Inquadramento delle diete chetogeniche: tipologie e modalità.
Pasti sostitutivi e integrazioni

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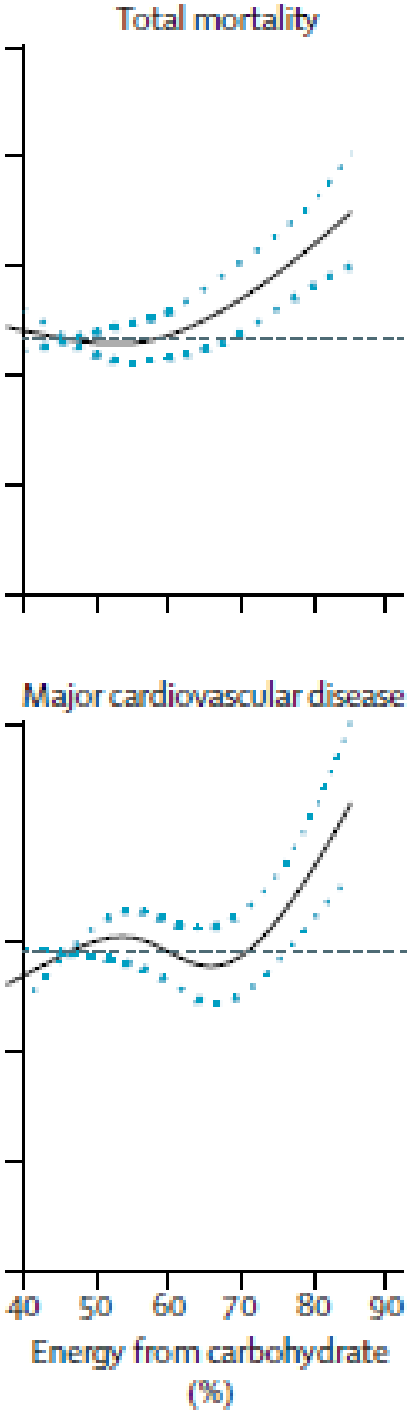
Carboidrati Killer ?
I dati dello studio PURE

Dati derivati da 18 paesi, 135 335 individui, follow-up mediano 7.4 anni

“Il rischio correlato alla modificazione % di intake di carboidrati (5% delle calorie totali) con qualunque altro nutriente non modifica la mortalità per cause cardiovascolari e totale.”

Lancet 2017;390(10107):2050-2062.



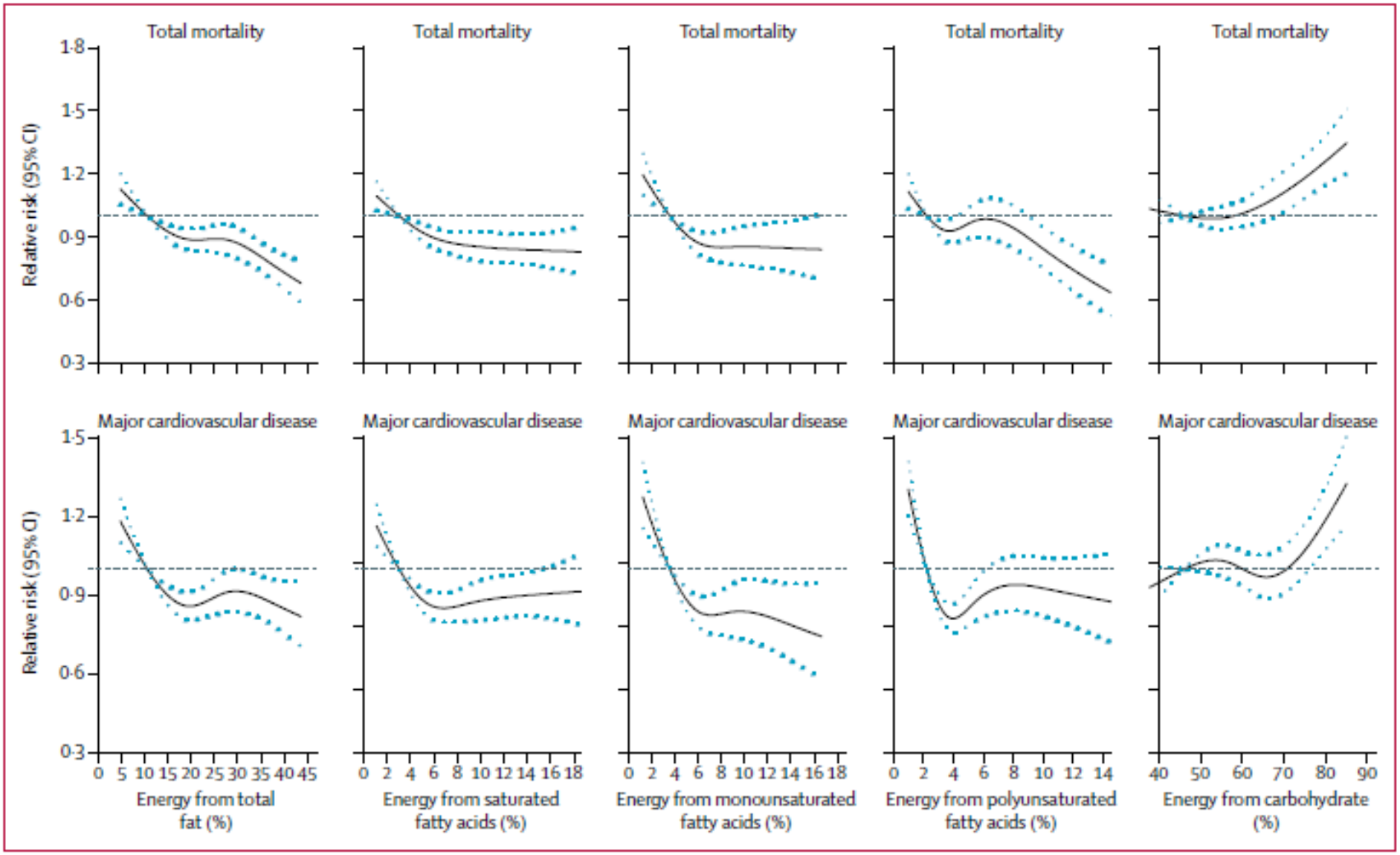
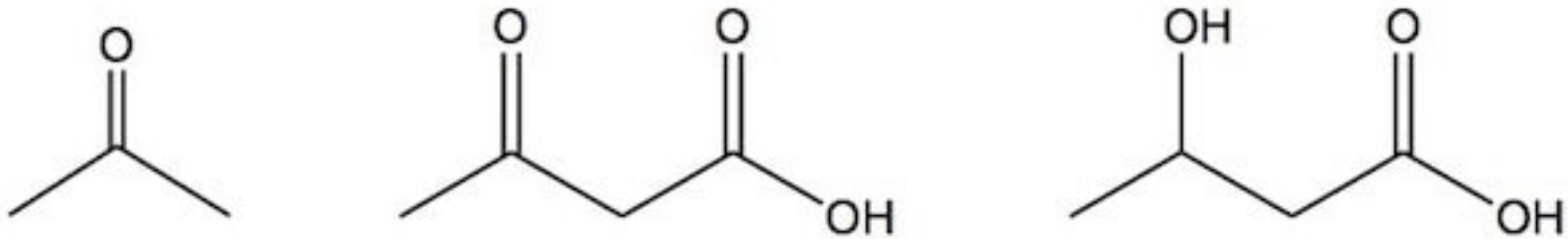


Figure 1: **Association between estimated percentage energy from nutrients and total mortality and major cardiovascular disease (n=135 335)**

Lancet 2017;390(10107):2050-2062.

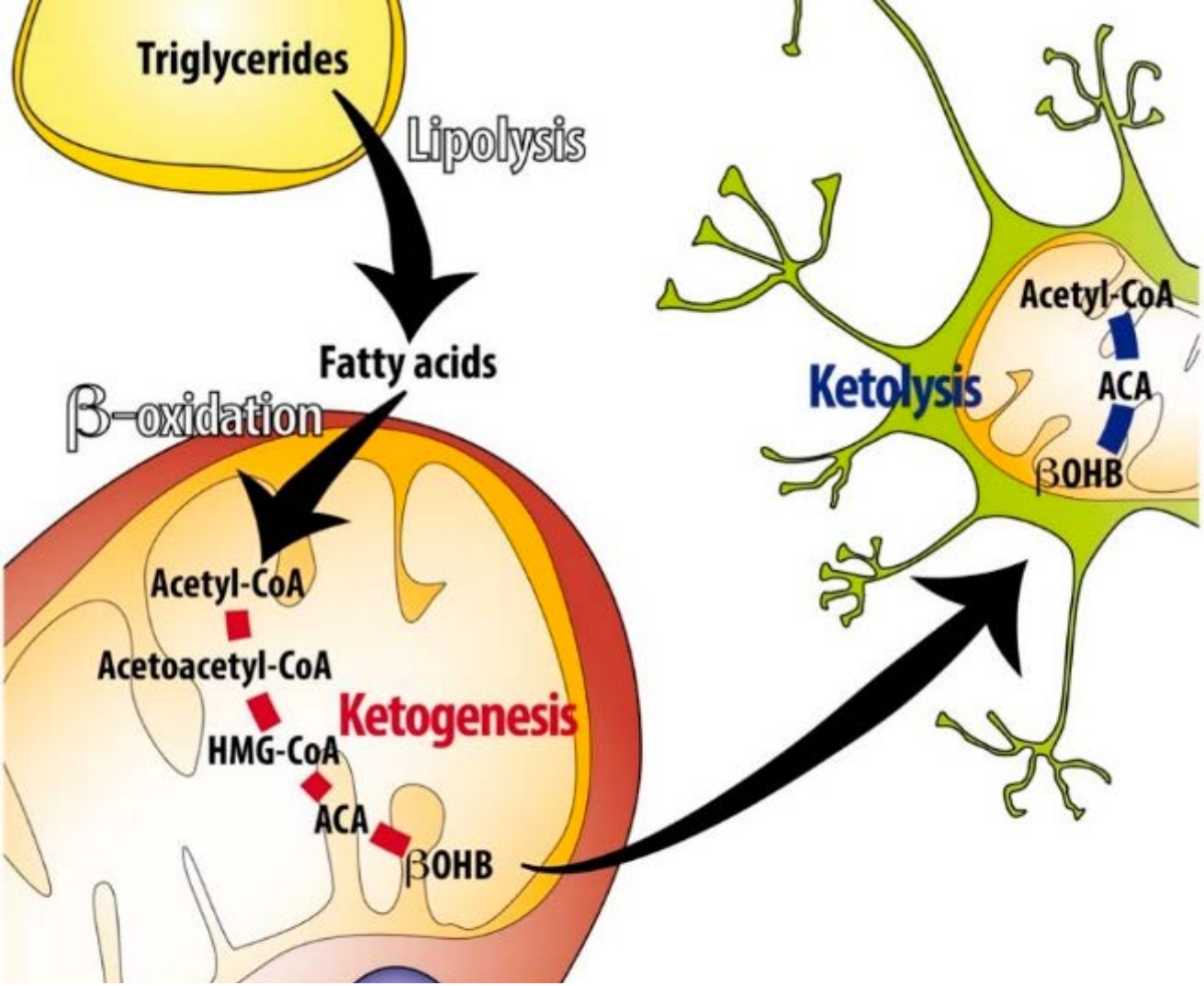
COSA E' UNA DIETA CHETOGENICA ?

E' un regime dietetico che genera chetoni



acetone acetoacetato beta-idrossibutirrato

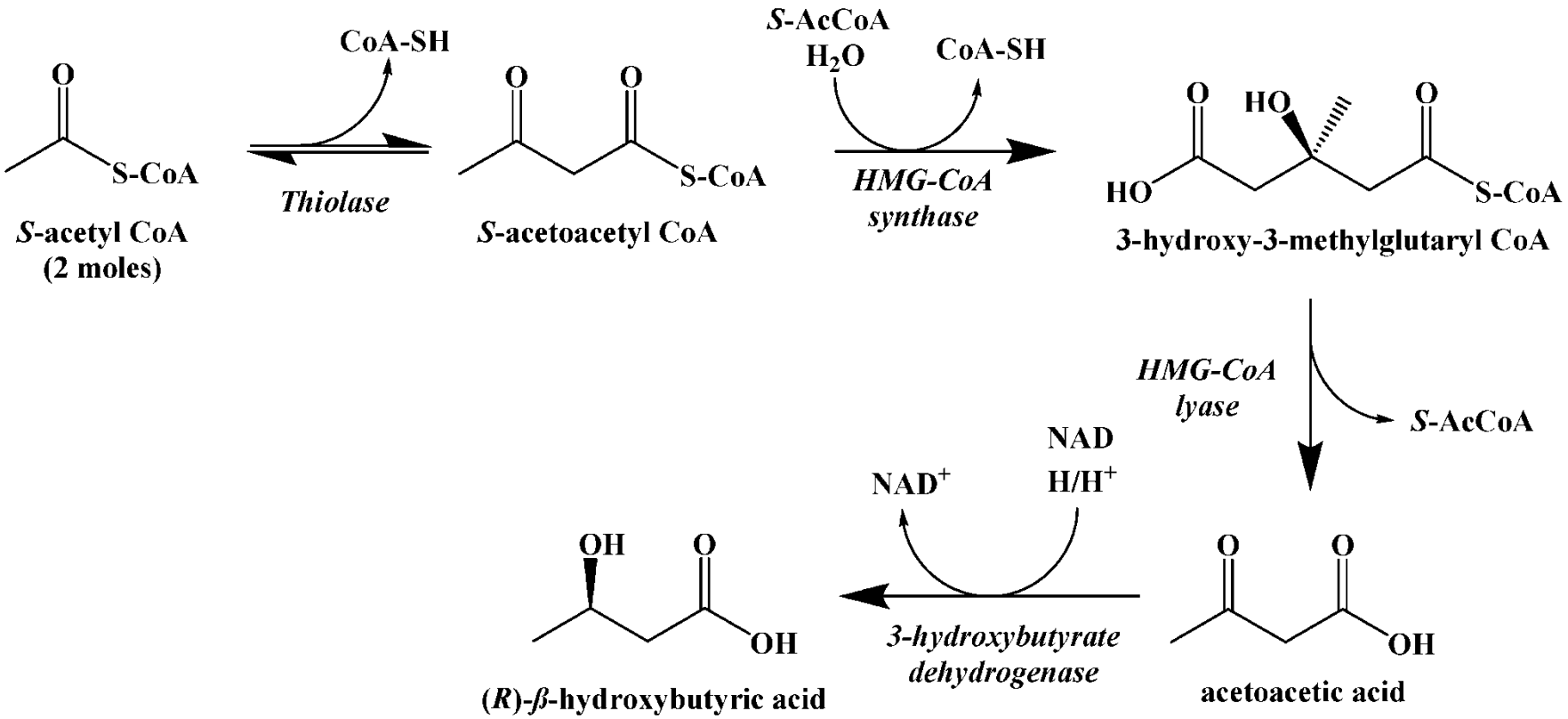
L'unico requisito indispensabile per la generazione di chetoni è l'assenza o la forte restrizione dei carboidrati dalla dieta

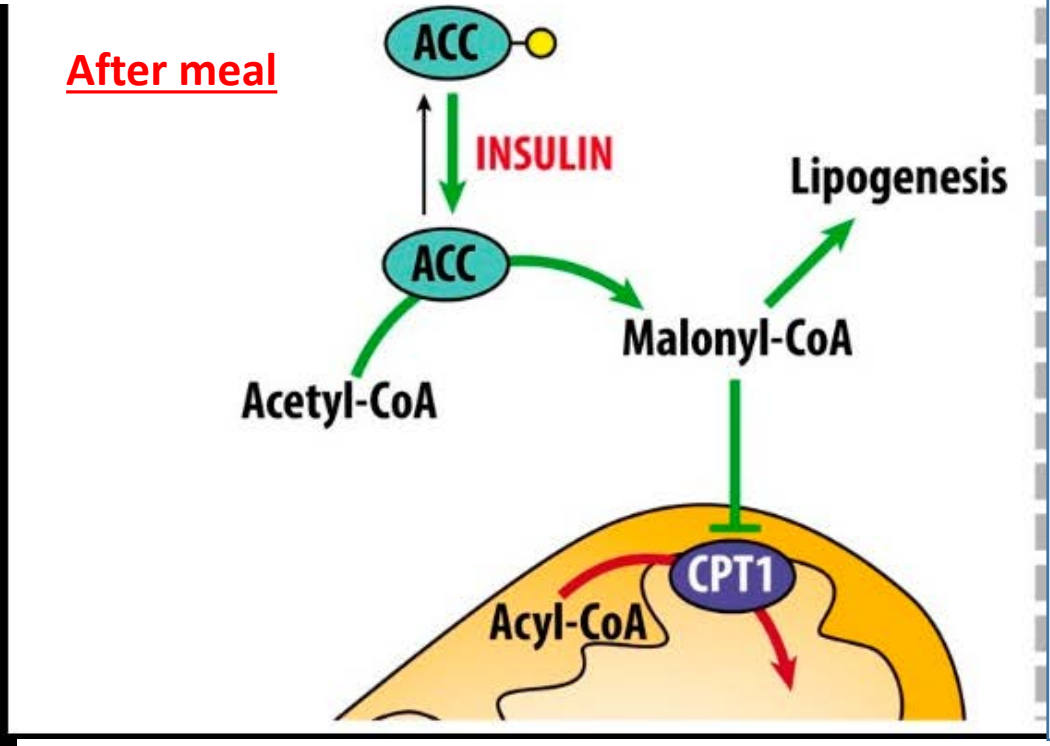


During fasting or prolonged exercise fatty acids are released from adipose tissue via lipolysis of TGs. Fatty acids can be internalized and beta-oxidized in hepatocytes.

Subsequently, acetyl-CoA derived from fatty acid oxidation is used as precursor for ketone body synthesis (acetoacetate [ACA] and beta-hydroxybutyrate [OHB]). OHB is released in the circulation and, after internalization in extra-hepatic tissues (here represented by the neuron) via MCT1 (monocarboxylate transporter 1) is used as a substrate to obtain acetyl-CoA and to produce energy via tricarboxylic acid cycle and electron transport chain.

Genesis of ketone bodies from Acetil-CoA

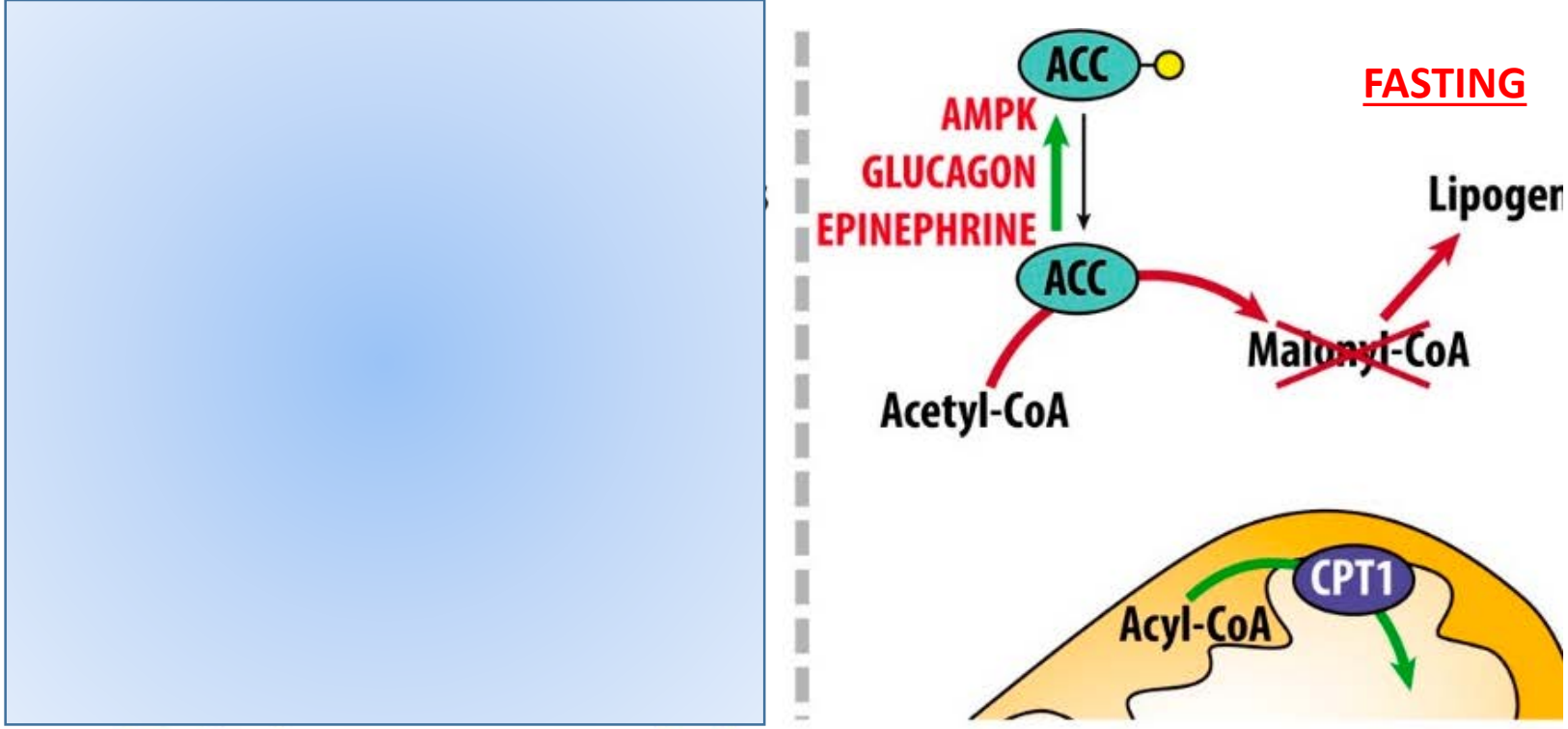




After a meal, insulin release promotes the dephosphorylation (phosphate group = yellow dot) and activation of acetyl-CoA carboxylase (ACC), therefore increasing malonyl-CoA levels.

This metabolite is the precursor for fatty acid synthesis but it also inhibits carnitin-palmitoyl transferase 1 (CPT1) activity and, consequently, fatty acid beta-oxidation.

Under this condition ketogenesis does not occur because of the lack of production of mitochondrial acetyl-CoA from fatty acid beta-oxidation.



<u>During fasting</u>, AMP kinase (AMPK), glucagon and epinephrine contribute to increase the phosphorylation and inactivation of acetyl-CoA carboxylase (ACC) activity.
Therefore, carnitin-palmitoyl transferase 1 (CPT1) activity is unlocked and fatty acid beta-oxidation occurs, thus producing high amount of mitochondrial acetyl-CoA, which can be used as precursor for ketone body production.

Il problema delle definizioni

- La chetogenesi si induce fondamentalmente via forte restrizione carboidratica.
- Le possibili declinazioni sono essenzialmente:

- Low-Energy/Very Low Carb diet
- Low-Fat/Very Low Carb diet
- High Fat/Very Low Carb diet
- High Protein/Very Low Carb diet
- High Fat/High Protein/Very Low Carb diet

Essenziale per capire la letteratura (e i suoi timori!!!)

Ketogenic diet

The ketogenic diet was first developed in the 1920s for the treatment of diabetes and pediatric epilepsy. It is now associated with weight loss and blood glucose control for patients with prediabetes and type 2 diabetes.

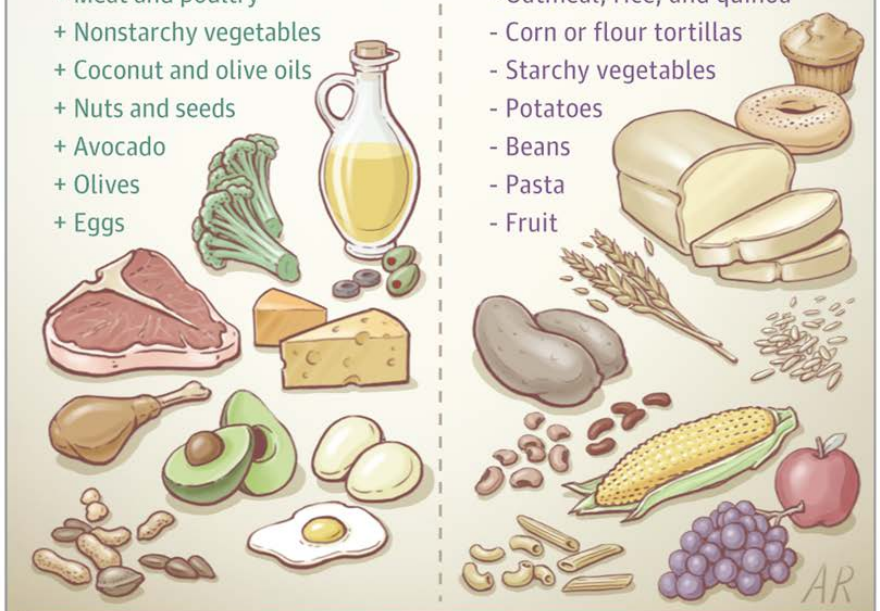
Recommended calorie sources

Foods to eat

+ Full-fat dairy products
+ Meat and poultry
+ Nonstarchy vegetables
+ Coconut and olive oils
+ Nuts and seeds
+ Avocado
+ Olives
+ Eggs

Foods to avoid

- Grains (bread products)
- Oatmeal, rice, and quinoa
- Corn or flour tortillas
- Starchy vegetables
- Potatoes
- Beans
- Pasta
- Fruit



Potential risks and adverse effects

Low physical and mental energy, hunger, sleep disturbance, muscle cramps, constipation, and stomach discomfort during the first 2 weeks of the diet

Increased urine production and fluid shifts in the body may require adjustment of blood pressure, heart failure, and diabetes medications.

JAMA. 2020;323(4):386.

Ketogenic diet

The ketogenic diet was first developed in the 1920s for the treatment of diabetes and pediatric epilepsy. It is now associated with weight loss and blood glucose control for patients with prediabetes and type 2 diabetes.

Re rie sources

5% 75% %

Carbohyd t Protein

Foods t oid

+ Full-fat dairy p products)
+ Meat and poultr ce, and quinoa
+ Nonstarchy vegeta our tortillas
+ Coconut and olive o vegetables
+ Nuts and seeds
+ Avocado
+ Olives
+ Eggs

Potential risks and adverse effects

Low physical and mental energy, hunger, sleep disturbance, muscle cramps, constipation, and stomach discomfort during the first 2 weeks of the diet

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JAMA. 2020;323(4):386.

Quale rapporto fra i macronutrienti?

- **In realtà non esiste un rapporto ideale fisso …**
- **Dipende da metabolismo basale del soggetto, risposta alla dieta impostata, timing della chetosi …**

-> Enorme importanza del «seguire il paziente» !!!

The Journal of Nutrition
Issues and Opinions

The Ketogenic Diet: Evidence for Optimism but High-Quality Research Needed

David S Ludwig

New Balance Foundation Obesity Prevention Center, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

TABLE 1 Conditions under study with a ketogenic or low-carbohydrate diet[1]

Condition	Proposed mechanisms[2]
Cancer (ancillary treatment)	Warburg effect; reduced concentration of insulin and other growth-stimulating hormones and factors; immune modulation; reduced side effects of chemotherapy, radiation
Brain	
Breast	
Colon	
Endometrial	
Lymphoma	
Pancreaticobiliary	
Prostate	
Cardiovascular	Weight loss; reduced postprandial glycemia, insulinemia; anti-inflammatory effects of ketones
Chronic inflammation	
Dyslipidemia	
Endothelial dysfunction	
Insulin resistance	
Endocrine	
Diabetes, type 1	Reduced postprandial glycemic excursions, lower insulin requirement
Diabetes, type 2	As above; weight loss
Obesity	Reduced anabolic stimulation of adipose; partitioning of metabolic fuels
Gastrointestinal	
Fatty liver, nonalcoholic	Reduced postprandial glycemia, insulinemia; enhanced fat oxidation
Irritable bowel syndrome	Microbiome; carbohydrate fermentation
Neurological	Neuroprotective effects of ketones through reduced inflammation, edema oxidative damage, apoptosis, amyloid deposition; neural energy metabolism; epigenetic effects; microbiome
Alzheimer disease	
Epilepsy	
Mild cognitive impairment	
Multiple sclerosis	
Oxygen toxicity (underwater diving)	
Traumatic brain injury	
Spinal cord injury	
Psychological/psychiatric	Reduced withdrawal symptoms; reduced craving and reward, mediated by nucleus accumbens; reduced neuroinflammation; neuronal metabolism; microbiome
Alcoholism	
Autism spectrum disorder	
Bipolar disorder	
Mood disorders	
Schizophrenia	
Well-being/quality of life	
Miscellaneous	
Exercise tolerance, physical performance	Improved access to metabolic fuels
Gangliosidoses	Increased efficacy, reduced side effects of primary treatment
Infectious endocarditis, diagnosis	Enhanced signal-to-noise ratio with ^{18}F-FDG PET scan
Lymphedema	Endothelial cell function; lymphatic transport
Obstructive sleep apnea	Weight loss; decreased visceral fat

I livelli di evidenza scientifica a supporto della KD

- Modelli preclinici
- Case reports
- Case series
- Studi in aperto
- RCTs
- Overviews
- Reviews
- Revisioni sistematiche
- Meta-analisi

I livelli di evidenza scientifica a supporto della KD

- Modelli preclinici X
- Case reports X
- Case series X
- Studi in aperto X
- RCTs X
- Overviews X
- Reviews X
- Revisioni sistematiche X
- Meta-analisi X

Efficacia e sicurezza della VLCKD in pazienti sovrappeso o obesi: una revisione sistematica e metanalisi

- **12 RCTs.**
- **VLCKD <4 settimane: - 10 kg**
- **VLCKD>4 settimane= - 15.6 kg**
- **BMI= -5.3 kg/m2, WC= -12.6 cm, HbA1c= -0.7%, TC= -28 mg/dL, TG= -30 mg/dL, AST= - 7 U/L, ALT= -8 U/L, gGT= -8 U/L, PAS= -8 mmHg, PAD= - 7 mmHg**
- **Non modificazione di LDL-C, HDL-C, Creatininemia, SUA, K**
- **Aumento Sodiemia durante VLCKD (+1.6 mEq/L)**
- **% Discontinuazione VLCKD= 7.5% (simile a soggetti in dieta ipocalorica standard, p= 0.83)**
- **Non cambiamento di peso dalla fine della fase chetogenica a 2 anni di follow-up**

Castellana M et al. Rev Endocr Metab Disord. 2020 Mar;21(1):5-16.

Simulazione cambiamento classe di rischio CV a 10 anni

- Uomo, 65 anni, non fumatore
- 95 kg -> 80 kg
- PA= 152/90 mmHg -> 144/83 mmHg
- CT= 224 mg/dL -> 198 mg/dL

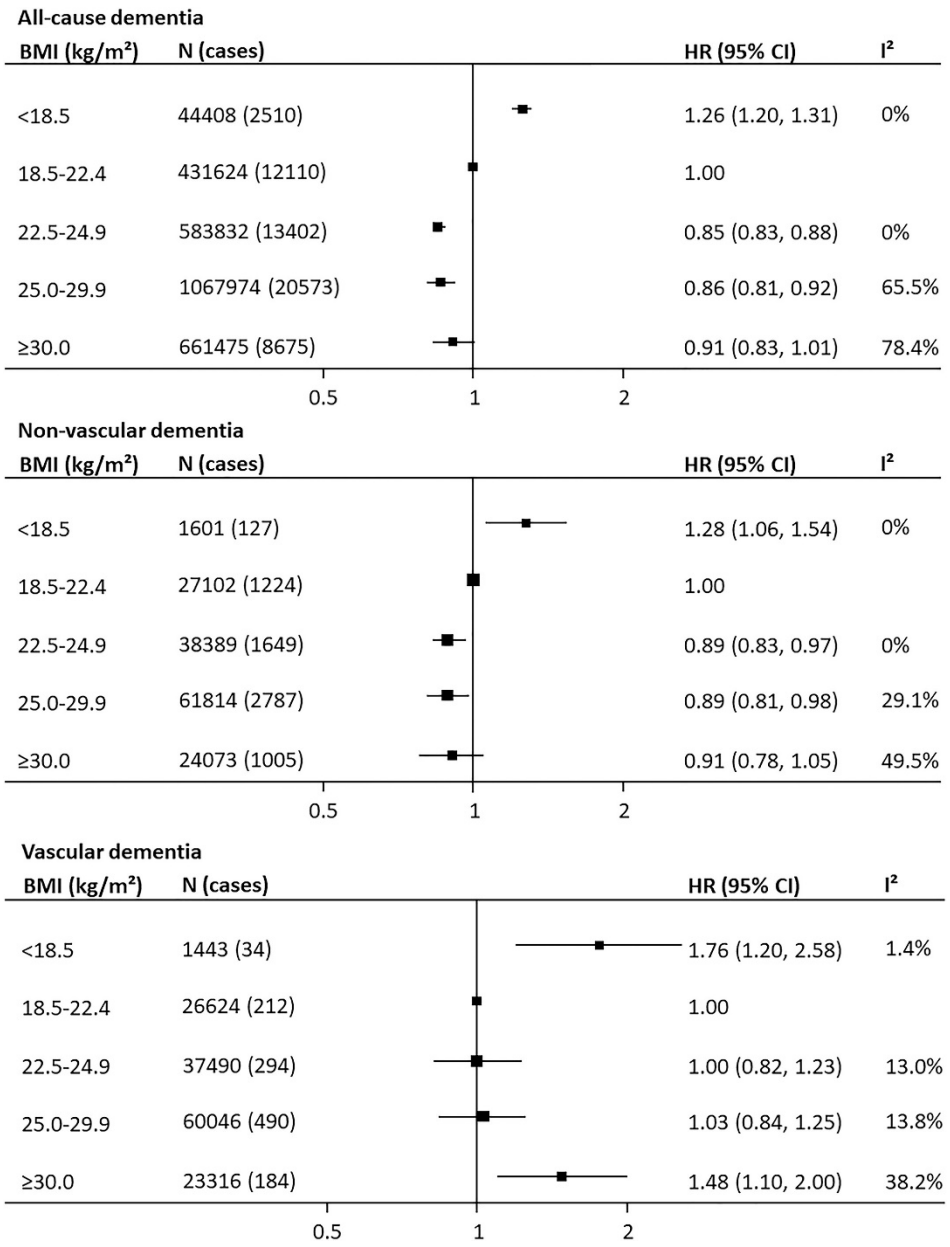
Simulazione cambiamento classe di rischio CV a 10 anni

- Uomo, 65 anni, non fumatore, iperteso in terapia
- 95 kg -> 80 kg
- PA= 152/90 mmHg -> 144/83 mmHg
- CT= 224 mg/dL -> 198 mg/dL

- Rischio CV: 20,9% -> 15,8%

-> -25% rischio relativo !!!

Associazione di antropometria e cambio di peso col rischio di demenza: una metanalisi di dati su 2.8 millioni di adulti con 57 294 casi incidenti di demenza



Obesity Reviews, First published: 03 January 2020, DOI: (10.1111/obr.12989)

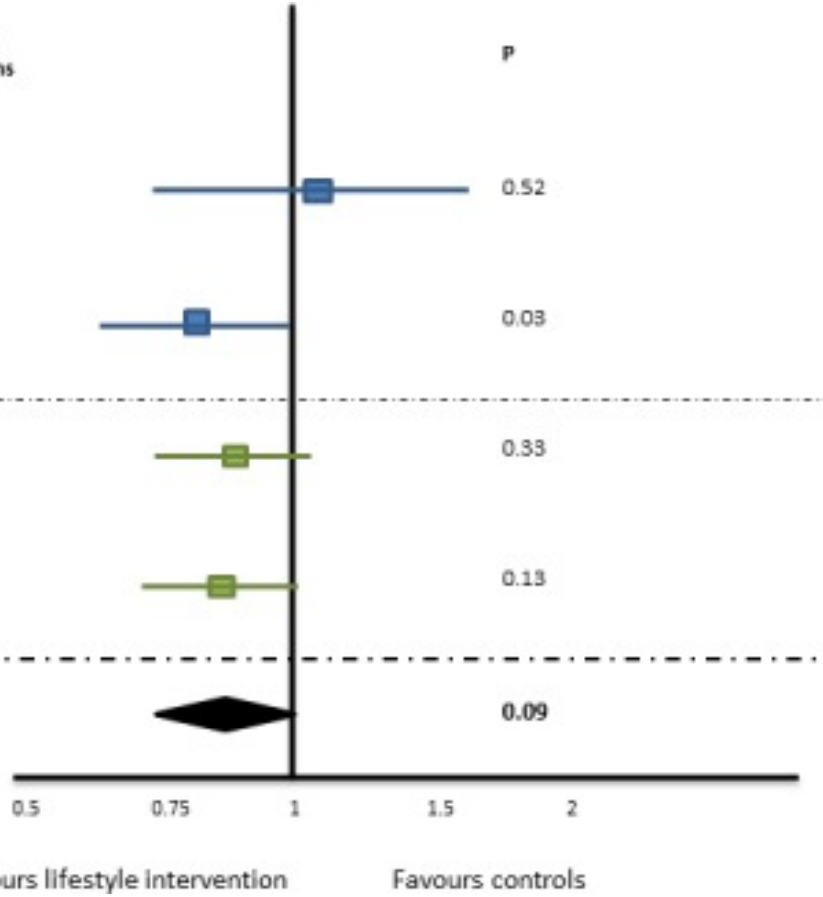
Effetto del calo ponderale su rischio e gravità della fibrillazione atriale: una metanalisi di studi clinici controllati

- 5 studi con un totale di 548 pazienti.
- I pazienti che riescono a perdere ≥10% del loro peso iniziale presentano:
- ↓ 29% rischio di ricorrenza di una FA (risk ratio 0.29; 95% CI 0.19 a 0.44)
- ↓ durata degli episodi (MD 2.14; 95% CI 0.04 a 4.23)
- ↓ severità globale degli episodi (MD 1.89; 95% CI 1.34 a 2.45)
- ↓ severità dei sintomi (MD 5.36; 95% CI 3.75 a 6.97)

Am J Cardiol. 2019 Nov 15;124(10):1568-1574.

Effetto della perdita di peso sulla mortalità per tutte le cause in un follow-up medio pesato di 9.2 anni

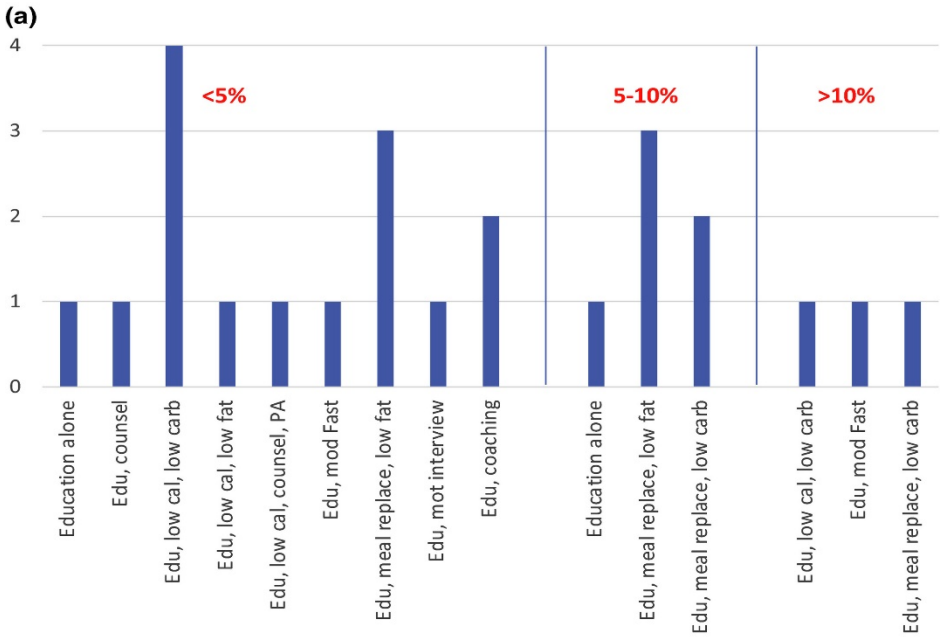
	Number of studies	N Intervention	N control	Odds ratio (95% CI)	Total deaths	P
Intervention ≤28 per year	18	5063	5227	1.11 [0.80, 1.56]	153	0.52
Intervention > 28 per year	18	4860	4589	0.81 [0.66, 0.98]	440	0.03
Weight loss ≤ 3.67Kg	20	4425	3844	0.89 [0.68, 1.16]	192	0.33
Weight loss > 3.67kg	12	5400	6605	0.86 [0.72, 1.04]	391	0.13
Total mortality	**33**	**9923**	**9816**	**0.86 [0.73, 1.02]**	**593**	**0.09**

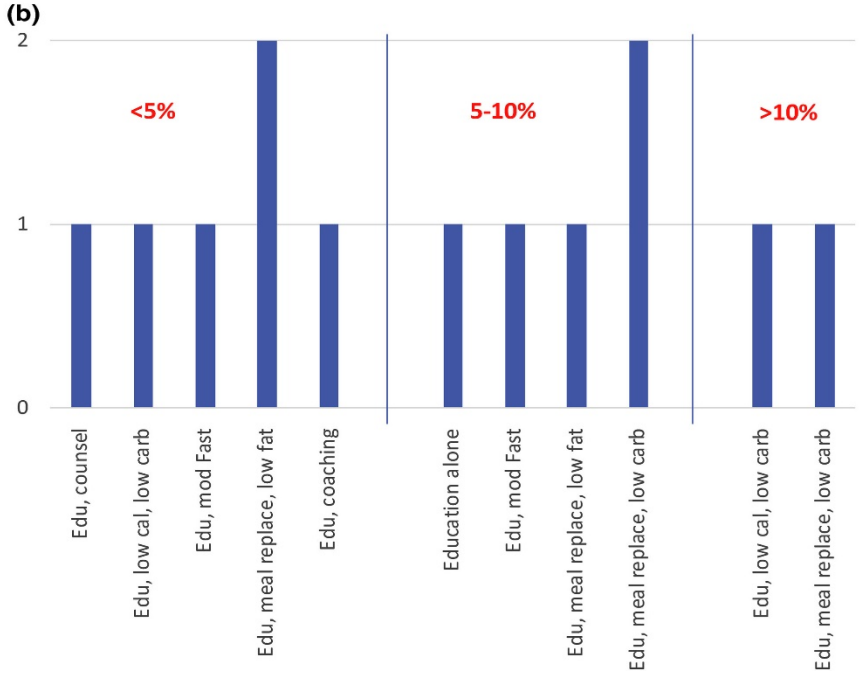


BMJ Open. 2019; 9(8): e029966.

Educational weight loss interventions in obese and overweight adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

49 RCTs (n = 12 461 participants)





Diabetic Medicine, First published: 30 November 2019, DOI: (10.1111/dme.14193)

Weight loss and body composition changes through ketogenic diet and physical activity: a methodological and systematic review

Evelyn Martín-Moraleda[1], Christine Delisle[2], Daniel Collado-Mateo[3] y Susana Aznar[1]

[1]Grupo de investigación PAFS. Universidad de Castilla La-Mancha. Toledo, España. [2]Department of Biosciences and Nutrition. Karolinska Institutet. NOVUM. Huddinge, Sweden. [3]Facultad de Ciencias del Deporte. Universidad de Extremadura. Cáceres, España

Objective: the objective of this review was to investigate the work done with obese patients who undertook a ketogenic diet and a physical exercise program, as well as to calculate the overall effect size in terms of improvements in fat mass, through a meta-analysis.

Methods: the selection of studies was based on the following criteria: experimental studies; a) experimental studies (randomized controlled designs) and quasi-experimental (e.g. pre-test/post-test); b) studies with low-carbohydrate diet (< 30%) or very low in carbohydrates (5-10%) (< 50 g Ch) and/or high in fats (> 35%); c) studies were admitted exclusively with subjects that facility overweight or obesity (BMI > 25; and d) with measurements of body composition and/or Lipid profile at the beginning and end of the intervention.

Results: for the methodological review, 7 articles and 3 reviews were analyzed. All studies, whether by establishing aerobic or strength training and show significant weight loss in all outcomes.

Conclusions: comparing different types of exercise, we could say that interventions based on endurance exercise reported a decrease in muscle mass, however there was a maintenance, and even an increase, in studies with resistance exercises. Meta-analysis showed significant results at the global level with a medium heterogeneity, therefore, there will be greater reduction of fat mass in groups that realize diets with low carbohydrates and exercise that in those who do not undertake this type of diet, and those only perform exercise.

KD associata ad esercizio di resistenza comporta mantenimento o aumento della massa magra, mentre l'esercizio di endurance calo !

Martín-Moraleda E, Delisle C, Collado-Mateo D, Aznar S. Cambios en la pérdida de peso y la composición corporal con dieta cetogénica y práctica de actividad física: revisión narrativa, metodológica y sistemática. Nutr Hosp 2019;36(5):1196-1204

nutrients

MDPI

Article

The Effect of Low Carbohydrate Diets on Fertility Hormones and Outcomes in Overweight and Obese Women: A Systematic Review

Melanie McGrice [1,2,*] and Judi Porter [3,4]

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2 Nutrition Plus Enterprises, 1004/1 Queens Road, Melbourne VIC 3004, Australia
3 Allied Health Research Office, 5 Arnold Street, Box Hill VIC 3128, Australia; Judi.Porter@easternhealth.org.au
4 Department of Nutrition, Dietetics and Food, Monash University, Level 1, 264 Ferntree Gully Road, Notting Hill VIC 3168, Australia

Nutrients **2017**, *9*, 204; doi:10.3390/nu9030204

Studies of low carbohydrate diets in overweight and obese women measuring fertility hormones and other reproductive outcomes

Author, Year, Location	Participants; Study Duration	Cause of Infertility	Study Design	Intervention	Comparators	Fertility Outcomes (Pregnancy Rate/Other)
Mavropoulos et al. 2005, USA [18]	11 women with PCOS and BMI >27 from the community; 24 weeks	PCOS	Two arm pre/post study	<20 g carbohydrate/day, ad libitum MJ/day (<6% carbohydrate if consuming 5 MJ/day)	Own control on usual diet (pre-intervention)	Reproductive hormones; Pregnancy rates
Moran et al. 2003, Australia [20]	45 overweight women with PCOS; 12 weeks	PCOS	Matched control trial	High protein, low carbohydrate (6 MJ—40% carbohydrate, 30% protein, 30% fat)	Usual diet (55% carbohydrate, 15% protein, 30% fat) but limited to 6 MJ/day	Reproductive hormones; Ovulation rates
Palomba et al. 2008, Italy [19]	20 obese PCOS patients with anovulatory infertility; 24 weeks	PCOS	Two arm pre/post study	High protein, low carbohydrate diet (35% protein, 45% carbohydrate, 20% fat) with 3.3 MJ deficit	Usual diet and 3 physical activity sessions per week	Reproductive hormones; Ovulation rates; Pregnancy rates
Palomba et al. 2010, Italy [22]	96 overweight or obese Clomiphene citrate resistant women; 2 weeks intervention, 4 weeks clomid (±intervention)	PCOS	Three arm randomised parallel controlled trial	Structured exercise + 35% protein, 45% carbohydrate, 20% fat diet with 4.2 MJ/day deficit + clomiphene citrate	Usual diet followed by clomiphene citrate	Reproductive hormones; Ovulation rate
Sim et al. 2014, Australia [3]	49 obese women planning ART; 12 weeks intervention, 12 month follow up	Mixed	Randomised controlled trial	Very low energy diet (2.5 MJ/day, 34% carbohydrate) for 6/52 followed by 6/52 hypocaloric diet	Usual diet	Pregnancy rates
Stamets et al. 2004, USA [21]	35 obese women with PCOS; 1 month	PCOS	Randomised controlled trial	Diet (40% carbohydrate, 30% protein, 30% fat with 4.2 MJ/day energy deficit)	Usual diet (55% carbohydrate, 15% protein, 30% fat) with a 4.2 MJ/day energy deficit	Reproductive hormones
Thomson et al. 2008, Australia [23]	94 overweight and obese women; 20 weeks	PCOS	Randomised parallel study (only one arm, "Diet Only" was included in this review)	Diet (5–6 MJ/day, 30% protein, 40% carbohydrate, 30% fat)	Own control on usual diet (pre-intervention)	Reproductive hormones; Ovulation rates

Nutrients 2017, *9*, 204; doi:10.3390/nu9030204

Study (Author, Year)	Intervention Group	Control Group	*p*-Value
Reproductive hormones			
Mavropoulos, 2005 [18]	Free testosterone ng/dL 1.7	Free testosterone ng/dL 2.19	0.04
	Luteinizing Hormone/Follicle Stimulating Hormone ratio 1.21	Luteinizing Hormone/Follicle Stimulating Hormone ratio 2.23	0.03
	Fasting serum insulin mcIU/mL 8.2	Fasting serum insulin mcIU/mL 23.5	0.002
Moran, 2003 [20]	Fasting glucose (mmol/L) 5.42 ± 0.13	Fasting glucose (mmol/L) 5.31 ± 0.17	NS
	Fasting insulin (mU/L) 16.6 ± 2.4	Fasting insulin (mU/L) 12.8 ± 2.0	<0.01
	Sex Hormone Binding Globule (nmol/L) 25 ± 2.5	Sex Hormone Binding Globule (nmol/L) 35 ± 5	0.027
	Testosterone (nmol/L) 1.45 ± 0.2	Testosterone (nmol/L) 1.3 ± 0.1	0.01
	Free Androgen Index (nmol/L) 7 ± 1.5	Free Androgen Index (nmol/L) 4.5 ± 1	0.004
Palomba, 2008 [19]	Follicle Stimulating Hormone (mIU/mL) 4.2 ± 13.2	Follicle Stimulating Hormone (mIU/mL) −1.2 ± 3.2	NS
	Testosterone (nmol/L) −28.7 ± 11.7	Testosterone (nmol/L) −33.4 ± 14.3	<0.05
	Sex Hormone Binding Globule (nmol/L) 41.9 ± 19.1	Sex Hormone Binding Globule (nmol/L) 82.5 ± 30.6	<0.05
	Free Androgen Index (%) −18.1 ± 9.7	Free Androgen Index (%) −27.2 ± 9.2	<0.05
	Fasting glucose (mmol/L) 1.2 ± 8.6	Fasting glucose (mmol/L) 0.4 ± 4.1	NS
	Fasting insulin (pmol/L) −13.1 ± 8.6	Fasting insulin (pmol/L) −23.4 ± 10.0	<0.05
Palomba, 2010 [22]	Follicle Stimulating Hormone (mIU/mL) 4.9 ± 3.1	Follicle Stimulating Hormone (mIU/mL) 4.2 ± 1.2	NS
	Testosterone (nmol/L) 2.2 ± 0.6	Testosterone (nmol/L) 2.51 ± 0.9	<0.05
	Sex Hormone Binding Globule (nmol/L) 25.3 ± 3.2	Sex Hormone Binding Globule (nmol/L) 17.4 ± 3.1	<0.05
	Free Androgen Index (%) 10.8 ± 3.5	Free Androgen Index (%) 11.6 ± 3.7	<0.05
	Fasting glucose (mmol/L) 4.0 ± 1.7	Fasting glucose (mmol/L) 4.0 ± 1.5	NS
	Fasting insulin (pmol/L) 15.8 ± 3.9	Fasting insulin (pmol/L) 17.9 ± 4.2	<0.05
Stamets, 2004 [21]	Testosterone (ng/dL) −9 ± 21	Testosterone (ng/dL) −9 ± 18	0.96
	Luteinizing hormone (mIU/mL) 7 ± 30	Luteinizing hormone (mIU/mL) 2 ± 11	0.59
	Follicle Stimulating Hormone (mIU/mL) −1 ± 5	Follicle Stimulating Hormone (mIU/mL) 2 ± 4	0.12
	Area under Curve Insulin 3 h Oral Glucose Tolerance Test −2912 ± 13,562	Area Under Curve Insulin 3 h Oral Glucose Tolerance Test −8734 ± 12,218	0.26
	Area Under Curve Glucose 3 h Oral Glucose Tolerance Test −87 ± 2803	Area Under Curve Glucose 3 h Oral Glucose Tolerance Test −93 ± 2049	0.99
Thomson, 2008 [23]	Glucose (mmol/L) 4.96 ± 0.6	Glucose (mmol/L)5.32 ± 0.49	<0.01
	Insulin (mU/L) 13.5 ± 9.9	Insulin (mU/L) 17.7 ± 8.2	<0.01
	Testosterone (nmol/L) 2.09 ± 0.98	Testosterone (nmol/L) 2.36 ± 0.71	NS
	Sex Hormone Binding Globule (nmol/L) 31.5 ± 17.5	Sex Hormone Binding Globule (nmol/L) 27.4 ± 15.9	NS
	Free Androgen Index (%) 8.4 ± 6.6	Free Androgen Index (%) 11.2 ± 5.5	<0.01

Ovulation rates			
Moran, 2003 [20]	Improved menstrual cyclicity 6/14 42%	Improved menstrual cyclicity 5/14 35%	NR
Palomba, 2008 [19]	Menses frequency (# observed menses/no expected cycles, %) 18/118 15.3%	Menses frequency (# observed menses/no expected cycles, %) 28/107 26.2%	0.043
	Ovulation rate (# ovulatory cycles/# observed cycles, %) 18/119 15.1%	Ovulation rate (# ovulatory cycles/# observed cycles, %) 28/113 24.8%	0.032
Palomba, 2010 [22]	Ovulation rate 12/32 37.5%	Ovulation rate 3/32 9.4%	0.020
Thomson, 2008 [23]	Improved menstrual cyclicity 3/14 21.4%	Improved menstrual cyclicity 0/14 0%	NR
Pregnancy rates			
Mavropoulos, 2005 [18]	Pregnancy 2/5 40%	Pregnancy 0/5 0%	NR
Moran, 2003 [20]	Pregnancy (# pregnancies/# patients, %) 2/14 14%	Pregnancy (# pregnancies/# patients, %) 1/14 7%	NR
Palomba, 2008 [19]	Pregnancy (# pregnancies/# patients, %) 2/20 10%	Pregnancy (# pregnancies/# patients, %) 7/20 35%	0.058
Sim, 2014 [3]	Natural conception 3/27 0.1%	Natural conception 0/22 0%	0.11
	Pregnancy rate 13/27 48.1%	Pregnancy rate 3/22 13.6%	0.007

Allora … perché «high-quality research is needed»?

- **Studi eterogenei per tipologia di soggetti considerati, composizione delle diete testate, durata dei protocolli testati**

- **Carenza di dati di efficacia (a breve e su outcomes forti) su ripetizione cicli di KD e KD di lunga durata, specie su pazienti con comorbidità renale e cardiovascolare (potenziali target della KD)**

- **Difficoltà di strutturazione di vero doppio cieco**

Una «guerra senza fine» alla ricerca di una comunicazione corretta

Epidemiologia ⟷ RCTs

Pattern dietetici ⟷ Componenti

Dieta Lifetime ⟷ Dieta per la cura

Pasti sostitutivi e integrazioni

RAZIONALE E NECESSITA’

Si può ottenere chetosi con la sola dieta ?

- Si ma ….

1) Lentamente (maggiore esposizione al disagio iniziale: astenia, fame, craving…)
2) Difficoltà di bilanciare la dieta (spettro aminoacidico), specie per necessità di diversità di alimenti e tempi di reperimento/preparazione
3) Rischio deficit micronutrienti

KD adverse events

Short-term effects
Nausea/vomiting
Constipation
Dehydration
Anorexia
Lethargy
Hypoglycemia
Acidosis
Long-term effects
Disruptions in lipid metabolism
Severe hepatic steatosis
Hypoproteinemia
Mineral deficiencies
Increase redox imbalance
Cardiomyopathy
Nephrolithiasis

J Postgrad Med. 2017 Oct-Dec;63(4):242-251.

Supplementazioni ?

- **Meno di quanto spesso si creda …**
- **Acqua (!)**
- **Multivitaminici/Multiminerali**
- **Magnesio (citrato)**
- **Potassio citrato**
- **Quercetina/Vitamina C**
- **Calcio + Vitamina D**
- **Acidi grassi Omega 3**
- **Pre/Pro/Sinbiotici**

Effects of Vitamin and Mineral Supplementation on Stress, Mild Psychiatric Symptoms, and Mood in Nonclinical Samples: A Meta-Analysis

Supplementation reduced the levels of:

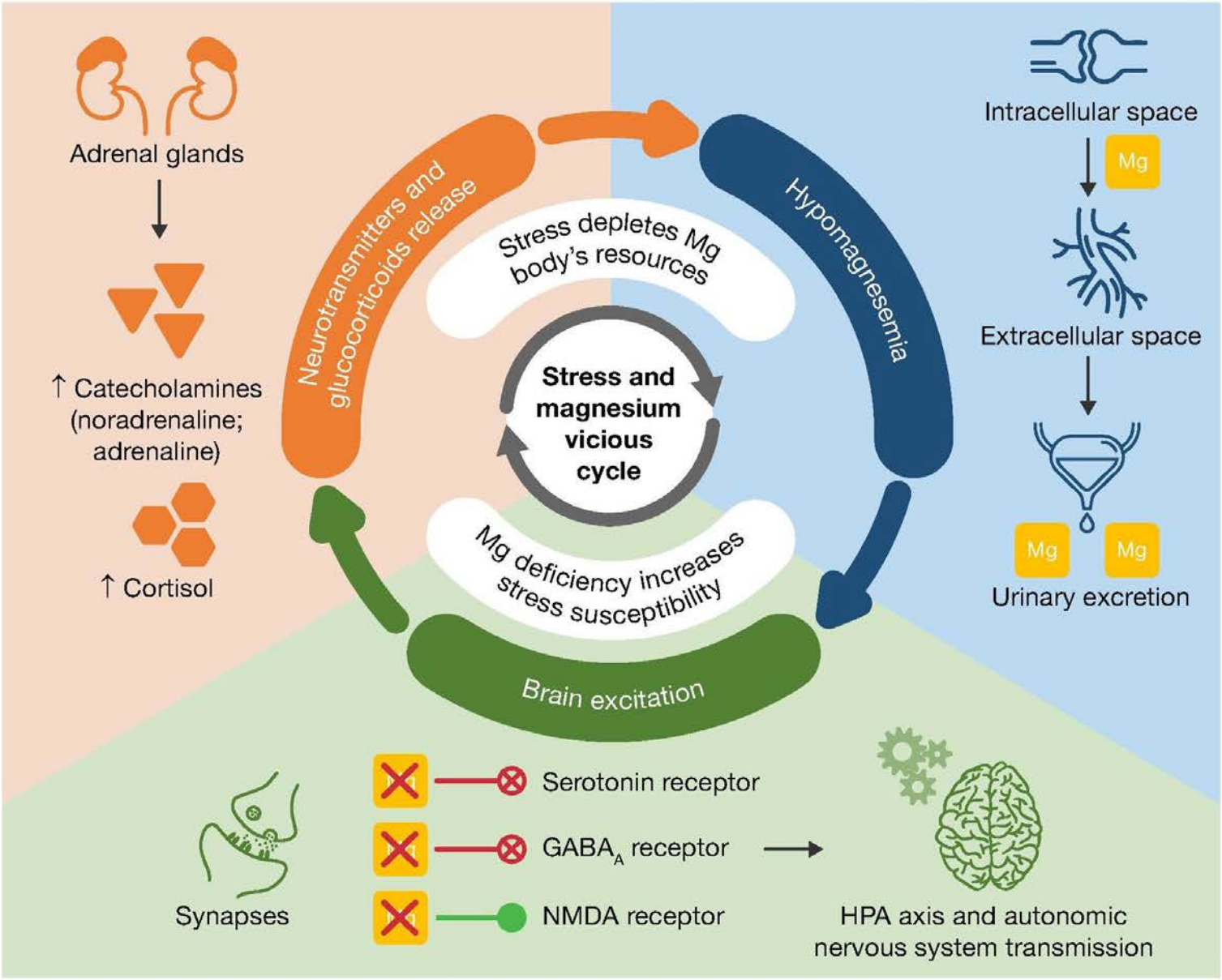
- **Perceived stress (SMD = 0.35; 95%CI 0.47–0.22; *p*= 0.001)**
- **Mild psychiatric symptoms (SMD = 0.30; 95%CI 0.43–0.18; *p* = 0.001)**
- **Anxiety (SMD = 0.32; 95%CI 0.48–0.16; *p* < 0.001)**
- **Fatigue (SMD = 0.27; 95%CI 0.40–0.146; *p* < 0.001)**
- **Confusion (SMD = 0.225; 95%CI 0.38–0.07; *p* < 0.003)**

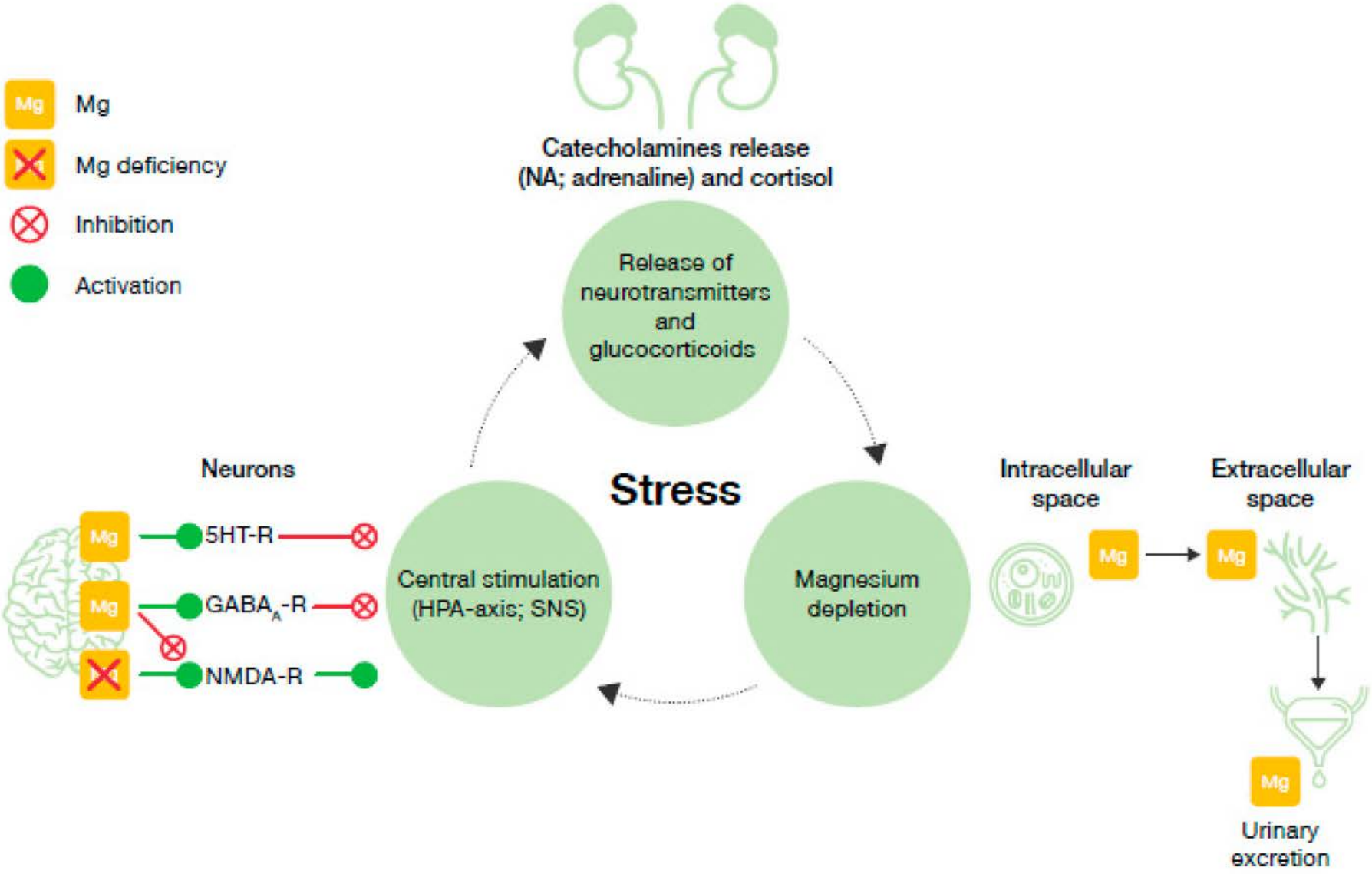
Psychosom Med. 2013 Feb;75(2):144-53.

Symptoms of magnesium deficiency and stress are very similar

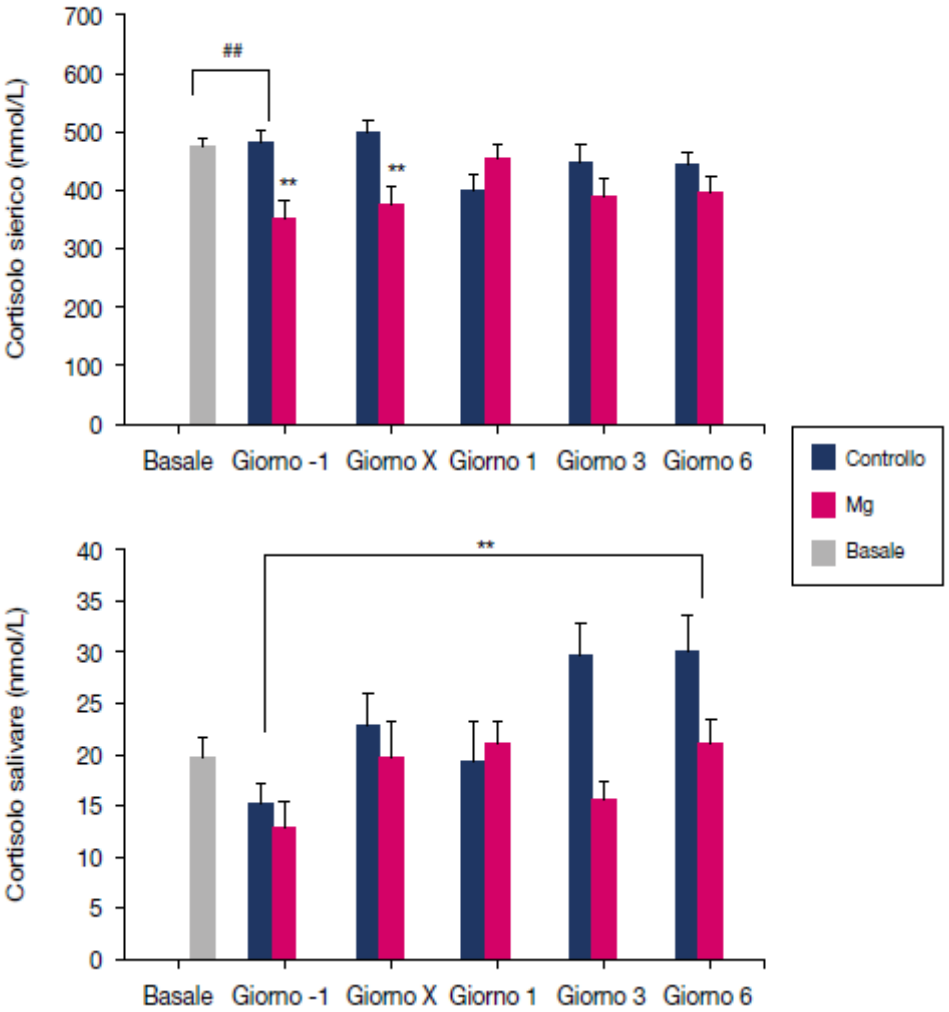
Fatigue
Irritability
Mild anxiety
Headache
Upset stomach

$GABA_A$, γ-aminobutyric acid; HPA, Hypothalamic-pituitary-adrenal axis; Mg, magnesium; NMDA, N-methyl-D-aspartate



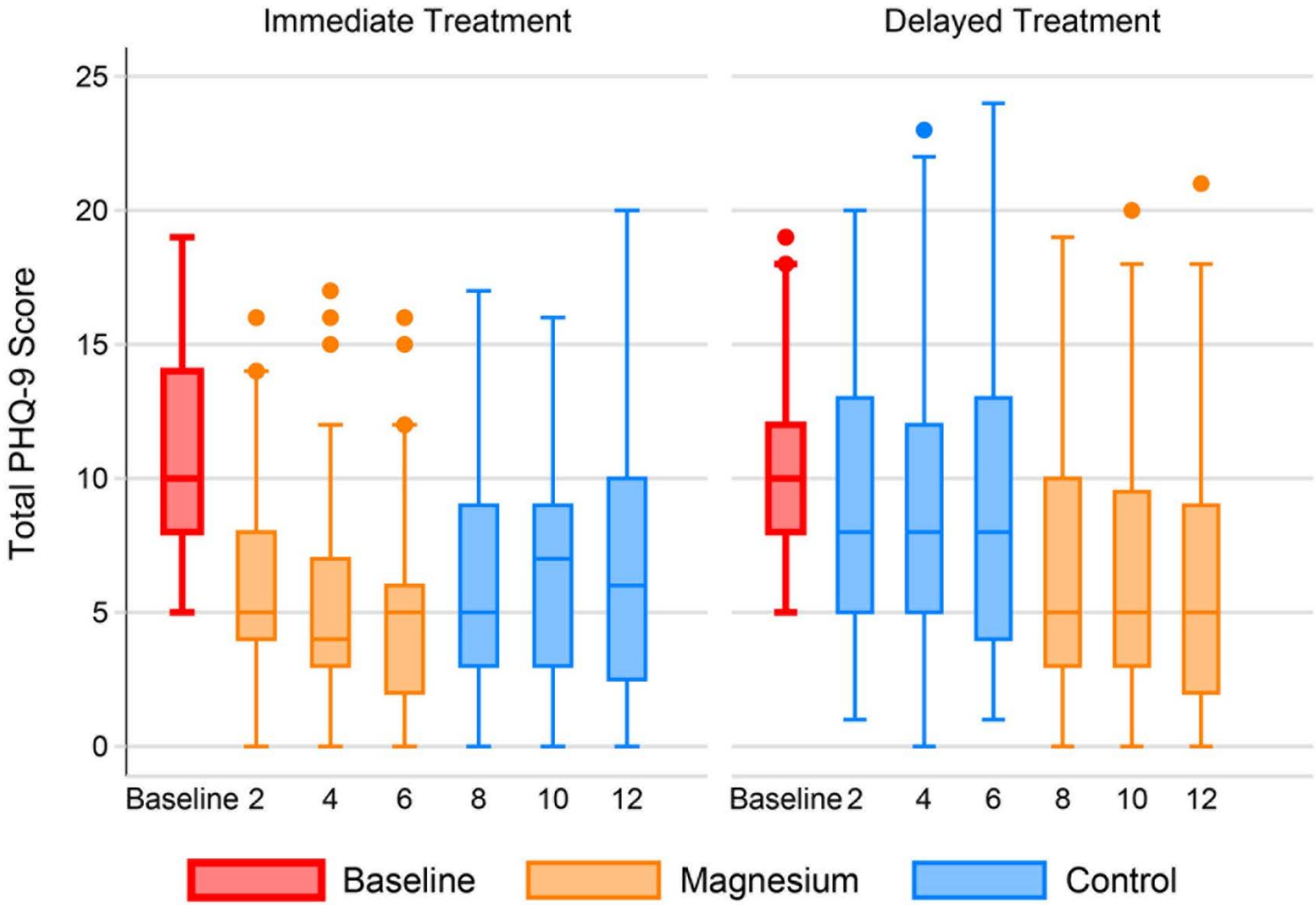

Mg
Mg
Mg deficiency
Inhibition
Activation
Catecholamines release
(NA; adrenaline) and cortisol
Release of
neurotransmitters
and
glucocorticoids
Stress
Central stimulation
(HPA-axis; SNS)
Magnesium
depletion
Neurons
5HT-R
GABA$_A$-R
NMDA-R
Intracellular
space
Extracellular
space
Urinary
excretion

Effetto della supplementazione con magnesio sulla cortisolemia pre-stress e post-stress di atleti sani



Biol Trace Elem Res. 2008 Mar;121(3):215-20.

Role of magnesium supplementation in the treatment of depression: A randomized clinical trial

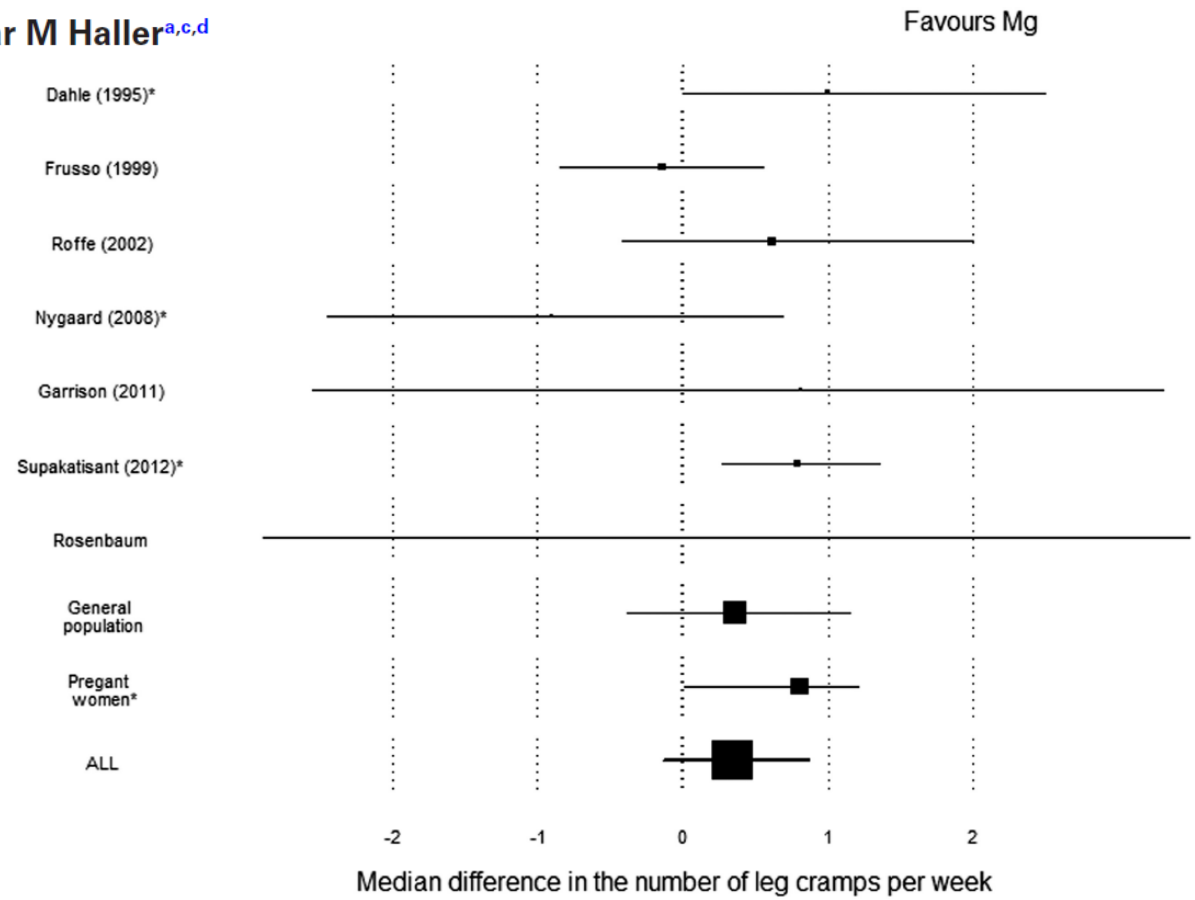


PLoS One. 2017 Jun 27;12(6):e0180067.

Family Practice, 2014, Vol. 31, No. 1, 7–19
doi:10.1093/fampra/cmt065
Advance Access publication 26 November 2013

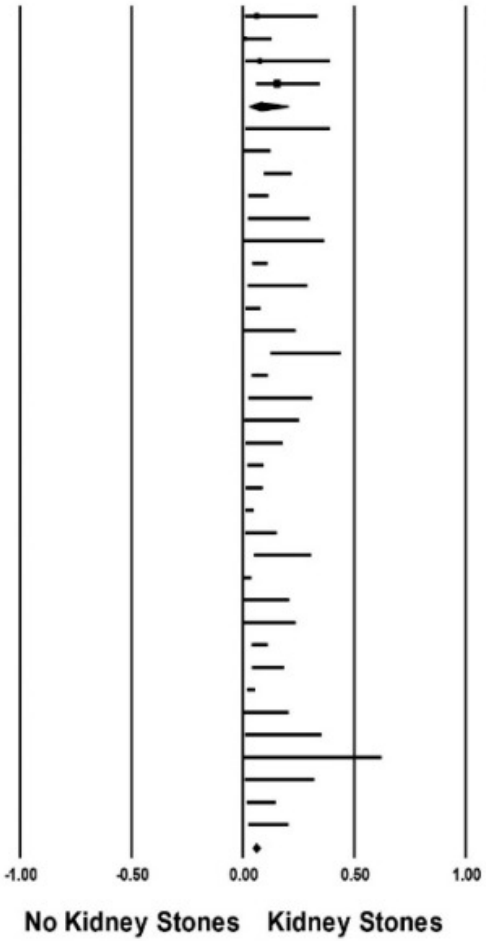
Effect of magnesium therapy on nocturnal leg cramps: a systematic review of randomized controlled trials with meta-analysis using simulations

Paul Sebo[a,*], Bernard Cerutti[b] and Dagmar M Haller[a,c,d]



Incidence of kidney stones during long-term KD

Group by Population	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Adult	Park et al	0.063	0.009	0.335	-2.622	0.009	21.04
Adult	Roehhl et al	0.009	0.001	0.127	-3.315	0.001	12.65
Adult	Attar H et al	0.077	0.011	0.391	-2.387	0.017	20.80
Adult	Lapp et al	0.154	0.059	0.345	-3.136	0.002	45.50
Adult		0.079	0.028	0.201	-4.474	0.000	
Children	Mak et al	0.077	0.011	0.391	-2.387	0.017	1.49
Children	Hassan et al	0.019	0.003	0.124	-3.894	0.000	1.56
Children	Furth et al (1)	0.145	0.093	0.219	-6.955	0.000	6.26
Children	Furth et al (2)	0.054	0.024	0.114	-6.843	0.000	4.63
Children	Rios et al	0.091	0.023	0.300	-3.105	0.002	2.48
Children	Takeoka et al	0.033	0.002	0.366	-2.341	0.019	0.86
Children	Kossoff et al (1)	0.068	0.041	0.110	-9.796	0.000	6.13
Children	Kossoff et al (2)	0.087	0.022	0.289	-3.177	0.001	2.48
Children	Kang et al (1)	0.031	0.012	0.080	-6.776	0.000	3.89
Children	Mackay et al	0.019	0.001	0.236	-2.781	0.005	0.87
Children	Groesbeck et al	0.250	0.124	0.439	-2.517	0.012	4.48
Children	Sampath et al	0.067	0.039	0.111	-9.193	0.000	5.93
Children	Raimann et al	0.095	0.024	0.311	-3.028	0.002	2.47
Children	Sharma et al	0.043	0.006	0.252	-3.023	0.003	1.53
Children	Kang et al (2)	0.050	0.013	0.179	-4.059	0.000	2.55
Children	Caraballo et al	0.043	0.019	0.092	-7.443	0.000	4.66
Children	Dressler et al	0.035	0.013	0.089	-6.530	0.000	3.88
Children	Hallbook et al	0.024	0.012	0.050	-9.669	0.000	4.98
Children	Wibisono et al	0.042	0.010	0.152	-4.341	0.000	2.57
Children	Khoo et al	0.133	0.051	0.306	-3.485	0.000	3.67
Children	Lim et al	0.010	0.002	0.038	-6.495	0.000	2.62
Children	Simm et al	0.034	0.005	0.208	-3.274	0.001	1.54
Children	Lambrechts et al	0.019	0.001	0.236	-2.781	0.005	0.87
Children	McNally et al	0.067	0.039	0.111	-9.193	0.000	5.93
Children	Draaisma et al	0.088	0.040	0.183	-5.462	0.000	4.56
Children	Guzel et al	0.031	0.018	0.054	-11.756	0.000	5.87
Children	Holler et al	0.016	0.001	0.206	-2.907	0.004	0.87
Children	Rener et al	0.067	0.009	0.352	-2.550	0.011	1.50
Children	Felix et al	0.083	0.005	0.622	-1.623	0.105	0.82
Children	Nerurkr et al	0.059	0.008	0.320	-2.690	0.007	1.51
Children	Nangia et al	0.051	0.016	0.146	-4.939	0.000	3.29
Children	Gainza et al	0.073	0.024	0.204	-4.234	0.000	3.25
Children		0.058	0.044	0.075	-19.824	0.000	



36 studies with 2795 patients on ketogenic diets were enrolled. The estimated pooled incidence of kidney stones was 5.9% (95% CI, 4.6–7.6%) in patients on KD at a mean follow-up time of 3.7±2.9 years.
48.7% (95% CI, 33.2–64.6%) of kidney stones were uric stones, 36.5% (95% CI, 10.6–73.6%) were calcium-based (CaOx/CaP) stones, and 27.8% (95% CI, 12.1–51.9%) were mixed uric acid and calcium-based stones.

Diseases. 2021 Jun; 9(2): 39.

Approccio empirico alla prevenzione della nefrolitiasi

- **Idratazione**
- **Potassio citrato**
- **Vitamina C/Quercetina (?)**

Urolithiasis 2019 Feb;47(1):107-113.

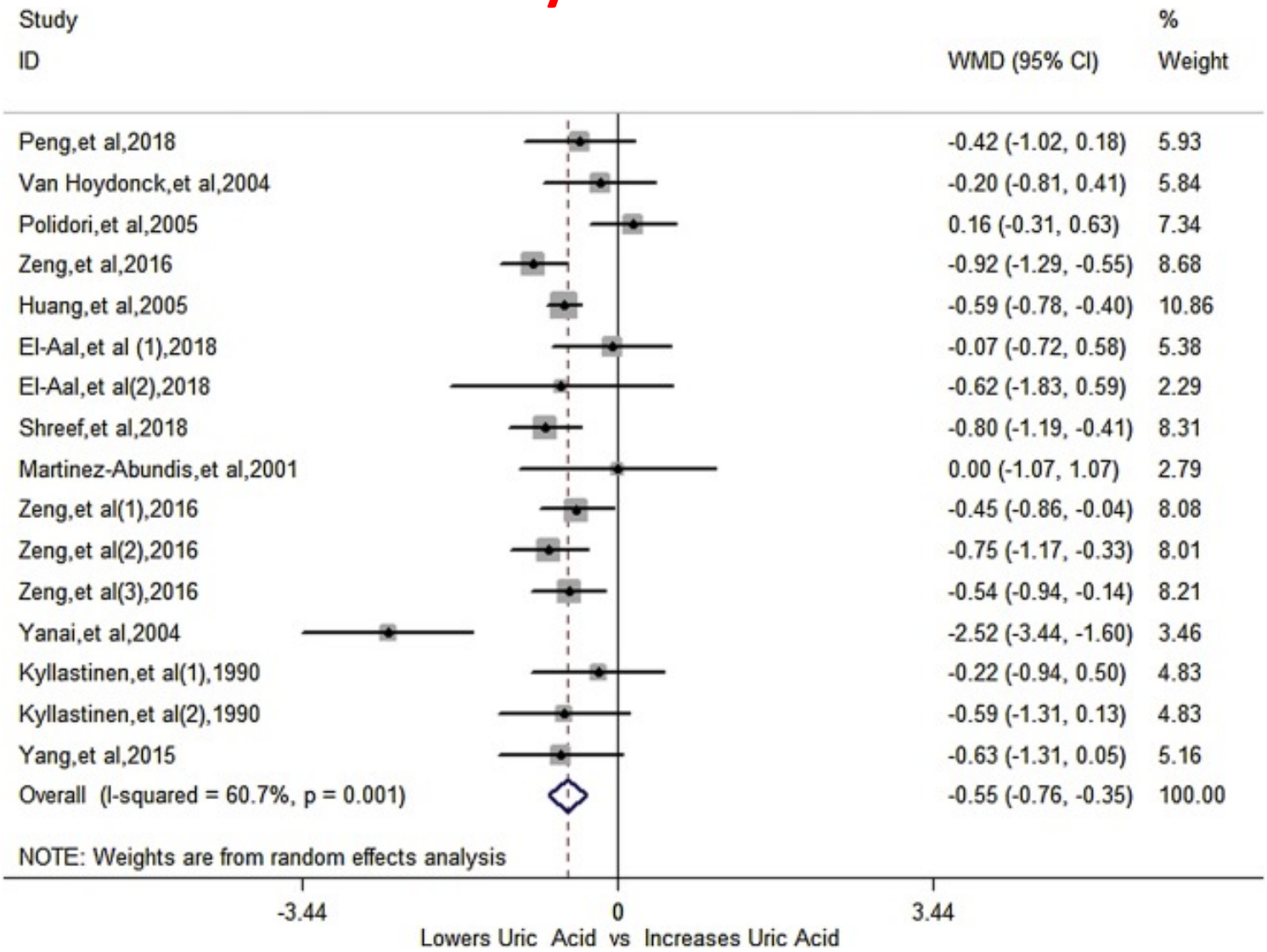
Pediatrics. 2009 August ; 124(2): e300–e304. doi:10.1542/peds.2009-0217.

Empiric use of Oral Potassium Citrate Reduces Symptomatic Kidney Stone Incidence with the Ketogenic Diet

Demographics, kidney stone prevalence, and laboratory values as based on the two treatment approaches.

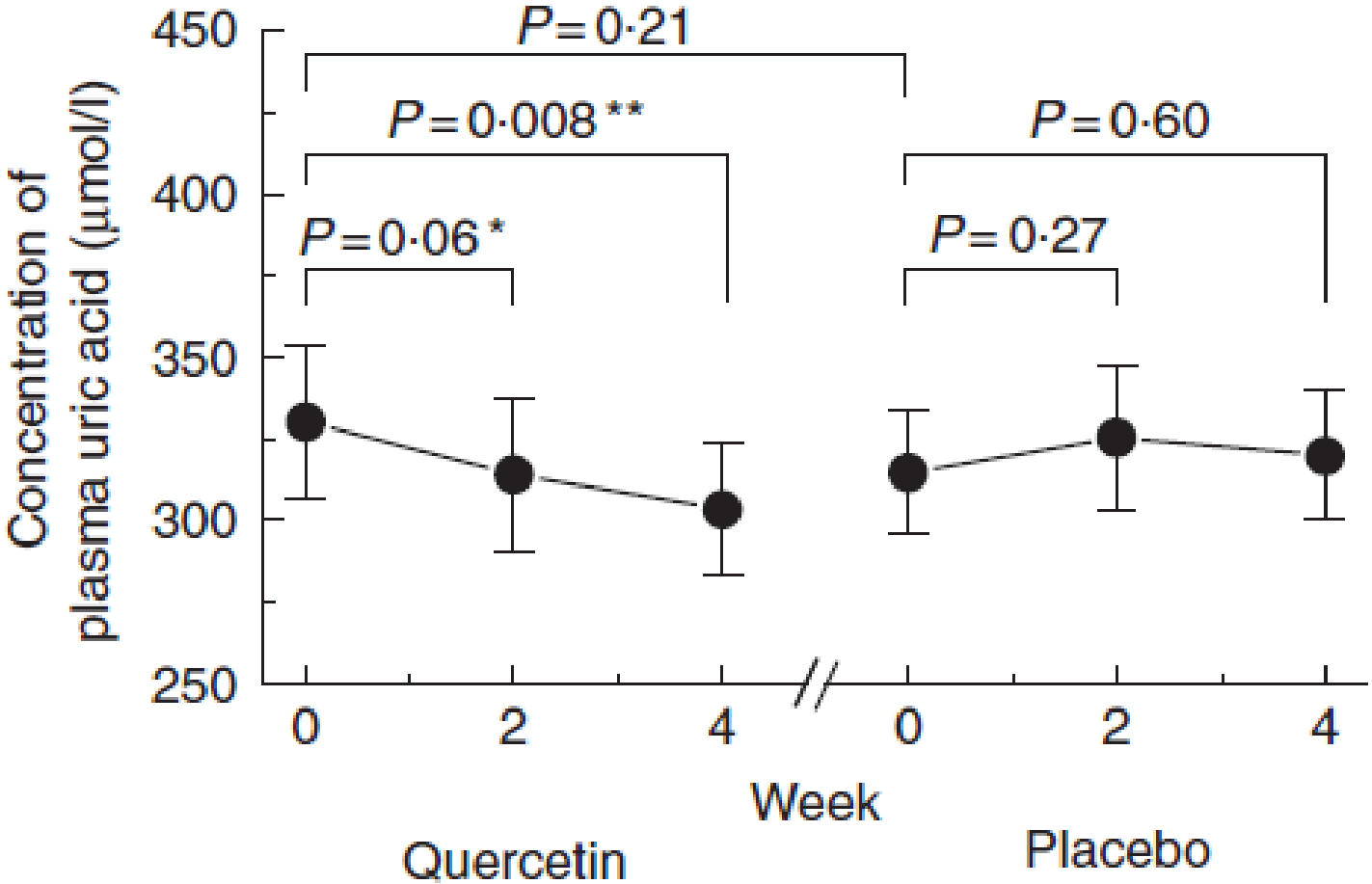
	'Reactive' approach, 2000–2005 (*n*=195)	'Empiric' approach, 2006–2008 (*n*=106)	*P* value
Baseline demographics			
Age, years (mean, SD)	4.3 (3.4)	4.1 (3.6)	.50
Diet duration, months (mean, SD)	15.6 (13.1)	13.3 (9.4)	.11
Gender, female (%)	90 (46%)	56 (52%)	.57
Immobile (%)	47 (24%)	28 (26%)	.76
Carbonic anhydrase use (%)	82 (42%)	53 (50%)	.19
Seizure reduction >50% (%)	128 (66%)	72 (67%)	.78
Results			
Stones, overall (%)	13 (6.7%)	1 (0.9%)	.02
Urine pH (mean, SD)	6.2 (0.7)	6.8 (0.9)	.002
Serum CO_2 (mean, SD)	20.5 (3.8)	20.1 (3.7)	.61

Vitamin C supplementation and SUA levels: a meta-analysis of RCTs



Complement Ther Med. 2021 Aug;60:102761.

Quercetina ed iperuricemia



Br J Nutr. 2016 Mar 14;115(5):800-6.

Mar. Drugs **2015**, *13*, 996-1009; doi:10.3390/md13020996

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Article

Effects of *n*-3 Polyunsaturated Fatty Acids (ω-3) Supplementation on Some Cardiovascular Risk Factors with a Ketogenic Mediterranean Diet

Antonio Paoli [1,*], Tatiana Moro [1], Gerardo Bosco [1], Antonino Bianco [2], Keith A. Grimaldi [3], Enrico Camporesi [4,5,6] and Devanand Mangar [5,6]

	KD Pre	KD Post	Δ TR Pre-Post Tukey's t	KDO3 Pre	KDO3 Post	Δ CTR Pre-Post Tukey's t	Between Treatment ANOVA t
Weight (kg)	92.25 ± 12.53	87.55 ± 10.03	$p < 0.05$	94.5 ± 15.2	90.48 ± 12.71	$p < 0.05$	n.s.
BMI	29.34 ± 2.41	27.87±1.70	$p < 0.05$	29.17 ± 2.38	27.96 ± 1.80	$p < 0.05$	n.s.
LBM (kg)	58.06 ± 14.68	58.77±12.02	n.s.	58.87 ± 18.19	60.41 ± 15.09	n.s.	n.s.
FM (kg)	34.19 ± 3.93	28.78 ± 4.37	$p < 0.005$	35.93 ± 6.76	30.06 ± 5.09	$p < 0.005$	n.s.
IL-6 (pg/mL)	6.13 ± 0.81	4.38 ± 1.05	n.s.	6.55 ± 1.41	3.65 ± 1.27	$p < 0.05$	$p < 0.05$
IL-1β (pg/mL)	2.77 ± 0.85	1.88 ± 0.5	n.s.	3.05 ± 0.51	1.2 ± 0.73	$p < 0.05$	$p < 0.05$
TNF-α (pg/mL)	5.63 ± 0.82	4.1 ± 0.73	$p < 0.05$	5.23 ± 0.67	2.8 ± 0.34	$p < 0.001$	$p < 0.05$
IL-1Ra	287 ± 101.54	307 ± 89.57	n.s.	299 ± 72.36	301 ± 88.95	n.s.	n.s.
IL-10	5.10 ± 3.8	6.25 ± 2.25	n.s.	4.7 ± 4.3	5.15 ± 3.37	n.s.	n.s.
Insulin (μIU/mL)	9.3 ± 2.00	7.4 ± 0.90	$p < 0.05$	11.1 ± 1.90	6.3 ± 1.10	$p < 0.05$	$p < 0.05$
Glucose (mg/dL)	103.5 ± 5.30	85.3 ± 4.70	$p < 0.05$	107.8 ± 6.30	82.1 ± 7.20	$p < 0.05$	n.s.
Adiponectin (μg/mL)	7.18 ± 0.67	7.83 ± 0.39	n.s.	6.55 ± 1.02	7.85 ± 0.37	$p < 0.05$	$p < 0.05$
Tot Chol (mg/dL)	217.25 ± 15.84	201.28 ± 6.79	$p < 0.05$	222.39 ± 6.10	204.52 ± 9.78	$p < 0.05$	n.s.
HDL-c (mg/dL)	36.28 ± 2.23	39.25 ± 1.37	n.s.	39.55 ± 2.99	40.25 ± 2.63	n.s.	n.s.
LDL-c (mg/dL)	133.41 ± 15.86	123.60 ± 7.99	$p < 0.05$	136.98 ± 7.06	127.56 ± 7.19	P < 0.05	n.s.
TG (mg/dL)	237.81 ± 20.26	197.27 ± 6.1	$p < 0.05$	230.79 ± 25.66	185.54 ± 9.64	P < 0.05	$p < 0.05$

Effect of Synbiotic Supplementation in a Very-Low-Calorie Ketogenic Diet on Weight Loss Achievement and Gut Microbiota: A Randomized Controlled Pilot Study

Increase in short-chain fatty aciding producing bacteria and anti-inflammatory mediator signals such as Odoribacter and Lachnospira is shown.
The administration of Bifidobacterium animalis subsp. lactis and prebiotics fiber during the LCD is significantly associated with the percentage of weight loss and change in glucose, C-reactive protein and lipopolysaccharide-binding protein.

Mol Nutr Food Res. 2019 Oct;63(19):e1900167.

Ha senso utilizzare fitoterapici e nutraceutici potenzialmente facilitanti il calo ponderale ?

- **Se la KD impostata è razionale, adeguata al paziente e funziona … NO!!!**
- **In genere hanno minimo effetto e spesso richiedono dosaggi elevati, non sempre sicuri**
- **Possono avere qualche razionale nelle fasi di mantenimento….**

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www.glasbergen.com

“Dottore, io cerco di mangiare sano: non aggiungo mai sale al tiramisù, mangio solo pizza decaffeinata e la mia birra è priva di colesterolo…