Cover letter:

Official project title:
Efficacy of Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Plus Forest Bathing (FB) on blood pressure and cognitive health for those who are aged 50 and above with hypertension

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Study protocol

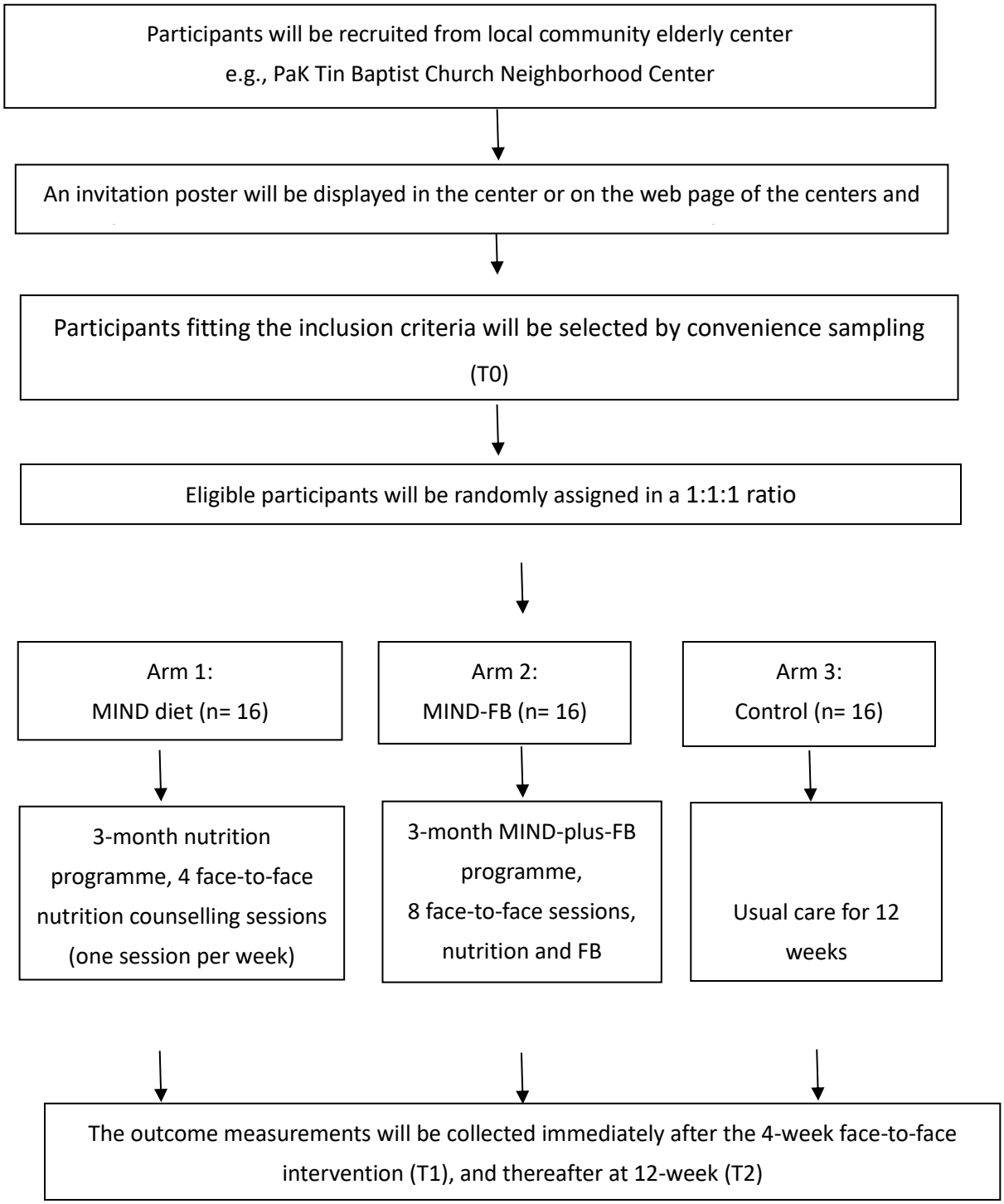

Figure 1: A flow diagram of the study

Work done by others
Nonpharmacological interventions are effective in controlling BP with weight loss, the Dietary Approaches to Stop Hypertension diet (DASH), increase physical activity and a reduction in alcohol consumption (1;2).

Dietary Intervention
DASH diet is combination of high intake of whole-grain cereals, low-fat dairy products, fish, chicken and lean meats, with moderately high in protein and high in mineral and dietary fibre (3:4). The bioactive compounds of DASH are high in minerals (magnesium, potassium, calcium and phosphorus), vitamins (vitamin C and folate) and other phytochemicals including flavonoids and inorganic nitrate, which have antioxidant properties (4;5;6). The protective effects of DASH diet may be due to the multiple physiological mechanisms including anti-inflammatory effect (8), antioxidant capacity (9), generation of nitric oxide (10), sympathetic activation (11). Recent systematic review and meta-analysis of RCT (30 RCTs, n=5545 participants) showed that moderately strong evidence that DASH diet reduced both SBP and DBP [difference in means (MD): -3.2 mmHg and -2.5 mmHg] compared with a control diet (12). Adherence to DASH diet was inversely associated with odds of cardiovascular disease (RR, 0.80), diabetes (0.80) in prospective cohort studies; decrease systolic BP (MD, -5.2 mmHg) and diastolic BP (MD, -2.6 mmHg), HbA1c (-0.53%) and body weight (-1.42 kg) in controlled trials (9). Mediterranean diet (MedDi) refers to high intake of olive oil, rich in green leafy vegetables and fruits, cereals, nuts, and legumes/pluses, moderate amount of fish and other meat, dairy products, red wine and low intake of eggs and sweets (10). Five potential metabolic and molecular mechanisms of high intake of flavonoids are lipid-lowering effect, protective against oxidative stress, inflammation and platelet aggregation, modification of hormones and growth factors involved in the pathogenesis of cancer, inhibition of nutrient sensing pathways by specific amino acid restriction and gut-microbiota-mediated production of metabolites influencing metabolic health (10;11;12).

Two recent systematic reviews and meta-analyses showed that MedDi play a significant role in prevention of cardiovascular disease incidence (RR: 0.62), mortality (RR: 0.79) and stroke (RR: 0.73) (14;15). Although DASH and MedDi have shown plausible prospective evidence to support the benefits on cardiovascular health, it is necessary to be adapted to different geographic settings and cultural preferences and health conditions. The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet (16;17) is a hybrid of the MedDi and DASH diet. Unlike DASH or MedDi, MIND diet emphasizes 10 brain-healthy foods including green leafy vegetables, other vegetables, berries, nuts, beans, whole grains, seafood, poultry, olive oil and wine) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). Evidence from epidemiologic studies (1 cross-sectional and 5 longitudinal) observed that adherence to MIND dietary pattern is associated with better cognitive performance and lower risk of cognitive performance in older adults but inconsistently with cognitive decline (17). Several biological mechanisms of MIND may influence cognitive function (18;19). The blood brain barrier guards the brain from environmental insults that leads to oxidative stress and inflammation. Accumulation of amyloid-beta (Aβ) leads to neuritis plaques within neuron cells and finally induces brain atrophy. Limiting intake of butter, margarine, pastries and sweets, low consumption of saturated fats and trans-fat may result in improving the blood-brain barrier function and decreasing amyloid-beta (Aβ) aggregation (19). Long-chain n-3 fatty acids from fish may reduce Aβ formation and oxidative damage (20). The components of berries and green leafy vegetables are rich in flavonoids, folate and vitamin E and carotenoids and it have been shown to be antioxidant and anti-inflammatory effect in inhibition of formation of Aβ (21;22). These mechanisms directly impact brain health and may be indirectly via cardioprotective effects of the

related food components. Recent cross-sectional study found that MIND diet score is inversely associated with odds of reduced HDL cholesterol and general obesity (23). Comparing to DASH and MedDi, it does not include the consumption of fast foods, fried foods, butter, margarine and pastries and sweets. These foods are common in urban cities like HK. To our best knowledge, the cognitively protective or cardioprotective effects of the MIND diet has not been tested or compared in Asian. Cross-country variation in food supply, dietary behaviour and lifestyle are different from western and Asian, studies of the MIND are required in Asian and Chinese population.

FB intervention

Shinrin-Yoku, known as Forest Bathing (FB), it is a traditional Japanese practice of mindfully usage of five senses by immersing into nature. Recent review, 11 of 14 RCT and experimental studies measured blood pressure as the primary outcome. Six of the studies reported FB significant decreases in SBP (5.4 – 24.6%) and DBP (7 – 29.5%) among the participants after the intervention (24). Another meta-analysis included 20 trials with 732 participants shown that SBP and DBP of the forest environment was significantly lower (MD -3.15 mmHg and -1.75 mmHg) than that of the non-forest environment (25). The possible therapeutic effects on FB including increasing in natural killer cells in cancer prevention, improvement in hypertension/coronary artery disease, improve allergies and respiratory conditions, improvement in mood disorders and stress and mental relaxation. The hypothesis mechanism is originally from concept of nature therapy, FB has a direct effect on increasing the parasympathetic nervous system by exposing to naturally occurring stimuli of five senses. Increasing the parasympathetic nervous system in turns to decreasing sympathetic nervous activity, cortisol levels and salivary amylase activity and leads to a stage of relaxation (24;25;26). These results indicated that FB is effective at reducing the blood pressure of participants, suggesting that they can potentially be used to manage hypertension. A feasibility study was conducted to measure and compare the psychological and physiological benefits of FB and DDBE among community middle-aged hypertensive adults. The intervention was conducted over four weeks to establish its feasibility and logistics, and the effects were measured pre-intervention (as the baseline) and immediately after completion of intervention at 4 weeks. The sustained effect of interventions was measured at eight weeks after the intervention. The findings of this feasibility study provided a preliminary evidence that, after 4-week intervention, FB was more effective than DDBE in lowering SBP of 7.45 mmHg ($t=2.44$; $p<0.05$) and the score of state anxiety level of 11.5 ($t=5.12$, $p<0.001$), trait anxiety levels of 6.4 ($t=3.21$, $p<0.01$), the total mood states of 14.8 ($t=4.93$, $p<0.001$), in the study population (30). Also, FB have been tested out in China and Taiwan and showed that FB enhanced heart rate and blood pressure functions. This relaxation strategy is suitable for middle-aged and elderly individuals (27;28).

MIND plus FB intervention

MIND diet has been tested the enhancing cognitive function on western hypertensive population, but it has not been tested in Asian prehypertensive and hypertensive population. We hypothesis that MIND diet has effective of lower BP and maintain/enhance cognitive function on Chinese populations. FB is the additional effects of MIND in this proposed study. To the best of our knowledge, there is no study related to the effect of MIND plus FB in non-Chinese and Chinese studies. Thus, a pilot study to test out the effects of MIND and MIND plus FB is necessary.

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4. Project plan and methodology: (max. 3 pages)

Quantitative arm – Setting and Participants: A block randomization, single-blind design will be used. A three-arm RCT with equal allocation between the intervention and control groups (1:1:1) will be used; only the assessors will be blinded to the treatment assignment. Convenience sampling with

fitting the inclusion criteria will be selected as subjects. Potential participants will be screened for blood pressure and health history at baseline assessment. The potential participants who meet the inclusion criteria will be asked to sign a consent form before participation in this study.

Primary and secondary outcomes

The primary outcomes will be systolic BP and the secondary outcomes will be point of care test (POCT) of lipid panel (HDL-cholesterol, triglycerides and LDL-cholesterol), cognitive function, waist-to-hip ratio, body fat percentages and body mass index.

Systolic BP will be determined by digital automatic device, Omron M6 Comfort (HEM-7221-E), for BP measurement (29). BP will be obtained in sitting position after enough rest (at least 10-15 min) and based on the mean of two measurements of participant. The POCT of lipid panel (HDL-cholesterol, triglycerides and LDL-cholesterol) will be measured by the Food and Drug Administration (FDA) cleared and Centers for Disease Control and Prevention, Cholesterol Reference Method Laboratory Network (CRMLN) certified CardioChek PA (30). Body fat percentages and body mass index will be measured via bioelectrical impedance analysis (BIA) (31). Cognitive function will be assessed via Hong Kong version of the Montreal Cognitive Assessment (HK-MoCA) (Cronbach alpha: 0.767; high sensitivity rate: 92.3% and good specific of 91.8%) for global cognition testing at baseline and each measurement. A cut-off score of 21/22 after adjustment of education level is recommended as indication for further evaluation of cognitive impairment and dementia (32). Waist circumference will be measured between the lower rib and iliac crest by tape meter. Waist to hip ratio will be calculated as waist circumference (cm) divided by hip circumference (cm) (33). The outcome measurements will be recorded before the intervention (T0), immediately after the 4-week face-to-face intervention (T1) and 12 (T2) post-intervention to determine its short-term effects.

Demographic and other covariates

In addition to sociodemographic data (age, marital status, sex and education attainment), we will also collect data on physical activity, alcohol consumption, self-reported medical diagnosis, current use of medications, number of chronic diseases and cognitive levels.

Diet scores

Dietary intake will be assessed by using a validated 163-item semi-quantitative Harvard Food Frequency Questionnaire (FFQ) (50;51). There is no FFQ specifically for MIND diet. Morris's group, the origin of MIND diet, is used Harvard FFQ to assess diet scores. Although it has not been used in Hong Kong Chinese population, the food list is user-friendly to Chinese culture with common food groups of green leafy vegetables, rice, fruits etc. Adherence to MIND dietary pattern will be assessed by calculating summation scores using predefined criteria (19:20). MIND score consists of 15 dietary components, namely 10 brain healthy food groups (green leafy vegetables, other vegetables, berries, nuts, beans, whole grains, seafood, poultry, olive oil and wine) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). A value of 0.0. 0.5 or 1.0 has been assigned to each group. For high intake of brain healthy food group, participants will receive a score of 1 and the score is reversed for unhealthy food group. The total MIND diet score will be computed by summing all food groups, with a maximum score of 15 representing the highest adherence to the MIND diet.

Inclusion and exclusion criteria

A total of 48 those who are aged 50 and above and meet the inclusion criteria will be asked to sign a consent form before participation in this study. The inclusion criteria are (i) aged 50 and above; (ii) Chinese ethnicity; (iii) ability to speak and understand Chinese; (iv)fulfilment of the AHA

criteria for stage 1 and stage 2 hypertension; and (v) physical fitness to take part in mild-intensity exercises e.g. slow walking, standing light work etc. The exclusion criteria are (i) poorly controlled chronic disease, including chronic obstructive pulmonary disease, cardiovascular disease, kidney disease and diabetes, (ii) have allergy to more than one type of food (nuts, berries, olive oil, or fish), (iii) Use of medications to treat Alzheimer's disease or Parkinson's disease, (iv) pregnant, (v) participation in any dietary or relaxation programme within the past 3 months, (vi) experienced chronic pain and muscle weakness, and (vii) were unable to walk independently were excluded. All screening tests will be carried out by a trained research assistant. Based on AHA criteria, stage 1 hypertension is suggested to be defined as SBP 130-130 mmHg or DBP 80-89 mmHg, and stage 2 is suggested to be defined as SBP ≥140 mmHg or DBP ≥ 90 mmHg.

Interventions

MIND diet group

The MIND diet intervention used for this study is based on the MIND diet developed by Morris and colleagues in 2015 (16;17). We adapted Arjmand group's 3-month MIND diet intervention (24). MIND diet intervention will be a 3-month nutrition programme consisting of 4 face-to-face nutrition counselling sessions (one session per week, 60 min per session) in the activity room of each participating community centre. All intervention sessions will be conducted by a registered nutritionist and trained student helpers. In the nutrition sessions, the participants will learn to modify their diet to meet MIND diet guidelines. MIND diet promotes 10 healthy foods and limits 5 unhealthy food groups. A 7-day sample menu is developed, meeting the required number of servings per day every week, as reference. Each intervention session will be conducted by a nutritionist with the help of a research assistant. To maintain consistency, one nutritionist, with one research assistant (with a degree in nursing or nutrition), will deliver all the interventions. Topics covered during the programme including how to promote behaviour change strategies; overview of MIND diet; discussion of establishing rapport with participants and instruction regarding dietary adoption and adherence checks using logbook to enable informed decision making and adherence to nutritional recommendations.

MIND-plus-FB intervention

The MIND-plus-FB intervention will last 4 weeks, consisting of 8 sessions (two sessions per week). The MIND diet will follow the steps mentioned in the previous section. MIND diet intervention will be one session per week, 60 min per session, in the activity room of each participating community centre. FB will be another session per week, 2 hours forest bathing sessions on 4-consecutive weekends in a country park at daytime with sunny, cloudy or drizzling conditions. The walking distance for each forest bathing is one to two kilometres. The session will be rescheduled to the next weekend if there is heavy rainy day. The best temperatures for forest bathing session are ranging from 11 to 25 °C. In view of humidity and temperatures in HK, FB is suitable to be conducted between January to June, and September to December respectively. On the day of FB, participants will gather at the entrance of the country park for briefing and measuring physical parameters e.g., BP and pluses.

FB coach will begin the FB intervention by a set of experiential thresholds, called Standard Sequence (25;26) to facilitate participants' deeper connection to the nature via sensory activity along the path. Each intervention session will follow an identical invitation: (i) sharing experience for the forest (20 minutes) (ii) center yourself at the pleasure of moment using five senses (20 minutes), (iii) wander down the designed forest path to slow down both physically and mentally (20 minutes) and (iv) build up a deeper connection to forest by alertness what happen of the surrounding (20 minutes). Participants will be given around 20 minutes of rest and sharing time

between each activity change. The tea Ceremony, as second threshold, is incorporated at the end of each session. All intervention sessions will be conducted by a certified FB coach with wilderness first aid certificate by the Association of Nature & Forest therapy (ANFT). The FB coach will ensure safety during FB. The coach-to-participant ratio is approximately 1:16. Participants will then be required to self-practice 2h FB in the country park at daytime at the weekends of 8th week and 12th week of the intervention.

Control group

A control group with routine care will be added to illuminate the effect of MIND and MIND-plus-FB.

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Sample size

There is no previous RCT on the MIND diet intervention. We first calculate the effect size (f=0.43) by using results from the DASH trial using systolic BP as a primary outcome variable (50); we consider the type I error of 5% ($\alpha = 0.05$), type II error of 20% ($\beta = 0.2$, power = 80%). A total of 48 participants will be required (i.e., 16 per group) for this pilot study. The sample size calculation was based on the F test using G*Power 3.1.9.4.