Effects of nicotinamide riboside on NAD+ levels, cognition, and symptom recovery in long-COVID: a randomized controlled trial

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Summary

Background Long-COVID often involves cognitive difficulties, immune dysregulation, and mitochondrial dysfunction. Studies suggest nicotinamide adenine dinucleotide (NAD+) precursors like nicotinamide riboside (NR) may reduce inflammation and support mitochondrial and neurological function. This double-blind, placebo (PBO)-controlled clinical trial with a placebo lead-in phase evaluated the effects of NR (2000 mg/day) on NAD+ and changes in cognitive and long-COVID symptoms.

Methods This was a 24-week, double-blind, placebo-controlled trial at a single center in Boston, USA, between August 2021 and September 2023. 58 community-dwelling participants with long-COVID were randomized 2:1 to the NR-NR group (NR for 20 weeks) or the PBO-NR group (PBO for 10 weeks, followed by NR for 10 weeks). The primary outcome was cognition, assessed using the Everyday Cognition scale (ECog), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Trail Making Test-B (TMT-B). Secondary outcomes included the Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Pittsburgh Sleep Quality Index. We conducted a mixed model for repeated measures to compare groups, then post-hoc and unadjusted for multiplicity, combined both groups to explore changes from baseline after 10 weeks of NR. This trial was registered with ClinicalTrials.gov (NCT04809974) in 2021.

Findings 37 participants (64%) were assigned to NR-NR, and 21 participants (36%) to PBO-NR. There was a 32.4% and 51.4% dropout in the NR-NR group at 10 weeks and 20 weeks, respectively, vs. 14.3% dropout at each timepoint in the PBO-NR group. In the NR-NR group, NAD+ levels increased by 2.6- to 3.1-fold after 5–10 weeks of supplementation, respectively, and remained elevated at 20 weeks. In the PBO-NR group, NAD+ levels remained close to baseline (0.93- to 1.0-fold change, 95% CI: 0.5–1.4) during the initial 5 and 10 weeks of PBO. After switching to NR, levels rose to a 2.6-fold and 2.1-fold increase after 5 and 10 weeks of NR, respectively. No significant between-group differences were observed for cognitive outcomes (ECog, RBANS, TMT-B; p-values = 0.47–0.74). There were no significant differences in fatigue severity (p = 0.59), sleep quality p = 0.69), and symptoms of anxiety (p = 0.84) or depression (p = 0.20) between PBO and NR groups. In post-hoc exploratory analysis, examining within-group changes during 5 and 10 weeks of NR intake by grouping all participants during the first 10 weeks of the NR phase, there were significant differences from baseline after 10 weeks of NR in executive functioning, fatigue severity, sleep quality, and symptoms of depression (compared with no significant changes in TMT-B, FSS, PSQI, BAI, or BDI scores during the PBO phase). One serious adverse event was reported, deemed unrelated to the study drug or trial.

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Interpretation In long-COVID, NR increased NAD+ within 5 weeks but did not significantly improve cognition, fatigue, sleep, or mood vs. PBO. Exploratory analyses suggested within-group benefits after 10 weeks of NR, supporting the need for larger trials.

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Keywords: PASC; SARS-CoV-2; Fatigue; Depression; Sleep; Nicotinamide adenine dinucleotide

Research in context

Evidence before this study

We searched PubMed for articles containing information on the effect of Nicotinamide Riboside (NR) after acute coronaviruses SARS-CoV-2 infection, using the keywords: ("SARS-CoV-2" OR "SARS-CoV" OR "COVID-19" OR "COVID" OR "Long COVID" OR "PASC") AND ("Nicotinamide" OR "Nicotinamide Riboside" OR "NR" OR "nicotinamide adenine dinucleotide" OR "NAD" or "NAD+") AND ("clinical trial" OR "randomized controlled trial" OR "RCT" OR "trial" OR "treatment" OR "intervention"). We applied no language restriction and included articles published from database inception up until June 10, 2025. Our search yielded 533 results, including six human clinical trials investigating the effects of nicotinamide or nicotinamide adenine dinucleotide (NAD+) supplementation on acute COVID-19 symptoms (n = 4) and long-COVID symptoms (n = 2). We have not identified human clinical trials evaluating the impact of NAD + supplementation specifically on both objective and subjective cognitive function in adults with long-COVID.

Added value of this study

To address this gap, we conducted a 24-week double-blind, randomized, placebo-controlled trial, measuring NAD+ absorption levels every 5 weeks and cognition every 10 weeks. This study provides evidence on the effects of 2000 mg/day NR supplementation on NAD+ levels and cognitive functioning (objective and subjective), sleep quality, fatigue severity, and mood symptoms (depression, anxiety) in individuals experiencing long-COVID symptoms. Our findings indicate that NR supplementation did not significantly alter cognitive function compared to placebo. However, exploratory analyses showed potential within-group improvements in executive functioning and sleep quality, as well as reductions in fatigue severity and depression symptoms after 10 weeks of NR supplementation, emphasizing the need for larger clinical trials to further evaluate the role of NAD+ augmentation in long-COVID recovery.

Implications of all the available evidence

Previous studies in animal models and human trials, along with the current study, have shown that NAD+ precursors, including NR, effectively increase NAD+ levels. Our findings demonstrate that NR is effective at increasing NAD+ in people with long-COVID. While we did not find differences between the intervention and placebo in cognition, sleep, fatigue, or mood, post hoc exploratory analysis combining everyone taking 10 weeks of NR showed improvements in executive functioning, fatigue, sleep disturbances, and depression symptoms. These findings highlight the need for larger trials to further investigate NAD+ as a therapeutic target for enhancing recovery in individuals with long-COVID.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has produced over 770 million reported cases worldwide, according to the World Health Organization (WHO). While most individuals recover from the acute phase of infection, it is estimated that at least 7% of survivors experience persistent and often debilitating symptoms lasting for months or even years post-infection, a condition referred to as Post-Acute Sequelae of COVID-19, Post-COVID-19 Condition, or long-COVID.[1–3] Long-COVID affects individuals across all age groups and severities of acute illness, with the highest proportion of diagnoses occurring in middle-aged and non-hospitalized patients who had mild to moderate acute illness.[3,4] It manifests as a multi-systemic condition, with neurological symptoms, such as cognitive difficulties (i.e., attention, executive functioning, and memory deficits), headaches, and sleep disruptions, among the most prominent and incapacitating.[4–6] Additional common symptoms include fatigue, shortness of breath, muscle aches, and psychiatric symptoms including depression and anxiety.[3,7] These persistent symptoms often result in substantial declines in quality of life and long-term disability,[8] underscoring the urgent need to identify treatment targets and develop effective interventions.

Several pathophysiological mechanisms contribute to long-COVID, including immune dysregulation, characterized by elevated pro-inflammatory cytokines, alterations in T-cell populations, and autoantibody production, along with mitochondrial dysfunction, oxidative stress, and disruptions in energy metabolism.[9–11] One emerging target in this context is nicotinamide adenine dinucleotide (NAD+), a critical coenzyme involved in cellular metabolism, immune regulation, and inflammation control that is found in every cell of the human body.[3,12] As a key electron carrier in the mitochondrial respiratory chain, NAD+ regulates essential metabolic pathways, including glycolysis, the Krebs cycle, and fatty acid oxidation.[13,14] It also plays a vital role in DNA repair and cellular resilience by activating poly (ADP-ribose) polymerase (PARP) enzymes, which help maintain genomic stability and prevent excessive cell death.[13] SARS-CoV-2 infection has been shown to dysregulate NAD+-dependent pathways.[9,12,15] Specifically, the virus activates PARP family genes, increasing NAD+ consumption and depletion.[16] A study measuring NAD+ and its metabolites in hospitalized COVID-19 patients found significantly lower NAD+ levels compared to control groups, along with altered levels of NAD+ metabolites such as 1-methyl nicotinamide and nicotinamide.[17] Gene expression analyses further revealed disruptions in immune response, metabolism, apoptosis, redox balance, and mitochondrial function, some of which are present in long-COVID.[17] Given NAD+'s role in mitochondrial function and immune regulation, its sustained depletion could help explain the lingering metabolic and neurological symptoms observed in long-COVID.

Supplementation with NAD+ precursors, such as nicotinamide riboside (NR), has been shown to effectively increase NAD+ levels and confer various health benefits. Preclinical studies indicate that NR reduces peripheral inflammation, cellular senescence and neuroinflammation and enhances oxidative metabolism, cognition, muscle function, motor coordination, and synaptic plasticity.[14,18–20] In humans, it has been shown to reduce circulating inflammatory cytokines in older adults.[21,22] A phase I clinical trial in Parkinson's disease patients demonstrated that NR supplementation enhanced the NAD+ metabolome and upregulated pathways associated with mitochondrial, lysosomal, and proteasomal function in blood cells and skeletal muscle.[23] Moreover, NR supplementation was associated with reduced inflammatory cytokine levels in both serum and cerebrospinal fluid. In addition, a small randomized, open-label, placebo-controlled phase II trial investigating the effects of a combination of metabolic cofactors (NR, L-serine, N-acetyl-L-cysteine, and L-carnitine tartrate) in people during acute COVID-19 found that this combination significantly reduced symptom duration.[24] However, since NR was administered alongside other cofactors, its independent effects remain unclear. Further research is needed to determine whether NR supplementation alone can improve long-COVID symptoms by boosting NAD+ levels.

We conducted a double-blind, placebo (PBO)-controlled clinical trial with a PBO lead-in phase to evaluate the effects of NR on NAD+ levels in non-hospitalized individuals with long-COVID. We hypothesized that NR supplementation would enhance NAD+ levels, which in turn would be associated with improvements in cognitive function and a reduction in long-COVID symptoms.

Methods

Study design

This 24-week, double-blind, placebo-controlled clinical trial with a placebo lead-in phase (NCT04809974) was conducted at the Massachusetts General Hospital (MGH, Boston, MA, United States). The trial protocol is provided in the Supplementary Materials.

Ethics statement

Study approval was obtained from the Institutional Review Board (IRB) at Massachusetts General Brigham (2021P000158), and all participants provided written informed consent.

Participants

Participants were mostly recruited through flyers, physician referrals, word-of-mouth, clinicaltrials.gov, and Rally, an online platform developed by MGH and affiliates where individuals can find enrolling studies. Inclusion criteria included: (1) age 18–65 years; (2) a self-reported history of SARS-CoV-2 PCR+ at least 2 months prior to study entry; (3) SARS-CoV-2 negative (PCR) at study entry; (4) persistent self-reported cognitive difficulties (esp. "brain fog") that began around the time of the acute COVID-19; (5) at least two neurological and/or physical symptoms that started around COVID-19 infection and are ongoing at study entry (e.g., fatigue, headache, loss of smell, tingling/numbness, shortness of breath, palpitations/tachycardia, musculoskeletal and/or chest pain; and (6) not pregnant or lactating. Exclusion criteria included: (1) any specific central nervous system disease history (e.g., major clinical stroke, brain tumor, normal pressure hydrocephalus); (2) unstable medical condition that could affect safety or compliance with the study; (3) intubation due to COVID-19; (4) major active or chronic unstable psychiatric illness (e.g., depression, bipolar disorder, obsessive-compulsive disorder, schizophrenia) within the previous year; (5) history of alcohol or other substance abuse or dependence within the past two years; (6) current use of medications with psychoactive properties that, 54 in the opinion of the clinician, may deleteriously affect cognition; (7) any

known hypersensitivity to NR, or its principal metabolite, nicotinamide mononucleotide; (8) use of other investigational agents or interventions one month before study entry and for the duration of the trial; (9) pregnant women or women who are planning to become pregnant within 7 months from study entry; (10) had <80% compliance; and (11) consumption of dietary supplements containing more than 100 mg of niacin, NR, or nicotinamide mononucleotide (NMN) as the primary agents 30 days prior to baseline and for the duration of the trial. Sex data were self-reported, with male and female options.

Randomization and masking

The randomization schedule was prepared and implemented by the MGH clinical trials pharmacy. Participants were randomized 2:1 to the NR-NR or PBO-NR sequence groups without *a priori* stratifications. NR and matching PBO were provided by ChromaDex, Inc., a Niagen Bioscience company (Los Angeles, CA). The NR and PBO bottles and labels were identical in appearance. Research assistants and clinicians delivering the interventions, outcome assessors, and data analysts were all blinded to group assignments.

Procedures

The trial consisted of a screening visit, a 2-week PBO lead-in period followed by a baseline visit, 4 visits every 5 weeks, and an end-of-study phone call 2 weeks after the last visit, for a total of 24 weeks. After the initial screening visit, all participants were provided PBO (4 pills twice daily) for 2 weeks. After the PBO lead-in period, participants had a baseline assessment visit and were assigned, based on their sequence, to receive 2000 mg of NR (4 capsules of 250 mg twice daily) or PBO (4 capsules twice daily) for 10 weeks. After 10 weeks, people in the PBO group switched to the NR phase (PBO-NR), while people in the NR group continued to stay in the NR phase (NR-NR). A check-in about safety was performed at every visit.

Outcomes

Extraction of NAD+ metabolites and NAD+ quantification (LC-MS)

Participants provided blood samples at every visit after screening. 2 μL of 5 μM Immucillin H (Cayman Chemical, Ann Arbor, MI, USA) was transferred into 1 mL Nunc cryogenic tubes (Thermo Fisher Scientific, Inc., Waltham, MA, USA) and placed on ice. 100 μL of freshly drawn whole blood was transferred from a 10 mL BD vacutainer with K2 EDTA (Becton Dickinson, Franklin Lakes, NJ, USA) into the 1 mL Nunc cryogenic tubes (Thermo Fisher Scientific, Inc.) and mixed with the 5 μM Immucillin H (Cayman Chemical). Immediately after, the blood-Immucillin H samples were snap-frozen in a dry ice/ethanol bath and stored in the –80 °C freezer until analysis. Q-NAD Blood NAD+ assay kits (NADMED Ltd., Helsinki, Finland) were shipped with dry ice from the manufacturer for quantitative NAD+ measurement of whole blood. Following the manufacturer's procedure, blood-Immucillin H samples were thawed in an ice-water bath and NAD+ metabolites were extracted, individually stabilized with protection from light, and measured through an enzymatic assay with colorimetric detection. Absorbance measurement was done at 573 nm using a BioTek Cytation 5 imaging reader with Gen5 software (Agilent, Santa Clara, CA, USA).

Safety and compliance

Participants received identical bottles with either PBO or NR provided by ChromaDex, Inc. from study staff and discussed any questions about tolerability or adverse events (AEs) with a licensed clinician during every visit. AEs, safety, and tolerability were assessed and recorded during all visits and at the end-of-study follow-up. Weight, vital signs (pulse and blood pressure), and physical and neurological examinations were conducted at baseline, visit 2, and visit 4. To assess compliance, a licensed clinician counted the number of pills that were returned at each visit and subtracted the total from the number of pills that were given to the participant at the previous visit. The difference was then divided by the number of pills that the participant was supposed to take between visits multiplied by 100%.

Cognitive assessments

The primary outcomes of the clinical trial were the Everyday Cognition (ECog) scale, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) index scores, and the Trail Making Test-Part B (TMT-B) score in seconds. Participants completed the ECog at every visit, and the RBANS and TMT-B at baseline, visit 2 and visit 4. All tests were conducted by clinical research coordinators who were trained by a licensed clinical neuropsychologist.

The ECog is a 29-item self-report questionnaire that assesses subjective cognitive decline, including a global factor and six domain-specific factors related to everyday function and cognition (e.g., memory, planning, organization, language, attention, visuospatial). Instructions were modified to ask participants to rate their current cognitive functioning compared to before COVID-19 infection on a four-point scale: 1 = better or no change compared to before COVID-19 infection, 2 = questionable/occasionally worse, 3 = consistently a little worse, 4 = consistently much worse. An option marked "9" for "I Don't Know" is not assigned a value and is excluded from scoring. Scores for each cognitive domain were determined by averaging the responses to the items within a cognitive domain and dividing them by the number of questions that they answered. A total ECog score (i.e., global factor) was calculated by adding the rating value of all items and dividing it by the number of questions that they answered.

The RBANS is a commonly used standardized neurocognitive battery consisting of 12 tests that assess functioning across 5 cognitive domains, including immediate memory (word list learning, story learning), visuospatial/constructional (line orientation, figure copy), language (naming, semantic fluency), attention (digits forward, coding), and delayed memory (word list recall, word list recognition, story recall, figure recall). The index scores for total and subdomains range from 40 to 160, with a higher score indicating better cognitive performance. Different versions of the RBANS were administered at baseline (Version A), visit 2 (Version B), and visit 4 (Version C).

The TMT-B measures executive functioning, particularly cognitive flexibility and set-shifting. It requires participants to connect a series of 25 circles containing alternating numbers (1–13) and letters (A–L) in sequential order (e.g., 1-A-2-B-3-C). The total score was recorded as the time to completion, with a longer time reflecting a worse performance.

Assessment of sleep, fatigue, and mood symptoms

Participants completed self-reported questionnaires about fatigue severity, sleep quality, and symptoms of anxiety and depression at every visit.

We assessed fatigue using the Fatigue Severity Scale (FSS), a 10-item self-report measure evaluating the impact of fatigue on daily functioning that has been validated in this population. Participants rated each statement on a 7-point scale, with 1 indicating "Strongly Disagree" and 7 indicating "Strongly Agree." Higher scores reflect greater fatigue severity and its effect on daily activities. A total score of less than 36 suggests that the individual may not suffer from fatigue.

Participants also completed the Beck Anxiety Inventory (BAI), a 21-item self-reported questionnaire assessing anxiety symptom severity. Participants rated the severity of each symptom on a scale from 0 (none) to 3 (severe) based on the past month, with total scores ranging from 0 to 63. Higher scores indicate more severe anxiety symptoms. Anxiety severity was classified into minimal (0–7), mild (8–15), moderate (16–25), and severe anxiety (≥26).

We administered the Beck Depression Inventory (BDI), a 21-item self-reported measure used to assess symptoms of depression. Participants rated the severity of each symptom on a scale from 0 (none) to 3 (severe) based on the past 2 weeks, with total scores ranging from 0 to 63. Higher scores indicate more severe depressive symptoms, with established clinical cutoffs categorizing minimal (0–9), mild (10–18), moderate (19–29), and severe depression (≥30).

Finally, we assessed sleep quality using the Pittsburgh Sleep Quality Index (PSQI), a self-report questionnaire measuring subjective sleep quality over the past month. The PSQI includes seven component scores assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. These components were summed to yield a global score ranging from 0 to 14, with a higher score indicating worse sleep quality. A global score greater than 5 indicates poor sleep quality and significant sleep difficulties.

Statistical analysis

Descriptive statistics were used to characterize the cohort's demographic and clinical variables. We conducted independent sample t-tests to examine between-group differences in demographic variables at baseline and analysis of variation (ANOVA) to test for between-group differences in treatment compliance for each study visit.

Primary analysis

For all outcomes, we performed mixed-effects model repeated measures (MMRM) analysis under intention-to-treat (ITT) principle. Treatment group (NR-NR vs. PBO-NR sequence), time (treated as a categorical variable), and group-by-time interaction were included as fixed effects. The study's primary outcomes were changes from baseline in the ECog, RBANS, and TMT-B scores, and blood NAD+ levels. Secondary outcomes included changes from baseline in the FSS, BAI, BDI, and PSQI scores. An unstructured covariance matrix was used to model the within-subject correlation of repeated measures. Age, sex assigned at birth, and years of education were included as covariates in all models. Least-squares means and their corresponding 95% confidence intervals were reported for each outcome at all post-baseline time points. Missing data were assumed to be missing at random and were implicitly handled by the MMRM framework without imputation.

Sensitivity analysis

A per-protocol (PP) analysis was conducted as a sensitivity analysis to assess the potential impact of missing data, particularly in the context of data that may have been missing not at random (MNAR). This analysis included only participants who completed visit 4 (n = 36). By restricting the analysis to study completers, we aimed to estimate treatment effects independently of assumptions about the missing data mechanism.

Post-hoc analysis

The sequential block design provided the opportunity to examine the effects of NR using a larger sample size, as all participants ultimately received 10 weeks of NR (baseline to visit 2 for the NR-NR group; visits 2–4 for the PBO-NR group). In addition to the standard MMRM analysis, we combined the data from the two randomized groups and explored the pre-post changes in outcomes after 5 and 10 weeks of NR intake compared to baseline. Further, we ran MMRM model

with only the NR-NR group to understand the changes in symptoms (i.e., BAI, BDI, FSS, PSQI) over 4 visits, up to 20 weeks of follow-up post-baseline. To explore the potential impact of NAD+ levels on change in outcomes, we performed linear regression analyses of change scores and NAD+ levels measured after 10 weeks, controlling for age, sex, education, and time since acute COVID-19 infection. We did not apply multiple-testing corrections given the exploratory nature of the analyses. All analyses were conducted using SAS 9.4 (Cary, NC), and the threshold for statistical significance was set at $p < 0.05$.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, or data interpretation. Team members of Niagen Bioscience reviewed the manuscript. None of the authors was paid to write this article.

Results

Participants were enrolled in the clinical trial between August 2021 and September 2023. A total of 72 potential participants were screened for eligibility. Of those, 61 were enrolled and randomized, and 58 completed baseline testing (Fig. 1). Of the total that completed the baseline visit, 37 participants (64%) were assigned to follow the NR-NR sequence, and 21 participants (36%) followed the PBO-NR sequence (Fig. 2). NR-NR and PBO-NR groups did not differ in baseline characteristics, except for sex assigned at birth, which was included as a covariate in all models (Table 1). In the NR-NR group, 25 and 18 participants remained in the study at 10 and 20 weeks after baseline, corresponding to dropout rates of 32.4% and 51.4% from baseline, respectively. The most common reason for study withdrawal was COVID-19 reinfection, followed by AEs, changes in medications that could affect cognition, inability to comply with the study time commitment, relocation out of state, or loss to follow-up (Supplementary Table S1). In the PBO-NR group, 18 participants remained at 10 and 20 weeks after baseline, with a dropout rate of 14.3% at each timepoint. Of the three people who withdrew from the study on this group, one was reinfected with COVID-19, one experienced an AE, and one had a change in a

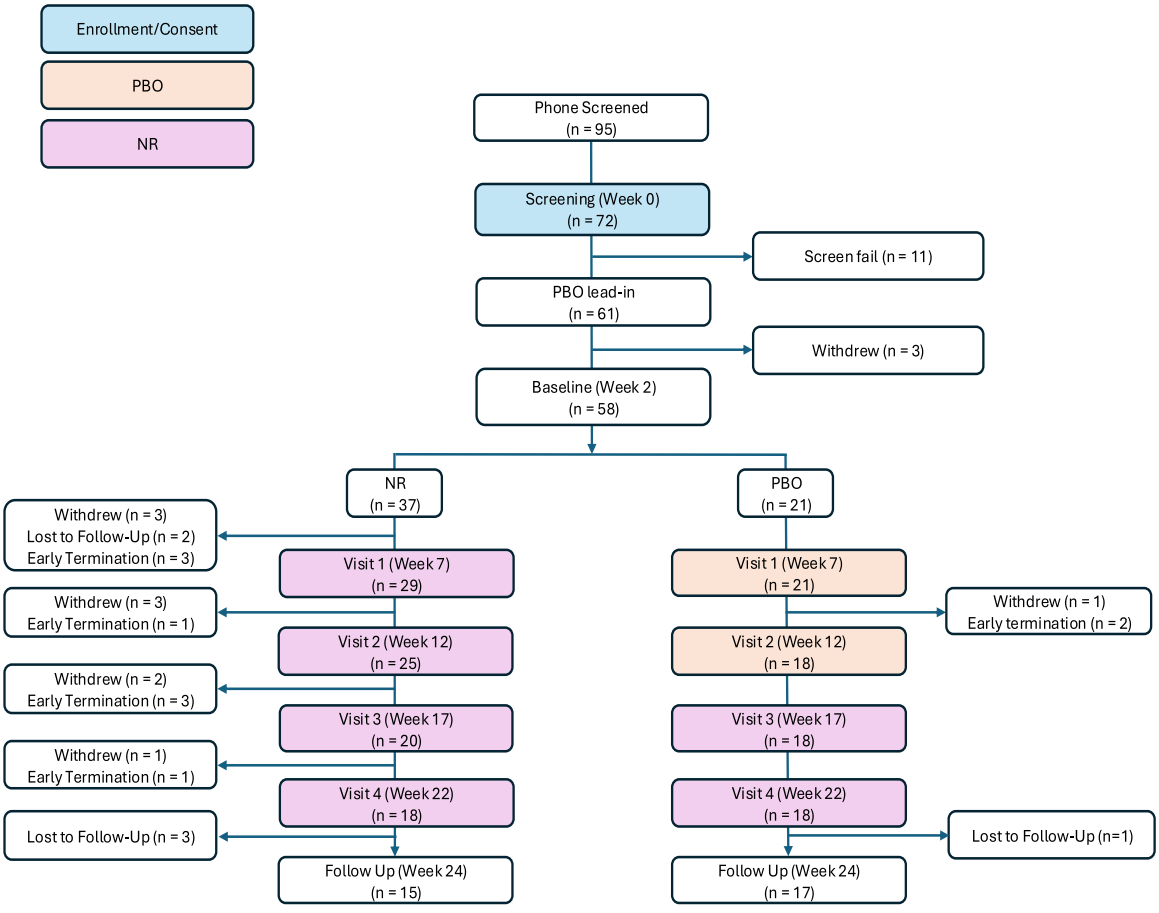

Fig. 1: **Consort diagram**.

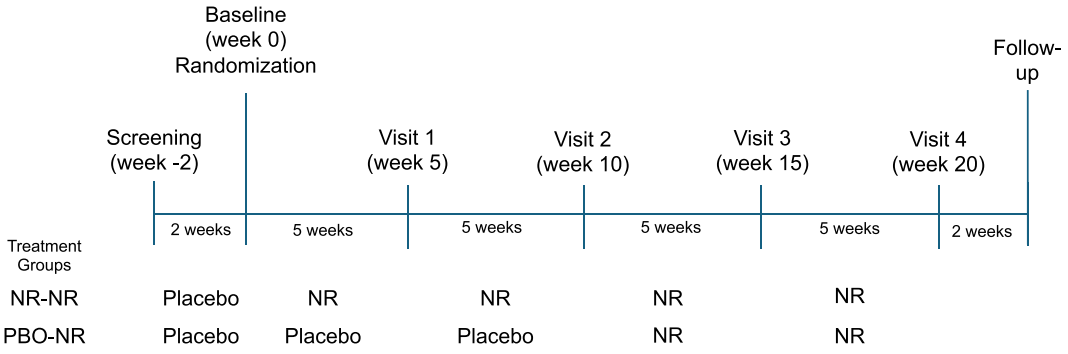

***Fig. 2:* Clinical trial design:** Participants completed a screening visit to determine eligibility and were started on PBO. Baseline data were collected 2 weeks after the screening visit and participants were randomized 2:1 (NR:PBO). Those randomized to the NR group continued on NR for 20 weeks, while those in the PBO group continued on PBO for 10 more weeks and then took NR for 10 weeks. A follow-up call was made to assess for adverse events 2 weeks after the last visit.

medication that could affect cognition (Suplementary Table S1). Standard medical care continued if initiated and stable before enrollment. Several participants in the trial were taking medications known to have potential cognitive effects; however, a licensed clinician determined that these were unlikely to interfere with study outcomes, typically due to their low dosage and stable use. These medications included amphetamines (n = 7), an anticonvulsant (n = 1), tricyclic antidepressant (n = 1), and benzodiazepines (n = 5). All participants had been on a stable dose for at least 2 months prior to the screening visit and were required to maintain that dosage throughout the study.

The average compliance rates were 96.7 ± 4.8% and 96.6 ± 6.1% in the NR-NR and PBO-NR groups, respectively. There were no differences in the compliance rate between the two groups and across time (group * time interaction term; p = 0.72).

We then examined changes in NAD+ levels in each group. In the NR-NR group, NAD+ levels increased by an average of 3.1-fold after both 5 and 10 weeks of NR supplementation (95% CI: 2.7–3.5, p < 0.001). These levels remained elevated, with a 2.6-fold (95% CI: 1.9–3.3, p < 0.001) and 2.1-fold (95% CI: 1.6–2.7, p < 0.001) increase at 15 and 20 weeks of NR supplementation, respectively (Fig. 3). In the PBO-NR group, NAD+ levels remained close to baseline (0.93- to 1.0-fold change, 95% CI: 0.5–1.4) during the initial 5 and 10 weeks of PBO. After switching to NR, levels rose to a 2.6-fold and 2.1-fold increase after 5 and 10 weeks of NR supplementation, respectively (95% CI: 1.9–3.3 and 1.6–2.7, p < 0.001; Fig. 3).

At baseline, 10.34% of participants in the NR-NR group had RBANS Immediate or Delayed Memory Index scores at least 2 standard deviations below the mean, and 6.9% had scores in the Visuospatial Index within this impaired range. In the PBO-NR group, 9.52% of participants had Visuospatial Index scores and 4.76% had Attention Index scores at least 2 standard deviations below the mean. For the primary analysis examining group differences in changes in the primary outcomes (i.e., cognition), there were no significant differences between the NR and PBO groups in the ECog total score (β = 0.08; 95% CI: −0.16 to 0.33; p = 0.49), RBANS total scaled score (β = 6.08; 95% CI: −10.86 to 23.01; p = 0.47), and TMT-B completion time (β = −1.83; 95% CI: −13.04 to 9.39; p = 0.74) (Fig. 4). Similarly, no group differences were observed in any ECog or RBANS subdomains (Fig. 4). Within the PBO-NR group, there were no significant differences in the changes observed during the NR and PBO phases for the ECog total (ΔPBO − ΔNR = −0.07, p = 0.47), RBANS total (Δ = 23.56, p = 0.10), and TMT-B (Δ = −0.72, p = 0.91) scores (Fig. 4). There were also no significant differences between the PBO and NR phase in ECog or RBANS subdomains, except for RBANS immediate memory, where participants improved more in the PBO phase than in the NR phase (Δ = 11.33, p = 0.04) (Fig. 4).

We then examined between and within-group differences in changes in secondary outcomes, including fatigue severity, sleep quality, and symptoms of depression and anxiety. The scores of self-reported questionnaires at baseline indicated that 94% of participants experienced poor sleep quality, and 78% had potentially severe fatigue. On the BDI, 60% reported minimal symptoms of depression, 24% mild, 14% moderate, and 2% severe depression. On the BAI, 30% reported minimal symptoms of anxiety, 34% mild, 14% moderate, and 22% severe anxiety.

For the primary analysis examining changes in the secondary outcomes, there were no significant differences between the NR and PBO groups in fatigue severity (β = −1.45; 95% CI: −6.76 to 3.86; p = 0.59), sleep quality (β = −0.27; 95% CI: −1.60 to 1.07; p = 0.69), and symptoms of anxiety (β = 0.45; 95% CI: −4.01 to 4.91; p = 0.84) or depression (β = −2.21; 95% CI: −5.63 to 1.21; p = 0.20) (Fig. 5). Within the PBO-NR group,

	Randomized groups		
	NR-NR	PBO-NR	p-value
	(n = 29)	(n = 21)	
Age (years) [*M* ± SD]	48.5 ± 13.0	41.7 ± 12.33	0.12
Sex (female) [n (%)]	24 (83%)	12 (57%)	0.047
Race/ethnicity [n (%)]			0.19
White	27 (93.1%)	17 (81.0%)	
Black or African American	1 (3.5%)	1 (4.8%)	
More than one race	1 (3.5%)	0 (0.0%)	
Unknown race or not reported	0 (0.0%)	3 (14.3%)	
Hispanic	2 (6.9%)	3 (14.3%)	
Education [n (%)]			0.67
High school	1 (3.4%)	0 (0%)	
Some college	4 (13.8%)	1 (4.8%)	
Associate or technical degree	2 (6.9%)	3 (14.3%)	
College	12 (41.4%)	12 (57.1%)	
Professional studies	10 (34.5%)	5 (23.8%)	
Occupation [n (%)]			
Sales and office	3 (10.34%)	2 (9.52%)	
Service	3 (10.34%)	6 (28.57%)	
Management, professional, and related	19 (65.52%)	9 (42.86%)	
Other	3 (10.34%)	2 (9.52%)	
Unemployed	1 (3.45%)	2 (9.52%)	
ECog [*M* ± SD][a]			
Total	2.07 ± 0.60	2.21 ± 0.86	0.53
Memory	2.29 ± 0.61	2.63 ± 1.04	0.15
Language	2.19 ± 0.75	2.24 ± 0.94	0.81
Visuospatial	1.50 ± 0.63	1.66 ± 0.82	0.43
Planning	1.84 ± 0.76	1.92 ± 0.93	0.74
Organization	2.03 ± 0.79	2.14 ± 1.03	0.68
Attention	2.64 ± 0.84	2.62 ± 0.99	0.94
RBANS (index scores) [*M* ± SD][b]			
Sum of index scores	482.9 ± 45.8	489.6 ± 48.4	0.62
Immediate memory	97.4 ± 15.2	100.8 ± 11.6	0.40
Delayed memory	94.1 ± 14.2	97.4 ± 12.9	0.41
Attention	96.2 ± 13.3	98.7 ± 17.3	0.57
Language	102.6 ± 11.6	101.0 ± 14.1	0.65
Visuospatial	92.7 ± 15.3	91.7 ± 17.4	0.83
Trail-making-test B [*M* ± SD]	70.7 ± 24.6	64.7 ± 22.9	0.38
Long-COVID symptoms and severity [*M* ± SD]			
Days since COVID-19 infection	447.2 ± 244.7	434.0 ± 191.9	0.84
BAI total	13.6 ± 8.8	15.0 ± 11.4	0.62
BDI total	14.0 ± 6.8	11.5 ± 6.7	0.20
FSS total	47.9 ± 13.2	46.8 ± 13.2	0.77
PSQI total	10.2 ± 3.0	9.4 ± 3.8	0.44
NAD+ (μmol/L)[c]	19.5 ± 3.7	18.9 ± 4.0	0.62

Note: M, mean; SD, standard deviation; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; FSS, Fatigue Severity Scale; PSQI, Pittsburgh Sleep Quality Index. [a]Sample sizes for NR-NR and PBO-NR are 28 and 19, respectively. [b]Sample sizes for NR-NR and PBO-NR are 28 and 21, respectively. [c]Sample sizes for NR-NR and PBO-NR are 21 and 16, respectively.

Table 1: **Demographic and clinical characteristics of the participants at baseline.**

there were no significant differences between the PBO and NR phase in fatigue severity (Δ = 3.89, p = 0.11), sleep quality (Δ = −0.50, p = 0.62), or symptoms of depression (Δ = 2.28, p = 0.34) and anxiety (Δ = 0.44, p = 0.84).

In the sensitivity analysis limited to participants who completed all study visits, no significant differences were observed between the NR and PBO groups in ECog total score (β = 0.12; 95% CI: −0.16 to 0.39; p = 0.40), RBANS total scaled score (β = 5.18; 95% CI: −14.17 to 24.52; p = 0.59), or TMT-B completion time (β = −1.26; 95% CI: −12.36 to 9.83; p = 0.82). There were also no significant group differences in any ECog or RBANS subdomains. Similarly, there were no statistically significant differences in fatigue severity (β = −3.08; 95% CI: −8.65 to 2.50; p = 0.27), sleep quality (β = −0.30; 95% CI: −1.77 to 1.16; p = 0.69), and symptoms of anxiety (β = −0.48; 95% CI: −5.97 to 5.01; p = 0.86) or depression (β = −2.22; 95% CI: −6.33 to 1.90; p = 0.28) between the PBO and NR groups.

We then conducted post-hoc analysis, where we grouped all participants during the first 10 weeks of the NR phase (n = 43) and examined within-group changes in primary and secondary outcomes during 5 and 10 weeks of NR intake. There were significant reductions in the ECog total (Δ = −0.12, p = 0.02), ECog attention (Δ = −0.23; p = 0.01), ECog memory (Δ = −0.19; p = 0.01), and ECog language (Δ = −0.16; p = 0.01) scores (Fig. 4). However, similar changes were also seen during the 10-week PBO phase (ECog total score Δ = −0.21, p = 0.03; ECog memory Δ = −0.28, p = 0.047; ECog language Δ = −0.29, p = 0.01), indicating that these changes were not specific to NR. In neuropsychological tests, there were no significant changes in RBANS scores after 10 weeks of either NR or PBO (Fig. 4). However, there was a significant decrease in TMT-B completion time by 8.36 s (Δ = −8.36, p = 0.01) after 10 weeks of NR. This effect was not observed after 10 weeks of PBO (Δ = −6.6, p = 0.07) (Fig. 4).

For the secondary outcomes in the post-hoc analysis, participants demonstrated statistically significant differences from baseline after 10 weeks of NR in fatigue severity, sleep quality, and symptoms of depression. Specifically, FSS scores decreased by 3.77 points (Δ = −3.77, p < 0.01), PSQI scores decreased by 0.74 points (Δ = −0.74, p = 0.03), and BDI scores by 1.67 points (Δ = −1.67, p = 0.04) (Fig. 5). In contrast, there were no significant changes in FSS, PSQI, BAI, or BDI scores during the PBO phase (FSS Δ = −0.39, p = 0.85; BDI Δ = 0.17, p = 0.90; BAI Δ = −0.72, p = 0.26).

When examining changes within the NR-NR group only, participants showed significant improvement in sleep quality after 10 (p = 0.02) and 15 weeks (p = 0.01) of NR intake, as well as significant reduction in depressive symptoms at 5 weeks of NR intake (p = 0.01) but no changes in primary outcomes, fatigue severity or symptoms of anxiety (Supplementary Figure S1).

We then further explored the association between changes in NAD+ levels, cognition and long-COVID symptoms. There were no significant associations between changes in NAD+ levels and changes in the ECog or RBANS scores (Supplementary Tables S2 and S3).

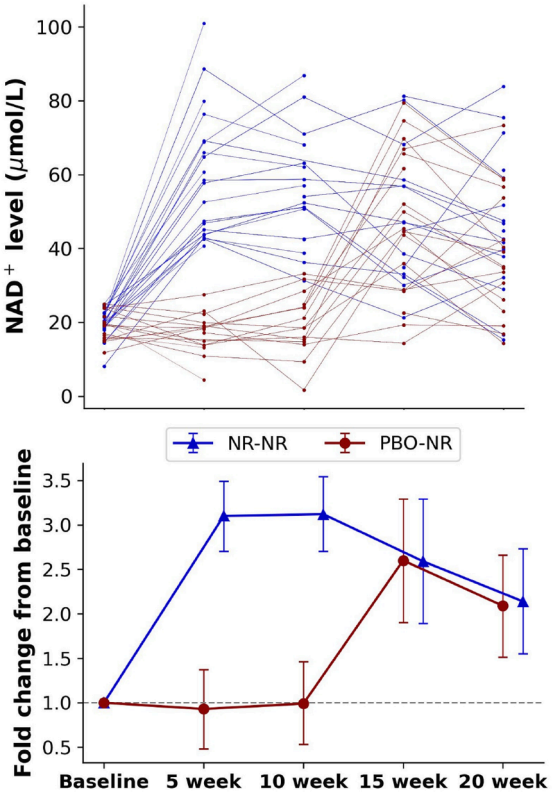

Fig. 3: **Change of NAD+ levels:** Blue lines represent individuals in the NR-NR group, and red lines represent individuals in the PBO-NR group. The top figure exhibits change in NAD+ levels for each individual at baseline, 5, 10, 15 and 20 weeks. Participants in the PBO-NR group switched to NR at 10 weeks (visit 2). The bottom figure shows the average fold change from baseline and standard deviations per group for each visit of the clinical trial.

There was a significant association between the PSQI change score and NAD+ levels after 10 weeks of NR intake ($p = 0.03$), when controlling for age, sex assigned at birth, education, and time since acute COVID-19 infection (Supplementary Table S4). Among the seven PSQI subdomains, changes in self-reported sleep quality (domain 1), sleep latency (domain 3), and use of sleep medication (domain 6) showed significant associations with NAD+ levels at 10 weeks (Supplementary Table S5). There were no significant associations between changes in NAD+ levels and changes in the FSS, BAI, or BDI scores (Supplementary Table S4).

Finally, AEs that occurred during the clinical trial are shown in Table 2 and Supplementary Table S6. One serious adverse event (SAE) was reported during the study, which was determined to be unrelated to the study drug or clinical trial. In total, 104 AEs were reported throughout the study. Among these, 63 were reported in the NR-NR group and 41 in the PBO-NR group. The AEs reported that were considered possibly related, probably related, or related to the study while participants were taking NR included muscle cramps, nausea, bruising, worsening of headaches, leg cramps, flushing, rash, and vertigo.

Discussion

We conducted a 24-week double-blinded, PBO lead-in, randomized, parallel-group, PBO-controlled design study to test the effect of NR on NAD+ levels and symptom recovery in individuals with long-COVID. Specifically, we assessed changes in subjective cognitive decline and objective cognitive functioning, as well as other common symptoms of long-COVID, including fatigue severity, sleep quality, and mood symptoms. Participants reported having mild-to-moderate symptoms during acute SARS-CoV-2 infection and experiencing severe fatigue, poor sleep quality, and elevated symptoms of depression and anxiety at baseline. NR was well tolerated, with no significant differences in AEs between the NR and PBO phases.

We found that 2000 mg a day of NR was highly effective at boosting NAD+ levels, as these increased by 2.6- to 3.1-fold in at least 5 weeks. Notably, NAD+ levels declined at certain time points in some individuals. Since compliance rates were consistent across visits, these fluctuations are unlikely to be due to missed doses of NR. One possibility is that some participants may not have taken NR on the day of the visit. Alternatively, transient declines in NAD+ could reflect increased physiological demand, such as during an adverse event or secondary infection, which may temporarily lower circulating NAD+ levels.

We did not observe significant changes in subjective cognitive decline or objective cognitive functioning between the PBO and NR groups, or between the PBO and NR phases within the PBO-NR group, in our primary analysis. Since all participants received at least 10 weeks of NR, we were able to treat the entire study as a single-arm design and assess changes from baseline within group after 10 weeks of NR supplementation. This enabled us to increase the sample size and gain additional insight with greater statistical power. We found a PBO effect on perceived cognitive functioning as participants self-reported feeling less subjective cognitive decline compared to before COVID-19 infection during both the PBO and NR phases. In contrast, having taken NR for 10 weeks was associated with a slightly improved performance on a measure of executive functioning. While studies in preclinical models show cognitive benefits with NR supplementation,[18,20] human studies have been mixed, with some showing no improvement in older adults with mild cognitive impairment.[25,26] Overall, our findings suggest that increasing NAD+ levels with NR does not meaningfully improve cognitive functioning in long-COVID.

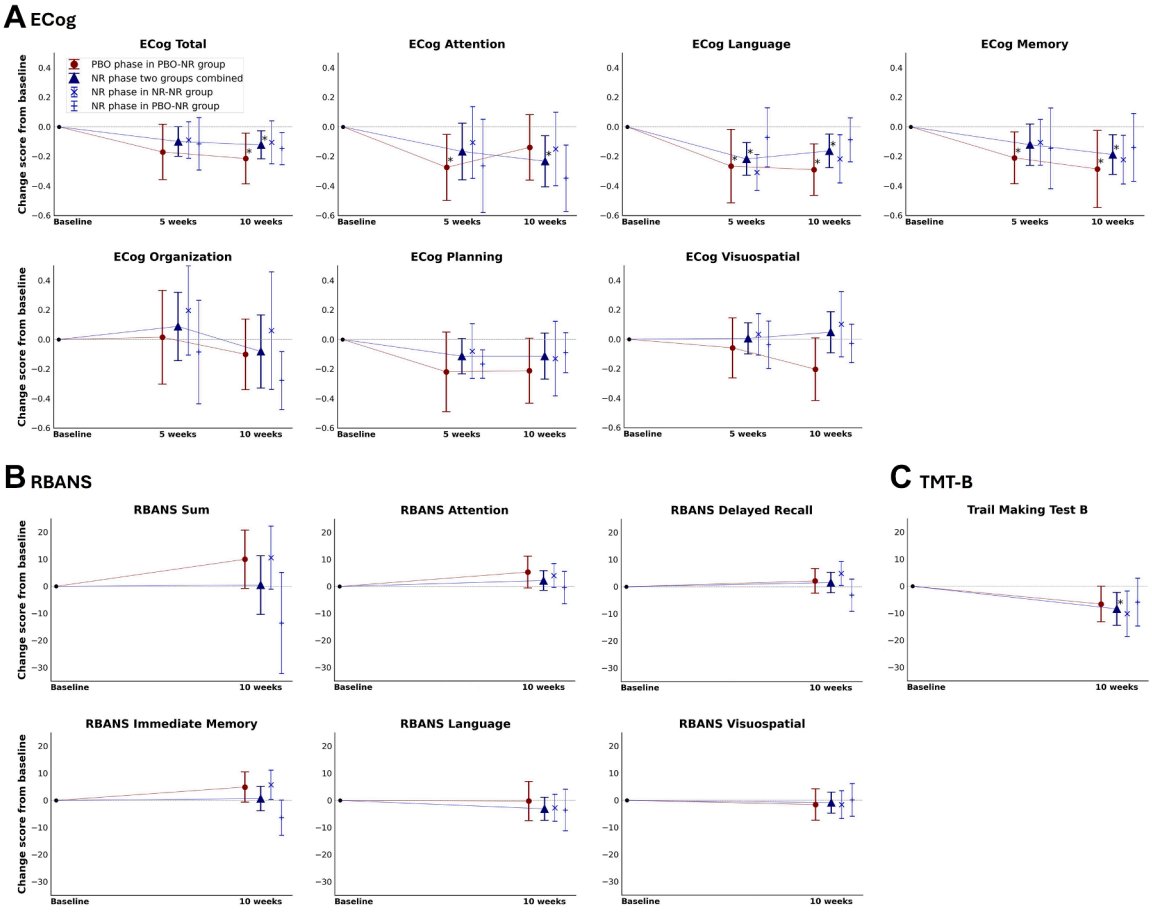

Fig. 4: **Changes in subjective cognitive decline and objective cognitive functioning:** Blue lines represent the first 10 weeks of the NR phase. The darker blue line represents the first 5 and 10 weeks of NR when combining all participants (n = 47 at 5 weeks, n = 43 at 10 weeks). The x group represents average values in the NR phase for people in the PBO-NR group, and + represents the average values in the NR phase for people in the NR-NR group. Red lines represent individuals in the PBO phase (n = 21 at 5 weeks, n = 18 at 10 weeks). The dotted line represents no change from baseline. The * represents statistically significant differences from baseline at $p < 0.05$. (A) Change from baseline in the Everyday Cognition scale (ECog) total and six domain-specific factors. (B) Change from baseline in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores. (C) Change from baseline in the Trail Making Test-B (TMT-B) scores.

In addition to cognitive deficits, individuals with long-COVID reported severe fatigue, disrupted sleep, and mood symptoms when they entered the study. This is consistent with other studies where these symptoms are highly endorsed and described to interfere significantly with daily functioning.[5,7] As such, we also tested the effect of NR and increased NAD+ levels on perceived fatigue severity, sleep quality, and symptoms of depression and anxiety. There were no significant differences in change scores between the NR and PBO groups or within the PBO-NR group, suggesting that NR may not have an effect on these symptoms. However, post-hoc analyses with all participants who completed 10 weeks of NR supplementation revealed reductions from baseline in self-reported fatigue severity, fewer depressive symptoms, and improved sleep quality after taking NR for at least 10 weeks. Further, post-hoc analysis showed that a greater increase in NAD+ levels was associated with improved perceived sleep quality. To date, few studies have investigated the link between NAD+ and sleep quality, fatigue, and mood,[27–30] and the underlying mechanisms remain largely uncharacterized. Overall, while the primary analyses did not show significant differences between NR and PBO on perceived sleep quality, fatigue severity, or mood, the post-hoc findings suggest that 10 weeks of NR supplementation may benefit some individuals with long-COVID. Notably, these results should be interpreted with caution and considered exploratory and hypothesis-generating. Further research with larger samples is warranted to better understand the role of

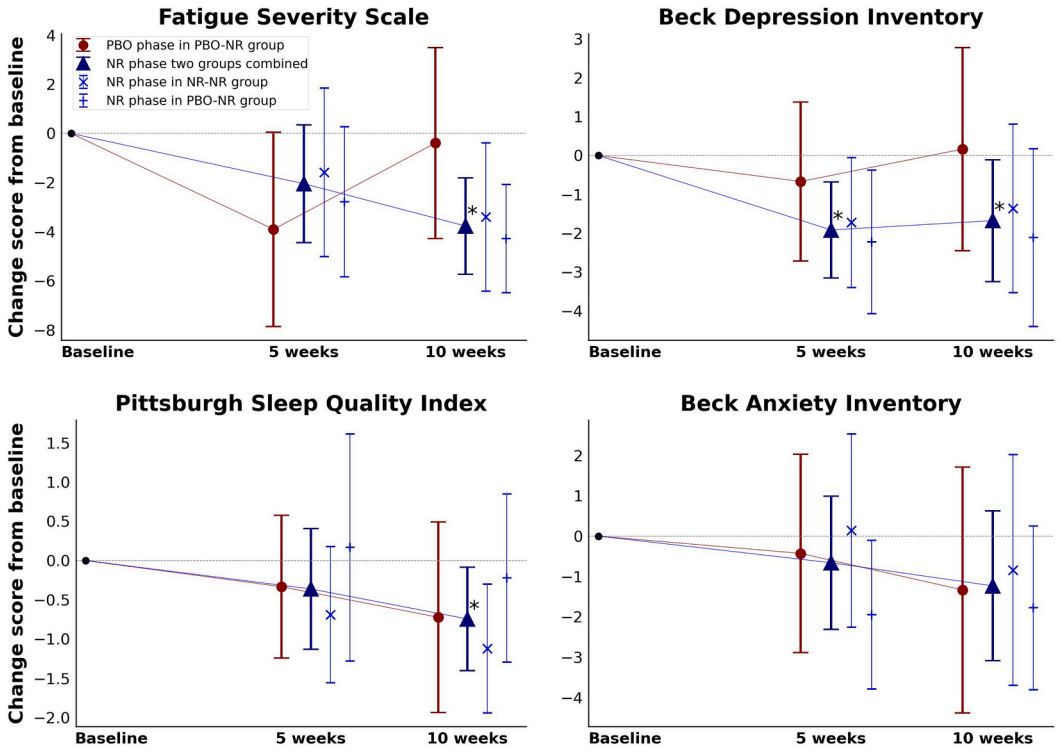

Fig. 5: **Changes in sleep, fatigue, and mood symptoms:** Blue lines represent the first 10 weeks of the NR phase. The darker blue line represents the first 5 and 10 weeks of NR intake when combining all participants (n = 43 at 5 weeks, n = 43 at 10 weeks). The x group represents average values in the NR phase for people in the PBO-NR group, and + represents average values in the NR phase for people in the NR-NR group. Red lines represent individuals in the PBO phase (n = 21 at 5 weeks, n = 18 at 10 weeks). The dotted line represents no change from baseline. The * represents statistically significant changes from baseline at $p < 0.05$.

NAD+ augmentation with NR in these common long-COVID symptoms.

Our clinical trial had several strengths. First, the inclusion of a PBO lead-in phase helped minimize the influence of PBO responders on the study outcomes. Second, the study design allowed for both between-group comparisons (PBO vs. NR) and within-group changes, enhancing the robustness of our findings. This design provided several benefits. The between-group design allows to isolate the effect of NR by accounting for PBO effects and natural recovery, which may be highly variable for people with long-COVID. In turn, the within-group offers insights into individual or subgroup responses that might not be apparent in between-group comparisons alone and that could be worth exploring in future, larger trials. Additionally, participants underwent a comprehensive clinical evaluation and completed validated self-report questionnaires and neuropsychological assessments to evaluate several common symptoms of long-COVID. We also directly measured blood NAD+ levels, providing an objective biomarker of NR's biological effects. Lastly, participant compliance was high, and only a few individuals discontinued the study due to NR-related AEs.

Our study had several limitations. First, the sample size of individuals who completed the clinical trial was relatively small, and the study experienced a high dropout rate. Withdrawals occurred for a range of reasons, including COVID-19 reinfection, AEs, changes in medications that could affect cognition, and personal circumstances such as time constraints or relocation. Although most of these dropouts appeared random rather than systematically related to treatment or outcomes, they may have reduced statistical power, limiting the ability to detect true between-group differences. Further, COVID-19 infection status was based on self-report. Additionally, our sample lacked substantial sociodemographic diversity, which may limit the generalizability of our findings. To fully understand the impact of NR on NAD+ levels and long-COVID recovery, larger and more diverse clinical trials are needed. Future studies should also explore the relationship between NAD+ restoration, inflammation, and immune regulation in long-COVID, as well as whether alternative NR dosing regimens, beyond 2000 mg daily, may be equally or more effective.

In conclusion, in individuals with long-COVID, NR was safe and effective in increasing NAD+ levels within

Event (overall—no. (%))	NR-NR (n = 37)	Relatedness NR-NR	PBO-NR (n = 21)	Relatedness PBO-NR
Any AE	26 (70.3)	NA	19 (90.5)	NA
Serious AE	1 (2.7)	1 Not Related	0 (0)	NA
AE leading to discontinuation	8 (21.6)	5 Not Related; 1 Possibly; 2 Definitely	2 (9.5)	2 Possibly
AE that occurred in ≥5% of participants in either group				.
Allergic reaction	2 (5.4)	2 Not Related	0 (0)	NA
COVID-19 infection	4 (10.8)	4 Not Related	1 (4.8)	1 Not Related
GI discomfort	4 (10.8)	3 Not Related; 1 Possibly	1 (4.8)	1 Possibly
Headache	1 (2.7)	1 Probably	2 (9.5)	2 Possibly
Heartburn	2 (5.4)	2 Possibly	0 (0)	NA
Injury	0 (0)	NA	3 (14.3)	3 Not Related
Leg cramps	2 (5.4)	1 Not Related; 1 Probably	0 (0)	NA
Muscle strain	0 (0)	NA	2 (9.5)	1 Not Related
Nausea	3 (8.1)	1 Possibly; 1 Probably; 1 Definitely	2 (9.5)	1 Possibly; 1 Probably
Pruritus	2 (5.4)	2 Not Related	0 (0)	NA
Rash	4 (10.8)	1 Not Related; 2 Possibly; 1 Definitely	0 (0)	NA
Upper respiratory infection	7 (18.9)	7 Not Related	4 (19.0)	4 Not Related
Vertigo	2 (5.4)	1 Not Related; 1 Definitely	1 (4.8)	1 Not Related
Worsening insomnia	2 (5.4)	2 Not Related	0 (0)	NA
Worsening sleep	2 (5.4)	1 Not Related; 1 Possibly	1 (4.8)	1 Not Related

Note: Relatedness, or whether the adverse event was related to NR, was assessed by licensed clinicians and categorized as Definitely Related, Probably Related, Possibly Related, or Not Related. AE, adverse event; NA, not applicable; NR, nicotinamide riboside; PBO, placebo.

Table 2: **Safety—adverse events.**

5 weeks. However, NAD+ augmentation did not produce statistically significant between-group differences (NR vs. PBO) in objective cognitive outcomes or in self-reported measures of fatigue severity, sleep quality, or mood. Exploratory post-hoc within-group analyses revealed improvements in self-reported fatigue, sleep, and depressive symptoms, and slightly better performance in executive functioning, following 10 weeks of NR supplementation. These findings highlight the need for larger trials to further investigate the role of NAD+ augmentation in long-COVID recovery.

Contributors

Chao-Yi Wu: Formal analysis, Writing—original draft; W. Cody Reynolds: Data curation, Investigation, Writing—review and editing; Isabel Abril: Writing—review and editing, Investigation; Alison McManus: Investigation, Writing—review and editing; Charlie Brenner: Writing—review and editing; Gabriel González-Irizarry: Writing—review and editing, Investigation; Leidys Gutiérrez-Martínez: Writing—review and editing, Investigation; Olivia Sun: Writing—review and editing, Investigation; Jonathan Rosand: Conceptualization, Writing—review and editing, Funding acquisition; Rudolph E. Tanzi: Conceptualization, Writing—review and editing, Funding acquisition; Steven E. Arnold: Conceptualization, Writing—review and editing, Funding acquisition; Edmarie Guzmán-Vélez: Conceptualization, Project administration, Supervision, Methodology, Writing—original draft. There was no patient or public involvement in the design, conduct and reporting of the trial. Dr. Guzmán-Vélez and Mr. Reynolds accessed and verified the underlying data reported in the manuscript.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The study protocol is available in the Supplementary Materials.

Declaration of interests

Drs. Brenner and Tanzi are on the scientific advisory board and hold equity in Niagen Bioscience. Dr. Arnold has received grants or contracts from AbbVie, AC Immune, Alzheimer's Association, Athira, Challenger Foundation, Novartis, Seer Biosciences, Venture Well, ChromaDex, Ionis Pharmaceuticals, Janssen Pharmaceuticals, John Sperling Foundation, NIH, Gatehouse Bio, Eli Lilly/Fortrea, and Superfluid Dx. He is also a consultant for Allyx Therapeutics, BioVe, Bob's Last Marathon, Merck, Jocasta Neuroscience, Sage Therapeutics, Sanofi, and Vandria, and has received payment for expert testimony for Foster and Eldredge, and ProSelect Insurance Co. All other authors have no declarations of interest directly related to the contents of the work presented herein.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103633.

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