STEATOSI EPATICA: MALATTIA EMERGENTE

CAM Monza, 10 MAGGIO 2014

STILI DI VITA COME TERAPIA

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Presidente Brain and Malnutrition Association

Steatosi - Definizione

- **Accumulo vacuolare di lipidi (+TG) in oltre il 5% degli epatociti**

- Eziopatogenesi multifattoriale
  - Tossica
  - Metabolica
  - Infettiva

- Istologia e prognosi variabili

steatosi→flogosi/necrosi→fibrosi→cirrosi→HCC

Steatosi - eziopatogenesi

- **Tossica**
  - Alcool
  - Farmaci (steroidi, amiodarone, tetracicline,etc)
- **Endocrino-Metabolica**
  - Iperinsulinismo
  - Obesità
  - Diabete
  - Dislipidemia
  - Ipercorticosurrenalismo
- **Malnutrizione e Malassorbimento**
  - Digiuno, celiachia, cachessia, by pass digiuno ileale
- **Infettiva**
  - HCV
  - Endotossina gram-

Alcool e steatosi epatica

-Alcool (etanolo)
-SNC deprime i centri inibitori
-Gastrico effetto infiammatorio

A livello epatico ha i peggiori effetti:

Etanolo-------metabolizzato------ Acetaldeide

TIPO DI BEVANDA	QUANTITÀ UNITARIA	GRAMMI DI ALCOOL
Vino (12 gradi)	1 bicchiere (125 ml)	11,7
Birra (4,5 gradi)	1 lattina (330 ml)	11,9
Champagne (11 gradi)	1 coppa (100 ml)	9
Superalcolici (40 gradi)	1 bicchiere (40 ml)	12,8
Amari (30 gradi)	1 bicchiere (30 ml)	7,2

Steatosi - eziopatogenesi

- **Tossica**
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- **Infettiva**
  - HCV
  - Endotossina gram-

Steatosi – eziopatogenesi comune

- **Tossica**
  - Acool
  - Farmaci (steroidi, amiodarone, tetracicline,etc)
- **Endocrino-Metabolica**
  - Iperinsulinismo

Tabella 1

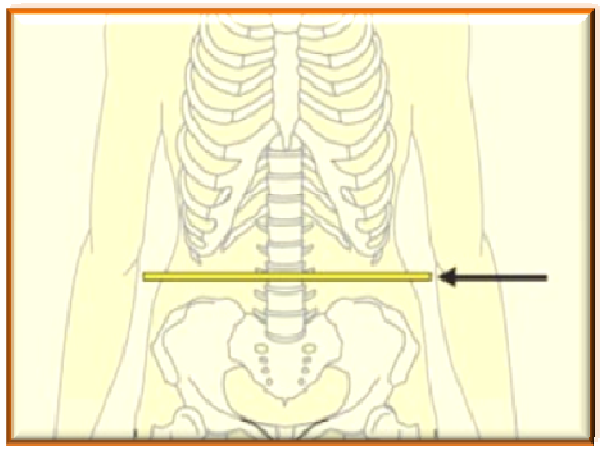
Confronto tra parametri per la definizione di sindrome metabolica

Parametri	OMS (1999)	NCEP ATP III (2001)	IDF (2005)
Body mass index	>30 kg/m^2 (4)		
Circonferenza addominale		P 102 cm - O 88 cm	P 94 cm - O 80 cm
Trigliceridi	≥150 mg/dl	≥150 mg/dl	≥150 mg/dl (1)
HDL colesterolo	P <35 mg/dl - O<39 mg/dl	P <40 mg/dl - O<50 mg/dl	P <40 mg/dl - O<50 mg/dl (1)
Pressione arteriosa	≥140/90 mmHg	≥130/85 mmHg	PAS ≥130 o PAD ≥85 mmHg (1)
Glicemia a digiuno	Diabete o IGT	>110 mg/dl	>100 mg/dl (2,3)
Microalbuminuria	≥20 g/min (5)		
Insulino-resistenza	Iperinsulinemia (6)		

1: Oppure trattamento specifico in atto
2: Oppure pregressa diagnosi di diabete di tipo 2
3: Se glicemia a digiuno<100 mg/dl raccomandata OGTT ma non necessaria per definire la presenza di sindrome metabolica
4. Oppure rapporto circonferenza addome/anche: P>0,90 - O >0,85
5: Oppure rapporto albumina/creatinina ≥30
6: In condizione di normoglicemia con uptake del glucosio al quartile inferiore per la popolazione studiata

- Endotossina gram-

MISURARE LA CIRCONFERENZA VITA



Bedogni et al., 2001

Si misura a metà tra l'ultima costa e la cresta iliaca (indicazioni WHO).

Il soggetto deve rimanere senza scarpe e con l'addome scoperto.

Il metro si applica senza comprimere i tessuti molli.

CIRCONFERENZA VITA E RISCHIO CARDIOVASCOLARE

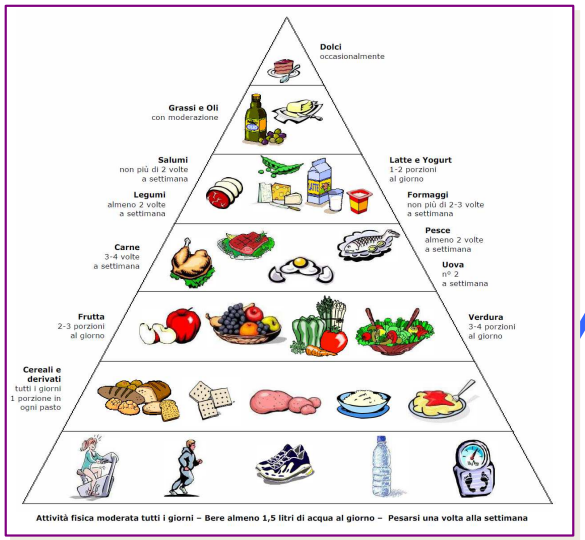
	Rischio Aumentato	Rischio Sostanzialmente Aumentato
Uomini	≥ 94 cm	≥ 102 cm
Donne	≥ 80 cm	≥ 88 cm

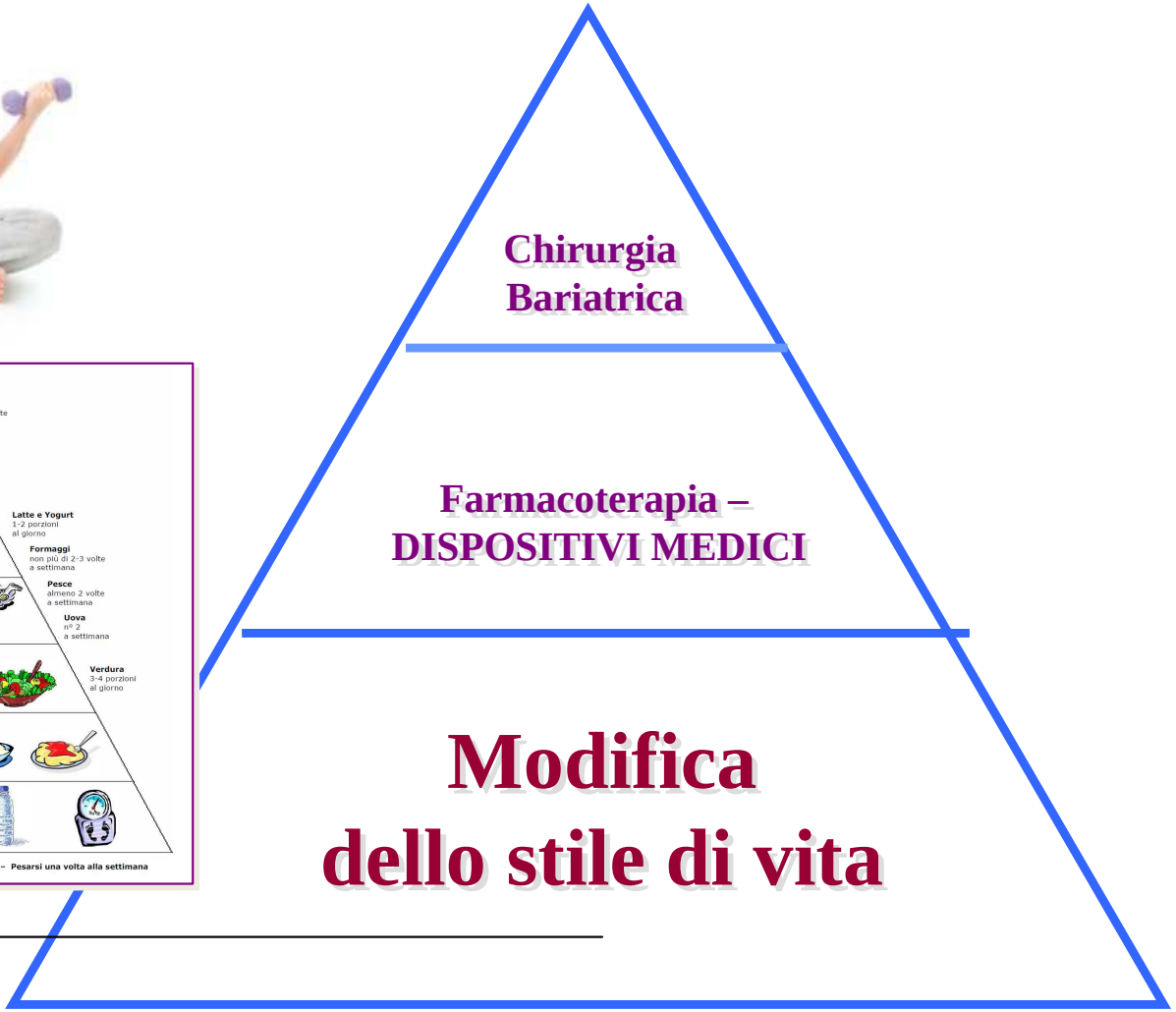
Bedogni et al., 2001

Ruolo dell'adipe centrale

- Drenaggio venoso portale → fegato
- Minor sensibilità all'effetto anti-lipolitico dell'insulina
- Lipolisi e liberazione di FFA più spiccata
- Secrezione di Adipo-citochine:
  - TNF-α: correlato a obesità ed insulinoresistenza
  - Leptina: correlata ad insulinoresistenza
  - Iperleptinemia in obesità, DM, epatopatia alcolica, cirrosi HCV: effetto pro-fibrotico
- FFA e TNF-α → insulinoresistenza ed iperinsulinemia
  - Inibizione del segnale insulinico post-recettore

Trattamento sindrome metabolica





Dietoterapia

Ha come obiettivo la riduzione del peso corporeo

Consiste nella riduzione degli introiti alimentari

Deve essere realistica e accettabile

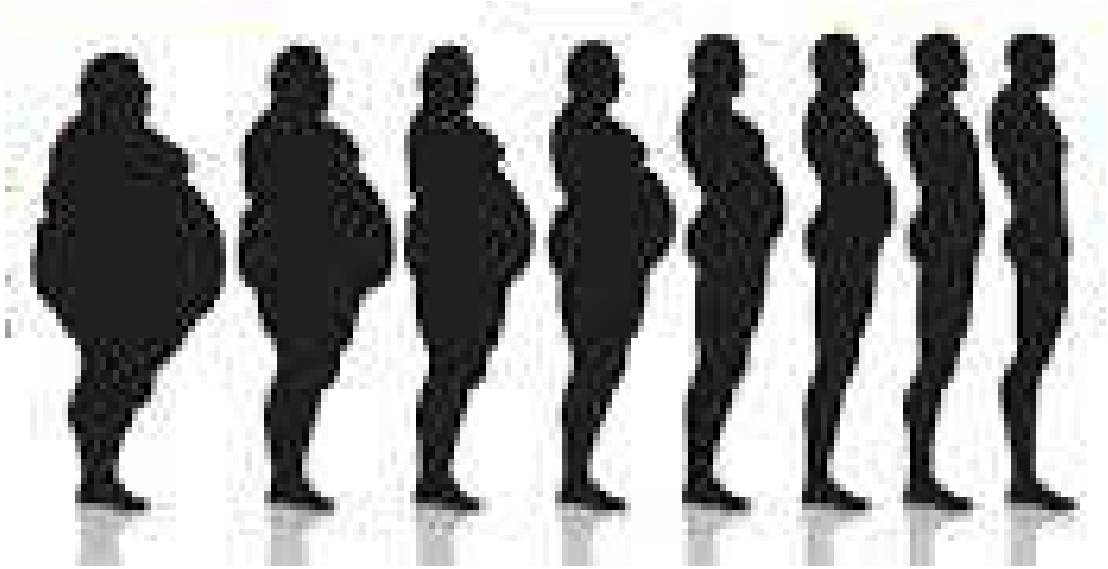
Ha come finalità una riduzione della mortalità e delle complicanze

1- Kastorini CM, Panagiotakos DB. Front Biosci 2010; 2:1320-33
2- Sarwer DB, Wadden TA, J Womens Healt Gend Based Med 1999; 8:483-93
3- Gregg EW et al, Ann Intern Med 2003; 138: 383-89

Autori	Terapia	Dose	Casi	Tempo	Enzimi epatici	Istologia
Eriksson (32)	Dieta		3	1 anno	Migliorati	Migliorata
Andersen (33)	Dieta		41	4-23 mesi	Migliorati	Variabile
Palmer (34)	Dieta + ex		39	2-11 mesi	Migliorati	nv
Vajro (35)	Dieta + ex		9	30 mesi	Migliorati	Migliorata
Ueno (36)	Dieta + ex		25	3 mesi	Migliorati	Migliorata
Franzese (37)	Dieta + ex		58	6 mesi	Migliorati	nv
Marchesini (38)	Metformina	500 × 3	20	4 mesi	Migliorati	nv
Coyle (39)	Metformina	500 × 4	2	4-11 mesi	Migliorati	Migliorata
Acosta (40)	Pioglitazone	nd	8	2-12 mesi	Migliorati	nv
Azuma (41)	Pioglitazone	15 mg	7	3 mesi	Migliorati	Migliorata
Neuschwander-Tetri (42)	Rosiglitazone	4 mg × 2	30	48 sett	Migliorati	Migliorata
Laurin (43)	UDCA	13-15 mg/kg	24	12 mesi	Migliorati	Migliorata
Horlander (44)	Atorvastatina	30 mg	7	21 mesi	Migliorati	Migliorata
Saibara (45)	Bezafibrato	400 mg	2	10 mesi	Migliorati	Migliorata
Lavine (46)	Vitamina E	400-1200 UI	11	4-10 mesi	Migliorati	nv
Harrison (47)	Orlistat	360 mg	3	6 mesi	Migliorati	Migliorata
Desai (48)	Flebotomia		8	3-24 mesi	Migliorati	nv
Nitecki (49)	Flebotomia		9	6-12 mesi	Migliorati	Migliorata
Facchini (50)	Flebotomia		17	—	Migliorati	nv

nv = non valutata; ex = esercizio fisico

Dietoterapia e Steatosi



Calo ponderale 10 %

Calo ponderale 5%

Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002;123:1705-1725.

Classificazione delle diete

- ❑ **NORMOCALORIC DIET**
- ❑ **LOW-CALORIE DIET**
- ❑ **HIGH-CALORIE DI**

- ❑ **BALANCED DIET**
- ❑ **LOW-FAT DIET**
- ❑ **LOW-PROTEIN DIET**
- ❑ **HIGH-PROTEIN DIET**
- ❑ **KETOGENIC DIET**

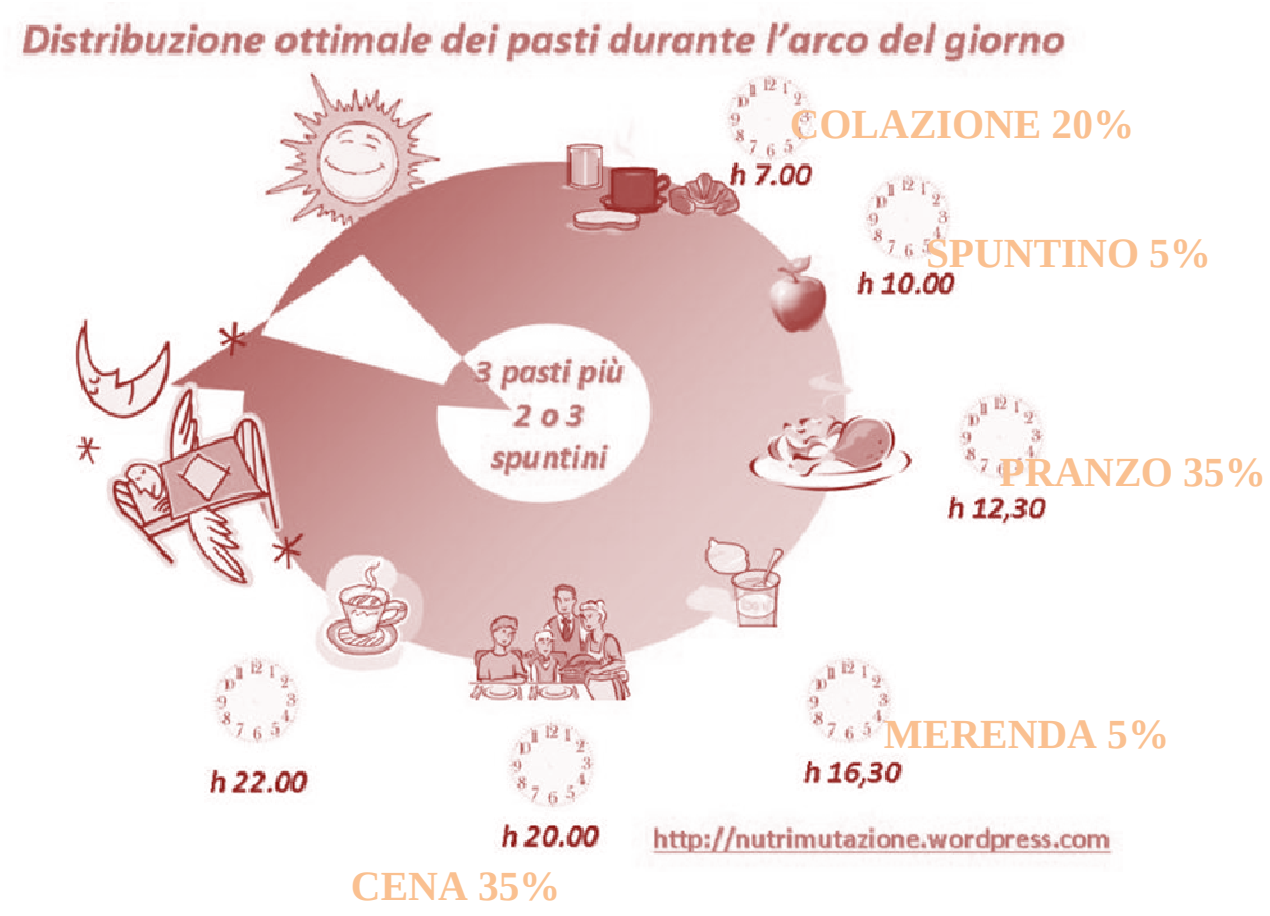
Attenzione Regimi restrittivi

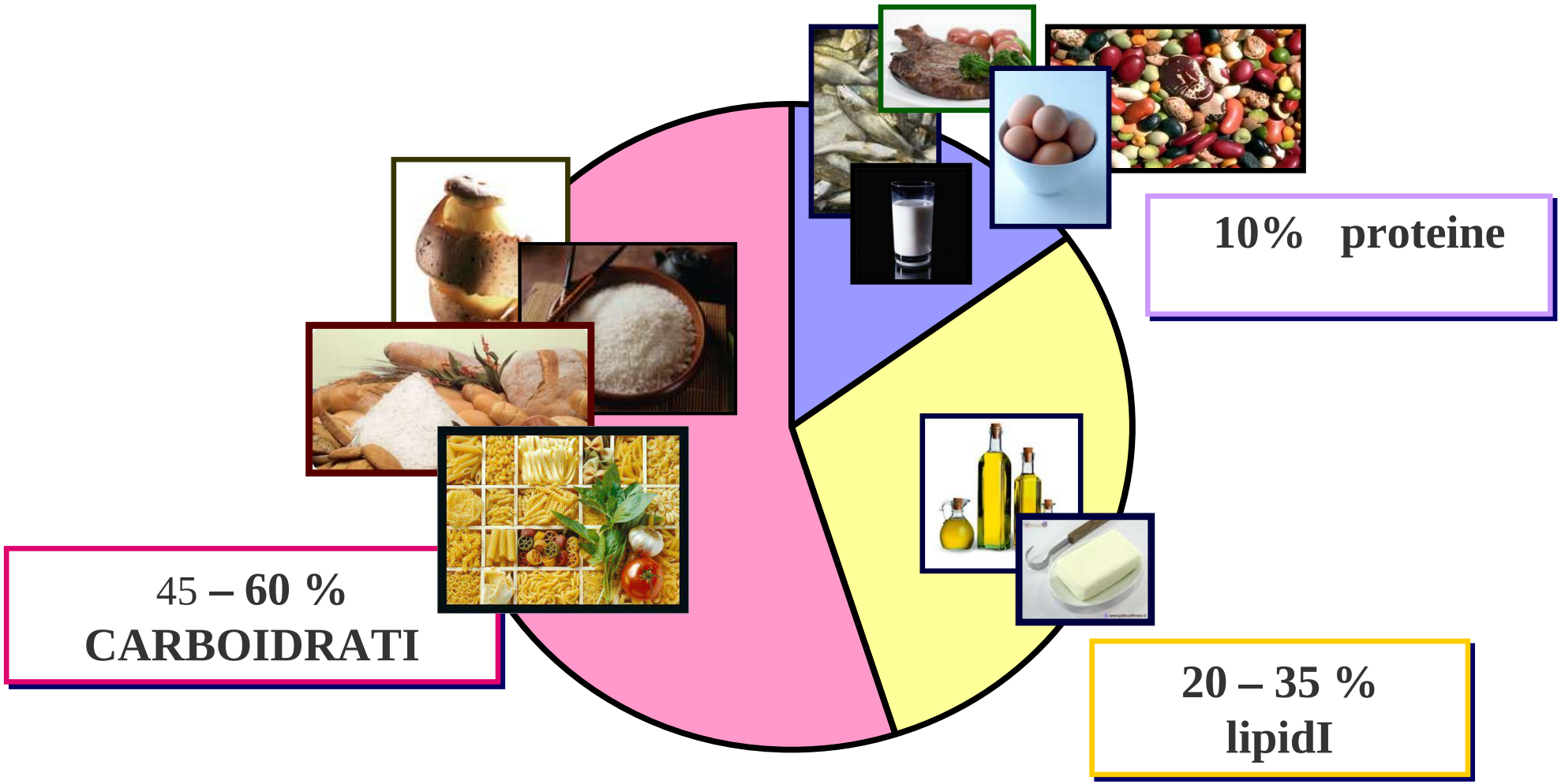
Perdita > 1.6 Kg/sett

Peggiore quadro epatica

Rischio litiasi biliare

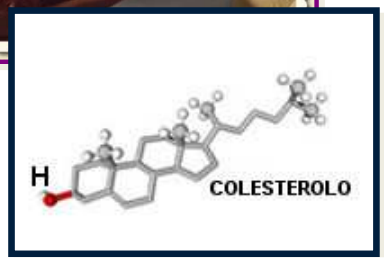
L’energia (intesa come calorie) assunta nella giornata deve essere suddivisa in cinque momenti fondamentali.




10% proteine
20 – 35 %
lipidI
45 – 60 %
CARBOIDRATI

Grassi < 30 %

Saturi < 7 %



< 300 mg / die

Monoinsaturi

polinsaturi

OMEGA - 3

Carboidrati 50 – 60 %

Complessi
ed
Integrali

Semplici
≤ 10 %

FIBRA > 15g / 1000 Kcal

DA CEREALI

Ricca in MAGNESIO

antiossidanti

Frutta e verdura

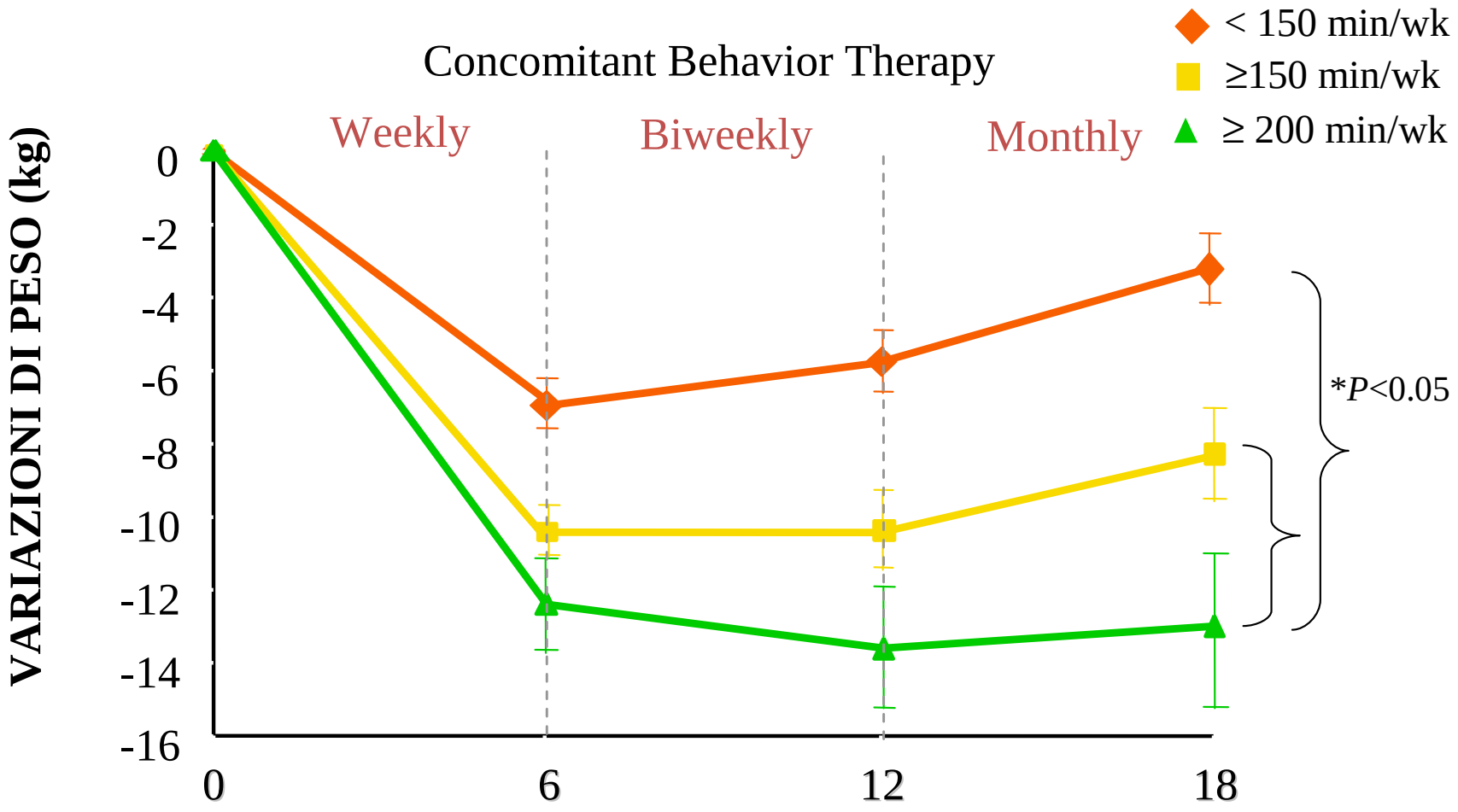
Attività fisica

AUMENTO SENSIBILITÀ INSULINICA

MAGGIORE UTILIZZO SUBSTRATI A LIVELLO MUSCOLARE

Physical Activity

TO MAINTAIN WEIGHT LOSS

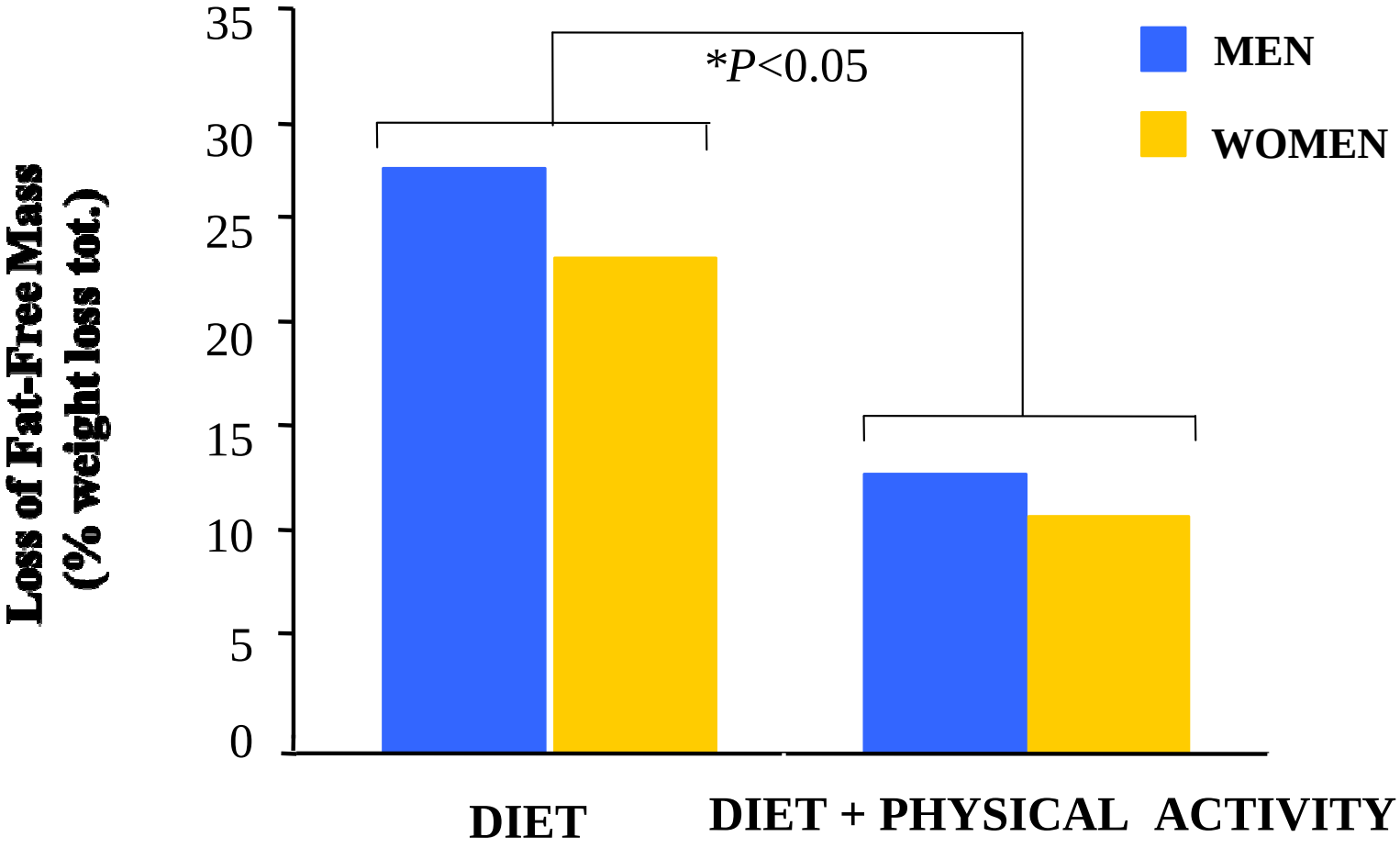


Jakicic et al. *JAMA* 1999;282:1554.

Physical Activity

REGULAR PHYSICAL ACTIVITY

FAT-FREE MASS



Ballor and Poehlman. *Int J Obes Relat Metab Disord* 1994;18:35.

Physical Activity

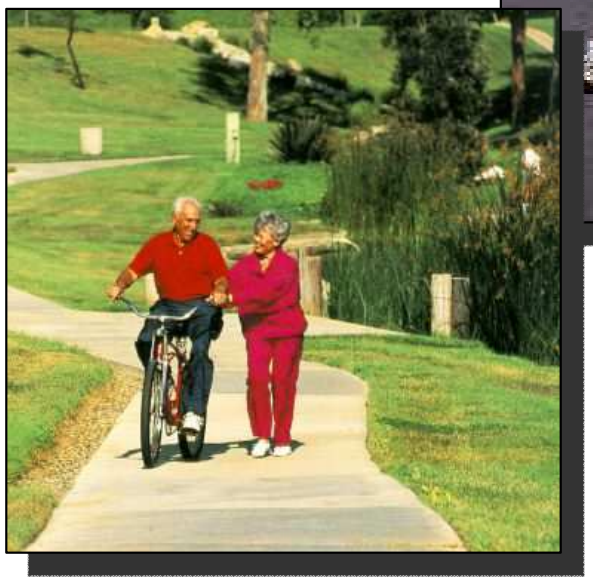
REGULAR PHYSICAL ACTIVITY

LONG-TERM WEIGHT MAINTENANCE

BENEFICIAL HEALTH EFFECTS

30-60 minutes

3-4 times a week



Attenzione al fruttosio

COMMENT

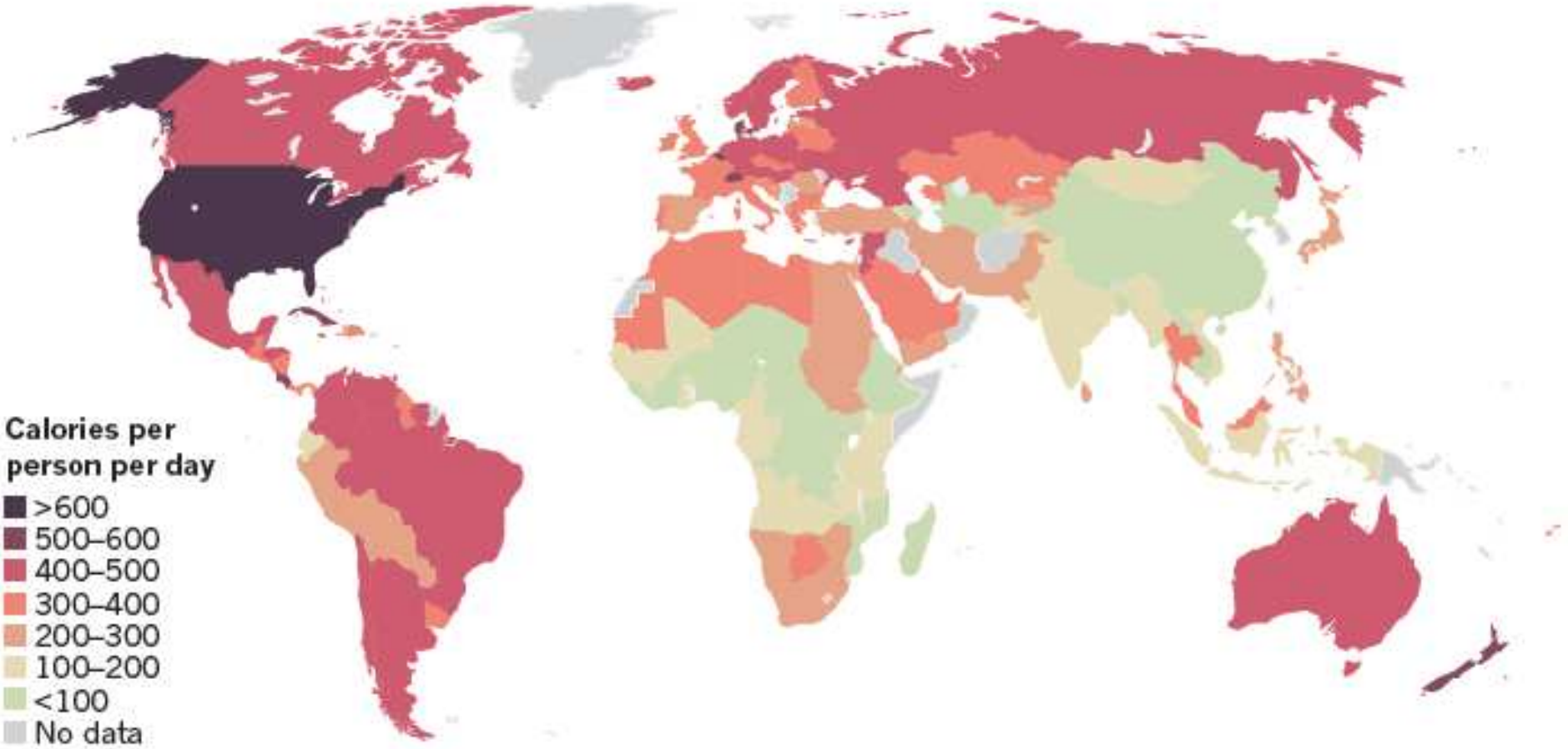
ILLUSTRATION BY MARK SMITH

The toxic truth about sugar

Added sweeteners pose dangers to health that justify controlling them like alcohol, argue **Robert H. Lustig**, **Laura A. Schmidt** and **Claire D. Brindis**.

THE GLOBAL SUGAR GLUT

Global sugar supply (in the form of sugar and sugar crops, excluding fruit and wine) expressed as calories per person per day, for the year 2007.



SOURCE: FAO

Meets Learning Need Codes 2000, 2100, and 2040. To take the Continuing Professional Education quiz for this article, log in to ADA's Online Business Center at www.eatright.org/obc, click the "Journal Article Quiz" button, click "Additional Journal CPE Articles," and select this article's title from a list of available quizzes.

Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol

ROBERT H. LUSTIG, MD

ABSTRACT

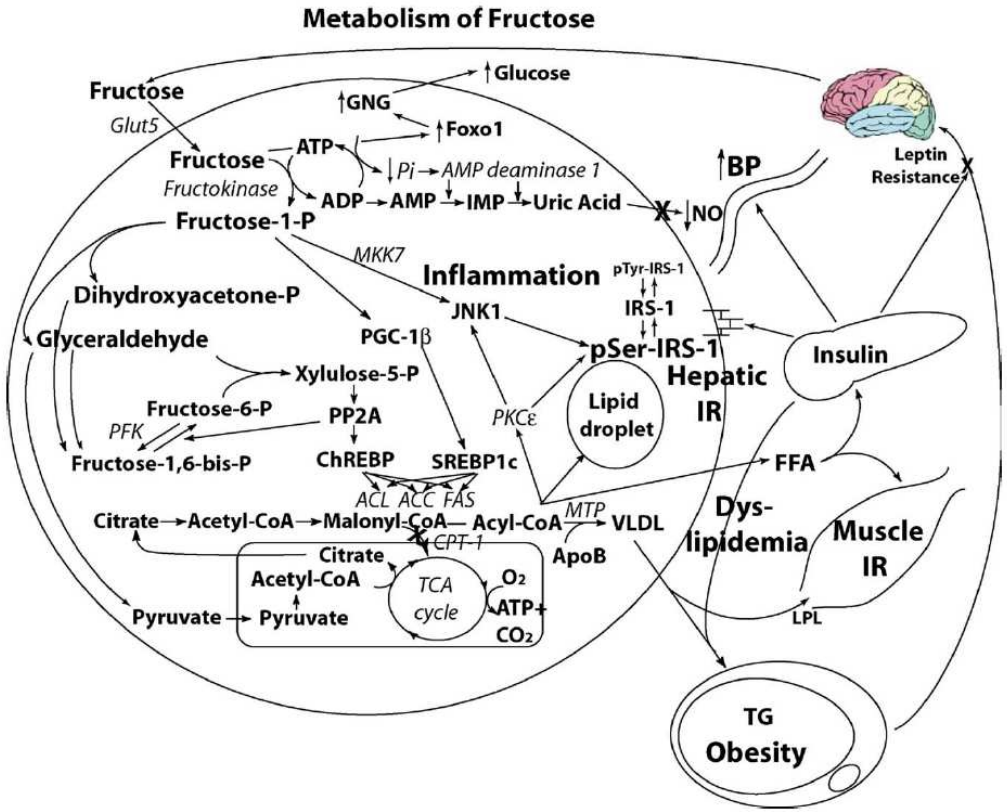
Rates of fructose consumption continue to rise nationwide and have been linked to rising rates of obesity, type 2 diabetes, and metabolic syndrome. Because obesity has been equated with addiction, and because of their evolutionary commonalities, we chose to examine the metabolic, hedonic, and societal similarities between fructose and its fermentation byproduct ethanol. Elucidation of fructose metabolism in liver and fructose action in brain demonstrate three parallelisms with ethanol. First, hepatic fructose metabolism is similar to ethanol, as they both serve as substrates for de novo lipogenesis, and in the process both promote hepatic insulin resistance, dyslipidemia, and hepatic steatosis. Second, fructosylation of proteins with resultant superoxide formation can result in hepatic inflammation similar to acetaldehyde, an intermediary metabolite of ethanol. Lastly, by stimulating the "hedonic pathway" of the brain both directly and indirectly, fructose creates habituation, and possibly dependence; also paralleling ethanol. Thus, fructose induces alterations in both hepatic metabolism and central nervous system energy signaling, leading to a "vicious cycle" of excessive consumption and disease consistent with metabolic syndrome. On a societal level, the treatment of fructose as a commodity exhibits market similarities to ethanol. Analogous to ethanol, societal efforts to reduce fructose consumption will likely be necessary to combat the obesity epidemic.

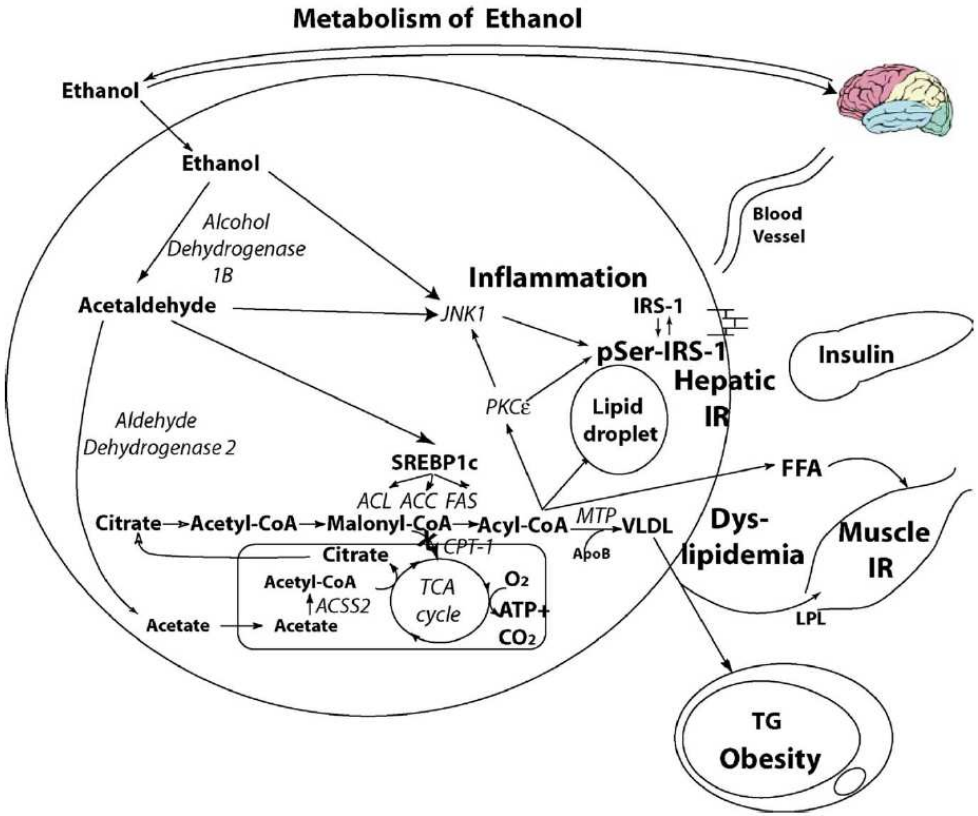
J Am Diet Assoc. 2010;110:1307-1321.

Meets Learning Need Codes 2000, 2100, and 2040. To take the Continuing Professional Education quiz for this article, log in to ADA's Online Business Center at www.eatright.org/obc, click the "Journal Article Quiz" button, click "Additional Journal CPE Articles," and select this article's title from a list of available quizzes.

Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol

ROBERT H. LUSTIG, MD





DEADLY EFFECT

Excessive consumption of fructose can cause many of the same health problems as alcohol.

Chronic ethanol exposure	Chronic fructose exposure
Haematological disorders	
Electrolyte abnormalities	
Hypertension	Hypertension (uric acid)
Cardiac dilatation	
Cardiomyopathy	Myocardial infarction (dyslipidaemia, insulin resistance)
Dyslipidaemia	Dyslipidaemia (*de novo* lipogenesis)
Pancreatitis	Pancreatitis (hypertriglyceridaemia)
Obesity (insulin resistance)	Obesity (insulin resistance)
Malnutrition	Malnutrition (obesity)
Hepatic dysfunction (alcoholic steatohepatitis)	Hepatic dysfunction (non-alcoholic steatohepatitis)
Fetal alcohol syndrome	
Addiction	Habituation, if not addiction

Source: ref. 1

Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women

CL Cox[1], KL Stanhope[1,2], JM Schwarz[3], JL Graham[1,2], B Hatcher[1], SC Griffen[4], AA Bremer[5], L Berglund[4], JP McGahan[6], PJ Havel[1,2] and NL Keim[1,7]

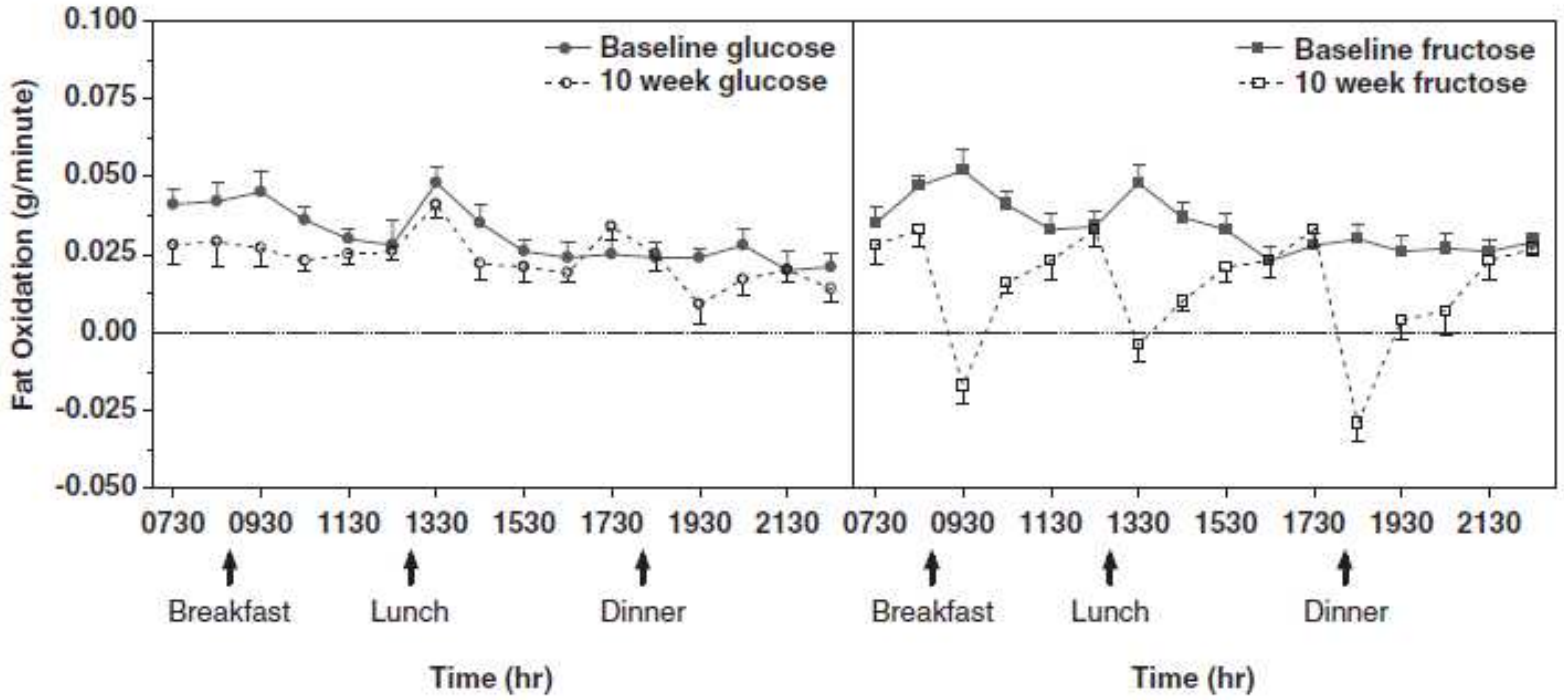
Background/Objectives: The results of short-term studies in humans suggest that, compared with glucose, acute consumption of fructose leads to increased postprandial energy expenditure and carbohydrate oxidation and decreased postprandial fat oxidation. The objective of this study was to determine the potential effects of increased fructose consumption compared with isocaloric glucose consumption on substrate utilization and energy expenditure following sustained consumption and under energy-balanced conditions.

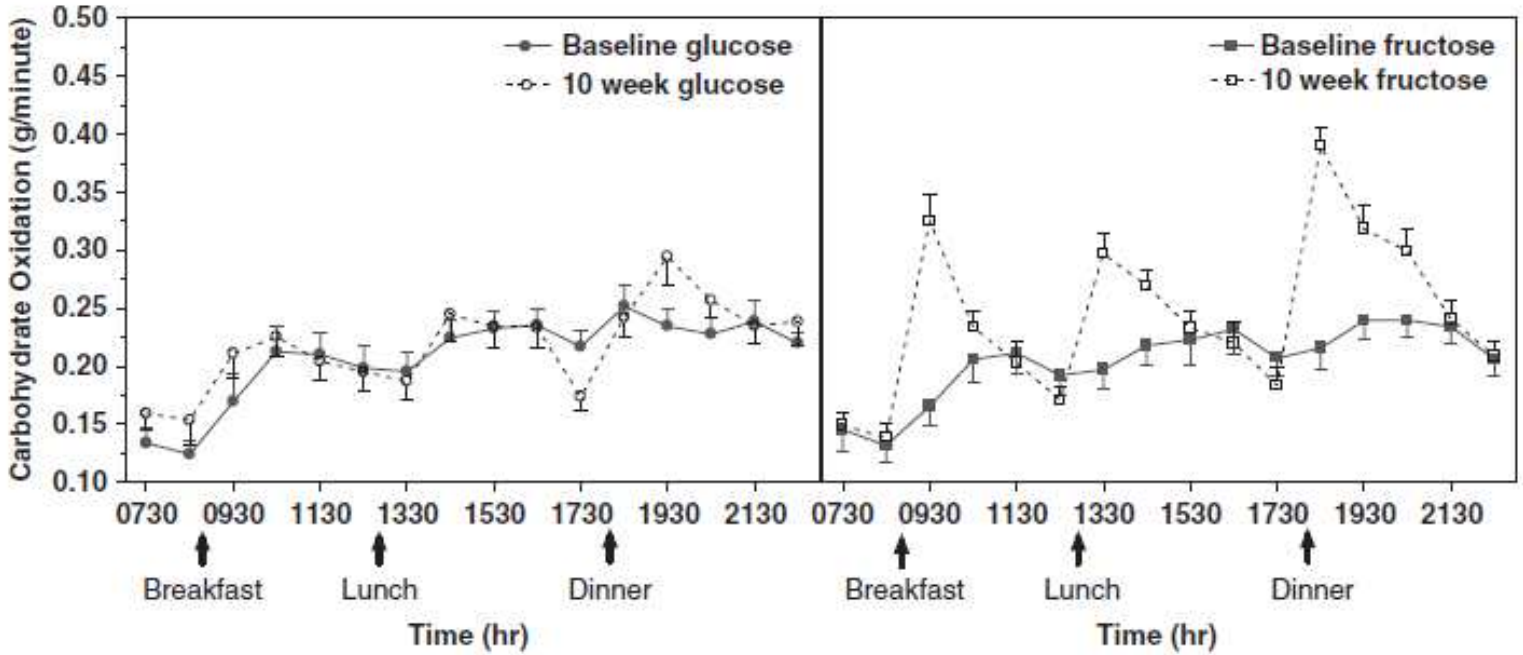
Subjects/Methods: As part of a parallel arm study, overweight/obese male and female subjects, 40–72 years, consumed glucose- or fructose-sweetened beverages providing 25% of energy requirements for 10 weeks. Energy expenditure and substrate utilization were assessed using indirect calorimetry at baseline and during the 10th week of intervention.

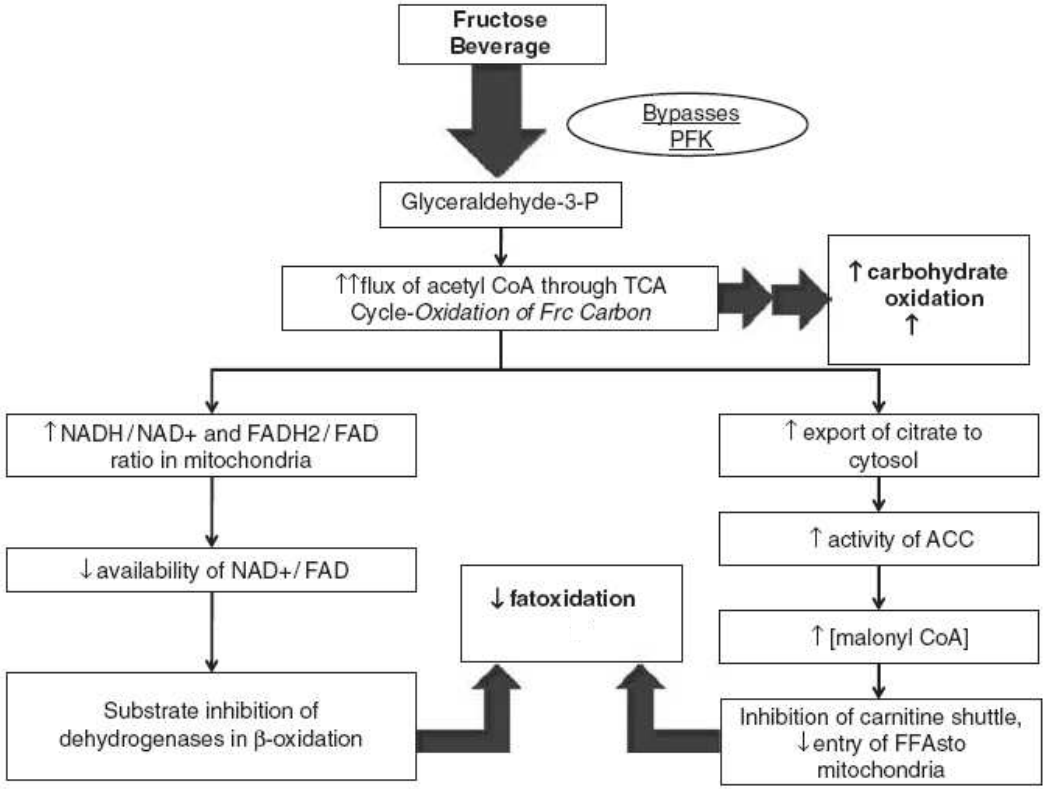
Results: Consumption of fructose, but not glucose, led to significant decreases of net postprandial fat oxidation and significant increases of net postprandial carbohydrate oxidation ($P<0.0001$ for both). Resting energy expenditure (REE) decreased significantly from baseline values in subjects consuming fructose ($P=0.031$) but not in those consuming glucose.

Conclusions: Increased consumption of fructose for 10 weeks leads to marked changes of postprandial substrate utilization including a significant reduction of net fat oxidation. In addition, we report that REE is reduced compared with baseline values in subjects consuming fructose-sweetened beverages for 10 weeks.

European Journal of Clinical Nutrition (2012) **66**, 201–208; doi:10.1038/ejcn.2011.159; published online 28 September 2011


Fat Oxidation (g/minute)
0.100
0.075
0.050
0.025
0.00
-0.025
-0.050
Baseline glucose
10 week glucose
Baseline fructose
10 week fructose
0730 0930 1130 1330 1530 1730 1930 2130
Breakfast
Lunch
Dinner
Time (hr)


Carbohydrate Oxidation (g/minute)
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
Baseline glucose
10 week glucose
Baseline fructose
10 week fructose
0730 0930 1130 1330 1530 1730 1930 2130
Breakfast
Lunch
Dinner
Time (hr)



Proposed mechanisms contributing to observed changes of substrate utilization in subjects consuming fructose-sweetened beverages. In the liver fructose is phosphorylated by fructokinase (which is not regulated by cellular energy status) and largely bypasses phosphofructokinase (PFK), the enzyme catalyzing the rate-limiting step of glycolysis (which is subject to inhibition by ATP and citrate). Ultimately fructose enters the glycolytic pathway as glyceraldehyde-3-phosphate. Following a high-fructose meal, an unregulated flux of fructose (Frc) carbon upregulates carbohydrate metabolism in the liver (increased CHO-Ox), leading to an increased flux of acetyl CoA through the tricarboxylic acid (TCA) cycle and a concomitant increase in cellular energy status (increased ATP/ADP ratio and NADH/NAD^+ ratio). A high NADH/NAD^+ ratio in the mitochondria results in substrate inhibition of isocitrate dehydrogenase in the TCA cycle, leading to increased export of citrate to the cytosol, activation of acetyl-CoA carboxylase (ACC), and increased production of malonyl-CoA, the precursor to fatty acid synthesis (DNL). Elevated cytosolic concentrations of malonyl-CoA inhibit the carnitine shuttle via carnitine palmitoyl transferase, leading to reduced entry of fatty acids into the mitochondria, and decreased fat oxidation. The elevation of cellular energy status following a high-fructose meal would also lead to reduced mitochondrial availability of the fixed pool of oxidized cofactors NAD^+ and FAD, which are required substrates for β-oxidation, also resulting in reduced fat oxidation (Williamson and Cooper, 1980; Mayes, 1993; McGarry, 1995; Locke *et al.*, 2008).

Consumption of Fructose and High Fructose Corn Syrup Increase Postprandial Triglycerides, LDL-Cholesterol, and Apolipoprotein-B in Young Men and Women

Kimber L. Stanhope, Andrew A. Bremer, Valentina Medici, Katsuyuki Nakajima, Yasuki Ito, Takamitsu Nakano, Guoxia Chen, Tak Hou Fong, Vivien Lee, Roseanne I. Menorca, Nancy L. Keim, and Peter J. Havel

Context: The American Heart Association Nutrition Committee recommends women and men consume no more than 100 and 150 kcal of added sugar per day, respectively, whereas the Dietary Guidelines for Americans, 2010, suggests a maximal added sugar intake of 25% or less of total energy.

Objective: To address this discrepancy, we compared the effects of consuming glucose, fructose, or high-fructose corn syrup (HFCS) at 25% of energy requirements (E) on risk factors for cardiovascular disease.

Participants, Design and Setting, and Intervention: Forty-eight adults (aged 18–40 yr; body mass index 18–35 kg/m^2) resided at the Clinical Research Center for 3.5 d of baseline testing while consuming energy-balanced diets containing 55% E complex carbohydrate. For 12 outpatient days, they consumed usual *ad libitum* diets along with three servings per day of glucose, fructose, or HFCS-sweetened beverages (n = 16/group), which provided 25% E requirements. Subjects then consumed energy-balanced diets containing 25% E sugar-sweetened beverages/30% E complex carbohydrate during 3.5 d of inpatient intervention testing.

Main Outcome Measures: Twenty-four-hour triglyceride area under the curve, fasting plasma low-density lipoprotein (LDL), and apolipoprotein B (apoB) concentrations were measured.

J Clin Endocrinol Metab, October 2011, 96(10):E1596–E1605

Fruttosio e insulino-resistenza 1

Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance

Kimber L. Stanhope[a,b] and Peter J. Havel[a,b]

Current Opinion in Lipidology 2008, 19:16–24

Fructose Consumption: Considerations for Future Research on Its Effects on Adipose Distribution, Lipid Metabolism, and Insulin Sensitivity in Humans[1,2]

Kimber L. Stanhope and Peter J. Havel*

J. Nutr. 139: 1236S–1241S, 2009.

Fructose consumption: Recent results and their potential implications

Ann N Y Acad Sci. 2010 March ; 1190: 15–24.

Kimber L. Stanhope[1,2] and Peter J. Havel[1,2]

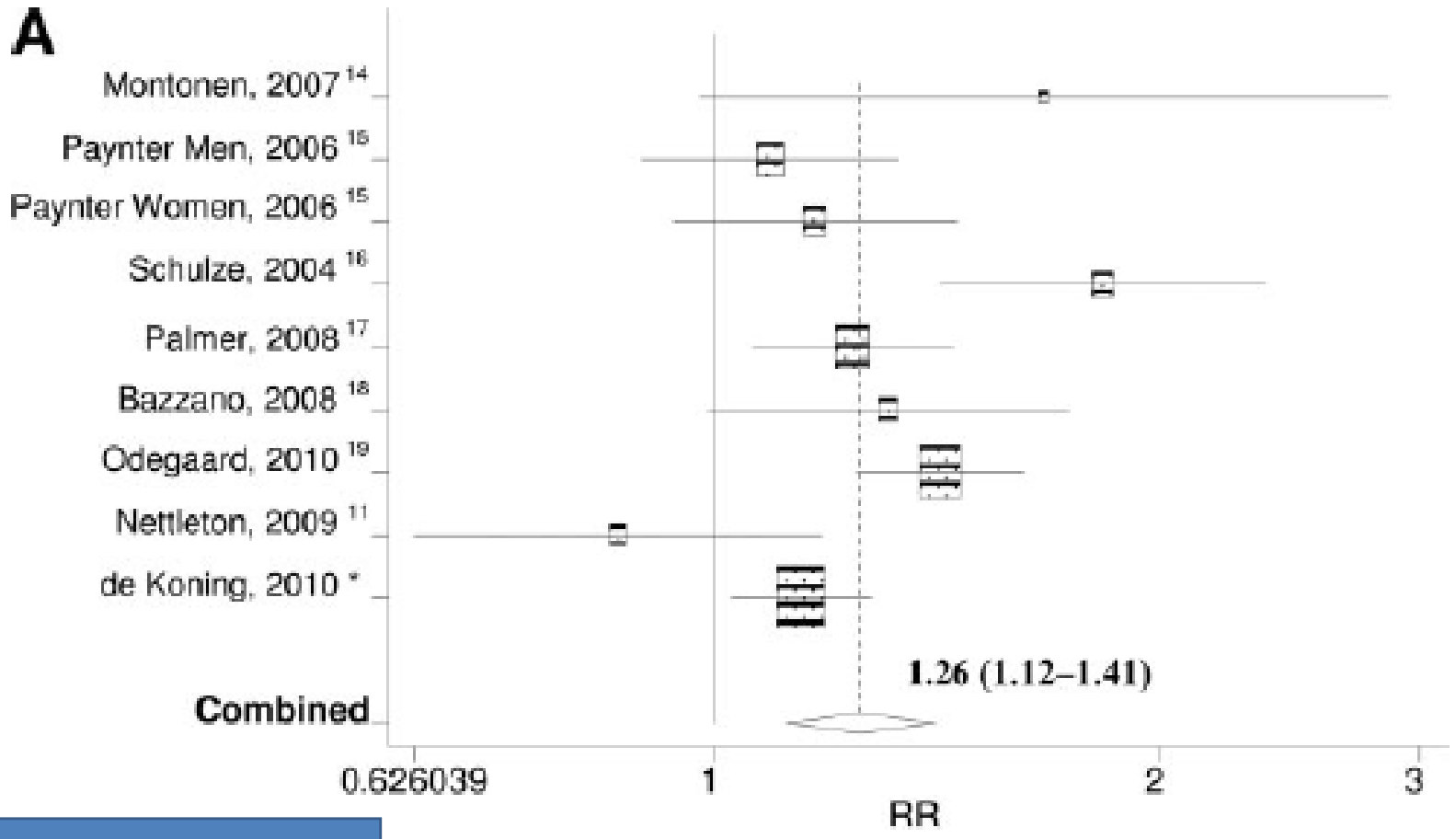
Fructose induced lipogenesis: from sugar to fat to insulin resistance

Varman T. Samuel[1,2]

Trends in Endocrinology and Metabolism February 2011, Vol. 22, No. 2

Diabete mellito tipo 2

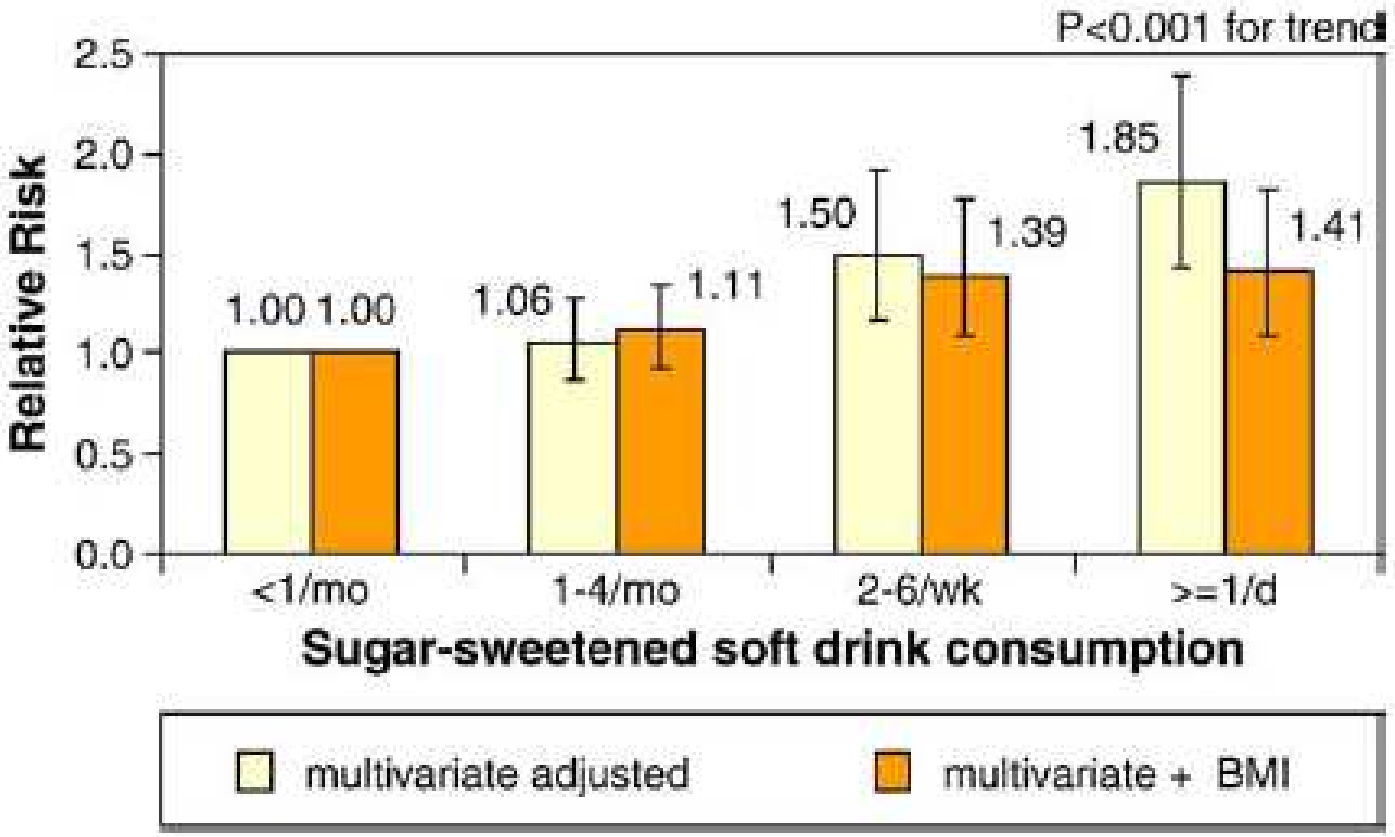
Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes



310.000 pazienti

DIABETES CARE, VOLUME 33, NUMBER 11, NOVEMBER 2010

Diabete mellito tipo 2



ENTITA' CONSUMO

INDIPENDENZA DA BMI

Fig. 4. Multivariate relative risks (RRs) of type 2 diabetes according to sugar-sweetened soft drink consumption in the Nurses' Health Study II 1991–1999 (Multivariate RRs were adjusted for age, alcohol (0, 0.1–4.9, 5.0–9.9, 10+ g/d), physical activity (quintiles), family history of diabetes, smoking (never, past, current), postmenopausal hormone use (never, ever), oral contraceptive use (never, past, current), intake (quintiles) of cereal fiber, magnesium, trans fat, polyunsaturated:saturated fat, and consumption of sugar-sweetened soft drinks, diet soft drinks, fruit juice, and fruit punch (other than the main exposure, depending on model). The data were based on Ref. [50]).

F.B. Hu, V.S. Malik / Physiology & Behavior 100 (2010) 47–54

Fumo e steatosi

Il fumo blocca l’azione AMPK (adenosian monofosfato chinasi)

↓

Accumulo di grassi

↓

STEATOSI

Journal of Hepatology

Educazione alimentare

Ringrazio
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Michela Barichella

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