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Review Article

Effect of Dietary Protein Intake on Hand Grip Strength in Healthy Adults - A Systematic Review

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Abstract

Background: Effect of protein intake on hand grip strength (HGS) is predominantly yielded using protein supplements for critically ill elderly population. In the midst of increasing chronic diseases and functional decline worldwide, we conducted a systematic review to assess the effect of dietary protein on HGS in healthy adult's ≥ 18 years old to fill in the significant knowledge gap.

Methods: A comprehensive database search e.g. MEDLINE, EMBASE, and Cochrane Library was performed until April 2016 to assess dietary protein effect alone or with exercise. A structured data synthesis was adopted as meta-analysis of the data was not appropriate due to the wide heterogeneity in the studies.

Results: Six studies (n = 7352) were included of which only one was located in a developing country (India). Overall, studies were judged at unclear (RCT), high (intervention study), moderate (3 cohort studies), and high (one cohort study) risk of bias. We found mixed evidence on the effect of dietary protein on HGS in healthy adults. The GRADE evidence quality was moderate (trial, intervention study) and very low (cohort studies).

Conclusion: The evidence on the impact of dietary protein on HGS is inconsistent for the healthy adults. To avert globally rising functional limitations and disabilities, further investigations preferably using RCT design including healthy adults are essential.

Keywords: Dietary Intake; Protein; Food Frequency Questionnaire (FFQ); Endurance Exercise; Hand Grip Strength (HGH); Healthy Adults; Global Health

Abbreviations

PURE: The Prospective Urban and Rural Epidemiological; CVD: Cardiovascular Disease; HGS: Hand Grip Strength; RCTs: Randomized Controlled Trials; RDA: The Recommended Daily Allowance; WHO: World Health Organization; g: Gram; kg: Kilogram; BW: Body Weight; HIV/AIDs: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; FFQs: Food Frequency Questionnaires; Q 5: Quintile 5; DRs: Dietary Recalls; BMI: Body Mass Index; I: Intervention; C: Control; BW: Body Weight; %E: Percent Energy; NE: No-Snack Exercise; SE: Snack-Exercise; SS: Snack-Sedentary; GLM: General Linear Model; HP: High Protein; UP: Usual Protein; MRA: Multiple Regression Analysis; %E: Percent Energy; GEE: Generalized Estimating Equations; %: Percent; MLR: Multivariate Regression Analysis; AoV: Analysis of Variance; SES: Socio-Economic Status

Introduction

Sarcopenia is prevalent among the aging population, chronic disease patients and some healthy adults [1-6]. In 2000, sarcopenia caused US$18.5 billion spending in health care [7] and the financial burden is estimated to grow exponentially with the globally increasing elderly population [8]. Loss of muscle mass and strength affect functionality through multiple factors such as age, sedentary lifestyle and suboptimal diet [7,9,10], and protein supplement is suggested preventive to frailty by preserving lean body mass in older adults [1]. Observational studies indicated benefits of higher protein intake for improved HGS and associated health outcomes [11-13]. However, results are inconclusive from RCTs and quasi-experimental studies [14-17]. Furthermore, although WHO's RDA of protein intake is 0.83 g/kg BW for the adult population [18], higher intake has been suggested beneficial for the prevention of sarcopenia and weight management [19]. Indeed, a meta-analysis of RCTs [20] administering higher protein to frail and hospitalized elderly observed a 1.76 kg (95% CI 0.36 to 3.17, n = 219, 4 RCT) increase in HGS (1.25g ± 0.17 g/kg BW). Additionally, adverse events of higher protein administration are seldom reported in previous studies. Recent evidence from the PURE study concluded that low-

er muscle strength, measured by HGS, predicted risks of CVD and all-cause mortality in adults aged 35 - 70 years [21]. Although the use of HGS as a clinical marker for cause-specific and total mortality has been previously studied [11,22] there is lack of information on the relationship between protein intake and HGS. Moreover, the relationship was primarily focused on protein supplements and including critical elderly, obese individuals, or young athletes, but not healthy adults especially for dietary protein. Intervention studies often included frail, undernourished, or malnourished institutionalized elderly observational studies assessed relatively healthy elderly [11,26-28] dietary protein intake especially by healthy population are least frequently studied. We hypothesize that higher dietary protein will prolong loss of muscle mass and strength and thereby declining functionality which will eventually prevent CVD events and associated in healthy general population. The present study seeks to conduct a systematic review and meta-analysis to understand the association of dietary protein intake with HGS in healthy adults aged > 18 years old.

Materials and Methods

This review is developed in accordance with the Cochrane Collaboration [29] and PRISMA guidelines [30].

Search Strategies

We developed a systematic search strategy and performed it in the following electronic databases: MEDLINE, MEDLINE in Process, EMBASE, Health star, CINAHL, AARP Age Line, and Cochrane Library from 1996 and up to April 2016. The search term combinations included 'diet', 'dietary intake', 'nutrition', 'malnutrition', 'nutritional status', 'food fortified', 'hand grip strength', 'randomized controlled trials', etc., using MESH and EMTREE equivalent of the terms. A more detailed search strategy is provided (Supplemental Material). We considered studies published only in English. We also hand searched reference lists of eligible studies, conference proceedings, abstracts, and relevant SR and MA for further identification of eligible studies.

Study Eligibility Criteria

Inclusion criteria: (1) full journal papers reporting RCTs, feeding trials, and cohort studies; (2) individuals aged > 18 years (mean age < = 60) without a critical health condition; (3) dietary protein intake alone or combined with other interventions, compared to placebo or other intervention e.g. calorie intake, exercise training or none; (4) interventions with at least two weeks in operation as previously reported [15,31].

Exclusion Criteria: (1) animal studies; (2) pregnant and lactating women, infectious disease and unique physiologic populations e.g. HIV/AIDs, tuberculosis, cancer patients, athletes, and astronauts; (3) cross-sectional design; (4) studies in other languages than English, including unpublished studies e.g. abstracts, meeting briefs, seminar notes; (5) interventions examining supplements or amino acids, fitness, exercise, weight reduction/management; dietary counselling alone, anabolic steroids, parenteral nutrition or enteral feeding.

Outcome: Handgrip strength [in kg].

Data Extraction and Management

Eligible abstracts were independently screened by two review authors (SS, YG), applying inclusion and exclusion criteria. Full texts of the potentially eligible studies were retrieved for in-depth assessment by SS and MD. Data abstraction were performed using a structured prescribed form [29], and pilot-tested for accuracy in duplicate by two review authors (SS, YG). Any disagreement between the review authors over the study eligibility was resolved through discussion with a third review author (MD). Wherever applied, multiple papers of the same study were reviewed and collated in, and detailed data were extracted mainly including general information, study eligibility, methods, population, setting, intervention/exposure groups, outcome, and findings. Review authors (SS, MD) critically reviewed the papers for any overall discrepancies or unusual patterns before reaching a final consensus for each of the included studies. A PRISMA diagram is added to document the step-by-step study selection process including study exclusion to provide a comprehensive snap-shot of process [30].

Data Collection and Quality Assessment

Analytical data mainly on socio-demographics, exposure type, dietary measurement method, and end point statistics were extracted by SS and double checked by MD. We reported the findings following a structured format including design, sample size, setting, participants, intervention/exposure and outcome as recommended for enhanced reporting quality [29].

The methodological quality of the included trials was assessed by SS and validated by MD, applying the Cochrane Collaboration's Risk of Bias Tool [29], with an added criteria specific to this review: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, baseline similarity in char-

acteristics and outcome, selective reporting, other bias, and compliance with the diet. These were ranked as 'high risk', 'unclear risk' or 'low risk' based upon each of the criterion reported by the trial authors. To assess design-specific validity threats of cohort studies, the Newcastle-Ottawa Scale [32] was used with minor modifications: of the exposed cohort with respect to the community, selection of the non-exposed cohort, adequacy of follow-up, baseline exposure/assessment method, baseline outcome/assessment method, factors adjusted and not adjusted for, funding, and conflicts of interest. The studies were then ranked for either 'high risk' or 'moderate risk': high risk was assigned for minimum two evidence apparent in representativeness of the exposed cohort; adequacy of follow-up; baseline exposure/assessment method; baseline outcome assessment; and factors adjusted and not adjusted for i.e. cohort was selected from a single clinic or urban location; > 20% participants were lost to follow-up; protein intake was assessed using a non-validated or unclear method; HGS assessment method was unclear; and important risk factors e.g. age, sex, ethnicity, and energy intake weren't adjusted for in the final model. Moderate risk of bias suggested otherwise.

Finally, the evidence quality (very low, low, moderate, and high) in relation to the outcome was assessed using the GRADE criteria by investigating study limitations, consistency of effect, imprecision, indirectness and publication bias [33]. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. We used the GRADE pro software [34] to generate a summary evidence quality. Additionally, two review authors (SS, MD) independently evaluated which studies were eligible for inclusion in the meta-analysis and if data pooling was deemed appropriate.

Data Synthesis and Statistical Analysis

We planned to carry out statistical analysis using the Review Manager Version 5.3.5 [35]. We felt meta-analysis inappropriate to pool the effect estimates across studies because studies differed mainly with respect to participants, sample size, follow-up durations, and risk factors adjusted for. We therefore adopted a structured data synthesis approach and presented them in a consistent manner as recommended [29]. We presented findings of continuous data with mean ± standard deviation (SD) or as reported by the study authors. We assessed the evidence quality (as very low, low, moderate and high) using the GRADE criteria [33].

We also assessed studies to infer lost to follow-up or missing data wherever appropriate and presented the data as how it was reported with sufficient explanations. We were unable to conduct meta-analysis; however, we planned to assess statistical heterogeneity in each meta-analysis using Tau^2, I^2 and Chi^2 statistics. We would regard heterogeneity as substantial if an I^2 is greater than 30% and either a Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity. We were also unable to investigate publication bias and sensitivity analyses to test the robustness of the results or a pre-specified subgroup analyses e.g. protein dosage (low or ≥ to the RDA, 0.83 g/kg BW/day) and follow-up duration (< 6 months, 6 to < 1 year, ≥ 1 year).

Results

Search Findings

We retrieved 1630 studies from the database and hand-searches, of which 6 [12,13,17,36-38] were included (Figure 1).

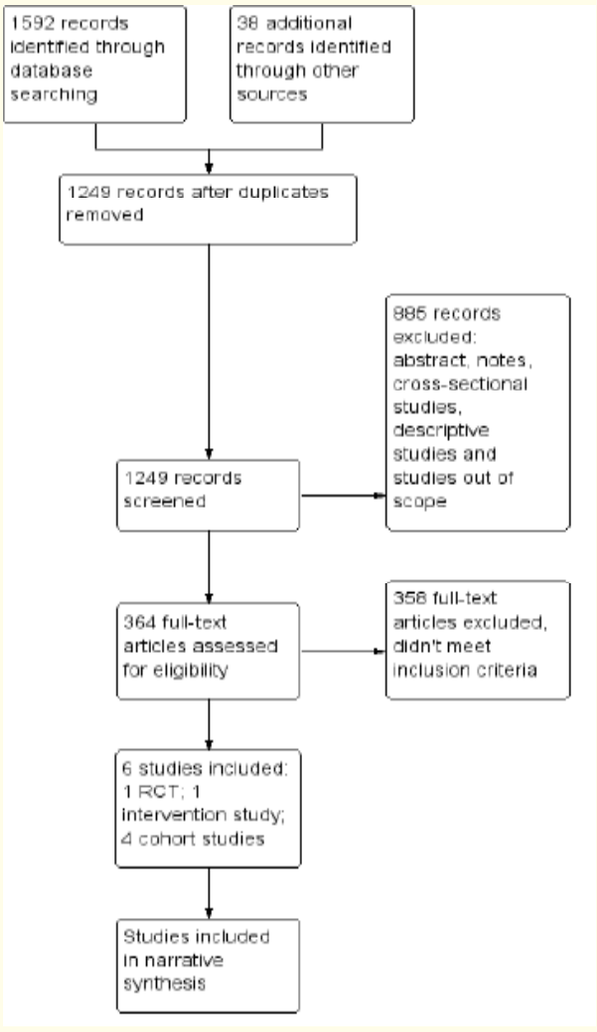

Figure 1: Study flow diagram.

Included Studies

See characteristics (Table 1) and summary findings of the included studies (Table 2).

Author/ Country	Setting		Participants			Intervention/ Exposure		Comparison
		N	Mean age ± SD	Gender	Health status	Type	Dosages	
Jacobsen 2011 RCT Denmark	Copenhagen University	23 11 (I) 12 (C)	24.7y ± 3.6 (I) 23.7y ± 3.5 (C)	Male	Healthy	Animal protein	About 3.0g/kg BW	About 1.5g/kg BW
Kulkarni 2014 Intervention study India	Villages, Hyderabad	1 384 (final model)	20.8y ± 1.1 (I) 20.8y ± 1.2 (C) 21.0y ± 1.1 (I) 21.1y ± 1.2 (C)	Male Female	Healthy Healthy	Plant supplementation	Protein g/d (mean±SD) Male: 82 ± 30 (I); 78 ± 27 (C) Female: 51 ± 17 (I); 49 ± 15 (C)	No supplementation
Beasley 2013[a] Cohort USA	40 clinical centers	905	59.5y ± 6.3	Female	Healthy	Animal, plant	%E from protein: 14.3 ± 1.4% total energy (mean biomarker calibrated protein intake)	
McLean 2016 Cohort USA	6 communities	1 542	58.7y ± 9.2 (range 29–85)	Both	Healthy	Animal, plant	Mean total protein g/d: 79 ± 27	
Mulla 2013 Cohort England	3 communities	3 488	53y	Both	Healthy	Animal, plant	%E from protein: Male 14.6 ± 2.3 Female 15.5 ± 3.0	
Kato 2011 Cohort Japan	Waseda University, Saitama	10	24.5y ± 1.2	Male	Healthy	Animal, plant	Protein g/d (mean ± SE): 82.5 ± 2.4 [NE]; 83.5 ± 3.3 [SE] 83.9 ± 2.3 [SS]; and dumbbell exercise for 30 - 60 minutes 5 times a week SE and NE groups]	

Table 1: Characteristics of the included studies (N = 6).

RCT: Randomised Controlled Trial; I: Intervention; C: Control; BW: Body Weight; %E: Percent Energy; NE: No-Snack Exercise; SE: Snack-Exercise; SS: Snack-Sedentary [a]Quintile 5 included only

Author/ Country	Inclusion/exclusion criteria	Follow-up duration	Analysis method/Effect estimates/ Analytical sample	Findings
Jacobsen 2011 RCT Denmark	20 - 40 year olds in good health based on a physical examination, with stable weights at screening. Excluded for smoking, overweight (BMI ≥ 25), heavy exercise, presence of any chronic disease, and etc.	3 weeks	GLM adjusted for baseline values: 53.8kg ± 7.3 (HP); 51.8kg ± 8.9 (UP). n = 23	No improvement in HGS was found in the HP group versus the UP
Kulkarni 2014 Intervetion study India	All births occurred during the study period and pregnant women were included. Exclusion criteria not specified	1 year	MRA: multivariable association between supplemental nutrition and HGS in young: β -0.70; 95% CI -1.27 to-0.12; p = 0.02. n = 1 384	After adjusting for potential confounders, the intervention group had lower HGS versus the control
Beasley 2013 Cohort USA	Postmenopausal women of stable residence, unlikely to die within 3 years, plus other criteria. Excluded for drug dependency, mental illness, risk factors e.g. stroke, breast cancer, etc.	6 years	GEE: yearly % change in HGS by Q of calibrated protein intake (%E): β -0.45; 95% CI -0.53 to -0.38; p = 0.028 (Q5 vs Q1). n = 905	Higher protein intake showed slower declines in HGS
McLean 2016 Cohort USA	All family members living in a HH in the identified sample and of eligible age. Exclusion criteria unmentioned.	5.8 years ± 1.0 (range 1- 8)	MLR: yearly % change in HGS by intake of total prtein: β 0.021 ± 0.01; p = 0.02 animal protein: β 0.02 ± 0.01; p = 0.03 plant protein: β 0.074 ± 0.03; p = 0.01. n = 1 542	In ≥ 60 years old, higher total and animal protein intake prevented declines in HGS
Mulla 2013 Cohort England	All birth registrants during the study in the catchment area. Participants excluded for incomplete data on confounders	17 years	MLR: association between protein intake and HGS: β 0·01; 95% CI -0.74 to 0.76; p = 0.98 (protein intake at 43 years). n = 1 717 β 0·06; 95% CI -0.64 to 0.76; p = 0.87(protein intake at years 36). n = 1 771	After adjustment for energy intake, the positive association (initial model) was attenuated
Kato 2011 Cohort Japan	Not specified	5 weeks	AoV: significant difference in HGS was found in SE and NE groups; p = < 0.01, < 0.05 respectively. n = 10	A marked increase in HGS was detected only in SE and NE groups

Table 2: Summary Findings of The Included Studies (n = 6).

BMI: Body Mass Index; GLM: General Linear Model; HGS: Hand Grip Strength; HP: High Protein; UP: Usual Protein; MRA: Multiple Regression Analysis; 95% CI: 95% Confidence Intervals; RCT: Randomised Controlled Trial; Q: Quintile; %E: Percent Energy; GEE: Generalized Estimating Equations; %: Percent; MLR: Multivariate Regression Analysis; AoV: Analysis of Variance; kgs: Kilograms; SE: Snack-Exercise; NE: No-Snack Exercise

Design

The included studies (one RCT, 1 intervention, 4 cohort) were published between 2010 and 2015. We did not identify any cluster-randomized or cross-over trials eligible for inclusion.

Sample Size

We included a total of 33797 participants, and with hand grip strength: 3488 [36]; 1542 [13]; 1384 [37]; 905 [12]; 23 [17]; and 10 [38].

Setting

The studies were based in villages, communities, and clinical centers with the majority from high-income countries i.e. the United States of America (USA), England, Denmark, and Japan, except for India [37].

Participants and Length of Follow-Up

The studies included healthy participants with diverse age range, where mean age varied from 20.8 ± 1.1 to 24.7 ± 3.6 years

(intervention groups, trials) and 20.5 ± 1.2 to 59.5 ± 6.3 years (cohorts). Findings presented by male [17,38] and female [12] participants. The follow-up duration was 3 weeks to 1year (trials) and 5 weeks to 17 years (cohort studies).

Interventions/Exposure

Studies defined dietary intervention as protein alone, combined with other macronutrients or exercise training. The reported protein intake was varying e.g. 3.0 g/kg BW and 14.3 ± 1.4% of total energy. The RCT tested high protein diet (approx. 3.0g protein/kg BW) versus usual protein (approx. 1.5g protein/kg BW) [17]. Cohort studies assessed high protein e.g. 15g snack diet and dumbbell exercise using 3 groups [38]. Studies mostly assessed both animal and plant protein (4 cohorts). Only one cohort provided HGS by protein type i.e. animal and plant [13]. Dietary assessment tools used were validated FFQs [12,13,37], dietary records/recalls, or food diaries.

Outcome

Hand grip strength (kg) was measured by electronic dynamometer.

Risk of Bias in Included Studies

Among the 6 included studies, the RCT in overall was judged to be of unclear risk of bias [17] and there was high risk in the intervention study [37]. The cohort studies were judged to be of moderate [12,13,36] to high [38] bias risk. Summary risk of bias assessments for trials (Figures 2,3) and cohort studies (Table 3) are presented.

Risk of Bias Assessment in Clinical Trials

See Figures 2, 3. Detailed assessment is available (Supplemental Material).

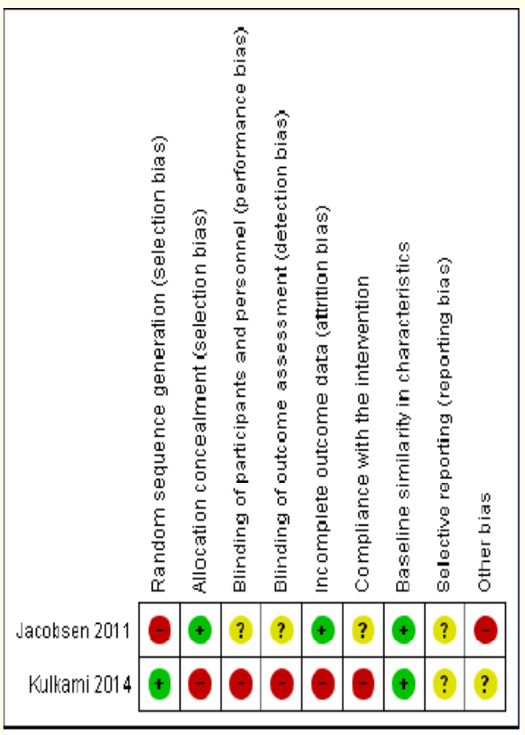

Figure 2: Judgements about each risk of bias item for each included study (one RCT, one Intervention study).

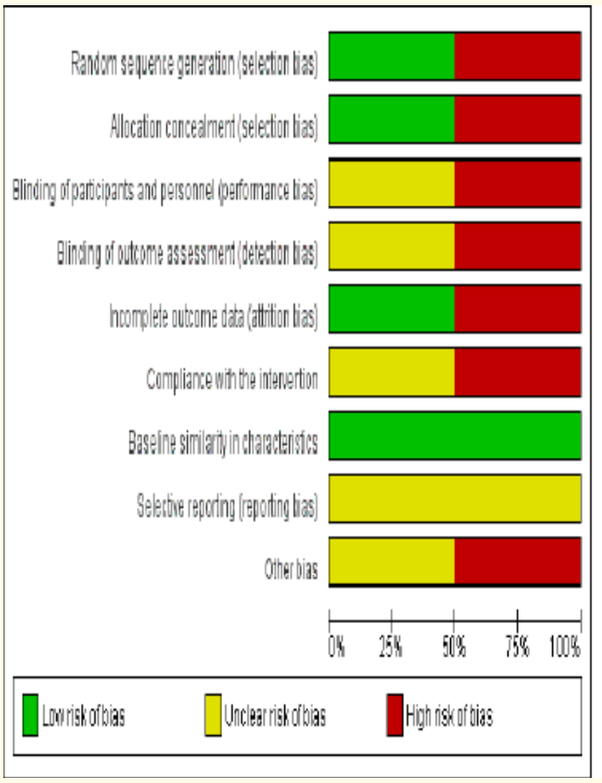

Figure 3: Judgements about each risk of bias item presented as percentages across all included studies (one RCT, one Intervention study).

Risk of Bias Assessment in Cohort Studies

We considered cohort studies to be overall at moderate or high risk of bias (Table 3): moderate [12,13,36] and high [38] risk. Detailed assessment is available (Supplemental Material).

Effects of Dietary Protein on HGS

We found data pooling across studies was inappropriate because they differed mainly due to sample size, dietary measurement method, follow-up durations, and risk factors adjusted for. A 'Summary of findings' assessing the effects of dietary protein alone or combined with exercise is narratively presented (Table 4).

Clinical Trials

In the RCT [17], a high protein (HP: approx. 3.0 g protein/kg BW) diet was compared with a usual protein (UP: approx. 1.5g protein/kg BW) among healthy young males (n = 26) for 3 weeks. The HGS in the HP group showed no improvements compared to the controls: HP 53.8 kg ± 7.3 versus UP 51.8 kg ± 8.9, general linear models adjusted for baseline measurements. In the intervention villages [37], protein was provided on average 20-25g to women and 8-10g to children aged < 6 years and compared with no intervention (control villages). Further adjustment for potential confounders showed that compared to their controls, the intervention group had lower grip strength: β -0.70; 95% CI -1.27 to -0.12; p = 0.02; n = 1384 [37] (Table 2).

Author Country	Representativeness of the exposed cohort with respect to the community	Selection of the non-exposed cohort	Adequacy of follow-up	Baseline exposure/ Assessment method	Baseline outcome/ Assessment method	Factors adjusted/unadjusted for	Funding/ Conflicts of interests	Risk of bias assessment[a]
Beasley 2013 The Women's Health Initiative Observational Study USA	Yes - as per study objective. Postmenopausal women N = 26 992 (Q5) recruited from 40 clinical centers across the USA	None	Numbers lost - 16%. HGS data - 84.0% (3 visits), completed grip strength measure: 5331; available measurement in the final model: 4527; 905 (Q5). Reasons of lost numbers weren't specified	Biomarker calibrated protein intake (15.4-22.3%, Q5). Four 24-hour dietary recalls and a 4-day food record assessed by the 122-item WHI validated FFQ	Yes - baseline mean HGS (kg) was slightly higher in women with higher calibrated protein intake; $P = 0.036$ (Q5). Blinding not specified. Jamar handheld dynamometer; Lafayette Instruments, Lafayette, IN	Age, income, education, race, BMI, smoking status, alcohol consumption, physical activity, self-reported history of medical conditions (e.g. diabetes, hypertension, cancer), calibrated total energy intake and clinical trial arm. Calibrated protein intake and HGS association was stratified at baseline by median age, recreational physical activity, BMI, or protein source (animal: total protein ratio)	The National Heart, Lung, and Blood Institute, National Institutes of Health, and U.S. Department of Health and Human Services, and other grants. No conflicts of interests declared	Moderate
McLean 2016 The Framingham Offspring Cohort USA	Yes - healthy participants N = 1746 from 6 communities across USA	None	12% was lost: 5124 enrolled; 1746 with valid diet data, and 1542 with baseline HGS. Reasons not specified	Past year's usual diet history at baseline and follow-up, by a semi-quantitative, validated 126-item Willett FFQ mailed out to the participants. Single assessment, checked by clinic staffs	Yes - baseline mean HGS (kg) wasn't statistically significant, and no significant differences found in pairwise comparisons (quartile analyses) for any protein source. Blinding not specified. HGS measured by an adjustable Jamar isometric handheld dynamometer	Age, sex, height, total energy, BMI, physical activity, health status, sex/ menopause status and baseline HGS. Models also adjusted for fruit and vegetable intake (servings/d), without plant protein. Animal and plant protein intakes were adjusted for each other in the same model. Interaction test done by sex, including a sex × protein interaction term for all models (no statistically significant sex interactions found).Not adjusted for history of medical condition, SES or education and income. HGS measurement was stratified by age and protein source	General Mills Bell Institute of Health and Nutrition; the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Aging (grant numbers R01 AR53205 and R01 AR/ AG41398); and the Heart, Lung and Blood Institute's Framingham Heart Study (contract number HHS-N268201500001I).Conflicts of interests not reported	Moderate
Mulla 2013 The MRC National Survey of Health andDevelopment (NSHD) – the British birth cohort England, Wales, and Scotland	Yes - occupational social class stratified nationally representative sample of all singleton births N = 3577 from 3 large communities in the UK	None	In 1999 follow-up, 3386 participants contacted, of which 3035 provided data (at 53 years). 35% was lost (1976) for refusal to participate, living abroad, untraced or died. Final analysis sample: 1771 (at 36 years) and 1717 (at 43 years), after excluding incomplete data observations on confounders	Two day diet recalls (48 h; instructed by the nurses) and a 5 day food diary (unweighted; self-reported, sent by post) of usual food eaten (at years 36 and 43). The intakes were calculated (standard reference works for the UK) using the authors' in-house suite of programs DIDO based on published guidelines	Yes - baseline mean HGS (kg): Male 47.4 ± 12.2, female 28.1 ± 7.8 (% of total energy), comparable at both time points. Blinding not specified. HGS assessment at ages 53 years, by Northern Coast Medical Precision Instruments, Gilroy, CA	Sex, height, weight, energy intake (except in the model where energy intake is the main explanatory factor), childhood social class, adult social class, education and interaction terms between sex and height and sex and weight. Factors not adjusted for race, community, and morbidity e.g. CVD, diabetes	The Nuffield Foundation and the National Birthday Trust Fun. Conflicts of interests not reported	Moderate

Kato 2011 Japan	Severely limited - young healthy adult males N = 10 were recruited from only one urban university in Tokyo	None	No information was explicitly provided, but most probably none occurred as small sample size was included	1)SE: high-protein snack (HPS): 15 g protein, 18 g sugar, daily 3 h after breakfast and dumbbell exercise for 30-60 min, 5 times a week; 2)SS: HPS 3 h after breakfast daily and no dumbbell exercises; 3)NE: dumbbell exercise similar to the SE group and ingested one-half of HPS with both breakfast and lunch. Eating habit recorded at 1st and 5th wks. Dietary questionnaire type not reported	Yes. Blinding not specified. HGS assessed using a digital grip strength meter	No covariates adjusted for or discussed	Not reported	High

Table 3: Risk of Bias Assessment of the Included Cohort Studies (n=4).

Q 5: Quintile 5 Only; HGS: Hand Grip Strength; Drs: Dietary Recalls; FFQ: Food Frequency Questionnaire; BMI: Body Mass Index; SES: Socio-Economic Status; CVD: Cardiovascular Disease

[a] Risk Was Suggested for Minimum Two Bias Evidence Apparent in 5 Out of the 7 Domains - Representativeness of the Exposed Cohort; Adequacy of Follow-Up; Baseline Exposure/Assessment Method; Baseline Outcome Assessment Method; And Factors Adjusted and Not Adjusted for Cohort was Selected from a Single Clinic or Urban Location; > 20% Participants were Lost to Follow-Up; Protein intake was Provided using a Non-Validated or Unclear Assessment Method; HGS Assessment Method was Unclear; And on the Basis of Previous Literature Any of the Important Risk Factors E.G. Age, Sex, Ethnicity, Energy Intake, and SES (Includes Educational) Weren't Adjusted for in the Final Model. Moderate Risk of Bias Suggested Otherwise.

Dietary protein intake alone or combined with exercise training for hand grip strength in healthy adults			
Patient or population: Adults > 18 years old (mean age < = 60) **Setting**: Denmark, USA, England, Japan, and India. Universities, Villages, Communities, and Clinical centers **Intervention**: Dietary protein intake alone or combined with exercise training **Comparison**: Protein, placebo or exercise training			
Outcomes	**Impact**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**
Hand grip strength (HGS) assessed with: Electronic dynamometer follow up: 3 weeks	Dietary protein showed no improvement in the HGS of young healthy male participants: 53.8kg ± 7.3 (high protein) versus 51.8kg ± 8.9 (usual protein)	23 (1 RCT)	⊕ ⊕ ⊕ ◯ MODERATE [1,2,3,4,5]
Hand grip strength (HGS) assessed with: Electronic dynamometer follow up: 1 year	After adjusting for potential confounders, the intervention group showed lower grip strength compared to the control: β -0.70; 95% CI -1.27 to -0.12; p = 0.02	1384 (1 intervention study)	⊕ ⊕ ⊕ ◯ MODERATE [6,7,8,9,10]
Hand grip strength (HGS) assessed with: Electronic dynamometer follow up: 5 weeks to 17 years	The effect of dietary protein intake on HGS is inconsistent: positive impact of high dietary protein (3 cohorts), and no impact (1 cohort) of dietary protein	5945 (4 observational studies)	⊕◯ ◯ ◯ ◯ VERY LOW [11,12,13,14,15,16]
GRADE Working Group grades of evidence **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect			

Table 4: Summary of findings.

1. Sequence generation method wasn't explained. Diet compliance was unspecified and seems to be a concern as weekend food and beverages weren't supervised by the staffs

2. Because of risk of bias, the RCT has limitations for unexplained heterogeneity

3. The RCT included small population/events and didn't provide 95% CI estimates

4. The protocol was identified on the clinical trial registry but outcome specification was absent

5. General linear models were adjusted for baseline characteristics e.g. age, height, BMI, weight and protein intake. But other important factors e.g. health condition, SES or education weren't adjusted for and thus, we are uncertain if the intervention effect in was not confounded

6. Non-random assignment of the intervention villages and no allocation concealment performed. But all births during the study period were eligible to include in the study, regardless of their birth weight record from the initial trial. Blinding the group assignment from fieldworkers mentioned as non-optional, participants' blinding was not specified. Blinding of outcome wasn't specified. 44% was lost to follow-up. Compliance with the intervention was unclear because the participants weren't obliged to consume the protein on the spot. However, a high intake was indicated as likely due to the considerable efforts inserted during the original trial

7. Not very small sample size i.e. 1384 participants were included and a little wide 95% CI was estimated

8. Unsure as no protocol was identified

9. p value 0.02 was reported

10. Models not adjusted for race and community covariates

11. Cohort studies were at risks of bias inherent to their design i.e. lack of blinding, lost to follow-up as Suggested Otherwise.

12. Results were inconsistent across studies because of unexplained heterogeneity due mainly to varying population, intervention, and study method i.e. risk of bias

13. Kato 2010 included small sample and didn't provide 95% CI estimates

14. Protocol found for only one large study (Beasley 2013, the WHI study, USA)

15. Three large studies reported p values of ≤0.5 and 0.02

16. Only three studies with relatively large samples adjusted for important risk factors, but some factors weren't considered e.g. SES, race, income, urban/rural and morbid conditions.

Cohort Studies

Three studies found a positive effect of protein intake on HGS (n = 2457): for calibrated protein β -0.45; 95% CI -0.53 to -0.38; p = 0.028 (Q5 vs Q1) [12]; total and animal protein p for trend < 0.03 (≥ 60 years only) [13]; and13.0g high protein and dumbbell exercise for snack-exercise (SE) and no-snack exercise (NE) groups [38]. However, there was no effect of dietary protein (animal, plant) on HGS: β 0.01; 95% CI -0.74 to 0.76; p = 0.98 (n = 1 717, age 43 years) [36] (Table 2).

Discussion

This review is based on six studies, identified through an inclusive search methods and showed mixed effect of dietary protein on hand grip strength. The single RCT was unable to detect an intervention effect on HGS for Danish young males; though an increasing trend was observed in both groups [17]. No adverse events were observed. The Indian intervention [37] found lower HGS following a plant-based protein diet. Three cohorts detected greater HGS for higher dietary protein intake (older adults [USA], young [Japan]), and by age and protein type [13]. The association was not significant for older adults (England) [36].

We found that the overall bias risks were unclear (RCT), high (intervention study), moderate (3 cohorts), and high (one cohort). Most of the cohort studies followed participants for many years and were published between 2011 to 2016. This perhaps indicates that long-term follow-up of dietary protein in relation to HGS of this design are receiving increasing attention to capture underlying contextual mechanism for practical health policy recommendations. Cohorts showing positive association with the largest HGS data (n = 1542) spanned from elderly followed for > 5.8 years and 6 years for postmenopausal women (n = 905) [12]. However, the Japanese study [38] with only 10 healthy subjects reporting a marked increase in HGS for two groups requires caution in interpretation. Moreover, cohort studies did not report potential adverse effects of higher protein; whereas, a previous systematic review on healthy elderly population highlighted the need for cohort studies to investigate protein intake intolerance above 20 - 23 E% [5]. Furthermore, although the models in the RCT [17] were adjusted for baseline characteristics e.g. age, BMI, and protein intake, other important risk factors e.g. health condition or education were not adjusted for and thus, we are uncertain if the intervention effect in this trial was not confounded by any of these unadjusted risk factors. The GRADE evidence quality was judged to be moderate (RCT), moderate (intervention) and very low (cohorts). The outcome was downgraded for design limitations e.g. inadequate follow-up, unexplained heterogeneity or inconsistency of results, and imprecision (cohort studies); and study limitations e.g. allocation concealment and imprecision of results (trials).

According to our review, the evidence effectiveness of dietary protein alone or combined with exercise on HGS is mixed: any direct comparison for the RCT [17] reporting non-significant findings for young males is unavailable. Parallel findings exist but for chronic disease patients, where protein and exercise combo did not improve HGS [39,40]. Also, dietary advice to increase energy and protein intake and supplements compared with dietary advice alone improved HGS among a diverse population, mean difference -1.67 kg (95% CI -2.96 to -0.37) [16]; also, 12 healthy sedentary to moderately active females (aged 66-79 years) randomized to low protein (0.45 versus 0.92 g/kg BW) showed a significant drop in their HGS after 9 weeks [41]. The latter is consistent to one included cohort showing lower HGS for protein g/d (mean ± SD): Male 82 ± 30; Female 51 ± 17 (N = 1384) [37]. For their findings, the authors indicated of ecological fallacy inherent to the study design and the effective supplemental dosage which was possibly diluted over the years by changes in diet and other lifestyle factors. Yet, for the discrepancies in the findings, we cannot rule out the influence of other factors like dietary measurement method, sample size, and protein type. For instance, dietary assessment method was varying and yielded from recording five days of DRs, validated FFQs or other method; whereas, dietary condition in the included RCT was controlled [17].

Additionally, only one cohort study addressed dietary recall bias per participants' characteristics using calibrated protein intake [12]. Furthermore, it is suggested that individual dietary pattern and other macro and micro-nutrients could also influence muscle and functional performance [26,42]. Moreover, because of the wide heterogeneity of different aspects as discussed above, we did not consider data pooling across studies.

The positive associations between higher dietary protein alone or with exercise and greater HGS in our cohorts [12,13,38] are consistent with other observational studies for instances, high animal protein diet by older women resulted in greater net protein synthesis compared to those who consumed high plant protein [16,43,44]. Animal protein therefore may provide greater benefits for muscle mass and strength as this source has a complete amino acid profile and thus studying this can add more compelling evidence in future. The attenuation of the positive association in one study [36] was however thought to be due to an independent effect of protein. Parallel to this study, no significant association between energy-adjusted protein intake and muscle strength was found in a community-dwelling older cohort (mean age 62 ± 7 years) [26].

Despite our systematic methods [29], for instance in minimum two review authors' independent assessment in eligible study selection, we cannot eliminate the possibility that additional published or unpublished studies exist and were not identified. Our study ineligibility criteria left out a small number of studies for inclusion and might have excluded some potentially relevant studies e.g. weight reduction or fitness-exercise programs and non-English studies. However, considering the likely complexity of nutrition studies due mainly to potential confounders and unpredictable life-style behaviour, we believe that our review still offers reliable evidence precise to the study objective primarily because of the fine tuning of study eligibility criterion. Furthermore, our consideration of studies with minimum two weeks in operation could have excluded some insightful studies with a shorter length; however, we believe that a subtle change in HGS was impossible to detect over a short period.

Conclusion

The available evidence involving 7352 participants is inconsistent for dietary protein intake alone or combined with exercise in healthy adults. To avert globally increasing functional disabilities, more studies are needed to further understand the effect of dietary protein on hand grip strength in healthy adults. Studying protein source and safe dosages using a rigorous dietary measurement method are also essential for this population as the knowledge gap is still significant. Such study should include vulnerable sub populations from both developed and developing regions to identify individuals at increased risk as well as to ensure health equity. Future studies should also ensure methodological rigor such as designing of RCTs with larger sample size, longer follow-up and possibly uncontrolled diet intake, including explanations of loss to follow-up in cohort studies.

Supplemental Material

Search Strategy	
Measures of Nutritional Intake/ Intervention	1. nutrition/ or nutrition.mp. 2. diet.mp. or diet/ 3. dietary intake.mp. or dietary intake/ 4. food/ or food.mp. 5. food intake.mp. or food intake/ 6. meal/ or meal.mp. 7. nutritional intake.mp. 8. nutritional status.mp. or nutritional status/ 9. nutritional support.mp. or nutritional support/ 10. nutritional counseling.mp. or nutritional counseling/ 11. nutritional health.mp. or nutritional health/ 12. diet therapy.mp. or diet therapy/ 13. diet supplementation/ or dietary supplement*.mp. 14. dietary advice.mp. 15. nutritional supplement*.mp. 16. nutrition intervention.mp. 17. nutritional intervention.mp. 18. nutritional program.mp. 19. supplement*.mp. 20. food fortification.mp. 21. (food and fortified).mp. [mp = title, original title, abstract, name of substance word, subject heading word] 22. (food and formulated).mp. [mp = title, original title, abstract, name of substance word, subject heading word] 23. (food and supplemented).mp. [mp = title, original title, abstract, name of substance word, subject heading word] 24. (food and enriched).mp. [mp = title, original title, abstract, name of substance word, subject heading word] 25. nutrient/ or nutrient.mp. 26. macronutrient*.mp. or macronutrient/ 27. macro-nutrient*.mp. 28. micronutrient*.mp. 29. micro-nutrient*.mp. 30. dietitian.mp. or dietitian/
Protein	31. protein intake.mp. or protein intake/ 32. dietary protein*.mp. 33. protein supplementation.mp. 34. protein consumption.mp. 35. oral protein.mp. 36. protein-supplemented.mp. 37. protein-enriched.mp. 38. protein-rich.mp. 39. protein-energy.mp.
Hand grip strength	40. grip strength.mp. or grip strength/ 41. hand strength/ or hand strength*.mp. 42. pinch strength/ or pinch strength*.mp. 43. pinch.mp. 44. Dynamometer.mp. or dynamometer/ 45. dynamometry.mp. or dynamometry/ 46. muscle strength/ or muscle strength*.mp. 47. jamar.mp. 48. hand grip.mp. or hand grip/ 49. hand grip strength.mp. 50. handgrip.mp. 51. hand-grip.mp. 52. physical performance.mp. or physical performance/

Search Strategy (April 18, 2016):

1. nutrition/ or nutrition.mp.
2. diet.mp. or diet/
3. dietary intake.mp. or dietary intake/
4. food/ or food.mp.
5. food intake.mp. or food intake/
6. meal/ or meal.mp.
7. nutritional intake.mp.
8. nutritional status.mp. or nutritional status/
9. nutritional support.mp. or nutritional support/
10. nutritional counseling.mp. or nutritional counseling/
11. nutritional health.mp. or nutritional health/
12. diet therapy.mp. or diet therapy/
13. diet supplementation/ or dietary supplement*.mp.
14. dietary advice.mp.
15. nutritional supplement*.mp.
16. nutrition intervention.mp.
17. nutritional intervention.mp.

18. nutritional program.mp.

19. supplement*.mp.

20. food fortification.mp.

21. (food and fortified).mp. [mp = title, original title, abstract, name of substance word, subject heading word]

22. (food and formulated).mp. [mp = title, original title, abstract, name of substance word, subject heading word]

23. (food and supplemented).mp. [mp = title, original title, abstract, name of substance word, subject heading word]

24. (food and enriched).mp. [mp = title, original title, abstract, name of substance word, subject heading word]

25. nutrient/ or nutrient.mp.

26. macronutrient*.mp. or macronutrient/

27. macro-nutrient*.mp.

28. micronutrient*.mp.

29. micro-nutrient*.mp.

30. dietitian.mp. or dietitian/

31. protein intake.mp. or protein intake/

32. dietary protein*.mp.

33. protein supplementation.mp.

34. protein consumption.mp.

35. oral protein.mp.

36. protein-supplemented.mp.

37. protein-enriched.mp.

38. protein-rich.mp.

39. protein-energy.mp.

40. grip strength.mp. or grip strength/

41. hand strength/ or hand strength*.mp.

42. pinch strength/ or pinch strength*.mp.

43. pinch.mp.

44. Dynamometer.mp. or dynamometer/

45. dynamometry.mp. or dynamometry/

46. muscle strength/ or muscle strength*.mp.

47. jamar.mp.

48. hand grip.mp. or hand grip/

49. hand grip strength.mp.

50. handgrip.mp.

51. hand-grip.mp.

52. physical performance.mp. or physical performance/

53. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52

54. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

55. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

56. 53 and 54 and 55

57. remove duplicates from 56

58. limit 57 to humans

Newcastle - Ottawa Quality Assessment Scale Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community

b) somewhat representative of the average _____ in the community

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records)

b) structured interview

c) written self-report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor)

b) study controls for any additional factor (These criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment

b) record linkage

c) self-report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest)

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost)

c) follow up rate < ___% (select an adequate %) and no description of those lost

d) no statement

Risk of bias assessment in clinical trials

Sequence generation was unclear in the RCT [17] as the method was not explained, but was at low risk [37] as all live births were included during the study period. Allocation concealment was adequate as a sealed, opaque envelope for randomisation was used [17]; however, it was not performed [37]. In the RCT, the participants and researchers were blinded to the knowledge of intervention, but the assigned randomization code had to keep by a kitchen staff for facts and thus was judged at unclear risk. High risk of blinding was judged [37] as masking the group as-

signment from fieldworkers was not an option as mentioned by the study authors; also, participants' blinding from the intervention wasn't specified.

Blinding of outcome assessment was unclear [17] as the randomization envelopes were divided into two lots indicating the weaker or stronger participants than the overall mean HGS. There was high risk [37] as it looks that blinding of outcome assessment wasn't performed. High risk was assigned [37] for incomplete outcome data: 44% was lost to follow-up; the RCT was at low risk for this bias. Compliance with the intervention was unclear [17] because all food was allocated under the hospital supervision except for weekends, which were supplied to the participants on Fridays. Since participants weren't obliged to consume the supplementation at the allocation spot [37], we judged this study for high risk, although authors mentioned that adequate consumption was ensured through considerable efforts during the trial. Baseline characteristics were comparable at baseline [17] as there were no obvious differences in anthropometry, energy requirements, HGS, or educational level. There were only minor deviations mentioned from the estimated energy requirements during the run-in and intervention period. Low risk was assigned [37] as participants were indifferent in their socioeconomic characteristics.

However, dietary energy and protein intakes (in men only) were higher in the intervention group, including intervention women with higher schooling years. Studies were at unclear risk for selective outcome reporting: outcome specification was absent in the clinical trial registry [17]; and no protocol was identified [37]. For other potential sources of bias, high risk [17] as it included small sample size and short follow-up duration to detect a subtle change in HGS over time, including exclusion of female population. Kulkarni et al. 2014 was unclear as villages were non-randomly selected at baseline; there might be selection bias as participants have been following up for decades may differ from the general population; differences in protein intake level i.e. low, medium, high; and differential misclassification of the subjects with respect to their exposure or disease status can lead to an over- or under-estimate of the effect between the exposure and outcome.

Risk of bias assessment in cohort studies

Overall, the cohort studies had design-specific concerns e.g. high loss to follow-up or reasons weren't explained, unclear or weak protein intake assessment method, important risk factors were not adjusted for or not discussed. We suggested high risk of bias where a minimum of two pieces of evidence were apparent in 5/7 domains as described above e.g. > 20% participants were lost to follow-up and risk factors not adjusted for. Moderate risk was suggested otherwise. Kato et al. 2011 did not specify the validity of their dietary tool, small samples were considered, and conflicts of interests were not reported [12,13,38].

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