BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036394
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2019
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Keywords:	NUTRITION & DIETETICS, Hypertension < CARDIOLOGY, DIABETES & ENDOCRINOLOGY

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Rational and design of a multicenter, single-blind, randomized, parallel controlled feeding trial evaluating the effect of a Chinese cardiovascular health (CCH) diet in lowering blood pressure and other cardiovascular risk factors

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Abstract

Introduction: Unhealthy diet has been identified the number one attributor of total mortality in China, accounting for >20% of total deaths. Although DASH and Mediterranean diets have been proved beneficial in managing cardiovascular disease (CVD) risk factors in Western countries, whether similar healthy diet can be developed that keeps Chinese diet culture but is able to reduce CVD risk factors remains unknown.

Methods/design: The Diet, ExerCIse and CarDiovascular hEalth (DECIDE)-Diet trial is a multicenter, single-blind, randomized controlled feeding trial to evaluate the effect of the Chinese Cardiovascular Health (CCH) diet, in comparison with the Chinese usual diet, in lowering CVD risk factors among community residents with higher cardiovascular risk. A total of 360 adults aged between 25−75 years old and with systolic blood pressure (SBP) at 130−159 mm Hg will be recruited from four centers located in four major Chinese cuisines: Beijing, Shanghai, Guangzhou and Chengdu. After one week of running period with local usual diet, the compliant participants will be randomized into the intervention and control groups on 1:1 ratio for additional four weeks of intervention and follow-up. Body weight will be maintained during the intervention. The primary outcome is 4-week change in SBP from baseline to the end of the study. DECIDE-Diet trial will be the first randomized controlled trial to evaluate the effect of a healthy Chinese diet in lowering CVD risk factors. It will inform the public and policy makers that cardiovascular health is achievable through a healthy diet that remains Chinese food culture unchanged.

Ethics and dissemination: This trial adheres to the Declaration of Helsinki and guidelines of good clinical practice. Signed informed consent would be obtained from all participants. The current trial has been approved by the Peking University Institutional Review Board (Approval Number: IRB00001052-18094).

Trail registration number: ClinicalTrials.gov identifier: NCT03882645.

Strengths and limitations of this study

- This trial will be the first randomized controlled trial to evaluate the effect of a healthy Chinese diet in lowering cardiovascular risk factors.
- The Chinese Cardiovascular Health (CCH) diet includes different versions according to the major Chinese cuisines to ensure the likeness by local people.
- We will investigate the effect of CCH diet on gut microbiome in this trial and the results might provide additional information linking healthy diet and health outcomes.
- We do not use chemical analyses of the menus during the trial to validate the nutrient targets of CCH diet.

Introduction

Cardiovascular disease (CVD) including ischemic heart disease and stroke remains the leading cause of death worldwide, but its mortality has declined in high-income countries.[1] In contrast, cardiovascular burden in China increased rapidly since 1980, as a consequence of rapid changes in lifestyle, environment, and population aging.[2,3] Among these changes, dietary changes might be one of the biggest changes and one of the biggest drivers to the increase in the burden of CVD in China. National Nutrition Surveys showed that the average consumption of pork among Chinese residents increased from 37.1 g/day in 1992 to 64.3 g/day in 2012, dietary energy from fat increased from 22.5% to 33.1% in the same period.[4] Conversely, Chinese are eating much less grains and vegetables in 2012 than in 1992.[4] Such dramatic changes in food patterns have been confirmed in multiple studies.[5,6] According to the Global Burden of Diseases (GBD) study 2013, poor diet and high systolic blood pressure (SBP) ranked the first and second risk factor leading to total death and the loss of disability-adjusted life-years (DALYs).[7] More recently, the GBD study reported that dietary risk factors accounted for 11 million deaths and 255 million DALYs worldwide in 2017.[8] Among the world's 20 most populous countries, China ranked the 1st on the age-standardized rates of diet-related CVD deaths.[8] Clearly, China needs to develop effective dietary strategies to improve the health status of the people.

Studies have demonstrated that high intake of sodium, low intake of whole grains, and low intake of fruits are the leading dietary risk factors for deaths and DALYs worldwide.[8] Several well-known healthy diets with low-sodium, high fruits

and vegetables, and fibers, such as DASH diet and Mediterranean diet, have been developed in Western countries, and their effects in lowering blood pressure, lipids, glucose, and cardiovascular events have been proved by randomized controlled trials (RCTs).[9-13] However, these Western diets are hardly accepted by Chinese due to the different diet culture. China has one fifth of the world total population and Chinese food is popular around the world. A healthy diet that fits into Chinese culture, tastes good by Chinese people, affordable to common people, and proved effective in improving cardiovascular health could bear great significance in prevention and control of CVD in China, in oversea Chinese communities, and people who like Chinese food globally. Thus, developing a healthy Chinese diet should also have a big impact on the global health.

To develop effective lifestyle interventions for prevention and control of CVD in China, the Diet, ExerCIse and CarDiovascular hEalth (DECIDE) project was initiated in 2016. As one of five independent DECIDE studies, the DECIDE-Diet trial aims to develop a tasty, affordable and healthy Chinese diet - Chinese Cardiovascular Health (CCH) diet - that could improve cardiovascular health of Chinese people. Specifically, the primary study aim is to determine whether the CCH diet is effective in reducing SBP, compared with the usual Chinese diet. The secondary study aims include: 1) to evaluate the effect of the CCH diet in lowering diastolic blood pressure (DBP), blood glucose, serum lipids, and estimated 10-year risk of cardiovascular disease; 2) to understand if the intervention effects would be modified by the types of Chinese cuisine; 3) to compare the participants' likeness of CCH diet with that of

usual Chinese diet; 4) to explore the possible impact of the CCH diet on gut microbial community, including microbial composition and abundance.

Methods

Study design

The DECIDE-Diet trial is a four-center, single-blind, randomized controlled feeding trial among community residents with higher risk of cardiovascular disease. Eligible participants will be recruited from four centers majored in different style of Chinese cuisines (Cantonese, Szechuan, Huaiyang, and Shandong), 90 from each. Participants will be randomized with stratification by center in a 1:1 ratio into intervention and control, after one week of a running period on local usual diet. The intervention group will receive the CCH diet and the control group will receive local usual diet. Both diets will be prepared by cooks hired by the study, according to the menus and recipes developed by the study nutritionists. Both diets will use food materials available on the local markets at the season, and will be provided free of charge. The interventions will last for 4 weeks, and both groups will be followed up on the same time schedules for all outcomes measurements. Figure 1 shows the flowchart of this trial.

Participant recruitment

Four cities selected as the study sites in accordance with the four typical Chinese cuisines are: Beijing (Shandong cuisine), Shanghai (Huaiyang cuisine), Guangzhou (Cantonese cuisine), and Chengdu (Szechuan cuisine). Including different diet sites increases the generalizability of our study results in the future and also gives us

opportunity to examine the possible impact of different Chinese cuisines on the intervention effect.

Men and women aged between 25 and 75 years old, living in the target communities for the past six months, with SBP in 130−159 mm Hg are eligible for this trial. Please refer to the Tables 1 and 2 for details of inclusion and exclusion criteria. Potential participants will be screened twice for eligibility before participating in the run-in phase. At the first screening, a trained lay recruiter will screen out the potential participants using a simple questionnaire. At the second screening, a trained research staff will confirm the eligibility by measuring blood pressure and checking on the full list of questions on the inclusion and exclusion criteria.

Run-in period

Only participants that passed the second screening will be invited to participate in a 1-week run-in phase in which they are provided the usual local diet. During this run-in period, the diet will be measured daily to assess the total energy, salt and cooking oil intake, and participants will be asked, on a daily basis, of food preference and likeness, in particular the saltiness, and adjustments will be made to best fit in their own favorable taste of food. The total energy and nutrients composition, amount of salt and cooking oil used daily during the run-in phase will be kept unchanged during the whole study period in the control group. The total energy intake level of each participant will be maintained in both groups throughout the next four weeks to avoid significant weight changes. At the end of the run-in phase, the participants will be

assessed again for their eligibility to the study and adherence to the study protocol. Any participant who failed to take three or more study meals for any reason during the week and any participant with mean SBP measured on three occasions (8:00-10:00 am, 14:00-16:00pm and 18:00 to 20:00pm), 3 readings for each, within 24 hours <130 or ≥160 mm Hg will be excluded from the trial.

Randomization

Participants who pass the run-in phase and complete the baseline data collection on the last two days of the run-in, will be randomly assigned in a 1:1 ratio to the intervention and control group. We will use a centrally concealed randomization procedure stratified by study sites and batches of study participants. We assume that each study site need to implement the trial in multiple batches of participants for the reason of feasibility. However, the multiple batches will introduce possible variances in foods by seasons. Thus, the randomization stratified by batches of participants and study sites is considered necessary. An statistician centrally based at the study coordinating center in Peking University Clinical Research Institute will be responsible for generating the random allocation sequence using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Blinding

Due to the nature of dietary intervention, it is impractical to blind the cook, dietitian and the study staff who are responsible for preparing the foods and taking all measurements of the diets. However, staffs conducting the outcome assessments will be blinded to the allocation of intervention assignments. In addition, every effort is

made to blind the study participants to their intervention assignment too. First, they will not be told which group that they belong to. Second, the two groups will take their meals in separate rooms. Third, the same menus using similar food materials will be used for both groups. For example, both groups will have Kung Pao Chicken at the same meal, but the one for the intervention group will be the healthy version and the one for control will be the regular version. In some occasions, a look-like but nutrients different food materials will be used to replace.

Intervention

A 4-week study diet with energy levels measured during the running phase and kept unchanged for each individual will be used immediately after the run-in phase in both groups. Both intervention and control diets will be prepared in the study kitchen, and then delivered to the dining rooms and distributed to each study participant. Standardized energy foods ranging from 80 kcal to 200 kcal each will be used to adjust individual energy level when there is a need. The participants will be required to eat all meals on site except for the breakfast, during the entire study period. But study meals are allowed to be taken home to eat when the participants are unable to present and the site investigators agree. In both cases, the photos of the remaining foods need to be taken and submitted for the amount assessment by trained staff. In any case, the study participants should consume at least the lunch each day on site, and more than 80% of study meals during each week. Otherwise, the participant is considered non-compliant to the study protocol.

China has a unique blend of culturally and geographically diverse regional

cuisines. To maximize the generalizability, four different versions of CCH diet have been developed according to four major Chinese cuisines: Shandong cuisine (north of China), Huaiyang cuisine (east of China), Cantonese cuisine (south of China), and Szechuan cuisine (southwest of China). All four versions of the CCH diet share the same nutrient targets (Table 3). The healthy version dishes list was based on a survey of local residents on the most common and popular local foods, and to ensure the likeness of flavor by participants the cooking method for each dish was designed by two registered Chinese national master chefs in collaboration with local cooks.

The control group will receive local usual diet with the same 4-week menus as CCH diet, but the targets of nutrient compositions, salt, and cooking oil will be kept the same as that in the run-in phase.

Measurements and data collection

The formal baseline data collection should be performed on the last two days of the run-in phase, which includes a questionnaire interview on demography (age, sex, occupation, education, marital status, household income, and health insurance), lifestyle and health behaviors (smoking, drinking, physical activity, and dietary habits), history of diseases (stroke, myocardial infarction, angina, atrial fibrillation, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and cancer), medications use (antihypertensive drugs, antidiabetic drugs, and lipid-lowering drugs), food likeness; physical examinations (blood pressure, height, weight, pulse rate); fasting blood tests (fasting blood glucose [FBG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol

[HDL-C], triglycerides, and serum potassium); spot urine tests (sodium and potassium excretion); and fecal sample tests on gut microbial community.

The questionnaire will be developed by the study group employing standard questions from previous studies. For food likeness assessment, a food likeness scale ranged from 0 to 10 will be developed and used.

Methods of physical measurements: We will use Omron HEM-7136 blood pressure monitor to measure SBP, DBP and pulse rate. Blood pressure will be taken 3 times within 24 hours at baseline and at the end of this trial: one in the morning between 8:00 am to 10:00 am, one in the afternoon between 2:00 pm to 4:00 pm, and one in the evening between 6:00 pm to 8:00 pm, respectively. In each time, 3 readings should be taken with at least one minute intervals. The average of the nine mean SBP will be used in our analysis. We will use Tanita HD-366 digital weight scale to measure weight. We will stick a Hoechstmass-99202 tape measure vertically to a vertical wall and a triangle to measure height.

Blood sample and spot urine tests: All blood samples of participants from the four centers will be collected in their fasting state by qualified nurses. The second morning urine will be collected to estimate population mean levels of sodium excretion which reflects dietary sodium intake using Kawasaki's formula.[14] Participants will be carefully instructed on how to accurately collect spot urine by research staff. Centrifuged serum samples and urine samples will be frozen and transported to Beijing through complete cold chain and measured in the central laboratory, Beijing Lawke Health Laboratory. Analysis of FBG (using hexokinase

method), TC, LDL-C, HDL-C (using enzymatic colorimetric assay) and triglycerides (using colorimetric assay), serum potassium as well as sodium and potassium in urine (using ISE method) will be carried out on a Roche Cobas c501 automatic biochemistry analyzer.

Fecal sample collection and tests: Stool collection supplies including sampling bowl, gloves, fecal collection tube will be given to participants on the day prior to the sampling. Meanwhile, issues that required attention will be verbally informed to the participants as well as a paper instruction with figure illustrations. Once the participant defecates the next morning, the feces of 50 grams per person will be collected into sterile fecal collection tubes (40ml), and placed in ice box immediately for storage, and then transported to the central laboratory in Beijing. Fecal DNA will be extracted from each sample using QIAamp Fast DNA Stool Mini Kit (QIAGEN, cat. 51604). To investigate the microbial community, shotgun metagenomic and amplicon sequencing strategies will be utilized.

Dietary intake of foods and nutrients: During the run-in phase, we will record the actual intake of every food item in every meal of all seven days for all participants, in order to measure the actual intake of total energy and its compositions, nutrients, and foods. We will weigh every raw food material after they were cleaned up and before they were cooked for any particular dish. We will further count on the total number of shares from that dish and weight the standard share after the cooking is done. In this way we could calculate the total energy and its compositions and amount of nutrients intake for the standard share of every study dish as well as every meal that each

participant take in, based on the China Food Composition (2nd Edition).[15] We will then weigh the leftovers of every dish after the participants finish every meal and calculate the proportion of leftover accounts for each particular dish shared by the participant. When weighing the leftover is not applicable, the proportion of leftovers will be estimated by the visual observation method by the trained staff. In our study, the mean difference in the estimated proportion was 0.5% (95% confidence interval: −1.1 to 2.1%) by the leftover visual observation and −0.4% (95% confidence interval: −1.9 to 1.0%) by leftover photo visual observation (observing photos of leftovers), respectively, from that by weighing. The intra-observer correlation coefficient (ICC) of the leftover visual observation with weighing ranged from 0.714 to 0.960 and the ICC of the leftover photo visual observation ranged from 0.756 to 0.959. We will also collect information or photos of foods that our participants take from outside of the study when it occurs during the study period. Each participant's nutrients intake will be calculated with adjustment for the leftovers and the external foods the participant consumed.

Follow up schedules

The same questionnaire interview and examinations will be repeated at the end of this trial with the same methods by a staff independent to the intervention delivery. In addition, foods intake including foods other than study foods will be recorded every day, and blood pressure, body weight and food likeness assessment will be taken weekly during the trial. The schedule of measurements and visits of this trial has been summarized in Table 4.

Data Management

A Web-based Data Management System (DMS) will be used to facilitate data collection and central management during the whole process of the trial. Data will be subjected to a full set of Web-based Data Management System (DMS) validation checks and additional manual data checking procedures to assure quality of data entry. Access to stored information is restricted to authorized personnel only. Paper forms with participant-identifiable information are held in secure, locked filing cabinets within a restricted area of each site. Trial documentation and data will be archived for at least 5 years after the completion of the trial.

Outcomes

The primary outcome is the change in SBP from baseline to the end of study. The mean of nine readings will be used for the calculation of the changes in each participant. The secondary outcomes include change in DBP, fasting blood glucose (FBG), total cholesterol (TC), 10-year CVD risk, gut microbial community, and food likeness, from baseline to the end of study. The 10-year CVD risk will be calculated according to 10-year risk prediction models for ischemic cardiovascular disease derived from the USA-PRC Collaborative Study of Cardiovascular Epidemiology cohort.[16]

Sample size

We assume that CCH diet will have an effect size of 3.0 mm Hg in reducing SBP in comparison with the control diet. And we further assume the standard deviation of SBP change will be 8 mm Hg in the control group according to our previous cohort

studies.[16,17] To have 90% power with a type I error rate of 5% to detect the difference of 3.0 mm, we would need 165 participants in each arm. Assuming that 10% of study participants will be lost by the end of the study, we will recruit a total of 360 participants (90 from each center).

Statistical analysis

All analyses will follow the intention-to-treat principle. We will adopt the multiple imputation, chained-equations method to impute missing values of primary and secondary outcomes if participants are lost to the follow-up at the end of this study. Variables used to impute the missing values of each outcome will include participants' available values of this outcome (such as baseline values and weekly measurements) and other variables which are associated with this outcome. We will create 20 imputed data sets for each outcome and the mean value of this outcome will be used in our analysis. The primary analysis is linear regression which will be used to estimate the absolute differences between two groups in both primary and secondary outcomes, reported as least squared means after adjusting for centers. The differences in baseline variables between groups will be calculated by using a t-test, Wilcoxon rank test, or chi-square test. Sensitivity analyses will be performed with modified intention-to-treat population including participants with observations at the end of the study, with per-protocol population including those who will consume more than 80% of study meals. Subgroup analyses will be performed to identify potential modifiers of the intervention effect, including type of Chinese cuisine (center), gender, age, baseline blood pressure, glucose, lipids, and estimated 10-year

risk of ischemic cardiovascular disease.

Ethical and dissemination

This trial adheres to the Declaration of Helsinki and guidelines of good clinical practice. Signed informed consent would be obtained from all participants. Participant data in the DMS are protected by password and only available to users designated by the study with appropriate authorization levels. De-identified data will be used for statistical analysis. The current trial has been approved by the Peking University Institutional Review Board (Approval Number: IRB00001052-18094) and registered in clinicaltrials.gov (Identifier: NCT03882645).

The results of this trial will be disseminated through academic conferences, and will be published in an international peer-reviewed journal.

Quality control

Quality control team was established before the initiation of this study. All the researchers participating in this study must attend the technical training and pass the examination organized by the coordinating center, including study protocol, informed consent, CRF, standard operating procedures of participants' data collections, collection and preservation methods of biological samples, etc.

All biological samples will be tested in our central laboratories located in Beijing. The biochemist who performs the measurements will be blinded to the participant allocation. And 10% of urine and blood samples will be taken as split samples to control the quality of laboratory test results. On-site and on-line monitoring for data verification will be used. Each site will have at least two on-site

monitoring visits, one at the beginning of the trial and one at the end of the trial, to ensure the implementation of the study according to the protocol and standard operating procedures. During the study, an appointed staff in the coordinating center will monitor the major nutrients of study diet, changes of body weight and medications of each participant in both two groups based on the data in the DMS. Quality control team could convene executive committee teleconferencing for quality control if necessary.

Current status

The first participant was enrolled on March 22, 2019.

Patient and public involvement

No patients or public were involved in design, or conduct, or reporting, or dissemination of our research.

Discussion

To the best of our knowledge, DECIDE-Diet trial will be the first randomized controlled feeding trial to evaluate the effect of a healthy Chinese diet in reducing blood pressure and improving CVD risk factor profile among community-based individuals with higher risk of cardiovascular disease. Previous RCTs in Western populations have demonstrated that healthy diets such as DASH diet and Mediterranean diet could reduce CVD risk factors and hence reduced CVD risk.[9,10] The meta-analysis that pooled data of 1917 participants from 20 trials found that DASH diet was associated with a significant decrease in SBP (−5.2 mm Hg), DBP

(−2.6 mm Hg), TC (−0.20 mmol/L), and LDL-C (−0.10 mmol/L). These changes predicted a reduction of 13% in the 10-year of Framingham CVD risk.[18]

On the basis of evidences from the previous studies on healthy diets in the Western populations, the DASH diet in particular, we developed the CCH diet with similar nutrients structure in terms of energy proportions from fat, protein and carbohydrate, as well as the amount of sodium, potassium, fiber, vegetables and fruits, in order to achieve the goal beneficial to cardiovascular health. The major difference of the CCH diet from the Western healthy diets is that we see the likeness of food by Chinese equally important to ensure its widely acceptability. Thus, the CCH diet uses local food materials, prepared with local ingredients and condiments and traditional ways of cooking, according to a menu developed on the basis of a survey of local residents. Comparing to the Western diet, Chinese diet is special in many aspects. First, Chinese usually prefer well cooked and hot meals, but Westerners are used to have fresh and cool foods. Second, Chinese do not use table salt but salt has critical role in Chinese diet. Chinese cooks often cite 'A good cook has a handful of salt', and that might be a reason why the salt intake level is so high in China. Third, there are more varieties of methods of cooking for Chinese diet. In addition to boiling, frying, roasting and baking, Chinese uses stewing, braising, steaming, sauteing, pickling, etc. Fourth, the ingredients or seasonings are significantly different between Chinese and Western diets. A lot of ingredients or seasonings are commonly used in Chinese cuisine, such as soy sauce, black or yellow bean sauce, monosodium glutamate, ginger, spring onion, garlic, mint, coriander, white pepper, and Chinese red pepper,

which are rarely used in Western dietary. Meanwhile, cheese, butter, cream or milk are hardly found in traditional Chinese diet. Fifth, unlike the Western diet serves sweet desserts often after every meal, Chinese diet includes sweet dishes but usually only for festivals or banquets treating guests. Last, Chinese often diet together sharing their dishes. These differences between Chinese and Western diets indicate the significance of developing a healthy diet for Chinese, who account for one-fifth of the world's total population.

Beside the commonalities, Chinese living in different parts of China had their own specialties in foods, tastes, and ways of cooking, namely different cuisines. Thus, the CCH diet includes different versions according to the major Chinese cuisines to ensure the likeness by local people. Due to the same reason, our control diet may vary from center to center, which was prepared according to the average local nutrients intake but adjusted according to the participants' likeness of the food taste during the run-in period, to better reflect their usual diet. However, different versions of the CCH diet follow the same targets of nutrients (Table 3) as much as possible. Due to time and resource constraints we could not develop more versions to cover all Chinese local cuisines, which should be done when the current version of CCH diet is proved effective.

In addition to the consideration on the likeness of the CCH diet, we also considered the affordability important to its scalability. The CCH diet was developed with a daily total price of 30 to 50 RMB (4 to 7 USD) using local commonly available food materials. The price is affordable for the wage-earning class in the cities where

the study is conducted. With this consideration, the menus and recipes of CCH diet would be possible to be accepted by the common people and generate real impact from the public health point of view.

Although previous trials proved that dietary intervention could improve cardiovascular health, the mechanisms that links the intervention and outcomes are still unclear. Recently, several studies reported that gut microbiome might play a key role linking dietary intervention and cardiovascular risk reduction.[19-21] However, none of them used RCT design and thus could establish the causal relationship. Thus, we will investigate the effect of CCH diet on gut microbiome in this trial and the results might provide additional information linking healthy diet and health outcomes.

In summary, this trial is the first randomized controlled feeding trial to rigorously investigate the effects of a Chinese diet (the CCH diet) on cardiovascular health among community living individuals. The attention paid to the low cost and good food likeness of the CCH diet makes it bearing huge potential in impacting the public's cardiovascular health if its expected effects can be proven with the current study.

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. Circulation 2018;137(12):e67-e492.
2. Liu S, Li Y, Zeng X, et al. Burden of Cardiovascular Diseases in China, 1990-2016: Findings From the 2016 Global Burden of Disease Study. JAMA cardiology 2019;4(4):342-352.
3. Johnson CO, Nguyen M, Roth GA, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology 2019;18(5):439-458.
4. He Y, Yang X, Xia J, Zhao L, Yang Y. Consumption of meat and dairy products in China: a review. Proc Nutr Soc 2016;75(3):385-391.
5. Zhai FY, Du SF, Wang ZH, Zhang JG, Du WW, Popkin BM. Dynamics of the Chinese diet and the role of urbanicity, 1991-2011. Obes Rev 2014;15 Suppl 1:16-26.
6. Zhao L, Hu J, Zheng R, Tian X, Ren F, Wu Y. The trends of dietary cholesterol intake and its food sources among workers and farmers in Beijing. Acta Nutrimenta Sinica 2009;31(6):556-559.
7. GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(10010):2287-2323.
8. GBD 2017 Risk Factors Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;393(10184):1958-1972.
9. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. New England Journal of Medicine 1997;336(16):1117-1124.
10. Obarzanek E, Sacks FM, Vollmer WM, et al. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. American Journal of Clinical Nutrition 2001;74(1):80-89.

11. De Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99(6):779-785.
12. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. New England Journal of Medicine 2013;368(14):1279-1290.
13. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. British Journal of Nutrition 2015;113(1):1-15.
14. Han W, Sun N, Chen Y, Wang H, Xi Y, Ma Z. Validation of the Spot Urine in Evaluating 24-Hour Sodium Excretion in Chinese Hypertension Patients. American Journal of Hypertension 2015;28(11):1368-1375.
15. Yang Y, Wang G, Pan X. China Food Composition 2004 (Book 1, 2nd Edition). In: Beijing: Peking University Medical Press; 2005.
16. Wu Y, Liu X, Li X, et al. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. Circulation 2006;114(21):2217-2225.
17. Xie W, Liang L, Zhao L, et al. Combination of carotid intima-media thickness and plaque for better predicting risk of ischaemic cardiovascular events. Heart 2011;97(16):1326-1331.
18. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. Br J Nutr 2015;113(1):1-15.
19. Cotillard A, Kennedy SP, Kong LC, et al. Dietary intervention impact on gut microbial gene richness. Nature 2013;500(7464):585.
20. Wilck N, Matus MG, Kearney SM, et al. Salt-responsive gut commensal modulates T H 17 axis and disease. Nature 2017;551(7682):585.
21. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011;334(6052):105-108.

Authors' contributions

Y. Wang and Y. Wu conceived of the original idea for the trial, has been part of the trial design and protocol writing, edited the paper and were overall guarantors. W. Xie obtained ethical approval and has been part of the trial design as well as drafted the protocol. J. Sun, G. Zeng, H. Zhu, Z. Yang, J. Yang, L. Feng, P. Gao, P. Lin, J. Xu, and J. Chen have contributed to the study design, interpretation of the results and commented the paper. All authors approved the final manuscript.

Funding statement

This study is funded by the National Key Research and Development Program, Ministry of Science and Technology of China, through the research grant "Diet, ExerCIse and CarDiovascular hEalth, DECIDE project" (2016YFC1300200). The authors are solely responsible for the design and conduct of this study. The funding has no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Acknowledgement

The Steering Committee of DECIDE-Diet study: Yanfang Wang, Jianqin Sun, Guo Zeng, Huilian Zhu, Zhenquan Yang, Pei Gao, Guansheng Ma, Keji Li, Pao-Hwa Lin, Junshi Chen, and Yangfeng Wu

Competing interests statement

The authors declare that there is no conflict of interest.

Figure legends

Figure 1. The flowchart of the Diet, ExerCIse and CarDiovascular hEalth (DECIDE)-Diet trial. CCH, Chinese Cardiovascular Health; CVD, cardiovascular disease.

Table 1. Inclusion criteria.

1. Men and women aged 25 to 75 years old.
2. Living in the study communities for the past six months and having no plan to move or travel in the next three months.
3. Having a mean systolic blood pressure in 130-159 mm Hg, regardless of medication use.
4. Agreed to keep the current medications and dosages unchanged throughout the study.
5. Promised to follow the study diets for 5 weeks, and eat at least 18 study meals per week.
6. Able to have at least one meal per day taken on site;
7. Signed informed consent.

Table 2. Exclusion criteria.

1. Fasting blood glucose ≥10.0 mmol/L.
2. Total cholesterol ≥7.2 mmol/L.
3. Any changes in dose and/or type of oral medication for antihypertensive, hypoglycemic or lipid-lowering in the past 3 months.
4. Insulin injection within 1 month.
5. Unable or unwilling to change diet for any reason (such as vegetarians).
6. Relatives of researchers or study administrators.
7. Already having family members in this study.
8. Alcohol consumption ≥8 drinks per week for women, ≥15 drinks per week for men.
9. BMI ≥30 Kg/m^2, or currently losing weight.
10. Acute cardiovascular and cerebrovascular events within the past 6 months.
11. A history of chronic kidney disease, intestinal irritation or asthma.
12. Current or planned pregnancy prior to end of study, or breast-feeding.
13. Other serious chronic disease thought to interfere with the effect of the diet or with participation, such as tumor, chronic heart failure, severe depression or other mental disorders, immobilization or unable to move freely.
14. Allergy of common food (e.g. eggs, seafood, peanuts, etc.).
15. On special diet due to medical needs.
16. Acute diseases such as upper respiratory tract infection, fever, severe diarrhea, etc.
17. Deafness, dementia, and inability to communicate.

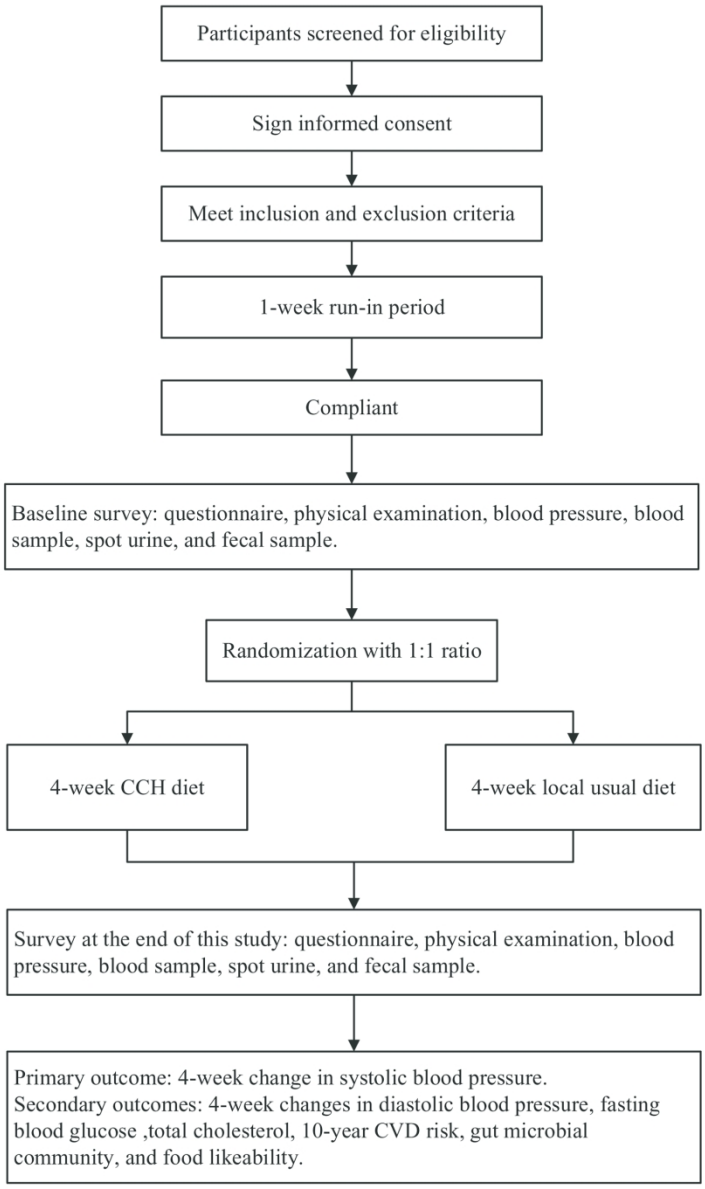
Table 3. Nutrient targets of Chinese cardiovascular health (CCH) diet.

Nutrients	CCH diet
Fat（% of total kcal）	25-27
Saturated	6
Monounsaturated	12
Polyunsaturated	8
Carbohydrates (% of total kcal)	55-60
Protein (% of total kcal)	17-19
Fiber (g/day)	30
Sodium (mg/day)	3000
Potassium (mg/day)	3700
Magnesium (mg/day)	500
Calcium (mg/day)	1200

Table 4. The schedule of measurements and visits of this trial.

	Screening	Run-in*	Follow-up (week)			
			1	2	3	4
Signed informed consent	√					
Eligibility confirmation	√	√				
Questionnaire	√	√				√
Dietary record		√	√	√	√	√
Food likeness assessment		√	√	√	√	√
Height	√					
Weight	√	√	√	√	√	√
Blood pressure and pulse rate	√	√	√	√	√	√
Blood sample		√				√
Spot urine		√				√
Fecal sample		√				√
Reasons for withdrawal		√	√	√	√	√

*Baseline data are collected on the last two days of the run-in period.



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	25
	5b	Name and contact information for the trial sponsor	25
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	25
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1, 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12-15

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol of a multicenter, single-blind, randomized, parallel controlled feeding trial evaluating the effect of a Chinese Healthy Heart (CHH) diet in lowering blood pressure and other cardiovascular risk factors

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036394.R1
Article Type:	Protocol
Date Submitted by the Author:	06-May-2020
Complete List of Authors:	Xie, Wuxiang; Peking University Health Science Centre Wang, Yanfang; Peking University Health Science Centre Sun, Jianqin; Huadong Hospital Affiliated to Fudan University Zeng, Guo; Sichuan University Zhu, Huilian; Sun Yat-Sen University Yang, Zhenquan; Yangzhou University GAO, Pei; Peking University Health Science Centre, Department of Epidemiology and Biostatistics Yang, Jing; National Institute for Communicable Disease Control and Prevention Feng, Lin; Peking University First Hospital; Peking University Health Science Centre, Lin, Pao-Hwa ; Duke University Medical Center Li, Ming; Chinese Preventive Medicine Association Xu, Jianguo; National Institute for Communicable Disease Control and Prevention Chen, Junshi; China National Center for Food Safety Risk Assessment Wu, Yangfeng; Peking University Health Science Centre, Epidemiology
Primary Subject Heading:	Public health
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	NUTRITION & DIETETICS, Hypertension < CARDIOLOGY, DIABETES & ENDOCRINOLOGY

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Protocol of a multicenter, single-blind, randomized, parallel controlled feeding trial evaluating the effect of a Chinese Healthy Heart (CHH) diet in lowering blood pressure and other cardiovascular risk factors

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Abstract

Introduction: Unhealthy diet has been identified as the number one attributor of total mortality in China, accounting for more than 20% of total deaths. Although the DASH and Mediterranean diets have been proven beneficial in managing cardiovascular risk factors in Western countries, whether healthy diets with similar cardiovascular benefits can be developed that are consistent with Chinese food culture remains unknown.

Methods/design: The Diet, ExerCIse and CarDiovascular hEalth (DECIDE)-Diet trial is a multicenter, single-blind, randomized controlled feeding trial to evaluate the effect of the Chinese Healthy Heart (CHH) diet, in comparison with the Chinese usual diet, in lowering cardiovascular risk factors among community residents with increased cardiovascular risk. A total of 360 adults aged between 25−75 years old and with systolic blood pressure (SBP) between 130−159 mm Hg will be recruited from four centers located in four areas representing four major Chinese cuisines: Beijing, Shanghai, Guangzhou and Chengdu. After one week of run-in period with local usual diet, the compliant participants will be randomized to the intervention group with CHH diet or the control group with usual local diet, on 1:1 ratio, for four weeks. Body weight of study participants will be maintained during the entire study period. The primary outcome is the change in SBP from the baseline to the end of the study. DECIDE-Diet trial will be the first randomized controlled feeding trial to evaluate the effect of a CHH diet in lowering cardiovascular risk factors. This trial will provide compelling evidence on the CHH diet in effect of improving cardiovascular health

among Chinese food consumers all around the world.

Ethics and dissemination: This trial adheres to the Declaration of Helsinki and guidelines of Good Clinical Practice. Signed informed consent will be obtained from all participants. The trial has been approved by the Peking University Institutional Review Board (Approval Number: IRB00001052-18094). The results will be disseminated through academic conferences, and publications in international peer-reviewed journals.

Trail registration number: ClinicalTrials.gov identifier: NCT03882645.

Strengths and limitations of this study

- This trial will be the first randomized controlled feeding trial to evaluate the effect of a Chinese Healthy Heart (CHH) diet in lowering cardiovascular risk factors.
- The CHH diet includes different versions according to four major Chinese cuisines to ensure the preference by local people.
- We will investigate the effect of CHH diet on gut microbiome in this trial and the results might provide additional information linking healthy diet and health outcomes.
- The food nutrients in the CHH diet will be calculated according to the China Food Consumption Table, instead of using chemical analyses of the whole dishes.

Introduction

Cardiovascular disease (CVD) including ischemic heart disease and stroke remains the leading cause of death worldwide, but its mortality has declined in high-income countries.[1] In contrast, cardiovascular burden in China has increased rapidly since 1980s, as a consequence of rapid changes in lifestyle, environment, and population aging.[2,3] Among these changes, dietary changes might be one of the biggest changes and one of the biggest drivers to the increase in the burden of CVD in China. Data from the China National Nutrition Surveys showed that the average consumption of pork among Chinese residents increased from 37.1 g/day to 64.3 g/day, and dietary energy from fat increased from 22.5% to 33.1% from 1992 to 2012.[4] Conversely, Chinese people are eating much less grains and vegetables during the same time period.[4] Such dramatic changes in food pattern have been confirmed in multiple studies.[5,6] According to the Global Burden of Diseases (GBD) study 2013, unhealthy diet and high systolic blood pressure (SBP) ranked the top 1 and 2 risk factors leading to total death and the loss of disability-adjusted life-years (DALYs).[7] More recently, the GBD study reported that dietary risk factors accounted for 11 million deaths and 255 million DALYs worldwide in 2017.[8] Among the world's 20 most populated countries, China ranked the 1st on the age-standardized rates of diet-related CVD deaths.[8] Clearly, China needs to develop effective dietary strategies to improve the health status of its people.

Studies have demonstrated that high intake of sodium, low intake of whole grains and fruits are the leading dietary risk factors for deaths and DALYs worldwide.[8]

Several healthy diets with low-sodium, high fruits/vegetables, and fibers, such as the DASH diet and Mediterranean diet, have been proven to lower blood pressure, lipids, glucose, and the risk of CVD with randomized controlled trials (RCTs).[9-13] However, these diets have not been tested within Chinese food culture. China has one fifth of the world total population and Chinese food is popular around the world. A healthy diet that fits into Chinese food culture and well received by Chinese people and is affordable and effective in improving CVD health, could bear great significance in prevention and control of CVD in China, in oversea Chinese communities, and people who like Chinese food globally. The development and evidences in health benefit gained on such a diet has the potential to impact a large segment of people globally.

To develop effective lifestyle interventions for prevention and control of CVD in China, the Diet, ExerCIse and CarDiovascular hEalth (DECIDE) program was initiated in 2016. As one of five independent DECIDE projects, the DECIDE-Diet trial aims to develop a tasty, affordable and healthy Chinese diet – the Chinese Healthy Heart (CHH) diet – that could improve CVD health. Specifically, the primary study aim is to determine the effect of the CHH diet in reducing SBP, compared with the usual Chinese diet. The secondary study aims are: 1) to evaluate the effect of the CHH diet in lowering diastolic blood pressure (DBP), blood glucose, serum lipids, and estimated 10-year risk of CVD; 2) to understand whether the intervention effects would be modified by the types of Chinese cuisines; 3) to compare the participants' preference of CHH diet with that of usual Chinese diet; 4) to explore the possible impact of the CHH diet on gut microbial community, including microbial composition

and abundance. Recent studies have reported that gut microbiome might play a key role in linking the healthy dietary intakes with CVD risk reduction.[14,15] But the causal relationships between dietary intakes, gut microbial community, and CVD risk factors have not been rigorously studied in randomized controlled studies.

Methods

Study design

The DECIDE-Diet trial is a four-center, single-blind, randomized controlled feeding trial among community residents with increased risk of CVD. Eligible participants, 90 from each center, will be recruited from four centers in four geographical locations representing four different style of Chinese cuisines (Cantonese, Szechuan, Huaiyang, and Shandong). Participants will be randomized with stratification by center in a 1:1 ratio into intervention and control, after one week of a run-in period on local usual diet. The intervention group will receive the CHH diet and the control group will receive local usual diet. Both diets will be prepared by cooks hired by the study, according to the menus and recipes developed by the study nutritionists. Both diets will use food materials available on the local markets at the season and will be provided free of charge. The interventions will last for 4 weeks, and both groups will be followed up on the same time schedules for all outcome measurements. Figure 1 shows the flowchart of the study participants.

Participant recruitment

Four cities selected as the study sites representing four typical Chinese cuisines are: Beijing (Shandong cuisine), Shanghai (Huaiyang cuisine), Guangzhou (Cantonese cuisine), and Chengdu (Szechuan cuisine). Inclusion of different cuisines increases acceptability of the CHH diet in local residents and demonstrates the generalizability of the CHH diet.

Men and women aged between 25 and 75 years old, living in the target communities for at least 6 months prior of the study, with SBP between 130−159 mm Hg are eligible for this trial. Tables 1 and 2 list the details of inclusion and exclusion criteria. Potential participants will complete two screening visits for eligibility before entering the run-in phase. At the first screening visit, a trained lay recruiter will screen the potential participants using a simple questionnaire. At the second screening visit, a trained research staff will confirm the eligibility by measuring blood pressure and checking every inclusion and exclusion criteria.

Run-in period

Only participants that passed the second screening will be invited to participate in the 1-week run-in phase during which all participants will be provided with the usual local diet. During the run-in period, amounts of food consumed will be measured daily to assess the total energy, salt and cooking oil intake. Participants will be asked, on a daily basis, of food preference, in particular the saltiness, and adjustments will be made to best fit their preferred taste. The total energy and nutrients composition, amount of salt and cooking oil used daily during the run-in phase will be kept unchanged during the rest of the study period in the control group.

The total energy intake level of each participant will be maintained for all individuals in both groups throughout the study to avoid significant weight changes. At the end of the run-in phase, the participants will be assessed again for their eligibility to the study and adherence to the study protocol. Any participant who failed to consume three or more study meals for any reason during the week and any participant with mean SBP measured on three occasions (8:00-10:00 am, 14:00-16:00 pm and 18:00 to 20:00 pm), 3 readings for each, within 24 hours and with an averaged reading of <130 or ≥160 mm Hg will be excluded from further participating the trial.

Randomization

Participants who pass the run-in phase and complete the baseline data collection on the last two days of the run-in, will be randomly assigned in a 1:1 ratio to the intervention and control group. We will use a centrally concealed randomization procedure stratified by study sites and batches of study participants. We assume that each study site needs to implement the trial in multiple batches of participants for the reason of feasibility. However, the multiple batches may introduce possible variances in foods and blood pressure by seasons. Thus, the randomization stratified by batches of participants and study sites is considered necessary. A statistician centrally based at the study coordinating center in Peking University Clinical Research Institute will be responsible for generating the random allocation sequence using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Blinding

Due to the nature of dietary intervention, it is impractical to blind the cook, dietitian

and the study staff who are responsible for preparing the foods and taking all measurements of the diets. However, staffs conducting the outcome assessments will be blinded to the allocation of intervention assignments. In addition, every effort is made to blind the study participants to their intervention assignment. First, they will not be told of their group assignment. Second, the two groups will consume their meals in separate rooms. Third, the same dishes using similar food materials will be used for both groups at the same meal. For example, both groups will have Kung Pao Chicken at the same meal, but the one for the intervention group will be the healthy version and the one for control will be the regular version. In some occasions, foods that look-alike but contain different nutrients may be used.

Intervention

Both intervention and control diets will be prepared in the study kitchen at each center, and then delivered to the dining rooms and distributed to each study participant. Standardized energy foods, with energy level ranging from 80 kcal to 200 kcal each, will be used to provide additional energy for the study participants when needed to assist with maintenance of body weight. The participants will be generally required to eat all their meals on site during the entire study period. Less than 20% of the study meals are allowed to be taken home to eat with investigators permission each week when the participants are unable to consume on site. In these cases, the photos of the remaining foods need to be taken and submitted to the study staff for assessment. Overall, the study participants should consume at least the lunch meal on site each day, and should have more than 80% of the study meals consumed on site

each week. Otherwise, the participant is considered non-compliant according to the study protocol.

China has a unique blend of culturally and geographically diverse regional cuisines. To maximize the generalizability and acceptability of the diet, four different versions of CHH diet have been developed according to four major Chinese cuisines: Shandong cuisine (north of China), Huaiyang cuisine (east of China), Cantonese cuisine (south of China), and Szechuan cuisine (southwest of China). All four versions of the CHH diet share the same nutrient targets (Table 3). The healthy version dishes menu was based on a survey of local residents on the most common and popular local foods, and to ensure the preference of flavor by the participants.

The recipes of CHH diet (intervention diet) were designed by the research team consisted of medical researchers, physician, nutritionists, registered dietitian, and chefs of each study center, according to the nutrient composition targets of CHH diet. See Table 3 for specific targets of each nutrient and the strategies to achieve these targets. The nutrients composition of a usual Chinese diet in urban China[16] are also listed in Table 3 for comparison. According to the nutrient targets, the resultant CHH diet will increase intakes of nuts, seeds and beans or bean product to 200 g per week, fruits to 150 g per day and vegetables to 300 g per day. A sample one-day menu of Shandong cuisine is shown in Table 4.

The CHH diet was designed to be easily adopted so that it can be applied in a variety of settings. Specifically, the CHH diet consists of a set of menus that include two weeks of non-repeating and exchangeable meals for breakfast, lunch and dinner.

With fixed recipes and standard cooking procedures, this diet can be easily learned and used by professional cooks and even individuals at home. The flavor and preference of each main dish had been tested before it is incorporated into the CHH diet, to ensure the acceptability by the study participants.

The control group will receive local usual diet with the same 4-week menus as CHH diet, but the targets of major nutrients, salt, and cooking oil will be kept the same as that in the run-in phase.

Measurements and data collection

The formal baseline data collection should be performed on the last two days of the run-in phase, which includes a questionnaire interview on demography (age, sex, occupation, education, marital status, household income, and health insurance), lifestyle and health behaviors (smoking, drinking, physical activity, and dietary habits), history of diseases (stroke, myocardial infarction, angina, atrial fibrillation, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and cancer), medication use (antihypertensive drugs, antidiabetic drugs, and lipid-lowering drugs), food preference; physical examinations (blood pressure, height, weight, pulse rate); fasting blood tests (fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and serum potassium); spot urine tests (sodium and potassium excretion); and fecal sample tests on gut microbial community.

The questionnaire has been developed by the study team employing standard questions from previous studies. For assessment of food preference, participants will

be asked at end of each week to rate their preference of the previous week's meals on a visual analogue scale ranging from 0 to 10 (10 represents "preferred the most"). We will further request more specific information about the foods if someone's scale is less than 7. Meanwhile, we will also regularly collect their comments about the food during this trial on site.

Methods of physical measurements: We will use Omron HEM-7136 blood pressure monitor to measure SBP, DBP and pulse rate. Blood pressure will be taken 3 times within 24 hours at baseline and at the end of this trial: one in the morning between 8:00 am to 10:00 am, one in the afternoon between 2:00 pm to 4:00 pm, and one in the evening between 6:00 pm to 8:00 pm, respectively. In each time, 3 readings should be taken with at least one-minute intervals. The average of the nine SBP readings will be used in our analysis. We will use Tanita HD-366 digital weight scale to measure body weight. We will stick a Hoechstmass-99202 tape measure vertically to a vertical wall and a Trigonometric ruler to measure height.

Blood and spot urine samples collection and tests: blood sample of participants from the four centers will be collected in their fasting state by qualified nurses. The over-night urine sample of each participant will be collected to estimate population mean levels of sodium excretion which reflects dietary sodium intake using Kawasaki's formula.[17] Participants will be carefully instructed on how to accurately collect spot urine by research staff. Centrifuged serum samples and urine samples will be frozen and transported to Beijing through complete cold chain and measured in the central laboratory, Lawke Health Laboratory in Beijing. Analysis of fasting blood

glucose (using hexokinase method), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (using enzymatic colorimetric assay) and triglycerides (using colorimetric assay), serum potassium and urinary sodium and potassium (using ISE method) will be carried out on a Roche Cobas c501 automatic biochemistry analyzer.

Fecal sample collection and tests: Stool collection supplies including sampling bowl, gloves, fecal collection tube will be given to participants, with verbal instructions delivered and written instructions distributed on how to collect and deliver the fecal sample to research center. Once the participant defecates the next morning, an approximate 50-gram feces sample per person will be collected into sterile fecal collection tubes (40 ml), and placed in ice box immediately for storage, and then transporting to the central laboratory in Beijing. Fecal DNA will be extracted from each sample using QIAamp Fast DNA Stool Mini Kit (QIAGEN, cat. 51604). To investigate the microbial community, shotgun metagenomic and amplicon sequencing strategies will be utilized.

Dietary intake of foods and nutrients: First, for each food/dish, raw food materials will be weighted after cleaning and before cooking. Then before the food serviced to the study participants it will also be measured and recorded. After each meal, the leftover from each participant will be weighted and recorded as well. The daily average total energy and dietary nutrients taken by each participants can be calculated using the China Food Composition (2nd Edition, volume 1).[18]

When weighing the leftover is not applicable, the proportion of leftovers will be

estimated by the visual observation method by the trained staff. The mean difference of the estimated from the weighted proportion was 0.5% (95% confidence interval: −1.1 to 2.1%) for onsite visual observation and −0.4% (95% confidence interval: −1.9 to 1.0%) for photo visual observation (observing photos of leftovers), respectively. The intra-observer correlation coefficient (ICC) of the estimated proportion of leftover for onsite visual observation with weighing ranged from 0.714 to 0.960 and the ICC of the estimated proportion of leftover for photo visual observation ranged from 0.756 to 0.959.

We will also collect self-reported information before every meal on foods that are taken by the participants but not provided by the study.

Follow up schedules

The same questionnaire interview and physical examinations will be repeated at the end of the trial with the same methods by staffs blinded to the interventions. In addition, blood pressure, body weight, and food preference will be assessed weekly during the trial. If a participant's weight changes more than 2 kg from baseline, we will adjust his/her energy intake right away in order to stabilize weight. The medication use will be monitored, and participants will be reminded to take their prescribed medication daily unless their physicians require to change. The schedule of measurements and visits of this trial has been summarized in Table 5.

Data Management

A Web-based Data Management System (DMS) will be used to facilitate data collection and central management during the whole process of the trial. Data will be

subjected to a full set of Web-based DMS validation checks and additional manual data checking procedures to assure quality of data entry. Access to stored information is restricted to authorized personnel only. Paper forms with participant-identifiable information are held in secure, locked filing cabinets within a restricted area of each site. Trial documentation and data will be archived for at least 5 years after the completion of the trial.

Outcomes

The primary outcome is the change in SBP from baseline to the end of study. The mean of nine readings will be used for the calculation of the changes in each participant. The secondary outcomes include change in DBP, fasting blood glucose, total cholesterol, 10-year CVD risk, gut microbial community, and food preference, from baseline to the end of study. The 10-year CVD risk will be calculated according to 10-year risk prediction models for ischemic cardiovascular disease derived from the USA-PRC Collaborative Study of Cardiovascular Epidemiology cohort.[19]

Sample size

According to the findings from the DASH diet that successfully reduced SBP by 5.5 mm Hg in 8 weeks,[9] we conservatively assumed that CHH diet will reduce SBP by 3.0 mm Hg in comparison with the control diet in 4 weeks. And we further assumed the standard deviation of SBP change will be 8 mm Hg in the control group according to our previous studies.[19,20] To have 90% power with a type I error rate of 5% to detect the assumed effect size, we would need 165 participants in each arm. Assuming that 10% of study participants will be lost by the end of the study, we will recruit a

total of 360 participants (90 from each center).

Statistical analysis

The primary analyses will follow the intention-to-treat principle and will be conducted among participants who have been randomized and also completed the final follow up. The linear regression will be used to estimate the absolute differences between two groups in both primary and secondary outcomes, reported as least squared means after adjusting for centers. The differences in baseline variables between groups will be evaluated by using a t-test, Wilcoxon rank test, or chi-square test. Sensitivity analyses will be performed to adjust for the imbalanced baseline variables if existed and to repeat the analyses with imputed missing values due to the lost to follow ups. We will adopt the multiple imputation, chained-equations method to impute missing values of primary and secondary outcomes if participants are lost to the follow-up at the end of this study. Variables used to impute the missing values of each outcome will include participants' available values of this outcome (such as baseline values and weekly measurements) and other variables which are associated with this outcome. We will create 20 imputed data sets for each outcome and the mean value of this outcome will be used in our analysis. Per-protocol analyses will be conducted among population including those who will consume more than 80% of study meals and completed the final follow up. Subgroup analyses will be performed to identify potential modifiers of the intervention effect, including type of Chinese cuisine, gender, age, baseline multi-morbidity, medications use, blood pressure, glucose, total cholesterol, and estimated 10-year risk of ischemic cardiovascular disease.

Patient and public involvement

No patients or public were involved in the design, conduct, reporting, or dissemination of this research study.

Ethical and dissemination

This trial adheres to the Declaration of Helsinki and guidelines of good clinical practice. Signed informed consent will be obtained from all participants. Participant data in the DMS will be protected by password and only available to users designated by the study with appropriate authorization levels. De-identified data will be used for statistical analysis. The current trial has been approved by the Peking University Institutional Review Board (Approval Number: IRB00001052-18094) and registered in clinicaltrials.gov (Identifier: NCT03882645).

The results of this trial will be disseminated through academic conferences, and publications in international peer-reviewed journals.

Quality control

Quality control team was established before the initiation of this study. All the researchers participating in this study must attend the technical training and pass the examination organized by the coordinating center, including study protocol, informed consent, case report form, standard operating procedures of participants' data collections, collection and preservation methods of biological samples.

All biological samples will be tested in our central laboratories located in Beijing. The biochemist who performs the measurements will be blinded to the participant's randomization allocation. In addition, 10% of urine and blood samples

will be taken as split samples to control the quality of laboratory test results. On-site and on-line monitoring for data verification will be used. Each site will have at least two on-site monitoring visits, one at the beginning of the trial and one at the end of the trial, to ensure the implementation of the study according to the protocol and standard operating procedures. During the study, an appointed staff in the coordinating center will monitor the delivery of the target nutrients of study diet, changes of body weight and medications of each participant in both two groups based on the data in the DMS. Quality control team will convene executive committee teleconferencing for quality control if necessary.

Data sharing plan

Data are available upon reasonable request (Yanfang Wang, pucri_wangyf1225@bjmu.edu.cn).

Current status

The first participant was enrolled on March 22, 2019.

Discussion

To the best of our knowledge, DECIDE-Diet trial will be the first randomized controlled feeding trial to evaluate the effect of a healthy Chinese diet in reducing blood pressure and improving CVD risk factor profile among community-based individuals with increased risk of CVD. Previous RCTs in Western populations have demonstrated that healthy diets such as the DASH diet and Mediterranean diet could reduce CVD risk by reducing CVD risk factors.[9,10] The meta-analysis that pooled data

of 1917 participants from 20 trials found that the DASH diet was associated with a significant decrease in SBP (−5.2 mm Hg), DBP (−2.6 mm Hg), total cholesterol (−0.20 mmol/L), and low-density lipoprotein cholesterol (−0.10 mmol/L). These changes predicted a 13% reduction in the 10-year Framingham CVD risk.[21]

Taken the evidences from the previous studies on healthy diets in the Western populations, the DASH diet in particular,[9] we developed the CHH diet with similar nutrients profile including energy proportions from fat, protein and carbohydrate, as well as the amount of sodium, potassium, fiber, vegetables and fruits, in order to achieve similar CVD benefit observed in previous research. The major difference of the CHH diet from the Western healthy diets is that it was developed with common local Chinese food items and cooking methods to ensure its wide acceptability.[22]

The menus of the CHH diet also incorporated feedback from surveys of local residents. Comparing to the Western diet, Chinese diet is special in many aspects. First, Chinese usually prefer well cooked and hot meals, but Westerners are used to have raw and cool foods.[23,24] Second, Chinese do not use table salt but salt has critical role in Chinese diet. Chinese cooks often cite “A good cook has a handful of salt”, and that might be a reason why the salt intake level is so high in China.[22] Third, there are more varieties of cooking methods for Chinese diet. In addition to boiling, frying, roasting and baking, Chinese uses stewing, braising, steaming, sauteing, pickling, etc.[25] Fourth, the ingredients or seasonings are significantly different between Chinese and Western diets.[24] A lot of ingredients or seasonings are commonly used in Chinese cuisine, such as soy sauce, black or yellow bean sauce, monosodium glutamate,

ginger, spring onion, garlic, mint, coriander, white pepper, and Chinese red pepper, which are rarely used in Western dietary. Meanwhile, cheese, butter, cream or milk are hardly found in traditional Chinese diet. Fifth, unlike the Western diet serves sweet desserts often after every meal, Chinese diet includes sweet dishes but usually only for festivals or banquets treating guests.[23] Last, Chinese often diet together sharing their dishes.[22] These differences between Chinese and Western diets indicate the significance of developing a healthy diet for Chinese, who account for one-fifth of the world's total population.

Beside the commonalities, Chinese living in different parts of China had their own specialties in foods, tastes, and ways of cooking, namely different cuisines. Thus, the CHH diet includes different versions according to the major Chinese cuisines to ensure its acceptability in different regions. Similarly, since local usual diet may vary from center to center, the control diet was prepared according to the average local nutrients intake but adjusted according to the participants' preference of the food taste during the run-in period, to better reflect their usual diet. Regardless, different cuisines versions of the CHH diet follow the same targets of nutrients (Table 3). The four major cuisines are estimated to cover over 80% of China's total population.[26]

In addition to the consideration on the acceptability of the CHH diet, we also considered the affordability of the diet which is important to its scalability. The CHH diet was developed with a daily total cost of 30 to 50 RMB (4 to 7 USD) per person using local commonly available food materials. The price is affordable for the wage-earning class in the cities where the study will be conducted. With this

consideration, the menus and recipes of CHH diet will be possible to be accepted by the common people and generate real impact from the public health point of view.

Although previous trials proved that dietary intervention could improve cardiovascular health, the mechanisms that links the intervention and outcomes are still unclear. Recently, several studies reported that gut microbiome might play a key role linking dietary intervention and CVD risk reduction.[27-29] However, none of them used RCT design and thus could establish the causal relationship. Thus, we will investigate the effect of CHH diet on gut microbiome in this trial and the results will enhance understanding the role of gut microbiome in the links between healthy diets and health outcomes.

In summary, this trial is the first randomized controlled feeding trial to rigorously investigate the effects of a healthy Chinese diet (the CHH diet) on cardiovascular health among community living individuals. This trial is designed with considerations including not only the health effect of CHH diet, but also its acceptability, feasibility and affordability. Findings from this trial has a great potential in impacting the cardiovascular health of many individuals.

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation.* 2018;137(12):e67-e492.
2. Liu S, Li Y, Zeng X, et al. Burden of Cardiovascular Diseases in China, 1990-2016: Findings From the 2016 Global Burden of Disease Study. *JAMA cardiology.* 2019.
3. Johnson CO, Nguyen M, Roth GA, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology.* 2019.
4. He Y, Yang X, Xia J, Zhao L, Yang Y. Consumption of meat and dairy products in China: a review. *Proc Nutr Soc.* 2016;75(3):385-391.
5. Zhai FY, Du SF, Wang ZH, Zhang JG, Du WW, Popkin BM. Dynamics of the Chinese diet and the role of urbanicity, 1991-2011. *Obes Rev.* 2014;15 Suppl 1:16-26.
6. Zhao L, Hu J, Zheng R, Tian X, Ren F, Wu Y. The trends of dietary cholesterol intake and its food sources among workers and farmers in Beijing. *Acta Nutrimenta Sinica.* 2009;31(6):556-559.
7. GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386(10010):2287-2323.
8. GBD 2017 Risk Factors Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2019;393(10184):1958-1972.
9. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *New England Journal of Medicine.* 1997;336(16):1117-1124.
10. Obarzanek E, Sacks FM, Vollmer WM, et al. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *American Journal of Clinical Nutrition.* 2001;74(1):80-89.

11. De Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* 1999;99(6):779-785.
12. Estruch R, Ros E, Salas-Salvado J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *The New England journal of medicine.* 2018;378(25):e34.
13. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. *British Journal of Nutrition.* 2015;113(1):1-15.
14. Wilck N, Matus MG, Kearney SM, et al. Salt-responsive gut commensal modulates TH17 axis and disease. *Nature.* 2017;551(7682):585-589.
15. Houghton D, Hardy T, Stewart C, et al. Systematic review assessing the effectiveness of dietary intervention on gut microbiota in adults with type 2 diabetes. *Diabetologia.* 2018;61(8):1700-1711.
16. National Health Family Planning Commission Disease Prevention Control Bureau. Report on nutrition and chronic diseases of Chinese residents. People's Medical Publishing House Beijing; 2015.
17. Han W, Sun N, Chen Y, Wang H, Xi Y, Ma Z. Validation of the Spot Urine in Evaluating 24-Hour Sodium Excretion in Chinese Hypertension Patients. *American journal of hypertension.* 2015;28(11):1368-1375.
18. Yang Y. China Food Composition Tables (Standard Edition, Book 1, 6th Edition). Beijing: Peking University Medical Press; 2018.
19. Wu Y, Liu X, Li X, et al. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. *Circulation.* 2006;114(21):2217-2225.
20. Xie W, Liang L, Zhao L, et al. Combination of carotid intima-media thickness and plaque for better predicting risk of ischaemic cardiovascular events. *Heart.* 2011;97(16):1326-1331.
21. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a

systematic review and meta-analysis. *Br J Nutr.* 2015;113(1):1-15.

22. Ma G. Food, eating behavior, and culture in Chinese society. *Journal of Ethnic Foods.* 2015;2(4):195-199.

23. Zili X. The Differences of Chinese and Western Food Cultures. *Chinese Language, Literature & Culture.* 2017;2(1):6.

24. Yang S, Zhang Y. The research of the differences between Chinese and Western diet cultures. *Cross-cultural communication.* 2010;6(2):75-83.

25. Li B. Comparison of Diet and Cooking based on Chinese and Western Culture. 2016.

26. Pan Y. Discussion on Chinese cuisines. *Science, Technology Vision.* 2016;4:202-206.

27. Cotillard A, Kennedy SP, Kong LC, et al. Dietary intervention impact on gut microbial gene richness. *Nature.* 2013;500(7464):585.

28. Wilck N, Matus MG, Kearney SM, et al. Salt-responsive gut commensal modulates T H 17 axis and disease. *Nature.* 2017;551(7682):585.

29. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334(6052):105-108.

Authors' contributions

Y. Wang and Y. Wu conceived of the original idea for the trial, has been part of the trial design and protocol writing, edited the paper and were overall guarantors. W. Xie obtained ethical approval and has been part of the trial design as well as drafted the protocol. J. Sun, G. Zeng, H. Zhu, Z. Yang, J. Yang, L. Feng, P. Gao, P. Lin, J. Xu, M. Li, and J. Chen have contributed to the study design, interpretation of the results and commented the paper. All authors approved the final manuscript.

Funding statement

This study is funded by the National Key Research and Development Program, Ministry of Science and Technology of China, through the research grant "Diet, ExerCIse and CarDiovascular hEalth, DECIDE project" (2016YFC1300200). The authors are solely responsible for the design and conduct of this study. The funding has no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Acknowledgement

The Steering Committee of DECIDE-Diet study: Yanfang Wang, Jianqin Sun, Guo Zeng, Huilian Zhu, Zhenquan Yang, Pei Gao, Guansheng Ma, Keji Li, Pao-Hwa Lin, Junshi Chen, and Yangfeng Wu

Competing interests statement

The authors declare that there is no conflict of interest.

Figure legends

Figure 1. The flowchart of the Diet, ExerCIse and CarDiovascular hEalth (DECIDE)-Diet trial. CHH, Chinese Healthy Heart; CVD, cardiovascular disease.

Table 1. Inclusion criteria.

1. Men and women aged 25 to 75 years old.
2. Living in the study communities for the past six months and having no plan to move or travel in the next three months.
3. Having a mean systolic blood pressure in 130-159 mm Hg, regardless of medication use.
4. Agreed to keep the current medications and dosages unchanged throughout the study.
5. Promised to follow the study diets for 5 weeks, and eat at least 18 study meals per week.
6. Able to have at least one meal per day taken on site;
7. Signed informed consent.

Table 2. Exclusion criteria.

1. Fasting blood glucose ≥10.0 mmol/L.
2. Total cholesterol ≥7.2 mmol/L.
3. The number of total oral medications for antihypertensive, hypoglycemic or lipid-lowering > 2 for the past 3 months.
4. Any changes in dose and/or type of oral medication for antihypertensive, hypoglycemic or lipid-lowering in the past 3 months.
5. Insulin injection within 1 month.
6. Unable or unwilling to change diet for any reason (such as vegetarians).
7. Relatives of researchers or study administrators.
8. Already having family members in this study.
9. Alcohol consumption ≥8 drinks per week for women, ≥15 drinks per week for men.
10. BMI ≥30 Kg/m^2, or currently losing weight.
11. Acute cardiovascular and cerebrovascular events within the past 6 months.
12. A history of chronic kidney disease, intestinal irritation or asthma.
13. Current or planned pregnancy prior to end of study, or breast-feeding.
14. Other serious chronic disease thought to interfere with the effect of the diet or with participation, such as tumor, chronic heart failure, severe depression or other mental disorders, immobilization or unable to move freely.
15. Allergy of common food (e.g. eggs, seafood, peanuts, etc.).
16. On special diet due to medical needs.
17. Acute diseases such as upper respiratory tract infection, fever, severe diarrhea, etc.
18. Deafness, dementia, and inability to communicate.

Table 3. The nutrients composition of a usual Chinese diet in urban China and Chinese Healthy Heart (CHH) diet, and strategies to achieve the CHH diet's nutrients' targets

Nutrients	Usual diet in urban China	CHH diet	Strategies to achieve the CHH diet's target
Energy (kcal)	2053	Individualized	Averaged intake assessed during run-in
Fat (% of total kcal)	33	25-27	Reducing the use of cooking oil by changing cooking method, e.g., replacing deep frying with steaming, and use low-fat or non-fat dairy products
Saturated	-	6	
Monounsaturated	-	12	
Polyunsaturated	-	8	
Carbohydrates (% of total kcal)	55	55-60	Increasing whole grains and limiting the use of monosaccharide
Protein (% of total kcal)	13.5	17-19	Increasing intake of protein from lean meat, beans & milk
Fiber (g/day)	11	30	Increasing use of foods with higher dietary fiber
Sodium (mg/day)	5859	3000	Using less salt in cooking, and replacing regular salt with salt substitute
Potassium (mg/day)	1660	3700	Increasing use of food that contain high amount of potassium, and use of salt substitute
Magnesium (mg/day)	-	500	Using food that contain high amount of Magnesium
Calcium (mg/day)	412	1200	Increasing use of dairy products, lean meat and beans

Table 4. An example of one-day menu of Shandong cuisine.

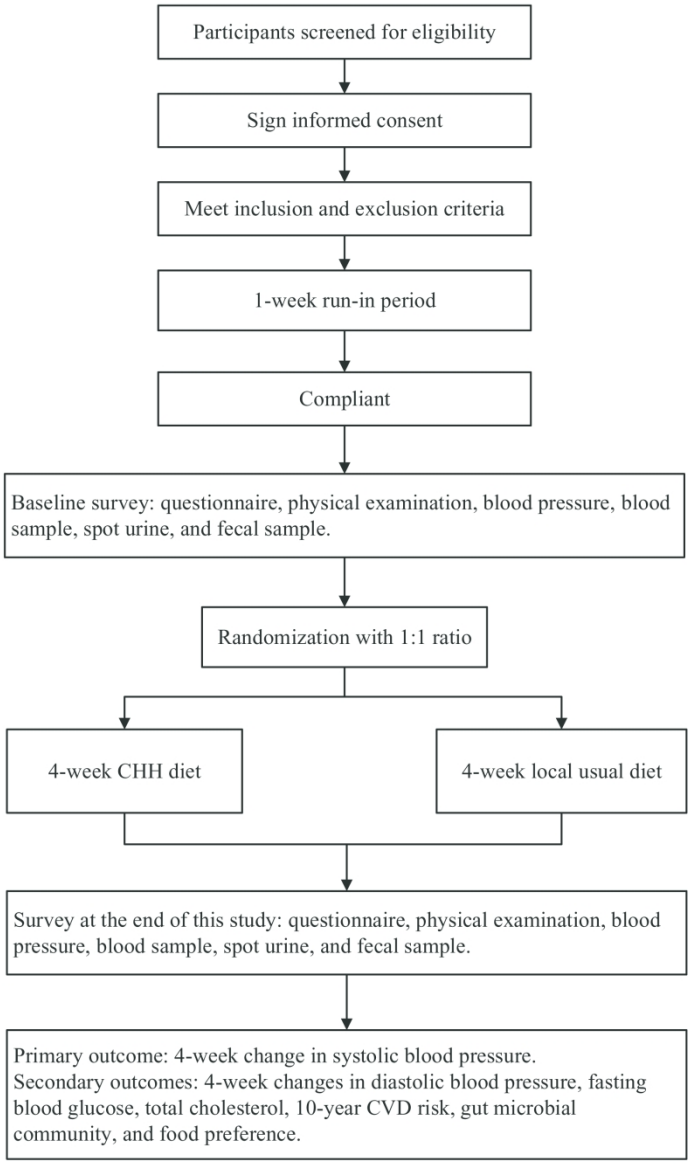
	Chinese Healthy Heart diet	Control diet
Breakfast	Steamed twisted roll mixed with vegetable	Steamed twisted roll
	Millet congee	Millet congee
	Boiled egg	Boiled egg
	Boiled Mung bean sprout in sauce with nuts	Boiled soybean sprouts in sauce
Lunch	Steamed rice with oats	Stir fried rice with meat and bean
	Stir fried cabbage with vermicelli	Stir fried cabbage with bean starch noodle
	Stewed tofu with shrimp & radish	Seaweed and egg soup
	Banana (half)	
	Skim milk	
Dinner	Steamed bun mixed with corn meal	Steamed bun stuffed with round pork and celery
	Rice congee with red bean	Rice congee
	Stir fried enoki mushroom with bell Pepper and dried bean curd	Stir fried mushroom with bell Pepper and dried bean curd
	Yogurt	Steamed twisted roll

Table 5. The schedule of measurements and visits of this trial.

	Screening	Run-in*	Follow-up (week)			
			1	2	3	4
Signed informed consent	√					
Eligibility confirmation	√	√				
Questionnaire interview	√	√				√
Dietary record**		√	√	√	√	√
Food preference assessment		√	√	√	√	√
Height	√					
Weight	√	√	√	√	√	√
Blood pressure and pulse rate	√	√	√	√	√	√
Blood sample		√				√
Spot urine		√				√
Fecal sample		√				√
Reasons for withdrawal		√	√	√	√	√

*Baseline data are collected on the last two days of the run-in period.

**Dietary data will be collected on the daily basis.



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	27
	5b	Name and contact information for the trial sponsor	27
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	27
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1, 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 5
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17-18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-11

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19-20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19-20

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19-20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13-16

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.