

NUTRITION REVIEWS

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Title: Effect of non-meat, high protein supplementation on quality of life and clinical outcomes for older people living in care homes: systematic review and meta-analysis.

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47 **ABSTRACT**

48

49 **CONTEXT:** Care home residents are at risk of malnutrition through reduced overall food intake, ‘anabolic
50 resistance’ in ageing muscle and high prevalence of medical morbidity and functional dependency.
51 There has been limited consensus regarding effectiveness of a high protein diet on quality of life or
52 clinical outcomes for care home residents.

53

54 **OBJECTIVE:** To evaluate the effectiveness of non-meat, high protein supplementation on Health-Related
55 Quality of Life (HRQOL) and relevant clinical and nutritional outcomes in older people in the care home
56 setting.

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58 **DATA SOURCES:** We searched EMBASE, AMED, CINAHL, MEDLINE, and the Cochrane Registry of Clinical
59 Trials, OpenGrey, clinicaltrials.gov, the WHO clinical trial registry and the ISRCTN and NIHR trial portfolio
60 (to February 2018) for randomised controlled trials.

61

62 **DATA EXTRACTION:** We extracted data from included trials if they assessed people aged 65 years and
63 over living in care homes, who received a protein supplementation compared to not.

64

65 **DATA ANALYSIS:** We assessed trial quality using Cochrane Risk of Bias tool and meta-analysis was
66 undertaken when appropriate.

67

68 **RESULTS:** 17 papers with 1,246 participants fulfilled the inclusion criteria. All studies were low or
69 moderate quality. No evidence of improving HRQOL when the SF-36 was used (Standardised Mean
70 Difference (SMD: -0.10; 95% CI: -0.51 to 0.31; p=0.62), although significant improvement was seen in
71 the single trial using EQ-5D (SMD: 2.58; 95% CI: 2.05 to 3.10; p<0.00001).

72

73 **CONCLUSIONS:** Non-meat, high-protein oral supplements can improve markers of nutritional status in
74 care home residents. However, there is insufficient high-quality evidence to determine the effect of
75 such interventions for older adults in care homes with regard to HRQOL.

76

77 **SYSTEMATIC REVIEW REGISTRATION:** PROSPERO - Reg No: CRD42015029313.

78

79 **KEYWORDS:** High protein; care homes; older people; quality of life; appetite

80

81 INTRODUCTION 82

83 In the UK 425,000 individuals live in care homes for older people. These are long-term care
84 facilities which may, or may not, have specialist nursing input but which universally provide care
85 for people with multiple morbidities and advanced functional dependency and who can no
86 longer be supported in their own home.¹ The care home bed-base is about three times that
87 for acute hospitals and care outcomes for care home residents are increasingly recognised to
88 impact upon all of health and social care.² An important source of morbidity for care home
89 residents is malnutrition, defined as a state of nutrition in which a deficiency, excess or
90 imbalance of energy, protein and other nutrients causes measurable adverse effects on
91 tissue/body form, function and clinical outcome.³ This affects approximately 30% of older
92 people living in care homes with a particular risk of protein energy malnutrition.⁴ The multitude
93 of poor outcomes attributable to inadequate nutrition include: increased risk of infections,
94 dehydration, falls, inability to perform activities of daily living (ADLs) and reduced health-
95 related quality of life (HRQOL).⁵ While malnutrition does not have to be an inevitability of
96 ageing, there are several factors putting older adults at risk, including reduced appetite, poor
97 dentition, swallowing problems, altered taste and smell.⁵ All of these may be addressed by high
98 protein oral nutritional supplements (ONS), which may be of particular use in care homes
99 because the care home staff supervise both dietary intake and administration of
100 medicines/supplements.^{6,7}

101

102 The most commonly administered ONS are protein enriched drinks which are easy to
103 administer, require no mastication and are less satiating than solids.⁸ Supplementation of
104 dietary protein from a non-meat source avoids matters of cultural beliefs around food choices,

105 as several religions and cultures prohibit consumption of particular meats, and this can be more
106 sustainable from an environmental perspective.^{9,10} While animal sources of protein deliver all
107 the essential amino acids, the environmental impact from producing livestock for meat is
108 almost double that associated with supporting a lacto-ovo-vegetarian diet.¹¹

109

110 While many older people are affected by multiple chronic diseases, most regard the presence
111 or absence of disease less important than their overall quality of life.¹² Numerous systematic
112 reviews have reported the prevalence of malnutrition among older adults. However, there is
113 little evidence from systematic reviews to establish the best nutritional support for older adults
114 in care homes.¹³ Older adults are at particular risk of protein energy malnutrition as a result of
115 reduced overall food intake and ‘anabolic resistance’ in ageing muscle.^{6,14} Additionally, few
116 papers have assessed the evidence regarding effectiveness of a high protein diet on quality of
117 life or clinical outcomes for care home residents.^{15,16} The primary purpose of this study was to
118 address this and to perform a systematic review to assess the effect of supplementation on
119 quality of life for older people living in care homes.

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123 **METHODS**

124

125 *Protocol*

126 The protocol for the review was registered on PROSPERO (Reg No: CRD42015029313).

127

128 *Reporting*

129 This systematic review has been reported in accordance with the PRISMA guidelines (Table
130 S1).¹⁷

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132

133 *Search Strategy*

134 A primary literature search was performed using the published literature databases: EMBASE,
135 AMED, CINAHL, MEDLINE, and the Cochrane Registry of Clinical Trials. In addition, unpublished
136 literature databases were also searched including OpenGrey, clinicaltrials.gov, the WHO clinical
137 trial registry and the ISRCTN and NIHR trial portfolio. We searched databases from their
138 inception to 1st February 2018. The MEDLINE search strategy is presented in Table S2 and was
139 modified for each database. We reviewed the reference lists of eligible studies and contacted
140 the corresponding authors from each included paper where contact details were available, to
141 identify any previously omitted trials. Three replies were received out of 13 enquiries.

142

143 *Eligibility*

144 We included studies which were: randomised controlled trials involving a non-meat, high-
145 protein dietary intervention; for people who were aged 65 years or over; and conducted on
146 residents in care homes. We defined high protein supplements as including >20g of protein and
147 >20% total calorie value from protein. We also included moderate protein supplements if
148 containing >10g protein or >10% of total calorie value from protein. We excluded trials where
149 participants were recruited during acute hospital or rehabilitation unit admissions or conducted
150 in sheltered housing settings. We included papers irrespective of country of origin, or language
151 or age of publication. We included all comparison arms which may have been controls assigned
152 to a standard diet or a placebo product, however we excluded trials where there were co-
153 interventions combined with a dietary intervention e.g. dietary intervention plus physical
154 activity. Where trials presented data on multiple intervention arms e.g. dietary intervention
155 vs. dietary intervention and physical activity vs. physical activity alone, data from the dietary
156 intervention alone group were extracted.

157

158 *Study Identification*

159 Two reviewers (AICD, SA) independently screened all titles and abstracts against the above pre-
160 defined eligibility criteria. We obtained the full-text of each paper which met the eligibility
161 criteria and these were re-reviewed independently by the two reviewers (AICD, SA). We
162 included those which met the criteria in the final analysis. Where disagreements occurred for
163 paper eligibility, these were discussed between the two reviewers and adjudicated by two
164 senior reviewers (TOS, PKM).

166 *Outcomes and Data Extraction*

167 The primary outcome was health related quality of life (HRQOL), including Short Form-36 (SF-
168 36), EQ-5D, and Dementia Quality of Life Measure (DEMqOL). Secondary outcomes included:
169 adverse events (including admissions to hospital, gastrointestinal symptoms), falls, functional
170 assessments, body weight, body mass index (BMI), mid-upper arm circumference (MUAC) and
171 grip strength. Data were extracted by one reviewer (AICD) and verified by a second reviewer
172 (SA). Disagreement was resolved by discussion and review of the source paper and adjudicated
173 by one senior reviewer (TOS). Data extracted included: participant characteristics, details of the
174 dietary intervention, trial design features and the outcomes of interest.

176 For body weight, BMI and MUAC, we recorded the change in each value for each group, and
177 where this value was not presented in the data, an estimate was made using the difference in
178 mean values for these outcomes from before and after intervention with an estimated standard
179 deviation (SD) using a correlation coefficient of 0.5.¹⁸

181 *Quality Assessment*

182 We assessed the quality of all included studies using the Cochrane Risk of Bias tool.¹⁹ This was
183 performed independently by two reviewers (AICD, SA). Any disagreement in appraisal score
184 was satisfied through discussion and adjudicated by a third reviewer (TOS).

185

186 *Data Analysis*

187 All the studies were RCTs. Effect size of such trials depends on how the ‘control’ has been
188 defined. Study heterogeneity was assessed through examination of the data extraction table,
189 assessing between-study variability in respect to participant, recruitment, intervention and any
190 co-interventions. We conducted a narrative analysis (reporting the trends in results (descriptive
191 and statistical) rather than pooling the data into a meta-analysis) when there was study
192 heterogeneity or insufficient data (less than two dataset presenting mean and standard
193 deviation or event count data for a specific outcome) to pool results. We performed a meta-
194 analysis when there was low risk of study heterogeneity. We assessed statistical heterogeneity
195 using the inconsistency-value (I^2) and Chi^2 . Where I^2 was 30% or less and Chi^2 $p > 0.10$, we
196 conducted a fixed-effects model analysis. When these were not met, we performed a random-
197 effects model. We evaluated all continuous outcomes of HRQOL, functional assessment, body
198 weight, BMI, MUAC and grip strength using mean difference (MD) for individual papers and
199 presented in forest plot or standardised mean difference (SMD) when trials used different
200 measurements to capture the same domain. We assessed categorical outcomes such as
201 adverse events and falls using a risk ratio (RR).

202

203 We presented all analyses with 95% confidence intervals (CI) and forest-plots. We performed
204 pre-defined sub-group analyses of study outcomes by duration of intervention ($>$ or \leq 12 weeks)
205 and total protein content. We classified protein content as high ($>20\text{g}$ protein), moderate (10-

206 20g protein) or low (<10g protein). We classified calorie content as high (>20% calories from
207 protein), moderate (10-20% calories from protein), or low (<10% calories from protein). Follow-
208 up intervals were up to two years post-randomisation. We planned to present a funnel plot for
209 the primary outcome analysed and/or any analysis where there was a minimum of 10 datasets,
210 to assess small sample size publication bias.¹⁹ We intended to examine the clustering effect if
211 the original papers reported the data accounted for clustering within a care home. We
212 conducted all analyses in collaboration for verification by two reviewers (AICD, TOS) using
213 Review Manager (RevMan).²⁰ For all analyses, a $P \leq 0.05$ was deemed statistically significant.

214
215 We made an analysis of the weight of the evidence for each individual outcome using the
216 GRADE approach.^{21,22} Through this, we categorised the strength of evidence underpinning
217 each analysis as high, moderate, low or very low, with evidence graded based on study design,
218 study quality, consistency, directness of evidence, precision and reporting bias.^{21,22}

219

220 RESULTS

221

222 *Study Selection*

223 The results of the search strategy are illustrated in the PRISMA flow-chart (Figure S1). As this
224 illustrates, the searches identified 431 potentially relevant papers, of which 17 fulfilled the
225 inclusion criteria.^{6,23-38} Two of the included papers reported on the same trial but participants
226 were only counted once.^{26,35} On stratifying the trials by protein content of the intervention, five
227 fulfilled our criteria of high protein (>20g protein and >20% of total calories from
228 protein)^{6,26,27,33,35,37} and 12 fulfilled our criteria of moderate protein (>10g protein or >10%
229 calories from protein).^{23-25,28-32,34,36,38}

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Study Characteristics

Study characteristics are summarised in Table 1. A total of 1246 participants were identified from 16 trials, (range: 34 to 175 participants).^{23,32} This included 271 males and 934 females; the gender of 41 participants was not documented in one trial.²⁹ The study mean ages ranged from 78.7 to 89.6 years.^{30,34} The presence of dementia or cognitive impairment indicated by Mini Mental State Examination (MMSE) score was described in 13 trials.^{23-32,35,36,38} In this systematic review, MMSE score of nine or below indicated severe cognitive impairment, 10 to 18 moderate cognitive impairment, 19 to 23 mild cognitive impairment and 24 to 30 as normal cognition.³⁹ In the included trials, mean baseline MMSE ranged from 18 to 26^{23,29} and in three trials 100% of participants had a diagnosis of dementia.³⁰⁻³² There was no consistent measure of frailty, but several trials provided information on the prevalence of chronic illness,^{25,28,32,34,35,37,38} ranging from a mean of 1.8 to five comorbid diseases.^{25,28}

The standard diet for participants prior to intervention contained a mean of 1560 kcal and 56g of protein daily. Interventions were mainly liquid: 10 studies used a milk based supplement,^{6,24-27,30,31,35-38} one used a soya drink,²⁸ three used an enriched diet or a choice of supplement,³²⁻³⁴ one used high protein cookies,²³ and one used an amino acid supplement²⁹. Intervention protein content ranging from 8g²⁹ to 40g³³ with total calories 32kcal²⁹ to 600kcal.^{26,33-36,21,28-31}

The duration of intervention ranged from four weeks⁶ to nine months.³⁷ The comparison used in 10 trials was standard diet,^{6,23,24,26,27,30-33,35,36} while four trials used a placebo non-calorie drink,^{25,30,37,38} one trial used a snack of unspecified content,²⁸ one trial used a placebo maltodextrin tablet,²⁹ and one provided dietary advice.³⁴

Risk of Bias

A summary of the Risk of Bias quality assessment is presented in Figure S2 and GRADE assessment of outcomes in Table 2. There was a strong risk of selection and performance bias due to the lack of blinding of participants and/or personnel in 14 trials,^{6,23,25-28,30,31,33-38} and unclear blinding in two further trials.^{24,30} A placebo supplement was employed in six trials,^{25,28-30,37,38} and blinding of the outcome assessor was described in five trials.^{25,29,36-38} The risk of reporting bias was largely unclear^{6,23-37} and risk of attrition bias was high with an attrition rate >15% in seven trials^{30,33-38} and not described in three.^{6,23,24}

Health Related Quality of Life

HRQOL was assessed by SF-36 in two trials^{29,33} and the EQ-5D in one trial.³⁴ Heterogeneity was too high to draw conclusions from meta-analysis of the three trials, although this can be seen in Figure 1 for interest only. On subgroup analysis, there was no evidence of improving HRQOL when the multi-dimensional assessment tool SF-36 was used (SMD: -0.10; 95% CI: -0.51 to 0.31; $p=0.62$; 2 trials), although significant improvement was seen in the single trial using EQ-5D for which the intervention was classed as moderate protein content (SMD: 2.58; 95% CI: 2.05 to 3.10; $p<0.00001$; 1 trial). Due to the significant heterogeneity between the trials ($I^2 = 96\%$) and based on the GRADE assessment, the evidence was graded low quality.

Adverse events, deaths and falls

Four trials reported data on death^{25,34,35,38} and eight reported data on adverse events.^{24-27,30,36,38} There was no significant difference in the number of reported adverse events (RR:

1.11; 95% CI: 0.70 to 1.76; Figure 2) and deaths (RR: 0.53; 95% CI: 0.22 to 1.25; Figure S3). There was no available data on the incidence of falls in any of the trials. Study heterogeneity was not significant for analysis of adverse events ($I^2 = 20\%$) or deaths ($I^2 = 0\%$). Based on the GRADE assessment, the evidence underpinning the assessment of adverse events, deaths and falls was graded low quality.

285

Functional Assessment

Two trials reported data on functional outcomes using the Barthel Index^{33,35} and two assessed this domain using an alternative ADL based score.^{24,30} Study heterogeneity was not significant ($I^2 = 0\%$). There were no significant differences between the control and intervention groups (SMD: -0.04; 95% CI: -0.29 to 0.22; $p=0.57$; Figure S4) including when limiting to the high protein studies^{33,35} (SMD: -0.11; 95% CI: -0.44 to 0.23; $p=0.41$). Based on the GRADE assessment, the evidence was graded low quality.

293

Body Weight

The mean change in mean body weight was reported in 13 trials.^{23-28,30,31,33-36,38} Meta-analysis showed significant increase in mean body weight with intervention across all included trials (MD: 1.11; 95% CI: 0.97 to 1.24; $p<0.0001$; Figure S5). This effect was also evident in the high protein group^{26,27,33} (MD: 2.12; 95% CI: 1.34 to 2.91; $p<0.00001$; Figure S5), and by a smaller magnitude in the moderate protein group (MD: 1.08; 95% CI: 0.94 to 1.21; $p<0.00001$; Figure S5).^{23-25,28,30,31,34-36,38} Based on the GRADE assessment, the evidence was graded moderate quality with overall substantial study heterogeneity ($I^2 = 75\%$).

302

303 *Body Mass Index*

304 The mean change in BMI was reported in eight trials.^{24,27,28,30,33,35-37} Meta-analysis showed
305 significant increase in mean BMI across all included trials (MD: 0.86; 95% CI: 0.61 to 1.10;
306 $p<0.00001$; Figure S6). This effect was seen in both the high protein group ^{27,33,37} (MD: 1.05;
307 95% CI: 0.68 to 1.41; $p=0.0004$; Figure S6) and in the moderate protein group ^{24,28,30,35,36} (MD:
308 0.70; 95% CI: 0.37 to 1.03; $p<0.00001$; Figure S6). The analyses on BMI were graded as
309 moderate quality evidence using the GRADE approach with low overall study heterogeneity (I^2
310 = 0%).

311

312 *Mid-upper-arm Circumference (MUAC)*

313 The mean change in MUAC was reported in six trials.^{24,26,28,30,35,36} The MUAC was maintained
314 better in the intervention group than the control group (MD: 0.51; 95% CI: 0.23 to 0.79;
315 $p=0.0004$; Figure S7). The GRADE assessment for change in MUAC measures was moderate
316 quality with substantial overall study heterogeneity ($I^2 = 73\%$).

317

318 *Grip Strength*

319 Grip strength was assessed in five trials. ^{24,27,32,33,35} These demonstrated substantial statistical
320 heterogeneity ($I^2 = 60\%$). There was a significant change in grip strength in the ‘moderate’
321 protein subgroup (MD: 1.29; 95% CI: 0.45 to 2.14; $p=0.003$; Figure S8), and although the change
322 in the ‘high protein’ subgroup was not statistically significant, there does appear to be a
323 tendency of an effect (MD: 0.63; 95% CI: -0.05 to 1.32; $p=0.07$; Figure S8). Based on the GRADE
324 assessment, the evidence was graded low quality.

325

326 *Duration of Interventions*

327 There were 12 trials (reported in 13 papers) with ≤ 12 week intervention duration^{6,23-27,29-35} and
328 four trials with intervention lasting >12 weeks.^{28,36-38} Minimum length of intervention was four
329 weeks⁶ and longest duration of intervention was nine months.³⁷ Subgroup analysis by duration
330 of intervention ($>$ or ≤ 12 weeks) was not significant for adverse events ($p=0.84$), deaths
331 ($p=0.61$), change in body weight ($p=0.12$) or change in BMI ($p=0.16$). However, there were
332 significant subgroup differences for MUAC ($p=0.005$) with stronger effect for > 12 weeks of
333 intervention (MD 0.95; 95% CI: 0.53 to 1.37; $p<0.00001$) compared to ≤ 12 weeks (MD 0.14;
334 95% CI: -0.24 to 0.52; $p=0.47$). There was insufficient data to examine the effect of duration of
335 intervention for grip strength.

336

337 **DISCUSSION**

338

339 The key finding of our systematic review is that whilst a non-meat, high protein enriched dietary
340 intervention appears to be effective for surrogate markers of clinical outcomes, there is a
341 paucity of high-quality evidence of the affect regarding HRQOL, an important health outcome
342 in old age.

343

344 Surprisingly, few trials objectively measured HRQOL. It was interesting to note that even within
345 the high protein subgroups, there was no evidence of improving HRQOL on a multidimensional
346 SF-36 assessment ($p=0.62$). Nonetheless the single trial which reported EQ-5D demonstrated
347 a significant improvement in HRQOL even at the moderate protein criteria ($p<0.00001$).³⁴ Since
348 this was only a single study which presented with a number of methodological limitations, the
349 evidence for EQ-5D remains limited, but does provide a signal which should be further

350 investigated. Notably, of those studies including HRQOL as an outcome measure, inclusion of
351 participants with a diagnosis of dementia was lacking. This absence of data on the effect of
352 high protein diet on HRQOL in care homes for those with cognitive impairment or dementia
353 must be addressed in future research given that this group comprises a significant proportion
354 of care home residents. Perhaps this paucity of data reflects the difficulties in assessing self-
355 reported measures like HRQOL in populations with a high prevalence of dementia using
356 validated tools without relying on a proxy. Even in relatively simple HRQOL measures with
357 validated proxy versions, most notably, the EQ-5D, there are acknowledged issues with relying
358 on proxy respondents in the care home setting.⁴⁰ However, dementia-specific HRQOL
359 measures, such as the DEMQoL, should be considered for future studies.⁴¹

360
361 Only four trials incorporated an objective measure of change in function ^{24,29,33,35} (Barthel Index
362 or ADL score) and it is possible that the time frame of the included trials was too short to show
363 any significant variation. Similarly, whilst there was a tendency for a difference, the study
364 interventions did not significantly differ by grip strength (p=0.07). However grip strength
365 measures have previously been noted to be very low among care home residents⁴² and may be
366 affected by both a floor effect and poor sensitivity to change. It could be that the relatively
367 invasive nature of the investigations to measure such outcomes, such as muscle biopsy and
368 DEXA scanning, in cohorts of older, frailer individuals has proved off-putting for researchers
369 working in the care home setting. More recent innovations in measuring muscle turnover,
370 including microbiopsy, ultrasonographic and excreted amino-acid derived indices of muscle
371 turnover could potentially allow more sensitive outcome measures to be employed in this very
372 frail cohort.⁴³

373

374 While no significant change in adverse effects or deaths were noted among participants
375 receiving a protein-rich nutritional intervention, a previous meta-analysis of protein and energy
376 supplementation in older people reported that there was a reduction in the mortality rate for
377 those malnourished at baseline.^{15,44} In the trials included in this review, generally only those in
378 the 'normal' BMI range were randomised, and therefore changes may have been apparent if
379 the low BMI, and therefore likely more malnourished group were also included.

380

381 It is important to consider that the population represented in the studies may have been a sub-
382 cohort of the care home population, rather than representative of the population as a whole.
383 Certainly the reported co-morbidities in those trials which described this, were significantly
384 lower than in most cohort studies of care home residents, suggesting that this may have been
385 a less comorbid and less frail sub-population. Of note, those studies which were conducted in
386 groups without dementia were almost certainly a subset, given that the estimated prevalence
387 of dementia in cohort studies of care home residents is between 69% and 80%.^{45,46}

388

389 Meta-analysis found small but statistically significant gains in both body weight (MD: 1.11kg)
390 and BMI (MD: 0.86 kg/m²), with a more significant effect noted in the higher protein group on
391 sub-analysis (MD: 2.12kg). Likewise, other meta-analyses also found significant increases in
392 body weight following protein supplementation in older adults.^{44,47} However, we recognise an
393 increase in skeletal muscle mass specifically, rather than body weight, would be the desired
394 outcome for improved function and HRQOL. While a meta-analysis by Dewansingh et al
395 showed a tendency to increase lean body mass from supplementing with >20g of protein per
396 day, a trial of long-term leucine supplementation in healthy older men did not improve skeletal
397 muscle mass or strength.^{47,48} Lean body mass is an important surrogate marker of nutritional

398 status, which should be included in future studies, this was omitted from this meta-analysis as
399 there were no results available for any of the studies.

400
401 It has been previously suggested that nutritional status can be improved by protein
402 supplementation.^{44,49,50,11,38,39} Our review supports that the macronutrient composition of
403 nutritional supplements, in terms of the protein content, may have a direct influence on the
404 extent of nutritional gains derived by older adults in residential care. Similarly, a study of protein
405 intake for more than 2,000 elderly participants demonstrated that those in the highest quintile
406 of protein intake lost significantly less lean body mass over three years than those in the lowest
407 quintile.⁵¹ This is particularly interesting given that protein rich diets have gained huge
408 popularity as a weight loss strategy, in part relying on the satiating effect of protein to prevent
409 excess calorie ingestion.⁵²

410
411 The strengths of this study relate to the systematic way in which we have approached the
412 literature. The main limitations relate to the narrow focus of our question, with focus on non-
413 meat protein supplementation and HRQoL related outcomes in a care home setting. The
414 paucity of data in this arena, whilst an important catalyst to further research, should not be
415 seen as representative of the broader literature on nutrition and patient outcomes.

416
417

418 **CONCLUSION**

419 High-protein oral supplements can improve markers of nutritional status (body weight and
420 BMI) in care home residents, but there is insufficient high-quality evidence to determine the

421 effect of non-meat, high protein interventions for older adults in residential care with regard
422 to HRQOL.

423 **DECLARATIONS**

424

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426 Witham, Reader in Ageing and Health, University of Dundee and Professor Alison Avenell,
427 Professor of Health Services Research, University of Aberdeen.

428

429 **Statement of Authorship:** AICD, PKM, AMJ and BDR conceived the study. AICD & SA performed
430 screening, selecting and extraction of data. AICD and SA also performed quality assessment.
431 AICD and TOS conducted analyses and AICD drafted the manuscript. All co-authors contributed
432 to the writing of the paper.

433

434 **Conflict of Interest Statement:** No author declared a conflict of interest in relation to this paper.

435

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439

440 **Ethical Approval:** No ethical approval was required to conduct or present this work.

441

442 **Data Availability:** We are able to provide the data which formed the basis of this analysis, on
443 request.

444 **Disclaimer:** The abstract was presented as an oral presentation at the BGS Spring meeting
445 2017 and will be published in the forthcoming supplementary issue of Age and Ageing.

446

447

448 **FIGURE AND TABLE LEGENDS**

449

450 **Figure 1:** Forest plot to assess quality of life assessments between the interventions on meta-
451 analysis

452 **Figure 2:** Forest plot to assess the adverse events reported between the interventions on
453 meta-analysis

454

455 **Table 1:** Summary of the characteristics of the included studies

456 **Table 2:** GRADE assessment of outcomes

457

458 **SUPPORTING INFORMATION**

459

460 **Table S1:** PRISMA Checklist

461 **Table S2:** Search strategy for MEDLINE

462

463 **Figure S1:** PRISMA flow diagram summarising the results of the search strategy

464 **Figure S2:** Results of the Risk of Bias assessment

465 **Figure S3:** Forest plot to compare the assessment of mortality between the interventions on
466 meta-analysis.

467 **Figure S4:** Forest plot to assess the functional assessment scores between the intervention
468 groups, on meta-analysis.

469 **Figure S5:** Forest plot to assess the change in mean body weight on meta-analysis

470 **Figure S6:** Forest plot to assess the change in mean body mass index on meta-analysis

471 **Figure S7:** Forest plot to assess the change in mean mid-upper-arm circumference (MUAC) on
472 meta-analysis

473 **Figure S8:** Forest plot to assess the outcome of grip strength measurement on meta-analysis.

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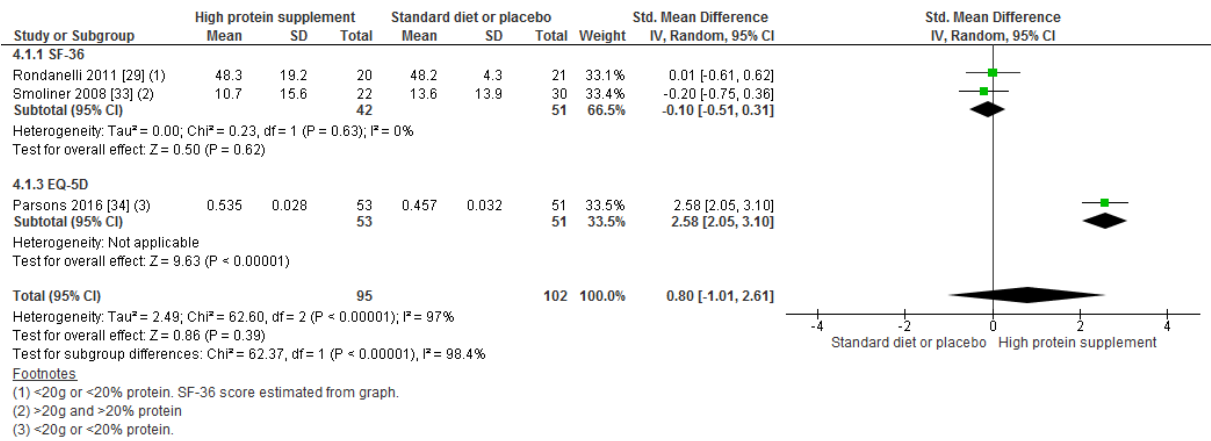
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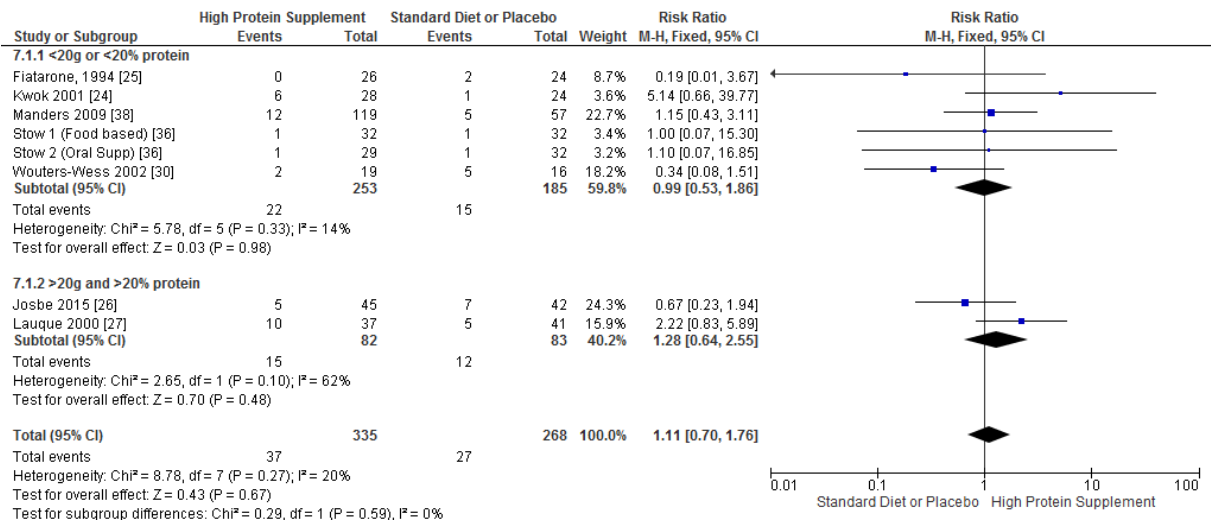
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Figure 1: Forest plot to assess quality of life assessments between the interventions on meta-analysis



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Figure 2: Forest plot to assess the adverse events reported between the interventions on meta-analysis



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Table 1: Summary of the characteristics of the included studies

Study	Country/ Setting	Number (control/ intervention)	Mean Age	Percentage female (%)	Baseline cognition	Mean baseline BMI	Baseline Diet	Dietary Intervention	Intervention protein content (g)	Intervention energy content (Kcal)	Placebo	Duration of intervention and follow-up
Smoliner et al ³³	Germany/ Nursing homes	52 (30/22)	85.2	73%	Not specified	CG: 22.5+-3.4 IG: 21.6+-3.6	2000kcal 80g protein	Enriched diet (using cream/oil) plus 300ml snacks	40 (from snacks alone)	600 (from snacks alone)	No	12 weeks
Bonnefoy et al ³⁷	France / Retirement home	57 (27/30)	83.0	88%	0% dementia (excluded)	CG: 27.32+-0.8 IG: 27.13+-0.9	2000kcal	400ml supplement drink	30	400	400ml non- calorie/ protein drink	9 months
Iuliano et al ⁶	Australia/ Low level care home	130 (62/68)	86.5	78%	Not specified	CG: 25.4+-4.9 IG: 23.7+-5.0	1497+-307kcal 56+-15g protein	2 servings of dairy foods (liquid/solid)	25+-12	215+-299	No	4 weeks
Josbe et al ²⁶ ; Stange et al ³⁵	Germany/ Nursing homes	87 (42/45)	87.0	91%	CG: 66% dementia IG: 80% dementia	CG: 22.5+-3.1 IG: 23.0+-3.4	1263+-374 kcal 41.3+-15.1g protein	250ml Fortimel Compact	24 (note one study reported as 48 but same intervention)	600	No	12 weeks
Lauque et al ²⁷	France/ Nursing homes	35 in comparable groups of same BMI status (22/13)	85.4 (estimated)	84%	CG: 68% dementia IG: 86% dementia	CG: 21.8+-0.9 IG: 22.3+-0.7	1573kcal 60g protein	300-400ml nutritional supplement drink	24	393+-23	No	60 days
Stow et al ³⁶	UK/ Care and nursing homes	93 (32/32+29)	Not described	82%	CG: 78% dementia IG(A): 78% dementia IG(B): 69% dementia	CG: 19 (17-20.5) IG(A): 20.1 (18.7-24.8) IG(B): 18.4 (17.6-21.6)	1553kcal 41g protein	A) 250-400ml food based liquid supplement B) 250-400ml liquid nutritional supplement	A) 20-25 B) 24	A) 600 B) 600	No	6 months
Kwok et al ²⁴	Hong Kong/ Nursing home	51 (24/28)	CG: 79.7 IG: 81.2	60%	CG: 9% dementia IG: 32% dementia	CG: 20.1+-3.1 IG: 19.1+-3.1	1198+-403kcal 61.6+-21.2g protein	2 cups of low-lactose milk	18.8	175	No	7 weeks

Parsons et al ³⁴	UK/ Care home	104 (51/53)	CG: 87.3 IG: 89.6	86%	0% dementia (excluded)	39% BMI <18.5 41% BMI 18.5-20	1360kcal 51.8g protein	Voluntary intake of range of supplements	Target 16	Target 600	Dietary advice	12 weeks
Fiatarone et al ²⁵	USA/ Care home	50 (26/24)	CG: 89.2 IG: 85.7	62%	Mean MMSE CG: 22.2+1 IG: 22.7+1.3	CG: 25.8+0.5 IG: 25.4+0.7	1485+-58kcal	240ml Supplement drink	15.3	360	240ml no calorie /protein drink	10 weeks
Pouyssegur et al ²³	France/ Nursing home	175 (87/88)	CG: 86.8 IG: 85.4	80%	Mean MMSE 18+-8.3	19.2+-2.9	Not specified	8 high protein cookies	11.5	244	No	6 weeks with 18 weeks follow-up
Young et al ³²	Canada/ Care home	34 (34/34) Crossover study	88.2	79%	100% dementia	23.8+-3.6	1514kcal 54.7+-17.4g protein	Various – mainly 75% of a supplement bar and a glass of juice	10.6	250	No	12 weeks
Wouters- Wess et al ³⁰	The Netherlands/ Psychogeriatric nursing home	34 (16/18)	82.7	85%	100% dementia	24.5+-4.2	1543+-377kcal 53.7+-18.3g protein	200ml supplement drink	11.2	300	No	5 weeks
Lee et al ²⁸	Taiwan/ Nursing home	92 (45/47)	CG: 80.2 IG: 78.9	58%	Mean MMSE CG: 14.1+-6.1 IG: 15.0+-5.5	CG: 20.31+-2.61 IG: 20.43+-2.50	Not specified	50g soy-protein based drink	9.5	250	Afternoon snack (content not specified)	24 weeks
Wouter- Wess et al ³¹	The Netherlands/ Psychogeriatric nursing home	35 (16/19)	CG: 78.7 IG: 85.3	89%	100% dementia	CG: 20.7+-2.7 IG: 20.7+-3.2	1496+-415kcal 55+-16g	250ml supplement drink	8.5	273	250ml non- calorie, no protein drink	3 months
Manders et al ³⁸	The Netherlands/ Care and nursing homes	176 (57/119)	CG: 81.0 IG: 81.0	74%	Mean MMSE CG: 24.0 (11.2-27.8) IG: 23.0 (9.6-27.4)	CG: 25.0+-3.5 IG: 26.1+-3.7	1793+-332kcal 58.8+-15.4g protein	250ml nutrient drink	8.75	250	250ml non- calorie, no protein drink	24 weeks
Rondanelli et al ²⁹	Italy/ Nursing home	41 (21/20)	CG: 79.9 IG: 83.5	Not specified	Mean MMSE CG: 21.1+-2.04 IG: 26.05+-2.09	CG: 22.1+-2.6 IG: 21.8+-2.3	59+-8g protein	8g Essential amino acid supplement	8	32	Maltodextrin tablet	8 weeks

Abbreviations: CG (control group); IG (intervention group); MMSE (mini mental state exam); BMI (Body mass index)

Table 2: GRADE Assessment of Outcomes

Outcome Measure	Quality Assessment				Number of Participants		Effect			EVIDENCE GRADE
	Design	Quality	Consistency	Directness	High protein intervention	Standard diet/ Placebo	MD/ SMD / RR (CI)	P value	I ²	
QOL (SF-36)	RCT	Low	Low	Moderate	42	51	SMD -0.10 (-0.51-0.31)	0.62	0%	LOW
QOL (EQ-5D)	RCT	Low	Low	Moderate	53	51	SMD 2.58 (2.05-3.10)	<0.00001	N/A	LOW
Adverse effects (group total)	RCT	Low	Low	High	335	268	RR 1.11 (0.70-1.76)	0.67	20%	LOW
Adverse effects (>20%/>20g protein)	RCT	Low	Low	High	82	83	RR 1.28 (0.64-2.55)	0.48	62%	LOW
Deaths (group total)	RCT	Moderate	Moderate	High	167	140	RR 0.53 (0.22-1.25)	0.15	0%	LOW
Deaths (>20%/>20g protein)	RCT	Moderate	Moderate	High	45	42	RR 0.40 (0.11-1.45)	0.16	N/A	LOW
Functional assessment (group total)	RCT	Low	Low	High	115	117	SMD -0.04 (-0.29-0.22)	0.79	0%	LOW
Functional assessment (>20%/>20g protein)	RCT	Low	Low	High	67	72	SMD -0.11 (-0.44-0.23)	0.53	0%	LOW
Change in mean body weight (group total)	RCT	High	High	High	446	440	MD 1.11 (0.97-1.24-)	<0.00001	75%	MODERATE
Change in mean body weight (>20%/>20g protein)	RCT	High	Moderate	High	50	87	MD 2.12 (1.34-2.91)	<0.00001	81%	MODERATE
Change in mean BMI (group total)	RCT	High	High	High	242	228	MD 0.86 (0.61-1.10)	<0.00001	0%	HIGH
Change in mean BMI (>20%/>20g protein)	RCT	High	High	High	65	79	MD 1.05 (0.68-1.41)	0.0004	0%	HIGH
Change in mean MAC (group total)	RCT	Moderate	Low	High	163	172	MD 0.51 (0.23-0.79)	0.0004	73%	LOW
Change in mean MAC (>20%/>20g protein)	RCT	Moderate	Low	High	57	70	MD 0.64 (0.11-1.18)	0.02	83%	LOW
Grip strength (group total)	RCT	Low	Low	High	122	128	MD 0.63 (-0.05-1.32)	0.07	60%	LOW
Grip strength (>20%/>20g protein)	RCT	Low	Low	High	77	87	MD -0.63 (-1.80-0.53)	0.29	33%	LOW

Figure S1: PRISMA flow diagram summarising the results of the search strategy

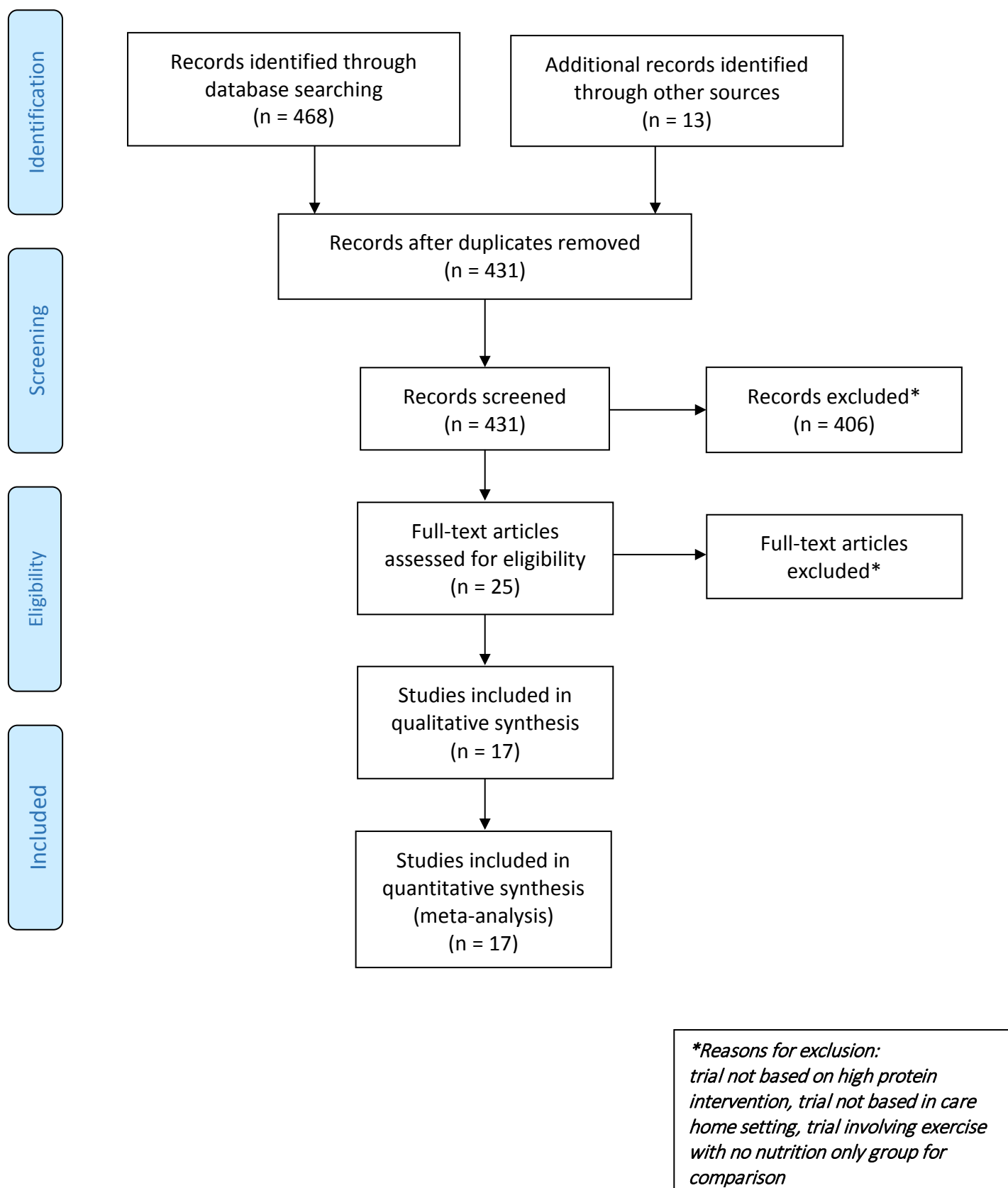


Figure S3: Forest plot to compare the assessment of mortality between the interventions on meta-analysis.

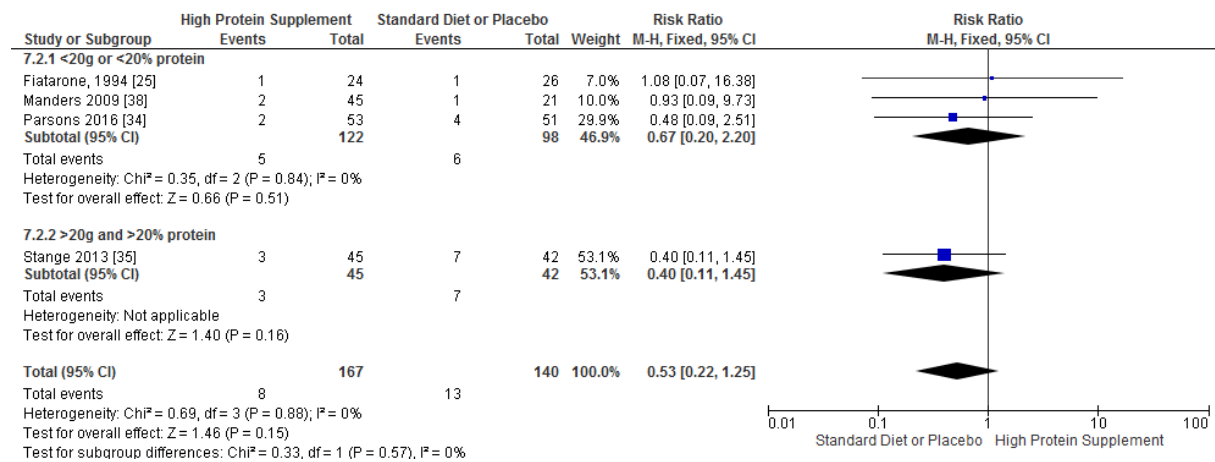


Figure S4: Forest plot to assess the functional assessment scores between the intervention groups, on meta-analysis.

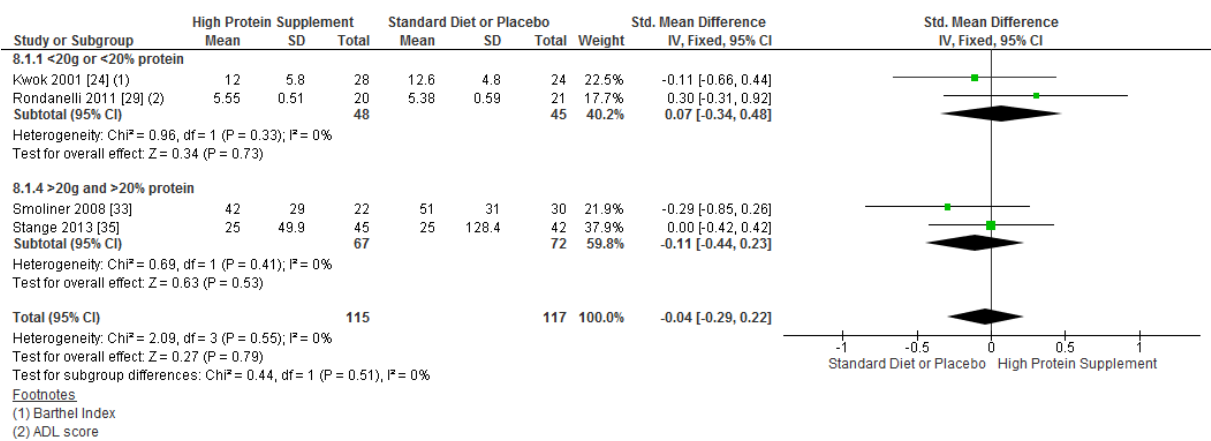


Figure S5: Forest plot to assess the change in mean body weight on meta-analysis

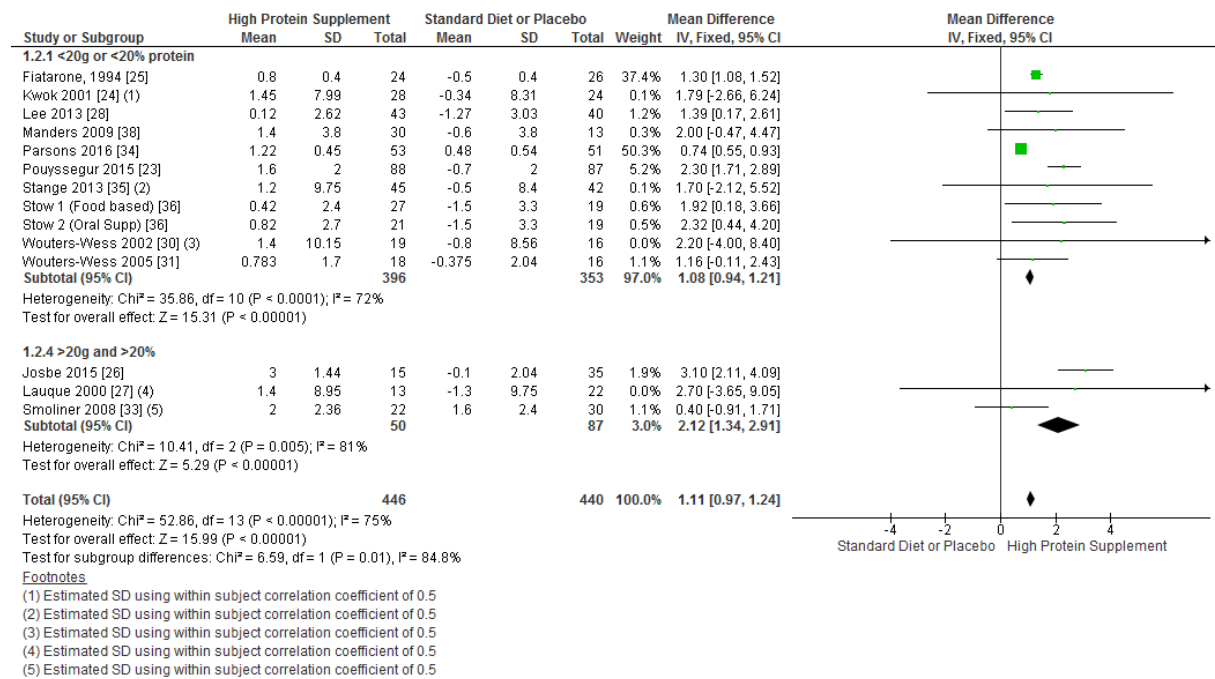


Figure S6: Forest plot to assess the change in mean body mass index on meta-analysis

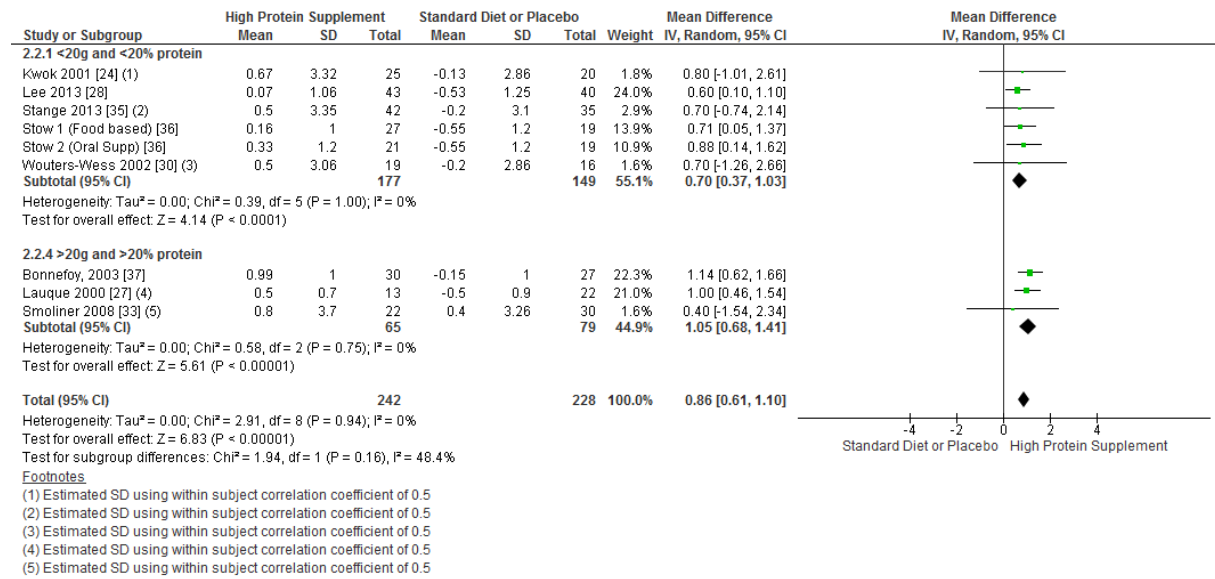


Figure S7: Forest plot to assess the change in mean mid-upper-arm circumference (MUAC) on meta-analysis

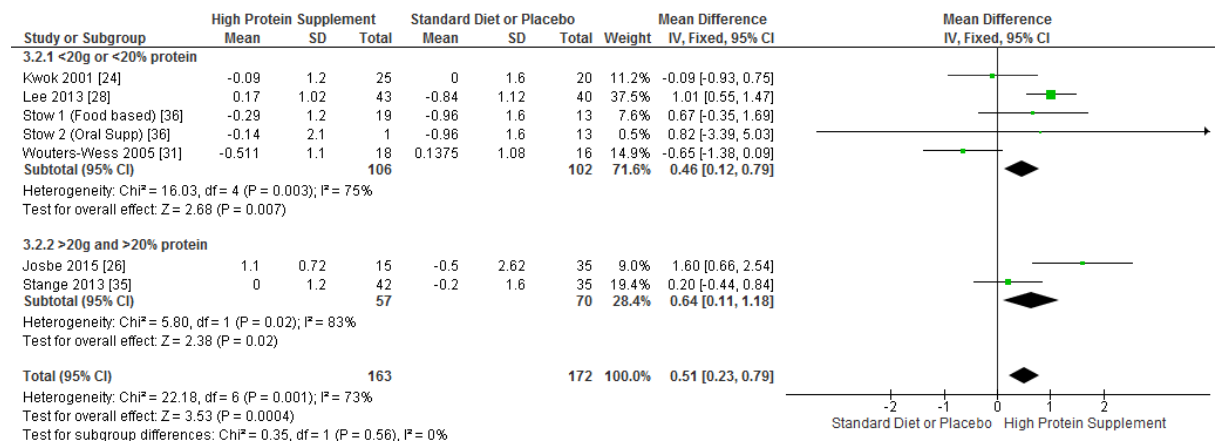


Figure S8: Forest plot to assess the outcome of grip strength measurement on meta-analysis

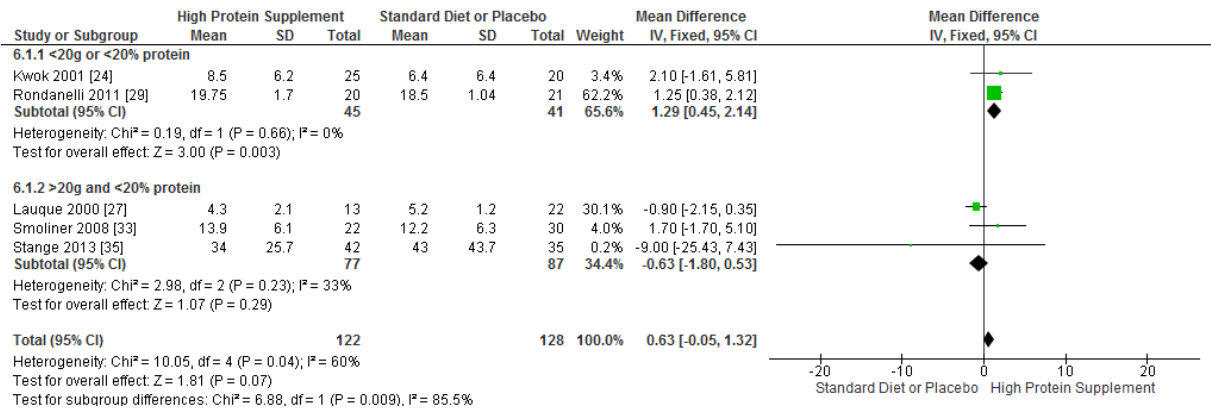


Table S1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	TITLE PAGE
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	ABSTRACT
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	INTRO Para 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	INTRO Para 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, Protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, Eligibility
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, Search Strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, Study Identification

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, Outcomes and Data Extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, Outcomes and Data Extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, Quality Assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, Data Analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, Data Analysis, Para 1

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, Data Analysis, Para 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, Data

			Analysis, Para 2
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplement Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, Figure 1,2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results, Figure 1,2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results, section throughout
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results, section throughout
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, Para 1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, Para 5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion Para 2-4

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Declarations

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Table S2: Search strategy for MEDLINE

PICOS Component	Search Strategy
Population	None Applied
Intervention	<ol style="list-style-type: none"> 1. Nutrit* 2. exp Nutrition Therapy/ 3. exp Diet/ 4. exp Diet Therapy/ 5. exp Eating/ 6. Oral nutritional supplement.ti.ab. 7. exp Dietary Supplements/ 8. exp Nutritional Support/ 9. Suppl*.ti.ab. 10. exp Dietary Proteins/ 11. (protein*) AND (feed* OR nutrit*)
Comparison	None Applied
Outcome	None Applied
Setting Design	<ol style="list-style-type: none"> 12. Care home*.ti.ab. 13. Old age home*.ti.ab. 14. Exp Homes for the Aged/ 15. Nursing home.ti.ab. 16. Residential home.ti.ab. 17. Residential facilities.ti.ab.
Design	<ol style="list-style-type: none"> 18. Randomised.ti.ab. 19. Randomized.ti.ab. 20. Controlled trials.ti.ab 21. RCT.ti.ab
	<ol style="list-style-type: none"> 22. OR/1-11 23. OR/12-17 24. OR/18-21 25. AND/22-24