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# Rationale and design of the frequency of eating and Satiety Hormones (FRESH) study: A randomized cross-over clinical trial

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ABSTRACT

*Background:* The goal of the Frequency of Eating and Satiety Hormones (FRESH) Study is to understand the relationship between eating frequency (EF) and biomarkers of appetite and disease risk. This report gives the study rationale and design.

*Methods:* The FRESH study was conducted in n = 50 overweight and obese, but otherwise healthy, male and female adults aged 18–50 years. The protocol included four in-person clinic visits for protocol instruction, blood draws, anthropometry, and meal testing; all other activities were done at home. Participants completed two 21-day phases in random order with a two-week washout between phases. One phase was high EF (6 eating occasions/day) and the other was low EF (3 eating occasions/day). Each phase specified time of day for each eating occasion. Participants prepared their own meals throughout the study using study-provided individualized, structured meal plans ensuring that calories, macronutrients and micronutrients were identical during both study phases. Fasting blood was collected before and after each phase to test intervention effects on the biomarkers. At the end of each phase participants also completed extended appetite testing with meals prepared by the study clinic.

*Results:* Participants were recruited using print, radio, and digital ads. 60 participants consented to enroll; 10 dropped out due to work or school scheduling conflicts and 50 (target sample size) completed the study. Compliance was assessed by completion of daily on-line meal plan checklists.

*Conclusions:* The FRESH study will provide data on whether higher vs. lower daily EF in the context of constant energy and nutrient intake may be harmful or beneficial based on intervention effects on biomarkers of health and disease risk.

## 1. Introduction

Current nutritional guidelines provide evidence-based recommendations for appropriate energy and nutrient intake across the lifespan for both males and females [1]. However, evidence-based recommendations are lacking for the optimal number of eating occasions per day. While there is wide speculation regarding the ideal number of daily eating occasions [2,3], there is no conclusive evidence supporting a relationship between eating frequency (EF) and health, independent of energy and nutrient intake. Several observational studies have found inverse associations between EF and disease risk factors including body weight, adiposity, and biochemical markers for heart disease and cancer [4–7]. However, as with all observational studies reliance on self-report of dietary intake and the inherent underreporting and measurement error in self-report is a barrier to drawing strong inferences from reported results [8–10]. Conversely, intervention studies comparing diets of high and low EF have found inconsistent results in relation to some of the same measures, including body weight, body composition, appetite, food intake, and biomarkers of metabolism and disease development [4]. Recommendations for increased EF are widely published in the popular diet literature as an approach to curbing appetite and reducing energy intake, but it remains unknown whether high or low EF best aids in regulation of appetite, energy balance and measures of long-term health. Therefore, we have designed and

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implemented a randomized controlled trial in healthy, free-living individuals that will test the effect of EF on blood-based biomarkers of inflammation, adiposity and satiety. These outcomes were selected based on our prior pilot work [11,12] as well as that of others [4,13–15]. Here we describe the study design and protocol.

## 2. Methods

### 2.1. Study design

The Frequency of Eating and Satiety Hormones (FRESH) Study is a randomized, cross-over clinical trial investigating the effects of low EF (three eating occasions/day) vs. high EF (six eating occasions per day) on blood-based biomarkers of inflammation, biomarkers of appetite regulation and food intake and self-reported perceived appetite. The study was registered at clinicaltrials.gov as NCT02392897. We will comply with NIH reporting requirements and NIH data sharing policies.

Study participants were normal (BMI-18.5- < 25.0 kg/m$^2$), overweight (BMI = 27.9–29.9 kg/m$^2$) and obese (BMI = 30.0–40.0 kg/m$^2$), but otherwise healthy adult males and females living in Seattle, WA, USA. Based on self-reported race/ethnicity, the study sample was 70% Caucasian (n = 35), 22% Asian (n = 11), 4% Black or African American (n = 2), and 4% more than one race (n = 2). Participants were randomly assigned to follow either low EF or high EF for 21 days (phase 1). Participants then completed a 14-day wash-out period followed by 21 days on phase 2 (see Fig. 1, study design). Participants attended study clinic visits at the beginning and end of both phase 1 and phase 2. All in-person procedures were conducted at the Fred Hutchinson Cancer Research Center Prevention Center clinic. Participants received $300.00 at the end of the study after completing all study activities.

### 2.2. Participants

Participants were healthy males and females 18–50 years of age. Exclusion criteria included: 1) fasting glucose greater than 100 mg/dL (tested at a screening clinic visit); 2) physician diagnosed medical conditions requiring dietary modification including but not limited to cardiovascular disease, diabetes mellitus; 3) current pregnancy, breastfeeding, or plans to become pregnant during the study period; 4) BMI < 18.5 kg/m$^2$, between 25.0 kg/$^2$ and 27.9, or > 40 kg/m$^2$; 5) history of eating disorder or restrained eating; 6) use of prescription or over-the counter medications that would interfere with accuracy of endpoint biomarkers or self-reported appetite; 7) tobacco or marijuana (recreational or medical) use; 8) any other conditions that would preclude successful completion of the protocol, such as work or school schedules.

### 2.3. Recruitment

Participants were recruited using print, radio, and digital ads. Print advertisements included various flyers, business cards, stickers, and reusable shopping totes featuring the study logo. These items were distributed at local organizations including the Fred Hutchinson Cancer Research Center, the Seattle Cancer Care Alliance, the University of Washington and other local colleges/universities, farmer's markets, fun runs and other community events, and local businesses (e.g., coffee shops, grocery stores, fitness studios, public libraries). Electronic advertisements were placed in digital news and entertainment publications, online classifieds such as Craigslist, and social media outlets including Facebook, Twitter, and university affiliated wellness blogs. Information about study recruitment was also listed on the Fred Hutchinson Cancer Research Center's volunteer website and the University of Washington-Medicine's Institute for Translational Health Sciences (ITHS) website. Recruitment began June 2015 and ended Fall, 2018.

A study website (http://www.thefreshstudy.org/) was created and used for additional aspects of study recruitment and initial eligibility screening. The posted recruitment flyers contained a QR code that took participants directly to the online screening form when scanned. Website tabs included an overall study description and requirements for

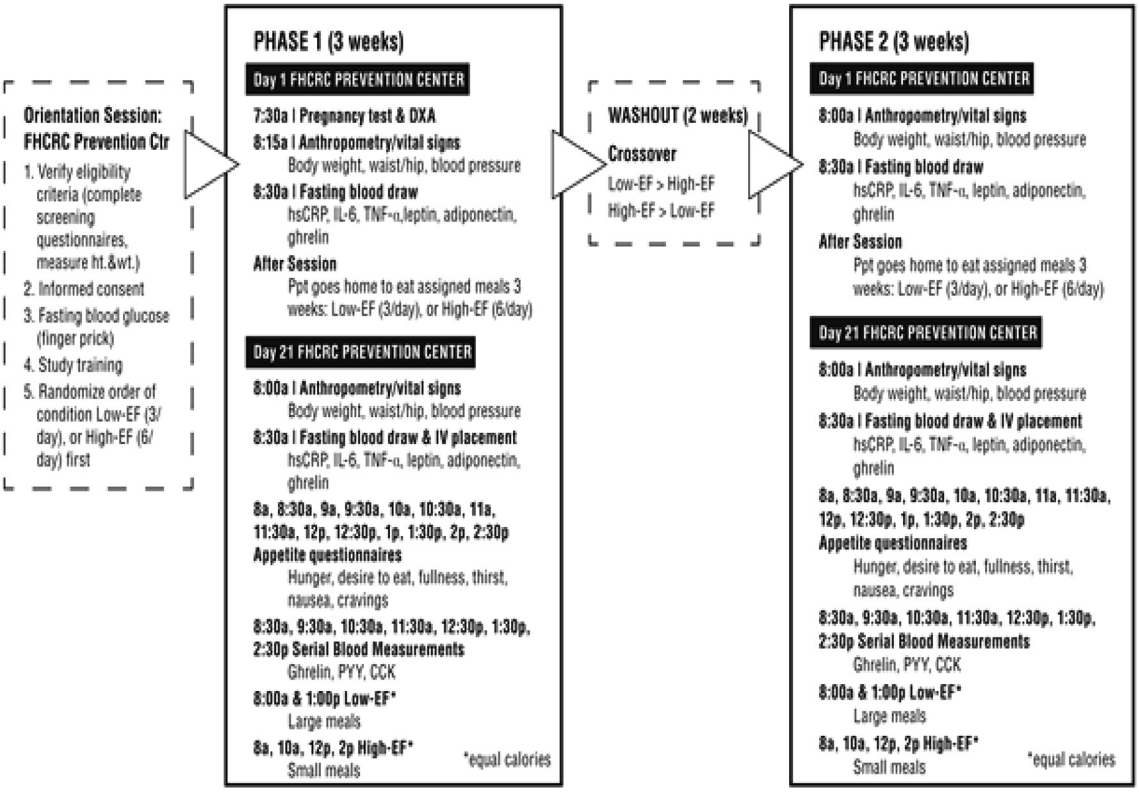


**Fig. 1.** Fresh study design.

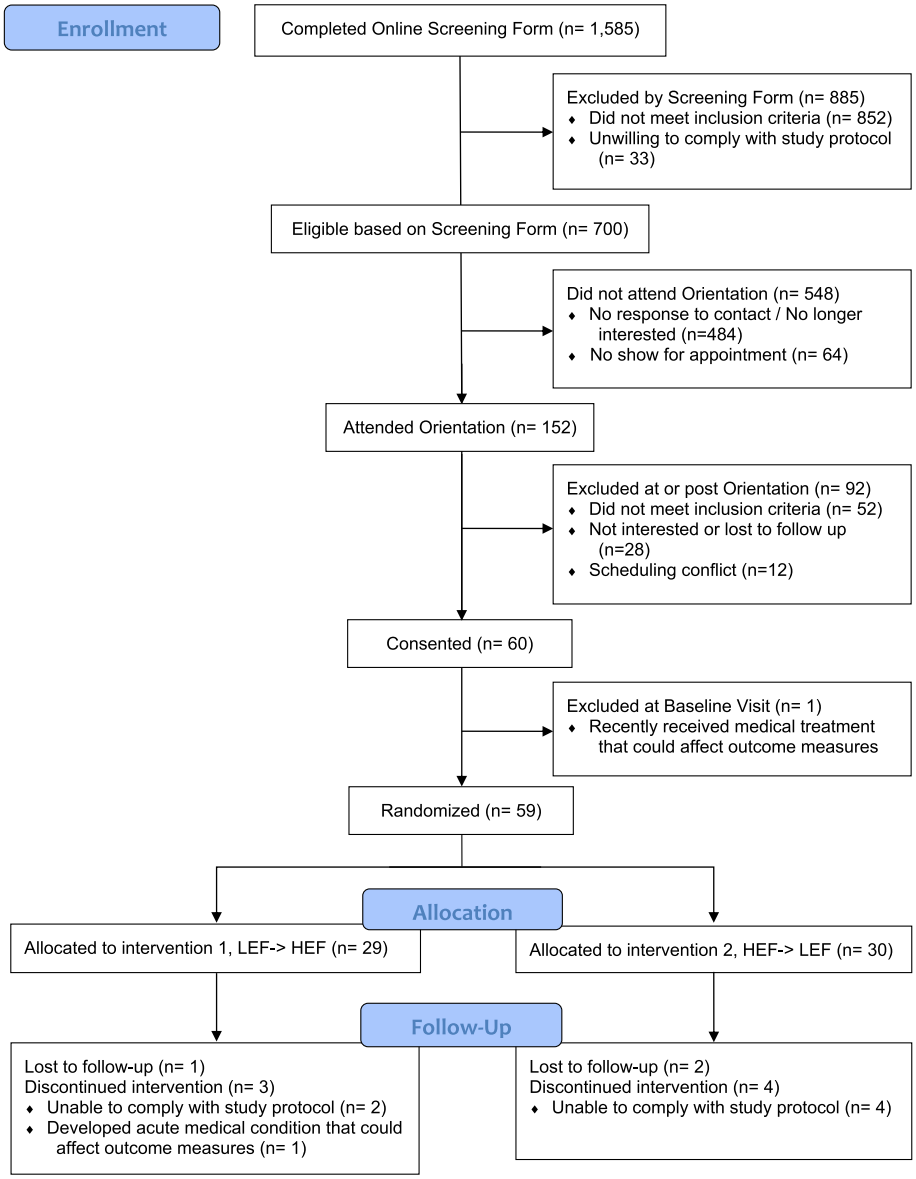


**Fig. 2.** The FRESH study CONSORT Flow Diagram.

participation and a secure on-line screening questionnaire that was built using REDCap® (Research Electronic Data Capture System). This eligibility screener included questions on current height and weight, age, sex, tobacco use, marijuana use, current medications, health status, usual physical activity, food allergies and food restrictions. Study staff reviewed the status of completed screening forms daily. Candidates who were ineligible based on the information they provided were not prompted to enter contact information and they received an automated message thanking them for their interest and informing them that they did not meet the study eligibility criteria. Those who were eligible were contacted by study staff via phone or email (per participant stated preference) and invited to a study orientation session at the Fred Hutchinson Cancer Research Center's Prevention Clinic. As of 10/29/2018 1,585 individuals completed the online screener and 700 were eligible based on their answers to this preliminary survey (see Consort diagram in Fig. 2).

### 2.4. Informed consent and intervention activities

Those who were eligible and remained interested after completing the online screener were scheduled for a 1-h final in-person eligibility screening and orientation session. Participants came to the Fred Hutch Prevention Center Clinic following a 12-h fast. They first completed a screening consent form that allowed staff to draw a small amount of blood for glucose measures (must be ≤ 100 mg/dL), conducted an in-person height and weight assessment (must meet study BMI criteria), and confirmed all other eligibility criteria such as no serious medical conditions or restrained eating (using the 3-factor eating questionnaire) [16]. Those who were eligible following these procedures received in-depth orientation about the study including expectations for participation, details about study activities, a calorie level assignment and associated eating pattern instruction, and instructions for their baseline study visit. The study nutritionist computed the daily energy needs of each participant using the Mifflin equation [17] together with the participant's usual activity level to estimate daily energy needs for weight maintenance. Staff then provided low and high EF sample menus and eating plans from a library of materials developed for a variety of energy needs (1200–3000 kcals/d in 200 kcal increments). The eating plans were based on a “food choice” system providing guidelines on the timing and amount of servings that should be consumed from the starch, milk, fruit, vegetable, fat and protein food groups. To facilitate scheduling and maximize compliance all four clinic

**Table 1**
Schedule of data collection in the FRESH study.

| Data element | On-Line screener | Orientation | Baseline 1 | Mid-point | Phase 1 End of Study | Baseline 2 | Phase 2 End of Study | Daily |
|---|---|---|---|---|---|---|---|---|
| Demographic characteristics | X | | X | | | | | |
| Current medications, recreational drugs | X | | | | | | | |
| General health status | X | | | | | | | |
| Food allergies or intolerances | X | | | | | | | |
| Usual physical activity | X | | | | | | | |
| Fasting blood glucose screen | | X | | | | | | |
| Height | | X | X | | | | | |
| Weight | | X | X | X | X | X | X | |
| 3-factor eating scale | | X | | | | | | |
| Dual-X-ray absorptiometry | | | X | | | | | |
| Fasting blood draw | | | X | | X | X | X | |
| Waist and hip circumference | | | X | | X | X | X | |
| Appetite testing with sequential blood draws | | | | | X | | X | |
| Pittsburgh Sleep Quality Index | | | | | X | | X | |
| On-line meal plan checklists | | | | | | | | X |
| Exit survey | | | | | | | X | |

visit appointments were made at the end of the orientation. Those who were not eligible were informed and, if excluded based on fasting blood glucose measures, were provided their results upon request and referred to their physician or a local sliding scale or free clinic.

Participants attended four in-person clinic visits and completed all other study activities at home. At baseline clinic visit 1, study staff obtained written informed consent prior to beginning any study activities. Following consent, participants completed a pregnancy test (females only) prior to undergoing whole body Dual X-Ray Absorptiometry. Staff also measured height, weight, body circumferences and obtained a 14 ml fasting blood draw. Participants wore light clothing and no shoes during the anthropometry measurements. Following these procedures, participants were randomized using a computer program to either the low or high EF arm during the first study phase. During the low EF arm, participants were asked to consume meals at evenly spaced times (8 a.m., 1 p.m., 6 p.m.) and to consume all food at each occasion within 15–30 min or less. During the high EF arm, participants also ate at evenly spaced intervals (8 a.m., 10 a.m., 12 p.m., 2 p.m., 4 p.m. and 6 p.m.) and were instructed to eat all food within 15–30 min or less. Participants were provided their first study meal, with calories commensurate with the low or high EF study arm assignment. For example, if participants were randomized to the low EF for the first phase, then they were provided with a full breakfast. If they were randomized to the high EF, then they were provided with half of the breakfast to eat immediately and provided the second half upon departure from the clinic to eat at the assigned time later in the morning. Other data collected at the baseline visit included self-report of race/ethnicity.

Phase 1 lasted 21 days. A midpoint visit was completed at approximately day 10. The goal of the midpoint visit was to check participant weight and adjust energy intake as needed to maintain baseline weight, and to help maximize compliance by discussing questions or concerns about the study protocol. While an in-person midpoint visit was preferred, a telephone visit was sometimes done instead. At the end of the 21 days, participants returned to the Prevention Center for an Endpoint visit for extended appetite testing that lasted 6 h. The meal frequency during the Endpoint visit corresponded to the randomization assignment that was just completed. Study staff first obtained a fasting blood draw, weight and waist circumference from all participants. Following these procedures, participants were escorted to a private room where staff placed an IV in participant's arm for serial blood draws. Meals were provided to the participant every 2 h from 8am to 2pm for the low EF arms, every 4 h for the high EF arms. Participants were asked to consume all food within 15 min of delivery. Twelve-ounce water bottles were provided at delivery of the first meal and again 4 h later and additional water was provided to participants upon request. All unconsumed food was weighed back and recorded; unconsumed water volume was also recorded. During the 7-h visit, self-reported appetite was reported every 30 min using a visual analog scale [11,18] and serial blood draws were obtained hourly to assess biomarkers of appetite and satiety. During the appetite testing, participants completed the Pittsburgh Sleep Quality Index instrument [19], but were otherwise free to read, work on-line or enjoy other quiet activities. At the end of the appetite testing session, appointments for the next phase were confirmed.

All participants completed a two-week wash-out period. Occasionally the wash-out was extended slightly to accommodate participants schedules. During this time, they ate per their personal preferences without regard to the study protocol. At the end of the washout period, participants returned to the Prevention Center for the baseline visit for phase two. All procedures were identical with the exception that the DXA was not repeated. Participants received instruction for following the second EF pattern that was not completed in phase one. They returned for a mid-point visit and again completed the Endpoint visit that included the appetite testing. At the final study visit, participants received their DXA results, a check for $300.00 and they completed an optional exit survey.

### 2.5. Other data collected

Data and biological specimens collected throughout the study are shown in Table 1. The biological samples will be assayed and used as the primary study endpoints. Since this is a randomized cross-over trial where each participant essentially acts as their own control, we expect minimal confounding by participant characteristics. Still we will check this assumption in the data analysis and use covariate data as needed.

### 2.6. Compliance

Compliance with an intervention protocol is a crucial aspect of any dietary intervention study [20]. We created procedures and systems to maximize compliance without overburdening participants and staff while also being cost effective. First, we created highly structured yet easy to follow low and high EF protocols. These eating plans were individualized to provide 100% of each participant's estimated energy needs for weight maintenance and approximately 90% of dietary reference intakes (DRI) for most other required nutrients. Food choices at each eating occasion were modeled after the Academy of Nutrition and Dietetics Food Exchange System and included specified amounts of the following food groups: starch, fruit, milk, vegetables, protein and fat (www.eatright.org/choose your foods). Participants were instructed on how many food choices were allotted at each eating occasion for both arms of the study. For example, a participant consuming 2000 kcals/day would consume five fruits, two milks, four vegetables, eight

proteins and six fat food choices in a given day. These choices would be distributed across three and six eating occasions for the low and high EF arms, respectively. At the orientation visit for each arm, participant received instruction on the food choice system and how to parse the food choices across the day's intake while maintaining comparable total calorie and nutrient intake on both arms. Sample menus and meal plans were also provided. The food choice system enhanced compliance with the protocol because it allowed participants to consume their own habitual foods. The second aspect of the study design that enhanced compliance was the on-line meal plan checklist. Each evening of the two three-week study phases, participants received a text message or email with a link to an on-line meal plan checklist. Here, participants completed a simple checklist of the food choices (food groups) that they were to have consumed that day per their prescribed meal plan. In addition, participants could add extra eating occasions and specify what type of food or beverage was consumed. These checklists were easy to complete and took no more than 5 min/each. The data from the meal plan checklists were sent directly to the study database where staff monitored completion of the checklists each day. Since we were primarily investigating compliance with the number of prescribed eating occasions per day, the on-line meal plan checklists were better suited to monitoring compliance than other measures often used in dietary intervention studies, such as 24-h dietary recalls.

### 2.7. Retention

To support participant retention, participants received an auto-generated email or text prior to each study visit via REDCap®, the study survey management system. Email or text reminders were also sent to participants up to two times for any meal checklist that was not filled out in a timely manner. Additionally, participants received email or text messages containing positive reinforcement statements or helpful meal planning tips three times a week on each phase of the study. Of 59 participants randomized into the FRESH study, only 9 dropped out, primarily due to work and school scheduling issues. The goal sample size was 50 participants with full and complete data.

### 2.8. Data management and quality control

A study database was created using REDCap® and most data elements, including questionnaires completed by participants, were entered directly into the system, by-passing the need for laborious and expensive data entry.

### 2.9. Planned analyses

The primary planned analyses for the FRESH Study will test the effects of low vs. high eating frequency inflammatory biomarkers [plasma C-reactive protein (*hs*-CRP), Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)] and an adipokine (adiponectin). We will compare the mean endpoint values of fasting *hs*-CRP, IL-6, TNF-α and adiponectin adjusted for baseline values for each 21-day intervention phase. Under the null hypothesis of no difference between the two intervention conditions on the changes in the outcome, the coefficient for the intervention condition in a linear regression model is equal to zero. We will consider analyses that include potential confounders for the purpose of further reducing any unexpected confounding effects, such as sex, DXA-derived body fat percentage, age, BMI and the baseline biomarker. The inclusion of the baseline biomarkers as an adjustment variable will reduce the effect that habitual usual eating frequency could exert on the outcome. All outcomes are *a priori*, hypothesis driven; thus, adjustments for multiple tests will not be required or recommended. We will also test the effects of low vs. high EF on appetite [daily Visual Analog Scale (VAS) ratings throughout intervention phases and serial ratings throughout the endpoint appetite testing session]), and biomarkers involved in appetite regulation and food intake [leptin, ghrelin, peptide YY (PYY), and cholecystokinin (CCK)]. Our sample size estimate of 50 participants considers a 10% drop out rate and a 5% non-adherence rate.

## 3. Results

The FRESH study flow and consort diagram is presented in Fig. 2. Recruitment began in 2015 and concluded in the Fall, 2018. Recruitment was carefully monitored weekly. Ineligibility reasons included presence of diseases requiring dietary modification, including physician diagnosed cardiovascular disease or diabetes mellitus, use of medications that may impact study results including non-steroidal *anti*-inflammatory drugs (NSAIDS), abnormal fasting glucose ($> 100$ mg/dL), tobacco or marijuana use within the past 3 months, a weight change of $\geq 10$ lbs in the past 6 months, a highly rigorous athletic training regimen, severe food allergies/intolerances, a history of disordered or restrained eating and severe food restrictions, a BMI of 25–27.9 or $\geq 40$ kg/m$^2$ and an inability or unwillingness to follow the study protocol. For potential participants who were excluded from randomization and enrollment following ths study orientation meeting, the most common reasons for ineligibility were abnormal fasting glucose out of range BMI (when measured in-person), recent tobacco/marijuana use, a history of disordered or restrained eating, and unwillingness or inability to follow protocol. These participants were informed at the orientation visit that their final screening ruled them ineligible and they were not randomized to the intervention.

## 4. Discussion

The FRESH study is a randomized cross-over intervention trial designed to test low vs. high EF on biomarkers of adiposity, inflammation and appetite. The study was designed to maximize participants compliance while maintaining scientific integrity. This was accomplished by allowing participants to complete most study activities with minimal disruption to usual work and leisure activities, asking participants to eat their own foods while adhering to the study's structured meal plan and reporting daily adherence via the on-line meal plan checklists.

Few previous clinical trials have tested EF in a randomized cross-over design. Current and completed trials have been conducted on intermittent fasting and time-restricted eating [21–23], but eating frequency is a distinct topic that is designed to answer the question of whether the total number of eating occasions per day affects health [24]. The FRESH study protocol required that foods on the meal plans for each study arm be consumed at specific times throughout the day. This contrasts with time-restricted protocols where eating is limited, for example, to 8 a.m. to 8 p.m. [25,26] but usually without consideration of the total number of meals or the timing between eating occasions throughout the day.

The FRESH study design has several strengths. First a randomized cross-over trial where each person acts as their own control is an efficient design and prevents contamination that often occurs in parallel arm trials [27]. Second, participants are free-living and consume their own foods and maintain personal food preferences, which maximizes compliance [20]. Third, each participant was provided with an individualized eating plan with a daily calorie level based on their height, weight and usual activity level. Since staff had frequent contact with participants throughout the study, calories were adjusted as needed for weight maintenance. Finally, the on-line meal plan checklists were an excellent way to monitor participant compliance without the cost and burden of 24-h recalls that are often used to monitor compliance in dietary intervention trials [20,28]. Limitations should also be noted. Current or planned pregnancy and lactation were exclusion criteria, but pregnancy and lactation in the recent past (i.e., past year) were not exclusions. Since appetite, metabolism and weight continue to change for many months post-partum, future protocols should expand the exclusions accordingly. Another limitation is that while this was a

rigorously conducted randomized controlled trial, we still relied on self-report for the daily on-line meal plan checklists. It is possible that some participants could have mis-reported their assigned daily eating occasions [20]. Finally, the study sample represents individuals in the greater Seattle area who were willing and able to complete the protocol, but who may not be representative of the general population.

Eating frequency in the United States has increased over the past several decades; on average adults consume multiple meals and snacks per day [4,29–31]. High EF leaves most individuals in a fed state for most of the day with unknown health effects. Whether this constant fed state has contributed to the high rate of diet-related chronic disease remains unknown.The FRESH study will contribute to the evidence base investigating EF and biomarkers of disease susceptibility. The FRESH study is a unique resource for testing the effect of EF on appetite and biomarkers of inflammation.

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## Clinical trials identifier

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2019.100334.

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