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Original Research

Reducing the Effects of Ageing on Cognition with Therapeutic Intervention of an Oral Multi-Nutrient: The REACTION Pilot Trial Study Design

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Abstract

BACKGROUND: Clinical benefits have been reported with a specific multinutrient intervention (Souvenaid) in Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease. The effects of Souvenaid in age-related cognitive decline are not established.

OBJECTIVE: To assess the feasibility of using virtual assessments to study the effects of a multinutrient on cognitive ageing.

DESIGN: This is a randomized, double-blind, placebo-controlled, parallel group virtual pilot trial performed over 6 months in a single-centre. Participants are randomly allocated (1:1) to receive the specific multinutrient (Souvenaid) or an isocaloric, same tasting, placebo.

SETTING: Trial visits are done virtually using secure online video communication.

PARTICIPANTS: English or Spanish speaking people aged 55–89 years from all ethnic groups and considered to have age-related cognitive decline are eligible.

MEASUREMENTS: Neuropyschological tests are done at baseline and after 6 months of intervention. Participants are contacted monthly by telephone to monitor safety, assess motivation and promote compliance. The primary outcome is feasibility determined by assessing recruitment rate, recruitment time, adherence rate and retention rate. A comprehensive set of neuropyschological measures will provide a broad assessment of cognitive function, including verbal memory, processing speed, and attention and executive function. Self-reported questionnaires are used to assess quality of life.

CONCLUSIONS: This pilot trial will provide data to guide inform selection of participants and outcome measures in future studies in age-related cognitive decline.

Key words: Healthy ageing, cognitive function, nutrients, Souvenaid, Fortasyn Connect, virtual Assessment, telemedicine.

Introduction

People worry about the prospect of losing their memory and independence as they get older (1). The risk between Alzheimer's disease (AD) and older age is well established (2), however, cognitive changes are also associated with healthy ageing. Age-related cognitive decline (ARCD) represents a distinct clinical entity, different from cognitive changes caused by primary neurodegenerative processes such as AD (3). ARCD afflicts a significant proportion of older adults and has an incidence 70% higher than dementia (3). Cognitive ageing is characterized by significant inter-individual variability, influenced by numerous factors such as cultural context, education, socio-economic status, and medical comorbidities, and may manifest with different profiles across cognitive domains (4). Moreover, there has been limited research in ARCD because of the absence of a clear clinical definition compared with conditions of impaired cognition.

The pathophysiological processes underlying cognitive changes seen in ARCD and AD are complex, although a common theme is a decline in synapse function and number, which manifests as changes in brain volume observable on neuroimaging (5). Studies of brain reserve and deterioration suggest that there is a critical threshold for the number of healthy, functioning synapses (6); loss of synapses to levels below the critical threshold leads to cognitive impairment and eventually to dementia (1, 7). Experimental studies suggest that a loss of synaptic plasticity (8-11) underlies ARCD in ageing human adults (5, 12, 13). Furthermore, these studies provide a scientific rationale to explore therapies aimed at rescuing dendritic spine density and increasing synaptic plasticity as potential strategies for ARCD, AD, and other dementias (1).

Synaptic membranes consist of specific phospholipids forming a bilayer also containing cholesterol, other lipids, and proteins (14, 15). It has been suggested that lifestyle, dietary, and other specifically targeted interventions may help to preserve neuronal functions and maintain cognitive performance by improving phospholipid metabolism (16). Furthermore, pioneering work by investigators at Massachusetts Institute of Technology showed how the metabolic pathways responsible for generating brain phospholipids can be positively influenced by supplying a combination of nutritional precursors and cofactors (17). A series of preclinical experiments showed that administering uridine, choline, and docosahexaenoic acid promotes neuro-regeneration, by increasing synaptic proteins, neurite and synapse

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formation, and neurotransmission, resulting in enhanced memory performance in animal models (reviewed in van Wijk et al., 2014). Importantly, these specific nutrients act synergistically, suggesting that a multinutrient intervention could be more effective than single-agent nutrient supplements (18).

Souvenaid (Fortasyn Connect; Nutricia, Zoetermeer, the Netherlands) is a multinutrient developed to support phospholipid synthesis. Taken as a once-daily drink, Souvenaid provides nutrients and cofactors (long-chain omega-3 fatty acids, uridine, choline, B vitamins, vitamin C, vitamin E, and selenium) to make neuronal membranes and synapses (18). Four randomized controlled trials have evaluated Souvenaid in subjects (n=1332) across the spectrum of AD, from mild cognitive impairment (MCI) due to AD to mild-moderate AD (19-24). Results from these trials showed high adherence rates and good tolerability when administered every day for between 12 weeks and 3 years (20-24). Furthermore, the benefits of Souvenaid on cognitive outcomes were most apparent when administered early in the disease course, notably in MCI due to AD (16).

The European LipiDiDiet Group investigated Souvenaid in a randomized, controlled, double-blind, parallel group, multicenter trial in patients with MCI due to AD (23). Results showed a significant benefit over a treatment period of 3 years as measured using a neuropsychological test battery (NTB) 5-item composite score, NTB memory domain, Clinical Dementia Rating scale Sum of Boxes (CDR-SB), and brain atrophy on neuroimaging (23, 24). Based on these findings, the authors suggested that long-term nutritional intervention and initiating early in the disease continuum might be factors contributing to the achievable benefits on reducing cognitive and functional decline (24).

Available preclinical evidence therefore shows that Souvenaid can promote the formation of new synapses, which may lead to improvements in cognitive symptoms associated with decreased synaptic plasticity (25). Following randomized controlled trials with Souvenaid in subjects with cognitive symptoms associated with AD, we hypothesize that Souvenaid can improve cognitive performance in ARCD. Since this is the first study of Souvenaid in ARCD, the most appropriate neuropsychological metrics, duration of therapy, and study design to test this hypothesis are unknown. Furthermore, as a result of the COVID-19 pandemic, there is a greater need for virtual assessments to allow cognitive ageing studies to operate within the context of social distancing and ongoing concerns about participants' safety. This trial therefore serves an exploratory purpose, and is largely informed by prior trials of Souvenaid in AD. The data produced by this trial can support the wider use of virtual assessments of cognitive function in ARCD and serve as a pilot for the design and implementation of future studies.

The 'Reducing the Effects of Ageing on Cognition with Therapeutic Intervention of an Oral Nutrient (REACTION)' trial is registered on ClinicalTrials.gov (Identifier: NCT04147624). The main objective of the REACTION trial is to assess the feasibility of virtual assessments to investigate the effect of a 6-month administration of a specific multinutrient oral supplement on cognitive ageing. In addition, the trial will evaluate whether the 6-month multinutrient intervention can delay or reverse the effects of normal cognitive ageing across different cognitive domains and will measure its effects on quality of life.

Methods and trial design

Participants

People with subjective memory complaints presenting at in-person or telemedicine clinics at the University of Miami Neurology clinics are invited to participate in the trial. English or Spanish speaking people aged 55–89 years from all ethnic groups and considered to have ARCD are eligible for inclusion. ARCD is determined based on a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Verbal Memory Retention score ≥70% on list learning retention and ≥80% on story memory retention and Subjective Cognitive Decline (SCD) 9-item brief screening tool score within the 25th percentile (SCD = 1) and 75th percentile (SCD = 6). In addition, participants are expected to score in the normal range of the Montreal Cognitive assessment (MoCA), defined in this trial as ≥24.

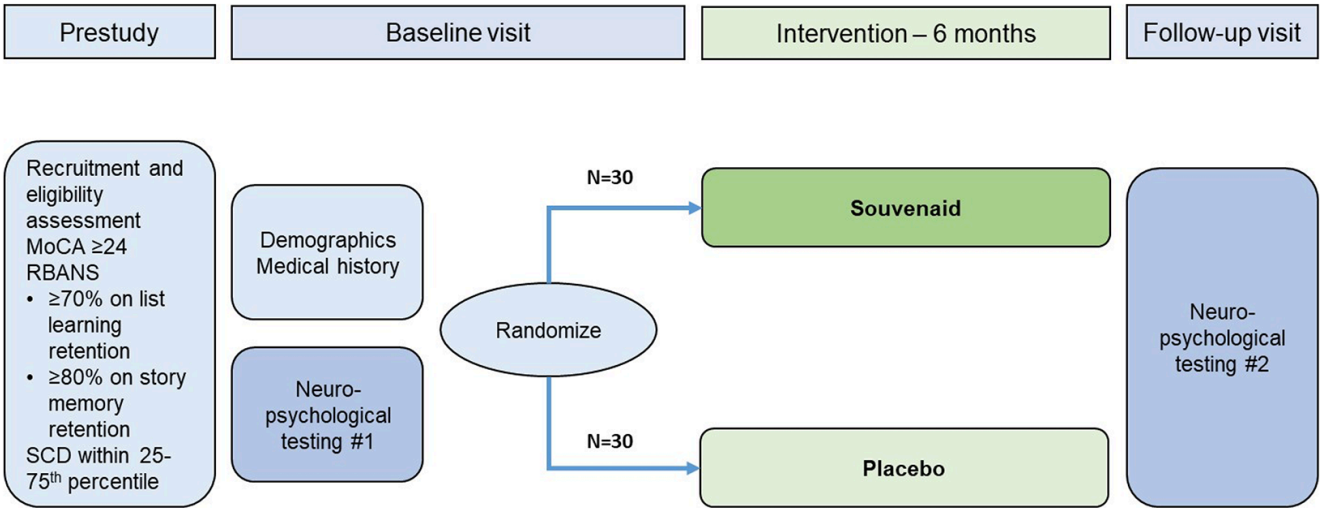
The trial excludes people with a diagnosis of dementia (according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition and/or the National Institute on Ageing and Alzheimer's Association criteria), prior stroke, cancer, untreated major depressive disorder that has not been in remission for at least 6 months prior to the study, any concurrent major medical or neurological illness, or history of abuse of illegal drugs and substances. Other exclusion criteria include enrolment in other cognitive therapeutic trials, the use of the nutritional supplements for cognitive improvements in the 24 days (folate, vitamins B6, B12, C, and E) or 30 days (omega-3 fatty acids) prior to participation, and treatment with any anti-AD medication or over-the-counter supplements or 'cognitive/memory' enhancers.

Participants must provide written consent. The study was approved by the University of Miami Institutional Review Board and is being done in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

Trial design

REACTION is a randomized, double-blind, placebo-controlled, parallel group virtual pilot trial performed

Figure 1. Trial design and timeline



RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SCD = Subjective Cognitive Decline; MoCA = Montreal Cognitive assessment.

Table 1. Outcomes to assess feasibility

Study milestones	+	±	–
Recruitment rate (% of potential eligible participants)	≥50%	25–50%	<25%
Recruitment time (% of planned time)	<110%	110–150%	>150%
Adherence to intervention (% of study product is consumed)	≥80%	60–80%	<60%
Retention rate (% of participants dropped out)	<30%	30–50%	>50%

For each of the feasibility variables being considered, the result will be determined to be feasible ("+"), feasible under certain conditions ("±"), or not feasible ("-") based on the cut-off values listed in the table. The overall feasibility of this study will be assessed taking into account all feasibility parameters: + This virtual study with Souvenaid seems to be feasible in ARCD; +/− This virtual study with Souvenaid seems to be feasible in ARCD but only under certain conditions – modification of protocol is required; − This virtual study with Souvenaid under specific conditions is unfeasible in ARCD

over 6 months in a single-centre (Figure 1). Participants are screened for eligibility and randomly allocated to receive the test product (specific multinutrient) or placebo (isocaloric and similar in appearance and flavor to the test product), both as a 125 mL once-daily drink, on a 1:1 basis. Trial visits are done in the clinic or virtually using a secure, Health Insurance Portability and Accountability Act (HIPAA)-compliant online video communication software (ZOOM). Participants will require a compatible device (e.g., computer or tablet device) and internet connection for virtual communication and remote neuropsychological testing. Participants are assessed at baseline and 6 months. In addition, they are contacted monthly by telephone to monitor safety, assess motivation, and promote compliance.

Primary outcomes

The primary outcome of the trial is feasibility determined by assessing recruitment rate, recruitment time, adherence rate, and retention rate (Table 1). The trial will be deemed feasible if recruitment rate is ≥50% of those who fulfil the eligibility criteria and are invited to participate, recruitment time is <110% of planned time, adherence is ≥80% of the test product consumed, and retention rate is <30% drop-out (Table 1). In addition, the percentage of participants in the "per-protocol" population defined as those without any protocol deviation, is tracked.

Main cognitive outcomes

Currently there are no cognitive assessments recognized as standard to evaluate the effect of a multinutrient intervention in ARCD. The cognitive outcome measures are secondary endpoints and have been selected to assess the effect of the intervention across several domains of interest. The main cognitive outcomes comprise a comprehensive set of measures assessed by several constructs to provide a broad assessment of cognitive function. Importantly, all these cognitive tests can be administered entirely via virtual communication. The cognitive domains assessed in this study include verbal memory, processing speed, and attention and executive function (Table 2).

Verbal learning, delayed memory, and recognition are measured using the Rey Auditory Verbal Learning Test (RAVLT), or for Spanish speakers the WHO/UCLA Auditory Verbal Learning Test (AVLT). The test takes

Table 2. Summary of cognitive and quality of life outcome measures

Tests administered virtually at baseline and at 6 months		Domains measured
Main cognitive outcomes	Verbal Learning Tasks (RAVLT for English or WHO/UCLA AVLT for Spanish)	Memory
	Digit Span (WAIS-IV)	Attention and executive function (working memory)
	Oral Trail Making Test B (TMT-B)	Attention and executive function (working memory and cognitive flexibility)
	Matrix Reasoning from the TMB research battery	Attention and executive function (fluid intelligence and non-verbal reasoning)
	Oral Trail Making Test A (TMT-A)	Processing speed
Exploratory cognitive outcomes	Visual Paired Associates from the TMB research battery	Visual memory
	MINT from the NACC neuropsychological battery	Language
	Verbal Fluency Tests (F, A, and S in English or P, T, and M in Spanish; animals)	Language (verbal and semantic fluency)
Exploratory quality of life outcomes	Amsterdam IADL Questionnaire	QoL (activities of daily living)
	Geriatric Depression Scale	QoL (depression)
	WHO-Quality of Life Scale	QoL
	PROMIS: Short Form v.1.0 (8b)	QoL (sleep disturbance)
	PROMIS: Short Form v.1.0 (8a)	QoL (fatigue)
	Frailty Trait Scale - Short Form	QoL (frailty)
	CHAMPS Physical Activity Questionnaire for Older Adults	QoL (lifestyle physical activity)
	Pandemic Stress Severity Index (PSSI)	QoL (stress)
	Person-Centric Questionnaire	QoL (to get more insight in the complaints of a healthy ageing population)

Notes: Age-based normative scores are available for cognitively intact individuals; 'Main' and 'Exploratory' designations are based on the authors' opinions concerning cognitive domains of interest hypothesized to be impacted by the investigational product. A 'Primary' outcome is not assigned due to lack of data needed to determine sample size necessary to power the study for a given primary outcome. By its pilot nature, this study is expected to generate the data to determine the sample size necessary for appropriately powering future studies. Abbreviations: AVLT = Auditory Verbal Learning Task; CHAMPS = Community Healthy Activities Model Program for Seniors; IADL = Instrumental Activities of Daily Living; MINT = Multilingual Naming Test; NACC = National Alzheimer's Coordinating Center; PROMIS = Patient-Reported Outcomes Measurement Information System; QoL = quality of life; RAVLT = Rey Auditory Verbal Learning Task; TMB = Test My Brain; UCLA = University of California, Los Angeles; WAIS-IV = Wechsler Adult Intelligence Scale Fourth Edition; WHO = World Health Organization

10–15 minutes plus a 30-minute delay during which time other measures can be done.

Attention and executive function are measured with three tests. The Digit Span subtest of the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) measures attention and working memory using exercises that require participants to recite a series of progressively longer sequence of numbers in forwards, backwards and sequencing order. The Oral Trail Making Test B (TMT-B) assesses working memory and cognitive flexibility. Participants are asked to verbally alternate between letters and numbers in sequential order as quickly as possible. The Matrix Reasoning from the Test My Brain (TMB) research battery task provides a measure of fluid intelligence and non-verbal reasoning. It is based on a well-validated and widely used matrix reasoning tasks but adapted for virtual administration.

Processing speed is measured using the Oral Trail Making Test A (TMT-A), which is a speeded mental control task that requires participants to recite the alphabet and a sequence of numbers as fast as possible. The time to complete each of these exercises is averaged.

Exploratory cognitive outcomes

Exploratory neurocognitive measures are done to evaluate if enhancing synaptic formation, the putative mechanism of the multinutrient intervention, affects performance in other cognitive domains (visual memory, language).

Visual episodic memory is assessed using the Visual Paired Associates from the TMB research battery. Participants are asked to learn and memorize 25 pairs of images. Following a distractor task, individuals choose corresponding pairs from a set of target and foil stimuli. The test takes approximately 6 minutes to complete.

Language is assessed using two tests. The Multilingual Naming Test (MINT) from the National Alzheimer's Coordinating Center's (NACC) neuropsychological battery is a research measure to assess word retrieval deficits. Trial participants are asked to name a series of individually presented line drawings that range from highly common (e.g. butterfly) to more obscure (e.g. axle). Verbal Fluency Tests are used evaluate phonemic and semantic fluency. In the phonemic fluency task, individuals are asked to produce as many words as they can that start with each of three letters (F, A, and S in English, or P, T, and M in Spanish) in one minute.

Semantic fluency is assessed by asking participants to name as many animals as possible in one minute.

The possibility of an age-differential effect of the study product on the cognitive outcomes will be examined based on decade of age and RBANS score.

Exploratory quality of life outcomes

Table 2 lists the self-reported questionnaires that are used to assess mood, quality of life, sleep quality, fatigue, frailty, level of daily activity, and ability to complete instrumental activities of daily living (IADLs).

Exploratory biomarkers

Optional biomarker testing could be done to measure plasma levels of AD biomarkers (P-Tau181, amyloid beta [Aβ]1-40, and Aβ1-42) and apolipoprotein E (ApoE) at baseline.

Safety

Adverse events and serious adverse events are recorded regardless of relationship with test product. Participants will be withdrawn if they experience unanticipated, life-threatening serious adverse events, or are deemed non-compliant with the study protocol.

Statistical considerations

No prior sample size calculation was performed because of the pilot nature of this study. The recruitment target is 60 participants (30 experimental arm, 30 placebo) based on conventional guidance for determining a pilot study size for a small to medium expected effect size in a two-group study (26). Descriptive statistics will be used for the primary endpoint variables of recruitment rate, recruitment time, adherence to intervention, and retention rate. Predefined cut-offs will be used to categorize the variable as either feasible ("+"), feasible under certain conditions ("+/-"), or not feasible ("-"). For secondary outcomes, the treatment effect will be tested by comparing the means of the cognitive change score between treatment groups using a two-sample t-test. If the outcome variable is not normally distributed, other statistical tests will be considered (e.g., Wilcoxon signed-rank test) or transforms will be applied to the dependent variable. The addition of other potential covariates will be considered if they are thought to influence the effect of intervention.

Discussion

The REACTION trial is designed to advance research in ARCD by objectively defining candidates for clinical studies in virtual and clinic settings, evaluating potentially informative outcome endpoints covering different cognitive domains, and assessing the effect of a specific multinutrient intervention on cognition. Although there have been many studies of lifestyle, dietary, and single-agent nutrients in ageing adults at risk for cognitive decline (27), this trial is one of the first to evaluate a specific multinutrient in a randomized, placebo-controlled setting.

ARCD does not have a universally accepted definition, therefore, the trial has been designed to enrich the population with ageing adults presenting with objective evidence of memory problems but without a clinical diagnosis of pathologic cognitive decline, for example, MCI or AD. Candidates are screened initially using the RBANS and SCD 9-item screening tool (28, 29). RBANS is designed to screen for dementia and a cut-off score of one standard deviation below the mean (Total Index score <85) has been proposed for identifying individuals with potential MCI (29); therefore, a logical screen for normal cognitive individuals would be a TI score >85. However, because the RBANS cannot be tested in its entirety in a virtual context, in this trial we are using the verbal memory retention subsections as an alternative screen, with screening cut-offs of ≥70% on list learning retention and ≥80% on story memory retention (30). The SCD 9-item brief screening tool is being used because it can screen cognitive function more broadly than RBANS (28) and provides information regarding participants' own perception of their cognitive status. AD biomarkers are being measured in some participants and may generate important data to help characterize the trial population in terms of any underlying disease pathology.

In this trial we are evaluating several established tests that track changes in cognitive function across different domains including memory, attention and executive function, processing speed, visual memory, language, and quality of life. Importantly, for the main cognitive outcomes used in the trial, age-specific normalized data are available for individuals without cognitive disorders. For example, as recall impairment is often an early sign of ARCD, we selected the RAVLT to assess this function. RAVLT is validated for MCI and AD and is sensitive for the detection of mild amnestic cognitive changes in early and preclinical stages (31). The secondary and exploratory endpoints explore changes in cognitive and quality-of-life scores at baseline and after 6 months of intervention to allow us to evaluate their potential to be used as primary or secondary efficacy outcomes in a future phase II trial. Determining the most appropriate outcome endpoints is an important challenge for studies of nutritional intervention in the setting of cognitive decline. The authors of the LipiDiDiet trial highlighted the difficulty in finding adequately sensitive outcome measures for trials in MCI due AD (23, 24). In the REACTION trial, we hope to provide useful data on the value of different outcome measures to guide future research in ARCD. Harmonization of trial design, particularly the most appropriate outcome measures, is an important goal for

future trials in large at-risk populations such as ARCD (32).

Like the criteria used to select candidates for the trial, it is important that the outcome measures can be done in a virtual setting. Recruitment and diversity in the study population can be improved by accommodating multiple languages and allowing participants living at a greater distance from the clinics to enrol in studies conducted in a virtual setting.

A possible limitation of this pilot study design is the lack of sample size calculation based on expected AD outcomes data. The AD population is in a pathologic state of cognitive decline and therefore it is challenging to apply outcomes data to an ARCD population. In addition, outcomes data in the ARCD population are not available to calculate an accurate sample size for this pilot study. It is also important to recognize that data from virtual study visits may not be identical to an equivalent in-person test. There are limited data for virtual cognitive testing in ARCD, and no such data exist in any Souvenaid trials. Conventional guidance for determining a pilot study size was therefore used for this study (26).

Conclusion

The REACTION pilot trial will determine the feasibility of a clinical trial conducted largely in a virtual setting to investigate the effects of a specific multinutrient on cognitive function in ARCD. The results from this trial will be valuable for the design of future research studies by providing useful data to guide selection of participants and outcome measures that are sensitive to detect effects on the trajectory of cognitive decline in ARCD.

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Ethical standards: The study was approved by the University of Miami Institutional Review Board and is being done in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

Conflict of interest: Dr. Camargo reports grants from American Academy of Neurology / McKnight Brain Research Foundation Clinical Research Training Scholarship, grants from Danone Nutricia Research during the conduct of the study. Ms. Merritt has nothing to disclose. Ms. Modjeski has nothing to disclose. Dr. Counotte was an Employee of Danone Nutricia Research during the conduct of the work. Dr. Fernández McInerney has nothing to disclose.

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