Protocols and Amendments as Submitted to the UCSF IRB

Original Study Protocol: Approved 7/25/2017

100 participants will be recruited from the Health eHeart Study cohort (CHR# 12-09993) by the Health eHeart Study team (refer to Section 10.6 for further information on the recruitment process). For the purposes of this study, participants will be asked to register for this study on the Eureka Research Platform (CHR# 16-19397) (refer to Section 10.8 for further information on the Eureka registration process and criteria). After registering and consent, the participants will be asked to answer a screening questionnaire to assess their eligibility to participate in the study.

Of the 100 total participants, 50 will be remote and 50 will be considered "local." These "local" individuals must live with 60 miles of UCSF and co-enroll in the Shape Up! Study (CHR# 15-18066). Shape Up! will be responsible for facilitating some of the in-person measurements. They must also be willing to visit the CTSI clinic at UCSF on four occasions for testing measurements. The purpose of the "local" group is to obtain more detailed measures that require a visit to the Shape Up! Lab for in-person measurements (see below).

Baseline Activities

During the baseline period, all 100 participants will be asked to fill out baseline questionnaires via the Eureka Research Platform from home. Participants will also be asked to connect a study-supplied iHealth Bluetooth scale, a MOCACARE Bluetooth blood pressure cuff, and a MOCACARE Bluetooth heart tracker (optional- hand held device that measures heart rate, blood oxygen, and pulse wave velocity with a quick scan of the thumb) to the study supported by the Eureka Research Platform. For local participants, connecting the devices will be facilitated in person by the study coordinator. For remote participants, detailed instructions will be provided to participants on how to connect the devices to the study. Additionally, a study coordinator will be available by phone or email to facilitate the remote connection of these devices. Local participants will also be supplied with a Breathometer device to measure breath acetone levels during the week leading up to the study. A study coordinator will assist the participant in connecting the device to their smartphone.

Remote Study Activities (for both Remote and Local groups)

Weight Measurements: Participants will be provided with an iHealth Bluetooth scale. Participants will measure their weight every morning after an overnight fast. Data will automatically be collected through the Eureka platform. Participants will receive daily reminders via the Eureka app.

Blood Pressure Measurements: Participants will be provided with a MOCAcare Bluetooth blood pressure cuff. Participants will be asked to measure their blood pressure at least twice per week at the same time they record their body weight. Text message reminders will be sent through the Eureka app.

Heart tracker activity (optional)- Participants will use the MOCACARE heart tracker device at the same time as blood pressure measurements are taken. Use of this device is optional and at the discretion of the participant. The heart tracker uses a quick scan of the thumb to measure heart rate, blood oxygen, and pulse wave velocity.

Daily Compliance question: Each day, participants will be directed to the Eureka app to answer one short question about compliance to their eating schedule that day.

Random 24-hour dietary recall: In order to assess caloric intake, we will have participants complete a random 24-hour dietary recall using the NCI ASA24. Subjects will have to report all caloric intake within the past 24 hours. The day of recall will be random, and each participant will complete the survey 3 times (once in every 4-week cycle)

Weekly Survey: Once per week, participants will complete a short survey through the Eureka app. This survey will only take a few minutes and will answer questions about the participants mood, energy level, and food cravings.

Monthly Sleep Questionnaire: To determine if eating habits affect sleep schedules, we will have each participant complete the Pittsburg Sleep Quality Index (PSQI) survey once per month of the study and also

at the beginning of the study to assess baseline sleeping habits (a total of 4 times). The survey should take no more than 10-15 minutes to complete.

Breath Acetone Measurements (Local participants only): Local participants will take daily breath acetone measurements for two weeks of the study. When participants visit the clinic 1 week prior to the diet start date, they will be given a Breathometer Breath Acetone device. The participants will be trained to properly use the device during this clinic visit. The device measures breath acetone levels simply by collecting a 10 second exhale of breath. Participants will measure their breath acetone level 3 times per day; 1) morning after an overnight fast 2) immediately before lunch 3) immediately after dinner. The device will be returned to the lab after one week. Participants will get the Breathometer device again on week 11 of the study when they visit the CTSI clinic. They will repeat the same measurement protocol as performed during week 1, and they will return the device to the lab at the completion of the study.

In-Person Study Activities (only for Local groups)

Local volunteers will undergo in-person body composition analyses, blood draws, muscle function testing, resting metabolic rate testing, and total energy expenditure testing. Please see the testing details (timelines, study activities, etc.) for the four visits for local participants below:

Note: The 3D-optical scans, DXA scans, muscle function tests, and blood draws are part of the Shape Up! Study and are covered under the Shape Up! protocol and informed consent.

Total Energy Expenditure (TEE) Measurements: To perform total energy expenditure measurements, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples. Participants will also collect urine/saliva samples after consuming the labelled water. One week later, participants will collect final urine samples for the total energy expenditure measurement. This procedure will require a total of 5 urine and saliva sample collections.

1. The first study visit will be one week prior to the study start. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the pre-intervention total energy expenditure (TEE) measurement.
2. One week later, at the start of the 12-week study, participants will return to the CTSI clinic for their second visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo extensive metabolic phenotyping (see below), which requires an overnight fast.
3. At the beginning of week 11 of the study, participants will return to the CTSI for their third clinic visit. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the post-intervention TEE measurement.
4. One week later and on the final day of the study (closeout), participants will return to the CTSI clinic for their fourth clinic visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo their second round of extensive metabolic phenotyping. The details of these procedures used for metabolic phenotyping are outlined below:

Resting Metabolic Rate (RMR) Measurements: To perform resting metabolic rate measurements, subjects will lay flat on gurney for up to 60 minutes. For 30 minutes, subjects will have their head under a clear plastic ventilated hood to collect oxygen and carbon dioxide levels.

The following measurements are all part of the Shape Up! Adults study:

DXA and 3D-optical scans: Participants will wear a consistent snug fitting-outfit for all DXA, and optical scans (shorts such as boxer briefs and sports bra for women only.) No shoes or socks will be worn during the measures. Hair will be held above the neckline when performing the optical scans. A swim cap, provided by the investigators, will be worn during some of the measures. The swim cap will be washed with soap and water and then sanitized using alcohol wipes between each use. The optical measures will involve multiple images of the whole body from different angles and positions and will take approximately 15 minutes. The subjects may stand against a green backdrop and/or on a rotating platform. For most of the images, they will stand with their backs straight, arms away from side and legs slightly apart. The researcher will then take optical images of the subjects from the front and side as well. The subjects will then be asked to reposition in order for more optical images to be taken for reproducibility assessment. The DXA scans

involve laying on the scanner for approximately 10 minutes and involves a very low amount of ionizing radiation. Total time for 3D-optical scans and DXA scans is approximately 30 minutes.

Muscle Function Tests: To perform the muscle function testing, participant will be seated in a chair to which her/his arm, feet or hip will be strapped. She/he will be asked to extend their leg or push and pull using their abdominal muscles at different speeds and/or various resistances. Participants will be encouraged to push and pull as hard and as fast as they can, and will feel local muscle fatigue, but no pain. This test takes approximately 20 minutes.

Blood Draw: Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Randomization and Interventions

All 100 participants, remote and local, will be randomized to one of the two study groups using a block randomization method. 50 participants will be randomized to the Time-Restricted Feeding (TRF) (treatment) group and 50 participants will be randomized to the Ad Libitum (control) group. Additionally, 25 of TRF group will be local participants and 25 of the control group will be local participants. The study interventions will last for a 12-week period.

Both cohorts will receive daily reminders of their assigned feeding times. Participants will also be reminded to measure their weight and blood pressure from home every morning using the study-supplied scale and blood pressure cuff. For participants who volunteer to use the Bluetooth heart tracker device, they will also take a measurement with that device. Additionally, participants may be asked to answer daily diet compliance questions, brief weekly surveys about their food cravings and mood, and a monthly questionnaire about sleep habits.

Time-Restricted Feeding (TRF) Group -- Treatment

The TRF group will be instructed to consume ad libitum from 12:00pm until 8:00pm every day and completely abstain from calorie consumption for the remainder of the day. Water, zero-calorie drinks, and coffee with calorie-free sweetener will be permitted during the fasting cycle. Using the Eureka mobile app, participants in this group will receive in-app messages notifying them when they should be abstaining and when they are able to eat. These messages are: "DO NOT eat between 8 pm tonight and 12 noon tomorrow" for the restricted time period (message to appear at 8 pm); "DO NOT eat until 12 noon today" (message appears at 8 am); "It is ok to eat now until 8 pm tonight" (message appears at 12 noon). They will also receive reminders to weigh themselves every Friday morning.

Ad Libitum Group -- Control

The control cohort will be instructed to eat three meals per day (6:00am-10:00am, 11:00am-3:00pm, 5:00pm-10:00pm). In order to control for the effect of messaging, this group will also receive three messages (as in-app messages) as part of the control group: "fruits and vegetables are healthy snacks" (message appears at 8 pm); "start your day with a healthy breakfast" (message appears at 8 am); "regular meals reduce snacking" (message appear at 12 noon).

Closeout

After the 12-weeks of intervention, participants will officially closeout of the study. All participants may be asked to fill out a series of questionnaires. Local participants will be asked to return to CTSI for their final in-person visit. The measurements are explained above (see In-Person Measurements section). Participants will be allowed to keep all study-supplied devices.

Inclusion Criteria

- Male or female ages 18-64
- BMI between 30 kg/m2 and 40 kg/m2
- Participants must regularly consume breakfast
- 50 participants will also be selected based on their location (live within 60 miles of UCSF)
- Must speak, read, comprehend English
- Access to reliable Internet and/or Wi-Fi
- Must have a valid email address and/or phone number

Exclusion Criteria

1. HIV or immunocompromised
2. Pregnancy, breastfeeding, or planned pregnancy in the next 6 months
3. Current diagnosis of type 1 or type 2 DM
4. Currently taking glucose-lowering drugs, statins, or oral steroids
5. History of gastric bypass surgery
6. Frequent travel across time zones or unusual work hours
7. Unable to fast for prolonged periods due to medical condition
8. Unable to stand for several minutes without aid
9. Cannot lie down on cushioned table for 30 minutes
10. No internal metal artifacts that would alter body composition (pacemakers, internal fixation, arthroplasty, etc.)
11. Unable to travel to UCSF Parnassus for in-person testing
12. Requires translator services

Note: Exclusion criteria 8-12 are for measurement purposes and only apply to local participants

Protocols and Amendments as Submitted to the UCSF IRB

Modification 1: approved 9/12/2017

We have updated our screening questionnaire, daily compliance survey and ICF. These documents will be attached to the modification.
The changes reflect updates to our inclusion/exclusion criteria. Additionally, we changed the study procedures so that participants will weigh themselves daily rather than weekly (using a home scale provided by the research team).

Additionally, we have added two cognitive tasks that will be completed by the local participants during their first and third study visits to the CTSI.

Lastly, we included in the protocol and ICF a modification to administer a bi-monthly dietary recall. This is a questionnaire from the NIH (called the ASA24) to record everything a person ate within the last 24 hours.

Study Protocol

100 participants will be recruited from the Health eHeart Study cohort (CHR# 12-09993) by the Health eHeart Study team (refer to Section 10.6 for further information on the recruitment process). For the purposes of this study, participants will be asked to register for this study on the Eureka Research Platform (CHR# 16-19397) (refer to Section 10.8 for further information on the Eureka registration process and criteria). After registering and consent, the participants will be asked to answer a screening questionnaire to assess their eligibility to participate in the study.

Of the 100 total participants, 50 will be remote and 50 will be considered "local." These "local" individuals must live with 60 miles of UCSF and co-enroll in the Shape Up! Study (CHR# 15-18066). Shape Up! will be responsible for facilitating some of the in-person measurements. They must also be willing to visit the CTSI clinic at UCSF on four occasions for testing measurements. The purpose of the "local" group is to obtain more detailed measures that require a visit to the Shape Up! Lab for in-person measurements (see below).

Baseline Activities

During the baseline period, all 100 participants will be asked to fill out baseline questionnaires via the Eureka Research Platform from home. Participants will also be asked to connect a study-supplied iHealth Bluetooth scale, a MOCACARE Bluetooth blood pressure cuff, and a MOCACARE Bluetooth heart tracker (optional- hand held device that measures heart rate, blood oxygen, and pulse wave velocity with a quick scan of the thumb) to the study supported by the Eureka Research Platform. For local participants, connecting the devices will be facilitated in person by the study coordinator. For remote participants, detailed instructions will be provided to participants on how to connect the devices to the study. Additionally, a study coordinator will be available by phone or email to facilitate the remote connection of these devices. Local participants will also be supplied with a Breathometer device to measure breath acetone levels during the week leading up to the study. A study coordinator will assist the participant in connecting the device to their smartphone.

Remote Study Activities (for both Remote and Local groups)

Weight Measurements: Participants will be provided with an iHealth Bluetooth scale. Participants will measure their weight every morning after an overnight fast. Data will automatically be collected through the Eureka platform. Participants will receive daily reminders via the Eureka app.

Blood Pressure Measurements: Participants will be provided with a MOCAcare Bluetooth blood pressure cuff. Participants will be asked to measure their blood pressure every day at the same time their weight measurement is recorded. Text message reminders will be sent through the Eureka app.

Heart tracker activity (optional)- Participants will use the MOCACARE heart tracker device at the same time as blood pressure measurements are taken. Use of this device is optional and at the discretion of the participant. The heart tracker uses a quick scan of the thumb to measure heart rate, blood oxygen, and pulse wave velocity.

Daily Compliance question: Each day, participants will be directed to the Eureka app to answer one short question about compliance to their eating schedule that day.

Random 24-hour dietary recall: In order to assess caloric intake, we will have participants complete a random 24-hour dietary recall using the NCI ASA24. Subjects will have to report all caloric intake within the past 24 hours. The day of recall will be random, and each participant will complete the survey bi-monthly (6 times throughout the 12-week study).

Weekly Survey: Once per week, participants will complete a short survey through the Eureka app. This survey will only take a few minutes and will answer questions about the participants mood, energy level, and food cravings.

Monthly Sleep Questionnaire: To determine if eating habits affect sleep schedules, we will have each participant complete the Pittsburg Sleep Quality Index (PSQI) survey once per month of the study and also at the beginning of the study to assess baseline sleeping habits (a total of 4 times). The survey should take no more than 10-15 minutes to complete.

Breath Acetone Measurements (Local participants only): Local participants will take daily breath acetone measurements for two weeks of the study. When participants visit the clinic 1 week prior to the diet start date, they will be given a Breathometer Breath Acetone device. The participants will be trained to properly use the device during this clinic visit. The device measures breath acetone levels simply by collecting a 10 second exhale of breath. Participants will measure their breath acetone level 3 times per day; 1) morning after an overnight fast 2) immediately before lunch 3) immediately after dinner. The device will be returned to the lab after one week. Participants will get the Breathometer device again on week 11 of the study when they visit the CTSI clinic. They will repeat the same measurement protocol as performed during week 1, and they will return the device to the lab at the completion of the study.

In-Person Study Activities (only for Local groups)

Local volunteers will undergo in-person body composition analyses, blood draws, muscle function testing, resting metabolic rate testing, and total energy expenditure testing. Please see the testing details (timelines, study activities, etc.) for the four visits for local participants below:

Note: The 3D-optical scans, DXA scans, muscle function tests, and blood draws are part of the Shape Up! Study and are covered under the Shape Up! protocol and informed consent.

Total Energy Expenditure (TEE) Measurements: To perform total energy expenditure measurements, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples. Participants will also collect urine/saliva samples after consuming the labelled water. One week later, participants will collect final urine samples for the total energy expenditure measurement. This procedure will require a total of 5 urine and saliva sample collections.

1. The first study visit will be one week prior to the study start. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the pre-intervention total energy expenditure (TEE) measurement.
2. One week later, at the start of the 12-week study, participants will return to the CTSI clinic for their second visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo extensive metabolic phenotyping (see below), which requires an overnight fast.
3. At the beginning of week 11 of the study, participants will return to the CTSI for their third clinic visit. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the post-intervention TEE measurement.
4. One week later and on the final day of the study (closeout), participants will return to the CTSI clinic for their fourth clinic visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo their second round of extensive metabolic phenotyping. The details of these procedures used for metabolic phenotyping are outlined below:

Resting Metabolic Rate (RMR) Measurements: To perform resting metabolic rate measurements, subjects will lay flat on gurney for up to 60 minutes. For 30 minutes, subjects will have their head under a clear plastic ventilated hood to collect oxygen and carbon dioxide levels.

Computerized cognitive task: The computerized cognitive task (called the NBACK) is a computer program developed by UCSF researchers to assess memory. Participants will be shown various stimuli on a computer screen and then later shown either the same stimulus or a different stimulus. Participants will then recall from memory whether the second stimulus is the same as the first. Researchers will record their ability to correctly remember the stimuli shown to them.

Computerized risk task: The computerized risk task (called the BART) is a computer program developed to measure risk taking. To complete this task, participants will inflate a virtual balloon by clicking a computer mouse. For each click, the balloon inflates more and the participant receives a hypothetical reward; however, with each click, they risk over-inflating and bursting the balloon, resulting in no reward. Researchers will use this test to measure impulsivity and risk-taking.

The following measurements are all part of the Shape Up! Adults study:

DXA and 3D-optical scans: Participants will wear a consistent snug fitting-outfit for all DXA, and optical scans (shorts such as boxer briefs and sports bra for women only.) No shoes or socks will be worn during the measures. Hair will be held above the neckline when performing the optical scans. A swim cap, provided by the investigators, will be worn during some of the measures. The swim cap will be washed with soap and water and then sanitized using alcohol wipes between each use. The optical measures will involve multiple images of the whole body from different angles and positions and will take approximately 15 minutes. The subjects may stand against a green backdrop and/or on a rotating platform. For most of the images, they will stand with their backs straight, arms away from side and legs slightly apart. The researcher will then take optical images of the subjects from the front and side as well. The subjects will then be asked to reposition in order for more optical images to be taken for reproducibility assessment. The DXA scans involve laying on the scanner for approximately 10 minutes and involves a very low amount of ionizing radiation. Total time for 3D-optical scans and DXA scans is approximately 30 minutes.

Muscle Function Tests: To perform the muscle function testing, participant will be seated in a chair to which her/his arm, feet or hip will be strapped. She/he will be asked to extend their leg or push and pull using their abdominal muscles at different speeds and/or various resistances. Participants will be encouraged to push and pull as hard and as fast as they can, and will feel local muscle fatigue, but no pain. This test takes approximately 20 minutes.

Blood Draw: Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Randomization and Interventions

All 100 participants, remote and local, will be randomized to one of the two study groups using a block randomization method. 50 participants will be randomized to the Time-Restricted Feeding (TRF) (treatment) group and 50 participants will be randomized to the Ad Libitum (control) group. Additionally, 25 of TRF group will be local participants and 25 of the control group will be local participants. The study interventions will last for a 12-week period.

Both cohorts will receive daily reminders of their assigned feeding times. Participants will also be reminded to measure their weight and blood pressure from home every morning using the study-supplied scale and blood pressure cuff. For participants who volunteer to use the Bluetooth heart tracker device, they will also take a measurement with that device. Additionally, participants may be asked to answer daily diet compliance questions, brief weekly surveys about their food cravings and mood, and a monthly questionnaire about sleep habits.

Time-Restricted Feeding (TRF) Group -- Treatment

The TRF group will be instructed to consume ad libitum from 12:00pm until 8:00pm every day and completely abstain from calorie consumption for the remainder of the day. Water, zero-calorie drinks, and coffee with calorie-free sweetener will be permitted during the fasting cycle. Using the Eureka mobile app, participants in this group will receive in-app messages notifying them when they should be abstaining and when they are able to eat. These messages are: "DO NOT eat between 8 pm tonight and 12 noon tomorrow"

for the restricted time period (message to appear at 8 pm); "DO NOT eat until 12 noon today" (message appears at 8 am); "It is ok to eat now until 8 pm tonight" (message appears at 12 noon). They will also receive reminders to weigh themselves every Friday morning.

Ad Libitum Group -- Control

The control cohort will be instructed to eat three meals per day (6:00am-10:00am, 11:00am-3:00pm, 5:00pm-10:00pm). In order to control for the effect of messaging, this group will also receive three messages (as in-app messages) as part of the control group: "fruits and vegetables are healthy snacks" (message appears at 8 pm); "start your day with a healthy breakfast" (message appears at 8 am); "regular meals reduce snacking" (message appear at 12 noon).

Closeout

After the 12-weeks of intervention, participants will officially closeout of the study. All participants may be asked to fill out a series of questionnaires. Local participants will be asked to return to CTSI for their final in-person visit. The measurements are explained above (see In-Person Measurements section). Participants will be allowed to keep all study-supplied devices.

Inclusion Criteria

- Male or female ages 18-64
- BMI between 30 kg/m2 and 40 kg/m2
- Participants must regularly consume breakfast
- 50 participants will also be selected based on their location (live within 60 miles of UCSF)
- Must speak, read, comprehend English
- Access to reliable Internet and/or Wi-Fi
- Must have a valid email address and/or phone number

Exclusion Criteria

1. HIV or immunocompromised
2. Current or past cancer diagnosis
3. Pregnancy, breastfeeding, or planned pregnancy in the next 6 months
4. Beginning or ending hormonal contraception in next 6 months
5. Current diagnosis of type 1 or type 2 DM
6. Currently taking glucose-lowering drugs, statins, or oral steroids
7. History of gastric bypass surgery
8. History of anorexia or bulimia
9. Frequent travel across time zones or unusual work hours
10. Unable to fast for prolonged periods due to medical condition
11. Unable to stand for several minutes without aid
12. Cannot lie down on cushioned table for 30 minutes
13. No internal metal artifacts that would alter body composition (pacemakers, internal fixation, arthroplasty, etc.)
14. Unable to travel to UCSF Parnassus for in-person testing
15. Requires translator services

Note: Exclusion criteria 8-12 are for measurement purposes and only apply to local participants

Modification 2: approved 1/23/2018

We will remove all study activities involving Breathometer. The company that produces these devices is no longer in business, so we cannot use their devices.

We will exclude potential participants that answer "other" as their gender. This pilot study is too small to include other genders into our stratification scheme.

In exclusion criteria, we will change "history of gastric bypass surgery" to "history of weight loss surgery" in order to include all weight loss surgeries in our exclusion criteria.

In our study protocol, we will add a blood draw to the end of the study. We need to perform a blood draw of after the diet intervention to determine if there are changes in metabolic markers between our two study arms.

We will make changes to our key study personnel to reflect recent changes in our study team staff.

Study Protocol

100 participants will be recruited from the Health eHeart Study cohort (CHR# 12-09993) by the Health eHeart Study team (refer to Section 10.6 for further information on the recruitment process). For the purposes of this study, participants will be asked to register for this study on the Eureka Research Platform (CHR# 16-19397) (refer to Section 10.8 for further information on the Eureka registration process and criteria). After registering and consent, the participants will be asked to answer a screening questionnaire to assess their eligibility to participate in the study.

Of the 100 total participants, 50 will be remote and 50 will be considered "local." These "local" individuals must live with 60 miles of UCSF and co-enroll in the Shape Up! Study (CHR# 15-18066). Shape Up! will be responsible for facilitating some of the in-person measurements. They must also be willing to visit the CTSI clinic at UCSF on four occasions for testing measurements. The purpose of the "local" group is to obtain more detailed measures that require a visit to the Shape Up! Lab for in-person measurements (see below).

Baseline Activities

During the baseline period, all 100 participants will be asked to fill out baseline questionnaires via the Eureka Research Platform from home. Participants will also be asked to connect a study-supplied iHealth Bluetooth scale and a MOCACARE Bluetooth blood pressure cuff to the study supported by the Eureka Research Platform. For local participants, connecting the devices will be facilitated in person by the study coordinator. For remote participants, detailed instructions will be provided to participants on how to connect the devices to the study. Additionally, a study coordinator will be available by phone or email to facilitate the remote connection of these devices.

Remote Study Activities (for both Remote and Local groups)

Weight Measurements: Participants will be provided with an iHealth Bluetooth scale. Participants will measure their weight every morning after an overnight fast. Data will automatically be collected through the Eureka platform. Participants will receive daily reminders via the Eureka app.

Blood Pressure Measurements: Participants will be provided with a MOCAcare Bluetooth blood pressure cuff. Participants will be asked to measure their blood pressure every day at the same time their weight measurement is recorded. Text message reminders will be sent through the Eureka app.

Daily Compliance question: Each day, participants will be directed to the Eureka app to answer one short question about compliance to their eating schedule that day.

Random 24-hour dietary recall: In order to assess caloric intake, we will have participants complete a random 24-hour dietary recall using the NCI ASA24. Subjects will have to report all caloric intake within the past 24 hours. The day of recall will be random, and each participant will complete the survey bi-monthly (6 times throughout the 12-week study).

Weekly Survey: Once per week, participants will complete a short survey through the Eureka app. This survey will only take a few minutes and will answer questions about the participants mood, energy level, and food cravings.

Monthly Sleep Questionnaire: To determine if eating habits affect sleep schedules, we will have each participant complete the Pittsburg Sleep Quality Index (PSQI) survey once per month of the study and also at the beginning of the study to assess baseline sleeping habits (a total of 4 times). The survey should take no more than 10-15 minutes to complete.

In-Person Study Activities (only for Local groups)

Local volunteers will undergo in-person body composition analyses, blood draws, muscle function testing, resting metabolic rate testing, and total energy expenditure testing. Please see the testing details (timelines, study activities, etc.) for the four visits for local participants below:

Note: The 3D-optical scans, DXA scans, muscle function tests, and blood draws are part of the Shape Up! Study and are covered under the Shape Up! protocol and informed consent.

Total Energy Expenditure (TEE) Measurements: To perform total energy expenditure measurements, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples. Participants will also collect urine/saliva samples after consuming the labelled water. One week later, participants will collect final urine samples for the total energy expenditure measurement. This procedure will require a total of 6 urine and 1 saliva sample collections.

1. The first study visit will be one week prior to the study start. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the pre-intervention total energy expenditure (TEE) measurement.
2. One week later, at the start of the 12-week study, participants will return to the CTSI clinic for their second visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo extensive metabolic phenotyping (see below), which requires an overnight fast.
3. At the beginning of week 11 of the study, participants will return to the CTSI for their third clinic visit. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the post-intervention TEE measurement.
4. One week later and on the final day of the study (closeout), participants will return to the CTSI clinic for their fourth clinic visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo their second round of extensive metabolic phenotyping. The details of these procedures used for metabolic phenotyping are outlined below:

Resting Metabolic Rate (RMR) Measurements: To perform resting metabolic rate measurements, subjects will lay flat on gurney for up to 60 minutes. For 30 minutes, subjects will have their head under a clear plastic ventilated hood to collect oxygen and carbon dioxide levels.

Blood Draw: All local participants will undergo a blood draw on their final study visit. Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Computerized cognitive task: The computerized cognitive task (called the NBACK) is a computer program developed by UCSF researchers to assess memory. Participants will be shown various stimuli on a computer screen and then later shown either the same stimulus or a different stimulus. Participants will then recall from memory whether the second stimulus is the same as the first. Researchers will record their ability to correctly remember the stimuli shown to them.

Computerized risk task: The computerized risk task (called the BART) is a computer program developed to measure risk taking. To complete this task, participants will inflate a virtual balloon by clicking a computer mouse. For each click, the balloon inflates more and the participant receives a hypothetical reward; however, with each click, they risk over-inflating and bursting the balloon, resulting in no reward. Researchers will use this test to measure impulsivity and risk-taking.

The following measurements are all part of the Shape Up! Adults study:

DXA and 3D-optical scans: Participants will wear a consistent snug fitting-outfit for all DXA, and optical scans (shorts such as boxer briefs and sports bra for women only.) No shoes or socks will be worn during the measures. Hair will be held above the neckline when performing the optical scans. A swim cap, provided by the investigators, will be worn during some of the measures. The swim cap will be washed with soap and water and then sanitized using alcohol wipes between each use. The optical measures will involve multiple images of the whole body from different angles and positions and will take approximately 15 minutes. The subjects may stand against a green backdrop and/or on a rotating platform. For most of the images, they will stand with their backs straight, arms away from side and legs slightly apart. The researcher will then take optical images of the subjects from the front and side as well. The subjects will then be asked to reposition in order for more optical images to be taken for reproducibility assessment. The DXA scans involve laying on the scanner for approximately 10 minutes and involves a very low amount of ionizing radiation. Total time for 3D-optical scans and DXA scans is approximately 30 minutes.

Muscle Function Tests: To perform the muscle function testing, participant will be seated in a chair to which her/his arm, feet or hip will be strapped. She/he will be asked to extend their leg or push and pull using their abdominal muscles at different speeds and/or various resistances. Participants will be encouraged to push and pull as hard and as fast as they can, and will feel local muscle fatigue, but no pain. This test takes approximately 20 minutes.

Blood Draw: Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Randomization and Interventions

All 100 participants, remote and local, will be randomized to one of the two study groups using a block randomization method. 50 participants will be randomized to the Time-Restricted Feeding (TRF) (treatment) group and 50 participants will be randomized to the Ad Libitum (control) group. Additionally, 25 of TRF group will be local participants and 25 of the control group will be local participants. The study interventions will last for a 12-week period.

Both cohorts will receive daily reminders of their assigned feeding times. Participants will also be reminded to measure their weight and blood pressure from home every morning using the study-supplied scale and blood pressure cuff. For participants who volunteer to use the Bluetooth heart tracker device, they will also take a measurement with that device. Additionally, participants may be asked to answer daily diet compliance questions, brief weekly surveys about their food cravings and mood, and a monthly questionnaire about sleep habits.

Time-Restricted Feeding (TRF) Group -- Treatment

The TRF group will be instructed to consume ad libitum from 12:00pm until 8:00pm every day and completely abstain from calorie consumption for the remainder of the day. Water, zero-calorie drinks, and coffee with calorie-free sweetener will be permitted during the fasting cycle. Using the Eureka mobile app, participants in this group will receive in-app messages notifying them when they should be abstaining and when they are able to eat. These messages are: "DO NOT eat between 8 pm tonight and 12 noon tomorrow" for the restricted time period (message to appear at 8 pm); "DO NOT eat until 12 noon today" (message appears at 8 am); "It is ok to eat now until 8 pm tonight" (message appears at 12 noon). They will also receive reminders to weigh themselves every Friday morning.

Ad Libitum Group -- Control

The control cohort will be instructed to eat three meals per day (6:00am-10:00am, 11:00am-3:00pm, 5:00pm-10:00pm). In order to control for the effect of messaging, this group will also receive three messages (as in-app messages) as part of the control group: "fruits and vegetables are healthy snacks" (message appears at 8 pm); "start your day with a healthy breakfast" (message appears at 8 am); "regular meals reduce snacking" (message appear at 12 noon).

Closeout

After the 12-weeks of intervention, participants will officially closeout of the study. All participants may be asked to fill out a series of questionnaires. Local participants will be asked to return to CTSI for their final in-person visit. The measurements are explained above (see In-Person Measurements section). Participants will be allowed to keep all study-supplied devices.

Inclusion Criteria

- Male or female ages 18-64
- BMI between 30 kg/m2 and 40 kg/m2
- Participants must regularly consume breakfast
- 50 participants will also be selected based on their location (live within 60 miles of UCSF)
- Must speak, read, comprehend English
- Access to reliable Internet and/or Wi-Fi
- Must have a valid email address and/or phone number

Exclusion Criteria

1. HIV or immunocompromised
2. Current or past cancer diagnosis
3. Pregnancy, breastfeeding, or planned pregnancy in the next 6 months
4. Beginning or ending hormonal contraception in next 6 months
5. Current diagnosis of type 1 or type 2 DM
6. Currently taking glucose-lowering drugs, statins, or oral steroids
7. History of gastric bypass surgery or any weight loss surgery
8. History of anorexia or bulimia
9. Frequent travel across time zones or unusual work hours
10. Unable to fast for prolonged periods due to medical condition
11. Answer "other" gender on study screening questionnaire
12. Unable to stand for several minutes without aid
13. Cannot lie down on cushioned table for 30 minutes
14. No internal metal artifacts that would alter body composition (pacemakers, internal fixation, arthroplasty, etc.)
15. Unable to travel to UCSF Parnassus for in-person testing
16. Requires translator services

Note: Exclusion criteria 8-12 are for measurement purposes and only apply to local participants

Modification 3: Approved 6/26/2018

We will add the Oura ring to a procedures. The Oura ring is a wearable device worn on the finger that tracks heart rate variability, body temp, and sleep patterns. In-person participants will be given the option to use this device throughout the 12-week study.

Study Protocol

120 participants will be recruited from the Health eHeart Study cohort (CHR# 12-09993) by the Health eHeart Study team (refer to Section 10.6 for further information on the recruitment process). For the purposes of this study, participants will be asked to register for this study on the Eureka Research Platform (CHR# 16-19397) (refer to Section 10.8 for further information on the Eureka registration process and criteria). After registering and consent, the participants will be asked to answer a screening questionnaire to assess their eligibility to participate in the study.

Of the 120 total enrollees, 60 will be remote and 60 will be considered "local." These "local" individuals must live with 60 miles of UCSF and co-enroll in the Shape Up! Study (CHR# 15-18066). Shape Up! will be responsible for facilitating some of the in-person measurements. They must also be willing to visit the CTSI clinic at UCSF on four occasions for testing measurements. The purpose of the "local" group is to obtain more detailed measures that require a visit to the Shape Up! Lab for in-person measurements (see below).

Baseline Activities

During the baseline period, all 100 participants will be asked to fill out baseline questionnaires via the Eureka Research Platform from home. Participants will also be asked to connect a study-supplied iHealth Bluetooth scale and a MOCACARE Bluetooth blood pressure cuff to the study supported by the Eureka Research Platform. For local participants, connecting the devices will be facilitated in person by the study coordinator. For remote participants, detailed instructions will be provided to participants on how to connect the devices to the study. Additionally, a study coordinator will be available by phone or email to facilitate the remote connection of these devices.

Remote Study Activities (for both Remote and Local groups)

Weight Measurements: Participants will be provided with an iHealth Bluetooth scale. Participants will measure their weight every morning after an overnight fast. Data will automatically be collected through the Eureka platform. Participants will receive daily reminders via the Eureka app.

Blood Pressure Measurements: Participants will be provided with a MOCAcare Bluetooth blood pressure cuff. Participants will be asked to measure their blood pressure every day at the same time their weight measurement is recorded. Text message reminders will be sent through the Eureka app.

Daily Compliance question: Each day, participants will be directed to the Eureka app to answer one short question about compliance to their eating schedule that day.

Random 24-hour dietary recall: In order to assess caloric intake, we will have participants complete a random 24-hour dietary recall using the NCI ASA24. Subjects will have to report all caloric intake within the past 24 hours. The day of recall will be random, and each participant will complete the survey bi-monthly (6 times throughout the 12-week study).

Weekly Survey: Once per week, participants will complete a short survey through the Eureka app. This survey will only take a few minutes and will answer questions about the participants mood, energy level, and food cravings.

Monthly Sleep Questionnaire: To determine if eating habits affect sleep schedules, we will have each participant complete the Pittsburg Sleep Quality Index (PSQI) survey once per month of the study and also at the beginning of the study to assess baseline sleeping habits (a total of 4 times). The survey should take no more than 10-15 minutes to complete.

Food Attitudes Survey: Participants will complete a short, 9 question survey at the beginning and end of the study. This survey will ask participants about their eating habits and attitudes about food and eating.

In-Person Study Activities (only for Local groups)

Local volunteers will undergo in-person body composition analyses, blood draws, muscle function testing, resting metabolic rate testing, and total energy expenditure testing. Please see the testing details (timelines, study activities, etc.) for the four visits for local participants below:

Note: The 3D-optical scans, DXA scans, muscle function tests, and blood draws are part of the Shape Up! Study and are covered under the Shape Up! protocol and informed consent.

Total Energy Expenditure (TEE) Measurements: To perform total energy expenditure measurements, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples. Participants will also collect urine/saliva samples after consuming the labelled water. One week later, participants will collect final urine samples for the total energy expenditure measurement. This procedure will require a total of 6 urine and 1 saliva sample collections.

1. The first study visit will be one week prior to the study start. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the pre-intervention total energy expenditure (TEE) measurement.
2. One week later, at the start of the 12-week study, participants will return to the CTSI clinic for their second visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo extensive metabolic phenotyping (see below), which requires an overnight fast.
3. At the beginning of week 11 of the study, participants will return to the CTSI for their third clinic visit. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the post-intervention TEE measurement.
4. One week later and on the final day of the study (closeout), participants will return to the CTSI clinic for their fourth clinic visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo their second round of extensive metabolic phenotyping. The details of these procedures used for metabolic phenotyping are outlined below:

Resting Metabolic Rate (RMR) Measurements: To perform resting metabolic rate measurements, subjects will lay flat on gurney for up to 60 minutes. For 30 minutes, subjects will have their head under a clear plastic ventilated hood to collect oxygen and carbon dioxide levels.

Breath Acetone Measurements: To measure breath ketone levels, participants will exhale into a hand-held device that measures acetone levels. The measurement will be done three times each visit, and the participant will complete this activity on all four of their study visits. This will only take 1-2 minutes.

Blood Draw: All local participants will undergo a blood draw on their final study visit. Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Computerized cognitive task: The computerized cognitive task (called the NBACK) is a computer program developed by UCSF researchers to assess memory. Participants will be shown various stimuli on a computer screen and then later shown either the same stimulus or a different stimulus. Participants will then recall from memory whether the second stimulus is the same as the first. Researchers will record their ability to correctly remember the stimuli shown to them.

Computerized risk task: The computerized risk task (called the BART) is a computer program developed to measure risk taking. To complete this task, participants will inflate a virtual balloon by clicking a computer mouse. For each click, the balloon inflates more and the participant receives a hypothetical reward; however, with each click, they risk over-inflating and bursting the balloon, resulting in no reward. Researchers will use this test to measure impulsivity and risk-taking.

Oura Ring: The Oura ring is a wearable device on the finger that tracks heart-rate variability, body temperature, and sleep patterns. In-person participants have the option to use this device during the 12-week study. If the participant agrees to participate, they will be fitted for the ring and given the appropriately sized ring during their first study visit.

The following measurements are all part of the Shape Up! Adults study:

DXA and 3D-optical scans: Participants will wear a consistent snug fitting-outfit for all DXA, and optical scans (shorts such as boxer briefs and sports bra for women only.) No shoes or socks will be worn during the measures. Hair will be held above the neckline when performing the optical scans. A swim cap, provided by the investigators, will be worn during some of the measures. The swim cap will be washed with soap and water and then sanitized using alcohol wipes between each use. The optical measures will involve multiple images of the whole body from different angles and positions and will take approximately 15 minutes. The subjects may stand against a green backdrop and/or on a rotating platform. For most of the images, they will stand with their backs straight, arms away from side and legs slightly apart. The researcher will then take optical images of the subjects from the front and side as well. The subjects will then be asked to reposition in order for more optical images to be taken for reproducibility assessment. The DXA scans involve laying on the scanner for approximately 10 minutes and involves a very low amount of ionizing radiation. Total time for 3D-optical scans and DXA scans is approximately 30 minutes.

Muscle Function Tests: To perform the muscle function testing, participant will be seated in a chair to which her/his arm, feet or hip will be strapped. She/he will be asked to extend their leg or push and pull using their abdominal muscles at different speeds and/or various resistances. Participants will be encouraged to push and pull as hard and as fast as they can, and will feel local muscle fatigue, but no pain. This test takes approximately 20 minutes.

Blood Draw: Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Randomization and Interventions

All 100 participants, remote and local, will be randomized to one of the two study groups using a block randomization method. 50 participants will be randomized to the Time-Restricted Feeding (TRF) (treatment) group and 50 participants will be randomized to the Ad Libitum (control) group. Additionally, 25 of TRF group will be local participants and 25 of the control group will be local participants. The study interventions will last for a 12-week period.

Both cohorts will receive daily reminders of their assigned feeding times. Participants will also be reminded to measure their weight and blood pressure from home every morning using the study-supplied scale and blood pressure cuff. For participants who volunteer to use the Bluetooth heart tracker device, they will also take a measurement with that device. Additionally, participants may be asked to answer daily diet compliance questions, brief weekly surveys about their food cravings and mood, and a monthly questionnaire about sleep habits.

Time-Restricted Feeding (TRF) Group -- Treatment

The TRF group will be instructed to consume ad libitum from 12:00pm until 8:00pm every day and completely abstain from calorie consumption for the remainder of the day. Water, zero-calorie drinks, and coffee with calorie-free sweetener will be permitted during the fasting cycle. Using the Eureka mobile app, participants in this group will receive in-app messages notifying them when they should be abstaining and when they are able to eat. These messages are: "DO NOT eat between 8 pm tonight and 12 noon tomorrow" for the restricted time period (message to appear at 8 pm); "DO NOT eat until 12 noon today" (message appears at 8 am); "It is ok to eat now until 8 pm tonight" (message appears at 12 noon). They will also receive reminders to weigh themselves every Friday morning.

Ad Libitum Group -- Control

The control cohort will be instructed to eat three meals per day (6:00am-10:00am, 11:00am-3:00pm, 5:00pm-10:00pm). In order to control for the effect of messaging, this group will also receive three messages (as in-app messages) as part of the control group: "fruits and vegetables are healthy snacks" (message appears at 8 pm); "start your day with a healthy breakfast" (message appears at 8 am); "regular meals reduce snacking" (message appear at 12 noon).

Closeout

After the 12-weeks of intervention, participants will officially closeout of the study. All participants may be asked to fill out a series of questionnaires. Local participants will be asked to return to CTSI for their final in-person visit. The measurements are explained above (see In-Person Measurements section). Participants will be allowed to keep all study-supplied devices.

Protocols and Amendments as Submitted to the UCSF IRB

Modification 4: Approved 8/14/2018

1) We are expanding our inclusion criteria from BMI between 30 and 40 to between 27-43 in order to increase the number of eligible participants. (Section 10.7)

2) From our Screening Questionnaire, we are removing the question "In the next 6 months, do you plan to fast for at least 12 hours/day, more than once per month?".

Study Protocol

120 participants will be recruited from the Health eHeart Study cohort (CHR# 12-09993) by the Health eHeart Study team (refer to Section 10.6 for further information on the recruitment process). For the purposes of this study, participants will be asked to register for this study on the Eureka Research Platform (CHR# 16-19397) (refer to Section 10.8 for further information on the Eureka registration process and criteria). After registering and consent, the participants will be asked to answer a screening questionnaire to assess their eligibility to participate in the study.

Of the 120 total enrollees, 60 will be remote and 60 will be considered "local." These "local" individuals must live with 60 miles of UCSF and co-enroll in the Shape Up! Study (CHR# 15-18066). Shape Up! will be responsible for facilitating some of the in-person measurements. They must also be willing to visit the CTSI clinic at UCSF on four occasions for testing measurements. The purpose of the "local" group is to obtain more detailed measures that require a visit to the Shape Up! Lab for in-person measurements (see below).

Baseline Activities

During the baseline period, all 100 participants will be asked to fill out baseline questionnaires via the Eureka Research Platform from home. Participants will also be asked to connect a study-supplied iHealth Bluetooth scale and a MOCACARE Bluetooth blood pressure cuff to the study supported by the Eureka Research Platform. For local participants, connecting the devices will be facilitated in person by the study coordinator. For remote participants, detailed instructions will be provided to participants on how to connect the devices to the study. Additionally, a study coordinator will be available by phone or email to facilitate the remote connection of these devices.

Remote Study Activities (for both Remote and Local groups)

Weight Measurements: Participants will be provided with an iHealth Bluetooth scale. Participants will measure their weight every morning after an overnight fast. Data will automatically be collected through the Eureka platform. Participants will receive daily reminders via the Eureka app.

Blood Pressure Measurements: Participants will be provided with a MOCAcare Bluetooth blood pressure cuff. Participants will be asked to measure their blood pressure every day at the same time their weight measurement is recorded. Text message reminders will be sent through the Eureka app.

Daily Compliance question: Each day, participants will be directed to the Eureka app to answer one short question about compliance to their eating schedule that day.

Random 24-hour dietary recall: In order to assess caloric intake, we will have participants complete a random 24-hour dietary recall using the NCI ASA24. Subjects will have to report all caloric intake within the past 24 hours. The day of recall will be random, and each participant will complete the survey bi-monthly (6 times throughout the 12-week study).

Weekly Survey: Once per week, participants will complete a short survey through the Eureka app. This survey will only take a few minutes and will answer questions about the participants mood, energy level, and food cravings.

Monthly Sleep Questionnaire: To determine if eating habits affect sleep schedules, we will have each participant complete the Pittsburg Sleep Quality Index (PSQI) survey once per month of the study and also

at the beginning of the study to assess baseline sleeping habits (a total of 4 times). The survey should take no more than 10-15 minutes to complete.

Food Attitudes Survey: Participants will complete a short, 9 question survey at the beginning and end of the study. This survey will ask participants about their eating habits and attitudes about food and eating.

In-Person Study Activities (only for Local groups)

Local volunteers will undergo in-person body composition analyses, blood draws, muscle function testing, resting metabolic rate testing, and total energy expenditure testing. Please see the testing details (timelines, study activities, etc.) for the four visits for local participants below:

Note: The 3D-optical scans, DXA scans, muscle function tests, and blood draws are part of the Shape Up! Study and are covered under the Shape Up! protocol and informed consent.

Total Energy Expenditure (TEE) Measurements: To perform total energy expenditure measurements, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples. Participants will also collect urine/saliva samples after consuming the labelled water. One week later, participants will collect final urine samples for the total energy expenditure measurement. This procedure will require a total of 6 urine and 1 saliva sample collections.

1. The first study visit will be one week prior to the study start. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the pre-intervention total energy expenditure (TEE) measurement.
2. One week later, at the start of the 12-week study, participants will return to the CTSI clinic for their second visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo extensive metabolic phenotyping (see below), which requires an overnight fast.
3. At the beginning of week 11 of the study, participants will return to the CTSI for their third clinic visit. During this visit, participants will drink stable-isotope labeled water (2H218O) and collect baseline urine and saliva samples for the post-intervention TEE measurement.
4. One week later and on the final day of the study (closeout), participants will return to the CTSI clinic for their fourth clinic visit to collect urine and saliva samples to complete the TEE measurements. Participants will also undergo their second round of extensive metabolic phenotyping. The details of these procedures used for metabolic phenotyping are outlined below:

Resting Metabolic Rate (RMR) Measurements: To perform resting metabolic rate measurements, subjects will lay flat on gurney for up to 60 minutes. For 30 minutes, subjects will have their head under a clear plastic ventilated hood to collect oxygen and carbon dioxide levels.

Breath Acetone Measurements: To measure breath ketone levels, participants will exhale into a hand-held device that measures acetone levels. The measurement will be done three times each visit, and the participant will complete this activity on all four of their study visits. This will only take 1-2 minutes.

Blood Draw: All local participants will undergo a blood draw on their final study visit. Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Computerized cognitive task: The computerized cognitive task (called the NBACK) is a computer program developed by UCSF researchers to assess memory. Participants will be shown various stimuli on a computer screen and then later shown either the same stimulus or a different stimulus. Participants will then recall from memory whether the second stimulus is the same as the first. Researchers will record their ability to correctly remember the stimuli shown to them.

Computerized risk task: The computerized risk task (called the BART) is a computer program developed to measure risk taking. To complete this task, participants will inflate a virtual balloon by clicking a computer mouse. For each click, the balloon inflates more and the participant receives a hypothetical reward;

however, with each click, they risk over-inflating and bursting the balloon, resulting in no reward. Researchers will use this test to measure impulsivity and risk-taking.

Oura Ring: The Oura ring is a wearable device on the finger that tracks heart-rate variability, body temperature, and sleep patterns. In-person participants have the option to use this device during the 12-week study. If the participant agrees to participate, they will be fitted for the ring and given the appropriately sized ring during their first study visit.

The following measurements are all part of the Shape Up! Adults study:

DXA and 3D-optical scans: Participants will wear a consistent snug fitting-outfit for all DXA, and optical scans (shorts such as boxer briefs and sports bra for women only.) No shoes or socks will be worn during the measures. Hair will be held above the neckline when performing the optical scans. A swim cap, provided by the investigators, will be worn during some of the measures. The swim cap will be washed with soap and water and then sanitized using alcohol wipes between each use. The optical measures will involve multiple images of the whole body from different angles and positions and will take approximately 15 minutes. The subjects may stand against a green backdrop and/or on a rotating platform. For most of the images, they will stand with their backs straight, arms away from side and legs slightly apart. The researcher will then take optical images of the subjects from the front and side as well. The subjects will then be asked to reposition in order for more optical images to be taken for reproducibility assessment. The DXA scans involve laying on the scanner for approximately 10 minutes and involves a very low amount of ionizing radiation. Total time for 3D-optical scans and DXA scans is approximately 30 minutes.

Muscle Function Tests: To perform the muscle function testing, participant will be seated in a chair to which her/his arm, feet or hip will be strapped. She/he will be asked to extend their leg or push and pull using their abdominal muscles at different speeds and/or various resistances. Participants will be encouraged to push and pull as hard and as fast as they can, and will feel local muscle fatigue, but no pain. This test takes approximately 20 minutes.

Blood Draw: Subjects will have been instructed to fast beginning at 8:00pm the night before the CTSI visit. We will collect 10 cc of blood via direct venipuncture to quantify biomarkers now and an additional 30 cc will be collected and stored for future testing. The blood draw takes approximately 10 minutes.

Randomization and Interventions

All 100 participants, remote and local, will be randomized to one of the two study groups using a block randomization method. 50 participants will be randomized to the Time-Restricted Feeding (TRF) (treatment) group and 50 participants will be randomized to the Ad Libitum (control) group. Additionally, 25 of TRF group will be local participants and 25 of the control group will be local participants. The study interventions will last for a 12-week period.

Both cohorts will receive daily reminders of their assigned feeding times. Participants will also be reminded to measure their weight and blood pressure from home every morning using the study-supplied scale and blood pressure cuff. For participants who volunteer to use the Bluetooth heart tracker device, they will also take a measurement with that device. Additionally, participants may be asked to answer daily diet compliance questions, brief weekly surveys about their food cravings and mood, and a monthly questionnaire about sleep habits.

Time-Restricted Feeding (TRF) Group -- Treatment

The TRF group will be instructed to consume ad libitum from 12:00pm until 8:00pm every day and completely abstain from calorie consumption for the remainder of the day. Water, zero-calorie drinks, and coffee with calorie-free sweetener will be permitted during the fasting cycle. Using the Eureka mobile app, participants in this group will receive in-app messages notifying them when they should be abstaining and when they are able to eat. These messages are: "DO NOT eat between 8 pm tonight and 12 noon tomorrow" for the restricted time period (message to appear at 8 pm); "DO NOT eat until 12 noon today" (message appears at 8 am); "It is ok to eat now until 8 pm tonight" (message appears at 12 noon). They will also receive reminders to weigh themselves every Friday morning.

Ad Libitum Group -- Control

The control cohort will be instructed to eat three meals per day (6:00am-10:00am, 11:00am-3:00pm, 5:00pm-10:00pm). In order to control for the effect of messaging, this group will also receive three messages (as in-app messages) as part of the control group: "fruits and vegetables are healthy snacks" (message appears at 8 pm); "start your day with a healthy breakfast" (message appears at 8 am); "regular meals reduce snacking" (message appear at 12 noon).

Closeout

After the 12-weeks of intervention, participants will officially closeout of the study. All participants may be asked to fill out a series of questionnaires. Local participants will be asked to return to CTSI for their final in-person visit. The measurements are explained above (see In-Person Measurements section). Participants will be allowed to keep all study-supplied devices.

Inclusion Criteria

- Male or female ages 18-64
- BMI between 27 kg/m2 and 43 kg/m2
- Participants must regularly consume breakfast
- Participants will also be selected based on their location (live within 60 miles of UCSF)
- Must speak, read, comprehend English
- Access to reliable Internet and/or Wi-Fi
- Must have a valid email address and/or phone number

Exclusion Criteria

1. Current or past cancer diagnosis
2. Pregnancy, breastfeeding, or planned pregnancy in the next 6 months
3. Current diagnosis of type 1 or type 2 DM
4. Currently taking glucose-lowering drugs
5. History of gastric bypass surgery or any weight loss surgery
6. History of anorexia or bulimia
7. Frequent travel across time zones or unusual work hours
8. Unable to fast for prolonged periods due to medical condition
9. Answer "other" gender on study screening questionnaire
10. Unable to stand for several minutes without aid
11. Cannot lie down on cushioned table for 30 minutes
12. No internal metal artifacts that would alter body composition (pacemakers, internal fixation, arthroplasty, etc.)
13. Unable to travel to UCSF Parnassus for in-person testing
14. Requires translator services

Note: Exclusion criteria 8-12 are for measurement purposes and only apply to local participants

Statistical Analysis Plan

All measurements collected in this study will collected at baseline and at study completion for the control group and the treatment group. We will analyze each parameter using a two-way analysis of variance (two-way ANOVA) to examine the mean differences in pre- and post-intervention values between the control group and the treatment group. The model specifications will include parameters to estimate the diet main effect (control and treatment group), time main effect (pre- and post-intervention), and their interaction effect. For home weight and blood pressure measurements, we will perform an analysis of covariance (ANCOVA) to compare changes in weight and blood pressure between the two treatment diets. Statistical analyses will be performed using the STATA software.