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Article

Design and implementation of a time-restricted feeding intervention in a randomized, controlled feeding study

Karen White [1], Beiwen Wu [1], Scott J. Pilla [2,3], Jeanne Charleston [1,2,5], May Thu Thu Maw [2], Lawrence Appel [2,4], Jeanne M. Clark [2,4], and Nisa M. Maruthur [2,4,5]*

[1] ProHealth Clinical Research Unit, School of Medicine, Johns Hopkins University, Baltimore, MD 21207, USA; kwhite33@jhmi.edu (K.W.); bwu19@jhu.edu (B.W.); jeannec@jhmi.edu (J.C.)
[2] Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD 21205, USA; spilla1@jhmi.edu (S.J.P.); mmaw1@jhmi.edu (M.T.T.W.); lappel1@jhmi.edu (L.A.); jclark@jhmi.edu (J.M.C.)
[3] Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA
[4] Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA
[5] School of Nursing, Johns Hopkins University, Baltimore, MD 21205, USA
* Correspondence: maruthur@ jhmi.edu

Abstract: The efficacy of time-restricted feeding for weight loss has not been established as prior studies were limited by lack of controlled isocaloric designs. This study describes the design and implementation of a controlled feeding study evaluating time-restricted feeding. We designed a randomized, controlled, parallel-arm, feeding study comparing time restricted feeding (TRF) to a usual feeding pattern (UFP) for the primary outcome of weight change. Participants were aged 18-69 years with prediabetes and obesity. TRF consumed 80% of calories by 1300, and UFP consumed ≥50% of calories after 1700. Both arms consumed identical macro- and micro-nutrients, based on a healthy palatable diet. We calculated individual calorie requirements which were maintained throughout the intervention. We randomized 41 participants who all completed the study. The desired distribution of calories across feeding windows in both arms was achieved, as were weekly averages for macronutrients and micronutrients. All randomized participants completed the study. We actively monitored participants and adapted diets to facilitate adherence. We provide the first report, to our knowledge, on the design and implementation of a feeding study that isolated the effect of meal timing on weight, while maintaining constant caloric intake and identical diets during the study period.

Keywords: time-restricted feeding, controlled feeding study, study design, nutrition interventions

1. Introduction

Time-restricted feeding (TRF), in which caloric intake is restricted to specific times of the day, is a promising but unproven intervention to address obesity and associated metabolic risk factors [1,2]. In particular, timing of feeding during the active period (daytime in humans), consistent with circadian rhythms, may improve metabolic outcomes [3-6]

Several randomized clinical trials have evaluated the cardiometabolic effects of TRF in humans [7-16]. These prior trials of TRF were either not feeding studies [12-19] or feeding studies with substantial limitations including short duration of intervention [8,9,11], small sample size [10] and low retention rates [7,10,11], limiting the inferences that can be drawn. These limitations make it difficult to assess whether prior promising results of TRF are due to reductions in caloric intake or other confounding factors rather than timing of food intake. A critical issue is whether a benefit of TRF on weight results from reduced caloric intake; if so, then TRF is just another means to reduce calories.

Feeding studies, in contrast to strictly behavioral interventions, have the potential to address these issues by providing precise, controlled calorie and nutrient intake. In a feeding study, all the participants' food is provided to them for the duration of the study

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period. This is the ideal study design to evaluate the efficacy of TRF as the same caloric intake and nutrient balance can be maintained between arms, thereby isolating the effect of meal timing on outcomes.

Our metabolic kitchen has a long history of feeding studies and is best known for participation in the multi-center DASH feeding study [20]. Most prior feeding studies, including ours, have focused on evaluating the impact of dietary patterns on health outcomes. A study comparing responses to two feeding patterns composed of the same menus, but with different distribution of calories over the day, presents a unique challenge, which to our knowledge has not been described elsewhere.

In this article, we describe the design and implementation of a randomized, controlled, isocaloric feeding study (Time-Restricted Intake of Meals (TRIM) Study) comparing the effect of TRF (eating earlier in the day) versus a usual feeding pattern (UFP; eating later in the day) on weight and other cardiometabolic outcomes.

2. Materials and Methods

2.1 Overall design

We conducted a randomized, parallel-arm, 12-week, feeding study of two dietary interventions: 1) TRF arm – in which participants consumed all calories between 0800 and 1800, with 80% prior to 1300; 2) UFP arm – in which participants consumed calories throughout the day (between 0800 and 0000), with 50% after 1700. We included adults in this study who had obesity (BMI 30-50 kg/m2) and prediabetes or diabetes not requiring medications. Potential participants completed one week of run-in feeding, to test their acceptance of both timing-of-feeding patterns prior to randomization. We took a constant clinical research diet approach in which we specified and calculated intake for the planned menus prior to the study using specialized software; weighed controlled portions; ensured consistent food sources and constant food preparation procedures in our metabolic research kitchen; and discouraged any food replacements to the extent possible [21]. We advised participants to maintain their usual level of activity throughout the intervention period.

The primary outcome for the clinical trial was weight and secondary outcomes were measures of glucose homeostasis. The outcomes of this paper are the distributions of calories throughout the meal-timing windows.

Trial registered at clinicaltrials.gov (NCT03527368).

2.2 Diet composition and menu planning

The major objective of this trial was to determine the effect of timing of feeding, therefore, in order to reduce the effect of confounding from other aspects of diet, the composition of the TRF and UFP interventions were identical in foods and nutrient content. These dietary interventions only differed in the timing of food distribution throughout the day (Figure 1). We focused on developing a diet that would be both healthy and palatable. The nutrient composition of the diets was similar to the OMNI Heart Unsaturated Fat Diet [22] and the SPICE Study [23]. In Omni Heart [22], we modified the original DASH Diet, which was previously shown to be beneficial for blood pressure reduction [20], to understand the impact of varying macronutrients on cardiovascular disease risk factors. In Omni Heart, the diet richer in unsaturated fat, the "Omni Heart Unsaturated Fat Diet," had beneficial effects on estimated cardiovascular risk [22]. In SPICE, the focus of the intervention was taste perception in the setting of low sodium intake, and thus a particular emphasis was placed on flavor [23].

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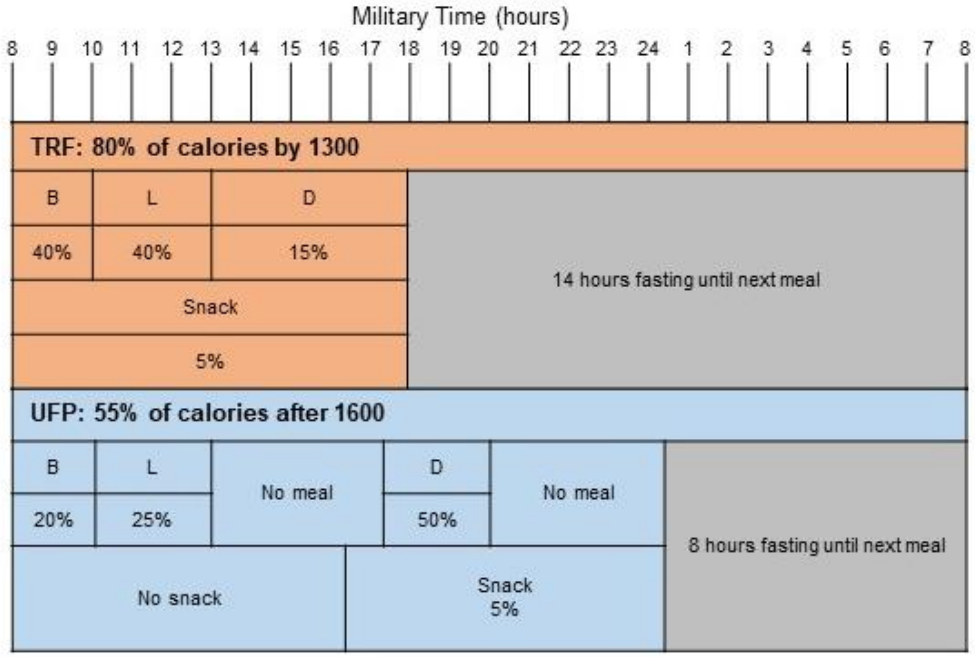

Figure 1. Feeding windows and distribution of calories throughout the day. In the TRF arm, participants consumed all calories between 0800 and 1800 and fasted for 14 hours beginning at 1800; participants consumed 40%, 40%, and 15% of total daily calories at breakfast, lunch and dinner, respectively. In the UFP arm, participants consumed all calories between 0800 and 2000 and fasted for 8 hours beginning at 2000; participants consumed 20%, 25%, and 50% of total calories at breakfast, lunch, and dinner, respectively.

We developed a 7-day menu cycle at 5 calorie levels (1600, 2000, 2500, 3000 and 3500 kcal). Table 1 shows the nutrient targets by kcal level. We used the energy method to establish the ranges for micronutrients at each energy level as follows [24]. We set nutrient targets at the 2000 calorie level based on previous studies and then indexed to the other calorie levels using the nutrient density at 2000kcal. For example, the sodium target at 2000kcal was set to 2300mg, thus the sodium density was 2300mg/2000kcal, or 1150mg/1000kcal. This density was then used to calculate the target value for menus at other energy levels. For example, sodium target at 2500kcal was calculated as 2875mg, which had the same sodium density as sodium target at 2000kcal.

Due to the percentage of calories allotted to each meal, we divided servings of many foods and recipes between meals; for example, one day participants in both arms would have part of a serving of lentil kale bean salad at breakfast and part of a serving of lentil kale bean salad at lunch (Table S1). We developed 100-calorie unit foods ("energy cookies") to match the dietary nutrient targets and used these to meet calculated calorie needs that fell between the calorie levels listed above. We created two recipes for these unit foods to minimize taste fatigue. Although we did not set meal-specific macronutrient targets, we planned to achieve our nutrient goals across all meals each day.

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Table 1. Nutrient Targets by Calorie Level

	1600 kcal		2000 kcal		2500 kcal		3000 kcal		3500 kcal	
Diet component	**Target**	Mean (SD)	**Target**	Mean (SD)	**Target**	Mean (SD)	**Target**	Mean (SD)	**Target**	Mean (SD)
Calories, kcal	**1600**	1616.2 (13.4)	**2000**	2010.3 (18.5)	**2500**	2507.2 (20.3)	**3000**	3001.4 (30.7)	**3500**	3499.0 (9.3)
Protein, %kcal	**15-18**	17.3 (1.0)	**15-18**	16.6 (0.4)	**15-18**	17.7 (1.2)	**15-18**	16.8 (1.0)	**15-18**	17.2 (0.6)
Carbohydrate, %kcal	**45-50**	45.3 (1.2)	**45-50**	46.1 (1.4)	**45-50**	45.1 (1.3)	**45-50**	46.1 (1.3)	**45-50**	46.5 (1.3)
Fat, %kcal	**32-37**	37.3 (0.9)	**32-37**	37.3 (1.4)	**32-37**	37.2 (1.7)	**32-37**	37.0 (0.9)	**32-37**	36.3 (1.2)
Saturated	**<10**	7.0 (1.6)	**<10**	6.7 (1.3)	**<10**	6.9 (1.7)	**<10**	6.8 (1.6)	**<10**	6.8 (1.3)
Calcium, mg/d	**560-800**	764.8 (137.1)	**700-1000**	896.1 (135.7)	**875-1250**	1200.6 (210.2)	**1050-1500**	1392.0 (222.6)	**1225-1750**	1513.8 (251.8)
Potassium, mg/d	**2000-2800**	2637.3 (137.2)	**2500-3500**	3179.9 (203.4)	**3125-4375**	4015.2 (167.4)	**3750-5250**	4686.9 (290.5)	**4375-6125**	5509.4 (350.9)
Sodium, mg/d	**1840**	1854.4 (19.2)	**2300**	2241.8 (34.7)	**2875**	2711.2 (92.4)	**3450**	3146.3 (93.0)	**4025**	3889.3 (143.7)
Fiber, g/d	**>20**	23.9 (3.7)	**>25**	29.9 (3.7)	**>30**	36.1 (4.6)	**>38**	43.9 (6.8)	**>44**	49.5 (5.6)

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While recipes were planned to be flavorful, we acknowledged that participants may want additional spices and herbs to use as needed on their foods. We provided participants with a list of allowed spices and herbs that were free of sodium and calories (Handout S1) and provided a minimal amount of potassium. Regarding beverages, there were some days when milk and juice were part of the planned menus. Water was encouraged as the additional beverage of choice. To encourage adherence, participants were provided with guidelines for allowed beverages (Handout S2). This included the allowance of one serving of alcohol; 8 ounces of plain coffee or tea and 12 ounces of diet soda daily. Specific powdered drinks were allowed as desired; these drinks had to be free of sodium and potassium and less than 5 calories per serving. They were allowed one individual serving of nondairy coffee creamer daily.

We planned menus on a one-week cycle using the ESHA software program [version 11.4.548]. Most recipes came from previous studies, primarily the SPICE study, which consisted of recipes that were well accepted by participants [23]. The nutrients we targeted in this study include protein, total carbohydrate, total fat, saturated fat, dietary fiber, calcium, potassium, and sodium. Although many of these nutrients are required to be listed on the Nutrition Facts labels by U.S. Food and Drug Administration (FDA), there are some exceptions. To ensure we had a complete nutrient profile for each product used in study menus, research dietitians first searched for the product in ESHA software. If the product was not available in ESHA or had missing information, then research dieticians would input the nutrient profile from the Nutrition Facts label, the manufacturer's website, and/or general USDA values, in that order.

Using the calculated menu, the research dietitians created recipes and production sheets for use by the kitchen staff. We trained kitchen staff on accuracy of measurement for research food preparation. Next, we tested the recipes and determined cooked factors. The cooked factor [25], also known as the cooking yield and retention factor, is a critical part of the nutrient calculation for cooked foods when composition data are not available. Cooked factors are used to reflect the changes in food weights resulting from moisture and fat losses during cooking and cooling processes. Our protocol for establishing a cooked factor is shown in Table S2 based on the type of cooking method for a given recipe.

We obtained foods from a central vendor and specific grocery stores to achieve consistency of nutrients across successive cohorts and simplify the process for updating nutrients if there was a change in product through the vendor.

2.3 Timing of feeding

We developed feeding windows (Figure 1) with the following principles in mind: 1) prioritizing consuming more calories earlier in the day for the TRF arm and later in the day for the UFP arm; 2) prioritizing testing of time-restricted feeding rather than intermittent fasting; 3) achieving high participant adherence; and 4) implementation of a usual feeding pattern based on the literature [26,27]. To be consistent with these principles, we planned for 80% of calories to be consumed by 1300 in the TRF arm (with all calories consumed by 1800), and at least 50% of calories to be consumed after 1700 in the UFP arm.

2.4 Screening and run-in

The focus of our screening procedures was to select and randomize participants who were likely to safely and successfully complete this efficacy trial. Research staff conducted a telephone screening with potential study participants. Participants meeting initial eligibility criteria were invited for in-person screening to determine eligibility. After confirmation of clinical eligibility based on medical history and physical measures at the initial in-person visit, participants completed a dietary questionnaire at a second in-person visit, which asked about food allergies and intolerances and barriers to completing the study's dietary interventions (Handout S3). A research dietitian reviewed this questionnaire in detail with the participant to assess dietary eligibility for the study.

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After in-person screening, participants had to successfully complete a seven-day run-in period prior to randomization. Day 1 of run-in began with a 60-minute study orientation conducted by a research dietitian, study coordinator, and the Principal Investigator. Orientation included an overview of the feeding study details and requirements, as well as food demonstrations of meal completion expectations. During the study orientation, participants were provided samples of specific foods that were found to be problematic in prior feeding studies (e.g., cottage cheese, nuts and milk). Orientation hand-outs included Safe Foods to Go (Handout S4); Allowed Beverages (Handout S2); Allowed Seasonings (Handout S1); a sample food diary for monitoring adherence; and timing of meals for both study arms. After orientation was completed, participants received study food to be eaten until their next visit to the research site. During the run-in period, participants ate a meal on-site three times on three separate days and were provided food for four days of TRF (including two weekend days) and three days of UFP. Participants had the opportunity to try all study meals and the different timing of feeding interventions during the run-in period. During the run-in period, research dietitians observed participants and assessed their ability to attend on-site meals and willingness to eat all study foods during the various feeding time windows covered by both interventions. This phase also provided dietitians an opportunity to get to know the participants and communicate with them regarding the importance of only going forward to randomization if they could truly commit to the 12 weeks of the study.

After the completion of run-in, the Principal Investigator, lead research dietitian, director of recruitment and retention, and study coordinator overseeing data collection met in-person to assess final eligibility of each participant prior to randomization. During this case conference, the lead research dietitian was asked to confirm eligibility of each participant from a dietary intervention perspective. At the time of randomization, the director of recruitment and retention again confirmed each participant's willingness to participate in the 12-week intervention regardless of intervention assignment.

2.5 Assessment of daily caloric needs

Since the effect of timing of feeding on weight was the primary study aim, we sought to determine baseline daily caloric need for each participant prior to randomization. This calorie level was then held constant throughout the intervention period to assure that changes in weight and other outcomes were related to timing of feeding and not changes in caloric intake. We used the Mifflin-St. Jeor equation to determine daily caloric need [28], this method entails different equations for men and women. Variables in the equation are age, height (cm) and weight (kg). This equation provides a basal caloric need, which is multiplied by an activity factor (see below) to determine the daily caloric need.

We determined activity level using the IPAQ-SF [29]. A research dietitian met with each participant to review their IPAQ-SF at which time the dietitian asked the participant to further elaborate on their activities and eating habits. The dietitian then assigned an activity factor. Typical activity factors used include 1.2 for sedentary, 1.4 for moderate activity, and 1.6 for very active [30]. We selected the following activity factors for this study: 1.3 for very low/sedentary, 1.4 for low, 1.5 for moderate activity, and 1.6 for high activity (Table S3). We selected these factors because of the younger population in our study (eligibility range: 18-69) and our experience with prior studies [22,31]. Research dietitians used clinical judgement to assign activity factors based on the IPAQ-SF and discussions with participants.

2.6 Controlled Feeding

Participants ate lunch or dinner on-site in a central dining room three weekdays each week. They were provided with the study foods to take home for the other days, including weekends. Participants were asked to complete a daily diary to monitor their adherence to the study diet each day of the intervention which included checking off the time they consumed each meal each day, and reporting any study food that was not eaten or food that was eaten that was not provided by the study. At each onsite meal day, we

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provided participants with a tray of food for the meal, which was fully cooked and only required microwave reheating. Participants were observed by a monitor to be sure they fully completed their meal, and they were asked to notify the dietitians when they finished their meals. If any food was left on the tray or in the container by a participant, the participant would be asked to finish the meal, and reasons for not completing the meal were noted if participant was unable to complete the meal. If any food was dropped on the table or on the floor, the food was weighed by a dietitian and replaced with the same food if possible; otherwise, the food and the quantity of food would be recorded on the daily diary form.

2.7 Staffing

We dedicated significant effort to the onboarding and training of study staff and implemented specific staffing patterns to support the safety and success of the feeding intervention. We required all kitchen staff to obtain and maintain food safety certification (ServSafe®). With this background in place, we trained each kitchen staff member on the standardized preparation of study recipes; this included learning and preparing each recipe using specific cooking techniques and measurements with observation by a dietitian. A study dietitian was in the kitchen at all times to observe and ensure the safety and standardized preparation of study meals. Staffing patterns consisted of a morning shift and evening shift to ensure sufficient staffing in the preparation of the metabolic kitchen at the start of each day and the close-out of the kitchen at the end of each day.

2.8 Adherence and retention

A full description of methods for assessing and optimizing adherence and adherence results is provided in an accompanying report. Briefly, dietitians were available to answer questions, clarify aspects of diet and timing, review daily diaries during the on-site feeding and assist with problem-solving around adherence to the intervention. The principal investigator and clinic director also ate regularly with participants in the study dining room. This helped to establish rapport and encourage participants to adhere to the intervention. We did not exclude participants because of lactose intolerance; the study provided Lactaid® (lactase enzyme supplement) and Beano® (alpha galactosidase supplement) for participants as needed. For participants who had raised intolerances as a possible concern (e.g., lactose intolerance), the dietitians spent extra time confirming that the lactase enzyme supplementation was sufficient. To encourage adherence to the intervention during holidays, we prepared special menus for those days that were close in nutrient content to the regular menu but included foods that were commonly eaten on those holidays.

This study was approved by [the institution blinded] Institutional Review Board, and all participants provided informed consent.

3. Results

Of 76 participants who completed dietary screening, we excluded 10 for dietary reasons (not willing and able to eat only study diet during intervention, n=4; food preference, allergy, or intolerance, n=4; not willing to adjust timing of feeding for study, n=2). Of 45 participants who completed screening for the study and started run-in, 41 completed run-in, and 41 were randomized.

Although there was some day-to-day variation, the actual weekly averages for macronutrients and micronutrients were very close to our planned targets as shown in Table 1. Table S4 and Table S5 display that we achieved the desired distribution of calories across feeding windows in both arms. Four participants requested and received a substitution of chicken for pork during the intervention; we made this substitution given that we could assure that nutrient targets would still be met.

Five of the randomized participants reported lactose intolerance during screening but were adherent to the intervention, including consumption of dairy products by using lactase supplements as needed.

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All 41 participants (100%) completed final data collection.

4. Discussion

In this publication, we describe the design and successful implementation of a time-restricted feeding intervention that addressed many of the challenges of prior studies of time-restricted feeding. We developed a palatable, acceptable, healthy diet with timing of feeding windows that were feasible for a 12-week intervention. Notably, 100% of participants were retained. We provided all food for participants throughout the study and required them to eat on-site for 3 meals each week; this controlled setting provides scientific validity without requiring an inpatient stay for the entire study. In total, these features enabled this study to deliver valid results on the true impact of time-restricted feeding on cardiometabolic outcomes.

This report provides important details on the procedures underlying successful implementation of the study interventions, including building in flexibility to the intervention (e.g., offering substitutions when possible) and devoting extra resources to retention such as special planning for conduct of the intervention during holidays. Operational details important to our success included the consolidation of food acquisition from a few sources and assuring that staff were well-trained in cooking techniques and food safety which provided for a smooth food preparation flow.

While our research dietitians and staff at this facility were experienced in planning research diets [20,22,23,31,32], the design of the menus to accommodate different distributions of calories throughout the day provided a new challenge. First, we had to consider what time windows for the intervention and comparison groups would allow us to answer our scientific questions while also being feasible. We considered work schedules and typical times of food intake in the US [26,27] to select windows. The next challenge was to provide the exact same menu of foods to both arms: the TRF group had large breakfasts and lunches and small dinners while the opposite was true for the comparison groups. In some cases, breakfast and lunch foods were not traditional (e.g., participants received kale bean salad for breakfast on Thursdays), and the different timing windows also posed an additional logistical challenge for intervention staff when packing food to be eaten off-site.

Given the resources that are necessary to recruit participants willing and able to participate in a feeding study (i.e., consume only study food for the entire study period), consideration of palatability and some flexibility in intervention delivery is important. In this trial, participants were required to eat the same food with the same timing of feeding pattern for 12 weeks. Also, there were participants who found it difficult to eat the large amount of food in one meal and some participants reported that they could not exercise as usual, due to being too full after the larger meals. To encourage participant adherence for this lengthy study, special attention was paid to utilizing prior feeding study recipes that were diverse and had been met with the greatest acceptance. The feeding patterns required time manipulations for many participants, such as needing to arrange their study designated mealtimes around their work schedule and church service times. We also made accommodations to the study foods when it was determined that the changes would not significantly affect nutrient targets. These features of our study allowed us to achieve our recruitment goal and 100% retention despite an intervention that was challenging to participants.

Estimating participants' caloric needs was a difficult task in this study. In most feeding studies testing dietary patterns, weight is held constant; participants are typically weighed at each clinic visit and calories adjusted to maintain weight. The primary outcome of this study was weight, and we sought to keep calories constant while only varying timing of feeding to understand how timing affects weight. Under- or over-estimation of caloric needs could result in increased hunger or difficulty eating all study food, respectively. Nonetheless, if there was an error in estimating calorie intake, the error would be random and would unlikely bias the results of our trial.

Another potential limitation of this study is the selection of feeding windows. We selected these to optimize having a contrast between intervention arms consistent with our study question while also seeking to have both interventions be feasible. While our choice of windows was informed by the literature, multiple windows could be considered as time-restricted feeding, and we decided to evaluate one set of feeding windows in this study.

5. Conclusions

We provide the first report, to our knowledge, on how to design and implement research diets in a feeding study to test the isolated effect of timing of feeding on weight and other cardiometabolic outcomes. Our intervention design addresses many of the challenges of prior studies and should inform future studies in this area.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Sample TRIM Menu Items for Single Day; Table S2: Standardized Procedure for Obtaining Recipe Cooked Factors; Table S3: Physical Activity Factors, Categories, and Definitions; Table S4: Average Percentage of Daily Calories by Meal in the Time-Restricted Feeding Arm; Table S5: Average Percentage of Daily Calories by Meal in the Usual Feeding Pattern Arm; Handout S1: Guidelines for Allowed Seasonings and Flavorings; Handout S2: Guidelines for Allowed Beverages; Handout S3: General Dietary Information Questionnaire; Handout S4: Safe Foods to Go.

Author Contributions: KW, BW, SJP, JC, JMC, LJA, and NMM contributed to study design. KW, BW, SJP, JC, and NMM implemented the intervention protocol. MTTM provided analysis of data. KW, BW, and NMM wrote the first draft of the manuscript. All authors reviewed and commented on subsequent drafts of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Johns Hopkins University.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

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Conflicts of Interest: Lawrence J. Appel, MD receives payments from Wolters Kluwer for chapters in UpToDate on the relation of blood pressure with weight and lifestyle factors. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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