

## Is non-adherence unique to weight loss?

### Predictors of adherence to a heart-healthy diet in lean vs. obese individuals

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Volunteers	150	M/F	≥18

**Uses Ionizing Radiation?** Yes  
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**Requires IND/IDE?** No

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**Uses “Durable Power of Attorney”** No

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**PRECIS**

Adherence, or "sticking to your diet" is important for successful initial weight loss and keeping off the weight over the long term (1). While early behavioral and dietary adherence have been associated with greater weight loss, sticking to a diet plan is difficult. It is not clear if adherence to any diet plan (even one which does not produce weight loss) is hard or whether people who are overweight have more difficulty with adhering to diet plans compared to people who are relatively lean.

The main aim of this study is to evaluate dietary adherence in 3 groups of individuals participating in a 6-week heart-healthy dietary intervention program. Two groups [1. Lean (BMI < 25 kg/m<sup>2</sup>) and 2. Obese (BMI ≥ 30 kg/m<sup>2</sup>)] will receive a heart-healthy diet designed to maintain their weight, and the third group [3. Obese] will be given a heart-healthy diet that is 35% *less* than their daily calorie needs to lose weight. Participants will attend one counseling session per week and will be contacted randomly 1x/week by study staff for completion of a 24-hour dietary recall. They will complete daily food diaries and daily records using smart-phones. Prior to starting the assigned heart-healthy dietary intervention, participants will complete questionnaires that include questions about how motivated they are to follow a diet, lose weight, and change eating patterns. These findings may help us understand what factors affect adherence, and help us design weight loss studies that improve people's ability to stick to diet interventions.

## A. INTRODUCTION

Obesity, defined by the NHLBI in 1998 (2) as a body mass index [BMI, in  $\text{kg/m}^2$ ]  $> 30$ , has become a medical epidemic in the US (3), and is reaching pandemic proportions in most industrialized countries. Obesity is linked to a number of medical complications and is a leading cause of preventable death in America, contributing to over 150,000 excess deaths per year (4). At any given time of the year, between 15 and 35% of the adult population in the US is reportedly attempting to lose weight (5), yet, successful weight reduction and maintenance of weight loss remain elusive goals for many dieters. In fact, a relatively small maximum average weight loss is common even in very low calorie long-term treatments (6). This low treatment efficacy has been consistently observed, and while some do achieve weight loss success, only about 20% of overweight individuals maintain the weight loss (7).

Adherence is defined as the “extent to which patients follow the instructions that are given to them for prescribed treatments” and is intended to be non-judgmental, a statement of fact rather than of blame of the patient, prescriber, or treatment (8).” Adherence is widely recognized as essential for achieving successful health outcomes yet non-adherence is the primary treatment barrier for most medical conditions. A recent review found that rates of non-adherence to treatment recommendations are 20%-40% for acute conditions, 30% to 60% for chronic conditions and 80% for prevention (9). Rates of non-adherence are substantially lower for lifestyle prescriptions and other more behaviorally demanding regimens (10). Lack of adherence is a pervasive problem in clinical research. This lack of adherence to assigned interventions results in intention to treat analyses, which are biased towards null findings (11).

For the treatment of obesity, there is a consensus that adherence is critical for successful initial weight loss and long term weight maintenance (1). Many studies have sought to identify

predictive demographic, psychosocial and behavioral characteristics that lead to weight loss success and successful weight loss maintenance. Age, income, marital status, ethnicity, employment status, previous dieting and weight history, dietary restraint, binge eating disorder, self-motivation and familial support, early weight loss success, and weight loss expectations are among the multitude of variables that have been studied (12). Ultimately, poor adherence to calorie-reduced diets is one of the most plausible explanations for less than predicted weight loss in clinical studies. In one review, Heymsfield and colleagues (6) concluded that participant adherence to the prescribed diet was the most likely explanation for the observed low efficacy of low-calorie diets, even after considering metabolic adaptations. Another recent study comparing four popular diets found a highly significant relationship between self-reported dietary adherence and weight loss, such that participants who scored in the top third of adherence lost an average of 7% of body weight. However, no single diet produced satisfactory adherence rates and the progressively decreasing mean adherence scores over time were practically identical among the 4 diets (13).

Factors predicting adherence have been moderately studied. Cognitive skills, the underlying brain skills that make it possible for individuals to think, remember and learn, have recently been found to predict adherence (14-16). To examine neuropsychological and cognitive factors, traditional neuropsychological tests and measures designed to stimulate real-world situations (everyday cognitive measures) are often administered. Poor neurocognitive performance as measured by various neuropsychological performance tests, has been associated with decreased medication adherence in many clinical populations, including HIV, type II diabetes, older adults and individuals taking antidepressants (14).

The neuropsychological factors which are most predictive of medication non-adherence are poor executive functioning (necessary for goal-directed behavior e.g. ability to initiate/stop actions, monitor/change behavior, plan future behavior, anticipate outcomes, think abstractly), followed by working memory (availability of information needed to complete immediate and short-term tasks) and processing speed (a measure of learning and thinking efficiency) (14). Poor performance on an everyday problem solving questionnaire was associated with poorer self-reported medication adherence (14). Moreover, problem-solving skills as measured by the Social Problem Solving Inventory partially mediated the relationship between treatment adherence and weight loss outcome in one recent study (15) and were significantly related to greater overall weight loss and long term weight loss maintenance in another study (16). In addition to evidence relating cognitive skills to adherence and weight loss, recent observations support a relationship between obesity status and performance on tests measuring decision-making (17;18) (Iowa Gambling Task), problem solving and working memory (Wisconsin Card Sorting Task) and inhibition/attention (Go/No Go task; (19)).

Personality is another factor significantly influencing health. The most common relationship between these variables is based on the Five Factor Model dimensions (FFM; (20)) - Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness, which are empirically derived clusters that capture the major axes of psychological and behavioral variation in humans (21;22). FFM factors have been linked with many health-related behaviors and outcomes, including medication non-adherence. One recent study found that neuroticism was the second strongest predictor of non-adherence to CPAP treatment for obstructive sleep apnea (23). Previous studies have shown that medication non-adherence (24) as well as emotional and external eating behaviors (25) were most frequently associated with lower levels of



Conscientiousness and higher levels of Neuroticism. However, no study to date has measured FFM with weight loss and/or dietary adherence.

Successful weight management appears to require adherence across a wide variety of behaviors yet measuring adherence poses a significant problem. While objective behavioral measures are superior to subjective self-report measures, objective measures are often difficult to obtain. Both early behavioral (e.g. attendance) and self-reported dietary adherence were predictors of changes in body weight, waist circumference and body fat, but for dietary adherence the magnitude of the effect was smaller (26). It is widely accepted that adherence to weight management strategies is critical for successful weight loss and for long-term maintenance (1). However, it is not clear whether problems with adherence occur more frequently with diets to promote weight loss versus weight maintenance, any diet prescription, and whether increased adiposity might in itself predispose to more difficulty with dietary and behavioral adherence. Our study aims to address these questions.

### **Summary:**

Adherence is essential for initial weight loss and long-term weight maintenance. It is unclear whether adherence to dietary protocols differs between lean and obese individuals and whether non-adherence is specific to weight loss intervention diets (compared to weight maintenance diets). Several predictors of adherence to medical treatments have been described, including associations with memory, problem solving, neuropsychological factors, personality traits and levels of motivation. To understand how adherence may differ by adiposity and diet, we will examine differences in dietary adherence between lean and obese individuals and within the obese group between those prescribed a heart-healthy weight maintenance versus reduced calorie

diet. We will also examine predictors of adherence and the relationship between dietary adherence and weight loss.

## **B. AIMS**

The primary goal of the current study is to determine whether or not there are differences in dietary adherence between lean and obese individuals and between two groups of obese individuals assigned different heart-healthy dietary prescriptions (weight maintaining diet [WMEN] vs. underfeeding [UF]). Thus 3 groups will be compared:

1. Lean WMEN
2. Obese WMEN
3. Obese UF

The secondary aim is to:

1. Examine predictors of adherence in general (e.g. motivation, self-efficacy, social support, personality traits, stress, neuropsychological/cognitive factors)

## **C. HYPOTHESES**

The primary hypothesis for the study is that:

1. Adherence to a heart-healthy dietary intervention will be greatest in the lean WMEN group, followed by the WMEN obese group, and subsequently lowest in the UF obese group

The secondary hypotheses are that:

1. Within the UF group, individuals with higher adherence scores will lose more weight than those with lower scores

2. Poor performance on neuropsychological tests and problem solving questionnaires will be associated with decreased adherence across all groups
3. Higher levels of neuroticism will be associated with lower levels of dietary adherence in all 3 groups
4. Higher levels of motivation and self-efficacy will predict greater adherence

#### **D. RESEARCH DESIGN & METHODS:**

**Study Design:** This is a study of lean and obese individuals undergoing a 6-week heart-healthy dietary intervention to examine dietary adherence. This design will allow us to determine whether or not levels of adherence are different between lean and obese individuals as well as between obese individuals receiving weight maintenance energy needs and those being underfed. Findings will also help us determine factors that influence dietary adherence.

**1. Subjects and Recruitment:** Non-diabetic individuals aged 18-70 years who are in good health and living in the greater Phoenix, AZ, metropolitan area are eligible to participate in this study. All subjects will be fully informed of the methods and risks of the study prior to giving written informed consent. Consent will be obtained by the principal investigator, co-investigators, study physicians or physician assistant, who will be well informed about the protocol and the intervention. Subjects will also be specifically advised that the results of testing for drug usage will be filed in the medical record and would, therefore, be available as part of this record. We do not plan or anticipate the enrollment of non-English speaking subjects; however they are not excluded from participation either. Should a non-English speaking subject be eligible for enrollment, IRB approval will be obtained for use of the short form consent

process in the absence of a fully translated consent document as outlined in SOP 12.9.1, under the provisions of 45 CFR 46.117(b)(2). IRB approval will be obtained according to IRB guidance prior to obtaining informed consent from the potential study participant/s.

Subject recruitment for this study will be through advertisement in local newspapers and through postings of the included flyers in various public places such as, but not limited to, libraries, public universities, hospitals, health clubs, and local health fairs. Additionally, advertisements may be placed in some national newspapers or websites (Craigslist) to reach a wider audience, particularly for the lean, weight-maintaining arm of the study. We aim to recruit 50% women for each study arm. A review of previous enrollment in our studies indicates that we typically have an even distribution of ethnic groups in our study samples (e.g. control versus treatment) even when the representation of ethnic categories is not equal. Thus, we expect to have at least 33% of volunteers represented by African American, Hispanic, Asian, or Native American groups in each of our study arms. We plan to enroll 60 individuals and in order to enroll this many, we will likely need to screen many more. We have therefore set our anticipated number to be screened at 180, equal to three times the number enrolled. For randomization, we will stratify the groups by gender and age, using a block design.

## **2. Inclusion Criteria:**

### **1. BMI**

- a.  $\text{BMI} \geq 30 \text{ kg/m}^2$  for the obese WMEN and UF groups but body weight less than 350 pounds to accommodate the DXA scanner
- b.  $\text{BMI} \leq 25 \text{ kg/m}^2$  (and  $\text{BMI} \geq 18.5 \text{ kg/m}^2$ ) for the lean WMEN group

2. Age  $\geq 18$  years. Minors under the age of 18 will be excluded because growth and pubertal issues are significant parameters that could affect our outcomes and also because the time requirements of the study are such that they would interfere with school schedules.  
Participants must be healthy, as determined by medical history, physical examination, and laboratory tests.
3. Weight stable ( $\pm 2\%$ ) for last 3 months

### **3. Exclusion Criteria:**

Candidates will be screened by phone to exclude those with BMI  $\geq 26$  kg/m<sup>2</sup> and BMI  $\leq 29$  kg/m<sup>2</sup>, significant health problems, including cancer, hypertension, diabetes, current and past 3-month use of certain prescribed medications, especially those that could affect body weight, such as antidepressants and stimulants as well as smoking, or excess alcohol ( $> 3$  drinks/d). Women must not be pregnant or lactating, and be at least 1 year postpartum. Candidates with a history of psychotic disorder or hospitalization for psychiatric illness within the past 1 year will not be eligible. They will need to be weight stable for the past 3 months ( $\pm 2\%$ ) and cannot be in treatment for obesity or currently receiving psychotherapy. Individuals who meet criteria according to the phone screen will be invited to come to the unit for a screening visit and their screening sheets are placed in a locked filing cabinet. Forms from potential volunteers who are ineligible are shredded.

### **4. Experimental Design:**

Screening visit: Participants will arrive on the unit in a fasting state. Written informed consent will be obtained from the participant prior to any screening visits, study procedures or

treatments. The Principal Investigator or other designated qualified protocol investigators (listed on the protocol face page) will explain the study in language understandable to the subject.

Because there are both clinical and technical areas that comprise this protocol, we will ensure both areas are fully addressed to the subjects by the research team with a clinical and technical member present during screening and consenting. We have designated on the protocol face page which investigators will obtain informed consent for this protocol. The investigator signature on the informed consent will be signed by the principal investigator or a designated clinical investigator.

Sufficient time and opportunity will be given for discussion of the research as well as to answer any questions they may have, taking care to minimize or eliminate the perception of coercion or undue influence. The participant and the investigator will sign the current IRB-approved informed consent document. A witness will also sign the consent document to attest only to the validity of the signature of the subject, not the validity or quality of the consent. This visit will then include:

- Height, weight, and blood pressure measurements
- A physical exam with a medical history component, including questions about medications and alcohol/substance use history. Those meeting criteria for current substance abuse or dependence or current suicidal ideation will be excluded.
- Research chemistry profile, including complete blood cell count, serum creatinine, ALT, AST, GGT, TSH, fasting plasma glucose and HbA1c. If fasting glucose is  $\geq 125$  mg/dL or HbA1c  $> 6.5$  and thus, suggestive of diabetes, volunteers will not be eligible for participation in this study and will be referred to their personal physician for follow-up care.
- A urine sample for urinalysis, drug screen, nicotine test, and pregnancy test (if female)

- Brief meeting with a study counselor who will review the diet requirements and other protocol requirements such as the food pick-up schedule, phone contacts and self- monitoring requirements. Physical activity will be assessed using the Physical Activity Recall (PAR) Questionnaire (Wilson et al., 1986).

Following the screening visit, the study staff will meet to discuss the volunteer's eligibility for participation in the study, as set forth by the inclusion and exclusion criteria (detailed above) and will contact him/her to set up the baseline visit if accepted into the study.

The main goal of this study is to determine whether or not there are differences in dietary adherence between lean and obese individuals and between two groups of obese individuals assigned different heart-healthy dietary prescriptions (weight maintaining diet [WMEN] vs. underfeeding [UF]). The experimental design is comprised of a 6-week outpatient heart-healthy dietary intervention with 2 clinic visits per week. To achieve our study goals we will measure the following:

*Baseline Visit 1:*

1. Weight, waist, thigh circumferences & vitals
2. Body composition using dual energy X-ray absorptiometry (DXA)
3. Breakfast
4. Behavioral Questionnaires
5. Psychological performance tests
6. Meet with study counselor to discuss weight maintenance diet instructions and study procedures

These parameters are described in detail below:

- Body composition by dual-energy X-ray absorptiometry (DXA): DXA will be used to accurately measure body composition. DXA is an X-ray device which non-invasively assesses both skeletal density and soft tissue composition by region with a precision of <1% for bone and 4-5% for soft tissue densities. Total body scan requires 10-50 minutes depending on the stature and thickness of the subject. The major limitation of the apparatus is the width of the scanning table. We validated the use of a half-body scan as an indicator of whole body composition in obese subjects who do not fit entirely on the scanning area. This half body method is valid for individuals weighing as much as 350 pounds (27). During the procedure, the subject is asked to lie flat on the table and to remain motionless, because the subject's movement can compromise the precision of the measurement during the scan. Proper subject positioning is also important. Once the proper alignment is determined, the subject's ankles and knees are loosely strapped to maintain the position. When the machine is turned on, a 188 mA current flows through the X-ray tube to produce X-rays. As the scan table arms move from the top of the subject's head downward towards the subject's feet, the shutter opens and a narrow beam of radiations projects upward through the table top and subject. After the scan, the arm clears the subject's feet, the scanner stops, and the source shutter closes. The software then calculates body composition in grams of fat tissue and lean tissue and percentage of body fat. The operator remains in the room with the subject during the scan.
- Psychological Assessment: We will administer a battery of behavioral questionnaires and psychological performance tests to assess constructs related to adherence, eating-related behaviors, personality and additional psychopathology. These assessments will be used to



determine predictors of adherence and weight loss. Scores will be related to outcome measures and may be used as covariates in data analysis.

- Behavioral questionnaires:
  - Gormally Binge Eating Scale (28): a self-report questionnaire to assess binge eating behavior. Subjects are asked to choose 1 response from a set of 4 possible choices in 16 instances. This scale can successfully discriminate among persons having no, moderate or severe binge eating problems
  - The Questionnaire on Eating and Weight Patterns - Revised (QEWP-R) (29): a self-report instrument used for diagnosis of binge eating disorder (BED), designed to describe both behavioral manifestations and feelings/cognitions surrounding a binge episode. Volunteers will be excluded from the study if they have purging behaviors or have anorexia nervosa.
  - Perceived Stress Scale (PSS) (31): a 14-item self-reported questionnaire used to assess stress and an individual's perceived ability to cope with such stress over the last 28 days
  - The Inventory for Depressive Symptomatology (IDS –SR)(32): a measure of depressive signs and symptoms, applicable to atypical depression which has been associated with overeating. Those who report suicidal ideation or have scores consistent with major depression will be referred for appropriate treatment and follow-up. The clinical research unit employs a licensed psychologist, but the Phoenix Indian Medical Center also has on-call behavioral health available 24 hours/day

- Barratt Impulsivity Scale -11 (BIS-11) (33;34): a self-report scale which contains 30 questions and has shown internal consistency across populations (34). There are 3 subscales of the BIS, which categorizes impulsivity into 3 main aspects and has 3 subscale scores: motor (acting without thinking), cognitive (quick decisions), and non-planning (present orientation)
- Power of Food Scale (PFS: (35;36): is a 15-item self-report measure of individual differences in the appetitive drive to consume highly palatable food, independent of homeostatic hunger
- The Social Problem-Solving Inventory - Revised (SPSI-R; (37): is a 52-item self-report measure that uses a 5-point Likert scale to assess problem solving abilities. It has 5 subscales: 1) Positive Problem Orientation; 2) Negative Problem Orientation; 3) Rational Problem Solving; 4) Impulsivity/Carelessness Style; and 5) Avoidance Style
- The NEO-FFI Neo-Five Factor Inventory (38): is a 60-question validated questionnaire to assess the five major dimensions of personality (Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness)
- Weight Efficacy Lifestyle Scale (WEL; (39)): a 20-item questionnaire to rate confidence in ability to avoid eating on a 10-point Likert Scale
- Treatment Self-Regulation Questionnaire (TSRQ; (40): to determine autonomous motivation (internal reasons for change) and controlled motivation (extrinsic reasons for change)
- The Three-Factor Eating Questionnaire (TFEQ) (77): a 51-item questionnaire composed of 3 subscales. These subscales measure dietary restraint (i.e., the cognitive control of eating, 21 items), disinhibition (i.e., the tendency to have an uninhibited

response to food, 16 items), and perceived hunger (i.e., the susceptibility of eating in response to subjective feelings of hunger; 14 items) using “true/false” or multiple-choice items.

- Emotional Appetite Questionnaire (EMAQ) (78): used to examine eating response to both positive and negative emotions and situations.
- The Childhood Trauma Questionnaire (CTQ; 120): is a 28-item self-report inventory that assesses abuse and neglect during childhood.
- Physical Anhedonia Scale (PAS) (85): a 61-item scale to assess sensitivity to reward (STR). It is designed to reflect the degree to which individuals take pleasure from, and are motivated to engage in, rewarding behaviors. High scores on this scale reflect the anhedonic end of the STR dimension while low scores reflect ‘hedonia’ or the enhanced ability to seek out and enjoy natural rewards.
- MacArthur Scale of Subjective Social Status (119): contains 2 ladders measuring subjective socio-economic status. Studies have indicated that ladder rankings are more powerful determinants of health-related outcomes than traditional measures of SES (121).
- U.S. Adult Food Security Survey Module: Six-Item Short Form: a 6-item self-report version of the original 18-item module for the assessment of food insecurity over the past 12-months. It classifies households into 3 categories of food security status according to the U.S. food security scale (120). It has been shown to identify food-insecure households and very low food security with reasonably high specificity and sensitivity and minimal bias compared with the 18-item measure (122) and shows significant association between food insecurity and obesity.

- Psychological performance tests:
  - Iowa Gambling Task (41;42): to evaluate decision-making. Subjects will be instructed to try to gain as much fake money as possible by drawing 100 selections from a choice of 4 decks of cards, while starting with a loan. The decisions to choose from the decks should become motivated by reward and punishment schedules inherent in the task. Two of the decks are disadvantageous, producing immediate large rewards but these are (after a pre-punishment phase of about 10–15 cards) accompanied by significant money loss due to extreme punishments. The other 2 decks are advantageous; reward is modest but more consistent and punishment is low.
  - Stroop Color Word Test (43): to assess selective attention. Words are presented on the screen in either a congruent (color screen with words printed in color) or incongruent set (color-word screen where the color and the word do not match [for example, the word “green” is printed in blue ink]). The subject has to either read the words or name the ink colors as quickly as possible within a time limit. A second Stroop task will be administered that will include food words that are printed in varying colors. Subjects will be asked to name the color rather than the name of the food.
  - Wisconsin Card Sorting Test (44): to examine cognitive executive functioning. Subjects are presented with 4 stimulus cards and 128 response cards. They are instructed to respond with response cards to match each of the 4 stimulus cards (based on either color, form or number, but directions are ambiguous), and are told if they are right or wrong. Once a certain number of correct answers are made, the sorting

principle is changed without warning, requiring the subject to figure out the new sorting strategy

- Go/No Go Task (45): to examine inhibitory control. Subjects are required to press a key whenever a target stimulus is presented and to refrain from pressing the key when a non-target stimulus is presented
- Meeting with study counselor: The counselor will review the weight-maintenance heart-healthy dietary prescription and provide the volunteer with 3 days of food. The volunteer will be instructed to eat only the foods provided, consume no additional foods, maintain their current levels of physical activity, and to keep track on a self-monitoring food record form.
- Weight Maintenance Dietary Prescriptions:
  - Recent studies have found that using free prepared meals facilitated greater adherence (16) and weight loss compared with a control group (17). Therefore, because the primary aim of our study is to compare differences between lean and obese groups and WMEN versus UF diets (rather than investigate real-world learning), all food items will be provided by the CRU, primarily as prepackaged meals and snacks for the volunteers to take home (see Table 2 for sample menu).
  - All diets will have 20%, 30%, and 50% of daily calories provided as protein, fat and carbohydrate, respectively. They are designated as "heart-healthy" because they will be balanced diets, which are also low in cholesterol and saturated fat.
    - During the baseline week, all participants will be fed their weight maintaining energy needs (WMEN), equal to the number of calories calculated for each participant based on the WHO equation with an activity factor (1.3-1.5)(46;47), based on results from the PAR questionnaire.

- *Women:* 18 to 30 y:  $EE = 13.3 \times \text{weight (kg)} + 344 \times \text{height (m)} + 35$   
30 to 60 y:  $EE = 8.7 \times \text{weight (kg)} - 25 \times \text{height (m)} + 865$
- *Men:* 18 to 30 y:  $EE = 15.4 \times \text{weight (kg)} - 27 \times \text{height (m)} + 717$   
30 to 60 y:  $EE = 11.3 \times \text{weight (kg)} + 16 \times \text{height (m)} + 901$
- During the first week, and prior to randomization, all patients will come for 2 outpatient visits to be weighed
- If their weight changes by 2%, their caloric intake will be adjusted by 200 kcal accordingly

#### Baseline Visit 2:

1. Weight
2. Adjust calories by 2%, if needed

#### Outpatient Visits (6 weeks):

- *Randomization:* During the first outpatient study visit, participants will meet with a study counselor to discuss randomization assignment. They will be provided with 4 days of food and will again be instructed to eat only the foods provided, consume no additional foods, maintain their current levels of physical activity, and to keep track on a self-monitoring food record form. Additionally, they will be instructed on how to use the smart-phone system
  - Heart-Healthy Dietary Prescriptions:
    - Both the lean and obese WMEN groups will continue to eat the same number of calories that were calculated for them during the baseline weight maintenance period

- The obese UF group will be assigned a diet of 35% of the calculated energy needs
- *Weight and BP*: obtained at each visit
- *Meal pick-up*: meals will be prepared by the metabolic kitchen and picked up on a twice weekly basis
- *Meeting with Study Counselor*: Participants will meet 1x/week with a study counselor to review food records and dietary adherence. The counselor will rate the participants adherence and participant will rate his/her adherence to the dietary prescription and to behavioral aspects on a 5- point Likert Scale (0 = low; 5 = high). Counselors will also obtain a rating of subjective hunger over the last week on the same Likert Scale (0 = low; 5 = high) and assess change in physical activity. Sessions will last 15-30 minutes.
- *Assessment of Adherence*: Subjects will complete additional assessments of adherence:
  - 24-hour recall: this will be conducted by a member of the study staff other than the primary counselor to avoid bias
  - Computerized confessional: participants will complete a computerized battery of questions that will include a 24-hour recall with prompts to encourage recall of various foods possibly consumed at various times during the day. Questions about other weight and eating behaviors will be included. Data from this procedure will enable us to compare with the in-person interview version of the 24-h recall and assess reliability

*Outpatient Adherence Contacts:*

- 24-h recall by phone: a member of the study staff will call at a random time, 1x/week to conduct a 24-h food recall

- Ecological Momentary Assessment (EMA) using Smart-phones: participants will use Smart-phones to monitor adherence. In brief, EMA research techniques reflect repeated, real-time (momentary) assessment in the participants' typical environment (48). Recent studies have shown that anger predicted binge episodes (Engel et al., 2007) and overall negative moods were higher on binge days than on non-binge days (Wegner et al., 2002). Signal contingent recordings will be used, which involves respondents recording experiences whenever signaled at semi-random times throughout the day. Signals will occur two times/day: once between 8am and 3pm and once between 3pm and 9pm and will be randomly dispersed.

When signaled, volunteers will be asked:

- Since the last time you were signaled, have you eaten anything?
- If yes, did you eat the study food provided to you?
  - If yes, did you finish the food?
  - If no, which foods didn't you eat?
- Did you eat anything else (in addition to the food provided)?
  - If yes, what did you eat?
- Mood will be assessed using the short version of the Positive and Negative Affect Scale (PANAS, Watson & Clark, 1989). Each item will be rated on a 7-point scale (0, none; 3 moderately; 6 extremely; Engel 2007; Wegner et al., 2002)
- Phones will have a data service plan to allow for transfer of data from the phone to a stored network. GPS and/or other tracking systems will not be installed and volunteers will not be monitored or tracked via the smart phone. Participants will have the option of using their own smart phones if they already have one.



After completion of the 6-wk outpatient study, volunteers will repeat the following tests during their final outpatient visit:

*Post-Intervention Visit:*

- weight, blood pressure
- Lab work; CBC, Research chemistry profile, urine HCG (for females)
- Repeat DXA
- Repeat behavioral measures and psychological performance tests
- Final adherence measurement and exit interview

**5. Patient monitoring:**

**5.1 Criteria for individual subject withdrawal:**

Any subject experiencing (1) clinically apparent deterioration or severe side effects resulting from the dietary interventions or (2) who develops any medical problem that poses a safety risk for further participation will be withdrawn.

**6. Data Analysis and Sample Size:**

The design of this study will allow us to look at differences in levels of adherence to a heart-healthy dietary prescription in lean vs. obese individuals. We will also be able to compare adherence levels in obese individuals who are being fed a WMEN diet compared to an UF diet. Additionally, we will measure predictors of adherence and the relationship between adherence and weight loss.

**Data Analysis:**

**Measuring Adherence: (see Appendix B):** for all measures, adherence will be examined as a binary variable (adherent versus non-adherent). Each measure will be awarded 0 points if non-adherent and 1 point if adherent.

1. Attendance: two sessions per week: (adherent = attended; non-adherent = not attended; 12 possible total points over the study).
  - a. counseling
  - b. food pick-up
2. Food Diaries: volunteers will turn in diaries during their weekly counseling visit. For each weekly diary there will be three scores (18 possible total points over the study):
  - a. *Completion of records*: adherent = completed diary; non-adherent = missing or incomplete diaries
  - b. *Dietary Adherence to Foods provided*: adherent = consumed all; non-adherent = did not consume all
  - c. *Adherence to Additional Foods*: adherent = did not consume any; non-adherent = consumed additional foods
3. 24-hour recall in-person interview: once per week on day of counseling session. For each session there will be three scores (18 possible total points over the study):
  - a. *Completion of interview*: adherent = completed interview; non-adherent = did not complete interview
  - b. *Dietary Adherence to Foods provided*: adherent = consumed all; non-adherent = did not consume all
  - c. *Adherence to Additional Foods*: adherent = did not consume any; non-adherent = consumed additional foods

4. 24-hour recall using computerized confessional: once per week on day of counseling session. For each session there will be three scores (18 possible total points over the study):
  - a. *Completion of records*: adherent = completed interview; non-adherent = did not complete interview
  - b. *Dietary Adherence to Foods provided*: adherent = consumed all; non-adherent = did not consume all
  - c. *Adherence to Additional Foods*: adherent = did not consume any; non-adherent = consumed additional foods
5. 24-hour recall (telephone): once per week. For each phone session there will be three scores (18 possible total points)
  - a. *Completion of recall*: adherent = completed recall; non-adherent = did not complete recall
  - b. *Dietary Adherence to Foods provided*: adherent = consumed all; non-adherent = did not consume all
  - c. *Adherence to Additional Foods*: adherent = did not consume any; non-adherent = consumed additional foods
6. EMA recordings: there will be two contacts per day. For each contact there will be three adherence scores. To avoid having EMA be more heavily weighted in the total score, the total weekly score will be divided by 7 to obtain an average weekly EMA score (42 possible total points per week; 6 possible total average points):

- a. *Completion of recording*: adherent = completed recording; non-adherent = did not complete recording. We will define incomplete or missing entries as non-adherent for that day.
  - b. *Dietary Adherence to Foods provided*: adherent = consumed all; non-adherent = did not consume all
  - c. *Adherence to Additional Foods*: adherent = did not consume any; non-adherent = consumed additional foods
7. Additional Non-Intervention Related Adherence Measure (once per week. For each rating there will be 1 score (6 possible total points over the study): We will also track the arrival time for weekly counseling session as a measure of adherence that is not directly related to the study intervention. Appointment adherence will be scored as the arrival within 5 minutes of the scheduled time and actual arrival time will be documented as a continuous measure of adherence. This measurement will allow us to examine the relationship between adherence to the dietary protocol and adherence to "other" factors (e.g. punctuality) and it will be included in the total adherence score.
- a. Appointment adherence: adherent = arrived within 5 minutes of scheduled appointment; non-adherent = did not arrive within 5 minutes of scheduled appointment

**Adherence Score:** The above variables will be totaled up to calculate a total adherence score out of a possible 21 points during each week. A percent (%) adherence score will also be calculated by dividing the total score by the number of variables assessed (21) and multiplying by 100 ( $[\text{total}/21] \times 100$ ).

### **Statistical Analysis:**

For our primary hypothesis, a one-way ANOVA will be performed with total adherence score as the dependent variable and group status (lean WMEN, obese WMEN, obese UF) as the independent variable. In addition, linear regression models adjusted for covariates including age, sex, race, socioeconomic status (SES) and baseline weight or percent body fat will also be used to examine the relationship of adherence and behavioral factors. Correlations between adherence scores, behavioral test scores and weight, fat mass and fat free mass loss will be calculated. Pearson's  $r$  will be calculated for data that are normally distributed and Spearman's correlation will be used if the distributions are non-normal. This will be an intention to treat study such that everyone who completes the run-in phase will be included in the final analysis. Missing data will be completed using a multiple imputation method utilizing the SAS procedures, PROC MI and MIANALYZE. This method introduces variability into the imputed values to reduce the risk of a type 1 error. All tests will have a 2-sided Type I error of  $p = 0.05$ .

### **Power Calculation:**

Sample size calculations are based on the number of individuals needed to demonstrate a significant difference in adherence scores over the 6-week intervention period between the 3 diet groups (lean WMEN, obese WMEN, obese UF).

We based our expected percent adherence score on a recent paper by Williamson et al (26) who observed 52% adherence in a group of obese dieters. Our maximum possible adherence score is 21 per week. To account for the increased adherence we expect to see because food is being provided in the study, we have increased the proposed adherence from the 52%

adherence observed in the POUNDS LOST study by an additional 10% and applied this increase in score across all 3 groups. Thus, assuming 62% adherence, we would expect a mean weekly score of 13 in the calorie restricted group. If we in addition, consider a smaller a meaningful difference between the groups of 3 points; (lean WMEN = 19, obese WMEN = 16, obese UF = 13), assuming the same SD = 6, with a calculated sum of squares of the means = 32, across 3 treatment groups with a mean 16 +/- SD = 6, alpha = 0.05, the proposed total of 20 subjects per group (total n = 60) would allow us to achieve a power of 0.793 (**see table 3a**). If we assume a larger difference between the groups 3.5 points; lean WMEN = 20, obese WMEN = 16.5, obese UF = 13), the proposed total of 20 subjects per group (total n = 60) would allow us to achieve a power of 0.906 (**see Table 3a**). Because the drop-out rate in weight loss intervention studies averages around 25%, we plan to recruit a total of 150 subjects (25 per group) to account for both screening failures and attrition, and to ensure 60 completers (**see Table 3b**).

## **7. Benefits:**

This is a supervised dietary outpatient study being offered to lean and overweight/obese individuals. The prescribed diet is "Heart-healthy" and could improve metabolic and health outcomes in all 3 groups. In addition, those in the UF group who adhere to the diet may experience weight loss, which may lead to additional favorable future metabolic outcomes. All volunteers will receive information regarding some aspects of their health, including lab screening tests, a thorough physical examination, a measure of body fat, and an evaluation of their glucose tolerance status. The results of these tests will be available to the subjects and will be provided to their personal physician, if desired. Other expected benefits of this study include obtaining generalizable knowledge related to the difference in levels of adherence between lean

and overweight/obese individuals, which has not yet been examined. We will also gain knowledge about predictors of treatment adherence for weight loss and the relationship between adherence and weight loss. Moreover, we are proposing novel ways to measure adherence, which could be used in future studies. The information obtained from this study should be useful to scientists, physicians, and psychologists.

## **8. Human Subjects Precautions:**

### ***8.1. Recruitment and Minority Participation***

Participants will be recruited via advertising in local newspapers and on the internet, strategies which have proved successful in the past. Based on our previous studies, we expect the ethnic diversity of our volunteers to be approximately 40% Caucasian, 40% Native American, 10% Black and 10% Hispanic. Native Americans represent approximately 2% of the population in greater Phoenix area, and we anticipate over-representation because our unit is situated within the Phoenix Indian Medical Center. Additionally, Native Americans have previously participated in many of our studies. We anticipate recruiting approximately 5 volunteers per month (60/year) over the course of about 1.5 years.

### ***8.2. Safeguards for subjects:***

Subjects will have the option of discontinuing the study at any time. All data will be treated confidentially, and the identity of subjects will not be disclosed in publications. Participants will be monitored (weight and blood pressure) and seen by a counselor weekly. Any participant judged on clinical grounds to have suffered any adverse effect will be evaluated by a provider (physician, physician assistant, nurse practitioner, or psychologist).

### ***8.3. Risks and Discomforts:***

8.3.a Radiation exposure due to DXA: The DXA scans will take place on the GE Lunar iDXA machine. The radiation exposure for a 188 mA scan may be as much as 1 mrem as indicated by a January 2014 internal radiation exposure review. According to the manufacturer, the medium and fast slow scan speeds are likely to result in one-half the radiation exposure of the slow scan speed. A typical radiation dosage from this procedure is equivalent to 1.22 days (iDXA) of exposure to natural background sources, such as the sun and outer space, or radioactive materials found naturally within the earth's air and soil. For subjects who move excessively during the scans, a complete or partial repeat of the scan procedure may be necessary. Thus, subjects could receive a maximum of 2 mrem (iDXA, 2.5 days of exposure) if the slow scanning mode is used each time. Participants in this study will undergo 2 DXA scans over the study period therefore the maximum amount of radiation they will receive in the first year could be as high as 4 mrem (iDXA, 5 days of exposure). This exposure increases the percent cancer risk from 25 percent to 25.00016 (iDXA). This is well within the NIH Phoenix Radiation Safety Guidelines for research subjects of 3,000 mrem in a 13-week period and 5,000 mrem per year. A urine pregnancy test will be performed in all females who are able to become pregnant prior to each DXA scan.

8.3.e Dietary Intervention: The side-effects of consuming a pre-selected diet are minimal and might include boredom, lack of desire to eat the prescribed foods and/or increased feelings of hunger.

8.3.e Questionnaires and computer performance tests: There are no known risks associated with completing any of these questionnaires. However, some of the questions may be of a highly personal nature; thus, subjects will be informed that they do not have to respond to all the questions if they choose not to do so. If this is the case, notations to that effect will be noted in the patient's record.



8.3.f Urine Drug Screen: Results of this test will be used only to determine study eligibility. If the result is positive, patients will be confidentially informed of the results and a recommendation for follow-up will be made with their primary physician.

8.3.g Blood Withdrawal: The amount of blood that may be drawn from adult patients and volunteers (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period.

8.3.h Adherence Measurements: Receiving phone calls from study staff and completing EMA assessments and food records could be perceived as a nuisance, but there are no known risks. Recalling food eaten, associated moods and related activities could induce negative emotions but the risks are minimal.

#### **8.4. Disclosure of medical conditions:**

The participants will be informed of any medical conditions uncovered by the screening blood work performed and referred to their primary care provider. The information will also be entered into their medical records and, at the patient's request, sent to their physicians. In the event that during screening, participants are found to have psychotic symptoms and present a danger to themselves or others, behavioral health services (available on site in the facility) will be contacted for appropriate referrals. All information from the study will be made available to the patients and their physicians at the patients' request. Information will be treated with the same protection and confidentiality as all other medical records. All information from the study may be made available to insurance companies if the information is requested by the insurance company and the subject signs a release of information. This could affect future insurability and employment opportunities.

#### **8.5. Data and Safety Monitoring:**

8.5. a. Independent Data Safety Monitoring Board: Potential adverse events from this study are expected to be infrequent. Therefore, the principal investigator (PI) will act as the safety monitor and report these events to the NIDDK IRB. Study procedures will be subject to audits and/or monitoring visits to ensure compliance with the protocol and applicable regulatory requirements consistent with the PIMC quality assurance program plan. Audit and/or monitoring visits results will be reported to the Principal Investigator for further reporting as appropriate. Study documents and pertinent hospital or clinical records will be reviewed to verify that the conduct of the study is consistent with the protocol plan.

8.5.b. Adverse events, protocol deviations, unanticipated problems (UP), serious adverse events, are defined as described in NIH HRPP SOP 16 (“Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations”). All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded and assessed for relatedness to the study procedures or treatments, severity and whether or not they are expected (in nature, severity and frequency). Serious unanticipated problems and serious protocol deviations will be reported to the IRB and Clinical Director (CD) as soon as possible but not more than 7 days after the PI first learns of the event. Non-serious unanticipated problems will be reported to the IRB and CD as soon as possible but not more than 14 days after the PI first learns of the event. Non-serious protocol deviations will be reported to the IRB as soon as possible but not more than 14 days after the PI first learns of the event. Non-serious protocol deviations that result from the normal subject scheduling variations or technical issues associated with sampling that does not impact the health of the subject or the interpretation of the study data will not be reported. Deaths will be reported to the CD and the IRB within 7 days after the PI first learns of the event. Previously undiagnosed medical conditions discovered by laboratory testing or imaging will not be reported

as adverse events, but will receive appropriate follow-up and referral to the primary care provider.

- The PI is responsible for summarizing all adverse events at least possibly related to the research procedure and interventions at the time of Continuing Review. All deaths that have occurred among study participants since the previous review will be summarized at the time of continuing review.

#### ***8.6. Research Use of Stored Human Samples, Specimens or Data:***

Blood (stored as plasma or serum) and urine samples not immediately used for study purposes will be stored for future measurements. Remaining plasma, serum, and urine samples will be stored in freezers located on the premises at the NIH in Phoenix. Stored samples and specimens will be used only to measure factors which relate to obesity and its complications and weight loss interventions. Stored samples, specimens or data may be sent to collaborators for specific measurements or analyses. All stored samples, specimens, and data will be coded so that when sent for measurements the identity of the volunteer remains confidential. Identification of coded samples will be kept in a secure, password-protected database accessible only to investigators, but will be identifiable in case specific tests yield clinical information of importance to a particular volunteer or samples can be destroyed per volunteer request (see below). Samples will be used only for research and not for commercial purposes. Research volunteers will not be informed of individual results from analyses performed specifically for research purposes; unless there is clear evidence accepted by the medical community that these results will impact the volunteer's individual medical care or future health. Samples will be stored until used and will not be destroyed unless specifically requested in writing by the

volunteer. Reports of samples lost due to technical issues or destroyed secondary to volunteer request will be included in the annual renewal report.

At this time, there is a consultative relationship set up with Drs. Scott Engel and Ross Crosby of the Neuropsychiatric Research Institute in Fargo, North Dakota. Drs. Engel and Crosby will assist with implementing the Smartphone EMA protocol and will aid in analysis of the data. The data will be uploaded to a server that will be accessible to Dr. Gluck and her team, as well as to Drs. Engel and Crosby. Additionally, they will receive related study data, including adherence scores and other metabolic parameters collected during the study for assistance with the data analysis and interpretation of the results.

**8.7. Reimbursement:** Reimbursement will be offered to study participants who will get paid for their visit to the clinical research ward as follows, per local Ethics Committee guidelines:

Volunteers will be compensated \$25 for the screening visit. Total reimbursement for the 7 week study will be at a flat rate of \$625.00. A payout of \$50.00 will be given at the end of the 3rd study week with the balance of \$575.00 at completion of the study with return of the smart phone. If the smart phone is not returned for any reason, the balance of the payment will not be paid at the end of the study.\*

\*\* If discontinuation occurs prior to completion of the study (7 weeks), reimbursement will be at the rate of \$10.00 per visit, beginning with the first outpatient visit. This reimbursement rate goes into effect if the study is not completed for any reason, i.e. occurrence of illness, family emergency, or per investigator discretion in the event of noncompliance with study procedures.

**Screening Visit:**

Screening payment @ \$25.00/d	<b>\$25.00</b>
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**Baseline Visits**

Baseline Assessment visit (@\$35)	\$35.00
3 inconvenience units for psychological assessments (baseline visit)	\$75.00
Daily payment (@\$35) for outpatient visit x 2: weight maintaining period	\$70.00
<b>Total</b>	<b>\$185.00</b>

**Outpatient Visits:**

Daily payment (@\$35) for outpatient visit x 6 (counseling sessions)	\$210.00
Travel compensation (@\$10) for outpatient visit x 6 (food pick-up)	\$60.00
3 inconvenience units for repeat psychological assessments during final visit	\$75.00
Bonus for study completion	\$100.00
<b>Total</b>	<b>\$445.00</b>

**Total Reimbursement (including screening visit): \$ 650.00**

**TABLE 1: STUDY PROCEDURES**

**Baseline & Wt. Maintenance Visits**

**Outpatient Study Visits**

PROCEDURES	SV 1	BV1	BV2	WK 1	WK 2	WK 3	WK 4	WK 5	WK 6
Screening lab tests	X								X
DXA		X							X
Psychological assessments		X							X
Randomization & instructions				X					
Clinic Visit/ Food Pick-up		X	X	XX	XX	XX	XX	XX	X
Weight and BP	X	X	X	XX	XX	XX	XX	XX	XX
Meet w/counselor		X		X	X	X	X	X	X
24-h recall interview				X	X	X	X	X	X
Complete computerized recall				X	X	X	X	X	X
EMA assessments				XXXX XXXX	XXXX XXXX	XXXX XXXX	XXXX XXXX	XXXX XXXX	XXXX XXXX

				XXXX XX	XXXX XX	XXXX XX	XXXX XX	XXXX XX	XXXX XX
24-h food recall by phone				X	X	X	X	X	X

**TABLE 2:** Sample Menu

<b>Item Name</b>	<b>Quantity</b>	<b>Measure</b>	<b>Cals(kcal)</b>	<b>Prot(g)</b>	<b>Carb(g)</b>	<b>Fat-T(g)</b>
<b>Day 1 (1/3/2012)</b>			<b>2002</b>	<b>90</b>	<b>299</b>	<b>55</b>
<b><i>Breakfast</i></b>			<b>338</b>	<b>17</b>	<b>64</b>	<b>3</b>
Instant Breakfast, chocolate, pkt	1	Each	131	7	24	1
Banana, fresh, med, 7" to 7 7/8" long	1	Each	105	1	27	0
Milk, 1%, w/add vit A & D	1	Cup	102	8	12	2
<b><i>Lunch</i></b>			<b>651</b>	<b>26</b>	<b>103</b>	<b>16</b>
Lean Cuisine, Grilled Chicken & Penne	1	Each	385	23	61	5
Carrots, baby, fresh	3	Ounce-Wt	40	1	9	0
Apples, fresh, sliced	6	Ounce-wt	88	0	23	0
Heat & Serve Roll	1	Serving	53	2	10	1
Spread, buttery, Omega Plus	1	Tablespoon	85	0	0	9
<b><i>Dinner</i></b>			<b>622</b>	<b>28</b>	<b>82</b>	<b>21</b>
Dinner, chili & cornbread, ckd f/fzn	1	Each	560	27	67	21
Oranges, fresh, med, 2 5/8 " diameter	1	Each	62	1	15	0
<b><i>Evening Snack</i></b>			<b>391</b>	<b>18</b>	<b>51</b>	<b>14</b>
Formula, choc, rtu	1	Serving	250	9	40	6
Cheese, mozzarella, string, part skim	1	Each	80	8	1	6
crackers, original, Triscuit	0.5	Ounce-wt	61	2	10	2

**TABLE 3A & 3B: POWER CALCULATION****3A**

The SAS System

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The POWER Procedure  
Overall F Test for One-Way ANOVA

Fixed Scenario Elements

Method	Exact
Alpha	0.05
Group Means	13 16 19
Standard Deviation	6

Computed Power

N Per		
Index	Group	Power
1	10	0.458
2	12	0.543
3	14	0.619
4	16	0.686
5	18	0.744
6	20	0.793
7	22	0.834
8	24	0.868
9	26	0.896
10	28	0.918
11	30	0.936



**3B**

The SAS System

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The POWER Procedure  
 Overall F Test for One-Way ANOVA

## Fixed Scenario Elements

Method	Exact
Alpha	0.05
Group Means	13 16.5 20
Standard Deviation	6

## Computed Power

N Per		
Index	Group	Power
1	10	0.590
2	12	0.685
3	14	0.762
4	16	0.823
5	18	0.870
6	20	0.906
7	22	0.933
8	24	0.952
9	26	0.967
10	28	0.977
11	30	0.984

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<b>SCORE SHEET</b>	Week1 (0 no, 1 yes)	Week 2	Week 3	Week 4	Week 5	Week 6
Session #1 Attendance (weight, counseling, 24-h interview, computer confessional, food pick-up)	1					
▪ Food Diaries completed	0					
▪ Food Diary food supplied	0					
▪ Food diary consuming other food	0					
▪ 24-hr recall interview completed	1					
▪ 24-hr recall interview food supplied	1					
▪ 24-h recall interview consuming other foods	0					
▪ Computer confessional completed	1					
▪ Computer confessional food supplied	1					
▪ Computer confessional consuming other food	0					
Session Attendance (#2: wt, food pick-up)	1					
24-hr recall phone completion (1)	1					
24-hr recall phone food supplied (1)	1					
24-h recall phone consuming other foods (1)	0					
EMA daily completion of records (1)	7					
EMA daily adherence of foods supplied (1)	6					
EMA daily adherence of consuming other foods (1)	4					
EMA daily completion of records (2)	5					
EMA daily adherence of foods supplied (2)	5					
EMA daily adherence of consuming other foods (2)	2					
AVERAGE weekly EMA Score (total possible = 6)	4.1					
On Time Arrival for Session	1					
<b>Total Score</b>	<b>13.1</b>					
<b>% Adherence (total/21) *100</b>	<b>62%</b>					