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Exploratory functional and quality of life outcomes with daily consumption of the ketone ester bis-octanoyl (R)-1,3-butanediol in healthy older adults: a randomized, parallel arm, double-blind, placebo-controlled study☆

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ABSTRACT

Background: Ketone bodies are metabolites produced during fasting or on a ketogenic diet that have pleiotropic effects on the inflammatory and metabolic aging pathways underpinning frailty in vivo models. Ketone esters (KEs) are compounds that induce hyperketonemia without dietary changes and that may impact physical and cognitive function in young adults. The functional effects of KEs have not been studied in older adults.
Objectives: Our long-term goal is to examine if KEs modulate aging biology mechanisms and clinical outcomes relevant to frailty in older adults. Here, we report the exploratory functional and quality-of-life outcome measures collected during a 12-week safety and tolerability study of KE (NCT05585762).
Design: Randomized, placebo-controlled, double-blinded, parallel-group, pilot trial of 12-weeks of daily KE ingestion.
Setting: The Clinical Research Unit at the Buck Institute for Research on Aging, California.
Participants: Community-dwelling older adults (≥65 years), independent in activities of daily living, with no unstable acute medical conditions ($n = 30$).
Intervention: Participants were randomly allocated (1:1) to consume 25 g daily of either KE (bis-octanoyl (*R*)-1,3-butanediol) or a taste, appearance, and calorie-matched placebo (PLA) containing canola oil.
Measurements: Longitudinal change in physical function, cognitive function and quality of life were assessed as exploratory outcomes in $n = 23$ completers ($n = 11$ PLA, $n = 12$ KE). A composite functional outcome intended for interventional frailty trials was derived and calculated. Heart rate and activity was measured throughout the study using digital wearables.
Results: There were no statistically significant longitudinal differences between groups in exploratory functional, activity-based or quality of life outcomes.
Conclusion: Daily ingestion of 25 g of KE did not affect exploratory functional or quality-of-life end points in this pilot cohort of healthy older adults. Future work will address these endpoints as primary and secondary outcomes in a larger trial of pre-frail older adults.

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Abbreviations

1-RM	1 Repetition Maximum
400 M GS	400-meter gait speed
6MWT	6 Min Walk Test
ADL	Activities of Daily Living
AEs	Adverse Events
BDO	(*R*)-1,3-butanediol
BH-BD	Bis-hexanoyl (*R*)-1,3-butanediol
BHB	Beta-hydroxybutyrate
BMI	Body Mass Index
BO-BD	Bis-octanoyl (*R*)-1,3-butanediol
BTQ	Beverage Tolerability Questionnaire
CSHA	Canadian Study of Health and Aging
CRF	Case Report Form
D3Cr	Deuterated creatine
DSST	Digit Symbol Substitution Test
IADL	Instrumental Activities of Daily Living
ITT	Intention to treat
KEs	Ketone Esters
MAT-sf	Mobility Assessment Tool, Short Form
MoCA	Montreal Cognitive Assessment
PLA	Placebo
PP	Per protocol
QoL	Quality of Life
SASP	Senescence-associated Secretory Phenotype
SoF-IT	SOMMA Frailty — Interventional Trials
SPPB	Short Physical Performance Battery
V2F	Vigor to Frailty Score
VO_2peak	Oxygen consumption at peak exercise

1. Introduction

The Geroscience Hypothesis, though yet untested in clinical trials, postulates that intervening in common aging biological mechanisms could mitigate or prevent various chronic age-related diseases as well as geriatric syndromes such as frailty [1]. Frailty syndrome, characterized by diminished physiological reserves and heightened susceptibility to adverse health stressors, posing a significant risk for disability, institutionalization, and mortality [2]. The prevalence of frailty escalates with age, with around 15 % of adults over 65 years old in the United States meeting one standard definition [3]. Although the pathophysiology of frailty is multi-system and poorly elucidated, it is believed to encompass deficits in cellular energy production, chronic inflammation, and immune dysfunction ([4,5]) – all of which also comprise geroscience molecular mechanisms commonly recognized as the "Hallmarks of Aging" [6]. Presently, specific molecular therapies for frailty remain elusive, although interventions such as exercise programs, specialized geriatric care models, and nutritional strategies have shown the most promise in modulating the frailty phenotype and its sequalae [7].

A challenge in interventional studies of frailty is the choice of a primary outcome to capture clinically meaningful changes in function, especially as many outcomes focus on the frailest population, and poorly discriminate among those 'not frail'. Recently, Newman et al., [8] used a large ($n = \sim$900), well-characterized older adult population to develop a four-item continuous composite score (comprising digit symbol substitution, leg power, peak oxygen consumption and fatigability) that better captures the spectrum of function from vigorous to frail. The score was strongly associated with age, with lower scores predicting functional limitation [8]. Such composite scores both increase the chance of detecting intervention-driven differences in higher functioning people and avoid the selection of a single arbitrary outcome for a complex, multi-factorial condition such as frailty and pleiotropic interventions such as diet or exercise [9].

An increasing number of studies have explored the impact of dietary restriction and fasting on aging biology in animal models [10] and humans (e.g., CALERIE [11], HALLO-P (NCT05424042)). Whilst there are multiple physiologic changes that are triggered by these dietary changes, a notable key shared feature of dietary restriction and fasting is the presence of ketone bodies, such as beta-hydroxybutyrate (BHB), synthesized in the liver during fasting or carbohydrate restriction. The primary role of BHB is to provide an alternative energy source to various tissues, including the brain, muscle, and heart. However, ketones bodies have additional molecular signaling activities, including improving mitochondrial function ([12,13]) and regulating inflammatory activation, which alongside their energetic function support a mechanistic role in modulating aging and may be directly relevant to frailty [14]. Prior studies have demonstrated the potential of increasing circulating ketone concentrations in extending healthy lifespan and ameliorating age-related functional decline in animal models ([15,16]).

Ketone esters (KEs), such as bis-octanoyl (*R*)-1,3-butanediol, are examples of exogenous ketones, small molecules that deliver ketone bodies without other dietary changes ([17,18]). KEs are hydrolyzed in the gut to release ketone bodies or ketogenic precursors, which are then metabolized in the liver to release ketone bodies [19]. In preclinical models, ketone bodies and KEs attenuate muscle atrophy through anti-catabolic signaling activities [20], improve heart function in age-related heart failure ([21,22]), and promote healthy function of T cell subpopulations ([23,24]). Clinically demonstrated effects of acute KE administration range from blood glucose control ([25,26]) to physical ([27,28]), cognitive ([29,30]), immune [31], and cardiovascular ([30, 32]) function in younger adult populations under the age of 65. Whilst KE have not been tested in an older adult population, related ketogenic dietary interventions such as ketogenic fatty acids have shown a signal of beneficial effects on brain energy and cognition in older adults with mild cognitive impairment [33]. These observations have led to our central hypothesis, that ketone bodies delivered through KEs may ameliorate the frailty syndrome through multi-system energetic and signaling activities that improve metabolic and immune function. To date, there are no published studies describing the effects of KE on functional outcomes in an aging population.

To begin addressing this gap, and laying the foundation for future work testing the KE in a pre-frail and frail population (NIH funding ID: **1R01AG081226–01**, Clinicaltrials.gov ID: **NCT06645847)**, we undertook a 12-week randomized, placebo-controlled, double-blinded, parallel-group pilot clinical trial with the primary objective of generating the first long-term safety and tolerance data for KEs in an independent living, generally healthy population of older adults. Here we report data describing our exploratory aging-focused functional endpoints. We also calculated a four-item composite frailty outcome score inspired by the Vigor to Frailty work of Newman et al [8] to investigate functional changes on the more vigorous end of a continuum from vigorous to frail. Based on the positive data of short-term KE use in younger adults, we hypothesized that 12-weeks of KE consumption would improve functional outcomes in our older adult population.

2. Methods

2.1. Study design overview

The study design was preregistered on ClinicalTrials.gov (ID: NCT05595762) and previously reported [34]. Healthy older adults $\geq$ 65 years of age ($n = 30$) took part in this randomized, 12-week randomized, placebo-controlled, double-blinded, parallel-group, pilot clinical trial (Fig. 1). The full study design was powered to determine tolerance and safety as previously described, and these primary outcomes were reported seperately ([34,35]). The study included single-administration kinetics visits prior to starting and after completing the main 12-week protocol, results of which are reported separately [36]. Physical, cognitive, and quality of life (QoL) exploratory outcomes were measured at week 0 and week 12. Participants arrived at these visits fasted for blood draws, then were provided with a snack and, if desired, coffee or tea prior to beginning functional testing. Coffee and tea intake was standardized between Week 0 and Week 12 visits. Wrist based health and fitness monitors were distributed at the first kinetics visit (at least 7 days before baseline) and were worn continuously until the final visit. The study was approved by Advarra IRB on September 28th 2022 (Pro00065464). The first participant was randomized on January 31st 2023 and the final participant completed the trial on January 17th 2024, which ended the study. The study was conducted in accordance with the 2013 Declaration of Helsinki.

2.2. Participants

Participants were community dwelling older adults (≥ 65 years of age), independent in activities of daily living and in stable health. The full inclusion and exclusion criteria are listed in the Supplemental Information. Decisions on eligibility were made by an independent medical officer to ensure allocation was concealed, and eligible participants were randomized by the study team based on a statistician-generated block allocation sequence (block size 4, intended to equally randomize men and women). The flow of study participants is illustrated in the CONSORT diagram (Supplementary Figure 1). Sample size was determined a priori based on the primary outcome of the study, which was tolerance of the KE beverage [37], and feasibility of this pilot.

2.3. Study beverages

The study KE beverage was a tropical-flavored beverage containing the KE bis-octanoyl (*R*)-1,3-butanediol (Cognitive Switch, BHB Therapeutics Ltd, Dublin, IRE). Each bottle was 75 mL and contained 25 g of KE. Participants were instructed to consume the study beverage at home daily for 12 weeks within 5 min of their first meal of the day. Half of a bottle (12.5 g KE) was consumed daily during week 1, and a full bottle (25 g KE) for the remainder of the study. The placebo used in the study was custom manufactured by BHB Therapeutics. In the placebo the KE was replaced with a non-ketogenic canola oil and matched for volume, appearance, flavor and calories. Nutritional facts for study beverages are shown in Supplementary Table 1. Beverages were provided as single serving bottles and labeled with the coded group allocation (i.e., Drink A or Drink B). The key linking the intervention (i.e., KE or PLA) to the coded allocation (i.e., Drink A or Drink B) was concealed from all personnel involved with the data collection, participant assessment, analysis, and interpretation to ensure they were blinded to the nature of the intervention assigned to participants. However study personnel were not blinded to each participant's coded group allocation.

2.4. Frailty indices

All frailty indices were evaluated by self-report during an interview in the screening and final visits as follows: Katz Index of Independence in Activities of Daily Living (Katz ADL) [38], Lawton Instrumental Activities of Daily Living (Lawton IADL) [39], and Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (CFS) ([40,41]).

2.5. Physical function

Physical function measures were collected at the baseline and final visits as follows: 1 repetition maximum (1-RM) leg press strength, 70 % of 1-RM leg press fatigability (both using Matrix Versa, Matrix Fitness, Cottage Grove, USA), Short Physical Performance Battery (SPPB), 4 m gait speed (as part of the SPPB), 6-minute walk test, grip strength, and actigraphy (FitBit Inspire 2, FitBit, San Francisco, USA). Participants were familiarized with the 1-RM equipment during the first kinetics visit.

2.5.1. One repetition maximum (1-RM) leg press strength

Participants were instructed on proper positioning and form on the seated leg press machine. They were positioned with their back straight and against the back rest, their feet on the footplate so that knee and hip angles were approximately 90°and the weight sled was adjusted accordingly. Foot position and sled position were replicated for both visits. The Rating of Perceived Exertion (RPE) Category-Ratio Scale was used to measure effort [42], RPE of 9–10 was the target. First, participants performed 5 - 6 unweighted repetitions as familiarization and to correct positioning or form. Then, participants completed a decreasing number of repetitions (starting repetitions = 6 - 7) at a set weight (starting weight = 50 % body weight) and rated their exertion after each set. Weight increased and number of repetitions decreased incrementally until the target RPE was achieved and the participant could only perform one repetition. Standardized rest was timed between each set and participants were verbally encouraged throughout the test.

2.5.2. Leg press fatigability

Leg press fatigability was performed after the 1-RM leg press after at least 5 min of rest. Positioning was replicated from the 1-RM leg press strength test. Weight was set to 70 % of the 1-RM and participants were instructed to complete as many repetitions as possible whilst maintaining proper form and a consistent self-selected cadence, without pausing at either end of the movement. Improper form was corrected once; the test was ended if a second correction was required. Exertion was rated using the RPE Category-Ratio Scale [42] immediately following completion. Participants were given verbal encouragement throughout the test.

2.5.3. Short physical performance battery (SPPB)

The SPPB includes several short tests to evaluate lower extremity function, including measures of standing balance, 4-meter gait speed, and ability to rise from a chair 5 times, and was administered according to standard instructions [43].

2.5.4. 6-Minute walk test (6MWT)

A 10-meter-long course was measured and marked with tape at each meter interval and a cone at each end. Participants were instructed to

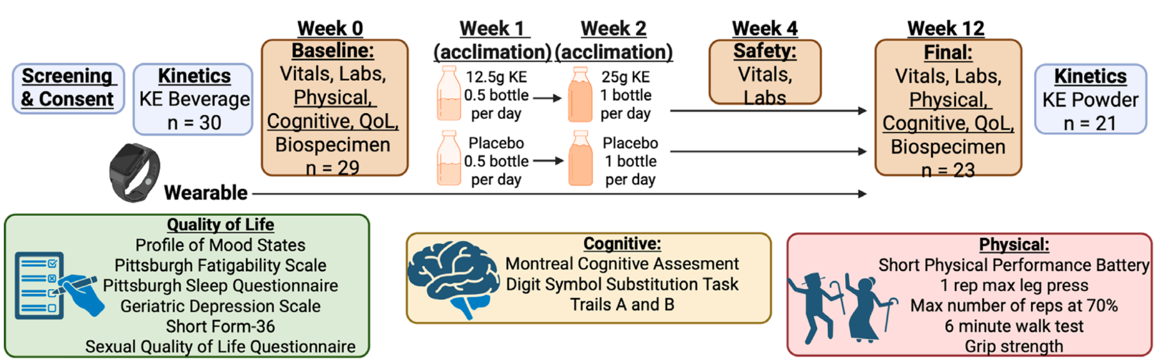

Fig. 1. Study schematic showing the schedule of visits and assessments described in this article. Abbreviations: KE, ketone ester; QoL, quality of life. Created using BioRender.com.

walk briskly from cone to cone, rounding the cones to invert direction, for 6 min. Participants were provided with standard encouragement throughout. Before walking began and immediately following completion, participants measured their exertion and breathing difficulty using the RPE Category-Ratio Scale and Modified Borg Dyspnea Scale [42]. After 6 min, participants stopped in place, and partial laps were recorded.

2.5.5. Grip strength

Grip strength was measured using a Jamar Hydraulic Hand Dynamometer (Jamar, Warrenville, IL, USA). Participants were sat in an armed chair and instructed to rest their arms on the arm rests with their elbow at a 90° angle. The dynamometer handgrip was adjusted to a setting comfortable for the participant, and a submaximal practice test was performed for familiarization. Three trials were performed per hand, and hands were alternated between trials. Measurements were recorded in kgs and rounded to the nearest 2 kg.

2.6. Health and fitness tracker

Wrist health and fitness trackers were dispensed at the kinetics visit at least 7 days before the baseline visit. Participants were instructed to wear the device throughout the 12-week trial, except for charging. The device was used to record heart rate, steps, sleep (total time asleep and sleep efficiency), and activity (sedentary, lightly active, moderately active, and very active minutes).

2.7. Cognitive function

Cognitive function measures were collected at the baseline and final visits as follows: Montreal Cognitive Assessment (MoCA) [44], Trails Test A and B [45], and Digit Symbol Substitution Test (DSST) ([46,47]). All cognitive function tests were conducted by trained study staff according to standard protocols, in a private, quiet room. The MoCA was scored by a study physician.

2.8. Quality of life

QoL measures were collected via self-rated questionnaire at the baseline and final visits as follows: Geriatric Depression Scale (GDS) [48], Pittsburgh Sleep Quality Index (PSQI) [49], 36-Item Short Form Health Survey (SF-36, Version 1, Rand) [50], Profile of Mood States—Short Form (POMS-SF) [51], Pittsburgh Fatigability Scale (PFS) [52]. All quality-of-life questionnaires were conducted on paper with pen in a private room. Questionnaires were scored by trained study staff.

2.9. General statistical design

Statistical analysis was carried out using R 4.3.1, except for actigraphy analysis, which was carried out in R and Python. Descriptive statistics (mean, standard deviation, sample size, minimum, and maximum) were calculated for pre- and post-intervention scores within each treatment group. Data were filtered to exclude any individual participant's endpoints with incomplete paired pre- and post-measurements. Assumptions for ANCOVA were tested, including linearity through scatter plots, homogeneity of variances with Levene's test, and homogeneity of regression slopes by examining interaction terms in a linear model. ANCOVA was performed using pre-intervention scores as a covariate to assess the treatment effect on post-intervention scores, with significance evaluated through F-tests.

2.10. Composite sof-it score

In an exploratory post-hoc analysis, we created a new composite outcome score for frailty intended for use in interventional trials, which we named SoF-IT (SOMMA Frailty — Interventional Trials). SoF-IT was inspired by the SOMMA Vigor to Frailty Score (V2F) of Newman et al [8], which was created using data from the Study of Muscle, Mobility and Aging (SOMMA) [53] to better capture the more vigorous end of a vigorous-to-frail spectrum in older adults.

SOMMA is a longitudinal cohort study of older adults aged ≥70 years (https://www.sommastudy.com), recruited between April 2019 and December 2021 at the University of Pittsburgh and Wake Forest University School of Medicine as previously described [53]. Briefly, individuals were eligible to participate in SOMMA if they were willing and able to complete a skeletal muscle biopsy and undergo magnetic resonance imaging and magnetic resonance spectroscopy. Individuals were excluded if they reported an inability to walk one-quarter of a mile or climb a flight of stairs; had BMI≥40 kg/m^2; had an active malignancy or dementia; or any medical contraindication to biopsy or magnetic resonance scanning. Finally, participants must have been able to complete the 400 m walk; those who appeared as they might not be able to complete the 400 m walk at the in-person screening visit completed a short distance walk (4 m) to ensure their walking speed as ≥0.6m/s. The protocol was reviewed and approved by the WIRB-Copernicus Group (WCG Institutional Review Board) and all participants gave informed consent.

The Newman et al. SOMMA V2F Score includes measures that map to the components of the frailty phenotype but have higher performance ceilings and are more sensitive to change than typical frailty phenotype components. The V2F score included both a 6-item version [endurance: weight-adjusted oxygen consumption at peak exercise (VO_2peak) [54]; sarcopenia: weight-adjusted skeletal muscle mass as measured by deuterated creatine (D3Cr) dilution [55]; muscle power: weight-adjusted leg press peak power [56]; cognitive speed: DSST [57]; fatigability: PFS Physical Score [52]; and sedentary time excluding time in bed from wrist-worn accelerometry [58]] and a 4-item parsimonious version comprising the same measures except D3Cr (sarcopenia) and sedentary time (fatigability). For clarity, here we refer to the original 6-item and parsimonious 4-item V2F variants as V2F-6 and V2F-4, respectively.

SoF-IT is inspired by the approach of V2F, particularly the parsimonious V2F-4, but adapted to use the measures available in our present study, which did not include D3Cr, VO_2peak, or leg press peak power. The nearest analogue in our data to the SOMMA measures for endurance (VO_2peak) and muscle power (leg press peak power) are 6MWT and 1RM leg press strength. These substitutions, or close analogues (400 M gait speed instead of 6MWT), are also available in SOMMA, enabling us to analyze the performance of this adaptation using SOMMA data, particularly focusing on the substitution of 6MWT/400MGS for VO_2peak (Supplementary Table 2). The SoF-IT score includes the same four domains as the parsimonious V2F-4 using measures that are analogous to those of V2F-4: leg strength (1RM leg press weight), endurance (400MGS in SOMMA data; 6MWT distance in our data), cognitive speed (DSST) and perceived Fatigability (PFS Physical Score). Given the strong association of VO_2peak alone with clinical outcomes, we also tested whether including it in addition to 400MGS/6MWT as endurance measures improved predictive power (SoF-IT plus VO_2peak).

As SoF-IT is intended for use as an outcome measure in the follow-up TAKEOFF randomized controlled trial (described in the Discussion), we first selected the subset of SOMMA participants with a baseline 4 m gait speed between 0.6–1.0 m/s, aligning with the proposed TAKEOFF inclusion criteria ($N = 441$ of the full SOMMA cohort $N = 879$ in the November 2024 data release, data available at https://sommaonline.ucsf.edu), then selected those who had complete baseline data for calculating both the V2F-4 and SoF-IT composite scores ($N = 369$) as these were central to the analysis goals. This subcohort of 369 formed the primary analytic sample (Supplementary Table 3). We calculated sex-specific pairwise Pearson correlations between each measure included in at least one of the composite scores (V2F-4, V2F-6, SoF-IT, and SoF-IT plus VO_2peak). For each individual, we calculated each composite score as the sum of the sex-specific z-scores for each component measure, with the z-scores for PFS Physical Score and Sedentary Time reversed so that lower values contributed to a higher composite score for these two measures. Longidtudinal changes in SoF-IT calculated in the SOMMA cohort were used to determine the sample size needed for the follow-up TAKEOFF randomized controlled trial; based on detection of a 0.4 SD difference in the mean 3-year change in the normally distributed, continuous outcome between treatment and placebo groups, accounting for 10 % dropout.

The approach of So-FIT differs from the method used by Newman et al. to create V2F. In V2F, sex-specific tertiles were assigned component scores of 0–2, which were then summed to create a discrete 0–12 total score. We reasoned that an interventional trial requires a fully continuous outcome measure to more sensitively detect differences, which a sum of z-scores provides. Because SoF-IT was designed with continuous outcomes in mind, we applied the same method for integrating component measures when creating V2F-4 and V2F-6 in this analysis, allowing for a fair comparison of the substituted measures between the composite scores. It is also important to note that SoF-IT and V2F are oriented in opposite directions. V2F, like classical frailty scores, assigns higher scores to those that are more frail (worse performance). In contrast, we oriented SoF-IT so that higher scores reflect greater vigor, while lower scores indicate greater frailty, making the interpretation of higher performance more intuitive.

In the baseline SOMMA cohort, we assessed sex-stratified cross-sectional associations between each score and age using linear regression, scatter plots, and Pearson correlations. Because the Mobility Assessment Tool-Short Form (MAT-sf)[59] is a validated marker of major mobility disability risk and was used as an outcome in creating the original V2F scores, we also examined it as an outcome to test the predictive power of each individual measure and of the composite scores using sex-stratified unadjusted Spearman correlations. Partial Spearman correlations were obtained by further adjusting for age, height, and weight. For longitudinal analysis, we calculated the SoF-IT score at the SOMMA 36-month follow-up visit using the same z-score methodology as at baseline, applying the baseline means and standard deviations to ensure comparability across time points. Change in z-scores for individual measures and for the SoF-IT score were summarized (mean $\pm$ SD) and annualized mean change was calculated. Then, SoF-IT was calculated using data from the current study. A simple linear regression was calculated for the baseline SoF-IT score vs. age and the pre- to post-change in So-FIT score vs. age in the current study. For all SOMMA analyses we used the November 2024 release of the SOMMA data and performed analyses in R (version 4.4.0).

2.11. Health and fitness tracker data analysis

Health and fitness tracker data was analyzed seperately for each variable of interest, data was compiled for all per protocol participants and duplicates were removed. Heart rate data was processed by filtering out low confidence measurements (confidence < 2). We determined sleep timing through the Fitbit's sleep staging, and mapped these time windows with the heart rate data to determine sleeping heart rate. We then calculated the sleeping heart rate (SHR) to be the mean value over each night-time sleep period for each individual. Time asleep was determined by the Ftibit's sleep staging, excluding all daytime naps (one dataset was missing). Minutes of sedentary, light, moderate and vigorous activity was determined through Fitbit's Active Minutes function that combines heart rate and movement data. Total minutes of each activity type per day was calculated by adding all data points per date. All data was analyzed by plotting the mean of each value per allocation, with bands generated using the standard error. Additional figures plotted each individual's time course with an aggregate mean value per allocation. These data were analyzed using R 4.3.1 and Python.

3. Results

3.1. Participants and completion

A total of 30 participants were randomized (mean age (range), Male $n = 15$; age = 76.5 y (65 – 90); mean BMI (range) = 25.2 (19.9 – 32.7); median Katz ADL (range) = 6 (5–6), median Lawton IADL (range) = 8 (8–8), median CSHA Frailty Score (range)= 1 (1 – 3)). Full participant anthropometric characteristics and frailty indices at baseline are shown in **Supplementary Table 4**.

Participant disposition is shown in a CONSORT diagram (**Supplementary Figure 1**). Briefly, 23 participants completed the 12-week protocol (the per-protocol population), 1 participant completed the acute kinetics visit but did not start the main study, without giving a reason, and 6 participants dropped out after Day 0 and did not complete the full protocol; repeat functional data was not available for participants who did not start or finish the study. Adherence with consumption of the study products for the per protocol population was high, with $n =$ 15 reporting 100 % adherence and a range of 94 – 99 % for the remaining 8 participants who completed the study, based on study logs and returned bottles. Blinding of participants was assessed by survey at the end of the study and 14/29 participants responded. Of those who responded, 7 correctly guessed their intervention group (50 % of respondants), indicating blinding was achieved.

3.2. Physical function

There were no signigicant differences between intervention groups in the post intervention physical function outcomes (Table 1): grip strength (KE = 32.8 (12.3) kg; PLA = 35.7 (14.8) kg, $p = 0.457$), Short Physical Performance Battery (KE = 10.6 (1.0); PLA = 10.7 (1.6), $p =$ 0.099) or leg press reps to fatigue at 70 % of maximal weight (KE = 26.2 (6.6); PLA = 40.4 (21.2), $p = 0.759$).

3.3. Cognitive function

There were no significant differences between intervention groups in the longitudinal change in the cognitive function outcomes (Table 1): Trails A (KE = −33.3 (7.3) s; PLA = 35.5 (11.2) s, $p = 0.403$), Trails B (KE = 81.3 (34.6) s; PLA = 68.7 (20.7) s, $p = 0.942$) or Montreal Cognitive Assessment (KE = 28.0 (1.7); PLA = 27.6 (1.9), $p = 0.244$).

3.4. Quality of life

There were no differences between study groups in the longitudinal change in any of the subdomains or global summary scores (where appropriate) of the Profile of Mood States, SF-36, Geriatric Depression Scale, Pittsburgh Sleep Quality Index (PSQI) or the Pittsburgh Fatigability Scale (**Supplementary Table 5**).

3.5. Health and fitness tracker

We observed a qualitative difference in sleeping heart rate (SHR, the mean heart rate during one sleep period; see **Methods**) trends between the KE and PLA groups, with the KE arm showing a sustained elevation in SHR (Fig. 2**A**). We did not see any differences in between groups trend in sleep minutes (Fig. 2**B**). There were no differences in steps (Fig. 2**C**) or total active minutes (Fig. 2**D**) between groups. For all measures, the small effect size of the cohort and the high inter-individual variability prohibited any meaningful quantification of the difference between the two arms.

3.6. SoF-IT exploratory composite outcome measure

For an exploratory post-hoc analysis on the effect of the ketone ester on overall function in frailty, we created SoF-IT, the SOMMA Frailty for

Table 1
Changes in physical and cognitive function outcomes from pre- to post- 12 weeks of daily consumption of ketone ester or placebo in $n = 23$ healthy older adults. **Abbreviations**: 1RM; 1-rep max, KE, ketone ester; PLA, placebo; MoCA, Montreal Cognitive Assessment; SPPB, Short Physical Performance Battery.* rows show Min/Max for Pre and Post data, or Lower and Upper 95 % CI for Change data.

		Pre		Post		Change		ANOCVOA Results			
		KE	PLA	KE	PLA	KE	PLA	SumSq	Df	F value	P value
PHYSICAL FUNCTION											
SPPB Score	Mean	10.42	10.36	10.64	10.73	0.00	0.36	0.57	1	3.013	0.099
	SD	1.24	1.86	1.03	1.62	0.45	0.50				
	Min / Lower 95 % CI*	8	6	8	7	−0.3	0.025				
	Max / Upper 95 % CI*	12	12	12	12	0.3	0.703				
	Median	11	11	11	11	0	0				
Reps at 70 % of 1RM	Mean	28.67	39.73	26.20	40.40	−0.70	−1.10	3.88	1	0.097	0.759
	SD	8.97	21.94	6.61	21.77	7.30	5.15				
	Min / Lower 95 % CI*	20	20	13	16	−5.92	−4.79				
	Max / Upper 95 % CI*	50	89	35	84	4.525	2.586				
	Median	25.5	30	26.5	35.5	0	0.5				
Grip Strength (kgs)	Mean	33.75	35.09	32.75	35.73	−1.00	0.64	17.14	1	0.575	0.457
	SD	12.90	13.90	12.31	14.78	4.82	5.99				
	Min / Lower 95 % CI*	12	11	17	12	−4.07	−3.39				
	Max / Upper 95 % CI*	50	54	56	60	2.065	4.659				
	Median	36	38	32	40	−1	0				
COGNITIVE FUNCTION											
MoCA Score	Mean	26.33	27.55	28.00	27.64	1.67	0.09	3.86	1	1.444	0.244
	SD	2.57	1.37	1.71	1.91	1.97	2.07				
	Min / Lower 95 % CI*	22	25	25	25	0.415	−1.3				
	Max / Upper 95 % CI*	30	30	30	30	2.918	1.483				
	Median	26.5	27	28.5	29	1.5	0				
Trails A Time (s)	Mean	39.08	37.00	33.25	35.36	−5.83	−1.64	44.85	1	0.729	0.403
	SD	12.66	19.89	7.34	11.24	11.77	15.07				
	Min / Lower 95 % CI*	21	21	23	21	−13.3	−11.8				
	Max / Upper 95 % CI*	67	92	52	57	1.644	8.491				
	Median	38.5	31	32	35	−4	0				
Trails B Time (s)	Mean	88.92	70.09	81.25	68.73	−7.67	−1.36	2.79	1	0.005	0.942
	SD	33.84	23.45	34.58	20.73	30.49	16.31				
	Min / Lower 95 % CI*	31	39	28	36	−27	−12.3				
	Max / Upper 95 % CI*	154	106	134	94	11.7	9.59				
	Median	81.5	62	71	77	1	−3				

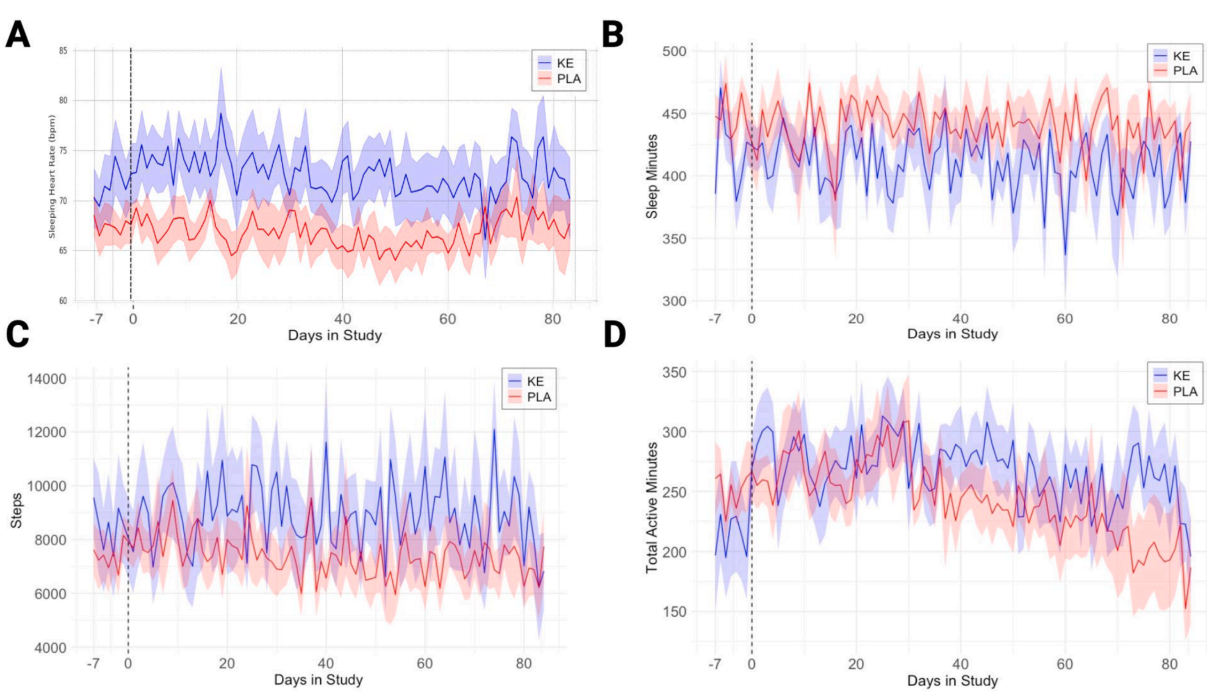

Fig. 2. Data from wearable health and fitness trackers worn by study participants who completed the 12-week protocol, showing mean and standard error for A) sleeping heart rate, B) sleep minutes, C) daily steps, D) total active minutes for 7 days before baseline visit, and for the remaining 12 weeks of the study. Abbreviations: KE, ketone ester; PLA, placebo.

Interventional Trials score, inspired by the parsimonious 4-item V2F score developed using SOMMA data by Newman et al. SoF-IT was designed to be more suitable as a trial outcome measure, being fully continuous (the mean z-score of its components rather than a discrete integer scale) and oriented so that higher scores are better, using analagous measures that are present in our data. V2F-4 comprises measures of edurance (weight-adjusted VO_2peak), muscle power (weight-adjusted leg press peak power), speed (DSST), and fatigability (PFS Physical Score). The nearest analogue to VO_2peak in our data is 6MWT time, and to leg press peak power is 1RM leg press strength. These substitutions, or close analogues (400 M gait speed [400 M GS] instead of 6MWT), exist in SOMMA data. This permitted us to use SOMMA data to determine the performance characteristics of SoF-IT, particularly focusing on the substitition of VO_2peak. First, we analyzed the pairwise Pearson correlations between variables, and found that 400 M GS was relatively highly correlated with VO_2peak ($r = 0.40$ for men, $r = 0.41$ for women) (**Supplementary Figure 2**). To test the predictive power of SoF-IT with or without including VO_2peak, we used MAT-sf as a outcome that represents disability in frailty. We calculated Spearman correlations between MAT-sf and each individual measure, SoF-IT, and SoF-IT plus VO_2peak. SoF-IT and SoF-IT plus VO_2peak were very highly correlated among individual participants (**Supplementary Figure 3**), displayed similar associations with MAT-sf (Table 2 and **Supplementary Figure 4**), and also displayed similar associations with age (**Supplementary Figure 5**), all suggesting that VO_2peak was not required in SoF-IT. Finally, we used the longitudinal change in SoF-IT score over 3 years in SOMMA participants to conduct an exploratory power analysis for the potential use of this composite as a clinical trial outcome (**Supplementary Table 6**). We found that detecting a medium effect size (0.4 standard deviations of the mean 3-year longitudinal change in the composite outcome) of an intervention would require 72 completing participants per arm. Therefore, our final SoF-IT score for quantifying vigor in frailty comprised 1RM leg press, 6MWT, DSST, and PFS Physical Score, and we analyzed this in data from the current study alongside our prespecified frailty index outcomes.

Shown are the observed Spearman and partial Spearman correlations, with 95 % confidence intervals estimated via bootstrapping. Partial Spearman correlations were adjusted for age, height, and weight (weight excluded for weight-adjusted measures). Abbreviations: 1RM, 1 repetition maximum; DSST, Digit Symbol Substitution Test; PFS, Pittsburgh Fatigability Scale; V2F, Vigor to Frailty Score; SoF-IT, SOMMA Frailty — Interventional Trials.

3.7. Frailty Indicies and frailty-vigor composite

No participants experienced a change in Katz ADL or Lawton IADL scores after the intervention. The CSHA Frailty Score was changed by one point in $n = 3$ participants (PLA = 2, one increase, one decrease, KE = 1, increase). There were no significant post-intervention differences, between groups in any of the individual items included in the composite score (Fig. 3**A-D)**: 1 rep max leg pres (KE = 153.7 (57.4) kg, PLA = 163.6 (41.9) kg, $p = 0.680$), Six Minute Walk Test (KE = 487.8 (57.4) m; PLA = 470.5 (70.0) m, $p = 0.461$), Digit Symbol Substitution Task (correct) (KE = 54.7 (11.4); PLA = 56.7 (5.6), $p = 0.693$), Pittsburgh Fatigability Scale (Physical) (KE = 8.45 (6.9); PLA = 11 (8.9), $p = 0.352$). When the items were converted to z-scores and combined into the SoF-IT composite outcome, there was no significant difference between groups post intervention (KE = 0.26 (0.40); PLA = 0.26 (0.58), $p = 0.824$, Fig. 3**E**). The baseline SoF-IT score trended lower (worse) with increasing age ($F = 2.037$; df = 1, 27; $P = 0.165$; $R^2 = 0.07$; Fig. 3**F**), and the change in SoF-IT score over the 12 week intervention was not related to the age of the participant ($F = 0.002$; df = 1, 21; $P = 0.967$; $R^2 = 8.26 \times 10^{-5}$); Fig. 3**G**).

4. Discussion

The main finding of this exploratory analysis of the effects of 12 weeks of KE consumption on functional outcomes in a pilot study of healthy older adults was that, in contrast to our hypothesis, there were no statistically significant effects of the KE intervention on individual items scoring physical or cognitive function, activity, resting heart rate or quality of life; or a composite score designed to capture the vigor-frailty continuum. However, this tolerability-focused pilot randomized controlled trial was not powered for functional outcomes, and enrolled non-frail, healthy older adults who were relatively high-functioning. As an example of an early-stage geroscience clinical trial, we discuss the rationale for intervention-specific outcome measures as well as the selection of common measures that broadly capture function in aging and

Table 2
Spearman correlations between outcomes and MAT-sf in the subset of SOMMA participants with gait speed 0.6–1.0 m/s.

Outcome	*Women*			*Men*		
	N	*Unadjusted*	*Adjusted*	*N*	*Unadjusted*	*Adjusted*
VO_2peak [Weight Adj]	222	0.386 (0.261, 0.498)	0.376 (0.251, 0.49)	132	0.42 (0.257, 0.555)	0.382 (0.221, 0.527)
400 M Gait Speed	222	0.392 (0.266, 0.509)	0.305 (0.177, 0.426)	132	0.483 (0.341, 0.619)	0.459 (0.309, 0.588)
Leg Power [Weight Adj]	222	0.413 (0.29, 0.514)	0.369 (0.241, 0.484)	132	0.303 (0.134, 0.452)	0.218 (0.04, 0.388)
1RM Leg Press	222	0.313 (0.185, 0.434)	0.303 (0.173, 0.422)	132	0.223 (0.055, 0.376)	0.219 (0.048, 0.38)
Muscle Mass [Weight Adj]	209	0.259 (0.116, 0.388)	0.254 (0.12, 0.383)	126	0.401 (0.232, 0.536)	0.349 (0.179, 0.504)
DSST	222	0.14 (0.007, 0.264)	0.059 (−0.07, 0.189)	132	0.203 (0.043, 0.363)	0.144 (−0.032, 0.312)
Sedentary Time	181	−0.052 (−0.192, 0.102)	−0.023 (−0.181, 0.137)	116	−0.125 (−0.319, 0.072)	−0.062 (−0.252, 0.134)
PFS Physical Score	222	−0.352 (−0.462, −0.236)	−0.309 (−0.425, −0.189)	132	−0.394 (−0.52, −0.244)	−0.374 (−0.516, −0.21)
V2F-6	174	0.488 (0.367, 0.596)	0.407 (0.272, 0.527)	113	0.489 (0.317, 0.629)	0.374 (0.185, 0.549)
V2F-4	222	0.502 (0.389, 0.595)	0.387 (0.269, 0.498)	132	0.485 (0.325, 0.615)	0.383 (0.214, 0.533)
SoF-IT plus VO_2peak	222	0.546 (0.44, 0.636)	0.44 (0.325, 0.546)	132	0.522 (0.377, 0.649)	0.470 (0.316, 0.602)
SoF-IT (without VO_2peak)	222	0.519 (0.412, 0.607)	0.435 (0.317, 0.545)	132	0.518 (0.375, 0.646)	0.484 (0.329, 0.614)

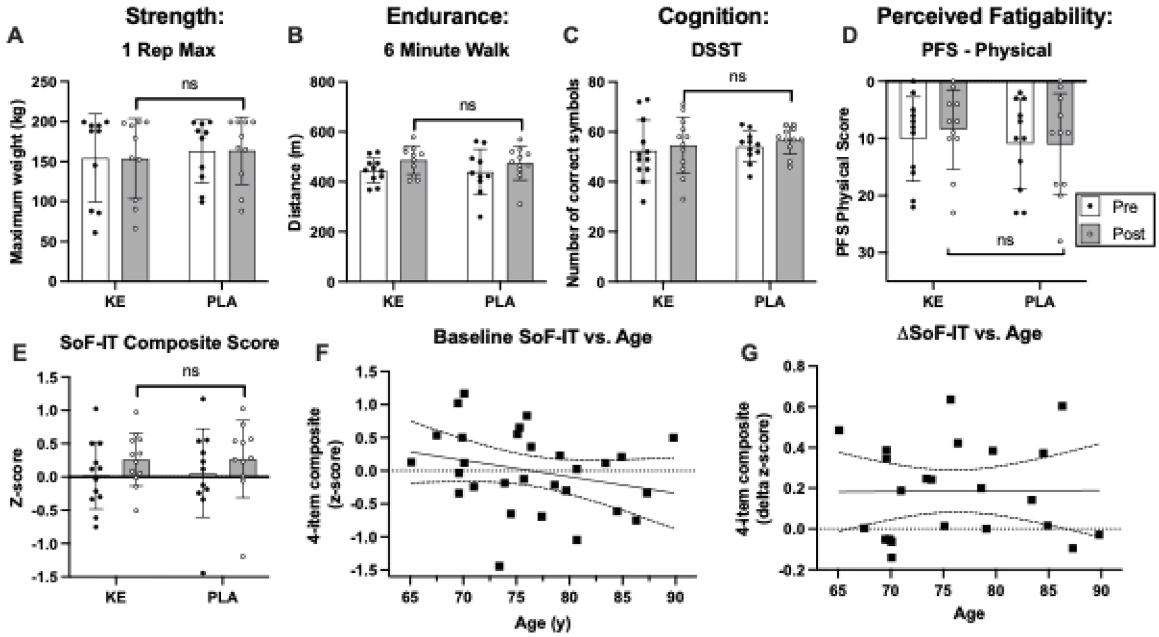

Fig. 3. Pre and post data in four functional outcomes following 12 weeks of daily consumption of ketone ester or placebo in $n = 23$ healthy older adult. **A:** 1 repetition maximum leg press, **B:** Six Minute Walk Test, **C:** Digit Symbol Substitution Test, **D** Pittsburgh Fatigability Scale - Physical Score. Change in the SoF-IT composite z-score resulting from the combination of these four outcomes (**E**), and characteristics of the SoF-IT score (**F,G**). **Abreviations**: KE, ketone ester; PLA, placebo; 1RM, 1 repetition maximum; DSST, Digit Symbol Substitution Test; PFS, Pittsburgh Fatigability Scale. Y-axes are oriented so higher is better in all panels.

represent a common toolbox for geroscience clinical trials ([60,61]).

Ketone bodies are expected to benefit physical function via multiple distinct mechanisms. Firstly, ketones might act as an alternative energy substrate that directly improved working muscle efficiency [12]. Secondly, there is a known acute effect of exogenous ketones on cardiac output and myocardial blood flow [62], which may indirectly facilitate physical function. Thirdly, ketones are known to be anticatabolic and may increase muscle protein synthesis and decrease muscle protein breakdown in the context of inflammatory stress [63,64], feasibly such as that seen during age-related or frailty-related inflammation, which could preserve or increase muscle mass and function with longer term use. Some, but not all, studies that administered exogenous ketones to young athletes immediately prior to endurance exercise found functional improvements ([27,28]). The only study of physical function with longer term exogenous ketone consumption found that KE could mitigate the performance decline and hormonal shifts triggered by 'over--reaching' endurance training in young adults [65]. Clinical evidence for a muscle sparing function of exogenous ketones is limited. Two studies used ketone infusions in healthy young men and found attenuated leucine oxidation and increased muscle protein synthesis [63], and a decreased muscle protein breakdown in the context of an inflammatory stressor [64]. A further study gave a ketone ester drink and found lowered post exercise AMPK phosphorylation and higher mTORC1 activation, suggesting greater protein synthetic potential [66]. None of these studies investigated functional changes in muscle strength.

While this study is part of a program to test the long-term effects of chronic daily use of KE in frailty, these data from athletes suggest that other approaches might be fruitful to pursue in parallel. For example, the greatest performance gains might be acutely during ketosis, perhaps relevant to scheduling the use of ketones as rehabilitation or exercise adjuvants. A concurrent stressor might increase the effects from ketones. Heart failure or other medical problems associated with energetic stress might be seen as examples of such stressors, but a more benign stressor might be resistance training. A parallel can be drawn with dietary protein supplementation, which alone does not consistently improve muscle mass and function in older adults [67], but increases the efficacy of resistance training compared to a placebo ([68,69]). Future work could address combinations of ketones, protein and resistance exercise to determine if there any synergistic effects of these strategies acutely and long-term.

The rationale for an effect of exogenous ketones on cognitive function is also multifactorial. Firstly, ketones act as an energy source in the brain and can mitigate the deficit in brain energetic needs that arises during age-related declines in glucose metabolism [70]. Secondly, ketones increase brain blood flow which would improve delivery of substrates and oxygen ([30,71]). Thirdly, ketones can trigger the release of neurotrophins, particularly brain derived neurotrophic factor (BDNF) [72]. Key clinical examples include a 12-month study of two 15 g daily servings of a ketogenic medium chain triglyceride, which found improved brain energy metabolism and cognition in adults with mild cognitive impairment [73], and a 14-day study of three 12 g daily servings of a ketone ester which found improved cerebral blood flow and elements of cognition in obese adults [30]. As there is a strong biological mechanism and both preclinical and clinical support for a neurocognitive effect of exogenous ketones, outcome measures relating to brain physiology and function will remain of keen interest in future work.

Whilst they are many steps removed from the underlying biological mechanisms and likely are influenced by multiple mechanisms, subjective self-assessment of quality of life is increasingly recognized as an important outcome in interventional geroscience trials that can distinguish functionally healthy and unhealthy aging [74]. To this end, we included a range of validated quality of life questionnaires, notably the SF-36, which has been proposed as a leading quality of life assessment tool [74].

We were inspired by the SOMMA Vigor to Frailty score to create and pilot the feasibility of a composite outcome measure that more might broadly capture and finely quantify the more vigorous end of the frailty phenotype in a clinical trial, compared to individual performance measurements or scales with few quantized steps. It is increasingly appreciated that many gerotherapeutic strategies, such as BO-BD, could have pleiotropic and potentially modest effects across a variety of individual organ systems (e.g., muscle strength, endurance, cognitive function) but have a clinically important overall effect on the whole person due to these integrated, potentially synergistic, multi-system effects [9]. It should be noted that the use of a composite is not without downsides, as a study using a composite score might fail to capture substantial changes within just one domain if not statistically powered for that endpoint alone. Composite outcomes are increasingly used in geroscience focused studies and range from composites of death or disease onset (e.g., a multi-disease composite endpoint for the planned Targeting Aging with Metformin trial – TAME), of combined blood and clinical biomarkers (e.g., in SGLT-2 trials) or of functional endpoints (e.g., Intrinsic Capacity). Composite cardiovascular outcomes (e.g. Major Adverse Cardiovascular Events, MACE) are widely used in clinical trials [75].

Given the frailty expertise of the SOMMA investigators, the size and richness of the SOMMA dataset, and the similarity of the SOMMA population to that we will target in a larger follow-up study, we created SoF-IT using as inspiration the SOMMA-derived Vigor to Frailty composite score. SoF-IT substitutes pragmatic and highly correlated measures: 1RM leg press weight rather than leg power for lower limb function and 6MWT distance instead of a direct VO_2peak measurement [76] for endurance. SoF-IT combines its 4 items in a fully-continuous, study-normalized manner (mean of z-scores calculated from trial baseline data) and is oriented so that improved performance results in higher scores – features we believe will be useful for interventional trials. We used SOMMA data to test So-FIT, and, given the powerful predictive value of VO_2peak for function and disability, to show that the composite would indeed be useful even without including VO_2peak. While SoF-IT specifically has not been validated in external longitudinal studies or other clinical trials, there are many examples of adapting composite frailty indices by substituting analogous measurements, such as the adaptation of a frailty index developed in the Study of Osteoporotic Fractures to the Lifestyle Interventions and Independence for Elders trial [77], and the adaptation of the Fried Frailty Index from the Cardiovascular Health Study to the Aspirin in Reducing Events in the Elderly study [78]. As we expected, baseline SoF-IT scores in our pilot trial showed a trend of being lower (worse) with higher age even in our small and functionally independent population. We did not see any difference in SoF-IT score between intervention groups, but importantly we did not see an age-effect on change in SoF-IT score. Overall, the data from this pilot trial of KE in older adults provided an interesting opportunity to explore the implementation of a frailty focused composite outcome which might have an increased likelihood of detecting any KE driven effects in future interventional trials.

The strengths of this trial include the free-living, pragmatic-inspired design (e.g. participants were instructed to maintain their usual diet and exercise habits) being highly relevant for future uses of KE as a geroscience intervention, the high adherence observed, the equal enrollment of men and women, the average age (76 y) being well over the lower limit (65 y), and the close matching achieved between the KE and PLA beverage, although the findings should be interpreted with the context that the lipid-based PLA was not truly 'inert' and thus does not offer a comparison to 'no intervention'.

There were several limitations of this study, many of which were inherent to its design as a "first in older adults" early-stage geroscience clinical trial [9], and that we plan to address in our follow-up study. The primary goals of this pilot study were to fill key gaps in kinetics, tolerability, and safety in older adults that would unlock the ability to design function-focused clinical trials with KE in older adults. The 12-week study duration was selected conservatively due to the longest prior study of any KE in any population being only 4 weeks, and the unknown feasibility and safety of the intervention in older adults. However, 12 weeks is relatively short to expect detectable changes in functional outcomes which often take months or years to manifest. Furthermore, whilst the 25 g once daily serving size was selected based on the previous studies of BO-BD in young adults, and the absence of any data on any dose of KE in older adults, studies of other KE in young adults have used servings of up to 75 g daily split across three doses. Further increasing blood ketone concentrations or overall exposure time with larger or more frequent dosing may increase response. It is also important to note that several types of exogenous ketones and KEs exist, with known differences in physical characteristics and possibly also functional effects, therefore our results using BO-BD may not apply to all types of exogenous ketones. In addition, the optimal outcome measures for early-stage geroscience clinical trials have not been defined. There is clear advantage to using measures that are well validated and commonly used in large longitudinal studies, though some of these may be best suited to much longer multi-year studies. Many of these outcomes also have considerable inter-individual variability across testing occasions, as well as training effects that limit repetition. Novel functional biomarkers may help bridge the gap between target engagement or kinetic outcomes (e.g. blood BHB levels) and clinically relevant, patient-centered, long-term functional outcomes. Notably, we chose to conduct all functional testing on days without KE consumption to focus on stable, sustained effects of KE rather than transient performance associated with acute ketosis (and to avoid confounding from the sequencing of study activities with respect to the peak of post-ingestion blood BHB concentrations). However, it is possible that ongoing ketosis is required for performance gains. Specific investigation will be required to answer this important question. Finally, the small sample size and relatively healthy and fit population, both determined by the primary study goals, were major limitations in our ability to detect a difference in these exploratory functional outcomes. It is possible that the lack of detectable effects in this study was the result of these methodological limitation and/or type II error from the limited sample size. We expect that a larger sample size, and a study population selected for increased vulnerability or with existing mild functional limitations, along with a longer or more intensive intervention, would together increase the likelihood of a detectable positive effect. These elements are all incorporated into the design of the larger, function-focused, follow-up study (TAKEOFF, NCT06645847).

In conclusion, consuming the KE, BO-BD, daily for 12 weeks did not impact exploratory quality of life, physical or cognitive functional outcomes in this pilot cohort of healthy older adults. Future work using a larger cohort of pre-frail and early frail older adults will seek to definitively test if the hypothesized benefits of exogenous ketones will be detectable against a functionally limited baseline.

4.1. Sources of funding, author declarations and conflict management

Funding for the study was provided by philanthropic donations from Dr. James B. Johnson and from members of the Buck Institute Impact Circle. Dr. Johnson assisted with conceptualization of the study and reviewed this manuscript but has no further role in study design, management, data collection, analysis, interpretation of data, decision to submit publications, or writing of publications. The Buck Institute Impact Circle had no role in conceptualization, study design, management, data collection, analysis, interpretation of data, decision to submit publications, review, or writing of publications.

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The KE intervention was provided gratis by BHB Therapeutics Ltd (Ireland). BHB Therapeutics also arranged for manufacture of the matched placebo, paid for by study funds. BHB Therapeutics (Ireland) markets formulated KE beverages to consumers. BHB Therapeutics (Ireland) provided no funding for the study, and had no role in the design, management, data collection, analysis, interpretation of data, decision to submit publications, or writing of publications.

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Author declarations and conflict management

The Buck Institute holds shares in BHB Therapeutics (Ireland) and Selah Therapeutics. B.J.S. has stock in H.V.M.N Inc, and stock options in Selah Therapeutics Ltd, BHB Therapeutics (Ireland) Ltd., and Juvenescence Ltd. J.C.N. has stock options in Selah Therapeutics Ltd and BHB Therapeutics (Ireland) Ltd. J.C.N and B.J.S. are inventors on patents related to the use of ketone bodies that are assigned to The Buck Institute. Individual and institutional conflict management plans were developed and approved by the Buck Institute and submitted to the reviewing IRB. Actions and decisions important to participant safety and study integrity were carried out by 'honest brokers' with no potential financial conflict. Participant consent was obtained by licensed registered nurses (L.A and W.S.M) who have no financial conflict. Decisions on participant enrollment, continuation, and were made by independent medical officers (J.M and M.Y) unaffiliated with Buck Institute and with no financial conflict. All other authors have no conflicts to report.

Data availability statement

The data presented here will be made available upon reasonable request from the corresponding author and in accordance with intellectual property considerations. Data from SOMMA are publicly available (https://sommaonline.ucsf.edu).

CRediT authorship contribution statement

Brianna J Stubbs: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft. **Elizabeth B Stephens:** Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **Tyler Mansfield:** Data curation, Formal analysis, Investigation, Writing – review & editing, Visualization. **Chatura Senadheera:** Data curation, Investigation, Writing – review & editing. **Stephanie Roa Diaz:** Data curation, Investigation, Writing – review & editing. **Sawyer Peralta:** Data curation, Investigation, Writing – review & editing. **Laura Alexander:** Investigation, Writing – review & editing. **Wendie Silverman-Martin:** Investigation, Writing – review & editing. **Jamie Kurtzig:** Data curation, Formal analysis, Writing – review & editing. **B.Ashen Fernando:** Formal analysis, Writing – review & editing, Visualization. **Thelma Y Garcia:** Project administration, Supervision, Writing – review & editing. **Michi Yukawa:** Investigation, Writing – review & editing. **Jennifer Morris:** Investigation, Writing – review & editing. **James T Yurkovich:** Formal analysis, Writing – review & editing. **Anne B. Newman:** Conceptualization, Writing – review & editing. **James B Johnson:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Peggy M. Cawthon:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **John C Newman:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2025.100106.

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