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SYSTEMATIC REVIEW AND META-ANALYSIS

Long term weight maintenance after advice to consume low carbohydrate, higher protein diets — A systematic review and meta analysis

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Abstract *Background:* Meta analysis of short term trials indicates that a higher protein, lower carbohydrate weight loss diet enhances fat mass loss and limits lean mass loss compared with a normal protein weight loss diet. Whether this benefit persists long term is not clear.
Methods and results: We selected weight loss studies in adults with at least a 12 month follow up in which a higher percentage protein/lower carbohydrate diet was either planned or would be expected for either weight loss or weight maintenance. Studies were selected regardless of the success of the advice but difference in absolute and percentage protein intake at 12 months was used as a moderator in the analysis. Data was analysed using Comprehensive Meta analysis V2 using a random effects analysis. As many as 32 studies with 3492 individuals were analysed with data on fat and lean mass, glucose and insulin from 18 to 22 studies and lipids from 28 studies. A recommendation to consume a lower carbohydrate, higher protein diet in mostly short term intensive interventions with long term follow up was associated with better weight and fat loss but the effect size was small-standardised means of 0.14 and 0.22, $p = 0.008$ and $p < 0.001$ respectively (equivalent to 0.4 kg for both). A difference of 5% or greater in percentage protein between diets at 12mo was associated with a 3 fold greater effect size compared with <5% ($p = 0.038$) in fat mass (0.9 vs. 0.3 kg). Fasting triglyceride and insulin were also lower with high protein diets with effect sizes of 0.17 and 0.22, $p = 0.003$ and $p = 0.042$ respectively. Other lipids and glucose were not different.
Conclusion: The short term benefit of higher protein diets appears to persist to a small degree long term. Benefits are greater with better compliance to the diet.
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Introduction

High protein weight loss diets are widely used but there is no consensus about the long term efficacy of these diets. Short to medium term studies have clearly shown that ad libitum high protein diets increase satiety and increase weight loss compared to high carbohydrate diets [1,2] but long term 1–2 year compliance with high protein diets is usually poor despite intensive support [3] but this is no different from compliance to any other macronutrient prescription. A recent meta analysis [4] showed a small benefit from high protein diets but this study selected only studies in which the dietary intervention was successful at achieving the planned macronutrient intake with a reported difference in protein

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intakes of 5% or more between groups. Another review came to a similar conclusion finding that when protein intake was increased by less than 5% no benefit was seen in weight loss outcomes while successful studies with greater weight loss with high protein diets had an increase in protein intake of 24% over baseline intakes [5]. As compliance to the protein prescription is very likely to be related to compliance to the energy prescription these positive findings do not show that adoption of a high protein weight loss or weight maintenance diet per se will necessarily lead to a better weight outcomes long term. However the positive findings of the weight maintenance phase of the DIOGENE study (especially the shop centres where food was provided) suggest that providing more protein moderates food intake in some circumstances and a change of 5% is all that is required [6]. Similarly short term isocaloric energy controlled weight loss studies show that high protein diets improve body composition compared with isocaloric high carbohydrate weight loss diets [7]. However it is not clear if providing only advice to consume a low carbohydrate, high protein diet for weight loss or weight maintenance with or without intensive support provides any advantages long term over any other type of advice and a recent selective meta analysis of low fat interventions in adults has suggested essentially no benefit over 12 months with the high protein diet other than a reduced fasting insulin Ref. [8]. The purpose of this review and meta analysis is to examine this question in more detail in a broader group of studies with no macronutrient or study design limitations.

Methods

Search strategy

We followed standard criteria for conducting and reporting meta-analyses of observational studies [9]. We conducted systematic literature searches, from the index date of each database through July 2013, of multiple databases including PubMed (http://www.ncbi.nlm.nih.gov/pubmed, since 1966), EMBASE (http://www.embase.com, since 1947), the Cochrane Library.

(http://www.thecochranelibrary.com/, since 1951) to identify all randomised controlled trials where the two diets potentially contained a different percentage of energy as protein. Studies were selected up until the end of July 2013 with the following keywords “Randomised controlled trial” AND “weight loss” or “weight maintenance” AND “protein” or “carbohydrate”. We thus searched for a very broad and heterogeneous range of weight loss interventions in which macronutrient composition was compared. There was no fixed definition of high or normal protein and we sought only a difference in protein between the two weight loss diets. Reference lists of identified publications and reviews were searched for citations of additional relevant articles. We restricted our searches to studies of adult humans in articles published in English and did not seek additional information from the authors.

Selection criteria

Articles were considered for selection if they were randomised controlled weight loss trials in adults of 18 or older and if they had [1] a follow up of 12 months or more and [2] advice was provided to either increase the absolute amount of protein or to keep the amount of protein constant and to reduce carbohydrate (thus to increase the percentage energy as protein) and this was compared to a second contrasting weight loss diet and [3] at a minimum weight measurements at the beginning and the end of the study were provided. The advice may have been just to reduce carbohydrate in which it would be expected that the percentage of energy from protein would increase. This includes studies with the Atkins or South Beach diet in an ad libitum or controlled energy diet. This advice could be as part of a weight loss program or as part of a weight maintenance program following weight loss with a different regime. Studies were included whether the advice was followed successfully or not and also included studies in which the assessment of dietary intake or objective measures of protein intake were limited or absent such that success of the advice could not be assessed. Studies involving participants with diabetes or PCOS were included or when the end points were focused on parameters other than weight such as bone density. A 12 month minimum duration was chosen as peak weight loss is usually achieved at 3–6 months and weight regain is often starting to occur at 6 months. Trials which used protein supplements to increase protein intake in a normal weight loss or maintenance diet were also included but meal replacement studies were excluded as these induce weight loss by a very different mechanism. When higher protein diets were used for weight maintenance then changes from the end of the standard weight loss period were used. Where multiple publications referred to the same trial the latest publication was used if possible even though participant numbers may have been significantly reduced compared with the original publications as long term data is the focus of this review. When the trial had more than two arms the lower carbohydrate arms were combined if appropriate and compared to the combined contrasting diets.

Outcomes

The primary outcomes were body weight and body composition (fat mass and fat free mass) assessed by either dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and air-displacement plethysmography. The secondary outcomes were blood lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), blood pressure, CRP, fasting plasma glucose, fasting insulin, and HbA1c for diabetics.

Data abstraction

Data was extracted for each identified article and entered by two researchers independently and cross verified.

Demographic characteristics of the study population and details of the study protocol and methodology were also extracted from all included studies. The prescribed and consumed relative daily protein content of treatment groups was calculated when possible. Completers' data was used as the primary data source but intention to treat data when available was used in a secondary analysis. Discrepancies were resolved by consensus.

Critical appraisal

Studies were evaluated for risk of selection, performance, and detection bias on the basis of a Cochrane risk of bias assessment [10].

Statistical analysis

Statistical analysis was conducted by using Comprehensive Meta analysis V2.2.064 (Englewood, NJ 07631). Data are reported as standardised mean differences (SMD) and 95% CIs. For all group comparisons significance was set at $p < 0.05$. Treatment effects were pooled, and the SMD was calculated for all outcome variables in the higher protein and usual protein groups (see Supplementary Data for Methods). Random effects analysis was used for all variables as the studies varied widely in design and considerable heterogeneity was expected. Heterogeneity between studies was examined by chi-square tests for significance, and measured inconsistency (I^2) statistics with a measurement >50% taken to indicate substantial heterogeneity [9].

Secondary analysis of the data set examined the relationship between achieved protein difference and weight outcomes both by diet record at the end of the study (protein difference between diets <5% or >5%, based on the inclusion criteria of the study of Santesso et al. [4]) and whether the result was modified by duration of study, concurrent planned or achieved level of carbohydrate restriction (mild − an absolute reduction <10% of energy from contrasting diet, moderate − 10–20% or severe − >20% of energy), diabetes or PCOS status. For these secondary analysis a mixed effects analysis was used. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is not assumed to be the same for all subgroups - this value is computed within subgroups and not pooled across subgroups. Publication bias was assessed with funnel plots using the Egger test [11].

Results

Searches identified (Embase 609, Cochrane 369, Pubmed 4103) potential articles of which all but 57 were excluded simply on the basis of title and abstract (Supplementary data Fig. 1). Most clinical weight loss trials identified were eliminated at the abstract stage because of their short duration. After eliminating multiple reports of the same study, a total of 34 separate articles (for 32 studies, one was a limited 6 year follow up and the other was a limited 3 year follow up) contained intervention groups that met the inclusion criteria [3,12–40]. At least 50% of the study reported intention to treat results as well as completer results. Study characteristics are shown in Table 1 while weight, fat mass and lean mass results are shown in Table 2. Many of the studies had an active intervention period that was <6 months with weight maintenance or passive follow up for the remainder of the time.

Study quality

Very few studies reported on the blinding of investigators during the intervention or analysis stage nor on the method of diet allocation or concealment of the randomisation so it was not possible to use study quality as a modifier in the analysis as all studies were very similar in quality. Most studies had very large amounts of missing data with 30–40% dropouts at 12 months and used a wide variety of methods for intention to treat analysis so all had a high risk of bias and the results need to be treated with caution.

Weight

As many as 32 studies contributed data on weight in the completers analysis-1681 randomised to a planned high protein diet (or a diet in which a higher percentage protein intake would be expected) and 1811 to a normal or standard protein diet (control group). Overall there was a small but significant effect with a standardised mean difference of − 0.138 (95% CI −0.231, −0.046) $p = 0.003$, $Q = 48$, $p = 0.023$ $I^2 = 36$ (Fig. 1). Back converted to absolute amounts this is 0.39 kg; use of intention to treat data did not alter the result. Sensitivity analysis showed that removal of Soenen et al. [41] reduced the effect size to SMD of −0.093 but this was still significant ($p = 0.008$). However using the DIRECT study 6 year intention to treat data [39] rather than the 2 year data from Shai et al. [40] and assuming the numbers are allocated evenly across the groups (numbers in each group were not stated in the short report) reduced the effect size SMD −0.075 ($p = 0.032$). Using the 3 year data from Cardillo et al. [15] instead of the 12 month data from Stern et al. [42] had virtually no effect on the SMD −0.130 ($p = 0.006$). There was no statistical difference between studies using very low carbohydrate arms and those not using them ($p = 0.9$). Although the 2 year (and longer) studies had a lower standardised mean than the 1 year studies they were not statistically different from the 1 year studies ($p = 0.3$). Similarly a greater protein intake at the end of the study (<5% vs. 5% and more difference) was associated with a 4 fold greater effect but this interaction was not statistically significant ($p = 0.13$). There was no difference between diabetic and non-diabetic subjects ($p = 0.3$). Examination of funnel plots showed no evidence of publication bias (Supplementary data Fig. 2).

Table 1 Summary of studies and treatment groups included in the meta-analysis.

Study	Diet group	Completed *n*	Dropouts *n* (%)	Duration (wks)	Age (y)[c]	P (%)‡	C (%)‡	F (%)‡	Energy intake (kJ)
Brinkworth 2004a[a] [12]	HP	19	14 (42)	64	60.9 ± 10.3	30	40	30	12 wk 6700, ad libitum
	LF	19	14 (42)	64	62.7 ± 10.3	15	55	30	12 wk 6700, ad libitum
Brinkworth 2004b [13]	HP	21	7 (25)	68	52 ± 13.8	30	40	30	12 wk 6500, 4 wk 8300, ad libitum
	LF	22	8 (27)	68	51.5 ± 8.8	15	55	30	12 wk 6500, 4 wk 8300 ad libitum
Brinkworth 2009 [14]	HP	33	22 (40)	52	51.5 ± 7.7	35	4	61	6000–7000
	LF	36	16 (31)	52	51.4 ± 6.5	24	46	30	6000–7000
Cardillo 2006 [15]	LC	27[b]	37(58)	156	52	53 ± 9		30 g	Not restricted
		26[b]	42 (65)	156	52	54 ± 9		<30	Restricted by 2100
Clifton 2008 [16]	HP	41	17 (29)	64	49.9 ± 9.7	34	46	20	5600
	LF	38	23 (38)	64	49.9 ± 9.6	17	64	20	5600
Dansinger 2005 [17]	LC	19	21 (48)	52	47 ± 12		20–50 g		ad libitum
	Ornish	20	20 (50)	52	49 ± 12			10	ad libitum
	Zone	14	26 (65)	52	51 ± 9	30	30	40	ad libitum
	WW	14	26 (65)	52	49 ± 10				Points system
Das 2007 [18]	HP	15	2 (12)	52	34 ± 5	30	40	30	24 wk restriction, 26 wk ad libitum
	HG	16	1 (6)	52	35 ± 6	20	60	20	24 wk restriction, 26 wk ad libitum
Davis 2009[a] [19]	LC	47	8 (15)	52	54 ± 6		20–25 g		ad libitum
	LF	44	6 (12)	52	53 ± 7			25	ad libitum
Delbridge 2009 [20]	HP	41	29 (41)	52	43.7 ± 11.7	30	40	30	Energy for weight maintenance
	HC	40	30 (43)	52	44.0 ± 9.2	15	55	30	Energy for weight maintenance
Due 2004[a] [21]	HP	36	14 (28)	104	39.8 ± 11.4	25	45	30	Energy ad libitum
	MP	31	19 (38)	104	39.4 ± 12.0	12	65	30	Energy ad libitum
Dyson 2010 [22]	LC	11	2 (15)	52	52 ± 9		40 g		
	LF	11	2 (15)	52	52 ± 9			LF	Diabetes UK Recommendations
Foster 2003 [23]	LCHP	20	13 (39)	52	44.0 ± 9.4		20 g		Energy ad libitum
	LF	17	13 (43)	52	44.2 ± 7.0	15	60	25	5040–6300 (F) 6300–7560 (M)
Foster 2010 [24]	LC	89	64 (42)	104	46.2 ± 9.2		20 g		Energy ad libitum
	LF	105	49 (32)	104	44.9 ± 10.2	15	55	30	Energy restricted
Frisch 2010 [25]	HP	82	18 (18)	52	47 ± 10.8	25	40	35	Energy reduction of 1680
	HC	83	17 (17)	52	47 ± 10.4	15	55	30	Energy reduction of 1680
Gardner 2007 [26]	Zone	61	18 (23)	52	40 ± 6	30	40	30	Energy restriction
	LEARN	61	18 (23)	52	40 ± 7		55–60	10	Energy restriction
	LC	68	9 (12)	52	42 ± 5		20–50 g		Low carbohydrate intake emphasised
	Ornish	59	17 (22)	52	42 ± 6			10	Low fat intake emphasised
Griffin 2013 [27]	HP	21	15 (42)	52	22.4 ± 2.4	32	41	25	5600
	HC	15	20 (57)	52	22.5 ± 2.4	20	58	21	5600
Guldbrand 2012[a] [28]	HP	26	4 (13)	104	61.2 ± 9.5	30	20	50	6694 (F), 7531 (M)
	HC	28	3 (10)	104	62.7 ± 11	10–15	55–60	30	6694 (F), 7531 (M)
Iqbal 2010[a] [29]	LC	28	42 (60)	104	60.0 ± 8.9		30 g		Energy ad libitum
	LF	40	34 (46)	104	60.0 ± 9.5			<7% SF	Energy reduction of 2000
Jesudason 2013[a] [30]	HP	21	10 (32)	52	59.4 ± 12.2	30	40	30	6000,≤7000 (M)
	SP	24	7 (26)	52	62.4±9.5	20	50	30	6000,≤7000 (M)
Keogh 2007b [31]	HP	7	8 (27)	52	48 ± 8	40	33	27	6000
	HC	6	8 (57)	52	46 ± 8	20	60	20	6000
Keogh 2007a [32]	HP	19	16 (46)	52	48 ± 13	40	30	30	6000
	HMF	19	17 (47)	52	52 ± 8	20	30	50	6000

(*continued on next page*)

Table 1 (*continued*)

Study	Diet group	Completed *n*	Dropouts *n* (%)	Duration (wks)	Age (y)[c]	P (%)‡	C (%)‡	F (%)‡	Energy intake (kJ)
Klemsdal 2010 [33]	HP	78	22 (22)	52	50.1 ± 9.3	25–35	30–35	30–55	Energy reduction of 2100
	HC	86	16 (16)	52	49.9 ± 8.4	15	55–60	<30	Energy reduction of 2100
Krebs 2010[a] [34]	HP	144	63 (30)	104	57.7 ± 9.9	30	40	30	Energy reduction of 2000
	HC	150	62 (29)	104	58.0 ± 9.2	15	55	30	Energy reduction of 2000
Larsen 2011[a] [35]	HP	48	9 (16)	52	59.6 ± 15.2	30	40	30	12 wk 6400, 40 wk energy balance
	HC	45	6 (12)	52	58.8 ± 20.1	15	55	30	12 wk 6400, 40 wk energy balance
Layman 2009 [36]	HP	41	23 (36)	52	45.2 ± 9.6	30	40	30	4 months 7100 (F), 7940 (M), 8 months weight maintenance
	HC	30	36 (48)	52	46.0 ± 8.1	15	55	30	4 months 7100 kJ (F), 7940 kJ (M), 8 months weight maintenance
Lim 2010 [37]	VLC	17	13 (43)	64	48.3 ± 7.6	36	4	60	6500
	VLF	18	12 (40)	64	48.6 ± 11.3	20	74	10	6500
	HUF	15	15 (50)	64	47.2 ± 10.5	20	50	30	6500
	Control	19	4 (17)	64	43.1 ± 10.7				No diet
McAuley 2006 [38]	HP	28	2 (7)	52	47 ± 7.9	30	40	30	2 months energy restriction
	HC	24	7 (23)	52	45 ± 7.5	15	55	30	ad libitum
	LC	24	8 (25)				20–50 g		ad libitum
Sacks 2009 [3]	HPHF	168	33 (16)	104	51 ± 9	25	35	40	Energy reduction of 3000
	HPLF	157	45 (22)	104	50 ± 10	25	55	20	Energy reduction of 3000
	HFAP	151	53 (26)	104	52 ± 9	15	45	40	Energy reduction of 3000
	LFAP	169	35 (17)	104	51 ± 9	15	65	20	Energy reduction of 3000
Schwarzfuchs 2012 [39]	LF	259[b]	63 (20)	208	51 ± 7			30	6300 (F), 7560 (M)
	Med D			208	53 ± 6			35	6300 (F), 7560 (M)
	LC			208	52 ± 7		20–120 g		Energy ad libitum
Shai 2008 [40]	LF	94	10 (9)	104	51 ± 7			30	6300 (F), 7560 (M)
	Med D	93	16 (15)	104	53 ± 6			35	6300 (F), 7560 (M)
	LC	85	24 (22)	104	52 ± 7		20–120 g		Energy ad libitum
Soenen 2012 [41]	HPNC	33	2 (6)	52	50 ± 12	60	35	5	3 months 33% of requirements
						30	45	25	9 months 67% of requirements
	HPLC	33	2 (6)	52	50 ± 12	60	5	35	3 months 33% of requirements
						30	25	45	9 months 67% of requirements
	NPNC	33	1 (3)	64	50 ± 12	30	35	35	3 months 33% of requirements
						15	45	40	9 months 67% of requirements
	NPLC	33	2 (6)	64	50 ± 12	30	5	65	3 months 33% of requirements
						15	25	60	9 months 67% of requirements
Stern 2004 [42]	LC	44	20 (31)	52	53 ± 9		30 g		Not restricted
	LF	43	25 (37)	52	54 ± 9			<30	Intake restricted by 2100
Sukumar 2011 [43]	HPNC	26	3 (10)	52	58 ± 4	24	48	28	5920 (2000–2400 deficit)
	NPHC	21	9 (33)	52	58 ± 4	18	54	28	5500 (2000–2400 deficit)
Wycherley 2013 [44]	HP	33	25 (43)	52	51.3 ± 9.4	35	40	25	7000
	HC	35	27 (44)	52	50.2 ± 9.3	17	58	25	7000

‡ Values are % of total energy intake.

Abbreviations: Protein (P), Carbohydrate (C), Fat (F), High protein (HP), Low fat (LF), Low carbohydrate (LC), Low carbohydrate, high protein (LCHP), Weight Watchers™ (WW), High glycaemic load (HG), High carbohydrate (HC), Medium protein (MP), High monounsaturated fat (HMF), Female (F), Male (M), High protein, high fat (HPHF), High protein, low fat (HPLF), High fat adequate protein (HFAP), Low fat adequate protein (LFAP), Mediterranean diet (Med D), High-protein normal-carbohydrate (HPNC), high-protein low-carbohydrate (HPLC), normal-protein normal-carbohydrate (NPNC), normal-protein low-carbohydrate, (NPLC), High protein, normal carbohydrate (HPNC), Saturated fat (SF), Weight Watchers (WW).

[a] Participants have diabetes.

[b] Data on which groups subjects withdrew from not provided.

[c] Values are mean ± SD.

Table 2 Changes in weight, lean mass and fat mass from baseline for High Protein diets.

Reference	Diet	Weight (kg)			Lean mass (kg)			Fat mass (kg)		
		Baseline	Final	Change	Baseline	Final	Change	Baseline	Final	Change
Brinkworth	HP	96.2 ± 17.4	92.4 ± 18.3	−3.7 ± 1.0	53.8 ± 11.3	51.5 ± 11.8	−2.3[b]	39.2 ± 12.2	37.8 ± 11.8	−1.4[b]
2004a[a] [12]	LF	91.2 ± 18.7	89.1 ± 17.4	−2.2 ± 1.1	50.0 ± 12.2	48.1 ± 11.8	−1.9[b]	38.2 ± 10.5	38.1 ± 11.3	−0.1[b]
Brinkworth	HP	94.0 ± 3.4	90[b]	−4.1 ± 0.3%	49.8 ± 13.7	50.2 ± 13.3	0.6 ± 3.2%	41.8 ± 8.1	37.6 ± 6.9	−9.4 ± 11.0%
2004b [13]	LF	94.0 ± 3.2	90[b]	−2.9 ± 0.8%	49.9 ± 13.1	50.0 ± 13.1	0.2 ± 4.2%	40.6 ± 8.9	38.0 ± 9.8	−7.0 ± 7.0%
Brinkworth	HP	93.9 ± 15.5	79.4	−14.5 ± 9.8	53.7 ± 12.6	50.5 ± 12.6	−3.2 ± 2.3	40.0 ± 9.8	28.7 ± 9.8	−11.3 ± 8.6
2009 [14]	LF	94.5 ± 12.7	83.0	−11.5 ± 7.2	55.9 ± 11.5	53.6 ± 12.0	−2.3 ± 1.2	39.2 ± 9.0	29.8 ± 9.6	−9.4 ± 7.2
Cardillo	LC	130 ± 23	129[b]	−1 ± 16[b]						
2006 [15]	HC	132 ± 27	130[b]	−2 ± 8[b]						
Clifton	HP	85.9 ± 11.4	81.3[b]	−4.6 ± 5.5	–	–	−1.1[b]	–	–	−3.5 ± 3.8
2008 [16]	LF	85.6 ± 11.7	81.2[b]	−4.4 ± 6.1	–	–	−0.9[b]	–	–	−3.5 ± 3.8
Dansinger	Zone	99 ± 18	94.4[b]	−4.9 ± 6.9	–	–	–	–	–	–
2005 [17]	Ornish	103±15	98.0[b]	−6.6 ± 9.3	–	–	–	–	–	–
	Atkins	100 ± 14	95.3[b]	−3.9 ± 6.0	–	–	–	–	–	–
	WW	97 ± 14	92.8[b]	−4.6 ± 5.4	–	–	–	–	–	–
Davis	LC	93.6 ± 18	90.5[d]	3.1±4.8	–	–	–	–	–	–
2009[a] [18]	LF	101 ± 19	96.9[d]	3.1±5.8	–	–	–	–	–	–
Das	HP	78.0 ± 9.4		−7.8 ± 5.0%				35.2 ± 8.7%		−17.9 ± 12.5%
2007 [19]	HG	78.5 ± 12.3		−8.0 ± 4.1%				35.0 ± 7.1%		−14.8 ± 8.8%
Delbridge	HP	95.5[b]	99.8[b]	4.3 ± 8.8	–	–	+0.34 ± 3.7	–	–	+4.2 ± 14.1
2009 [20]	HC	92.9	95.1[b]	3.0±7.4	–	–	+0.89 ± 2.7	–	–	+3.2 ± 8.8
Due	HP	87.0 ± 10.2	80.8[b]	−6.2 ± 6.4	54.6 ± 11.2	53.7[b]	−0.9 ± 2.9	28.5 ± 7.3	23.9[b]	−4.6 ± 1.8
2004 [21]	MO	88.6 ± 12.7	84.3[b]	−4.3 ± 5.3	54.4 ± 10.7	54.0[b]	−0.4 ± 2.04	30.5 ± 7.4	27.4[b]	−3.1 ± 1.8
Dyson	LC	105	105	0	–	–	–	–	–	–
2010 [22]	LF	95	95	0	–	–	–	–	–	–
Frisch	HP	100.3 ± 15.9	94	−6±5			−1.5 ± 2.5			−4.2 ± 4.9
2010 [23]	HC	98.8 ± 16.9	94.6	−4.2 ± 5			−1.3 ± 3.6			−3.3 ± 4.4
Foster	LC	98.7 ± 19.5		−4.4 ± 6.7%	–	–	–	–	–	–
2003 [24]	LF	98.3 ± 16.4		−2.5 ± 6.3%	–	–	–	–	–	–
Foster [25]	LC	103.3 ± 15.5		−6.34 (−8.06 to −4.63)			−2.35 (−3.07 to −1.08)			−3.99 (−5.50 to −2.79)
	LF	103.5 ± 14.4		−7.37 (−9.1 to −5.63)			−2.14 (−2.68 to −1.59)			−3.84 (−5.03 to −2.64)
Gardner	Zone	84 ± 12	82.4[b]	−1.6 ± 5.4				40 ± 6%		−1.3 ± 3.4%
2007 [26]	LEARN	85 ± 14	82.8[b]	−2.2 ± 5.4				38 ± 6%		−1.0 ± 3.4%
	Atkins	86 ± 13	81.3[b]	−4.7 ± 7.2				41 ± 6%		−2.9 ± 4.8%
	Ornish	86 ± 10	83.4[b]	−2.6±5.3				40 ± 6%		−1.5 ± 4.0%
Griffin	HP	96.2 ± 9.6	86.6[b]	−9.6 ± 13.6						
2013 [27]	HC	96.5 ± 12.6	92.1[b]	−4.1 ± 6.9						
Guldbrand	HP	91.4 ± 19.0	89.4 ± 22.0	−2.3 ± 5.1	–	–	–	–	–	–
2012[a] [28]	HC	98.8 ± 21.0	95.9 ± 21.0	−3.0 ± 4.9	–	–	–	–	–	–
Iqbal	LC	118.3 ± 21.3	118.1[b]	−0.2	–	–	–	–	–	–
2010[a] [29]	LF	115.5 ± 16.7	114[b]	−1.5	–	–	–	–	–	–
Jesudason	HP	108.1 ± 22.9	98.3[b]	−9.7 ± 13.4		–	−1.7 ± 2.7	–	–	−6.2 ± 7.7
2013[a] [30]	SP	104.7 ± 18.6	98.1[b]	−6.6 ± 67.1		–	−1.8 ± 2.9	–	–	−4.9 ± 5.1
Keogh	HP	91.5 ± 14.8	86.9[b]	−4.6 ± 5.6	–	–	–	–	–	–
2007a [31]	HC	97.6 ± 8.3	92.1[b]	−5.5 ± 3.4	–	–	–	–	–	–

(*continued on next page*)

Table 2 (*continued*)

Reference	Diet	Weight (kg)			Lean mass (kg)			Fat mass (kg)		
		Baseline	Final	Change	Baseline	Final	Change	Baseline	Final	Change
Keogh	HP	91.9 ± 11	86.6 ± 12.5	−5.3[b]	50.4 ± 13.0[f]	48.6 ± 11.9	−1.7 ± 2.9	38.0 ± 7.0	34.2 ± 9.7	−3.9 ± 4.8
2007b [32]	HMF	98.8 ± 15	91.3 ± 16.6	−7.5[b]	51.4 ± 11.4[f]	48.8 ± 11.9	−2.5 ± 2.4	41.5 ± 10.0	34.6 ± 10.4	−6.9 ± 6.1
Klemsdal	HP	100.0 ± 16	96.1 ± 17	−3.9[b]						
2010 [33]	HC	99.9 ± 15	95.6 ± 16	−4.3[b]						
Krebs	HP	103.4 ± 19.7	99.5 ± 17.2	−3.9[b]	42 ± 8.1%	41.1 ± 7.9%	−1.7[b]	43.9 ± 13.9	40.9 ± 11.9	−3[b]
2010[a] [34]	Control	101.9 ± 20.1	95.9 ± 17.1	−6.0[b]	43.8 ± 7%	42.6 ± 7.4%	−1.2[b]	45.2 ± 14.3	41.4 ± 12.8	−3.8[b]
							−0.19 (−0.9,0.53)			−0.45 (−1.56,0.66)
Larsen	HP	94.6 ± 15.6	92.4[b]	−2.23	–	–	–	–	–	–
2011[a] [35]	HC	95.5 ± 14.2	93.3[b]	−2.17	–	–	–	–	–	–
Layman	HP	91.7 ± 14.7	81.3[b]	−10.4 ± 7.7	57.2 ± 12.8	54.6[b]	−2.6 ± 3.2	32.0 ± 8.0	24.7[b]	−7.3 ± 5.8
2009 [36]	HC	93.8 ± 13.0	85.4[b]	−8.4 ± 4.9	57.8 ± 11.4	55.1[b]	−2.7 ± 3.2	33.8 ± 7.3	28.5[b]	−5.3 ± 3.3
Lim	LC	87.6 ± 2.3	84.6[b]	−3.0 ± 0.2	–	–	–	–	–	–
2010 [37]	LF	89.4 ± 2.5	87.4[b]	−2.0 ± 0.1	–	–	–	–	–	–
	HUF	93.0 ± 2.8	89.3[b]	−3.7 ± 0.1	–	–	–	–	–	–
McAuley	HP	93.7 ± 14.3	87.1 ± 15.6	−6.6	51.2[b]	48.4[b]	−2.8[b]	42.5 ± 7.9	38.7 ± 8.9	−3.8[b]
2006 [38]	HC	97.6 ± 16.4	93.2 ± 15.1	−4.4	51.7[b]	50.8[b]	−3.5[b]	45.9 ± 11	42.4 ± 10.3	−3.5[b]
	LC	97.2 ± 10.4	91.8 ± 11.3	−5.4	52.4[b]	50.4[b]		44.8 ± 6.8	41.4 ± 7.3	−3.4[b]
Sacks	HP	93.0	–	−4.5	–	–	–	–	–	–
2009 [3]	LP	93.0	–	−3.5	–	–	–	–	–	–
Schwarzfuchs	LF	91.3 ± 12.3		−0.6	–	–	–	–	–	–
et al. [39]	Med D	91.1 ± 13.6		−3.1	–	–	–	–	–	–
	LC	91.8 ± 14.3		−1.7	–	–	–	–	–	–
Shai	LF	91.3 ± 12.3		−2.9 ± 4.2	–	–	–	–	–	–
2008 [40]	Med D	91.1 ± 13.6		−4.4 ± 6.0	–	–	–	–	–	–
	LC	91.8 ± 14.3		−4.7 ± 6.5	–	–	–	–	–	–
Soenen	HP	107.1	95.3	−12.8 ± 4.0	60.3	57.6	−2.7	46.8	38.9	−9.1 ± 0.8
et al. [41]	LP	106.3	97.3	−8.9 ± 3.0	58.1	56.8	−1.3	48.2	40.6	−7.7 ± 0.6
Stern	LC	130 ± 23	124.9[b]	−5.1 ± 8.7	–	–	–	–	–	–
et al. [42]	HC	132 ± 27	128.9[b]	−3.1 ± 8.4	–	–	–	–	–	–
Sukumar	HP	88.5 ± 15.1	82.8 ± 15.4	−6.6 ± 4.0	–	–	–	–	–	–
et al. [43]	NP	82.7 ± 12.2	76.6 ± 11.7	−7.4 ± 5.2	–	–	–	–	–	–
Wycherley	HP	106.0 ± 12.9	93.7 ± 10.7	−12.3 ± 8.0	68.3 ± 7.1	65.6 ± 5.9	−2.6 ± 3.7	36.2 ± 7.4	26.2 ± 8.3	−9.9 ± 6.0
2012 [44]	HC	101.6 ± 14.	90.7 ± 12.4	−10.9 ± 8.6	68.2 ± 9.9	64.3 ± 7.8	−3.8 ± 4.7	33.6 ± 7.6	26.3 ± 7.9	−7.3 ± 5.8

Data are Mean ± SD.
[a] Participants have diabetes.
[b] Derived.

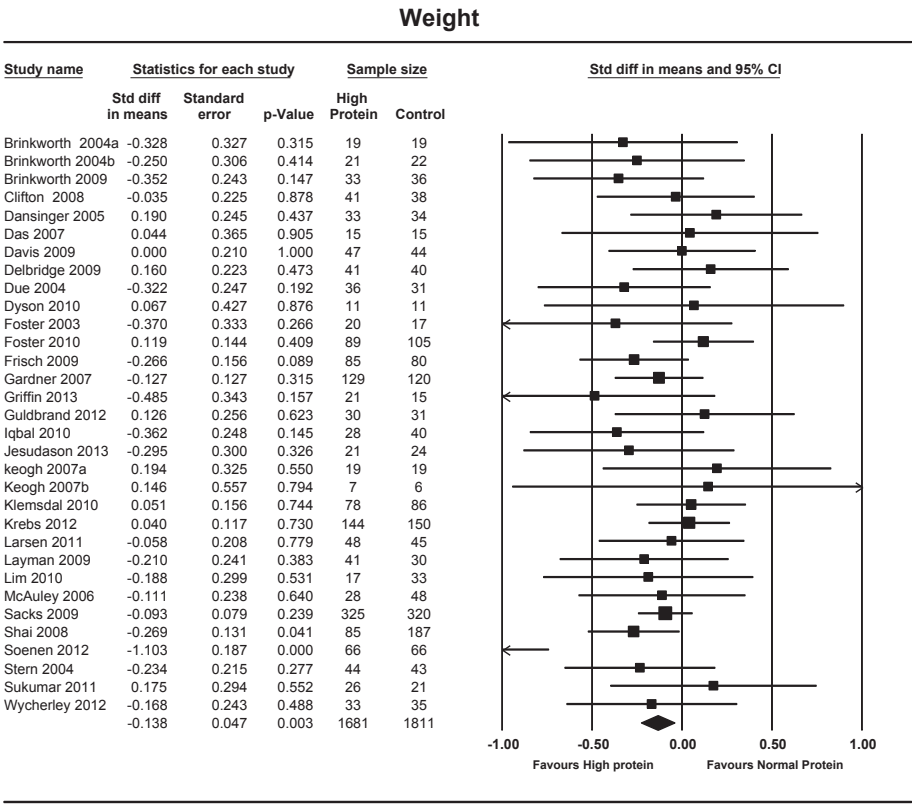

Figure 1 Random effects meta analysis of weight from 32 separate studies. Data shown are standardised means and 95% confidence intervals.

Fat mass

Eighteen studies contributed data to this section (Table 2 and Fig. 2). There was a small effect of low carbohydrate, high protein diets compared with contrasting diets on fat mass SMD −0.22 (95% CI −0.32, −0.12), $p = 0.000$ $I^2 = 0$. This is equivalent to about 0.44 kg using a back conversion from SMD. Those studies that had an initial low carbohydrate diet-energy controlled or ad libitum ($n = 4$) were not significantly different from the other 12 studies ($p = 0.5$). If reported protein intake at the end of the study was divided into two groups (<5% or 5% or greater

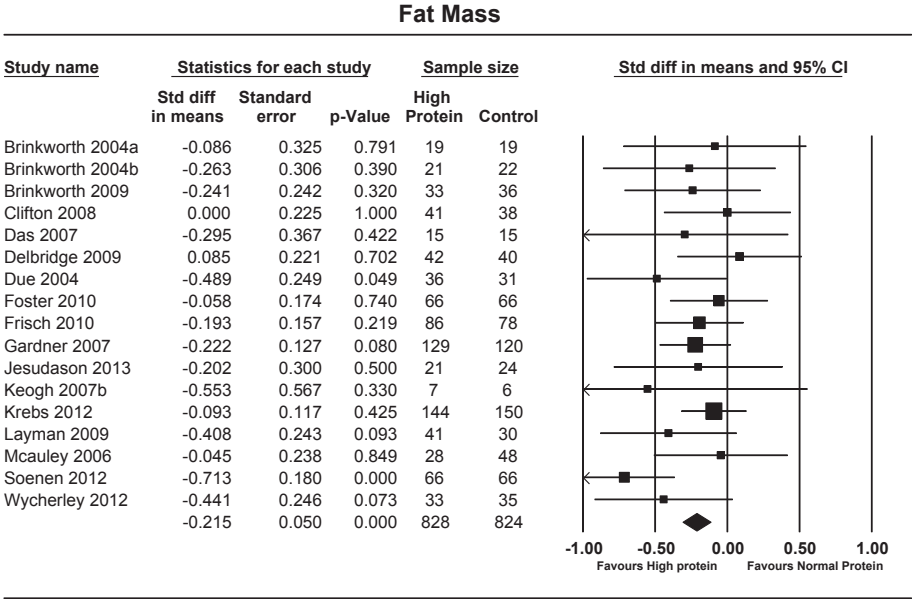

Figure 2 Random effects meta analysis of fat mass from 18 separate studies. Data shown are standardised means and 95% confidence intervals.

difference between the two diet groups) a higher protein intake was associated with a 3 fold greater reduction in fat mass (0.9 kg vs. 0.3 kg $p = 0.017$ for interaction but both groups were separately significant). This was true whether the difference was assessed by diet records or objective urine measures. There was no effect of either planned or recorded carbohydrate intake or planned protein intake on changes in fat mass. The 4 studies that included people with type 2 diabetes were not statistically different from the other 14 studies ($p = 0.51$). Sensitivity analysis showed no one study dominated the results and removal of which made the whole analysis negative. Examination of funnel plots showed no evidence of publication bias using the Egger test (Supplementary data Fig. 3).

Lean mass

Eighteen studies contributed data to this section. There was no significant effect of higher protein diets on lean mass: SMD −0.007 (95% CI −0.087, 0.102) $p = 0.94$, $I^2 = 0$ (Supplementary data Fig. 5).

Lipids

Twenty-nine studies had data on lipid values. For total cholesterol there was no significant effect of diet allocation: SMD −0.045 (95% CI −0.181, 0.090), $p = 0.51$, $I^2 = 63$ (Supplementary data Fig. 6).

Fasting triglyceride was influenced by diet (Fig. 3). There was a small effect of a high protein diet: SMD −0.19 (95% CI −0.30, −0.07), $p = 0.001$. $Q = 73$, $p = 0.000$, $I^2 = 60$. This represents a difference of 0.60 mmol/L. There was no significant effect of planned or achieved protein intake whether assessed by dietary records or by urinary urea or whether there was an initial ad libitum rather than controlled energy phase. There was also no significant effect of planned or achieved carbohydrate intake. Sensitivity analysis showed no one study dominated the results which remained significant after removal of individual studies. Testing of funnel plots showed no evidence of publication bias (Supplementary data Fig. 4).

There was no significant effect of diet on HDL cholesterol: SMD 0.21 (95% CI −0.016, 0.44) $p = 0.07$, $Q = 228$p $= 0.000$, $I^2 = 89$ or LDL cholesterol: SMD −0.007 (95% CI −0.11 0.09), $p = 0.89$, $I^2 = 34$ (Supplementary data Figs. 7 and 8). Very low carbohydrate diets were no different from moderate carbohydrate diets ($p = 0.11$ for interaction for HDL) although the effect size was 4 times greater.

Blood pressure

Nineteen studies contributed data and there was no significant effect on either systolic SMD 0.022 (95% CI −0.13, 0.09), $p = 0.69$; $I^2 = 33$ or diastolic blood pressure – SMD 0.11 (95% CI −0.23, 0.01), $p = 0.08$, $I^2 = 52$ (Supplementary data Figs. 9 and 10).

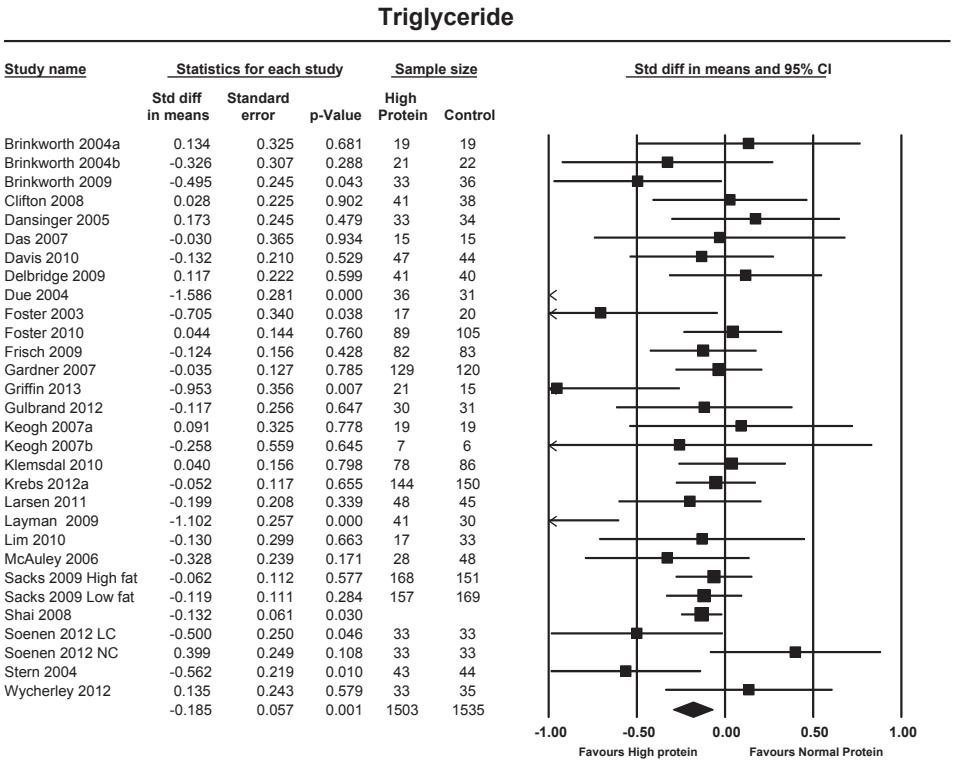

Figure 3 Random effects meta analysis of fasting triglyceride from 29 separate studies. Data shown are standardised means and 95% confidence intervals.

Glucose and insulin and HbA1c

Values were provided for these variables in 22 studies. There was no significant effect of diet on glucose: SMD −0.005 (95%CI −0.114, 0.124), $p = 0.93$. $I^2 = 61$ (Supplementary data Fig. 11). No difference was seen in studies with or without people with type 2 diabetes ($n = 3$). For insulin there was a significant effect of diet: SMD −0.21 (95% CI −0.41, −0.009) $p = 0.04$, $Q = 98$, $p < 0.001$, $I^2 = 78$ (Supplementary data Fig. 12). There was no statistical difference between the diabetics and non diabetics. Eight studies provided data on HbA1c. No significant effect of diet was seen: SMD −0.12 (95% CI −0.27, 0.04), $p = 0.15$, $I^2 = 36$ (Supplementary data Fig. 13).

C reactive protein (CRP)

Seven studies provided data and no significant effect of diet was seen on CRP: −0.22 (95%CI −0.87, 0.43), $p = 0.50$, $I^2 = 94$ (Supplementary Data Fig. 14).

(95%CI −0.87, 0.43), $p = 0.50$, $I^2 = 94$ (Supplementary Data Fig. 14).

Discussion

We have shown in this analysis that a recommendation to lower carbohydrate intake and to maintain or increase the amount of protein in a weight loss diet (or this increase in protein would be expected based on the reduction in carbohydrate) leads to a small long term effect on weight and fat mass compared to advice to reduce protein. This is unexpected given that many studies had active intervention periods of <6 months and the remainder of the time was weight maintenance strategies or passive follow up. Many volunteers revert to their usual diet once the main intervention has finished. Surprisingly there was no effect on lean mass which is in contrast to the meta regression of Krieger et al. [45] which examined mostly short term studies and only contained one 12 month study as well as the meta analysis of short term studies from Wycherley et al. [7]. This suggest that the apparent preservation of lean mass during short term intense weight loss is lost during weight regain in the follow up period where the normal protein group regains the lost lean mass, especially when the protein intake tends to rise in the normal protein group toward the value of the high protein group. As expected replacement of carbohydrate with protein (or protein and fat together) lowered fasting triglyceride but HDL cholesterol was not significantly increased. There was no effect on total cholesterol, LDL cholesterol or glucose but insulin was lowered. These results are in apparent contrast to a recent meta analysis from Schwingshackl and Hoffmann [8] who examined 15 twelve month studies contrasting a planned high protein (>25% protein) with a normal protein (<20% protein) with both arms being low fat (<30%). They found no significant effect of a high protein diet on weight, fat mass or waist circumference nor on any lipid parameters. Only insulin was lowered more in the high protein arms. Apart from more studies in our meta analysis some of which had low carbohydrate arms, we also used the low carbohydrate arms in the studies in their meta analysis which they omitted. However in examining mediators of the response exclusion of those which had a very low carbohydrate arm had no effect on the fat mass results and there was no statistical heterogeneity between study types for either weight or fat mass and the effect size was similar with both study designs. Thus our results are very similar to those of Schwingshackl and Hoffman [8] in terms of effect size and are statistically significant by virtue of the greater number of studies and participants. Although very low carbohydrate interventions produce greater weight loss at 6 months in virtually all studies except one this advantage has mostly disappeared by 12 months so inclusion of these studies did not influence our results. Bueno et al. [46] in a meta analysis of 13 very low carbohydrate weight loss diets found very similar effects in terms of weight and triglyceride levels as in our larger study. We did not see an effect on HDL cholesterol or LDL cholesterol nor was there a statistical difference in our study between the two different study designs. In many of the studies although an increase in percentage protein would be expected because of the advice in the Atkins diet book to limit only carbohydrate, there was a very small 0.5–1% difference between groups in percentage protein and absolute protein intake was sometimes reduced in the low carbohydrate groups. In a limited review of 8 studies longer than 6 months Lepe et al. [47] found no overall effect of high protein diets.

Many of these studies test the degree to which adherence to a lower carbohydrate, higher protein dietary pattern persists in the presence of minimal or no reinforcement of the diet after a well controlled 3–6 month weight loss intervention. Those studies in which closer dietary supervision was maintained for the whole 12 months achieved a greater than 5% difference in protein percentage energy between the groups at the end of the study and had greater differences in fat mass. Diet records taken just at the 12 month time point are not necessarily representative of the preceding 12 month and almost certainly under report the true difference in protein over this period but in some studies these are the only records reported. Similarly absolute amount of protein may be more important than percentage of energy as protein but not all studies report both. Nevertheless compliance to a protein prescription may be a marker of compliance to an energy prescription and the fat mass differences may be related to the latter rather than the former. The effect sizes in the previous meta analysis by Santesso et al. [4] which included short and long term studies are about twice those in this study reflecting the waning compliance with time.

Although total, LDL and HDL cholesterol were not different between the high and normal protein groups, as expected triglyceride was lower in the lower carbohydrate, higher protein groups although the effect was small and had disappeared when the follow up was longer than 12 months. This result again contrasts with those of the earlier meta analysis [8] where no lipid changes were seen but is similar to our meta analysis of short term energy

controlled high protein diets [7] where carbohydrate reduction was the main contributor to the triglyceride reduction as well as to the Santesso meta analysis [4].

We saw no effect on blood pressure, glucose or Hba1c which is similar to previous results. The effect on fasting insulin was small and is probably related to the small differences in fat mass between the two diets rather than being attributable to macronutrient differences especially when studies such as Brinkworth et al. [14] see absolutely no differences in fasting insulin despite very big differences in carbohydrate and protein intake.

In conclusion a recommendation to lower carbohydrate and increase protein still has persistent effects on weight and fat mass and fasting triglyceride after 12 months but the effect is small. Those studies where a difference of 5% energy from protein was still maintained at the end of the study had a 3 times greater effect on fat mass which was nearly 1 kg better than the normal protein diet. Strategies to maintain this protein difference are required as compliance to all the dietary regimes was poor. Sources of protein should include a mix of lean red meat, chicken, fish, dairy and vegetable protein. Processed meat should not be used. The strategies used by the Diogenes study [6] were effective over 6 months and did not require a greater than 5% absolute difference in protein.

Limitations of this analysis include the high dropout rate in all the studies limiting the assessment of the true effect of the interventions but there is no reporting bias evident even though most individual studies were negative. Epidemiological data suggest that low carbohydrate, high protein diets are associated with increased mortality [48] but most of the strength of this association is due to the low carbohydrate aspect of the diets. It is known that low carbohydrate diets can be low in fibre and fruit and vegetables but is possible to advise a healthy diet that is slightly higher in protein with higher quality carbohydrate sources, abundant in fibre and fruit and vegetables.

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PMC devised the study and analysed the data and drafted the manuscript while DC and JBK performed the data extraction and contributed to the manuscript. PMC is the Co author of several diet books that encourage a high protein diet while DC and JBK have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2013.11.006.

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