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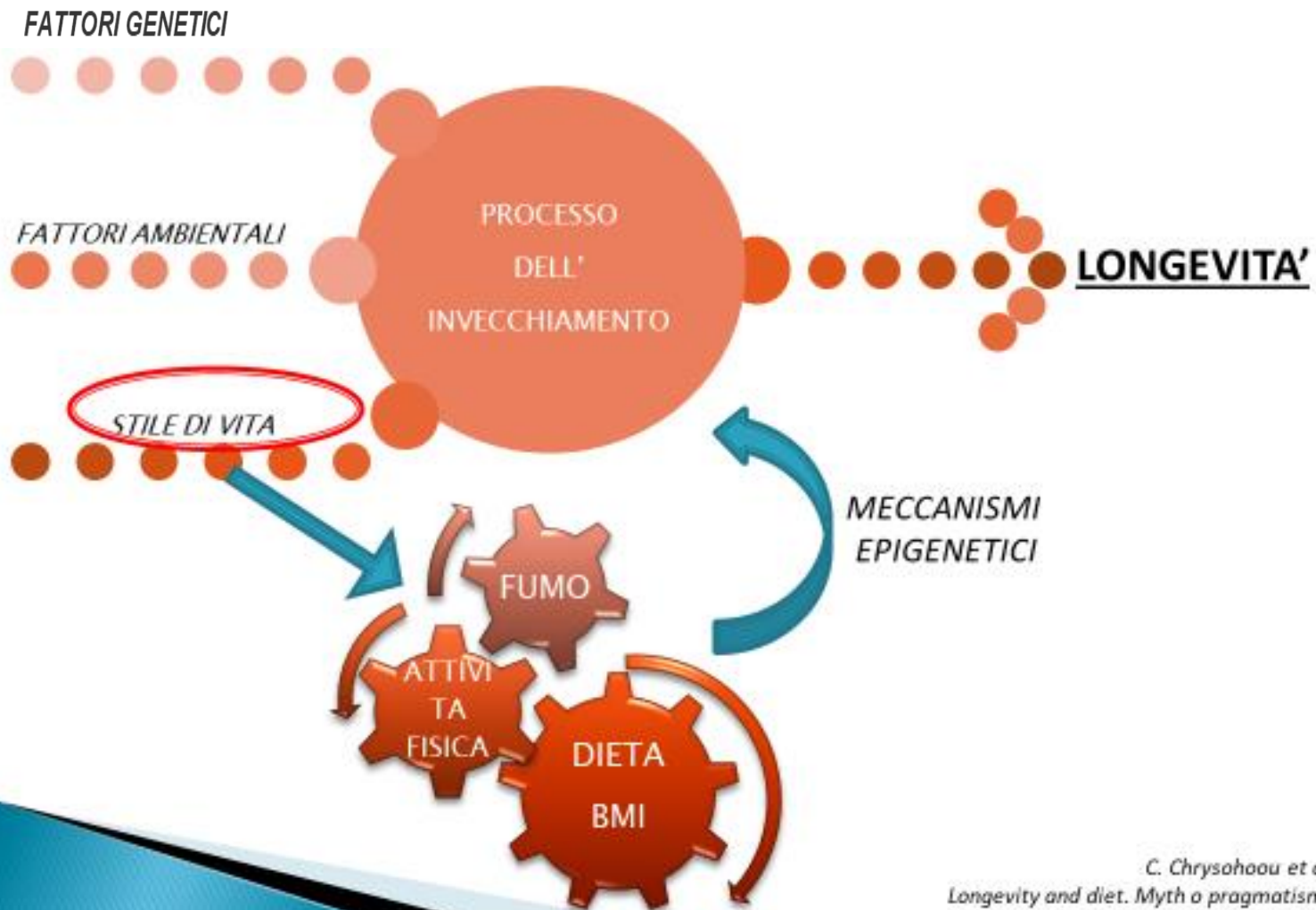
# LE DIETE DEI LONGEVI

**PROF. MAURO CACCIAFESTA**

DIPARTIMENTO DI SCIENZE CARDIOVASCOLARI,  
RESPIRATORIE, NEFROLOGICHE, ANESTESIOLOGICHE E  
GERIATRICHE

SAPIENZA UNIVERSITA' DI ROMA

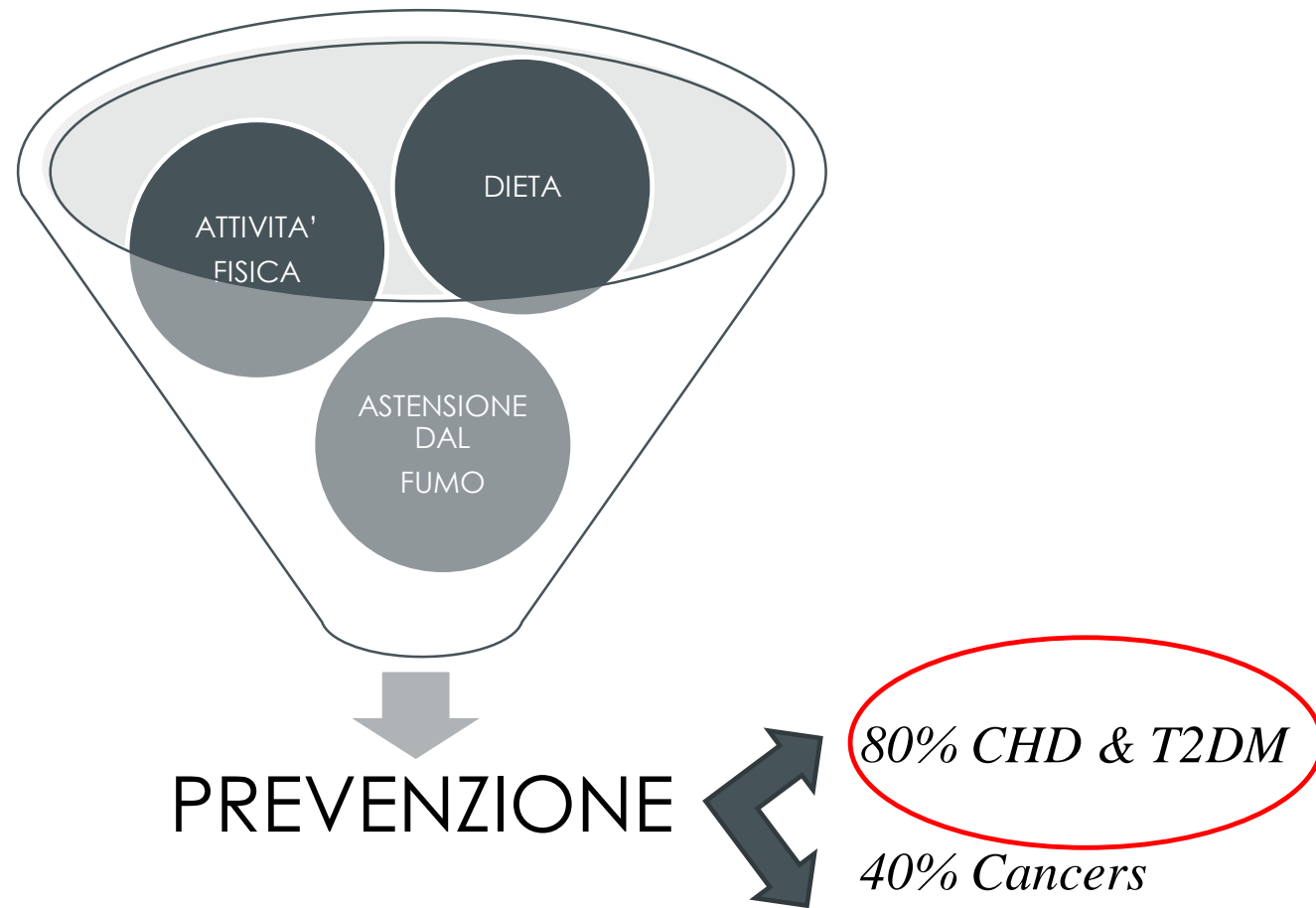




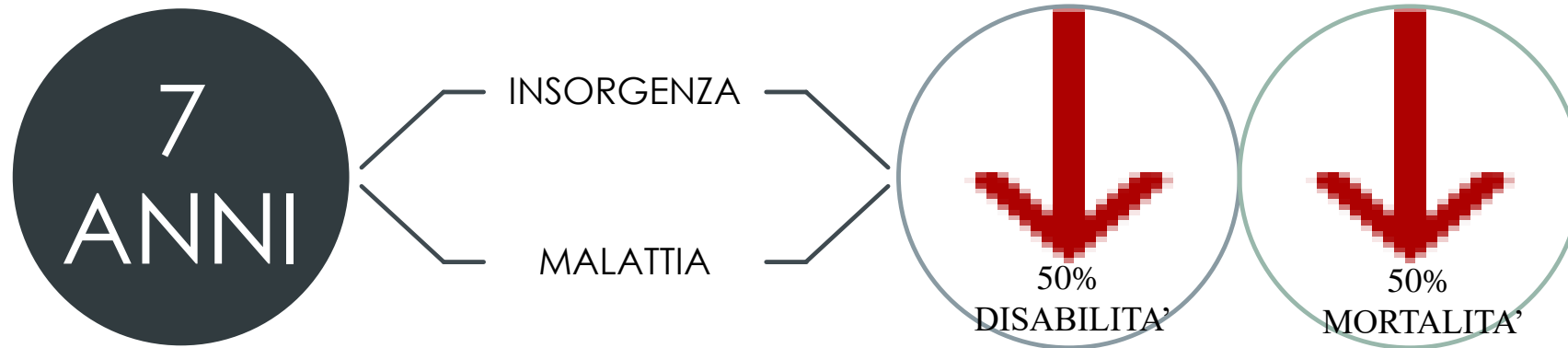
IL TEMPO DEL PASTO (...) È UN MOMENTO FONDAMENTALE DI "COSTRUZIONE" DEL NOSTRO STATO DI SALUTE, DI PREVENZIONE DELLE MALATTIE E, SE SI È MALATI, DI POSSIBILE CURA.

C. Chrysohaou et al.  
 Longevity and diet. Myth or pragmatism?  
 Maturitas 2013

C. TREVISANI, Curarsi con il cibo. Prevenire e curare i disturbi più comuni con l'alimentazione, Terra Nuova Edizioni, 2009



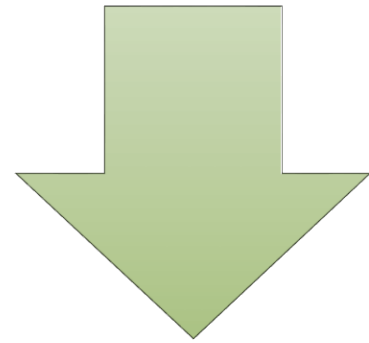
*World Health Organization, 2005; Centers for Disease Control and Prevention, 2009*



## *Life-span & Health- span*



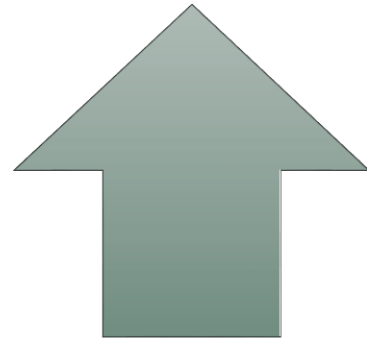
*Olshansky, S.J., et al. 2007. Pursuing the longevity dividend: scientific goals for an aging world. Ann. N.Y. Acad. Sci. 1114, 11–13.*



Restrizione  
calorica

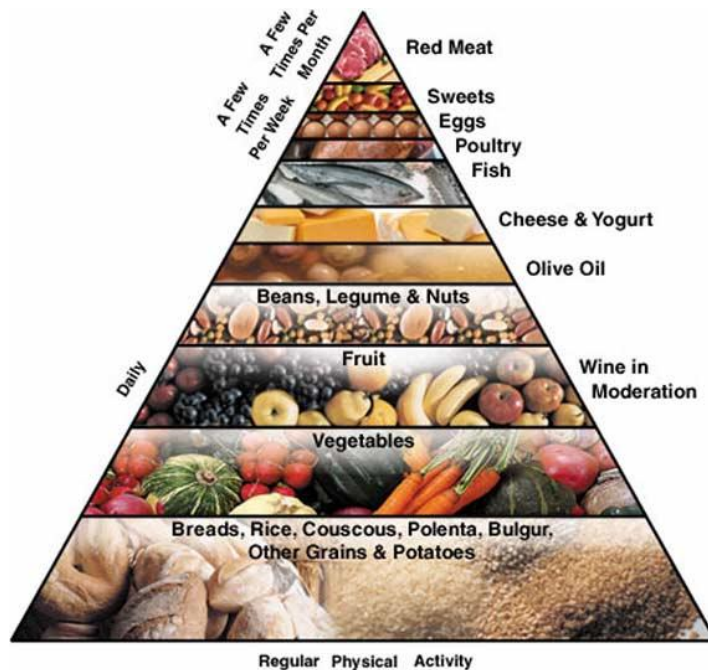
riduzione del 30-40% rispetto all'assunzione  
considerata "normale" per la specie in  
questione

Life-span



*E' un regime  
alimentare  
impegnativo,  
difficilmente  
applicabile!*

QUALE APPROCCIO NUTRIZIONALE?

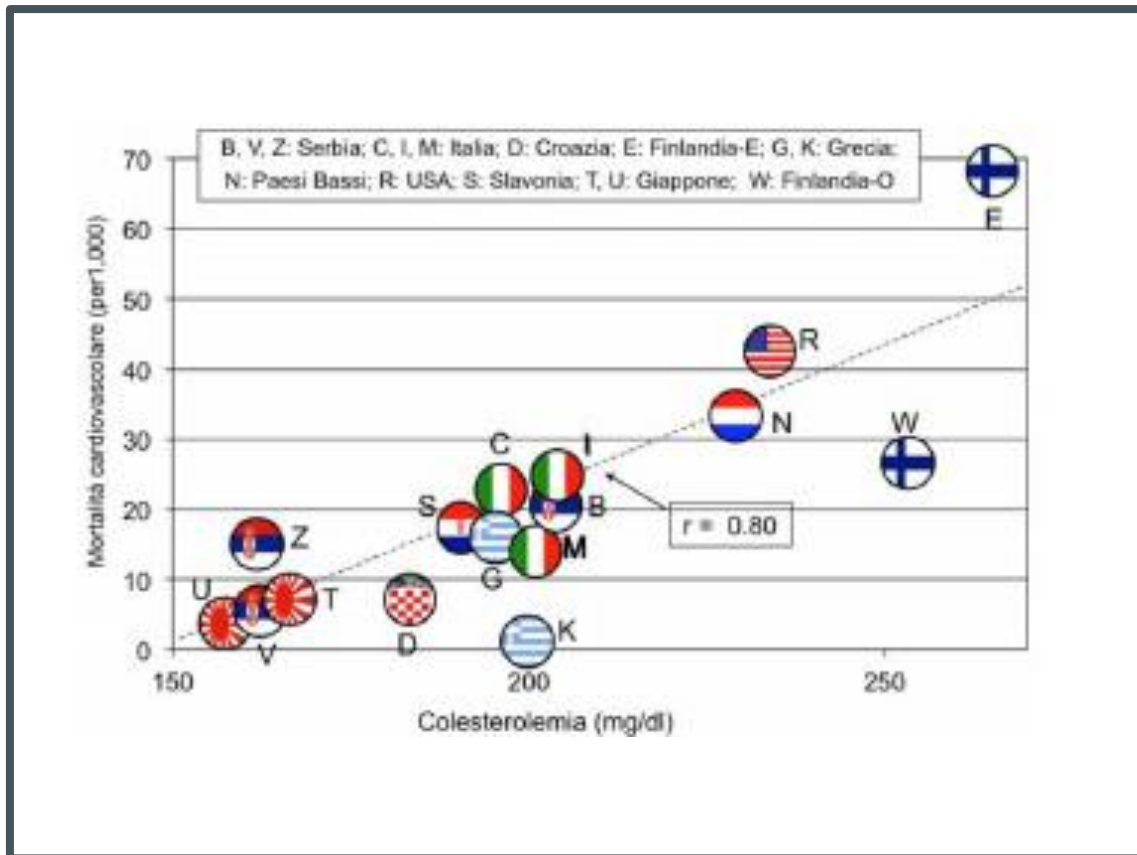


1. Elevato rapporto acidi grassi monoinsaturi/acidi grassi saturi
2. Consumo di vino rosso da basso a moderato
3. Alto consumo di legumi
4. Notevole consumo di grano e cereali
5. Notevole consumo di frutta e verdura
6. Basso consumo di carne e derivati, aumentato consumo di pesce
7. Moderato consumo di latte e latticini

*Vasanthi HR, ShriShriMal N, Das DK. 2012. Phytochemicals from plants to combat cardiovascular disease. Curr Med Chem 19: 2242–51.*

*Curr Cardiol Rep (2014) 16:491 Ischemic Heart Disease and the Mediterranean Diet  
Thomas F. Whayne Jr*

# LA DIETA MEDITERRANEA



*Keys, A., Seven Countries: a multivariate analysis of death and coronary heart disease, ed. A. Keys. 1980, Cambridge, Massachusetts: Harvard University Press*

# RIDUZIONE DEL 9% MORTALITA' PER TUTTE LE CAUSE E DEL 9% MORTALITA' PER CVD

BMJ 2008;337:A1344

DOI:10.1136/BMJ.A1344

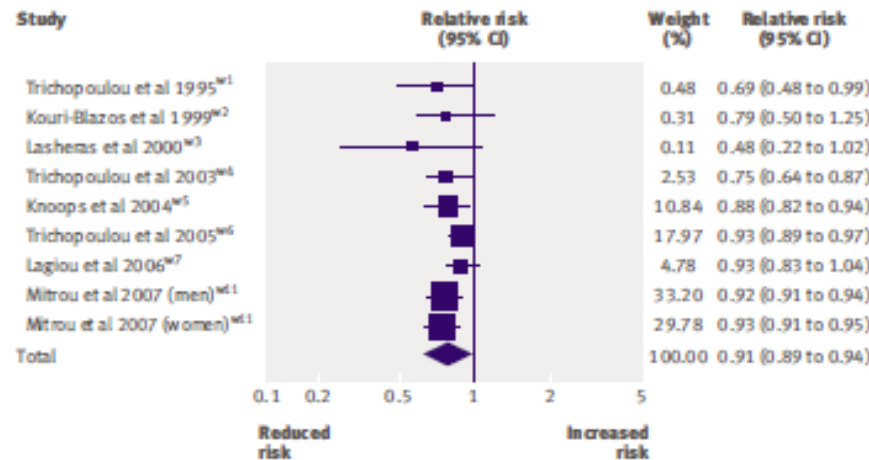


Fig 2 | Risk of all cause mortality associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size

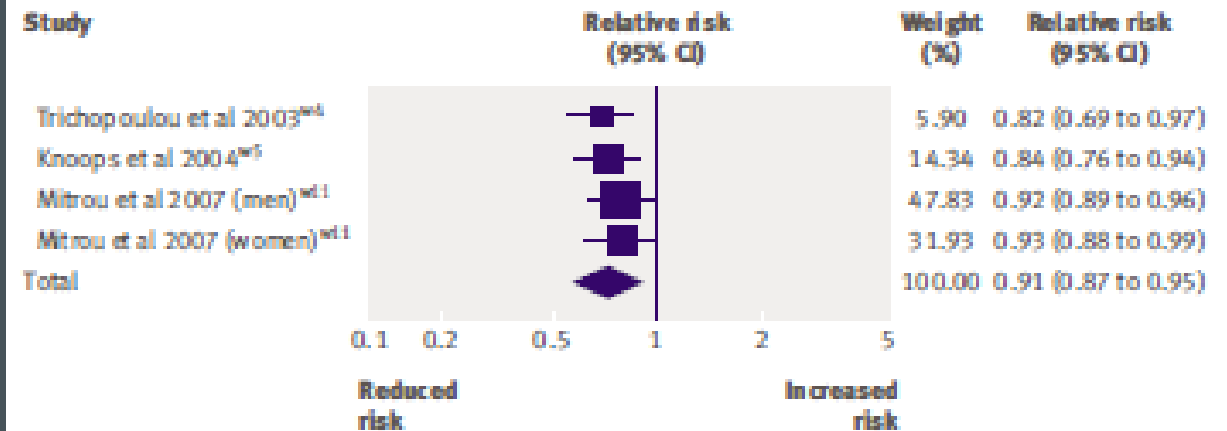


Fig 3 | Risk of mortality from cardiovascular diseases associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size



# RIDUZIONE DELLA MORTALITA' PER NEOPLASIA E DELL'INCIDENZA A DI PD E AD.

BMJ 2008;337:A1344

DOI:10.1136/BMJ.A1344

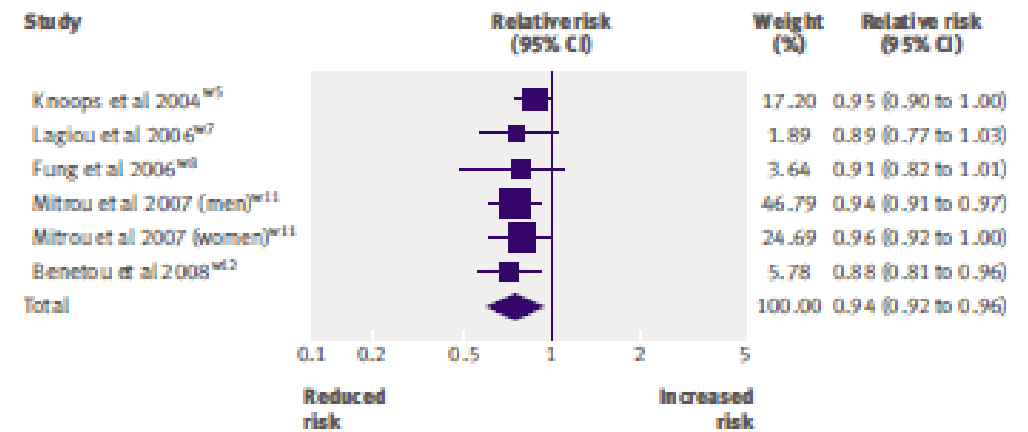


Fig 4 | Risk of occurrence of or mortality from cancer associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size

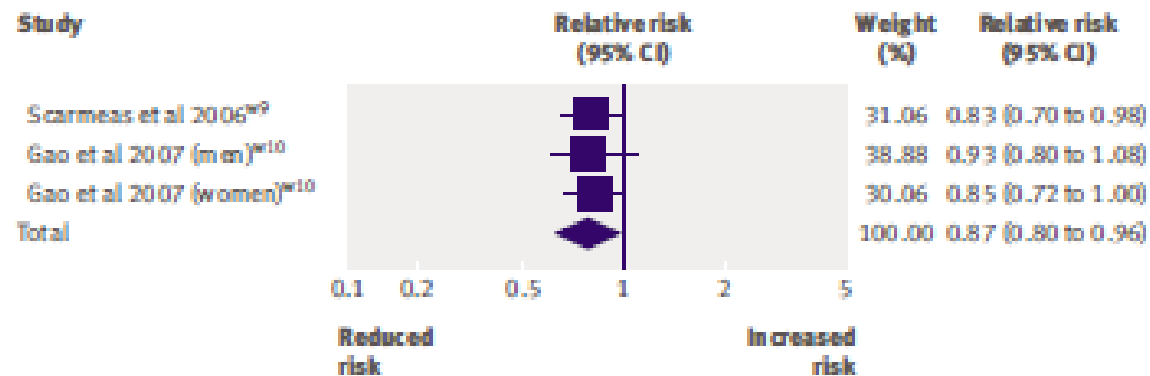


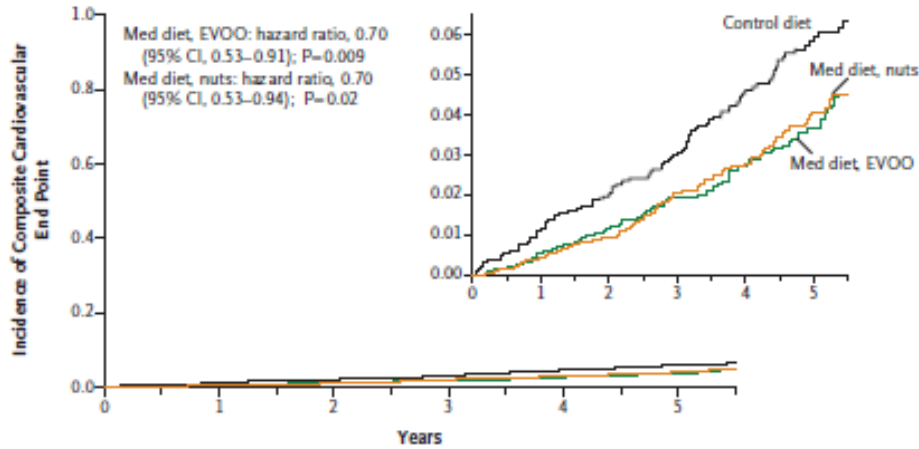
Fig 5 | Risk of Parkinson's disease and Alzheimer's disease associated with two point increase in adherence score for Mediterranean diet. Squares represent effect size; extended lines show 95% confidence intervals; diamond represents total effect size

## PREDIMED (Prevencion con Dieta Mediterranea)

- Trial randomizzato su **7747 persone ad alto rischio cardiovascolare** (diabetici di tipo I e di tipo II, soggetti con almeno tre dei maggiori fattori di rischio: fumo, ipertensione, alti livelli di LDL, bassi livelli di HDL, sovrappeso, obesità, familiarità per malattia coronarica precoce)
- 3 gruppi: 1) dieta Mediterranea supplementata con olio extravergine di oliva; 2) dieta Mediterranea supplementata con noci miste; 3) dieta controllata (con indicazione a basso introito di grassi).
- Obiettivo primario: era il numero di eventi cardiovascolari maggiori, composto da infarto del miocardio, ictus, morte da cause cardiovascolari.
- periodo di follow-up medio è stato di circa 5 anni.

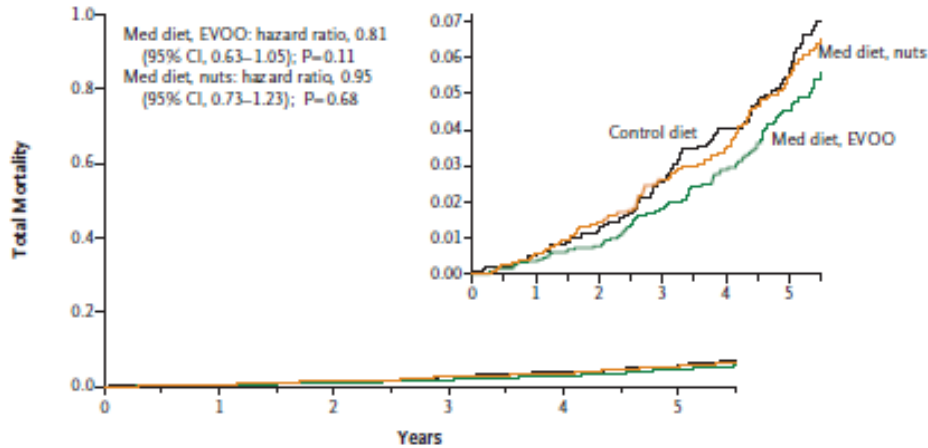
Estruch R, Ros E, Salas-Salvado´ J, Covas MI, et al. 2013.  
Primary prevention of cardiovascular disease with a Mediterranean diet.  
N Engl J Med 368: 1279–90.

**A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)**



No. at Risk	0	1	2	3	4	5
Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

**B Total Mortality**



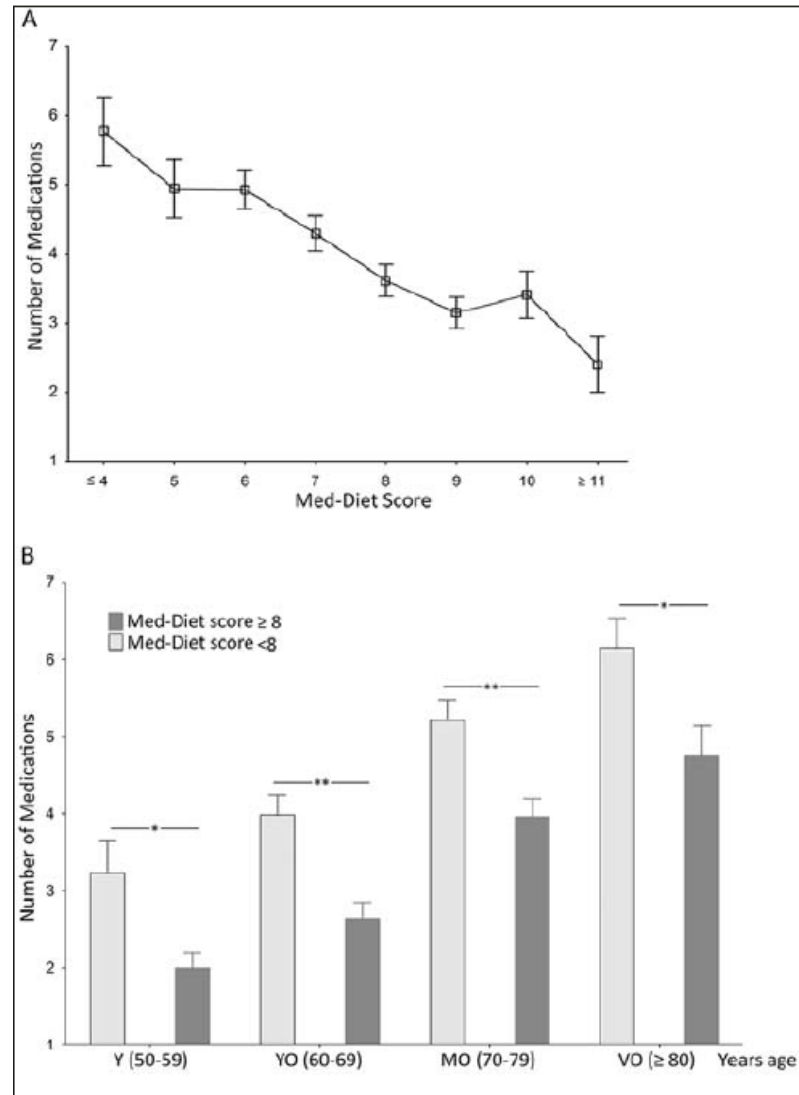
No. at Risk	0	1	2	3	4	5
Control diet	2450	2268	2026	1585	1272	948
Med diet, EVOO	2543	2485	2322	1988	1690	1308
Med diet, nuts	2454	2345	2097	1662	1395	1037

**Figure 1. Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.**

Panel A shows the incidence of the primary end point (a composite of acute myocardial infarction, stroke, and death from cardiovascular causes), and Panel B shows total mortality. Hazard ratios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.

*Riduzione del rischio relativo del 30% nei soggetti ad alto rischio cardiovascolare che seguivano la dieta mediterranea.*

Lo studio ribadisce l'efficacia della dieta mediterranea nel proteggere da eventi cardiovascolari, suggerendo possibili sinergie tra alimenti tipici di questa dieta e pathways intermedi del rischio cardiovascolare (profilo lipidico, sensibilità all'insulina, all'insulina, resistenza all'ossidazione, infiammazione e e vasoreattività).



Med-Diet was inversely associated with cardiometabolic disorders and with polypharmacy, suggesting that improved Med-Diet adherence might potentially delay the onset of age-related health deterioration and reduce the need of multiple medications

## Una possibile variante di dieta Mediterranea?



- ✓ la Kasherùt vieta la possibilità di assumere alcuni dei cibi che la dieta Mediterranea consente, sia pur in misura ridotta (ad esempio: maiale, insaccati ) e che possono impattare negativamente sul rischio cardiovascolare e sulla salute in generale perchè ricchi di allergeni
- ✓ La certificazione kosher garantisce una grande attenzione all'igiene e costanti controlli in ogni fase della filiera produttiva – dall'allevamento alla macellazione fino ad arrivare alla preparazione e cottura.
- ✓ La certificazione kosher garantisce un rigido controllo degli additivi alimentari aggiunti nella fase di produzione industriale degli alimenti.

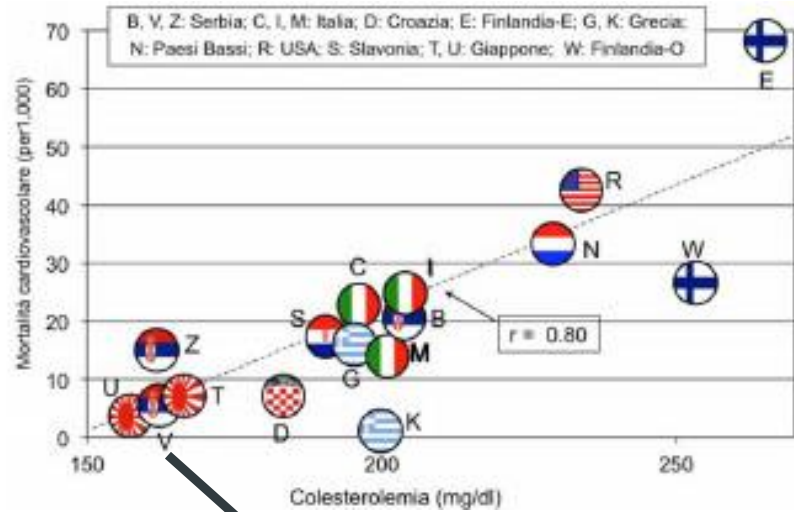
Table 1. Differences between Kosher Diet Group (Kos Diet Gr) and Mediterranean Diet Group (Med Diet Gr Old)

Variables	Kos Diet Gr n=20 M ±SD / n(%)	Med Diet Gr Old n=33 M ±SD / n(%)	χ <sup>2</sup> / F	P
Gender				
Female	15 (75%)	24 (72.70%)	0.033	.56
Male	5 (25%)	9 (27.30%)		
Central Obesity	5 (25%)	18 (54.55%)	4.425	.03*
Metabolic Syndrome	3 (15%)	14 (42.42%)	4.299	.04*
Arterial hypertension	10 (50%)	24 (72.70%)	2.797	.08
14-item Mediterranean diet score	11.25 ± .96	11.31 ± .99	.049	.82
Age	90.00 ± 3.98	82.80 ± 2.65	62.622	.001**
BMI	26.45 ± 4.07	25.82 ± 4.30	0.282	.59
FBG	83.70 ± 11.05	97.70 ± 21.58	7.221	.01*
TC	185.85 ± 44.52	187.58 ± 27.37	0.031	.86
HDLc	49.30 ± 13.21	49.06 ± 14.36	0.004	.95
TG	116.85 ± 48.47	106.76 ± 42.42	0.633	.43

\*p<.05 \*\*p<.001

Note: BMI= Body Mass Index; FBG= fasting blood glucose; TC= plasma total cholesterol; HDLc= high-density lipoprotein cholesterol; TG= triglycerides.

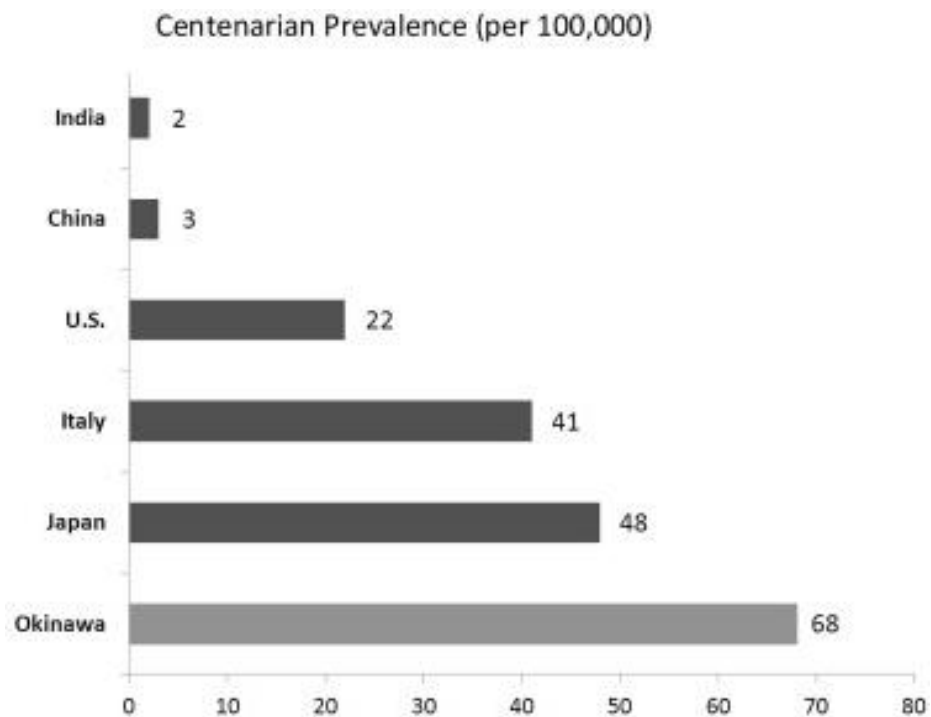
53 subjects (mean age=85.4; sd=4.7) with **high adherence to Mediterranean** diet and moderate-intensity weekly physical activity were enrolled. Of these, 20 patients (Kos Diet Gr) were compliant with **kosher** rules. Data regarding the metabolic profile and the health status were collected.



***IL SEGRETO DI OKINAWA***



**Centenarians in the World (Willcox et al., 2006).**



Okinawan nonagenarians and centenarians had higher prevalence of **anti-inflammatory** type-2 HLA **alleles** and a lower prevalence of proinflammatory alleles



**HHS Public Access**

Author manuscript

*Mech Ageing Dev.* Author manuscript; available in PMC 2017 April 24.

Published in final edited form as:

*Mech Ageing Dev.* 2014 ; 136-137: 148-162. doi:10.1016/j.mad.2014.01.002.

**Healthy aging diets other than the Mediterranean: A Focus on the Okinawan Diet**

Donald Craig Willcox<sup>a,b,c</sup>, Giovanni Scapagnini<sup>d</sup>, and Bradley J. Willcox<sup>b,c</sup>

<sup>a</sup>Okinawa International University, Department of Human Welfare, 2-6-1 Ginowan, Okinawa, Japan 901-2701

Marine-based Carotenoids: Fucoxanthin, Astaxanthin, and Fucoxanthin

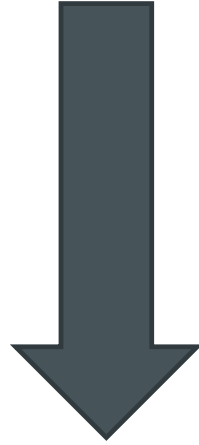
Marine-based carotenoids, such seaweed, algae, kelp are very low in caloric density, nutrient-dense, high in protein, folate, carotenoids, magnesium, iron, calcium, iodine, and have significant **antioxidant and anti-inflammatory properties.**





La dieta tradizionale di Okinawa si basa su verdure verdi e gialle, ortaggi a radice (patate dolci), alimenti a base di soia e altre piante, molte delle quali con proprietà medicinali

*“Something from the mountains  
and something from the sea”*



IL MINISTERO DELLA SALUTE  
GIAPPONESE CONSIGLIA DI  
CONSUMARE GIORNALMENTE ALMENO  
TRENTA 30 CIBI DIFFERENTI

## ALTRI MODELLI DIETETICI

La dieta **DASH** (Dietary Approaches to Stop Hypertension) è ricca di frutta e verdura, cereali, latticini a basso contenuto di grassi, pesce, carne bianca, noci e semi. Contiene anche **meno sodio**, zucchero, grassi e carne rossa rispetto alla solita dieta occidentale.

La **dieta del portfolio** è stata progettata dai ricercatori dell'Università di Toronto per testare l'efficacia di questo approccio dietetico vs la terapia farmacologica standard (statine) in soggetti ipercolesterolemici. È una dieta ricca di verdure e cereali.

Dietary patterns of selected healthy diets.

Major nutrient	Mediterranean <sup>b</sup>	Traditional Okinawa <sup>c</sup>	Okinawan elder's diet <sup>d</sup>	Modern Okinawa <sup>d</sup>	DASH <sup>e</sup>	Portfolio <sup>f</sup>
Carbohydrate (% kcal) <sup>a</sup>	43%	85%	58%	58%	55%	49%
Protein (% kcal) <sup>a</sup>	13%	9%	16%	15%	18%	20%
Fat (% kcal) <sup>a</sup>	42%	6%	26%	28%	27%	30%
Sat. fat (% kcal)	9%	2%	7%	7%	6%	6%
Cholesterol (mg/1000 kcal)	75 mg	–	156 mg	164 mg	72 mg	49 mg
Sodium (mg/d)	2157 mg <sup>g</sup>	1113 mg	3100 mg	3256 mg	1150 mg	1921 mg
Potassium (mg/d)	3637 mg <sup>g</sup>	5199 mg	1999 mg	1901 mg	4700 mg	3382 mg

<sup>a</sup> Macronutrient data may not equal exactly 100% due to unaccounted alcohol calories and/or rounding error.

<sup>b</sup> Kromhout et al. (1989).

<sup>c</sup> Willcox et al. (2007).

<sup>d</sup> Okinawa Prefecture (2013).

<sup>e</sup> Sacks et al. (2001).

<sup>f</sup> Jenkins et al. (2007a).

<sup>g</sup> Schröder et al. (2002).

1. Elevato consumo di carboidrati non raffinati , a basso indice glicemico
2. Elevato consumo di ortaggi , legumi e frutta.
3. Moderato consumo di pesce.
4. Bassa assunzione di carne.
5. Uso libero di piante medicinali , erbe , spezie o oli.
6. Consumo regolare di the o moderato di alcool .





FATTORI GENETICI



FATTORI AMBIENTALI



PROCESSO  
DELL'  
INVECCHIAMENTO

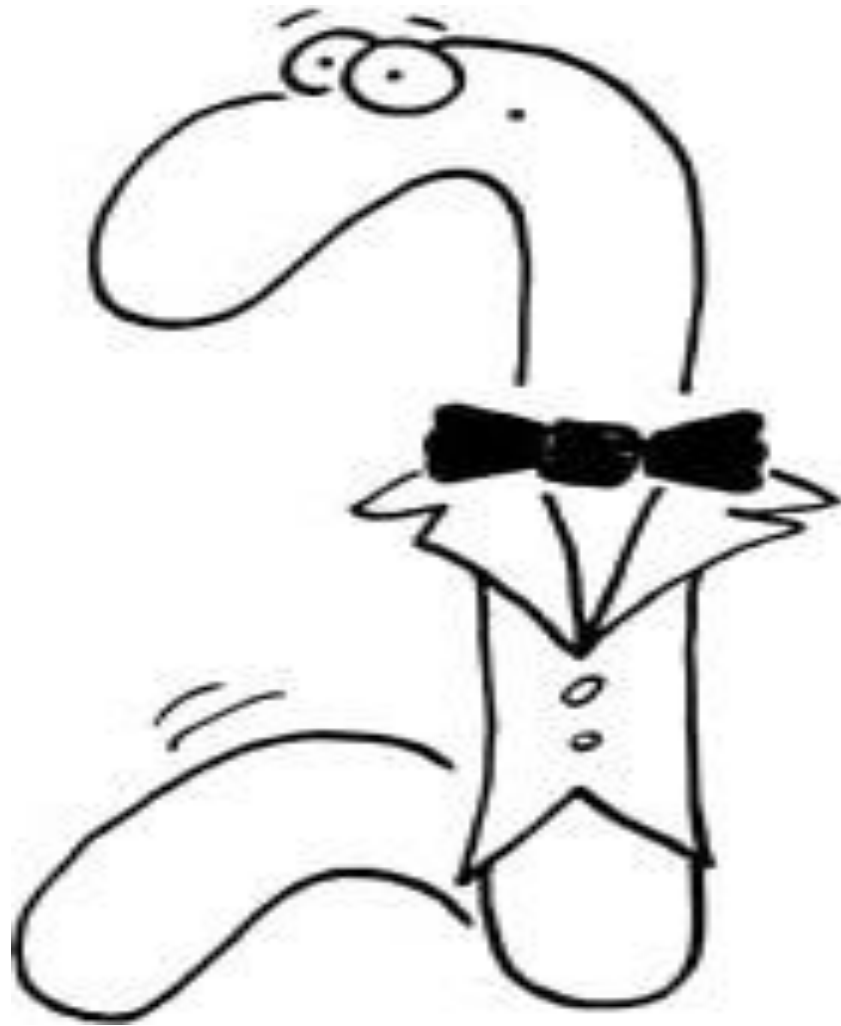
LONGEVITA'

STILE DI VITA

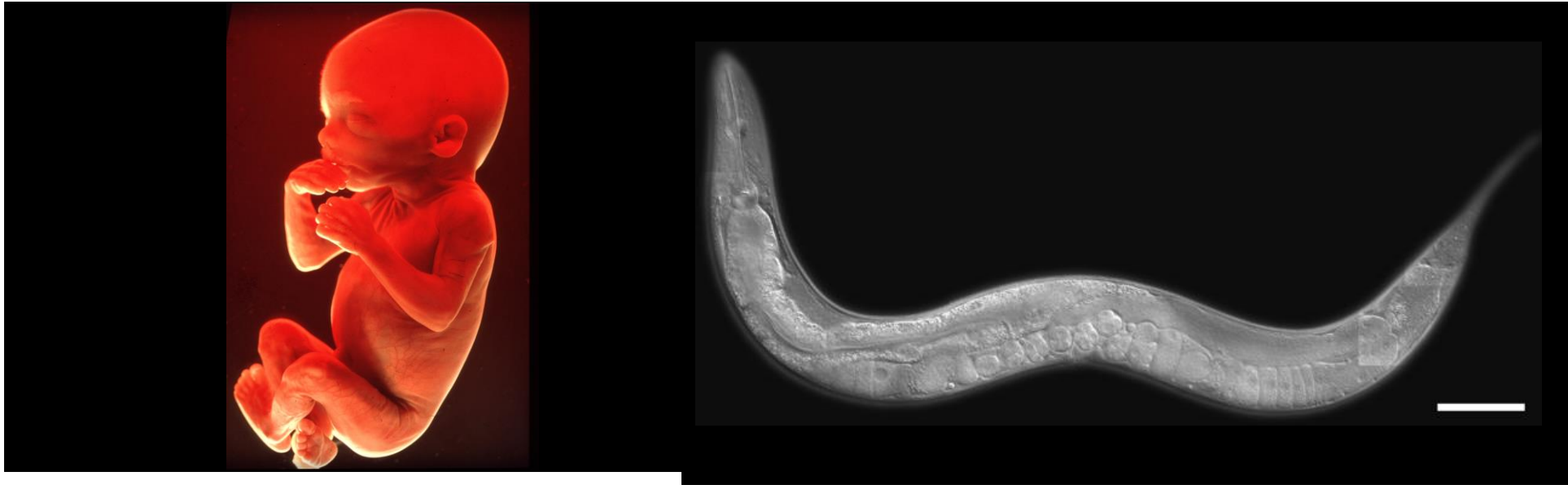


MECCANISMI  
EPIGENETICI

*C. Chrysohaou et al.  
Longevity and diet. Myth o pragmatism?  
Maturitas 2013*



## The genetic basis of developmental complexity

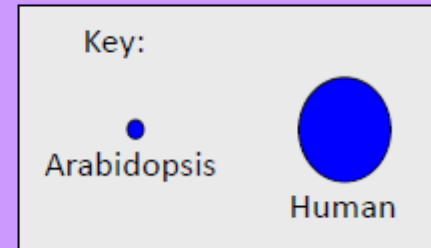
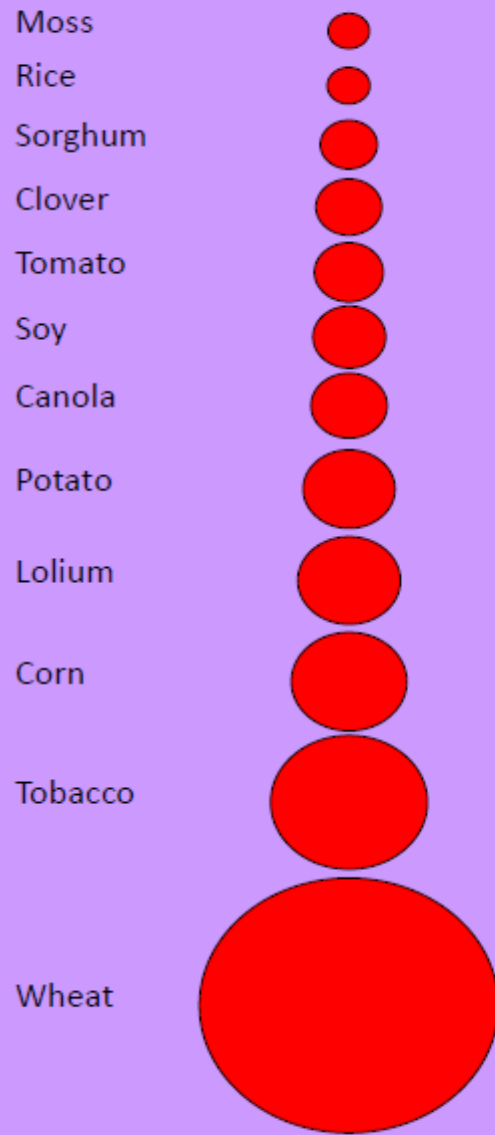


- Humans (and other vertebrates) have approximately the same number of protein-coding genes (~20,000) as *C. elegans*, and less than those of plants (Arabidopsis ~28,000, rice ~40,000) and protozoa (30,000).
- Most of the proteins are orthologous and have similar functions from nematodes to humans, and many are common with yeast.
- Where is the information that programs our complexity?



# I genomi della pianta possono essere più grandi del genoma umano

Dimensioni relative dei genomi

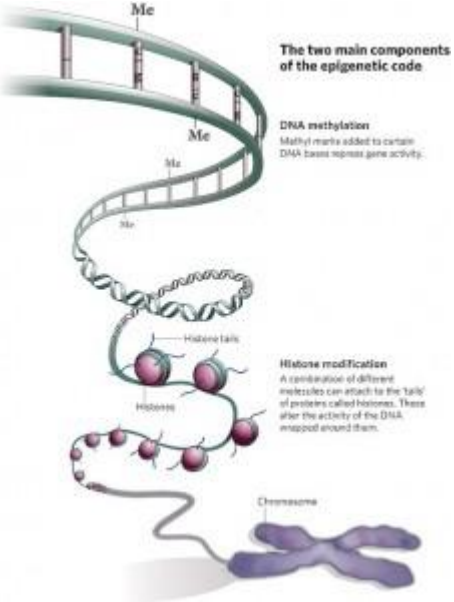


# DIETA MEDITERRANEA

METILAZIONE DEL DNA

MODIFICAZIONE DEGLI ISTONI

REGOLAZIONE DI microRNA



ENDOGENI

ESOGENI?

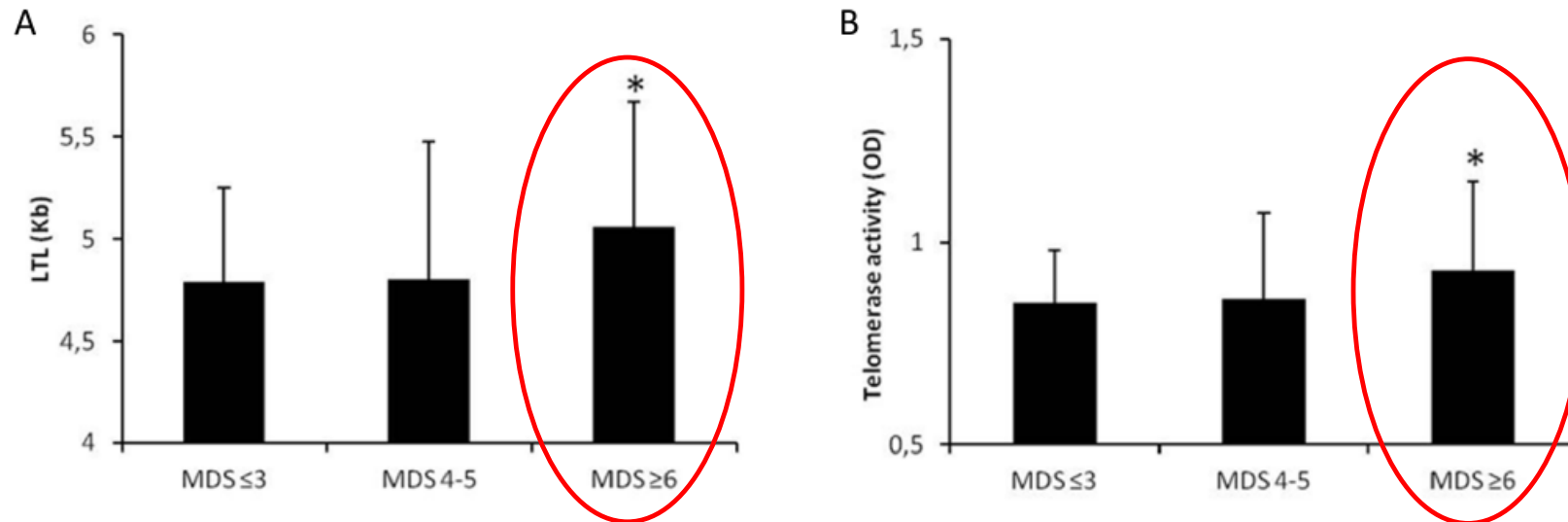
*Zhang L, et al. 2012. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. Cell Res 22: 107–26.*

*Prospects & Overviews 2014 How does the Mediterranean diet promote cardiovascular health? Current progress toward molecular Mechanisms.*

# LE SIRTUINE

Sirt1 induction by CR or by the “sirtfood”- constituent resveratrol has been shown to counteract elevated levels of inflammation and might lower cholesterol and triglyceride synthesis.

Various reports have shown that Sirt1 activation *in vitro* decreased the levels of proinflammatory mediators such as the tumour necrosis factor  $\alpha$ , interleukins 1 and 6, intercellular adhesion molecule 1, and inducible nitric oxide synthase (NOS)



**Figure 2. LTL and Telomerase Activity according Mediterranean Diet Score subgroups.** Data are means  $\pm$  standard deviation. MDS $\leq$ 3: n=70; MDS 4–5: n=68; MDS $\geq$ 6: n=79. *p* values were obtained using ANOVA followed by Bonferroni multiple testing correction. A) \**p* = 0.003; MDS $\geq$ 6 vs MDS $\leq$ 3 *p* = 0.009 and MDS $\geq$ 6 vs MDS 4–5 *p* = 0.011 B) \**p* = 0.013; MDS $\geq$ 6 vs MDS $\leq$ 3 *p* = 0.028 and MDS $\geq$ 6 vs MDS 4–5 *p* = 0.033. LTL, Leukocyte Telomere Length; MDS, Mediterranean Diet Score.  
doi:10.1371/journal.pone.0062781.g002

Boccardi V. et al, PLOS ONE, 2013 (4)

*possibilità di prevenire le patologie età-correlate come l'aterosclerosi, l'osteoartrite, la senescenza immunitaria e le demenze degenerative come l'Alzheimer.*

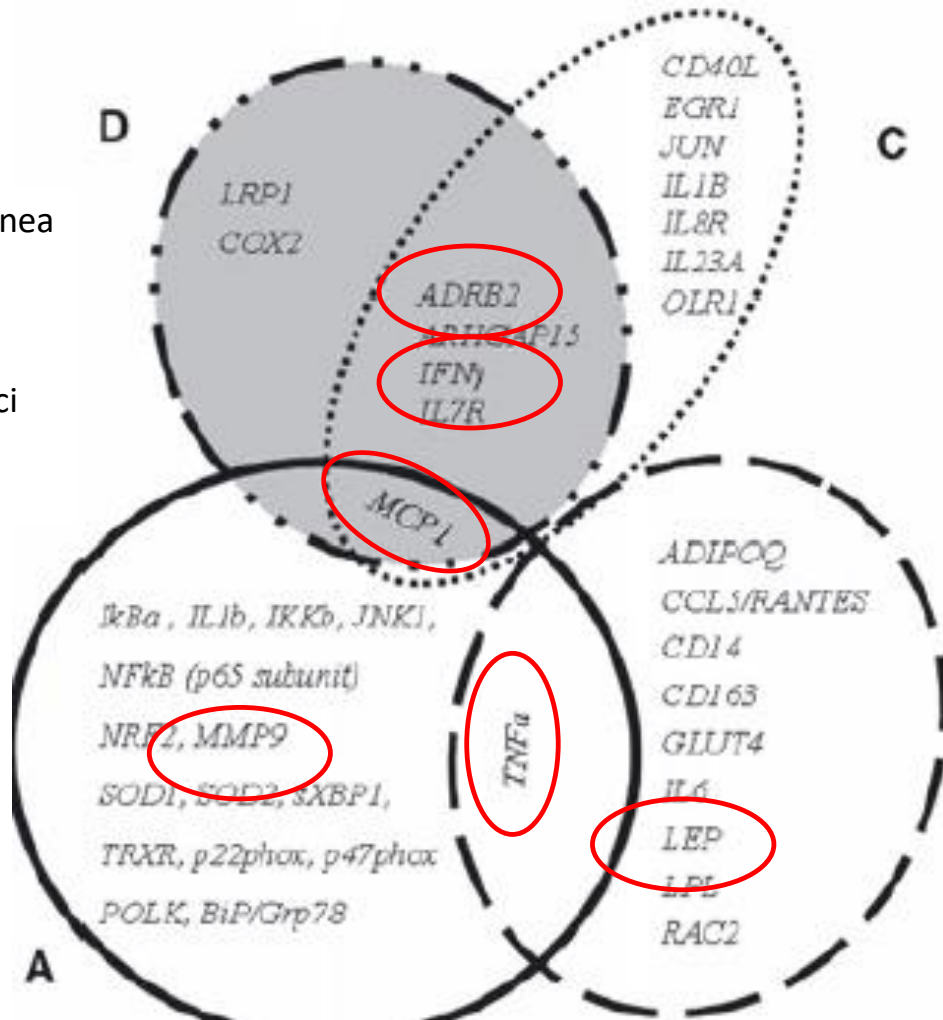
# INTERAZIONE DIETA – GENI

A: Dieta Mediterranea

B: Olio di Oliva

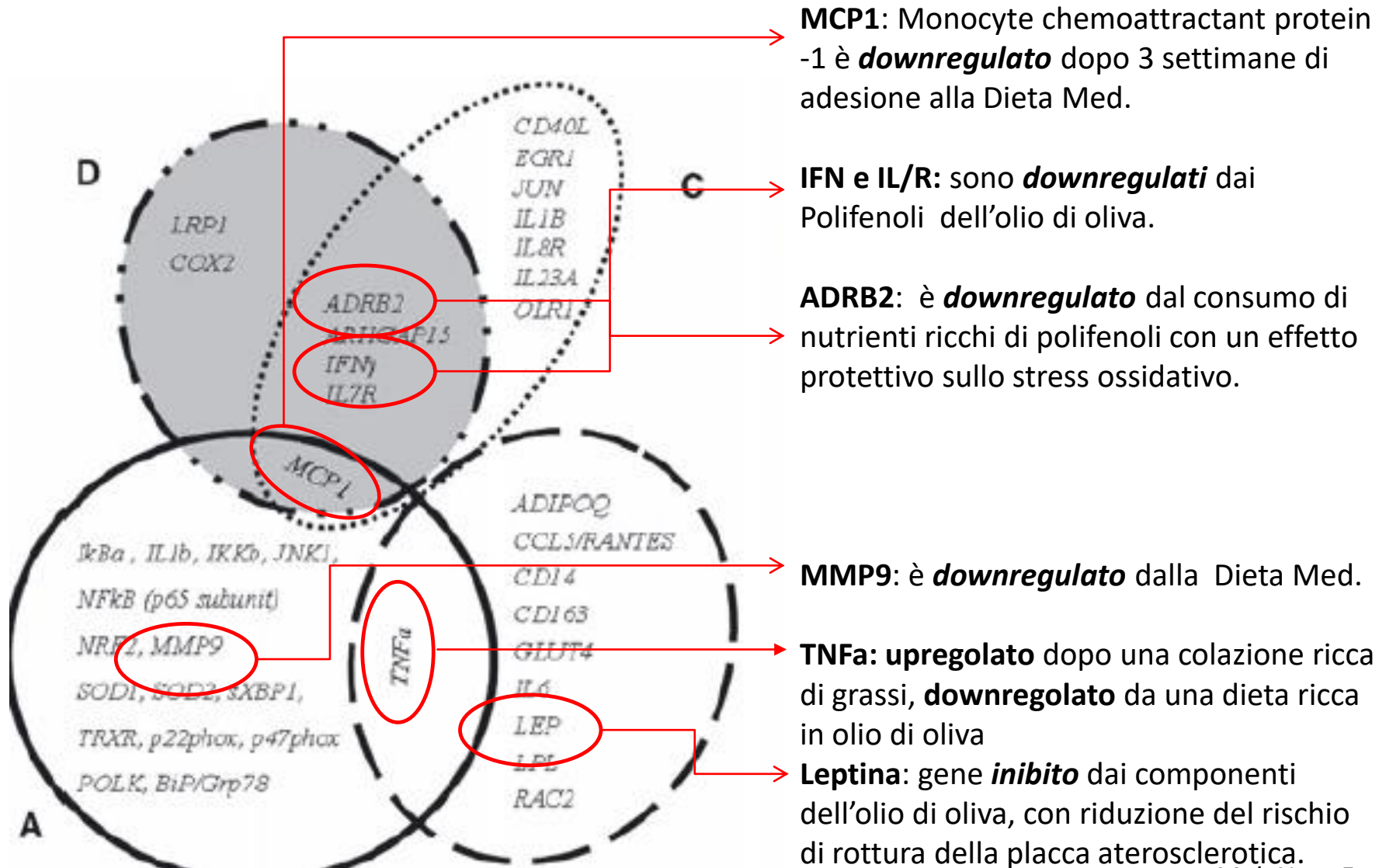
C: Composti fenolici

D: A+B



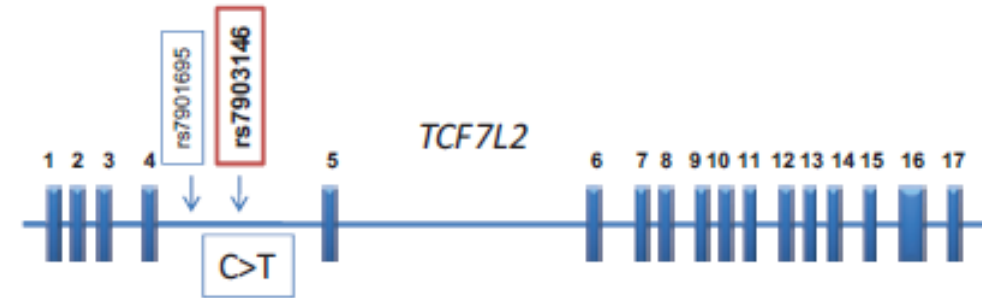
Despite a great diversity among studies, the attributed health benefits of the MedDiet and its components could be explained by a **transcriptomic effect on atherosclerosis, inflammation, and oxidative stress-related genes**

# INTERAZIONE DIETA – GENI

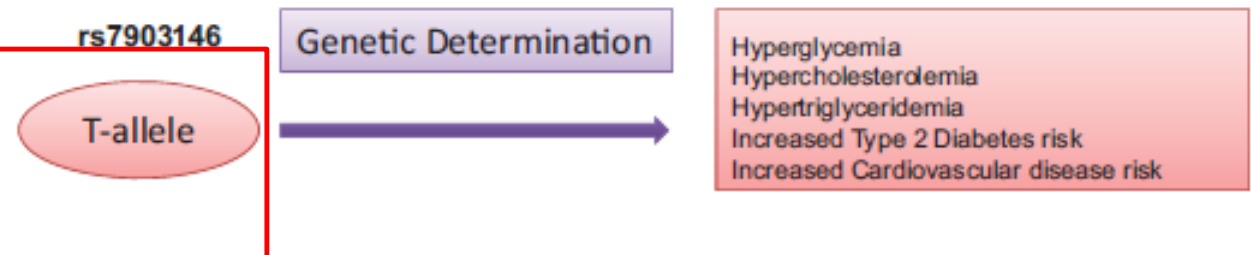


## PREDIMED (Prevencion con Dieta Mediterranea)

Il gene che codifica per il *Transcription Factor 7-like 2* (TCF7L2) ha dimostrato una forte associazione con la suscettibilità al DMT2. In particolare, è stato documentato che la variante allelica T del polimorfismo nucleotidico TCF7L2-rs7903146 è gravata da un più alto rischio di DMT2 ed è molto meno frequente rispetto alla variante C.



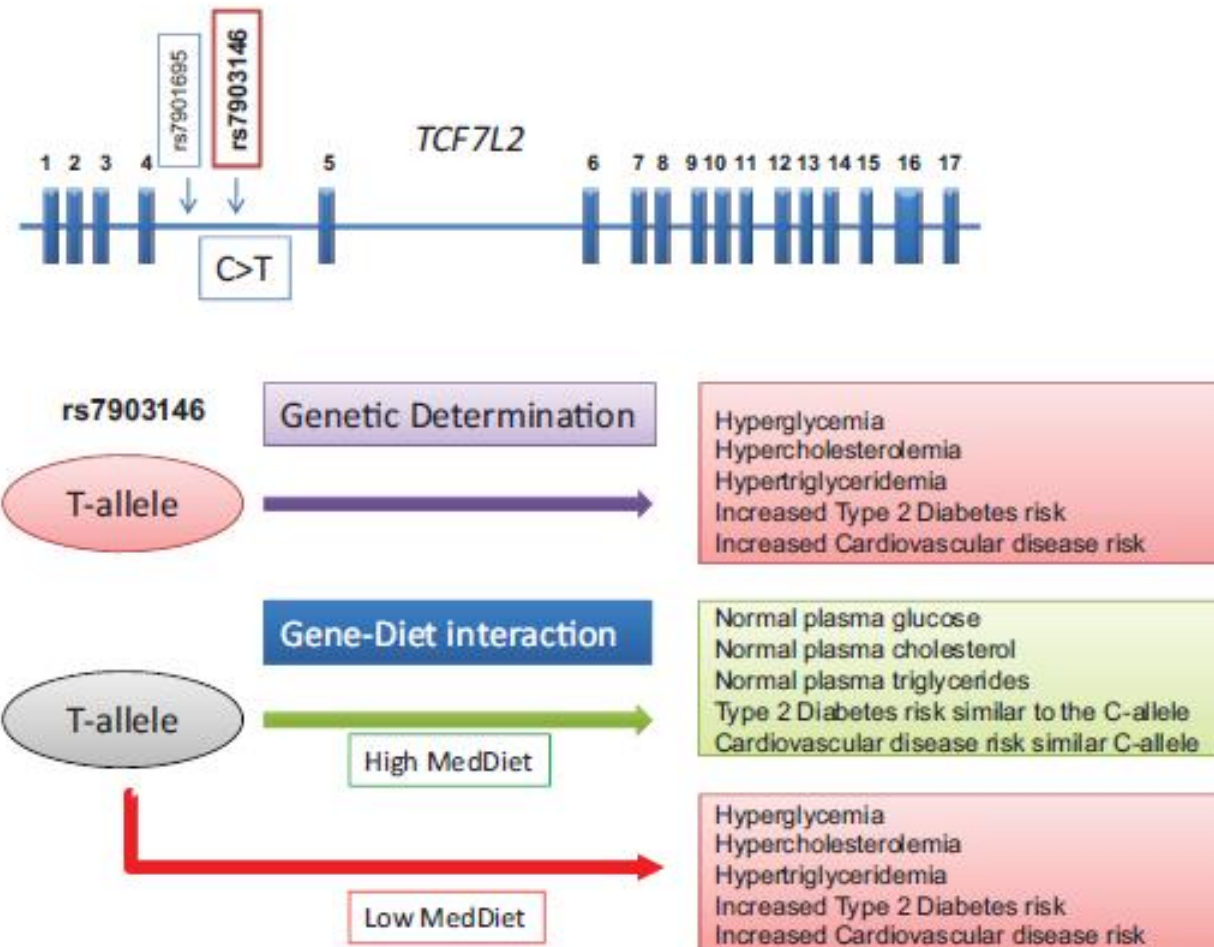
La **variante allelica T** è stata associata a maggiore prevalenza e gravità di malattia coronarica ed eventi cardiovascolari e cerebrovascolari.



**The north-south gradient for the 7903146T in Europe, the frequency of this allele being higher in Mediterranean Populations than in Northern Europeans.**

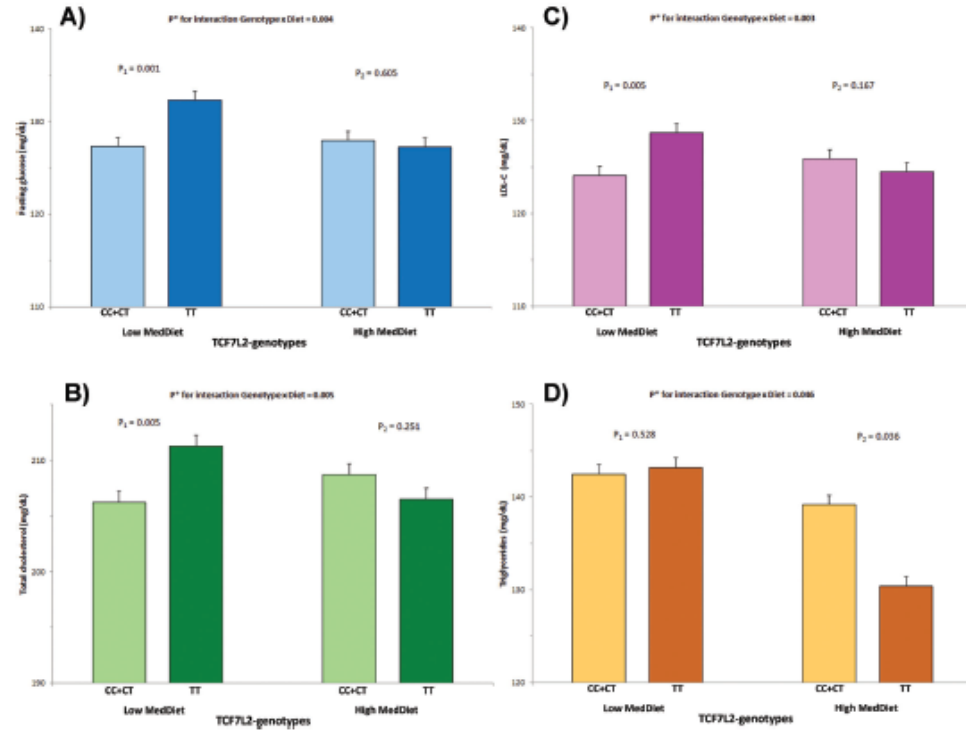
*Although there is evidence that the Mediterranean food pattern may reduce type 2 diabetes risk and cardiovascular disease incidence, no studies have investigated the influence of Mediterranean diet (MedDiet) on TCF7L2 gene effects.*



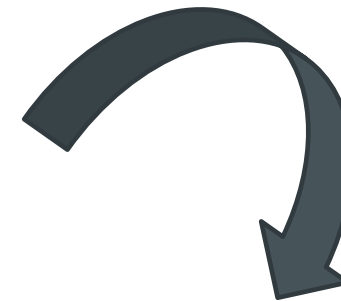


*Prospects & Overviews 2014 How does the Mediterranean diet promote cardiovascular health? Current progress toward molecular Mechanisms.*



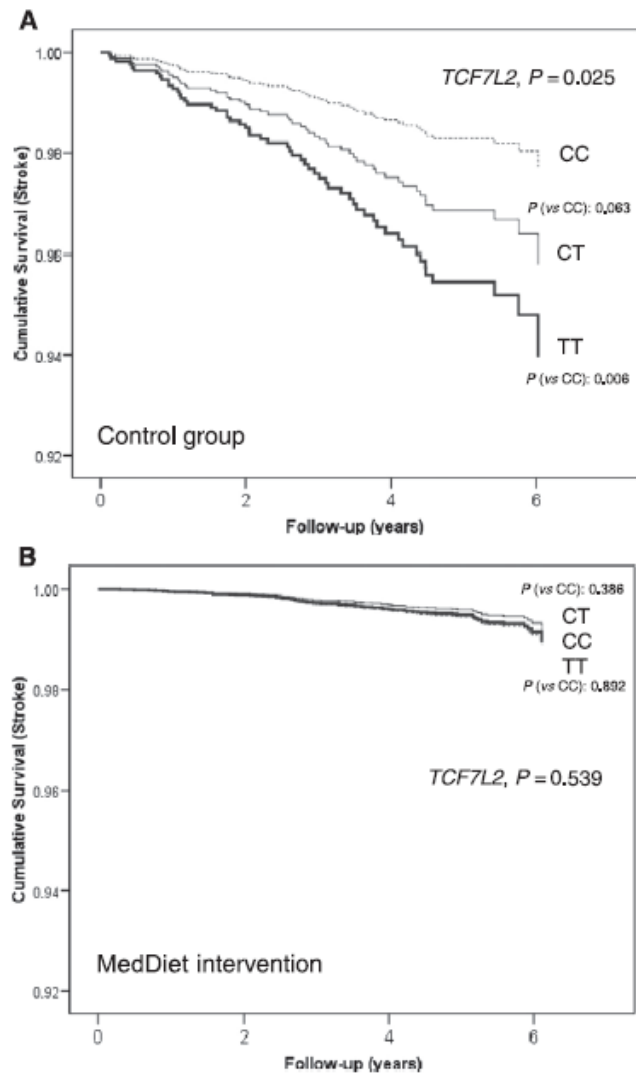


Follow-up 4.8 y



*Soggetti TT che avevano seguito la dieta Mediterranea non presentavano una maggiore incidenza di stroke*

*Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population. Diabetes Care 2013, 36: 3803–11.*



cumulative stroke free-survival per *TCF7L2*-rs7903146 genotypes in the control group (Fig. 1A) and the MedDiet intervention groups (Fig. 1B).



# QUALE APPROCCIO NUTRIZIONALE?

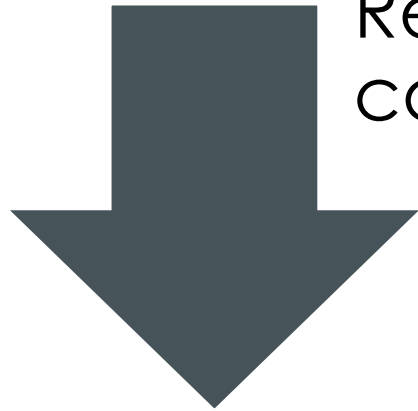


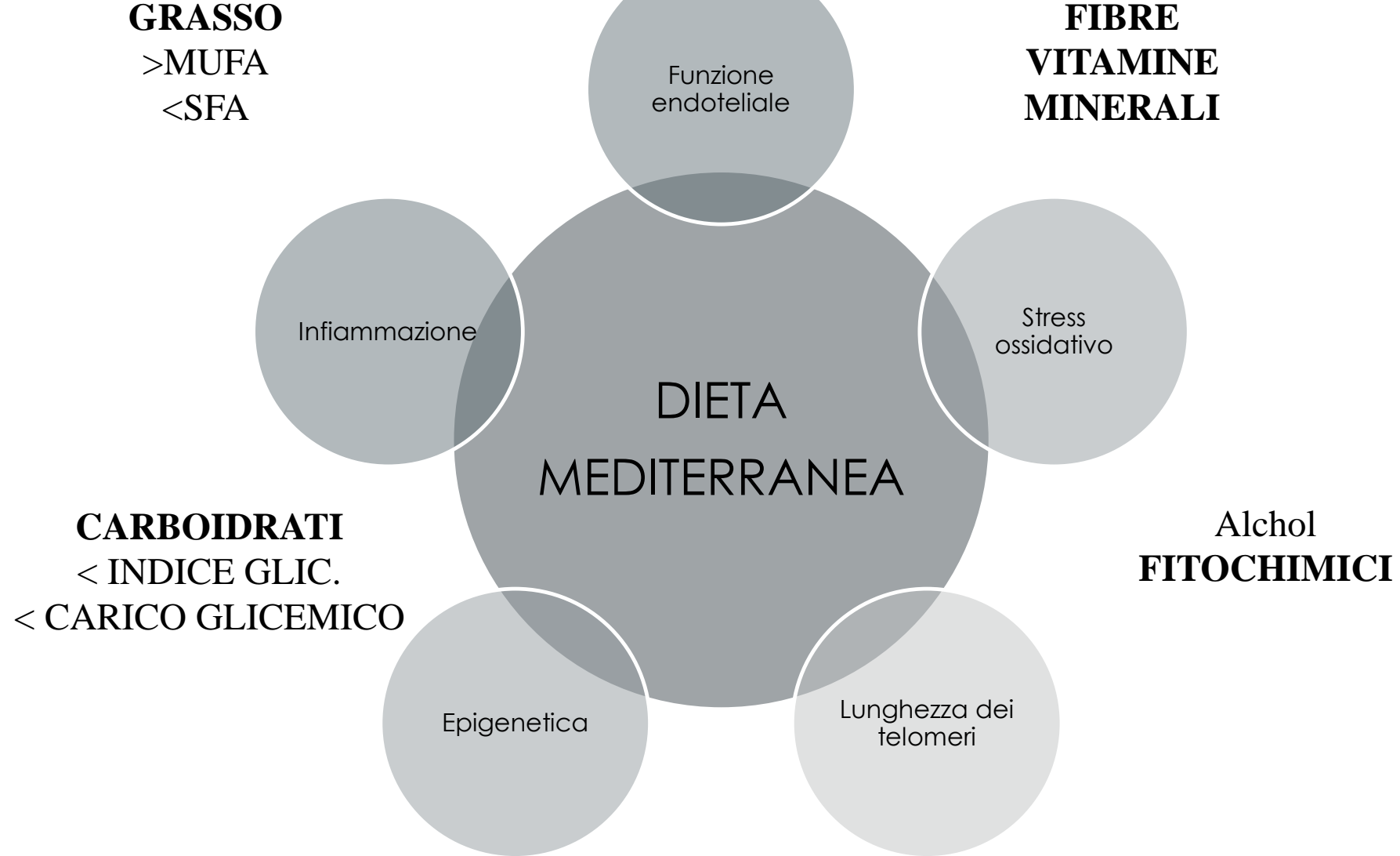
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Fitochimici  
(polifenoli,  
carotenoidi  
etc...)



Restrizione  
calorica





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**GRASSO**

>MUFA

<SFA

**FIBRE**

**VITAMINE**

**MINERALI**

Funzione  
endoteliale

DIETA

DI

OKINAWA

Infiammazione

Stress ossidativo

The verde

**FITOCHEMICI**

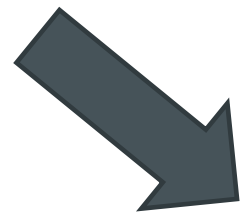
**CARBOIDRATI**

< INDICE GLIC.

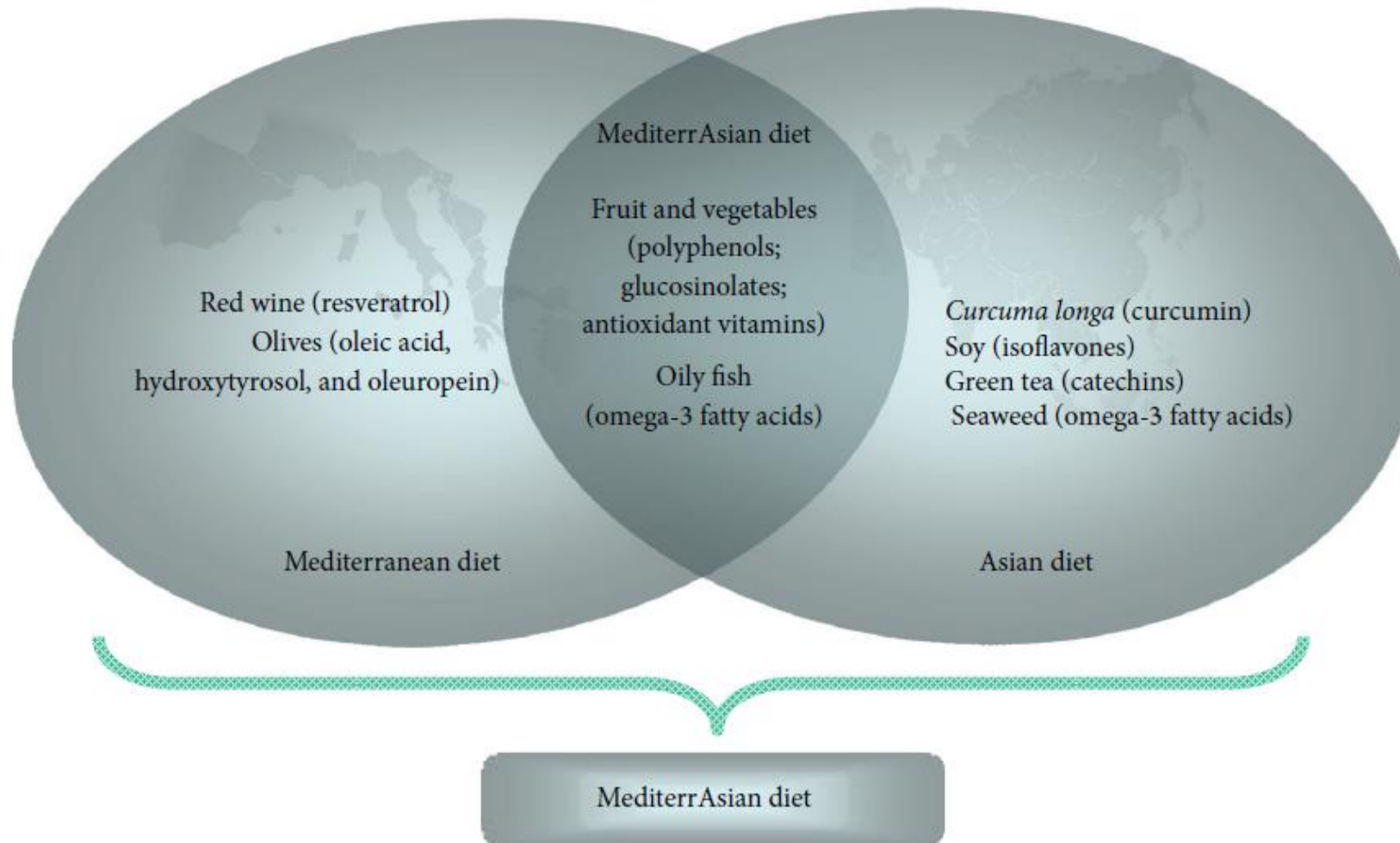
< CARICO GLICEMICO

Aging  
vascolare

CR mimetics	Fonte	Signalling Pathways
Idrossitirosolo	Olio di oliva	>Nrf2; Sirt1; <NFkB
Resveratrolo	Vino rosso, uva rossa	>Nrf2; Sirt1; <NFkB
Quercetina	Cipolle, mele, vino bianco	Sirt1
Curcumina	Radice	>Nrf2; Sirt1; <NFkB
Daidzeina	Soia	Sirt1



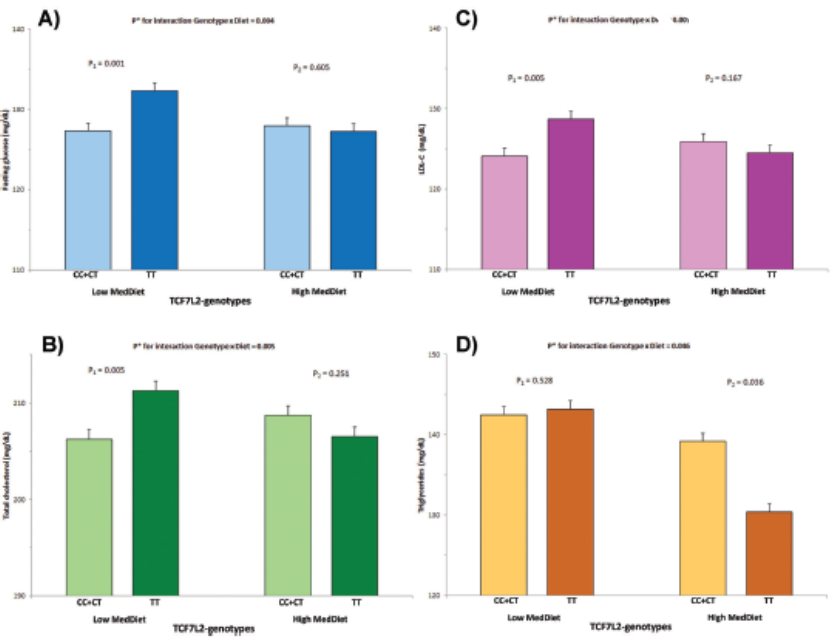
QUALE DIETA?





"Fa che il cibo sia la tua medicina  
e la medicina sia il tuo cibo."  
(Ippocrate)

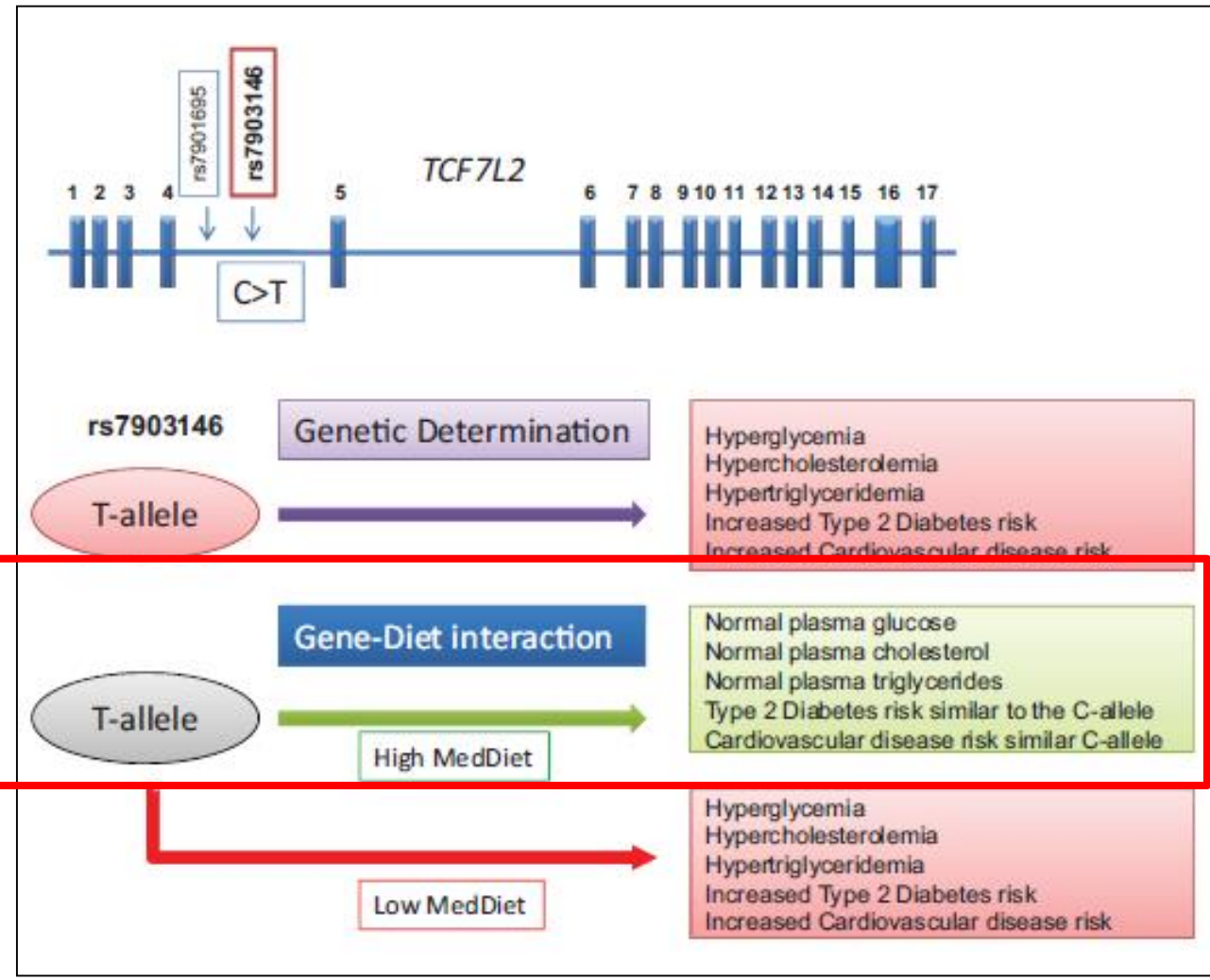




Follow-up 4.8 y



*Soggetti TT che avevano seguito la dieta Mediterranea non presentavano una maggiore incidenza di stroke*



*Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population. Diabetes Care 2013, 36: 3803–11.*