



University of Milan, Italy

School of Medicine

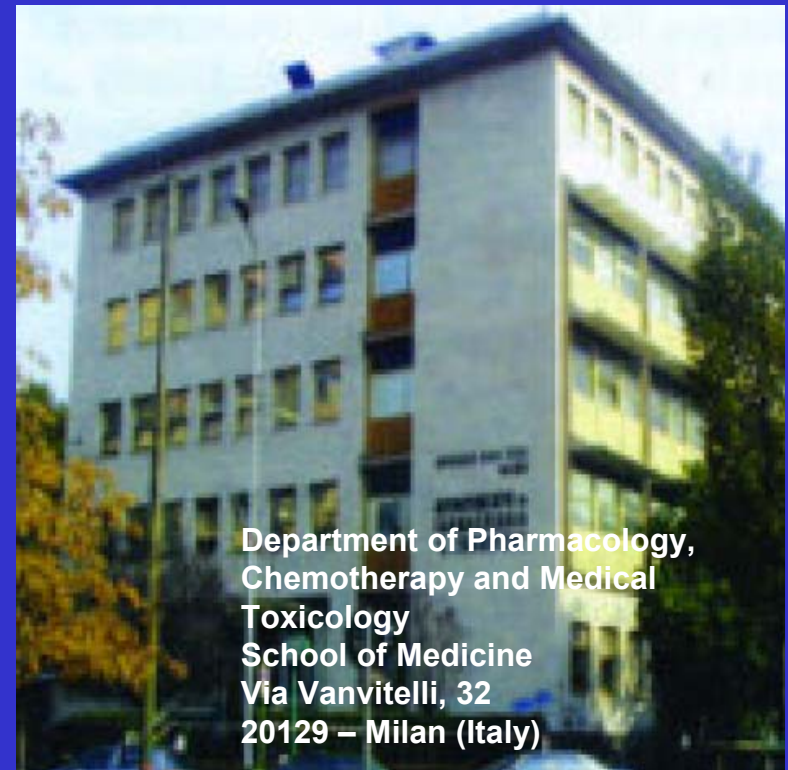
**Department of Pharmacology, Chemotherapy and
Medical Toxicology**

CENTER FOR STUDY AND RESEARCH ON OBESITY



STILI DI VITA ALIMENTAZIONE OBESITA' E SALUTE

Michele O. Carruba

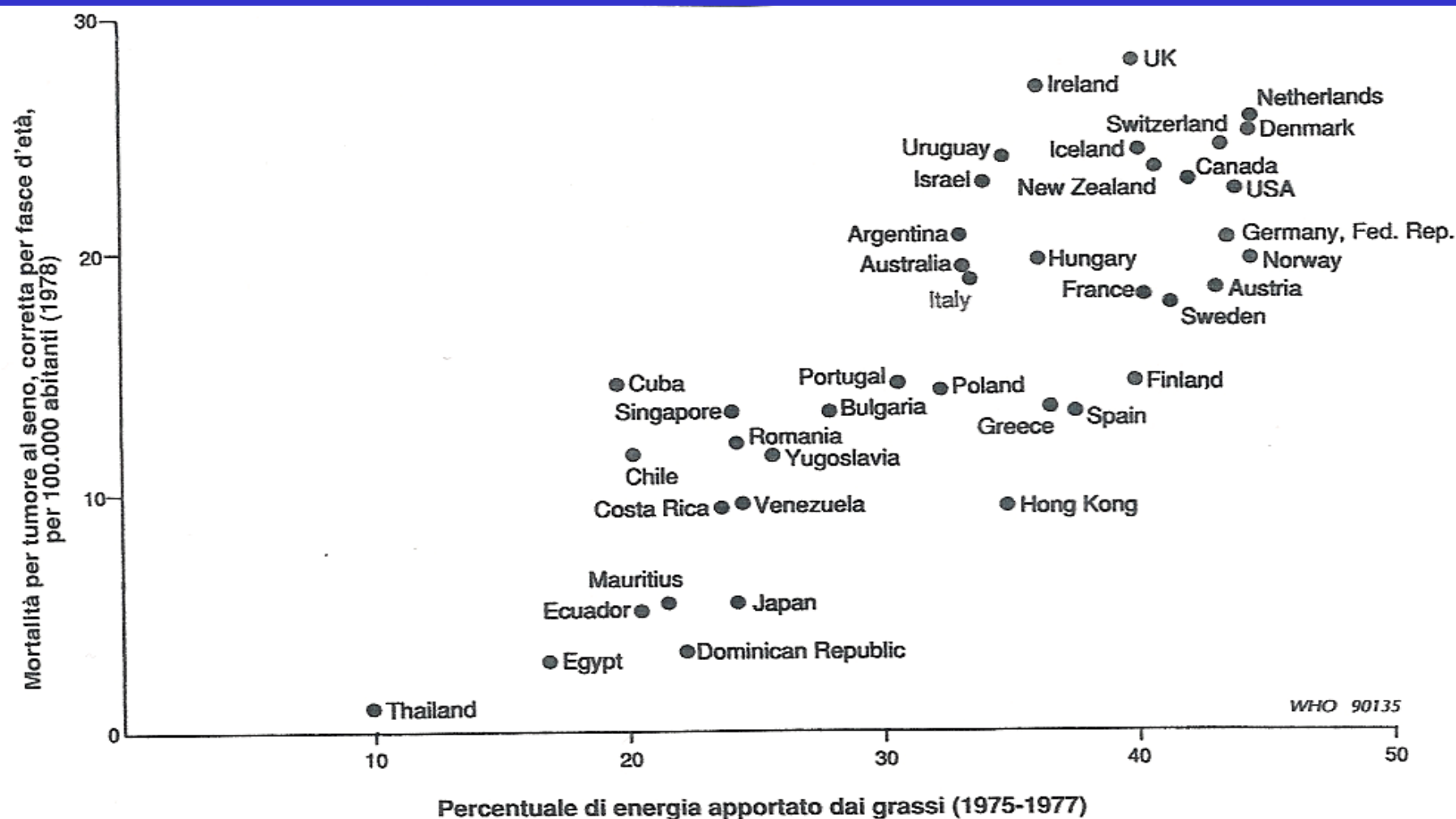


**Department of Pharmacology,
Chemotherapy and Medical
Toxicology
School of Medicine
Via Vanvitelli, 32
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Principali patologie croniche non comunicabili legate a cattiva alimentazione e a scorretti stili di vita

- Malattie cardiovascolari e ischemiche
- Obesità
- Disturbi del Comportamento Alimentare
- Diabete
- Tumori
- Osteoporosi
- Cirrosi ed altre patologie legate all'abuso di alcool
- Gozzo
- Anemie nutrizionali (ferro, folati vit. B12)
- Carie dentale
- Ipercolesterolemia familiare

Correlazione tra consumo di grassi alimentari e tassi di mortalità per tumore al seno



Correlazioni tra componenti selezionate della dieta e tumori

Sede del tumore	Grassi	Peso corporeo	Fibre	Frutta e ortaggi	Alcol	Cibi affumicati conservati sotto sale o salamoia
Polmoni				-		
Seno	+	+			+ / -	
Colon	++		-	-		
Prostata	++					
Vescica				-		
Retto	+			-	+	
Endometrio		++				
Cavità orale				-	+ ^b	
Stomaco				-		++
Cervice				-		
Esofago				-	++ ^b	+

+ = Correlazione positiva: apporto aumentato e incidenza maggiore.

- = Correlazione negativa: apporto aumentato e incidenza inferiore.

^a Tratto e approfondito dalla nota bibliografica 44.

^b Sinergia con il fumo.

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

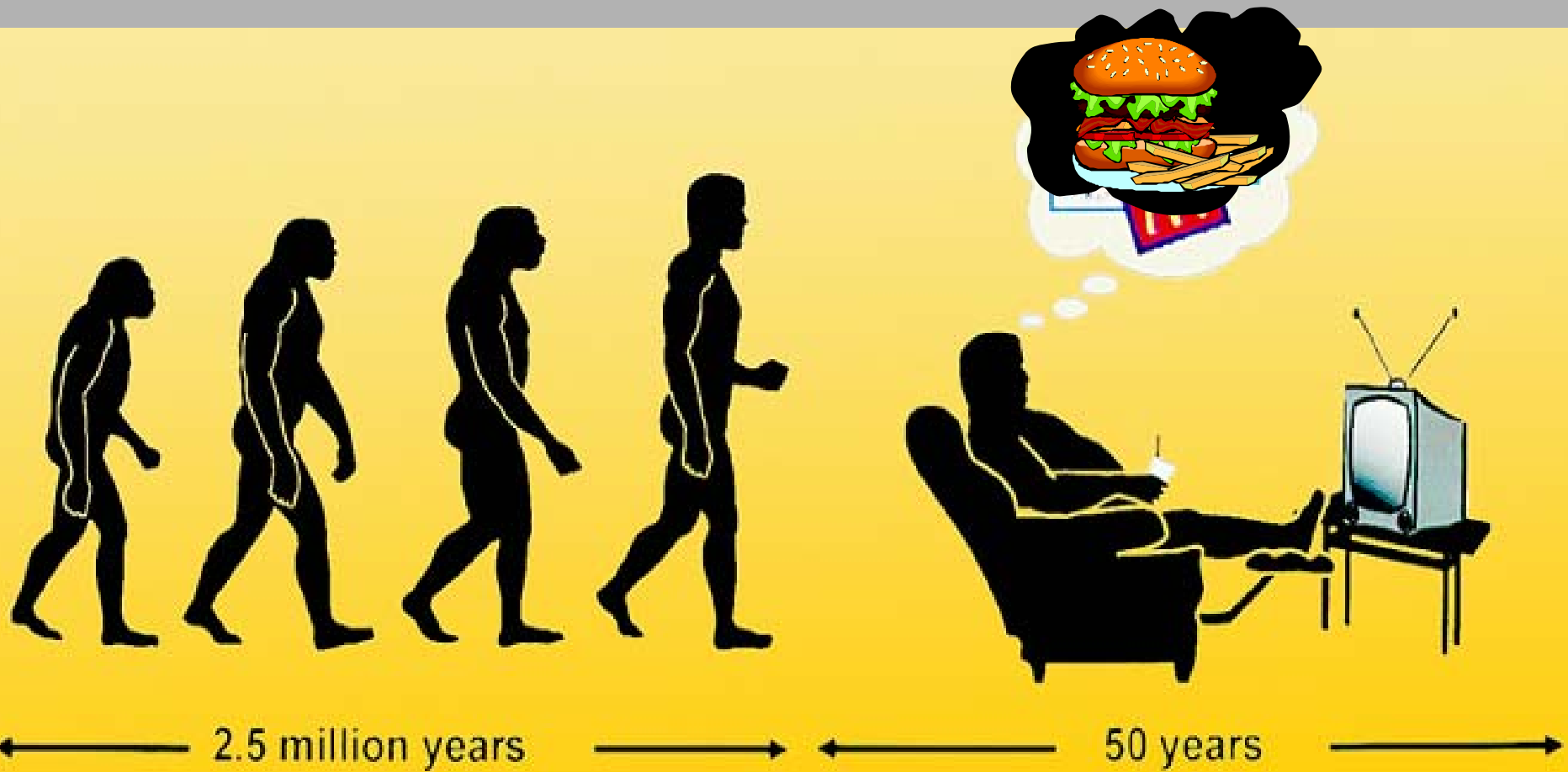
*Eugenia E. Calle, Ph.D., Carmen Rodriguez, M.D., M.P.H.,
Kimberly Walker-Thurmond, B.A., and Michael J. Thun, M.D.*

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.

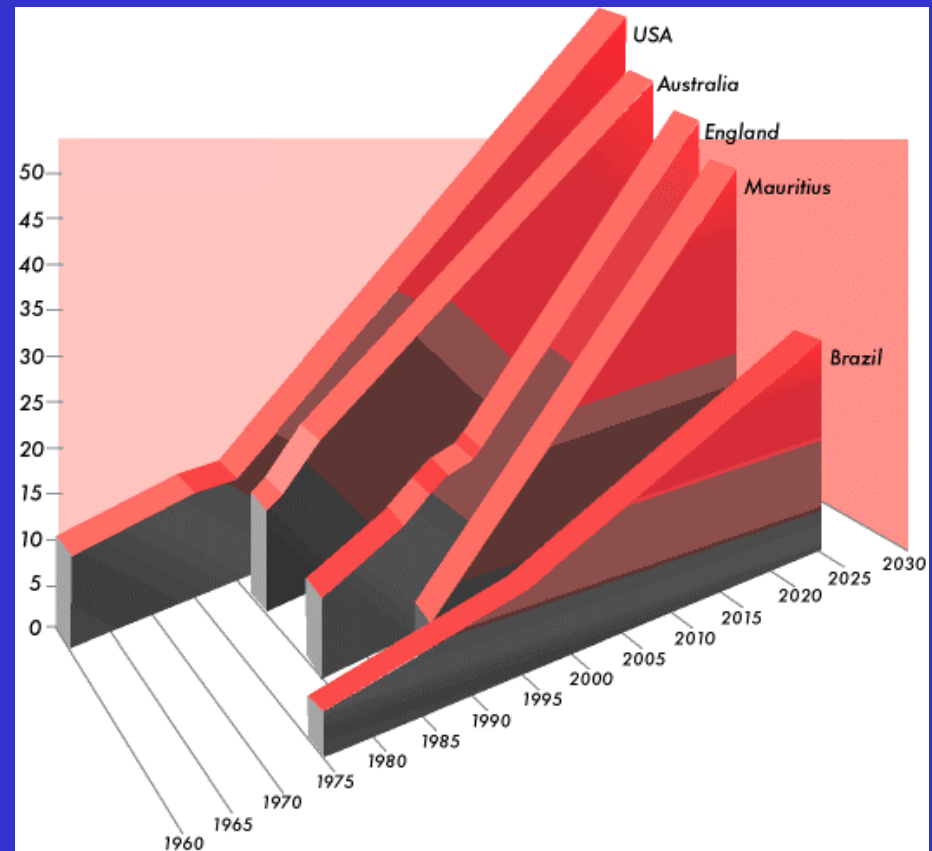
L'evoluzione della specie



Sovrappeso/Obesità— l'epidemia mondiale

% di Popolazione obesa
(BMI ≥ 30 kg/m²)²

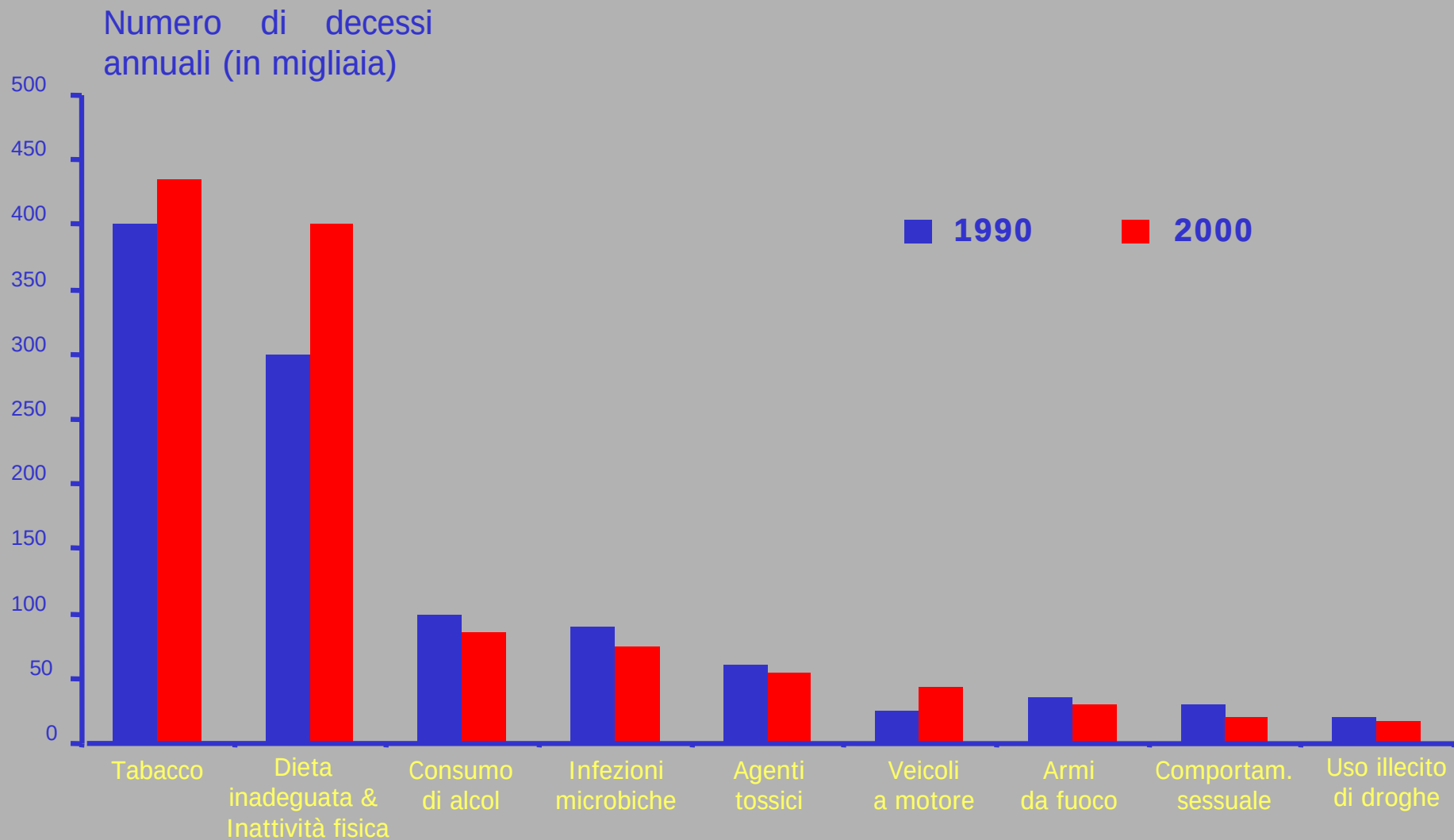
- >1 miliardo di adulti nel mondo erano in sovrappeso (BMI >25 kg/m²) nel 2002¹
- Almeno 300 milioni sono obesi (BMI >30 kg/m²)¹
- Regioni dell'incremento della prevalenza:¹
 - Abbondanza di cibo
 - Livelli più bassi di attività fisica



1. World Health Organization. Global strategy on diet, physical activity and health, 2003. Available at: http://www.who.int/hpr/NPH/docs/gs_obesity.pdf. Accessed November 11, 2003.

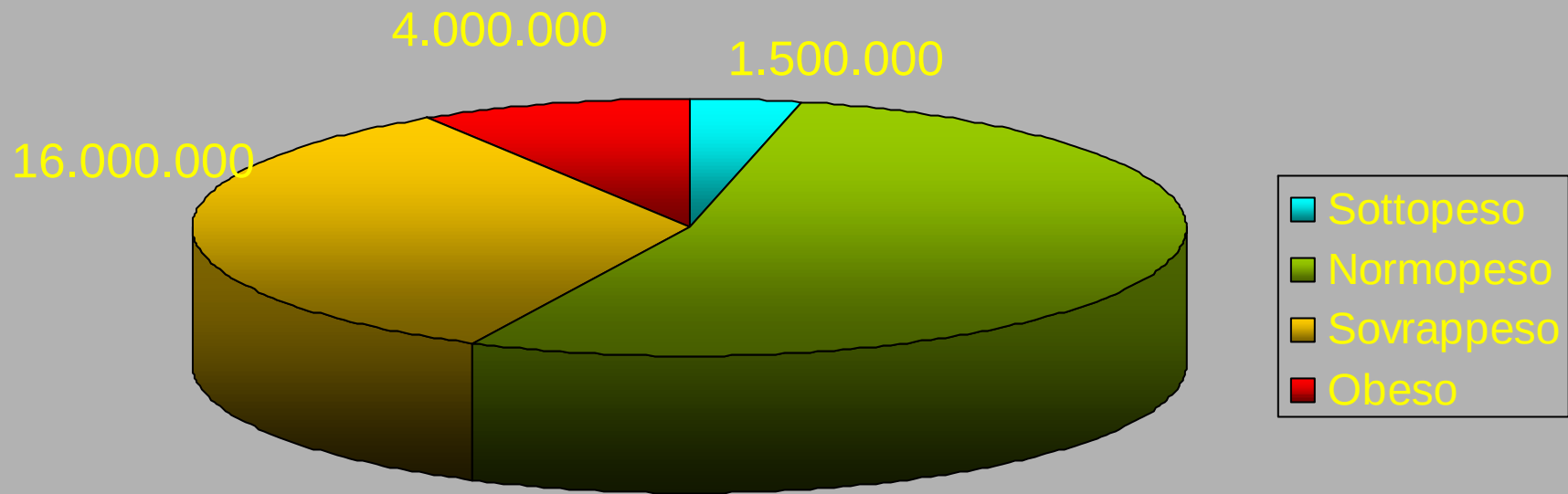
2. International Obesity Task Force. Available at: <http://www.ietf.org>. Accessed November 13, 2003.

Cause di morte negli U.S.A.

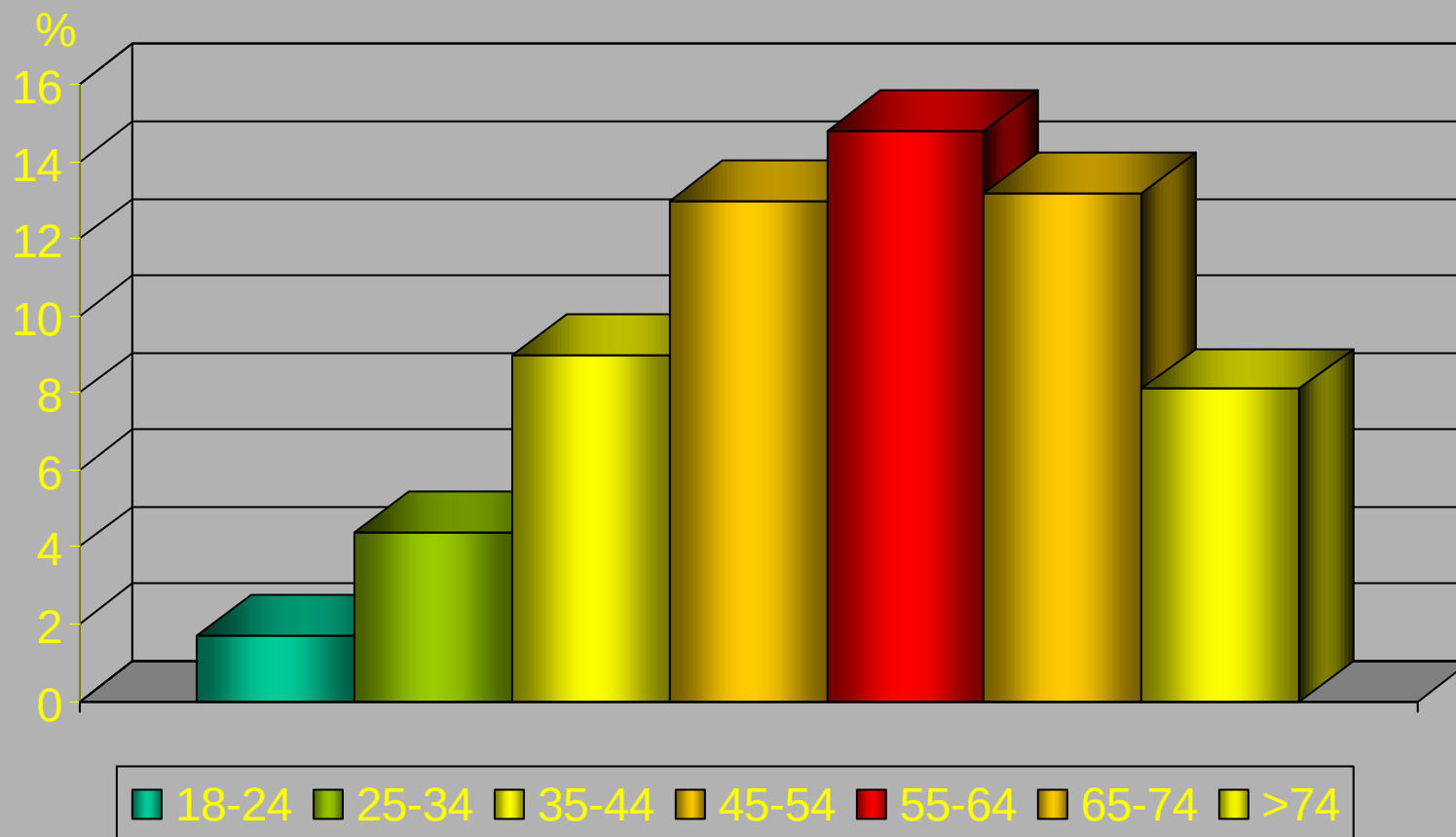


Adapted from Mokdad et al. *JAMA* 2004; 291: 1238-1245

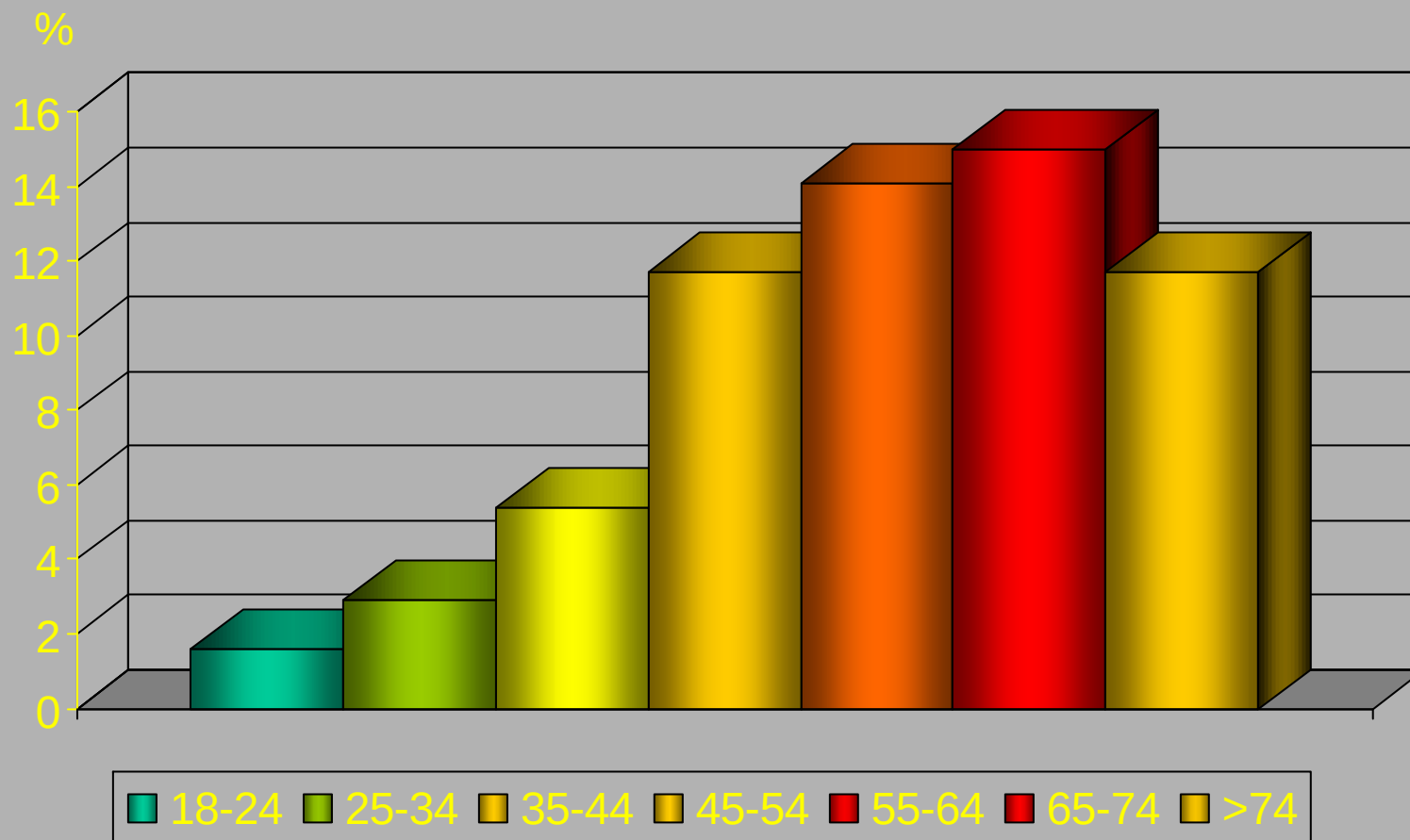
Distribuzione della popolazione italiana nelle varie condizioni di peso



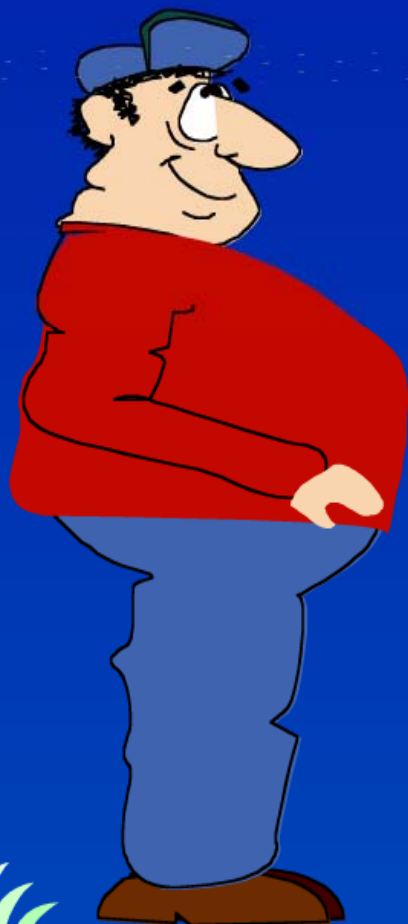
Prevalenza dell'obesità (IMC>30) in funzione dell'età negli UOMINI



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



L'obesità viene valutata mediante l'Indice di Massa Corporea (BMI)

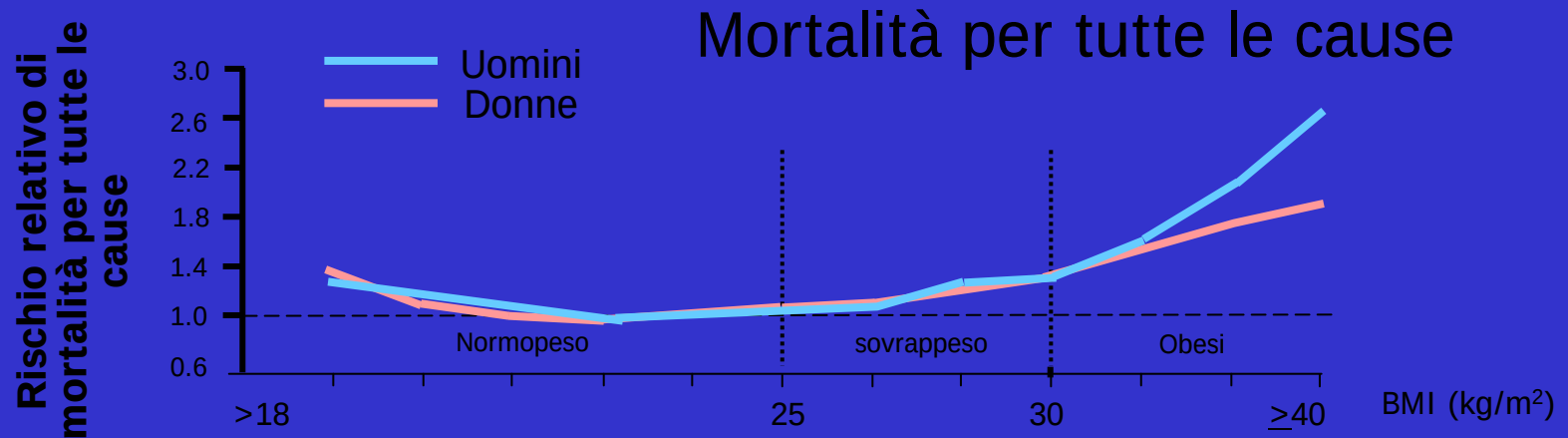
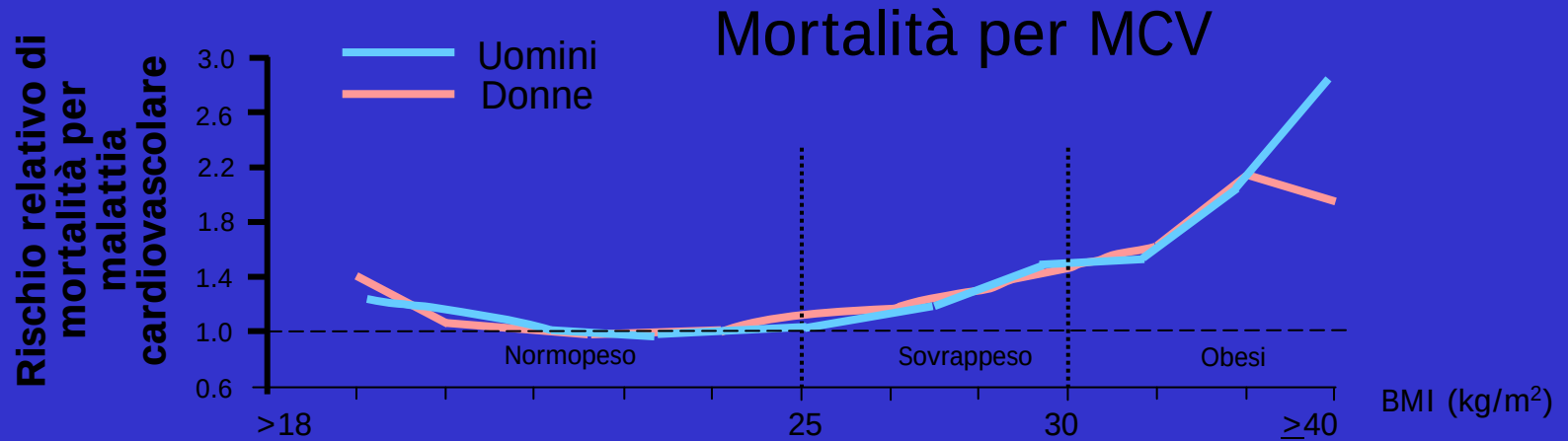


$$\text{BMI} = \frac{\text{Peso (kg)}}{\text{Altezza (m}^2\text{)}}$$

Classificazione	BMI (kg/m ²)	Rischio di comorbidità
Normopeso	18,5 - 24,9	Nella media
Sovrappeso	25,0 - 29,9	Aumentato
Obesità classe I	30,0 - 34,9	Moderato
Obesità classe II	35,0 - 39,9	Elevato
Obesità classe III	≥ 40,0	Molto elevato



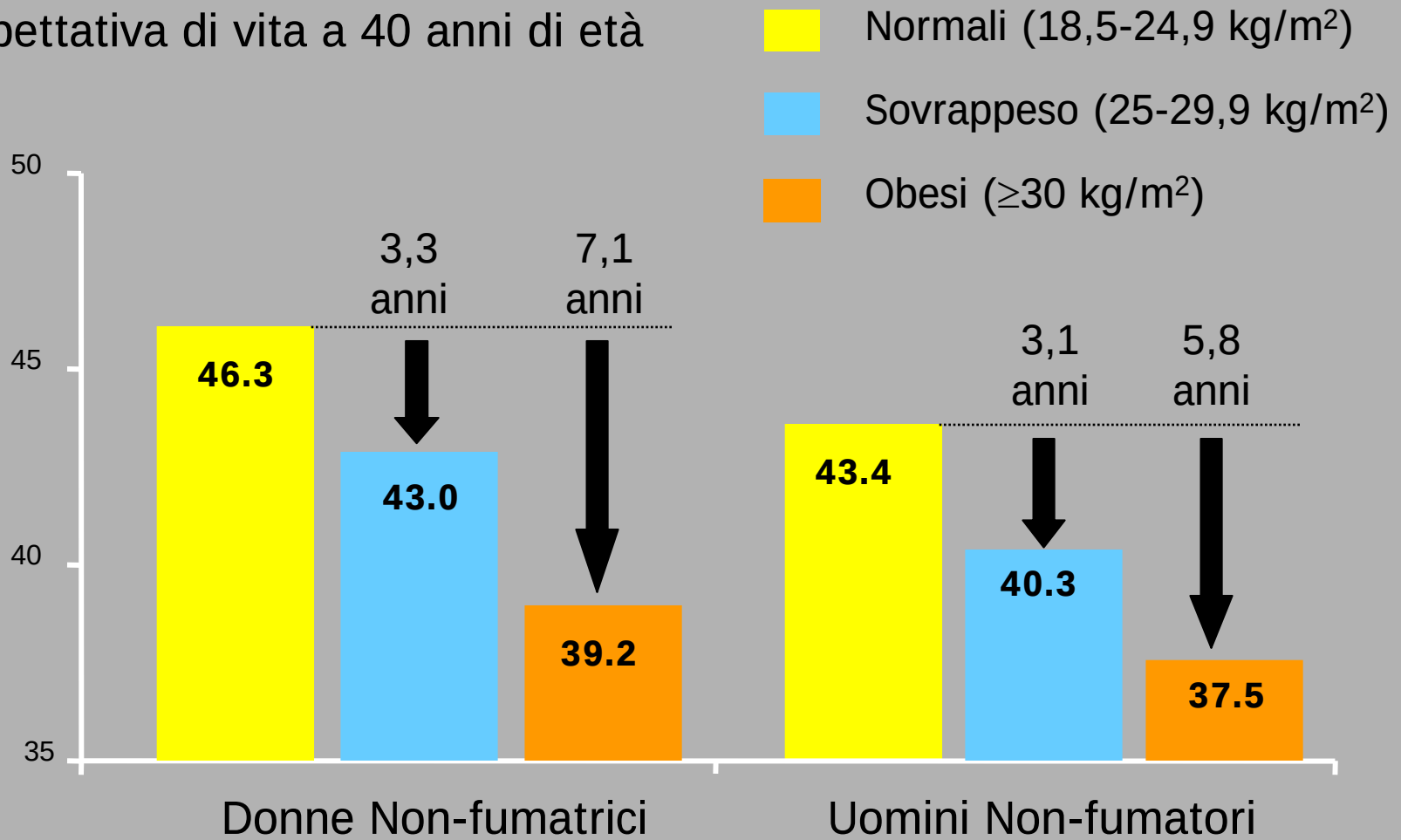
Sovrappeso e obesità aumentano il rischio di MCV e di mortalità per tutte le cause



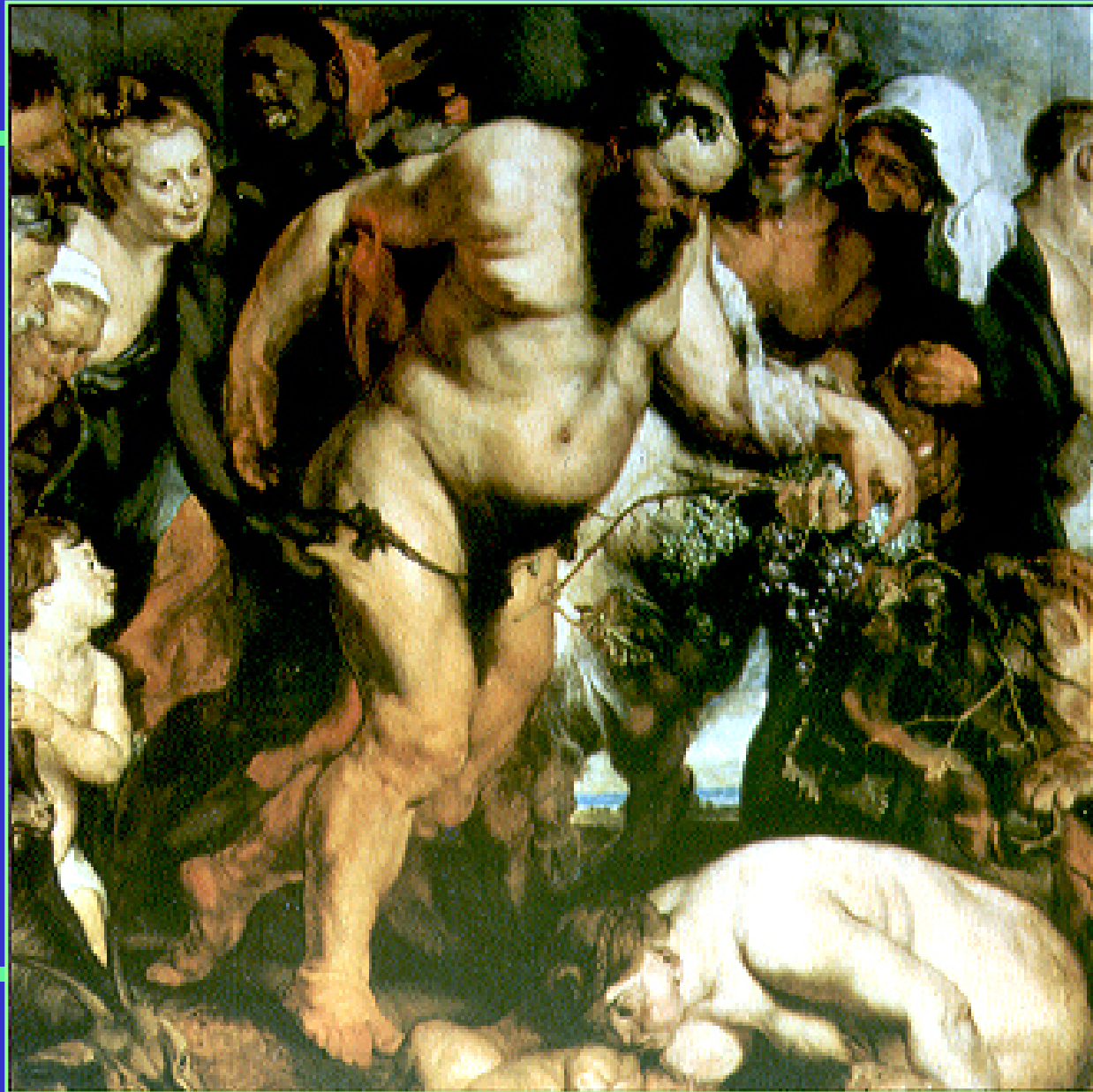
Dati relativi a 1 milione di uomini e donne seguiti per 16 anni con età media di 57 anni che non hanno mai fumato e non avevano una storia di malattia all'arruolamento.

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

Aspettativa di vita a 40 anni di età





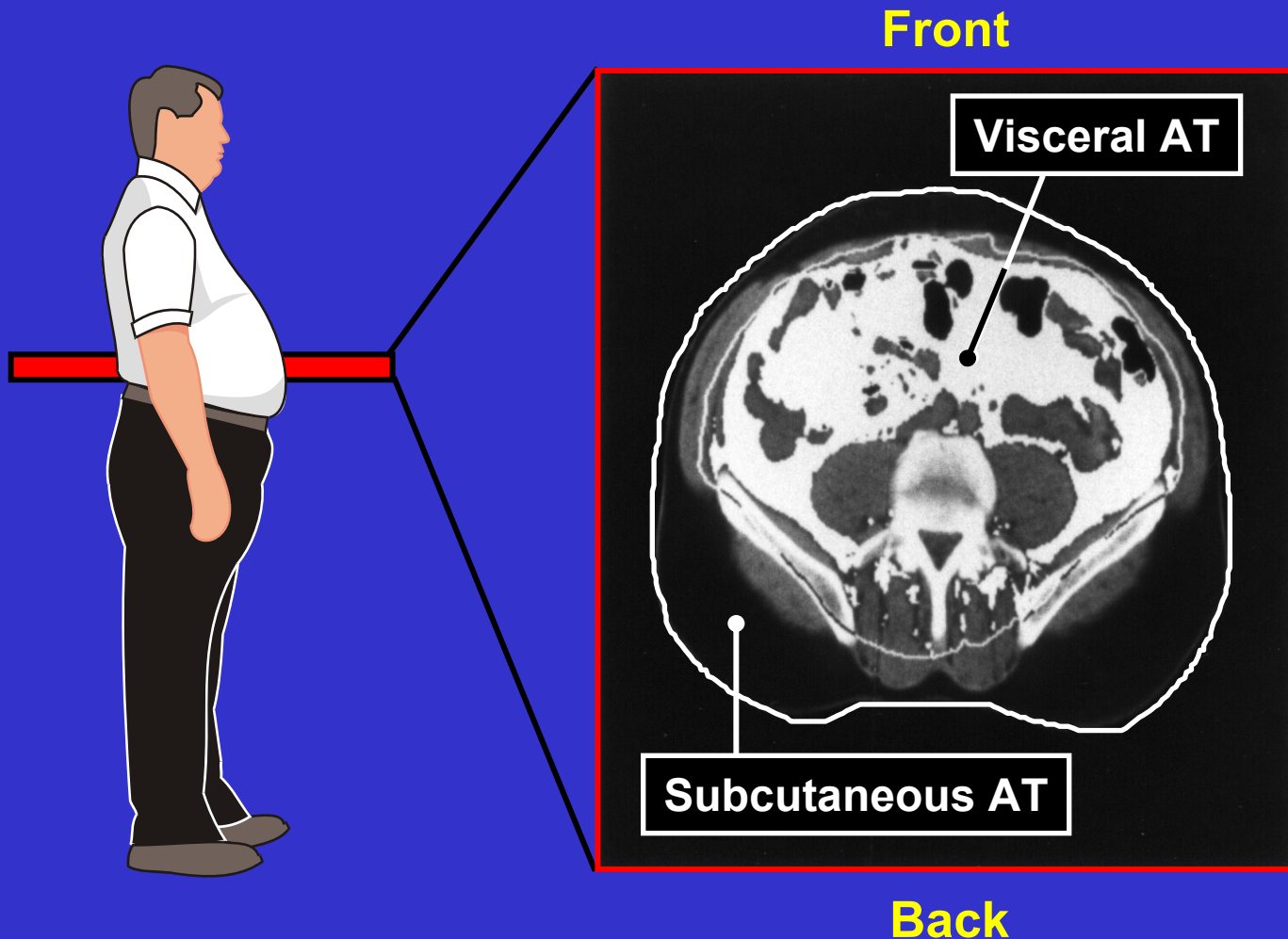


Un parametro fondamentale: la circonferenza addominale



Intra-Abdominal (Visceral) Fat

The dangerous inner fat!



La circonferenza vita è un indicatore del tessuto adiposo viscerale

Donne

>88 cm = Rischio aumentato¹



Uomini

>102 cm = Rischio aumentato¹



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

Rischio Relativo di Problemi di Salute Associati all'Obesità

RR >3 volte	RR tra 2-3 volte	RR tra 1-2 volte
Diabete di tipo 2 Problemi cistifellea Dislipidemie Apnee notturne	Pat. cardiovascolari Ipertensione Osteoartriti Gotta	Alterazioni dell'asse HPG Cancro Problemi lombosacrali Difetti alla nascita

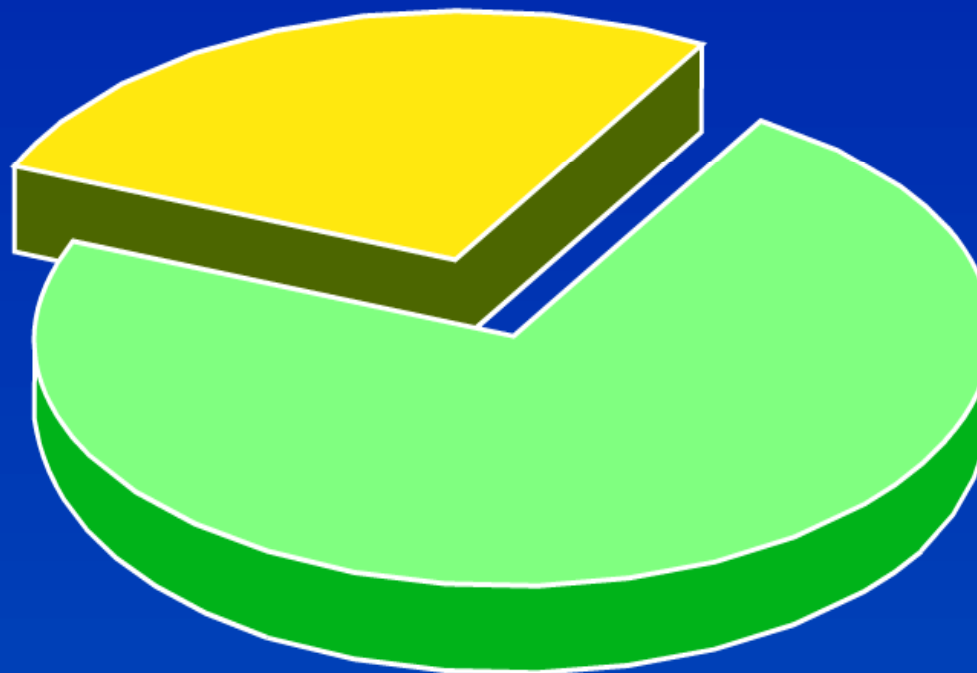
Tessuto adiposo sottocutaneo **Perdita di peso ~ 10 %**
Perdita di TA viscerale ~ 30 %



BMI e comorbidità

Pazienti con BMI ≥ 27 (%)

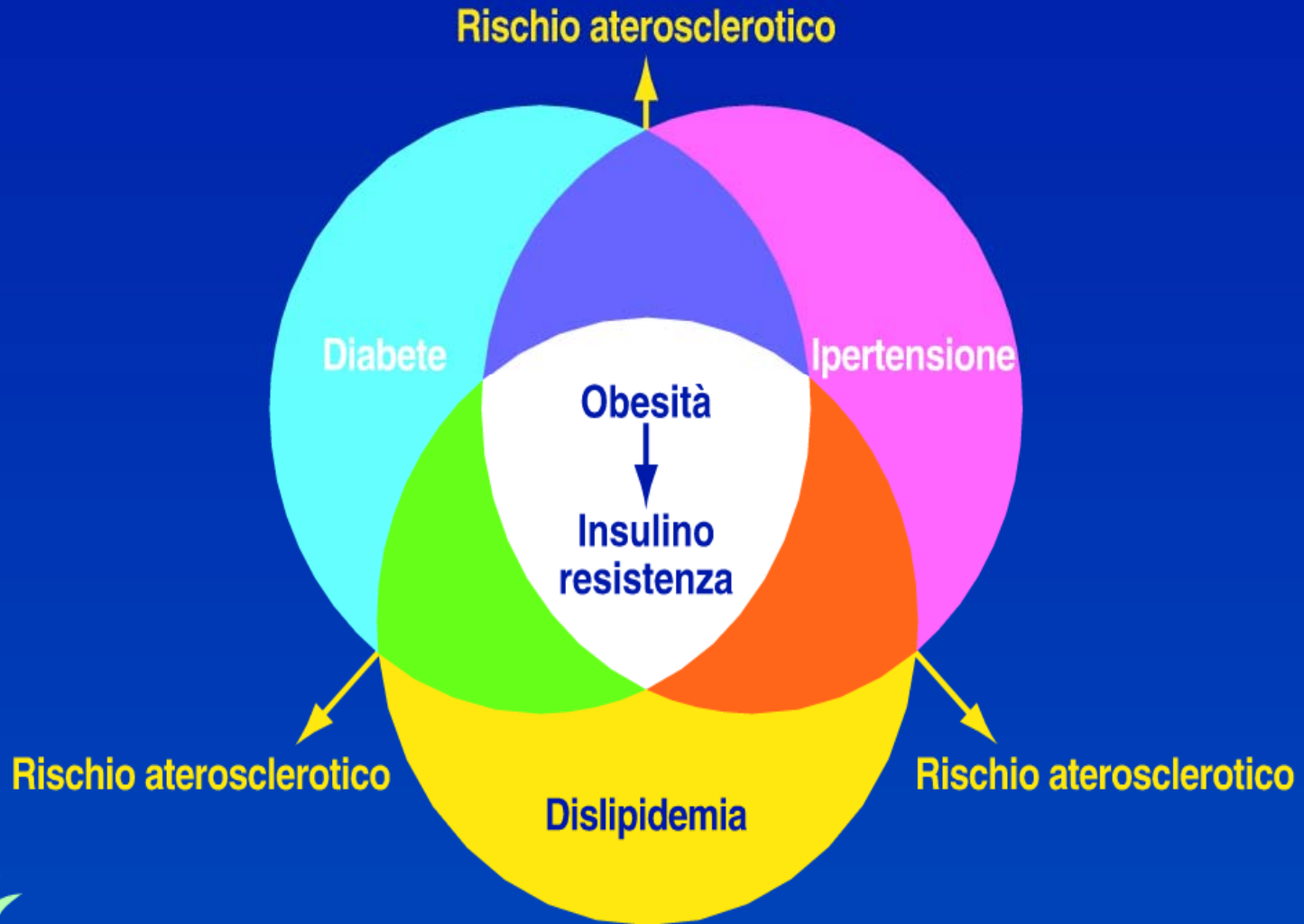
Nessuna
comorbidità



Comorbidità:
ipertensione
dislipidemia
diabete di tipo 2



Sindrome metabolica



Studio SPESA: composizione dei costi sanitari dell'Obesità

Tot 22,8 mld Euro/anno

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

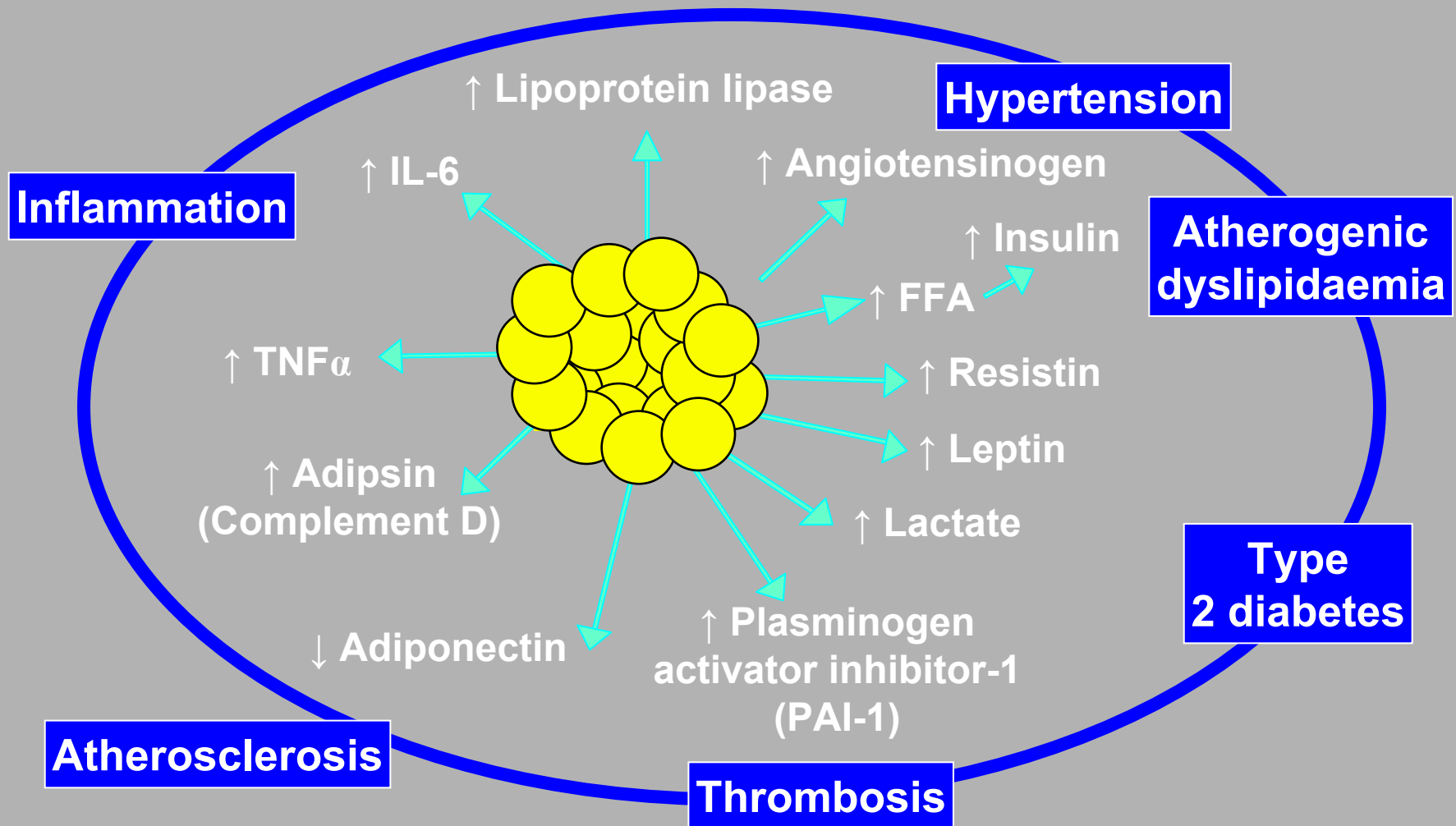
Elaborazioni: Centro di Farmacoeconomia

Impatto economico annuo dell'obesità

BMI	Costo	% pop	Totale
25 - 30	878	35	16 mld
30 - 40	1653	9	6 mld
40 o più	2220	1	1 mld
TOTALE			23 mld

Elaborazioni: Centro di Farmacoeconomia

Adverse cardiometabolic effects of products of adipocytes



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

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}

¹Integrated Laboratories Network, Center for Study and Research on Obesity, Department of Pharmacology, School of Medicine, University of Milan, Milan, Italy.

²Department of Preclinical Sciences, University of Milan, Milan, Italy. ³CEINGE Biotechnologie Avanzate, Naples, Italy. ⁴Istituto Auxologico Italiano, Milan, Italy.

⁵Stem Cell Research Institute, San Raffaele Scientific Institute, Milan, Italy. ⁶Istituto di Farmacologia e Farmacognosia, University of Urbino "Carlo Bo," Urbino, Italy. ⁷Eugenio Medea Scientific Institute, Lecco, Italy. ⁸Wolfson 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

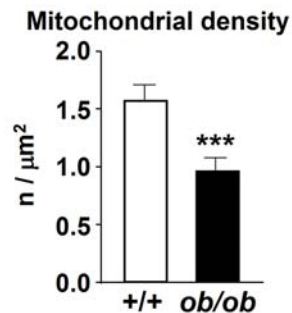
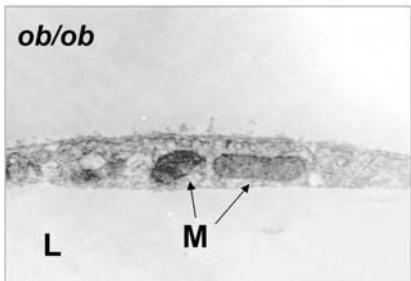
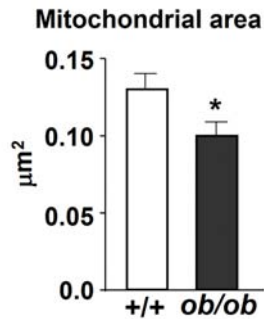
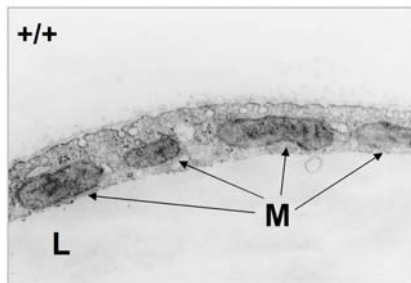
**Enzo Nisoli,^{1,2*†} Emilio Clementi,^{3,4*} Clara Paolucci,³
Valeria Cozzi,¹ Cristina Tonello,¹ Clara Sciorati,³
Renata Bracale,¹ Alessandra Valerio,⁵ Maura Francolini,⁶
Salvador Moncada,⁷ Michele O. Carruba^{1,2}**

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 1 α , 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.

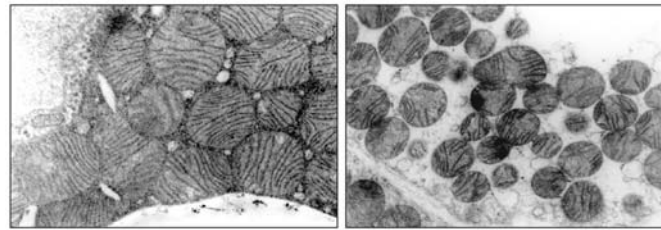
Science 299: 896-899, 2003

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

WAT

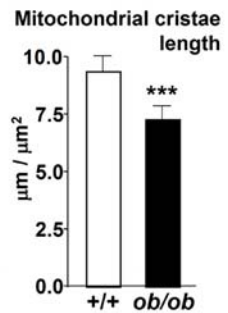
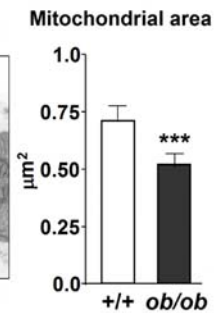


BAT

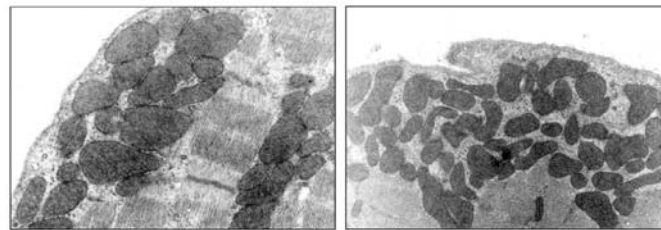


+/+

ob/ob

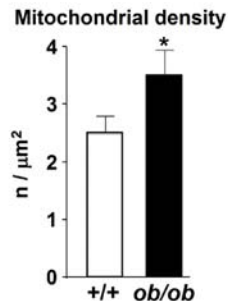
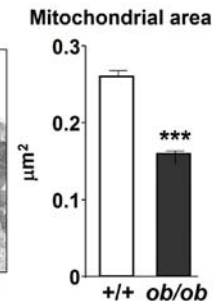


Soleus



+/+

ob/ob



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

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

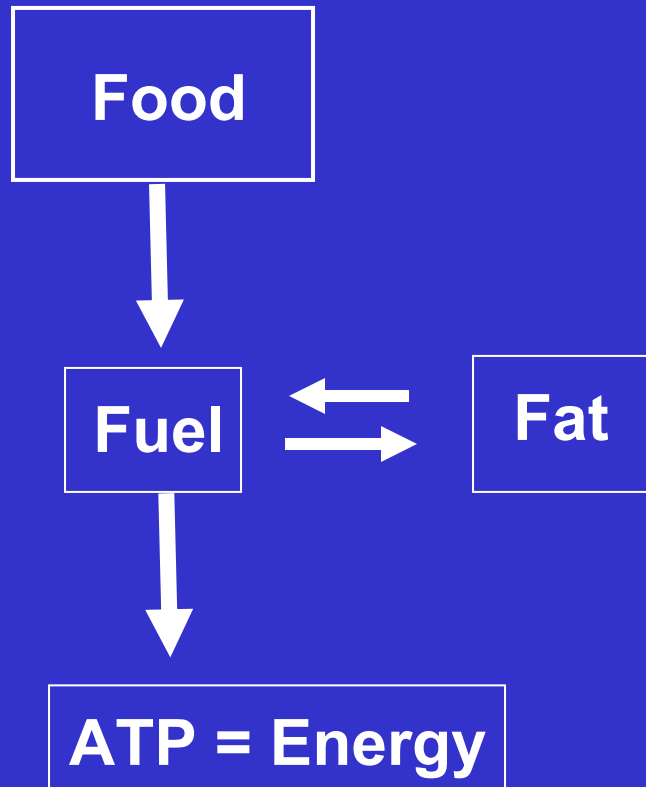
wt



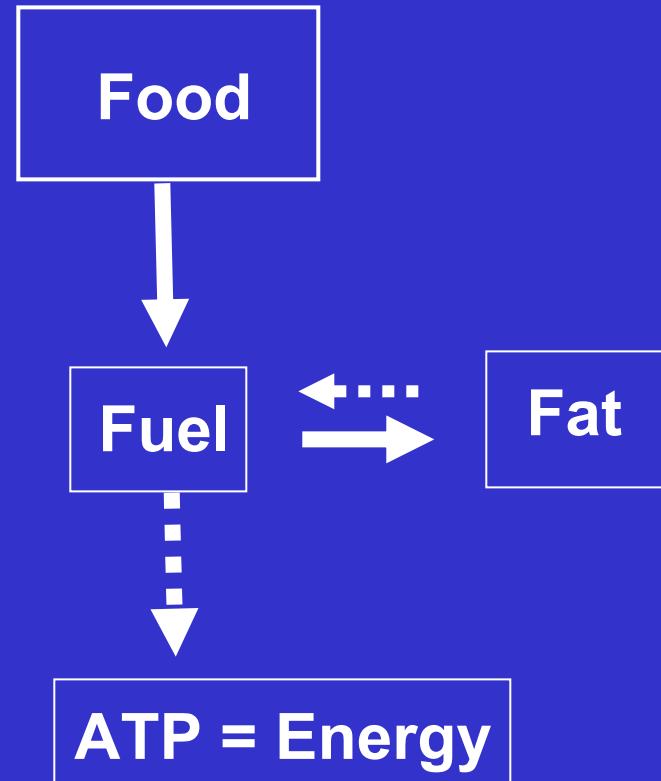
eNOS^{-/-}



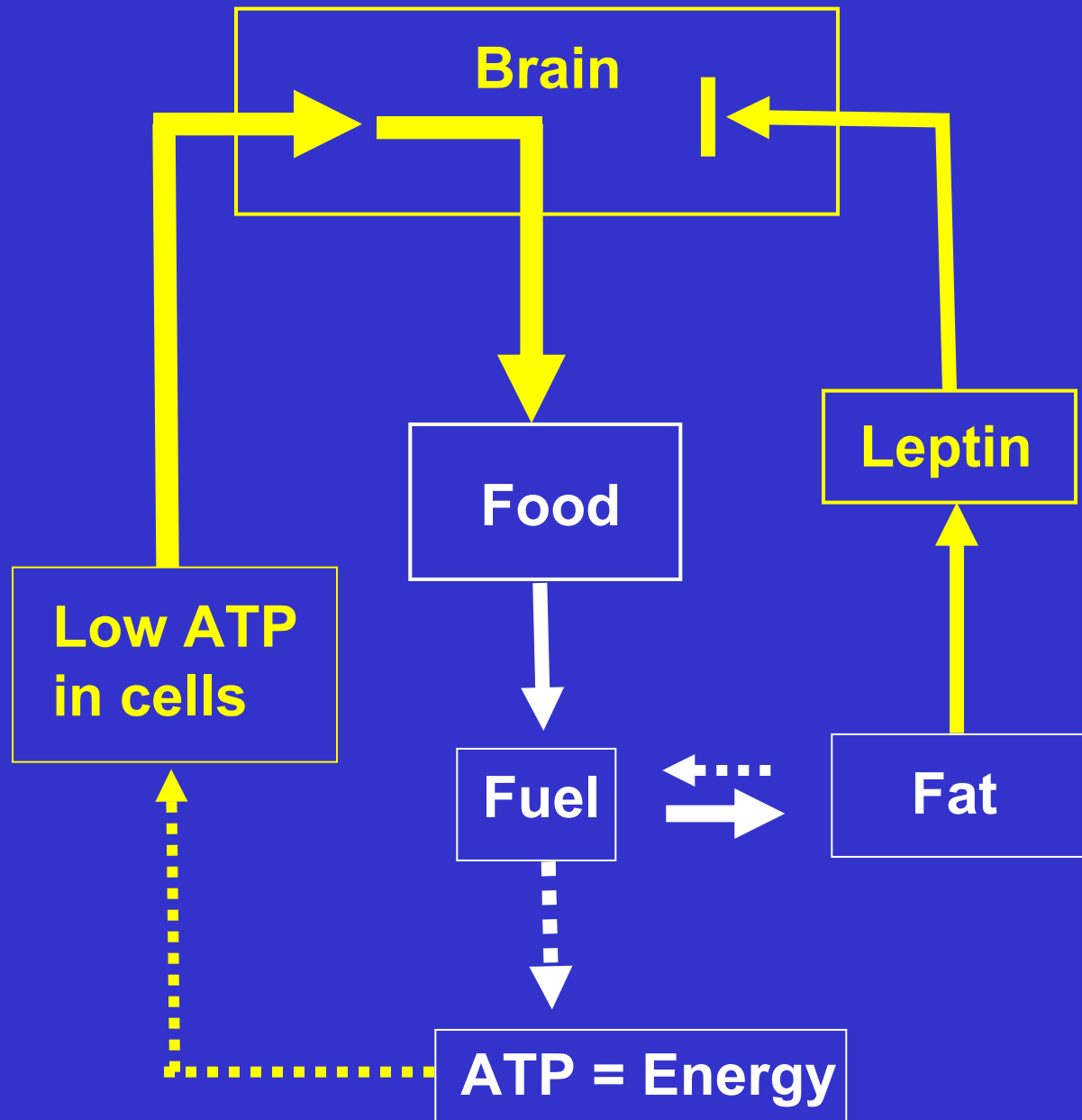
Decreased energy levels can cause and sustain obesity



Healthy subject



Obese subject



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.

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-Sánchez¹

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

Quindi? Stile di vita!

Abitudini alimentari

e

Attività fisica

Adherence to a Mediterranean Diet and Survival in a Greek Population

Antonia Trichopoulou, M.D., Tina Costacou, Ph.D., Christina Bamia, Ph.D., and Dimitrios Trichopoulos, M.D.

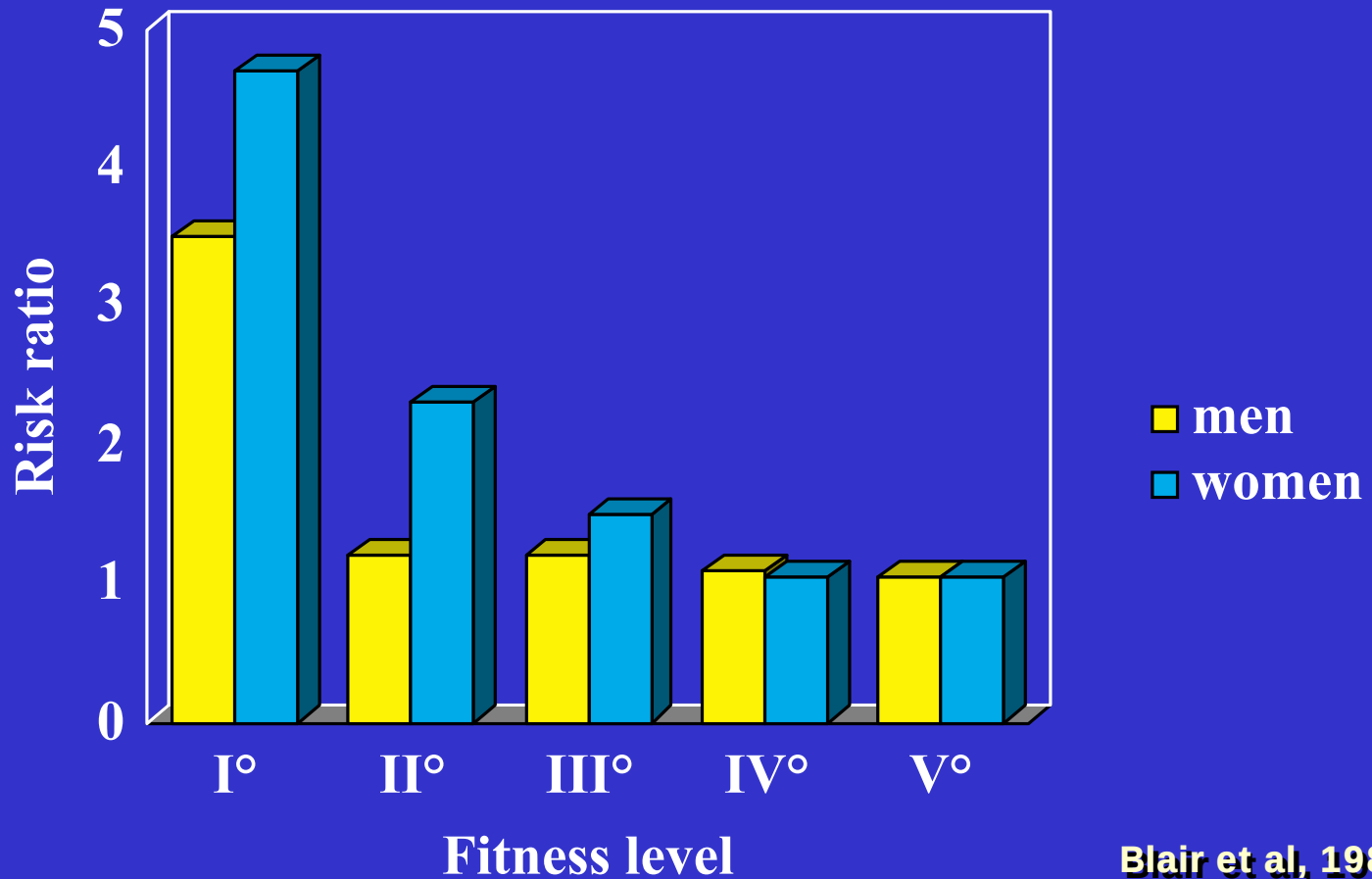
We conducted a population-based, prospective investigation involving 22,043 adults in Greece who completed an extensive, validated, food-frequency questionnaire at baseline.

During a median of 44 months of follow-up, there were 275 deaths. A higher degree of adherence to the Mediterranean diet was associated with a reduction in total mortality.

An inverse association with greater adherence to this diet was evident for both death due to coronary heart disease and death due to cancer.

Conclusions. Greater adherence to the traditional Mediterranean diet is associated with a significant reduction in total mortality.

Livello di attività fisica e rischio di mortalità



Blair et al, 1989

CAMPAGNA
STAMPA
sulla CORRETTA
ALIMENTAZIONE
IMMAGINI



**MAMMA,
DALLE TUTTO,
MA NON DARLE
TROPPO**

Benetton Group

'Sana e robusta costituzione' non vuol dire sovrappeso.

Vuol dire a tavola porzioni equilibrate, poco sale e meno grassi, tanta frutta e verdura.

La ricetta del benessere di tuo figlio è semplice.

Una dieta equilibrata migliora la vita.


Ministero della Salute
Campagna per gli stili di vita salutari

CAMPAGNA
STAMPA
sulla CORRETTA
ALIMENTAZIONE
IMMAGINI



**PAPÀ,
FALLO CORRERE...**

'Sana e robusta costituzione' non vuol dire sovrappeso.

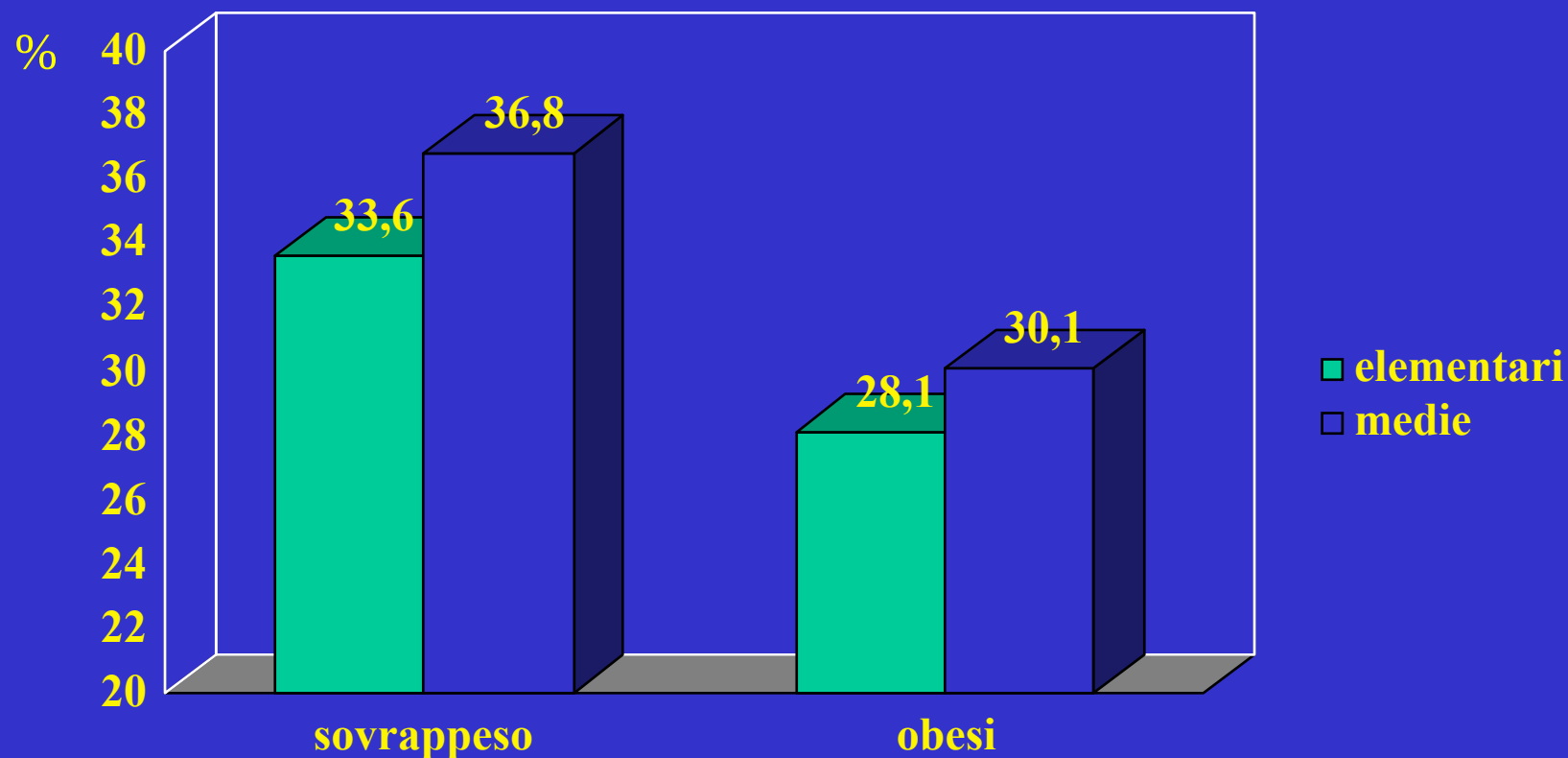
Vuol dire una dieta equilibrata, porzioni giuste e attività fisica
nella vita di tutti i giorni.

Combattere la pigrizia alimenta la vita.

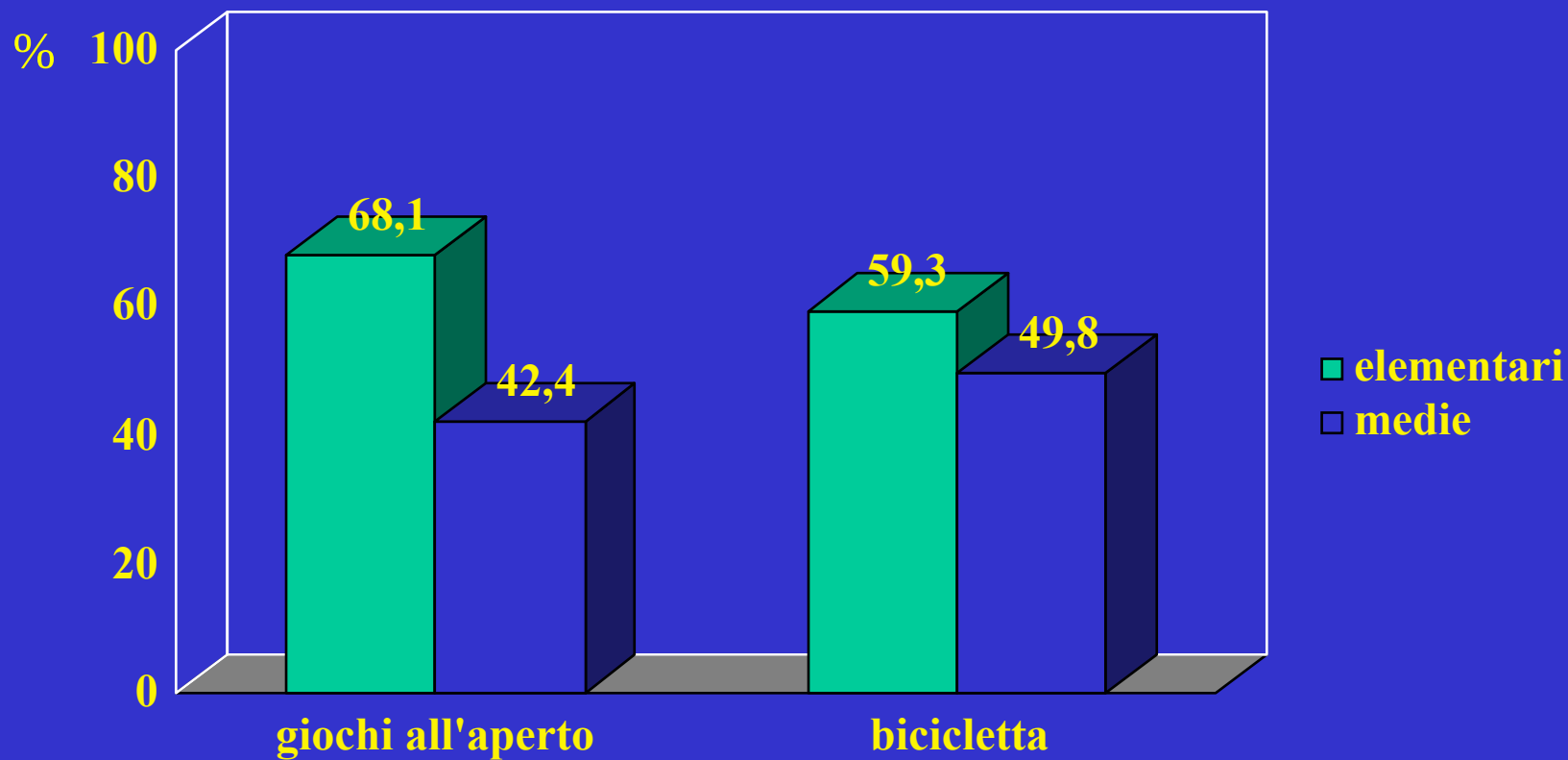
Il movimento è salute


Ministero della Salute
Campagna per gli stili di vita salutari

Prevalenza di sovrappeso e obesità in 1280 ragazzi di Legnago (2001, Vr)

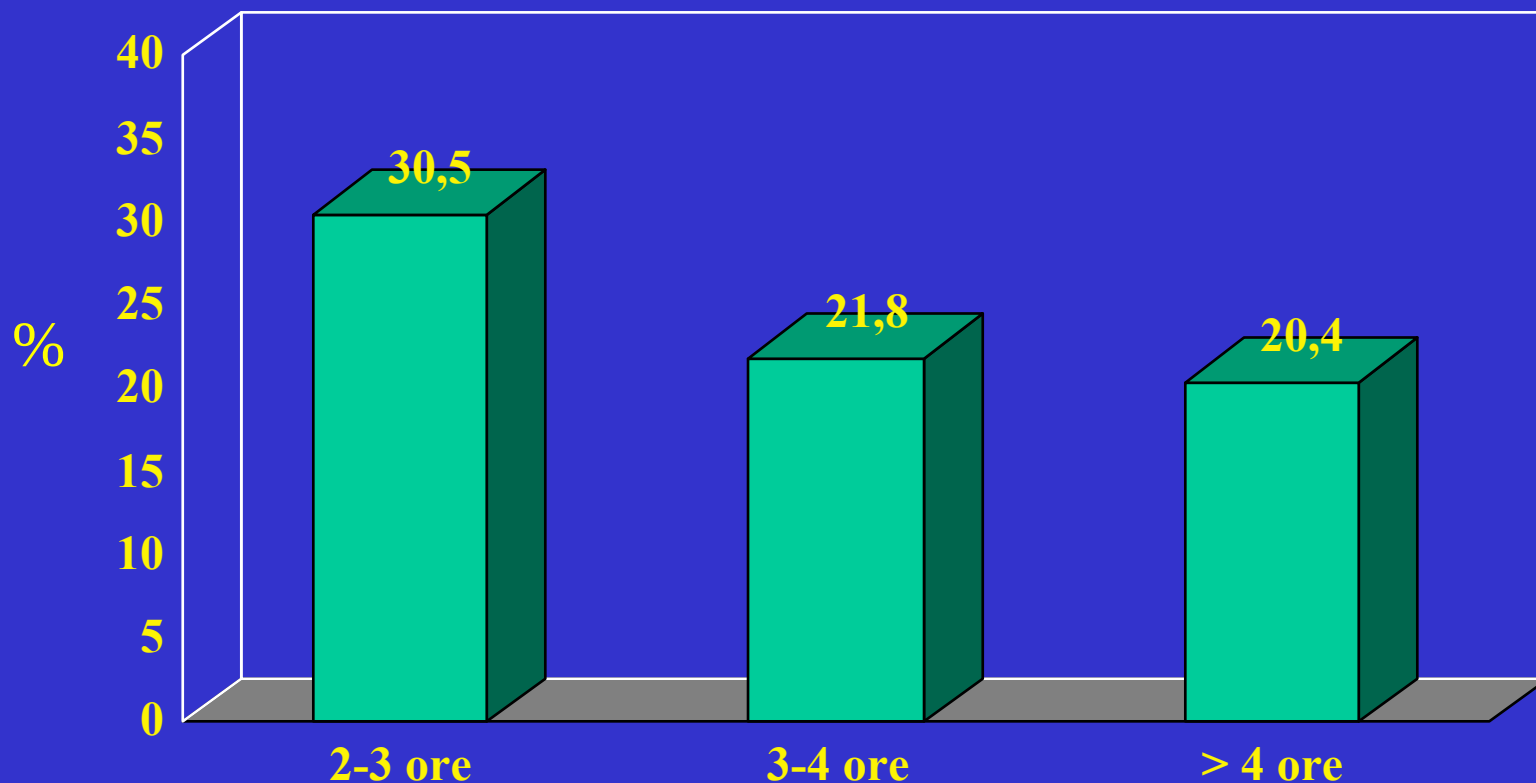


L'attività fisica in 1280 ragazzi di Legnago (2001, Vr)



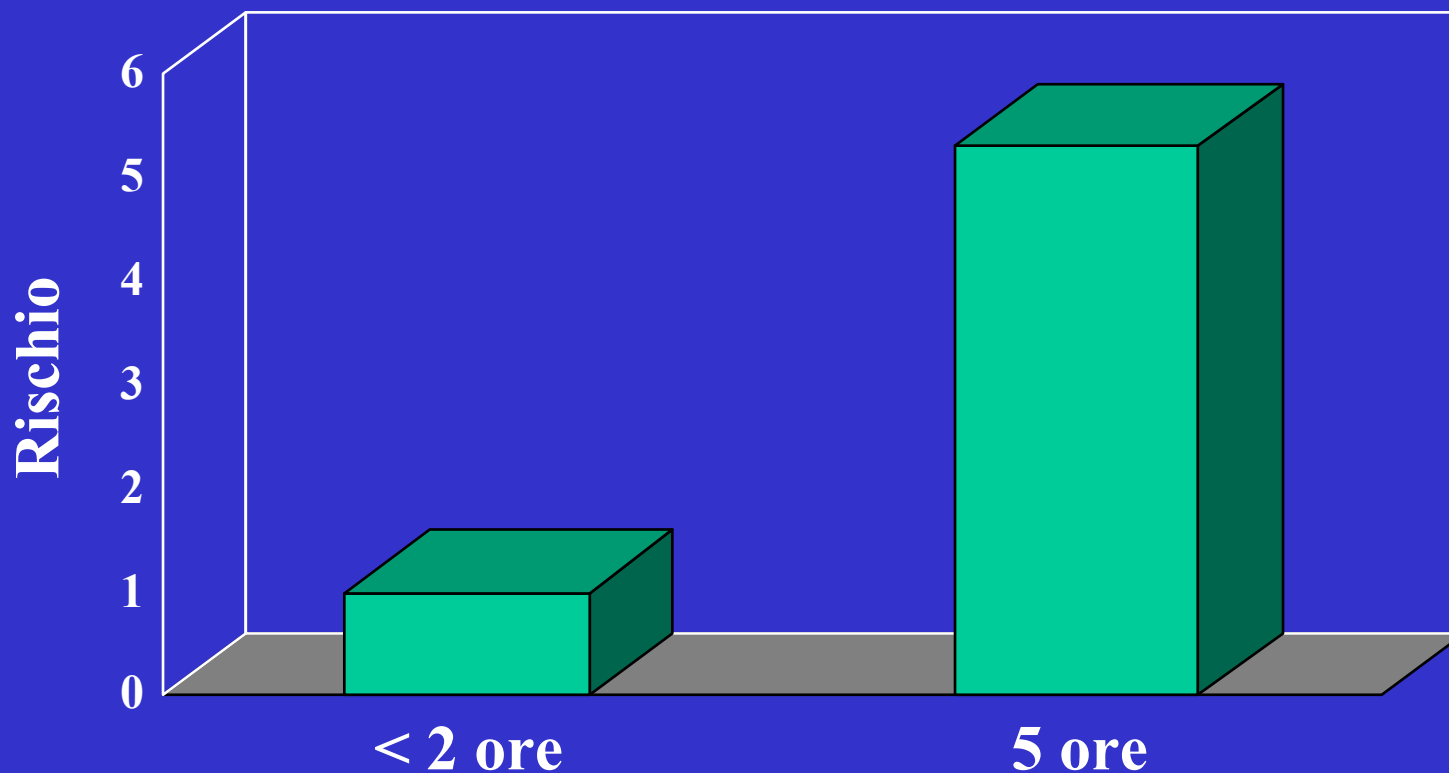
Tempo passato quotidianamente alla TV da ragazzi 6-14 anni

ISTAT, 2001

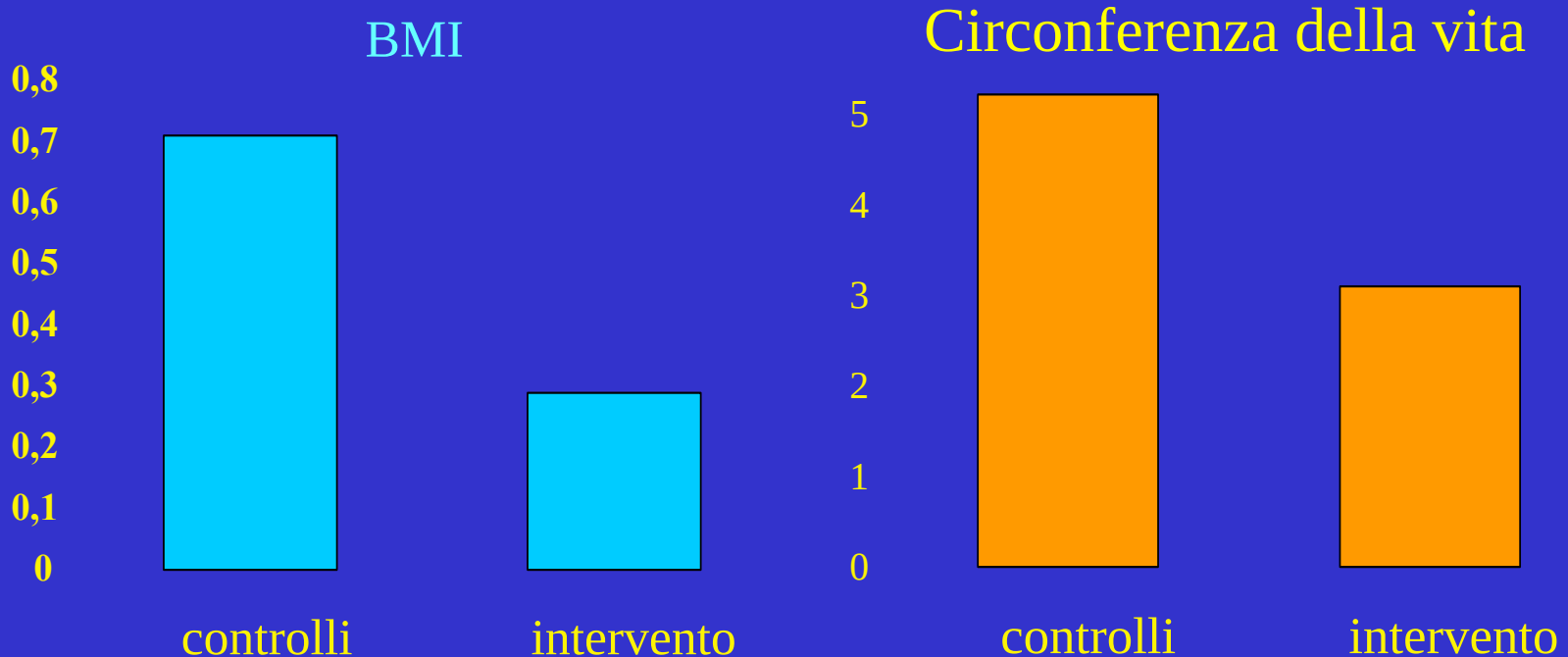


Tempo quotidiano dedicato alla TV e rischio di obesità in bambini di 6-10 anni

Dati pareggiati per livello socioeconomico



Effetto della riduzione del tempo dedicato alla Tv sull'aumento del BMI e della Circonferenza della vita in studenti di 3° e 4° elementare



Robinson, 1999