Luca Busetto

OBESITÀ COME MALATTIA CRONICA: IL RAZIONALE DELLE DICHIARAZIONI DI CONSENSO ALL'USO DELLE DIETE CHETOGENICHE

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Coordinatore della Obesity Management Task Force
European Association for the Study of Obesity

Presidente della Società Italiana delll'Obesità (SIO)

Il sottoscritto Luca Busetto
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

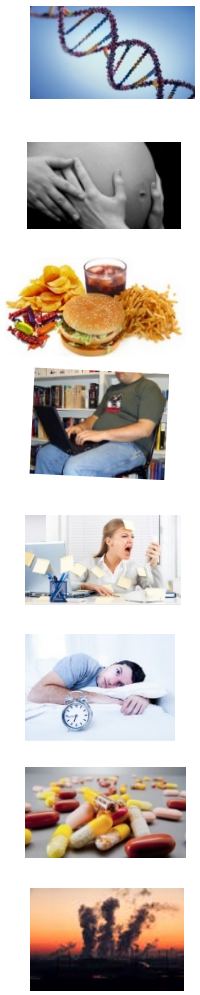
che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

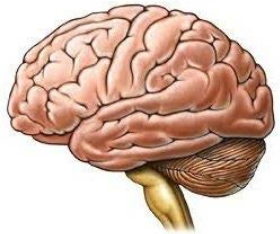
- *Novo Nordisk*
- *Bruno Farmaceutici*
- *Amryt Pharma*
- *Therascience*

OBESITÀ COME MALATTIA CRONICA: IL RAZIONALE DELLE DICHIARAZIONI DI CONSENSO ALL'USO DELLE DIETE CHETOGENICHE

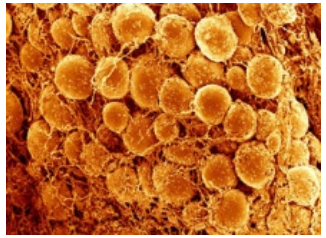
TOPICS

- L'obesità come malattia cronica recidivante
- I vantaggi tattici delle diete chetogeniche
- I documenti di consenso e le raccomandazioni

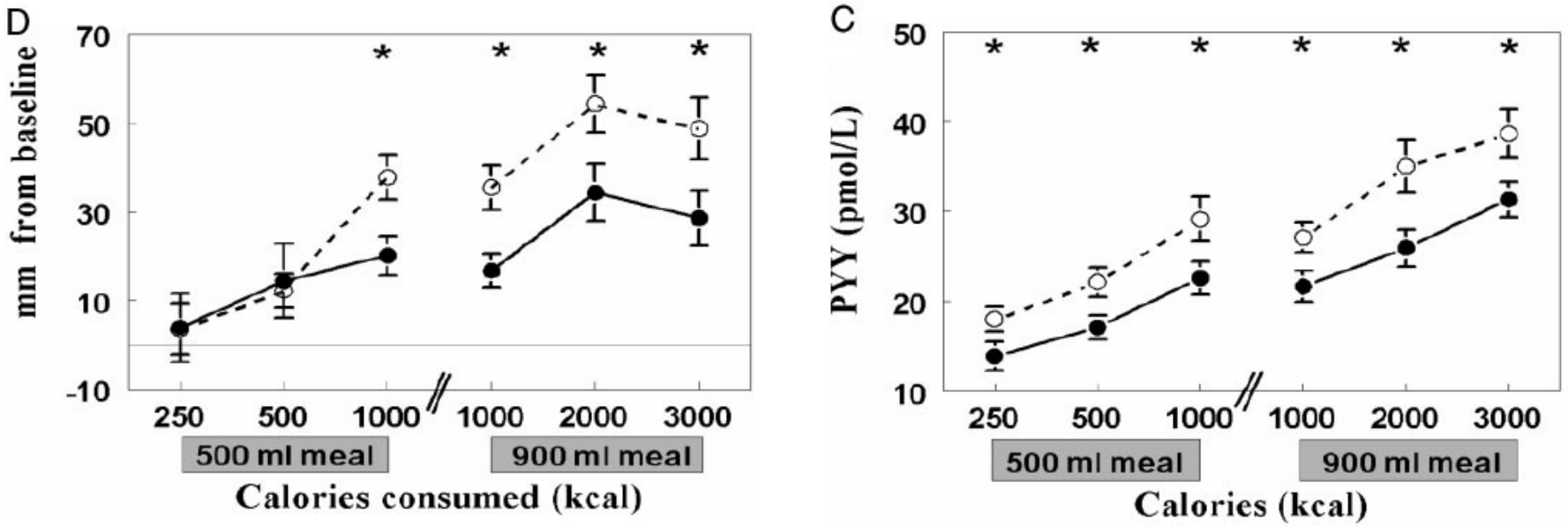




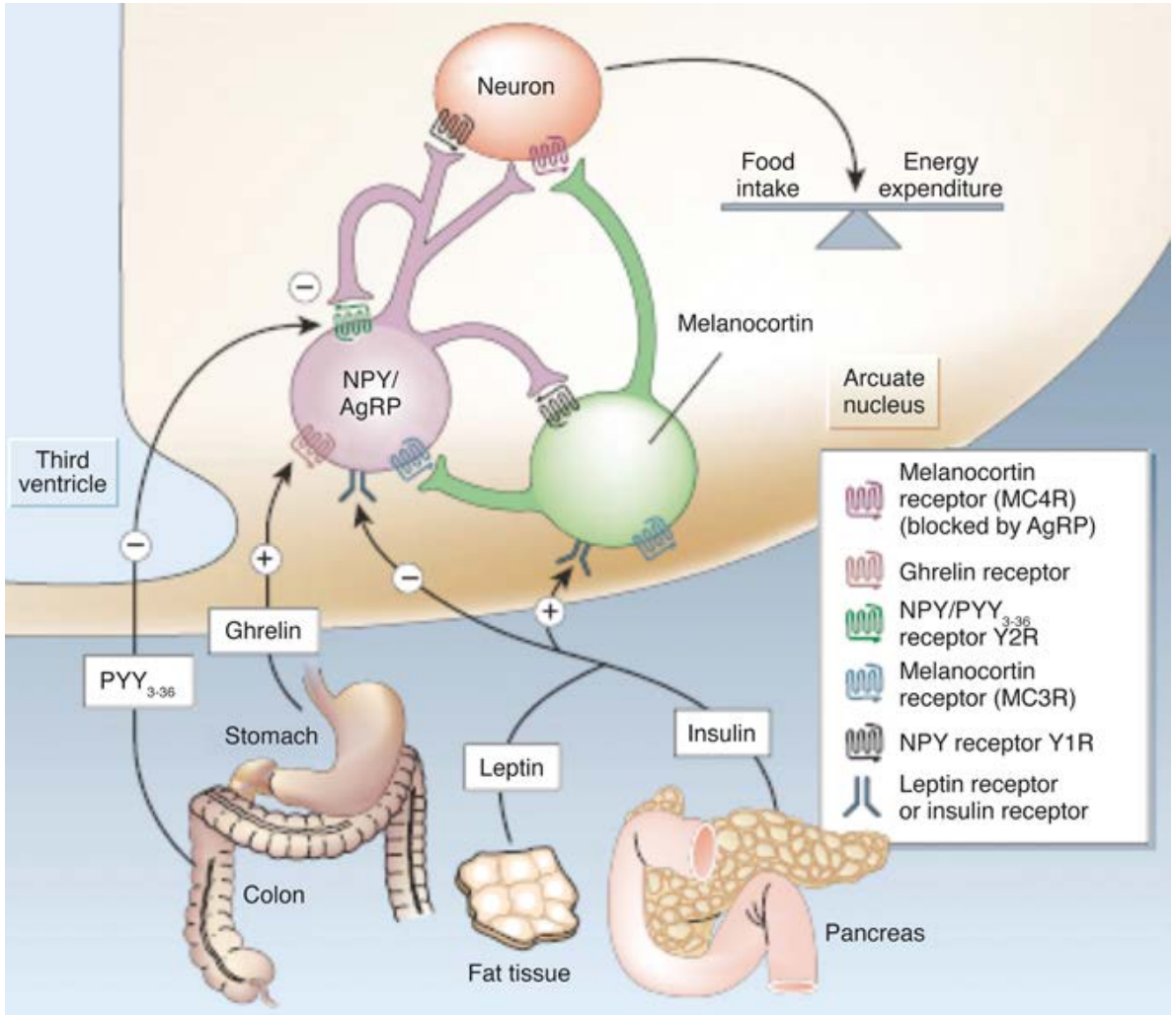
AUMENTO DELLA FAME
RIDUZIONE DELLA SAZIETA’



Attenuated Peptide YY Release in Obese Subjects Is Associated with Reduced Satiety



LeRoux CW et al. Endocrinology 2006;147:3-8


Neuron
Food intake
Energy expenditure
Melanocortin
NPY/ AgRP
Arcuate nucleus
Third ventricle
Melanocortin receptor (MC4R) (blocked by AgRP)
Ghrelin receptor
NPY/PYY3-36 receptor Y2R
Melanocortin receptor (MC3R)
NPY receptor Y1R
Leptin receptor or insulin receptor
Ghrelin
PYY3-36
Stomach
Leptin
Insulin
Colon
Fat tissue
Pancreas

Genetics of Obesity: What We Have Learned Over Decades of Research

TABLE 2 Examples of single-gene defects responsible for human Mendelian obesity cases

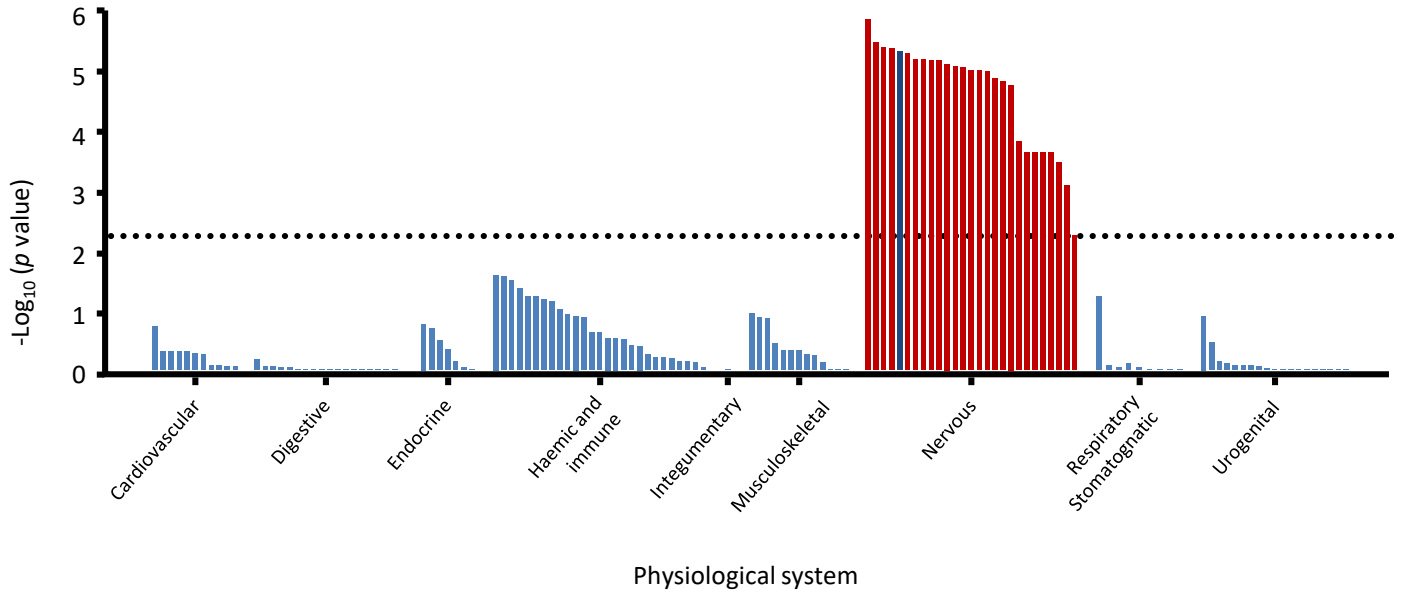
Gene	Mutation type	Prevalence	Associated phenotypes
Leptin	Autosomal recessive inheritance	<100 patients worldwide	Hyperphagia Gonadotropic and thyrotrophic insufficiency Alteration in immune function
LEPR	Autosomal recessive inheritance	<3% of patients with severe early-onset obesity	Hyperphagia Gonadotropic, thyrotrophic, and somatotropin insufficiency Alteration in immune function
MC4R	Heterozygous or homozygous loss of function	About 5% of children with severe obesity, 1% of adults with severe obesity, and 0.1% of the general population	Hyperphagia Hyperinsulinemia High lean mass and bone mineral density
NTRK2	Heterozygous missense mutation	<10 patients worldwide	Hyperphagia Developmental delay Behavioral disturbance Blunted response to pain
PCSK1	Autosomal recessive inheritance or compound heterozygotes	<20 patients worldwide	Hyperphagia Adrenal, gonadotropic, somatotropin, and thyrotrophic insufficiency Postprandial hypoglycemia
POMC	Autosomal recessive inheritance or compound heterozygotes	<10 patients worldwide	ACTH insufficiency Mild hypothyroidism Pale skin and red hair in Caucasian individuals
SIM1	Translocation between chromosome 1p22.1 and 6q16.2 or dominant inheritance	<50 patients worldwide	Neurobehavioral abnormalities Memory deficit, emotional lability, or autism-like behavior

Modified and amplified from Huvenne et al. (68).
ACTH, adrenocorticotropic hormone.

Bouchard C. Obesity 2021;29:802-20

Most Obesity Genes Are Related To The CNS

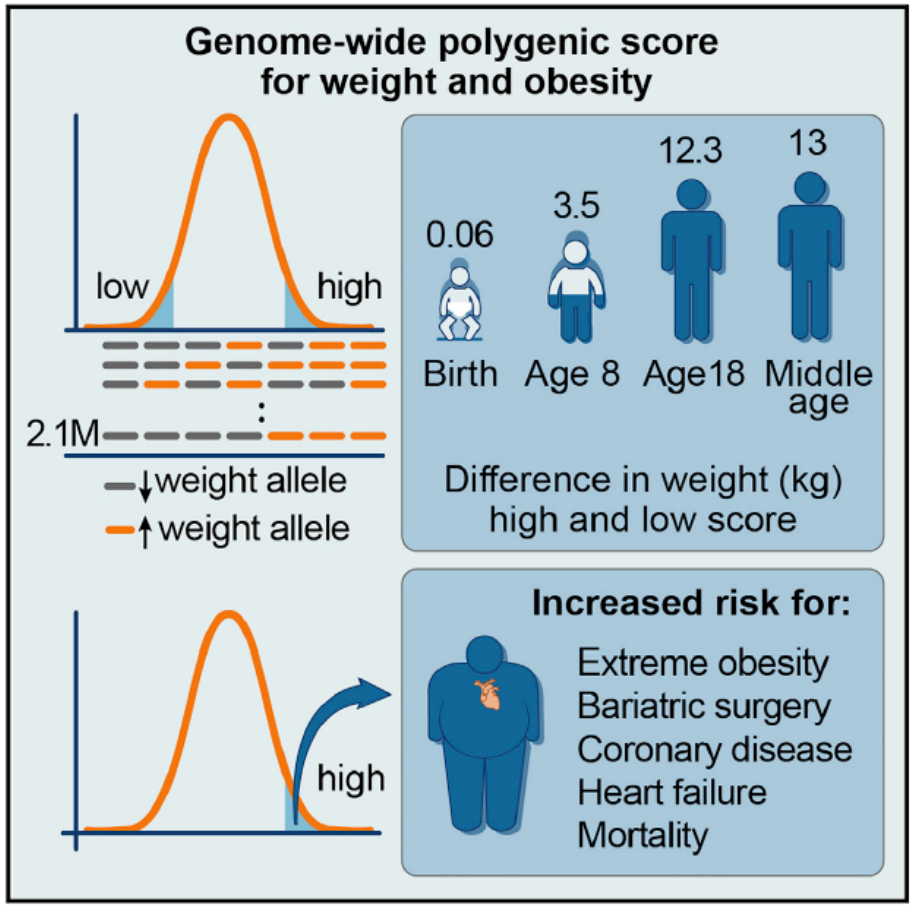
Tissues sorted by physiological system – genes from CNS showed association



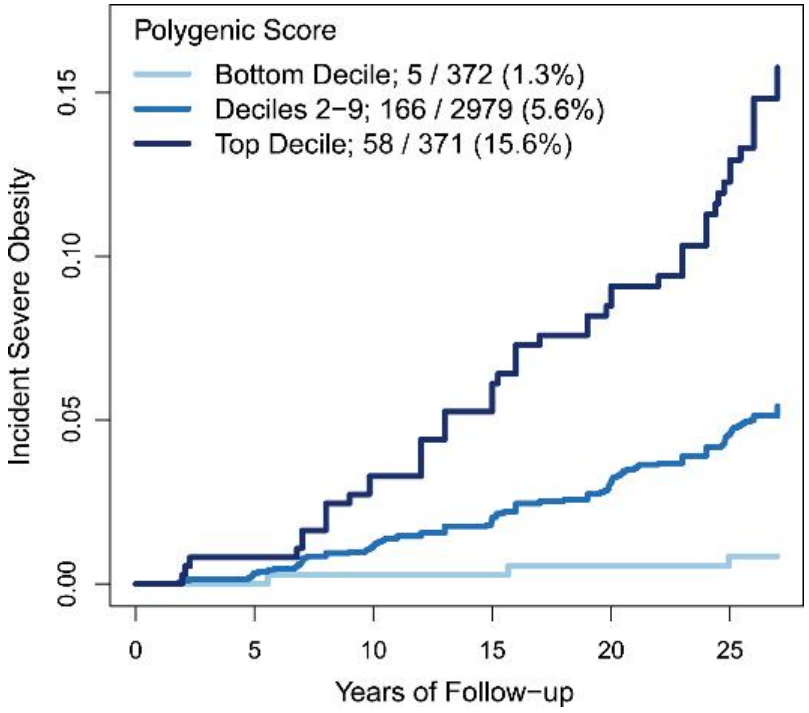
CNS, central nervous system; GWAS, Genome-Wide Association Study

Locke AE et al. Nature 2015;518:197–206

Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood



A genome-wide polygenic score quantifies inherited susceptibility to obesity, integrating information from 2.1 million common genetic variants to identify adults at risk of severe obesity.



Khera Av et al. Cell 2019;177:587-596

Environmental Drivers to Obesity

(3) Stress and distress

(direct impact on relevant areas of the brain)

(4) Drugs

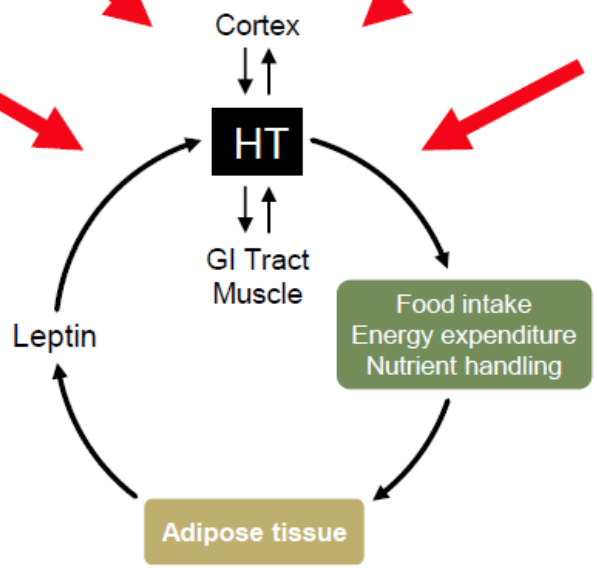
(accounts for up to 10%)

(2) Decreased physical activity

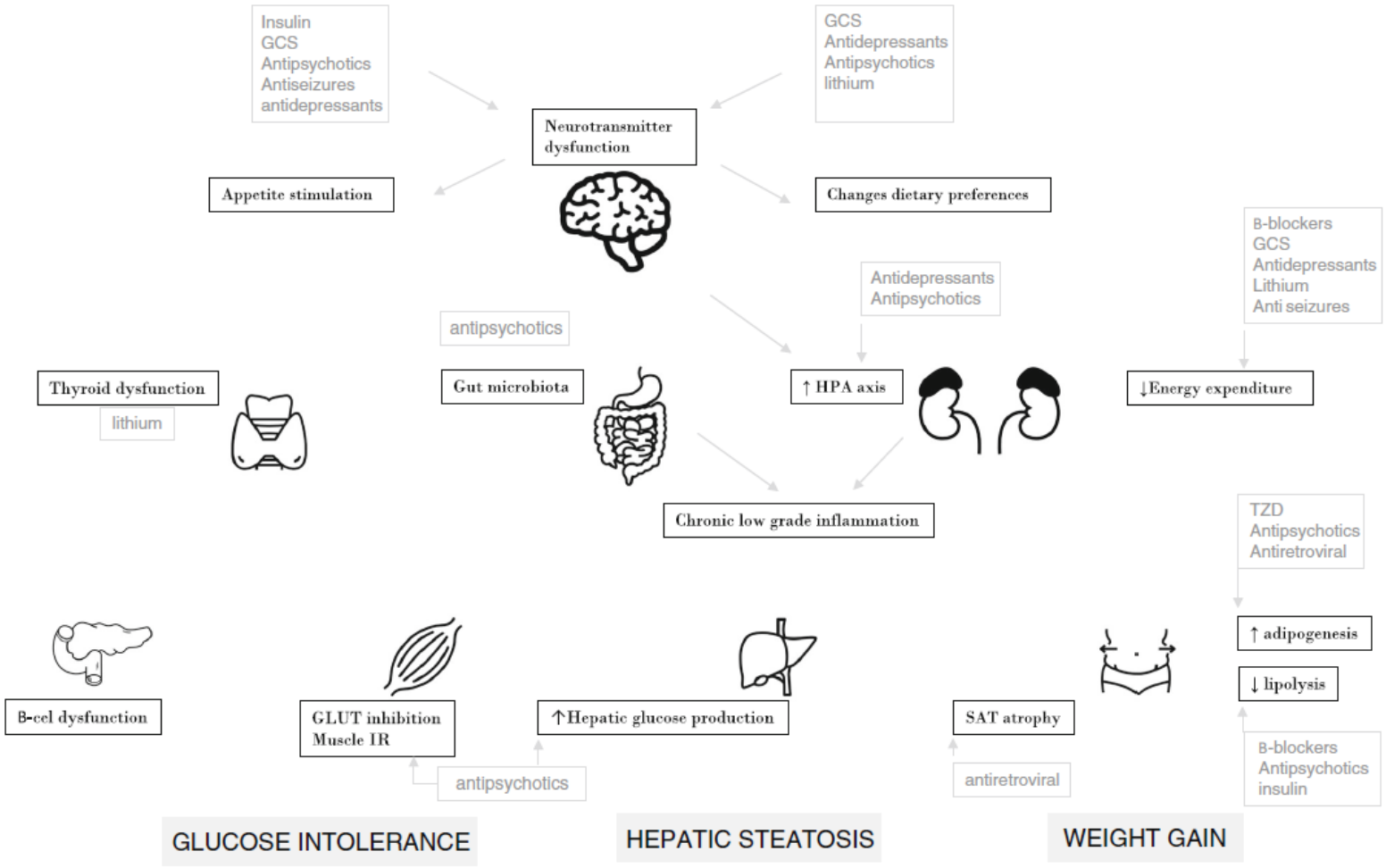
(effects on muscle more than calories)

(1) Altered food supply

(signaling more than calories)



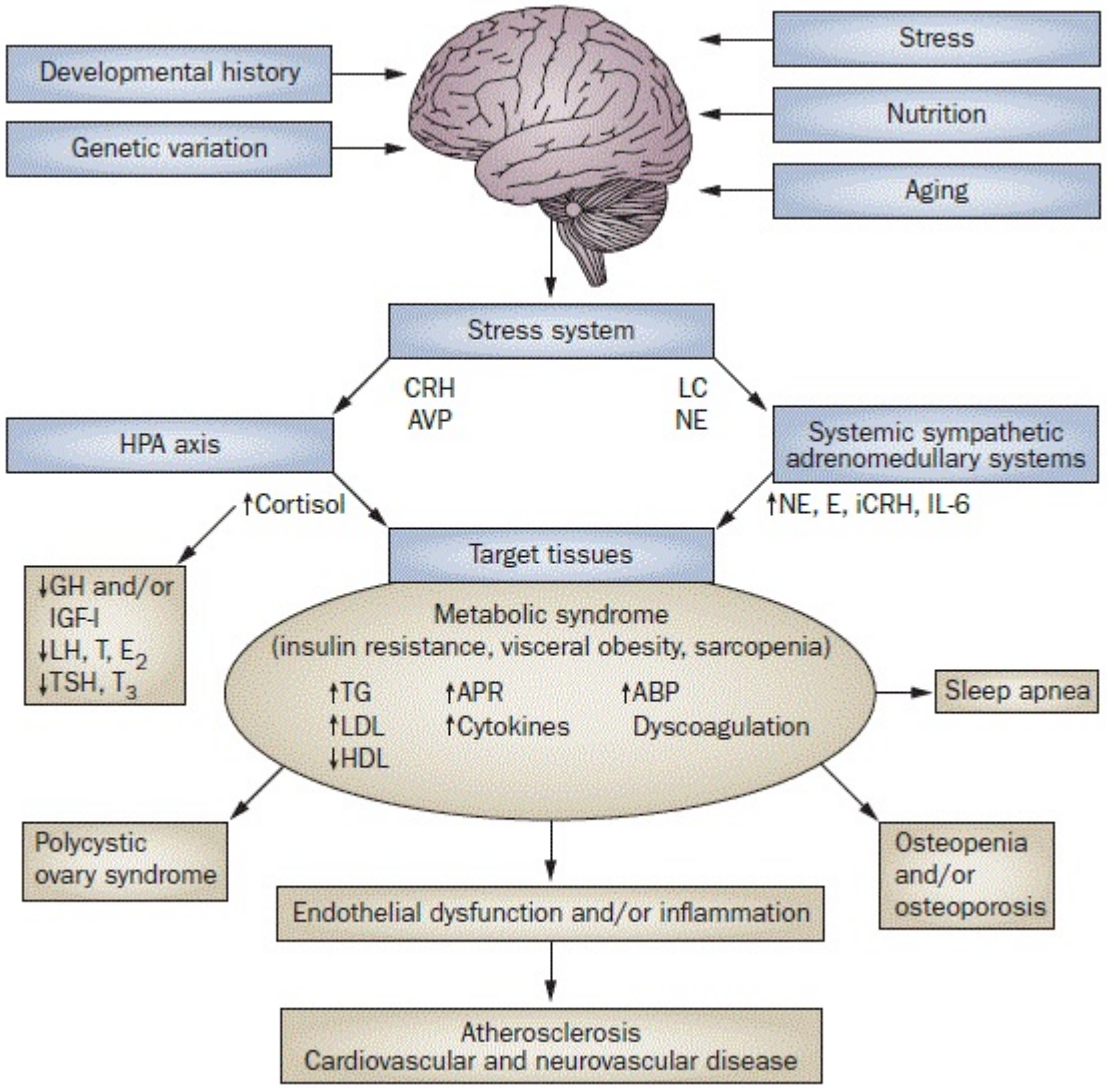
Drugs Affecting Body Weight, Body Fat Distribution, and Metabolic Function—Mechanisms and Possible Therapeutic or Preventive Measures: an Update

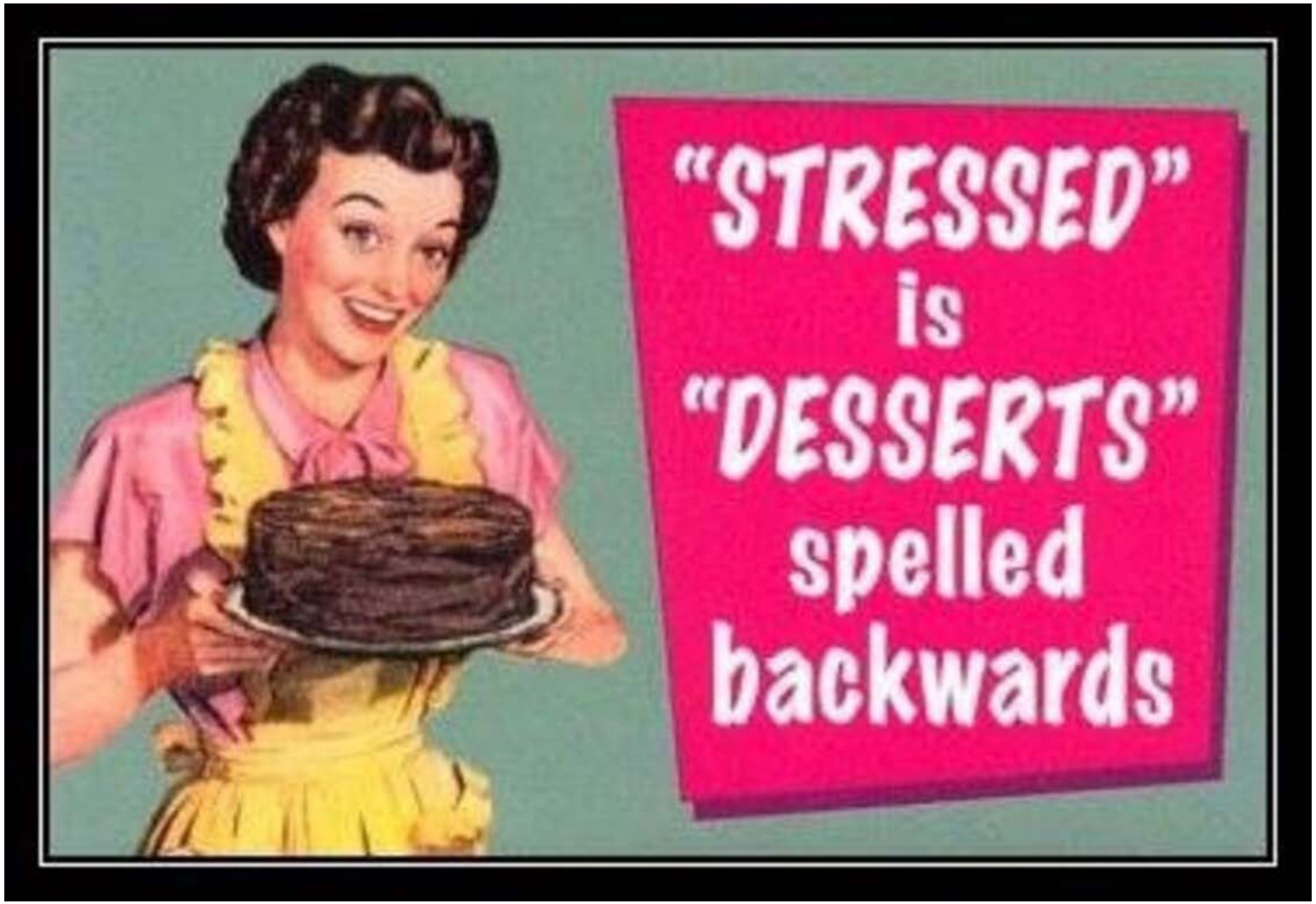


Verhaegen AA &van Gaal LF. Curr Obes Rep 2021;10:1-13

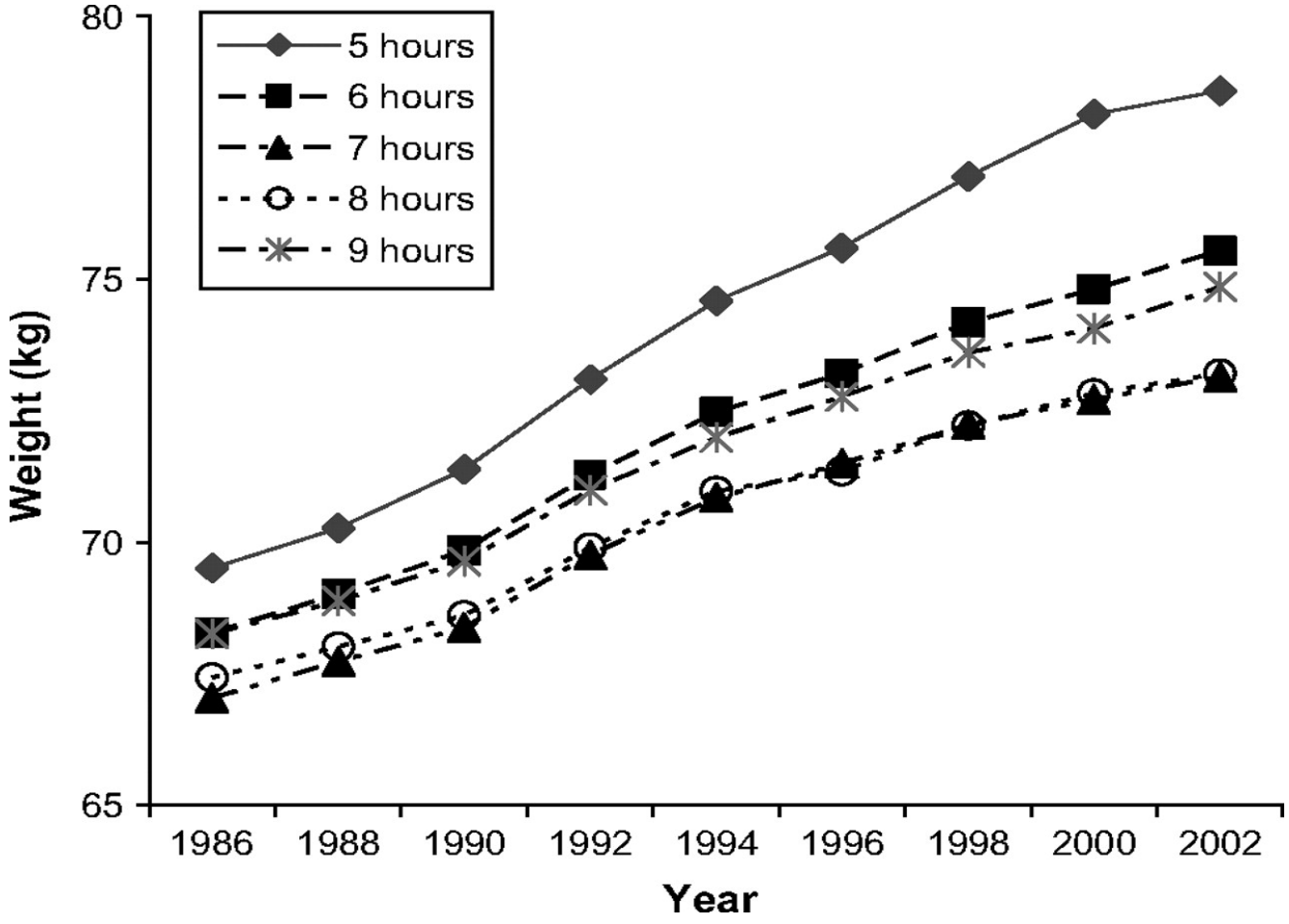
KDA Ketogenic Diet ACADEMY

SINut Società Italiana di Nutraceutica


Developmental history
Genetic variation
Stress
Nutrition
Aging
Stress system
CRH
AVP
LC
NE
HPA axis
Systemic sympathetic adrenomedullary systems
↑Cortisol
↑NE, E, iCRH, IL-6
Target tissues
↓GH and/or IGF-I
↓LH, T, E_2
↓TSH, T_3
Metabolic syndrome
(insulin resistance, visceral obesity, sarcopenia)
↑TG
↑LDL
↓HDL
↑APR
↑Cytokines
↑ABP
Dyscoagulation
Sleep apnea
Polycystic ovary syndrome
Osteopenia and/or osteoporosis
Endothelial dysfunction and/or inflammation
Atherosclerosis
Cardiovascular and neurovascular disease


"STRESSED"
is
"DESSERTS"
spelled
backwards

Andamento del peso nel Nurses' Health Study dal 1986 al 2002 in funzione delle ore di sonno



Patel S R et al. Am. J. Epidemiol. 2006;164:947

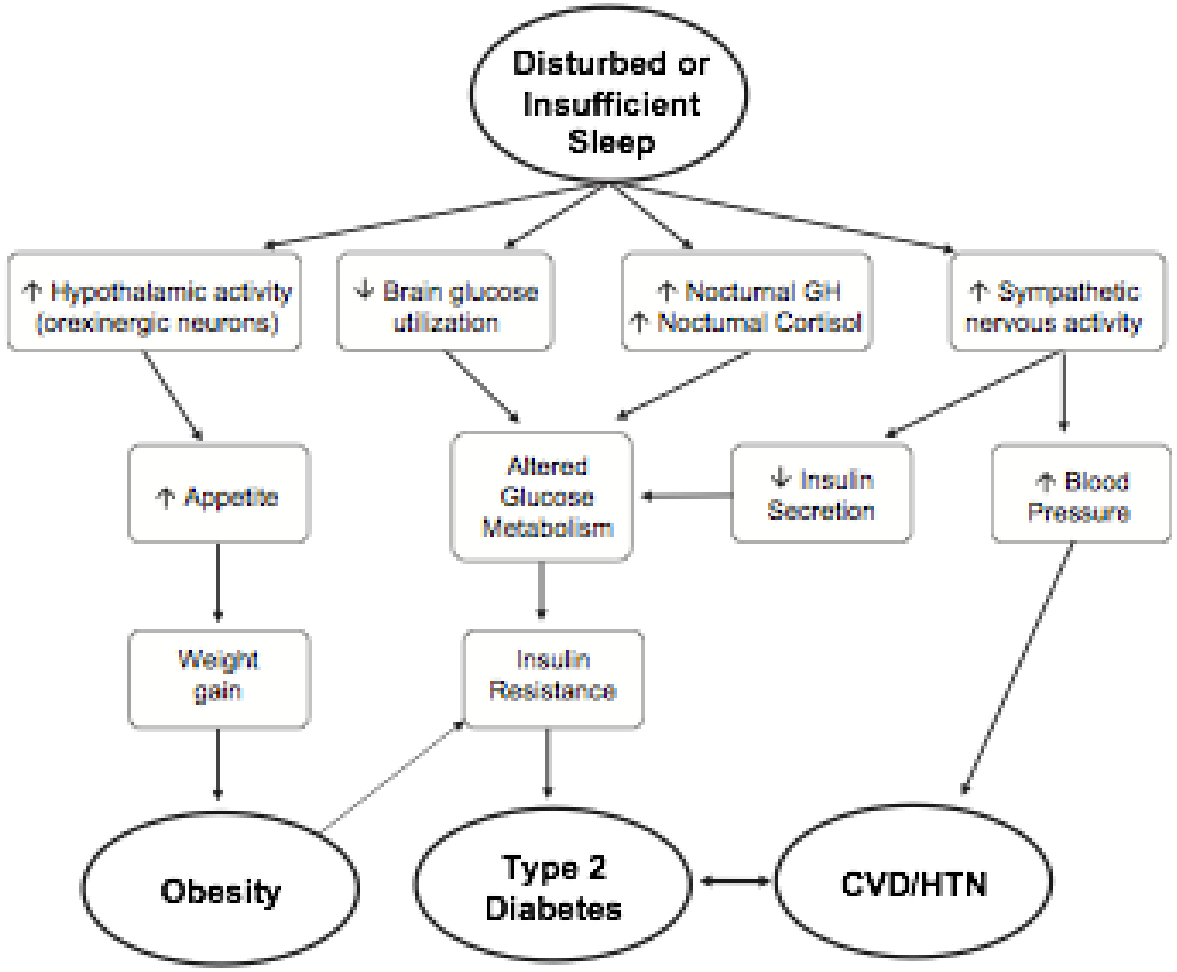
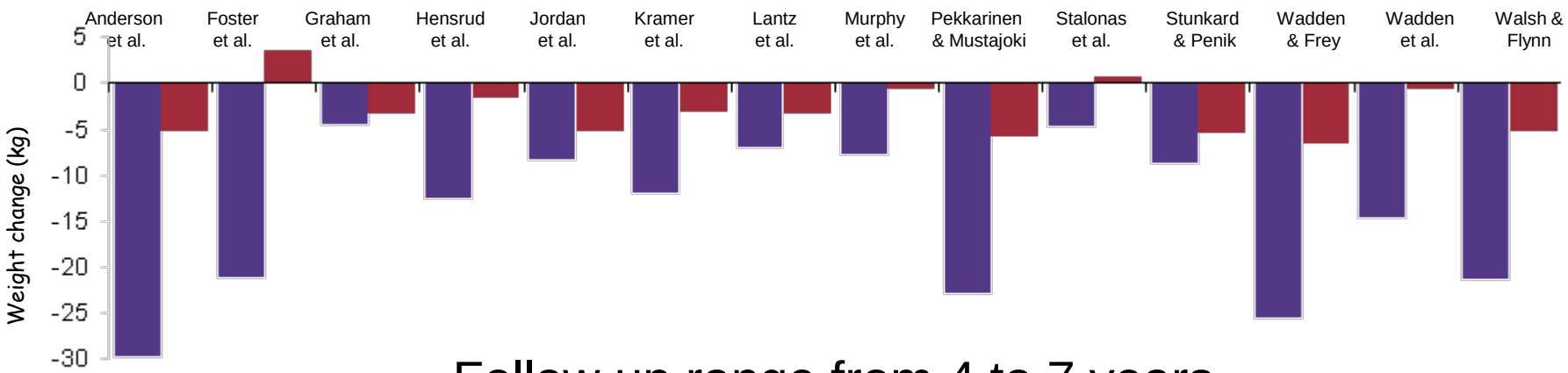


Fig. 1. Schematic representation of possible mechanistic pathways linking disturbed or insufficient sleep to obesity, diabetes, cardiovascular disease (CVD) and hypertension (HTN).

WEIGHT MAINTENANCE IS THE MOST RELEVANT PROBLEM IN OBESITY MANAGEMENT



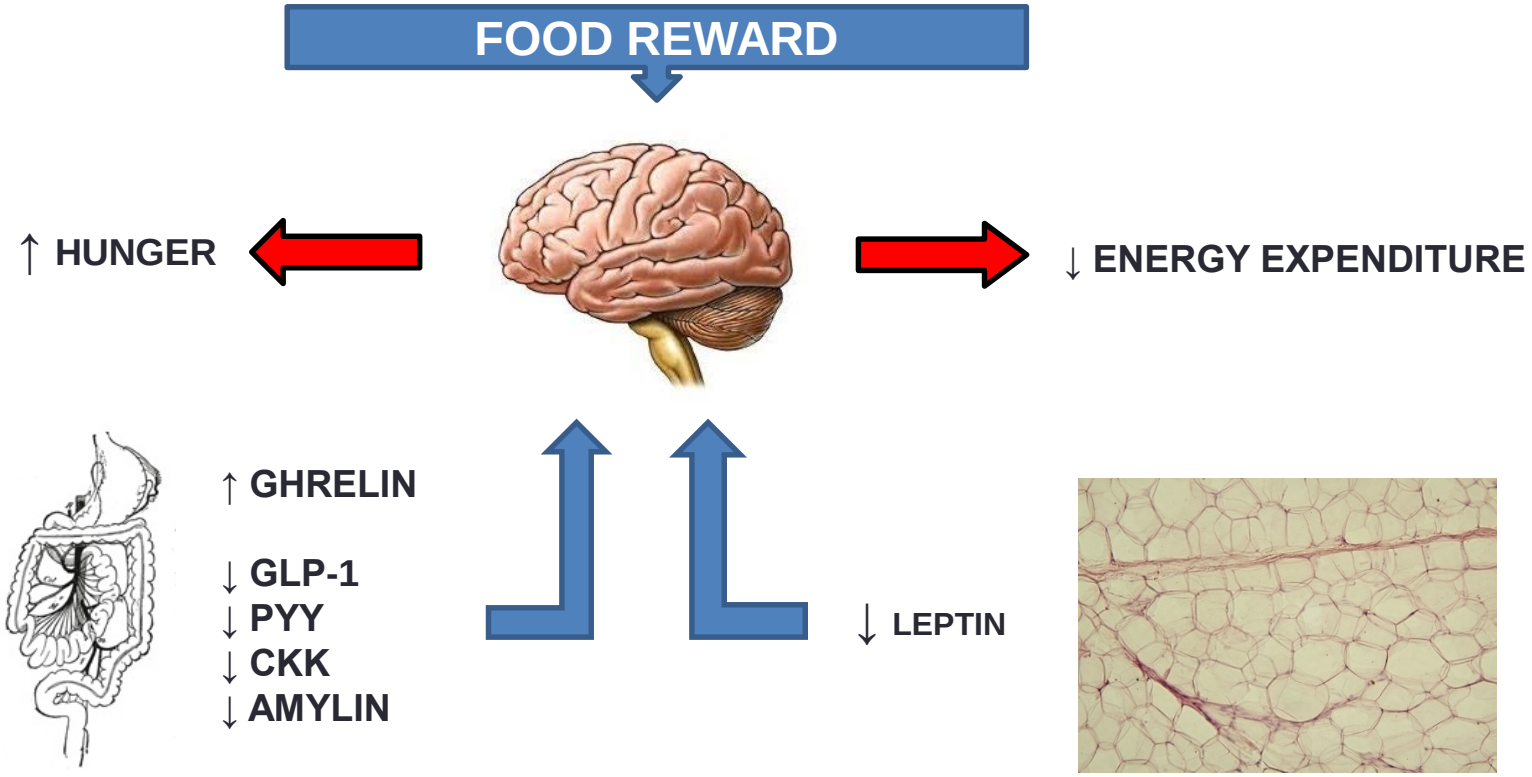
Follow up range from 4 to 7 years

Mean change from baseline to end of diet (kg)

Mean change from baseline to follow-up (kg)

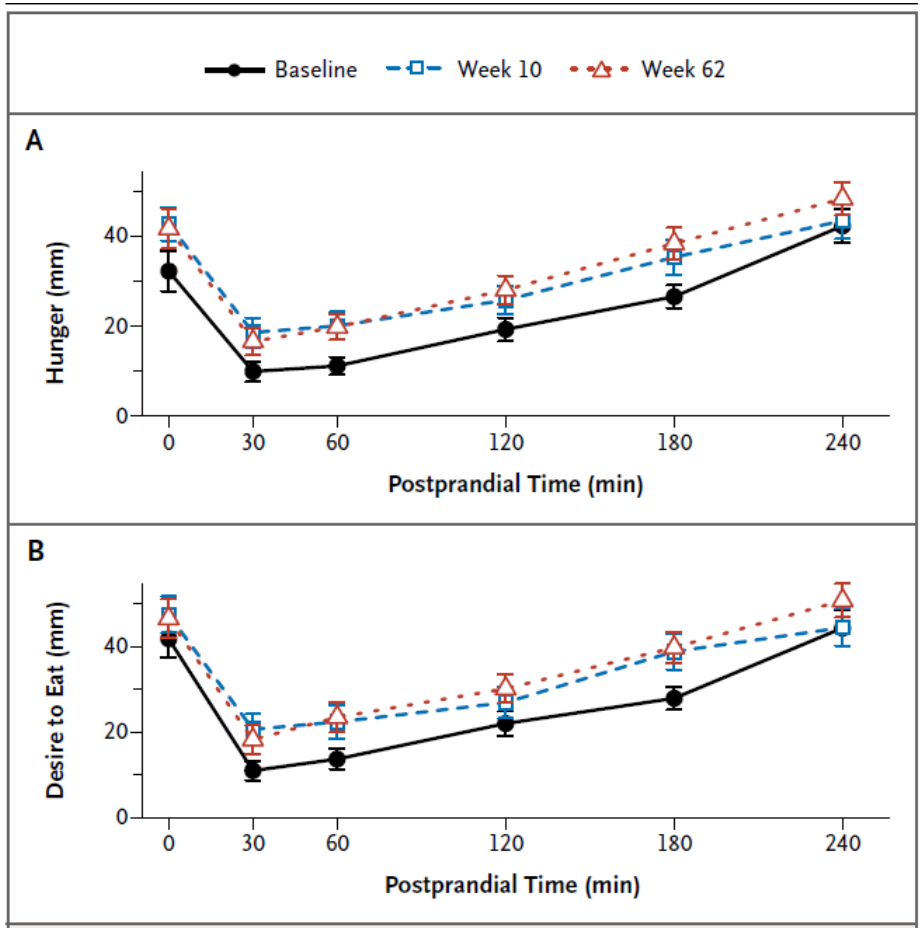
Mann et al. Am Psychol 2007

Mechanisms of weight regain



Busetto L et al. Eur J Int Med 2021 Jan 16

Long-Term Persistence of Hormonal Adaptations to Weight Loss



Sumithran P et al. N Engl J Med 2011;365:1597

Long-Term Persistence of Hormonal Adaptations to Weight Loss

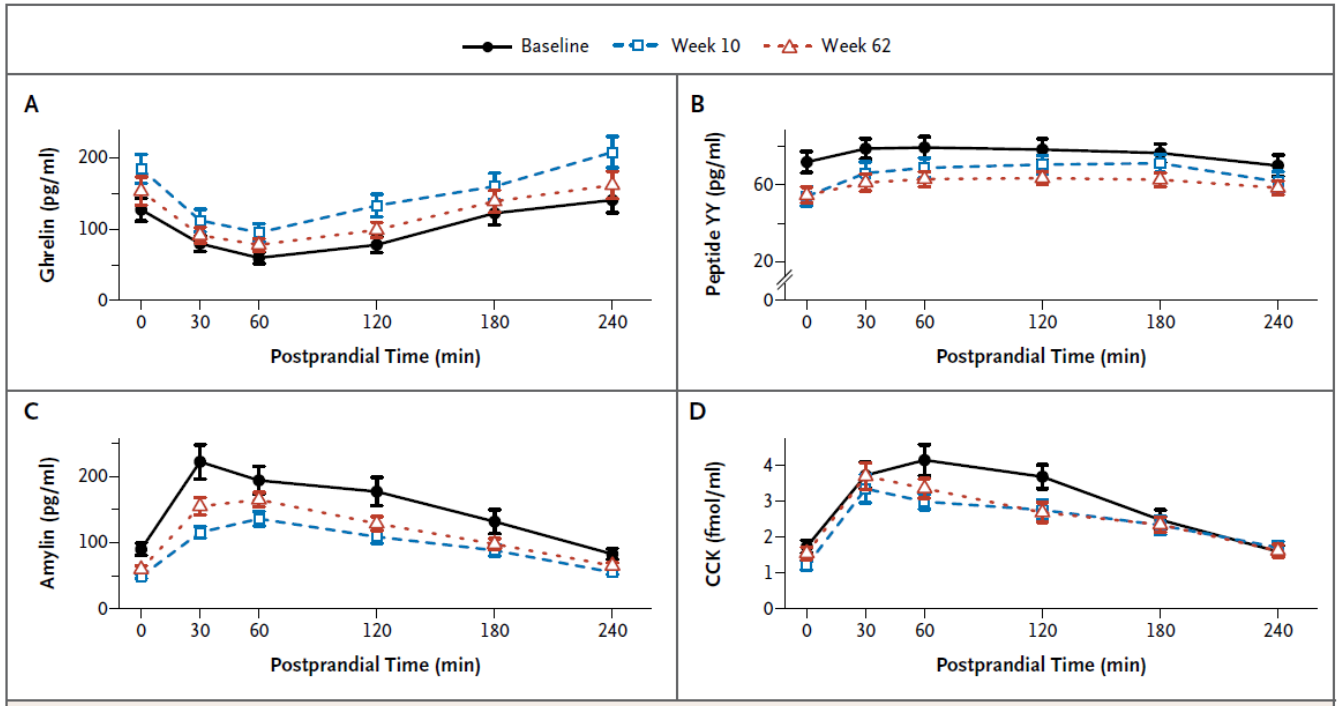


Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

Sumithran P et al. N Engl J Med 2011;365:1597

Gastro-intestinal hormones and their regulation of food intake

Table 2 Variations in the levels of gastrointestinal hormones induced by obesity and their changes after dietary restriction or physical exercise

Hormone	*Levels in obesity*	*After diet*	*After exercise*
Anorexigenic factors			
Cholecystokinin (CCK)	=?	↓	=↑
Glucagon-like peptide 1 (GLP-1)	↓	↓↓	↑
Oxyntomodulin (OXM)	?	?	?
Pancreatic polypeptide (PP)	=↓	↑	↑
Peptide YY (PYY)	↓	↓↓	=↑
Orexigenic factors			
Ghrelin	=↑	↑↑	?

Busetto et al. In "Encyclopedia of Endocrine Diseases, 2nd Ed. Huhtaniemi & Martini eds. Oxford Academic Press 2019;vol.1:398-405

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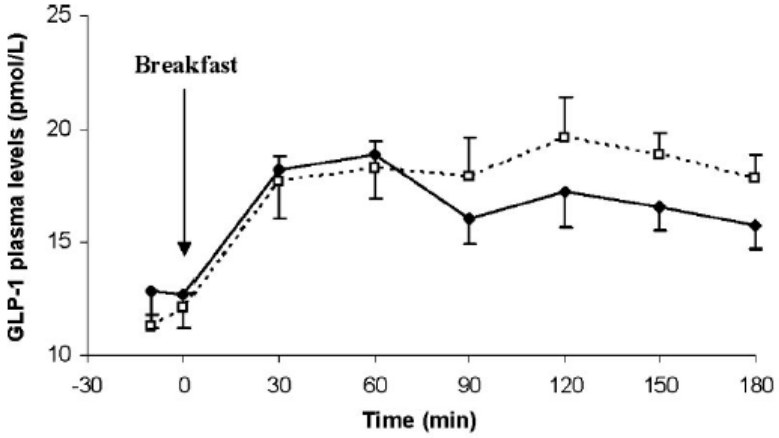
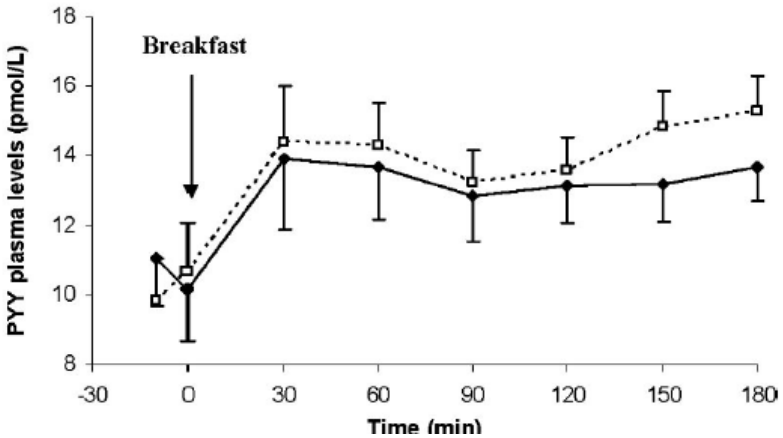
Oxyntomodulin (OXM)	?	?	?
Pancreatic polypeptide (PP)	=↓	↑	↑
Peptide YY (PYY)	↓	↓↓	=↑
Orexigenic factors			
Ghrelin	=↑	↑↑	?

Busetto et al. In "Encyclopedia of Endocrine Diseases, 2nd Ed. Huhtaniemi & Martini eds. Oxford Academic Press 2019;vol.1:398-405

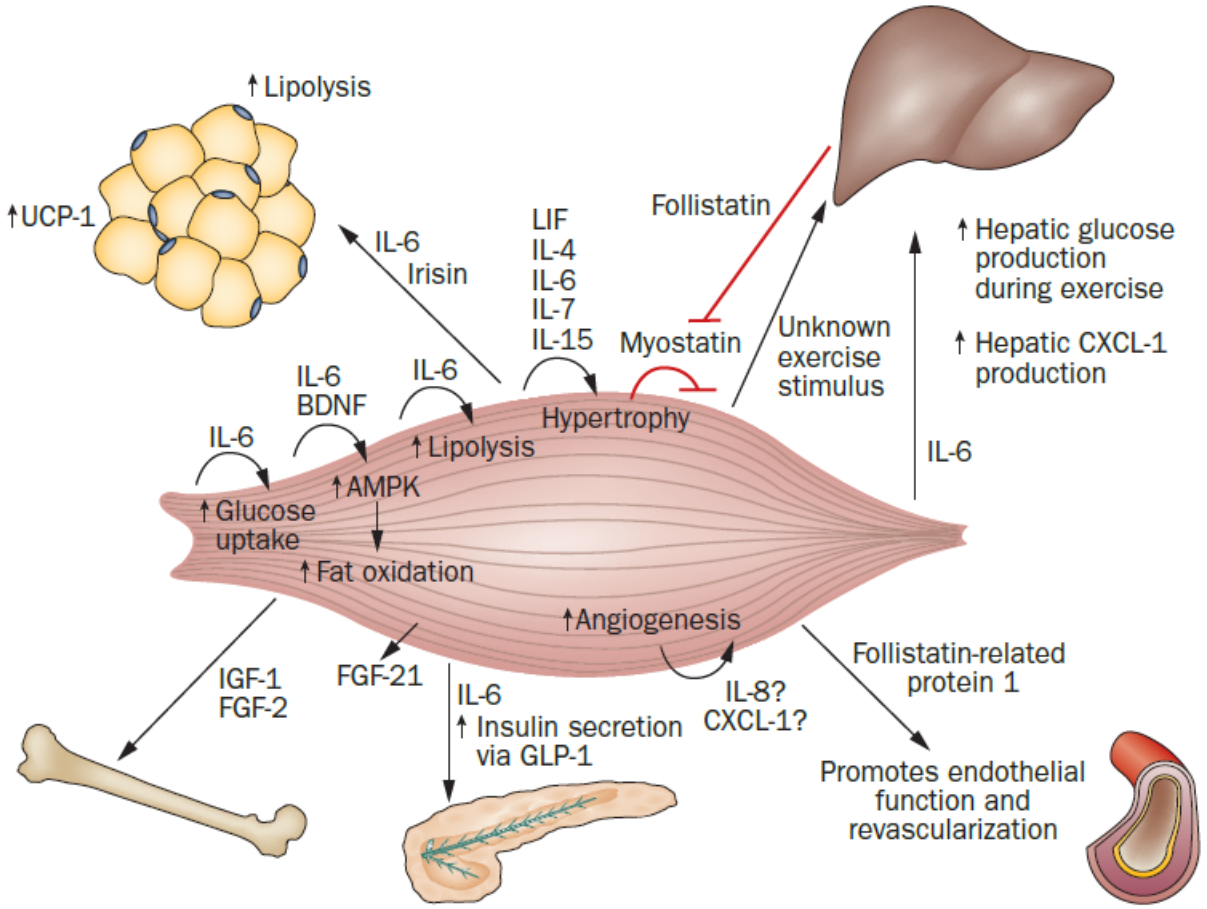
The Effects of Exercise-Induced Weight Loss on Appetite-Related Peptides and Motivation to Eat





Martins C et al. JCEM 2010;95:1609

Muscles, exercise and obesity: skeletal muscle as a secretory organ



Pedersen BK and Febbraio MA. Nat Rev Endocrinol 2012;8:457

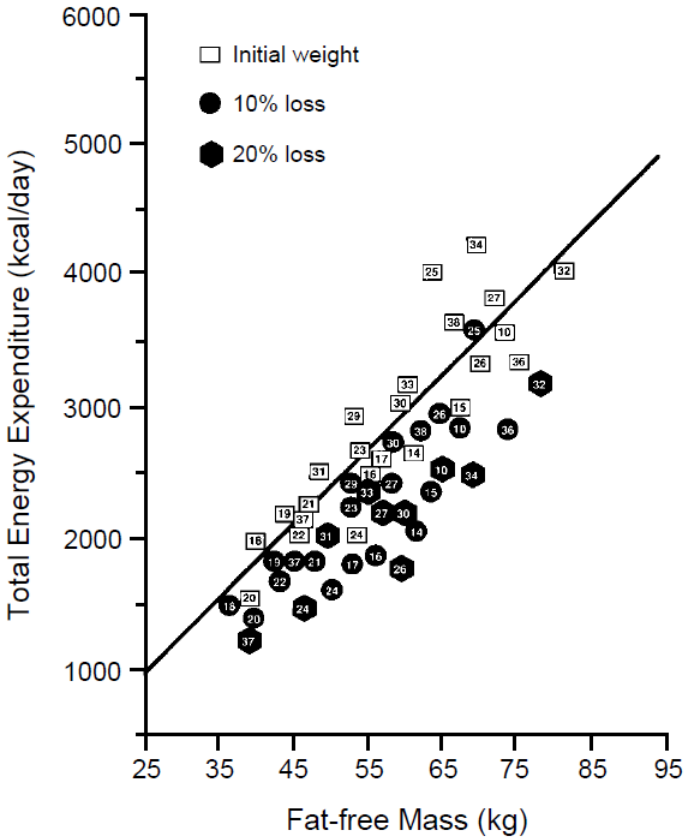
Gastro-intestinal hormones and their regulation of food intake

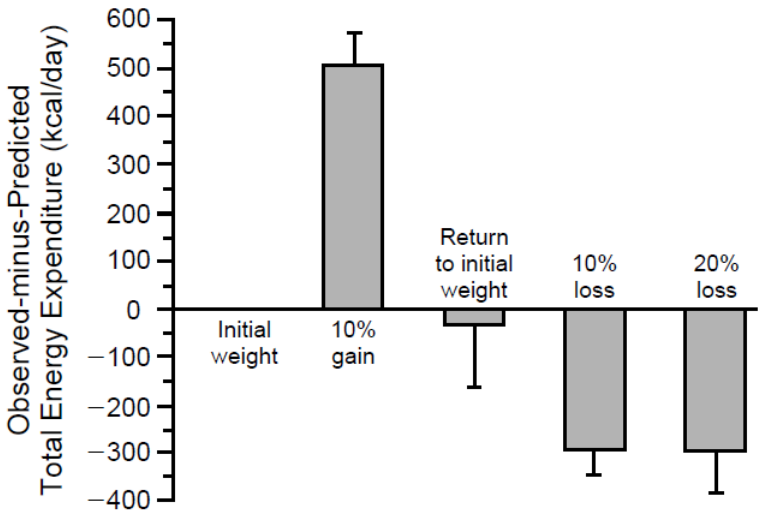
Table 3 Variations in the levels of gastrointestinal hormones after bariatric surgery procedures

Hormone	*LAGB*	*LSG*	*RYGB*
Anorexigenic factors			
Cholecystokinin (CCK)	?	↑↑	↑
Glucagon-like peptide 1 (GLP-1)	=↑	↑	↑↑
Oxyntomodulin (OXM)	?	?	↑
Pancreatic polypeptide (PP)	=	?	?
Peptide YY (PYY)	↑	↑	↑
Orexigenic factors			
Ghrelin	=	↓↓	↓

LAGB: Laparoscopic adjustable gastric banding; LSG: sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass.

Busetto et al. In "Encyclopedia of Endocrine Diseases, 2nd Ed. Huhtaniemi & Martini eds. Oxford Academic Press 2019;vol.1:398-405



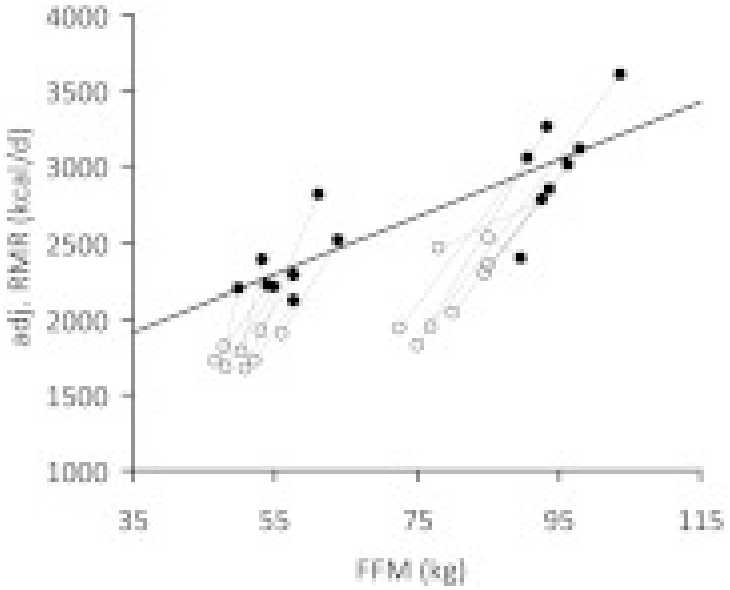


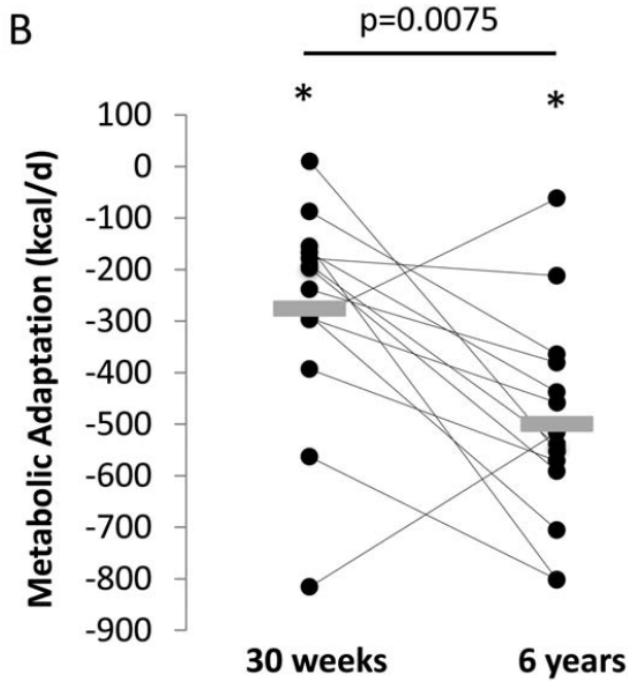
Metabolic Adaptation

A reduction in basal metabolism rate not accounted for the changes in either body mass or body mass components occurring with weight loss

Leibell RL et al. New Engl J Med 1995;332:621

Persistent Metabolic Adaptation 6 Years After "The Biggest Loser" Competition





Johannsen DL et al.
J Clin Endocrinol Metab 2012;97:2489

Fogthergill E et al.
Obesity 2016;24:1612

Modifications of Resting Energy Expenditure After Sleeve Gastrectomy

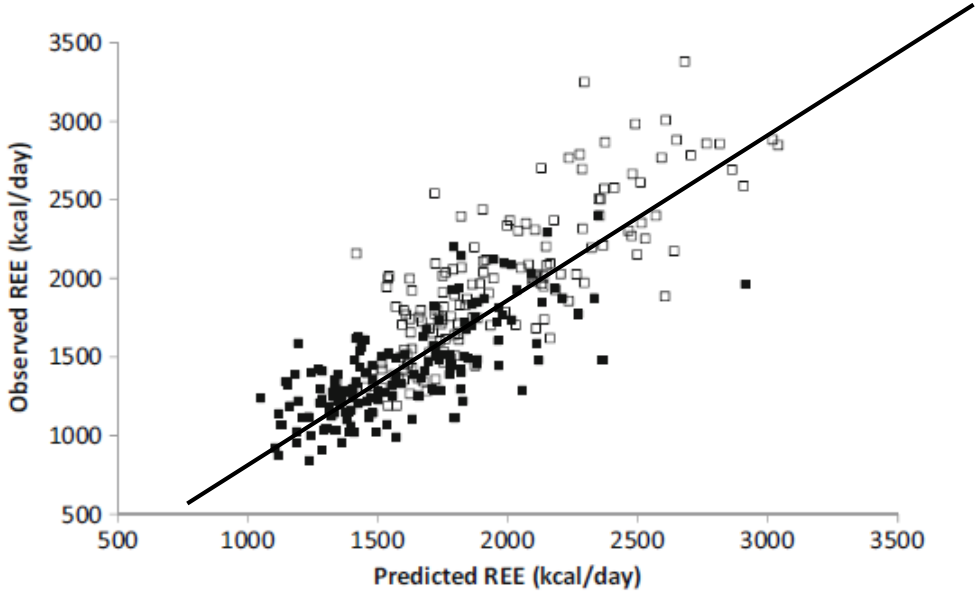


Fig. 1 Distribution of the predicted and observed REE values before (open symbols) and 12 months after sleeve gastrectomy (closed symbols). Most of the observed post-surgery REE values are distributed below the identity line, confirming the existence of a certain degree of metabolic adaptation

METABOLIC ADAPTATION

- 199 ± 238 kcal/day

Moreover, the level of metabolic adaptation after surgery was inversely related to postoperative percent weight loss ($r = -0.170$; $P < 0.05$) and FM loss ($r = -0.245$; $P < 0.01$).

Bettini S et al. Obes Surg 2018;28:2481

KDA Ketogenic Diet ACADEMY

SINut Società Italiana di Nutraceutica

European Guidelines for Obesity Management in Adults

Volkan Yumuk[a] Constantine Tsigos[b] Martin Fried[c] Karin Schindler[d] Luca Busetto[e] Dragan Micic[f] Hermann Toplak[g] for the Obesity Management Task Force of the European Association for the Study of Obesity

Table 2. A guide to deciding the initial level of intervention to discuss with the patient

BMI, kg/m^2*	WC, cm*		Co-morbidities
	men < 94, women < 80	men ≥ 94, women ≥ 80	
25.0–29.9	L	L	L ± D
30.0–34.9	L	L ± D	L ± D±S**
35.0–39.9	L ± D	L ± D	L ± D ± S
≥40.0	L ± D ± S	L ± D ± S	L ± D ± S

L = Lifestyle intervention (diet and physical activity); D = consider drugs; S = consider surgery.

*BMI and waist circumference cut-off points are different for some ethnic groups.

**Patients with type 2 diabetes on individual basis.

Obesity Facts 2015;8:402-424

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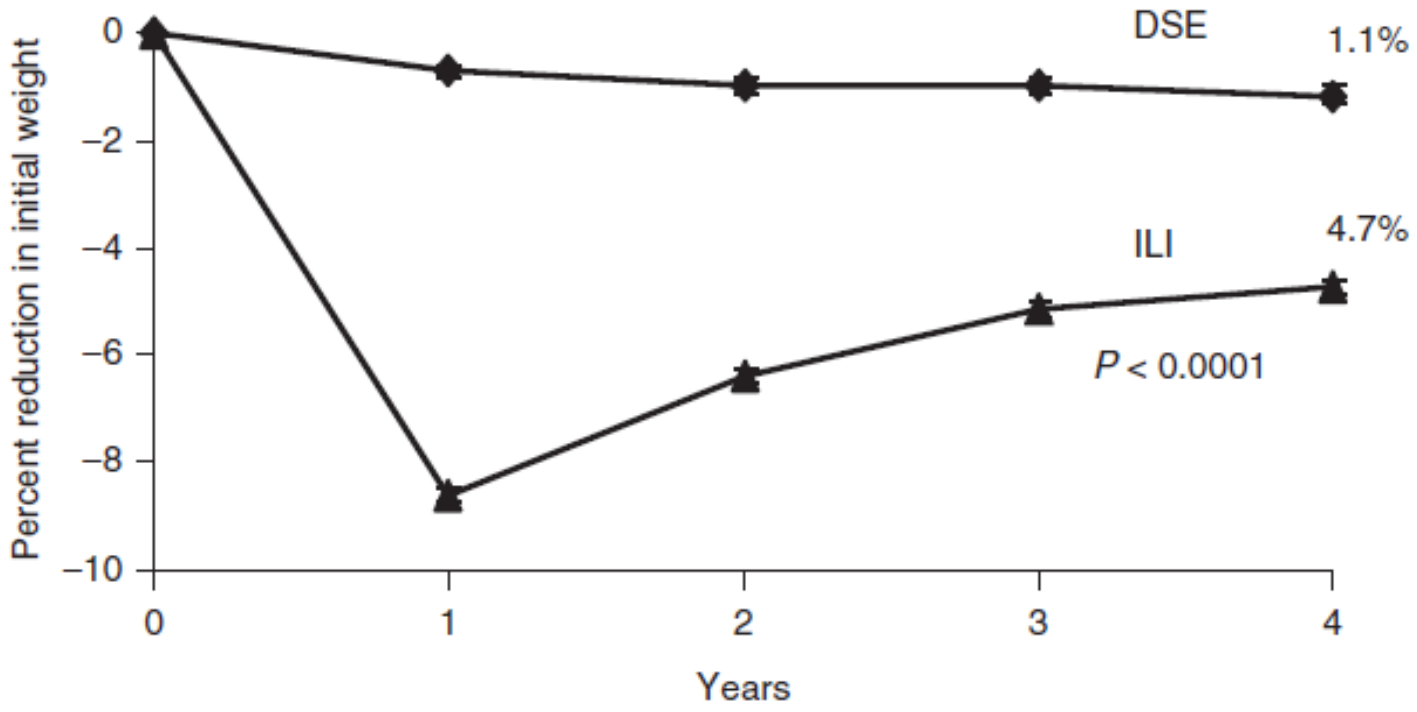
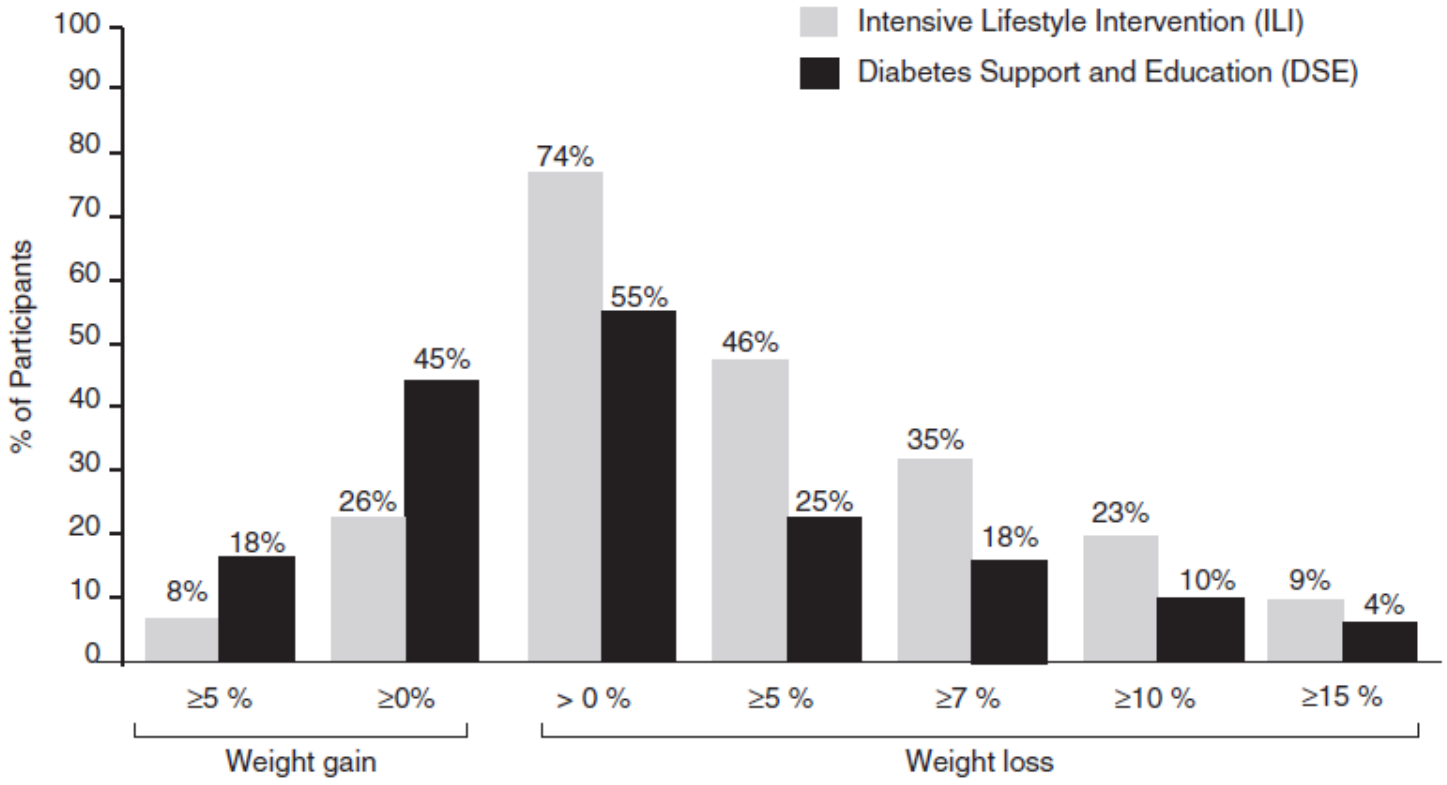
Four-Year Weight Losses in the Look AHEAD Study: Factors Associated With Long-Term Success



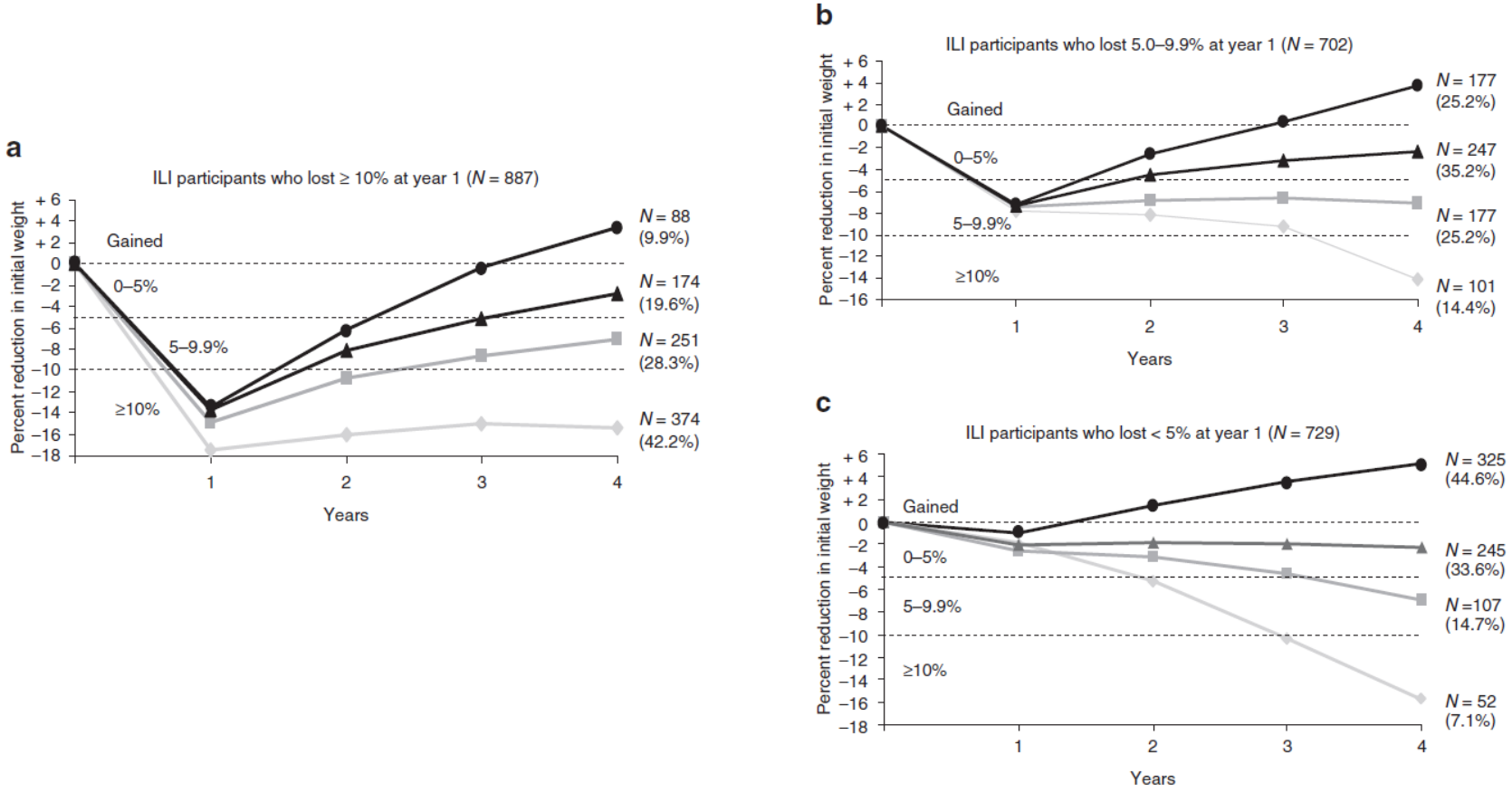
Wadden et al. Obesity 2011;19:1987-98

Four-Year Weight Losses in the Look AHEAD Study: Factors Associated With Long-Term Success



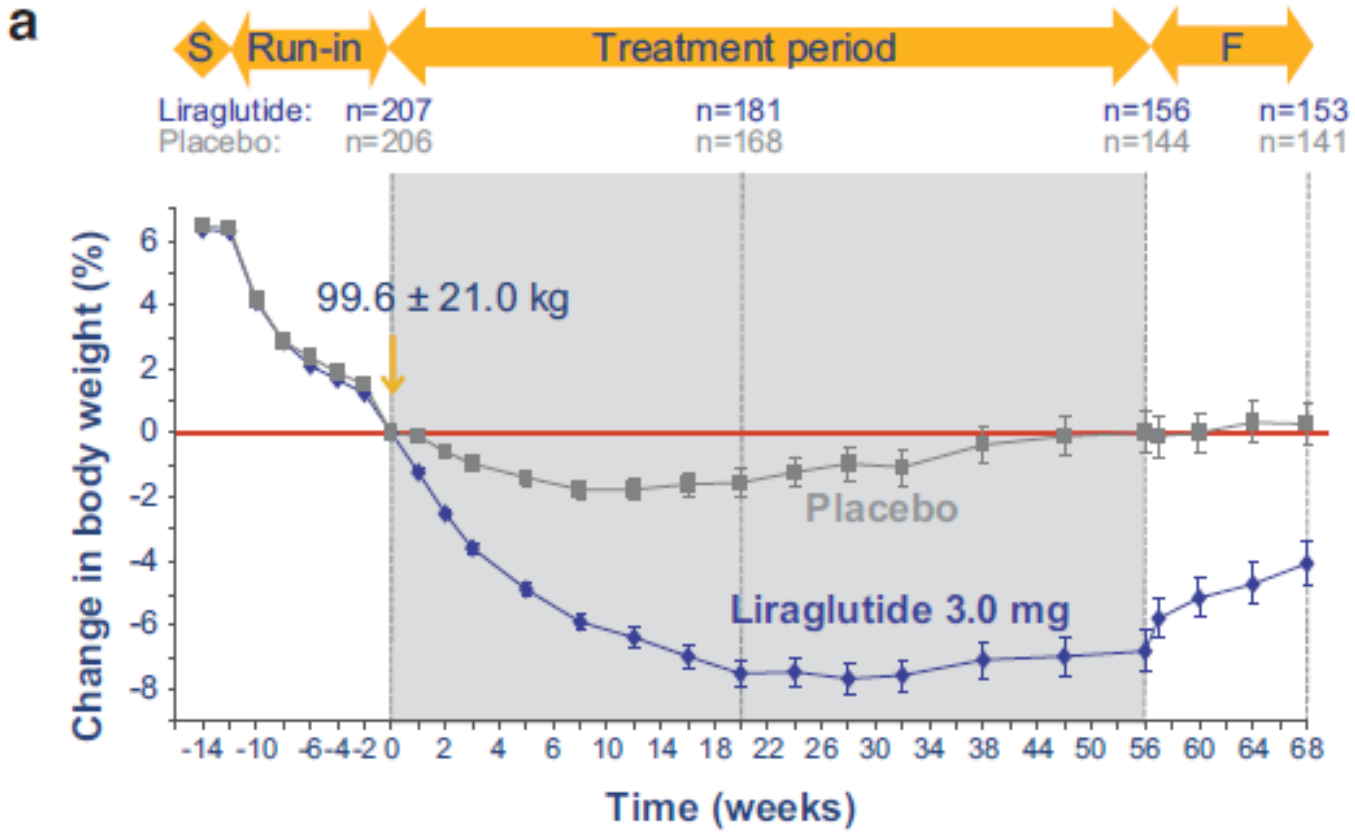
Wadden et al. Obesity 2011;19:1987-98

Four-Year Weight Losses in the Look AHEAD Study: Factors Associated With Long-Term Success



Wadden et al. Obesity 2011;19:1987-98

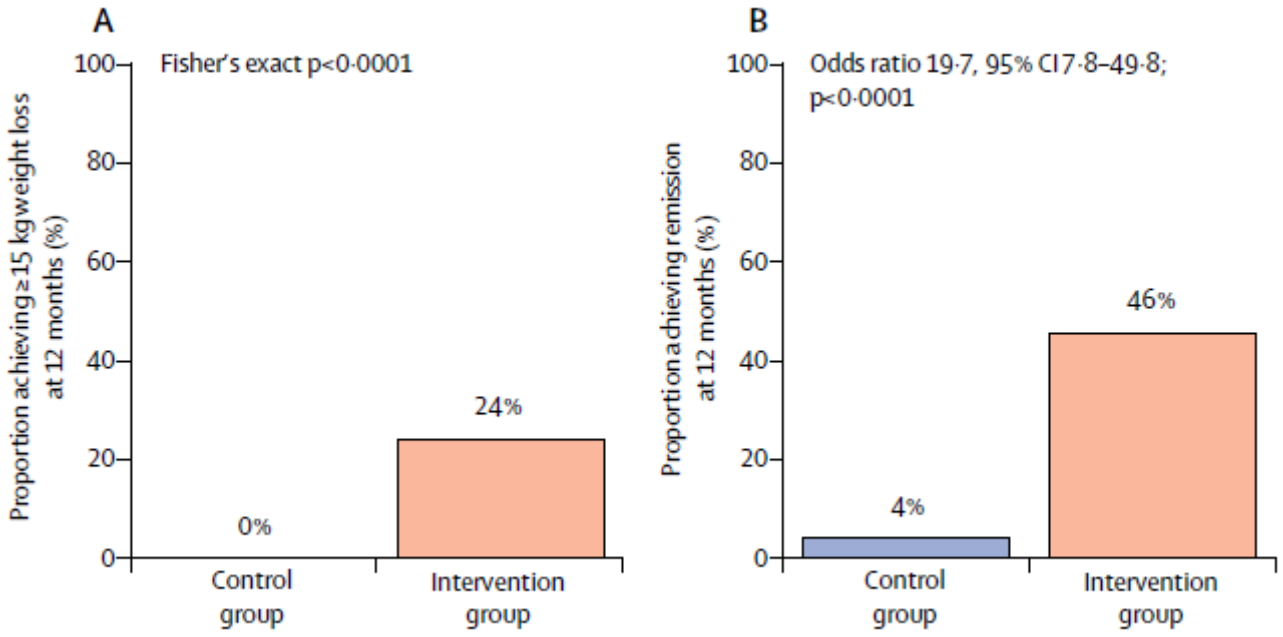
Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study



Wadden TA et al. Int J Obes 2013;37:1443

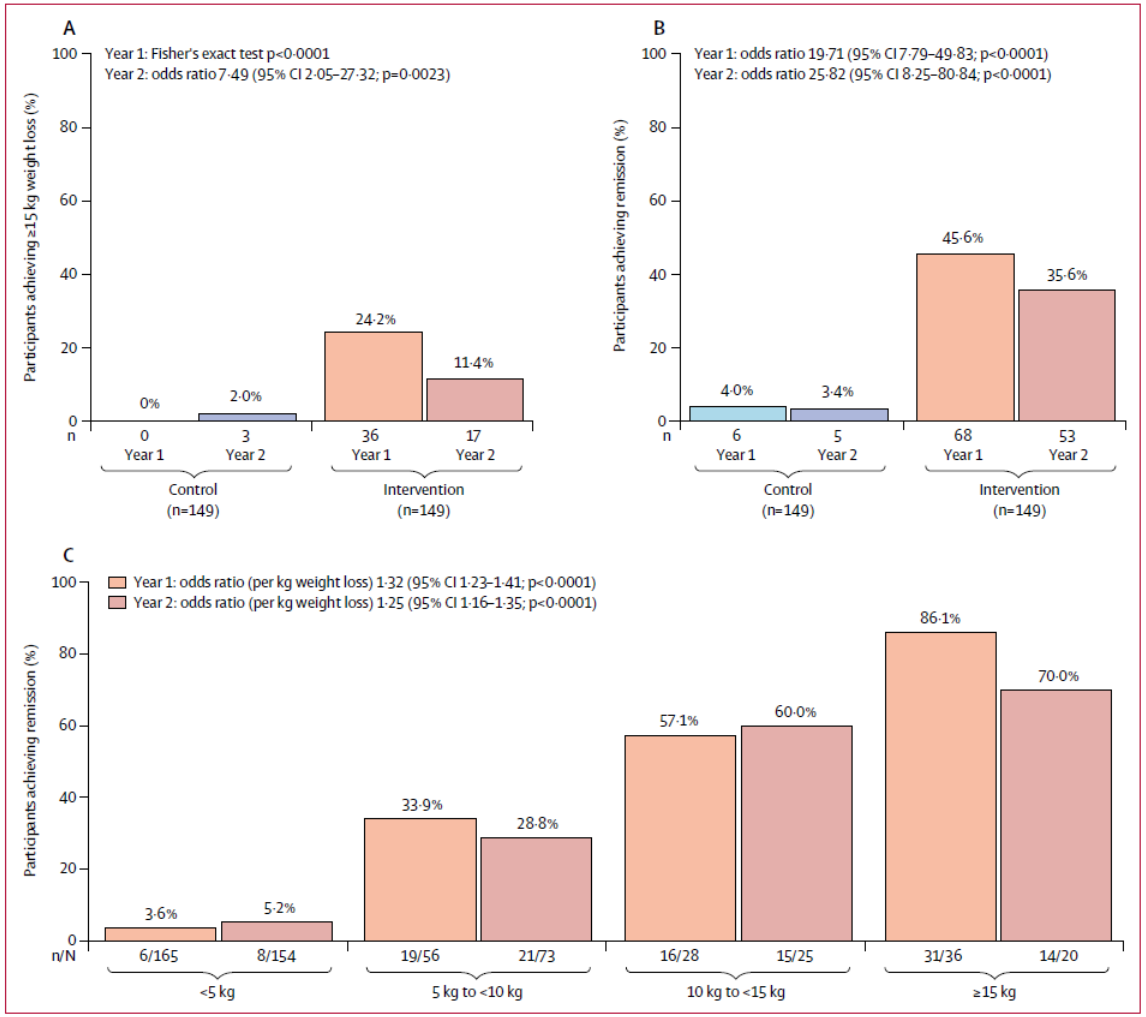
Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Control group (N. 149 with T2DM):	Best practice care by guidelines in 49 primary care practices in Scotland.
Intervention group (N. 149 with T2DM):	Weight management programme in 49 primary care practices in Scotland.



Lean MEJ et al. Lancet 2018;391:541-51

Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial



Lean MEJ et al. Lancet Endocrinol 2019;7:344-55

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Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

Table 3 Absolute contraindications to the use of VLCKD

Absolute contraindications
Type 1 diabetes mellitus, latent autoimmune diabetes in adults, β-cell failure in type 2 diabetes mellitus, use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk for euglycemic diabetic ketoacidosis)
Pregnancy and breastfeeding
Kidney failure and moderate-to-severe chronic kidney disease, liver failure, hearth failure (NYHA III-IV), respiratory failure
Unstable angina, recent stroke or myocardial infarction (< 12 months), cardiac arrhythmias
Eating disorders and other severe mental illnesses, alcohol and substance abuse
Active/severe infections
Frail elderly patients
48 h prior to elective surgery or invasive procedures and perioperative period
Rare disorders: porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders, pyruvate carboxylase deficiency

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Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

Table 2 Indications for the use of VLCKD in metabolic diseases

Strong recommendations	Strength of recommendations and quality of evidence according to GRADE system
Severe obesity	(1 ØØØO)
Management of severe obesity before bariatric surgery	(1 ØØØO)
Sarcopenic obesity	(1 ØØØO)
Obesity associated with type 2 diabetes (preserved beta cell function)	(1 ØØØO)
Obesity associated with hypertriglyceridemia	(1 ØØØO)
Obesity associated with hypertension	(1 ØØØO)
Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet	(1 ØØØO)
Weak recommendations	
Obesity associated with dysbiosis of the gut microbiota	(2 ØØØO)
Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol	(2 ØØØO)
Obesity associated with non-alcoholic fatty liver disease (NAFLD)	(2 ØØØO)
Obesity associated with heart failure (NYHA I–II)	(2 ØOOO)
Obesity associated with atherosclerosis	(2 ØOOO)
Male obesity secondary hypogonadism	(2 ØØØO)
Obesity associated with polycystic ovary syndrome (PCOS)	(2 ØOOO)
Menopausal transition-related obesity	(2 ØOOO)
Neurodegenerative disorders associated with sarcopenic obesity	(2 ØOOO)

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Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

Table 1 Parameters that need to be monitored before, during and at the end of a VLCKD regimen

Parameters	Frequency of monitoring	Rationale of monitoring
Complete blood count	At baseline and at the end of the VLCKD program	To exclude patients with severe alterations of blood count
Creatinine, BUN, uric acid (serum)	At baseline and during the ketogenic phase	Monitoring of kidney function and potential increase in uric acid
Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (serum)	At baseline and at the end of the VLCKD program	Excluding patients with uncontrolled diabetes, monitoring of lipid profile
ALT, AST, γ-GT, total and direct bilirubin (serum)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring of liver function and cholestatic parameters
Sodium, potassium, calcium, magnesium, inorganic phosphate (serum)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring for potential dehydration and electrolyte abnormalities
β-Hydroxybutyrate (capillary blood or urine)	During the ketogenic phase	Monitoring of ketosis
TSH, FT4 (serum)	At baseline	To exclude thyroid function abnormalities
25-Hydroxyvitamin D (serum)	At baseline	To treat vitamin D deficiency, if present
Complete urinalysis and microalbuminuria (urine)	At baseline, during the ketogenic phase and at the end of the VLCKD program	To exclude any potential kidney damage
Body composition and hydration status (by bioelectrical impedance analysis)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring of body composition (fat mass, fat-free mass, body cell mass, total body water, extracellular water)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *FT4* free thyroxine, *γ-GT* gamma-glutamyl transferase, *HDL-cholesterol* high-density lipoprotein cholesterol, *LDL* cholesterol, low-density lipoprotein cholesterol, *TSH* thyroid-stimulating hormone, *VLCKD* very-low-calorie ketogenic diet

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European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis

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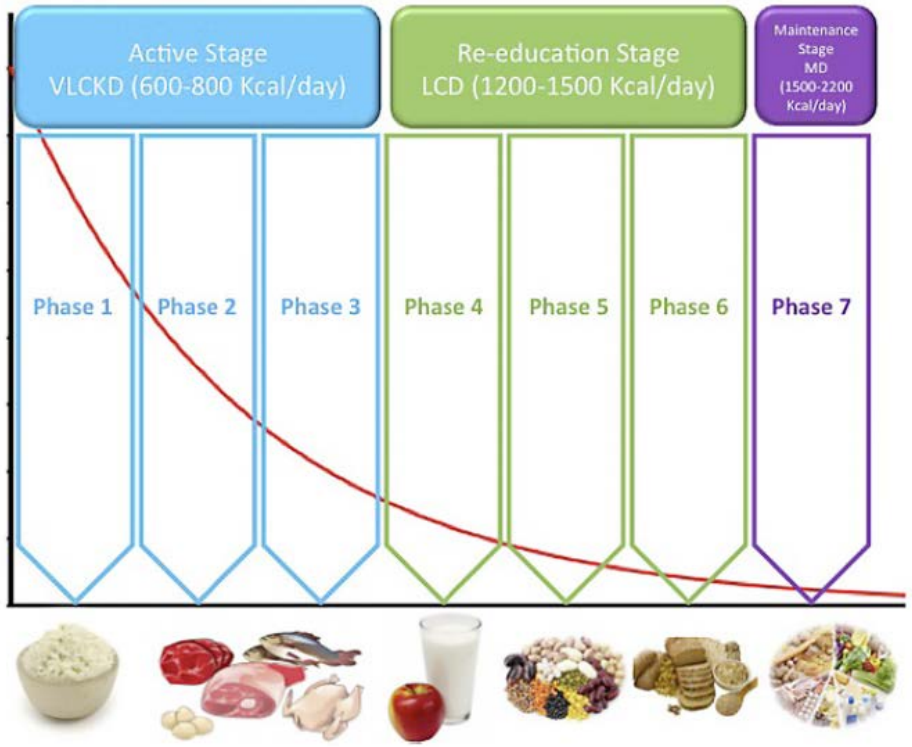
Maria Hassapidou[d] Volkan Yumuk[e] Luca Busetto[f] Obesity Management
Task Force (OMTF) of the European Association for the Study of Obesity (EASO)



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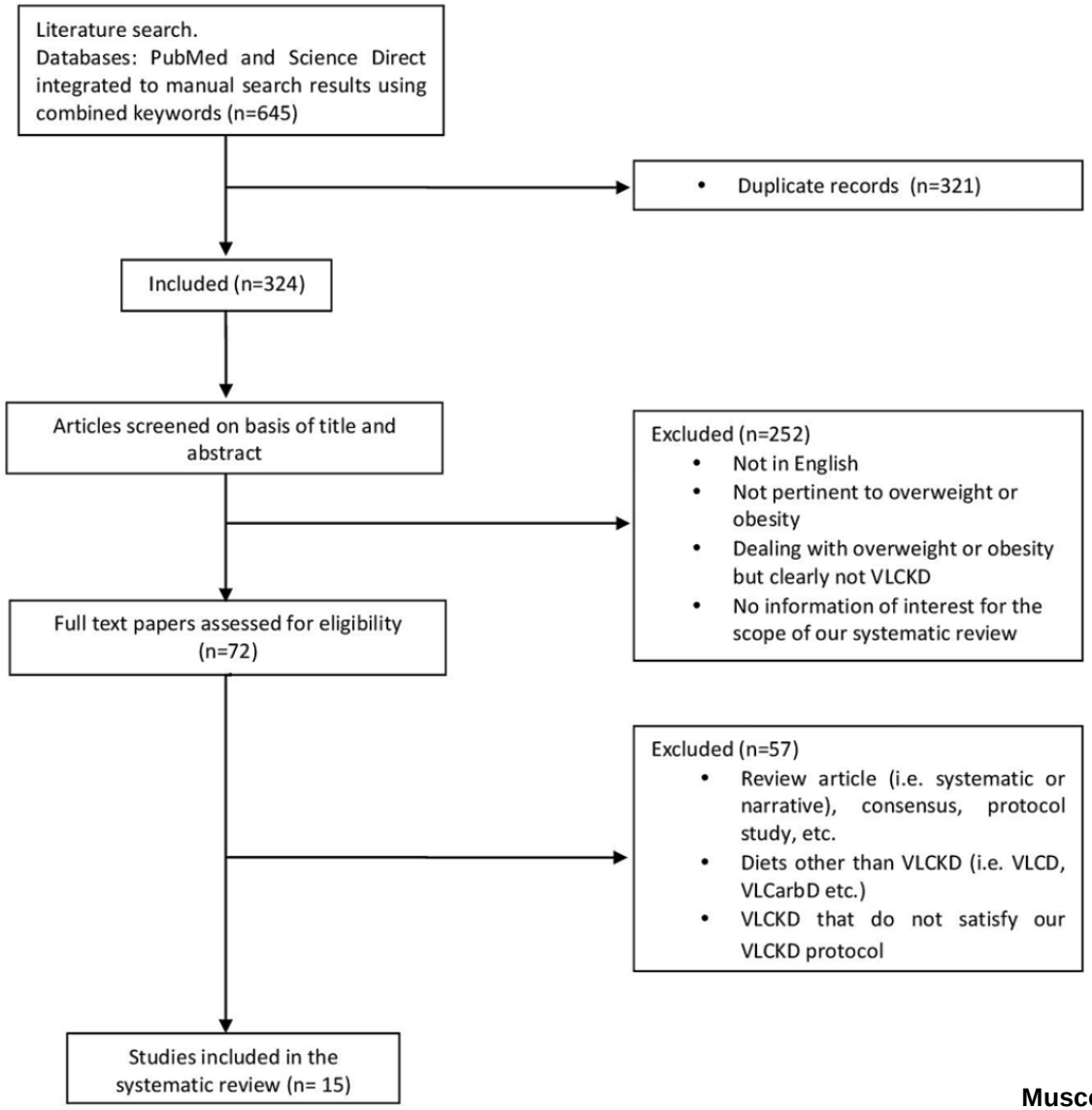

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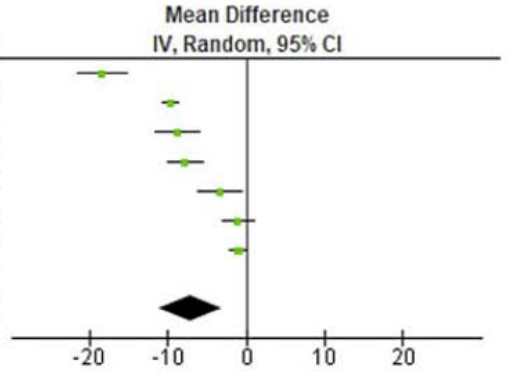
BW

Study or Subgroup	VLCKD Mean	VLCKD SD	VLCKD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Perticone 2019 [33]	-26.6	7.27	28	-8.2	4.6	28	13.7%	-18.40 [-21.59, -15.21]
Goday 2016 [28]	-14.67	2.18	45	-5.05	2.67	44	14.8%	-9.62 [-10.63, -8.61]
Moreno 2014 [32]	-13.7	5.7	27	-4.9	4.65	26	14.0%	-8.80 [-11.60, -6.00]
Sajoux 2019 [35]	-11.8	4.66	20	-4	2.91	39	14.3%	-7.80 [-10.04, -5.56]
Rubini 2015 [34]	-8.5	4.42	16	-5.1	3.63	16	14.0%	-3.40 [-6.20, -0.60]
Merra 2016 [13]	-6.98	2.2	9	-5.97	2.2	9	14.4%	-1.01 [-3.04, 1.02]
Albanese 2019 [24]	-5.8	3.89	72	-4.8	2.94	106	14.8%	-1.00 [-2.06, 0.06]
Total (95% CI)			**217**			**268**	**100.0%**	**-7.06 [-11.16, -2.97]**

Heterogeneity: Tau² = 29.22; Chi² = 225.21, df = 6 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.38 (P = 0.0007)

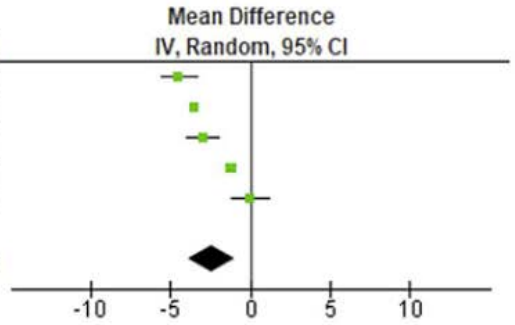


i.

BMI

Study or Subgroup	VLCKD Mean	VLCKD SD	VLCKD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Perticone 2019 [33]	-7.2	2.75	28	-2.7	1.37	28	18.9%	-4.50 [-5.64, -3.36]
Goday 2016 [28]	-5.4	0.35	45	-1.9	0.41	44	21.4%	-3.50 [-3.66, -3.34]
Moreno 2014 [32]	-4.8	2.06	27	-1.8	1.58	26	19.5%	-3.00 [-3.99, -2.01]
Albanese 2019 [24]	-2.4	1.02	72	-1.2	0.94	106	21.3%	-1.20 [-1.50, -0.90]
Merra 2016 [13]	-2.33	1.67	9	-2.31	0.57	9	18.9%	-0.02 [-1.17, 1.13]
Total (95% CI)			**181**			**213**	**100.0%**	**-2.45 [-3.88, -1.01]**

Heterogeneity: Tau² = 2.48; Chi² = 212.53, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.35 (P = 0.0008)



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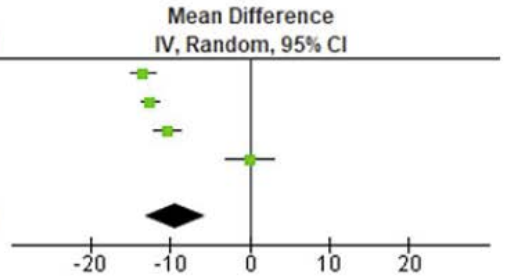
FM

Study or Subgroup	VLCKD Mean	VLCKD SD	VLCKD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Perticone 2019 [33]	-19.9	3.58	28	-6.5	2.61	28	25.5%	-13.40 [-15.04, -11.76]
Sajoux 2019 [35]	-16.5	2.43	20	-3.9	1.47	59	26.1%	-12.60 [-13.73, -11.47]
Moreno 2014 [32]	-16	3.65	27	-5.6	2.71	26	25.4%	-10.40 [-12.13, -8.67]
Merra 2016 [13]	-2.45	4.41	9	-2.47	1.71	9	22.9%	0.02 [-3.07, 3.11]
Total (95% CI)			**84**			**122**	**100.0%**	**-9.35 [-13.29, -5.41]**

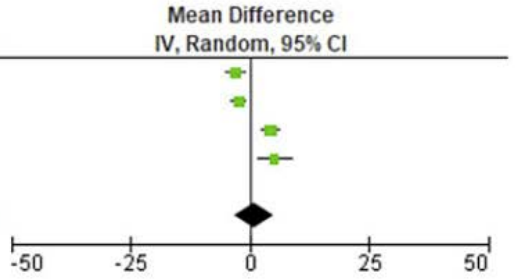
Heterogeneity: Tau² = 15.11; Chi² = 63.74, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.66 (P < 0.00001)



FFM

Study or Subgroup	VLCKD Mean	VLCKD SD	VLCKD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Moreno 2014 [32]	-3	4.43	27	0	3.26	26	25.5%	-3.00 [-5.09, -0.91]
Sajoux 2019 [35]	-3.7	3.16	20	-1.4	2.11	59	26.3%	-2.30 [-3.79, -0.81]
Perticone 2019 [33]	3.6	4.35	28	-0.8	3.14	28	25.6%	4.40 [2.41, 6.39]
Merra 2016 [13]	1.92	5.22	9	-3.3	1.44	9	22.6%	5.22 [1.68, 8.76]
Total (95% CI)			**84**			**122**	**100.0%**	**0.94 [-3.10, 4.97]**

Heterogeneity: Tau² = 15.49; Chi² = 44.18, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 0.46 (P = 0.65)



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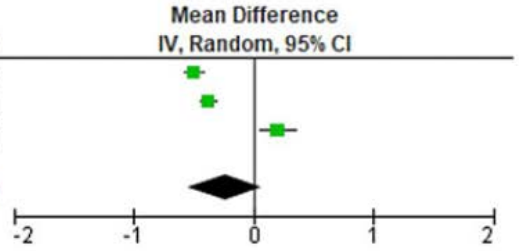
HbA1c

Study or Subgroup	VLCKD Mean	VLCKD SD	VLCKD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Goday 2016 [28]	-0.9	0.19	45	-0.4	0.19	44	33.9%	-0.50 [-0.58, -0.42]
Moreno 2014 [32]	-0.01	0.16	27	0.37	0.09	26	34.0%	-0.38 [-0.45, -0.31]
Perticone 2019 [33]	-0.9	0.27	28	-1.1	0.29	28	32.1%	0.20 [0.05, 0.35]
Total (95% CI)			**100**			**98**	**100.0%**	**-0.23 [-0.54, 0.07]**

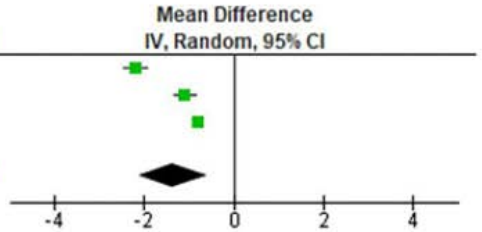
Heterogeneity: Tau² = 0.07; Chi² = 68.32, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.49 (P = 0.14)



HOMA

Study or Subgroup	VLCKD Mean	VLCKD SD	VLCKD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Goday 2016 [28]	-3.4	0.71	45	-1.2	0.58	44	32.9%	-2.20 [-2.47, -1.93]
Sajoux 2019 [35]	-2.72	0.55	20	-1.63	0.23	59	33.1%	-1.09 [-1.34, -0.84]
Perticone 2019 [33]	-4.7	0.14	28	-3.9	0.19	28	34.1%	-0.80 [-0.89, -0.71]
Total (95% CI)			**93**			**131**	**100.0%**	**-1.36 [-2.14, -0.57]**

Heterogeneity: Tau² = 0.47; Chi² = 95.44, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.38 (P = 0.0007)



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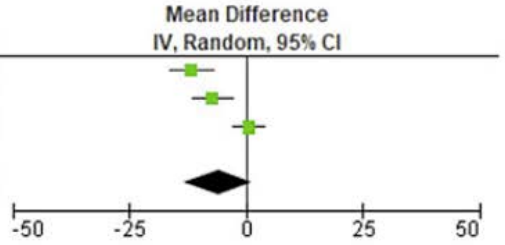
LDL

Study or Subgroup	T1 Mean	T1 SD	T1 Total	T0 Mean	T0 SD	T0 Total	Weight	Mean Difference IV, Random, 95% CI
Moreno 2014 [32]	-13.6	9.42	27	-1.9	7.6	26	32.5%	-11.70 [-16.30, -7.10]
Perticone 2019 [33]	-17.6	6.8	28	-10.4	9.82	28	32.8%	-7.20 [-11.62, -2.78]
Goday 2016 [28]	-2.1	7.61	45	-2.7	8.21	44	34.6%	0.60 [-2.69, 3.89]
Total (95% CI)			**100**			**98**	**100.0%**	**-5.96 [-13.42, 1.50]**

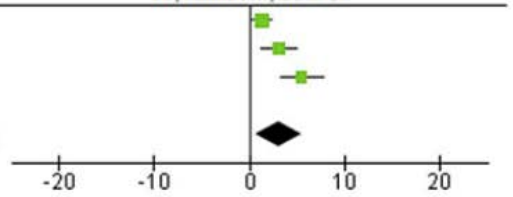
Heterogeneity: Tau² = 39.01; Chi² = 20.07, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 1.57 (P = 0.12)



HDL

Study or Subgroup	VLCKD Mean	VLCKD SD	VLCKD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Goday 2016 [28]	-1.4	2.36	45	-2.7	2.32	44	37.8%	1.30 [0.33, 2.27]
Perticone 2019 [33]	4.3	3.31	28	1.2	4.12	28	32.0%	3.10 [1.14, 5.06]
Moreno 2014 [32]	7.8	4.44	27	2.3	3.78	26	30.2%	5.50 [3.28, 7.72]
Total (95% CI)			**100**			**98**	**100.0%**	**3.14 [0.70, 5.59]**

Heterogeneity: Tau² = 3.86; Chi² = 12.61, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 2.52 (P = 0.01)



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Parameters	Baseline	During the active stage	At the end of the active stage	At the end of the reintro-duction stage
Antropometric assessment				
Weight, height, and BMI	X	X	X	X
Body composition and hydration status (by bioelectrical impedance analysis)	X	X	X	X
Laboratory assessment				
Complete blood count with platelets	X	X	X	X
Sodium, potassium, magnesium, and inorganic phosphate	X	X	X	X
Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine, γ-GT, and total and direct bilirubin)	X	X	X	X
Fasting lipid profile	X			X
25(OH)D, calcium	X			X
Glucose and insulin	X			X
β-hydroxybutyrate (capillary blood or urine)		X		
TSH and FT4	X			
Complete urinalysis and microalbuminuria (urine)	X	X	X	X

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Conclusions and Recommendations

After a careful systematic review and meta-analysis of the current evidence, and considering the potential side effects, VLCKD can be recommended as an effective dietary treatment for individuals with obesity, in particular for patients with severe obesity and/or comorbidities (joint diseases, preoperative period of bariatric surgery, and cardiovascular and metabolic diseases) who need immediate and substantial weight loss. Therefore, VLCKD can be prescribed targeting a specific population of patients with obesity after consideration of the potential contraindications and under medical surveillance. However, it is important to personalize the diet, based on the patient's preferences, allowing food choices within the VLCKD protocol. After achievement of the weight target with VLCKD, implementation of long-term lifestyle strategies (physical activity and nutritional counselling) is strongly recommended to reduce the risk of weight regain in the long term.

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KDA Ketogenic Diet ACADEMY

SINut Società Italiana di Nutraceutica

Grazie per l'attenzione !!!

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