

76° CONGRESSO NAZIONALE

**PROSSIMITÀ E ORGANIZZAZIONE DELLE CURE:
LA MEDICINA GENERALE DI DOMANI TRA DEMOGRAFIA E CRONICITÀ**

FI&MG
M

Metis

**PERCORSI SIMP e SV PER UN
AMBULATORIO DEGLI STILI DI VITA**

**Dieta chetogenica e sue
applicazioni cliniche**
I dati della letteratura

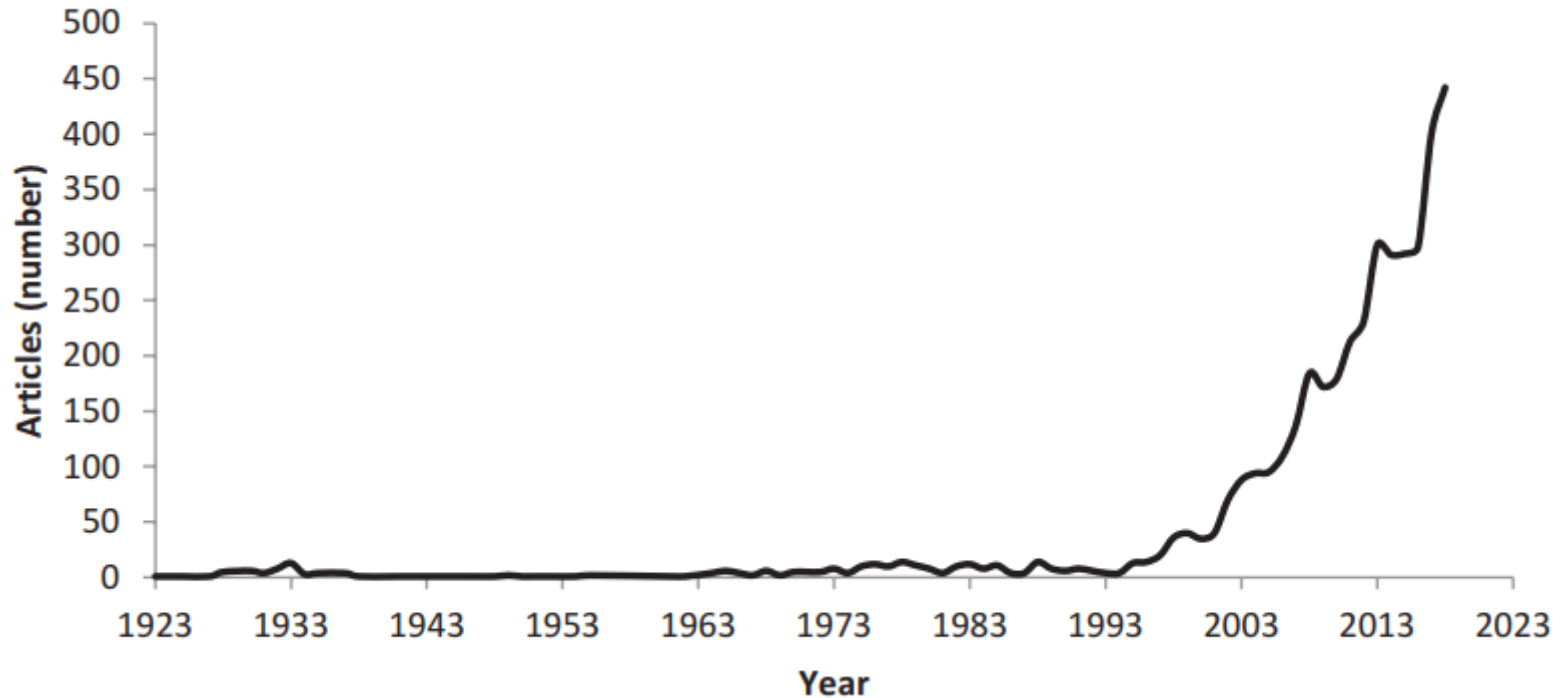
Franca Marangoni
Nutrition Foundation of Italy,
Milano

7- 12 OTTOBRE 2019 - Tanka Village - Villasimius (CA)

**SIMP
e SV**

Società Italiana di Medicina
di Prevenzione e degli Stili di Vita

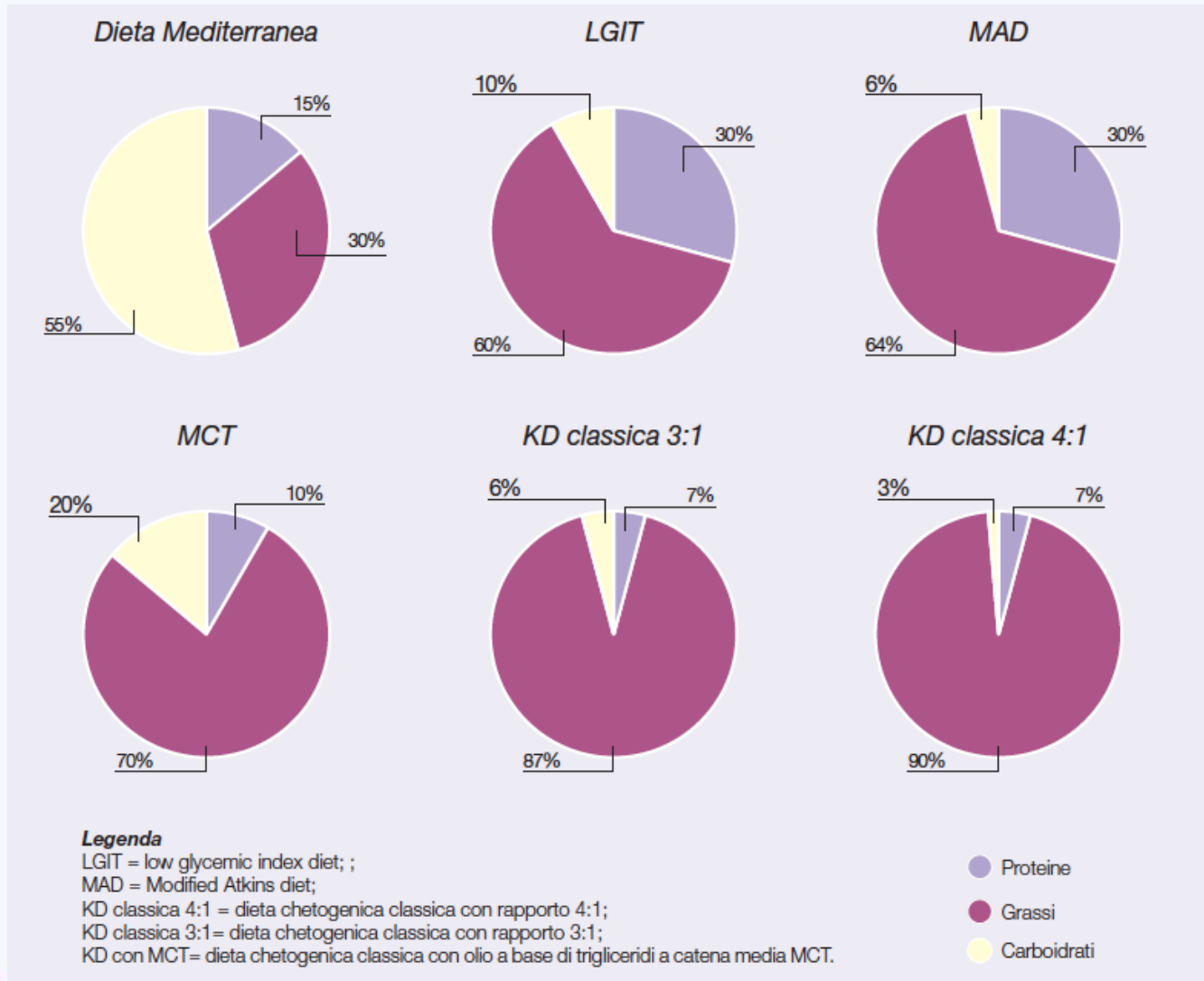
Number of articles published on the ketogenic diet over 1923–2018 (Scopus)



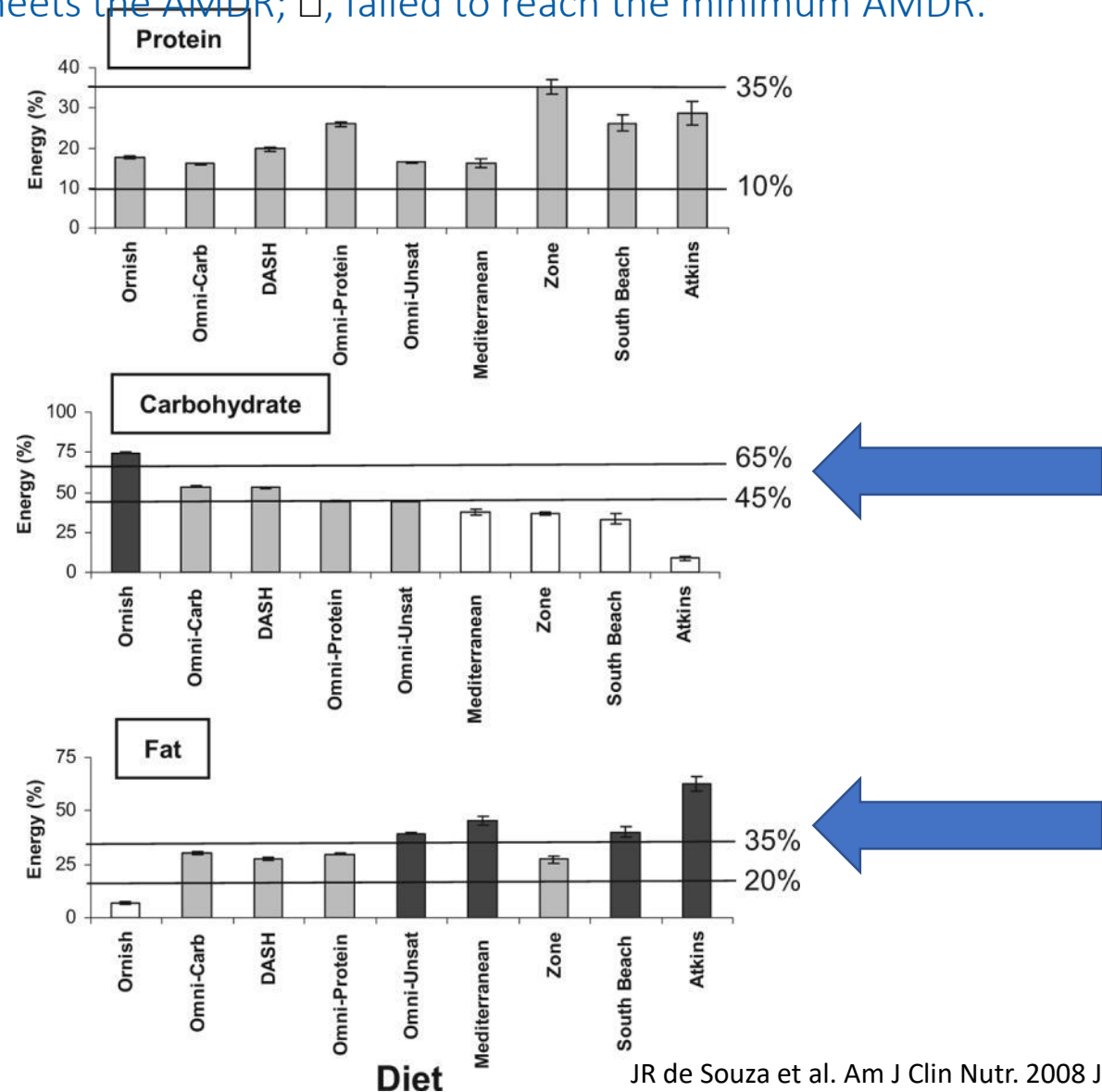
Kraeuter et al. *Advances in Experimental Medicine and Biology* 1178, 2019

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Contenuto di macronutrienti nei diversi protocolli dietetici



Comparison of the calculated macronutrient profiles (mean \pm SEM) of various diet plans with the Institute of Medicine's Acceptable Macronutrient Distribution Ranges (AMDR). Solid horizontal lines represent the upper and lower limits of the AMDR for the macronutrient. ■, exceeds the AMDR; ■, meets the AMDR; □, failed to reach the minimum AMDR.



AHA Protein Criteria	Atkins ²⁹	Zone ³⁰	Protein Power ³¹	Sugar Busters ³²	Stillman ²⁸
Total protein is not excessive (average 50–100 g/d, proportional 15–20% kcal/day to carbohydrates and fat)	No.	No.	No.	No.	No.
	1st 2 weeks = 125 g/d (36%)	127 g/d (34%)	91 g/d (26%)	71 g/d (27%)	162 g/d (64%)
	Ongoing weight loss = 161 g/d (35%)				
	Maintenance = 110 g/d (24%)				
Carbohydrates are not omitted or severely restricted. Minimum of 100 g/d	No.	Yes.	No.	Yes.	No.
	1st 2 weeks = 28 g/d (5%)	135 g/d (36%)	56 g/d (16%)	114 g/d (52%)	7 g/d (3%)
	Ongoing weight loss = 33 g/d				
	Maintenance = Yes 128 g/d				
Total fat (30%) and saturated fat (10%) are not excessive	No.	Yes.	No.	Yes.	No.
	1st 2 weeks = 53% fat, 26% saturated fat per day	29% total calories, 4% saturated fat per day	54% total fat, 18% saturated fat per day	21% total calories, 4% saturated fat per day	33% total calories, 13% saturated fat per day
Total diet can be safely implemented over the long term by providing nutrient adequacy and support a healthful eating plan to prevent increases in disease risk	No.	No.	No.	No.	No.
	Limited food choices. Diet low in fiber, vitamin D, thiamine, pantothenic acid, copper, magnesium, manganese, potassium, calcium. High in total fat and saturated fat	Food must be eaten in required proportions of protein, fat, carbohydrates. Menus not appealing, vegetable portions very large. Low in copper	Not practical for long term. Rigid rules. Diet low in calcium, fiber, pantothenic acid, copper, manganese. High in total fat and saturated	Eliminates many carbohydrate foods. Discourages eating fruit with meals. Low in calcium, vitamin D, vitamin E, pantothenic acid, copper, potassium	Eliminates many foods. Diet low in fiber, vitamin A, thiamine, vitamin C, vitamin D, folate, pantothenic acid, calcium, copper, magnesium,

Available evidence of diseases through-out life

Disorder	Preclinical	Case study	Uncontrolled trial	Randomised, controlled trial
<i>Childhood</i>				
Epilepsy	✓	✓	✓	✓
ADHD	✓	✓	✓	
ASD	✓	✓	✓	
<i>Adolescence/Early adulthood</i>				
Schizophrenia	✓	✓		
<i>Adult</i>				
Obesity/Type-2 diabetes	✓	✓	✓	
<i>Elderly</i>				
Alzheimer's	✓	✓	✓	
Parkinson's	✓	✓	✓	

ADHD attention-deficit hyperactivity disorder, ASD autism spectrum disorder, ✓published evidence available

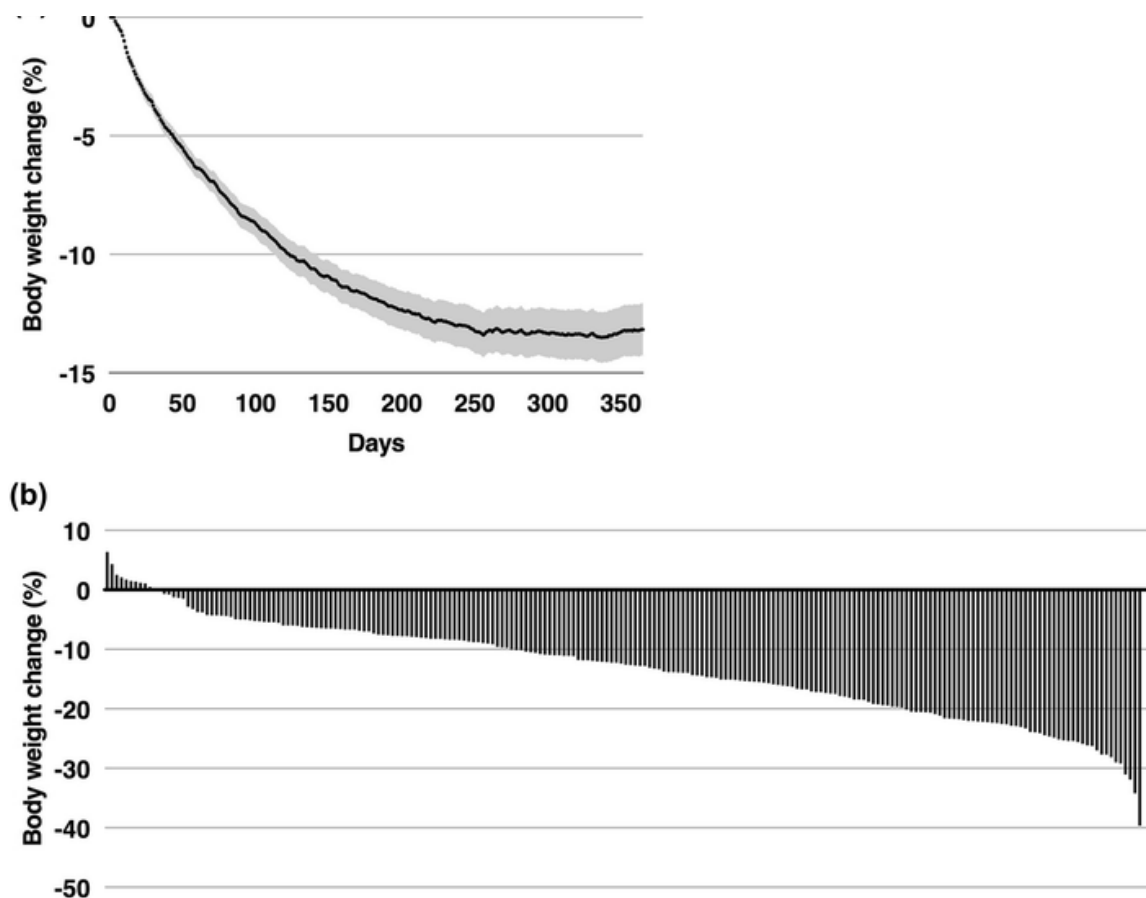
Kraeuter et al. Advances in Experimental Medicine and Biology 1178, 2019

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ORIGINAL RESEARCH

Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study

Sarah J. Hallberg · Amy L. McKenzie · Paul T. Williams ·
Nasir H. Bhanpuri · Anne L. Peters · Wayne W. Campbell · Tamara L. Hazbun ·
Brittanie M. Volk · James P. McCarter · Stephen D. Phinney ·
Jeff S. Volek



Systematic Review with Meta-analysis

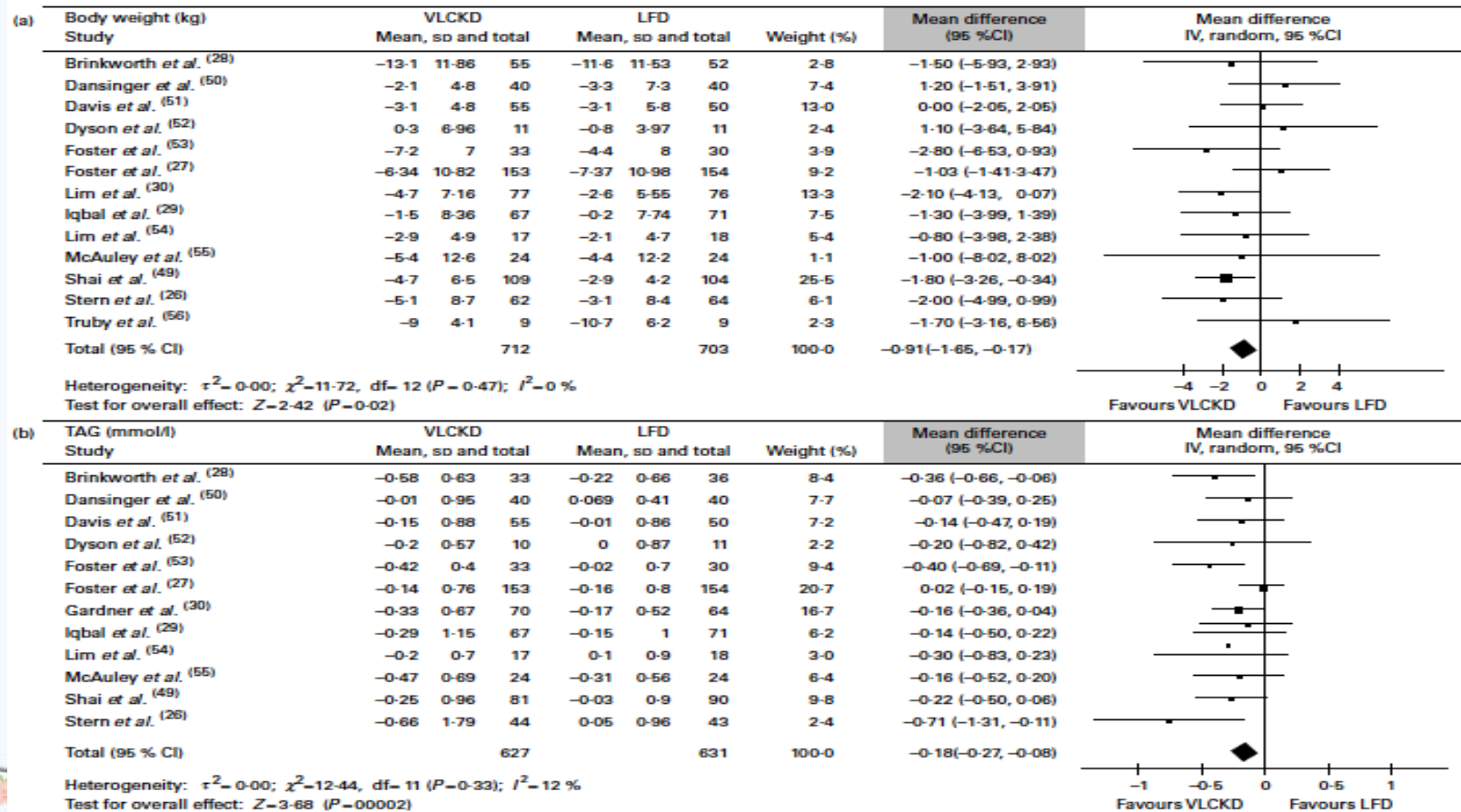
Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials

Nassib Bezerra Bueno*, Ingrid Sofia Vieira de Melo, Suzana Lima de Oliveira and Terezinha da Rocha Ataide

- BMI greater than 27.5 kg/m²
- LFD (i.e. a restricted-energy diet with less than 30% of energy from fat) or VLCKD (i.e. a diet with no more than 50 g carbohydrates/d or 10% of daily energy from carbohydrates);
- follow-up period 12 months or more
- a total of thirteen studies met the inclusion/exclusion criteria

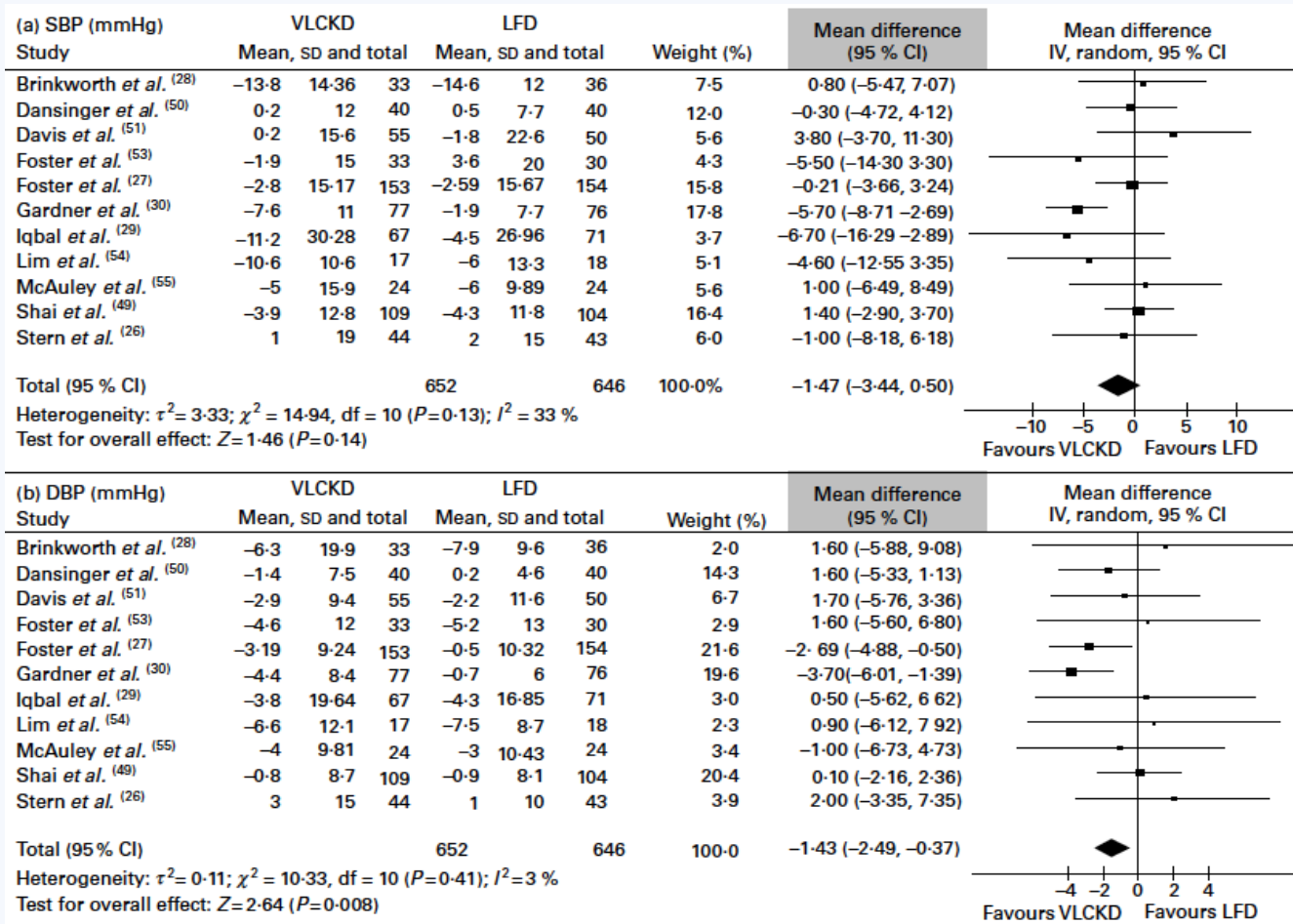


Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials



British Journal of Nutrition (2013), 110, 1178–1187

Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials



British Journal of Nutrition (2013), 110, 1178–1187

Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials

- ..., these findings must be carefully interpreted regarding its clinical significance. For example, a typical 1.70 m-tall adult with a BMI of 30 kg/m² weighs 87 kg; hence, a weight loss of 0.91 kg, as observed here, would represent only 1.04% of the initial body weight.
- However, large randomised clinical trials with long-term dietary interventions aiming weight loss showed that individuals under intensive lifestyle interventions lose about 4.8 kg... Hence, the further reduction of 0.9 kg in the individuals assigned to a VLCKD would represent almost 20% of the awaited weight loss achieved with long-term dietary interventions.
- ...
- The extra reduction of 1.43mmHg in DBP achieved by individuals assigned to a VLCKD is similar to the reductions promoted by other dietary interventions, such as Mg supplementation or consumption of flavonol-rich products.

British Journal of Nutrition (2013), 110, 1178–1187



Behavior/Etiology

**Do ketogenic diets really suppress appetite?
A systematic review and meta-analysis**

A. A. Gibson¹, R. V. Seimon¹, C. M. Y. Lee¹, J. Ayre^{1,2}, J. Franklin³, T. P. Markovic^{1,3}, I. D. Caterson^{1,3}
and A. Sainsbury¹

Study

WMD (95% CI)

This systematic review and meta-analysis provides evidence that VLEDs significantly reduce appetite during weight loss. KLCD also show promise, but only a limited number of studies have addressed this question within the scope of our review. The findings of this study have important implications for the communication of information by clinicians to patients. Based on this meta-analysis, clinicians can advise patients that although they may indeed feel slightly less hungry (or more full or satisfied) while on VLED, the true benefit of VLED is in preventing an increase in appetite, and that this can help them to comply with a severe restriction of energy intake in order to achieve substantial weight losses, rather than the absence of hunger altogether.

The hypothesized mechanisms of KD's weight loss effect

- Reduction in appetite due to higher satiety effect of proteins, effects on appetite control hormones and to a possible direct appetite suppressant action of the ketone bodies;
- Reduction in lipogenesis and increased lipolysis;
- Greater metabolic efficiency in consuming fats highlighted by the reduction in the resting respiratory quotient;
- Increased metabolic costs of gluconeogenesis and the thermic effect of proteins

Paoli, *Int. J. Environ. Res. Public Health* 2014, 11, 2092-2107;



Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes

Ole Snorgaard,¹ Grith M Poulsen,² Henning K Andersen,³ Arne Astrup²

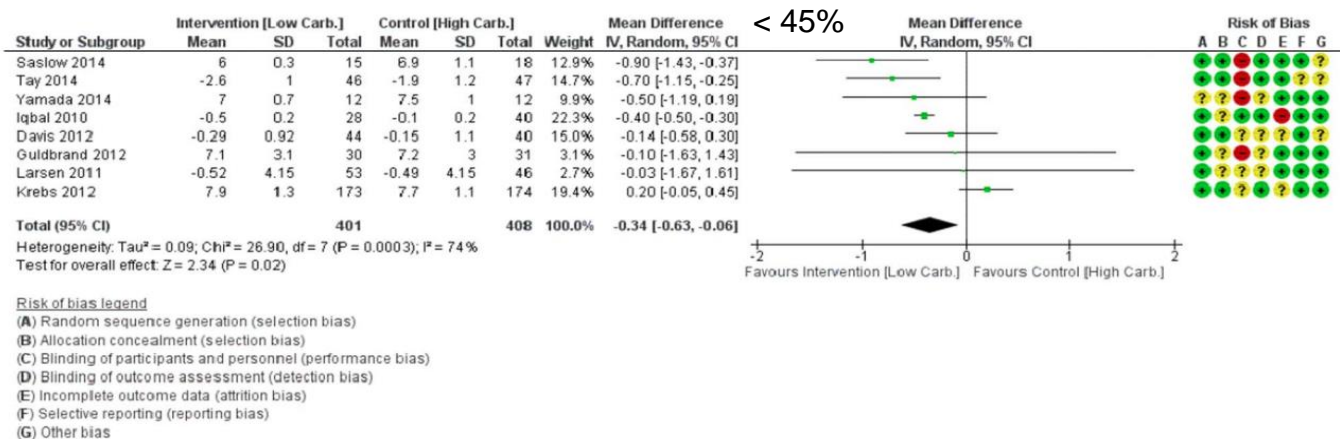


Figure 2 Forest plot of change in HbA1c (%-point) after 3 or 6 months of low to moderate carbohydrate diet compared with high-carbohydrate diet in type 2 diabetes.

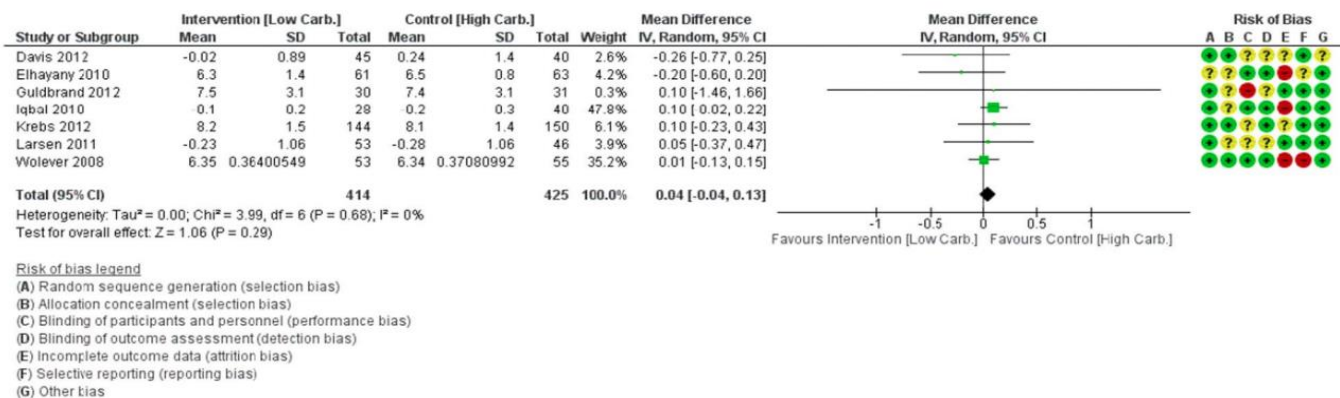


Figure 3 Forest plot of change in HbA1c (%-point) after 12 months of low to moderate carbohydrate diet compared with high-carbohydrate diet in type 2 diabetes.



Key messages

- The ideal amount of carbohydrates in the diet in the management of type 2 diabetes is unclear.
- The current meta-analysis conducted according to the GRADE system of rating quality of evidence shows that low to moderate carbohydrate diets have greater glucose-lowering effect compared with high-carbohydrate diets.
- The greater the carbohydrate restriction, the greater glucose lowering.
- Apart from improvements in HbA1c over the short term, there is no superiority of low-carbohydrate diets in terms of glycemic control, weight, or LDL cholesterol.

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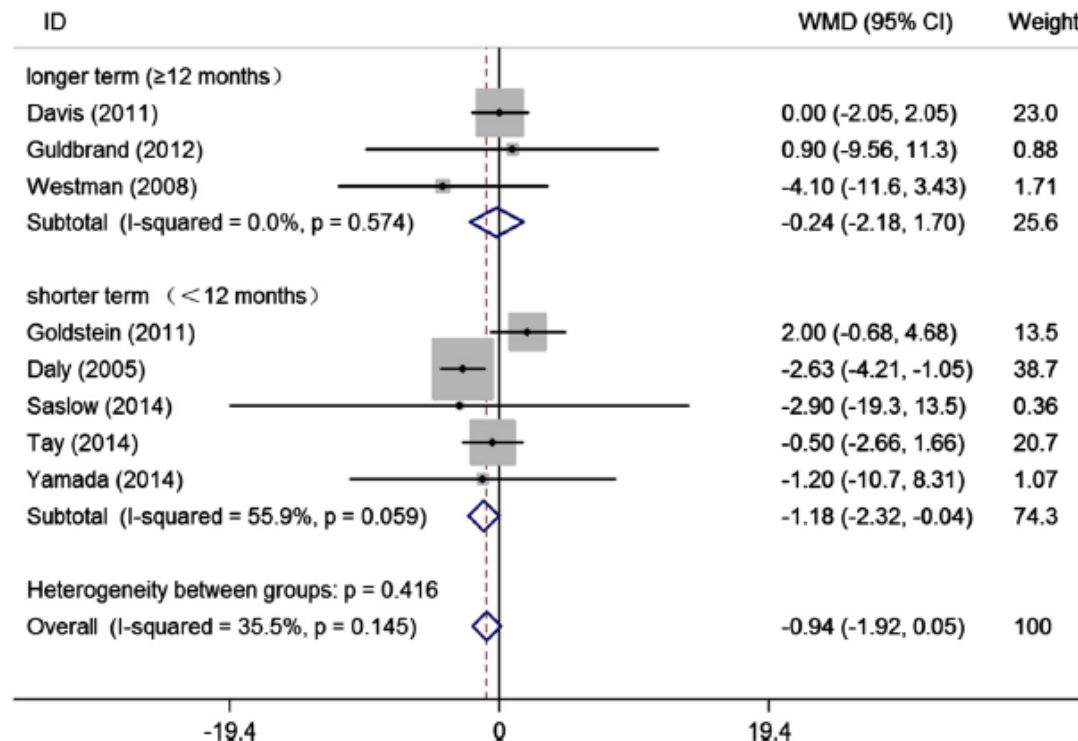
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Review

Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials



Subgroup analyses of the effect of low carbohydrate diet (<26% E) on weight loss in different study duration



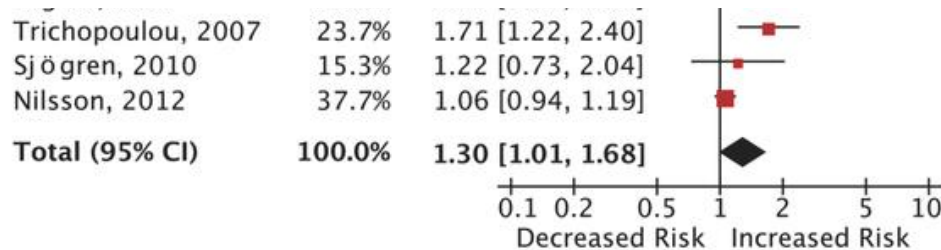
Adjusted risk ratios for all-cause mortality associated with low-carbohydrate diets.

(A) Low-carbohydrate score

Study	Weight	Risk Ratio IV, Random, 95% CI
Lagiou, 2007	11.4%	1.69 [1.01, 2.81]
Trichopoulou, 2007	12.5%	1.75 [1.08, 2.82]
Fung, 2010	45.2%	1.12 [1.01, 1.24]
Nilsson, 2012	31.0%	1.32 [1.06, 1.65]

Conclusion

Low-carbohydrate diets were associated with a significantly higher risk of all-cause mortality and they were not significantly associated with a risk of CVD mortality and incidence. However, this analysis is based on limited observational studies and large-scale trials on the complex interactions between low-carbohydrate diets and long-term outcomes are needed.

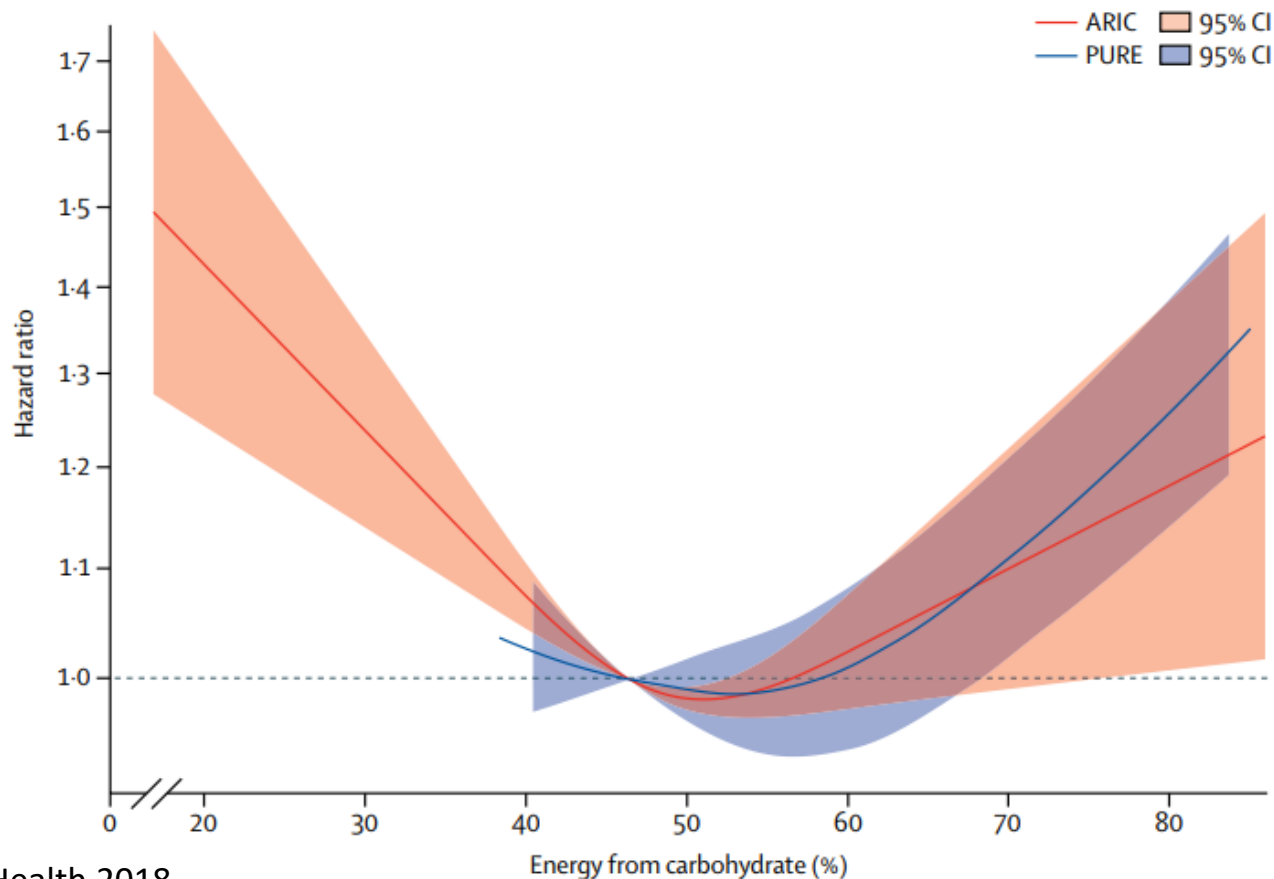


Heterogeneity: $\text{Tau}^2 = 0.04$; $\text{Chi}^2 = 8.55$, $\text{df} = 3$ ($P = 0.04$); $I^2 = 65\%$
 Test for overall effect: $Z = 2.01$ ($P = 0.04$)

Noto H, Goto A, Tsujimoto T, Noda M (2013) Low-Carbohydrate Diets and All-Cause Mortality: A Systematic Review and Meta-Analysis of Observational Studies. PLOS ONE 8(1): e55030. <https://doi.org/10.1371/journal.pone.0055030>
<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0055030>

Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis

Sara B Seidelmann, Brian Claggett, Susan Cheng, Mir Henglin, Amil Shah, Lyn M Steffen, Aaron R Folsom, Eric B Rimm, Walter C Willett, Scott D Solomon



Lancet Public Health 2018

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VIEWPOINT

The Ketogenic Diet for Obesity and Diabetes— Enthusiasm Outpaces Evidence

JAMA Internal Medicine September 2019 Volume 179, Number 9

Although the ketogenic diet has garnered much attention for the dietary treatment of chronic diseases such as **obesity and type 2 diabetes**, the **evidence supporting its use is currently limited and the diet's potential risks are real**. Physicians and patients should continue to judiciously appraise the benefits and risks of the ketogenic diet in accordance with the evidence, not the hype.



Ketogenic diets compared to control for people with epilepsy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Ketogenic diets				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 2 months to 12 months	Proportion of individuals achieving seizure freedom ranged from 0% to 9% in the control groups	Proportion of individuals achieving seizure freedom ranged from 0% to 15% in the KD groups	Not estimable	350 (4 studies)	⊕⊕⊕⊕ Low ^{1,2}	No studies reported a statistically significant difference between KD and control.
Seizure reduction (50% or greater reduction in seizure frequency) Follow-up: 2 months to 16 months	Proportion of individuals achieving 50% or greater reduction in seizure frequency ranged from 0% to 18% in the control groups	Proportion of individuals achieving 50% or greater reduction in seizure frequency ranged from 35% to 56% in the KD groups	Not estimable	452 (5 studies)	⊕⊕⊕⊕ Low ^{1,2}	All five studies reported a statistically significant advantage to the KD group over the control group.
Adverse effects Follow-up: 2 months to 16 months	The most frequent adverse effects reported by participants in dietary intervention groups were: vomiting and constipation. Other adverse effects reported included diarrhoea, dysphagia, lethargy, lower respiratory tract infection, hyperammonaemic encephalopathy, weight loss, nausea, infections (pneumonia, sepsis), acute pancreatitis, decrease in bone matrix density, gallstones, fatty liver, nephrocalcinosis, hypercholesterolaemia, status epilepticus, acidosis, dehydration, tachycardia, hypoglycaemia, hunger, abdominal pain, clinically relevant reduction in height, hypercalcaemia and renal stones.		Not estimable	452 (5 studies)	⊕⊕⊕⊕ Low ^{1,2}	Few statistically significant differences were found between the KD groups and control groups.

Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN.
 Ketogenic diets for drug-resistant epilepsy.
 Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD001903.
 DOI: [10.1002/14651858.CD001903.pub4](https://doi.org/10.1002/14651858.CD001903.pub4).

Ketogenic diets compared to control for people with epilepsy

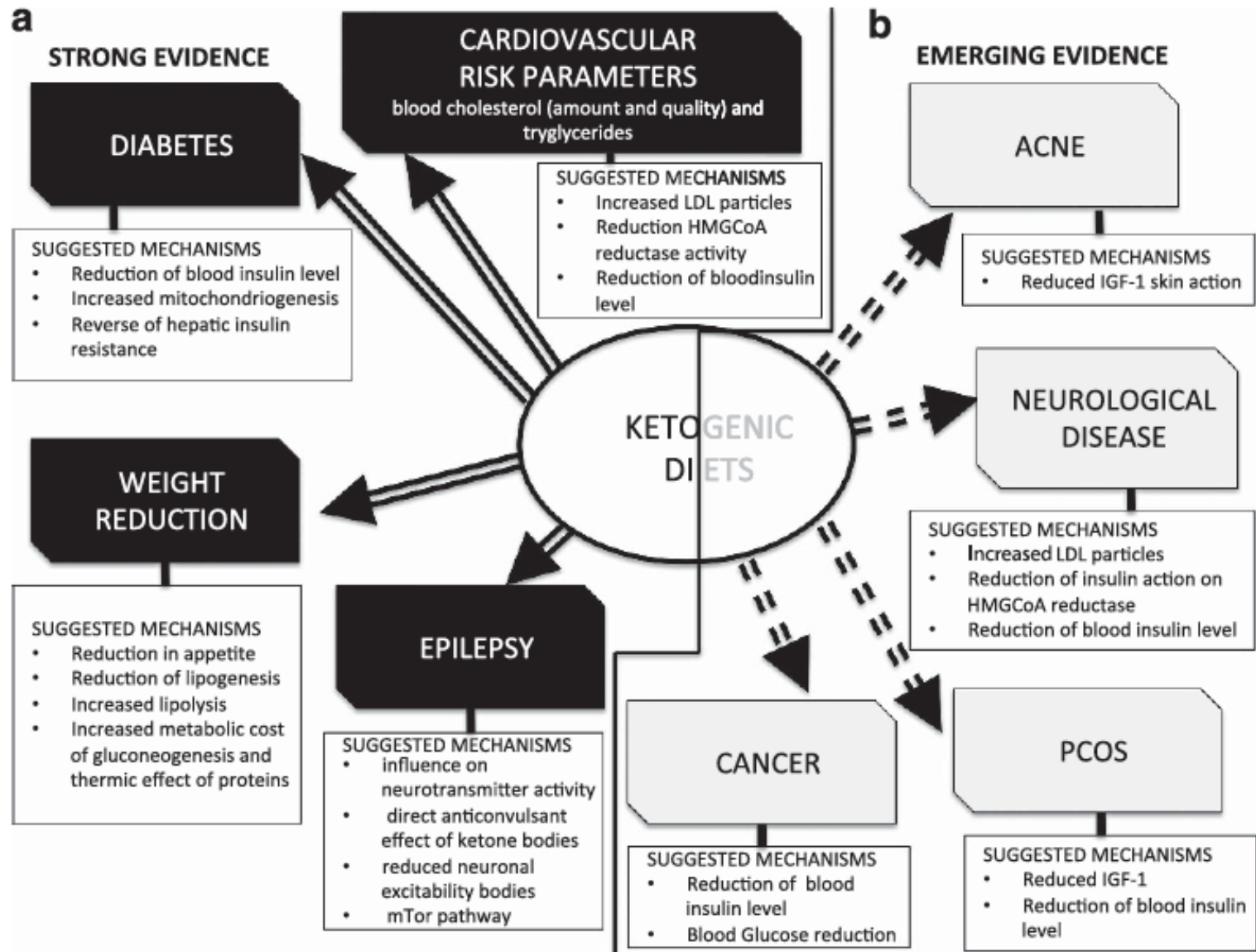
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Ketogenic diets				

Quality of the evidence

The studies included in this review were limited by small numbers of participants and only children were included in 10 of the 11 studies, therefore, we judged the quality of the evidence to be low to very low.

There is little research at present into the use of these diets in adults, therefore, more research is required in this area.

Follow-up: 16 months			(1 study)			
Attrition rate	Proportion of individuals withdrawing from the control group ranged from 0% to 40%	Proportion of individuals withdrawing from the KD group ranged from 8% to 35%	Not estimable	452 (5 studies)	⊕⊕⊕⊕ Low ^{1,2}	No studies reported a statistically significant difference between KD and control.
Follow-up: 2 months to 16 months						



La dieta chetogenica

Andrea Pezzana¹,
 Maria Luisa Amerio²,
 Giuseppe Fatati³,
 Lorenza Caregaro Negrin⁴,
 Fabrizio Muratori⁵,
 Giuseppe M. Rovera⁶,
 Michela Zanardi¹

Indicazioni

- Obesità grave o complicata (ipertensione, diabete tipo 2, dislipidemia, OSAS, sindrome metabolica, osteopatie o artropatie severe)
- Obesità severa con indicazione alla chirurgia bariatrica (nel periodo pre-operatorio)
- Pazienti con indicazioni a rapido dimagrimento per severe comorbidità
- *Non-alcoholic fatty liver disease* (NAFLD)
- Epilessia farmaco-resistente

Controindicazioni

- Gravidanza e allattamento
- Anamnesi positiva per disturbi psichici e comportamentali, abuso di alcol e altre sostanze
- Insufficienza epatica o renale
- Diabete tipo 1
- Porfiria, angina instabile, IMA recente



Conclusioni

In un mondo sempre più affetto da sovrappeso e obesità, in cui il diabete tipo 2 è in preoccupante aumento, la dieta chetogenica si pone come un'interessante alternativa ad altri percorsi terapeutici.

Non si può al momento prevederne un utilizzo routinario come prima scelta in tutte le forme di sovrappeso e obesità, ma è da considerare soprattutto laddove sia richiesto un calo ponderale rapido, che aiuti al contenimento del rischio globale di salute e alla motivazione del paziente.

Deve essere proposto a pazienti accuratamente selezionati, sia per caratteristiche cliniche sia per prevista compliance, e richiede un'adeguata conoscenza del-

ADI 2014;6:38-43

FONDAZIONE ADI: POSITION PAPER

La dieta chetogenica

Andrea Pezzana¹,
Maria Luisa Amerio²,
Giuseppe Fatati³,
Lorenza Caregaro Negrin⁴,
Fabrizio Muratori⁵,
Giuseppe M. Rovera⁶,
Michela Zanardi¹

Ketogenic Diet for Weight Loss

Allowed

- Strong emphasis on fats at each meal and snack to meet the high-fat requirement. Cocoa butter, lard, poultry fat, and most plant fats (olive, palm, coconut oil) are allowed, as well as foods high in fat, such as avocado, coconut meat, certain nuts (macadamia, walnuts, almonds, pecans), and seeds (sunflower, pumpkin, sesame, hemp, flax).
- Some dairy foods may be allowed. Although dairy can be a significant source of fat, some are high in natural lactose sugar such as cream, ice cream, and full-fat milk so they are restricted. However, butter and hard cheeses may be allowed because of the lower lactose content.
- Protein stays moderate. ...grass-fed beef (not grain-fed) and free-range poultry that offer slightly higher amounts of omega-3 fats, pork, bacon, wild-caught fish, organ meats, eggs, tofu, certain nuts and seeds.
- Most non-starchy vegetables are included: Leafy greens ... cauliflower, broccoli, Brussels sprouts, asparagus, bell peppers, onions, garlic, mushrooms, cucumber, celery, summer squashes.
- Certain fruits in small portions like berries. ...
- Other: Dark chocolate (90% or higher cocoa solids), cocoa powder, unsweetened coffee and tea, unsweetened vinegars and mustards, herbs, and spices.

Ketogenic Diet for Weight Loss

Not Allowed

- **All whole and refined grains** and flour products, added and natural sugars in food and beverages, starchy vegetables like potatoes, corn, and winter squash.
- **Fruits** other than from the allowed list, unless factored into designated carbohydrate restriction. All fruit juices.
- **Legumes** including beans, lentils, and peanuts.
- Although some programs allow small amounts of hard liquor or low carbohydrate wines and beers, most restrict full carbohydrate wines and beer, and drinks with added sweeteners (cocktails, mixers with syrups and juice, flavored alcohols).



Ketogenic diet: Unanswered Questions

- What are the long-term (one year or longer) effects of, and are there any safety issues related to, the ketogenic diet?
- Do the diet's health benefits extend to higher risk individuals with multiple health conditions and the elderly? For which disease conditions do the benefits of the diet outweigh the risks?
- As fat is the primary energy source, is there a long-term impact on health from consuming different types of fats (saturated vs. unsaturated) included in a ketogenic diet?
- Is the high fat, moderate protein intake on a ketogenic diet safe for disease conditions that interfere with normal protein and fat metabolism, such as kidney and liver diseases?
- Is a ketogenic diet too restrictive for periods of rapid growth or requiring increased nutrients, such as during pregnancy, while breastfeeding, or during childhood/adolescent years?

<https://www.hsph.harvard.edu/nutritionsource>



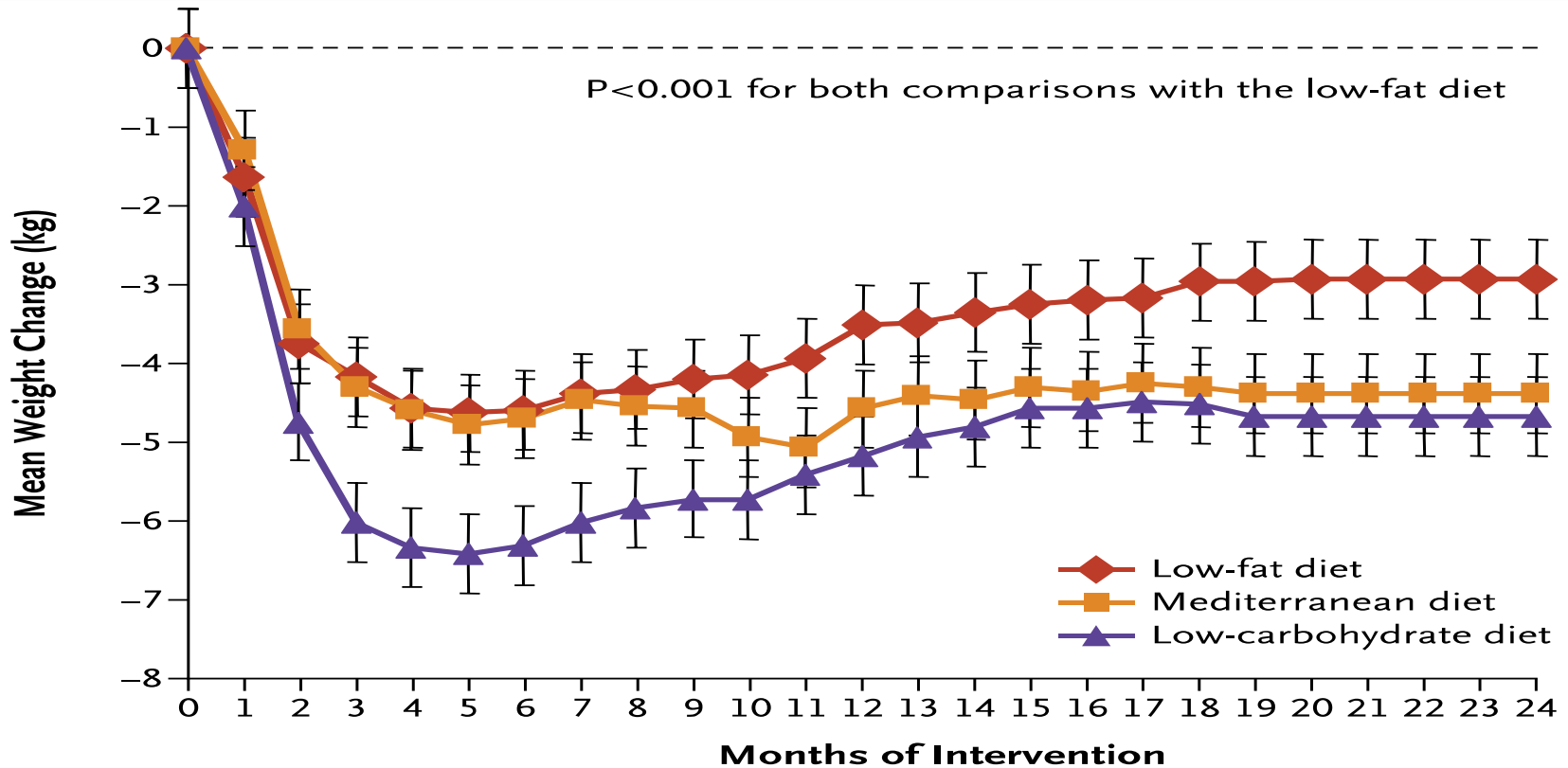
The Ketogenic Diet for Obesity and Diabetes— Enthusiasm Outpaces Evidence

JAMA Internal Medicine September 2019 Volume 179, Number 9

- The greatest risk, however, of the ketogenic diet may be the one most overlooked: the opportunity cost of not eating high-fiber, unrefined carbohydrates. Wholegrains, fruits, and legumes are some of the most health promoting foods on the planet. They are not responsible for the epidemics of type 2 diabetes or obesity, and their avoidance may do harm.
- The risks posed by the ketogenic diet may explain why the majority of, if not all, populations consume enough carbohydrates to avoid chronic ketosis.
- In contrast, some of the longest-living populations, the so-called Blue Zone communities (eg, Greece, Japan), subsist on a carbohydrate fare that exceeds 50% of daily calories.

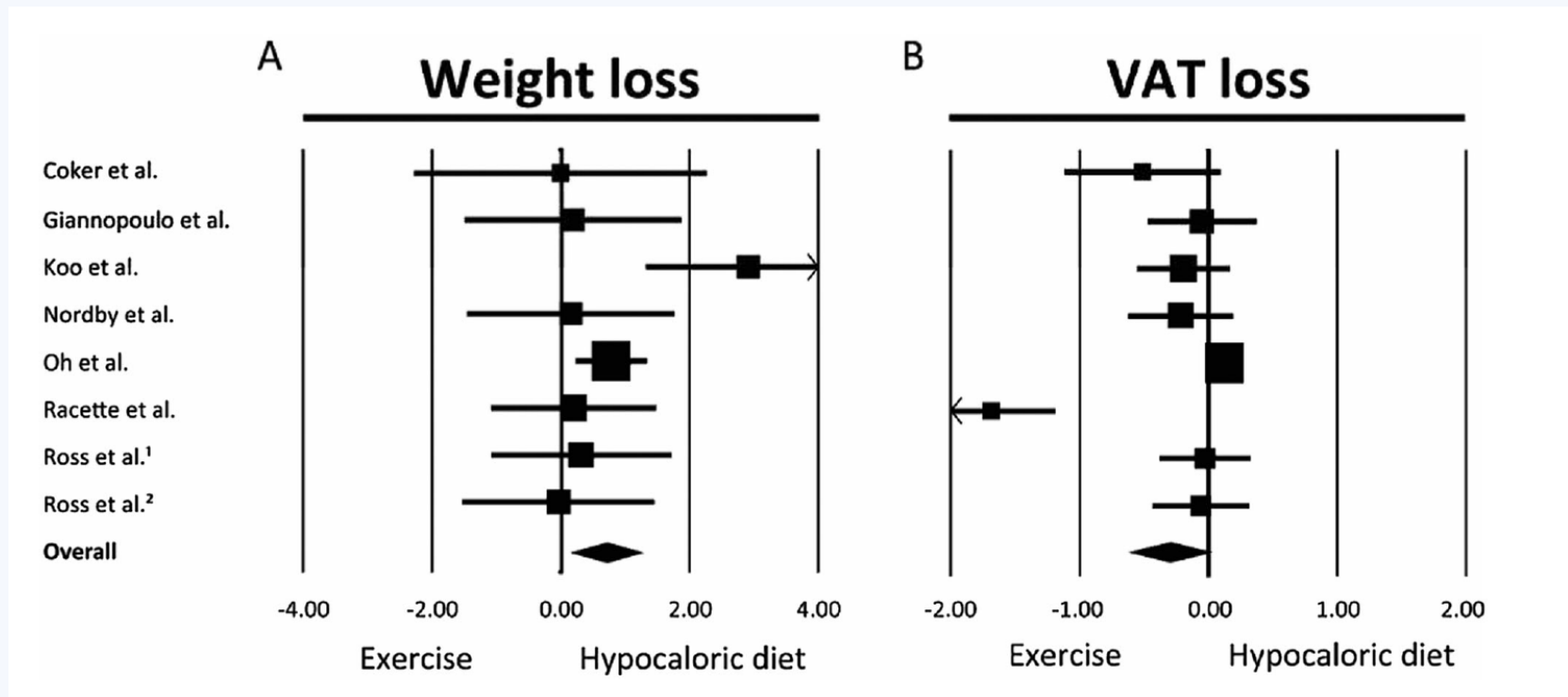


Med Diet is as effective as Low Carb diet in weight loss



Shai I et al, N Engl J Med 2008

A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue



Forest plot of the effect size (SMD) of (a) exercise training versus caloric restriction on weight loss and (b) exercise training versus caloric restriction on visceral adiposity (VAT) loss. The effect size (SMD) and 95% confidence interval for individual studies and the pooled estimate (assessed with the use of random effects model) are depicted.

Verheggen, 2017



Position of the Academy of Nutrition and Dietetics

POSITION STATEMENT

Overview

ABSTRACT

It is the position of the Academy of Nutrition and Dietetics that successful treatment of overweight and obesity in adults requires adoption and maintenance of lifestyle behaviors contributing to both dietary intake and physical activity. These behaviors are influenced by many factors; therefore, interventions incorporating more than one level of the socioecological model and addressing several key factors in each level may be more successful than interventions targeting any one level and factor alone.

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Academy of Nutrition and Dietetics
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