#### 76° CONGRESSO NAZIONALE

PROSSIMITÀ E ORGANIZZAZIONE DELLE CURE:

LA MEDICINA GENERALE DI DOMANI TRA DEMOGRAFIA E CRONICITÀ



## PERCORSI SIMPeSV PER UN AMBULATORIO DEGLI STILI DI VITA

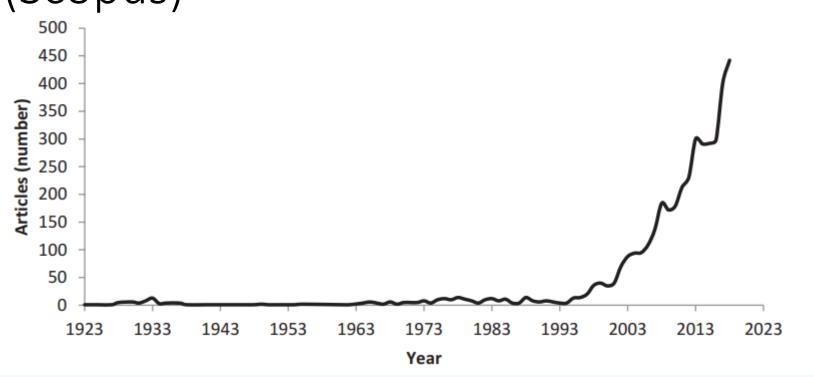
# Dieta chetogenica e sue applicazioni cliniche

I dati della letteratura

Franca Marangoni
Nutrition Foundation of Italy,
Milano



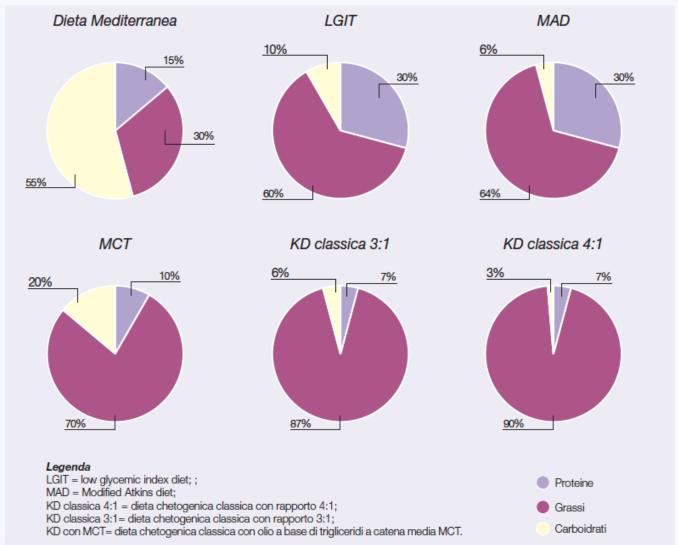
# Number of articles published on the ketogenic diet over 1923–2018 (Scopus)







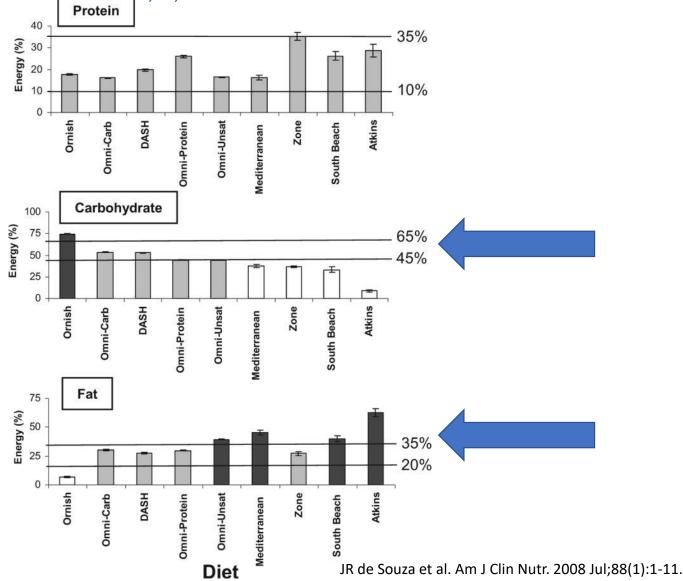
#### Contenuto di macronutrienti nei diversi protocolli dietetici







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.  $\blacksquare$ , exceeds the AMDR;  $\blacksquare$ , meets the AMDR;  $\square$ , failed to reach the minimum AMDR.



AHA Protein Criteria	Atkins <sup>29</sup>	Zone <sup>30</sup>	Protein Power <sup>31</sup>	Sugar Busters <sup>32</sup>	Stillman <sup>28</sup>
Total protein is not excessive average 50–100 g/d, proportional L5–20% 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				
otal fat (30%) and saturated fat 10%) are not excessive	No.	Yes.	No.	Yes.	No.
	-	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 nealthful eating plan to prevent ncreases in disease risk	No.	No.	No.	No.	No.
	Diet low in fiber, vitamin D, thiamine, pantothenic acid,	protein, fat, carbohydrates. Menus not appealing, vegetable portions very	low in calcium, fiber, pantothenic acid, copper,	Eliminates many carbohydrate foods. Discourages eating fruit with meals. Low in calcium, vitamin D, vitamin E, pantothenic acid, copper, potassium	vitamin D, folate, pantothenic acid, calcium, copper,

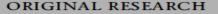
# Available evidence of diseases through-out life

		Case	Uncontrolled	Randomised, controlled
Disorder	Preclinical	study	trial	trial
Childhood				
Epilepsy		√		
ADHD	V	√	V	
ASD	V	V	V	
Adolescence/Early a	dulthood			
Schizophrenia	√	√		
Adult				
Obesity/Type-2 diabetes	V	V	√	
Elderly				
Alzheimer's	√	√		
Parkinson's	V	<b>√</b>	V	

ADHD attention-deficit hyperactivity disorder, ASD autism spectrum disorder,  $\sqrt{\text{published}}$  evidence available

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







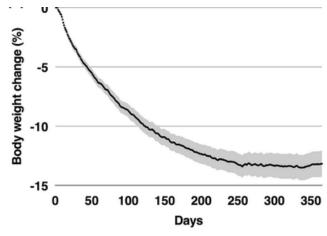
#### Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study

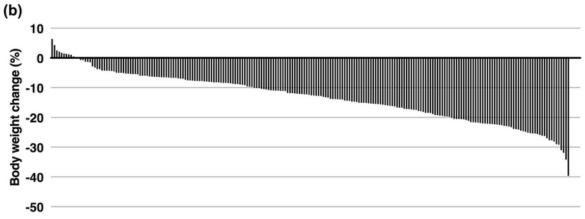
Sarah J. Hallberg · Amy L. McKenzie · Paul T. Williams ·

Nasir H. Bhanpuri · Anne L. Peters · Wayne W. Campbell · Tamara L. Hazbun ·

Brittanie M. Volk  $\cdot$  James P. McCarter  $\cdot$  Stephen D. Phinney  $\cdot$ 

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

)	Body weight (kg)		VLCKD			LFD			Mean difference	Mean difference
_	Study	Mean	, so and	total	Mean	, so and	total	Weight (%)	(95 %CI)	IV, random, 95 %CI
	Brinkworth et al. (28)	-13-1	11-86	55	-11-6	11-53	52	2-8	-1.50 (-5.93, 2.93)	<del></del>
	Dansinger et al. (50)	-2-1	4-8	40	-3.3	7.3	40	7-4	1-20 (-1-51, 3-91)	<del> </del>
	Davis et al. (51)	-3-1	4.8	55	-3-1	5.8	50	13-0	0-00 (-2-05, 2-05)	<del></del>
	Dyson et al. (52)	0-3	6-96	11	-0-8	3.97	11	2-4	1-10 (-3-64, 5-84)	<del>-   •</del>
	Foster et al. (53)	-7-2	7	33	-4-4	8	30	3-9	-2-80 (-6-53, 0-93)	<del></del>
	Foster et al. (27)	-6.34	10-82	153	-7-37	10-98	154	9-2	-1-03 (-1-41-3-47)	<del>-   -</del>
	Lim et al. (30)	-4-7	7-16	77	-2.6	5-55	76	13-3	-2-10 (-4-13, 0-07)	<del></del>
	lqbal et al. (29)	-1-5	8-36	67	-0-2	7-74	71	7-5	-1-30 (-3-99, 1-39)	<del></del>
	Lim et al. (54)	-2-9	4.9	17	-2-1	4.7	18	5-4	-0.80 (-3.98, 2.38)	<del></del>
	McAuley et al. (55)	-5-4	12-6	24	-4-4	12.2	24	1-1	-1.00 (-8.02, 8.02)	
	Shai et al. (49)	-4-7	6-5	109	-2.9	4.2	104	25-5	-1-80 (-3-26, -0-34)	— <del>-</del> -
	Stern et al. (26)	-5-1	8-7	62	-3-1	8-4	64	6-1	-2-00 (-4-99, 0-99)	<del></del>
	Truby et al. (56)	-9	4-1	9	-10-7	6.2	9	2-3	-1-70 (-3-16, 6-56)	<del>-   -</del>
	Total (95 % CI)			712			703	100-0	-0-91(-1-65, -0-17)	•
	Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2$ .		(P = 0-4	7); I <sup>2</sup> -	0 %					-4 -2 0 2 4
, –	Heterogeneity: $\tau^2$ = 0-00; $\chi^2$ . Test for overall effect: $Z$ =2-4: TAG (mmol/l)	2 (P=0-02)	(P = 0-4		0 %	LFD			Mean difference	-4 -2 0 2 4 Favours VLCKD Favours LFD Mean difference
_	Test for overall effect: Z=2-4:	2 (P=0-02)				LFD , so and	i total	Weight (%)	Mean difference (95 %CI)	Favours VLCKD Favours LFD
_	Test for overall effect: Z=2-4: TAG (mmol/l)	2 (P=0-02)	VLCKD				i total	Weight (%) 8-4		Favours VLCKD Favours LFD  Mean difference
_	Test for overall effect: Z=2-4: TAG (mmol/l) Study	2 (P=0-02) Mean	VLCKD , so and	Itotal	Mean	, so and			(95 %CI)	Favours VLCKD Favours LFD  Mean difference
_	Test for overall effect: Z=2-4: TAG (mmol/l) Study Brinkworth et al. (28)	2 (P=0-02) Mean -0-58	VLCKD , so and 0-63	I total	Mean	0-66	36	8-4	(95 %CI) -0·36 (-0·66, -0·06)	Favours VLCKD Favours LFD  Mean difference
, - -	Test for overall effect: Z=2-4: TAG (mmol/l) Study Brinkworth et al. (28) Dansinger et al. (50)	2 (P=0-02)  Mean  -0-58  -0-01	VLCKD , so and 0-63 0-95	33 40	Mean -0-22 0-069	0-66 0-41	36 40	8-4 7-7	(95 %CI) -0-36 (-0-66, -0-06) -0-07 (-0-39, 0-25)	Favours VLCKD Favours LFD  Mean difference
, - -	Test for overall effect: Z=2-4: TAG (mmol/l) Study Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51)	Mean, -0-58 -0-01	VLCKD , sp and 0-63 0-95 0-88	33 40 55	Mean -0-22 0-069 -0-01	0-66 0-41 0-86	36 40 50	8-4 7-7 7-2	(95 %CI) -0-36 (-0-66, -0-06) -0-07 (-0-39, 0-25) -0-14 (-0-47, 0-19)	Favours VLCKD Favours LFD  Mean difference
, - -	Test for overall effect: Z=2-4: TAG (mmol/l) Study  Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52)	Mean -0-58 -0-01 -0-15 -0-2	VLCKD , sp and 0-63 0-95 0-88 0-57	33 40 55	Mean -0-22 0-069 -0-01	0-66 0-41 0-86 0-87	36 40 50	8-4 7-7 7-2 2-2	(95 %CI)  -0-36 (-0-66, -0-06)  -0-07 (-0-39, 0-25)  -0-14 (-0-47, 0-19)  -0-20 (-0-82, 0-42)	Favours VLCKD Favours LFD  Mean difference
-	Test for overall effect: Z=2-4: TAG (mmol/l) Study  Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52) Foster et al. (53)	Mean, -0-58 -0-01 -0-15 -0-2 -0-42	VLCKD , sp and 0-63 0-95 0-88 0-57 0-4	33 40 55 10 33	Mean -0-22 0-069 -0-01 0 -0-02	0-66 0-41 0-86 0-87 0-7	36 40 50 11 30	8-4 7-7 7-2 2-2 9-4	(95 %CI)  -0-36 (-0-66, -0-06)  -0-07 (-0-39, 0-25)  -0-14 (-0-47, 0-19)  -0-20 (-0-82, 0-42)  -0-40 (-0-69, -0-11)	Favours VLCKD Favours LFD  Mean difference
-	Test for overall effect: Z=2-4: TAG (mmol/l) Study  Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52) Foster et al. (53) Foster et al. (27) Gardner et al. (30)	Mean, -0-58 -0-01 -0-15 -0-2 -0-42 -0-14	VLCKD , sp and 0-63 0-95 0-88 0-57 0-4 0-76	33 40 55 10 33 153	Mean -0-22 0-069 -0-01 0 -0-02 -0-16	0-66 0-41 0-86 0-87 0-7	36 40 50 11 30 154	8-4 7-7 7-2 2-2 9-4 20-7	(95 %CI)  -0-36 (-0-66, -0-06)  -0-07 (-0-39, 0-25)  -0-14 (-0-47, 0-19)  -0-20 (-0-82, 0-42)  -0-40 (-0-69, -0-11)  0-02 (-0-15, 0-19)	Favours VLCKD Favours LFD  Mean difference
, -	Test for overall effect: Z=2-4: TAG (mmol/l) Study  Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52) Foster et al. (53) Foster et al. (27)	Mean, -0-58 -0-01 -0-15 -0-2 -0-42 -0-14 -0-33	VLCKD , sp and 0-63 0-95 0-88 0-57 0-4 0-76 0-67	33 40 55 10 33 153 70	Mean -0-22 0-069 -0-01 0 -0-02 -0-16 -0-17	0-66 0-41 0-86 0-87 0-7 0-8 0-52	36 40 50 11 30 154 64	8-4 7-7 7-2 2-2 9-4 20-7 16-7	(95 %CI)  -0-36 (-0-66, -0-06)  -0-07 (-0-39, 0-25)  -0-14 (-0-47, 0-19)  -0-20 (-0-82, 0-42)  -0-40 (-0-69, -0-11)  0-02 (-0-15, 0-19)  -0-16 (-0-36, 0-04)	Favours VLCKD Favours LFD  Mean difference
, -	Test for overall effect: Z=2-4: TAG (mmol/l) Study Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52) Foster et al. (27) Gardner et al. (30) Iqbal et al. (29)	Mean, -0-58 -0-01 -0-15 -0-2 -0-42 -0-14 -0-33 -0-29	VLCKD , sp and 0-63 0-95 0-88 0-57 0-4 0-76 0-67 1-15	33 40 55 10 33 153 70	Mean -0-22 0-069 -0-01 0 -0-02 -0-16 -0-17 -0-15	0-66 0-41 0-86 0-87 0-7 0-8 0-52	36 40 50 11 30 154 64 71	8-4 7-7 7-2 2-2 9-4 20-7 16-7 6-2	(95 %CI)  -0-36 (-0-66, -0-06)  -0-07 (-0-39, 0-25)  -0-14 (-0-47, 0-19)  -0-20 (-0-82, 0-42)  -0-40 (-0-69, -0-11)  0-02 (-0-15, 0-19)  -0-16 (-0-36, 0-04)  -0-14 (-0-50, 0-22)	Favours VLCKD Favours LFD  Mean difference
-	Test for overall effect: Z=2-4: TAG (mmol/l) Study Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52) Foster et al. (53) Foster et al. (27) Gardner et al. (30) Iqbal et al. (54) McAuley et al. (55)	Mean -0-58 -0-01 -0-15 -0-2 -0-42 -0-14 -0-33 -0-29 -0-2	VLCKD , sp and 0-63 0-95 0-88 0-57 0-4 0-76 0-67 1-15 0-7	33 40 55 10 33 153 70 67	Mean -0-22 0-069 -0-01 0 -0-02 -0-16 -0-17 -0-15 0-1	0-66 0-41 0-86 0-87 0-7 0-8 0-52 1	36 40 50 11 30 154 64 71	8-4 7-7 7-2 2-2 9-4 20-7 16-7 6-2 3-0	(95 %CI)  -0-36 (-0-66, -0-06)  -0-07 (-0-39, 0-25)  -0-14 (-0-47, 0-19)  -0-20 (-0-82, 0-42)  -0-40 (-0-69, -0-11)  0-02 (-0-15, 0-19)  -0-16 (-0-36, 0-04)  -0-14 (-0-50, 0-22)  -0-30 (-0-83, 0-23)	Favours VLCKD Favours LFD  Mean difference
, -	Test for overall effect: Z=2-4: TAG (mmol/l) Study Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52) Foster et al. (27) Gardner et al. (30) Iqbal et al. (29) Lim et al. (54)	Mean -0-58 -0-01 -0-15 -0-2 -0-42 -0-14 -0-33 -0-29 -0-2 -0-47	VLCKD , sp and 0-63 0-95 0-88 0-57 0-4 0-76 0-67 1-15 0-7	33 40 55 10 33 153 70 67 17	Mean -0-22 0-069 -0-01 0 -0-02 -0-16 -0-17 -0-15 0-1 -0-31	0-66 0-41 0-86 0-87 0-7 0-8 0-52 1 0-9	36 40 50 11 30 154 64 71 18 24	8-4 7-7 7-2 2-2 9-4 20-7 16-7 6-2 3-0 6-4	(95 %CI)  -0-36 (-0-66, -0-06)  -0-07 (-0-39, 0-25)  -0-14 (-0-47, 0-19)  -0-20 (-0-82, 0-42)  -0-40 (-0-69, -0-11)  0-02 (-0-15, 0-19)  -0-16 (-0-36, 0-04)  -0-14 (-0-50, 0-22)  -0-30 (-0-83, 0-23)  -0-16 (-0-52, 0-20)	Favours VLCKD Favours LFD  Mean difference
, -	Test for overall effect: Z=2-4: TAG (mmol/l) Study  Brinkworth et al. (28) Dansinger et al. (50) Davis et al. (51) Dyson et al. (52) Foster et al. (53) Foster et al. (27) Gardner et al. (29) Lim et al. (54) McAuley et al. (49) Shai et al. (49)	Mean -0-58 -0-01 -0-15 -0-2 -0-42 -0-14 -0-33 -0-29 -0-2 -0-47 -0-25	VLCKD , sp and 0-63 0-96 0-88 0-57 0-4 0-76 0-67 1-15 0-7 0-69 0-96	33 40 55 10 33 153 70 67 17 24	Mean -0-22 0-069 -0-01 0 -0-02 -0-16 -0-17 -0-15 0-1 -0-31 -0-03	0-66 0-41 0-86 0-87 0-7 0-8 0-52 1 0-9 0-56	36 40 50 11 30 154 64 71 18 24	8-4 7-7 7-2 2-2 9-4 20-7 16-7 6-2 3-0 6-4 9-8	(95 %CI)  -0-36 (-0-66, -0-06) -0-07 (-0-39, 0-25) -0-14 (-0-47, 0-19) -0-20 (-0-82, 0-42) -0-40 (-0-69, -0-11) 0-02 (-0-15, 0-19) -0-16 (-0-36, 0-04) -0-14 (-0-50, 0-22) -0-30 (-0-83, 0-23) -0-16 (-0-52, 0-20) -0-22 (-0-50, 0-06)	Favours VLCKD Favours LFD  Mean difference

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

(a) SBP (mmHg)	,	VLCKD			LFD			Mean difference	Mean difference
Study	Mean	, SD and	total	Mean	, SD and	total	Weight (%)	(95 % CI)	IV, random, 95 % CI
Brinkworth et al. (28)	-13⋅8	14.36	33	-14.6	12	36	7.5	0.80 (-5.47, 7.07)	
Dansinger <i>et al.</i> <sup>(50)</sup>	0.2	12	40	0.5	7.7	40	12.0	-0·30 (-4·72, 4·12)	<del>- +</del> -
Davis <i>et al.</i> <sup>(51)</sup>	0.2	15-6	55	-1.8	22.6	50	5.6	3.80 (-3.70, 11.30)	<del>-   -</del>
Foster et al. (53)	-1.9	15	33	3.6	20	30	4.3	-5·50 (-14·30 3·30)	<del></del>
Foster et al. (27)	-2.8	15.17	153	-2.59	15-67	154	15⋅8	-0.21 (-3.66, 3.24)	<del>-+</del>
Gardner <i>et al.</i> <sup>(30)</sup>	-7.6	11	77	-1.9	7.7	76	17.8	-5.70 (-8.71 -2.69)	<del></del>
lqbal <i>et al.</i> <sup>(29)</sup>	-11.2	30.28	67	<b>-4</b> ⋅5	26.96	71	3.7	-6.70 (-16.29 -2.89)	<del>- +</del>
Lim <i>et al.</i> <sup>(54)</sup>	-10.6	10.6	17	-6	13-3	18	5⋅1	-4.60 (-12.55 3.35)	<del></del>
McAuley et al. (55)	-5	15.9	24	-6	9.89	24	5.6	1.00 (-6.49, 8.49)	<del></del>
Shai <i>et al.</i> <sup>(49)</sup>	-3.9	12.8	109	<b>-4</b> ⋅3	11.8	104	16-4	1.40 (-2.90, 3.70)	<del></del>
Stern et al. (26)	1	19	44	2	15	43	6-0	-1.00 (-8.18, 6.18)	
Total (95 % CI)				652		646	100-0%	-1.47 (-3.44, 0.50)	•
Heterogeneity: τ²= 3.3	33; $\chi^2 = 1$	4.94, df	= 10 ( <i>F</i>	P=0·13)	$I^2 = 33$	%			10 5 10
Test for overall effect:	Z=1.46	(P=0·14)							-10 -5 0 5 10 Favours VLCKD Favours LFD

(b) DBP (mmHg)	VLCKD			LFD			Mean difference	Mean difference	
Study	Mean,	, SD and	total	Mean	, SD and	total	Weight (%)	(95 % CI)	IV, random, 95 % CI
Brinkworth et al. (28)	-6⋅3	19-9	33	-7.9	9.6	36	2.0	1.60 (-5.88, 9.08)	
Dansinger <i>et al</i> . <sup>(50)</sup>	-1.4	7.5	40	0.2	4.6	40	14.3	1.60 (-5.33, 1.13)	<del></del>
Davis <i>et al.</i> <sup>(51)</sup>	-2.9	9.4	55	-2.2	11.6	50	6.7	1.70 (-5.76, 3.36)	<del></del>
Foster et al. (53)	-4.6	12	33	-5⋅2	13	30	2.9	1.60 (-5.60, 6.80)	
Foster <i>et al.</i> (27)	-3.19	9.24	153	-0.5	10.32	154	21.6	-2. 69 (-4.88, -0.50)	<del></del>
Gardner <i>et al.</i> <sup>(30)</sup>	-4.4	8.4	77	-0.7	6	76	19-6	-3.70(-6.01, -1.39)	<b></b>
lqbal <i>et al</i> . (29)	-3.8	19-64	67	<b>-4·3</b>	16.85	71	3.0	0.50 (-5.62, 6 62)	
Lim <i>et al.</i> <sup>(54)</sup>	-6.6	12.1	17	-7.5	8.7	18	2.3	0.90 (-6.12, 7 92)	<del> </del>
McAuley et al. (55)	-4	9.81	24	-3	10.43	24	3.4	-1.00 (-6.73, 4.73)	
Shai <i>et al.</i> <sup>(49)</sup>	-0⋅8	8.7	109	-0.9	8.1	104	20.4	0.10 (-2.16, 2.36)	<del></del>
Stern <i>et al.</i> <sup>(26)</sup>	3	15	44	1	10	43	3.9	2.00 (-3.35, 7.35)	-
Total (95 % CI)				652		646	100-0	-1.43 (-2.49, -0.37)	•
Heterogeneity: τ²= 0·1		•		e0·41);	I <sup>2</sup> =3 %				-4 -2 0 2 4
Test for overall effect:	Z=2.64 (	P=0.008	B)						Favours VLCKD Favours LFD

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



besity reviews

doi: 10.1111/obs.12230

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. Ayre¹², J. Franklin³, T. P. Markovic¹³, I. D. Caterson¹³ 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, Grith M Poulsen, Henning K Andersen, Arne Astrup

	Interventi	on [Low C	arb.]	Control	[High Ca	arb.]		Mean Difference	< 45% Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Saslow 2014	6	0.3	15	6.9	1.1	18	12.9%	-0.90 [-1.43, -0.37]		<b></b>
Tay 2014	-2.6	1	46	-1.9	1.2	47	14.7%	-0.70 [-1.15, -0.25]		
Yamada 2014	7	0.7	12	7.5	1	12	9.9%	-0.50 [-1.19, 0.19]		? ? <b>.</b> ?
lqbal 2010	-0.5	0.2	28	-0.1	0.2	40	22.3%	-0.40 [-0.50, -0.30]	+	● 2 ● ● ● ●
Davis 2012	-0.29	0.92	44	-0.15	1.1	40	15.0%	-0.14 [-0.58, 0.30]	-	<ul><li>• • ? ? ? • ?</li></ul>
Guldbrand 2012	7.1	3.1	30	7.2	3	31	3.1%	-0.10 [-1.63, 1.43]		
Larsen 2011	-0.52	4.15	53	-0.49	4.15	46	2.7%	-0.03 [-1.67, 1.61]		• ? ? ? • • •
Krebs 2012	7.9	1.3	173	7.7	1.1	174	19.4%	0.20 [-0.05, 0.45]	<del>  •</del>	
otal (95% CI)			401			408	100.0%	-0.34 [-0.63, -0.06]	•	
Heterogeneity: Tau <sup>2</sup> =			= 7 (P = 0	).0003); l²	= 74%				-2 -1 0 1	<del>1</del> 2
Test for overall effect:	Z = 2.34 (P =	= 0.02)							Favours Intervention [Low Carb.] Favours Control [High Carl	b.]

#### Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

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.

	Interv	ention [Low Car	rb.]	Con	trol [High Carb	-]		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	Mean SD Total		Mean SD		Total	Weight	IV, Random, 95% C	IV, Random, 95% CI	ABCDEFG
Davis 2012	-0.02	0.89	45	0.24	1.4	40	2.6%	-0.26 [-0.77, 0.25]		<ul><li>3 3 3 9 3</li></ul>
Elhayany 2010	6.3	1.4	61	6.5	0.8	63	4.2%	-0.20 [-0.60, 0.20]	<del></del>	220002
Guldbrand 2012	7.5	3.1	30	7.4	3.1	31	0.3%	0.10 [-1.46, 1.66]		
lqbal 2010	-0.1	0.2	28	-0.2	0.3	40	47.8%	0.10 [ 0.02, 0.22]	<del>  -</del>	<b>878888</b>
Krebs 2012	8.2	1.5	144	8.1	1.4	150	6.1%	0.10 [-0.23, 0.43]	<del></del>	$\bullet \bullet ? \bullet ? \bullet \bullet$
Larsen 2011	-0.23	1.06	53	-0.28	1.06	46	3.9%	0.05 (-0.37, 0.47)	<del></del>	lacksquare
Wolever 2008	6.35	0.36400549	53	6.34	0.37080992	55	35.2%	0.01 [-0.13, 0.15]	+	•••••
Total (95% CI)			414			425	100.0%	0.04 [-0.04, 0.13]	•	
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 3.99, df = 6 (F	= 0.68);	$I^2 = 0\%$					- t J. J. J.	_
Test for overall effect: 2	Z = 1.06 (F	P = 0.29)							-1 -0.5 0 0.5 1 Favours Intervention [Low Carb.] Favours Control [High Carb.]	

#### Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

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.



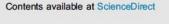
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- The ideal amount of carbohydrates in the diet in the management of type 2 diabetes is unclear.
- The current meta-analysis conducted according to the GRADE system of rating quality of evidence shows that low to moderate carbohydrate diets have greater 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 lowcarbohydrate diets in terms of glycemic control, weight, or LDL cholesterol.









#### Diabetes Research and Clinical Practice

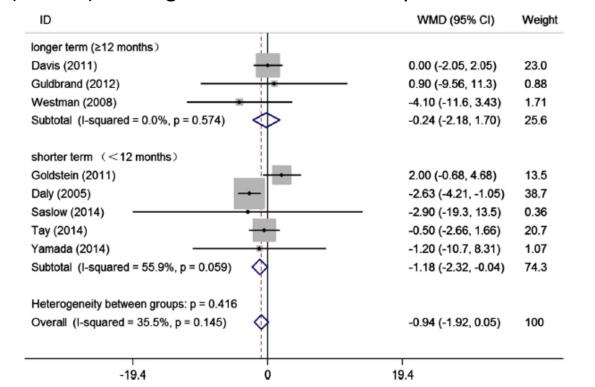






#### Review

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





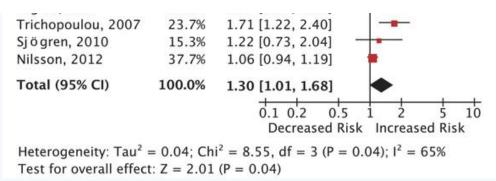


#### Adjusted risk ratios for all-cause mortality associated with low-carbohydrate diets.

(A) Low-carbohydrate score  Risk Ratio										
Study	Weight	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.

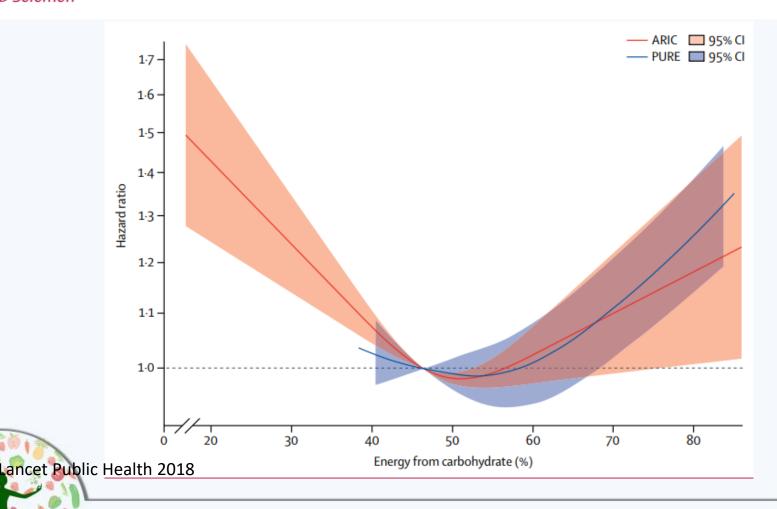


Noto H, Goto A, Tsujimoto T, Noda M (2013) Low-Carbohydrate Diets and All-Cause Mortality: A Systematic Review and Meta-Analysis of Observational Studies. PLOS ONE 8(1): e55030. https://doi.org/10.1371/journal.pone.0055030

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





#### 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* (9	5% CI)	Relative ef-	No. of partic-	Quality of the evidence	Comments
	Assumed risk	Corresponding risk	(95% CI)	(studies)	(GRADE)	
	Control	Ketogenic diets				
Seizure freedom (100% reduction in seizure frequency) Follow-up: 2 months to 12 months	Proportion of individuals achiev- ing seizure freedom ranged from 0% to 9% in the control groups	Proportion of individuals achiev- ing seizure freedom ranged from 0% to 15% in the KD groups	Not estimable	350 (4 studies)	⊕⊕⊝⊝ Low <sup>1,2</sup>	No studies report- ed a statistically significant differ- ence 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 <sup>1,2</sup>	All five studies re- ported a statisti- cally significant ad- vantage to the KD group over the con- trol group.
Adverse effects Follow-up: 2 months to 16 months	fects reported included diarrhoea, of tory tract infection, hyperammonae nausea, infections (pneumonia, sep bone matrix density, gallstones, fatt lesterolaemia, status epilepticus, ad	and constipation. Other adverse ef- dysphagia, lethargy, lower respira- emic encephalopathy, weight loss, osis), acute pancreatitis, decrease in ty liver, nephrocalcinosis, hypercho- cidosis, dehydration, tachycardia, pain, clinically relevant reduction in	Not estimable	452 (5 studies)	⊕⊕⊝⊝ Low <sup>1,2</sup>	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.

## Ketogenic diets compared to control for people with epilepsy

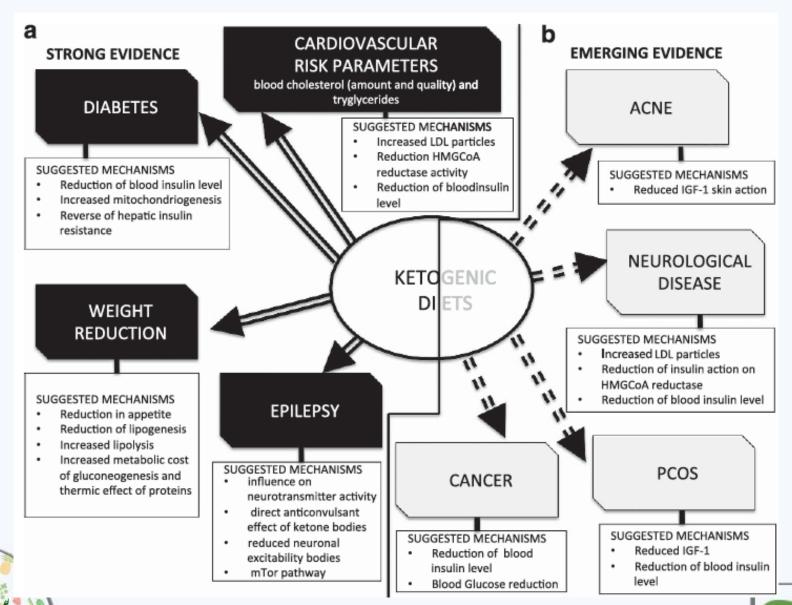
Outcomes	Illustrative comparative risks* (95	% CI)	Relative ef- fect (95% CI)	No. of partic- ipants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Ketogenic diets				

#### 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 Follow-up: 2 months to 16 months	Proportion of individuals with- drawing from the control group ranged from 0% to 40%	Proportion of individuals with- drawing from the KD group ranged from 8% to 35%	Not estimable	452 (5 studies)	⊕⊕⊝⊝ Low <sup>1,2</sup>	No studies report- ed a statistically significant differ- ence between KD and control.



Paoli et al. European Journal of Clinical Nutrition (2013) 67, 789



#### FONDAZIONE ADI: POSITION PAPER

#### La dieta chetogenica

Andrea Pezzana<sup>1</sup>, Maria Luisa Amerio<sup>2</sup>, Giuseppe Fatati<sup>3</sup>, Lorenza Caregaro Negrin<sup>4</sup>, Fabrizio Muratori<sup>5</sup>, Giuseppe M. Rovera<sup>6</sup>, Michela Zanardi<sup>1</sup>

#### 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 comorbilità
- 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 delADI 2014;6:38-43

#### FONDAZIONE ADI: POSITION PAPER

#### La dieta chetogenica

Andrea Pezzana¹,
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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).





# Ketogednic 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





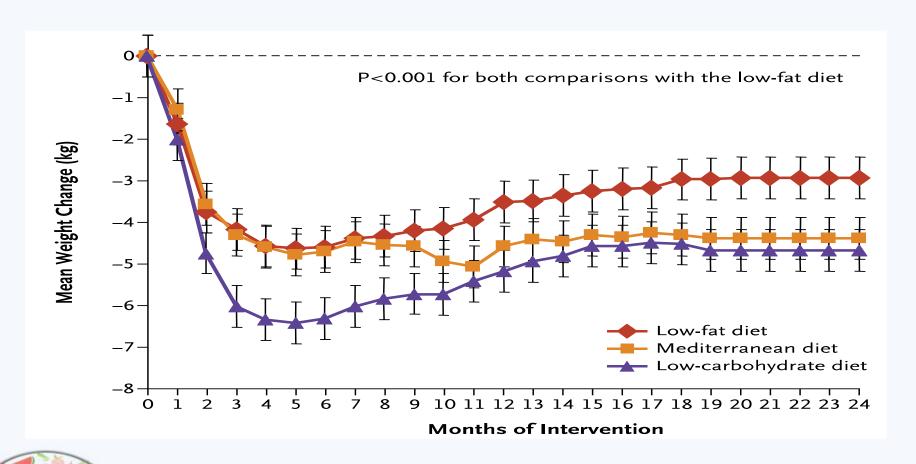
#### The Ketogenic Diet for Obesity and Diabetes– Enthusiasm Outpaces Evidence

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.



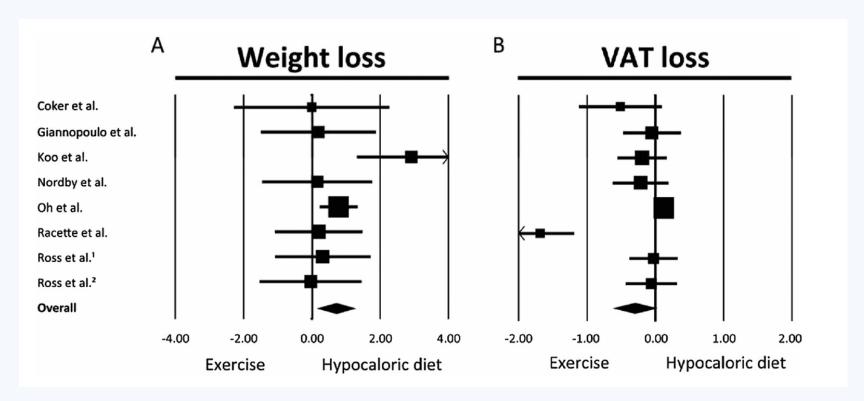
# Med Diet is as effective as Low Carb diet in weight loss



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





#### FROM THE ACADEMY

**Position Paper** 

#### Position of the Academy of Nutrition and

#### Dietetic Position STATEMENT

Overwe It is the position of the Academy of Nutrition and Dietetics that successful treatment of overweight and obesity in adults requires overweight and ob adoption and maintenance of lifestyle behaviors contributing haviors contributing to both dietary intake of the socioecologic and physical activity. These behaviors are incores; therefore, indietitian nutritionis influenced by many factors; therefore, inepidemic. Using the terventions incorporating more than one and factor alone mendations for the level of the socioecological model and



Academy of Nutrition cessful treatment of y in adults requires ance of lifestyle beboth dietary intake ng more than one ological model and and factor alone.

#### ABSTRACT

It is the position of in weight managen Evidence Analysis I personal influence addressing several key factors in each level tensity of treatmen strengthen existing may be more successful than interventions ronments that supr targeting any one level and factor alone.



