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Remote, lower-intensity, multidomain lifestyle intervention for subjective cognitive decline or mild cognitive impairment (APPLE-Tree): a multicentre, single-masked, randomised controlled trial

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Summary

Background Trials of high-intensity, multidomain interventions show that modifying lifestyle and psychological risk factors can slow cognitive decline. We aimed to evaluate the effectiveness of a lower-intensity, personally-tailored dementia prevention programme in improving cognition in adults with subjective cognitive decline or mild cognitive impairment.

Methods We conducted a single-masked, multisite, randomised controlled clinical trial recruiting older adults with subjective cognitive decline or mild cognitive impairment across 11 sites in England. Participants were randomly assigned (1:1) to the 12-month Active Prevention in People at Risk of Dementia through Lifestyle, Behaviour Change and Technology to build Resilience (APPLE-Tree) intervention or to the control condition (usual care plus brief written information about dementia prevention). Randomisation was blocked and stratified by site, with allocations assigned via a remote web-based system. The intervention promoted healthy lifestyles, social connections, enjoyable activities, and self-management of long-term conditions. It comprised ten 1-h group video-call sessions over 6 months, supplemented with alternating, informal, 40-min video-call sessions (termed tea breaks) and individual goal-setting calls between sessions. From months 6 to 12, participants continued with monthly online tea breaks. The primary outcome was cognition (Neuropsychological Test Battery [NTB] score) at 24 months, analysed using an intention-to-treat approach. This trial was pre-registered with the ISRCTN Registry (ISRCTN17325135); further analyses are ongoing.

Findings Between Oct 5, 2020, and Dec 31, 2022, we screened 1287 individuals for eligibility and randomly assigned 746 to the APPLE-Tree intervention (n=374) or control treatment (n=372). There were 177 (47%) women and 194 (52%) men in the intervention group and 173 (47%) women and 198 (53%) men in the control group. The primary outcome analysis included 635 (85%) of 746 participants. Mean NTB scores increased in both groups over time, with greater improvement in the intervention group than in the control group (mean 24-month NTB 0·33 [SD 0·67] *vs* 0·21 [0·75]; adjusted mean difference 0·06 [95% CI –0·001 to 0·128]; p=0·055). Serious adverse events occurred in 35 (9%) participants in the intervention group and 30 (8%) participants in the control group; none were intervention-related.

Interpretation APPLE-Tree is an accessible intervention associated with small improvements in cognition, although these results were not statistically significant. Low-intensity interventions that can be delivered remotely by non-clinical facilitators have the potential for wide-scale implementation to support adults with memory concerns. However, further work is needed to optimise the intervention for delivery in routine settings.

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Introduction

About 982 000 people in the UK have dementia.[1] In the absence of a cure, therapies that delay cognitive decline and might prevent or delay dementia onset are a health priority. The most effective approach involves group-based, multimodal interventions.[2] The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER),[3] a randomised controlled trial, found that a 2-year, intensive, multicomponent intervention (diet, exercise, cognitive training, and vascular risk monitoring)

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Research in context

Evidence before this study

We previously published a systematic review of evidence exploring whether psychosocial or lifestyle interventions changed cognitive function and dementia risk in people aged 50 years and older and people with subjective cognitive decline or mild cognitive impairment of any age. We searched PubMed, EMBASE, PsycINFO, CINAHL, and Web of Science from database inception to April 4, 2019, limited to studies in English. We applied key terms describing age, study type (randomised controlled trial), type of intervention (early medical intervention, therapeutics, medical informatics), outcome (cognitive dysfunction, dementia, Alzheimer disease, mild cognitive impairment), and modifiable risk factors addressed (diabetes, exercise, BMI, bodyweight, smoking cessation, alcohol consumption, social isolation, depression, anxiety, cardiovascular diseases, vascular diseases, blood pressure, and hypertension). We synthesised evidence, prioritising results from studies rated as at lower risk of bias and assigning Centre for Evidence-Based Medicine grades. We included 64 papers, describing psychosocial (n=12), multidomain (n=10), exercise (n=36), and dietary (n=6) interventions. We found Grade A evidence that, over a period of 4 months or longer, twice-weekly aerobic exercise had a moderate effect on global cognition in people with or without mild cognitive impairment and that interventions that integrate cognitive and motor challenges (eg, dance and dumbbell training) had small-to-moderate effects on memory or global cognition in people with mild cognitive impairment. Grade B evidence showed small positive effects on global cognition from 4 months or longer of creative art or story-telling groups in people with mild cognitive impairment, 6 months of resistance training in people with mild cognitive impairment, and a 2-year multidomain intervention (diet, exercise, cognitive and social training) in people with or without mild cognitive impairment. Effects for some interventions persisted up to 1 year beyond facilitated sessions.

Added value of this study

This multicentre, single-masked, randomised controlled trial conducted in England evaluated the effectiveness of the Active Prevention in People at Risk of Dementia through Lifestyle, Behaviour Change and Technology to build Resilience (APPLE-Tree) intervention in people with cognitive concerns but without dementia over 2 years. Compared with a control condition consisting of participants receiving information about dementia prevention, APPLE-Tree was associated with a small, albeit not statistically significant, improvement in cognition.

Implications of all the available evidence

APPLE-Tree could provide an accessible, scalable model for dementia prevention in older adults with subjective cognitive decline or mild cognitive impairment. Although not attaining statistical significance over 2 years, the effect size was similar to that observed with previous, higher intensity interventions.

improved cognition in older adults with vascular risk factors compared with controls. A South Korean study found that an intensive intervention for people with mild cognitive impairment improved cognitive outcomes relative to a control condition over 6 months' follow-up.[4] Similarly, in a pilot randomised controlled trial that randomly assigned older adults with at least two dementia risk factors to personalised risk-reduction goals (with health coaching and nurse visits) or to a health education control, the intervention was superior to the control in terms of the composite cognitive outcome.[5] The US POINTER trial[6] (based on FINGER) showed that a group-structured, higher-intensity intervention had a greater cognitive benefit than a self-guided, low-intensity intervention over 2 years of intervention and follow-up.

Multidomain dementia prevention trials often fail to preferentially include those at the highest risk of dementia; indeed, many exclude those who might benefit most.[7] Moreover, few dementia prevention trials have focused on recruiting diverse samples.[4,8] To address these issues, we co-designed and piloted an acceptable, inclusive dementia prevention programme, Active Prevention in People at Risk of Dementia through Lifestyle, Behaviour Change and Technology to build Resilience (APPLE-Tree).[9,10] APPLE-Tree is a group-based, lower-intensity intervention that involves setting personalised goals to promote a healthy diet and adequate hydration, increase physical activity, enhance pleasurable activities and social connections, reduce alcohol and smoking, improve self-care of physical conditions, and improve sleep and mental wellbeing. We recruited older adults experiencing mild cognitive impairment (defined by objective cognitive symptoms and absence of dementia) or subjective cognitive decline (characterised by self-reported memory problems without objective impairment)—conditions affecting 18% and 25%, respectively, of people aged 60 years and older.[11,12] An evaluation of the trial process[13] reported high adherence: 305 (82%) of 374 participants in the intervention group attended at least five main sessions (ie, the a priori determined minimum dose) and met over two-thirds of their self-set goals; only 49 (13%) used the cognitive training app.

Here, we report on the primary objective of evaluating the clinical effectiveness of APPLE-Tree in community-dwelling older adults with subjective cognitive decline or mild cognitive impairment in terms of improving cognition over 24 months compared with treatment-as-usual plus written information.

Methods

Study design

We conducted a parallel-group, single-masked, multisite, superiority randomised controlled trial across 11 sites in

England. Sites were primarily NHS primary and secondary care organisations, with additional recruitment from online and media sources and non-governmental organisations serving older people. The study was preregistered on Nov 27, 2019 (ISRCTN17325135), and the trial protocol has been published.[14] The London (Camden and Kings Cross) Research Ethics Committee (19/LO/0260) and UK Health Research Authority approved the study in April 2019.

Participants

We recruited participants through multiple channels: UK National Health Service (NHS) primary care practices and memory clinics within 2 h of London or Essex (with sites purposely selected for ethnic and sociodemographic diversity), the recruitment database Join Dementia Research, non-governmental organisations for older people, X (formerly Twitter), the APPLE-Tree website, and local and national newspapers.

The trial included adults aged 60 years and older with mild cognitive impairment or subjective cognitive decline, identified using the quick mild cognitive impairment screen (Qmci),[15] which has shown validity in distinguishing mild cognitive impairment from normal cognition and dementia. Mild cognitive impairment was defined as a score of 50–62 (out of 100), a cutoff previously shown to yield 90% sensitivity and 87% specificity for cognitive impairment (mild cognitive impairment or dementia).[15] Participants scoring 62 or higher (indicating that mild cognitive impairment was less likely) were classified as having subjective cognitive decline if they responded "yes" to at least two of the following three questions: Has your memory deteriorated in the last 5 years, or has someone close to you noticed a decline? Is your memory persistently poor, or has someone else observed this? Are you concerned about your memory, or are others concerned? We adapted this approach from published subjective cognitive decline measures.[16] For instances when researchers considered that Qmci scores might not be representative of a participant's cognitive ability—eg, because English was their second language or they had few years of formal education—they discussed with CC (an old age psychiatrist), who agreed exceptions where context supported mild cognitive impairment or subjective cognitive decline. Where disagreement arose, the researcher and CC consulted the trial clinical psychologist to reach consensus.

Other inclusion criteria were a Functional Activities Questionnaire (FAQ) score lower than 9 (with 9 indicating no meaningful cognition-related impairment), with a case-by-case review when researchers considered that functional impairment due to a non-cognitive pathology was affecting scores,[17] and having a relative or friend in at least monthly contact with the participant who was able to act as an informant (to complete informant-rated measures such as the FAQ). Individuals were excluded if they were diagnosed with dementia or a terminal condition; scored 8 or higher on the Alcohol Use Disorders Identification Tool-Consumption (AUDIT-C) scale, indicating hazardous or harmful alcohol use;[18] were in regular contact with a group facilitator outside of the study (which could occur if NHS staff or non-governmental organisations were co-delivering the intervention, and risked contamination of the control arm); or where participants judged that they had insufficient understanding of spoken English or a severe hearing impairment that would prevent them from benefitting from the intervention. Sex (with options of male, female, or other) and ethnicity (Office of National Statistics categories) were self-reported.

At baseline, trained researchers obtained written or audio-recorded informed consent from participants and informants, with capacity to consent being an inclusion criterion. Participants were asked to nominate a personal consultee for the research team to approach if they were to lose capacity during the trial. If a participant was deemed to have lost capacity, researchers asked the participant's nominated personal consultee whether they considered that the participant would wish to continue. If the consultee assented to the participant continuing in the study, they were asked to sign a consultee declaration form.

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Donations of blood (using a dried blood spot sample card) and saliva samples were optional. We used standard methods to measure apolipoprotein E from saliva samples; Alzheimer's disease polygenic risk scores and blood-based biomarkers will be reported separately.

Randomisation and masking

Participants were randomly assigned (1:1) to either the APPLE-Tree intervention or control condition with a remote web-based system (Sealed Envelope) provided by PRIMENT Clinical Trials Unit. Randomisation used a permuted block design (block sizes two and four), with stratification by site. Due to the nature of the intervention and clustering within the intervention arm, it was not possible to mask participants, informants, facilitators, or statisticians because group allocation was apparent during data management. Researchers collecting outcome measures were masked to randomisation status and were asked to guess participants' allocation after completing assessments to evaluate masking success.

Procedures

The development and content of the APPLE-Tree intervention was informed by a behaviour change framework and co-designed with public and patient involvement, academic and clinical involvement, and representatives from older people's advocacy groups. The main part of the intervention comprised ten manualised 1-h group video-call sessions held fortnightly over 6 months with groups of four to nine participants, with a 40-min tea break (ie, an unstructured, informal, social session) in the weeks between intervention sessions. Participants also received a telephone call (lasting up to 30 min) after each main session from a facilitator, to discuss and set new goals or revise existing goals; participants were supported to record progress in their goal-setting booklet. Group sessions and goal

calls focused on promoting a healthy diet (based on Mediterranean diet principles and the MedEx-UK trial[19]), hydration, physical activity, increasing pleasurable activities and social connections, reducing alcohol and smoking, improving self-care of long-term physical conditions, and enhancing sleep and mental wellbeing. Designed to be fun, informative, and interactive, sessions included short video demonstrations of recipes included in the intervention manual and videos of suggested physical activities. Participants were invited to bring healthy food and drinks to the tea breaks and share how they had adopted the intervention into their daily lives. We encouraged participants to include relatives or friends to support their plans, and they could choose to invite them to group sessions. Participants who missed a session were invited to catch up with that session content at the next goal call.

Before the first intervention session, participants received a one-off food delivery (eg, olive oil, frozen salmon, and brown pasta) to support adherence to the suggested dietary advice and recipes. Substitutes were provided where necessary to accommodate food allergies, intolerances, personal preferences, or lack of freezer access. Participants were sent the intervention manual, a structured booklet for recording goals and progress, and a pedometer and had access to the study website, which included resources to support wellbeing, including cognitive training. Any participants without a device were able to borrow one to access the intervention via video call and the study website.

The intervention was delivered by two non-clinical facilitators, and groups were organised so that participants were allocated to groups with others from similar localities where possible. At non-NHS sites, the intervention was delivered by a university-based researcher and a facilitator from a non-governmental organisation working with older people. At NHS sites, it was delivered by two assistant psychologists. All facilitators were trained by the research team via role play to deliver the intervention as defined in the facilitator manual (which included health and clinical psychology, psychiatry, primary care, and nutrition expertise). Facilitators attended online group supervision with a clinical psychologist every fortnight. Monthly nutrition supervision was provided by a trained nutritionist. A researcher or third-sector worker provided additional technical support during groups, providing help for participants to access the video call and for facilitators to show videos; this support for facilitators was conducted as a training or shadowing activity to onboard new facilitators.

See Online for appendix

Due to COVID-19 pandemic-related restrictions imposed before fieldwork started, consent was obtained and assessments (all cognitive function tests and other questionnaires) were completed via telephone or video call, depending on the individual's preference; from April, 2021, when restrictions were lifted, we also offered in-person assessments. Saliva and blood samples were sent by post. We collected data at baseline, 6 months (for diet only, to provide additional information regarding a key anticipated intervention mechanism), 12 months, and 24 months after randomisation. Participants were offered a £20 voucher per assessment. 10% of intervention sessions were randomly selected for audio recording (subject to consent of all participants) and used to assess fidelity to the intervention manual.[13] Participants in the control group received a booklet about dementia prevention produced by the Alzheimer's Society. Participants in both groups received routine care; no other structured programmes were provided by the study team. Monitoring and grading of adverse events were completed as per the protocol by the site Principal Investigator, and processes were overseen by the Clinical Trials Unit.

People with lived experience of memory concerns contributed to the APPLE-Tree research programme, including project management and co-design of the intervention.

Outcomes

The primary outcome was the total composite Neuropsychological Test Battery (NTB) score at 24 months, with higher scores reflecting better cognitive performance. The NTB is highly sensitive to change, has excellent internal consistency and test–retest reliability,[20] and is validated for video-call delivery.[21] NTB cognitive domains (ie, memory and executive function) at 12 months and 24 months were secondary outcomes. Other secondary outcomes were diet (Mediterranean Diet Adherence Screener total score), sleep (Pittsburgh Sleep Quality Index [PSQI] total score), mood (Hospital Anxiety and Depression Scale [HADS] total score), anxiety (HADS-Anxiety subscale), depression (HADS-Depression subscale), loneliness (Brief Loneliness Scale), social support (primary support network size), alcohol intake (AUDIT-C total score), activity (assessed via number of daily steps, average resting heart rate, and average high heart rate obtained from wrist-worn wearable sensors [Garmin; Olathe, KS, USA]), and weight and BMI (self-reported). Health-related quality of life information (via the EuroQoL 5-dimension 5-level questionnaire) and self-reported health and social care resource use were collected to inform our health economic analysis and will be reported separately. We also asked informants to complete the General Health Questionnaire (GHQ-12) regarding their own psychological health and the FAQ to report changes in participant functioning. Details of these scales, including how they are scored, and handling of missing items are described in the appendix (pp 7–8). Outcomes (primary and secondary) were analysed in all participants for whom any follow-up data were available.

Statistical analysis

Our a priori sample size calculation indicated that 704 participants (352 per arm) were sufficient to detect a difference of 0·15 in NTB score (effect size 0·25 [SD 0·6]) between intervention and control groups at 24 months with 90% power and 5% significance (based on the FINGER trial[3]). This calculation allowed for baseline adjustment (assumed correlation coefficient 0·6), intervention-group clustering

(intracluster correlation coefficient 0·03, design effect 1·93), and 10% drop out (full details are in the appendix [p 6]).

Analyses were prespecified in the statistical analysis plan (appendix pp 1–12), which was approved, with the trial protocol, by the trial steering committee. We summarised outcomes and effect measures by randomised group, using standard statistics. We described the intervention effect as the between-group difference in mean 24 month NTB score, calculated with a 95% CI and p value. This estimate was obtained from a three-level, linear mixed-effects multiple regression model with random effects to allow for repeated outcome measurements at 12 months and 24 months and therapy group clustering in the intervention arm. Treatment group, baseline NTB score, site, a time indicator, and treatment × time interaction were included in the model as fixed effects. We analysed secondary clinical outcomes using similar approaches. We used all available outcome data at 12 months and 24 months, assuming that missing values were missing at random (MAR).

We refitted the primary analysis model using imputed data. We imputed missing values (assuming MAR) using multiple imputation methods. The imputation model included baseline and repeated measurements of the outcome, site, and variables related to missingness. We performed imputations by study arm and combined estimates using Rubin's rules.[22]

In sensitivity analyses, the primary and secondary outcome models were refitted with adjustment for baseline variables found to be associated with missing scores, which we identified using logistic regression models (with missing yes/no as the outcome). We used pattern mixture models for sensitivity analyses considering missing not at random (MNAR) scenarios. MAR imputed data were displaced by a specified factor d to reflect a scenario; the primary model was refitted and estimates combined using Rubin's rules. We anticipated that missing outcomes mainly related to cognitive function and physical or mental ill health and, hence, planned for d to take values between –1 and 0 times the SD of NTB scores (0·7).

We conducted the following supportive analyses for the primary outcome: (1) we estimated the treatment effect from a simple, single-level regression model adjusting for site and baseline NTB; (2) the main analysis model was refitted with adjustment for educational attainment and baseline FAQ as fixed effects; (3) we used complier average causal effect analysis to estimate the treatment effect relevant to the subgroup of participants who attended at least five sessions in the intervention group (considered compliers); and (4) we repeated the primary analysis excluding outcome data collected outside the prespecified assessment window (±4 weeks around the 12 month and 24 month follow-up dates, relative to baseline).

For the primary outcome, we examined whether the treatment effect differed according to baseline FAQ score (using groups predefined by scores <10 and ≥10, with these cutoffs denoting lesser or greater functional impairment, respectively), genetic classification in five groups

	Control group (n=372)	Intervention group (n=374)
Site		
North London	22 (6%)	22 (6%)
North-East London	8 (2%)	10 (3%)
Brighton	31 (8%)	32 (9%)
Barnet, Enfield, and Haringey	59 (16%)	60 (16%)
Essex	55 (15%)	55 (15%)
Hounslow	42 (11%)	41 (11%)
Kent	59 (16%)	58 (16%)
Suffolk	61 (16%)	62 (17%)
Berkshire	11 (3%)	10 (3%)
Norfolk	18 (5%)	18 (5%)
Hertfordshire	6 (2%)	6 (2%)
Age, years	74·4 (7·2)	74·3 (6·6)
Missing data	2 (1%)	2 (1%)
Sex		
Male	198/371 (53%)	194/372 (52%)
Female	173/371 (47%)	177/372 (48%)
Other	0	1/372 (<1%)
Missing data	1 (<1%)	2 (1%)
Ethnicity		
White UK	299/370 (80%)	300/372 (81%)
White other	32/370 (9%)	25/372 (7%)
Asian	27/370 (7%)	23/372 (6%)
Black	3/370 (1%)	10/372 (3%)
Mixed	4/370 (1%)	12/372 (3%)
Arab	2/370 (1%)	1/372 (<1%)
Other	3/370 (1%)	1/372 (<1%)
Missing data	2 (1%)	2 (1%)
First language		
English	333/370 (90%)	339/371 (91%)
Not English	37/370 (10%)	32/371 (9%)
Missing data	2 (1%)	3 (1%)
Marital status		
Single	22/370 (6%)	24/372 (6%)
Married or in civil partnership	231/370 (62%)	233/372 (63%)
Living with partner	19/370 (5%)	11/372 (3%)
Widowed	51/370 (14%)	57/372 (15%)
Divorced	46/370 (12%)	46/372 (12%)
Unable to specify	1/370 (<1%)	1/372 (<1%)
Missing data	2 (1%)	2 (1%)
Highest level of education		
No education	1/370 (<1%)	1/372 (<1%)
Primary	4/370 (1%)	6/372 (2%)
Secondary*	81/370 (22%)	86/372 (23%)
Further†	99/370 (27%)	100/372 (27%)
Degree	109/370 (29%)	95/372 (26%)
Postgraduate	67/370 (18%)	80/372 (22%)
Other	8/370 (2%)	3/372 (1%)
Unable to specify	1/370 (<1%)	1/372 (<1%)
Missing data	2 (1%)	2 (1%)
Employment		
Full-time employment	19/370 (5%)	13/372 (3%)
Part-time employment	24/370 (6%)	30/372 (8%)

(Table 1 continues on next page)

	Control group (n=372)	Intervention group (n=374)
(Continued from previous page)		
Retired	301/370 (81%)	306/372 (82%)
Unemployed or unable to work	9/370 (2%)	8/372 (2%)
Other	16/370 (4%)	13/372 (3%)
Unable to specify	1/370 (<1%)	2/372 (1%)
Missing data	2 (1%)	2 (1%)
Living situation		
Living alone	96/370 (26%)	102/372 (27%)
Living with partner or relatives	266/370 (72%)	266/372 (72%)
Living with friends or other people	3/370 (1%)	3/372 (1%)
Other	5/370 (1%)	1/372 (<1%)
Missing data	2 (1%)	2 (1%)
Accommodation		
Council rented	19/370 (5%)	14/372 (4%)
Private rented	19/370 (5%)	21/372 (6%)
Own home	327/370 (88%)	326/372 (88%)
Supported living	3/370 (1%)	9/372 (2%)
Other	2/370 (1%)	2/372 (1%)
Missing data	2 (1%)	2 (1%)
APOE genotype		
E2E2	1/331 (<1%)	0
E2E3	35/331 (11%)	35/339 (10%)
E2E4	5/331 (2%)	5/339 (1%)
E3E3	206/331 (62%)	206/339 (61%)
E3E4	78/331 (24%)	86/339 (25%)
E4E4	6/331 (2%)	7/339 (2%)
Missing data	41 (11%)	35 (9%)
Cognitive function		
Mild cognitive impairment	155 (42%)	153/373 (41%)
Subjective cognitive decline	217 (58%)	220/373 (59%)
Missing data	0	1 (<1%)

Data are n (%), n/N (%), or mean (SD). Percentages may sum to more than 100% because of rounding. *For example, General Certificate of Education Ordinary Level or General Certificate of Secondary Education. †For example, A level, Business and Technology Education Council qualification, or National Vocational Qualification.

Table 1: **Baseline characteristics of participants**

according to *APOE* genotype (ie, genotypes E2E3, E2E4, E3E3, E3E4, and E4E4; E2E2 was removed from the analysis as only one participant had this genotype]), and subjective versus objective cognitive impairment. Subgroup effects were formally considered by including the appropriate interaction terms in the main analysis model.

Role of the funding source

The study funders had no role in study design, data collection, analysis, interpretation, or writing of the report.

Results

Between Oct 5, 2020, and Dec 31, 2022, we assessed 1287 older adults for eligibility, excluding 539 (42%). Of the 748 who were eligible and consented to participate, one participant was randomly assigned twice by mistake and was excluded after review by the trial steering committee, resulting in 374 participants randomly assigned to the intervention and 372 to the control group. 34 participants were included despite scoring outside the inclusion criteria ranges for the FAQ and/or Qmci. Mean participant age was 74·4 years (SD 6·9). 350 (47%) of 746 participants were women, 392 (53%) were men, and one participant identified as other (table 1; clinical characteristics [baseline questionnaire scores] are in the appendix [pp 15–16]). Of the 742 participants who provided ethnicity data, 599 (81%) identified as White British, 57 (8%) identified as other White ethnic groups, 50 (7%) identified as Asian, 13 (2%) as Black, 16 (2%) as mixed, three (<1%) as Arab, and four (<1%) as belonging to other ethnic groups. The baseline characteristics of the informants are provided in the appendix (p 17).

There were similar numbers of discontinuations in the intervention group and control group by 12 months (53 in the control group and 57 in the intervention group) and 24 months (99 in the control group and 121 in the intervention group; figure 1). The proportion of data collected outside the prespecified window at each follow-up point is reported in the appendix (p 13). The primary analysis included 635 (85%) of 746 participants who had at least one NTB measurement after random assignment. Reasons for missing NTB data, characteristics of those with missing data, and item missingness are summarised in the appendix (pp 14, 20–23, 41–42). Compared with participants who had complete data at 24 months, participants with missing data generally had lower baseline NTB scores, were educated to a lower level, were less likely to be married or living with a partner, and were older (as were their informants).

The number of intervention sessions participants attended is reported in the appendix (p 18) and elsewhere.[13] There were 55 intervention therapy groups with a mean of 6·3 participants (range four to nine) per group, facilitated by a total of 31 non-clinical facilitators. Most participants in the intervention group attended at least one intervention session (346 [93%]), with 305 (82%) attending five or more sessions (appendix p 18).

Mean NTB scores increased from baseline to 24 months, with a greater increase in the intervention compared with the control group (figure 2, appendix p 19). Mean NTB scores at 24 months were 0·33 (SD 0·67) in the intervention group and 0·21 (0·75) in the control group; the adjusted mean difference from the primary analysis model was 0·06 (95% CI –0·001 to 0·13) but was not significant (p=0·055; table 2). A similar difference between groups was seen at 12 months (0·06 [0·00–0·12]; p=0·049). NTB scores were missing for 226 participants at 24 months and for 137 at 12 months.

Sensitivity analyses consistently showed that mean NTB scores in the intervention group increased more than in the control group at 12 months and 24 months under different assumptions for missing NTB data, with a small effect size. These included analyses adjusting for variables (ie, education status, marital status, participant's age, and informant's age) significantly associated with NTB missingness at

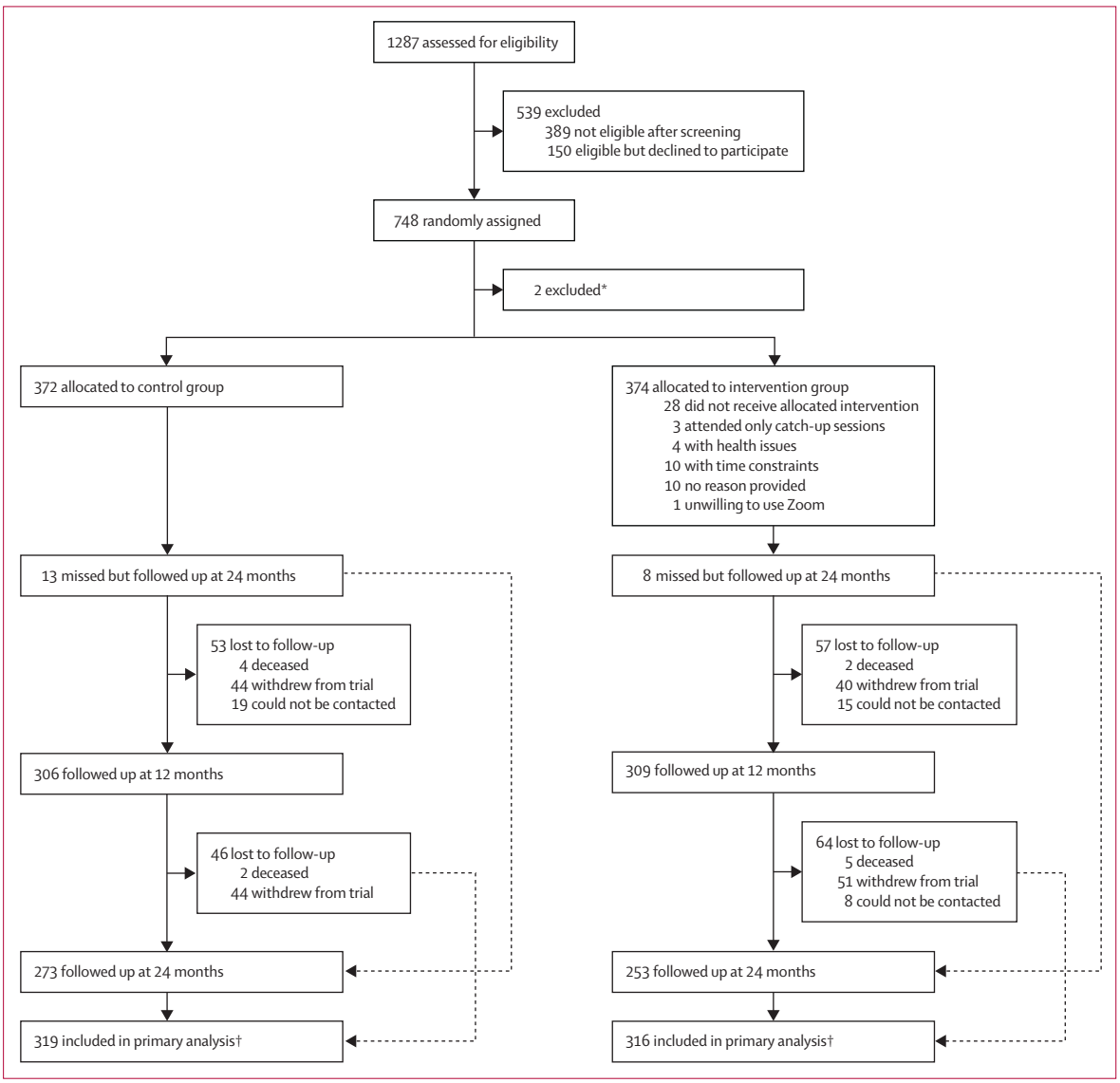


Figure 1: **Trial profile**
*One participant was randomly assigned twice in error. †On the basis of repeated measurement data at 12 months and 24 months.

12 months (adjusted mean difference 0·07 [95% CI 0·01 to 0·133] at 12 months and 0·07 [0·003 to 0·133] at 24 months; appendix p 24) and multiple imputation under the MAR assumption at 12 months (0·06 [–0·01 to 0·12]) and 24 months (0·06 [–0·01 to 0·13]). In our pattern mixture sensitivity analysis under MNAR, differences in means favoured the intervention group for all scenarios, although these results were not significant but were notably smaller for extreme cases (appendix p 25).

Estimates for the effect at 24 months obtained in planned supportive analyses were not substantially different from the primary result, with an adjusted mean difference of 0·08 (95% CI 0·01–0·15; n=520) for single-level regression of NTB at 24 months, 0·06 (0·00 to 0·13) with additional adjustment for educational attainment and baseline FAQ as fixed effects, 0·09 (0·01 to 0·16; n=520) with complier average causal effect analysis, and 0·07 (–0·01 to 0·15]; n=350) with exclusion of data collected outside the pre-specified assessment window.

Secondary outcomes and analyses are provided in the appendix (pp 26–33). Compared with the control group, the intervention had better average NTB memory subdomain scores at 12 months (adjusted mean difference 0·06 [95% CI –0·01 to 0·13]) and 24 months (0·07 [–0·01 to 0·14]), although neither reached statistical significance. Findings on the NTB executive subdomain were similar. No significant between-group differences were observed for function (FAQ), sleep (PSQI), anxiety and depression (HADS), or general health (GHQ-12).

Considering wellbeing and lifestyle factors targeted by the intervention, we observed a beneficial intervention effect at 6 months (adjusted mean difference 1·35 [1·05–1·65]),

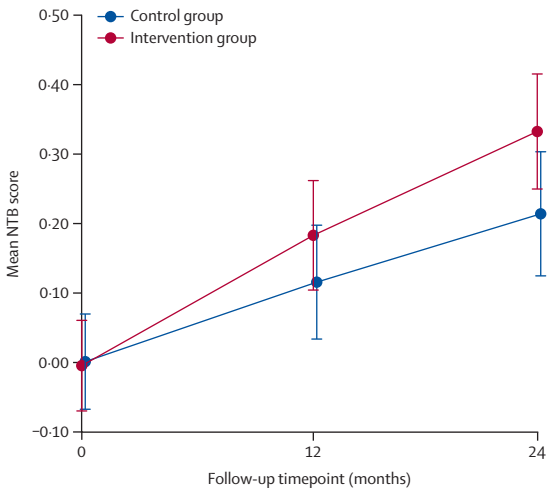


Figure 2: **Profile plot of NTB scores at baseline, 12 months, and 24 months**
Dots are mean scores; lines are 95% CIs. NTB=Neuropsychological Test Battery.

	Control		Intervention		Adjusted mean difference (95% CI)*	p value
	Participants, n	Mean (SD)	Participants, n	Mean (SD)		
Baseline	371	0·001 (0·67)	373	−0·005 (0·64)		
Baseline-imputed†	372	0·001 (0·67)	374	−0·005 (0·64)		
12 months	302	0·12 (0·73)	307	0·18 (0·70)	0·06 (0·0002 to 0·123)	0·049
24 months	271	0·21 (0·75)	249	0·33 (0·67)	0·06 (−0·001 to 0·128)	0·055

*Estimated from a three-level mixed-effects model adjusting for treatment arm, time indicator, interaction between treatment and time indicators, baseline Neuropsychological Test Battery score, and site as fixed effects and group clustering and repeated outcomes as random effects; n=635. Intracluster correlation coefficient for the primary model within the intervention group <0·001. †In two cases of participants with missing Neuropsychological Test Battery score at baseline, missing values were imputed using the overall mean for all subjects.

Table 2: **Results of primary analysis of Neuropsychological Test Battery scores**

	Control group (n=33 events)	Intervention group (n=45 events)
Severity		
Mild	2 (6%)	3 (7%)
Moderate	9 (27%)	21 (47%)
Severe	22 (67%)	21 (47%)
Status		
Resolved	17 (52%)	31 (69%)
Resolved with sequelae	7 (21%)	2 (4%)
Ongoing	3 (9%)	5 (11%)
Fatal	6 (18%)	7 (16%)
Intervention action		
None	25 (76%)	25 (56%)
Temporarily interrupted	0	7 (16%)
Permanently withdrawn	8 (24%)	13 (29%)

Table 3: **Severity, status, and action taken for the 78 reported serious adverse events**

12 months (0·63 [0·33–0·93]), and 24 months (0·69 [0·38–1·01]) on the Mediterranean Diet Adherence Screener score. No evidence of between-group differences were observed for other variables (ie, loneliness [Brief Loneliness Scale], alcohol intake [AUDIT-C], or measures of step count, heart rate, weight, or BMI).

For each secondary outcome, the main analysis model was refitted, with adjustment for baseline characteristics associated with missingness (appendix p 34). Findings were very similar to those obtained in the original analyses (appendix p 35). Some secondary outcomes were reported without formal comparisons, as prespecified in the statistical analysis plan. Social support, smoking status, and life events reported at each timepoint were similar between groups (appendix p 36).

The planned subgroup analysis for participants based on predefined FAQ groups was not conducted as few participants were in the greater impairment category (ten [3%] for the intervention group and five [1%] for the control group at baseline). Investigation of subgroup effects by *APOE* genotype category or by subjective versus objective cognitive impairment showed no evidence of differing treatment effects between these groups (appendix pp 37–38).

There were 142 adverse events (table 3; appendix p 39). 78 serious adverse events were reported by 65 participants (30 [8%] in the control group and 35 [9%] in the intervention group); none were related to the intervention, and all were unexpected side-effects of the intervention. No serious adverse events were deemed to be associated with the intervention. Correct guesses of group allocation by study researchers were only slightly higher than would have been expected by chance at both timepoints (appendix p 40).

Discussion

The APPLE-Tree intervention was associated with modest improved cognitive outcomes over 2 years in older adults with subjective or objective cognitive impairment without dementia. However, these results should be interpreted cautiously as the observed improvement in cognition was small and not statistically significant.

To our knowledge, this intervention is the first dementia prevention programme conducted by non-clinical facilitators and delivered remotely—characteristics that can increase feasibility and decrease costs—to yield findings that might indicate improved cognition in this population. However, improvements in cognition were also observed in the control group. We compared the APPLE-Tree intervention with an informational control; as information can be beneficial, the intervention effect could be underestimated. Although APPLE-Tree was less intensive than interventions in other trials[3,6] and was delivered over 1 year, the between-group difference in NTB total score in this study was similar to those obtained in the FINGER[3] and US POINTER trials,[6] which were delivered over 2 years.

Albeit small and not statistically significant, cognitive effects of this magnitude (calculated using FINGER[3] trial data) have been equated to a relative dementia risk

reduction of around 6% in 20-year dementia risk if extrapolated to a larger population;[23] however, the risk profile of our population might have differed from the FINGER cohort. The FINGER intervention planned 360 h of nutritionist, physiotherapist, and nursing time,[24] whereas APPLE-Tree participants were offered 31 h with non-clinical facilitators, delivered remotely. We designed APPLE-Tree as an inclusive, briefer intervention, tailored to individual goals. This type of approach has the potential to be more cost-effective and accessible compared with more intensive interventions and to better reach those populations who need it most. Dementia prevalence is higher in under-served groups, who are likely to face financial and other barriers to engaging in longer, more intensive interventions.

National health policies are shifting focus towards prevention.[25] A challenge when planning national dementia prevention strategies is how to interpret so-called black box evidence from multimodal interventions, whereby effects on diet, exercise, social and cognitive stimulation, and physical and mental wellbeing can be hard to disentangle. Our process evaluation describes how APPLE-Tree sessions supported behaviour change through increasing participants' knowledge and providing space for them to plan, implement, and evaluate new strategies and make social connections.[13] The goals that were set mostly pertained to diet, followed by exercise. Aligning with existing literature, our findings suggest that dietary change and greater adherence to the principles of a Mediterranean diet might be a key mechanism of action, related to the impact of Mediterranean diet foods and bio-actives on cerebrovascular function, brain insulin sensitivity, and glucose use and reduced amyloid β and tau pathology, inflammation, and oxidative stress.[19] However, evidence that dietary change interventions alone improve cognition is modest and inconclusive.[26] Dietary advice might be best contextualised within a multidomain intervention.[3,27] The small cognitive improvements observed with APPLE-Tree could also be explained by the personalised goal-setting element, which enabled participants to select personally meaningful goals. As with other similar intervention studies, cognition also improved in the control group, most likely due to practice effects.

As national dementia policy promotes timely diagnosis, more people with mild memory concerns are seeking help from health services. Raised awareness of cognitive concerns in people without dementia can feel like an illness in itself.[10] Approaches such as the APPLE-Tree intervention delivery with third sector and community organisations represent a potential treatment pathway for older people with mild memory concerns that could be cost-effective, supportive, acceptable and complement current medicalised pathways via memory clinics. Community-delivered cognitive wellbeing groups could provide an alternative treatment pathway to costly and low benefit health encounters, with referral to memory services potentially built in for those who decline in cognition despite receiving the intervention.

APPLE-Tree was designed to be inclusive. Compared with census data for adults aged 65 years and older, we included more participants from non-White ethnic groups (11·6% versus 6·4%). This diversity strengthens the relevance to under-represented groups, helping to address long-standing disparities in dementia prevention research. However, the study population was highly educated and more likely to own their home relative to the general population, indicating risks of recruitment bias and suggesting that our aim of inclusivity was only partly met. The potential influence of cognitive reserve on outcomes should be considered.[28]

There are important limitations to this study. Despite a modest increase in NTB score, the results were not statistically significant and the utility of the intervention was not unequivocally shown. Although there is no universally agreed minimally clinically important difference for the NTB, the observed effect size (and CI) was smaller than the threshold we defined as clinically meaningful in our power calculation, albeit similar to effect sizes from more intensive trials.[3,6] Despite these findings indicating that the small benefits on cognition associated with more intensive multidomain interventions can be enabled with more scalable models, this approach is only actionable if those benefits are meaningful to society. Simulation models often assume that the risk reductions observed in trial populations can be extrapolated to real-world, at-risk populations and that intervention effects will persist after active delivery ends. These assumptions risk over-estimating cost-effectiveness. We plan further investigations to include a cost-effectiveness evaluation and are following participants for 5 years, enabling us to report longer-term outcomes, including effects on dementia incidence. Future studies are now needed to replicate these findings in larger samples and real-world settings; adaptation studies should consider potential modifications to the intervention before further studies in larger, real-world populations.

Despite strong retention, data were missing for 30% of participants at 24 months, requiring assumptions to be made about missing data in analyses, which might not fully reflect participants' outcomes. However, we explored multiple approaches to handling missing data, and findings remained consistent across methods, supporting the robustness of our results. Finally, as in all psychological treatment trials, we could not mask participants to allocation status.

In the future, we will explore how to improve and translate these findings into practice—at a crucial and hopeful time for dementia prevention. Emerging disease-modifying pharmacological treatments are likely to drive earlier diagnoses and delay disease progression, including conversion from mild cognitive impairment to dementia in a proportion of people with Alzheimer's disease who are eligible for and able to tolerate these new drugs. However,

most people with memory problems will not meet the eligibility criteria for these medications. Strengthening the evidence base for non-pharmacological therapies and expanding their delivery would provide supportive and beneficial treatment for those unable to access medical treatments and complement the care of those who can. A sufficiently powered hybrid effectiveness–implementation trial of the APPLE-Tree intervention to optimise strategies for moving from this trial evidence to practice would be a valuable next step.

Contributors

CC was Chief Investigator. JAB, EA, NB, HB, ABu, PH, RMH, JH, JR, HCK, IL, NLM, SM-T, A-MM, PR, MR, IP, ZW, and KW were coapplicants on the funding application and contributed to trial conceptualisation and methodological development. MPo, SA, JB, and LD were trial managers. MPa, JR, PR, and CC contributed to intervention co-design workshops. MA conducted the statistical analysis, and JAB was the senior statistician; both MA and JAB verified the data. HC, RIEJ, OK, MM, and SZ collected data and contributed to data curation. HD-K and CC drafted the paper. NB led genetic data collection and analysis. All authors contributed to manuscript review and editing. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

JAB reports support from the University College London Hospitals National Institute for Health and Care Research (NIHR) Biomedical Research Centre. HB declares consulting fees from Eisai, Eli Lilly, Medicines Australia, Roche, Skin2Neuron, and Cranbrook Care. JR declares grants from the Alzheimer's Society, Alzheimer's Research UK, and the NIHR clinical research network. RMH declares grants from NIHR; consulting fees from the Ministry of Justice, UKHSA, University of Nottingham and QuidelOrtho; and chairs the Transforming Health and Care Systems EU funding board. SB declares grants from NIHR, the Economic and Social Research Council, Engineering and Physical Science Research Council, and Canadian Institute for Health Research; honoraria from Lundbeck Neuratorium and Lilly; and has held the following positions: Trustee of the Alzheimer's Society, Advisor to Alzheimer Europe, and Advisor to the Alzheimer's Association. All other authors declare no competing interests.

Data sharing

Data collected for the study, including the statistical analysis plan, de-identified participant data, and a data dictionary defining each field in the set, will be made available to others on receipt by Priment Clinical Trials Unit ([CTU] priment@ucl.ac.uk) of a reasonable request at any date after publication of this Article. All requests will be reviewed by Priment CTU in line with Priment CTU guidance on sharing data and anonymising data. This process is to ensure that the request is reasonable and that the dataset is suitably anonymised. The study protocol is available on an open-access basis. Intervention materials are available without cost, subject to a CC BY-NC-ND license held by CC.

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