Title: APPLE-Tree (Active Prevention in People at risk of dementia: Lifestyle, bEhaviour change and Technology to REducE cognitive and functional decline) programme: protocol

Running title: APPLE-Tree protocol

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Abstract

Background: Observational studies indicate that approximately a third of dementia cases are attributable to modifiable cardiometabolic, physical and mental health, social and lifestyle risk factors. There is evidence that intensive behaviour change interventions targeting these factors can reduce cognitive decline.

Methods and analysis: We will design and test a low intensity, secondary dementia-prevention programme ('APPLE-Tree') to slow cognitive decline in people with Subjective Cognitive Decline with or without objective cognitive impairment. We will embed our work within social science research, to understand how dementia prevention is currently delivered and structured. We will carry out systematic reviews and around 50 qualitative interviews with stakeholders, using findings to co-produce the APPLE-Tree intervention. We plan a 10-session group intervention, involving personalised goal-setting, with individual sessions for those unable or unwilling to attend groups, delivered by psychology assistants who will be trained and supervised by clinical psychologists. The co-production group (including PPI (Public and Patient Involvement), academic and clinical/third sector professional representatives) will use the Behaviour Change Wheel Theoretical Framework to develop it.

We will recruit and randomly allocate 704 participants, 1:1 to the intervention: informational control group. This sample size is sufficient to detect a between-group difference at 2 years of 0.15 on the primary outcome (cognition: modified Neuropsychological Test Battery; 90% power, 5% significance, effect size 0.25, standard deviation 0.6).

Dissemination We will work with Public Health England and third sector partners to produce an effective national implementation approach, so that if our intervention works, it is used in practice.

Key words: dementia prevention, Mild Cognitive Impairment, Subjective Cognitive Decline, RCT

Introduction

The hypothesis that dementia incidence can be reduced by targeting modifiable dementia risk factors is increasingly accepted. There is now robust evidence from observational studies that potentially modifiable risk factors predict dementia. According to the recent Lancet Commission on Dementia Prevention, Intervention and Care, around 35% of dementia is attributable to nine risk factors (education, midlife hypertension, midlife obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation) [(1)]. An earlier study similarly concluded that around a third of Alzheimer's disease cases were attributable to modifiable risk factors, and estimated that relative reductions of 10% per decade in the prevalence of each of seven key risk factors could reduce Alzheimer's disease prevalence in 2050 by 8.3% [(2)]. It is estimated that delaying Alzheimer's disease onset by one year would reduce the number of cases in people over 60 years old in 2050 by 11% worldwide [(3)].

Attributable does not mean preventable; not every case of diabetes or depression can be avoided and not everyone will be amenable to dietary and other lifestyle changes, but recent research findings provide grounds for optimism. These include significant reductions in the UK age-standardised dementia incidence over 20 years, alongside increased availability of education and preventive health care [(4)]. There is less evidence from clinical trials supporting the effectiveness of interventions targeting modifiable risk factors, though two trials provide promising results. In the SPRINT-MIND trial, intensive antihypertensive treatment (aiming for systolic <130mm Hg) decreased incidence of MCI or dementia over three years, relative to standard treatment (systolic <140mmHg) [(5)]. Secondly, in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, a two-year lifestyle and behavioural intervention reduced cognitive decline over two years (effect size 0.25) in people aged 60-77 years with a Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) risk score ≥6 [(6)]. Intervention adherence was modest: two-thirds of participants attended at least half of nutritional and group cognitive training sessions, while adherence to self-directed cognitive training was lower, with only 30% completing more than half of the sessions [(6)]. Intervention effects did not vary with baseline sociodemographic, socioeconomic, cognitive or cardiovascular status [(7)]. The FINGER trial provides proof of concept that reducing risk factors can reduce cognitive decline in populations with elevated vascular risk but it involved over 200 hours of expert time, so could not be implemented across whole populations. Time-intensive interventions are expensive to deliver and unacceptable to many. Those with healthier lifestyles are more likely to use them, with lower uptake in those who may benefit most.

Effectiveness of less time-intensive, multi-domain lifestyle and behaviour interventions intended for large scale implementation has not yet been definitively demonstrated. This may be because these trials have recruited healthy trial populations with high cognitive reserve who are at low risk of cognitive decline and have evaluated interventions that were unacceptable or ineffective at achieving targeted behaviour changes. In the Multi-domain Alzheimer Preventive Trial (MAPT), an intervention comprising nutritional advice, physical exercise and cognitive stimulation delivered in 12 small group sessions over two months, then a once monthly group for the remainder of the trial, did not reduce cognitive decline in frail participants aged 70 years and older over three years. The authors described their population as "particularly well-educated" and only 53% of participants attended at least three-quarters of group sessions. There was some evidence of greater achievement of targeted behavioural change, in terms of increased exercise levels in intervention versus control groups. In a sub-group analysis in participants with baseline CAIDE scores of 6 or greater, cognitive decline was less in the intervention relative to control groups.

In the PreDiva (Prevention of Dementia by Intensive Vascular Care) study, participants aged 70 and over, receiving an intervention comprising of visits to a nurse every four months for six years, with motivational interviewing and lifestyle advice, achieved limited vascular risk reduction relative to the control group. The intervention did not significantly improve cognition relative to the control group. A number of other internet based lifestyle intervention trials in older people have just been completed (in people aged 65+) [8] or are underway (in people aged 55-77) [9].

The APPLE-Tree (Active Prevention in People at risk of dementia: Lifestyle, bEhaviour change and Technology to REducE cognitive and functional decline) programme will design and test a secondary dementia prevention programme to slow cognitive decline, based on the strategy and evidence described in the Dementia roadmap [10] and Lancet Commission on dementia prevention, intervention and care [1]. We want to find out whether a lower intensity, personally tailored intervention that targets older people with subjective memory decline, is flexible in delivery format (with individual sessions for those unable or unwilling to attend groups) and informed by best available behaviour change techniques, can effectively reduce cognitive decline.

We will embed our intervention development and trial within a programme of social science research, to understand how dementia prevention is currently delivered and structured. In stream 1, we will use ethnographic and qualitative research to explore debates around 'limited but limitless ageing': concepts that physical, mental or cognitive limitations reconfigure policies and practices of active ageing. We will explore how social inequities influence individual and societal motivations for active dementia prevention.

In stream 2, we will use existing NHS (National Health Service) primary care data to understand to what extent patients who report memory concerns and are at high risk of dementia currently receive relevant preventative care. In streams 3 and 4, we will develop intervention and implementation strategies that we will test in stream 5. We aim to produce an effective national implementation approach in collaboration with Public Health England so that if the intervention is successful, not only healthy early adopters but vulnerable groups will use and benefit from it. Our programme will be relatively low cost because facilitators without formal clinical training will deliver it. They will be trained and supervised by clinical behavioural specialists. It will be less intensive and more personally tailored than FINGER, and will use and integrate with existing third-sector and NHS services to support implementation and maintenance of behaviour change.

We will target older adults at high dementia risk, with Mild Cognitive Impairment (MCI) or Subjective Cognitive Decline (SCD). MCI (objective cognitive symptoms and absence of dementia) affects 20% of people over 65 [11]. SCD, without objectively impaired cognitive performance, affects half of people over 65 [12, 13]. MCI and SCD are rarely identified: a missed opportunity for secondary prevention. We find that memory concerns strongly motivate many people to make lifestyle changes to delay dementia. We will also address inequities in research participation [14]. Recruitment strategies will be designed to include vulnerable, deprived and minority ethnic older people, who have higher rates of dementia risk factors and dementia but receive less preventive care [15-17]. The most deprived fifth of adults are 50% more likely to develop dementia than the fifth least deprived [18]. We will build on our previous work developing and testing behaviour-change interventions in groups comparable to our target population [19-21] and ongoing work on the SCD-WELL (NCT03005652) and MedEx-UK studies (NCT02525198).

Our small, embedded technology innovation and feasibility project looks to the future. We risk excluding vulnerable groups and widening inequities by digitalising interventions and care without addressing inclusion barriers. In a competitive manner, we will challenge and support the best new

engineers to design and build an app to record and support the behavioural changes our intervention enables. We will explore its feasibility in trial participants, to understand how digital participation barriers are structured. If feasible, we will develop it further in legacy work.

Research questions

Stream 1: How do social inequities impact societal and individual motivations for active dementia prevention? How could statutory and third-sector organisations and civil society support people from marginalised groups to prevent dementia?

Stream 2: Do people with reported memory concerns and high risk of dementia receive relevant preventative care? Are there social inequities in care delivery, having memory concerns recorded or in specialist referral? What are the facilitators and barriers to primary care patients and practitioners engaging in dementia prevention?

Stream 3: How do people with SCD/MCI and stakeholders in older people's wellbeing think our active prevention intervention should be designed and delivered, so it is acceptable and used by vulnerable groups? How can we understand and overcome contextual constraints/barriers to behaviour change and trial recruitment in marginalised groups? Is the APPLE-Tree intervention feasible to deliver in practice? Which app design has most potential to record and support targeted behaviour changes? Is it feasible? How are barriers to digital participation structured?

Stream 4: How can we optimise the intervention for fast and easy implementation and spread while supporting our aspiration to reduce population inequities in dementia prevention?

Stream 5: How can we best measure behaviour change in the APPLE-Tree intervention? Does the APPLE-Tree intervention reduce cognitive decline over two years? What are the mechanisms? Is it cost-effective? What effective strategies do our third sector, NHS and social care partners and participants use to maintain behavioural and lifestyle changes during and beyond the facilitated sessions?

Methods

Recruitment

We will recruit through NHS primary and secondary care services, Join Dementia Research register and third-sector partners. We will over-sample people from minority ethnic and more deprived backgrounds (people living in social or private rented housing). We will select trial sites to include rural-urban, deprivation, and ethnic diversity. Half will be NHS sites (memory services, and Improving Access to Psychological Therapies (IAPT) services). The other half of the trial sites will be hosted in community settings (e.g. third-sector organisations).

Stream one (Conceptual)

This will interact with other streams to situate conceptual thinking in the wider sociological context. We will explore how active ageing policies and practices apply to people with cognitive symptoms, the dialectic between enablement and frailty, and how active ageing approaches are structured by social inequalities. We will use step-in step-out ethnographic methods [22] to understand how older people with memory concerns and professionals communicate, understand and situate dementia prevention advice. We will undertake participant observation in five settings before, during and after our intervention: existing health promotion groups, co-production workshops, the trial intervention and after the six-month facilitated intervention period finishes, to explore how people do or do not engage

with strategies to facilitate and maintain change. We will theoretically sample, based on observations, people with memory concerns and other stakeholders for 8-10 qualitative interviews to triangulate findings. We will analyse field notes and interviews inductively for relevant themes (see later analysis section).

Stream two (Naturalistic study of dementia prevention)

This explores how the NHS currently engages in dementia prevention. We will use The Health Improvement Network (THIN) national database of over 14 million patients' primary care electronic health records to compare 'usual care' that may prevent dementia, of people (without a dementia diagnosis) with and without memory concerns, and at higher and lower risk of dementia, defined using a risk score [23]. We will investigate socioeconomic, neighbourhood and gender differences in the likelihood of having memory concerns recorded and receiving preventative treatment.

We will explore barriers and facilitators to engaging with dementia prevention in qualitative interviews using topic guides with around 15 people with memory concerns and 10 multi-disciplinary clinicians (e.g. GPs, community nurses and allied health professionals). Patients will be purposively recruited for maximum diversity in socio-demographic characteristics and existing engagement in healthy lifestyle (e.g. exercise levels) from NHS primary care.

Stream three (Co-production of the intervention)

Work Package 1 (scoping reviews): We are mapping the current evidence on: (1) psychosocial interventions for dementia prevention, risk reduction or delay; and (2) existing apps (and any associated evidence base) supporting behavioural change (Prospero registration CRD42019133614). Researchers are searching databases, extracting data, and two researchers will independently rate study validity with standard tools. We will narratively synthesise results.

Work package 2: (qualitative interviews): We are interviewing older people with SCD/MCI, their family members and professionals working with older people in third -sector, NHS and statutory organisations. Data collection will continue until data saturation is reached. We estimate we will recruit:

- 15-20 people with memory problems and 10 family members, purposively selected for diversity in gender, age, ethnicity and presence of long-term mental and physical health conditions.
- 10 health and social care professionals who are stakeholders/commissioners in older people's community care.
- 10 third-sector workers, purposively selected for diversity in gender, age, ethnicity and professional experiences.

We have developed a topic guide focussed on identifying important components of an active dementia prevention intervention and potential barriers and facilitators to achieving the targeted behaviour changes. We are audio-recording and transcribing the interviews.

Work Package 3 (Co-production): Work package 1 and 2 and attendee expertise will inform this. The co-production group includes five PPI, and 11 academic, clinical (Public Health England and NHS) and third-sector representatives. It will meet regularly to develop the intervention, convene workshops and seek the input of other expert stakeholders. The group will use the **Behaviour Change Wheel Theoretical Framework** to select intervention strategies, linked to techniques aimed at achieving specified behaviour changes [24].

Behavioural targets: Intervention participants will develop personalised plans to achieve behaviour change targets in sessions 1-7. For each target, there will be bronze, silver and gold achievement

levels, set so that gold targets are reached by the end of the six-month facilitated session period. Sessions 8-10 will embed changes and ensure participants have plans to sustain or work towards gold targets beyond the facilitated sessions.

For the following areas, the level and time-frame of **bronze, silver and gold achievement** on the specified targets will be standardised and follow UK recommendations:
Nutrition targets: to achieve an increase on the 14-point Mediterranean Diet Score (MDS) which measures adherence to a Mediterranean-style diet [25], of one point within two months (bronze); two points (from baseline) by four months (silver); and three points (from baseline) by six months (gold). Other targets will be: eating regular meals and maintaining adequate fluid intake; participants outside a healthy weight range (defined by NHS criteria) will be referred to NHS services if they are willing, and supported to set targets to reduce or gain weight according to NHS protocols.
Moderate physical activity target: to attain 100 minutes of moderate intensity activity per week after two months (bronze), 120 minutes after four months (silver) and 150 minutes after six months (gold) (26). This change rate was achieved by *Brainfood* participants [20], and is associated with lower incidence of the metabolic syndrome [27].
Alcohol and smoking targets: to reduce to current UK targets of 14 alcohol units per week or less consumed over 3+ days and smoking cessation.

For **mental wellbeing (mood and sleep), reducing social isolation and cardiometabolic function targets**, facilitators will work with participants in sessions to develop specified behaviour targets with personalised levels and time frames set for bronze, silver and gold attainment, and plans to help them reach these. Targets may focus on: improving self-monitored mood and/or sleep; enjoyable social engagement; diabetic control;or uptake and adherence to antihypertensive regimes (set in collaboration with primary care).

Intervention content: The intervention will be fully manualised and delivered face-to-face. We will encourage participants to include relatives or friends who support them in sessions and incorporate support for family and friends. Content will address key risk factors for dementia in older age [1]:

Nutrition*:* Participants will share healthy food and drinks at each session. Intervention development will learn from Brainfood and the ongoing MedEx-UK trial, and include swap suggestions and recipes ideas to facilitate target attainment.
Moderate physical activity: We will develop a tailored home activity programme, facilitate participants to join local exercise group activities or set up their own walking groups and maintain this activity over time. We will focus on aerobic exercise, which has the strongest evidence base, with reference to the importance of strength exercise in line with recent Public Health England policy [27].
Alcohol/smoking: We will support participants to use local NHS and third-sector smoking-cessation and alcohol-reduction services.
Mental well-being: We will address sleep problems as they decrease wellbeing. We will use behavioural activation and mindfulness techniques, plus techniques to increase daytime activity, physical activity and light exposure and incorporate environmental changes.
Social isolation: Strategies include reducing sensory deprivation (signposting for hearing aids/vision correction – glasses/cataracts, etc); facilitating social connections (e.g. joining shared-interest groups); and overcoming barriers to participation including continence concerns.
Cardiometabolic function: We will develop strategies to support participants to benefit from existing services, including medication reviews and care planning for people with long-term conditions. For participants with diabetes, we will incorporate strategies to improve self-management. We will signpost participants with hypertension (measured at baseline) to primary care; facilitators will follow this up at group sessions. Participants will be supported to liaise with primary care to optimize treatment and set targets.

Cognitive training: We will agree in co-production whether to include basic memory strategies to reduce disability from symptoms. Participants will have access to an online cognitive-training battery. The extent that use of this battery is included as a behavioural target will depend on results of our evidence syntheses and decisions by the coproduction group.

[Figure 1 here]

Intervention format: The intervention package will include participant and facilitator versions of workbooks for each session, a facilitator training schedule and plans to engage non-attenders with individual catch-up sessions. We will build an internet resource (for access to cognitive training, our new app (see work package 4) and other resources), using agile design, with iterative user testing to develop a beta version for further development. We will plan with our community partners how to support maintenance of behavioural change beyond the first six months of facilitated sessions.

We plan 10 group sessions over six months (every two weeks for sessions 1-7, then monthly), delivered by two facilitators, trained and supervised by a clinical/health psychologist and behaviour specialist, to groups of 10-12 participants; with catch-up sessions for participants unable or unwilling to attend groups. Catch-up sessions (individual or small group) will take place when participants attend the next group or as a home visit. We will train facilitators to deliver the intervention as per the manual (intervention fidelity). They will demonstrate, by role-play, competence in delivering the intervention after a short training programme. Facilitators will attend group supervision every fortnightand there will be additional individual supervision sessions as requested by facilitators or the study team.

Trying it out: The initial drafts for 10 manualised group sessions will be piloted by two facilitators, with a group of 10-12 people with memory concerns, recruited from our partner organisations. We will hold a focus group post-intervention and use it to revise and finalise the manuals.

Work Package 4 (Technology): The PPI group, sociology, clinical and engineering collaborators will plan a brief for engineering students to respond to in a ***Challenge Weekend***. This will be to design a new app to support trial participants by recording and encouraging targeted behavioural changes. The scoping review from stream 3 will be accessibly presented to inform competitors. We will look for the design likely to be most useful for end users, including marginalised groups. We will guide the successful student(s) to design a beta version, which will be made available to all trial participants on the study website. To test acceptability, we will report app usage data, and carry out additional qualitative evaluation within our trial process evaluation.

Stream four (Implementation science)

We will work with our collaborators and partners and learn from our process evaluation and health economic analyses to increase the likelihood that research benefits are translated into practical benefits, guided by the ***Knowledge-to-Action Framework*** [28]. Streams 1-3 will inform our conceptual approach and strategies for reaching marginalised groups. We will hold six-monthly implementation group meetings, which will include Public Health England, academic, NHS, social and third-sector organisation leads, frontline staff and two PPI group representatives. Groups will consider evidence emerging from other streams and carry out targeted additional qualitative interviews (up to 5) to further inform our theoretical model, for example in services not participating in the trial to explore how they would implement the findings.

Stream 5 (Randomised Controlled Trial)

Work package 1:

We will invite co-applicants and our PPI group to a one-day consensus workshop to finalise the APPLE-Tree battery of cognitive, cardiovascular, biological, social and environmental measures to assess the efficacy of the intervention. We will conduct a scoping review, to present at the workshop, regarding readily available blood-based vascular health biomarkers that can predict risk of dementia progression and intervention response (we have not yet specified these to ensure selection is based on latest science in this fast-moving field).

Work package 2 (Randomised Controlled Trial with internal pilot)

Inclusion criteria: These are designed to recruit a population with average cognitive functioning comparable to the FINGER trial population (which had a mean MMSE score of 26.7 points): (a) Age 60+; (b) Cognitive Change Index score>16 indicating subjective cognitive impairment [29]; (c) Quick MCI score within educational and age normal range for MCI or SCD [30]; CAIDE Dementia Risk Score ≥6 points (modifiable risk factors); (d) No dementia diagnosis; (e) Functional Assessment Questionnaire score <9 (no significant impairment); and (f) a relative, friend or professional in at least monthly contact who is willing to act as an informant.

Exclusion criteria: AUDIT (Alcohol Use Disorders Identification Tool) score of 8+ (hazardous or harmful use of alcohol); primary neurodegenerative disease; advanced, severe unstable or terminal medical condition; severe mental illness; lack of capacity to consent to take part at baseline. We will exclude participants who have regular contact with one of the group facilitators. Unwillingness to donate the blood sample will not be a reason for exclusion.

Individual randomisation 1:1 to the APPLE-Tree intervention: informational control group, blocked and stratified by site using a web-based randomisation service.

Internal pilot (first six months): Progression criteria will guide the stop/go decision process for proceeding to a full trial: proportion of participants adhering to the intervention (attending at least half of sessions) [expected value 70% (continue protocol as is); minimum criteria (consider not progressing) 50%; 51-69%: alter study design]; and achieving planned recruitment rate [expected value >80% (continue protocol as is); minimum criteria (consider not progressing) 60%; 61-80%: alter study design].

Study procedures: Clinical Research Network staff and third-sector partners will identify potential participants. Trained, masked researchers will complete study assessments (at baseline, 6 months and 24 months post-randomisation) with eligible participants who have given written, informed consent and collect 30ml of blood (3 tubes: serum, EDTA plasma, heparin plasma) at each time point if participants agree. The isolated plasma, serum, red blood cells and buffy coat (for DNA extraction) will be stored at -80^{o}C for biological and genetic analyses.

We will randomise after baseline assessment. Group facilitators will contact intervention-allocated participants and invite them to the next available group series. Group facilitators will complete individual catch-up sessions with participants who do not attend sessions. We will offer taxis to participants who need them.

Intervention*:* This is described above. Facilitators will, with the supporter/patients' permission, record a random group-intervention session from each cohort. A researcher not involved in the therapy will use this to rate fidelity to the manual using a standard checklist. ***Control condition****:* Usual care plus written information about dementia prevention, including the behavioural-change targets, with signposting information.

Outcomes: Measured at baseline, post intervention (six months) and 24 months. ***Primary:*** Cognition at 24 months, using the modified Neuropsychological Test Battery (mNTB) composite z-score. This comprises a series of computer-based tests assessing memory, executive function and paired associates learning. It is sensitive to change with excellent internal consistency and test-retest reliability [31]. ***Secondary:*** Cost-effectiveness: care costs, measured using the Client Service Receipt Inventory (CSRI) [32] and the EQ-5D to generate QALYs (quality of life adjusted health years)[33]; The Functional Assessment Questionnaire, to measure activities of daily living [34] and Neuropsychiatric Inventory [35] will be completed with an informant.

Measures of effect mechanisms: We will use the APPLE-Tree battery to measure effect mechanisms at baseline, six and 24 months. This will be finalised (and additional biomarkers specified) at the consensus conference but is likely to include: *Hospital Anxiety and Depression Scale* [36]; *Mediterranean Diet Score:* to assess consumption of Mediterranean diet elements; e.g., olive oil, wine, fruits, legumes and whole-grain intake. Low consumption of meat, coffee, commercial sweets and fizzy drinks is reverse scored. Higher scores indicate greater dietary adherence [25, 37]; AUDIT (Alcohol Use Disorders Identification Tool); smoking status; measures of primary support-network size, life events [38, 39] and the revised UCLA loneliness scale [40]. We will measure mobility limitations and physical functioning using the Short Physical Performance Battery (standing balance test, timed sit-to stand test, 4-m comfortable walking time); and blood pressure, weight and Body Mass Index (BMI), and hip and waist circumference. We will record physical activity over one week (after baseline assessment), using wearable sensors; and download cognitive training use from the website. Blood indices: We will measure: red blood cell omega-3 index and vitamin C to evaluate dietary compliance and cardiovascular and cognitive biomarkers of risk including plasma total, LDL and HDL-cholesterol, triglycerides, glucose, HBA1c, BDNF (marker of neuronal function) and insulin. The Global Screening Array (Illumina) will be used to generate genome-wide genotype data for each participant and derive Alzheimer's disease polygenic risk scores. We will record adverse events and measure physical health outcomes, including cardiovascular events, diabetes incidence and mortality, and current medication. We will record data on eligibility, uptake and non-respondents at each stage, adherence, and loss to follow-up and document these in a CONSORT flow-diagram. Outcome assessors will be asked to guess group allocation to test blinding. We will ask participants to name a personal consultee at baseline whom we can contact if they lose capacity during the trial.

Work package 3: process evaluation

We will conduct a mixed-methods process evaluation examining how the intervention is implemented (content/fidelity, frequency/duration and coverage/reach), informed by the ***Consolidated Framework for Implementation Fidelity*** [41], and potential impact mechanisms. We will conduct case studies at two intervention sites after post-intervention outcomes are complete, interviewing 8-10 participants, 3-5 relatives/ friends and 5-6 staff involved in intervention delivery at each site. We will also interview 5-6 participants who leave the study before completion and their family members where possible. The case study design will allow us to investigate how intervention components interact, with each other and the context. We will use a combination of theoretical sampling of sites and participants based on streams 1-3 findings, with purposive sampling to ensure we interview participants from vulnerable groups and those who accessed the trial website (including our new app) on their own devices, devices we provided, or did not access it. We will use qualitative analysis techniques as above. We will triangulate qualitative data with fidelity ratings and six-month quantitative outcomes, and with intervention adherence. We will explore uptake of the intervention in disadvantaged groups.

Analytic approaches

Qualitative (streams 1, 2 and 3): We will use inductive thematic analytic approaches [42]. Researchers will enter all transcribed interviews into NVivo software. Two researchers will familiarise themselves with the data, then independently, systematically code transcripts into meaningful fragments and label these initial codes, discussing and resolving discrepancies. The team will then search for, review and define themes and sub-themes, according to Braun and Clarke's stages of analysis [42]. We will send participants summaries of findings, inviting them to comment on the accuracy and credibility of interpretations.

Quantitative (stream 5): Analysis will be described in a predefined plan. We will use a random-effects multiple regression model to compare mNTB scores between randomised groups at two years, adjusting for baseline scores and site and allowing for facilitator clustering in the intervention arm. We will carry out all analyses on an intention-to-treat basis and check modelling assumptions. We will investigate missing data and use multiple imputation if appropriate. We will use similar models for the secondary clinical outcomes. For both primary and secondary outcomes we will conduct exploratory analyses for potential effect modifiers, including biological indices of dietary compliance and chronic disease and Alzheimer's disease polygenic risk score (and polygenic risk scores for other subtypes of dementia as they become available). *Sample size:* 352 participants per arm is sufficient to detect, with 90% power and 5% significance, a difference of 0.15 on mNTB score (effect size=0.25, standard deviation of 0.6) [6] between intervention and control at 2 years. This calculation allows for baseline adjustment (assumed correlation coefficient 0.6), clustering in intervention arm only (36 patients per facilitator team (32 after drop out), ICC 0.03); and 10% drop out (design effect 1.93). *Health economic analyses:* We will compare costs between groups; cost-effectiveness analyses will combine costs with: (a) cognitive score and secondary outcomes; (b) QALY measures generated from the EQ-5D, allowing comparison with other interventions.

Approach to engagement of research users and patient and public involvement

Age UK and the Alzheimer's Society will co-lead Public and Patient Involvement (PPI). We are inviting people who have personal or family experience of memory problems to join our **community of interest (**through partner organisations, social media and local radio). From 25 attendees at our initial community meeting in April 2019, we purposively selected nine people from diverse ethnic, socioeconomic and professional backgrounds to be our PPI group, of whom five will be invited to be in the co-production group and two in each of the implementation, programme management and trial steering committee groups. The PPI group will meet together every six months for peer support and to share experiences across the groups from a PPI perspective.

Conclusions

Our broad collaboration plans the first large-scale behavioural change intervention in the UK targeting cognition. We intend that our findings will inform UK public health policy and contribute to growing global understanding of how dementia can be prevented. We will disseminate our findings through regular knowledge exchange events and work with Public Health England and third sector partners to produce an effective national implementation approach, so that if our intervention works, it is used.

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