Protein intake and changes in whole-body lean/fat-free mass, measures of muscle size or mass, strength, and physical function in healthy adults: an updated systematic review and Bayesian model averaged dose-response meta-analysis*

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Abstract

Background: Previous dose-response meta-analyses of protein intake have generally assumed linear relationships or imposed a fixed "breakpoint", rendering inferences conditional on a particular functional form. We therefore estimated the dose-response associations between protein intake and changes in whole-body lean/fat-free mass, measures of muscle size or mass, strength, and physical function in healthy adults, with and without resistance training (RT), while accounting for uncertainty about the shape of these associations. **Methods:** We performed an updated systematic review of parallel-group randomised controlled trials that assigned participants to dietary or supplemental protein interventions, placebo, or control conditions. We searched MEDLINE, Embase, CINAHL, and Web of Science Core Collection through 14 September 2026 and assessed risk of bias with Cochrane RoB 2. Standardised mean changes were synthesised using hierarchical arm-based Bayesian meta-regression. For each outcome, we fit 26 candidate models representing no association, linear relationships, linear splines with a knot at 1.6 g/kg/day, and nonlinear smooth functions. Models were then averaged using leave-one-out cross-validation stacking weights. Pairwise contrasts between protein intakes were evaluated against a preregistered smallest effect size of interest of ±0.1 standardised units, using a 95% posterior-probability criterion. We additionally fit a range of sensitivity analyses including Mundlak regression, strict within-study contrasts, common sample models of achieved- or assignment-derived protein intake, errors-in-variables models, residual-correlation models, and intervention strategy (addition or energy matched substitution). Finally, primary dose-response models examined body-mass relative total protein intake (g/kg/day) and thus we also examined models with protein as absolute total intake and absolute supplementation (both in g/day). **Results:** We identified 119 eligible studies, of which 95 included sufficient data to contribute 254 study arms, 4,931 participants, and 1,864 eligible baseline-to-follow-up contrasts to the primary analyses. Primary dose-response functions across outcomes generally showed modest positive associations, particularly with RT. However, no supported contrast between a current and proposed protein intake resulted in a conclusively meaningful gain in outcome from increasing intake or a meaningful loss from decreasing it. Increases or decreases of approximately 0.2 to 0.5 g/kg/day from a current intake were generally supported as practically equivalent. Contrasts between more widely separated intakes were uncertain rather than demonstrably meaningful or equivalent. We could not identify a clearly optimal intake. Inference was robust across the completed sensitivity families, although stricter within-study analyses produced dose-response functions of attenuated magnitude. The absolute total intake and absolute supplementation dose analyses did not materially alter the overall interpretation based on relative total intake. Most trials raised some concerns or were at high risk of bias. Publication-bias adjustment attenuated outcome-level estimates towards zero, and certainty was low or very low for all GRADE-assessed contrasts. **Conclusions:** Protein intake showed a modest positive association with outcomes and so those wishing to maximise outcomes may see it as reasonable to aim for higher protein intakes. However, the estimates were not sufficiently precise to establish that the gain from increasing intake, or the loss from decreasing it, exceeds a practically meaningful threshold. Comparisons between more widely separated intakes, and the extent to which the observed associations represent causal dose effects, remain uncertain particularly as data are sparse at low and high intakes (2.0% of primary-analysis arms were below 0.8 g/kg/day and 8.3% were above 2.2 g/kg/day). As such, whilst our results do not establish adequacy of the RDA, we suggest that practical recommendations for changes to intakes from typical habitual values should be based upon considerations other than just their effectiveness for the outcomes examined here (e.g., cost, appetite and food preferences, energy restriction). Lastly, we suggest that future research should make concerted attempts to address the shortcomings of the current body of literature. **Funding:** Kieser Australia provided in-kind support through consultancy and employment. **Registration:** Open Science Framework, w2qpx.

Keywords: protein, lean soft tissue mass, fat free mass, muscle, strength, physical function, dose-response, resistance training, bayesian

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Introduction

Protein intake recommendations increasingly vary as the evidence base has grown and typically according to life stage, physical activity, and clinical context. The long-standing and widespread recommended dietary allowance for healthy adults has been ~0.8 g/kg/day, whereas recent expert guidance commonly advocates ~1.0–1.2 g/kg/day for healthy older adults, ~1.2–1.5 g/kg/day during acute or chronic illness, and higher intakes for physically active adults or during intentional weight loss[1–3]. The Dietary Guidelines for Americans, 2025–2030, released in January 2026, went further by introducing a general protein target of 1.2–1.6 g/kg/day in addition to emphasizing nutrient-dense animal and plant protein sources[4]. Recent perspectives have however reached different judgements about the numerical target while questioning whether evidence centred on weight management is sufficient for universal application[5,6], and the latest systematic review conducted to update the protein dietary reference intakes found the available evidence insufficient to redefine requirements across life stages[7]. There are similarly varied recommendations regarding protein targets across different athletic populations and those engaged in practices such as resistance training (RT) ranging ~1.4-2.2 g/kg/day[8–13]. Across general and athletic populations, protein-intake recommendations have typically been derived from a heterogeneous evidence base consisting of nitrogen-balance and indicator amino-acid oxidation studies, acute tracer studies of muscle protein synthesis, observational evidence, small or indirect intervention trials, and expert consensus, whereas recommendations for specific health or performance outcomes should, wherever possible, be anchored in appropriately conducted meta-analyses of high-quality randomised controlled trials (RCTs) that directly manipulate protein intake and measure outcomes of interest. The noted divergent recommendations are also reflected in the lack of recent expert consensus on acceptance of whether global upper and lower protein intake recommendations can be made or are appropriate[14], and this underscores the need to quantify how both relative and absolute protein exposure relates specifically to changes in whole-body lean/fat-free mass, measures of muscle size or mass, strength, and physical function.

A number of systematic reviews and meta-analyses of RCTs examining protein intake have been conducted aimed at examining dose-response relationships to support recommendations. In a recent systematic review and meta-analysis Nunes et al.[15] examined the dose-response association of protein intake relative to body mass upon whole-body lean/fat free mass, measures of muscle size or mass, strength, and function both with and without concomitant RT. However, whilst they examined both categorical protein intakes ('<1.2 g/kg/day', '1.2–1.59 g/kg/day' and ' 1.6 g/kg/day') as well as continuous (as g/kg/day) in the latter only linear functional forms were utilised which imply a constant slope of proteins relationship with outcomes across varied intakes. It may be the case that some kind of non-linear functional form may better describe the dose-response relationship. For example, in earlier work Morton et al.[16] used a piecewise linear model and estimated a so-called "breakpoint" where a plateau in protein intakes relationship might occur for whole body fat free mass (breakpoint = 1.62 g/kg/day [95%CI: 1.03, 2.20]). Tagawa et al.[17,18] have also reported possible non-linear functional forms using piecewise splines but inflection points were selected arbitrarily; 1.3 g/kg/day for strength outcomes without RT and for whole body lean mass with RT, and 1.5 g/kg/day for strength outcomes with RT. Both these approaches are somewhat limited in specifically forcing a single "breakpoint" or "flex" in the modelled functional forms.

The meta-analyses noted above have generally examined protein intake relative to body mass (i.e., g/kg/day). Although this scaling facilitates interpretation of the intake that may be adequate or optimal for an individual of a given body mass, absolute total protein intake (i.e., g/day) has received less attention and addresses the complementary question of whether outcomes vary with the total quantity consumed irrespective of body mass. In free-living RCTs, however, achieved total protein intake, whether expressed in relative or absolute terms, is usually a post-randomisation exposure derived from reported dietary intake, sometimes combined with the amount supplemented where this is the intervention strategy, and may therefore reflect adherence, dietary compensation, measurement error and, depending on its calculation, changes in body mass. Associations with achieved intake consequently do not retain the full causal protection afforded by randomisation. By contrast, the absolute supplementation dose assigned to each trial arm is a pre-specified component of the randomised intervention and is therefore more closely aligned with an intention-to-treat, treatment-policy causal estimand. Nevertheless, it estimates the effect of assignment to that supplementation dose rather than the effect of the amount actually consumed or of total protein intake, and comparisons of

assigned doses across trials remain observational at the trial level. Some prior meta-analyses have examined absolute supplementation but typically analysed categorical supplement doses[19–22] with fewer examining supplement values using continuous models, whether linear or nonlinear[17,18,23–25]. However, none to our knowledge have examined the dose-response association of absolute total protein intake.

Whilst the dose-response models previously explored in meta-analyses may have some plausibility, at least over the range of data available, these previous analyses have also not made any attempts at comparing functional forms implied by different models. Other recent meta-analyses have taken a further step when exploring dose-response models by using model comparison approaches for the selection of the best fitting function form specification by whatever criteria were chosen to guide selection (e.g., Pelland et al.[26]; Robinson et al.[27]; Refalo et al.[28]). However, even comparing amongst different candidate models with regards to the relative evidence for, and against, different functional forms as being the underlying data generating process has limitations. Any predictions or contrasts are conditional on the candidate model selected and the selection process used. Indeed, in the inductive process of fitting models to data, even when all selected have some *a priori* plausibility, unless a specific model is being tested there is uncertainty in which of the possible models best fit and the selection process used to choose the best model. However, with Bayesian approaches to modelling it is simple to combine, in a weighted fashion determined by their relative evidence, estimates from all models examined and directly incorporate this uncertainty into the inductive model choice[29]. Adopting a Bayesian approach for evidence synthesis also allows the incorporation of prior information that might be relevant to inference. For example, we also have precise estimates of the effects of RT without additional protein intervention from previous meta-analyses for whole-body lean/fat-free mass, measures of muscle size or mass, strength, and physical function[30,31]. Most, though not all, previous protein intake intervention studies have examined RT as a concomitant intervention. As such we can also utilise these estimates, in addition to those from non-RT control groups in randomised trials, to set informative priors for the expected effect sizes at habitual protein intakes (i.e., the typical protein intakes of people taking part in intervention research examining RT without a concomitant intervention to increase protein intake).

Thus, we sought to revisit the randomised controlled trials that were included in the review of Nunes et al.[15], in addition to updating searches since the date of their last search to include any newer trials, replicating and extending the systematic searches conducted previously. Our aim was to explore, estimate, and average a range of candidate dose-response relationships between protein intake, experimentally manipulated by assignment to diet or supplementation, and whole-body lean/fat-free mass, measures of muscle size or mass, strength, and physical function in healthy adults. We primarily focus upon relative total protein intakes (i.e., g/kg/day) though include secondary exploratory analyses examining absolute total intake and absolute supplementation dose (i.e., g/day).

Methods

This systematic review was originally pre-registered in July 2025 on the Open Science Framework following the structure for registration with the International Prospective Register of Systematic Reviews (PROSPERO). The pre-registration and any updates to it is available at: https://osf.io/w2qpx/overview. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[32].

Updates to/deviations from pre-registration

Some updates were made to our pre-registered plan after initial pre-registration. These are detailed in full in the preregistration deviations supplementary documentation and also noted throughout the methods section where relevant.

Search Strategy

We replicated the databases and database-specific search strings used by Nunes et al.[15], applying the update date limits described below. Two reviewers (EAN, ML) worked independently at each screening stage. A third reviewer (JS) was available to resolve disagreements. None arose. The original strategy is available in the supplementary materials for Nunes et al.. The previous review searched through to September 2020.

We first updated the searches in MEDLINE, Embase, CINAHL, and Web of Science Core Collection on 13 July 2025, covering the period since the previous search. We reran the same database search families on 14 September 2026 to capture records added since the July 2025 update; because month-level restriction was not available in MEDLINE, Embase, or Web of Science, those searches covered publication years 2025-2026 and records already identified in 2025 were removed after deduplication. The CINAHL update began on 1 July 2025. Records were managed in EndNote and Rayyan[33]. Papers not identified in the database searches but known to the author team and meeting the inclusion criteria were also included. The PRISMA supplement reports search sources, date limits, and yields.

Inclusion/exclusion criteria

We examined studies including healthy adults and which manipulated protein intake experimentally by assignment to dietary or supplementation intervention with or without inclusion of a concomitant RT intervention performed in any settings. The following population, intervention, comparator, and outcomes (PICO) was used to guide inclusion:

- Population
  - Adult participants (healthy) aged 18 years or older.
- Intervention(s) or exposure(s)
  - Additional protein ingestion with or without the addition of resistance exercise (increasing protein ingestion as the primary intervention using nutritional supplements or diet at any dose or level).
- Comparator(s) or control(s)
  - Placebo or no intervention (control).
- Outcomes[a]
  - Whole body lean/fat free mass, measures of muscle mass/size, muscle strength, and performance in tests of physical function.

In the updated searches, studies including participants with decreased mobility, frailty, obesity, or any chronic or infectious diseases were not included[b]. Also, interventions were carefully screened for the presence of any potential active ingredient that might impact changes in the eligible body-composition or muscle outcomes other than protein (i.e. creatine, phosphatidic acid, omega-3 fatty acids, anabolic steroids, and beta-hydroxy-beta-methylbutyrate [HMB]) or if they were intended to cause weight loss (e.g., energy restriction). If a particular study testing potential active supplements had intervention groups fitting our inclusion criteria, the study was included and assessed to extract the respective arm based data of protein and control/placebo interventions only. No restrictions were imposed regarding additional protein dose or the duration of the intervention protocol. Only randomised controlled trials using parallel arm designs (i.e., where arms were independent) were included.

For primary outcomes we considered the following as valid operationalisations of these constructs: for whole body lean/fat free mass (or device-estimated muscle mass), dual-energy X-ray absorptiometry (DXA), hydrodensitometry, bioimpedance analysis (BIA), skinfolds, and/or whole-body air plethysmography (BodPod®); for measures for muscle size or mass, magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), regional[c] measures of muscle mass using DXA or BIA, and any muscle biopsy measures for

[a] In comparison to the pre-registration terminology i.e., "Whole body lean soft tissue mass (or a closely related measure i.e., fat-free mass[34]), direct measures of muscle mass/size (both whole muscle and muscle fiber), muscle strength, and performance in tests of physical function", we have, after discussion, updated the terminology throughout the manuscript and supplementary materials. Instead we use "whole-body lean/fat-free mass" and "measures of muscle size or mass". Lean soft tissue excludes bone mineral, whereas fat-free mass includes it; these terms therefore describe related but distinct body compartments[34]. Neither is a muscle-specific measure. The separate muscle-outcome group included MRI, CT, ultrasound, and muscle-biopsy measurements of muscle or fibre size, together with regional body-composition estimates, including appendicular DXA/BIA measures used as proxies for muscle mass. We refer to this mixed group as measures of muscle size or mass, rather than direct measures throughout. See the outcome terminology in the preregistration deviations.

[b] Four studies were carried over from Nunes et al.[15] which did include these populations, two of which contributed to analysis. This is detailed in the pre-registration deviations supplement.

[c] An error in extraction and coding data meant that, contrary to our initial pre-registration which detailed "appendicular" measures, all regional measures including six trunk region outcomes and also six skinfold derived regional measures were included. The primary models as well as the expanded sensitivity analyses described below were fit to the entire dataset including these and so, as noted below, we include a supplementary re-analysis of the primary models only for measures of muscle size or mass

fiber cross sectional area; for strength, any repetition-maximum (isotonic), maximal isometric, or maximal isokinetic testing for all tasks/exercises; and for physical function, timed up and go (TUG), chair-based testing (i.e., sit to stand), sit-to-stand tests, gait speed tests, balance tests, short physical performance battery tests, stair climb tests, time or distance-limited walking tests, jump tests, agility tests, flexibility tests, and any other tests involving activities of daily life.

Data extraction/coding

It was originally planned that data would be extracted by at least two investigators, after random allocation of newly identified studies, with discrepancies checked by a third (JS). However, two members of the original extraction team were unable to complete their extraction and so two authors (LR, AVM) extracted the studies allocated to them with a third (JS) going back through all included studies, including re-extracting data from the original studies included in Nunes et al.[15] in addition to all newly identified studies, such that all studies had been checked and extracted by at least two authors.

For each study we extracted bibliometric data including pubmed ID, DOI, authors, corresponding author email, journal, year of publication, title of article, and how many arms from the study were to be included in our analysis. For each arm within each study data was extracted for participant characteristics, including location (i.e., means) and scale (i.e., standard error, or standard deviations), for any continuous variables, which included sex (proportion male), age and body mass, sample size at baseline, intervention characteristics including protein source and what the placebo arm consisted of, whether concomitant RT was performed, and protein intakes (at baseline and during the study i.e., after intervention). Protein intake was reported too heterogeneously to use a single derivation. Directly reported total intake in g/kg/day and/or g/day were extracted; otherwise intake was reconstructed from absolute dietary intake in g/day, supplement dose and schedule, energy intake, percentage energy from protein, and body mass as appropriate. When available, reported uncertainty around protein intake was extracted. Otherwise, SDs or SEs were derived and propagated using first-order delta-method calculations. Prescribed fixed absolute supplement doses were treated as having no additional sampling variance unless the study reported variation in consumed dose or adherence. Because correlations and covariances required for protein-intake error propagation were almost never reported, all relevant propagation assumed independence. This is a transparent assumption and is not necessarily conservative. The protein calculations supplement documents how intake was derived and how uncertainty was propagated.

On an arm by arm basis, and for each time point reported in the study, all whole body lean/fat free mass and measures of muscle size or mass outcomes, strength outcomes, and function outcomes in addition to the outcome group[d] they belong to (whole body lean/fat free mass; measures of muscle size or mass; strength; function), the measurement method, the units of measurement, samples sizes, and means and either standard deviations, standard errors, or confidence intervals were extracted in addition to contrasts between each time points mean deltas (e.g., for two timepoints 1 and 2, timepoint 2 – timepoint 1) and their standard deviations or standard errors, t statistics, p values, confidence intervals, and correlation between timepoints. If not available in tables or the text, data was extracted from figures using the online tool WebPlotDigitizer (all data extracted from figures is available in the project repository: https://github.com/jamessteeleii/protein_dose_response_meta/tree/master/data/graphical_data). Authors were contacted for key missing aggregate data. We originally planned to contact all authors to request individual participant level data, however ultimately opted not to pursue this due to resource and time constraints for the author team to commit to this though may do so in a future update.

Risk of bias and certainty of evidence assessment

Risk of bias was assessed using the Cochrane RoB 2 tool[35] for the effect of assignment to intervention in both the studies included by Nunes et al.[15] and the newly identified studies. Because RoB 2 is result-specific, whereas our synthesis used a dose-response meta-regression as our primary estimand spanning

with these excluded to check sensitivity against the pre-registered plan as exactly worded.

[d]With outcome-group labels in the data indicating the terminology of preregistered synthesis groups rather than equivalence of the tissues or quantities measured by each method or the terminology adopted by convention in this manuscript.

multiple outcome-contrast clusters, we pragmatically assessed one prespecified index result per trial rather than every contributing result. Index results were selected hierarchically: whole-body lean/fat-free mass, measures of muscle size or mass where whole-body lean/fat-free mass mass was unavailable, and strength where neither body-composition outcome was available. Within each outcome family, selection prioritised a result contributing to the primary model, followed by the longest follow-up, greatest number of included arms, largest follow-up sample, and a lexical tie-break where required. One reviewer (MM) completed all assessments and a second reviewer (JS) independently assessed a random 10% sample, with discrepancies resolved through discussion. Domain-level assessor overrides were retained only when accompanied by sufficient domain-specific justification; otherwise, the RoB 2 algorithm judgement was used. Overall judgements were regenerated from the final five domain judgements. This constituted a documented deviation from the preregistered approach and provides a proxy indication of risk of bias at the study level in the broader trial evidence rather than an assessment formally applicable to every contributed result. The risk-of-bias methods supplement details index-result selection and judgement rules.

Potential publication bias was assessed separately for each outcome family using one highest-versus-lowest achieved-intake contrast per study and outcome. Contrast selection followed a deterministic hierarchy based on achieved-intake separation, follow-up duration, sample size, and fixed identifier-based tie-breaking. We compared matched publication-bias-unadjusted Bayesian random-effects and robust Bayesian model-averaged meta-analysis (RoBMA) models and examined contour-enhanced funnel plots and posterior-predictive zplots[36]. All eligible protein-versus-comparator and active-dose-versus-active-dose contrasts were displayed descriptively, but algebraically redundant or shared-arm contrasts were not treated as independent publication units. A clustered, moderator-adjusted analysis across outcome families was treated as a supporting sensitivity analysis rather than as the basis for an individual GRADE judgement. The supplement documents contrast construction and the model specifications.

Certainty was appraised using the GRADE[37] domains of risk of bias, inconsistency, indirectness, imprecision, publication bias, and other considerations. The unit of appraisal was an outcome, resistance-training condition, and model-derived relative-intake contrast. For RT, we assessed contrasts from 0.8 g/kg/day to 1.2, 1.6, 2.0, and 2.4 g/kg/day and 0.4-g/kg/day increments above a 1.6-g/kg/day reference while remaining within the pooled observed range. For conditions without RT, proposed intakes were restricted to the outcome-specific observed range. Population effects used the complete primary 26-model stacking ensemble, whereas inconsistency was evaluated by re-stacking the candidates that permitted study-specific dose slopes or smooths and examining study-specific contrasts and leave-one-study-out results. Evidence started at high certainty because the contributing studies were randomised trials and was downgraded according to the recorded domain judgements. Domain judgements and their rationales were entered explicitly; diagnostic flags did not automatically determine downgrading, and no automatic upgrade was applied for a dose-response gradient given this was the primary aim of our analysis anyway and typically such upgrading is applied in the context of non-randomised evidence[38].

Statistical analysis

Statistical analyses were performed in R version 4.4.3[39] and RStudio version 2026.07.0 (Posit). The code for data preparation and analysis is available on the Open Science Framework and GitHub. The reference list includes software citations compiled using `grateful`[40]. Package versions and full software citations are available in the software supplement.

Primary pre-registered analyses (relative intakes)

Though we have specific criteria for the selected models described below and despite pre-registration, our analysis should be considered exploratory and aimed at principled dose-response model estimation. Analysis was aimed at effect estimation within a Bayesian meta-analytic framework[41]. For all analyses, the model estimates and their precision, along with conclusions based upon them, are interpreted continuously and probabilistically, considering the data quality, the plausibility of effect, and the previous literature, all within the context of our model candidate set.

The primary models estimate conditional associations between arm-level protein intake and standardized

change in outcomes across the included trial arms. Because the dose-response function parameters may contain both within-study randomized information and between-study information, alone the resulting function from the primary pre-registered analysis is interpreted as an exploratory candidate model rather than as a causally identified dose effect. We therefore distinguish within-study from between-study dose associations in subsequent sensitivity analysis detailed in a later section below to determine the extent to which it may be tentatively considered causally.

Effect size calculation

Standardised mean changes with small sample bias correction were calculated within each arm and for each outcome for each timepoint contrast relative to baseline using Becker's[42] d (i.e., where the numerator is the mean change contrast between timepoints or the mean for a given follow-up timepoint n, after baseline minus the mean for baseline; timepoint_{0+n} - timepoint_{0}). However, given we are including only randomised controlled trials we used the pooled baseline standard deviations as the denominator, akin to Morris'[43] PPC_2, given that participants come from the same population at randomisation. When baseline, follow-up, and change score standard deviations were available $r_{pre:post}$ was recovered exactly using $r = (SD^2_{pre} + SD^2_{post} - SD^2_{change})/(2SD_{pre}SD_{post})$. We imputed missing correlations using a multilevel meta-analysis of observed correlations on the Fisher-z scale, which gave a pooled r of 0.947. We used standardised mean change scores due to the varying outcome operationalisations for the constructs considered (i.e., in both specific method of observation and in the units of measurement) that were extracted and also directionally recoded all outcomes such that positive effects consistently represented improvement in a given outcome. Further, given the nature of the constructs of interest this facilitated comparison with other large scale meta-analytic estimates (e.g., Steele et al.[30]) to support interpretation of the magnitude of effects identified.

Models

We retained the preregistered `brms` candidate-model analysis as our primary analysis with sensitivity analyses added later (and described below). Before fitting the final models, we audited the implementation against the stated model specifications and corrected any specifications that did not represent the intended models as defined in the pre-registration. We then conducted a pilot fit of every model–outcome combination using strict diagnostic criteria to ensure that our candidate model set was suitable for subsequent stacking and inference. Where the preregistered parameterisation produced unresolved sampling geometry, we applied the smallest diagnostic-driven modification required, typically either removing correlations among study-level random coefficients or adding regularising priors to variance components, while retaining the original fixed-effects functional form and estimand. The model-by-model deviation register records those decisions and the corresponding diagnostics. We used four Monte Carlo Markov Chains each with 2000 warmup and 6000 sampling iterations for each model. Note this also deviated from our pre-registration in order to reduce the time required for model fitting given that in retrospect we realised we were primarily interested in estimation rather hypothesis testing and so did not calculate Bayes Factors. Candidate models and stacking ensembles were fitted separately for each of the four outcome groups. Whole-body lean/fat-free mass was not pooled with the muscle-outcome group; within the latter, direct measurements and regional body-composition proxies were pooled after standardisation.

Data was hierarchical across three levels (i.e., effects within arms within studies), and so, we included random (i.e., cluster) intercepts using explicitly nested coding across these levels in all models. We then examined a selection of models for the functional form of dose-response association of protein intake. For each model, protein intake was included as a fixed (i.e., population) effect in g/kg/day and centred at the median value for protein intake across all control and placebo arms i.e., considered to be the habitual protein intake, which was 1.1 g/kg/day. In all models we included a fixed effect for whether the study included a RT intervention or not and set informative priors based on the effect estimates for whole body lean/fat free mass, measures of muscle size or mass, strength, and functional outcomes based on estimates from previous meta-analyses using similar arm based models as those described[30,31]. These priors reflect the typical effect magnitudes for these outcomes under either RT or non-RT conditions with habitual protein intakes. Sampling errors for different outcomes were treated as independent conditional on the hierarchical model because the required

outcome covariance matrices are almost never reported in this literature. The sensitivity of the findings to residual within-study dependence was examined separately as noted below.

Priors for all other fixed effect coefficients were pre-registered to be set as weakly regularising using a student t distribution with 3 degrees of freedom, mu of 0, and sigma of 1 permitting a reasonable range of prior values of standardised mean effects[e]. Priors for random effects followed a half student-t prior with 3 degrees of freedom and a scale parameter set to 2.5 centred at a mu of 0. However, as documented in the prior scale correction, priors were rescaled to match model rescaling where required and where set to be more regularising to address model diagnostic issues. The diagnostic remedies included more regularising priors for selected parameters where required to address model fitting issues. The prior sensitivity checks showed that dose-contrast estimates across the primary relative-intake candidates were robust to the tested prior changes, with only occasional shifts in classification near the 95% posterior probability threshold.

We began by fitting a selection of possible dose-response functional forms for the association of protein intake in g/kg/day with standardised mean changes as follows:

1. Intercept only model i.e., a model assuming no dose-response association of protein intake
2. Linear model i.e., a model assuming a linear dose response association of protein intake
3. Linear splines with knot at 1.6 g/kg/day i.e., a model assuming linear dose-response associations that differ in magnitude below or above a protein intake of 1.6g/kg/day (similarly to previous "breakpoint" models)
4. Nonlinear smooth model using splines i.e., a model assuming a dose-response association that is a non-linear smooth function of protein intake with three basis functions

Each of these describes the functional form for the dose-response association of protein intake with standardised mean change from baseline in outcomes and vary in the extent to which they restrict the shape of the function[f]. We then fit each of these functional forms across four groupings of models varying in parameters included:

1. Models with only fixed (i.e., population) level effects for protein intake
2. Models with only fixed (i.e., population) level effects for protein intake, and also including fixed effects for intervention duration in weeks and age in years
3. Models with both fixed (i.e., population) level effects for protein intake in addition to random (i.e., cluster) level effects for protein intake at the study level
4. Models with both fixed (i.e., population) level effects for protein intake in addition to random (i.e., cluster) level effects (slopes or smooths) for protein intake at the study level, and also including fixed effects for intervention duration in weeks and age in years

The exception being the intercept only model which of course cannot be fit with random slopes or smooths for protein intake.

Lastly, we also fit all the above models with the inclusion of a fixed interaction term (either linear, or fixed factor smooths by each level) between protein intake and whether the study included a RT intervention to include the possibility that protein intake requirements may differ if participating in resistance training. The exception to this was also the intercept only model being that protein intake was not included.

As such, a total of 26[g] models across each of the four outcome groups varying in complexity regarding the functional forms for dose-response association of protein intake with standardised mean change, the inclusion of additional study and arm level moderators, whether or not the dose-response association of protein intake are modelled as varying between studies, and whether or not the association of protein intake varies with

[e] A typo was noticed in the pre-registration plan and analysis code for the priors where the scale for weakly regularising priors on coefficients other than the effects of RT was set to 10 when it should have been 1 given the former allows for completely implausible standardised mean changes.

[f] Note, we originally planned to also examine a model assuming dose-response effects are a function of both a linear and logarithmic transformation of protein intake to allow a parametrised non-linear function permitting a plateau, but the use of priors that were based on habitual protein intake required centring of the protein intake meaning we could not log transform the predictor given zero or negative signed values. However, we felt the inclusion of the smooth function spline models enabled sufficient flexibility to allow for this kind of functional form to emerge.

[g] The original pre-registration contains a miscounting error and states 28 models.

and without the concomitant inclusion of a RT intervention, were fit and compared in terms of the evidence supporting them relative to one another as the data generating process. Candidate models with age and duration included them additively. The model-fitting audit documents their original centring and subsequent standardisation in the remediated candidates.

As noted, we utilised Bayesian model averaging across the set of candidate models noted above in order to account for uncertainty in the model selection process. Across these models we used leave-one-out cross-validation (LOO-CV)[h] to estimate the expected log predictive density (ELPD) and calculate weights using the stacking approach[44,45]. We then took posterior draws of the conditional global grand means (i.e., the expectation of effect size, without the inclusion of random effects) for predictions and contrasts across different values of protein intake and calculate the means with 95% quantile intervals. These draws for each model were then be combined using the LOO-CV weights to generate our Bayesian model averaged predictions and contrasts.

We evaluated the primary population curves and dose contrasts at the outcome-specific median age across distinct study arms and median follow-up across distinct study–follow-up records. Each outcome used the same profile for RT and no RT. The profiles were 30 years and 10 weeks for whole-body lean/fat-free mass, 63.4 years and 12 weeks for muscle size or mass, 48.5 years and 10 weeks for strength, and 70.3 years and 12 weeks for physical function. Additive age and duration terms cancel when subtracting predictions at the same profile within a posterior draw. Arm-conditional estimates use the observed arm profiles. Primary dose support uses the pooled observed intake range within each outcome and RT condition. The age and duration supplement separately reports support in the neighbourhood of each age and duration profile.

Inference criteria

We collectively agreed as an author group upon the pre-registered smallest effect size of interest (SESOI) on the standardized mean change scale as $\delta = 0.1$ and thus set this as our region of practical equivalence (ROPE) i.e., $(-0.1, 0.1)$. We prespecified 0.1 standardised units as a deliberately small threshold for practical relevance in line with other recent work[46–48]. We present illustrative raw-unit equivalents in the supplementary materials to make this judgement explicit for readers across outcomes and populations. We deviate from our pre-registration which noted the comparison of model-averaged local slopes to instead report sequential contrasts between protein intakes along each dose response function. Contrasts are more directly interpretable for nonlinear models and avoid treating a derivative at a point as a sustained change over a practical intake interval. Model-averaged contrasts were estimated for all possible pairs of current and proposed protein intakes across the observed data range and plotted as heatmaps. Throughout, the outcome contrast Δ is expressed as the predicted standardised mean change at the proposed intake minus that at the current intake. Thus, the sign of Δ describes the direction of the outcome difference, not the direction of the protein-intake change. In the heatmaps, cells above the diagonal represent an increase in protein intake and cells below it a decrease. Given the generally positive posterior mean dose-response functions, the two directional inferences therefore correspond to a meaningful outcome gain from increasing intake and a meaningful outcome loss from decreasing intake. We drew these inferences, together with practical equivalence, when at least 95% of the posterior distribution lay within the following regions relative to the ROPE:

Meaningful outcome gain from increasing intake (above the diagonal):

$$P(\Delta > \delta) \geq 0.95$$

Practical equivalence after moving intake in either direction:

$$P(-\delta < \Delta < \delta) \geq 0.95$$

Meaningful outcome loss from decreasing intake (below the diagonal):

[h]The leave-one-observation-out audit documents the remedies for high Pareto-k values before stacking and model averaging.

$$P(\Delta < -\delta) \geq 0.95$$

We then present all these contrasts in their heatmap depicting the posterior mean outcome contrast, with contour lines enclosing the regions that meet the 95% posterior-probability criterion for an outcome gain from increasing intake, practical equivalence, or an outcome loss from decreasing intake.

Supplementary sensitivity analyses (relative intakes)

The preregistered primary analysis relates achieved arm-level protein intake to outcome change and therefore combines within-study randomised information with between-study differences. Achieved intake is also measured after randomisation and can reflect adherence, baseline diet, co-interventions, and other prognostic differences. We consequently conducted a retrospective programme of complementary sensitivity analyses to test whether the substantive conclusion depended on the primary estimand or modelling assumptions. Each family retained the same four outcomes and, where applicable, the same 26 candidate-model identities and outcome-specific LOO stacking procedure as the primary analysis.

First, Mundlak models decomposed every protein basis term into a study mean and an arm-level deviation from that mean[49], reducing the influence of between-study differences while retaining the arm-level model. Second, strict within-study models related matched intervention-minus-comparator outcome effects to their achieved-intake contrasts, restricting identification to comparisons among randomised arms within the same trial. Third, we fitted paired common-sample models in which the same observations were analysed using either achieved intake or assignment-derived intake, defined as baseline dietary protein plus the randomised prescribed increment. This separated the influence of sample restriction from the choice of a post-randomisation achieved exposure versus an intention-to-treat-like assigned exposure. Fourth, errors-in-variables models treated true arm intake as latent and propagated the reported or derived uncertainty in measured intake. Fifth, residual-correlation models estimated dependence among multiple effects contributed by the same study. Finally, arm-level and strict within-study strategy models allowed the dose-response function to differ between interventions that added protein and those that substituted protein for other macronutrients and thus whether or not the estimand was one of addition or substitution with respect to energy intake[50]. The strategy comparison was treated as study-level effect modification rather than a randomised head-to-head comparison. These analyses test complementary assumptions; none alone identifies the causal per-protocol effect of sustaining a particular protein intake but collectively inform the extent to which the primary analyses are sensitive to these assumptions and thus whether they can be tentatively treated as causal estimates. Full specifications, diagnostics, model weights, figures, and contrast data are provided in the relative-intake sensitivity analysis register.

Direct muscle size or mass sensitivity analyses (relative intakes)

We conducted two additional analyses of measurement eligibility, specified after registration. First, we refitted the primary muscle-outcome models after excluding trunk DXA/BIA estimates and skinfold-derived measures, which were included by extraction and coding error in the original primary analysis run and the above described sensitivity analyses, retaining appendicular DXA/BIA proxies alongside imaging and biopsy measurements to restore the registered eligibility definition. Second, we restricted the same models to MRI, CT, ultrasound, and muscle-biopsy measurements, excluding all DXA/BIA and skinfold estimates, to examine sensitivity to pooling direct measurements with body-composition proxies. Whole-muscle and muscle-fibre measurements remained combined in this second analysis. Both analyses retained the primary 26-candidate framework, priors, sampling schedule, diagnostic criteria, and inference thresholds, with new LOO stacking weights estimated separately for each restricted dataset after any required exact case-deletion refits. The other expanded model families retained the original measurement eligibility. Full details are provided in the muscle-measurement eligibility audit.

Absolute-intake and absolute-supplementation analyses

We also specified two exploratory absolute-scale analysis programmes because expressing intake relative to body mass may conceal clinically useful absolute-dose patterns and can couple the exposure to body size.

The first examined total protein intake in g/day; the second examined the prescribed supplemental protein dose in g/day, assigning zero to eligible control or placebo arms without a protein supplement. For each scale, the candidate models set retained the intercept-only, linear, and flexible nonlinear forms and their prespecified moderator, RT-interaction, and study-varying variants. The eight linear-spline candidates with a fixed knot at 1.6 g/kg/day were omitted because that relative-intake threshold has no invariant meaning on an absolute g/day scale, leaving 18 candidates per outcome and 72 initial fits per applicable family.

For total intake, the planned programme mirrored the primary, Mundlak, strict within-study, common-sample achieved-versus-assignment, errors-in-variables, residual-correlation, and arm-level and within-study protein-strategy families. These analyses tested whether the conclusions depend on body-mass scaling and whether the same confounding, exposure-definition, measurement-error, dependence, and intervention-strategy assumptions matter on the absolute total-intake scale. For prescribed supplementation, the primary, Mundlak, strict within-study, residual-correlation, and two protein-strategy families were applicable. Separate common-sample achieved and assignment models are not fitted because prescribed supplement dose is already the assignment exposure and systematically measured achieved supplement dose is unavailable; an errors-in-variables family is also not fitted because a fixed prescribed dose has no corresponding dietary measurement-error input. The absolute analyses are reported in full in the separate online supplements for absolute total intake and absolute supplementation.

Age and duration interaction analyses (relative, absolute, and supplementation intakes)

We also conducted exploratory, post-registration analyses of whether protein dose-response associations varied with mean participant age and intervention duration. For relative total intake, absolute total intake, and prescribed absolute supplementation, we expanded only the corresponding primary model families. Covariate-adjusted dose models included protein interactions with age, duration, or both, retaining both additive covariates, the inherited dose functions and dependence structures, and body-mass adjustment where applicable. Joint candidates included both protein interactions without an age-by-duration interaction, and RT-specific candidates allowed these interactions to differ by RT condition. Following sampling diagnostics, predictive checks, and corrected observation-level LOO, we estimated fresh stacking weights over the original and additional candidates separately within each exposure and outcome on identical observations.

We compared conditional predictions and paired differences in protein contrasts at outcome-specific median and quartile age and duration profiles, alongside the original 25-year/12-week reference profile and primary-only averages evaluated at the same profiles. Age quartiles were calculated across distinct study arms, and duration quartiles across distinct study/follow-up records. Posterior draws were paired across profiles. Examination of local empirical support required at least three studies within 10 years and four weeks of each profile, with both compared protein doses within the neighbourhood's observed range. We similarly applied a threshold of 0.1 standardised units and the 95% posterior probability criterion descriptively to differences between protein contrasts across these moderators. The age and duration interaction methods describe the expanded candidate sets and support criteria.

Training-status analyses (relative, absolute, and supplementation intakes)

Finally, for each outcome and protein-dose definition (relative total intake, absolute total intake, and absolute supplementation), we refitted the primary candidate models on RT arms with study-reported trained or untrained participants. We excluded arms classified as active or with unreported status. Training status replaced the RT main effect and RT-by-dose interactions. We estimated new stacking weights using corrected observation-level leave-one-out cross-validation and paired population-level protein contrasts within posterior draws to estimate trained-minus-untrained differences. Both doses had to fall within each group's observed range, with at least three studies per group. We applied the 0.1-standardised-unit threshold and 95% posterior-probability criterion descriptively. See the training-status methods supplement.

Table 1: Primary-analysis dataset by outcome.

Outcome	Studies	Arms	Participants	Contrasts	Duration, weeks
Whole-body lean/fat-free mass	82	220 (32/55/133)	4066 (808/870/2388)	283	10.5 [8, 12]
Measures of muscle size or mass	53	145 (22/36/87)	3072 (549/685/1838)	425	12 [10, 12]
Strength	87	231 (34/56/141)	4490 (833/1012/2645)	794	12 [8, 12]
Function	33	93 (17/20/56)	2598 (603/487/1508)	362	12 [12, 24]

Note:
Values in parentheses for arms and participants are control/placebo/protein; duration is the longest eligible follow-up per study, reported as median [first quartile, third quartile] in weeks. Participants were counted once per contributing study arm using the largest analysed sample for that arm. Outcome-specific participant counts overlap where an arm contributed more than one outcome and therefore should not be summed. Similarly, an arm was counted once within each outcome irrespective of the number of measurements or follow-ups it contributed. The muscle-outcome group includes direct imaging and biopsy measurements and regional body-composition proxies; whole-body outcomes are summarised separately.

Results

All supplementary materials accompanying the results presented here are available in full on the supplementary materials landing page.

Systematic Review

The July 2025 systematic search update identified 12,917 database records. After deduplication and preliminary screening in EndNote, 608 records were transferred to Rayyan. A further 36 duplicates were removed and 572 titles and abstracts were screened. Fifty-five reports were assessed in full, of which 32 were retained and represented 30 studies not already included in the previous review. Four additional studies were known to the authors. Together with 75 historical study records from the dataset shared directly by Nunes et al.[15], this brought the register to 109 records before the September update. The September 2026 database search identified 4,894 records. After removing 2,722 internal duplicates and 305 records already identified in 2025, 1,867 new records were screened. Of 22 reports assessed in full, 12 were excluded and 10 were retained. Nine represented new trials and one was a follow-up of the previously included Ioannidou et al. trial. A colleague alerted us to one further eligible trial, Bagheri et al. The September update thus added ten trials, bringing the review total to 119 study records[51–169]. The PRISMA supplement provides the study-selection flow diagram, full-text exclusion reasons, and characteristics of the included studies.

Of the identified studies, 95 contributed 1,864 eligible baseline-to-follow-up contrasts from 254 study arms and 4,931 participants to the primary analyses. The arms comprised 39 control, 61 placebo, and 154 protein conditions, contributing 919, 1,095, and 2,917 participants, respectively. Across studies, the median longest eligible follow-up was 12 weeks (IQR 8 to 12). Outcome-specific totals are shown in Table 1.

Of 2,210 candidate contrast rows generated from the extracted data, 1,864 were eligible for the primary analysis and 346 were excluded because at least one required analysis component was unavailable. The recorded reasons were missing protein intake ($n = 228$); effect size not estimable ($n = 120$); missing baseline standardisation SD ($n = 101$); missing mean change ($n = 19$); missing outcome sample size ($n = 18$); excluded by author-group decision ($n = 12$); missing mean age ($n = 6$); missing resistance exercise code ($n = 2$); missing duration ($n = 0$); missing pre-post correlation ($n = 0$). Reasons were not mutually exclusive: every applicable reason was retained for each row, so the reason-specific counts can exceed the number of excluded contrasts. The review audit provides exclusion counts by outcome and the downloadable row-level audit.

Risk of bias, publication bias, and certainty of evidence

Risk-of-bias assessments were available for all 119 included trials. Overall risk of bias was low for 28 trials (23.5%), raised some concerns for 69 (58.0%), and was high for 22 (18.5%). Selection of the reported result was the most frequent source of concern: 67 trials raised some concerns and 10 were at high risk in this domain. These judgements are study level indicators and apply to the prespecified index result for each trial

and should not be interpreted as assessments of every contributed outcome, timepoint, or contrast (Figure 1). See the study-level RoB 2 judgements for each trial's index result and domain ratings.

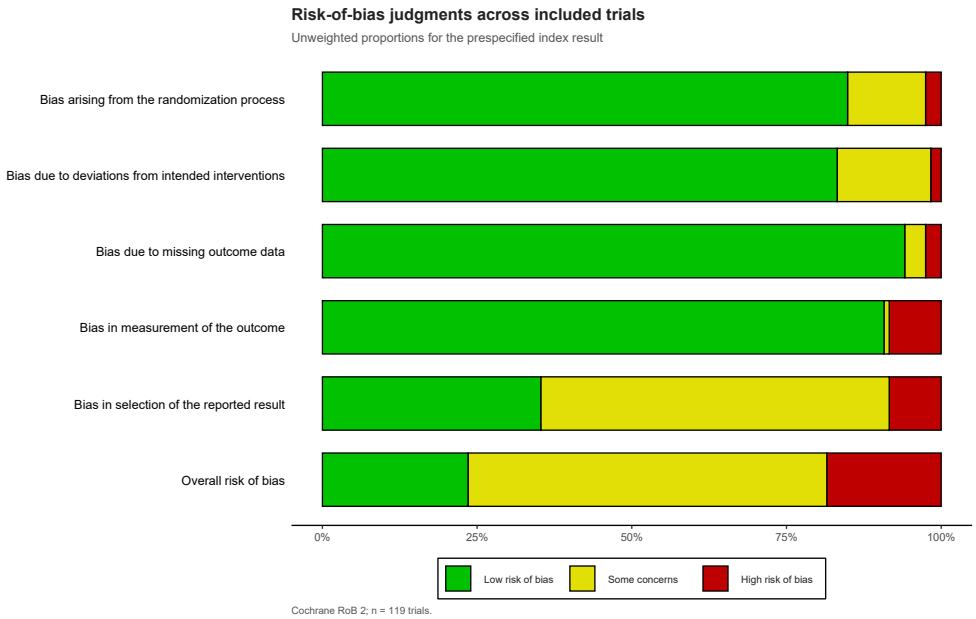


Figure 1: Unweighted proportions of included trials rated low risk, some concerns, or high risk of bias for each RoB 2 domain and overall. One prespecified index result was assessed per trial (n = 119). D1, randomisation process; D2, deviations from intended interventions; D3, missing outcome data; D4, outcome measurement; D5, selection of the reported result.

Across the four outcome families, the publication-bias-unadjusted Bayesian random-effects estimates ranged from 0.058 to 0.120 standardised units. The corresponding RoBMA-adjusted estimates ranged from -0.002 to 0.007 and were close to the null for every outcome. Adjustment attenuated the estimated association by approximately 0.057 to 0.118 standardised units. This pattern, considered together with the search and visual and posterior-predictive diagnostics, led us to judge publication bias as strongly suspected for GRADE. It is evidence compatible with selection and attenuation, rather than proof that a single publication mechanism generated the observed results. The supplement reports the outcome-specific estimates and zplots, funnel plots, and supporting clustered analysis.

GRADE was completed for 41 prespecified outcome-, RT-, and dose-specific relative-intake contrasts. Certainty was low for 2 contrasts and very low for 39; no contrast was rated moderate or high certainty. Risk of bias was judged serious and publication bias strongly suspected for every contrast, with further downgrading where inconsistency, indirectness, or imprecision warranted it. See the GRADE evidence profile and judgement rationales and the leave-one-study-out and empirical-support checks.

Primary pre-registered results (relative intakes)

The top panels of Figure 2, Figure 3, Figure 4, and Figure 5 show the model-averaged population dose–response curves, with points showing only the arm-conditional posterior means. These means are expected standardised changes at the observed arm profiles, retaining the fitted study- and arm-level effects. The primary dose–response supplement also shows the original observed effect sizes, with a thin line linking each observation to its corresponding arm-conditional mean. The bottom panels of Figure 2, Figure 3, Figure 4, and Figure 5 show the posterior mean for every pairwise contrast between a proposed and current protein intake with the contrasts that met the 95% practical-equivalence criterion denoted as inside the dashed contour lines. These plots can be read by taking a current protein intake on the x-axis, a proposed protein intake on the y-axis, and then identifying the point defined by these coordinates with the colour scale denoting the magnitude of the posterior mean. Where this point lies within the contour lines around the diagonal the contrast is practically equivalent and where this point lies outside the contrast is uncertain (i.e., neither

Table 2: Model-averaged contrasts with resistance training at the outcome-specific median profiles. Each cell gives the posterior mean (95% credible interval) in standardised units. The second line gives posterior percentages for meaningful gain (above 0.10 SD), practical equivalence (within ±0.10 SD), and meaningful loss (below −0.10 SD), in that order. FFM, fat-free mass.

Contrast (g/kg/day)	Whole-body lean/FFM	Muscle size or mass	Strength	Physical function
0.8 to 1.1	0.025 (0.000 to 0.060) 0.4 / 99.6 / 0.0	0.037 (-0.005 to 0.102) 2.9 / 97.1 / 0.1	0.045 (-0.008 to 0.110) 3.5 / 96.4 / 0.1	0.062 (-0.024 to 0.142) 17.7 / 82.2 / 0.1
1.1 to 1.6	0.044 (0.000 to 0.104) 3.0 / 97.0 / 0.0	0.054 (-0.001 to 0.119) 5.5 / 94.5 / 0.0	0.074 (0.000 to 0.162) 26.5 / 73.4 / 0.1	0.096 (-0.036 to 0.223) 49.1 / 50.7 / 0.1
1.6 to 2.2	0.068 (0.000 to 0.169) 15.6 / 84.4 / 0.0	0.061 (-0.024 to 0.157) 13.5 / 86.2 / 0.4	0.043 (-0.037 to 0.135) 6.8 / 92.9 / 0.2	-0.061 (-0.284 to 0.160) 7.6 / 54.5 / 37.9

a clearly meaningful gain from increasing intake or meaningful loss from decreasing intake). The raw-unit reference supplement shows how the prespecified ±0.10 SD threshold and an example protein-intake contrast translate to original units across reference populations and measurement protocols.

Because the analysis comprised all supported pairwise dose contrasts we qualitatively describe the dose-response functions and inferential pattern rather than select a single post hoc "headline" contrast. Across all outcomes and both with and without RT, neither increasing nor decreasing intake within the observed range produced a supported contrast that attained at least 95% posterior probability of a meaningful outcome change relative to the pre-registered SESOI: specifically, a meaningful gain from increasing intake or a meaningful loss from decreasing it. Regions supporting practical equivalence were concentrated around the heatmap diagonal, where the compared intakes were most similar. Each local-equivalence distance is the median of the pooled lower and upper one-sided reaches across supported current intakes. These summaries vary by outcome and RT condition and need not describe a symmetric interval around every current intake. More widely separated comparisons of current and proposed protein intakes were generally uncertain rather than demonstrably meaningful or equivalent. The outcome-specific posterior mean patterns are described below; all statements refer to the observed intake ranges displayed in the corresponding panels. Note, sequential pairwise contrasts from the recommended dietary allowance of 0.8 g/kg/day and also 1.6 g/kg/day in 0.4 g/kg/day intervals from the primary models can be seen in the GRADE supplementary materials summary of findings under the "Effect (95% CrI)" column and Table 2 presents three representative contrasts across outcomes.

The 1.1 g/kg/day habitual-intake reference in Table 2 is the median across control and placebo arms. For physical function, 0.8 g/kg/day is below the pooled observed RT range, and 2.2 g/kg/day exceeds the range observed near the median age and follow-up.

Whole-body lean/fat-free mass

For whole-body lean/fat-free mass, the model-averaged posterior mean changes increased modestly with protein intake with RT but the dose-response function was flatter without resistance training. Local equivalence between current and proposed protein intakes spanned approximately ±0.41 g/kg/day for RT and ±0.46 g/kg/day for without RT whereas more widely separated intake contrasts remained uncertain. Neither increasing nor decreasing intake produced a contrast meeting the probability criterion for a meaningful outcome gain or loss, respectively (Figure 2).

Measures of muscle size or mass

For the primary muscle-outcome group, the model-averaged posterior mean changes tended to increase modestly across the observed protein-intake range with and without RT. Local equivalence between current and proposed protein intakes spanned approximately ±0.40 g/kg/day for RT and ±0.22 g/kg/day for without RT whereas more widely separated intake contrasts remained uncertain. Neither increasing nor decreasing intake produced a contrast meeting the probability criterion for a meaningful outcome gain or loss, respectively (Figure 3).

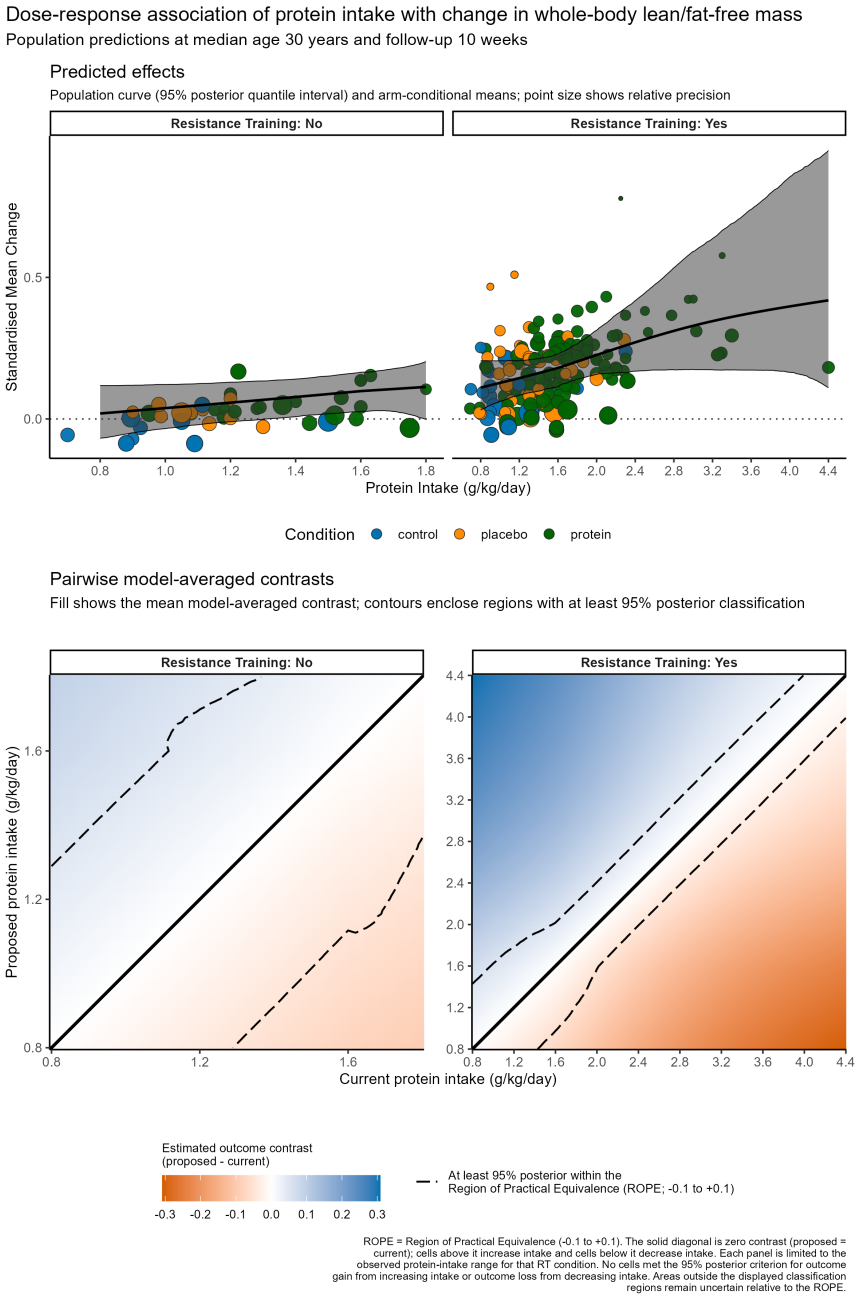


Figure 2: Model-averaged population dose-response curve at the median profile and means at observed arm profiles (top), and paired dose contrasts at the median profile (bottom) for whole-body lean/fat-free mass. Included methods estimate different body compartments. Contrasts are proposed minus current intake, so cells above the diagonal increase intake and cells below it decrease intake. Bands are 95% posterior intervals for the population curve. Dashed contours enclose dose pairs attaining the 95% practical-equivalence criterion. No supported pair attained the criterion for a meaningful outcome gain from increasing intake or outcome loss from decreasing it. Panels show observed intake ranges within each resistance-training condition.

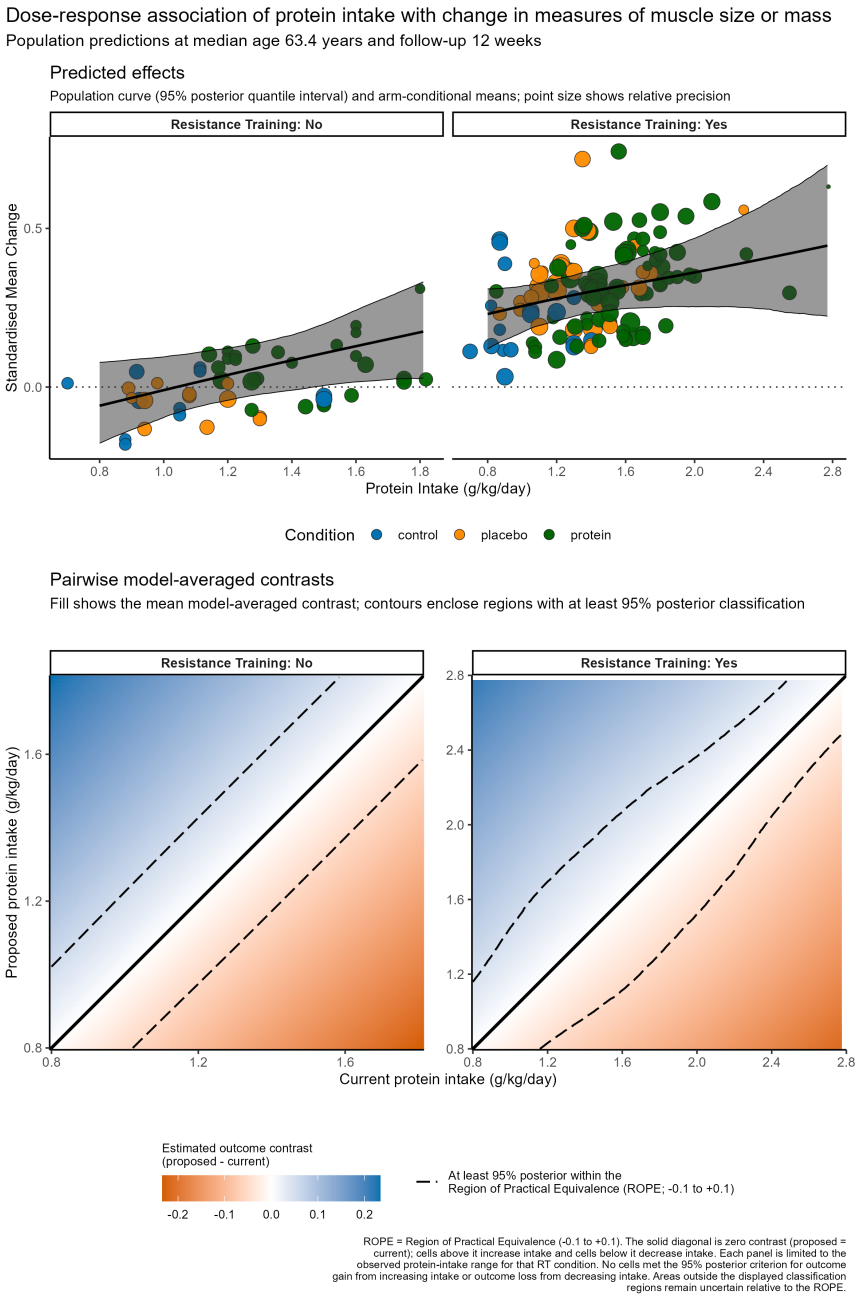


Figure 3: Model-averaged population dose-response curve at the median profile and means at observed arm profiles (top), and paired dose contrasts at the median profile (bottom) for measures of muscle size or mass. This group includes direct imaging and biopsy measurements and regional body-composition proxies, including appendicular DXA/BIA measures. Contrasts are proposed minus current intake, so cells above the diagonal increase intake and cells below it decrease intake. Bands are 95% posterior intervals for the population curve. Dashed contours enclose dose pairs attaining the 95% practical-equivalence criterion. No supported pair attained the criterion for a meaningful outcome gain from increasing intake or outcome loss from decreasing it. Panels show observed intake ranges within each resistance-training condition.

Strength

For strength, the model-averaged posterior mean changes tended to increase modestly across the observed protein-intake range with and without RT. Local equivalence between current and proposed protein intakes spanned approximately ±0.44 g/kg/day for RT and ±0.28 g/kg/day for without RT whereas more widely separated intake contrasts remained uncertain. Neither increasing nor decreasing intake produced a contrast meeting the probability criterion for a meaningful outcome gain or loss, respectively (Figure 4).

Function

For function, the model-averaged posterior mean changes tended to increase modestly up to ~1.6 g/kg/day both with and without RT, though past this dose there was minimal data and thus the posterior is far less certain. Local equivalence between current and proposed protein intakes spanned approximately ±0.23 g/kg/day for RT and ±0.22 g/kg/day for without RT whereas more widely separated intake contrasts remained uncertain. Neither increasing nor decreasing intake produced a contrast meeting the probability criterion for a meaningful outcome gain or loss, respectively (Figure 5).

Supplementary sensitivity results (relative intakes)

The completed body-mass-relative sensitivity analyses did not overturn the primary analyses substantive conclusions. Mundlak, errors-in-variables, residual-correlation, and common-sample achieved and assignment-derived models remained broadly compatible with the primary curves and inferential pattern. The strict within-study curves were generally more attenuated in magnitude, indicating that part of the primary arm-level association may reflect between-study differences or non-random variation in achieved intake; critically, they did not reveal a large or clearly meaningful outcome gain from increasing intake that was hidden by the primary analysis. The similarity of the paired achieved- and assignment-derived analyses suggests that neither restriction to studies with reconstructible assignment nor the achieved-versus-prescribed exposure definition materially changed the broad conclusion. Models distinguishing protein addition from macronutrient substitution did not show a consistent advantage for either strategy across outcomes, RT conditions, and arm-level versus within-study estimands. Together, the sensitivities strengthen the robustness of the conclusion that large outcome gains from increasing intake, or losses from decreasing it, are not supported while reinforcing that, whilst the overall positive dose-response pattern is supported, the exact magnitude of the primary achieved-intake curve should not be interpreted as a causal per-protocol effect. See the primary, Mundlak, and strict within-study comparison, arm-level sensitivity curves, and addition-versus-substitution results.

Direct muscle size or mass sensitivity results (relative intakes)

Restricting eligibility to the registered measurement methods (i.e., excluding regional trunk or skinfold derived outcomes) for the relative intake analyses produced dose-response estimates and inferential conclusions similar to those of the original measures of muscle size or mass-outcome analysis. The imaging/biopsy-only analysis also yielded similar intake contrasts with RT; without RT, the estimated association was steeper but substantially less precise. Neither restriction identified a supported contrast meeting the posterior-probability criterion for a meaningful outcome gain from increasing intake or loss from decreasing it. Local practical equivalence remained supported, although the equivalence regions were narrower in the imaging/biopsy-only analysis, particularly without RT. These comparisons reflect changes in both the measurements and the contributing studies, and therefore do not necessarily isolate measurement method as the cause of differences. The supplement shows the dose–response curves for the three eligibility definitions and local practical equivalence.

Absolute-intake and absolute-supplementation results

The exploratory primary analyses of absolute total protein intake and prescribed absolute supplemental protein dose broadly reproduced the pattern of the relative-intake analysis. Dose-response functions were generally modestly positive for whole-body lean/fat-free mass, measures of muscle size or mass, and strength,

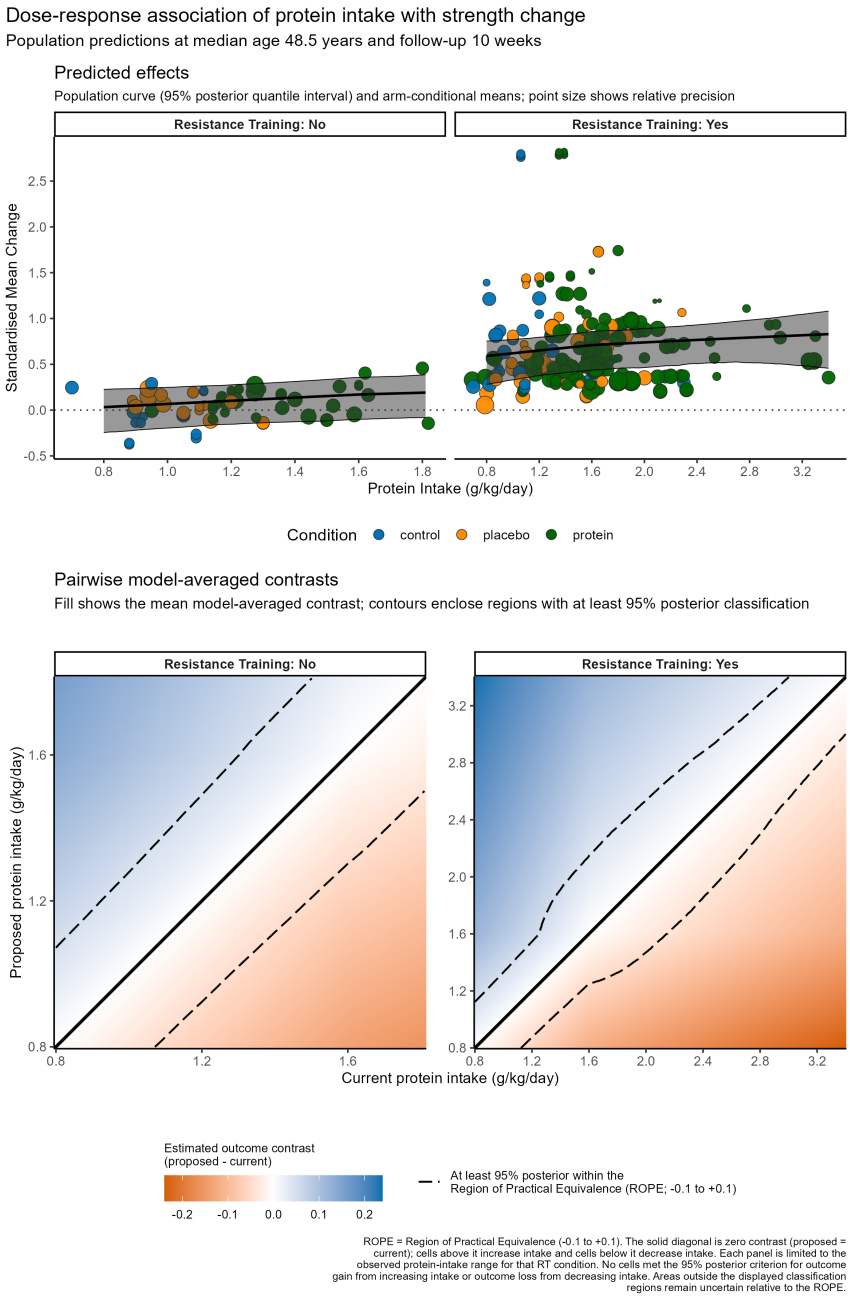


Figure 4: Model-averaged population dose-response curve at the median profile and means at observed arm profiles (top), and paired dose contrasts at the median profile (bottom) for strength. Contrasts are proposed minus current intake, so cells above the diagonal increase intake and cells below it decrease intake. Bands are 95% posterior intervals for the population curve. Dashed contours enclose dose pairs attaining the 95% practical-equivalence criterion. No supported pair attained the criterion for a meaningful outcome gain from increasing intake or outcome loss from decreasing it. Panels show observed intake ranges within each resistance-training condition.

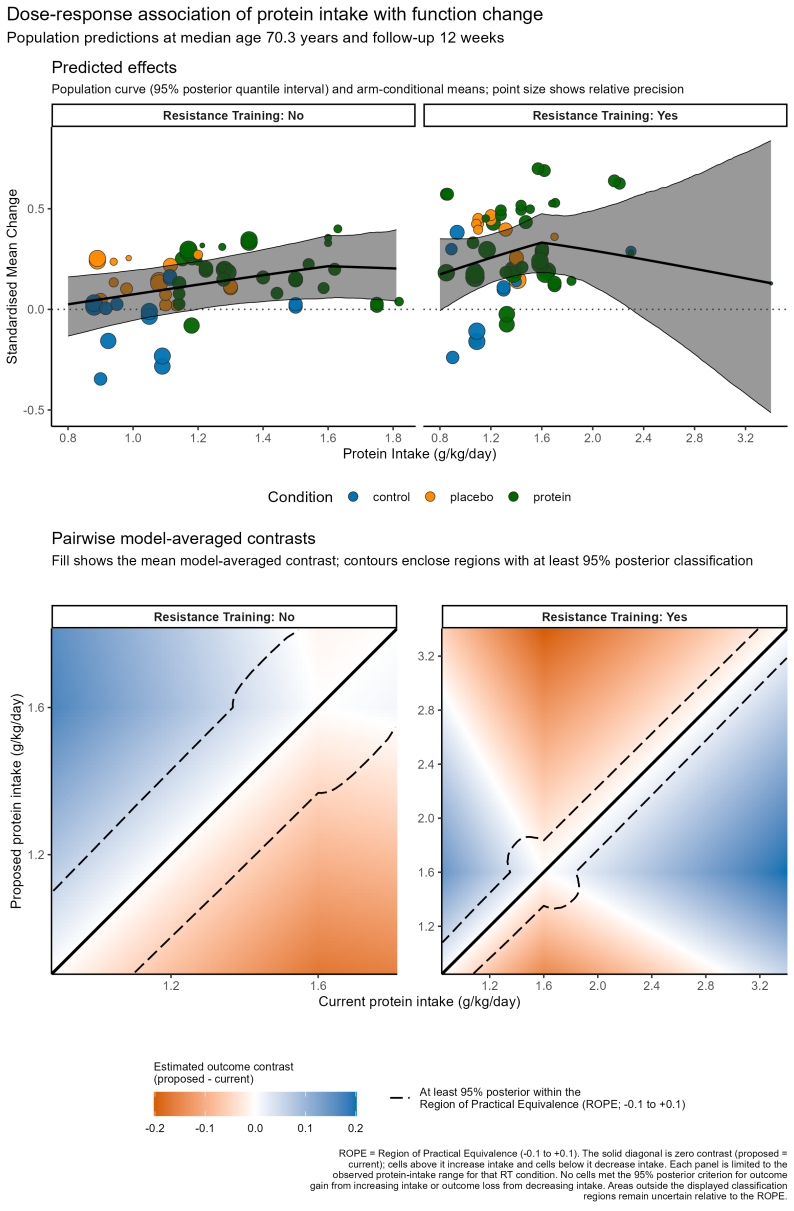


Figure 5: Model-averaged population dose-response curve at the median profile and means at observed arm profiles (top), and paired dose contrasts at the median profile (bottom) for physical function. Contrasts are proposed minus current intake, so cells above the diagonal increase intake and cells below it decrease intake. Bands are 95% posterior intervals for the population curve. Dashed contours enclose dose pairs attaining the 95% practical-equivalence criterion. No supported pair attained the criterion for a meaningful outcome gain from increasing intake or outcome loss from decreasing it. Panels show observed intake ranges within each resistance-training condition.

while function showed shallow curvature, and nearby absolute-dose contrasts were commonly supported as practically equivalent. No supported contrast attained the 95% posterior-probability criterion for a meaningful gain or loss for direct muscle size or mass, strength, or function. The exception was whole-body lean/fat-free mass within the RT category, where some very widely separated contrasts met the criterion for a meaningful difference; low intakes of 51–67 g/day versus approximately 202–265 g/day or more of total intake, and 0–7 g/day supplementation versus approximately 88–106 g/day. However, these contrasts occurred in the sparsely represented exposure tails and none lay wholly within the central 90% exposure range. The supplements show the dose–response curves and supported contrasts for absolute total intake and absolute supplementation.

Age and duration interaction results (relative, absolute, and supplementation intakes)

Across the four outcomes and three protein-dose definitions, posterior mean differences in protein contrasts between the upper and lower age or duration quartile profiles were generally small within locally supported dose ranges. No locally supported comparison met the posterior-probability criterion for a difference exceeding 0.1 standardised units in either direction. Many differences met the practical-equivalence criterion, while others remained uncertain, particularly where empirical support was limited. See the conditional predictions, paired contrasts, and profile support and the candidate counts and stacking weights.

Training-status results (relative, absolute, and supplementation intakes)

Across the three protein-dose definitions, no supported trained-minus-untrained difference in a protein contrast reached the 95% posterior-probability criterion for meaningful moderation of whole-body lean/fat-free mass, measures of muscle size or mass, or strength. Many differences met the practical-equivalence criterion. Uncertainty remained, particularly for strength in the relative- and absolute-total-intake analyses. Physical-function comparisons were descriptive because only one or two trained studies contributed per dose definition and no comparison met the support criterion. The supplement shows the dose–response curves and paired contrasts and study counts and dose support.

Discussion

To our knowledge this is the largest systematic review and dose-response meta-analysis of randomised controlled trials conducted to date exploring the association of protein intake with changes in whole body lean/fat free mass, measures of muscle size or mass, strength, and physical function in healthy adults. For our primary analyses of relative intake (i.e., g/kg/day), across all outcomes, whilst dose-response functions were typically modestly positive, particularly with RT, neither increasing nor decreasing intake within the observed range met our criterion for a meaningful change in outcome, whether a gain from increasing intake or a loss from decreasing it. Thus, despite directional dose-response associations, it is far less clear that differences in protein intakes across the ranges examined in the included studies are associated with meaningful differences in outcomes. Instead, there is clearer evidence for local practical equivalence between protein intakes. The local equivalence between protein intakes does not imply that protein intake has no impact upon the outcomes examined, but that changes within these local regions are likely to yield outcomes that are practically equivalent, at least according to our registered SESOI. Across all outcomes our results suggest that, from a current protein intake within the ranges examined, increases or decreases of approximately 0.2 to 0.5 g/kg/day do not result in meaningfully different outcomes. Outside these local ranges, neither increases nor decreases in intake met our pre-registered SESOI for a meaningful outcome change; instead, estimates for more widely separated intakes were far less certain, reflecting the lack of current data for such comparisons.

We examined a range of candidate dose-response models in our analysis and utilised a Bayesian model-averaging approach[29] in order to incorporate uncertainty about the function form which might best describe the data. Previous modelling of dose-response functions has often implicitly included sharp "breakpoints" in the analyses (~1.2 to 1.6 g/kg/day) either through categorical treatment of intakes[15], estimation of single

breakpoints from piecewise models[16], or using fixed inflexion points in non-linear modelling[17,18]. In contrast, our model-averaged dose response function did not identify a specific optimal intake nor any clear plateau in the association between protein intake and outcomes. This was despite including some candidate models with a function form implying a precise "breakpoint" (i.e., the linear-spline models with a knot at 1.6 g/kg/day). The distributed model weights (see final stacking weights) instead demonstrate genuine function form uncertainty in the underlying data generating process meaning no single dose response shape should be treated as established. The overall model averaged dose-response function then should be treated as a candidate to take forward for further severe testing of its implied contrasts, and the implied magnitude of these could be used in ensuring that sufficiently powered/precise RCT designs are used for these tests.

We examined several variables that had physiological plausibility as moderators of the protein intake dose-response considering previous research examining acute muscle protein synthetic response including participation in RT, age, study duration, and training status. For example, previous studies show that RT increases muscle protein turnover and enhances the protein-synthetic response to amino acid provision, providing a plausible basis for an interaction between protein availability and the exercise stimulus[170,171], whereas in the absence of an RT stimulus muscle protein synthesis saturates at modest protein doses[172,173]. Similarly older adults require a larger relative protein dose in a single meal to maximise muscle protein synthesis than younger adults[174]. Further, during RT, early increases in muscle protein synthesis partly reflect repair following unaccustomed exercise; as muscle damage subsides, synthesis becomes more closely associated with hypertrophy[175]. But, the effects of RT itself tend to diminish over duration of exposure[176,177] resulting in strongly attenuated effects in well trained participants[46,48]. This provides a physiological reason to consider both exposure duration and prior training experience as both may affect not only RTs effects but plausibly the effects of protein too. However, despite their plausibility, comparison of dose-response functions between conditions with participation of RT compared to no RT, across ages, study durations, and both untrained and trained participants, revealed little in the way of moderating effects across outcomes. The exception was for whole body lean/fat free mass and RT where there was a somewhat clearer tendency for modest association between higher protein intakes and outcomes when participating in RT as compared to a flatter function without. However, given participation in RT is a principally more effective adaptive stimulus for this outcome the overall modest effects of protein intake in comparison retain biological plausibility. When not participating in RT protein intake may have even less influence when habitual intake is already adequate consistent with adaptive metabolic demand and protein-stat accounts of regulation[178]. Yet, the present evidence does not clearly establish that protein intake dose-response associations across outcomes differ meaningfully when participating, or not, in RT. Additionally, in exploratory model-averaged analyses restricted to RT studies, we also found little moderating effect of study-reported training status comparing trained and untrained groups[i]. This held for relative protein intake, absolute total intake, and absolute supplementation. Many supported differences met the criterion for practical equivalence, while others remained uncertain, particularly for strength in the relative and absolute total intake analyses.

Despite the generally trivial effects of differing protein intakes and the lack of moderating effects by participation in RT, age, study duration, and training status in our results, the uncertainty in aspects of our findings is particularly relevant to well-trained participants and competitive athletes who may be seeking to optimise outcomes. Short trials, limited sample sizes, and sparse evidence jointly covering trained participants, direct contrasts between low and high intakes, and lack of long follow-up periods leave the question of whether a worthwhile benefit from higher intakes over longer periods remains possible for experienced participants in strength and aesthetic sports, including bodybuilding, despite trivial average effects. Further, individuals in such populations may hold different personal SESOIs in comparison to our pre-registered SESOI used here and so may still reasonably interpret the trivial average effects reported as meaningful to them and their context. But, it should be noted that even with smaller SESOIs most contrasts would remain uncertain for the kinds of contrasts described i.e., low versus high intakes in trained populations participating in RT. Evidence remains sparse for contrasts implied by these areas of the dose-response curves presented and so future research should perhaps be directed at these but be aware that the typical sample sizes in the present body of literature are woefully inadequate with respect to power/precision to detect the magnitudes of average effects estimated in our present results[j]. Further, these populations typically also seek to maximise muscle

[i]Physical-function estimates were descriptive because too few studies included trained participants to support the comparison.

[j]For each dose comparison, we used the smallest absolute posterior mean contrast across whole-body lean/fat-free mass,

gain while reducing fat mass, and therefore undertake periods of energy deficit. We excluded interventions intended to induce weight loss and did not model energy balance directly as a moderator, so the present findings do not resolve protein dose responses during deliberate energy restriction. Short-term energy deficit can suppress resting muscle protein synthesis[179]. Previous syntheses addressing this context suggest that intakes above the RDA can attenuate lean-mass loss during energy restriction[180], and that higher intakes are associated with more favourable fat-free-mass changes in energy-restricted, resistance-trained participants, although the latter findings remain exploratory[28]. Preserving fat-free mass during a deficit is also a distinct objective from maximising muscle gain. Neither those findings nor our results establish an optimal intake for athletes pursuing both goals, and our local equivalence findings should not be assumed to generalise to that setting. Again, this is a further area that future research should target.

The sensitivity analyses, across all protein exposure definitions, clarify the causal interpretation of the primary dose-response results. The Mundlak and strict within-study models moved identification towards randomised comparisons within trials, and the latter were generally more attenuated in magnitude than the primary arm-level associations. This suggests that the magnitude of the primary dose-response results may include at least some between-study differences or post-randomisation components and may in fact overstate the magnitude of the causal effect of changing intake. Conversely, the paired achieved- and assignment-derived analyses were broadly similar, and explicitly modelling intake measurement error or residual within-study correlation did not reveal any substantively different association. The addition-versus-substitution protein intake strategy analyses, examined to determine if energy adjustment (i.e., protein intake either increased energy intake or protein intake substituted other macronutrients) was conducted to see if the dose response associations differed when these different estimands were considered[50]. However, it also did not identify a consistent strategy advantage. When comparing the results of analyses examining different measurement approaches for muscle size or mass the shape and magnitudes of the dose-response curves were similar when including regionally derived outcomes from DXA, BIA, or skinfolds and sensitivity analyses including only direct MRI, CT, US, and biopsy muscle measurements; though the latter estimates were far less precise and may also be influenced by study-level confounding given the contributing studies differed between this and the other measurement analyses. Overall then the broad small-effect conclusion was robust across complementary assumptions for relative intakes. The primary absolute-intake and absolute supplementation dose analyses also did not materially alter the overall interpretation based on relative intake. This was also consistent across the sensitivity analyses for these exposure definitions. They provide a limited indication that extremely widely separated absolute doses may be associated with a meaningful difference in whole-body lean/fat-free mass during RT, but this was limited to contrasts with sparse high-dose observations and was not reproduced across the other outcomes. The risk-of-bias, publication-bias, and GRADE findings further qualify the strength of our conclusions. Most trials raised some concerns or were at high risk of bias for their index result, publication-bias-adjusted estimates were appreciably attenuated towards zero, and certainty was low or very low for every assessed dose contrast. The failure to establish a meaningful outcome gain from increasing intake, or loss from decreasing it, should therefore not be interpreted as precise evidence that all more widely separated intakes are equivalent. Rather, the clearest positive inference is local practical equivalence, while estimates for larger contrasts remain uncertain and the overall evidence base warrants caution.

This review both inherits strengths from the previous review of Nunes et al.[15] and adds several new strengths in comparison with that and other previous evidence syntheses. The evidence base was expanded to include studies published since the previous review, and data extraction and modelling were expanded to include more data than previously used from the included studies; compared with the previous review, the updated dataset contained approximately five times as many whole-body lean/fat free mass or measures of muscle

measures of muscle size or mass, and strength among the primary RT estimates in Table 2. We used pooled RT estimates because the lowest observed intake in trained RT samples was 0.87 g/kg/day. For 0.8 to 1.1, 1.1 to 1.6, and 1.6 to 2.2 g/kg/day, the selected effects were 0.0250, 0.0445, and 0.0435 baseline SDs, respectively. The first two were for whole-body lean/fat-free mass and the third was for strength. If these were the true between-arm differences in mean change, a two-sided two-sample t-test at $\alpha = 0.05$ with equal allocation, equal baseline and follow-up SDs, and the pooled baseline-to-follow-up correlation used for imputation ($r = 0.947$) would have conditional power of 5.3%, 6.1%, and 6.0% at 11 participants per arm (trained RT median), and 5.4%, 6.4%, and 6.3% at 14 per arm (all RT median), respectively. Achieving 80% power would require 2,638, 836, and 875 analysable participants per arm, respectively. Repeated measurements and adjustment for baseline prognostic covariates may improve precision though sample sizes required would likely still exceed the typical trial considerably.

size or mass contrasts, over four times as many strength contrasts, and nearly six times as many function contrasts. We also directly incorporated uncertainty about dose-response functional form through model averaging and provide cautious interpretations based on our preregistered SESOI. Lastly, although some deviations were required to address model-fitting diagnostic issues in the final dataset, all are thoroughly and transparently reported.

There are, however, still limitations to this review and the broader body of evidence regarding the effects of protein intake. As already noted, data remain sparse at the extremes of intake, both below the RDA and very high intakes (of 254 primary-analysis arms, 5 [2.0%] were below 0.8 and 21 [8.3%] were above 2.2 g/kg/day), and thus it is difficult to draw certain inferences regarding comparatively high or low protein intakes. Most included studies examined relatively short intervention durations, typically 10-12 weeks. Although the exploratory duration analyses did not identify meaningful moderation within locally supported ranges, they do not establish whether protein contrasts become smaller or larger over substantially longer exposure, either with or without participation in RT. The heterogeneity of outcome measures required standardisation and limits interpretation in original units. The raw-unit reference supplement illustrates how translations vary by measure and reference sample. Further, and specific to the whole body outcomes in addition to influencing the measures of muscle size and mass including regional proxies from DXA, BIA, and skinfolds, is that these are multi-compartment measures[34] in which values of lean/fat free mass overstate the specific skeletal muscle component[181–184]. Outcome covariances were not reported within studies and were therefore treated as independent. A proportion of eligible contrasts also had to be excluded, most commonly because protein intake or sufficient outcome data were unavailable, so resulting selection bias cannot be ruled out. Characteristics such as age, training status, sex, energy balance, clinical conditions such as frailty, protein quality and distribution, and RT programme design may modify responses but cannot all be resolved reliably from study-level synthesis. Lastly, though only indicative, our results suggest high risk of bias, including possible publication bias or other selection bias effects, in this trial literature and as such even our strongest conclusions retain at best a low level of certainty following GRADE.

Future trials provide severe tests of the implied dose-response functions and contrasts from our model-averaged results while addressing limitations of the present literature including risks of bias. Pre-registered studies of longer interventions, with larger samples, repeated dietary measurements, adherence assessment, and standardised RT prescriptions, together with better reporting of baseline, follow-up, and change-score variability, within-participant correlations, and outcome covariances, would strengthen subsequent synthesis. Open data would enable some missing quantities to be recovered and facilitate individual-participant-data analyses of potential effect modification by baseline intake, age, training experience, sex, body composition, and energy status. Most studies randomise participants to additional absolute supplementation or a prescribed intake target, for which intention-to-treat effects can be estimated, whereas achieved intake is post-randomisation and may be confounded by determinants of adherence and diet. Trials intended to estimate per-protocol effects of sustained intake should therefore collect the longitudinal intake, adherence, prognostic, and co-intervention information needed for appropriate adjustment. Future studies should also target the more uncertain contrasts implied by the model-averaged functions, especially comparisons between lower and higher intakes across the empirically supported ranges. They should also consider approaches to help achieve the relatively large sample sizes required for their detection when testing against a point zero null (e.g., multi-site randomised trials), improve power through other means (e.g., pre-registered prognostic covariates or higher frequency outcome measurement and covariance handling), or consider determining *a priori* a justifiable SESOI for which to test equivalence against if the effect magnitudes estimated by our models are deemed to be too small to be practically meaningful for a given population and context.

Conclusion

The results of this updated systematic review and dose-response meta-analysis suggest that, within the protein-intake ranges represented in the available trials, the evidence more clearly supports local practical equivalence than a meaningful change in outcome from moving intake in either direction i.e., increasing or decreasing intake. The model-averaged functions showed a modest positive association between protein intake and the examined outcomes and so those wishing to maximise outcomes may see it as reasonable to aim

for higher protein intakes. However, the estimates were not sufficiently precise to establish that the gain from increasing intake, or the loss from decreasing it, exceeded our *a priori* determined practically meaningful threshold. From a given current intake, directional changes of approximately 0.2 to 0.5 g/kg/day were generally supported as practically equivalent. More distant comparisons were generally uncertain rather than demonstrably meaningful or equivalent. The sensitivity analyses supported this broad conclusion but indicated that the primary achieved-intake curves should not be interpreted as fully causal and may overestimate the magnitude of causal effects. Together with some or high risk of bias, attenuation of effects towards zero after publication-bias adjustment, and low or very low GRADE certainty, these findings suggest a lack of certainty regarding the effects of varied protein intakes; though they would appear most likely to be small with no clear evidence to support an optimum intake. Comparisons between more widely separated intakes, and the extent to which the observed associations represent causal dose effects, remain uncertain. As such, whilst our results do not establish adequacy of the RDA, we suggest that practical recommendations for changes to intakes from typical habitual values should be based upon considerations other than just their effectiveness for the outcomes examined here (e.g., cost, appetite and food preferences, energy restriction). Lastly, we suggest that future research should make concerted attempts to address the shortcomings of the current body of literature.

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Competing Interests

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Data and Supplementary Material Accessibility

The GitHub repository contains the analysis code, public reporting data and instructions for obtaining archived analysis inputs. All supplementary materials accompanying the results presented here are available in full on the supplementary materials landing page.

Declaration of Generative AI Use in the Research and Manuscript Preparation Process

During the conduct and preparation of this work, the authors used OpenAI's ChatGPT and Codex (including GPT-5.6/6.1 Sol) to assist with developing, reviewing, and debugging R and Stan code and the reproducible workflow including initial auditing of the pre-registered pipelines and ensuring accurate implementation of the pre-registrations intended analyses; auditing protein-intake calculations and extracted data against source reports; and drafting, restructuring, and language editing of manuscript components and supplementary materials. All AI-assisted outputs used in the project were critically reviewed and edited by the authors and, where relevant, verified against the source reports, data, and reproducible computational outputs. The authors retained full control over all study decisions, choice of analyses and their rationale, interpretations, and conclusions and take full responsibility for the accuracy, integrity, originality, and final content of the work.

Author Contributions (CRediT)

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- **Formal analysis** — JS
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- **Methodology** — JS
- **Project administration** — JS
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- **Software** — JS
- **Supervision** — JS
- **Validation** — JS
- **Visualization** — JS
- **Writing – original draft** — JS
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