NUTRITIONAL EPIDEMIOLOGY

POSSIBILITIES AND LIMITATIONS

Definition of epidemiology

Epidemiology is the study of the distribution and determinants of diseases and other health outcomes in human populations. Epidemiology also deals with the natural history of diseases and it can provide evidence that contributes to their prevention.

Specific characteristics of nutritional epidemiology

Nutritional epidemiology can be defined as the study of the nutritional determinants of disease in human populations. It is one of the most exciting – and most difficult – types of epidemiological research.

Epidemiological studies showing protection by fruits and vegetables against cancer

Cancer site	Fraction of studies showing protection
Epithelial	
Lung	24/25
Oral	9/9
Larynx	4/4
Esophagus	15/16
Stomach	17/19
Pancreas	9/11
Cervix	7/8
Bladder	3/5
Colorectal	20/35
Miscellaneous	6/8
Hormone-dependent	
Breast	8/14
Ovary/endometrium	3/4
Prostate	1/14
Total	129/172

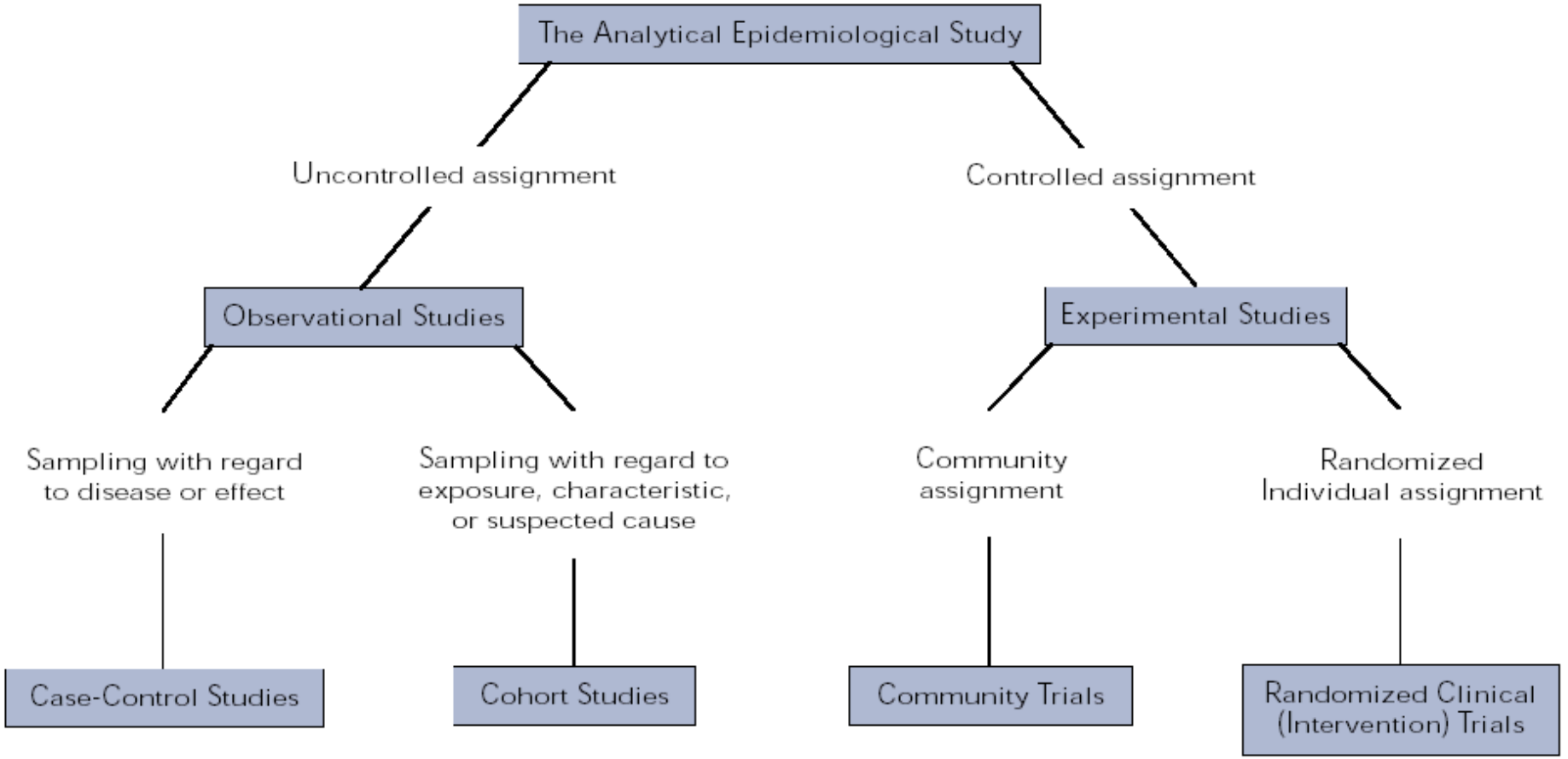
The complex nature of diet

A major difficulty of nutritional epidemiology lies in the extremely complex nature of diet. To appreciate this complexity, it is helpful to compare diet with another exposure that also influences the risk of many of the same diseases – cigarette smoking.

An epidemiologist who is studying tobacco can obtain a great deal of useful information simply by asking people, "Do you smoke?" By collecting a few additional pieces of information – the number of cigarettes smoked per day, the types or brands of cigarettes smoked, the age at which the person began (or stopped) smoking and any changes that may have occurred in the pattern of cigarette use – the researcher can obtain a clear, reasonably accurate picture of an individual's smoking history.

FIGURE 3

Types of epidemiological studies

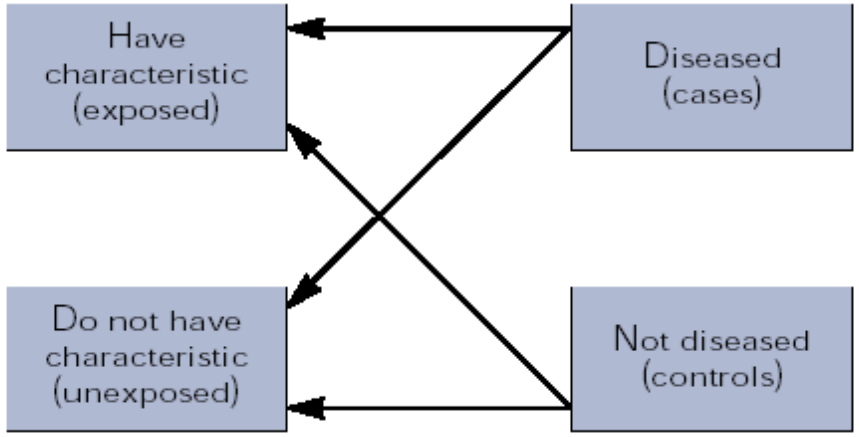


Source: Lilienfeld DE, Foundations of Epidemiology, © D. Lilienfeld 1994 (Used by permission of Oxford University Press)

Observational Studies

FIGURE 4

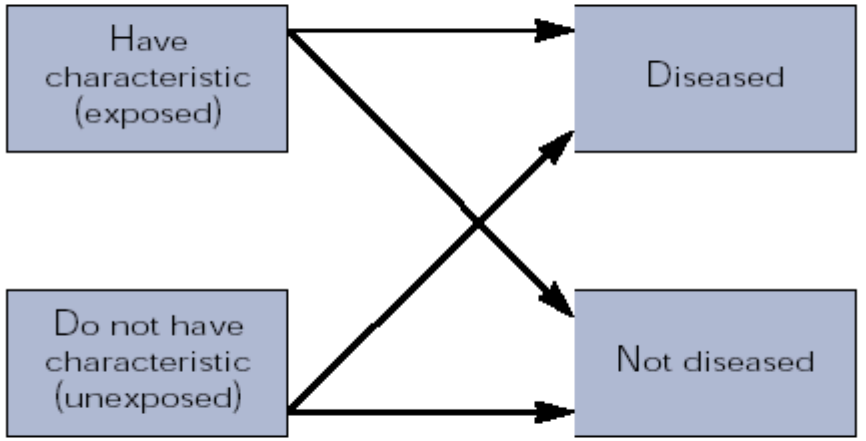
The basic principle of case-control studies



Source: Ahlbom A, Norell S, Introduction to Modern Epidemiology, (© Newton Lower Falls, MA: Epidemiology Resources, Inc., 1984).

FIGURE 5

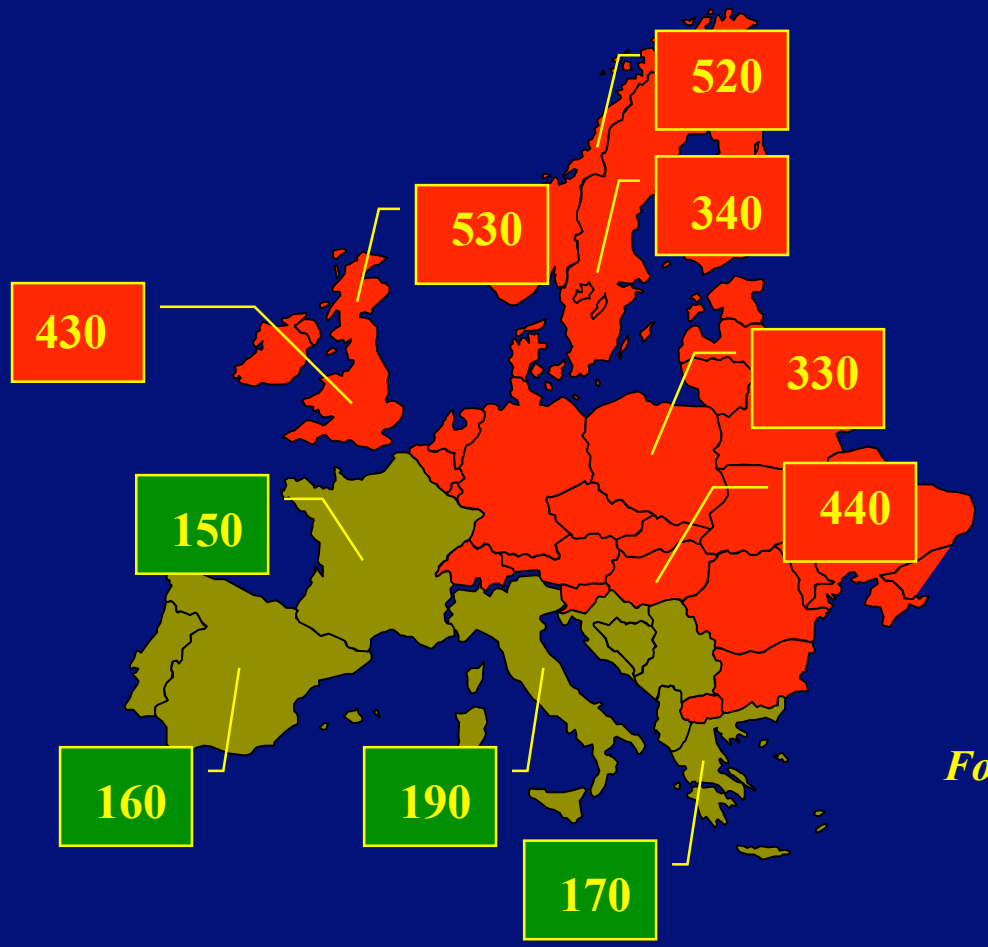
The basic principle of cohort studies



Source: Ahlbom A, Norell S, Introduction to Modern Epidemiology, (© Newton Lower Falls, MA: Epidemiology Resources, Inc., 1984).

MORTALITA' PER MALATTIE CARDIOVASCOLARI IN EUROPA

(per 100.000 persone/anno)



Fonte: OMS, 1985

Golfo di Biscaglia
PIRENEI
Golfo del Leone
MAR LIGURE
Bocche di Bonifacio
BALEARI
MINORCA
MAIORCA
Bacino Algerino
M A R
MAR TIRRENO
PENISOLA ITALIANA
MAR ADRIATICO
PENISOLA BALCANICA
Alpi Transilvane
Valacchia
Bulgaria
Tracia
MAR IONIO
Peloponneso
CRETA
PANTELLERIA
MALTA
LAMPEDUSA
M E D I T E R R A N E O
Atlante del Tell
A L G E R I A
Atlante Sahariano
G. di Gabès
Tripoli
Gebel Nefusa
Tripolitania
Golfo della Sirte
Bengasi
Cirenaica
Marmarica
Grande Erg Occidentale
Grande Erg Orientale

The Seven Countries Study of Cardiovascular Diseases

The origins

- Created and coordinated by Prof Ancel Keys, University of Minnesota
- Started in the late 1950's, early 1960's
- 16 cohorts of men aged 40-59 enrolled in 7 countries (8 nations) for a total of 12763 subjects in:
- United States, Finland, the Netherlands, Italy, Croatia (former Yugoslavia), Serbia (former Yugoslavia), Greece, Japan

The Seven Countries Study of Cardiovascular Diseases

Objectives

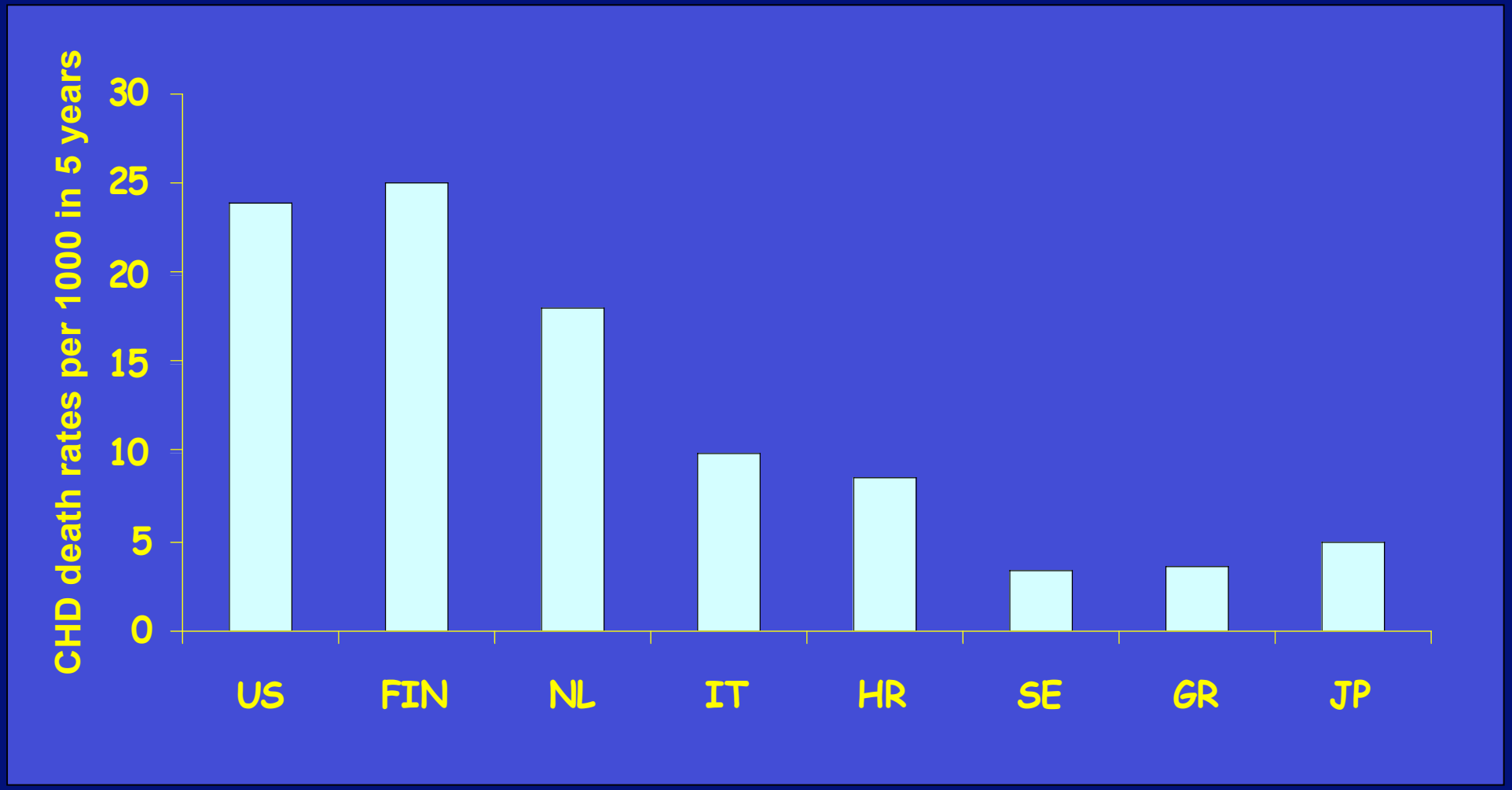
- To establish whether culturally different populations suffer different amount of the disease (prevalence, incidence, mortality).
- To establish whether these differences, if true, are explained by life-style, eating habits and other characteristics of the populations.
- To establish whether, within populations, some personal characteristics (risk factors) were predictive of subsequent cardiovascular events.

The Seven Countries Study of Cardiovascular Diseases

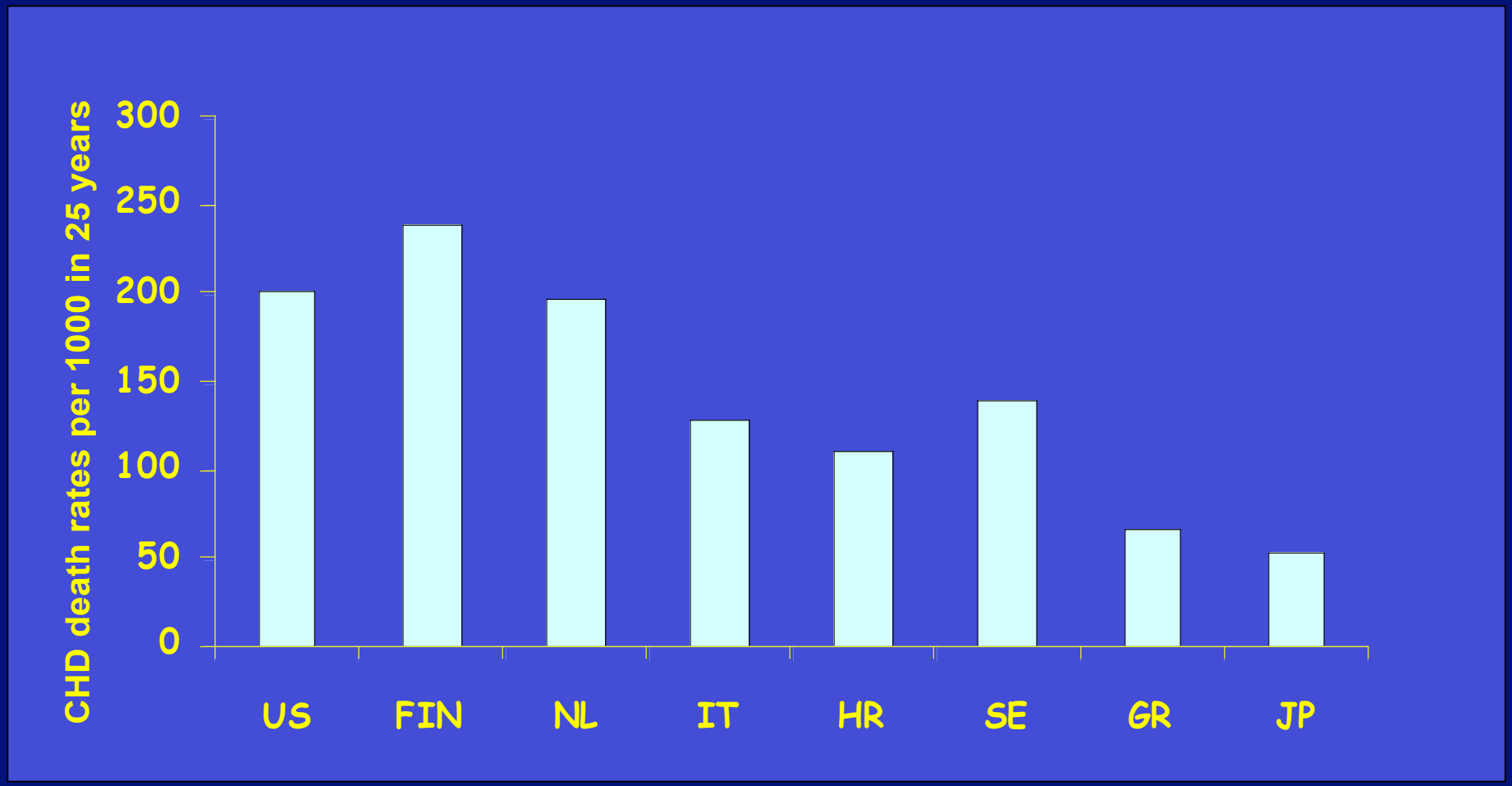
Dietary data collection

- Was run on sub-samples of each cohort.
- In 13 cohorts the 7-day record method was used.
- In 1 cohort (US) the 1-day record method was used.
- In 2 cohorts (Japan) the 4-day record method was used.

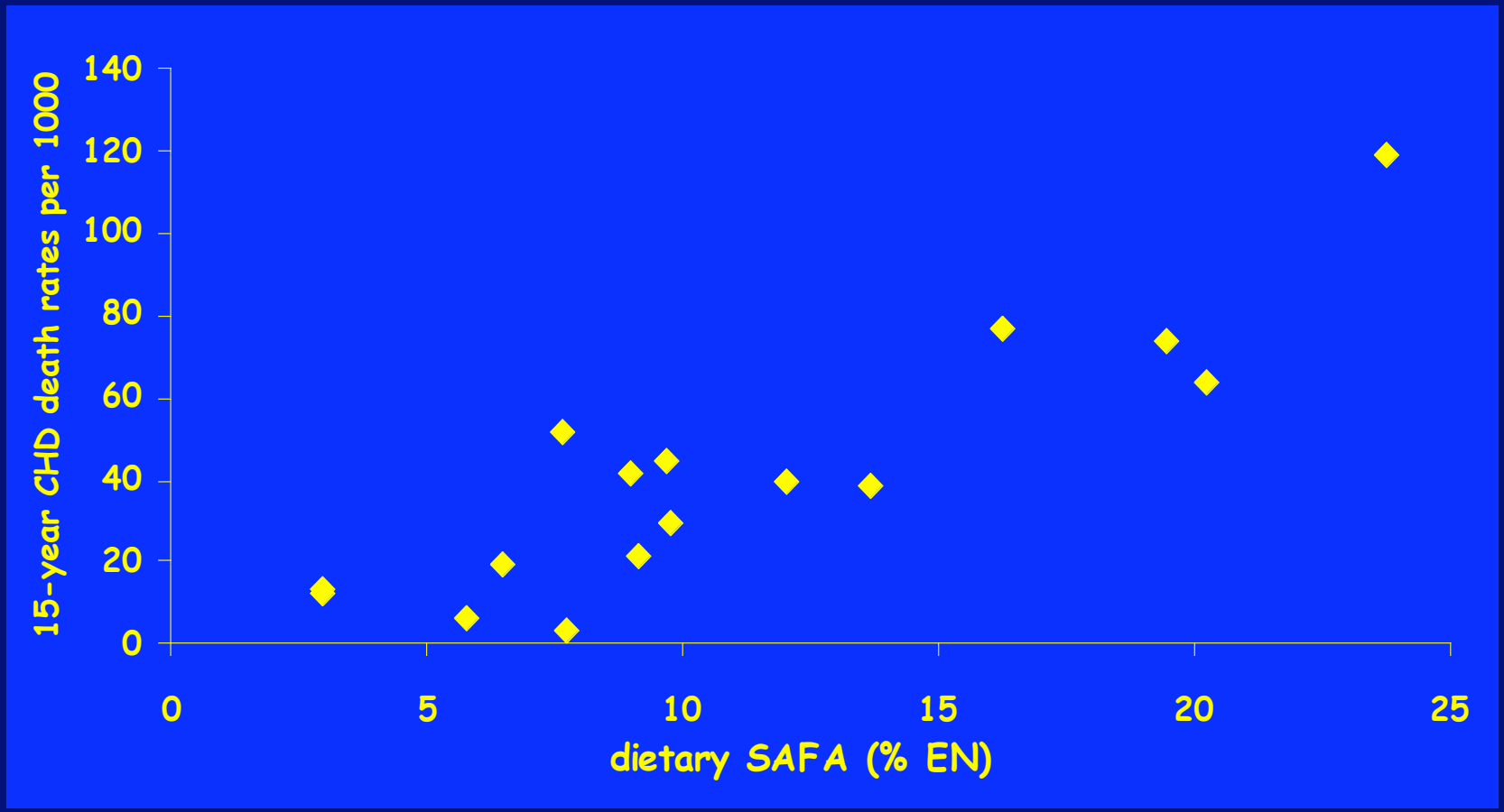
CHD mortality rates in 5 years in 8 nations of the Seven Countries Study.



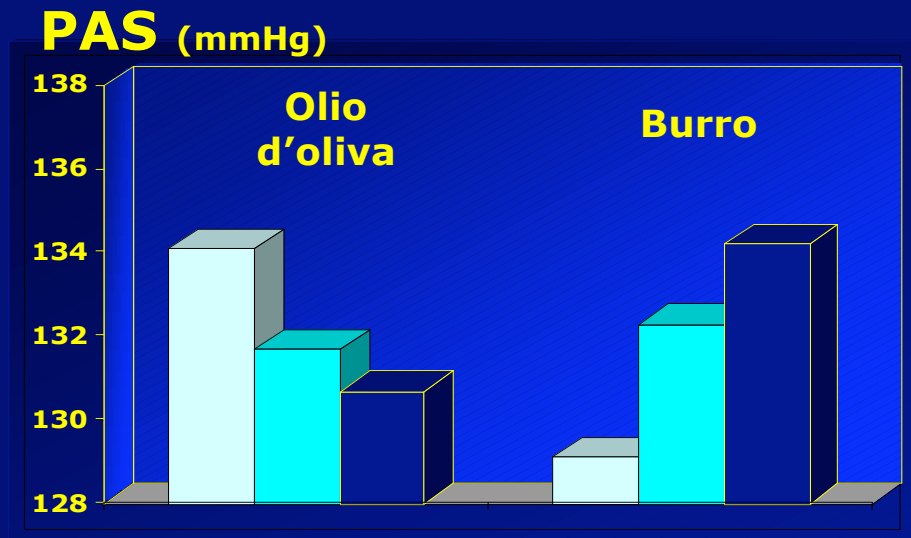
CHD mortality rates in 25 years in 8 nations of the Seven Countries Study.

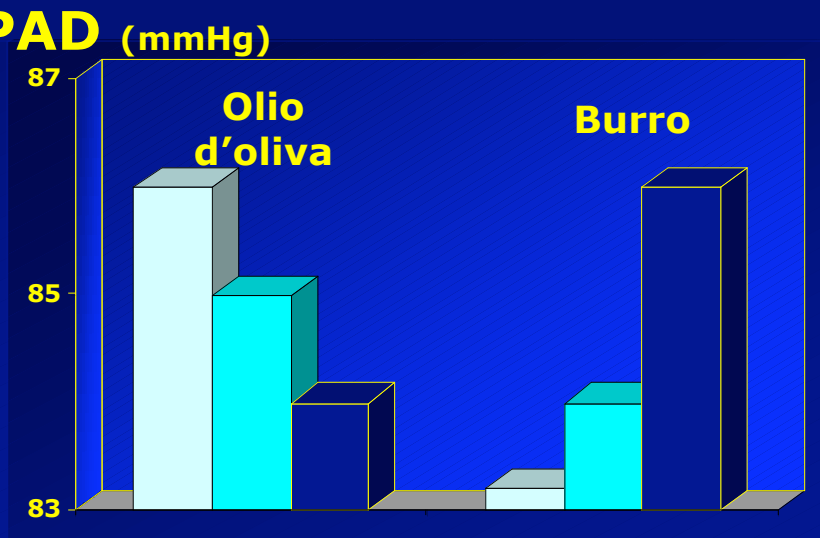


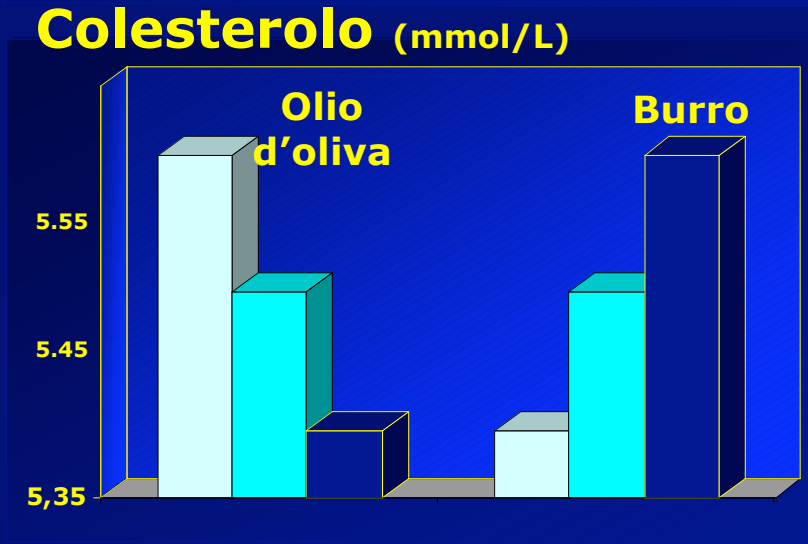
Correlation between dietary SAFA and 15-year CHD mortality in 16 cohorts of the Seven Countries Study

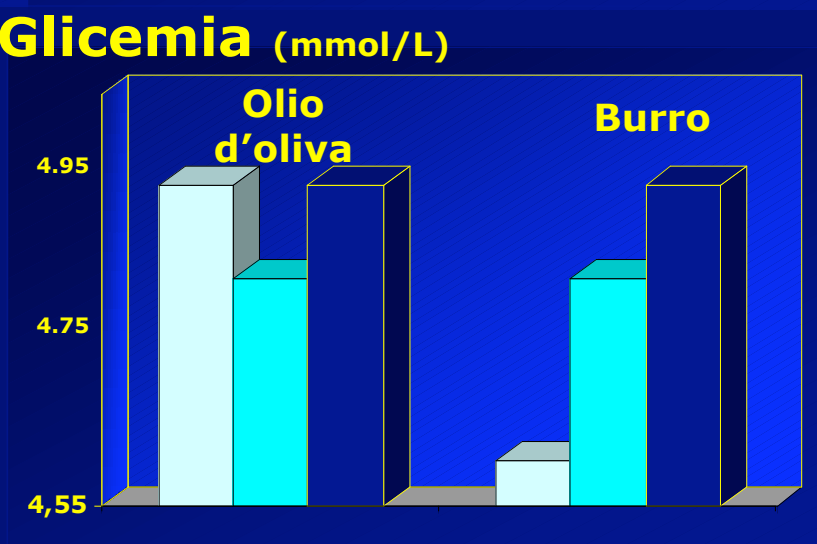


Fattori di rischio per cardiopatia ischemica in base al consumo di grassi *(The Italian Nine Communities Study)*





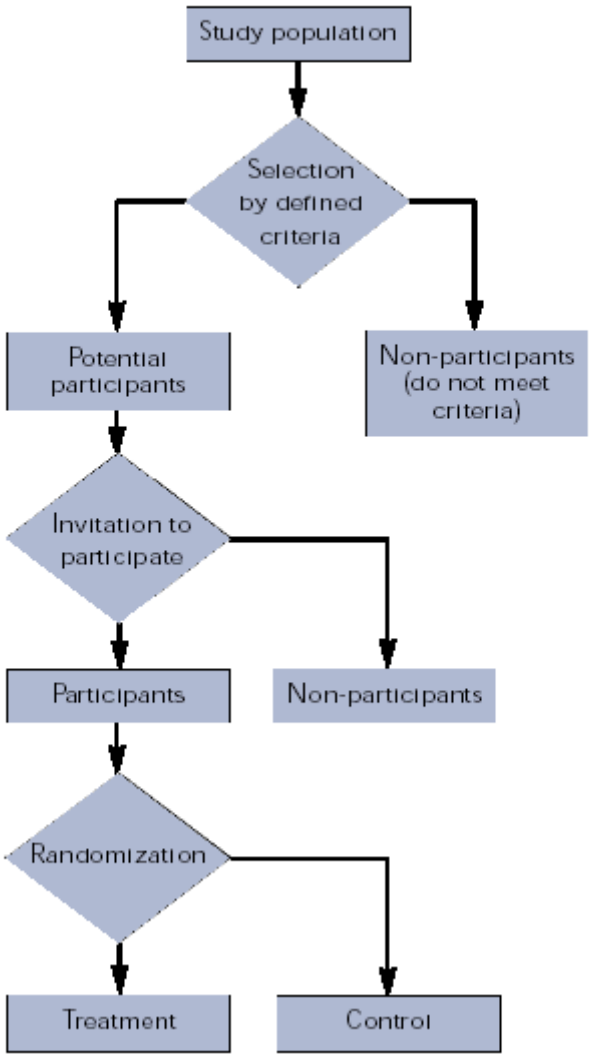




Categorie di consumo: Basso Medio Elevato

M. Trevisan et al. JAMA, 199

Design of a randomized intervention trial



Advantages of intervention trials

The key advantage of intervention trials is that they can provide direct evidence of a cause-and-effect relationship. If the subjects are randomly assigned to the treated and control groups and if blinding is successful, one can assume that any difference that develops between the members of the two groups is directly attributable to the factor under investigation.

CHANGING THE MEDITERRANEAN DIET...
The POLLICA Study

ISA, Epidemiologia e Genetica delle Popolazio

CHANGING THE MEDITERRANEAN DIET...
The POLLICA Study

SCOPO

- valutare gli effetti di modificazioni dei grassi alimentari sui lipidi plasmatici e sulla pressione arteriosa

POPOLAZIONE

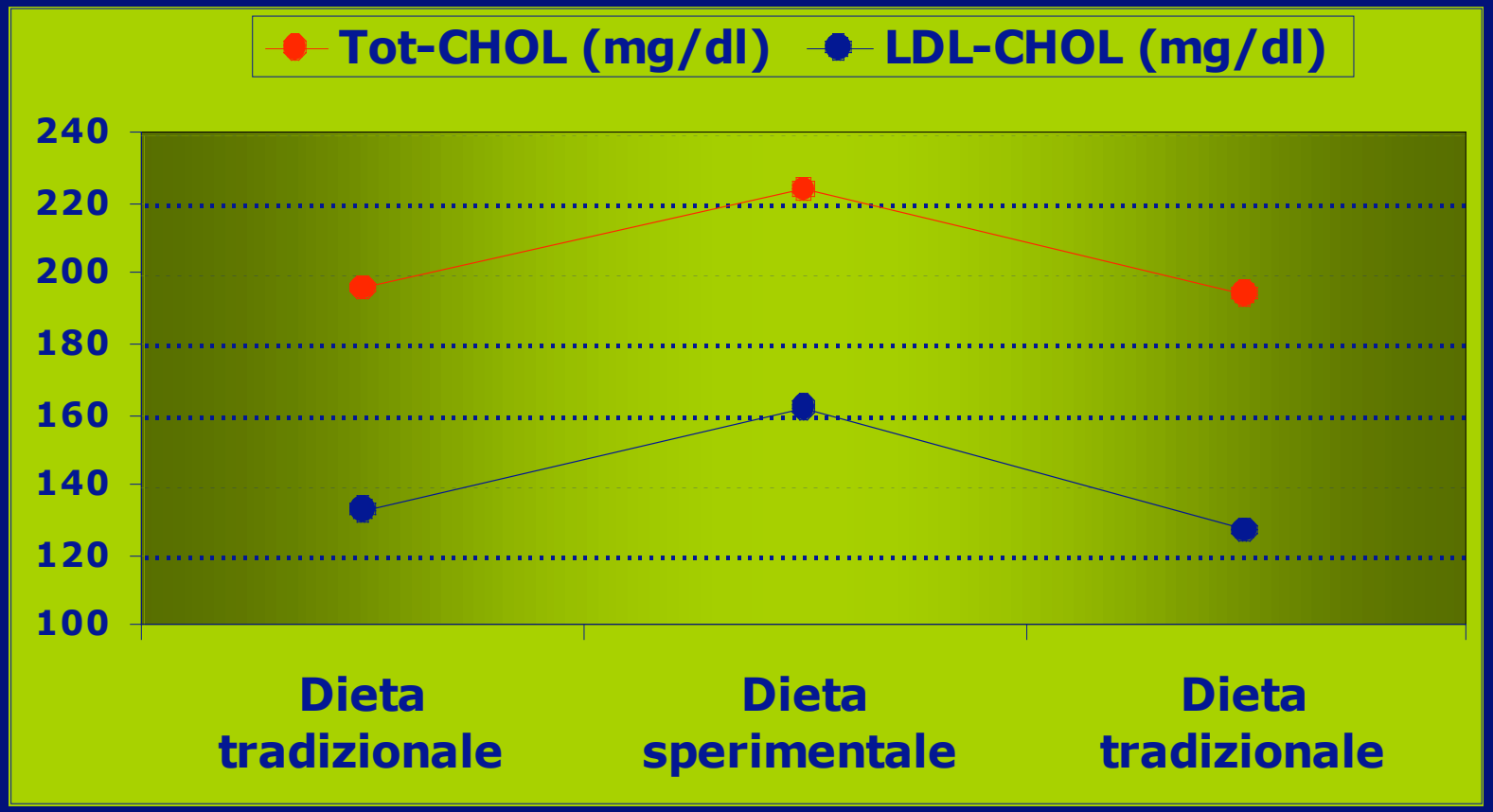
- 58 volontari sani abitanti nel comune di Pollica (Parco Nazionale del Cilento, Salerno)

DIETA SPERIMENTALE

- MENO cibi tradizionali di origine vegetale (in particolare olio d'oliva)
- PIU' alimenti ricchi di grassi saturi di origine animale (burro, panna)

CHANGING THE MEDITERRANEAN DIET: EFFETTI SUI LIPIDI PLASMATICI

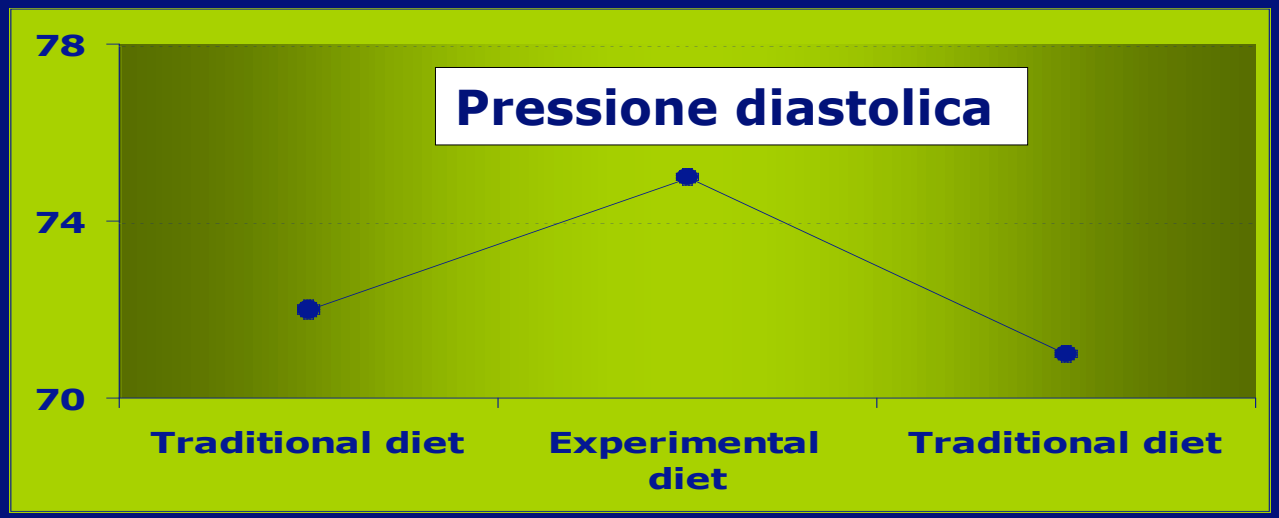
The Pollica Study



Ferro-Luzzi et al, Am J Clin Nutr, 1984

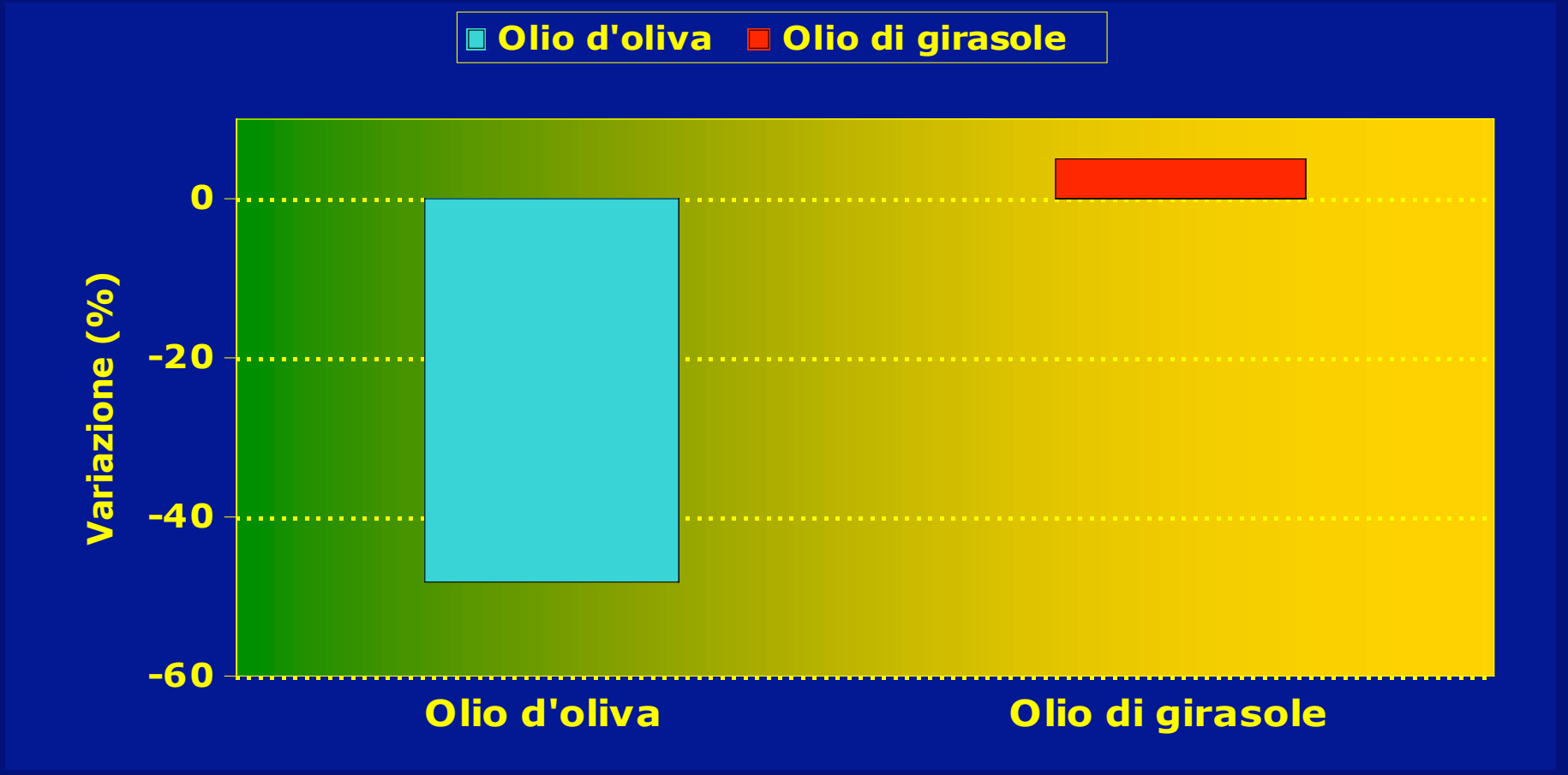
CHANGING THE MEDITERRANEAN DIET: EFFETTI SULLA PRESSIONE

The Pollica Study



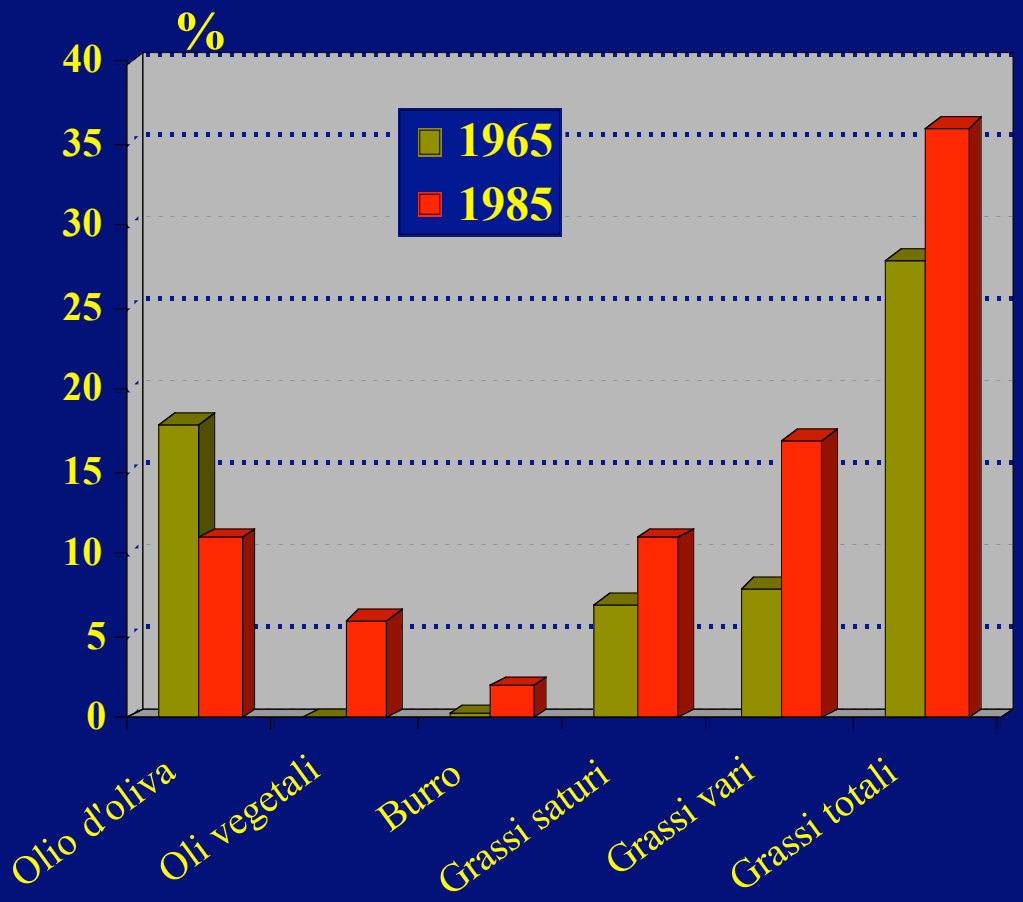
Strazzullo et al, J Hypertension, 1986

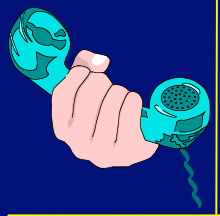
Variazioni nel consumo quotidiano di farmaci in pazienti ipertesi in corso di 6 mesi di dieta ricca in olio extra-vergine d'oliva o olio di girasole



Ferrara et al. *Arch Intern Med* 2000; 160: 837-842

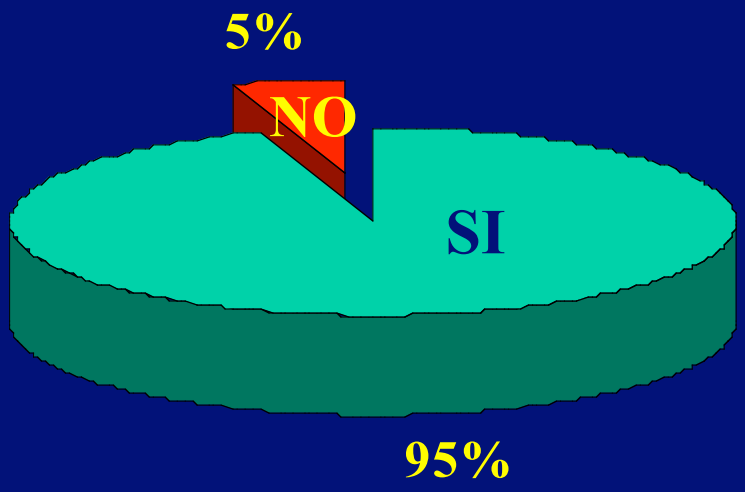
VARIAZIONI DEL CONTENUTO IN GRASSI NELLA DIETA DELL'ITALIA MERIDIONALE E INSULARE



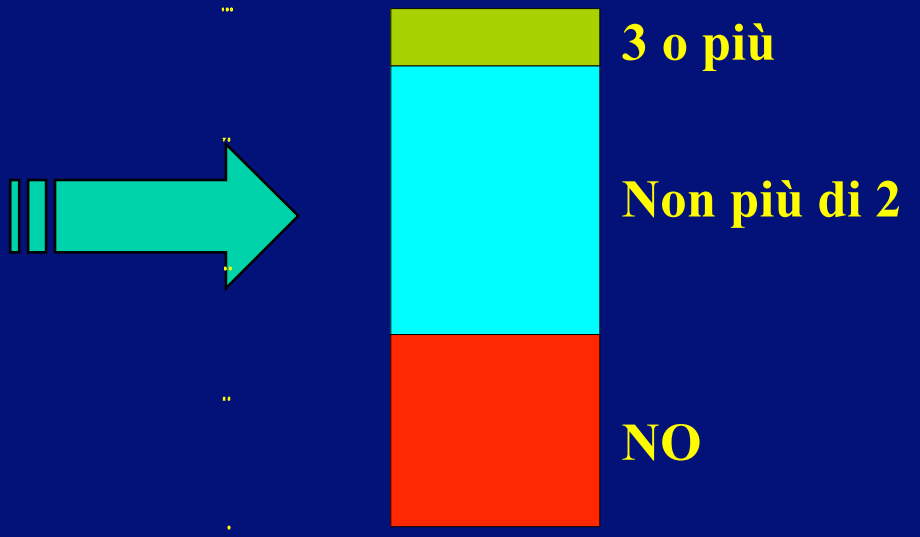


INFORMAZIONE & SALUTE: ***indagine conoscitiva sul livello di conoscenza de ruolo della nutrizione nella prevenzione delle malattie cardiovascolari condotta in aree urbane e rurali dell'Italia meridionale*** *(Barba et al, Ital Heart J 2001; 2:546-552)*

Pensate che un elevato contenuto di grassi animali nella dieta sia pericoloso per la salute ?



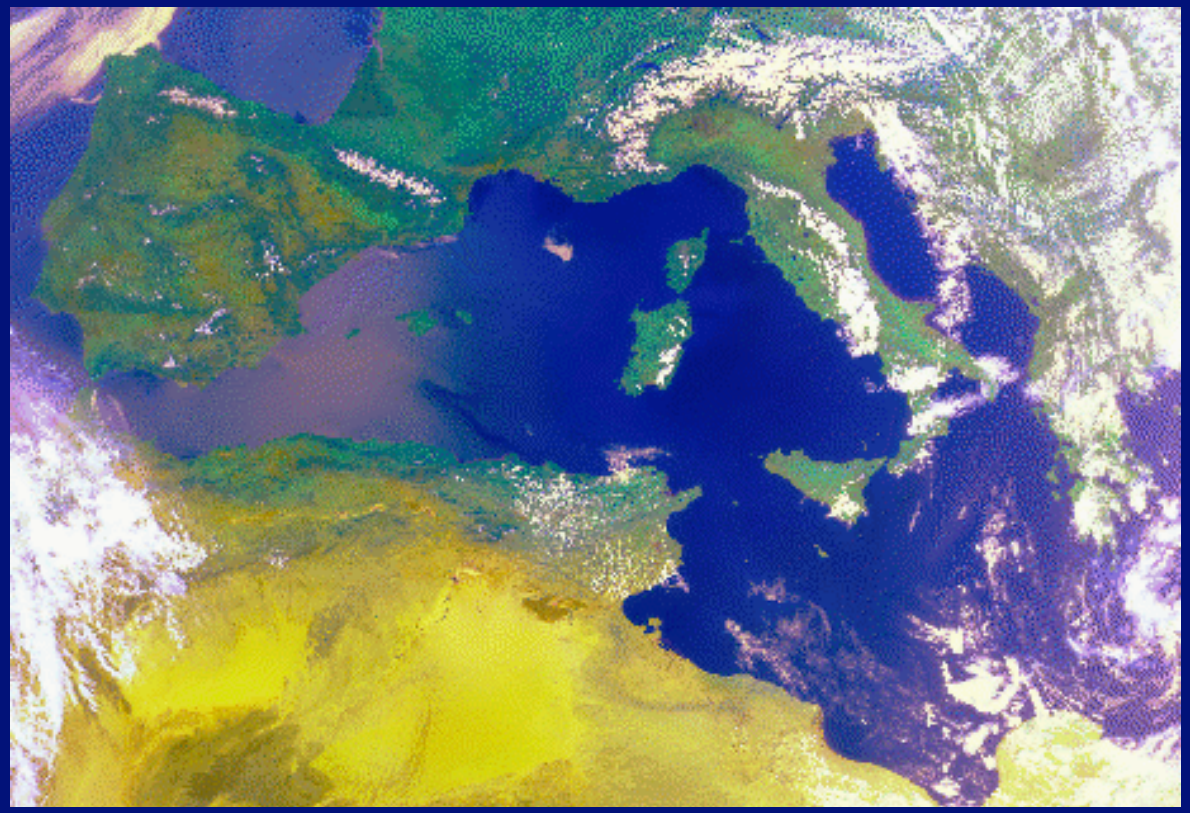
Sapete indicare uno o più alimenti ricchi in grassi animali ?



Summary:

- Numerous comparisons between populations have shown that there is a strong correlation between the intake of saturated fatty acids (SFA) and CHD morbidity and mortality.
- A customary diet high in SFA is associated with high levels of CHD. This is the case for the most Western and Northern European countries.
- On the other hand, in the Mediterranean countries, where people consume their traditional diet in which the majority of fat calories is derived from olive oil, there is a low incidence of CHD.

Consiglio Nazionale delle Ricerch



LA DIETA MEDITERRANEA:

PATRIMONIO DELLA TRADIZIONE E RISORSA PER IL FUTURO

ISA, Epidemiologia e Genetica delle Popolazion

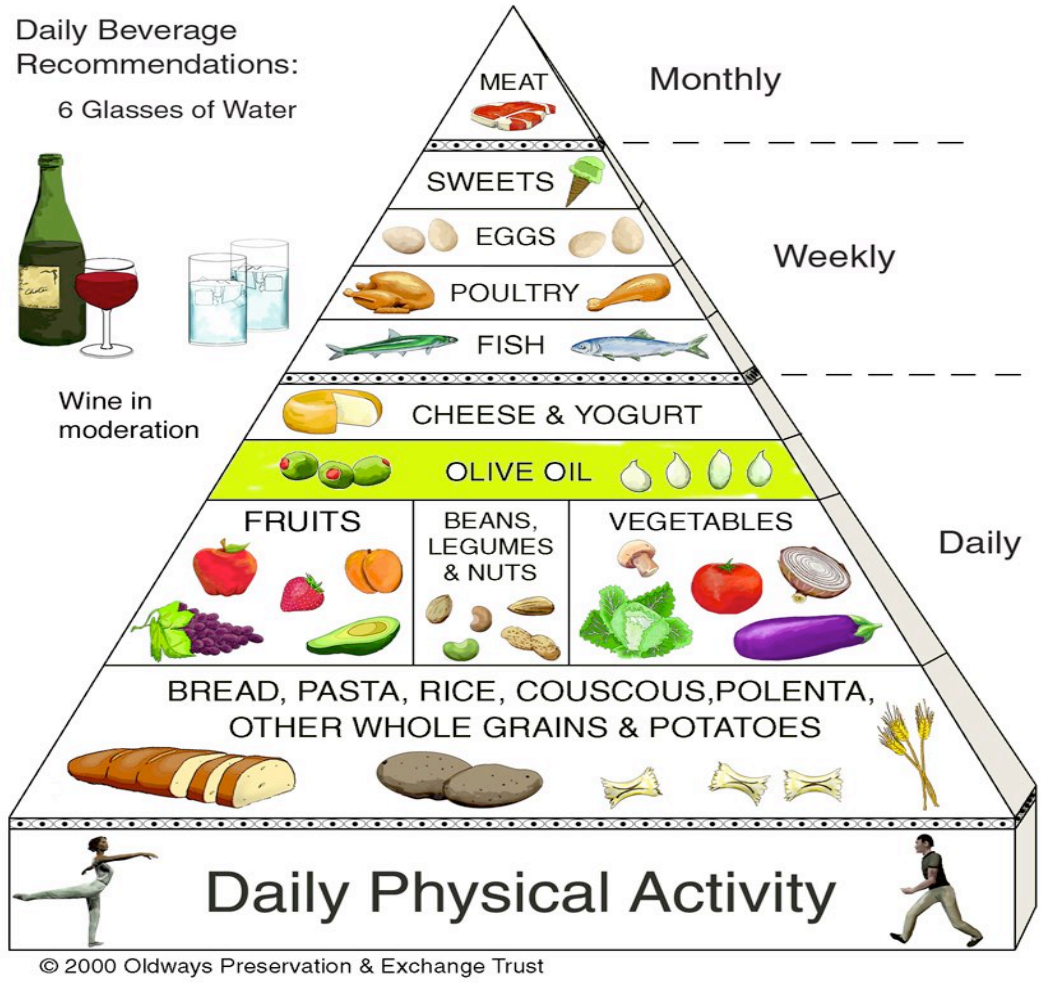
Documento di Consenso Internazionale "Olio di oliva e Dieta Mediterranea: implicazioni per la salute in Europa".

•Da un punto di vista scientifico, si definisce DIETA MEDITERRANEA la diet abitualmente consumata in Italia Meridionale e Insulare e in Grecia durante g anni '50.

•La dieta mediterranea tradizionale è caratterizzata dall'abbondanza di alimenti vegetali come pane, pasta, verdure, insalate, legumi, frutta e frutti secchi; olio di oliva come fonte primaria di grassi, un moderato consumo di pesce, di carne bianca, di latticini e uova, moderate quantita di carne rossa e modesto consumo di vino durante i pasti.

•Questa dieta ha un basso contenuto di acidi grassi saturi, è ricca in carboidrati e fibra, e ha un alto contenuto di acidi grassi monoinsaturi che derivano principalmente dall´olio d´oliva.

The Traditional Healthy Mediterranean Diet Pyramid



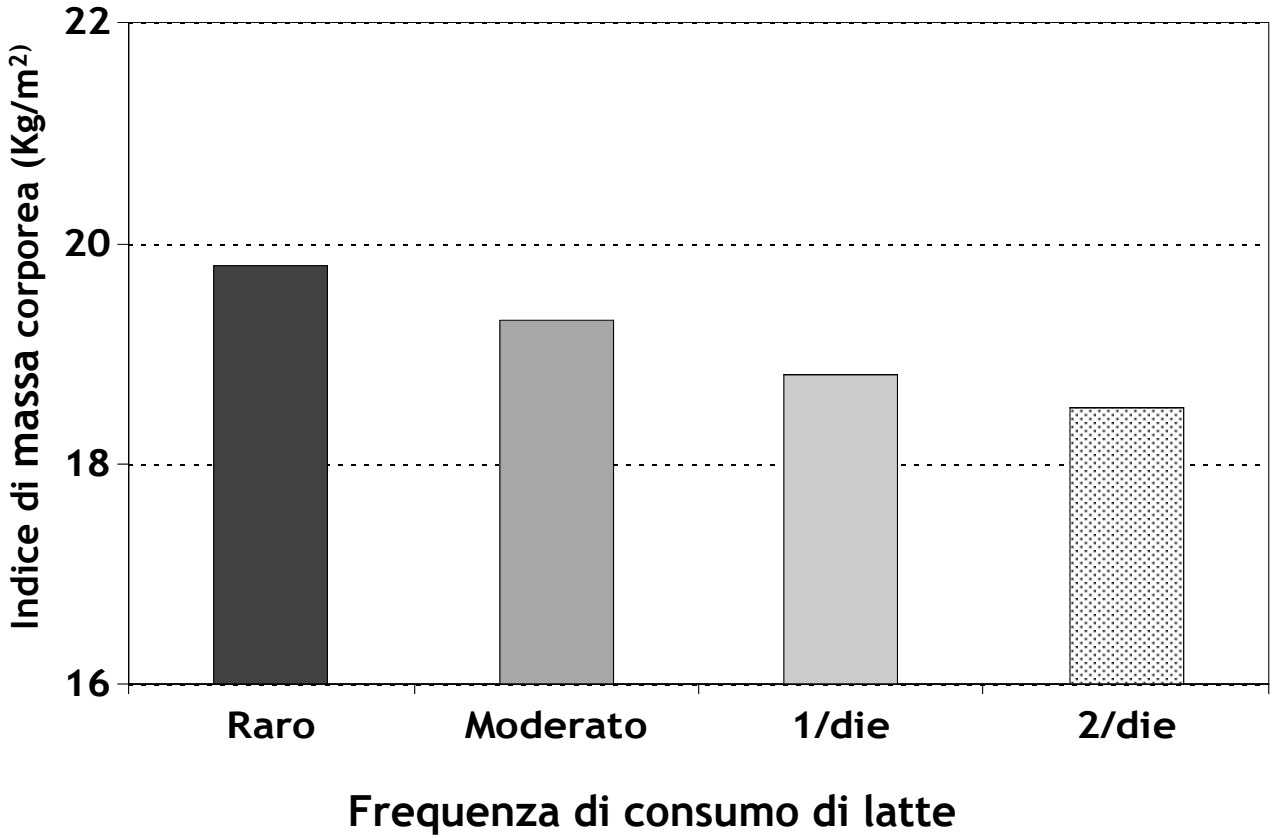
Guidelines for causation

Temporal relation	Does the cause precede the effect?
Plausibility	Is the association consistent with other knowledge?
Consistency	Have similar results been shown in other studies?
Dose-response relationship	Is increased exposure to the possible cause associated with increased effect?
Reversibility	Does the removal of a possible cause lead to reduction of disease risk?
Study design	Is the evidence based on a strong study design?
Judging the evidence	How many lines of evidence lead to the conclusion?

Inverse association between body mass and frequency of milk consumption in children

British Journal of Nutrition (2005), **93**, 15–19

Gianvincenzo Barba*, Ersilia Troiano, Paola Russo, Antonella Venezia and Alfonso Siani



Working hypotheses….

Calcium-linked mechanisms

- Low dietary Ca intake stimulates lipogenesis and fat accumulation
- Calcitrophic hormones, such as parathyroid hormone and 1,25 dihydroxyvitamin D, migh influence lipid metabolism in the adipocyte, independently of dietary Ca
- Supplemental dietary Ca has been shown to influence dietary fat absorption

Other plausible mechanisms:

- Bioactive compounds in milk (ACE inhibitory peptides).They limit angiotensin II product and thereby the angiotensin II stimulation of adipocyte lipogenesis.
- Milk also promotes insulin-like growth factor production

Finally, milk consumption could be a marker of other factors either not measured (or mismeasured) in the present study or as yet unidentified.

> Regardless of the mechanisms, our findings may encourage further research on the mechanisms of the milk-mediated regulation of body mass and might have important implications for the prevention of both childhood and adult obesity.

Nuove frontiere dell'epidemiologia nutrizionale: la nutrigenomica

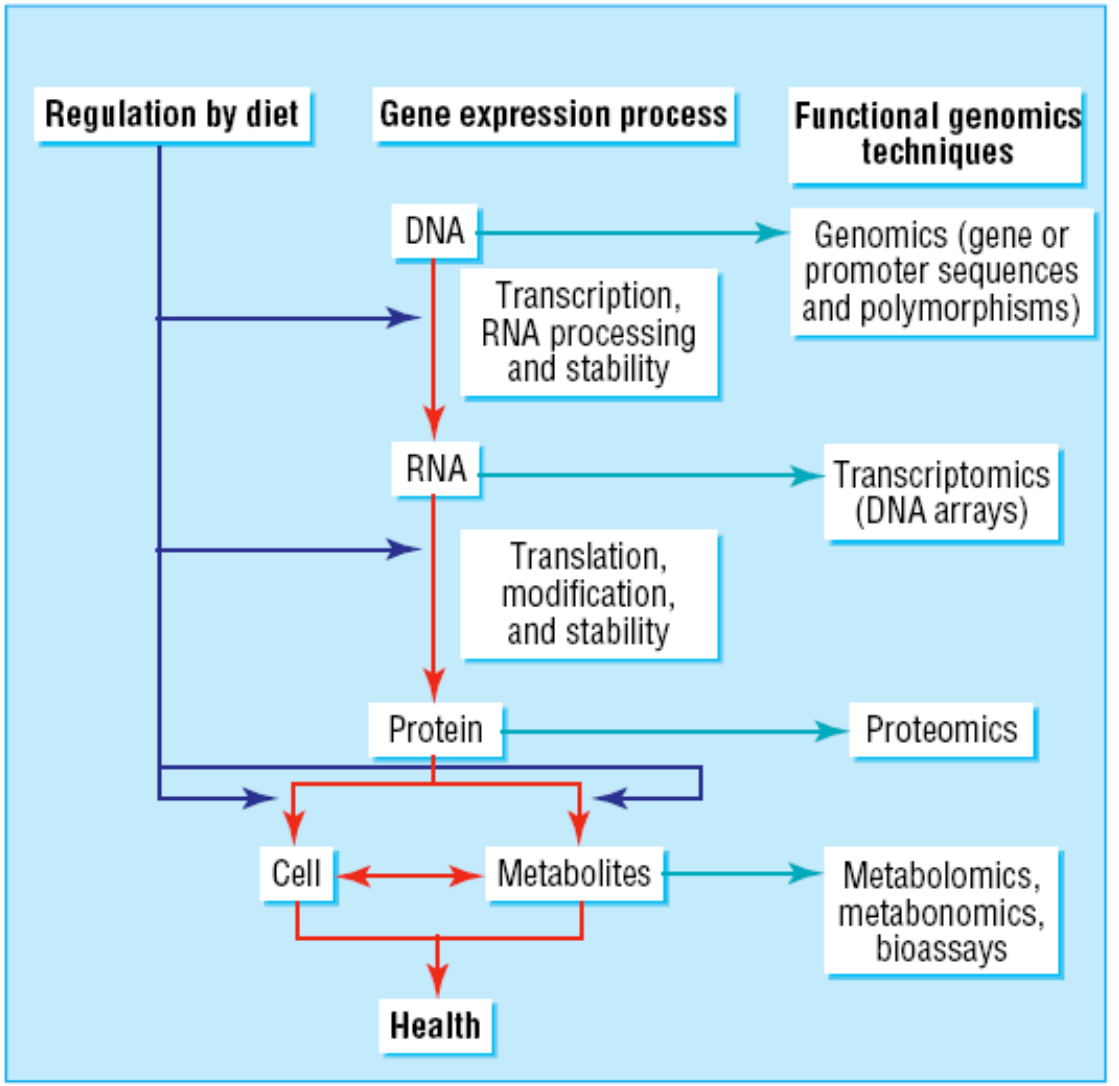


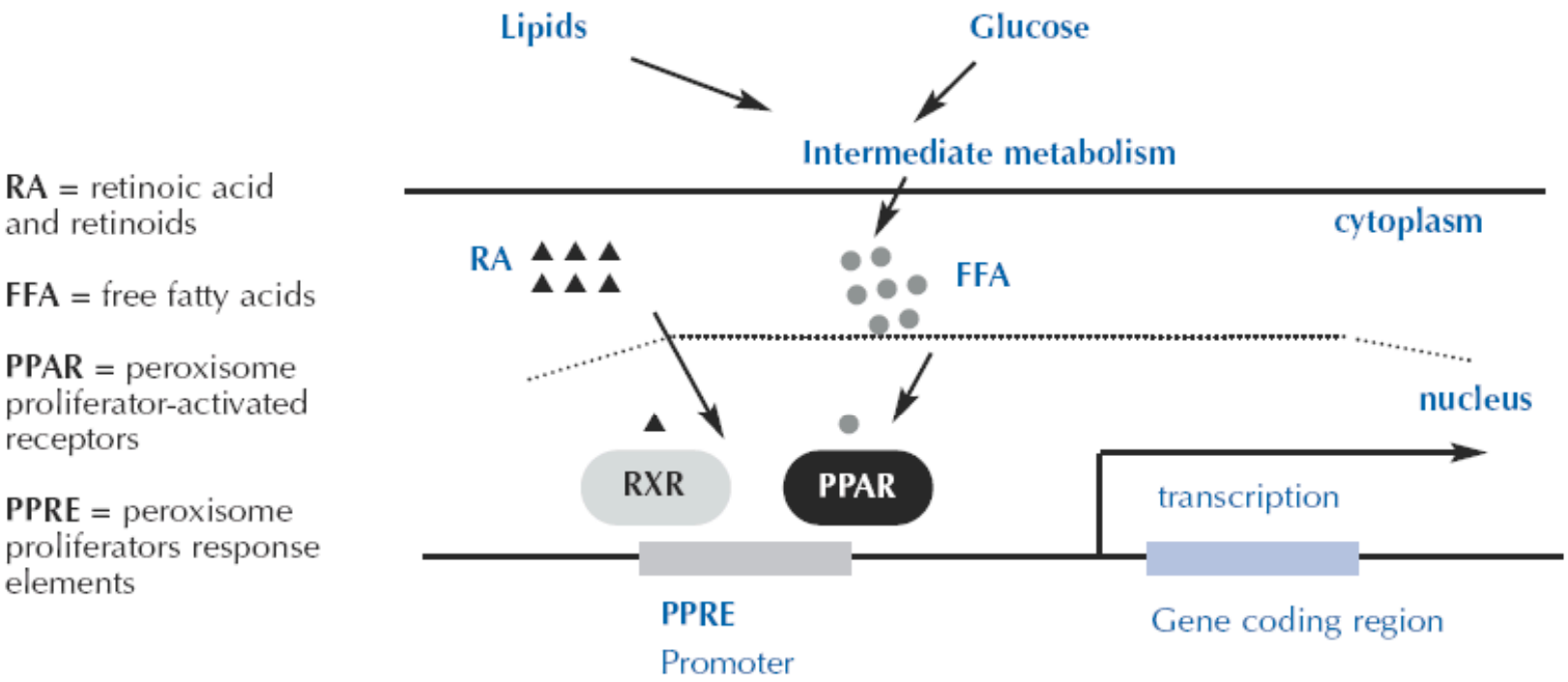
Fig 1 Schematic representation of the steps involved in gene expression (centre), the stages at which diet can modulate these processes (left), and the functional genomics techniques used to analyse each stage (right)

"Regardless of the type of diet-gene interaction, nutritive and non-nutritive components of food influence the abundance and function of cellular proteins by governing gene expression at a variety of levels"

Points in the pathway of protein expression regulated by dietary constituents

Targeted Site	*Examples of Nutrient Regulator*
Gene transcription	Fatty acids, glucose, cholesterol, retinoids, vitamin D
mRNA stability	Fatty acid, glucose, selenium, iron
mRNA processing	Polyunsaturated fatty acids, glucose
mRNA translation	Iron, amino acids
Post-translational modification	Vitamins and minerals

FIGURE 8. A generalised scheme for the PPAR signalling pathway



A general scheme of PPAR signaling pathway. Agonists for the system include free fatty acids, deriving from glucose or lipid intermediary metabolism, and retinoic acid and retinoids, binding to PPAR and RXR, respectively. The heterodimeric complex bound to the respective agonists is thus able to bind PPRE in the promoter region of responsive genes, thus driving transcription. See text for further details.

Source: De Caterina, R.D., Madonna, R., Hassan, J. and Propcopio, A.D., (2001). Nutrients and Gene Expression, in Nutrition and Fitness: Die Genes, Physical Activity and Health. ed Simopoulos, A. P. and Pavlou, K.N. *World Rev Nutr Diet.* **89**,23-52. Reproduced with permission from S. Karger AG.

- Which components of the diet have important health promoting effects?
- How, where and when are these effects exerted?
- Can some of these components also have adverse effects?
- How much and in what form and combination do we need to eat such components to obtain the maximum health benefit with minimum risk?
- How do individuals' dietary recommendations vary depending on their genetic profile, age, gender and lifestyle?

Salt-sensitivity of blood pressure: a paradigm of gene-environment interaction

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(Ital Heart J 2000; 1 (Suppl 3): S15-S19)

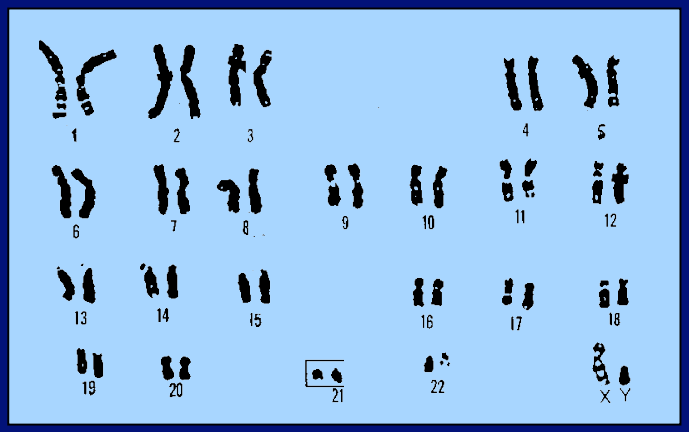

Table I. Candidate genes for arterial hypertension.

Angiotensin-converting enzyme*[18,19]
Angiotensinogen*[20,21]
Angiotensin II type 1 receptor[22]
Atrial natriuretic peptide*[23]
Natriuretic peptide clearance receptor*[24]
Aldosterone synthase*[25,26]
Na^+/K^+ ATPase*[27]
β subunit epithelial sodium channel*[28]
α-adducin*[29,30]
α_{1B}-adrenergic receptor[31]
α_2-adrenergic receptor*[32]
β_2-adrenergic receptor*[33]
β_3-adrenergic receptor*[13,34]
Glucocorticoid receptor[35]
Insulin receptor[36]
Glucagon receptor*[37]
Lipoprotein lipase[38]
Pancreatic phospholipase[39]
Growth hormone[40]
Complement C3F[41]
Type 1A dopamine receptor[31]
Endothelial nitric oxide synthase*[42]
SA gene[43]
G-protein β_3 subunit*[44]
Prostacyclin synthase[45]
Hp1-haptoglobin*[46]

* genes more likely to be involved in the salt-sensitivity of blood pressure.

Combination of Renin-Angiotensin System Polymorphisms Is Associated With Altered Renal Sodium Handling and Hypertension

(*Hypertension*. 2004;43:598-602.)

Alfonso Siani, Paola Russo, Francesco Paolo Cappuccio, Roberto Iacone, Antonella Venezia, Ornella Russo, Gianvincenzo Barba, Licia Iacoviello, Pasquale Strazzullo

TABLE 2. Indices of Tubular Sodium Handling: Comparison Between Carriers of MM AA CC DD/ID and All Other Allelic Combinations

Indices of Tubular Sodium Handling	MM AA CC DD/ID	All	*P* Value	Difference (99% CI)
Lithium FE (%)*	20.0±5.9	25.0±7.5	0.004	−4.9 (−9.3 to −0.6)
Uric Acid FE (%)	6.3±2.0	8.2±2.7	0.001	−1.9 (−3.3 to −0.4)
Sodium FE (%)	0.96±0.41	1.22±0.61	0.004	−0.26 (−0.5 to −0.02)

Values are Mean±SD.

MM AA CC DD/ID indicates homozygosity for M allele of angiotensinogen (*AGT*), A allele of angiotensin II type 1 receptor (*AT1R*), and C allele of *CYP11B2* in presence of D allele of *ACE*; FE, fractional excretion.

As many polymorphisms identified appear to be linked to increased disease susceptibility, better understanding of the mechanisms involved would allow scope for better targeting of more appropriate dietary advice to the relevant population sub-groups.

Where links are established between nutrients or dietary practice and SNP, it is conceivable that people at risk could be identified early in life, if rapid and inexpensive screening methods were available. This would enable a lifelong dietary approach that may improve both longevity and quality of life.