University of Milan, Italy

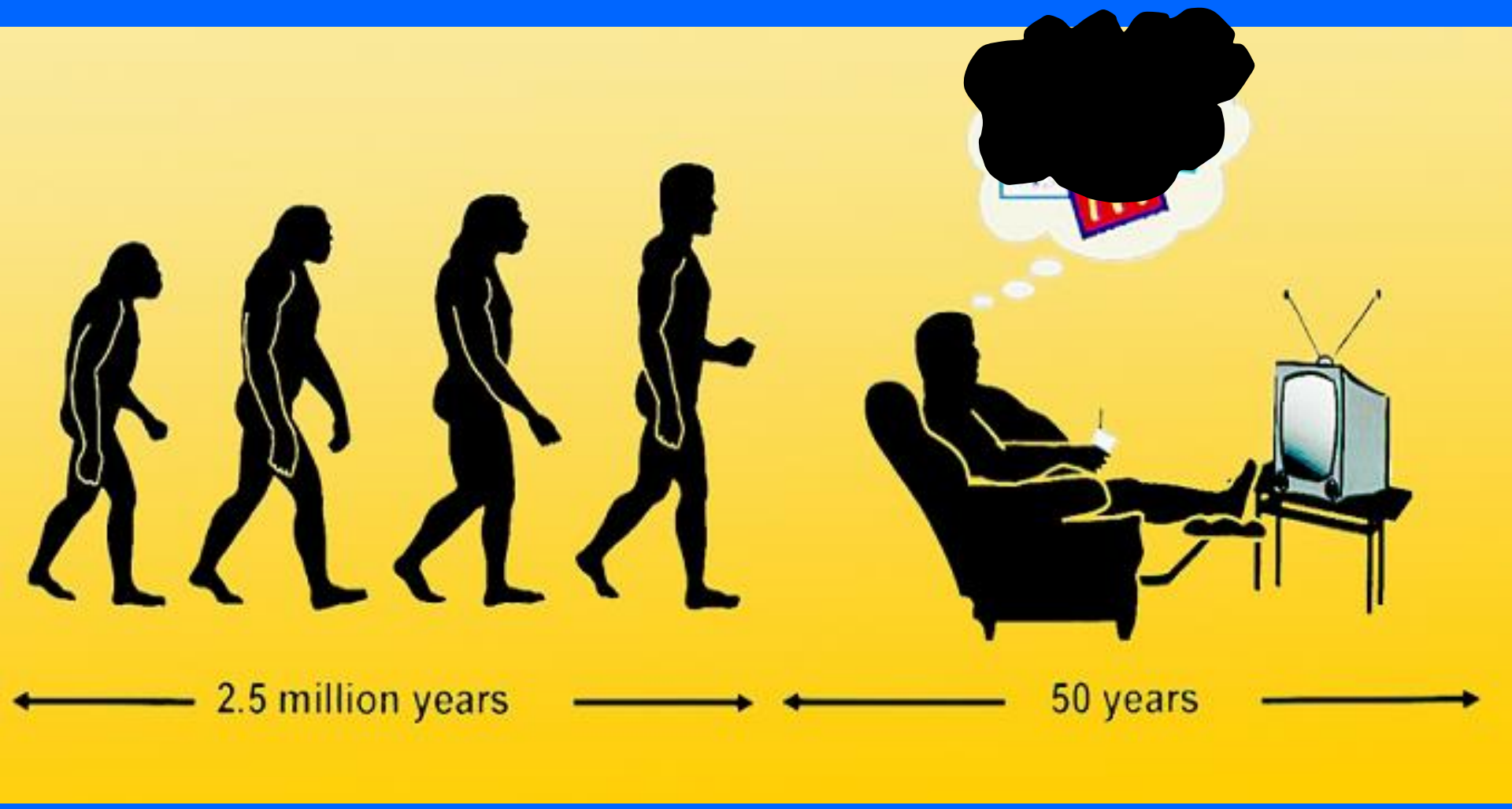
Department of Biotechnology and Traslational Medicine

CENTER FOR STUDY AND RESEARCH ON OBESITY

OBESITY: EPIDEMIOLOGY, PATHOPHISIOLOGY AND CLINICAL PICTURE

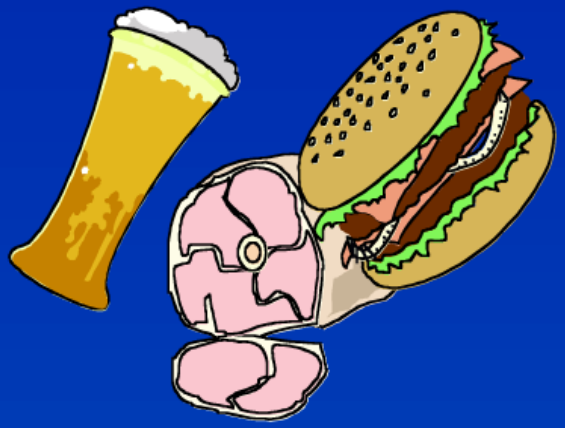
Michele O. Carruba

L’evoluzione della specie



IL BILANCIO ENERGETICO

Introduzione di Energia



Dispendio di Energia

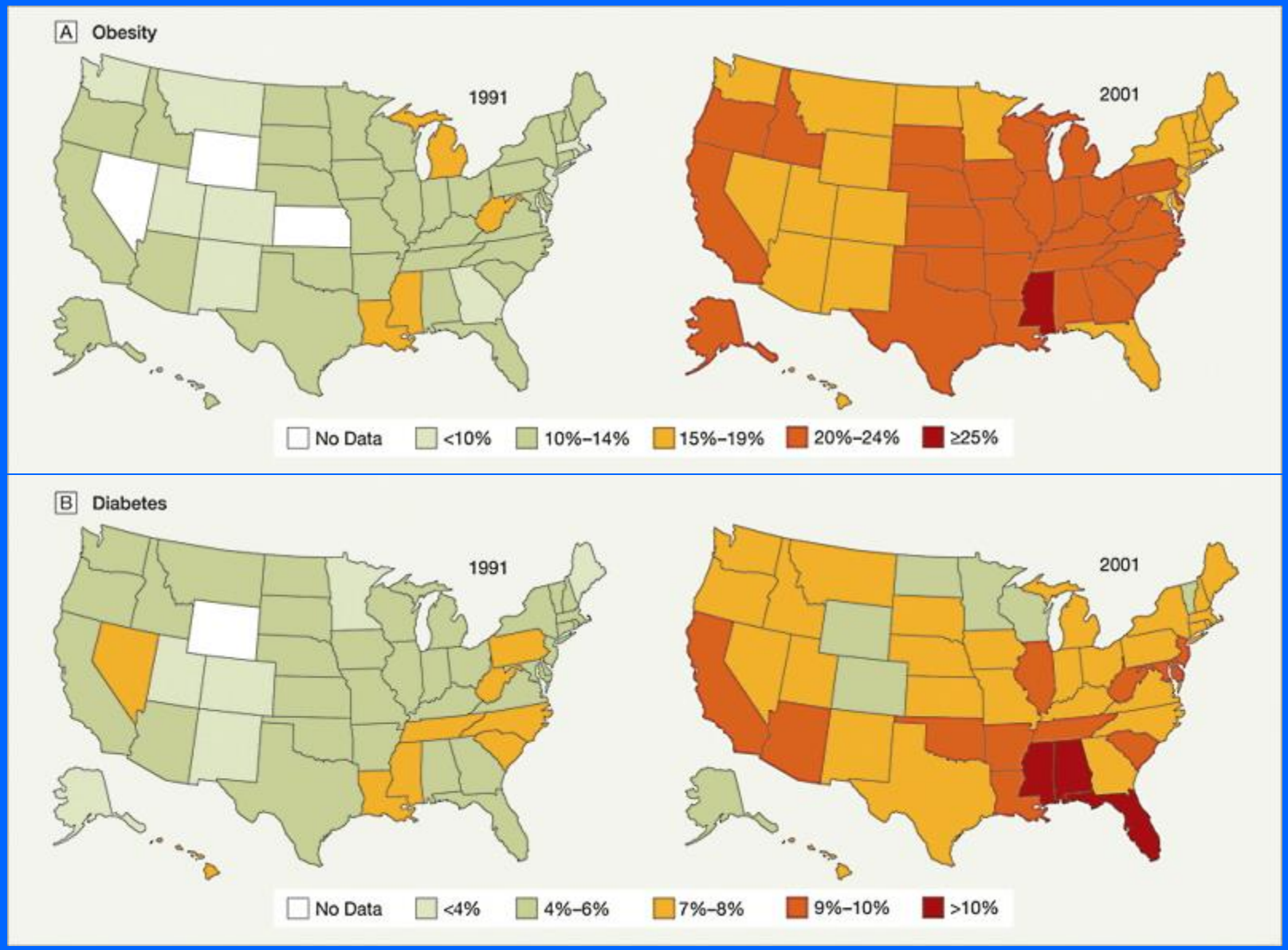
Fattori di controllo

Predisposizione genetica
Alimentazione

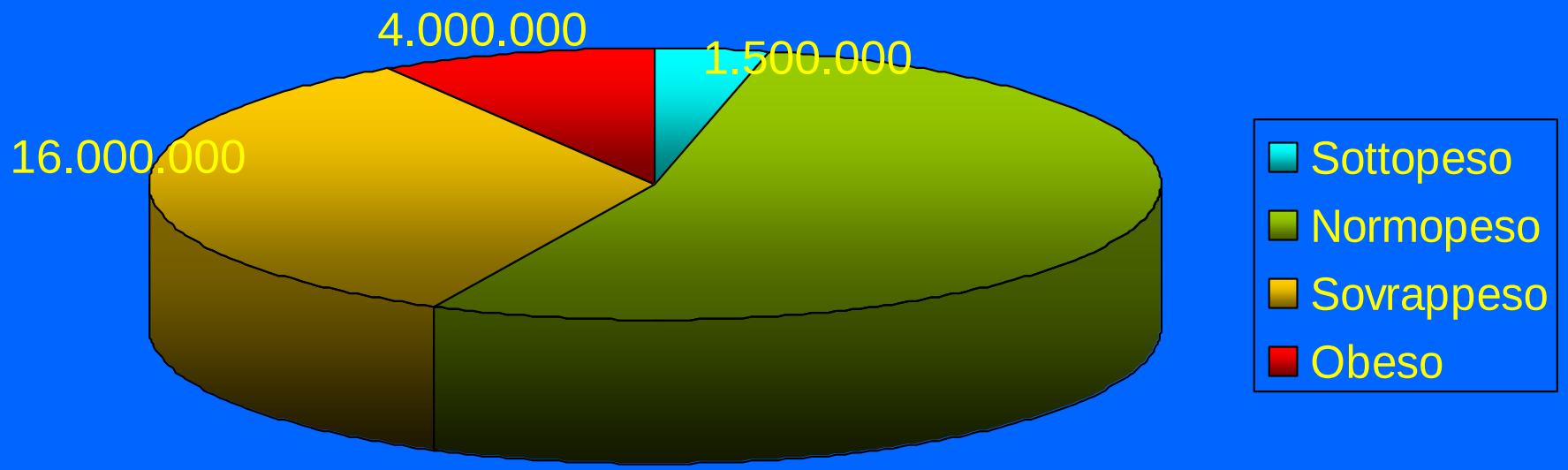
Esercizio fisico
Metabolismo Basale
Termogenesi

Centro Studio e Ricerca sull'Obesità (C.S.R.O.)
Dipartimento di Farmacologia, Chemioterapia e Tossicologia Medica,
Università degli Studi di Milano, Via Vanvitelli 32, Milano
Prof. **Michele Carruba**

Prevalence of Obesity and Diagnosed Diabetes Among US Adults, 1991 and 2001

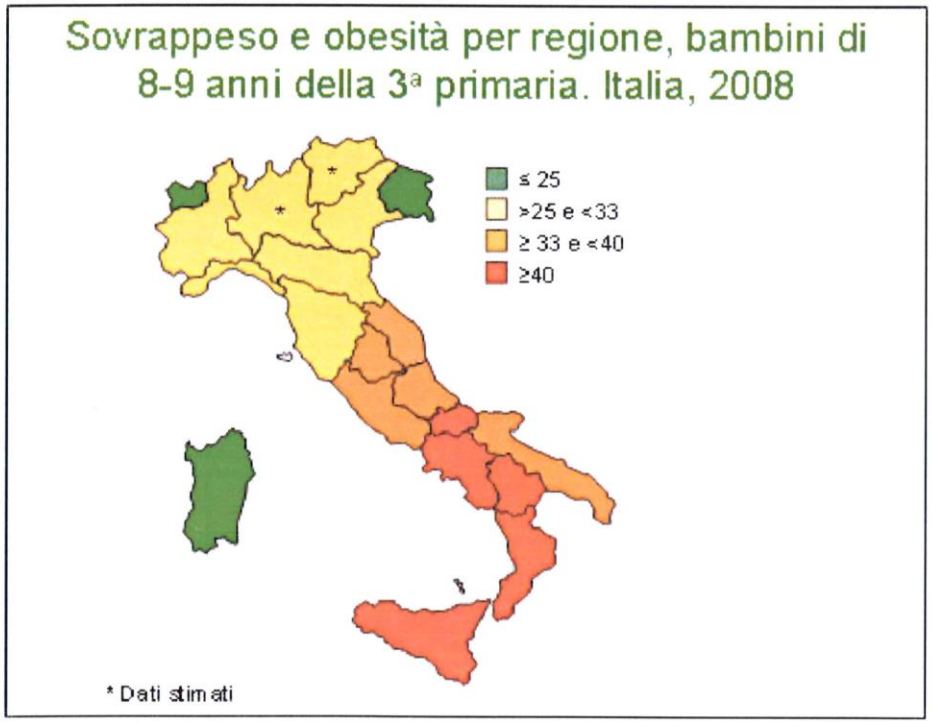


Distribuzione della popolazione italiana nelle varie condizioni di peso



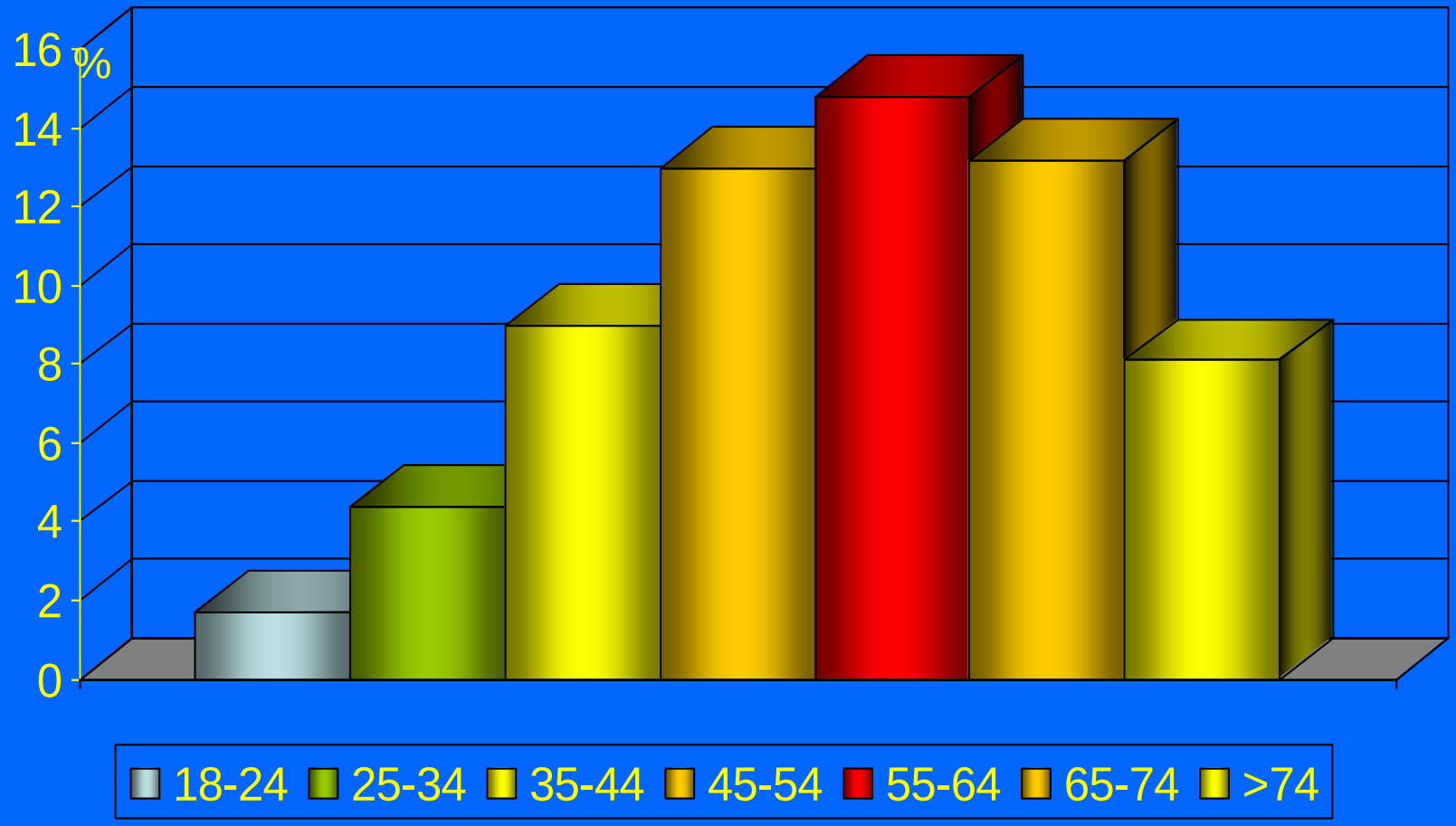
Fonte: ISTAT, 4° Rapporto sull'Obesità in Italia. Istituto Auxologico Italiano, 2002


MICHELIN



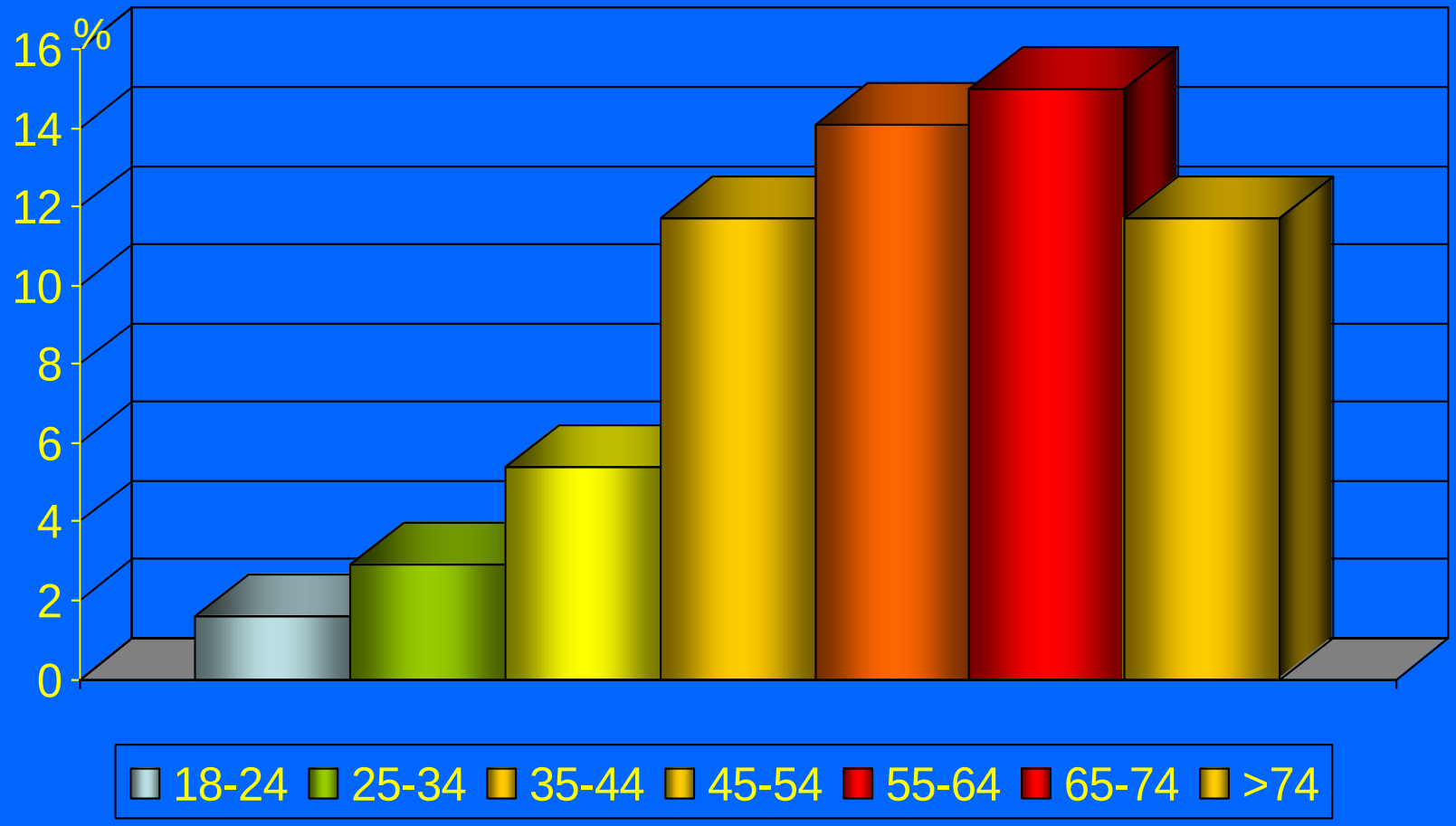
Fonte: “OKkio alla Salute” - Istituto Superiore di Sanità

Prevalenza dell'obesità (IMC>30) in funzione dell'età negli **UOMINI**



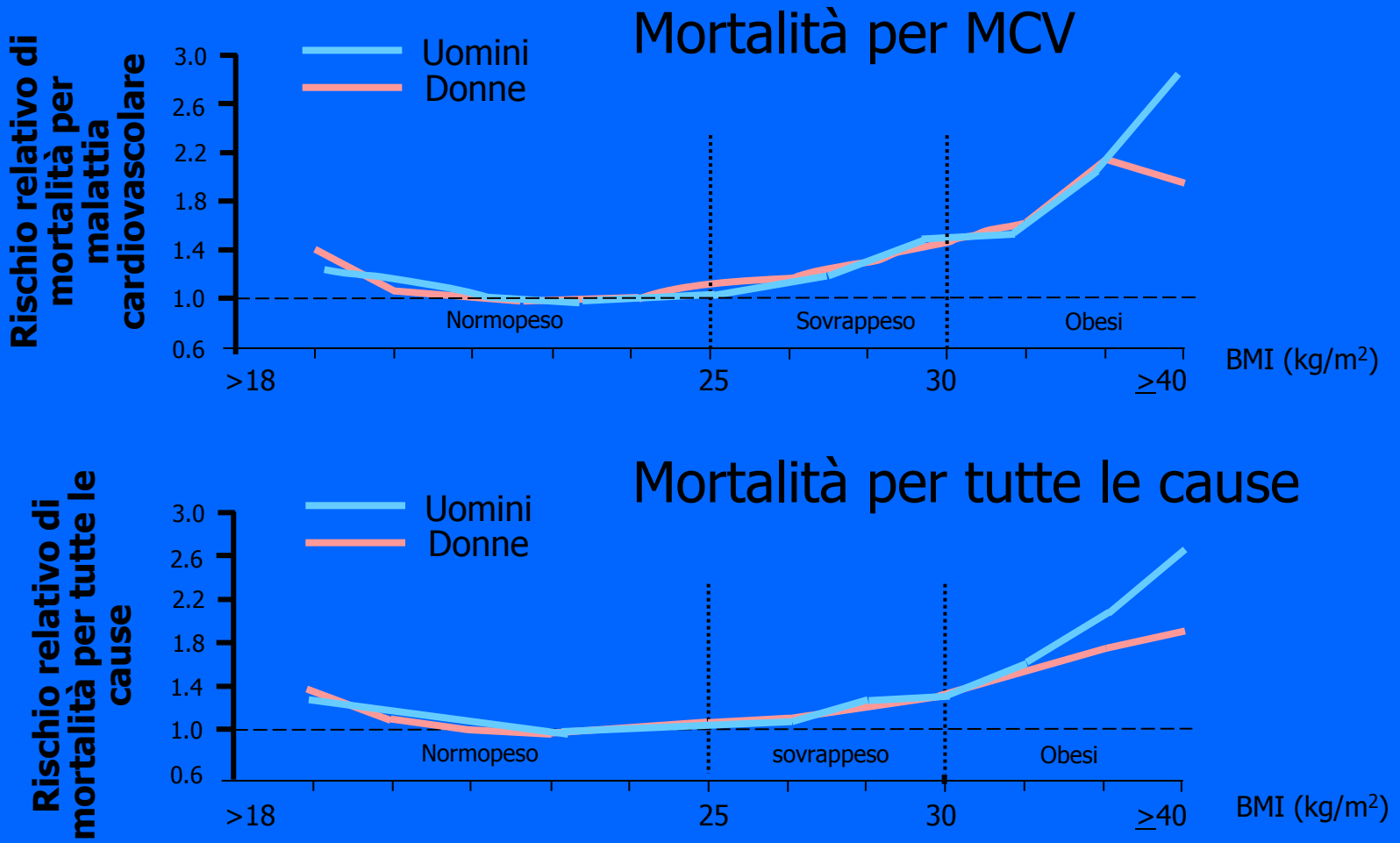
Fonte: ISTAT, 4° Rapporto sull'Obesità in Italia. Istituto Auxologico Italiano, 2002

Prevalenza dell'obesità (IMC>30) in funzione dell'età nelle **DONNE**



Fonte: ISTAT, 4° Rapporto sull'Obesità in Italia. Istituto Auxologico Italiano, 2002

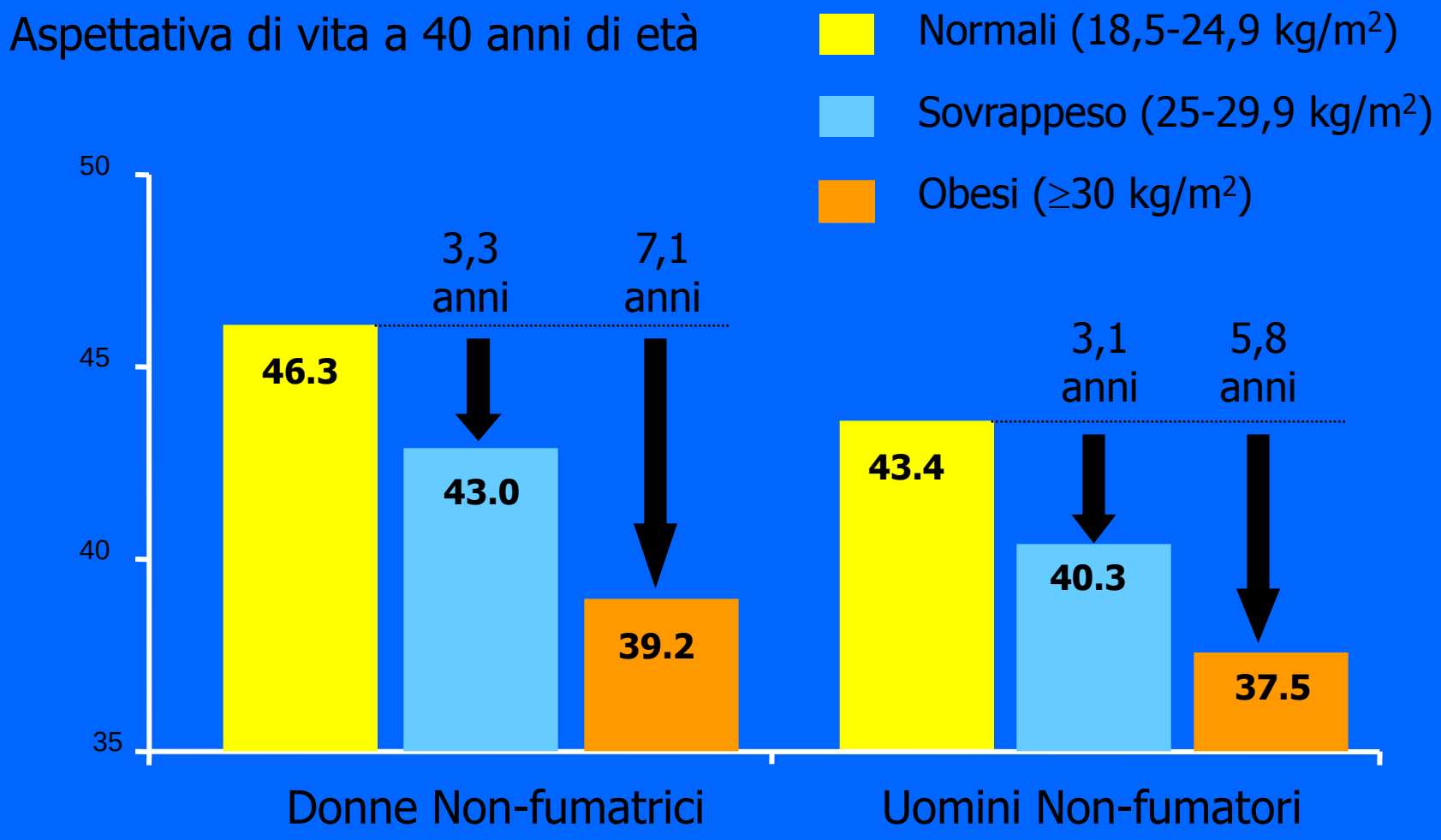
Sovrappeso e obesità aumentano il rischio di MCV e di mortalità per tutte le cause



Dati relativi a 1 milione di uomini e donne seguiti per 16 anni con età media di 57 anni che non hanno mai fumato e non avevano una storia di malattia all'arruolamento.

Calle et al. *N Engl J Med.* 1999;341:1097-1105

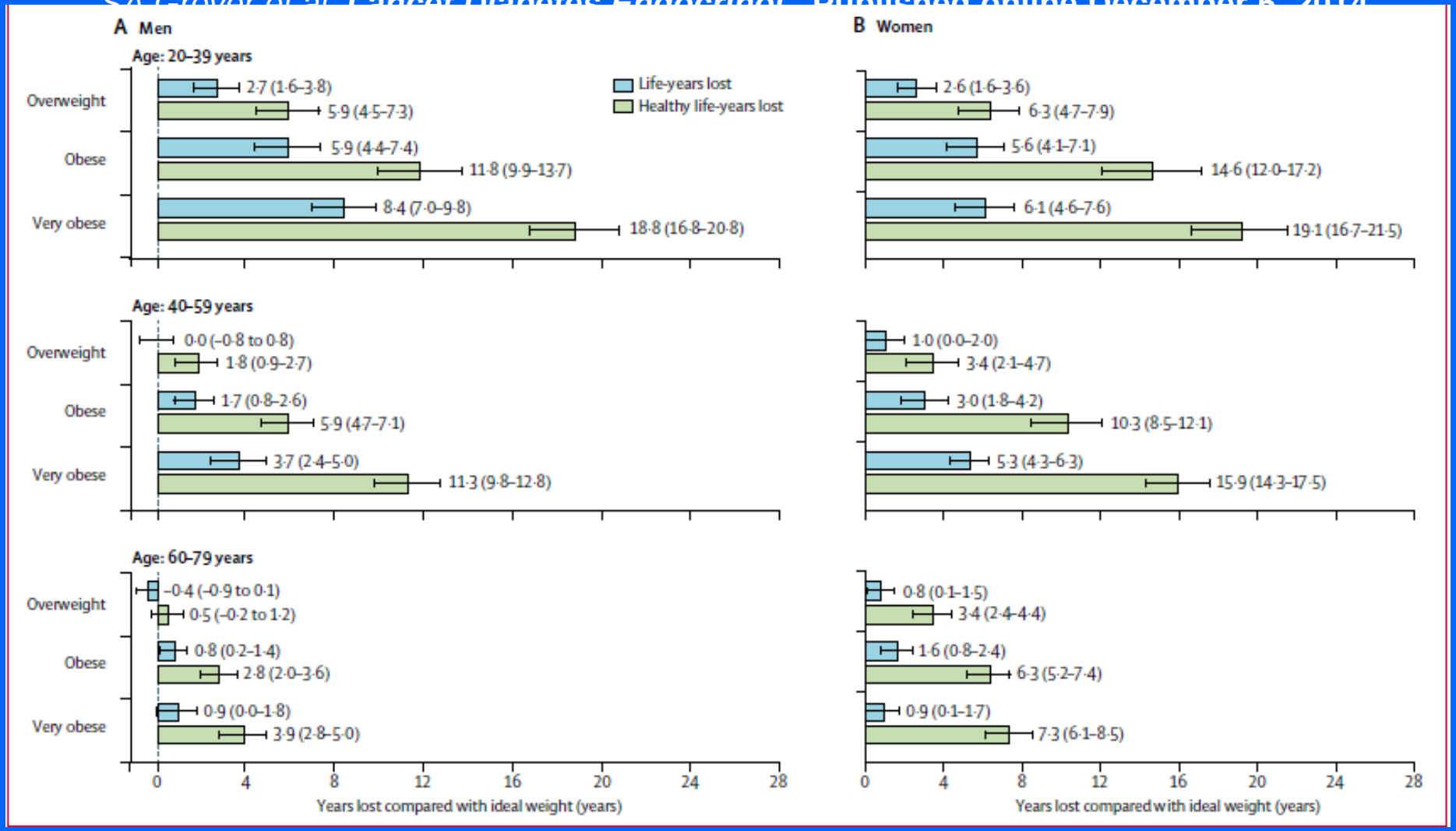
Aspettativa di vita a 40 anni: impatto dell'eccesso di peso corporeo

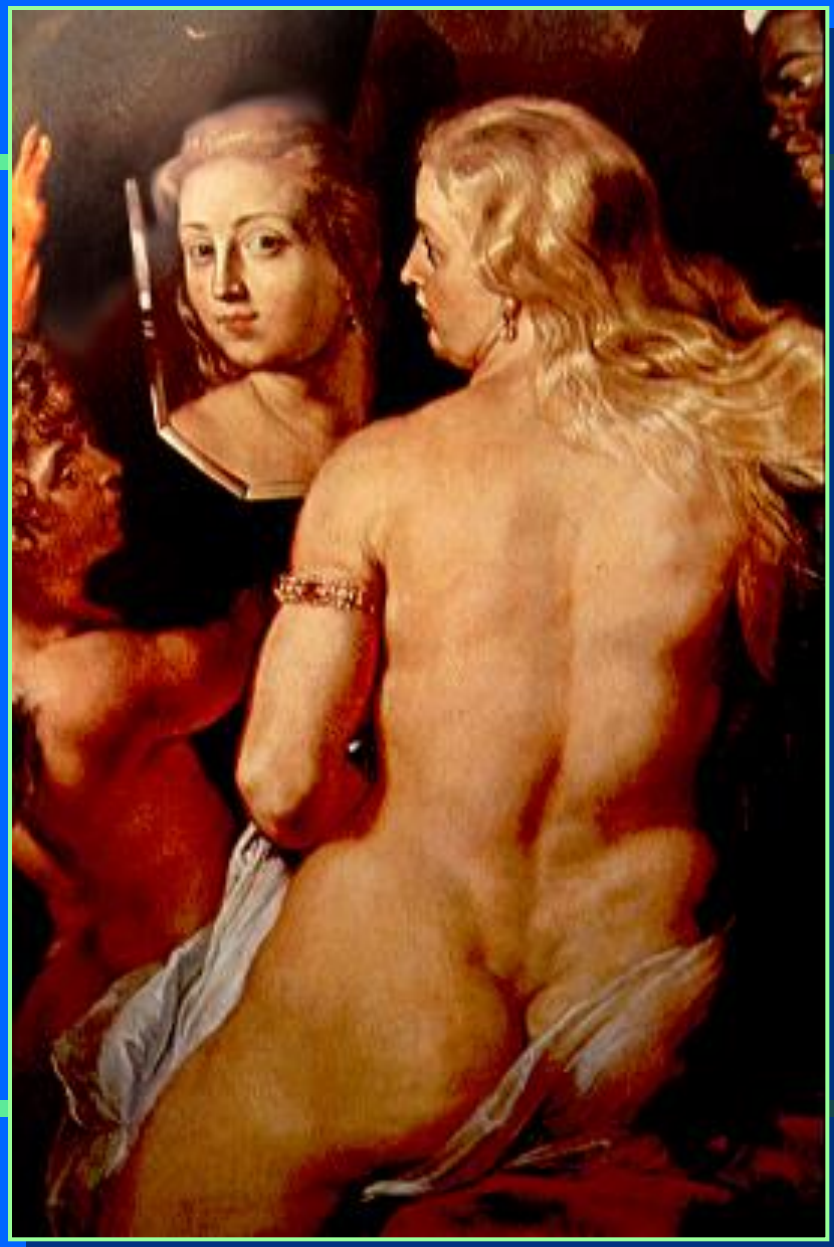


Peeters et al. *Ann Intern Med* 2003; 138: 24-32

Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in overweight and obese people: a modelling study

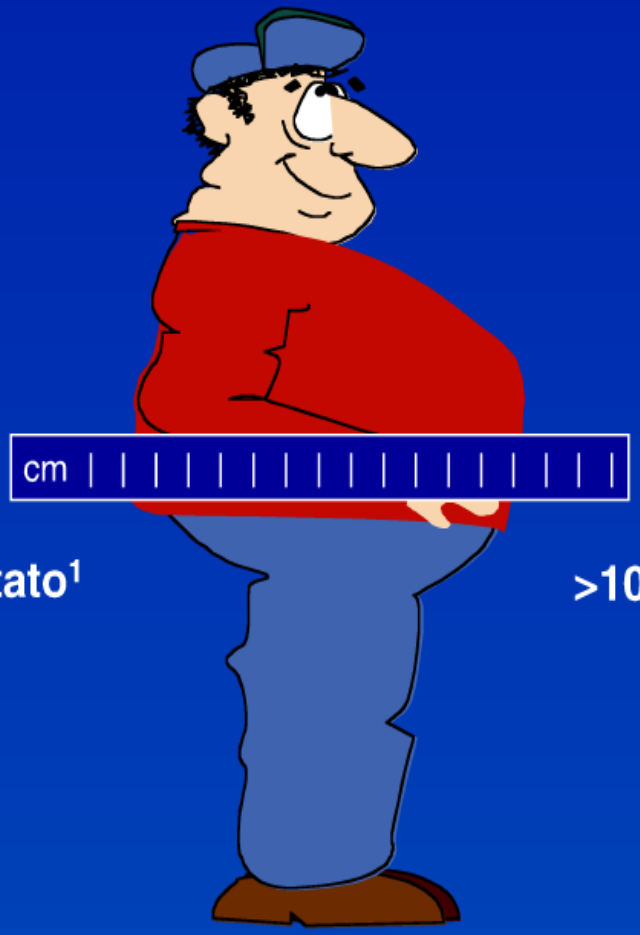
SA Grover et al. *Lancet Diabetes Endocrinol*. Published online December 5, 2014





Un parametro fondamentale: la circonferenza addominale

La circonferenza vita è un indicatore del tessuto adiposo viscerale



Donne

>88 cm = Rischio aumentato[1]

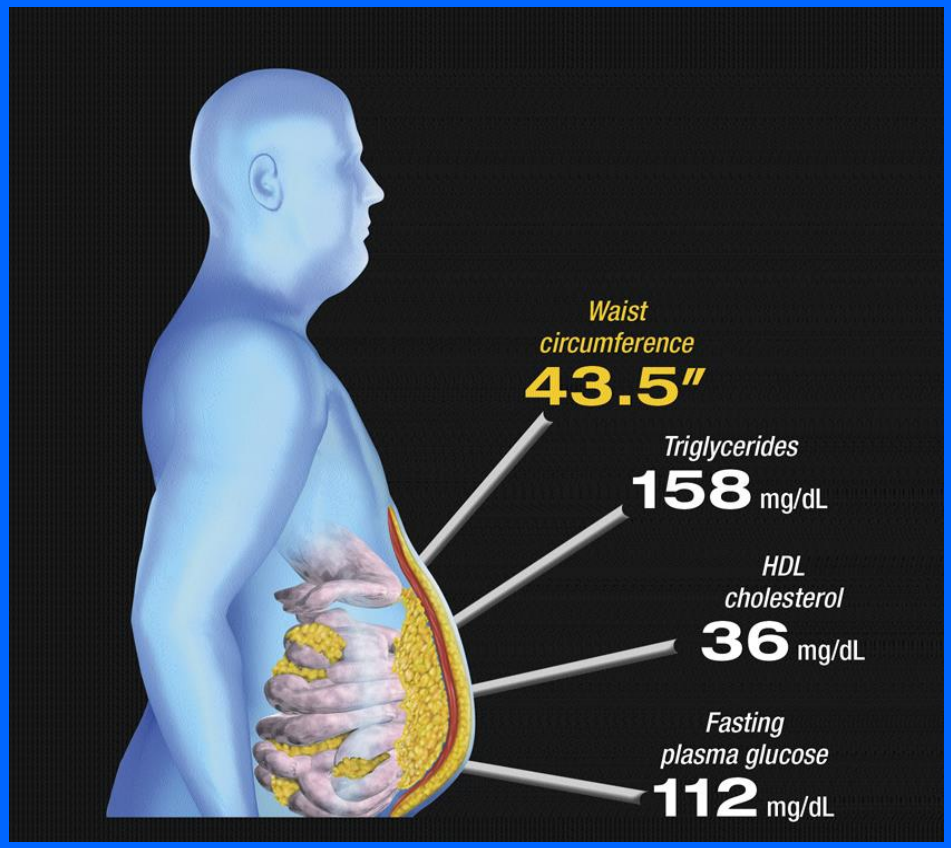
Uomini

>102 cm = Rischio aumentato[1]

[1]Lean MEJ, et al. Lancet;1998:351:853–6

Unmet clinical need associated with abdominal obesity

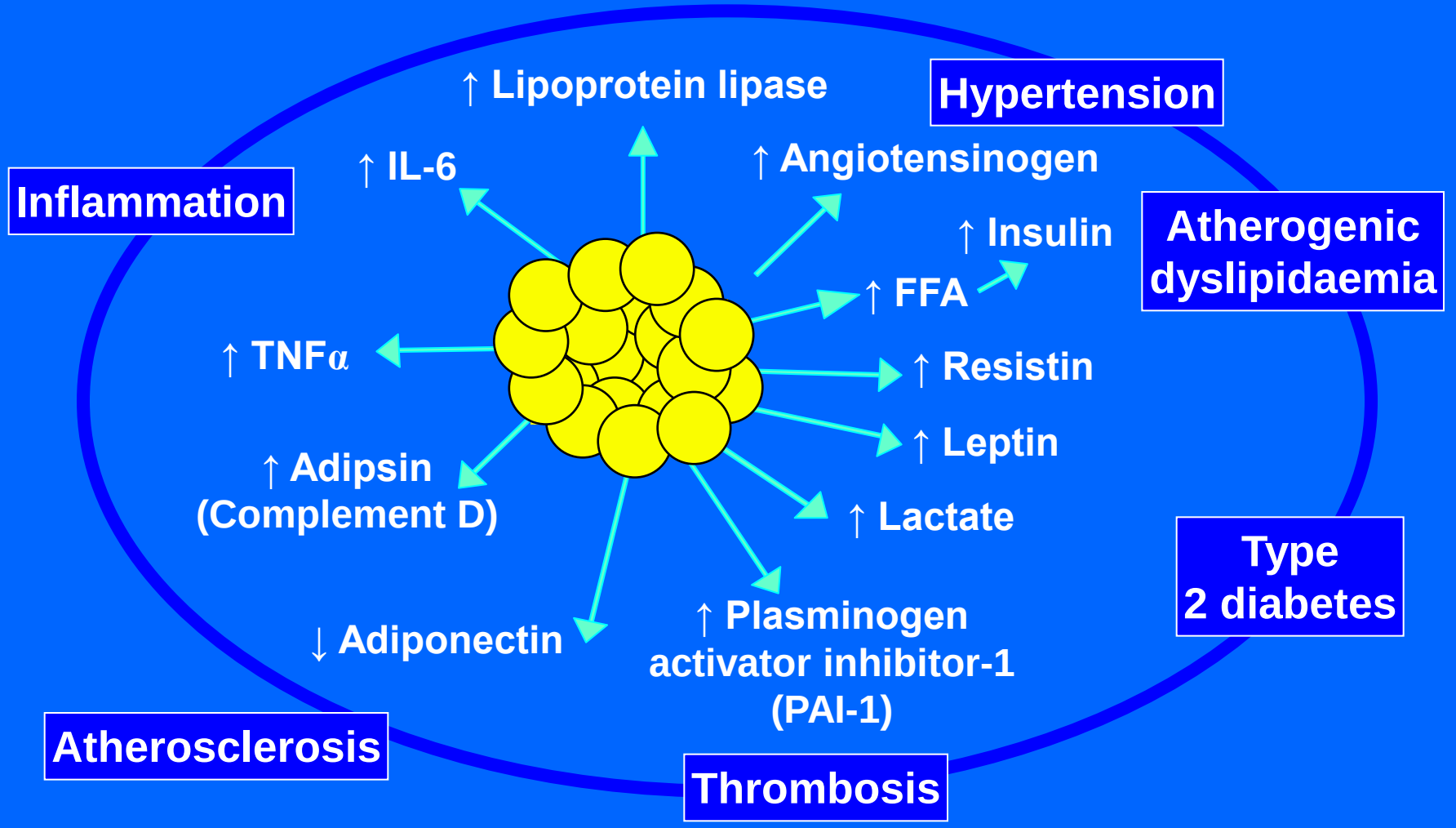
CV risk factors in a typical patient with abdominal obesity



Patients with abdominal obesity (high waist circumference) often present with one or more additional CV risk factors

NHANES 1999–2000 cohort (data on file)

Adverse cardiometabolic effects of products of adipocytes



Lyon 2003; Trayhurn et al 2004; Eckel et al 2005

Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

Eugenia E. Calle, Ph.D., Carmen Rodriguez, M.D., M.P.H., Kimberly Walker-Thurmond, B.A., and Michael J. Thun, M.D.

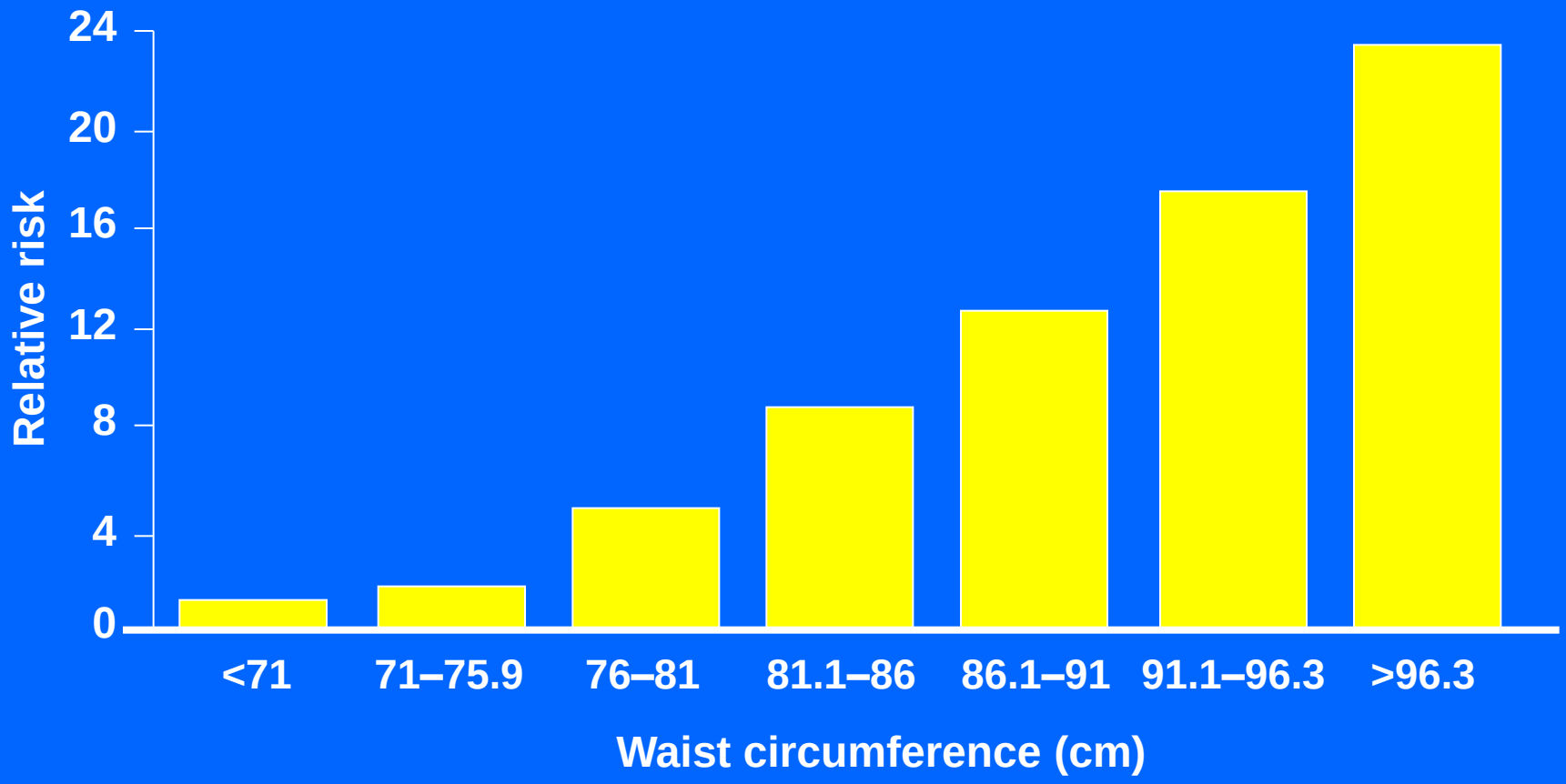
The heaviest members of this cohort (body-mass index of at least 40) had death rates from all cancers combined that were 52 percent higher (for men) and 62 percent higher (for women) than the rates in men and women of normal weight.

In both men and women, body-mass index was also significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney; the same was true for death due to non-Hodgkin's lymphoma and multiple myeloma. Significant trends of increasing risk with higher body-mass-index values were observed for death from cancers of the stomach and prostate in men and for death from cancers of the breast, uterus, cervix, and ovary in women.

Conclusions. Increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites.

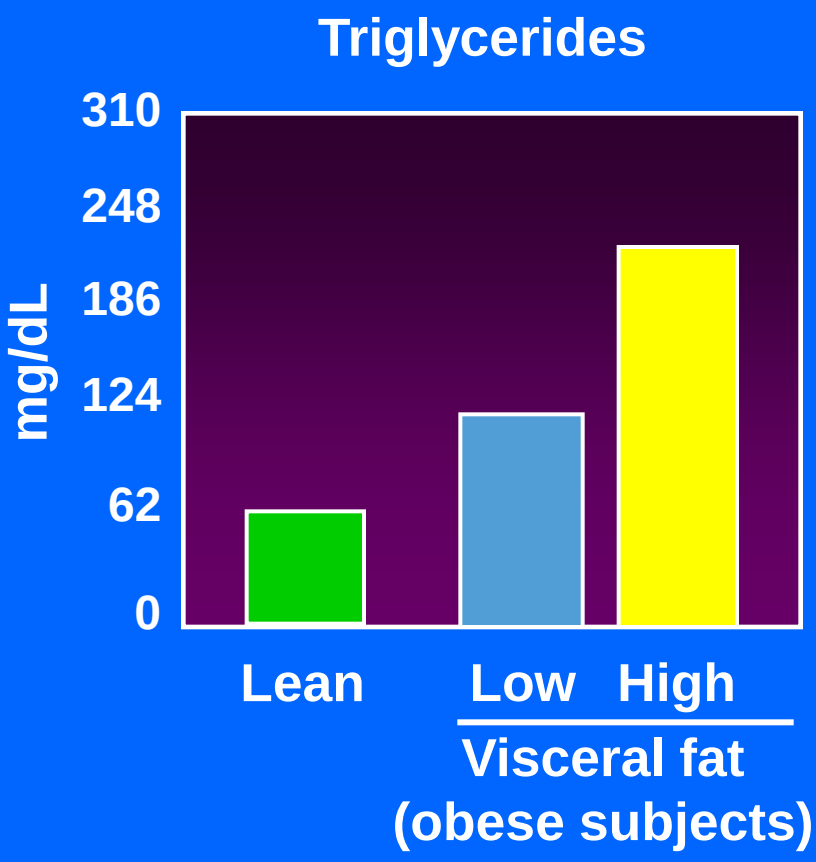
The New England Journal of Medicine, 348: 1625-1638, 2003

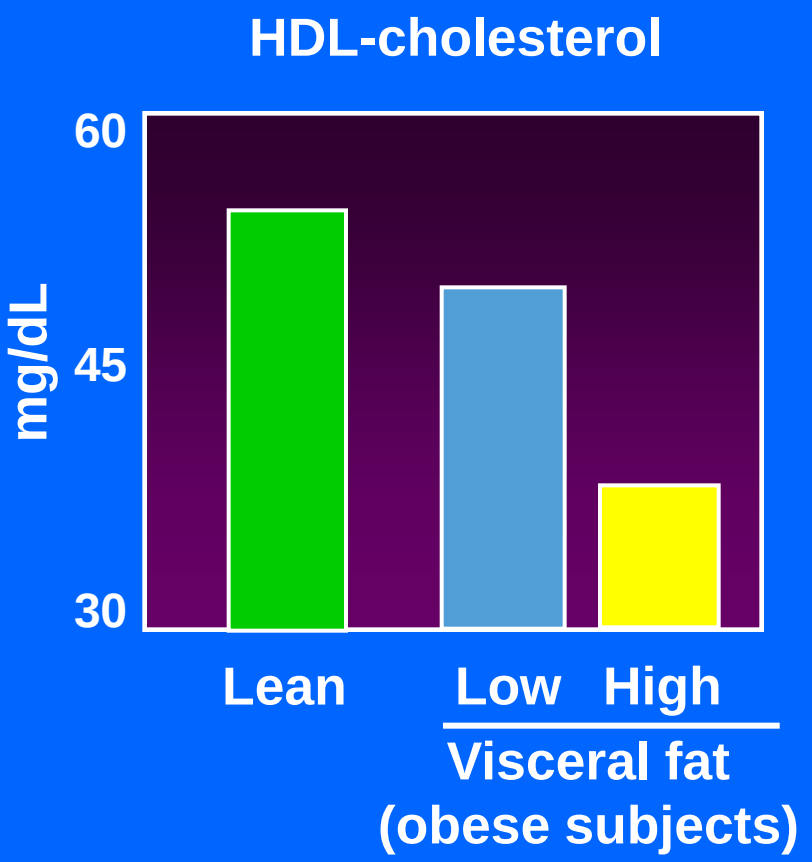
Abdominal obesity increases the risk of developing type 2 diabetes



Carey et al 1997

Intra-abdominal adiposity and dyslipidaemia

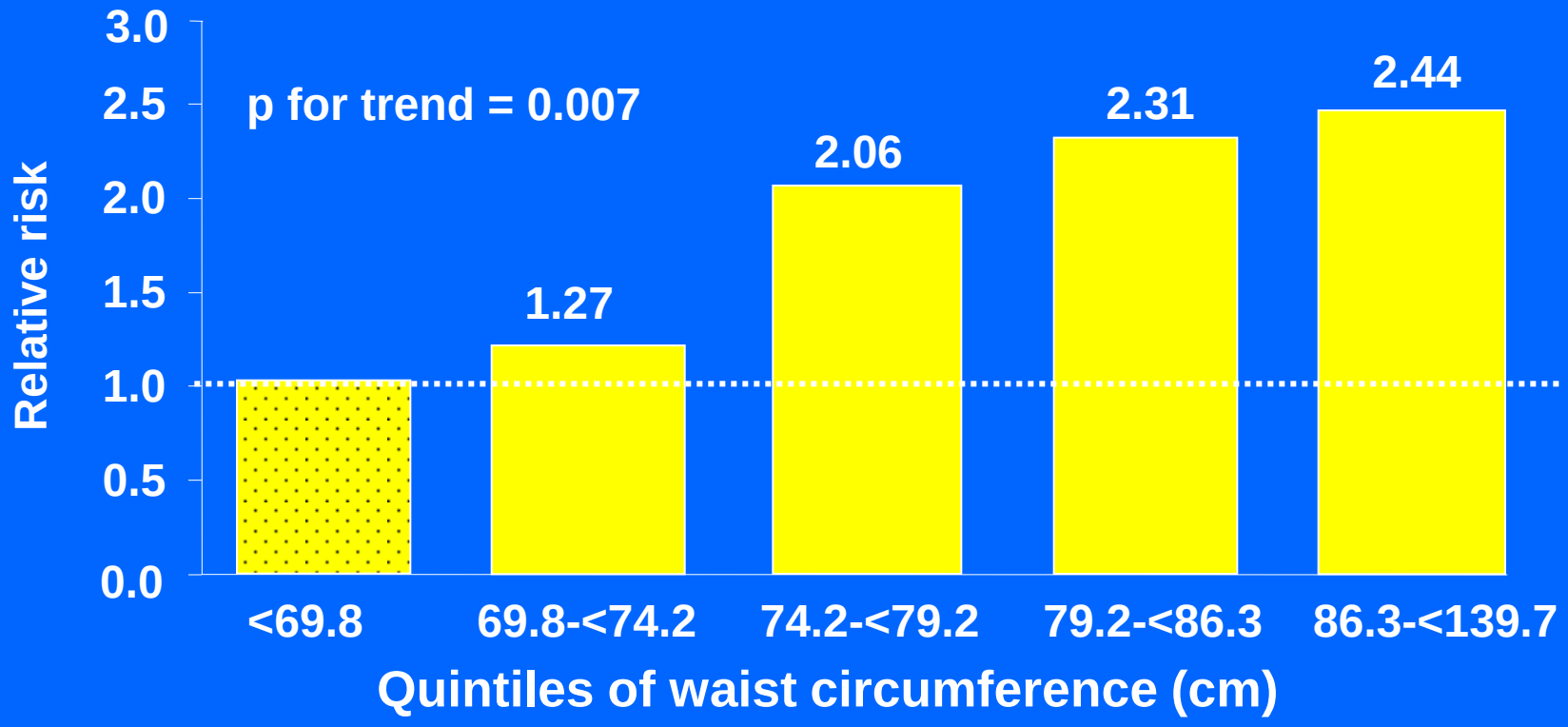




Pouliot et al 1992

Abdominal obesity and increased risk of CHD

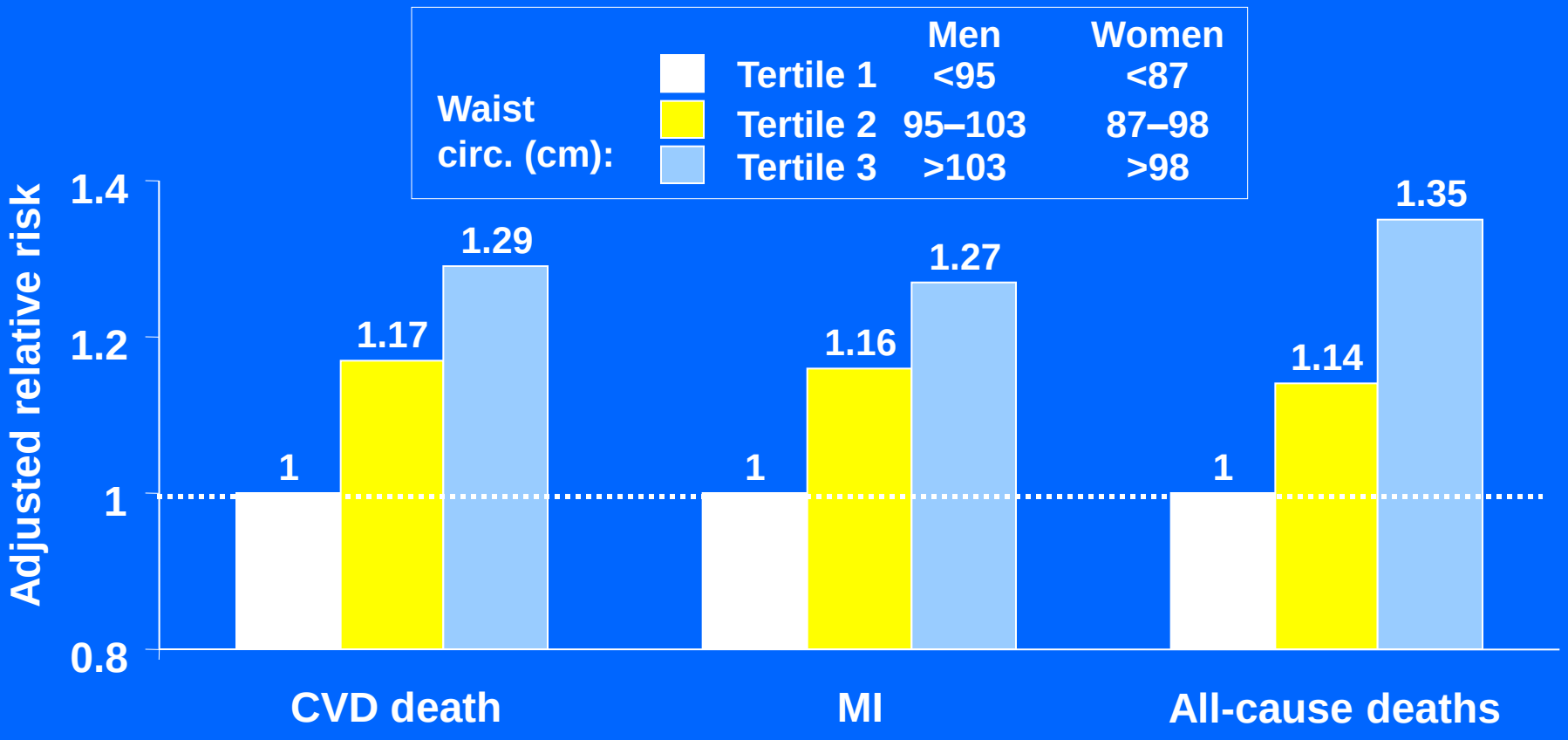
Waist circumference was independently associated with increased age-adjusted risk of CHD, even after adjusting for BMI and other CV risk factors



Rexrode et al 1998

Abdominal obesity and increased risk of cardiovascular events

The HOPE Study

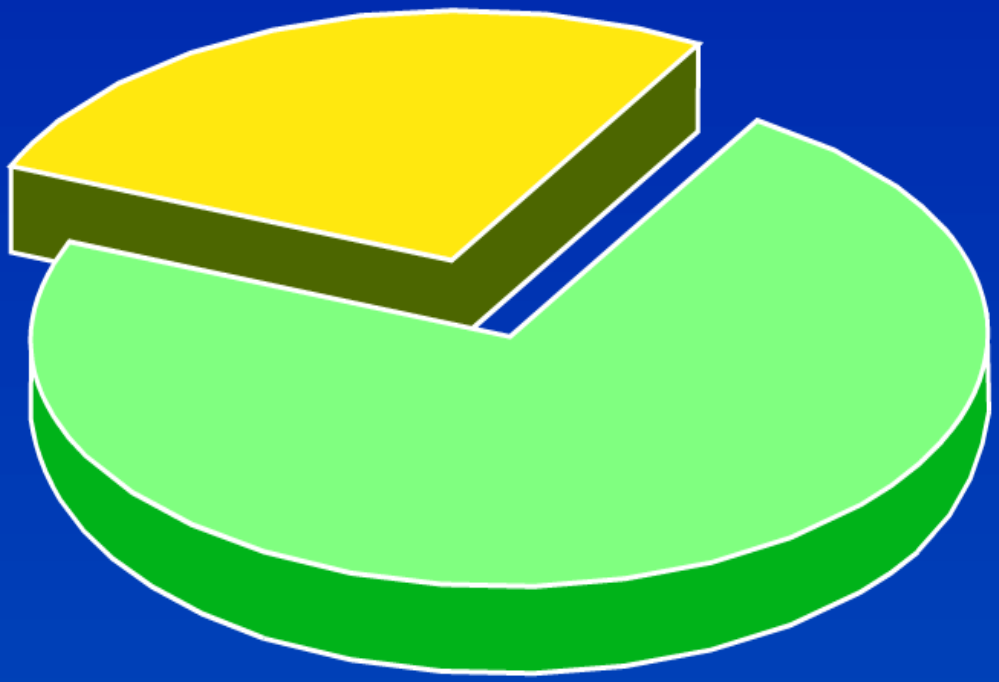


Adjusted for BMI, age, smoking, sex, CVD, disease, DM, HDL-C, total-C

Dagenais et al 2005

BMI e comorbilità

Pazienti con BMI ≥27 (%)



Dati non pubblicati NHANES III

Sindrome metabolica

Reaven GM. Annu Rev Med 1993; 44:121–31

"STUDIO SPESA" : COSTI DIRETTI ANNUI DELL'OBESITÀ IN ITALIA

BMI	Costo tot (€)	Pazienti (mlo)	%	Tot (mld)
25-29,9	984	17,5	35	17,2
30-39,9	2.136	4,5	9	9,6
> 40	2796	0,5	0,9	1,4
				28,2

Studio SPESA: composizione dei costi dell'Obesità Tot 28,2 mld Euro/anno

Voce di costo	Percentuale
Ospedalizzazioni	64%
Diagnostica	12%
Farmaci	7%
Visite	6%
Altro	11%

Nel 2025 costo Tot (mld) da 11 a 15,7 (+43%) con obesità infantile + 205%

Elaborazione Centro Studi Ricerca Obesità (CSRO) e Farmacoeconomia UniMI

Centro Studio e Ricerca sull'Obesità (C.S.R.O.)
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Università degli Studi di Milano, Via Vanvitelli 32, Milano
Prof. **Michele Carruba**

TNF-α downregulates eNOS expression and mitochondrial biogenesis in fat and muscle of obese rodents

Alessandra Valerio,[1] Annalisa Cardile,[1,2] Valeria Cozzi,[1,2] Renata Bracale,[1,2,3] Laura Tedesco,[1,2,4] Addolorata Pisconti,[2,5] Letizia Palomba,[6] Orazio Cantoni,[6] Emilio Clementi,[2,5,7] Salvador Moncada,[8] Michele O. Carruba,[1,4] and Enzo Nisoli[1,4]

[1]Integrated Laboratories Network, Center for Study and Research on Obesity, Department of Pharmacology, School of Medicine, University of Milan, Milan, Italy. [2]Department of Preclinical Sciences, University of Milan, Milan, Italy. [3]CEINGE Biotecnologie Avanzate, Naples, Italy. [4]Istituto Auxologico Italiano, Milan, Italy. [5]Stem Cell Research Institute, San Raffaele Scientific Institute, Milan, Italy. [6]Istituto di Farmacologia e Farmacognosia, University of Urbino "Carlo Bo," Urbino, Italy. [7]Eugenio Medea Scientific Institute, Lecco, Italy. [8]Wolfson Institute for Biomedical Research, University College London, London, United Kingdom.

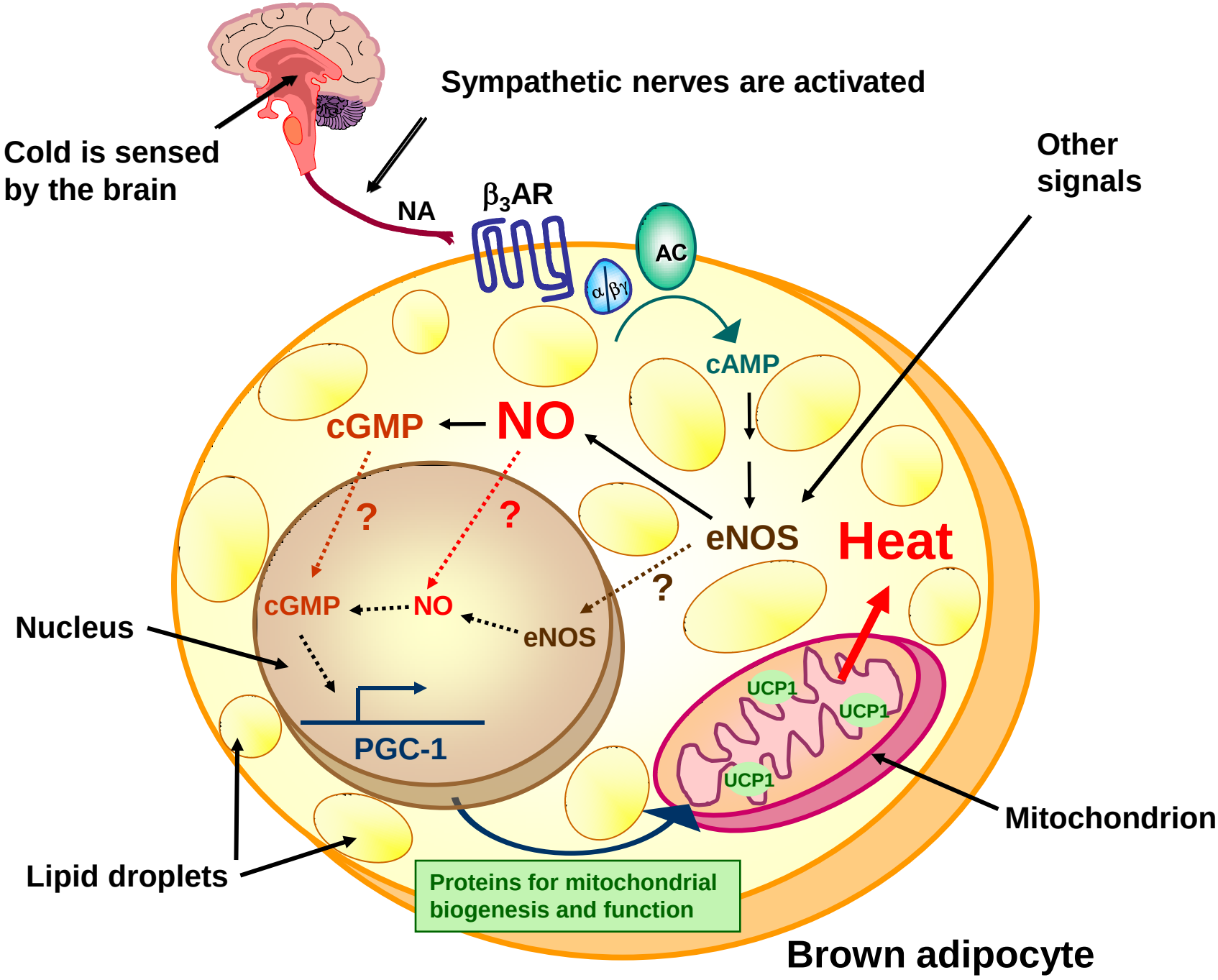
The Journal of Clinical Investigation

Mitochondrial Biogenesis in Mammals: The Role of Endogenous Nitric Oxide

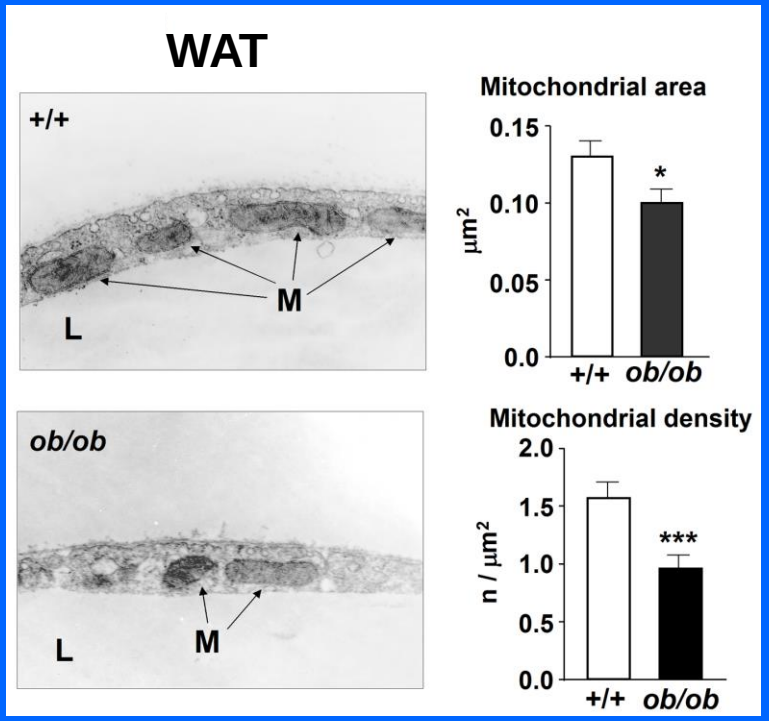
Enzo Nisoli,[1,2*†] Emilio Clementi,[3,4*] Clara Paolucci,[3] Valeria Cozzi,[1] Cristina Tonello,[1] Clara Sciorati,[3] Renata Bracale,[1] Alessandra Valerio,[5] Maura Francolini,[6] Salvador Moncada,[7] Michele O. Carruba[1,2]

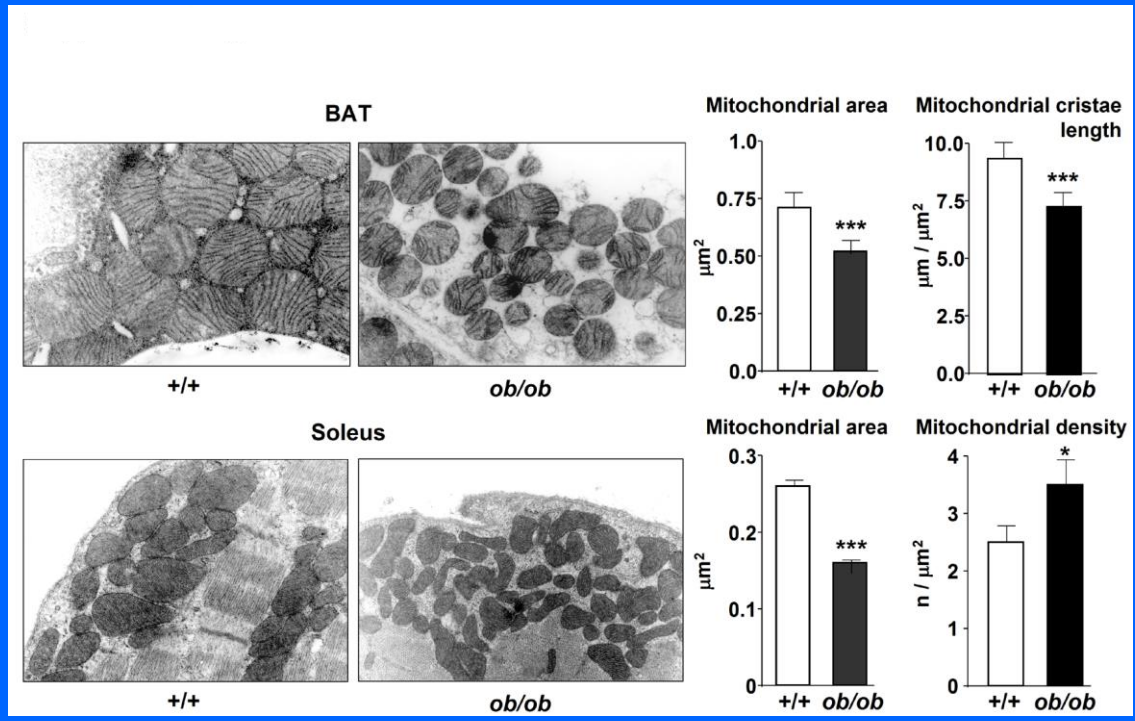
Nitric oxide was found to trigger mitochondrial biogenesis in cells as diverse as brown adipocytes and 3T3-L1, U937, and HeLa cells. This effect of nitric oxide was dependent on guanosine 3′,5′-monophosphate (cGMP) and was mediated by the induction of peroxisome proliferator–activated receptor γ coactivator 1α, a master regulator of mitochondrial biogenesis. Moreover, the mitochondrial biogenesis induced by exposure to cold was markedly reduced in brown adipose tissue of endothelial nitric oxide synthase null-mutant ($eNOS^{-/-}$) mice, which had a reduced metabolic rate and accelerated weight gain as compared to wild-type mice. Thus, a nitric oxide–cGMP–dependent pathway controls mitochondrial biogenesis and body energy balance.

Science 299: 896-899, 2003


Sympathetic nerves are activated
Cold is sensed by the brain
Other signals
NA
β3AR
AC
α βγ
cAMP
cGMP
NO
?
?
?
eNOS
Heat
cGMP
NO
eNOS
Nucleus
PGC-1
UCP1
UCP1
UCP1
Mitochondrion
Lipid droplets
Proteins for mitochondrial biogenesis and function
Brown adipocyte

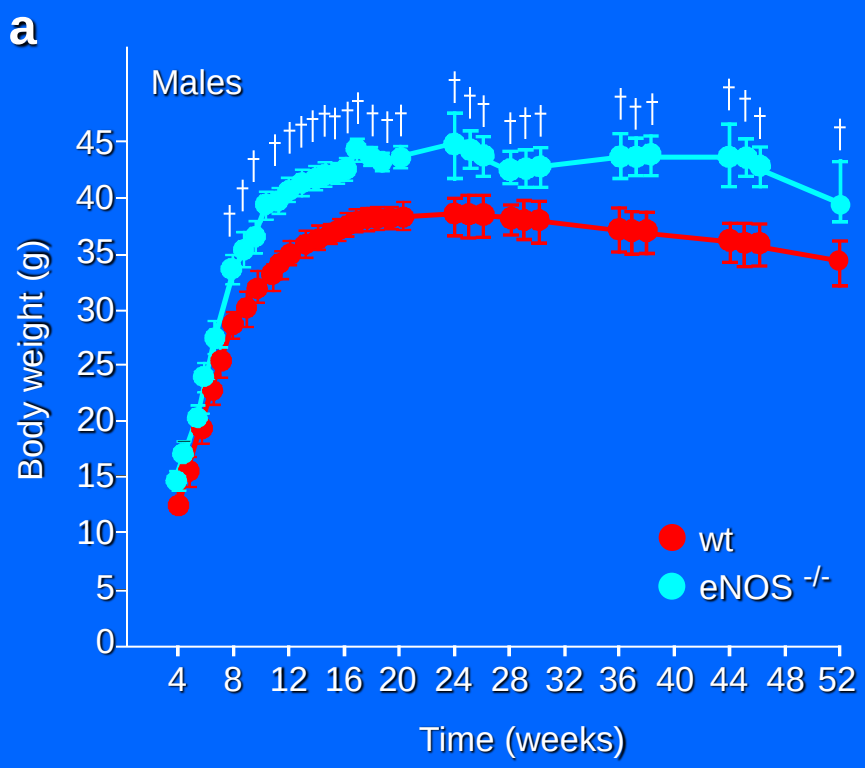
Electron microscopy analysis of WAT, BAT and muscle in *ob/ob* mice

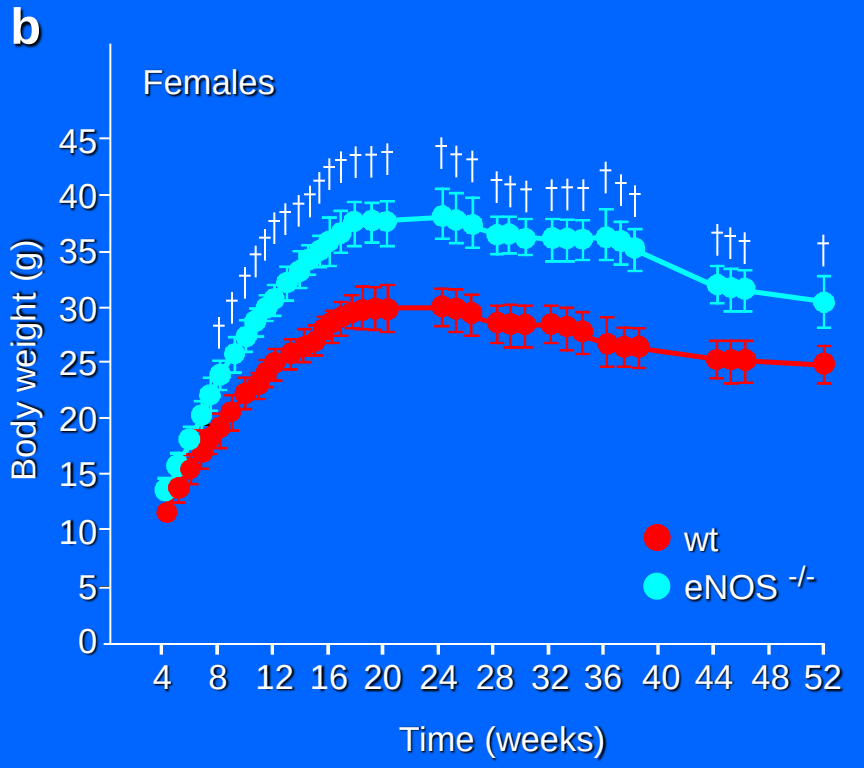




Valerio et al., J. Clin. Invest., Oct. 2006

Growth curves of wild-type and eNOS$^{-/-}$ mice





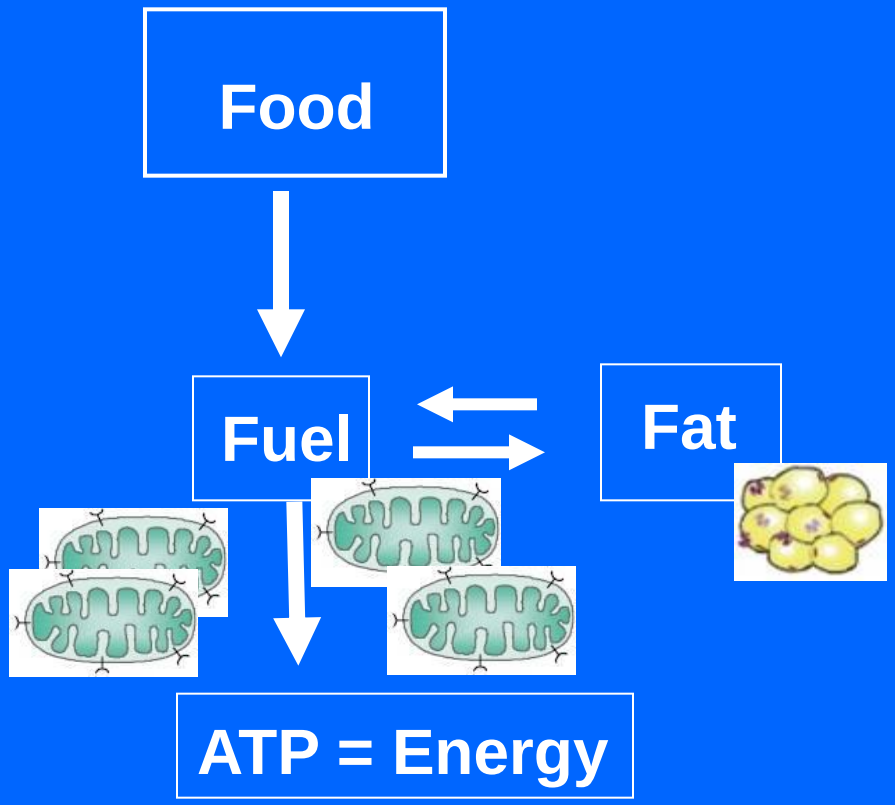
Nisoli et al., Science 299, 896–899, 2003

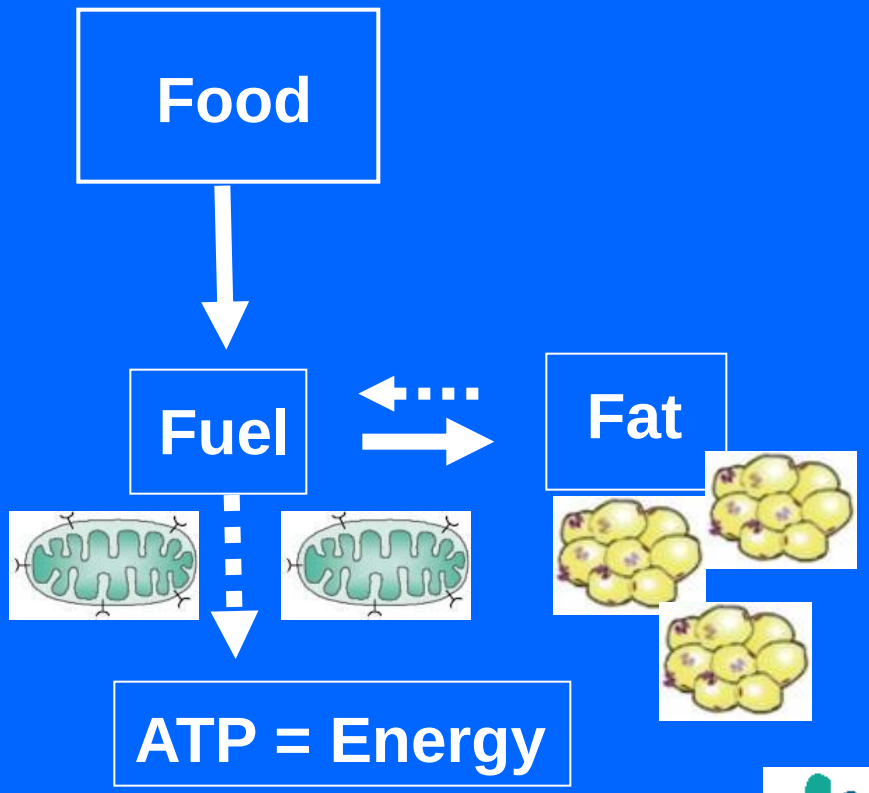
Visceral fat depot in eNOS$^{-/-}$ *vs.* wild-type mice

wt

eNOS$^{-/-}$

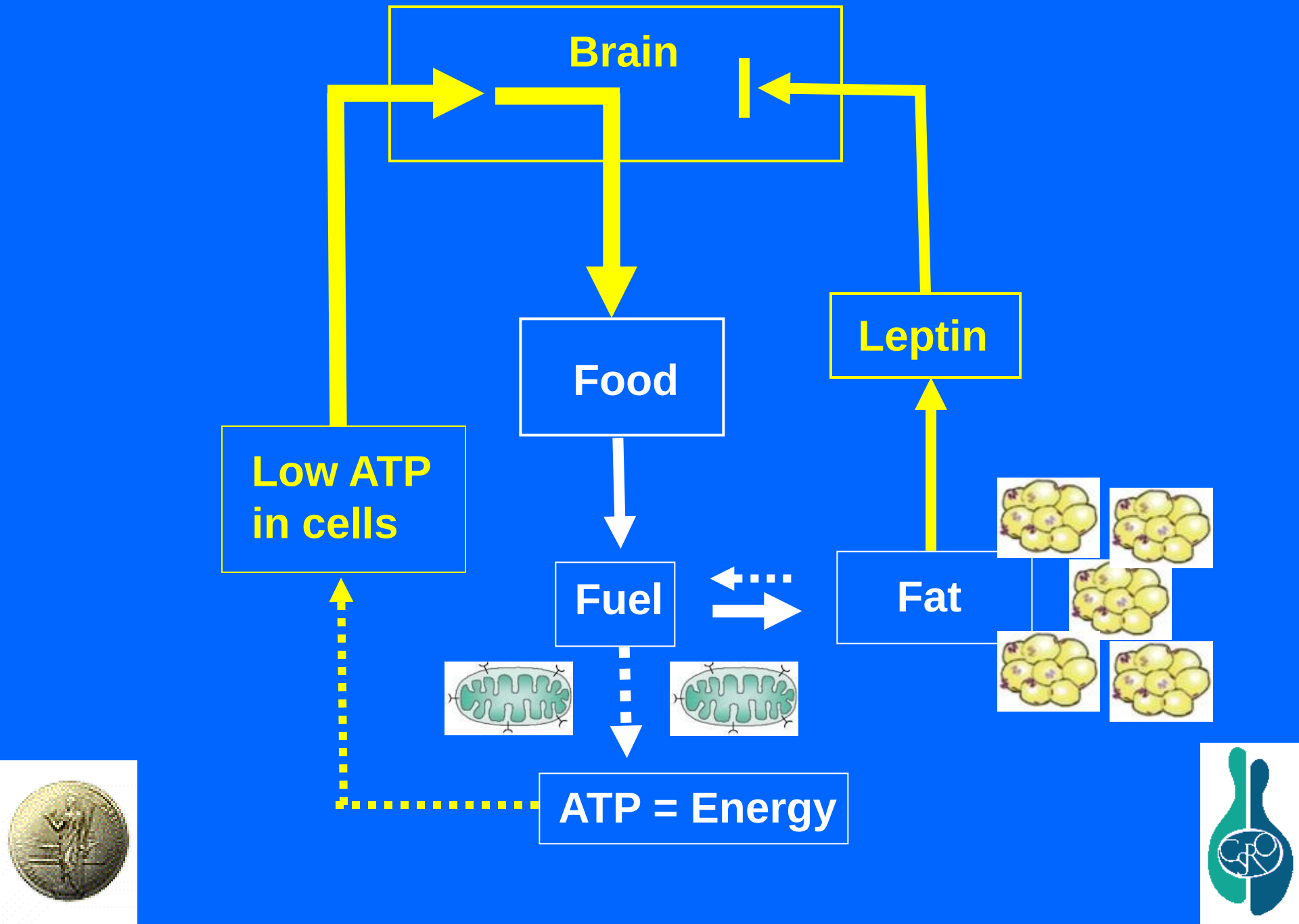
Decreased energy levels can cause and sustain obesity





Healthy subject

Obese subject

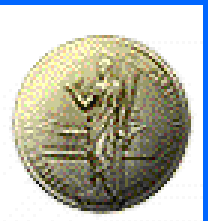

Brain
Food
Leptin
Low ATP
in cells
Fuel
Fat
ATP = Energy

Calorie Restriction Promotes Mitochondrial Biogenesis by Inducing the Expression of eNOS

Enzo Nisoli,[1,2*] Cristina Tonello,[1] Annalisa Cardile,[1]
Valeria Cozzi,[1] Renata Bracale,[1] Laura Tedesco,[1]
Sestina Falcone,[1,3] Alessandra Valerio,[1] Orazio Cantoni,[4]
Emilio Clementi,[1,3,5] Salvador Moncada,[6] Michele O. Carruba[1,2]

Calorie restriction extends life span in organisms ranging from yeast to mammals. Here, we report that calorie restriction for either 3 or 12 months induced endothelial nitric oxide synthase (eNOS) expression and 3′,5′-cyclic guanosine monophosphate formation in various tissues of male mice. This was accompanied by mitochondrial biogenesis, with increased oxygen consumption and adenosine triphosphate production, and an enhanced expression of sirtuin 1. These effects were strongly attenuated in eNOS null-mutant mice. Thus, nitric oxide plays a fundamental role in the processes induced by calorie restriction and may be involved in the extension of life span in mammals.

Sience October 14, 2005



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Università degli Studi di Milano, Via Vanvitelli 32, Milano
Prof. **Michele Carruba**

Skeletal muscle mitochondrial DNA content in exercising humans

A. Marcuello,[1] J. González-Alonso,[2] J. A. L. Calbet,[3]
R. Damsgaard,[2] M. J. López-Pérez,[1] and C. Díez-Sánchez[1]

[1]*Department of Biochemistry, Molecular and Cell Biology, University of Zaragoza, Zaragoza, Spain;*
[2]*The Copenhagen Muscle Research Centre, Rigshospitalet, University of Copenhagen, Denmark; and*
[3]*Department of Physical Education, University of Las Palmas de Gran Canaria, Canary Islands, Spain*

Several weeks of intense endurance training enhances mitochondrial biogenesis in humans.

***J Appl Physiol* 99: 1372–1377, 2005**

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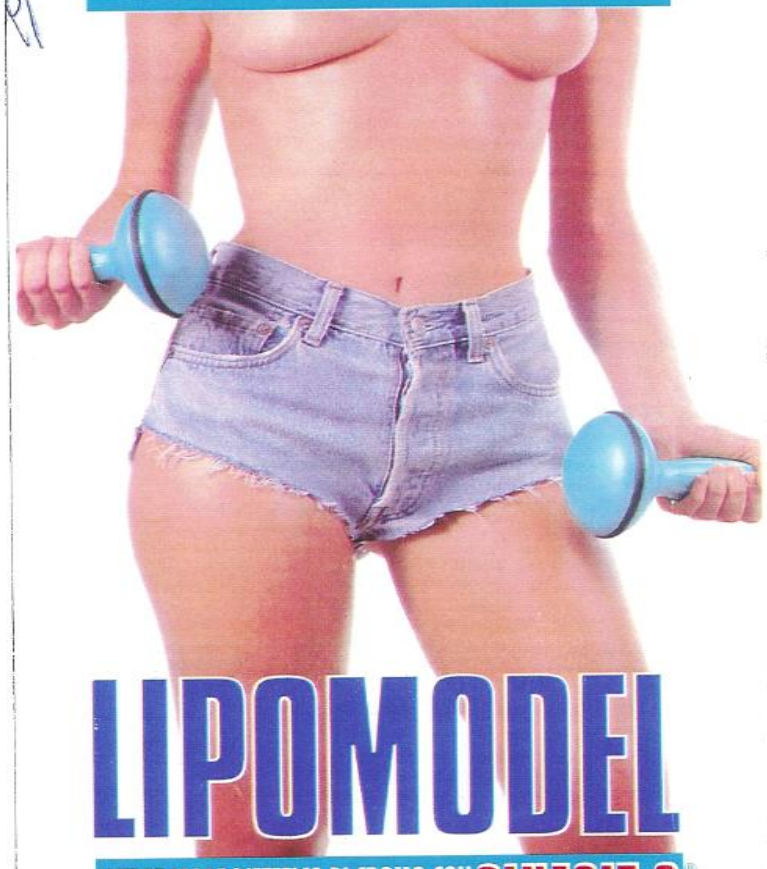
Università degli Studi di Milano, Via Vanvitelli 32, Milano
Prof. **Michele Carruba**

DIETA + PALESTRA =



LIPOMODEL

INTEGRATORE DIETETICO DI CROMO CON SINECIT 6®

1 AZIONE DIETA

Controlla il senso dell'appetito.

Aumenta la termogenesi cellulare con riduzione della massa grassa.

2 AZIONE PALESTRA

Stimola la sintesi delle proteine, con conseguente aumento della massa magra.

DIETALINEA
Salute e bellezza del corpo

P.N. PRODOTTI NATURALI S.r.l.
Tel. 010/72 02 15

Not. Min. San.

Integrated Laboratories Network (InLaNe)

Center for Study and Research on Obesity, University of Milan (Italy)

Enzo Nisoli, M.D. Ph.D.
Laura Tedesco, Ph.D.
Maurizio Ragni, Ph.D.
Renata Bracale, Ph.D.
Andrea Fossati, Ph.D.
Annalisa Cardile, Ph.D.
Chiara Ruocco, Ph.D.

Michele O. Carruba, M.D. Ph.D.

Department of Medicine, University of Padua, Padua (Italy)

Roberto Vettor, M.D.
Elisabetta Trevellin, Ph.D.
Marnie Granzotto, Ph.D.
Massimiliano Olivieri, Ph.D.
Roberto Fabris, M.D.
Roberto Serra, M.D.

Department of Biomedical Sciences and Biotechnology, University of Brescia, Brescia (Italy)

Alessandra Valerio, M.D. Ph.D.

Fracesca Fenaroli, Ph.D.
Mattia Bicelli, Ph.D.