overseeing large-scale production projects. These include the yeast knockout consortium, the Yale CEGS, a protein production project that led to a new Biotechnology company, etc. He has extensive experience working with patients samples for nucleic acid and protein analysis.

Dr. Tracey McLaughlin, Assistant Professor of Medicine, will be responsible for the clinical aspects of this study by sharing her expertise in endocrinology and metabolism, including diabetes.

Dalia Perelman is a dietitian and certified diabetes educator with many years of experience counseling people with different nutritional needs. She has much experience using continuous glucose monitors in patients.

Alessandra Celli is a CRCII with extended experience in clinical research coordination. Together with the other coordinators, Caroline Bejikian and Manjot Kaur, they will be responsible for participants enrollment, study visits schedule and diet cycle preparation.

Dalia Perelman is a study dietitian with extensive experience in nutritional and diabetes counseling.

b) Training.

Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.

All participating personnel have already taken required training (HIPAA, HealthStream and CITI, as well as mandatory laboratory trainings) supervised by Stanford University.

c) Facilities.

Provide the location(s) where the research will be conducted, including physical address if not conducted on site at Stanford University, Stanford Hospital on Pasteur Dr., Lucile Packard Children's Hospital on Welch Rd. or VAPAHCS. Describe the facilities and resources available to conduct the research at these sites.

Facilities:

Dr. Snyder's laboratory space occupies ~2000 sq ft of laboratory space in the third floor Alway wing of the Stanford School of Medicine as well as ~2000 sq ft at 1501 California Avenue. Dr. Snyder has an office at each site. The laboratory research will be conducted at the Alway site; the DNA sequencing will be performed at the California avenue site. These sites contain all of the necessary laboratory benches equipment for this project, including molecular building equipment, incubators and shakers for growing cells. They also have dishwashing, cold rooms, autoclaves, darkrooms and tissue culture rooms with incubators at each site and are available for the project.

The Genetics department has administrative support and facilities (e.g. copying), and the School of Medicine has a library. Stanford has supercomputer facilities in both the BioX building and Main Campus. A fully staffed mass spectrometer facility (which houses the mass spectrometer is located in the Chemistry department directly across the street from the Always site.

Stanford Clinical Translational Research Unit - CTRU, and laboratory are required for metabolic tests; we use the sterile hood, special iv tubing, special nurse protocols, beckman glucose analyzer for immediate glucose values, sample processing/labeling for storage, clinical data collection/filing. The CTRU nurses are highly skilled in assisting with the prctcol procedures, we would not be able to do our study testing anywhere else besides the CTRU.

d) Sufficient time.

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Explain the time that you and your research team will allocate to perform the research activities, including data analysis.

Our research group is very experienced in recruitment, plus we have a focused group to recruit from and 3 years will be sufficient to complete the study.

e) Access to target population.

Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.

We have access to a generally healthy volunteer population for this study through Stanford University and Stanford Hospital and Clinics.

f) Access to resources if needed as a consequence of the research.

State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.

There are no expected severe adverse consequences from this trial. If patients developed a side effect from one of the procedures or from the medications they will contact our research group and if it is not an emergency can be seen by one of the research group in the CTRU. Severe symptoms of any kind, related or unrelated, that present in our patients may necessitate referral to emergency room. Study physicians and NP are available to make determination if more comprehensive evaluation in the emergency room is necessary.

g) Lead Investigator or Coordinating Institution in Multi-site Study.

Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.

1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.

With this study we want to understand the physiological differences for people developing pre-diabetes and diabetes. We Hypothesize that different individuals go through different paths in the development of the disease. By understanding the personal mechanism for developing disease, we will find a personalized approach to prevent that development. We are also hoping to be able to find a biomarker that will pinpoint to the particular defect and thus, diagnose the problem at an earlier stage and have the information to give personalized diet recommendations to prevent the development of diabetes more effectively.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

With more than 1/3 of the US population developing prediabetes, it is imperative that we get a better understanding of the reasons why individuals develop this disorder. at present these individuals are lumped together as a single entity, but almost certainly they represent a mix of different gene-environment interactions that lead to one of four dominant physiologic mechanisms underlying their dysglycemia. 1- liver insulin resistance, 2- muscle insulin

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resistance, 3- impaired insulin secretion, 4- impaired incretin hormone secretion. Gaps that we are addressing here are extremely important – first, we will define a composite biomarker to identify different subphenotypes of prediabetes based on the four known physiologic mechanisms that contribute differentially in each individual to glucose elevations, which we hypothesize will also be reflected in their "glucotype". Importantly, because both continuous glucose monitor and administration of standardized meal testing and metabolic tests are not practical in the clinic, the development of a composite biomarker comprised of select multi-omics measures and clinical variables will enable clinicians and possibly patients (without clinician) to easily identify the specific diet that will yield optimal health results. What we learn from this study can be scaled to the entire worldwide population.

Also, sleeping patterns are very much involved with glucose regulation. To investigate so we will ask participants to complete the Alliance Sleep Questionnaire (ASQ) at baseline to figure out participants' sleeping patterns. After, we will ask to wear a portable polysomnography system for 1 or 2 nights to detect EEG (brain activity), EMG (muscle movement), EOG (eye movement), etc.

- c) **Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)**

We would like to understand the pathophysiology of insulin resistance in humans. In vitro or animal studies would not give us the answers we are seeking.

2. Study Procedures

- a) **Please SUMMARIZE the research procedures, screening through closeout, which the research participant will undergo. Sections in the protocol attached in section 16 can be referenced, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care. For research involving collaborators, please specify the respective roles of Stanford and each collaborator on the protocol.**

Screening:

We will review their medical history, have their height, and weight measured, and have their blood pressure and heart rate taken and a lab test to check their fasting glucose level. This visit will occur at Stanford University Medical Center in the Clinical Translational Research Unit CTRU. To allow for an easier flow, some participants will have the opportunity to choose to consent through our e-consent system on Redcap.

We will enroll 3 types of participants cohorts:

- people with pre-diabetes
- people with type 2 diabetes
- healthy control.

If they qualify, participants will be scheduled for the following procedures:

3 METABOLIC TESTS (all cohorts)

1) The Oral Glucose Tolerance Test. This test is approximately 3-4 hours in length. The subject drinks a standard amount of glucose (75gr) and blood sugars will be measured at 15,30,60,90,120,150,180 min after drinking the solution. Subjects will also be given 1 gram of acetaminophen to consume along with the

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glucose. The acetaminophen given at baseline is given as it is a surrogate and safe way of testing gastric emptying. Before the test, the subject will meet with the study dietitian who will show them how to use a continuous glucose monitor. The subjects will be advised to use this device for 7 to 10 days. During this time, the subject will be instructed to keep track of food eaten. The subject will wear the CGM while undergoing the OGTT + will be asked to repeat the test at home (drinking 75g of a solution of water and glucose as first thing in the morning and waiting for 2-3h before eating anything else). This at-home OGTT will be done twice (3 times if one of the first 2 times will not produce high enough quality data). Participants will then use the Dexcom continuous glucose monitor and will keep track of their foods using the "cronometer" app.

2) The Insulin Sensitivity Test (SSPG: Steady State Plasma Glucose): This test is approximately 6-7 hours in length. Participants will be asked to fast for 12 hours. The insulin sensitivity test is designed to measure how well your cells remove glucose from your blood in response to insulin. This test will involve the infusion of sugar (glucose), insulin, and octreotide by vein for three to four hours. During this test participants will have two small catheters (tubing) placed in their veins (I.V. lines). One of these will be used for blood drawing and the other for giving the infusion of glucose, insulin, and octreotide. Blood samples will be taken every 30 min until 90 min into the study, then every 10 min at 100, 110, and 120 min. The glucose infusion will then be changed and samples will be taken every 30 min until 210 min, then every 10 min at 220, 230, and 240 min. The total amount of blood that will be drawn during this test will be 140 mL of blood (approximately 9.5 tablespoons). Insulin is a natural hormone, and octreotide (a synthetic hormone) is a drug that temporarily blocks the secretion of insulin from your pancreas.

3) The Isoglycemic Intravenous Glucose Infusion (IIGI): This test will be approximately 4-5 hours in length. Participants will be asked to fast for 12 hours. This test is designed to measure the effect of glucose in the blood independent of the effect it has when ingested orally by way of the intestinal tract. Participants will have two catheters placed in their veins: one for a glucose infusion in one arm and the other for taking small blood measurements to adjust the glucose infusion. Small amounts of blood will be taken from that catheter during the testing to analyze for insulin and c-peptide measurement (product of insulin synthesis). The total amount of blood that will be drawn during this test will be 60 mL of blood (approximately 4 tablespoons).

The order of these tests will be determined by participants' preference and availability at the CTRU. Each test requires a separate visit, and they will have to be done 7 days or more apart from each other.

DIET CYCLES (for pre-diabetic and healthy controls, optional for the diabetic participants):

Diet cycle 1, 10 days.

During this first diet cycle, participants will be asked to follow their normal diet, plus consume the special meals described below.

In order to better compare individual responses to various different types of carbohydrates, we will provide them with 3-4 different foods or "meals" to consume at home. These will be different types of carbohydrates such as: rice, potatoes, and bread. Each portion will contain 50g of total carbohydrates. We will ask them to consume these special meals for breakfast.

Diet cycle 2, 10 days.

During the second diet cycle, participants will be provided additional portion of rice and asked to consume this 6 more times with provided supplemental fiber (two times), cream (two times), and egg whites (two times) to see if fiber, fat, and/or protein can attenuate the glucose response.

Right after the test meals, participants will be asked to not eat any food for 3h after the consumption of the provided meals for diet cycles 1 and 2. They will work with a dietitian who will help them follow these different diets.

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During the time participants are using the CGM monitor, we will ask them to keep detailed logs of their food intake, including the time they ate, and the portions of all food consumed using the "Cronometer" app. This is to help us link the food they've consumed with their corresponding glucose values on the monitor. We will send them a link to use the research food logging app and they will have an opportunity to consent to send us their food logs.

Glucose data will be analyzed to determine which foods caused a pronounced peak ("bad") versus those that did cause a high glucose response ("good").

Participants will be also asked to complete some questionnaires related to physical activity, stress (STRAIN questionnaire), and sleeping pattern (ASQ questionnaire).

Lastly, we will ask participants to collect blood microsampling during the 2 diet cycles. Specifically, we will provide them with 20 devices and ask them to use the kits during 4-time points:

- One time during cycle 1 (rice);
 - Three times during cycle 2 (rice+fiber, rice+fat, and rice+protein). For every time point, they will be asked to collect the samples 5 times: right before eating, 30 min, 1h, 2h, and 3h after finishing the provided meal. The total of microsampling collected is 20 (4 timepoints * 5 kits).
- To do so, they will be given a Tasso arm-prick microsample kit, containing all the supplies and instructions. They will return the collected samples to the research team by the end of the 2 cycles.

STUDY UPDATE AFTER COVID19 PANDEMIC:

Unfortunately, our study was heavily affected by the COVID19 Pandemic and the mandatory shelter in place (SIP), starting March 2020. We are now authorized to retrieve research activities at the CTRU. The the research team is facing 2 issues:

- 1- Funds are running low, and this study is very expensive
- 2- Some data collected from participants right before March 2020 can't be used anymore, as the metabolic profiles of our research participants are most likely not the same after 1 year of SIP and stressful events such as COVID19 pandemic.

Due to these factors, the research team decided to modify this protocol in the following way:

1- We want to repeat the OGTT test at the CTRU for participants who already completed it. Adding to that, we want to perform 2 OGTTs "at home", about 1 week apart. We will also have them wear the CGM Dexcom G6 during both OGTTs. Each time they will wear the CGM monitor for 10 days total. During each time, participants will be asked to complete a daily food log using the Cronometer app and might be asked to check their blood sugar with the glucose meter and fingerprick. That will allow the study team to interpret the CGM readings.

2- For participants who signed up right before March 2020, who could do no test or only part of them, we would like to just do a smaller version of the above protocol. We will STILL perform all metabolic tests. For those who have done 1 or 2 out of the 3 metabolic tests, we will repeat the test(s) that were already done again.

After the 3 metabolic tests will be completed, we will do the following:

- i- One visit at the CTRU for a blood draw, urine, stool, and swab collection.

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ii- Two diet cycles (instead of 3) while wearing the CGM G6 Dexcom monitor (10 days each time). For cycle 1 we will test 3-4 meals (instead of 7) and for cycle 2 we will test rice for everyone (instead of the worst carb as previously done). During each diet cycle, participants will be asked to complete a daily food log using the Cronometer app. That will allow the study team to interpret the CGM readings.

Participants will also be asked to complete the study-related surveys.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

All procedures have been performed before and those doing the procedures are highly skilled and safety measures are in place for all procedures. SSPG has no alternative besides euglycemic clamp, which is not less risky.

c) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).

No deception will be used.

d) State if photo, audio or video recording will occur. Describe what will become of the photos or recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.

No audio or video recording will occur.

e) Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).

There are no alternative treatments other than not participating in the study. The advantages to the subjects are that they will have the opportunity to see how their blood sugars vary through the day and how they react to different foods. They will learn what meals work best for them.

f) Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

During the course of the study they might learn of a personalized diet that works best for their health and they will be able to follow that if they choose. Participants with diabetes will know if the monitor is helpful for them to better control blood sugars and they can then discuss this option with their physicians.

g) Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?

The only treatments in this study are trying different diets to find the optimal one for each subject. The design of the study is to personalize the diets and we do not have one placebo and one treatment group- each person will be their own control.

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The study will not be terminated before the projected total participant population has been enrolled and completed the study.

3. Background

a) Describe past experimental and/or clinical findings leading to the formulation of the study.

Most studies measuring blood sugars continuously, have been done in people with diabetes. One of the few studies done on healthy individuals was led by Eran Segal and Eran Elinav of the Weizmann Institute of Science, where they studied 800 people in their responses to different meals. They found that individuals react differently to the same meals. They report that post prandial glucose responses (PPGR) were associated with several risk factors, including BMI, HbA1c%, and fasting glucose. They also found several associations between microbiome features and variability in PPGRs across people. In some cases, such as for Actinobacteria, Proteobacteria, and Enterobacteriaceae, the direction of their associations are consistent with previous associations reported between these taxa and higher-level phenotypes such as dietary habits, obesity and overall glycemic control. In our study, we want to look for patterns from glucose levels that are measured in a continuous fashion in order to predict long-term outcomes. We are looking specifically for insulin resistance role in the pathophysiology of this disorder and we are hoping we can develop clinical guidelines to diagnose individuals with higher risk at a much earlier stage.

b) Describe any animal experimentation and findings leading to the formulation of the study.

There have been some animal studies on glucose response to meals, but these don't translate well to human responses.

4. Radioisotopes or Radiation Machines

a) List all standard of care procedures using ionizing radiation (radiation dose received by a subject that is considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during the entire study. More Info

Identify Week/Month of study	Name of Exam	Identify if SOC or Research
------------------------------	--------------	-----------------------------

b) For research radioisotope projects, provide the following radiation-related information:

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Identify the radionuclide(s) and chemical form(s).

For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.

If not FDA approved provide dosimetry information and reference the source documents (package insert, MIRD calculation, peer reviewed literature).

- c) **For research radiation machine projects, provide the following diagnostic procedures:**

For well-established radiographic procedures describe the exam.

For the typical subject, identify the total number of times each will be performed on a single research subject.

For each radiographic procedure, provide the setup and technique sufficient to permit research subject dose modeling. The chief technologist can usually provide this information.

For radiographic procedures not well-established, provide FDA status of the machine, and information sufficient to permit research subject dose modeling.

- d) **For research radiation machine projects, provide the following therapeutic procedures:**

For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants' medical condition or whether it is being performed because the research participant is participating in this project.

For a therapeutic procedure that is not well-established, provide FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions.

5. Devices

- a) **Please list in the table below all Investigational Devices (including Commercial Devices used off-label) if they are being studied.**
- b) **Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) to be used on participants.**

6. Drugs, Reagents, or Chemicals and Devices

- a) **Please list in the table below all investigational drugs, reagents or chemicals if they are being studied.**
- b) **Please list in the table below all commercial drugs, reagents or chemicals if they are being studied.**

6.1 Drug Name : Ocreotide/Sandostatin

Source (i.e. Pharmacy, Sponsor, Pharmacy
etc.) :

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If not pre-mixed, where will the material be mixed and by whom:

Manufacturer : Novartis

IND# (if available) :

Dosage : 25 micrograms and 0.27 micrograms

Administration Route:

first dose is given over 5 minutes. Second is given over 3 hours by IV infusion.

IND Exemption

N Is this new and different uses of this commercially available drug, reagent or chemical?
Y Are all of these IND Statements true?

Revising the IND Regulations section for consistency with the 21 CFR 312.2(b).

The IND Regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product is exempt from the requirements for an IND if all of the following apply:

- The Drug used in the investigations is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of new indication for use nor intended to support any other significant change in the labeling for the drug.
- The investigation is not intended to support a significant change in the advertising of the product.
- The investigation does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50].
- The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7], e.g., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

6.2 Drug Name : regular insulin

**Source (i.e. Pharmacy, Sponsor, Pharmacy
etc.) :**

If not pre-mixed, where will the material be mixed and by whom:

Manufacturer : Elli Lilly

IND# (if available) :

Dosage : 6 mU/m2/min and 32 mU/m2/min

Administration Route:

Intravenous

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IND Exemption

N Is this new and different uses of this commercially available drug, reagent or chemical?
Y Are all of these IND Statements true?

Revising the IND Regulations section for consistency with the 21 CFR 312.2(b).

The IND Regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product is exempt from the requirements for an IND if all of the following apply:

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- The investigation is not intended to be reported to FDA as a well-controlled study in support of new indication for use nor intended to support any other significant change in the labeling for the drug.
- The investigation is not intended to support a significant change in the advertising of the product.
- The investigation does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50].
- The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7], e.g., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

6.3 Drug Name : acetaminophen

Source (i.e. Pharmacy, Sponsor, sponsor

etc.) :

If not pre-mixed, where will the material be mixed and by whom:

Manufacturer : McNeil Consumer Healthcare

IND# (if available) :

Dosage : 1000 mg

Administration Route:

oral

IND Exemption

Y Is this new and different uses of this commercially available drug, reagent or chemical?
Y Are all of these IND Statements true?

Revising the IND Regulations section for consistency with the 21 CFR 312.2(b).

The IND Regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product is exempt from the requirements for an IND if all of the following apply:

- The Drug used in the investigations is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of new indication for use nor intended to support any other significant change in the labeling for the drug.

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- The investigation is not intended to support a significant change in the advertising of the product.
- The investigation does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50].
- The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7], e.g., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

7. Medical Equipment for Human Subjects and Laboratory Animals

If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.

8. Participant Population

- a) **State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii) the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.**

i) we expect to enroll 130 participants:

- people with pre-diabetes 40
- people with type 2 diabetes 30
- healthy control 60

ii) no other sites, this study will be done at Stanford only

iii) we will accept individuals with normal blood sugars, prediabetes or diet-controlled type 2 diabetes. These can be students, staff, people from our community, or anyone willing to come to Stanford to do the study.

- b) **State the age range, gender, and ethnic background of the participant population being recruited.**

The participants must be 18 years of age or older. There is no limitation on gender, or ethnic background for the participant population being recruited.

- c) **State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

We will not enroll potentially vulnerable subjects in our study.

- d) **If women, minorities, non-English speaking individuals, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).**

We are not enrolling children as we expect this would put a high burden for any healthy child.

- e) **State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.**

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Any personnel or employee that qualifies for the study will be treated exactly the same as outside participants. They will receive the same consent to sign and given the same high quality care we will give all our subjects.

- f) State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

We are studying the response to different foods in people with the full range of glucose regulation: normal, prediabetes and diabetes. There is no greater than minimal risk for any volunteers due to the design of our study.

- g) Describe your plan to identify and recruit potential participants including who will inform them about the study and how they will be initially contacted by the researchers (e.g., Research Engagement services; chart review; treating physician; ads including social media posts). All final or revised recruitment materials must be approved by the IRB before use. Contacting potential participants is not permitted prior to IRB approval. See Recruitment Guidance for additional information.**

Recruitment methods include:

1- Advertise on social media platforms, such as Facebook, Instagram, Nextdoor, LinkedIn, etc. (please see section 16 for the attached script we will plan to post).

2- We may place flyers (attached in section 16) in public spaces with appropriate permission from the owner of the space, for example, a flyer in a hospital department or staff meeting room.

3- Primary care physicians, nurses, and other healthcare workers may, if they agree, tell patients/colleagues about this study.

4- Participants who enrolled in other studies in the Snyder's Lab and McLaughlin's Lab or other Stanford collaborating labs and consented to be contacted for future research opportunities.

5- We will use the Stanford Diabetes Research Center (SDRC) Registry as a method of recruitment. Flyer/email (attached in section 16) will be sent to people who have signed up through the SDRC website to be contacted for research studies relating to diabetes. The list of potential participants will be obtained directly from the SDRC.

6- Established research registries, email listservs, and newsletters with appropriate permission from the moderator of those registries/listservs/newsletters, including non-profit organizations that operate in the field.

7- Snowball recruitment through word of mouth (for example a study investigator may share the study or lab website with their friends, who may, in turn, choose to pass on that information to their family/friends).

- h) Inclusion and Exclusion Criteria.**

Identify inclusion criteria.

Persons eligible for this study must:

- Be 18 years of age or older;
- Not be pregnant, if female;
- Can be prediabetic or normal blood sugar control

For the Diabetic cohort (type 2), people will be eligible for the study if they are:

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- Between 30 and 69 yrs of age;
- Have diet-controlled type 2 diabetes defined as:
 - i) fasting blood glucose ≥ 126 -150 mg/dL or A1c $\geq 6.5\%$ or OGTT 2 hour glucose ≥ 200 mg/dL;
 - ii) Plasma or Finger-Stick Blood Glucose <150 mg/dl and A1c between 6.0% and 7.9% off antidiabetic medications
 - iii) Metformin-treated patients with A1c $<7.0\%$ may undergo a 2-week washout with permission from their physician and will be eligible if post-washout fasting plasma or FSBG glucose is <150 mg/dL. BMI 23-42 kg/m²

Identify exclusion criteria.

A person may not participate in this study if any of the following applies to him/her:
 They have major organ disease, hypertension defined as $>160/100$, pregnant/lactating, diabetogenic medications, malabsorptive disorders like celiac sprue, others, heavy alcohol use, use of weight loss medications or specific diets, weight change > 2 kg in the last three weeks, history of bariatric surgery. Any medical condition that physicians believe would interfere with study participation or evaluation of results.
 Mental incapacity and/or cognitive impairment on the part of the patient that would preclude adequate understanding of, or cooperation with, the study protocol.

For the diabetic cohort, the following exclusion criteria will apply:

- Active (symptomatic or uncontrolled) cardiovascular disease,
 - active cancer,
 - other major organ disease (liver, pulmonary, or kidney failure),
 - unstable body weight defined as self-reported weight change >2 kg over the past 6-8 weeks,
 - unstable hypertension (defined as BP $>160/100$ mm Hg),
 - hematocrit $< 33\%$,
 - use of medications known to alter blood glucose,
 - insulin sensitivity, or inflammation.
 - Pregnancy, lactation
 - prior bariatric surgery,
 - active eating disorder,
 - current substance abuse,
 - untreated psychiatric disease
- i) **Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).**
- Subjects will be contacted from our database of past participants who agreed to be contacted. If they agree to be screened for this study, we will use our screening protocol (protocol # 35935) to do a telephone screening call to review current medical history.
- j) **Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.**
- The study consent specifically asks the question - Are you participating in other studies and Yes or No has to be checked.
- k) **Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations**
- Participants will receive no payment.
- l) **Costs. Please explain any costs that will be charged to the participant.**

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Other than time to participate in the study and travel costs there are no direct study costs.

m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.

The total duration of this study will be 4 years.

The screening time for the participant will be up to 1 hour, active participation in the study for each participant will be 5-6 months.

Analysis of participant data will take approximately 12 months after the final subject completes the study.

9. Risks

- a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

i. The risks of the Investigational devices.

No investigational devices will be used.

ii. The risks of the Investigational drugs. Information about risks can often be found in the Investigator's brochure.

No investigational drugs will be used.

iii. The risks of the Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.

Potential risks to healthy volunteers:

Risks involving the insulin sensitivity test: Using glucose, insulin

Hypoglycemia- Blood sugars monitoring is done at regular intervals per the study and more frequently if needed. The procedure for monitoring blood sugars is described below.

Blood glucose levels are measured every 30 min for the first 2 & 1/2 hrs and more frequently if needed. In the last 1/2 hr they are measured every ten minutes.

The test will be terminated early if the blood glucose is < 60 mg/dL and or a patient becomes symptomatic with a glucose < then 70 mg/dL.

20% Dextrose will be administered at 75 ml/hr after completion of the test if the blood glucose is < 120 mg/dL and the participant will be served lunch immediately.

Blood glucose levels are checked 30 and 60 minutes upon completion of the meal and the level must be at or above 100 mg/dL before the individual can be discharged.

Participants also receive a snack to take home with them consisting of juice and graham crackers to be eaten several hours after the test with written instructions regarding signs and symptoms of hypoglycemia.

Octreotide -Transitory side effects can be- metallic taste and nausea (5-10% of our study population), rare side effect 5-10% or our study population- abdominal cramping and diarrhea after discharge. This is explained to participants during consenting and during the procedure.

Possible effects of the continuous glucose measurement CGM sensor include redness, bleeding, pain, tenderness, irritation, or inflammation at the

insertion site. There is also a possibility of infection at the insertion site. We will educate subjects on the early symptoms of infection and have them contact us if they see these.

Acetaminophen: besides possible sensitivity to the medication in general it is well tolerated.

Hepatic side effects including severe and sometimes fatal dose dependent hepatitis have been reported. In general occurs at doses of 4GM and chronic use. In this study the participants will receive 1GM once.

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Gastrointestinal side effects have included nausea (34%) and vomiting (15%).

Renal

Renal side effects are rare and have included acute renal failure, acute tubular necrosis, and interstitial nephritis.

Hypersensitivity side effects including anaphylaxis and fixed drug eruptions have been reported rarely in association with acetaminophen use.

Hematologic side effects including rare cases of thrombocytopenia associated with acetaminophen have been reported.

Dermatologic

Dermatologic side effects including erythematous skin rashes associated with acetaminophen have been reported, but are rare.

Respiratory

Respiratory side effects have included dyspnea and a case of acetaminophen-induced eosinophilic pneumonia.

Cardiovascular

Two cases hypotension have been reported following the administration of acetaminophen.

Cardiovascular side effects including hypertension and hypotension have been reported following the administration of acetaminophen.

Dr. McLaughlin's associates are present and monitoring the results along with with nursing staff of the CTRU. Participants are told they can call one of the associates if there is any problems when they are discharged.

iv. The risks of the Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

Risks from taking blood from the participants' arm is minimal, which may involve a little pain, a bruise or local infection at the site. There is no risk of taking nasal, tongue and skin swabs or for saliva, urine and stool collection, except of minor and temporary discomfort. Reversibility of potential risks of procedures to be performed does not apply for blood draws or saliva/urine/stool collections.

Risks of using continuous glucose monitor are minimal. Very few participants have reported slight redness and swelling. If this happens, participants might feel discomfort in the area the sensor is inserted.

Microsampling: risks of micro-sampling using the microlet lancet are minimal. There may be minor discomfort and slight redness or swelling at the site of lancing.

v. The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

N/A

vi. The risks of the Physical well-being.

Potential risk of procedures is minimal. Risks to physical well being would be discomfort during the insulin resistance test. The use of the continuous monitor might incur the discomfort of having the adhesive on the skin and carrying the monitor with them most of the time.

Microsampling may cause slight discomfort but are not harmful in nature.

vii. The risks of the Psychological well-being.

N/A

viii. The risks of the Economic well-being.

N/A

ix. The risks of the Social well-being.

N/A

Overall evaluation of Risk.

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Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

- b) If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Provide an explanation as to why the research must be completed at this location and complete the [LINKFORINTERNATIONALRESEARCHFORM] International Research Form. If not applicable, enter N/A.**

N/A

- c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.**

1. IVs are started by qualified nurses in the CTRU who have been doing this for over 10 years. This minimizes the risk of bruising or infection.
 2. For insulin, glucose levels are monitored throughout the study, guidelines for stopping are as follows:
 -for glucose readings in the 60s, if patients are symptomatic, the test is stopped
 -for glucose readings in the 50s, the test is automatically stopped
 -in both of these instances 20% dextrose is run at 75mL per hour and the patient is given food immediately
 -blood sugars are then checked at 30 and 60 min after completing their meal before patients are allowed to go home; blood sugars have to be minimally between 95 and 100 ml/dL before patient is discharged
 -patients are also given a snack
 3. There are no major side effects for octreotide. Participants are informed of minor side effects of abdominal cramping, nausea and diarrhea. They are consented before the study and before the test is administered.

These tests have been part of our research for well-over 20 years and we have had no adverse events.

All patient information is kept in books not shared with anyone else which is in a locked room. Some information may also reside on an encrypted computer. Everyone in the McLaughlin research group is HIPPA certified and follow confidentiality rules.

- d) Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.**

The study is of very short duration and it involves only monitoring with no intervention, thus we do not plan on terminating the study early.

- e) Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring.**

A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinical trials that involve interventions that have potential for greater than minimal risk to study participants also have a DSMB or DSMC.

The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data from all sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and the complexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safety officer, or by the Protocol Director (PD).

Describe the following:

- 1. What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?**

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Monitoring will include any expected side effects such as hypoglycemia resulting from SSPG or IVGTT tests. If these are of a serious nature (e.g. more than expected resulting in clinical deterioration or requiring medical assistance) they will be reported as adverse events, and then graded as to severity and likelihood of being related to study procedures/drug. Unexpected adverse events (eg. hospitalization or death) will be reported within 24 hours to the Stanford IRB.

2. Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).

The protocol director will fill this role. He is in close communication with the study physician, Dr. Tracey McLaughlin who oversees the clinical aspects of the study.

3. Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.

N/A

4. Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.

Any adverse event, death or hospitalization will be reported to the ME within 24 hours.

5. If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?

Dr. McLaughlin and associates meet weekly to review studies and study participants. Any issues of concern will be discussed at that time and can also be discussed at any time with Dr. Snyder.

6. Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See 2g'.

This is a short term study and unless something totally unexpected occurs, this study will not be terminated early. We do not anticipate any unusual events based on are previous experience and the short term nature of the study. If there is an unexpected adverse event, i.e. hospitalization or death we would re- evaluate regarding stopping the study early. Unintended identity leakage of the participants will lead to further investigation.

7. Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.

When a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem, the investigator will submit the adverse event(s) to the IRB with a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

8. Select One:

- Y The Protocol Director will be the only monitoring entity for this study.
This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

10. Benefits

- a) Describe the potential benefit(s) to be gained by the participants or by the acquisition of important

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knowledge which may benefit future participants, etc.

They will learn if they are insulin sensitive or insulin resistant, they will learn more about their risks for type 2 diabetes. If they have diabetes or prediabetes, they will learn about dietary measures to better control blood sugars. Participants will learn about their body's response to different meals and which (if any) would be healthier for them.

11. Privacy and Confidentiality

Privacy Protections

- a) **Describe the setting and method (e.g. crowded waiting room, patient exam room, telephone or email communication) in which interactions will occur and how the privacy interests of participants will be maintained. Note, high risk data such as PHI must be sent via "Secure:" email per Stanford policy.**

All procedures will be done in a private room with only the participant and the study administrators, physician and/or genetic counselors when explaining the study, obtaining consent, and administering questionnaires.

Confidentiality Protections

- b) **Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.**

We will be looking at the following categories of Health Information:

- A. Laboratory and Pathology Test Results with embedded identifiers
- B. Coded Diagnoses and Procedures
- C. Clinical Records with embedded identifiers
- D. Demographics with embedded identifiers
- E. Vital Status

We will be obtaining and using the following PHI:

- A. Laboratory and Pathology Test Results with embedded identifiers
- B. Clinical Records with embedded identifiers
- C. Demographics with embedded identifiers
 - 1. Names
 - 2. Telephone numbers
 - 3. Dates more precise than year only, e.g. date of birth or death, date of service, diagnosis, admission
 - 4. Electronic mail addresses
 - 5. Medical record numbers

The data will be secured by storing it on AMIE compliant desktop or laptop.

- c) **You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted.**

Stanford University IT approved platforms (<https://uit.stanford.edu/guide/riskclassifications>) should be used for data management. Consult with

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your Department IT representative for more information. For data security policies and links to encrypt your devices see <http://med.stanford.edu/irt/security> and [target=_blankhttp://www.stanford.edu/group/security/securecomputing/mobile_devices.html](http://www.stanford.edu/group/security/securecomputing/mobile_devices.html). Additionally, any PHI data on paper must be secured in a locked environment.

By checking this box, You affirm the aforementioned. Y

All records will be maintained electronically.

- PHI data will be stored as follows. (a) If the data is on devices such as laptop or desktop or drives, the device will follow Stanford School of Medicine protocols for computer security needed for PHI data. Only authorized researchers covered under IRB are allowed to store the data in this manner. (b) If PHI data is stored on a Stanford computational cluster, the cluster will be HIPAA compliant. PHI data access will be specific to authorized researchers covered under IRB. (c) If PHI data is stored in a Cloud environment, the Cloud provider will have a Business Associate Agreement (BAA) with Stanford that covers such data storage. PHI data access will be specific to authorized researchers covered under IRB.

- De-identified sequence data and other non-PHI data will be treated as confidential data and will be stored as specified above.

- d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.**

Tissue samples will be labeled with a letter and number code, date of test, and bar code and subject's initials. The reason subjects' initials remain is because there has been an error in the past in identifying samples.

- e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).**

All personnel involved in the study will have access to the collected and processed coded data. Only the Protocol Director and the key personnel will have access to the key to participant identification.

- f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.**

Tissue samples will be labeled with a letter and number code, date of test, and bar code and subject's initials. The reason subjects' initials remain is because there has been an error in the past in identifying samples (same as section D).

No one will have access to the code except key investigators.

- g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.**

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Data will be kept in encrypted files on secure computers. If we generate any paper documentation with PHI, these will be kept in a locked room which can be only accessed to study personnel. Only study personnel will have access to files.

- h) If sharing data with others, describe how data will be transferred or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, confirm a Stanford University IT approved platform will be used (see <https://uit.stanford.edu/guide/riskclassifications>) or that data will be encrypted while in transit. Additionally, confirm appropriate agreements are in place to allow for the sharing (see <https://ico.stanford.edu/stanford-researchers/who-will-handle-my-agreement>). If using or sharing PHI, refer to the following policies: <https://uit.stanford.edu/security/hipaa>**

No data with PHI will be shared with anyone outside of the study personnel.

- i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?**

Every staff is HIPPA certified and meets weekly. If there were confidentiality issues they would be discussed at this meeting.

12. Potential Conflict of Interest

Investigators are required to disclose any outside interests that reasonably appear to be related/li to this protocol.

Outside Interest Tasks

Investigators	Role	Potential COI?	Date Outside Interest Answered	Date OPACS Disclosure Submitted	COI Review Determination
Michael Snyder	PD	N	09/13/2023		N/A
Fahim Abbasi	OP	N	09/13/2023		N/A
Emmanuel Mignot	OP	N	09/15/2023		N/A
Sophia Miryam Schussler-Fiorenza Rose	OP	N	09/13/2023		N/A
Dr Tracey	OP	N	09/15/2023		

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Lynn McLaughlin					N/A
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13. Consent Background

13.1 Consent 43883 - Consent Form_Oct2023

Check if VA related

- a) Describe the informed consent process. Include the following.
- i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
 - ii) When and where will consent be obtained?
 - iii) How much time will be devoted to consent discussion?
 - iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
 - v) What steps are you taking to minimize the possibility of coercion and undue influence?
 - vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

no change We are now planning to use Adobe Sign as an alternative e-consent solution while COVID19 lockdown is reducing access on campus. The consent discussion will now be done via zoom instead of being in person at the CTRU (like it was before COVID), at the end of the orientation (which lasts always no less than 20-30min) participants will be sent the Redcap Link where he/she can e-sign the consent. Adobe Sign offers the e-form function, which will automatically prompt the participant to download and save/print the consent form with his/her own e-signature embedded in it. A stylus or finger-drawn signature will be obtained on the Adobe Sign consent form. The signed consent/assent forms will be printed, and that Adobe Sign will not be used for storage and document management. The document mirrors the approved consent form in section 13. Signature lines are included for the HIPAA Authorization and the main consent form. All participants are provided with a copy of the word doc before the orientation, where the HIPAA form is in the 14 font.

- b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter 12.2 for guidance.

no change

- c) What steps are you taking to determine that potential participants have the capacity to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

We do not plan to enroll participants who can't speak, read and write in English in this study.

13.2 Consent Consent Form_OGTT only_June 2022

Check if VA related

- a) Describe the informed consent process. Include the following.
- i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
 - ii) When and where will consent be obtained?
 - iii) How much time will be devoted to consent discussion?
 - iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
 - v) What steps are you taking to minimize the possibility of coercion and undue influence?
 - vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

i) ii) and iii) The research coordinator. We are now planning to use Adobe Sign as an alternative e-consent solution while COVID19 lockdown is reducing access on campus. The discussion of the consent will not change, but because it is now done via zoom instead of being in person at the CTRU (like it was before COVID), at the end of the orientation (which lasts always no less than 20-30min) participants will be sent

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the Adobe Sign link where he/she can e-sign the consent. The document mirrors the approved consent form in section 13. Signature lines are included for the HIPAA Authorization and the main consent form. All participants are provided with a copy of the word doc before the orientation, where the HIPAA form is in the 14 font. iv) yes v) Participants will be informed that participating in this extra portion of the study is completely volunteer and they can refuse to join. vi) N/A

- b) **What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter 12.2 for guidance.**

We are now planning to use RedCap as an alternative e-consent solution while COVID19 lockdown is reducing access on campus. Copy of the RedCap consent is attached on section 16. The discussion of the consent will not change, but because it is now done via zoom instead of being in person at the CTRU (like it was before COVID), at the end of the orientation (which lasts always no less than 20-30min) participants will be sent the Redcap Link where he/she can e-sign the consent. The document mirrors the approved consent form in section 13. Signature lines are included for the HIPAA Authorization and the main consent form. All participants are provided with a copy of the word doc before the orientation, where the HIPAA form is in the 14 font. We do not plan to enroll participants who can't understand, read and write in English.

- c) **What steps are you taking to determine that potential participants have the capacity to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.**

We are enrolling participants for this portion of the study who already consented, participated and completed the study less than a year ago.

14. Assent Background (less than 18 years of age)

15. HIPAA Background

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
Study Timeline	12/19/2017	daliap	
Ocreotide	01/09/2018	daliap	
regular insulin	01/09/2018	daliap	
email ad.1	03/05/2018	daliap	
Study Timeline.1	03/05/2018	daliap	
Physical Activity questionnaire	06/26/2018	daliap	
SSPG symptoms questionnaire	06/26/2018	daliap	
Study Timeline v.3	06/26/2018	daliap	
Acetaminophen	05/25/2019	daliap	
CGM study timeline	09/06/2019	celli	

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Flyer_Updated	09/10/2019	celli	
ASQ 3.0 2019-04-26 with instructions	02/06/2020	celli	
STRAIN questionnaire (1)	03/11/2020	celli	
STRAIN supplemental questionnaire #1 (1)	03/11/2020	celli	
STRAIN supplemental questionnaire #2 (1)	03/11/2020	celli	
Redcap_OGTT Only Consent Form June2021	06/30/2021	celli	
Dexcom G6 Pro instructions	10/12/2021	celli	
CGM participant presentation OGTT	10/12/2021	celli	
Redcap_Consent form Oct 2021	10/12/2021	celli	
CronometerBAA_2018-11-19	10/18/2021	celli	
CronometerDRA_229_report	10/18/2021	celli	
43883 Adobe Sign Message	11/16/2021	celli	
DEMOGRAPHICandMEDICALINFORMATI (1) (1)	01/20/2022	celli	
3. TASSO_Artwork	09/15/2022	celli	
Video instructions for participants (Tasso, Cronometer)	09/15/2022	celli	
Fitbit Versa 3_PDF Manual	09/15/2022	celli	
CGM participant presentation 2022	09/15/2022	celli	
Social Media Blurbs.	01/11/2023	celli	
MedTech Recruitment Flyer for Type 2 Diabetes	02/21/2023	ignacioj	

Obligations

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB
- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethical

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principles, regulations, policies and procedures

- Ensure all Stanford research personnel are adequately trained and supervised
- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made to re-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks to participants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk should be reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be written in language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

<https://stanfordmedicine.box.com/shared/static/qbsi8u8h47qsotxhdpuzz50xlrqa0sgo.pdf> Report promptly any new information, complaints, possibly serious and/or continuing noncompliance, or unanticipated problems involving risks to participants or others.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook,

<http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data>)

APPROVAL LETTER/NOTICE NOTE: List all items (verbatim) that you want to be included in your approval letter (e.g., Amendment date, Investigator's Brochure version, consent form(s) version(s), advertisement name, etc.) in the box below.

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD to certify that the PD has read and agrees to abide by the above obligations.