Original Article

Optimal dietary macronutrient distribution in China (ODMDC): a randomised controlled-feeding trial protocol

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Background and Objectives: Findings from observational studies in China show that increased dietary fat consumption might be a contributor to the developing obesity epidemic. However, some cohort studies suggest that carbohydrate intake, especially from white rice, is a risk factor for obesity, type 2 diabetes and coronary heart disease in China. Our study aims to determine whether the traditional lower-fat, higher-carbohydrate Chinese or the Western higher-fat, lower-carbohydrate dietary pattern is more effective for weight control and the related cardiometabolic profiles increasingly found among contemporary Chinese. **Methods and Study Design:** The Optimal Dietary Macronutrient Distribution in China (ODMDC) trial is a 6-month, multi-centre, three-arm controlled feeding study. Based on the macronutrient transition in the past 30 years in China, three isoenergetic diets with a spectrum of fat and carbohydrate intake, but same protein contents, have been formulated. Percentages of fat, carbohydrate, and protein energy are one of 20, 66 and 14%; 30, 56 and 14%; 40, 46 and 14%, respectively. Participants will be provided with all their food and most beverages for 6 months. **Results:** The study population is planned to be 300 healthy non-obese adults aged 18 to 35 years. The primary outcome is body weight and the secondary variables are waist circumference and cardiometabolic risk factors. **Conclusions:** The ODMDC trial will have implications for nutrition policy in regard to weight control and related cardiometabolic disturbances among otherwise healthy non-obese Chinese.

Key Words: macronutrients, dietary fat, carbohydrate, cardiometabolic risk factors, randomised controlled feeding trial

INTRODUCTION

Background

Obesity, an important modifiable risk factor for cardiovascular disease (CVD), has become a major public health concern worldwide. There is broad consensus that the epidemic of obesity and related cardiometabolic diseases are closely associated with dietary composition including the amount and type of macronutrients. In many of the European countries and North America, the prevalence of obesity and type 2 diabetes (T2D) has increased in parallel with a reduction in total and saturated fat intake, and a corresponding increased intake in carbohydrate.[1] The reduction in fat and increased carbohydrate consumption are considered by some to have increased the risk of obesity and T2D in these countries.[2-4] Some clinical trials and observational studies suggest that moderate restriction of carbohydrate intake and enrichment with unsaturated fat improve blood lipid profiles and lower coronary heart disease (CHD) risk among individuals with a high metabolic risk.[5-6] It is possible that carbohydrate restriction rather than fat reduction might be an appropriate nutritional approach to the reduction of obesity prevalence and of cardiometabolic risk.[7,8] These generally Western interpretations and views are highly food culturally-specific and represent dietary shifts in macronutrient composition predicated on ultra-processed food where companion bioactive components and food structure are lost.[9,10] Traditional diets, like most of those in China, provide a higher carbohydrate-intake from grains, root vegetable and beans; lower-fat energy intakes from a variety of animal and plant sources with little edible oil; and protein from beans, leafy greens and small amounts of animal-sourced foods like eggs, fish and pork.[11,12]

A very different, dynamic and intergenerational situation now prevails in China with increasing affluence and poverty reduction, where over a similar period to that in the West, the consequences of overnutrition have begun rapidly to replace those of malnutrition in parents and

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Manuscript received 27 May 2017. Initial review completed and revision accepted 28 June 2017.
doi: 10.6133/apjcn.072017.06

offspring.[13-16] The macronutrient shift in China is different in its antecedents, rapidity and characteristics from that in the West. In the 1960s, after wars extending for over a hundred years, China was poor, mainly rural and more physically active. Despite high death rates from hunger, China was known to have a lean population and extremely low prevalences of pre-diabetes, diabetes and cardiovascular disease (CVD).[17-20] In the 1980s, with the implementation of reform and open policy, and substantial socio-economic changes, traditional Chinese diets and lifestyles were chanlleged.[14,15] Now foreign so-called 'fast food', ultra-processed food, animal-sourced products, various edible oils and sugary soft drinks are increasingly used by Chinese families.[14] Unlike other East Asian countries, such as Japan and South Korea, which have generally maintained their traditional cuisines, China seems to be relinquishing its original dietary patterns.[21] From 1982 to 2011, energy intake from fat doubled from 18% to 37% in megacities and daily edible oil nearly tripled from 18 to 49 grams (Figure 1).[14,22] Correspondingly, carbohydrate energy intake decreased from 72% to 54%.[14]

Along with these diet changes, the burden of undernutrition has diminished, but an epidemic of obesity and diet-related cardiometabolic disease has emerged.[23-25] The prevalence of overweight has increased to 26%, which was rare in the past.[13,15,16] In parallel, waist circumference, an indicator of central fat distribution, has undergone an increase across all age groups in the past 30 years. Increased waist circumference is more strongly associated with CVD than body mass index in China, since Chinese tend to develop CVD and other diet-related disease at a younger age and a lower body mass index.[16,26-31] The China Health and Nutrition Survey in 2009, representing 56% of the Chinese population, showed that over three quarters of this national sample were at high risk of developing metabolic diseases, and all metabolic risk factors assessed were higher in overweight people.[16] This escalating epidemic of overweight and obesity has put the Chinese population at a higher risk of developing CVD, and diet-related chronic diseases than in any previous generation.[31,32]

In China, the relationship between diet and diet-related disease was not studied until 1983. A series of ecological studies conducted in China showed that consumption of a low-fat, high-carbohydrate diet was associated with lower risk of coronary heart diseases, type 2 diabetes, and diet-related cancer.[11,12] Findings from observational studies indicated that increased consumption of fat had been consistent with increase in overweight and obesity among Chinese.[24,33-35] Recent perspective cohort studies indicate that carbohydrate intake , particularly from white rice, is associated with increased CHD and T2D risk in Chinese adults.[36,37] Although it is not possible to know whether these observations in China represent true causation, it is an important, if unresolved question: which is to ask, whether the traditional lower-fat, higher-carbohydrate (LF-HC) diet is more effective than the Western higher-fat, lower-carbohydrate (HF-LC) diet at weight control among the otherwise non-obese healthy Chinese population?

Against this background of changing international dietary patterns, the trends in fat and carbohydrate consumption in China need evaluation their own right. To this end, we plan to conduct a randomised controlled feeding trial in China. The design entails three isoenergetic diets with different macronutrient compositions to simulate the dietary shift over the past 30 years in China. In these formulated diets, the energy intake from fat will range from 20% to 40% and that from carbohydrate ranges from 66% to 46% accordingly, with that from protein kept constant. Fat from food is complex and diverse, as are cooking or processing methods, and most typical Chinese dishes are comprised of mixed foods with varied garnishes. It is difficult to strictly control the source and amount of fat from the food without introducing other confounding factors. For feasible and comparable menu planning, we only use soybean oil, the most commonly consumed edible oil in China. We interchange soybean oil with white rice and white wheat flour, which are the most consumed carbohydrate sources in China and account for 70% and 17% of total carbohydrate in Chinese diets, respectively, in order to achieve the macronutrient distributions required for each diet group.

Though numerous randomised controlled trials and prospective cohort studies have compared fats with carbohydrates and several dietary approaches have been shown to be associated with lower cardiovascular risk, the source of dietary fat and type of carbohydrate in these studies have generally been poorly controlled and some have involved many dietary changes. In the current trial, we only interchange soybean oil with white rice and white wheat flour to reach the macronutrient targets in

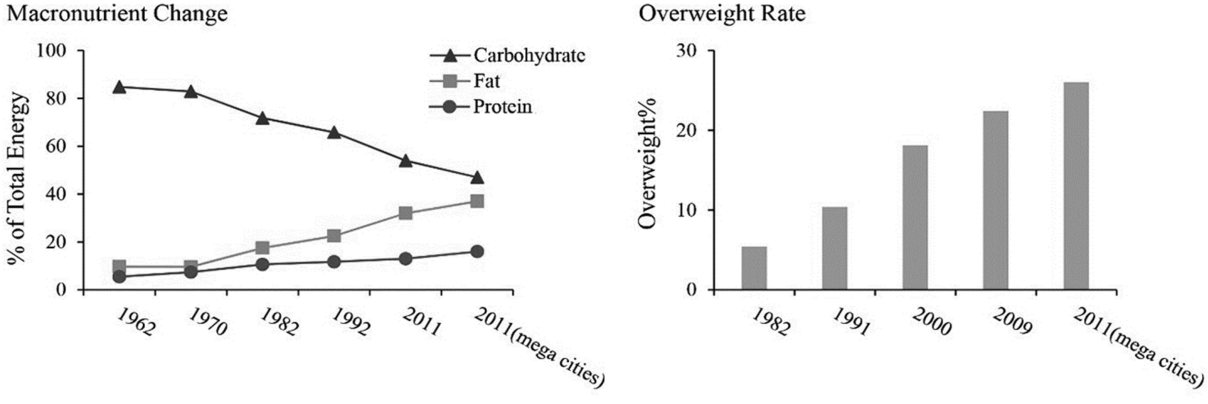

Figure 1. Changes of macronutrient composition and overweight rate in China.

each diet group. Except for white rice, white wheat flour and soybean oil, other foods are kept almost the same in each isoenergetic diet and all of them will encourage maximal adherence and limit dietary and behavioural confounders.

Primary specific aim

To determine whether the traditional Chinese LF-HC dietary pattern or its Western HF-LC counterpart is more effective at weight control in a non-obese healthy population in China.

Secondary aims

To determine the effects of macronutrient distribution on other cardiometabolic outcomes such as waist circumference, blood pressure, lipid profiles (total, LDL, HDL, and non-HDL cholesterol, ratio of total to HDL cholesterol, triglycerides, apolipoprotein A1, and apolipoprotein B), glycaemic traits (glucose, glycated serum protein, and insulin), adiponectin, and leptin.

Hypothesis

We hypothesize that the LF-HC diet which characterizes the macronutrient composition of the traditional diet of Chinese people is more favourable to health than the Western HF-LC diet.

METHODS

Design summary

ODMDC trial is a 6-mo, multi-centre, three-arm controlled feeding study. It is designed to determine whether the traditional LF-HC diet is more effective than the Western HF-LC diet at weight control among non-obese healthy population in China. The protocol consists of screening for eligibility, 7-day run-in feeding period, and a 6-mo intervention feeding period (Figure 2). Participants will be provided with all the food prepared in research kitchens and most beverages during the feeding period. This trial is to be conducted at two sites: Zhejiang University, Hangzhou, in south China and Chinese PLA General Hospital, Beijing, in north China. The primary outcome variable is body weight; the secondary outcomes are waist circumference, blood pressure, lipid profiles (total, LDL, HDL, and non-HDL cholesterol, ratio of total to HDL cholesterol, triglycerides, apolipoprotein A1, and apolipoprotein B), glycaemic traits (glucose, glycated serum protein, and insulin), adiponectin, and leptin. The study has been approved by the Ethics Committee of the College of Biosystem Engineering and Food Science at Zhejiang University, number ZJU-BEFS-2014006. The trial is registered at ClinicalTrials.gov, number NCT02355795.

Participants/eligibility criteria

The study sample is planned to be 300 healthy adults with equal number of men and women (half from northern and half from southern China in relation to the Qinling Mountains-Huaihe River Line) aged 18 to 35 years old. Major inclusion and exclusion criteria are shown in Table 1.

Recruitment

Participants are planned to be recruited using fliers, newspaper advertisements, and the internet posts that describe the study indicates that meals will be nutritious and free for 6 months. Because of the disproportionately greater burden of obesity and related metabolic diseases among northern than southern Chinese, an explicit goal is to include about half of the participants from each area. To reach this goal, participants will be recruited through Zhejiang University, Hangzhou, in the south of China and the Chinese PLA General Hospital, Beijing, in the north.

Screening visits, run-in period and randomisation

Participants eligibility for the trial will be determined from 3 screening visits and a 7-day run-in period. People who respond to recruitment will be interviewed by phone or through the internet by brief questions on major eligibility issues. Appropriate individuals from the pre-screen contact will be scheduled for the subsequent three formal screening visits and run-in period (Table 2).

Screening visit 1: At the first visit, informed consent will be obtained for subsequent procedures and exclusionary criteria applied except for the laboratory exclusions (blood lipid profiles and blood glucose). Eating habits and dietary preferences will be reviewed to assess a participant's willingness and ability to consume all 3 diets

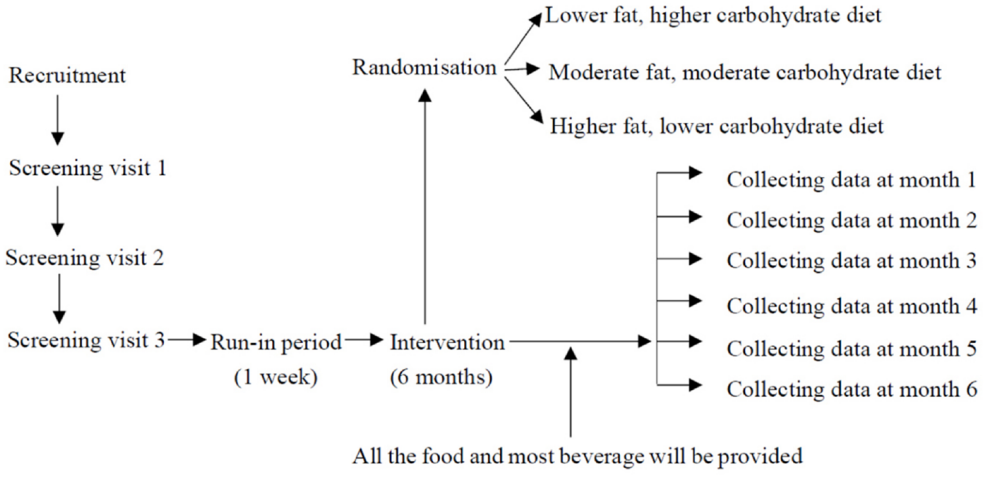

Figure 2. Summary of the ODMDC study protocol.

Table 1. Major inclusion criteria and exclusion criteria

Major inclusion criteria:
- Students in Zhejiang University or working staff in the Chinese PLA General Hospital
- 18≤age≤35
- Body mass index <28
- Are willing to eat all of the study foods even when full
- Are willing to eat only foods provided
- Are willing to avoid strenuous activity during the 6-month intervention

Major exclusion criteria:
- Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg
- Total cholesterol ≥6.19 mmol/L
- LDL cholesterol ≥4.12 mmol/L
- Triglycerides ≥2.25 mmol/L
- Blood glucose ≥6.11 mmol/L
- Change in body weight exceeding ±10% during the prior year
- Energy intake is too low or too high
- Unwillingness or special requirement for diet that could not be modified
- Poor adherence during the recruiting meeting or unsatisfactory completion of keeping food diary or filling questionnaire at any time before randomisation
- Eating disorder or any psychosocial or scheduling factors that could impede study outcomes
- Have a history of diagnosed CVD, diabetes, cancer or inflammatory diseases
- Have a history of a mental illness
- Have diagnosed endocrine, pulmonary or hematological disease
- Have diagnosed bowel disease or malabsorption that would prevent the participants from complying with the dietary restrictions of the feeding trial
- Renal or liver insufficiency
- Other chronic disease thought to interfere with the effect of the diet or with participation or adherence
- Current use of supplements or anti-inflammation medications or medications affecting glucose, lipid metabolism and blood pressure
- Smoking or alcoholic beverage intake >1 time per week
- Current or planned pregnancy prior to end of study, or breast-feeding
- Irregular menstrual cycles
- Have birth control medication

Table 2. Nutrient targets of the 3 study diets

Nutrient targets	LF-HC Diet	MF-MC Diet	HF-LC Diet
Total energy (male), kcal[†]	-	-	-
Total energy (female), kcal[†]	-	-	-
Carbohydrate, % of energy	66	56	46
Fat, % of energy	20	30	40
Protein, % of energy	14	14	14

LF-HC: lower-fat, higher-carbohydrate; MF-MC: moderate-fat, moderate-carbohydrate; HF-LC: higher-fat, lower-carbohydrate.
[†]Energy levels will be set based on participants' baseline energy intake.

and adhere to the feeding protocol.

Screening visit 2: All participants will have breakfast acceptability tests. They will be provided with breakfast samples (low-fat bread, moderate-fat and high-fat cookies) which will be the same as the breakfast during the feeding period; breakfast will not change throughout the whole trial. A 3-d (2 weekdays and 1 weekend day) food diary and physical activity questionnaire will be provided to complete off-site and returned by email or in person at the clinical site when completed. Daily energy intake will be determined from the 3-day dietary record.

Screening visit 3: Participants will undergo a clinical examination, and provide a 12-hour fasting blood and 24-h urine sample for eligibility testing.

Run-in period: Eligible participants will then enter into a 7-day run-in period during which they are fed the moderate-fat, moderate-carbohydrate (MF-MC) diet using the same procedures that will take place during the intervention period. The objective of run-in diet is to introduce participants to the feeding protocol, identify and exclude individuals who cannot adhere to the feeding regimen. During the run-in phase, participants will be provided with all the foods, including breakfast, lunch, dinner, and most beverages. Fruit intake will not be restricted, but participants will be instructed to maintain their usual level of fruit intake and keep records of daily fruit intakes. For each day of controlled feeding, participants will complete a daily diary which asks about the amount of study food not eaten, non-study food eaten, or beverages not consistent with the assigned diet. Questionnaires that ask for information on satiety, food craving, eating behaviour, and satisfaction with diet will be administered at day 4. Participants may be excluded during run-in for low adherence to the study protocol. Research staff will meet with participants to assess the questionnaires collected, review the progress and evaluate their interest in the trial in the subsequent 3 days.

Randomisation will take place on day 8 using a computer-generated random number list by a data manager. Each eligible participant will be randomised to one of the

three diets (1:1:1) stratified by clinic centre, age, sex, and body mass index. Clinical staff and laboratory personnel who did the measurements will be masked to group allocation. Meal providers will be aware of participant diet assignment, but they will not be involved in the rest of the trial, including later measurement and results analyses. Due to the obvious difference in the breakfast provided, blinding participants is not feasible, though they will not be informed of the allocated treatment.

Implementation of dietary intervention

On the first day after the run-in feeding period the 6-month intervention phase will begin, during which participants will be provided with all of their food and most beverages. Across the 6 months, the menu will change monthly, and within each month the menu will change every day in a week at two energy levels (one for female participants and the other for male participants), but repeat for 4 weeks. They will be asked to eat only the foods provided and to consume at least one meal per day (lunch or dinner) on site, and breakfast will be packaged for consumption off-site. At each daily visit (including weekend and holidays) for meals, participants will be required to complete a food diary to document deviations from study protocol. They will be allowed to consume up to 1 serving of tea, coffee or alcoholic beverage, and unlimited amount of water each day. At least two meal monitors will be present during all on-site feeding visits for the purpose of distributing take-away meals, meal box checks, and collecting daily data (daily diaries, questionnaires, etc.).

A regular group session about half an hour with 150 participants led by nutrition and psychology staff in each centre will be held every month, 7 days before clinical measures. They will record how satisfied the participants are with the food provided, their feelings and suggestions about the study, difficulties when complying with the study protocol, evaluate potential problems, and facilitate compliance. When participants fail to abide by protocols, we will initiate behavioural counseling. If the participant continues to deviate from the study protocol, he or she will be withdrawn from the trial. All outcome measurements will be administered on the weekend in the fourth week of every month, then they have one-day off from the diet regimen. During the breaks, participants will be allowed to return to their usual diets, and no specific guidelines will be provided to participants for what they should eat during these one-day breaks.

Adherence assessment

Adherence to the dietary intervention will be assessed by observation, and self-report of study participants. During the provision of on-site meals, adherence will be assessed by direct observation of the number of missed meals, the quantity of the uneaten food and the subjective judgment of the clinic staff. Self-report measures include a daily diary that records any deviations throughout the trial in addition to satisfactory questionnaires. Each day, an overall compliance score (on 10-cm visual analog scale with 0 indicating not at all and 10, extremely) will be calculated based on staff observation, and information from the daily diary and questionnaires.

Nutrient targets of study diets

The primary distinguishing feature of the three diets is that they are isoenergetic, while soybean oil, white rice, and white wheat flour intake from total energy vary in these three diets. Table 3 shows the targets of the three study diets. With white rice and white wheat flour replacing soybean oil, we designed three diet groups. Total energy intake from fat ranges from 20% to 40%, representing the trend of dietary transition in the past 30 years in China. The LF-HC diet group corresponds to the level 30 year ago during which obesity were rare; the MF-MC diet group is based on the current macronutrient intake in China and also the upper limit of fat intake recommended by the Chinese Nutrition Society; and the HF-LC diet group approximates to the current consumption of Chinese residents in some megacities.

Traditional Chinese cuisines include a staple (rice or noodles or steamed bread), stir-fried dishes, and sometimes soups. In order to alter the fat and carbohydrate content of the diet without participants having to make major changes in foods throughout the day while keeping the sources of other nutrients constant across the 3 diets, additional fat will be in the form of soybean oil (daily edible oil tripled in the past 30 years in China) and incorporated into cookies to be consumed at breakfast. For example, at the 2000 kcal energy level, the lower-fat group has low-fat bread without soybean oil, while the moderate-fat group replaces the low-fat bread with cook-

Table 3. Protocol for the screening, run-in periods, and randomisation

Screening visit 1 by telephone or internet interview
Informed consent for screening and run-in periods
Major eligibility questions
Medical history questionnaire
General dietary questionnaire
Screening visit 2 by face to face interview[†]
3-day food records
Physical activity questionnaire
Breakfast accessibility test
Screening visit 3[‡]
Weight, height, waist circumferences, blood pressure
12-hour fasting blood sample for eligibility testing
Run-in period (7 days)
Feed the participants the moderate-fat, moderate-carbohydrate diet
Lunch and dinner eaten on a dinning site
Prepared breakfast distributed for consumption off-site
Daily diet diaries
Compliance assessment, and adherence counseling as needed[§]
Side effects questionnaires
Randomisation takes place at the beginning of day 8

[†]The screening visit 2 is 7 days after previous visit. All potential participants will be informed to send the 3-day food records and physical activity questionnaire to our working email when finished.

[‡]The screening visit 3 is 10 days after previous visit.

[§]Adherence to the dietary intervention is assessed by observation and self-report of study participants. During the provision of on-site meals, adherence is assessed by direct observation of the number of missed meals, the quantity of the uneaten food and the subjective judgment of the clinic staff. Self-report measures include daily diary that records any deviations throughout the trial in addition to satisfaction level.

ies containing 23.5 grams of soybean oil and the higher-fat group does the same but their cookies contained 44.7 grams of soybean oil. Carbohydrate mainly with the form of white rice and white wheat flour will be added into the lower-fat group to balance the total energy of the three diets. Otherwise the menus for the 3 groups are almost identical. To enhance the public health relevance of the trial, the test diets will be constructed with naturally occurring foods and does not include supplements or unusual foods.

Food preparation

Daily menus will be developed for 2 energy levels: one for female and the other for male. In order to minimize the influence of food structure and cooking methods on the outcomes, these will be the same among three groups. Foods in the menu will be those commonly consumed, such as rice, bread, green vegetables, pork, beef, chicken, fish, shrimps, and so on. Cooking methods will be of traditional Chinese style – steamed, boiled, stir-fried and stewed, which are also commonly used by most people in China. The target nutrients in the menus will be chemically validated before feeding and monitored for drift over time. For production consistency and quality control, each site will purchase the same brand of each particular food item, and soybean oil will be the only edible oil used in food preparation. Standardized recipes and cooking procedures will be meticulously followed under sanitary conditions. As most Chinese dishes are mixed food with varied garnishes, each item will be prepared in batch quantities, individually portioned, and weighed to within 0.1 g for portions <10 g or within 0.5 g for those ≥10 g using electronic scales.

Data analysis plan

The selected minimal clinically significant between-group difference in weight change is 1.8 kg (approximately 3% for a 60-kg individual) and a 6.3-kg SD of weight change is selected based on previous study.[38] Thus, a total of 240 participants are able to detect this difference in weight change at a two-tailed significance level of 0.05 and a power of 90%. Considering a loss-to-follow-up rate of 20%, sample size is raised to 300.

Baseline demographic variables (age, sex, and centre), cardiovascular diseases risk factors (weight, body mass index, waist circumference, blood pressure, total, LDL, HDL, and non-HDL cholesterol, ratio of total to HDL cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B, glucose, glycated serum protein, insulin, adiponectin, and leptin), dietary characteristics (total energy intake, percentage energy from fat, carbohydrate, and protein, dietary cholesterol, and fiber) and physical activity level will be presented using descriptive statistics. Adherence measures include participant satisfaction score and self-report compliance, which will be presented as percent of perfect adherence.

Dietary intake, physical activity level over the course of the trial will be analysed by mixed-model analysis of variance, without imputing missing values. Within-participant correlation will be accounted for by a random effect (repeated measures with compound-symmetric covariance).[39] Age, sex and study centre will be included as covariates. The raw unadjusted means at each time point will be used for graphical presentation. The group x time interaction term (12 degrees of freedom) will provide a test of the hypothesis that dietary intake and physical activity level in 3 groups do not differ across the study period.

The primary outcome is body weight. The main analysis will be conducted applying an intention-to-treat approach, in which participants will be analysed according to their randomisation assignments, regardless of their actual adherence to the whole 6 months of intervention or measurement schedule. Main analysis will be supplemented with a per-protocol method, including only those who will complete the intervention.

As described above for dietary intakes, body weight will be analysed by mixed-model analysis of variance, with the same covariates (age, sex, and study centre) and covariance structure. Missing data will not be imputed as they can be handled by mixed-model. A parallel approach will be used for secondary outcomes including waist circumference, blood pressure, lipid profiles (total, LDL, HDL, non-HDL cholesterol, ratio of total to HDL cholesterol, triglycerides, apolipoprotein A1, and apolipoprotein B), glycaemic traits (glucose, glycated serum protein, and insulin), adiponectin, and leptin. For analyses of these secondary outcomes, only intention-to-treat analysis without imputing missing data will be used.

For exploratory purposes, ancillary analyses will be conducted after adjusting for change in weight in mixed-model. We will also perform sensitivity analysis for all outcome variables according to whether multiple imputation, mixed-model or the observed value (complete case) will be used at 6 months. Additionally, two subgroup analyses, namely male versus female and participants living in the south versus living in the north will be performed.

RESULTS

Measurement of outcome variables

Briefly, dietary intake data will be collected at baseline, while all the other outcome variables including physical activity, anthropometric and metabolic data will be collected at baseline and monthly thereafter. Data collection personnel will be masked to group assignment. Table 4 shows the detailed schedule of measurements.

Diet and physical activity assessment

Dietary intake will be assessed by a 3-day dietary record (2 weekdays and 1 weekend day) using Nutrition System of Traditional Chinese Medicine Combining with Western Medicine, version 11.0 (Medical College, Qingdao University, Shandong, China). This nutrition system includes food composition data, permitting calculation of nutrient intake from reported food intake.[40,41] Physical activity will be assessed by the Globe Physical Activity Questionnaire developed by WHO.

Anthropometric data

Weight will be measured to the nearest 0.1 kg in light clothing and without shoes using a digital scale, in the morning before breakfast and after urinating. Height will be measured to the nearest millimeter in bare feet using a

Table 4. Measurements schedule

	PSV	Screening Visits			Run-in	6-mo feeding intervention					
		SV1	SV2	SV3		M1	M2	M3	M4	M5	M6
Informed consent		√			√						
Major eligibility questionnaire		√									
General health questionnaire		√									
Dietary Information questionnaire		√									
Medication questionnaire		√									
3-d food records			√								
Physical activity questionnaire			√			√	√	√	√	√	√
Breakfast acceptability[†]			√								
Height				√	√	√	√	√	√	√	√
Weight				√	√	√	√	√	√	√	√
Waist circumference				√	√	√	√	√	√	√	√
Blood pressure				√	√	√	√	√	√	√	√
12-h fasting blood[‡]				√	√	√	√	√	√	√	√
Feeding activity					Daily						
Randomisation					√						
Food records								Daily			
Diet satisfaction					√	√	√	√	√	√	√
Fecal sample[§]				√	√						√

PSV: pre-screening visit; SV: screening visit.
[†]All the participants take breakfast acceptability tests, they are provided with breakfast samples (low-fat bread, moderate-fat cookies, high-fat cookies) which will be the same as the breakfast during the feeding period, and the breakfast will not change throughout the trial.
[‡]Blood samples will be obtained and at day 5 in the run-in period and at week 4 each month in intervention period. Samples of whole blood for DNA for later gene-diet interaction studies. Plasma and serum will be separated, aliquoted, and stored at -80 0C until later assay for metabolomics, proteomics, and inflammatory biomarkers.
[§]Fecal samples will be collected and then kept at -80 0C until extraction of genomic DNA for later gut microbiome studies.

wall-mounted stadiometer. Waist circumference will be measured halfway between the last rib and iliac crest with the use of a 150-cm anthropometric measuring tape.

Metabolic measures

Blood pressure and heart rate will be measured after 5 minutes of rest with the use of OMRON HEM-7112 device (OMRON Corp., Tokyo, Japan) which records blood pressure using an oscillometric technique.[42] Two measurements separated by 10 minutes will be taken as described elsewhere.[43] Each measurement will be obtained on the right arm of participants in a seated position, using an appropriate-sized cuff at the level of the heart. Blood samples will be collected (15 mL each time) by venipuncture after a 12-hour fast. Traditional lipid fractions and glycaemic traits (including total, LDL, HDL cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B, glucose, and insulin) will be measured. Glycated serum protein is a glycosylated protein and reaches a steady state within 2-3 weeks of change in blood glucose.[44] Therefore, as an integrated measure of blood glucose concentration, it will also be measured. We will also determine the adiponectin and leptin concentration, which might relate to lipid metabolism.[45] All of these measurements will be performed in the core laboratory.

Candidate assays

Samples of blood from each fasting blood collection will be stored at -800 ℃ for subsequent analyses. Candidate assays that might be performed include those related to metabolomics, proteomics, inflammation (e.g. interleukin-1, interleukin-6, prostaglandin, tumor necrosis factor), kidney function (e.g. creatinine, uric acid), and liver function. Specifically, samples of whole blood will be stored for DNA for gene-diet interaction studies and plasma or serum for metabolomics, proteomics, inflammation and other disease markers.

In order to evaluate the overall effects of these diets, fecal samples will be collected at baseline and month 6. Fresh fecal samples are expected to be collected in the morning before breakfast under anaerobic conditions and frozen immediately in liquid nitrogen, and transferred to laboratory within 1 h and stored at -80 ℃ until extraction of genomic DNA for later gut microbiome studies.

Monitoring plan

The Data Safety and Monitoring Board will be in charge of monitoring all aspects of the study. Data collected in screening, run-in and intervention periods, will be entered blindly by type of period at each centre using specific forms, and sent weekly to the data monitor. This data includes baseline characteristics, clinical measures, and questionnaires assessing adherence. The data monitor will check the form for completeness and appropriateness and records missing information of inappropriate entries. Data inconsistencies across recording forms will be resolved with the assistance of clinic staff. All investigators, staff and participants will be masked to all trial outcome data until the trial ends, with the exception of the trial statisticians and the Data safety and Monitoring Board.

Study administration and timeline

The research team includes 2 field centres (one at Zhejiang University in South China and another at The PLA General Hospital in North China), a data management and statistical unit in the PLA hospital, and a core laboratory at Zhejiang University. A steering committee will be responsible for the overall implementation, and

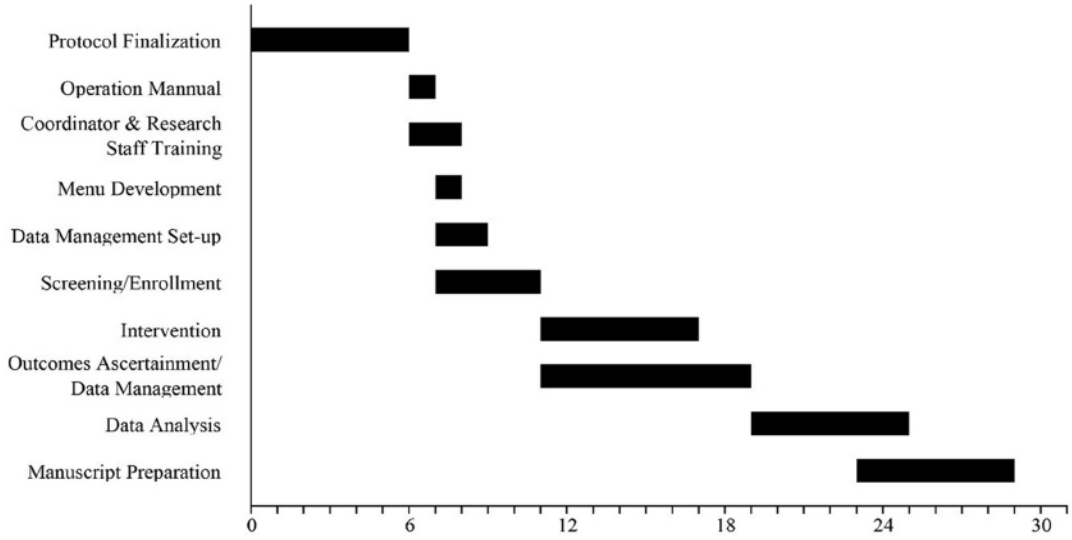

Figure 3. Study timeline.

will meet at least every month primarily by face-to-face and phone conference. Prof Li and Director Yuan co-chair the trial. Prof Li directs the field centre at Zhejiang University. Director Yuan directs the field centre at PLA General Hospital. Dr Huang and Dr Zheng direct the data management and statistical unit. As the proposed research is a multicentre randomised clinical trial, an independent Data Safety and Monitoring Board will be established. The schedule of key activities is depicted in Figure 3.

CONCLUSION

The trial is expected to will have implications for nutrition recommendations and policy for the weight control and related cardiometabolic disturbances among healthy non-obese Chinese.

ACKNOWLEDGEMENTS

We thank Prof Andrew J Sinclair at the School of Medicine, Deakin University, Victoria, Australia for helping to revise this manuscript.

AUTHOR DISCLOSURES

The authors declare that they have no conflicts of interest. This study is supported by the National Basic Research Program of China (973 Program: 2015CB553604). The funders have had no role in study design, and will have none in data collection or analysis, decision to publish, or preparation of the manuscript.

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