Diabetes, Obesity and Metabolism

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REVIEW ARTICLE

Effects of High-Protein Diets on Renal Function and Body Composition in Adults Without Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Randomised Trials

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ABSTRACT

Background: High-protein diets are widely prescribed for weight management and metabolic control, yet concerns persist regarding their impact on renal function, particularly due to diet-induced hyperfiltration.

Objective: We evaluated the effects of high-protein diets compared with normal- or low-protein (NPL) diets on renal function and body composition in adults without chronic kidney disease.

Methods: We systematically searched PubMed, Embase and the Cochrane Central Register of Controlled Trials from inception to May 2026 to identify randomised controlled trials comparing high-protein diets (typically ranging from approximately 25%–35% of total energy intake or ≥ 2.0 g/kg/day) with NPL diets in adults without chronic kidney disease. We defined estimated glomerular filtration rate (eGFR) and serum creatinine as primary outcomes. We evaluated body fat percentage, total fat mass and fat-free mass as secondary outcomes. We performed random-effects meta-analyses using restricted maximum likelihood estimation. We assessed risk of bias with the Cochrane RoB 2 tool and evaluated certainty of evidence using GRADE.

Results: We included 22 randomised controlled trials. High-protein diets increased eGFR compared with control diets (standardised mean difference 0.39, 95% confidence interval 0.09–0.69; $I^2 = 74.9\%$). However, because most studies relied on creatinine-based estimates of renal function, these findings should be interpreted cautiously and may primarily reflect short-term hemodynamic adaptations associated with increased protein intake. High-protein diets did not significantly change serum creatinine (19 trials; $n = 1044$; standardised mean difference 0.08, 95% confidence interval −0.09 to 0.25; $I^2 = 20.8\%$), without consistent biochemical evidence suggestive of renal injury. High-protein diets reduced body fat percentage and total fat mass, while they did not significantly affect fat-free mass.

Conclusions: High-protein diets were associated with increases in eGFR without consistent biochemical evidence of renal injury in adults without chronic kidney disease. However, because most available studies were of relatively short duration and frequently relied on creatinine-based estimates of renal function, the long-term renal implications of these findings remain uncertain.

Trial Registration: PROSPERO: CRD420251014114

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1 | Introduction

High-protein diets play a central role in contemporary strategies for weight management and metabolic control. Clinicians and patients widely adopt these dietary approaches because they promote weight loss, improve glycaemic control and favourably modify cardiometabolic risk factors across randomised controlled trials conducted in healthy individuals and in populations with obesity or type 2 diabetes [1–4]. However, despite these established metabolic benefits, clinicians continue to question the renal safety of sustained high-protein intake, particularly in individuals without pre-existing kidney disease.

Dietary protein intake acutely increases renal plasma flow and glomerular filtration rate, a response commonly described as physiological hyperfiltration [5]. While this adaptation may reflect normal renal physiology in healthy individuals, clinicians remain concerned that sustained hyperfiltration could contribute to renal stress, particularly in individuals with metabolic risk factors such as obesity and type 2 diabetes [5–7]. Randomised controlled trials have investigated the renal effects of high-protein diets, but these studies vary substantially in protein dose, intervention duration, population characteristics and methods used to assess renal function, which complicates clinical interpretation and limits the ability to generate clear recommendations.

Despite the growing number of randomised trials, important gaps remain. Existing studies report inconsistent findings regarding the impact of high-protein diets on renal function, with some suggesting adaptive increases in glomerular filtration and others raising concerns about potential renal harm [8–10]. In addition, substantial heterogeneity in study populations, intervention duration and methods used to assess renal outcomes limits clinical interpretation. Previous systematic reviews have also combined randomised and non-randomised evidence or relied on heterogeneous outcome definitions, which weakens causal inference [11, 12]. No recent synthesis has comprehensively evaluated randomised controlled trials to simultaneously assess renal function and body composition outcomes in adults without chronic kidney disease while accounting for these methodological limitations.

Therefore, we conducted a systematic review and meta-analysis of randomised controlled trials to evaluate the effects of high-protein compared with normal- or low-protein (NPL) diets on renal function and body composition in adults without chronic kidney disease. We specifically examined estimated glomerular filtration rate (eGFR) and serum creatinine as primary outcomes and assessed changes in adiposity and fat-free mass as clinically relevant secondary outcomes. By focusing on randomised evidence and applying rigorous methodological standards, we aimed to clarify whether high-protein diets induce clinically meaningful renal changes and to inform evidence-based dietary recommendations in metabolically diverse adult populations.

2 | Materials and Methods

2.1 | Study Design and Registration

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement [13]. The completed PRISMA 2020 checklist is provided in Table S2. We prospectively designed the study according to a predefined protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251014114). We followed all prespecified methodological steps, and when data limitations required deviations, we explicitly reported and justified them.

2.2 | Data Sources and Search Strategy

We systematically searched PubMed (MEDLINE), Embase and the Cochrane Central Register of Controlled Trials from database inception through May 2026 without language restrictions. We developed comprehensive search strategies using controlled vocabulary and free-text terms related to high-protein diets, protein intake, renal function, glomerular filtration rate, serum creatinine, body composition and randomised controlled trials. We manually screened reference lists of eligible studies and relevant reviews to identify additional records. We provide the complete search strategies in Supporting Information S1.

2.3 | Eligibility Criteria

We included randomised controlled trials with parallel-group or crossover designs that enrolled adults aged 18 years or older without diagnosed chronic kidney disease. We defined high-protein diets as dietary interventions providing protein intake substantially higher than comparator diets, typically ranging from approximately 25%–35% of total energy intake or ≥ 2.0 g of protein per kilogram of body weight per day, consistent with operational definitions commonly used in randomised dietary intervention trials. We acknowledge that these thresholds are not metabolically equivalent and may reflect different absolute protein exposures depending on total caloric intake, body composition and participant characteristics. Nevertheless, we adopted these definitions to maximise the inclusion of clinically relevant randomised evidence evaluating high-protein dietary strategies. We included studies that compared high-protein diets with NPL dietary interventions.

We excluded studies conducted exclusively in postmenopausal populations when the study objectives primarily focused on menopause-related hormonal or metabolic effects rather than the generalised effects of high-protein dietary interventions applicable to broader adult populations without chronic kidney disease.

We required that studies report at least one renal outcome, including eGFR or serum creatinine. We considered additional renal biomarkers, including urinary calcium, uric acid and urinary pH, as prespecified outcomes; however, insufficient data across trials precluded quantitative synthesis of these variables. We also included body composition outcomes, including body fat percentage, total fat mass and fat-free mass, as secondary outcomes.

We excluded non-randomised studies, acute interventions lasting fewer than 7 days, trials without a clear contrast in protein intake, studies enrolling participants with established chronic kidney disease and studies lacking sufficient data for quantitative analysis.

2.4 | Study Selection

Two reviewers independently screened titles and abstracts using Rayyan software. We retrieved full-text articles for potentially eligible studies and assessed them independently against the inclusion criteria. We resolved disagreements through discussion and, when necessary, consulted a third reviewer. We summarise the study selection process in the PRISMA flow diagram.

2.5 | Data Extraction

Two reviewers independently extracted data using a standardised and piloted data extraction form. We collected information on study design, sample size, participant characteristics, metabolic status, dietary composition, intervention duration, renal outcomes, body composition outcomes and methods used to assess renal function. When studies did not report data as means and standard deviations, we derived them from standard errors, confidence intervals, or test statistics using established methods. We extracted data from figures using *WebPlotDigitizer* when necessary and contacted corresponding authors to obtain missing information.

2.6 | Risk of Bias Assessment

Two reviewers independently assessed risk of bias using the Cochrane Risk of Bias 2 tool [14]. We evaluated bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement and selection of reported results. For crossover trials, we additionally evaluated potential period and carryover effects. We resolved disagreements through consensus. Detailed risk-of-bias assessments for parallel-group and crossover trials are provided in Table S1a,b.

2.7 | Outcomes

We defined eGFR and serum creatinine as primary outcomes. We extracted eGFR values derived from study-specific equations, including MDRD and CKD-EPI, as well as clearance-based measures when available. We defined body fat percentage, total fat mass and fat-free mass as secondary outcomes.

2.8 | Statistical Analysis

We performed all statistical analyses using RStudio with the metafor and dmetar packages. We conducted random-effects meta-analyses using restricted maximum likelihood estimation to account for expected clinical and methodological heterogeneity. We pooled continuous outcomes as standardised mean differences with 95% confidence intervals due to variability in measurement methods across studies. We selected this approach to ensure comparability across different equations and assessment techniques for renal function and body composition.

For crossover trials, we planned to use paired analyses when within-participant correlations were reported. However, none of the four included crossover trials [1, 8, 15, 16] reported within-participant correlations in a format that allowed paired-effect estimation for the outcomes included in the meta-analysis. Therefore, all crossover trials were analysed as parallel-group comparisons, a conservative approach intended to avoid overestimating precision.

We conducted prespecified sensitivity analyses excluding crossover trials. We quantified heterogeneity using the I^2 statistic and Cochran's Q test and calculated prediction intervals to estimate the expected range of effects in future studies [17]. We conducted subgroup analyses according to study design, diabetes status, intervention duration and age group, as prespecified in the protocol. We assessed publication bias through visual inspection of funnel plots and Egger's regression test [18].

2.9 | Certainty of Evidence

Two reviewers independently evaluated the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework [19]. We assessed risk of bias, inconsistency, indirectness, imprecision and publication bias to rate the certainty of evidence for each outcome. Detailed GRADE assessments for all outcomes are presented in Table S3.

3 | Results

3.1 | Study Selection

We identified 278 records across electronic databases (PubMed, $n = 116$; Embase, $n = 118$; Cochrane, $n = 44$). After removing 135 duplicate records, we screened 143 records by title and abstract and excluded 113 records. We assessed 30 full-text articles for eligibility and excluded eight studies for the following reasons: exclusive enrollment of postmenopausal women with specific hormonal and metabolic characteristics outside the predefined target population ($n = 2$), intervention not consistent with the prespecified dietary protein definition ($n = 1$), insufficient protein contrast between intervention groups ($n = 1$) and ineligible renal populations including chronic kidney disease, dialysis, or kidney transplantation ($n = 4$). We included 22 randomised controlled trials in the quantitative synthesis

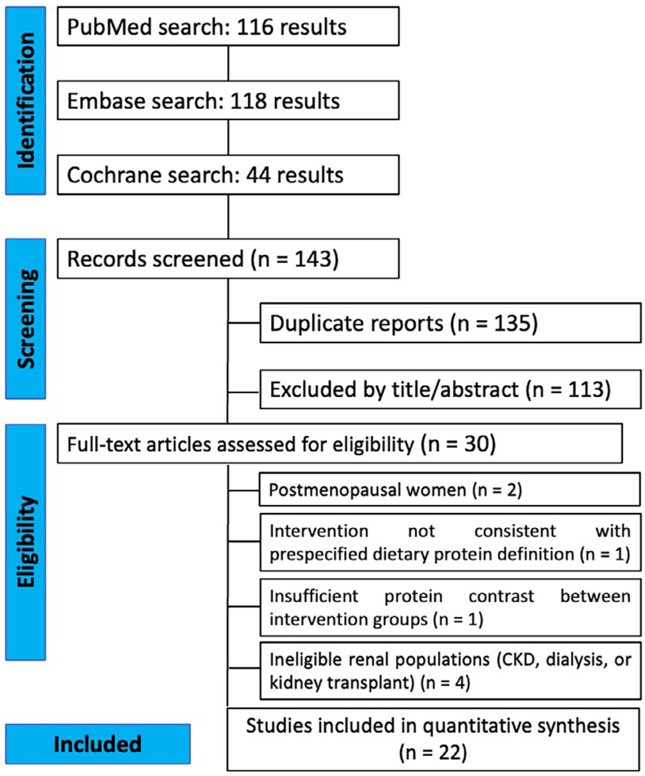


FIGURE 1 | PRISMA flow diagram of study selection. Flow diagram of study identification, screening, eligibility and inclusion according to PRISMA guidelines. We identified records through PubMed, Embase and Cochrane Library databases. After removing duplicates, we screened titles and abstracts, assessed full-text articles for eligibility and included randomised controlled trials in the quantitative synthesis.

[1–4, 8–10, 15, 16, 20–33]. Figure 1 presents the study selection process.

3.2 | Study Characteristics

The included trials enrolled adults without diagnosed chronic kidney disease and compared high-protein diets with NPL dietary interventions. Protein intake across high-protein interventions typically ranged from approximately 25%–35% of total energy intake or ≥2.0 g/kg/day. Study populations included healthy individuals, participants with overweight or obesity and individuals with type 2 diabetes. Intervention duration varied from short-term controlled feeding studies to trials lasting up to 2 years. Table 1 summarises the characteristics of the included studies.

3.3 | Primary Outcomes

3.3.1 | eGFR

Not all included studies contributed data to every outcome analysis because renal and body composition outcomes were inconsistently reported across trials. Twenty randomised controlled trials including 1478 participants contributed data on eGFR, whereas 19 studies contributed data to the serum creatinine analysis.

High-protein diets increased eGFR compared with control diets (standardised mean difference 0.39, 95% confidence interval 0.09–0.69), with substantial heterogeneity ($I^2 = 74.85\%$). The prediction interval ranged from −0.88 to 1.67, indicating considerable between-study variability. Figure 2a presents the pooled estimates.

We conducted prespecified subgroup analyses according to study design, diabetes status, intervention duration and age group. These analyses did not identify significant effect modification, although crossover trials showed numerically larger effects. Figure S1 presents subgroup analyses according to study design, diabetes status, intervention duration and age group.

3.3.2 | Serum Creatinine

Nineteen trials including 1044 participants reported serum creatinine outcomes. High-protein diets did not change serum creatinine compared with control diets (standardised mean difference 0.08, 95% confidence interval −0.09 to 0.25), with low heterogeneity ($I^2 = 20.8\%$). The prediction interval ranged from −0.33 to 0.48. Figure 2b presents these findings.

We conducted prespecified subgroup analyses according to study design, diabetes status, intervention duration and age group, which did not show significant effect modification (Figure S2).

3.4 | Secondary Outcomes

Although several included trials reported body composition-related variables, many did not provide extractable data for the specific prespecified outcomes included in the quantitative synthesis (body fat percentage, total fat mass, or fat-free mass). Some studies reported only body weight changes, whereas others presented body composition outcomes using incompatible metrics, incomplete dispersion measures, or non-convertible reporting formats that precluded reliable quantitative pooling.

3.4.1 | Body Fat Percentage

Six randomised controlled trials including 290 participants assessed body fat percentage. High-protein diets reduced body fat percentage compared with control diets (standardised mean difference −0.28, 95% confidence interval −0.51 to −0.05), with no observed heterogeneity ($I^2 = 0\%$). The prediction interval ranged from −0.59 to 0.02. Figure 3a presents the pooled estimates. Subgroup analyses according to study design and diabetes status showed consistent findings across strata (Figure S3).

3.4.2 | Total Fat Mass

Seven trials including 281 participants contributed data on total fat mass. High-protein diets reduced total fat mass compared with control diets (standardized mean difference −0.26, 95% confidence interval −0.50 to −0.02), with no observed heterogeneity ($I^2 = 0\%$). The prediction interval ranged from −0.55 to 0.04. Figure 3b presents these results. Subgroup analyses according to study design and diabetes status showed consistent results (Figure S4).

TABLE 1 | Characteristics of included randomised controlled trials evaluating high-protein diets in adults without chronic kidney disease.

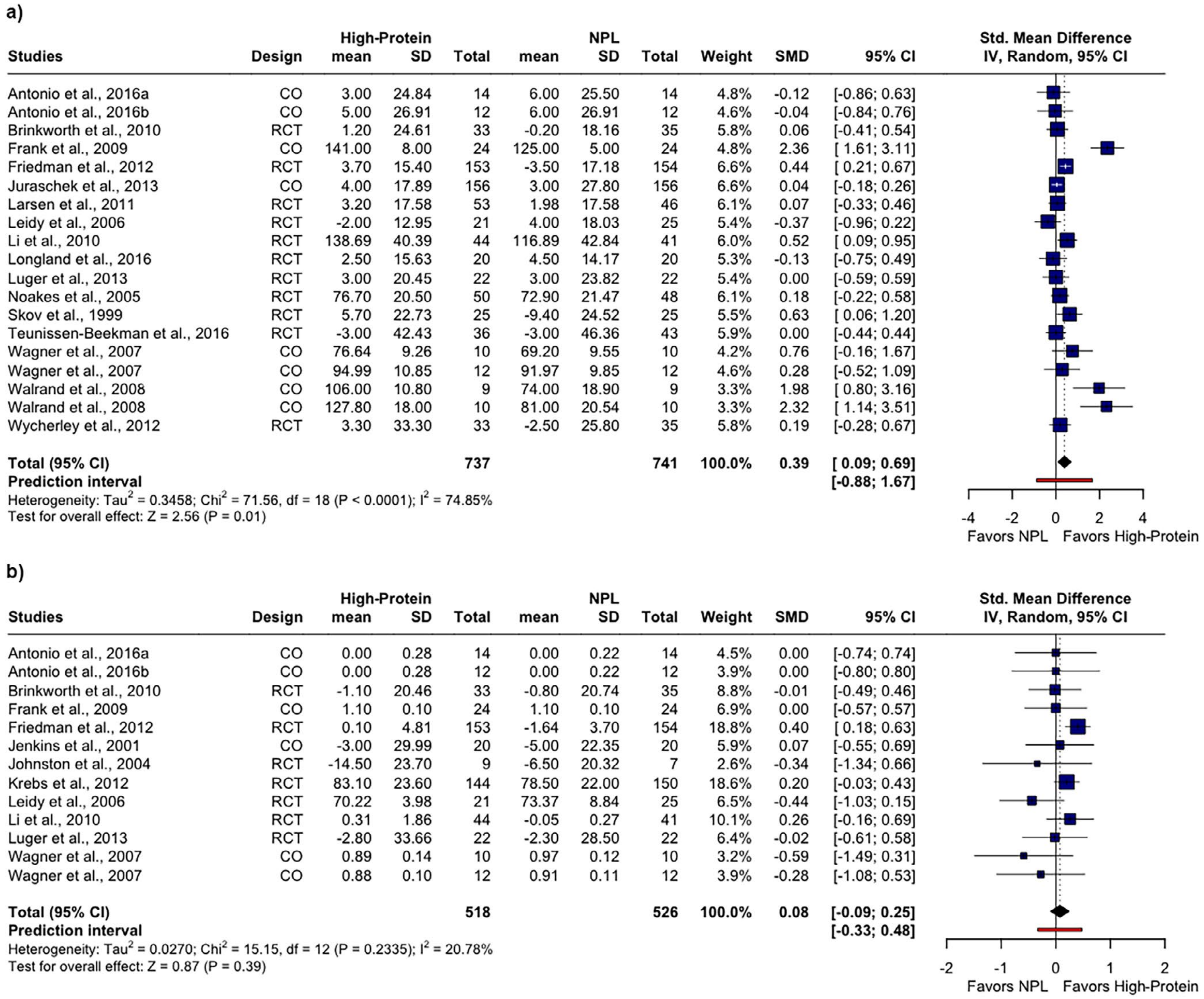
Study (year)	Country	Design	*N*	Population	Intervention (HP)	Control (NPL)	Duration	Renal outcomes	Body composition outcomes	GFR method
Antonio et al. 2016	USA	CO	14	Trained males	> 3.0 g/kg/day	Habitual protein intake	1 year	SCr, eGFR	Body weight, lean mass	MDRD
Antonio et al. 2016b	USA	CO	30	Trained adults	> 2.5 g/kg/day	Habitual protein intake	8 weeks	SCr, eGFR	FM, lean mass	MDRD
Brinkworth et al. 2004	AUS	PRCT	27	Obese adults	HP, LC	LF	12 weeks	SCr, urea	Body fat, FFM	Cockcroft–Gault
Brinkworth et al. 2010	AUS	PRCT	68	Abdominal obesity	HP: 30% of total energy intake	HC: 20% E	1 year	SCr, eGFR	FM, lean mass	MDRD
Frank et al. 2009	GER	CO	24	Healthy men	2.4 g/kg/day	1.2 g/kg/day	7 days	Inulin GFR, U-albumin	—	Inulin
Friedman et al. 2012	USA	PRCT	307	Obese adults	LC: 30% of total energy intake	LF: 15% of total energy intake	2 years	SCr, cystatin C, CrCl	FM, lean mass	MDRD/24 h
Jenkins et al. 2001	CAN	PRCT	43	Hyperlipidemic	HP (gluten-based)	LP	4 weeks	CrCl, SCr, uric acid	—	24 h CrCl
Johnston et al. 2004	USA	PRCT	20	Healthy adults	30% of total energy intake	15% of total energy intake	6 weeks	SCr, eGFR	Body weight	MDRD
Juraschek et al. 2013	USA	CO	164	Pre-HTN adults	25% protein	15% of total energy intake	6 weeks	SCr, eGFR, β2-M	—	CKD-EPI
Krebs et al. 2012	NZL	PRCT	419	T2D	HP: 30% of total energy intake	HC: 20% E	2 years	SCr, eGFR	Weight, lean mass	MDRD
Larsen et al. 2011	AUS	PRCT	57	T2D	30% of total energy intake	15% of total energy intake	1 year	SCr, eGFR	Weight, FM	MDRD
Leidy et al. 2007	USA	PRCT	24	Obese women	30% of total energy intake	15% of total energy intake	12 weeks	BUN, SCr	Body fat	Not reported
Li et al. 2010	USA	PRCT	100	Overweight adults	Meal replacement HP	LP	1 year	SCr, BUN, eGFR	FM	MDRD

(Continues)

TABLE 1 | (Continued)

Study (year)	Country	Design	*N*	Population	Intervention (HP)	Control (NPL)	Duration	Renal outcomes	Body composition outcomes	GFR method
Longland et al. 2016	CAN	PRCT	40	Young men, active	2.4 g/kg/day	1.2 g/kg/day	4 weeks	SCr	Lean mass, FM	MDRD
Luger et al. 2013	AUT	PRCT	17	T2D	HP: 30% of total energy intake	Control	6 weeks	SCr, insulin dose	Weight	Not reported
Luscombe-Marsh et al. 2005	AUS	PRCT	57	T2D	30% of total energy intake	15% of total energy intake	1 year	SCr, urea	FM, insulin	MDRD
Noakes et al. 2005	AUS	PRCT	93	Overweight	HP: 30% of total energy intake	LF: 15% of total energy intake	1 year	SCr, urea	FM	Cockcroft–Gault
Sargrad et al. 2005	USA	PRCT	21	T2D	30% of total energy intake	ADA diet	6 weeks	SCr, glucose	Weight	MDRD
Skov et al. 1999	DEN	PRCT	65	Overweight adults	25% protein	12% protein	6 months	GFR, U-albumin	—	CrCl
Teunissen-Beekman et al. 2016	NLD	PRCT	79	Overweight	HP vs. NP	NP diet	4 weeks	GFR, RBF, U-albumin	—	Para-aminohippurate
Wagner et al. 2007	GER	PRCT	21	Healthy adults	HP vs. NP	NP diet	6 weeks	GFR (iohexol), RPF	—	Iohexol
Walrand et al. 2008	FRA	PRCT	24	Healthy elderly	HP: 2.0 g/kg	0.8 g/kg	10 days	eGFR, SCr	—	MDRD
Wycherley et al. 2012	AUS	PRCT	120	Overweight and obese men without CKD	Energy-restricted high-protein, low-fat diet (35% protein, ~1.24 g/kg/day)	Isocaloric high-carbohydrate, low-fat diet (20% protein, ~0.82 g/kg/day)	52 weeks	Creatinine clearance, serum creatinine	Body fat mass, body fat percentage, fat-free mass	Creatinine clearance

Note: A dash indicates that the outcome was not reported in the original study.
Abbreviations: BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CO, crossover trial; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; FFM, fat-free mass; FM, fat mass; HPD, high-protein diet; MDRD, Modification of Diet in Renal Disease equation; NPL, normal- or low-protein diet; PRCT, parallel randomised controlled trial; RBF, renal blood flow; RPF, renal plasma flow; SCr, serum creatinine; T2D, type 2 diabetes mellitus.



a)

Studies	Design	High-Protein mean	High-Protein SD	Total	NPL mean	NPL SD	Total	Weight	SMD	95% CI
Antonio et al., 2016a	CO	3.00	24.84	14	6.00	25.50	14	4.8%	-0.12	[-0.86; 0.63]
Antonio et al., 2016b	CO	5.00	26.91	12	6.00	26.91	12	4.6%	-0.04	[-0.84; 0.76]
Brinkworth et al., 2010	RCT	1.20	24.61	33	-0.20	18.16	35	5.8%	0.06	[-0.41; 0.54]
Frank et al., 2009	CO	141.00	8.00	24	125.00	5.00	24	4.8%	2.36	[1.61; 3.11]
Friedman et al., 2012	RCT	3.70	15.40	153	-3.50	17.18	154	6.6%	0.44	[0.21; 0.67]
Juraschek et al., 2013	CO	4.00	17.89	156	3.00	27.80	156	6.6%	0.04	[-0.18; 0.26]
Larsen et al., 2011	RCT	3.20	17.58	53	1.98	17.58	46	6.1%	0.07	[-0.33; 0.46]
Leidy et al., 2006	RCT	-2.00	12.95	21	4.00	18.03	25	5.4%	-0.37	[-0.96; 0.22]
Li et al., 2010	RCT	138.69	40.39	44	116.89	42.84	41	6.0%	0.52	[0.09; 0.95]
Longland et al., 2016	RCT	2.50	15.63	20	4.50	14.17	20	5.3%	-0.13	[-0.75; 0.49]
Luger et al., 2013	RCT	3.00	20.45	22	3.00	23.82	22	5.4%	0.00	[-0.59; 0.59]
Noakes et al., 2005	RCT	76.70	20.50	50	72.90	21.47	48	6.1%	0.18	[-0.22; 0.58]
Skov et al., 1999	RCT	5.70	22.73	25	-9.40	24.52	25	5.5%	0.63	[0.06; 1.20]
Teunissen-Beekman et al., 2016	RCT	-3.00	42.43	36	-3.00	46.36	43	5.9%	0.00	[-0.44; 0.44]
Wagner et al., 2007	CO	76.64	9.26	10	69.20	9.55	10	4.2%	0.76	[-0.16; 1.67]
Wagner et al., 2007	CO	94.99	10.85	12	91.97	9.85	12	4.6%	0.28	[-0.52; 1.09]
Walrand et al., 2008	CO	106.00	10.80	9	74.00	18.90	9	3.3%	1.98	[0.80; 3.16]
Walrand et al., 2008	CO	127.80	18.00	10	81.00	20.54	10	3.3%	2.32	[1.14; 3.51]
Wycherley et al., 2012	RCT	3.30	33.30	33	-2.50	25.80	35	5.8%	0.19	[-0.28; 0.67]
Total (95% CI)				**737**			**741**	**100.0%**	**0.39**	**[0.09; 0.69]**
Prediction interval										**[-0.88; 1.67]**

Heterogeneity: $Tau^2 = 0.3458$; $Chi^2 = 71.56$, df = 18 ($P < 0.0001$); $I^2 = 74.85\%$
Test for overall effect: $Z = 2.56$ ($P = 0.01$)

b)

Studies	Design	High-Protein mean	High-Protein SD	Total	NPL mean	NPL SD	Total	Weight	SMD	95% CI
Antonio et al., 2016a	CO	0.00	0.28	14	0.00	0.22	14	4.5%	0.00	[-0.74; 0.74]
Antonio et al., 2016b	CO	0.00	0.28	12	0.00	0.22	12	3.9%	0.00	[-0.80; 0.80]
Brinkworth et al., 2010	RCT	-1.10	20.46	33	-0.80	20.74	35	8.8%	-0.01	[-0.49; 0.46]
Frank et al., 2009	CO	1.10	0.10	24	1.10	0.10	24	6.9%	0.00	[-0.57; 0.57]
Friedman et al., 2012	RCT	0.10	4.81	153	-1.64	3.70	154	18.8%	0.40	[0.18; 0.63]
Jenkins et al., 2001	CO	-3.00	29.99	20	-5.00	22.35	20	5.9%	0.07	[-0.55; 0.69]
Johnston et al., 2004	RCT	-14.50	23.70	9	-6.50	20.32	7	2.6%	-0.34	[-1.34; 0.66]
Krebs et al., 2012	RCT	83.10	23.60	144	78.50	22.00	150	18.6%	0.20	[-0.03; 0.43]
Leidy et al., 2006	RCT	70.22	3.98	21	73.37	8.84	25	6.5%	-0.44	[-1.03; 0.15]
Li et al., 2010	RCT	0.31	1.86	44	-0.05	0.27	41	10.1%	0.26	[-0.16; 0.69]
Luger et al., 2013	RCT	-2.80	33.66	22	-2.30	28.50	22	6.4%	-0.02	[-0.61; 0.58]
Wagner et al., 2007	CO	0.89	0.14	10	0.97	0.12	10	3.2%	-0.59	[-1.49; 0.31]
Wagner et al., 2007	CO	0.88	0.10	12	0.91	0.11	12	3.9%	-0.28	[-1.08; 0.53]
Total (95% CI)				**518**			**526**	**100.0%**	**0.08**	**[-0.09; 0.25]**
Prediction interval										**[-0.33; 0.48]**

Heterogeneity: $Tau^2 = 0.0270$; $Chi^2 = 15.15$, df = 12 ($P = 0.2335$); $I^2 = 20.78\%$
Test for overall effect: $Z = 0.87$ ($P = 0.39$)

FIGURE 2 | Effects of high-protein diets on renal function. Forest plots showing the effects of high-protein diets compared with NPL diets on renal function outcomes. (a) Estimated glomerular filtration rate (20 studies). (b) Serum creatinine (19 studies). Effect sizes are presented as SMDs with 95% CIs using a random-effects model. The diamond represents the pooled effect estimate, and horizontal lines indicate study-specific CIs. Prediction intervals are shown to reflect between-study variability. CI, confidence interval; NPL, normal- or low-protein diets; SMD, standardised mean difference.

3.4.3 | Fat-Free Mass

Five trials including 222 participants evaluated fat-free mass. High-protein diets showed a non-significant trend toward preservation of fat-free mass compared with NPL diets (standardized mean difference 0.19, 95% confidence interval −0.08 to 0.45), with no observed heterogeneity ($I^2=0\%$). The prediction interval ranged from −0.19 to 0.56. Figure 3c presents these findings. Subgroup analyses according to study design and diabetes status did not show significant differences (Figure S5).

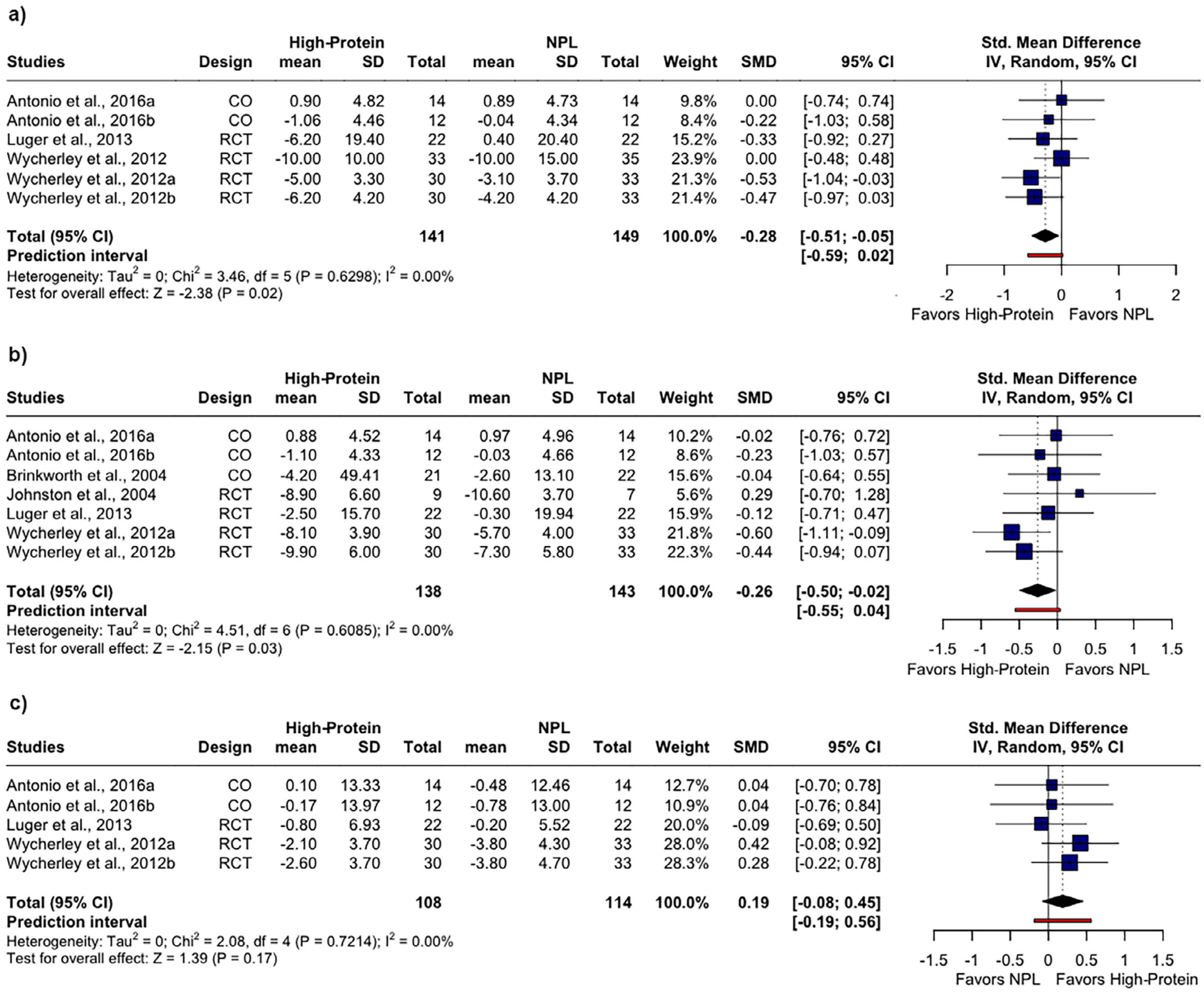
3.5 | Sensitivity Analyses and Publication Bias

Sensitivity analyses excluding crossover trials attenuated the pooled effect estimate and substantially reduced heterogeneity for eGFR; however, the direction and overall interpretation of the findings remained unchanged. Similar analyses for serum creatinine and body composition outcomes did not materially alter the pooled estimates or overall interpretation of the findings. Leave-one-out analyses demonstrated that no single study substantially altered the direction of the pooled estimates, although removal of Frank et al. reduced heterogeneity for eGFR (Tables S4–S6). Funnel plots and Egger's regression tests did not suggest small-study effects for outcomes with sufficient data.

4 | Discussion

4.1 | Main Findings

This systematic review and meta-analysis found that high-protein diets increased eGFR without consistent biochemical evidence suggestive of renal injury, as reflected by unchanged serum creatinine levels. At the same time, high-protein diets reduced body fat percentage and total fat mass, while they did not significantly



a)

Studies	Design	High-Protein mean	SD	Total	NPL mean	SD	Total	Weight	SMD	95% CI
Antonio et al., 2016a	CO	0.90	4.82	14	0.89	4.73	14	9.8%	0.00	[-0.74; 0.74]
Antonio et al., 2016b	CO	-1.06	4.46	12	-0.04	4.34	12	8.4%	-0.22	[-1.03; 0.58]
Luger et al., 2013	RCT	-6.20	19.40	22	0.40	20.40	22	15.2%	-0.33	[-0.92; 0.27]
Wycherley et al., 2012	RCT	-10.00	10.00	33	-10.00	15.00	35	23.9%	0.00	[-0.48; 0.48]
Wycherley et al., 2012a	RCT	-5.00	3.30	30	-3.10	3.70	33	21.3%	-0.53	[-1.04; -0.03]
Wycherley et al., 2012b	RCT	-6.20	4.20	30	-4.20	4.20	33	21.4%	-0.47	[-0.97; 0.03]
Total (95% CI)				**141**			**149**	**100.0%**	**-0.28**	**[-0.51; -0.05]**
Prediction interval										**[-0.59; 0.02]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.46$, df = 5 (P = 0.6298); $I^2 = 0.00\%$

Test for overall effect: Z = -2.38 (P = 0.02)

b)

Studies	Design	High-Protein mean	SD	Total	NPL mean	SD	Total	Weight	SMD	95% CI
Antonio et al., 2016a	CO	0.88	4.52	14	0.97	4.96	14	10.2%	-0.02	[-0.76; 0.72]
Antonio et al., 2016b	CO	-1.10	4.33	12	-0.03	4.66	12	8.6%	-0.23	[-1.03; 0.57]
Brinkworth et al., 2004	CO	-4.20	49.41	21	-2.60	13.10	22	15.6%	-0.04	[-0.64; 0.55]
Johnston et al., 2004	RCT	-8.90	6.60	9	-10.60	3.70	7	5.6%	0.29	[-0.70; 1.28]
Luger et al., 2013	RCT	-2.50	15.70	22	-0.30	19.94	22	15.9%	-0.12	[-0.71; 0.47]
Wycherley et al., 2012a	RCT	-8.10	3.90	30	-5.70	4.00	33	21.8%	-0.60	[-1.11; -0.09]
Wycherley et al., 2012b	RCT	-9.90	6.00	30	-7.30	5.80	33	22.3%	-0.44	[-0.94; 0.07]
Total (95% CI)				**138**			**143**	**100.0%**	**-0.26**	**[-0.50; -0.02]**
Prediction interval										**[-0.55; 0.04]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.51$, df = 6 (P = 0.6085); $I^2 = 0.00\%$

Test for overall effect: Z = -2.15 (P = 0.03)

c)

Studies	Design	High-Protein mean	SD	Total	NPL mean	SD	Total	Weight	SMD	95% CI
Antonio et al., 2016a	CO	0.10	13.33	14	-0.48	12.46	14	12.7%	0.04	[-0.70; 0.78]
Antonio et al., 2016b	CO	-0.17	13.97	12	-0.78	13.00	12	10.9%	0.04	[-0.76; 0.84]
Luger et al., 2013	RCT	-0.80	6.93	22	-0.20	5.52	22	20.0%	-0.09	[-0.69; 0.50]
Wycherley et al., 2012a	RCT	-2.10	3.70	30	-3.80	4.30	33	28.0%	0.42	[-0.08; 0.92]
Wycherley et al., 2012b	RCT	-2.60	3.70	30	-3.80	4.70	33	28.3%	0.28	[-0.22; 0.78]
Total (95% CI)				**108**			**114**	**100.0%**	**0.19**	**[-0.08; 0.45]**
Prediction interval										**[-0.19; 0.56]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.08$, df = 4 (P = 0.7214); $I^2 = 0.00\%$

Test for overall effect: Z = 1.39 (P = 0.17)

FIGURE 3 | Effects of high-protein diets on body composition. Forest plots showing the effects of high-protein diets compared with NPL diets on body composition outcomes. (a) Body fat percentage. (b) Total fat mass. (c) Fat-free mass. Effect sizes are presented as SMDs with 95% CIs using a random-effects model. The diamond represents the pooled estimate, and horizontal lines indicate study-specific CIs. Prediction intervals are presented where applicable. CI, confidence interval; NPL, normal- or low-protein diets; SMD, standardised mean difference.

affect fat-free mass. Overall, these findings suggest a pattern of adaptive renal response accompanied by favourable changes in adiposity in adults without chronic kidney disease.

4.2 | Interpretation of Findings

The increase in eGFR observed with high-protein diets may reflect physiological hyperfiltration associated with increased renal plasma flow and glomerular hemodynamic adaptation [5, 22]. However, interpretation of these findings requires caution because most included studies relied on creatinine-based estimates of renal function, which may be influenced by increased creatinine generation related to higher protein intake, dietary creatine exposure and changes in muscle metabolism [7].

Consequently, distinguishing adaptive physiological responses from early renal stress remains challenging based exclusively on creatinine-derived estimates. Importantly, the absence of significant changes in serum creatinine does not necessarily exclude subtle renal alterations, particularly because most included interventions were of relatively short duration. Although the available evidence does not demonstrate consistent biochemical evidence of renal injury in adults without chronic kidney disease, uncertainty remains regarding the long-term renal implications of sustained high-protein intake, particularly in individuals with obesity, insulin resistance, or type 2 diabetes, in whom baseline renal hemodynamics may already be altered and sustained hyperfiltration could contribute to progressive renal stress over time [5, 6, 18, 19].

From a clinical perspective, these findings remain relevant because concerns regarding renal safety frequently limit the implementation of high-protein diets in weight management and metabolic care. At the same time, the observed reductions in body fat percentage and total fat mass support the potential metabolic benefits of these dietary strategies. Although the pooled effect for fat-free mass did not reach statistical significance, the direction of effect was consistent with prior literature suggesting that higher protein intake may contribute to preservation of lean mass during dietary interventions [33]. Nevertheless, the current evidence primarily reflects short-term physiological and metabolic responses rather than definitive evidence of long-term renal safety.

Although hyperfiltration may initially represent a physiological adaptation to increased protein intake, persistent increases in intraglomerular pressure could theoretically contribute to progressive renal stress over time.

4.3 | Context With Previous Literature

Overall, this pattern aligns with prior randomised trials and controlled feeding studies showing that high-protein diets increase glomerular filtration without consistent evidence of renal harm in adults without chronic kidney disease [3, 8]. It also aligns with mechanistic studies describing hyperfiltration as a normal physiological response to increased protein intake [5].

However, observational and epidemiological studies have reported associations between long-term high-protein dietary patterns and adverse renal or cardiometabolic outcomes in some high-risk populations, particularly among individuals with preexisting renal dysfunction or metabolic disease [34–36]. These discrepancies likely reflect differences in study design, residual confounding and population characteristics, including baseline renal function and comorbidity burden. By restricting the analysis to randomised controlled trials in individuals without chronic kidney disease, the present study reduces these sources of bias and provides a more direct assessment of causality.

4.4 | Interpretation of Heterogeneity

The substantial heterogeneity observed for eGFR likely reflects differences in study populations, intervention characteristics and outcome assessment methods. Trials included individuals with varying metabolic profiles, ranging from healthy participants to those with obesity or type 2 diabetes, which could influence baseline renal hemodynamics. In addition, protein intake varied across studies, both in absolute terms and as a proportion of total energy intake, potentially influencing the magnitude of the renal response.

An additional source of heterogeneity relates to the operational definition of high-protein diets across studies. Some trials defined high-protein intake according to the proportion of total energy intake, whereas others used absolute protein intake expressed in grams per kilogram of body weight per day. These approaches are not physiologically equivalent, particularly across populations with different caloric intake, body composition and metabolic status, and likely contributed to variability in the magnitude of renal responses observed across studies.

Differences in intervention duration may also have influenced variability, as short-term feeding studies primarily capture acute hemodynamic adaptations, whereas longer trials may reflect more stable physiological responses. Furthermore, studies used different methods to estimate renal function, including creatinine-based equations and clearance-based techniques, which introduce additional measurement variability. Taken together, these factors likely contributed to the observed heterogeneity and should be considered when interpreting the pooled estimates.

Importantly, the present findings should not be extrapolated to long-term cardiovascular safety. Although high-protein diets may improve body composition and metabolic parameters in the short term, uncertainty remains regarding their long-term cardiovascular implications because currently available randomised trials remain relatively short in duration and are not designed to assess major cardiovascular outcomes.

4.5 | Strengths

The main strengths of this review include a comprehensive and systematic search strategy, a protocol-driven approach registered in PROSPERO and the exclusive inclusion of randomised controlled trials. We applied rigorous methods for risk of bias assessment using the Cochrane RoB 2 tool and evaluated the certainty of evidence using GRADE. The analysis included a relatively large pooled sample and assessed clinically relevant outcomes, including both renal function and body composition. In addition, we conducted prespecified subgroup and sensitivity analyses and reported prediction intervals to provide a more comprehensive assessment of between-study variability.

4.6 | Limitations

These findings should be interpreted in light of several limitations. First, the duration of most included trials was relatively short, which limits the ability to assess long-term renal outcomes and the potential cumulative effects of sustained hyperfiltration. Second, the included studies showed substantial variability in both the definition and dose of dietary protein exposure. High-protein interventions were variably defined according to relative protein intake as a proportion of total energy intake or absolute intake expressed in grams per kilogram per day. These approaches may represent different physiological exposures depending on total caloric intake and participant characteristics, which may have contributed to between-study heterogeneity and limited comparability across trials. Third, the number of studies and participants contributing to several body composition outcomes was relatively modest, which limits statistical precision and reduces confidence in the stability and generalizability of these pooled estimates. In addition, the inclusion of metabolically diverse populations, including exercise-trained and sedentary individuals, may introduce indirectness when interpreting body composition responses across different clinical settings.

Another important limitation relates to the assessment of renal function across included studies. Most trials relied on creatinine-based equations to estimate glomerular filtration rate, which may be influenced by increased creatinine generation associated with high-protein intake and changes in muscle metabolism. As a result, observed increases in eGFR may partly reflect physiological or analytical effects related to protein intake rather than isolated changes in intrinsic renal function. Finally, although we assessed publication bias when possible, the limited number of studies for some outcomes restricts the reliability of these assessments.

Importantly, most included interventions were relatively short in duration, with many trials lasting only a few weeks to months. Consequently, the available evidence primarily reflects short-term physiological and metabolic responses to increased protein intake and does not permit definitive conclusions regarding long-term renal safety.

4.7 | Remaining Gaps and Future Directions

Important uncertainties remain. Future studies should evaluate the long-term renal effects of high-protein diets, particularly in populations with metabolic risk factors such as obesity and type 2 diabetes. Studies should also standardize outcome definitions and measurement methods for renal function to improve comparability across trials. In addition, future research should explore dose–response relationships between protein intake and renal outcomes and assess whether specific protein sources influence renal and metabolic responses. Trials with longer follow-up and consistent reporting of clinically relevant outcomes will be essential to clarify the long-term safety profile of high-protein diets.

5 | Conclusion

In summary, the available evidence suggests that high-protein diets are associated with increases in eGFR without consistent biochemical evidence suggestive of renal injury in adults without chronic kidney disease. At the same time, these dietary interventions were associated with reductions in body fat percentage and total fat mass without significant effects on fat-free mass. However, because most available trials were relatively short in duration and frequently relied on creatinine-based estimates of renal function, these findings should be interpreted cautiously. The observed increases in eGFR may primarily reflect short-term hemodynamic adaptations associated with increased protein intake, whereas uncertainty remains regarding the long-term renal implications of sustained high-protein dietary exposure.

These findings may help inform dietary strategies for weight management and metabolic health while reinforcing the need for longer-term randomised studies using standardised and directly measured assessments of renal function.

Author Contributions

All authors contributed to the study design, data analysis, interpretation of data and manuscript preparation. All authors approved the final version of the manuscript.

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Ethics Statement

Ethical approval was not required because this study is a systematic review and meta-analysis of published data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request. All data included in this systematic review and meta-analysis were derived from previously published studies cited in the manuscript and Supporting Information.

Peer Review

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References

1. J. Antonio, A. Ellerbroek, T. Silver, et al., "A High Protein Diet Has no Harmful Effects: A One-Year Crossover Study in Resistance-Trained Males," *Journal of Nutrition and Metabolism* 2016 (2016): 1–5.

2. G. D. Brinkworth, M. Noakes, J. B. Keogh, N. D. Luscombe, G. A. Wittert, and P. M. Clifton, "Long-Term Effects of a High-Protein, Low-Carbohydrate Diet on Weight Control and Cardiovascular Risk Markers in Obese Hyperinsulinemic Subjects," *International Journal of Obesity* 28, no. 5 (2004): 661–670.

3. A. N. Friedman, L. G. Ogden, G. D. Foster, et al., "Comparative Effects of Low-Carbohydrate High-Protein Versus Low-Fat Diets on the Kidney," *Clinical Journal of the American Society of Nephrology* 7, no. 7 (2012): 1103–1111.

4. C. S. Johnston, S. L. Tjonn, and P. D. Swan, "High-Protein, Low-Fat Diets Are Effective for Weight Loss and Favorably Alter Biomarkers in Healthy Adults," *Journal of Nutrition* 134, no. 3 (2004): 586–591.

5. T. H. Hostetter, "Hyperfiltration and Glomerulosclerosis," *Seminars in Nephrology* 23, no. 2 (2003): 194–199.

6. L. Tonneijck, M. H. Muskiet, M. M. Smits, et al., "Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment," *Journal of the American Society of Nephrology* 28, no. 4 (2017): 1023–1039.

7. A. Basolo, G. Salvetti, D. Giannese, et al., "Obesity, Hyperfiltration, and Early Kidney Damage: A New Formula for the Estimation of Creatinine Clearance," *Journal of Clinical Endocrinology and Metabolism* 108, no. 12 (2023): 3280–3286.

8. S. P. Juraschek, L. J. Appel, C. A. M. Anderson, and E. R. Miller, "Effect of a High-Protein Diet on Kidney Function in Healthy Adults: Results From the OmniHeart Trial," *American Journal of Kidney Diseases* 61, no. 4 (2013): 547–554.

9. J. D. Krebs, C. R. Elley, A. Parry-Strong, et al., "The Diabetes Excess Weight Loss (DEWL) Trial: A Randomised Controlled Trial of High-Protein Versus High-Carbohydrate Diets Over 2 Years in Type 2 Diabetes," *Diabetologia* 55, no. 4 (2012): 905–914.

10. R. N. Larsen, N. J. Mann, E. Maclean, and J. E. Shaw, "The Effect of High-Protein, Low-Carbohydrate Diets in the Treatment of Type 2 Diabetes: A 12 Month Randomised Controlled Trial," *Diabetologia* 54, no. 4 (2011): 731–740.

11. M. C. Devries, A. Sithamparapillai, K. S. Brimble, L. Banfield, R. W. Morton, and S. M. Phillips, "Changes in Kidney Function Do Not Differ Between Healthy Adults Consuming Higher- Compared With Lower- or Normal-Protein Diets: A Systematic Review and Meta-Analysis," *Journal of Nutrition* 148, no. 11 (2018): 1760–1775.

12. L. Schwingshackl and G. Hoffmann, “Long-Term Effects of Low-Fat Diets Either Low or High in Protein on Cardiovascular and Metabolic Risk Factors: A Systematic Review and Meta-Analysis,” *Nutrition Journal* 12 (2013): 48.

13. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., “The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews,” *BMJ* 372 (2021): n71.

14. J. A. C. Sterne, J. Savovic, M. J. Page, et al., “RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials,” *BMJ* 366 (2019): l4898.

15. J. Antonio, A. Ellerbroek, T. Silver, L. Vargas, and C. Peacock, “The Effects of a High Protein Diet on Indices of Health and Body Composition—A Crossover Trial in Resistance-Trained Men,” *Journal of the International Society of Sports Nutrition* 13, no. 1 (2016): 3.

16. H. Frank, J. Graf, U. Amann-Gassner, et al., “Effect of Short-Term High-Protein Compared With Normal-Protein Diets on Renal Hemodynamics and Associated Variables in Healthy Young Men,” *American Journal of Clinical Nutrition* 90, no. 6 (2009): 1509–1516.

17. J. IntHout, J. P. Ioannidis, M. M. Rovers, and J. J. Goeman, “Plea for Routinely Presenting Prediction Intervals in Meta-Analysis,” *BMJ Open* 6, no. 7 (2016): e010247.

18. M. Egger, G. Davey Smith, M. Schneider, and C. Minder, “Bias in Meta-Analysis Detected by a Simple, Graphical Test,” *BMJ* 315, no. 7109 (1997): 629–634.

19. G. H. Guyatt, A. D. Oxman, G. E. Vist, et al., “GRADE: An Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations,” *BMJ* 336, no. 7650 (2008): 924–926.

20. G. D. Brinkworth, J. D. Buckley, M. Noakes, and P. M. Clifton, “Renal Function Following Long-Term Weight Loss in Individuals With Abdominal Obesity on a Very-Low-Carbohydrate Diet vs High-Carbohydrate Diet,” *Journal of the American Dietetic Association* 110, no. 4 (2010): 633–638.

21. D. J. Jenkins, C. W. Kendall, E. Vidgen, et al., “High-Protein Diets in Hyperlipidemia: Effect of Wheat Gluten on Serum Lipids, Uric Acid, and Renal Function,” *American Journal of Clinical Nutrition* 74, no. 1 (2001): 57–63.

22. H. J. Leidy, N. S. Carnell, R. D. Mattes, and W. W. Campbell, “Higher Protein Intake Preserves Lean Mass and Satiety With Weight Loss in Pre-Obese and Obese Women,” *Obesity* 15, no. 2 (2007): 421–429.

23. Z. Li, L. Treyzon, S. Chen, E. Yan, G. Thames, and C. L. Carpenter, “Protein-Enriched Meal Replacements Do Not Adversely Affect Liver, Kidney or Bone Density: An Outpatient Randomized Controlled Trial,” *Nutritional Journal* 9 (2010): 72.

24. T. M. Longland, S. Y. Oikawa, C. J. Mitchell, M. C. Devries, and S. M. Phillips, “Higher Compared With Lower Dietary Protein During an Energy Deficit Combined With Intense Exercise Promotes Greater Lean Mass Gain and Fat Mass Loss: A Randomized Trial,” *American Journal of Clinical Nutrition* 103, no. 3 (2016): 738–746.

25. M. Luger, B. Holstein, K. Schindler, R. Kruschitz, and B. Ludvik, “Feasibility and Efficacy of an Isocaloric High-Protein vs. Standard Diet on Insulin Requirement, Body Weight and Metabolic Parameters in Patients With Type 2 Diabetes on Insulin Therapy,” *Experimental and Clinical Endocrinology & Diabetes* 121, no. 5 (2013): 286–294.

26. N. D. Luscombe-Marsh, M. Noakes, G. A. Wittert, J. B. Keogh, P. Foster, and P. M. Clifton, “Carbohydrate-Restricted Diets High in Either Monounsaturated Fat or Protein Are Equally Effective at Promoting Fat Loss and Improving Blood Lipids,” *American Journal of Clinical Nutrition* 81, no. 4 (2005): 762–772.

27. M. Noakes, J. B. Keogh, P. R. Foster, and P. M. Clifton, “Effect of an Energy-Restricted, High-Protein, Low-Fat Diet Relative to a Conventional High-Carbohydrate, Low-Fat Diet on Weight Loss, Body Composition, Nutritional Status, and Markers of Cardiovascular Health in Obese Women,” *American Journal of Clinical Nutrition* 81, no. 6 (2005): 1298–1306.

28. K. R. Sargrad, C. Homko, M. Mozzoli, and G. Boden, “Effect of High Protein vs High Carbohydrate Intake on Insulin Sensitivity, Body Weight, Hemoglobin A1c, and Blood Pressure in Patients With Type 2 Diabetes Mellitus,” *Journal of the American Dietetic Association* 105, no. 4 (2005): 573–580.

29. A. R. Skov, S. Toubro, J. Bülow, K. Krabbe, H. H. Parving, and A. Astrup, “Changes in Renal Function During Weight Loss Induced by High vs Low-Protein Low-Fat Diets in Overweight Subjects,” *International Journal of Obesity and Related Metabolic Disorders* 23, no. 11 (1999): 1170–1177.

30. K. F. M. Teunissen-Beekman, J. Dopheide, J. M. Geleijnse, et al., “Effect of Increased Protein Intake on Renal Acid Load and Renal Hemodynamic Responses,” *Physiological Reports* 4, no. 5 (2016): e12687.

31. E. A. Wagner, G. A. Falciglia, H. Amlal, L. Levin, and M. Soleimani, “Short-Term Exposure to a High-Protein Diet Differentially Affects Glomerular Filtration Rate but Not Acid-Base Balance in Older Compared to Younger Adults,” *Journal of the American Dietetic Association* 107, no. 8 (2007): 1404–1408.

32. S. Walrand, K. R. Short, M. L. Bigelow, A. J. Sweatt, S. M. Hutson, and K. S. Nair, “Functional Impact of High Protein Intake on Healthy Elderly People,” *American Journal of Physiology-Endocrinology and Metabolism* 295, no. 4 (2008): E921–E928.

33. T. P. Wycherley, G. D. Brinkworth, P. M. Clifton, and M. Noakes, “Comparison of the Effects of 52 Weeks Weight Loss With Either a High-Protein or High-Carbohydrate Diet on Body Composition and Cardiometabolic Risk Factors in Overweight and Obese Males,” *Nutrition & Diabetes* 2, no. 8 (2012): e40.

34. E. L. Knight, M. J. Stampfer, S. E. Hankinson, D. Spiegelman, and G. C. Curhan, “The Impact of Protein Intake on Renal Function Decline in Women With Normal Renal Function or Mild Renal Insufficiency,” *Annals of Internal Medicine* 138, no. 6 (2003): 460–467.

35. J. H. Jhee, Y. K. Kee, S. Park, et al., “High-Protein Diet With Renal Hyperfiltration Is Associated With Rapid Decline Rate of Renal Function: A Community-Based Prospective Cohort Study,” *Nephrology, Dialysis, Transplantation* 35, no. 1 (2020): 98–106.

36. B. Haring, E. Selvin, M. Liang, et al., “Dietary Protein Sources and Risk for Incident Chronic Kidney Disease: Results From the Atherosclerosis Risk in Communities (ARIC) Study,” *Journal of Renal Nutrition* 27, no. 4 (2017): 233–242.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** (a) Effects of high-protein diets on estimated glomerular filtration rate (eGFR) stratified by study design, (b) effect of high-protein diets on eGFR stratified by diabetes status, (c) effect of high-protein diets on eGFR stratified by study duration and (d) effect of high-protein diets on eGFR stratified by age group. **Figure S2:** (a) Forest plot showing the effect of high-protein diets versus normal- or low-protein diets (NPL) diets on serum creatinine levels, stratified by study design (crossover [CO] vs. randomised controlled trials [RCT]). (b) Forest plot presenting subgroup analyses of serum creatinine changes in participants with and without diabetes mellitus. (c) Subgroup meta-analysis of serum creatinine according to intervention duration (follow-up < 12 vs. ≥ 12 weeks). (d) Stratified analysis of serum creatinine levels based on age groups (young, middle-aged and older adults). **Figure S3:** (a) Effect of high-protein diets on body fat reduction according to study design. (b) Effect of high-protein diets on body fat reduction stratified by diabetes status. **Figure S4:**. (a) Forest plot of the effects of high-protein versus NPL diets on fat mass (kg), stratified by study design and (b) forest plot of the effects of high-protein versus NPL diets on fat mass (kg), stratified by diabetes status. **Figure S5:** (a) Effect of high-protein diets on fat-free mass stratified by study design and (b) effect of high-protein diets on fat-free mass stratified by diabetes status. Forest plot showing subgroup analyses of the effect of high-protein diets compared with normal- or low-protein diets on fat-free mass according to diabetes status (participants with diabetes versus participants without diabetes). Effect estimates are presented as standardised mean differences with 95% confidence intervals using a random-effects model with restricted maximum likelihood estimation. **Table S1:** (a) Risk of bias assessment for parallel-group randomised controlled trials (RoB 2.0). (b) Risk of bias assessment for crossover trials (RoB 2.0 adapted for crossover design). **Table S2:** PRISMA 2020 checklist. **Table S3:** GRADE summary of findings table. **Table S4:** Sensitivity analyses excluding crossover trials. **Table S5:** Sensitivity analyses excluding studies with higher risk of bias. **Table S6:** Leave-one-out analysis for estimated glomerular filtration rate.