Effects of nicotinamide adenine dinucleotide precursors on measures of physical performance and physical frailty: A systematic review

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Abstract

Background Nicotinamide adenine dinucleotide (NAD) is a key molecule in muscle metabolism and energy production; skeletal muscle concentrations are low in older people with sarcopenia. Although preclinical data suggest beneficial effects of NAD precursor supplementation, the effects on skeletal muscle function and physical frailty in humans are unclear. This systematic review evaluated the effects of NAD precursor supplementation on measures of physical performance and physical frailty in humans.

Methods We included randomized controlled trials assessing outcomes relevant to either physical performance or any of Fried’s frailty phenotype domains: slowness, weakness, exhaustion, low physical activity and weight loss. All review stages were conducted independently by two separate authors. A systematic search strategy was used searching multiple databases (MEDLINE, EMBASE, CINAHL, CENTRAL, ISRCTN, ClinicalTrials.gov, NHS e-Library, and Google Scholar) to find appropriate trials. Risk of bias was assessed using the Cochrane Risk-of-Bias 2 tool. Results were grouped by intervention and phenotypic domain and were described through narrative synthesis. Sensitivity analyses were conducted for trials with a mean age >60 years and trials with low risk of bias.

Results Twenty-six trial populations across 23 studies met inclusion criteria; size ranged from 2 to 77 participants. No trials assessed frailty as a composite outcome, though at least one Fried frailty domain was assessed in almost all included trials. A range of interventions were investigated; niacin (n = 8) and nicotinamide riboside (n = 7) were the most commonly assessed. Most trials examined short-term interventions of up to 6 months duration, with 13 out of 26 trials lasting 1 week or less. A total of 96 primary outcomes were assessed across trials, 10 of which were in favour of an NAD precursor whereas 1 was in favour of placebo; the remainder were not statistically significant in any clear direction. Methodological heterogeneity across trials precluded meta-analysis for any outcome. Trial populations were heterogeneous and only four trials enrolled participants with a mean age ≥60 years. Risk of bias analysis found unclear or high risk of bias in all but one trial. There was no clear pattern as to whether NAD precursors improved any measure of physical performance or any domain of the frailty phenotype; the majority of trials reported neutral findings for most outcomes.

Conclusions There is insufficient evidence to ascertain whether NAD precursor supplementation can improve physical performance or physical frailty measures in humans. Future trials need to be longer, larger, and target older people with skeletal muscle dysfunction.

Keywords Physical frailty; Physical performance; Systematic review; Nicotinamide adenine dinucleotide
Introduction

Frailty is a health state characterized by increased vulnerability to stressors and is independently associated with adverse clinical outcomes including impaired quality of life, increased emergency hospital admission, disability and earlier death. One of the two major ways to conceptualize frailty is through a phenotype model of physical frailty, describing a state of impaired energy metabolism operationalized as a spiral of age-related weakness, exhaustion, low activity and weight loss. Levels of physical activity fall as the frailty phenotype progresses, and this reduced activity leads to further weakness and impaired physical performance. There are currently few treatments shown to prevent or improve frailty, with the exceptions of resistance exercise training and possibly high-protein nutritional interventions. Thus, there is a need for evidence-based treatments that are able to improve skeletal muscle function and which could slow or reverse patients’ progression to the state of frailty.

Nicotinamide Adenine Dinucleotide (NAD) is present in all human cells and plays a role in several key cellular processes including adenosine triphosphate (ATP) production and DNA repair. Older people are more likely to have low concentrations of intracellular NAD than younger people, possibly due to increased CD38 activity with ageing, and consequent metabolism of NAD. Concentrations of NAD in skeletal muscle biopsies from patients with sarcopenia are lower than those found in controls, and correlate with measures of muscle strength. Supplementation with NAD precursors has demonstrated encouraging results in older mice including improved physical function and delayed onset of chronic disease. It is possible that supplementation of NAD may be able to improve energy production across a range of tissue types including skeletal muscle, with consequent benefits to physical performance and frailty in older people.

To date there has not been a systematic review analysing human trials of NAD precursors to assess the effect of their supplementation on physical performance and frailty. The aim of this trial was therefore to systematically review the published literature to examine whether nicotine adenine dinucleotide (NAD) precursors have beneficial effects on these outcomes.

Methods

Protocol and systematic search activity

We conducted a systematic review according to a prespecified protocol, which was registered on the PROSPERO database of systematic review protocols (CRD1392864) prior to beginning the review process. Eight databases were searched [MEDLINE (Ovid), EMBASE (Ovid), CINAH, CENTRAL, ISRCTN, ClinicalTrials.gov, NHS e-Library, and Google Scholar] from the inception of each database up to 15th September 2021 using a systematic search strategy (provided in Supporting Information). References of all included trials were hand-searched to find additional appropriate papers.

Included studies, participants, interventions, and outcomes

The search strategy was limited to randomized controlled trials in human adults (≥18 years old) where at least one group received a single NAD precursor whereas another group received either placebo or usual care. No language restrictions were imposed. Trials with co-interventions were acceptable for inclusion provided that both trial arms received the same co-intervention. If an unpublished trial was found the authors were contacted on two occasions to request the data.

The range of outcomes to be included was drawn broadly to reflect the range of domains that form part of the frailty phenotype and the heterogeneity of physical performance measures used across clinical trials. Any measures with an association with either physical performance or one of the five Fried domains were therefore included (walk speed, strength, exhaustion, physical activity, and weight change). Populations from all clinical and community contexts were eligible for inclusion. No minimum follow-up time from baseline to outcome measurement was stipulated.

Inclusion assessment

Two reviewers (F. J. B. and A. H.) independently assessed each title retrieved through the systematic search and handsearching. Titles were screened for inclusion; if trial appropriateness remained unclear the abstract was retrieved, and if either reviewer deemed that the abstract was appropriate or of unclear appropriateness, the full text paper was reviewed. Where authors disagreed on trials appropriateness for inclusion, they discussed their rationale in attempt to reach consensus. If consensus was not reached a third reviewer assessed the paper (M. D. W.).

Risk of bias

The risk of bias was assessed independently by both reviewers to assess the risk of bias for each included trial manuscript. We extracted data on risk of bias from each paper onto a bespoke proforma using categories derived from the Cochrane Risk of Bias tool. Disagreements were resolved using the same method discussed for inclusion assessment. Papers were not excluded from analysis based on their risk of bias.
Data extraction

Two reviewers (F. J. B. and A. H.) independently extracted data from each included manuscript using a standard proforma. In addition to key outcomes, data including mean participant age, sex, adverse effects of trial medication, and sources of funding were extracted. Differences in data extraction were discussed to reach consensus; where consensus was not reached cases were resolved by a third reviewer (M. D. W.). Where papers did not provide sufficient data, we attempted to contact authors on a maximum of two occasions to request the missing information.

Outcomes were grouped into the most appropriate of the five Fried frailty phenotype domains. Walk speed outcomes on a short course (10 m or less) were grouped together. All measures of strength were grouped together, including outcomes where strength was likely to be the most significant factor (e.g. the maximum number of press-ups). Physical activity included self-reported or objective measures of overall work and leisure-time activity. Exhaustion included measures of subjective fatigue or subjective exhaustion to align with the original Fried phenotypic criteria. All measures of body mass, including measures of lean mass and fat mass, were included in the ‘body weight’ domain; in this domain, outcomes (such as BMI) were only considered positive if changes were towards a healthier state (such as approaching a healthier BMI). All other measures of physical performance that did not clearly fit into one of the five domains of the Fried frailty phenotype were included but reported under a separate non-frailty specific physical performance domain; this also included objective measures of fatigability which failed to adequately meet criteria for either the exhaustion or strength domains.

Data synthesis

Descriptive data on baseline trial characteristics and individual trial outcomes were tabulated. Tabulated summaries were generated combining results across trials for each NAD precursor and for each frailty domain. Where significance tests were not available in the published papers, significance was calculated using independent Student’s t-tests (for continuous data) or Fisher’s exact tests (for categorical data) where this was possible from reported results. A P-value of <0.05 (reported in the original paper or calculated) was required for a result to be deemed statistically significant and thus flagged as a favourable (statistically significant improvement in physical performance) or unfavourable (statistically significant worsening in physical performance) finding. Results not reaching statistical significance were flagged as neutral findings, as were results where significance could not be calculated.

Findings were tabulated into results tables according to both their intervention used and domain assessed. A description of adverse effects was generated but not subjected to statistical analysis due to a lack of information. Two pre-planned subgroup analyses were conducted. The first analysis included only trials with a mean age ≥60 years old, reflecting a demographic with a higher likelihood of having phenotypic frailty. The second analysis included only trials with a low risk of bias.

Results

Figure 1 shows the PRISMA diagram for trial selection. Five hundred and sixty-three titles were found from databases and 15 were found through handsearching; 31 full papers were assessed for eligibility. Of these, seven papers were removed because they did not present data for an appropriate outcome, and one was removed due to not being a controlled trial. We therefore included 23 papers in the data synthesis. Authors of two unpublished trials were unable to provide data as trials had not completed recruitment or analysis. Three included papers reported results from two different trial sub-populations. For these papers, sub-populations have been presented separately from each other as ‘series A’ or ‘series B’ and are counted as separate trials for the purposes of this analysis, giving a total of 26 included trials. The characteristics of each trial are listed in Table 1. Missing significance values could not be calculated due to a lack of suitable data in study reports.

Summary of included trials

Twelve trials were of parallel group design and 14 were crossover trials. Trial sizes ranged from 2 to 77 participants, with half of all trials enrolling 12 or fewer participants. Intervention duration ranged from 2 h to 6 months, with half of all trials lasting 2 weeks or less. Eight RCTs assessed niacin (NA) [19–22,25,31], of these four were placebo-controlled and four had usual care control groups. Seven trials assessed nicotinamide riboside (NR) against placebo [34–39]. Five trials assessed acipimox against placebo [23,24,30,32,33]. Three trials assessed reduced nicotinamide adenine dinucleotide (NADH) against placebo [26,28,29]. Two trials assessed nicotinamide mononucleotide (NMN) against placebo [40,41]. One trial assessed nicotinamide (NAM) against placebo [27]. All frailty domains were assessed across the included trials. In addition, several other outcomes were assessed that did not fit the five Fried phenotypic domains but were relevant to skeletal muscle function; such outcomes were reported under a separate ‘physical performance’ domain.
Risk of bias

Figure S1 displays the risk of bias assessed for each included trial. Only one trial was assessed to have a low risk of bias, whereas 10 had some concerns and 15 had a high risk of bias.

Summary of findings

One hundred and nine results were reported across the 26 included trials, summarized in Table 2. Of these, 96 assessed the main outcomes whereas 13 assessed adverse effects. Ten results showed a significant benefit of NAD precursors over placebo; one showed a significantly worse outcome than placebo; 51 were statistically non-significant and 34 provided insufficient data for significance to be confidently ascertained (also considered non-significant in this analysis). We did not attempt meta-analysis of any results, as heterogeneity of populations, trial methods and outcomes meant that such an analysis would not be meaningful.

Domain 1 – Gait speed

Two trials assessed various measures of gait speed.30,34 No assessments demonstrated any significant differences between placebo and treatment groups in this domain.

Domain 2 – Strength

Within this domain four trials assessed grip strength,26,34,37,41 one study assessed upper body strength in terms of number of press-ups achieved40 and five trials assessed measures of lower limb strength.28,34,36,41 Three of the 22 assessments showed significant benefits of NAD precursors in strength; no interventions were significantly unfavourable compared with placebo. The only significant improvements found in this domain were from assessments of lower limb strength.28,36

Domain 3 - exhaustion

Twelve trials assessed subjective measures of exhaustion or fatigue.19,24–26,28,29,34,36,39 Two trials assessed perceived fatigue while participants were at rest,26,29 both comparing NADH against placebo. All remaining trials assessed perceived ratings of exhaustion during physical activity.19,24,25,28,34,36,39 Exhaustion was assessed under a variety of levels of strenuous exercise. Only one of 20 results noted significant benefits from NAD precursor supplementation.26 In this trial of people with chronic fatigue, the NADH group had a significantly higher proportion of participants’ fatigue scores dropping by 10% over the course of the study compared with the placebo group.
| Authors, year | Country | Sample size | Mean age [median] | NAD precursor | Control | Dosing regimen | Trial type | Relevant outcomes included | Additional notes |
|---------------|---------|-------------|-------------------|---------------|---------|----------------|-----------|---------------------------|-----------------|
| Bergström et al. 1969 Series A | Sweden | 2 | Range: 20–33 | Niacin 1 g IV and 600 mg oral | Usual care | During a 2-hour break between exercises | Unblinded parallel trial | Physical performance while cycling | Subjective fatigue during >60 min of exercise Physical performance while cycling at submaximal rate Total workload performed during exercise (kcal) Time to exhaustion during intense exercise for 30–60 seconds |
| Bergström et al. 1969 Series B | Sweden | 13 | Range: 20–33 | Niacin 1 g IV and 600 mg oral | Usual care | During a 1-hour break between exercises | Unblinded parallel trial | Physical performance while cycling | |
| Pernow et al. 1971 | Sweden | 4 | 24 | Niacin 500 mg IV and 600 mg oral | Usual care | Between leg exercises | Unblinded crossover trial | Physical performance while cycling at submaximal rate Time to run 10 miles (s) | Time to reach exhaustion at 60% VO$_{2\text{max}}$ |
| Galbo et al. 1976 | Denmark | 7 | 24 | Niacin: 1 g IV and 200 mg oral with 250 mg IV in breaks between exercises | Usual care | Immediately before and during exercise | Unblinded crossover trial | Physical performance while cycling at submaximal rate | |
| Norris et al. 1978 | USA | 10 | Not provided | Niacin 2 g oral | Placebo | 2 h prior to outcome assessment | Single-blind crossover trial | Physical performance while cycling at submaximal rate | Time to run 10 miles (s) Adverse effects Total energy expenditure during 3 h of walking at 45% VO$_{2\text{max}}$ |
| Gautier et al. 1993 | Belgium | 6 | Range: 21–25 | Acipimox 250 mg oral | Placebo | Single dose 1 h before outcome assessment | Single-blind crossover trial | Physical performance while cycling at submaximal rate | Adverse effects Rate of perceived exertion after 120 min at 50% VO$_{2\text{max}}$ Energy expenditure at 50% VO$_{2\text{max}}$ over 120 min |
| Head et al. 1993 | UK | 8 | Range: 19–36 | Acipimox 250 mg oral | Placebo | 2 doses daily for 5 doses prior to outcome assessment | Single-blind crossover trial | Physical performance while cycling at submaximal rate | Participants were all medical students who ran daily |
| Murray et al. 1995 Series A (niacin vs placebo) | USA | 10 | 33 | Niacin 3.5 mg/kg of lean body weight every 15 min during exercise | Placebo | During outcome assessment | Double-blind crossover trial | Physical performance while cycling at submaximal rate | Time to cycle 3.5 miles Perceived exhaustion during 3.5 miles on cycling machine (10 item Borg scale[51]) |
| Murray et al. 1995 Series B (niacin + energy drink vs placebo + energy drink) | USA | 10 | 33 | Niacin 3.5 mg/kg of lean body weight every 15 min during exercise | Placebo | During outcome assessment | Double-blind crossover trial | Physical performance while cycling at submaximal rate | Both control and trial arms also given energy drink as co-intervention |

(Continues)
| Authors, year       | Country  | Sample size | Mean age [median] | NAD precursor | Control    | Dosing regimen | Trial type                              | Relevant outcomes included                                                                 | Additional notes                                                                                   |
|---------------------|----------|-------------|-------------------|---------------|------------|----------------|------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Forsyth et al. 1999 | Austria  | 26          | 39.6              | NADH 10 mg oral | Placebo    | Daily for 4 weeks | Double-blind crossover trial             | Frequency of 10% reduction in ‘fatigue score’ based on CDC chronic fatigue criteria [52]       | Grip strength                                                                                     |
| Osar et al. 2004    | Turkey   | 30          | 58                | Nicotinamide 50 mg/kg oral | Placebo | Daily for 1 month | Single-blind parallel group | BMI (kg/m²) Adverse effects | Participants all had poorly-controlled diabetes mellitus                                        |
| Mero et al. 2008    | Finland  | 8           | 25                | NADH 30 mg oral    | Placebo    | Daily for 4 weeks | Double-blind crossover trial             | Jump height during 5 points in time across trial Perceived rating of fatigue during 5 points in time across trial during breaks between exercises VO₂max | Subjective measures of fatigue: SF-36 ‘vitality’ [53] Fatigue impact scale ‘physical dimension’ [54] Fatigue intensity using a visual analogue scale 6 min hall walk test Physical performance during intense exercise Adverse effects Body weight Adverse effects | Participants all had ischaemic heart disease with reduced left ventricular ejection fraction |
| Alegre et al. 2010  | Spain    | 77          | 47                | NADH 20 mg oral | Placebo    | Daily for 2 months | Double-blind parallel group |                                                                                                  |                                                                                                  |
| Halbirk et al. 2010 | Denmark  | 24          | 59                | Acipimox 250 mg oral | Placebo | 4 times daily for 4 weeks (±1 day) | Double-blind crossover trial | Energy over 90 min of exercise at 50% VO₂max |                                                                                                  |
| Kim et al. 2011     | South Korea | 47       | 60 (trial 57; placebo 62) | Niacin 500 mg oral | Placebo | Daily for 4 weeks, then twice daily for 4 weeks | Double-blind parallel group | Body weight | Adverse effects                                                                                   |
| Nelleman et al. 2014 | Norway   | 8           | [30] Range: 23–46 | Acipimox 250 mg oral | Placebo | Four doses across 16 h prior to outcome assessment | Double-blind crossover trial | Energy over 90 min of exercise at 50% VO₂max |                                                                                                  |
| Makimura et al. 2015 | USA      | 31          | 46 (trial 47; placebo 45) | Acipimox 250 mg oral | Placebo | 3 times daily for 6 months | Double-blind parallel group | Chance in Bouchard physical activity record [52]                                               |                                                                                                  |
| Authors, year | Country | Sample size | Mean age [median] | NAD precursor | Control | Dosing regimen | Trial type | Relevant outcomes included | Additional notes |
|--------------|---------|-------------|------------------|---------------|---------|----------------|------------|---------------------------|-----------------|
| Martens et al. | USA     | 24          | 66               | NR 500 mg     | Placebo | Twice daily for 6 weeks | Double-blind crossover trial | %Change in BMI %Change in lean mass Adverse effects 4 m walk time 6 min walk distance Leg extension maximum torque Leg extension rate of torque development Leg flexion maximum torque Leg flexion rate of torque development Grip strength 5 times sit to stand test Rate of perceived exertion at various VO₂ levels Leg fatiguability (heel rise test) VO₂max Time to exhaustion during approximately 10 min of intense exercise | |
| Dollerup et al. | Denmark | 40          | 59 (trial 58, placebo 60) | NR 1 g oral | Placebo | Twice daily for 12 weeks | Double-blind parallel group | BMI Adverse effects Total body mass Total lean mass Total fat mass Fat mass percentage | All participants were men with obesity |
| Dolopikou et al. | Greece | 12          | 23.0             | NR 500 mg oral | Placebo | Single dose 2 h prior to exercise | Double-blind crossover trial | Isometric peak leg extension torque Concentric peak leg extension torque VO₂max | |
| Dolopikou et al. | Greece | 12          | 72.9             | NR 500 mg oral | Placebo | Single dose 2 h prior to exercise | Double-blind crossover trial | Isometric peak leg extension torque Concentric peak leg extension torque VO₂max | (Continues)

(Continues)
| Authors, year          | Country | Sample size | Mean age [median] | NAD precursor       | Control  | Dosing regimen | Trial type                                   | Relevant outcomes included                                                                 | Additional notes                                                                                       |
|-----------------------|---------|-------------|-------------------|---------------------|----------|----------------|----------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Elhassan *et al.* 2019 | UK      | 12          | [75]              | NR 1 g oral         | Placebo  | Daily for 3 weeks | Double-blind crossover trial                | Leg extension percentage decrease in torque following 30 repetitions                              | Grip strength BMI Adverse effects All participants were “marginally overweight but otherwise well older men” Double-blind crossover trial |
| Remie *et al.* 2020   | Netherlands | 13          | 59                | NR 1 g              | Placebo  | Daily for 6 weeks | Double-blind crossover trial                | Rate of perceived exertion (Borg scale [51] giving scores between 6–20 during 1 h of cycling at 60% maximum power output) Mean VO₂ during 1 h of cycling at 60% maximum power output | Grip strength Number of push-ups VO₂max VO₂ at first and second ventilatory thresholds Peak workload Peak power Power at first ventilatory threshold Power at second ventilatory threshold Single leg stance test (eyes closed) Body mass BMI Fat-free mass Body fat percentage Adverse effects Double-blind crossover trial |
| Stocks *et al.* 2021  | UK      | 21          | 23                | NR 1 g oral         | Placebo  | Daily for 7 days  | Double-blind crossover trial                |                                                                                                  | All participants were healthy amateur runners                                                                                                     |
| Liao *et al.* 2021    | China   | 48          | 36                | NMN 150 mg NMN 300 mg NMN 600 mg Oral | Placebo  | Daily for 6 weeks  | Double-blind parallel group                |                                                                                                  | All participants were healthy amateur runners                                                                                                     |
| Authors, year | Country | Sample size | Mean age [median] | NAD precursor | Control | Dosing regimen | Trial type | Relevant outcomes included | Additional notes |
|--------------|---------|-------------|------------------|---------------|---------|----------------|-----------|---------------------------|-----------------|
| Yoshino et al., 2021 | USA | 25 | Placebo 61, NMN 62 | NMN oral | Placebo | Daily for 10 weeks | Double-blind parallel group | Grip strength
Sum of peak isometric (at speeds of 60 and 80 degrees per second) and isokinetic torque of knee extensors and flexors of the dominant leg
Decline of isokinetic torque of the knee extensors during two consecutive phases of fatiguing exercise and recovery period
Recovery of isokinetic torque of the knee extensors during two consecutive phases of fatiguing exercise and recovery period
BMI
Fat mass
Fat-free mass
Adverse effects | Participants were all postmenopausal women with prediabetes |
Domain 4 – Physical activity

One trial assessed physical activity as an outcome, finding no significant differences in Bouchard’s activity scores between people taking 6 months of acipimox or placebo.33

Domain 5 – Measures of weight and body mass

Eight trials assessed measures of weight and body mass.27,31,33,35,37,38,40,41 Of these, seven did not report any significant differences in outcome measures between those taking NAD precursors and placebo. Remie et al. reported that although weight remained unchanged after 6 weeks of NR (P = 0.055), there was a significant decrease in fat percentage (mean change −1.34%, P = 0.02) and significant increase in fat-free mass (+1.34%, P = 0.02) across participants.38

Additional domain – Measures of physical performance

Nineteen trials reported results on other measures of physical performance.19–25,28,30,32,34,36,37,39–41 Trials of NR, acipimox, niacin, NADH and NMN assessed this domain. In total 28 outcomes were non-significant, four were favourable and one was unfavourable. One paper found significant differences in power output at two different ventilatory thresholds (P < 0.01 in both cases) and an improvement in oxygen uptake at ventilatory threshold (P = 0.03).40 In each case, a trend was present where groups taking higher doses of NMN demonstrated incrementally higher mean outcome point estimates. However, the trial did not find notable differences in several other outcomes such as peak power, peak workload or VO2max. One study noted significantly reduced levels of muscle fatiguing during weight exercises in its older cohort (NR 36.3, SE 1.1; placebo 42.6, SE 1.4 P < 0.05).21

Adverse effects – Note that significance was not assessed as part of this analysis

Thirteen included trials commented on adverse effects.21,23,30,31,33–38,40,41 Of these, 10 (77%) described higher frequencies of adverse effects in the intervention groups than in the control groups. Six trials commented on flushing in their results,22,23,30,31,33,34 though only four of these mentioned the frequency of this effect being higher in the trial group than the control group.22,23,30,33 The NAD precursors given in trials that commented on flushing were niacin and acipimox. NMN was the only NAD precursor to have shown lower or equal frequencies of adverse effects across the two trials that assessed them.
Subgroup analysis: Cohorts with mean age >60 years

Four trials assessed outcomes in cohorts with a mean age above 60 years. One of these trials assessed NAD concentrations in participants, no trials assessed any measures of sarcopenia or frailty. As shown in Table 3, only two of the 29 relevant reported results across these trials showed statistically significant improvements in outcomes for the NAD precursor compared with placebo (for concentric torque and leg strength fatigability, both from the same trial). 41

Subgroup analysis: Trials with a low risk of bias

Only one trial was considered to be at low risk of bias. This paper reported that although weight remained unchanged after 6 weeks of 500 mg NR, there was a significant decrease in fat percentage and significant increase in fat-free mass.

Discussion

Summary of findings

Our review found data on the effects of six NAD precursors on a broad range of physical performance and physical frailty outcomes. The majority of reported results were neutral, failing to find either a statistically significant benefit or worsening of outcomes from NAD precursor supplementation compared with control groups. Results that showed significant benefit did not cluster together under particular domains or with particular NAD precursors, suggesting that at present, there is no strong signal of benefit for any NAD precursor on domains of physical frailty or other measures of physical performance. These findings remained the case when analyses were restricted to trials of participants with a mean age of 60 years or over.

Limitations of included evidence

The existing evidence reviewed here has major limitations. Most included trials were very small in size (12 or fewer participants in half the trials), which severely limited their ability to detect clinically important improvements in outcome measures. Although combining results from different trials in meta-analysis would provide a way to partially address this issue, meta-analysis was not possible due to the range of different outcome measures and interventions employed. Most trials studied interventions given for a very short duration; a week or less in half the included trials, and several trials used acute administration of NAD precursors. The durations of interventions in several included trials were unlikely to be long enough to manifest changes in outcomes such as weight, physical activity levels or feelings of exhaustion. Significance levels were not available for some outcomes, and insufficient data were contained in papers to enable these missing significance levels to be calculated – many studies used a crossover design which precludes a simple comparison of presented mean and standard error summaries.

Most included trials had an uncertain or high risk of bias. Common reasons for this included a lack of numerical data and deficiencies in the completeness of reporting of methods or results. Several NAD precursors are known to cause flushing, which may compromise effective trial blinding and thus introduce bias. Aspirin can be used to mitigate the risk of flushing from NAD precursors but use of aspirin or related agents as adjunctive therapies was not reported in the included trials. Use of these agents may improve blinding for future trials. NMN and NR may demonstrate fewer adverse effects than other NAD precursors, which may reduce the risk of bias when using these agents. Adverse events were poorly reported, and even where reported were confined to known side effects of NAD precursors such as flushing. This information needs to be collected in a systematic way in future trials to enable a thorough assessment of the balance of benefits and risks of therapy to be made.
The majority of trials had a mean age of below 60 years, and most trials recruited healthy individuals. Only a very small number of trials have assessed NAD precursors’ effects on physical performance or components of physical frailty in older people, who are the group most likely to require such therapies in clinical practice. This is in part due to many included trials being conducted prior to the recognition of the therapeutic potential of this drug class in addressing age-related conditions, but also reflects the focus of most included trials understanding physiology in health rather than in disease.

Limitations of the review process

Despite conducting the review process across multiple databases, without language restriction, and with additional handsearching of references from included papers, it is possible that some literature was missed. Our ability to synthesize the findings was limited by the heterogeneous nature of the populations, trial designs and outcomes, and by the fact that included trials were not designed specifically to examine the domains of the physical frailty phenotype. Although our review found only a few favourable outcomes, it is possible that even this low number overestimates any benefit of NAD precursor supplementation. Some of the statistically significant findings from this review may represent type I error; from the 102 results reported, approximately 5 results would be expected to be significant at $P < 0.05$ by chance.

Implications for research

There is insufficient evidence at present to recommend, or to rule out, the use of NAD precursors as a treatment to improve physical performance or components of the physical frailty phenotype, particularly in older people who are most likely to experience impaired physical performance and other aspects of the physical frailty phenotype. Given that intracellular NAD concentrations are lower in older people, this is the group most likely to benefit from NAD replacement. Additionally, positive findings from studies in mice typically involve the rejuvenation of age-related pathologies and phenotypes rather than the improvement of physical function in young healthy mice. Future trials should therefore target older people and those with impaired physical performance or features of the physical frailty phenotype. In addition, NAD precursors should be administered for long enough to produce measurable differences in outcomes; for outcomes such as weight or fat mass, this is likely to require several months of treatment. Outcome measures should include commonly used measures relevant to the diagnosis of sarcopenia and phenotypic frailty such as handgrip strength, walk speed and sit-to-stand time. Trials need to be large enough to detect minimum clinically important differences in these measures; this is likely to require sample sizes of between 50 and 100 per arm depending on the measure used. Finally, future trials should consider the concomitant administration of aspirin in both arms to minimize side-effects and preserve blinding.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Search strategy.
Figure S2. Risk of Bias assessment.
Table S1. Niacin (NA) outcomes summary.
Table S2. Nicotinamide riboside (NR) outcome summary.
Table S3. Acipimox outcome summary.
Table S4. Reduced nicotinamide adenine dinucleotide (NADH) outcome summary.
Table S5. Nicotinamide mononucleotide (NMN) outcome summary.
Table S6. Nicotinamide (NAM) outcome summary.

Conflicts of interest

None to declare.
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