Feasibility and Preliminary Efficacy of the Lifestyle, Exercise and Diet (LEAD) Study: A Cluster Randomized Controlled Trial of a Combined Exercise and Diet Intervention in Older Adults with Vascular Risk Factors and Early Dementia Risk

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Abstract

Background:

Healthy diet and exercise are associated with reduced risk of dementia in older adults. Evidence for the impact of clinical trials on brain health is less consistent, especially with dietary interventions which often rely on varying intervention approaches. Our objective was to evaluate the feasibility and preliminary efficacy of a 6-month intervention combining exercise with a novel dietary counselling approach among older adults with vascular risk factors (VRFs) and early dementia risk.

Methods: Participants with VRF's and SCD or early MCI were cluster randomized into the intervention (exercise + Baycrest Brain-healthy Eating Approach (EX+DIET)) or control group (exercise + brain health education (EX+ED)). Both groups participated in 1-hour of supervised exercise per week and were prescribed additional exercise at home. EX+DIET involved 1-hour per week of group-based dietary counselling comprising didactic education focused on brain healthy eating recommendations, goal setting and strategy training. Whereas, EX+ED involved 1-hour per week of group-based brain health education. The primary outcome was change in hippocampal volume from baseline to 6 months. Secondary outcomes included fitness, diet, cognition, and blood biomarkers. Recruitment challenges and early discontinuation of the trial due to COVID-19 necessitated a revised focus on feasibility and preliminary efficacy.

Results: Of 190 older adults contacted, 14 (7%) were eligible and randomized, constituting 21% of our recruitment target. All participants completed the intervention and attended 90% of exercise and diet/education sessions on average. All 6-month follow-up assessments pre-COVID-19 were completed but disruptions to testing during the pandemic resulted in incomplete data collection. No serious adverse events occurred and all participants expressed positive feedback about the intervention. Mean improvements in peak oxygen consumption were observed in both EX+DIET (d = .98) and EX+ED (d =1.15) groups. Substantial improvements in diet and HbA1c were observed in the EX+DIET group compared to EX+ED (d = 1.75 and 1.07, respectively).

Conclusions: High adherence and retention rates were observed among LEAD participants and preliminary findings illustrate improvements in cardiorespiratory fitness and diet quality. These results indicate that a larger trial is feasible if difficulties surrounding recruitment can be mitigated.

Trial Registration: ClinicalTrials.gov identifier: NCT03056508

Key Messages Regarding Feasibility

What uncertainties existed regarding feasibility?

- Limited evidence on recruitment, retention, and adherence rates of older adults with VRF's and early dementia risk in combined exercise and diet intervention studies.

- The ability of an intensive dietary intervention (EX+DIET) involving goal setting and strategy changing to promote adherence to a brain-healthy diet.

What are the findings on feasibility of this study?

- A small portion of people contacted met inclusion criteria and the time commitment related to study visits deterred many people from participating.
- High retention, adherence, and satisfaction were observed for enrolled participants.
- The EX+DIET intervention resulted in improved adherence to a brain-healthy diet.

What are the implications for the design of the main study?

- Broader inclusion criteria may be warranted to reach recruitment targets.
- Outcome assessments and visit requirements need to be prioritized and reduced to lessen participant burden.
- EX+DIET is a feasible intervention for a larger trial investigating the effects of exercise and diet on cognition.

Background

Alzheimer's disease (AD) and related dementias are among the world's most prevalent and costly medical conditions (Prince et al., 2015). An early at-risk population for dementia are older adults with subjective cognitive decline (SCD) which describes people who are concerned that their memory or thinking has declined despite no objective signs of cognitive impairment (Jessen et al., 2014; Jessen et al., 2014). SCD is present in 25% of adults over 60 (Rohr et al., 2020), with 75% progressing to mild cognitive impairment or dementia over 10 years (Slot et al., 2019; Liew, 2020). The Alzheimer's Disease Neuroimaging Initiative (ADNI) defined a cohort of individuals as early mild cognitive impairment (EMCI) who are less amnestic than those with late MCI and progress more slowly to dementia (Aisen et al., 2010). SCD and EMCI are both early risk factors for developing dementia. In the absence of disease modifying-therapy for dementia, there is research interest in mitigating cognitive decline prior to dementia through lifestyle modification. Vascular risk factors (VRF's) such as hypertension, type 2 diabetes, high cholesterol, and obesity also increase dementia risk and are directly impacted by lifestyle (Livingston et al., 2020). Thus, older adults with SCD or EMCI and VRFs may benefit from lifestyle intervention before irreversible changes in brain health occur.

Exercise and adhering to a healthy diet are lifestyle behaviours that are strongly associated with reduced dementia risk (30-60%) in cross sectional and longitudinal studies (Samadi et al., 2019; Solfrizzi et al., 2011; Otaegui-Arrazola et al., 2014; Aridi et al., 2017; Blondell et al., 2014; Beckett et al., 2015; Hamer & Chida 2009). The intervention literature is less consistent, especially for dietary interventions which rely on varying approaches of dietary counseling (Otaegui-Arrazola et al., 2014). Randomized controlled trials (RCTs) of exercise across a range of modalities, frequencies and intervention durations suggest small to

moderate effects on cognition among older adults (Northey et al., 2018). The actions by which exercise affect the brain are suspected to be both indirect, such as improving health conditions, as well as more direct mechanisms, including increasing brain neurotrophic factors (Lista & Sorrentino, 2010), improving cerebrovascular function (MacIntosh et al., 2014), and enhancing brain plasticity (Ma et al., 2017). Multicomponent exercise programs that combine aerobic and resistance training may impact cognition over and above either alone (Northey et al., 2018).

Several high quality RCTs have demonstrated a small effect of diet on cognition (Valls-Pedret et al., 2015; Smith et al., 2010), while other trials using various intervention modalities resulted in inconsistent adherence and findings (Kwok et al., 2012; Rondanelli et al., 2012; Marseglia et al., 2018; Knight et al., 2016). Many trials relied on education alone and infrequent (bi-weekly to quarterly) counseling, which is likely insufficient to promote eating changes. There is a general consensus that it is the global diet attributes (i.e. high in fruits, vegetables, nuts, whole grains and fish as well as reducing consumption of saturated fats, sodium and highly processed foods) that are important for brain health rather than individual foods or nutrients (Samieri et al., 2013). Proposed mechanisms include reduced inflammation and oxidative stress (Vauzour et al., 2017) as well as neurogenesis and improved neuronal connectivity (Gomez & Tyagi, 2013). High adherence to a healthy diet is necessary for determining its effects on cognition (Bartachowski et al., 2020). Thus, it is important to understand how to optimize intervention delivery to achieve dietary change in at-risk populations.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first large, long term RCT to demonstrate that a multi-domain lifestyle intervention (diet, exercise, and cognitive training) can reduce the risk of cognitive decline in older adults at-risk for dementia (Nagndu et al., 2015). It is uncertain how each domain contributed to cognition as adherence or potential mechanisms were not investigated in detail. Given the complex, heterogenous nature of AD and dementia, interventions targeting several risk factors simultaneously may be required for optimal effects. We were particularly interested in whether a healthy diet intervention, when combined with exercise, would lead to better outcomes than an exercise intervention alone.

The purpose of this study was to investigate the effects of the Lifestyle, Exercise and Diet (LEAD) trial, a 6-month combined exercise and diet intervention on brain structure and function in older adults with VRFs and early dementia risk. Slow recruitment and early discontinuation of the trial to prevent virus transmission during the COVID-19 pandemic resulted in a revised focus toward the feasibility and preliminary efficacy of the LEAD trial. Feasibility measures included recruitment, retention, adherence, and safety. Effect sizes (Cohen's d) were used to characterize changes in outcome measures from baseline to 6-month follow-up within each group and differences in changes between groups.

Methods

Study Design

The LEAD trial took place in Toronto, Canada, from July 2018 to July 2020. Four groups of participants were cluster randomized into the intervention or control group: 1) a combined aerobic and resistance exercise intervention (EX) with additional group-based dietary intervention called the Baycrest Brain-healthy Eating Approach (BBEA) (EX+DIET), or 2) a combined aerobic and resistance exercise intervention (EX) with additional group-based brain health education (BHED) on brain aging and tips to support brain health (EX+ED). The BBEA encompasses didactic nutrition education regarding a specific brain-healthy dietary pattern combined with goal setting and strategy training to promote sustainable dietary change (Bar et al., 2021). BHED acted as a time-matched placebo and was designed to be of equal frequency, duration, and social interaction/engagement as the BBEA. Outcomes were measured at baseline, 6 months (post-intervention) and 12 months (follow-up).

The LEAD study was a sub-study of the Canadian Consortium on Neurodegeneration in Aging (CCNA; ccna-ccnv.ca) and participants were enrolled in the CCNA Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study (NCT03402919). COMPASS-ND is a longitudinal study involving comprehensive clinical and neuropsychological testing, as well as neuroimaging to determine cohort membership (e.g. healthy control, SCD, mild cognitive impairment, and various forms of dementia) at baseline and at 2-year follow-up (Chertkow et al., 2019). Refer to Additional file 2: Appendix 1 for a more detailed description of the COMPASS-ND study. Participation in LEAD was contingent on first completing the COMPASS-ND baseline assessments which took place over 4 visits at either the Centre for Memory and Aging or Baycrest memory clinic in Toronto. The LEAD study was a collaborative effort between Baycrest Hospital, Sunnybrook Hospital, and University Health Network's Toronto Rehabilitation Institute (TRI), all situated in a large urban centre in Toronto, Ontario, Canada. Baycrest was the lead site, responsible for recruitment. The intervention sessions took place at TRI's comprehensive Cardiovascular Prevention and Rehabilitation Program (CRP).

Participants

Recruitment

Participants were recruited through a research volunteer database at Baycrest, investigator talks, community advertisements, and clinically through the memory clinics and TRI's CRP. Following telephone contact and screening to determine inclusion criteria, participants attended the initial COMPASS-ND assessment to confirm eligibility and provide written consent to participate in COMPASS-ND and LEAD. Once participants completed baseline COMPASS-ND assessments they were enrolled into the LEAD study. Patients referred to TRI's CRP were informed about the LEAD trial and screened by LEAD researchers during their intake assessment. If they were deemed to be eligible and were interested in participating, they were invited to attend the initial COMPASS-ND assessment.

Inclusion criteria

Participants were aged 60–85 years old with SCD or EMCI and ≥2 vascular risk factors. The initial COMPASS-ND visit was used to establish a research diagnosis. SCD was determined by answering "Yes"

to the following Jessen questions: “Do you feel like your memory or thinking is becoming worse?” and “Does this worry you?” (Jessen et al. 2014; Jessen et al. 2014). They also had minimal or no cognitive deficit as indicated by having: (1) a delayed recall score on Story A of the Logical Memory subtest of the Wechsler Memory Scale—Revised (Wechsler, 1997) above the ADNI education-adjusted cutoffs (= 9 for 16+ years of education; = 5 for 8–15 years of education; = 3 for 0–7 years of education); (2) a Montreal Cognitive Assessment (MoCA) total score above 24 (Nasredine et al., 2005) ; (3) a delayed recall score on the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) word list above 5; and (4) a global Clinical Dementia Rating (CDR) score lower than 1.0. Although our original plan was to recruit only people with SCD, we expanded our inclusion criteria to include EMCI. The ADNI criteria (Aisen et al., 2010) was used to determine EMCI, and included individuals who scored between 20 and 24 on the MOCA and 5 on the CERAD. We report on the group assignment of SCD and EMCI in the manuscript. Participants were required to possess ≥2 of the following vascular risk factors: overweight (BMI>25), or physician diagnosed type 2 diabetes mellitus (T2DM) or pre-diabetes (HbA1c ≥ 6.0%) (Diabetes Canada, 2018); high cholesterol; or hypertension. They were also required to be reasonably sedentary at baseline (less than 75min per week of moderate or vigorous intensity physical activity assessed using the Godin Leisure Time Exercise Questionnaire (Godin & Shephard, 1985), be consuming a reasonably poor quality diet (Additional File 2: Appendix 2: Diet screening questionnaire), and be available for the whole intervention. Participants also had to have a study partner who knew them well enough to complete informant questionnaires (COMPASS-ND requirement). Exclusion criteria were: significant known chronic brain disease; major surgery within the past 2 months; major depression or clinical anxiety disorders; schizophrenia or other major psychiatric disorders; ongoing alcohol or drug abuse; inability to undergo an MRI scan; or contraindications to an exercise program (ACSM, 2000)

Intervention

Exercise

Exercise took place at TRI’s CRP in Toronto, Ontario. This clinical program services over 1800 adults/year and has demonstrated success in multiple vascular cohorts, notably coronary artery disease (Marzolini et al., 2008; Marzolini et al., 2012). The program is led by an interprofessional team of physicians, physiotherapists, nurses, kinesiologists, psychologists, and dietitians. All LEAD participants engaged in the standard CRP program which included aerobic and resistance training, education/counseling on exercise and cardiac health, and goal setting. Participants were required to complete 5 aerobic and 2-3 resistance training sessions per week. Participants attended 60-minute group supervised exercise sessions once per week, with the balance of the exercise being completed in the home/community. Thirty minutes of exercise education was provided before every supervised exercise session. Embedded into the exercise education sessions were 2.5 hours total of formal nutrition education which addressed fats, fibre, sodium, and food labels. Study participants also had access to clinical program’s psychosocial counseling upon request.

The initial walking prescription was set at a distance of approximately 1.6 km per day and an intensity equivalent to the ventilatory anaerobic threshold and/or 60-80% of $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$). Prescriptions were progressed to a maximum of 6.4 km and then increasing intensity to a maximum of 80% of $\dot{V}O_{2peak}$. The intensity was re-evaluated based on results of a 3-month CPA, which is a standard CRP assessment. Resistance training was started in week 8 of the program, and was performed 2 to 3 times per week (1-2 times at home in an unsupervised setting). Resistance was provided by hand-held dumbbells, the patient's body weight, and elastic bands of different thickness. Exercises included 3 lower body, 5 upper body, and 2 trunk-stabilizing exercises. In the first weekly class, a moderate load was selected for each of the ten exercises (the selected load was chosen to yield a value of <15 out of 20, i.e., <hard/heavy, on the Borg 6-20 rating of perceived exertion scale (RPE) on the last repetition of 10 repetitions). At home, the participants were required to perform 1 set of 10 repetitions for each exercise using the same load, twice over the following week and to gradually increase the number of repetitions from 10 to 15 over following weeks. Once they could perform 2 sets of 15 reps comfortably, they were advised to increase the weight/resistance load, but reduce the repetitions to 10, and then build again to 15.

Participants were required to log each exercise session, noting the precise distance walked/jogged, duration, resting and peak heart rate, Borg RPE, and any symptoms experienced during exercise. Participants were trained to measure resting and exercise heart rates during orientation to the program and accuracy was checked each week. Resistance training logs included the Borg RPE of the last repetition of the last set performed, any symptoms encountered, the amount of weight lifted, and the number of repetitions and sets performed for each workout. This record was submitted and cross validated by an exercise specialist during the participant's weekly visit.

Baycrest Brain-healthy Eating Approach

The BBEA encompassed didactic nutrition education, goal setting and strategy training to promote sustainable dietary change (Table 1). We first defined a dietary pattern which drew on contemporaneous scientific evidence linking diet to improved cognitive functioning in older adults with VRFs. In particular, the recommended dietary pattern encompassed key features of two dietary interventions associated with cognitive benefits as implemented in the PREDIMED (Valls-Pedret et al., 2015) and ENCORE (Smith et al., 2010) trials. Since neither trial published complete nutritional intake data for their cognitive subsamples, targeted and achieved levels of nutritional intake data from the larger trial populations were compared and formed the basis of the recommendations (Epstein et al., 2012; Zazpe et al., 2008). In some cases, evidence from prospective cohort studies, published at the time, was used to further refine the recommendations. The principal foods or food groups that were targeted were total vegetables; raw or leafy green vegetables; cruciferous vegetables; total fruit; berries; unsalted nuts or all natural butters with an emphasis on walnuts; fish or seafood; fatty fish; canned beans or cooked dried beans; meat and poultry; red or processed meat; butter, cream, or high fat dairy spreads; white bread; and processed foods. A translational product called the Brain Health Food Guide (BHFG) (Parrott, 2016; Additional File 2: Appendix 3) was created to educate individuals on the diet recommendations.

The BBEA builds upon a previously established program designed to manage age-related cognitive changes in older adults (Dawson et al., 2014). Once per week, participants attended a 1-hour group session with the study dietitian (Additional File 2: Appendix 4) who underwent formal training by individuals with expertise in this approach. The dietitian used guided discovery to help participants develop and adapt their own goals and identify ways to overcome barriers to implementation. Participants took part in an iterative process of working to attain their personalized diet goals using a meta-cognitive strategy (Goal-Plan-Do-Check). Participants self-selected goals on a weekly basis, which were rationalized within the context of the BHFG and individuals were expected to incrementally improve an aspect of their diet on a weekly basis. Guided discovery, goal-setting and the identified meta-cognitive strategy are key elements of the CO-OP Approach from which they were derived (Dawson, et al., 2017). The didactic education curriculum within the BBEA included some set topics around the BHFG, but also many open sessions where participants were given the chance to pick topics that would help them move towards their goals. There were also brainstorming sessions where the group came up with ideas, and the dietitian only acted as a facilitator, not education provider. Results from the baseline Canadian Diet History Questionnaire II (C-DHQ II) (Csizmadi et al., 2007), describing intake patterns according to BHFG food groupings were distributed to participants during the first or second session to help participants identify areas where their diet could be improved. Twice throughout the second half of the program, participants were allowed to schedule individual meetings with the study dietitian. If participants felt they needed to schedule additional individual sessions, they were accommodated on a case by case basis. Participants submitted weekly logs outlining diet goals, plans, successes and obstacles to help directly identify sequential goals. Every month, participants were asked to complete an eating pattern self-assessment to help them assess the degree of dietary change achieved (Additional File 2: Appendix 5).

BHED session

Once per week, participants in the BHED group participated in a 1-hour passive group discussion and education session surrounding lifestyle practices to support brain health which acted as the placebo to the BBEA (Additional File 2: Appendix 4). The BHED program was adapted from the DISCOVERY program used by our partner CCNA sub-study ENGAGE (NCT#03271190) as the placebo program to their intervention (Belleville et al., 2019). These classes were designed to be of equal frequency, duration, and social interaction/engagement compared to the BBEA sessions and were manualized to ensure consistency between trainers. During the classes, participants received information on the brain and cognitive processes, the effect of age on cognition, and tips to promote successful aging. Twice throughout the second half of program, participants were allowed to schedule individual meetings with a study dietitian. Individuals in these groups did not participate in strategy training to assist them in undertaking dietary changes nor receive the supplemental BHFG information.

Outcome measures

Feasibility

Feasibility measures included recruitment, retention, adherence, and safety. We report data on recruitment sources and the number of participants screened and enrolled. Retention rate post-intervention and after 6 and 12-month follow-up assessments was calculated as the percentage of enrolled participants. Since the assessment protocol was different for those who completed the intervention pre-COVID-19 versus during the COVID-19 pandemic (described below), retention rates through follow-up assessments are described separately by time point. Adherence was measured as the percentage of intervention sessions attended. We also report the percentage of exercise logs and diet self-assessments completed and the number of one-on-one sessions with the dietitian that were scheduled. Following the intervention, participants were asked to complete an anonymous feedback questionnaire (Additional File 2: Appendix 6,7,8) about knowledge/skills gained, the length of sessions, what they found most or least useful, and whether they would recommend the study to other individuals concerned about their memory.

Preliminary Efficacy

Original LEAD outcome measures included structural and functional MRI, fasting blood biomarkers, cognitive function, anthropometric measurements, dietary adherence, physical fitness, gait and balance assessment, and a variety of questionnaire-assessed lifestyle and psychosocial factors (Additional File 2: Appendix 9). Assessments were spread over 3 visits of approximately 2-3 hours each. These visits took place at Sunnybrook hospital except for fitness testing and blood draws which were done at TRI and the memory clinics, respectively. COVID-19 impacted the 6 month assessments for 3 participants in the EX+DIET intervention and the 12-month assessment for 3 participants in the BHED group. These individuals were invited to take part in a shortened assessment which included a diet assessment, graded exercise test, bloodwork, MRI, and a remote cognitive assessment. This resulted in incomplete data collection and a revised focus on preliminary efficacy, measuring change from baseline to 6 months using outcomes from the shortened assessment.

Fitness

Participants underwent symptom-limited, graded exercise tests on a cycle ergometer (Ergoline 800 P) or a treadmill (Quinton®) at the discretion of the cardiology technologist and physician depending on balance, mobility, and participant preference. Participants were tested using the same modality at baseline and follow-up. The Bruce protocol was used for patients being tested on the treadmill (Bruce et al., 1973) and for the cycle-ergometer protocol, the workload was increased by 50 kpm per minute. A 12-lead electrocardiogram (Quinton®, Q-Stress system) was monitored continuously and breath-by-breath gas samples were collected and averaged over 20-second periods via calibrated metabolic cart (VMAX Encore and Spectra – CareFusion, Yorba Linda, California, USA). Peak oxygen consumption ($\dot{V}O_{2peak}$) was determined.

Diet

Adherence to the BHFG was measured using the C-DHQ II (Csizmadi et al., 2007). The C-DHQ II is a web-based, 153-item questionnaire that takes approximately 1 hour to complete. Participants completed the

questionnaire during the first and last group session so that the study coordinator and dietitians were available to assist. Items from the C-DHQ II were mapped on to items from the BHFG and target ranges for 14 key foods were used to assess dietary adherence. For “foods to include”, we rated participants’ adherence to each of these items as either 1 = greater than or equal to the target, 0.5 = intake greater than equal to 50% of the target, 0 = below 50% of the target. For “foods to limit” we rated participant’s adherence as either 1 = intake less than or equal to the target, 0.5 = intake exceeding the target by an amount less than or equal to 50% of the target, or 0 = intake exceeding the target by an amount greater than 50% of the target. These ratings were summed to calculate a composite Brain-healthy Eating Index (BEI) representing a participant’s adherence to the BHFG (maximum scores = 14).

MRI

MRI data were collected according to the Canadian Dementia Imaging Protocol (Duchesne et al., 2019). A 60-minute brain MRI protocol consisted of: 1) high spatial resolution anatomical imaging sequences, 2) an attention-related task-based blood oxygenation level dependent functional MRI (fMRI) that involved button responses to visual stimuli during a Flanker test, 3) two functional sequences during a resting state, one of which used BOLD contrast while the other used arterial spin labeling (ASL) for cerebral blood flow, and 4) additional structural sequences to assess small vessel disease and white matter integrity, i.e. fluid attenuated inversion recovery and diffusion tensor imaging, respectively. The sequences are as follows: 3D T1-weighted MRI, PD/T2-weighted MRI, FLAIR, Gradient Echo, Resting State fMRI (BOLD), DTI, PCASL resting, Attention-based task fMRI (BOLD).

Images were acquired on a 3 Tesla Siemens Prisma scanner with a 12-channel head coil. Each participant’s head was restrained using cushions that fit inside the head coil. High-resolution structural images (T1-weighted three-dimensional magnetization-prepared rapid gradient-echo sequence; 3D-MPRAGE) were acquired with the following parameters: TR/TE = 2300/2.98, FOV = 256mm, slice thickness = 1mm, number of slices = 192. Whole hippocampal segmentation was performed using an established deep learning HippMapp3r algorithm (hippmapp3r.readthedocs.io) that was based on a convolutional neural network (Goubran et al., 2019). It uses a T1-weighted image as the only input and the outputs are segmentation masks for the left and right hippocampi.

Cognition

Our cognitive testing session lasted 2-3 hours and was based on a harmonized CCNA neuropsychological battery and other cognitive tests to harmonize with a concurrent CCNA sub-study (ENGAGE: NCT#03271190). Of the latter tests, the following were administered at baseline, 6, and 12 months: Direct Assessment of Functional Status – Revised (DAFS-R) (McDougall et al., 2009), Number-letter computer task, Memory toolbox task (Troyer, 2001), Geriatric Anxiety Inventory (GAI) (Pachana et al., 2007), Apathy Inventory (participant version) (Robert et al., 2002). The following were administered only at baseline: Beck Anxiety Inventory (BAI) (Beck et al., 1979), Beck Depression Inventory (BDI)-II (Beck et al., 1979).

Follow-up testing also included a selection of tests that were administered to participants during the CCNA - COMPASS-ND baseline assessment and these data were used to determine pre-post cognitive changes. These tests include the Jessen questions, Montreal Cognitive Assessment (MOCA), Rey Auditory Verbal Learning Test (RAVLT) – immediate and delayed recall (Schmidt, 1996), Trail Making Test (TMT) (Reitan & Wolfson, 1992), Digit Symbol Substitution test (DSST) (Weschler, 1997)), Face-Name Association test - immediate and delayed recall (adapted from a task being used in the CIMA-Q study, www.cima-q.ca/en/home), DKEFS Color Word Interference (Lippa et al., 2010), Geriatric Depression Scale (GDS) (Yesavage et al., 1983), Activities Specific Balance Confidence Scale (ABC) (Powell et al., 1995), Pittsburg Sleep Quality Index (PSQ) (Carpenter, 1998), MAYO clinic fluctuations scale, and Quality of Life – AD scale.

During the pandemic we administered remote cognitive assessments to 3 participants via the Zoom video conferencing application. Tests were administered by a trained assessor and participants were asked to set up their computer/camera in a quiet room without any distractions. A package with all testing forms and a return envelope was mailed to participants who were instructed not to open the package until the beginning of the scheduled session. At the beginning of the assessment, the assessor helped to work out any technical issues and made sure they had the proper camera angles in order to see the participant and the test forms depending on the test. All the follow up tests listed above were administered except for DAFS, Number-letter computer task, and Face-Name Association Task. At the end of the assessment, the participant was instructed to seal the testing forms in the return envelope while in camera view and mail it back. One participant was unable to set up video conferencing so they were sent a package of questionnaires to be filled out on their own and the RAVLT was administered over the telephone. The RAVLT was the only cognitive test for which we had complete data at baseline and 6-months.

Blood samples

Fasting blood samples were collected and analyzed for inflammatory cytokines, oxidative burden and BDNF and APOE status using CCNA platforms. The blood draw was done at the same memory clinic at baseline and follow-up and was drawn according to CCNA protocols. A tube for Vitamin K analysis was collected at all time points. Vitamin K was assessed by high-performance liquid chromatography (HPLC) (Presse et al., 2013). HbA1c and Vitamin K were processed, stored, and analyzed locally. Broader measures of biological markers (e.g., LDL, HDL, triglycerides, etc.) were drawn and stored by the CCNA but were not yet analyzed by the time this manuscript was prepared.

Sample size

Sample size was originally estimated to observe an overall effect of participation in an exercise intervention on brain structural, functional, and cognitive outcome measures. The *a priori* plan was to first compare the effect size associated with pre-post changes in individuals in this study, relative to comparable patient populations participating in either the exercise intervention or a stretching placebo control at the TRI and undergoing the same outcome measures. Based on an expected grey matter

volume effect size of 0.27 (partial eta-squared = 0.07), 3 time points, 2 groups, power = 0.9, alpha = 0.05 and correlation between repeated measures = 0.5, we required a minimum sample size of 60. The total sample size of 66 was used to accommodate a retention rate of approximately 90% and allow for the following covariates: inflammatory cytokines, oxidative burden, BDNF/APOE status and sex. Our effect size was derived from neuroimaging work that reported a grey matter volume increase in a time by group analysis among older sedentary adults (Erickson et al., 2011) and is comparable to other older adult exercise studies with functional, (Rosano et al., 2010) hemodynamic (Ivey et al., 2011) and cognitive (Baker et al., 2010) outcome measures.

Randomization and blinding procedure

We used cluster randomization whereby 4 groups of participants were randomly allocated into one of the two study arms. We chose to randomize in clusters in order to enrol groups of 6 participants at the same time and complete all their baseline measurements within a 2 to 4-week window before starting the intervention. We did not anticipate it would be feasible to simultaneously enrol and assess 12 participants (required for individual randomization) in COMPASS-ND and LEAD within this timeframe. Randomization was done using the Random.org online software. Assessors were blinded to group assignment and participants were asked not to mention their group assignment to assessors. To keep participants blinded from the hypotheses and group effect expectations, the content of the intervention and the wording of recruitment documents and consent forms did not convey the differences between EX+DIET and EX+ED conditions. Participants were specifically told that the groups would differ in the type of nutrition and brain health education that was provided.

Analysis

We performed statistical analyses using R (v.3.3.1) (R Core team, 2019). Demographic data are presented as means and standard deviations or frequencies/percentages where appropriate. Frequencies/percentages were used to summarize recruitment, retention, and adherence. Responses to quantitative questions from the surveys were summed and reported. For open ended questions, responses from 2 or more participants with similar themes were grouped together and reported.

Descriptive statistics and effect sizes (Cohen's d) were used to characterize changes from baseline to 6 months within each group and differences in changes between groups for outcomes included in our shortened follow-up assessment. These included diet (BEI scores), cardiorespiratory fitness ($\dot{V}O_{2peak}$), glycated hemoglobin (HbA1c), vitamin K, hippocampal volume, and the Rey Auditory Verbal Learning Test (RAVLT) - delayed recall.

Results

Participants

A total of 14 participants were randomized and equally assigned to EX+DIET (n = 7) and EX+ED (n = 7). Figure 1 outlines the flow of study participants. Participant baseline characteristics are displayed in Table 2. The mean age of our sample was 72 ± 5 years and included 10 (71%) females. Average years of formal education was higher in the EX+DIET group (18.0 versus 13.4 years). The difference was driven by one participant with 23 years of education in the EX+DIET group and one participant with 8 years of education in the EX+ED group. All other measures were comparable between study groups.

Feasibility

Recruitment

Recruitment started in July 2018 and ended when the trial was discontinued in March 2020. Of the 190 people screened, 14 (7%) were enrolled in the trial constituting 21% of our target enrolment. The main reasons for not participating were: 1) too much time commitment (18%), 2) not meeting criteria for vascular risk factors (17%), or 3) not meeting the criteria for being physically inactive or having a poor diet (11%). Of the 14 enrolled participants, 5 (36%) responded to newspaper advertisements, 4 (29%) responded to community advertisements/flyers, and 3 (21%) were recruited following public talks given by the study investigators. No participants were recruited through the Baycrest participant database, study memory clinics, or TRI's CRP. We had intended to run groups of 6 but due to recruitment difficulties, we ended up with two groups of 4 and two groups of 3 in both EX+DIET and EX+ED.

Retention

All 14 participants completed the intervention. All 6-month assessment visits before the COVID-19 outbreak were completed (11/11). Of the 3 participants scheduled for their 6-month follow-up assessment during COVID-19, one consented to take part in a graded exercise test, MRI, and blood draw. All 3 participated in the diet assessment (C-DHQ II) and the remote cognitive assessment. Two participants completed the remote cognitive assessment via video conferencing and one participant without internet access completed a shortened battery over the phone.

Out of 4 participants who were scheduled for their 12-month assessment before COVID-19, 3 completed the assessment and one declined to attend due to medical reasons. A total of 7 participants were invited to take part in our shortened 12-month follow-up assessment during COVID-19. Of these 7, 2 completed the assessment and 5 declined to participate. When the trial was discontinued in March 2020, the 12-month assessments scheduled for August 2020 were cancelled for 3 participants.

Intervention Adherence

Mean exercise class and BBEA session attendance was 90% and 92% in the EX+DIET group, respectively. Mean exercise class and BHED session attendance was 86% and 91% in the EX+ED group, respectively. COVID-19 restrictions forced us to supplement the once weekly in-person exercise sessions with at-home exercise during the last 6 weeks of the trial for our final EX+DIET cohort (n = 3). Study staff followed up with participants on the same day every week to collect exercise information and discuss any

questions/concerns with participants. The once-weekly BBEA sessions were moved online and over Zoom video conferencing with all participants and the dietitian in attendance. Attending the exercise follow-up calls and the group Zoom video conferencing sessions were considered as attending class for analysis purposes.

Participants in the EX+DIET group completed all of their monthly diet self-assessments (100%). Mean exercise log completion was 61% in the EX+DIET group and 39% in the EX+ED group. When attending weekly in-person exercise sessions, participants verbally confirmed they were completing their exercises at home which was evident by progression of their exercise prescriptions over time. Within the EX+DIET group, 5 participants scheduled 3 individual meetings with the study dietitian and 2 participants scheduled 1 session. In the EX+ED group, 2 participants scheduled 2 sessions with the study dietitian and 5 participants scheduled 1 session.

Safety

No serious adverse events were reported. Several participants with pre-existing osteoarthritis occasionally complained of mild-moderate discomfort associated with exercise. One participant in the EX+DIET group experienced knee pain resulting from back to back assessments of the 6-minute walk test and 5 times sit to stand test. This prevented the individual from participating in intense exercise for two weeks, restricting them to light walking and cycling. The aforementioned fitness assessments were not included in our shortened assessment during COVID-19 and therefore were not explored as preliminary efficacy outcomes.

Participant feedback

All participants answered “yes” when asked if the exercise class provided them with new or useful knowledge and if they were given adequate resources to continue their exercise routine outside of in-person sessions. When asked to describe what they found most useful, most common responses suggested: individualized exercise prescription, learning how to monitor heart rate, and exercise education (part of TRI’s CRP program). The most common aspects of the program they found most challenging were: maintaining a regular schedule/exercising daily, keeping up with resistance training, adjusting program to cater to health issues, and slowing down and not over-exercising. Twelve (86%) participants considered the length of the weekly in-person exercise sessions to be adequate, while one participant felt they were too long and another participant felt they were too short. All EX+DIET participants answered “yes” when asked if the BBEA provided them with new skills/useful knowledge and if they were given adequate information to follow the BHFG. They all answered “yes” when asked if the goal setting approach helped them make dietary change. Emphasis on fruits was a component of the BBEA equally reported to be most useful and most challenging by participants. Four (57%) participants found the length of the weekly BBEA sessions to be adequate, while 2 participants felt they were too short and one participant felt they were too long. All EX+ED participants answered “yes” when asked if the BHED sessions provided them with new skills/useful knowledge. When asked to describe what they found most useful, most common responses suggested: information on sleep. When asked about the length of the

weekly BHED sessions, 6 (86%) participants considered them to be adequate and 1 felt that they were too long. Six (86%) participants felt that there was an adequate number of individual sessions scheduled with the dietitian, and 1 stated that there were too few. All participants (n=14) answered “yes” when asked if they would recommend the study to others who were concerned about their memory.

Preliminary Efficacy

$\dot{V}O_{2peak}$

A total of 5 EX+DIET and 6 EX+ED individuals completed the graded exercise test at baseline and 6 months. One participant in the EX+ED group attended the 6-month assessment but did not complete their exercise test due to difficulties with the mouthpiece. Mean $\dot{V}O_{2peak}$ values at baseline were 22.16 ± 5.35 $mL \cdot kg^{-1} \cdot min^{-1}$ in the EX+DIET group and 20.13 ± 3.64 $mL \cdot kg^{-1} \cdot min^{-1}$ in the EX+ED group. At 6 months, mean $\dot{V}O_{2peak}$ values were 24.2 ± 5.82 $mL \cdot kg^{-1} \cdot min^{-1}$ in the EX+DIET group and 22.53 ± 3.23 $mL \cdot kg^{-1} \cdot min^{-1}$ in the EX+ED group, with relatively large mean differences of 2.04 $mL \cdot kg^{-1} \cdot min^{-1}$ (95%CI: .95 to 3.13, d = .98) and 2.4 $mL \cdot kg^{-1} \cdot min^{-1}$ (95%CI: -.55 to 5.35, d = 1.15), respectively (Figure 2). There was a negligible between-group effect (*d* = .17).

Brain-healthy Eating Index (BEI) score

At baseline, mean BEI scores (out of 14) were 6.43 ± 1.06 in the EX+DIET group and 7.21 ± 1.60 in the EX+ED group. The most common food items outside target ranges at baseline were raw leafy vegetables (86%), total fruit (86%), and fatty fish (86%). At 6 months, mean BEI scores were 9.36 ± 1.28 in the EX+DIET group and 7.07 ± 1.67 in the EX+ED group, mean differences of 2.93 points (95%CI: 1.88 to 3.98, d = 1.67) and -.14 points (95%CI: -2.17 to 1.88, d = -.08), respectively (Figure 3). There was a large between-group effect (*d* = 1.75) favouring the EX+DIET group. The most common food items that were improved within the EX+DIET group were cruciferous vegetables (33%) and fatty fish (25%). All participants whose cruciferous vegetable or total meat and poultry intake was outside-target at baseline improved to within-target ranges at post-intervention.

Hippocampal volume

A total of 5 EX+DIET and 7 EX+ED individuals participated in the MRI assessment at baseline and 6 months. Mean unadjusted hippocampal volume at baseline was 3336.16 ± 557.26 mm^3 in the EX+DIET group and 3155.94 ± 262.03 mm^3 in the EX+ED group. At 6 months, mean hippocampal volumes were 3337.95 ± 506.18 mm^3 in the EX+DIET group and 3165.69 ± 290.83 mm^3 in the EX+ED group, mean differences of 1.79 mm^3 (95%CI: -171.30 to 174.88, d = .02) and 9.74 mm^3 (95%CI: -73.80 to 93.28, d = .13). A negligible between-group effect was observed (*d* = .11)

RAVLT – delayed recall

Our analysis of cognitive function was limited to RAVLT scores as this was the only cognitive test with a full data set. These data included 3 remote assessments (2 video conference, 1 telephone) conducted at 6-months follow-up in the EX+DIET group. Mean RAVLT delayed recall scores at baseline were 9.00 ± 1.91 in the EX+BEAA group and 9.86 ± 2.27 in the EX+ED group. At 6 months, mean scores were 10.57 ± 2.51 in the EX+DIET group and 10.57 ± 2.15 in the EX+ED group, mean differences of 1.57 (95%CI: -1.30 to 4.44, d =.64) and 0.71 (95%CI: -.67 to 2.10, d = .29), respectively. There was a small between group-effect (*d* = .35) favouring the EX+DIET group.

HbA1c and Vitamin K

A total of 5 EX+DIET and 7 EX+ED individuals participated in a fasting blood draw at baseline and 6 months. Mean HbA1c values at baseline were 6.00 ± 0.29% in the EX+DIET group and 5.76 ± 0.57% in the EX+ED group. At 6 months, mean HbA1c levels were 5.52 ± 0.18% in the EX+DIET group and 5.78 ± 0.57% in the EX+ED group, mean differences of -.48% (95%CI: -.71 to -24, d = -1.11) and -.04% (95%CI: -.09 to .01, d = -.09), respectively. There was a large between-group effect (*d = 1.02)* favouring the EX+DIET group. Additionally, 4 of the 5 participants in the EX+DIET group who were in the pre-diabetic range (≥6.0) at baseline moved into the normal range (<6.0).

Mean serum vitamin K levels at baseline were 1.24 ± 0.39 nmol/L in the EX+BEAA group and 2.65 ± 1.61 nmol/L in the EX+ED group. At 6 months, mean vitamin K levels were 1.45 ± 1.24 nmol/L in the EX+DIET group and 1.93 ± 0.98 nmol/L in the EX+ED group, mean differences of .21 nmol/L (95%CI: -.88 to 1.30, d = .13) and -.90 nmol/L (95%CI: -2.05 to 0.26, d = -.57), respectively). There was a medium sized between-group effect (*d* = .70) driven by a decrease in Vitamin K levels in the EX+ED group.

Discussion

This study investigated the feasibility and preliminary efficacy of the LEAD trial. All participants completed the trial and attended 90% of exercise and diet/education visits on average. No serious adverse events occurred and all participants expressed positive feedback about the intervention. Recruitment difficulties owing to the perceived time commitment and narrow inclusion criteria resulted in a smaller than anticipated sample size. Preliminary findings indicate improvements in cardiorespiratory fitness and diet quality. We also observed a clinically significant decrease in mean HbA1c levels among EX+DIET participants. We conclude that the LEAD trial is feasible, however different recruitment strategies or location/method of delivery would be needed to meet realistic sample sizes required to assess efficacy.

Feasibility

Recruitment into the LEAD trial was challenging. The majority of our participants were recruited from newspaper and community advertisements and talks by our investigators. Recruiting through clinical practices (COMPASS-ND memory clinics or TRI's CRP) proved not to be feasible. Compared to individuals with greater cognitive impairment, those with SCD or EMCI are less likely to seek help and be

referred to memory clinics and the few individuals with SCD or EMCI that were referred to us from these sources did not meet our LEAD-specific inclusion criteria (i.e. risk factors, diet, exercise). Several patients were screened at TRI's CRP, however we could not complete their baseline assessments and organize an intervention group within an appropriate time (2-3 weeks) to have them wait before starting their exercise program. By shortening assessment frequency and duration this line of recruitment may be more feasible.

Most people at initial contact expressed that the once weekly in-person visits and the required assessments was too much of a time commitment. Travel to the study sites could also be quite challenging for some. The requirement to be enrolled and complete assessments for both LEAD and COMPASS-ND may have been a deterrent for potential participants. Another barrier was restricting inclusion criteria to four particular VRFs. Expanding eligibility criteria to include other VRFs associated with cognitive decline may help with recruitment. For example, smoking, transient ischemic attack, atrial fibrillation, and sleep apnea. (Anstey et al., 2007; Ganzer et al., 2016; Kalantarian et al., 2013; Gosselin et al., 2018). It may also be appropriate to include individuals with one VRF in addition to low physical activity and poor diet.

We attribute high adherence and retention to the close contact we kept with participants. Our research staff were always available to discuss any questions or concerns and participants were sent out appointment schedules and reminders about upcoming assessments. If a drop in attendance was noticed, the participant was contacted to discuss the reasons and/or barriers and help find solutions. Participants were satisfied with the video conferencing sessions conducted during the last 6 weeks of the trial. Attendance rates were the same as in-person sessions and there were no technical difficulties.

Participants in the EX+DIET group filled out 100% of monthly diet self-assessment and 61% of weekly exercise logs compared to 39% of exercise logs in the EX+ED group. Diet assessments were required less frequently and usually completed with the help of the study dietitian which may explain the discrepancy between exercise and diet reporting. This may also speak to the ability of the BBEA to motivate participants to track their dietary behaviours which may have extended to exercise tracking as well. Participants verbally confirmed that they were completing their exercises at home, but either forgot to fill out the logs or found them too onerous. $\dot{V}O_{2peak}$ changes seen in our sample support these claims. Objective measures such as pedometers or accelerometers are ways to overcome these challenges, however full time monitoring can be expensive, burdensome, and require greater staff involvement for support and analysis. Another strategy would be to have more supervision of the intervention where objective accounts of exercise participation could be recorded.

High assessment completion rates seen in our sample before the pandemic indicate that our extensive testing battery was manageable for participants. One study participant with pre-existing osteoarthritis experienced knee pain related to the fitness assessments. For older adults, especially those with chronic musculoskeletal conditions, it may be necessary to spread strenuous physical assessments further apart from each other.

Preliminary Efficacy

Changes in diet and fitness measures indicate the effectiveness of the LEAD trial in this population. Large improvements in fitness were observed in both study arms, but it is possible that a larger study may uncover group differences. The guided discovery, goal setting and strategy training employed in the BBEA has been used to assist with other lifestyle changes in other populations (Dawson et al., 2017) and it would be worthwhile to discern whether skills developed in the BBEA program transfer into other aspects of lifestyle, such as physical activity. The EX+DIET intervention resulted in substantial dietary changes in accordance with the BHFG recommendations compared to control. We attribute these promising results to our novel form of intervention delivery which combined dietary education with guiding participants to set, monitor and track their diet related goals. The dietary changes observed in LEAD are comparable to high quality interventions of brain healthy global diets such as Mediterranean, MIND and DASH diets. Relative to our 14-point BEI, the EX+DIET group increased their dietary adherence from an average 46% at baseline to 67% (range 50-79%) at 6 months, an absolute mean increase of 21%. In PREDIMED, diet adherence increased by ~25% following a 12-month intervention of a Mediterranean diet supplemented with either mixed nuts (30g/day) or extra virgin olive oil (1L/week) (Zazpe et al., 2008). In the 4-month ENCORE trial, adherence to the DASH diet increased by 30% and 22% in groups receiving DASH diet + weight management and DASH diet alone, respectively (Epstein et al., 2012). In the Nu-AGE trial, the intervention group increased their adherence to a Mediterranean-type diet by an average of 14% from 51.9% at baseline to 65.9% (range 25-96%) at 1-year follow-up (Marseglia et al., 2018).

While high quality diet interventions have observed associations between diet and brain changes, we were not powered to corroborate these findings. Effect size estimates revealed a small to moderate between-group effect in RAVLT- delayed recall performance in the EX+DIET group compared to EX+ED. This is a promising preliminary finding, however a larger study is required to statistically analyze cognitive differences associated with dietary intervention.

A large between-group effect in HbA1c reduction was observed in the EX+DIET compared to control. The average decrease in HbA1c levels among EX+DIET group represents a clinically meaningful reduction associated with a decreased risk of cardiovascular disease (Lenters-Westra et al., 2014). Reducing HbA1c levels has also shown to be associated with a decreased risk of incident all cause dementia and Alzheimer's disease (Ramirez et al., 2015). It would be worthwhile to further investigate whether reductions in HbA1c associated with the EX+DIET intervention are associated with cognitive changes. Green leafy and cruciferous vegetables are an important food source of vitamin K, and its levels in serum can provide information about dietary patterns (Ferland et al., 2020). Reduced vitamin K status has also been associated with poor cognitive function in older adults (Presse et al., 2013; Kiely et al. 2020). We observed a small between-group effect on serum Vitamin K levels, however this appears to have been driven by a regression in Vitamin K levels toward the mean among the EX+ED group. Although vegetable intake was a commonly altered component of diet, increased BEI scores in our sample also resulted from improvements in other aspects of diet such as increasing fatty fish consumption, or decreasing processed foods.

Limitations, Strengths, And Future Considerations

Slow recruitment and early trial discontinuation resulted in a much smaller than anticipated sample size and incomplete data collection from several participants. In addition, the BBEA was designed to accommodate groups of 4-6 participants, but we ended up running groups of 3-4. It is unknown if adherence rates would differ based on group size, however group of 4-6 were considered ideal based on prior work (Dawson et al. 2014) and we feel that these concerns may be minimal. Dietary changes and positive feedback received from participants suggest that the intervention was feasible with smaller groups. There is evidence for gender differences in exercise and dietary preferences and adherence rates (van Uffelin et al., 2017; Marsella & Malomi 2017). The small sample size limited our ability to examine these relationships, however this is an important consideration for a larger trial.

Further impacting the LEAD trial was the arrival of COVID-19 to Canada. We abruptly had to cancel follow-up assessments that were scheduled and put an indefinite pause on recruitment. When our assessment sites approved the restart of research activities, we asked participants to take part in a shortened assessment, but several participants declined to attend. As a result, we were unable to collect follow-up data for a significant portion of our sample. We also conducted an abridged remote cognitive assessment. It is likely that participants preform worse when being assessed remotely compared to being in the direct presence of an assessor. Only our EX+DIET group participated in remote cognitive assessments at 6 months and it is reasonable to suspect that they would have performed better if tested in person. Standardized forms of remote testing are becoming more necessary and may be more readily available for future trials.

Strengths of this study include the adoption of a brain-healthy diet based on empirical evidence and counseling approach that teaches goal setting strategies to achieve sustainable dietary change. We also created a composite BEI to assess dietary adherence utilizing a common diet assessment tool (C-DHQ II). Considering that the online diet counselling sessions appeared to be feasible within our study, one avenue to explore would be delivering EX+DIET intervention remotely. Technology use has rapidly increased among older adults during the COVID-19 pandemic and is expected to dramatically increase in the coming years (Age-Well, 2020; Statistics Canada, 2019). Online intervention delivery and assessment would allow studies to cast a wider net for recruitment and could also avoid potential future disruptions of face to face contact like we have seen with the COVID-19 pandemic.

Conclusions

High adherence and retention rates were observed among LEAD participants. Preliminary findings illustrate improvements in cardiorespiratory fitness and diet quality. We attribute successful dietary adherence to the novel form of intervention delivery which combines diet education with cognitive behavioural strategies. The results of this study indicate that the trial interventions are feasible if difficulties surrounding recruitment can be mitigated.

Declarations

Trial Registration

The LEAD study is registered with the US National Institutes of Health clinical trials registry (ClinicalTrials.gov identifier NCT03056508) and this report complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.

Ethics approval and consent to participate

The study was approved by Clinical Trials Ontario (application# 1336, last approval 21 July 2020. The lead REB site is Baycrest Health Science in Toronto (application #16–34, last approval 21 July 2020) and the COMPASS-ND portion of the study was approved by Clinical Trials Ontario (application #750, last approved June 23, 2020)

Consent for publication

All authors gave their consent for publication

Availability of data and materials

The data was uploaded to the CCNA LORIS database. Access to the data will be subjected to the CCNA data access policy. No datasets are included in this this manuscript.

Competing interests

The authors declare that they have no competing interests

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Author's contributions

Everyone that has significantly contributed to this work has been listed as coauthor. All authors have participated in the conceptualization of the study and design. CEG and NDA were the leaders of the trial. NDK was the project coordinator and oversaw all aspects of the project. MDP prepared and developed the dietary intervention and assisted CEG in creating the BHFG. DD developed and contributed the BBEA approach. FA administered the BBEA intervention, while NK (with the help of several student volunteers) administered the BHED intervention. PO is the medical director and SM supervised the exercise specialists at TRI's cardiac rehabilitation program. Exercise specialists at TRI supervised the group

exercise sessions. NK wrote the first version of the paper. All authors read, revised, and approved the final manuscript.

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References

1. Prince MJ, Wimo A, Guerchet MM, Ali GC, Wu YT, Prina M. World Alzheimer Report 2015 - The global impact of dementia: An analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International. 2015.
2. Jessen F, Wolfsgruber S, Wiese B, Bickel H, Mösch E, Kaduszkiewicz H, et al. AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. Alzheimers Dement. 2014;10(1):76–83.
3. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer’s disease. Alzheimers Dement. 2014;10(6):844–52.
4. Röhr S, Pabst A, Riedel-Heller SG, Jessen F, Turana Y, Handajani YS, et al. Estimating prevalence of subjective cognitive decline in and across international cohort studies of aging: a COSMIC study. Alzheimers Res Ther. 2020;12(1):167.
5. Slot RER, Sikkes SAM, Berkhof J, Brodaty H, Buckley R, Cavedo E, et al. Subjective cognitive decline and rates of incident Alzheimer’s disease and non-Alzheimer’s disease dementia. Alzheimers Dement. 2019;15(3):465–76.
6. Liew TM. Trajectories of subjective cognitive decline, and the risk of mild cognitive impairment and dementia. Alzheimers Res Ther. 2020;12(1):135.
7. Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, Jack CR Jr, Jagust W, Toga AW, Saykin AJ, Morris JC, Green RC, Weiner MW; Alzheimer's Disease Neuroimaging Initiative. Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans. Alzheimers Dement. 2010;6(3):239-46.
8. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–446.
9. Samadi M, Moradi S, Moradinazar M, Mostafai R, Pasdar Y. Dietary pattern in relation to the risk of Alzheimer's disease: a systematic review. Neurol Sci. 2019;40(10):2031-2043.
10. Solfrizzi V, Frisardi V, Seripa D, Logroscino G, Imbimbo BP, D'Onofrio G, et al. Mediterranean Diet in Predementia and Dementia Syndromes. CurrAlzheimer Res. 2011;8:520.

11. Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martínez-Lage P. Diet, cognition, and Alzheimer's disease: food for thought. Eur J Nutr. 2014;53(1):1-23.
12. Aridi YS, Walker JL, Wright ORL. The Association between the Mediterranean Dietary Pattern and Cognitive Health: A Systematic Review. Nutrients. 2017;9(7):674.
13. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC Public Health. 2014;14:510.
14. Beckett MW, Ardern CI, Rotondi MA. A meta-analysis of prospective studies on the role of physical activity and the prevention of Alzheimer's disease in older adults. BMC Geriatr. 2015;15:9.
15. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med. 2009;39(1):3-11.
16. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. Br J Sports Med. 2018;52(3):154-160.
17. Lista I, Sorrentino G. Biological mechanisms of physical activity in preventing cognitive decline. Cell Mol Neurobiol. 2010;30(4):493–503.
18. MacIntosh BJ, Crane DE, Sage MD, Saeed Rajab A, Donahue MJ, McIlroy WE, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and activation responses in healthy young adults. PLoS One. 2014;9(1):e85163.
19. Ma CL, Ma XT, Wang JJ, Liu H, Chen YF, Yang Y. Physical exercise induces hippocampal neurogenesis and prevents cognitive decline. Behav Brain Res. 2017;317:332-339.
20. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA Intern Med. 2015;175(7):1094-1103.
21. Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, et al. (2010) Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension. 2010;55:1331-1338.
22. Kwok TC, Lam LC, Sea MM, Goggins W, Woo A. randomized controlled trial of dietetic interventions to prevent cognitive decline in old age hostel residents. J Eur J Clin Nutr. 2012;66(10):1135-40.
23. Rondanelli M, Opizzi A, Faliva M, Mozzoni M, Antoniello N, Cazzola R, et al. Effects of a diet integration with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan in elderly patients suffering from mild cognitive impairment. Nutr Neurosci. 2012;15(2):46-54.
24. Marseglia A, Xu W, Fratiglioni L, Fabbri C, Berendsen AAM, Bialecka-Debek A, et al. Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults: A Randomized Controlled Trial. Front Physiol. 2018;9:349.
25. Knight A, Bryan J, Wilson C, Hodgson JM, Davis CR, Murphy KJ. The Mediterranean Diet and Cognitive Function among Healthy Older Adults in a 6-Month Randomised Controlled Trial: The MedLey Study. Nutrients. 2016;8(9):579.

26. Samieri C, Sun Q, Townsend MK, Chiuve SE, Okereke OI, Willett WC, et al. The association between dietary patterns at midlife and health in aging: an observational study. Ann Intern Med. 2013;159(9):584-91.
27. Vauzour D, Camprubi-Robles M, Miquel-Kergoat S, Andres-Lacueva C, Bánáti D, Barberger-Gateau P, et al. Nutrition for the ageing brain: Towards evidence for an optimal diet. Ageing Research Reviews. 2017;35:222-240.
28. Gomez P & Tyagi E. Diet and cognition: interplay between cell metabolism and neuronal plasticity. Curr Opin Clin Nutr Metab Care. 2013;16(6):726-733.
29. Bartachowski Z, Conway J, Wallach Y, Chakkamparambil B, Alakkassery S, Grossberg GT. Dietary Interventions to Prevent or Delay Alzheimer's Disease: What the evidence shows. Curr Nutr Rep. 2020;9:210-225.
30. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385(9984):2255-63.
31. Bar Y, Ajwani, F, Atlas B, Ricupero M, Greenwood C, Parrott M, et al. Promoting Adoption of Brain Heathy Eating Patterns: A Pilot Study Using Goal Setting and Strategy Training. 2021. Manuscript in preparation.
32. Chertkow H, Borrie M, Whitehead V, Black SE, Feldman HH, Gauthier S, et al. The Comprehensive Assessment of Neurodegeneration and Dementia: Canadian Cohort Study. Can J Neurol Sci. 2019;46(5):499-511.
33. Wechsler D. Wechsler Memory Scale–Third Edition manual. San Antonio: The Psychological Corporation; 1997.
34. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. JAGS. 2005;53:695-699
35. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.* Can J Diabetes. 2018;42(Suppl 1):S1-S325.
36. Godin G & Shephard RJ. A simple method to assess exercise behaviour in the community. Can J Appl. Sport. Sci. 1985;10:141-146.
37. *American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription, 11th Edition. Philadelphia: Lippincott Williams & Wilkins, 2010.*
38. Marzolini S, Brooks D, Oh PI. Sex differences in completion of a 12-month cardiac rehabilitation programme: an analysis of 5922 women and men. Eur J Cardiovasc Prev Rehabil. 2008;15:698-703.
39. Marzolini S, McIlroy W, Oh P, Brooks D. Can individuals participating in cardiac rehabilitation achieve recommended exercise training levels following stroke? J Cardiopulm Rehabil Prev. 2012;32:127-134.

40. Parrott M. Brain Health Food Guide. 2016. http://ccna-ccnv.ca/wp-content/uploads/2016/12/BHFG_legal_combined.pdf
41. Epstein DE, Sherwood A, Smith PJ, Craighead L, Caccia C, Lin PH, et al. Determinants and consequences of adherence to the dietary approaches to stop hypertension diet in African-American and white adults with high blood pressure: results from the ENCORE trial. J Acad Nutr Diet. 2012;112:1763-1773.
42. Zazpe I, Sanchez-Tainta A, Estruch R, Lamuela-Raventos RM, Schroder H, Salas-Salvado J, et al. A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study. J Am Diet Assoc. 2008;108:1134-1144.
43. Dawson D, Richardson J, Troyer A, Binns M, Clark A, Polatajko H, et al. An occupation-based strategy training approach to managing age-related executive changes: a pilot randomized controlled trial. Clin Rehabil. 2014;28(2):118-127.
44. Dawson D, Bar Y. Using the CO-OP Approach: Older adults with subjective cognitive complaints. In: Dawson D, McEwen S, Polatajko H, editors. Enabling participation across the lifespan: advancements, adaptations and extensions of the CO-OP Approach™. Bethesda, MD: AOTA Press; 2017. p119-134.
45. Csizmadi I, Kahle L, Ullman R, Dawe U, Zimmerman TP, Friedenreich CM, et al. Adaptation and evaluation of the National Cancer Institute's Diet History Questionnaire and nutrient database for Canadian populations. Public Health Nutr. 2007;10:88-96.
46. Belleville S, Moussard A, Ansaldo AI, Belchior P, Bherer L, Bier N, et al. Rationale and Protocol of the ENGAGE study: a double-blind randomized controlled preference trial using a comprehensive cohort design to measure the effect of a cognitive and leisure-based intervention in older adults with a memory complaint. Trials. 2019;20:283
47. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J. 1973;85(4):546–562.
48. Duchesne S, Chouinard I, Potvin O, Fonov VS, Khademi A, Bartha R, et al. The Canadian Dementia Imaging Protocol: Harmonizing National Cohorts. J Magn Reson Imaging. 2019;49(2):456-465.
49. Goubran M, Ntiri E, Akhavein H, Holmes M, Nestor S, Ramirez J, et al. Hippocampal segmentation for atrophied brains using three-dimensional convolutional neural networks. Hum Brain Mapp. 2020.;41(2):291-308.
50. McDougall GJ, Becker H, Vaughan PW, Acee TW, Delville CL. The revised direct assessment of functional status for independent older adults. Gerontologist. 2010;50(3):363–70
51. Troyer AK. Improving memory knowledge, satisfaction, and functioning via an education and intervention program for older adults. Aging Neuropsychol Cognit. 2001;8(4):256–68.
52. Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E. Development and validation of the Geriatric Anxiety Inventory. Int Psychogeriatr. 2007;19(1):103–14.
53. Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer’s disease, Parkinson’s disease and mild cognitive

impairment. Int J Geriatr Psychiatry. 2002;17(12):1099–105.

54. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: the Beck Anxiety Inventory. J Consult Clin Psychol. 1988;56:893–7.
55. Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression. New York: Guilford press; 1979.
56. Schmidt, M. *Rey auditory verbal learning test: A handbook.* Los Angeles, CA: Western Psychological Services; 1996.
57. Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation. 2nd ed. Tuscon, AZ: Neuropsychology Press; 1993.
58. Lippa SM, Davis RN. Inhibition/Switching Is not Necessarily Harder than Inhibition: An Analysis of the D-KEFS Color-Word Interference Test. *Arch Clin Neuropsychol.* 2010;25(2):146–152
59. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1983;17(1):37–49.
60. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) scale. J Gerontol A Biol Sci Med Sci. 1995;50(1):M28-34
61. Carpenter JS, Andryowski MA. Psychometric evaluation of the pittsburgh sleep quality index. J Psychom Res. 1998;45(1):5-13
62. Presse N, Belleville S, Gaudreau P, Greenwood CE, Kergoat M-J, Morais JA, et al. Vitamin K status and cognitive function in healthy older adults. Neurobiol Aging. 2013;34:2777-2783.
63. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011;108:3017-3022
64. Rosano C, Venkatraman VK, Guralnik J, Newman AB, Glynn NW, Launer L, et al. Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. J Gerontol A Biol Sci Med Sci. 2010;65:639-647.
65. Ivey FM, Ryan AS, Hafer-Macko CE, Macko RF. Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. Stroke. 2011;42:1994-2000.
66. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol. 2010;67:71-79
67. R Core Team. R: A Language and Environment for Statistical Computing. Vienna: R Core Team; 2019.
68. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol. 2007;166(4):367-78.
69. Ganzer CA, Barnes A, Uphold C, Jacobs AR. Transient Ischemic Attack and Cognitive Impairment: A Review. J Neurosci Nurs. 2016;48(6):322-327.
70. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med. 2013;158(5 Pt 1):338-46.

71. Gosselin N, Baril AA, Osorio RS, Kaminska M, Carrier J. Obstructive Sleep Apnea and the Risk of Cognitive Decline in Older Adults. Am J Respir Crit Care Med. 2019;199(2):142-148.
72. Lenters-Westra E, Schindhelm RK, Bilo HJ, Groenier KH, Slingerland RJ. Differences in interpretation of haemoglobin A1c values among diabetes care professionals. Neth J Med. 2014;72(9):462-6.
73. Ramirez A, Wolfsgruber S, Lange C, Kaduszkiewicz H, Weyerer S, Werle J, et al. Elevated HbA1c is associated with increased risk of incident dementia in primary care patients. J Alzheimers Dis. 2015;44(4):1203-12.
74. Ferland G. Vitamin K. In: Marriott B, Birt DF, Stalling V, Yates AA, editors, Present Knowledge in Nutrition, 11th edition. Washington, DC: Academic Press; 2020. p. 137-153.
75. Kiely A, Ferland G, Ouliass B, O'Toole PW, Purtill H, O'Connor EM. Vitamin K status and inflammation are associated with cognition in older Irish adults. Nutr Neurosci. 2020;23(8):591-599
76. Masella R, Malorni W. Gender-related differences in dietary habits. **Clin. Manag. Issues. 2017;11(2):59-62.**
77. van Uffelen JGZ, Khan A, Burton NW. Gender differences in physical activity motivators and context preferences: a population-based study in people in their sixties. BMC Public Health. 2017;17:624.
78. Age-Well. COVID-19 has significantly increased the use of many technologies among older Canadians: poll [cited 2020 Nov 24]. https://agewell-nce.ca/archives/10884.
79. Statistics Canada. Analytical Studies Branch Research Paper Series; Evolving Internet Use Among Canadian Seniors; July 10, 2019. https://www150.statcan.gc.ca/n1/pub/11f0019m/11f0019m2019015-eng.htm

Tables

Table 1. Key elements in the Baycrest Brain-healthy Eating Approach

Element	Description
1. Brain Health Food Guide	The BHFG was based on existing European and American epidemiologic and clinical trial results related to diet and cognitive function or dementia risk. It was designed as a practical, lifelong eating guide that does not eliminate any type of food but emphasizes variety and moderation and offers maximum flexibility for individual food choices and preferences. Recommendations on daily or weekly servings of foods to include and foods to limit is provided as part of the Guide
1. Didactic Education	Participants selected topics of interest and were provided details about the health benefits of particular foods, suggestions for how these foods might be incorporated into one's diet and making healthy food choices. Topics selected were incorporating legumes into one's diet, the health benefits of various plant foods, healthy fats and label reading
1. Individual Nutritional Counseling	Each participant was offered a 30-minute session with the dietitian to address individual concerns and barriers to change. Participants missed 30-minutes of group discussion to receive their individual counselling. If participants felt they needed to schedule additional individual sessions, they were accommodated on a case by case basis.
1. Individualized Goal Setting	Each week, participants selected a dietary change to align their diets more closely to the BHFG and put it into a goal statement
1. Meta-cognitive strategy us	The meta-cognitive strategy, GOAL-PLAN-DO-CHECK, provides the frame for behaviour change
1. Guided Discovery	This method of instruction is accomplished through having the group leader act as a facilitator rather than instructing participants. The group leader uses a series of questions to help participants identify plans that will achieve their goals in a way that will work for them and encourages participants to focus on "one thing at a time"
1. Dynamic Performance Analysis	While facilitating the plan development, the group leader encourages the active analysis of whether the proposed plan is feasible and do-able. Thus, the planning is an iterative process
1. Intervention Format	1-hour facilitated session that included goal setting, education, a brain-healthy snack break and group support

Note: Used with permission from Bar et al., 2021

Table 2. Participant characteristics at baseline

Demographics	EX+DIET	EX+ED
Age (years)	72.29 (4.54)	71 ± 4 (65-83)
Sex	4 females (57%)	6 females (86%)
Education (years)	18.00 (2.52)	13.43 (2.76)
Early MCI	1 (14%)	2 (29%)
MOCA (out of 30)	27.43 (3.1)	26.29 (3.09)
Body Mass Index (kg/m^2)	28.98 (4.98)	30.14 (5.13)
Overweight (n)	5 (71%)	6 (86%)
Hypertension (n)	5 (71%)	4 (57%)
High Cholesterol (n)	4 (57%)	4 (57%)
Type 2 Diabetes (n)	1 (14%)	1 (14%)
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	22.16 (5.35)	20.13 (3.64)
BEI diet score	6.43 (1.06)	7.21 (1.60)
Hippocampal volume (mm^3)	3336.16 (557.26)	3155.95 (262.03)
RAVLT scores (out of 15)	9.00 (1.91)	9.86 (2.27)
HbA1c (%)	6.00 (.29)	5.76 (.57)
Serum vitamin K (nmol/L)	1.24 (0.39)	2.65 (1.61)

Note: All data are reported in mean (SD) or frequency (%). BBEA = Baycrest Brain-healthy Eating Approach; BHED = Brain Health Education; MCI = mild cognitive impairment; MOCA = Montreal Cognitive Assessment; $\dot{V}O_{2peak}$ = peak oxygen uptake HbA1c = Hemoglobin A1c; BEI = Brain-healthy Eating Index. Overweight = BMI>25, Hypertension, High Cholesterol and Type 2 Diabetes were physician diagnosed. Hippocampal volumes, $\dot{V}O_{2peak}$, HbA1c, and vitamin K for EX+DIET group n = 5. $\dot{V}O_{2peak}$ for EX+ED group n=6. All other values n = 7

Figures

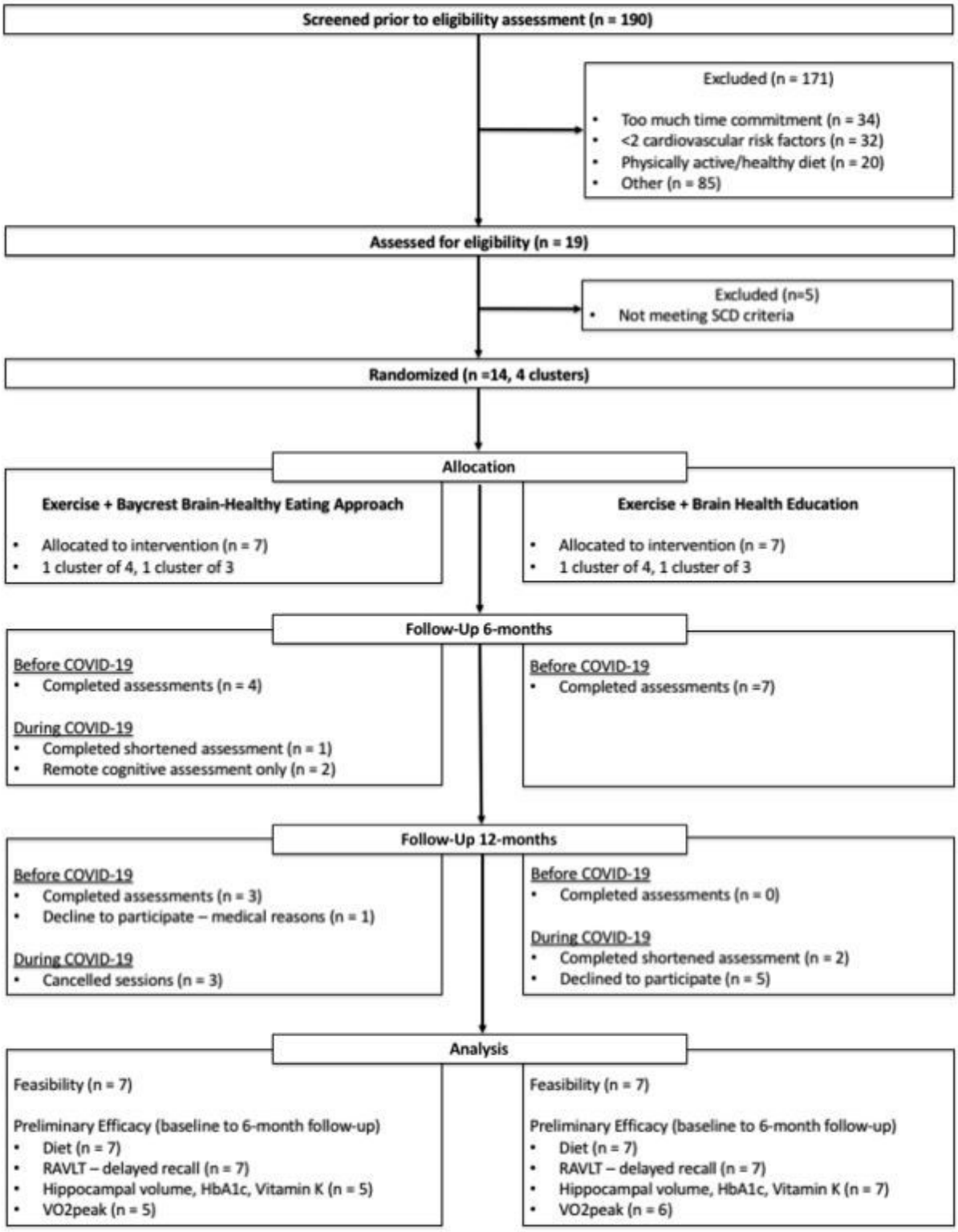

Figure 1

Study flow diagram

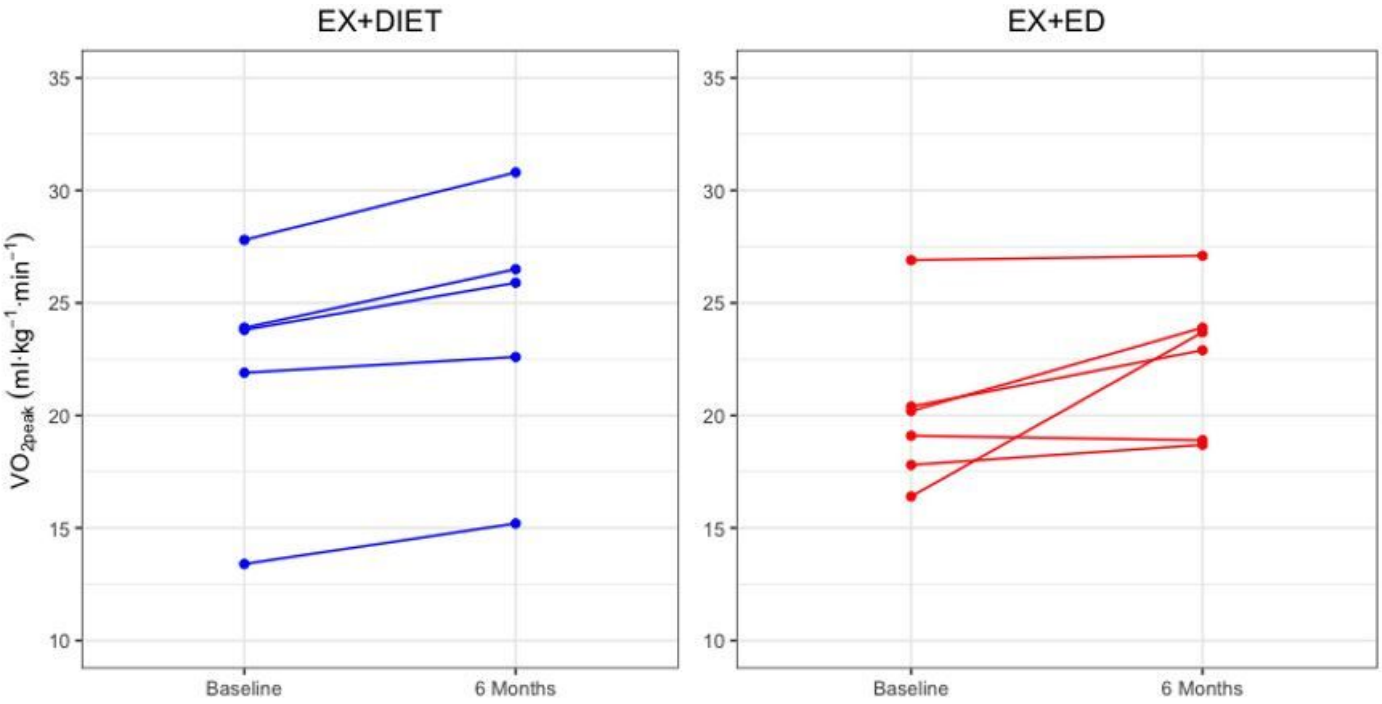

Figure 2

Individual changes in V̇O2peak

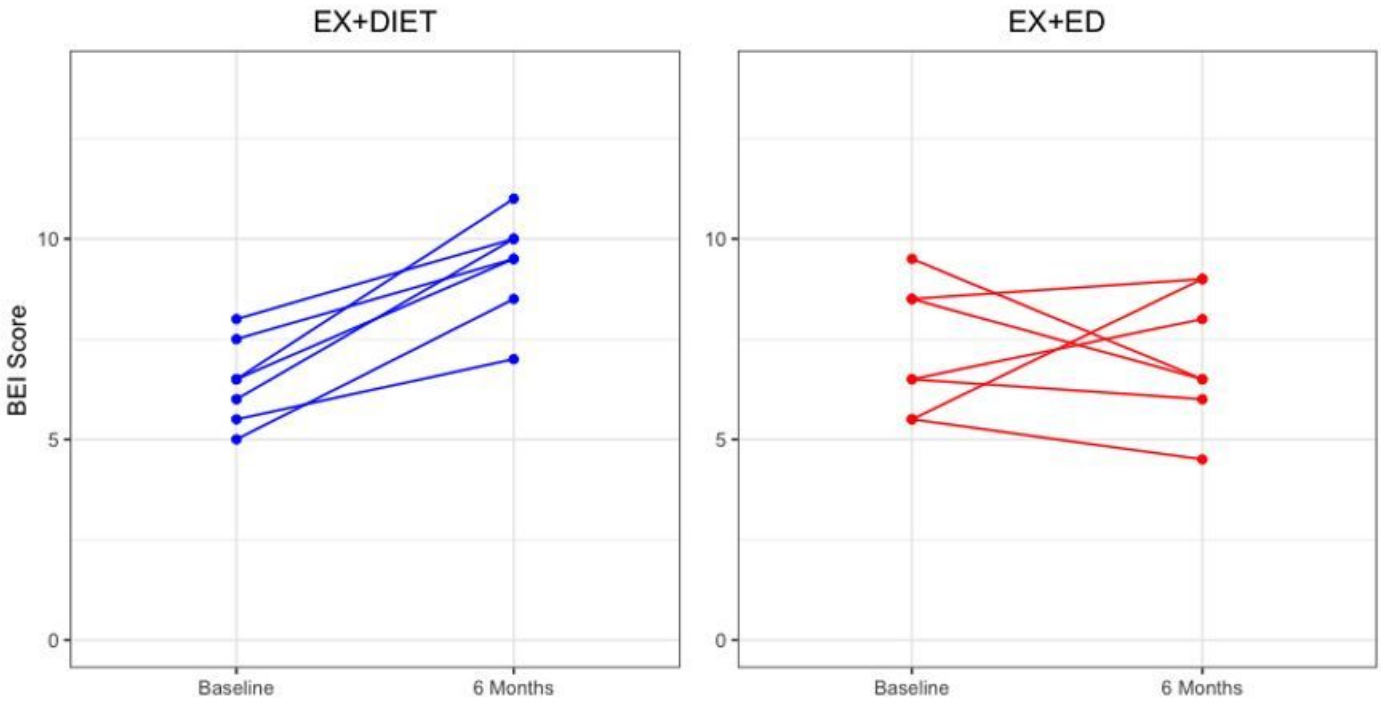

Figure 3

Individual changes in Brain-healthy Eating Index (BEI) scores

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTFeasibilityTrialsChecklistLEADJune15.pdf
- AdditionalFile1.docx