TITLE

Investigating the feasibility and acceptability of a multi-domain intervention to increase Mediterranean diet adherence and physical activity in older UK adults at risk of dementia: Protocol for the MedEx-UK randomised controlled trial.

AUTHORS

Oliver M Shannon[1*], Vivian YJ Lee[2*], Rafe Bundy[3], Rachel Gillings[3], Amy Jennings[3], Blossom CM Stephan[4,5], Michael Hornberger[6], George M Balanos[2], Stella-Maria Paddick[7], Sarah Hanson[3], Wendy Hardeman[3], Sarah Aldred[2,8], Mario Siervo[1,5], John C Mathers[1], and Anne Marie Minihane[3]

*Shared first authorship

AFFILIATIONS

1 Human Nutrition Research Centre, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK.

2 School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, B15 2TT, UK.

3 Department of Nutrition and Preventive Medicine, Norwich Medical School, University of East Anglia (UEA), Norwich, NR4 7TJ, UK.

4 Institute of Health and Society and Newcastle University Institute of Ageing, Newcastle University, Biomedical Research Building, Campus of Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK.

5 School of Life Sciences, The University of Nottingham Medical School, Queen's Medical Centre, Nottingham, NG7 2UH, UK.

6 Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK.

7 Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital and Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE27 0QJ, UK.

8 Centre for Human Brain Health, College of Life and Environmental Sciences, University of Birmingham, B15 2TT, UK.

CORRESPONDENCE:

Name: Prof. Anne Marie Minihane

Email: A.Minihane@UEA.ac.uk)

Telephone: 01603592389

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ABSTRACT

Introduction

Dementia prevalence continues to increase, and effective interventions are needed to prevent, delay, or slow its progression. Higher adherence to the Mediterranean diet (MedDiet) and increased physical activity (PA) have been proposed as strategies to facilitate healthy brain ageing and reduce dementia risk. However, to date, there have been no dementia prevention trials in the UK focused on combined dietary and PA interventions. This study aims to: 1) assess the feasibility and acceptability of a multi-domain intervention for dementia risk reduction in an 'at risk' UK cohort; 2) evaluate behaviour change responses to the intervention; and, 3) provide information on cognitive, neurological, vascular and physiological outcomes to inform the design of a follow-on, full-scale efficacy trial.

Methods

One hundred and eight participants aged 55-74 years with a QRISK2 score of ≥10% will be recruited to take part in this 24-week multi-site study. Participants will be randomised into three parallel arms: 1) Control; 2) MedDiet; 3) MedDiet+PA. The study will apply a personalised, multi-domain intervention to increase MedDiet adherence and/or PA levels in older adults at risk of dementia. Diet and PA will be monitored prior to, during, and following the intervention. Feasibility and acceptability of our multi-domain intervention will be assessed in addition to measures of cognitive function (extended Neuropsychological Test Battery), brain structure/perfusion (MRI), vascular function (blood pressure and endothelial function) and physiological changes (blood, urine and faecal) prior to, and following, the intervention.

Discussion

This trial will provide insights into the feasibility and acceptability of a multi-domain intervention for dementia risk reduction in an 'at risk' UK cohort.

Ethics and dissemination

The study has received NHS REC and HRA approval (18/NI/0191). Findings will be disseminated via conference presentations and peer-reviewed publications.

Trial registration number: ClinicalTrials.gov NCT03673722

STRENGTHS AND LIMITATIONS OF THIS STUDY

- MedEx-UK is the first feasibility and acceptability study of a Mediterranean diet (MedDiet) alone or in combination with physical activity (PA) intervention for dementia risk reduction in an ‘at-risk’ UK cohort.
- This study will provide detailed information on behavioural (dietary and objective measures of PA), cognitive, neurological, vascular and physiological outcomes to inform the design of a follow-on, full-scale efficacy trial.
- The study intervention is informed by evidence synthesis and was designed with input from patients and members of the public.
- It is not possible to blind participants to their experimental condition, and results may be influenced by expectation bias.
- It is beyond the scope of this trial to include a PA only arm so that the effects of PA alone cannot be elucidated.

INTRODUCTION

The worldwide prevalence of dementia continues to increase – an effect driven by expanding and ageing populations. Current estimates suggest that around 50 million individuals worldwide have dementia, with this figure forecast to increase to around 82 million by 2030 and 152 million by 2050 [1]. In England and Wales, dementia is the first and second leading cause of death in women and men, respectively, responsible for 16.7 % and 8.9 % of total mortality in 2018 [2]. Considering the health and social care burden and financial cost of dementia, estimated to be £26.3 billion (£32,250 per affected person) in the UK in 2014 [3], identifying ways to prevent, delay, or slow the progression of dementia is a major public health and research priority [4]. There is no cure for dementia, and there are few pharmacological options to improve symptoms [5]. However, an increasingly large body of evidence indicates that modifiable behaviours such as diet and physical activity (PA) could play an important role in preventing or delaying dementia onset [4,6]. Delaying the onset by 2 or 5 years is estimated to reduce the number of dementia cases by 19% and 33%, respectively, by 2050, with a lower prevalence of severe dementia [7].

The Mediterranean dietary pattern (MedDiet) is one of the healthiest dietary patterns and is characterised by high intakes of vegetables, fruits, nuts, seeds, and whole grains. Fish and other seafood are consumed at least twice per week, whilst red meat and confectionery are consumed infrequently. Olive oil is the principal cooking fat, whilst red wine is consumed in moderation with meals [8,9]. Several prospective cohort studies have reported reduced brain atrophy, better cognitive function and reduced risk of dementia, including Alzheimer's disease, with higher MedDiet adherence [10,11]. Adherence to a Mediterranean diet was identified to play a key role in dementia prevention, intervention and care by the Lancet commission [11]. Moreover, evidence from the Prevención con Dieta Mediterránea (PREDIMED) randomised controlled

trial (RCT) in Spain demonstrated beneficial effects on cognitive function of a MedDiet intervention supplemented with additional nuts or extra virgin olive oil [12–14]. Fewer studies have been conducted outside the Mediterranean basin. However, in a recent analysis of over 8000 participants from the EPIC-Norfolk cohort (UK), we demonstrated that a 3 point increase in MedDiet score on a 14- or 15-point scale was equivalent to between 1.5 and 5 fewer years of ageing on global cognition, with effects particularly evident in individuals at higher cardiovascular disease (CVD) risk [15]. Potential mechanisms of action for the MedDiet include improved cardiovascular health [16,17] and modulation of the gut microbiota [18] along with direct effects on brain glucose utilisation and β-amyloid load [19,20].

Increased PA has also been shown to reduce age-related cognitive decline and dementia risk [21,22]. In a recent dose-response meta-analysis, the risk of all-cause dementia and Alzheimer's disease was found to be 10% and 13% lower, respectively, for every 500 kcal or 10 metabolic equivalent (MET)-hours per week increase in leisure-time PA [21]. While there is strong evidence of a protective effect of PA in numerous observational studies, the limited number of RCTs and the heterogeneity of the exercises prescribed in these studies, limit our understanding of the effects [23–25]. Potential mechanisms for the effects of PA on cognitive health include induction of antioxidant pathways, reduced neuro-inflammation, neurogenesis, enhanced synaptic plasticity, decreased amyloid burden, improved vessel health and augmented cerebrovascular blood flow [26–30].

The effects of increased PA and improved diet on cognitive health are likely to be additive. To date, three large-scale multi-domain interventions have been completed which incorporated diet and increased PA [31–33]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial – which included dietary advice, PA, cognitive

training, social activity, and management of metabolic and vascular risk factors - observed 25-150 % improvement in cognitive outcomes [31]. In addition, the Prevention of Dementia by Intensive Vascular Care (preDIVA, The Netherlands), which included lifestyle (diet, PA, smoking cessation) and medical interventions (e.g. statins, anti-hypertensive medication), and the Multidomain Alzheimer Preventive Trial (MAPT, France) trial, which included dietary and PA changes alongside cognitive stimulation, observed protective effects in specific sub-groups including individuals with elevated vascular or dementia risk, brain amyloid positivity, or *APOE4* carriers [32,33]. Two ongoing studies – the Lifestyle Intervention in Independent Living Aged Care (LIILAC) [34] and Maintain Your Brain (MYB) [35] trials – are investigating the combined impact of a MedDiet and PA intervention on cognition in Australian populations.

To date, there have been no dementia prevention trials in the UK focused on MedDiet only or in combination with PA. Given a) the lack of success of pharmacological trials, b) the widespread calls for dementia risk reduction strategies in the UK, and c) the effectiveness of multi-domain interventions such as FINGER, preDIVA and MAPT in improving cognitive function, this research is strongly justified. The aims of the MedEx-UK are:

1) To assess the feasibility and acceptability of a multi-domain intervention by evaluating participant recruitment, engagement and retention on the trial.
2) To assess behavioural change in response to the intervention through changes in MedDiet scores and PA levels.
3) To assess various cognitive, neurological, vascular and biological outcomes to inform the design of a later full-scale efficacy trial.

METHODS AND ANALYSIS

This protocol has been written in accordance with the Standard Protocol Items for Randomised Trials (SPIRIT) guidelines [36]

Design

MedEx-UK is a 24-week multi-site (Norwich, Newcastle and Birmingham) RCT in older UK adults at risk of dementia. The study is a personalised, multi-domain intervention, with three parallel arms: 1) Control; 2) MedDiet; 3) MedDiet+PA.

Participants

We are recruiting 108 participants (36 per site) through Primary Care and direct-to-public advertisements such as via posters, leaflet distribution, social media and local media. Recruitment through Primary Care is in collaboration with local Clinical Research Networks (CRNs) at each study site.

Inclusion and exclusion criteria

Participants are aged 55 to 74 years. Cardiovascular health is highly prognostic of future dementia [37–40]. The QRISK2 score is routinely in UK primary care, to identify cardiovascular risk and is applied in MedEx to identify those 'at risk' for dementia. We included those with a QRISK2 score of ≥10%, which indicates a ≥10% risk of having a cardiovascular event in the next 10y. Participants will i) possess normal cognition (Montreal Cognitive Assessment (MoCA) score ≥23 [35]), ii) not diagnosed with mild cognitive impairment, dementia or any other severe neuropsychological complaints, iii) have a baseline MedDiet (Mediterranean Diet Adherence Screener (MEDAS)) score ≤9 [41]; and iv) undertake <90 minutes moderate-intensity PA per week. We estimate that our recruitment strategy will

identify 10-15% of the 55-74 year old UK population who are at risk of dementia and are likely to benefit from behavioural change. A full list of criteria is provided in Table 1.

Recruitment

Prior to enrolment, participants undergo several stages of screening to ensure they meet the study inclusion/ exclusion criteria (Figure 1).

Online screening

Participants provide online consent prior to completing an online screening questionnaire (~30 minutes duration). This questionnaire evaluates a MedDiet adherence score via an adapted version of the 14-point MEDAS questionnaire and levels of PA via the International Physical Activity Questionnaire (IPAQ). Additionally, participants provide information on age, height, weight, medical history, and whether they have regular access to the internet.

Telephone screening

Participants who satisfy all of the inclusion/exclusion criteria on the online screening questionnaire, except for the PA criteria, receive a telephone call (~10 minutes duration) from a research team member to probe PA levels, to minimise over-reporting and to improve the accuracy of PA estimates. Probing questions are based on Rzewnicki et al. [42], and involve enquiries around exercise duration and intensity (estimated via the effect on breathing). Eligible participants are invited to an onsite screening session.

Onsite screening

Onsite screening is conducted in a clinical facility at the participant's local study site (~90 minutes duration). Following informed consent (Online Supplementary Material), a series of measures are taken to evaluate participant eligibility (Table 2).

Height and weight are measured using standard laboratory techniques for calculation of body mass index (BMI), whilst blood pressure (BP) is determined as described in the *Outcome Measures* section. The MoCA is administered, and participants are assessed for subjective memory complains via the Cognitive Change Index (CCI) [43]. Further questionnaires are administered to ensure the absence of severe depression (Participant Health Questionnaire [PHQ-9] score≤10) and anxiety (General Anxiety Disorder questionnaire [GAD-7] score≤10). Additionally, a close friend or relative of the participant is asked to complete the Ascertain Dementia 8-item informant questionnaire (AD-8; score<2) and the Instrumental Activities of Daily Living questionnaire (IADL; score=8) to evaluate memory decline. Finally, participants recruited directly from the general public provide a 4 mL blood sample for determination of serum total- and HDL-cholesterol concentrations and provide additional medical history information for calculation of QRISK2 score.

Randomisation

Those who pass the onsite screening receive a written invitation to participate in the study. If they accept, they are allocated at random to one of the three study arms, with stratification for sex and MedDiet score (0-4 or 5-8) within each centre.

Intervention description

To promote adherence and efficacy, MedEx-UK is a personalised intervention based on an individual's baseline MedDiet profile and/or PA levels, alongside personal food and activity preferences. The study aims to increase the MedDiet score by a minimum of 3 points in both intervention arms. This target is based on the consistent observation of significant reductions in CVD risk and overall mortality associated with a 2-point increase in the score using the 9-point scale [44,45]; the cognitive benefits associated with a 1.4-1.8 point increase in score in the PREDIMED trial [12,14]; and our own analyses in the EPIC-Norfolk cohort showing that a 3 point increase in MedDiet score is equivalent to between 1.5 and 5 fewer years of ageing on global cognition in older, UK adults [15]. We also aim to increase PA levels (in the MedDiet+PA group) to at least 150 minutes of moderate-intensity exercise (or equivalent vigorous-intensity exercise minutes) per week and to maintain this level throughout the study, in line with World Health Organisation (WHO) recommendations [46].

Delivery of the intervention

The MedEx-UK study uses three complementary approaches to support behaviour change, namely a web-based intervention, group support sessions, and food delivery.

Web-based component

Participants in the MedDiet and MedDiet+PA groups are given access to an interactive, web-based, modular platform called LEAP^2, which serves as the primary method of delivering the behaviour change intervention. LEAP^2 is built upon the LEAP platform used in the LiveWell Programme (designed to enhance healthy ageing by improving diet, PA and social connectedness in older adults [47]) and includes the 'Eating Well' module (to increase MedDiet adherence) and the 'Moving More' module (to increase PA). Participants are encouraged to

revisit the Eating Well and Moving More modules frequently to monitor their progress. In addition, the LEAP^2 platform includes a diary feature to help participants plan their meals and PA, and serves as a central hub through which participants can 'link out' to the dietary assessment and food delivery elements of the MedEx-UK trial, alongside information on locally available PA opportunities. Members of the public provided feedback on iterations of the LEAP^2 platform to maximise efficacy and usability.

Eating Well

The Eating Well module begins with a dietary screening questionnaire (MEDAS), which provides an overall MedDiet score (on a 14 point scale). This allows LEAP^2 to identify those MedDiet goals that are being met, and to give recommendations on those goals that are not. The participant is asked to focus on increasing their score by ≥3 points. To facilitate this increase, the Eating Well module provides MedDiet-specific recipes, alongside suggestions for incorporating MedDiet food items into the participants favourite meals (so-called 'MedDiet Hacks'), advice on consuming takeaway and restaurant foods, and tips on overcoming key barriers associated with dietary change [48].

Moving More

The Moving More module follows a similar structure to the Eating Well module and begins with a PA questionnaire (IPAQ) to determine the participant's current PA levels. LEAP^2 allocates the participant bronze (≥100 minutes of moderate or 50 minutes of vigorous-intensity PA per week), silver (≥120 minutes of moderate or 60 minutes of vigorous-intensity PA per week) or gold level (≥150 minutes of moderate or 75 minutes of vigorous-intensity PA per week) awards for achieving set PA targets. Reflective of our inclusion criteria, participants begin the intervention below the bronze level, with aims to increase and maintain PA equivalent

to the gold level. Participants are asked to set a goal of moderate and/or vigorous activity in minutes per week and LEAP^2 provides tailored PA suggestions based around participants preferences for cost, intensity, and group or individual exercises (list of suggestions summarised in the Online Supplementary Material), and guides participants through overcoming key barriers associated with increasing PA levels.

Group sessions component

Participants in the two 'active' intervention arms (MedDiet and MedDiet+PA groups) receive face-to-face support via four, 2-2.5 hour group session (conducted at weeks 0, 2, 4, and 12) to complement the LEAP^2 platform. The inclusion of the group sessions is based on evidence that 'human support' in the form of group sessions improves adherence to internet-delivered interventions [49]. The content and delivery of the group sessions are informed by evidence synthesis and PPI consultation. Group sessions aim to empower participants to engage with the process of achieving ambitious behavioural targets and encourage them to access available support, including other participants and the LEAP^2 platform [50]. Each group consists of 6 participants and up to 6 'supportive others', who are encouraged to attend to provide social support for participants.

Group facilitators recruited from the community were provided with extensive training, including an in-person 2-day training course and training materials for at-home learning, in social interaction, group facilitation, and behaviour change theory and techniques. Evidence-based training strategies include instruction, demonstration, practice and feedback. We promote fidelity of delivery across sites and facilitators through standardised training, ongoing support, and use of group session materials and example 'script'. However, we are balancing fidelity (delivery of group sessions as planned) with the need to adapt the content and delivery

to context (e.g., geographical area) and participants (age, gender and culture). Such adaptations can promote engagement of the participants and gives them a sense of ownership over the group sessions and the process of behaviour change.

Food provision

Increasing MedDiet adherence in a 'real world' setting has only modest cost implications (high versus low MedDiet adherence was associated with an increased dietary cost of ~ £0.20/d in a UK cohort [51]). However, to ensure perceived cost or logistics is not a barrier to increasing MedDiet score, participants are provided with £30/ week in vouchers for an online food retailer or, in cases where online food delivery is not possible (e.g. due to delivery restrictions to rural areas), vouchers for a supplier of their choice. A link to the online food retailer is provided on the LEAP^2 platform, and participants are asked to use the vouchers to purchase foods contributing towards their MedDiet targets.

Control group

The control group, undergo 'usual care' and are thus provided with general guidelines for those with a moderately elevated QRISK2 score [52], comprising publically available dietary and PA advice viz. leaflets from the British Heath Foundation and links to the NHS 'Livewell' and 'Eatwell' websites. Participants are given a brief presentation on the importance of a control group, at an initial group session (week 0). At the end of the trial, the control group will receive shopping vouchers (£10 per week, totalling £240) for their participation, and to improve retention.

Outcome measures

Dietary intake

At baseline and week 24, participants complete five, non-consecutive 24-hour dietary recalls (~10-20 minutes duration per recall) on four weekdays and one weekend day, using the validated online dietary reporting software Intake24 [53–55]. At weeks 6 and 12, participants also complete 24-hour dietary recalls on three non-consecutive days, including two weekdays and one weekend day to monitor interim dietary changes. These dietary data are used to calculate a MedDiet score using the 14-point MEDAS scale. Participants also complete an online version of the 14-point MEDAS at each of these time points to allow comparison and cross-validation of the two assessment methods.

Physical activity

Participants are asked to wear an activity monitor (Vivosmart 3, Garmin) throughout the 24-week intervention period. The activity monitors are set to show the time and date; however, they are prevented from accessing any activity-based data because use of activity trackers alone has been shown to influence behaviour [56]. The participant's age, height and weight are entered when setting up the device to improve accuracy. The activity monitor monitors total step count, heart rate and energy expenditure.

Cognitive function

Global cognitive function, as determined by a composite score based on an extended version of the neuropsychological test battery (NTB; Table 3), is measured [59]. This is calculated as Z-scores standardised to the baseline mean and SD, with higher scores indicating better performance. Sub-domain Z-scores are evaluated for executive function, memory, and processing speed. The executive function domain is calculated using scores from the Controlled

Word Association Test (COWAT), Category Fluency Test (CFT), Trail Making Test (TMT) A and B, Hayling Sentence Construction Task, and Digit Span. The memory domain Z-score includes results from the Verbal Paired Associates (immediate and delayed), Visual Paired Associates (immediate and delayed), and Rey Auditory Verbal Learning Test (RAVLT; immediate and delayed), whilst the processing speed domain z-score is calculated from the Digit Symbol Substitution Task and Hayling Sentence Completion Task.

Extended NTB score was the primary outcome in the FINGER trial [35] where it was responsive to intervention. Its use in MedEx-UK will allow trial comparability, although in our study we have used the Hayling Sentence Completion Task as an alternative to the Stroop test and we have not included the Concept Shifting Test, as most of the related processes are covered via the TMT. We include assessments of spatial navigation via the virtual reality Supermarket Trolley Task [57–60] and the Sea Hero Quest Test [61]. Spatial navigation has been shown to be an earlier cognitive symptom in preclinical dementia than episodic memory [62,63]. The duration of each cognitive assessment is ~ 90 minutes.

Neuroimaging

Magnetic resonance imaging (MRI) is conducted at baseline and 24-weeks to assess regional structural integrity and blood flow (~60 minutes duration per scan). The following sequences are used; i) T1-weighted 3D gradient-echo MR sequence to evaluate brain structure, ii) T2-weighted scan, T2* and T2 FLAIR to allow for vascular characterisation, such as white matter hyperintensities, iii) Arterial Spin Labelling to measure regional cerebral blood flow, iv) Diffusion Tensor Imaging (DTI) involving a 30-direction diffusion-weighted echo-planar imaging scan to assess the integrity of white matter, v) resting-state functional MRI (fMRI) to

evaluate regional interactions in the brain that occur in a resting or task-negative state when a participant is not performing an explicit task.

Biological samples

Blood, urine and faecal samples are collected at baseline and at 24-weeks to establish *APOE* genotype and selected biomarkers of cardiometabolic and cognitive health (e.g. plasma glucose, lipids, antioxidant and inflammatory levels, BDNF and nitric oxide biomarkers, gut microbiota speciation, and metabolomic profiles in dry blood spots, urine, and faecal samples). A total of 29 mL blood is collected in the fasting state, and whole blood, red blood cells, plasma, serum and platelets are aliquoted and stored at -80C° until further analysis. Protein saver cards (Whatman, GE Healthcare, UK) are used to obtain dry blood spot samples. At-home spot urine samples are collected on 4 days/ week (3 x weekdays, 1 x weekend day), whilst faecal samples are collected on the day prior to the baseline and end-point visits. Both urine and faecal samples are stored at -80C° until further analysis

Blood pressure

Clinic-based blood pressure (BP) of the brachial artery is determined following a 5-minute rest period using calibrated, automated sphygmomanometers. BP is measured in triplicate, with one minute rest period between measures [64]. In addition, 24-hour ambulatory BP is measured using a portable monitor consisting of an inflatable cuff attached to a small monitoring device. Readings are taken every 20 minutes from 06:00 to 22:00 and every hour overnight from 22:00 to 06:00 the subsequent day.

Endothelial function

Endothelial function is measured using flow-mediated dilation (FMD), which assesses the response of the endothelia to shear stress [65]. The brachial artery is identified with an ultrasound transducer, and changes in the artery diameter in response to hyperaemia are recorded using border detection software. The diameter is recorded continuously throughout the procedure including for 3 minutes at baseline, followed by 5 minutes of occlusion of the forearm (sphygmomanometric cuff inflated to 220 mmHg to induce hyperaemia), then 5 minutes post-deflation.

Data storage, management, and dissemination

To maintain anonymity, participants are allocated a numerical identifier. All raw and analysed data from tests and questionnaires will be assigned a code and will not contain information that could enable identification of individual participants. Data will be stored in locked filing cabinets and any electronic information will have restricted access and/or password protection as appropriate. All adverse events and participant medication will be documented. Study results will be disseminated via conference presentations, peer-reviewed publications, and public outreach events. Participant data will be anonymised in all publications. Data will be retained for 15 years following publication. Access to data will be determined by a trial management committee consisting of AMM, JCM, MS and SA.

Statistics

This study aims to recruit 108 participants. Assuming a 20% drop-out rates, we predict about 90 will complete the study, 30 participants in each arm. Hence, we will obtain a 95% confidence interval for the mean difference between the TAU (treatment as usual) and combined treatment arms of + 0.75 points either side of the point estimate. The smallest

detectable change in MedDiet score with 90% power and 5% size is 1.23 points, well inside our minimum target for dietary change of 3 points, suggesting we will have a sufficiently precise estimate of whether a dietary change is achievable in this trial. We will also compare individual arms descriptively, to provide an indication of whether the PA intervention effects the MDP change achieved, and explore associations between intervention engagement ($LEAP^2$ and group sessions) and behavioural outcomes. A total of 90 participants to completion will have 90% power to detect a difference of 1.4 points between these groups.

DISCUSSION

The MedEx-UK trial aims to evaluate the feasibility and acceptability of a multi-dimensional intervention in an older, UK-based cohort at risk of dementia. This study will provide crucial information on behaviour change (MedDiet score and PA levels) and on cognitive, neurological, vascular, and physiological responses to the intervention, to inform the power and design of a follow-on, full-scale efficacy trial.

Strengths and limitations

A key strength of the MedEx-UK trial is the personalised nature of the intervention. To date, most multi-domain interventions have prescribed a 'one size fits all' approaches to behaviour change, where recommendations are made to consume specific food products [41] or to undertake specific exercises [34]. In contrast, MedEx-UK encourages participants to take an active role in selecting lifestyle changes which fit with their individual needs (identified through the diet and activity screening questionnaires) and personal food and activity preferences, which may help aid motivation and improve the efficacy of the intervention [66–69]. From a dietary perspective, results from our analysis of the EPIC-Norfolk cohort [15] indicate that the beneficial effects on cognition are related to consumption of the MedDiet as a

whole, rather than being driven by an individual food group. This suggests that individuals have a degree of dietary flexibility and are encouraged to focus on MedDiet components that meet their personal food preferences. The design of the PA intervention used in the study accommodates key practices identified in promoting PA in older adults, including the multidimensional approach, principles of behaviour change and gradual increases in intensity [70]. Furthermore, reducing barriers against inactivity identified in older adults [71], by allowing the participants to self-select activities, will promote adherence to PA. Such personalisation and flexibility may improve adoption of this dietary pattern and facilitate increased PA.

MedEx-UK targets individuals deemed to be 'at-risk' of dementia, based on their cardiovascular risk profile (QRISK2 score $\geq$ 10), given the strong links between poor cardiovascular health and increased risk of cognitive decline and dementia [37–40]. Such targeting will allow us to capture the most vulnerable population who are most likely to benefit from lifestyle modifications. Indeed, in our analysis of data from the EPIC-Norfolk cohort, we showed that associations between MedDiet adherence and reduced risk of poor cognitive performance were apparent only in individuals with a high CVD risk profile [15]. Furthermore, a recent systematic review found that exercise affected cognitive performance positively in those with known vascular disease [72].

Consistent with most other RCTs in this area [73], it is not possible to blind participants to the intervention. This increases the risk of expectation bias which could result in more favourable outcomes compared with the control group [74]. Additionally, this trial does not include a PA only arm, so the effects of PA alone (rather than the potentially additive effects of diet and PA) cannot be elucidated.

Conclusions

The MedEx-UK trial will provide insight into the feasibility and acceptability of a multi-dimensional lifestyle intervention to promote healthy brain ageing in a UK cohort. If successful, this feasibility trial will inform a longer and larger trial designed to test the efficacy of the lifestyle-based intervention in reducing dementia risk with the long-term aim of diminishing the mounting social and financial burden caused by this debilitating neurodegenerative disease.

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AUTHOR CONTRIBUTIONS

OMS, VL, and RB wrote the initial draft of the manuscript. RG, AJ, BCMS, MH, GMB, S-MP, SH, WH, SA, MS, JCM and AMM provided specific content and critically revised the manuscript. All authors approved the final version of the manuscript prior to submission.

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COMPETING INTERESTS

The authors declare no competing interests.

DEDICATION

We dedicate this paper to Dr Narelle Berry, our colleague and friend, who died on the 24th July 2019, aged 40y. Narelle was a Lecturer in Vascular Physiology, in Norwich Medical School, UEA. She was instrumental in preparing the original grant bid to ARUK, and was particularly focussed on delivered the MRI, BP and other vascular measures in MedEx. Being highly experienced in nutrition interventions, Narelle also made a large contribution to the design of the MedDiet intervention.

TABLES

Table 1: Inclusion and exclusion criteria for the MedEx-UK trial

Inclusion Criteria
• Male and female aged 55-74 years • QRISK2 score ≥ 10% • Stable use of any prescribed medication for at least four weeks • Understands and is willing and able to comply with all study procedures • Has access to, and able to use, the internet and a computer/tablet • Normal, or corrected to normal, vision and hearing • Fluent in written and spoken English
Exclusion Criteria
Health
• Diagnosis of Alzheimer's disease, other forms of dementia, Mild Cognitive Impairment, or other significant neurological disorder • Cognition not within the normal range, based on a score of less than 23 on the Montreal Cognitive Assessment (MoCA); or indication of cognitive decline, based on a score of 2 or more on Ascertain Dementia (AD-8) • Evidence of impairment of Instrumental Activities of Daily Living (IADLS) • Moderate to severe depression, assessed by the Patient Health Questionnaire (PHQ-9) • Moderate to severe anxiety, assessed by the Generalised Anxiety Disorder A (GAD-7) questionnaire • Current psychotic illness (delusional disorder/schizophrenia) • History of serious mental illness know to affect cognition (schizophrenia, schizoaffective disorder, bipolar disorder) • Subjects with other clinically diagnosed psychiatric disorders likely to affect the cognitive measures (as judged by a clinical advisor) • HIV positive • Past history or previous MRI evidence of brain damage, significant head trauma (including loss of consciousness as a result), brain surgery, stroke, or serious neurological disorders • History of alcohol or drug dependency in the last two years • Subjects with existing diagnosed gastrointestinal disorders likely to impact study results (as judged by a clinical advisor) • History of any major cardiovascular event, such as a myocardial infarction, stroke or TIA • Severe chronic obstructive pulmonary disease • Cancer, or cancer treatment within the last 12 months • Diagnosis of type 1 or type 2 diabetes diagnosed less than three months ago • Clinical diagnosis of liver or kidney disease (level 3 and above) • Diagnosed Epilepsy • Subjects with any other existing medical conditions likely to influence the study measures (as judged by a clinical advisor) • BMI of more than 40kg/m^2

Lifestyle

- Habitual Mediterranean Diet Score (MDS) of more than 8 (on the 14-point MEDAS questionnaire)
- Habitual physical activity of more than 90 minutes moderate activity per week, assessed using the International Physical Activity Questionnaire short form
- Currently engaged in a weight loss, other dietary, or physical activity intervention

Other

- Currently, a participant or have participated in any other study involving an investigational product in the last four weeks
- Metal implants, e.g. pacemaker that precludes MRI

Table 2: A summary of measures obtained during the onsite screening visit

Variable	Methods
Height (cm) and weight (kg)	Stadiometry and calibrated, electronic scales
Resting blood pressure (mmHg)	Calibrated, automated sphygmomanometers
Blood cholesterol	4 ml blood sample
Cognitive function	Montreal Cognitive Assessment (MoCA)
Subjective memory complaints	Cognitive Change Index (CCI)
Depression	Participant Health Questionnaire (PHQ-9)
Anxiety	General Anxiety Disorder questionnaire (GAD-7)
Memory decline	Ascertain Dementia 8-item informant questionnaire (AD-8) and Instrumental Activities of Daily Living questionnaire (IADL).

Table 3: Cognitive tests used in the MedEx-UK trial

Task	Time	Extended NTB sub-domain
	Part 1 Total 45-50 (including instruction time)	
Verbal Paired Associates	9-12	Memory
Visual Paired Associates	6	Memory
COWAT	3	Executive function
CFT	1	Executive function
Digit Symbol Substitution	2	Processing speed
TMT A & B	5	Executive function
Verbal Paired Associates, delayed recall*	5-8	Memory
Visual Paired Associates, delayed recall	6	Memory
	BREAK	
	Part 2 Total 45-50 (including instruction time)	
RAVLT	10-15	Memory
Hayling Sentence Completion	5-10	Executive function, Response inhibition
Digit Span	3-5	Executive function
Supermarket Trolley Task	10	Spatial navigation
RAVLT - delayed recall	3	Memory
Sea Hero Quest	10-15	Spatial navigation

FIGURE LEGENDS

Figure 1: Flow of participants through the MedEx-UK trial.