

Prevenzione primaria individuale. Farmaci e non solo... stili di vita... e non solo

Andrea Poli

Nutrition Foundation of Italy
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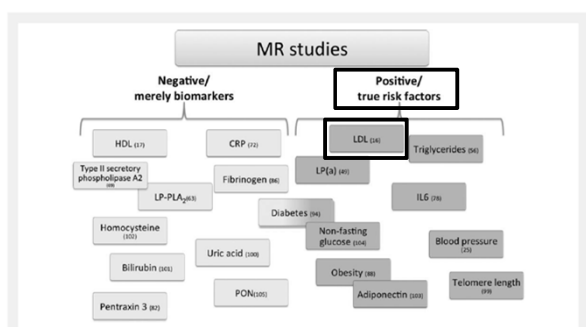
Fattori vs markers di rischio

Fattore di rischio vero: può essere oggetto di intervento, se lo controllo riduco il rischio

Indicatore di rischio: segnala la presenza di un rischio aumentato; trattarlo è in genere inutile

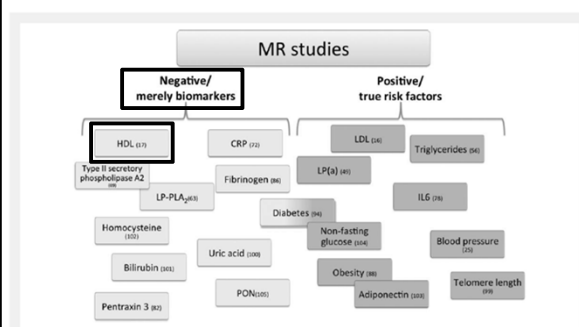
Come differenzio fattori da indicatori?
Mediante RCT o randomizzazioni Mendeliane

Mendelian Randomization studies on the risk of Coronary Heart Disease (CHD)



Henning J, et al. Eur Heart J 2014

Mendelian Randomization studies on the risk of Coronary Heart Disease (CHD)



Henning J, et al. Eur Heart J 2014

HDL: implicazioni pratiche

- Il ruolo di HDL-c nella stadiazione del rischio rimane del tutto invariato...
- ... ma il ruolo delle modificazioni dei livelli di HDL-c è da riconsiderare
- E' probabile che la stima dei flussi del colesterolo (in parte HDL mediati) possa correlare causalmente con le variazioni del rischio (Rothagi, NEJM 2014)...
- ... ma i livelli di HDL-c non correlano con i flussi!(Rothagi, NEJM 2014)

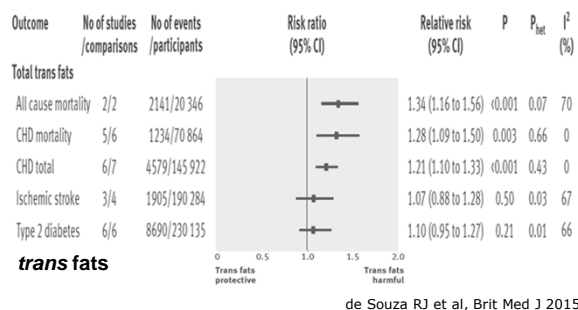
Acidi grassi e rischio cardiovascolare: come sono evolute le evidenze tra il 2000 ed oggi

	Associazione con il rischio CV la visione del 2000	Associazione con il rischio CV la visione del 2014
Grassi totali	++	=
Grassi saturi	++	+
Grassi insaturi trans	++	+++
Monounsaturi	-	=
Polinsaturi omega 6	-	--
Polinsaturi omega 3	--	--

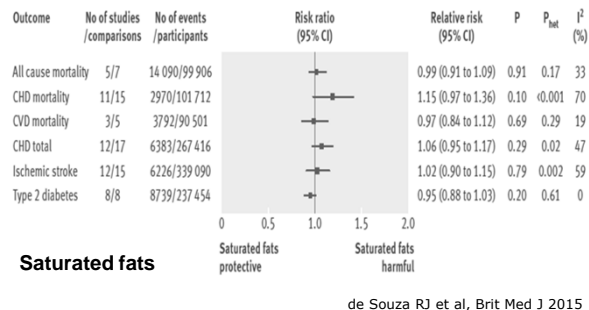
-: riduzione del rischio CV; ++: aumento del rischio CV; -: nessun effetto significativo.

Poli A, personal opinion, 2014

Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies



Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies



Lipidi Alimentari e Lipidi Plasmatici

△ colesterolo serico =

+ 0,0711 △ saturi

- 0,0365 △ polinsaturi

+ 0,0043 △ colesterolo alimentare

Hegsted, 1993

Total fat and different types of fat intake in spanish high risk patients of the PREDIMED cohort: effects on all-cause mortality

Total fat	1408 (5.3)	1408 (6.9)	1407 (5.3)	1408 (6.0)	1407 (6.0)
Cases, n (%)	31.3	36.7	40.2	43.5	48.2
Median, % of energy	31.3	36.7	40.2	43.5	48.2
Multivariable model 1	1 (Ref)	1.04 (0.77, 1.40)	0.73 (0.53, 1.01)	0.80 (0.58, 0.82)	0.57 (0.40, 0.82)
Multivariable model 2	1 (Ref)	1.02 (0.75, 1.37)	0.71 (0.51, 0.98)	0.75 (0.54, 1.05)	0.53 (0.37, 0.76)
MUFAs					
Cases, n (%)	1408 (6.3)	1408 (6.1)	1407 (5.9)	1408 (5.4)	1407 (5.4)
Median, % of energy	14.7	17.9	20.5	22.8	26.0
Multivariable model 1	1 (Ref)	0.85 (0.62, 1.16)	0.78 (0.56, 1.08)	0.70 (0.49, 1.00)	0.64 (0.43, 0.95)
Multivariable model 2	1 (Ref)	0.86 (0.63, 1.17)	0.78 (0.56, 1.09)	0.69 (0.48, 0.99)	0.64 (0.43, 0.94)
PUFAs					
Cases, n (%)	1408 (8.1)	1408 (5.9)	1407 (5.9)	1408 (4.9)	1407 (4.4)
Median, % of energy	4.2	5.3	6.2	7.2	9.0
Multivariable model 1	1 (Ref)	0.72 (0.53, 0.97)	0.71 (0.52, 0.97)	0.56 (0.40, 0.78)	0.50 (0.35, 0.71)
Multivariable model 2	1 (Ref)	0.73 (0.54, 0.99)	0.72 (0.53, 0.99)	0.56 (0.39, 0.80)	0.50 (0.35, 0.73)
SFAs					
Cases, n (%)	1408 (5.0)	1408 (5.8)	1407 (5.7)	1408 (6.2)	1407 (6.6)
Median, % of energy	6.9	8.3	9.4	10.5	12.1
Multivariable model 1	1 (Ref)	1.20 (0.86, 1.68)	1.17 (0.82, 1.67)	1.22 (0.84, 1.77)	1.21 (0.81, 1.80)
Multivariable model 2	1 (Ref)	1.16 (0.83, 1.62)	1.12 (0.78, 1.61)	1.12 (0.78, 1.60)	1.08 (0.74, 1.58)
trans Fat					
Cases, n (%)	1408 (4.8)	1408 (5.9)	1407 (4.7)	1408 (6.4)	1407 (7.5)
Median, % of energy	0.05	0.10	0.16	0.23	0.36
Multivariable model 1	1 (Ref)	1.15 (0.83, 1.60)	0.90 (0.64, 1.29)	1.22 (0.87, 1.72)	1.38 (1.06, 1.94)
Multivariable model 2	1 (Ref)	1.11 (0.80, 1.54)	0.86 (0.59, 1.24)	1.13 (0.78, 1.64)	1.29 (0.87, 1.90)

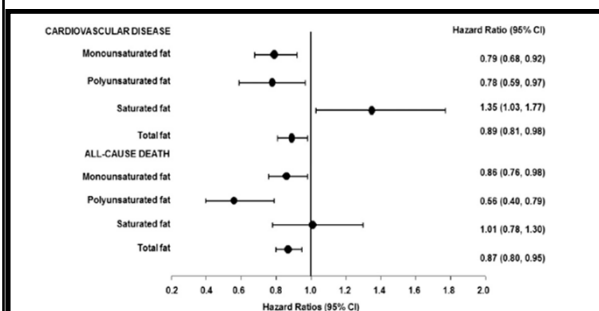
Guasch-Ferré M et al, Am J Clin Nutr 2015

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Guasch-Ferré M et al, Am J Clin Nutr 2015

Total fat and different types of fat intake in spanish high risk patients of the PREDIMED cohort: effects on all-cause mortality



Guasch-Ferré M et al, Am J Clin Nutr 2015

Dairy, total CVD and CHD: a metanalysis

Study name	Rate ratio	Lower limit	Upper limit
Kondo 2013 (F)	0.79	0.62	1.00
Kondo 2013 (M)	1.12	0.60	1.29
Louie 2013	0.76	0.56	1.03
Somewell 2011	0.89	0.78	1.01
Bornhals 2010	0.28	0.06	1.32
SRRE =	0.88	0.75	1.04



Fig. 2. Meta-analysis of total dairy intake and total CVD (high v. low intake analysis). SRRE, summary relative risk estimate. Individual studies required to report a composite total dairy variable and a composite total CVD variable. F, female; M, male.

Study name	Rate ratio	Lower limit	Upper limit
Bernstein 2010	0.99	0.91	1.08
Bostock 1999	0.94	0.66	1.34
Haring 2014	1.04	0.84	1.29
Kondo 2013 (F)	0.60	0.36	1.00
Kondo 2013 (M)	1.49	0.91	2.45
Louie 2013	0.71	0.51	0.99
Pattinson 2013	0.77	0.63	0.95
Soodanah-Mukhi 2012	0.91	0.68	1.22
SRRE =	0.91	0.80	1.04

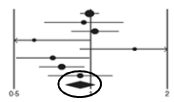
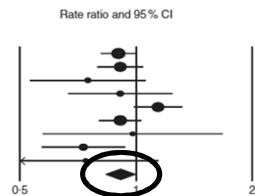


Fig. 3. Meta-analysis of total dairy intake and total CHD (high v. low intake analysis). SRRE, summary relative risk estimate. Individual studies required to report a composite total dairy variable and a composite total CHD variable. F, female; M, male.

Alexander DD et al, Brit J Nutr 2016

Dairy and stroke: a metanalysis

Study name	Rate ratio	Lower limit	Upper limit
Bernstein 2012 (F)	0.90	0.81	1.00
Bernstein 2012 (M)	0.91	0.79	1.04
Kondo 2013 (F)	0.75	0.53	1.06
Kondo 2013 (M)	0.91	0.67	1.24
Larsson 2009 (ischaemic)	1.14	0.99	1.32
Larsson 2012	0.91	0.80	1.03
Louie 2013	0.98	0.57	1.68
Sauvaget 2003	0.73	0.57	0.94
Lin 2013	0.74	0.48	1.14
SRRE =	0.91	0.83	0.99



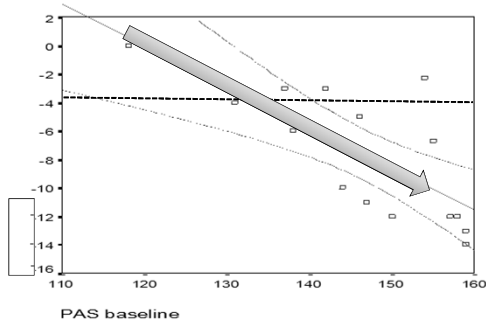
$P_H = 0.324$

$I^2 = 0.0$

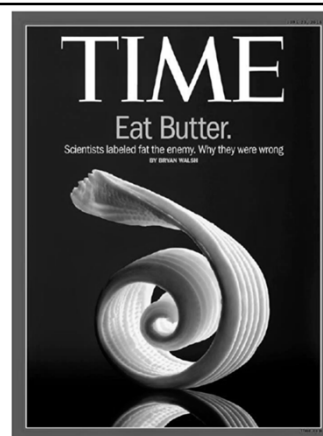
Removal of Larsson 2009 in a sensitivity analyses resulted in and SRRE of 0.88 (95% CI 0.83, -0.94) with no heterogeneity ($P_H = 0.73$, $I^2 = 0.00$)

Alexander DD et al, Brit J Nutr 2016

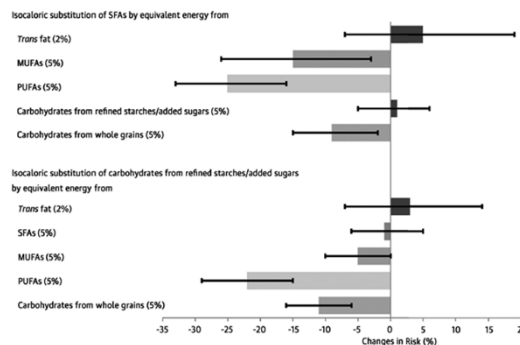
Tripeptidi del latte: riduzione PAS e PAS basale negli studi controllati disponibili



Cicero A et al, personal communication, 2009



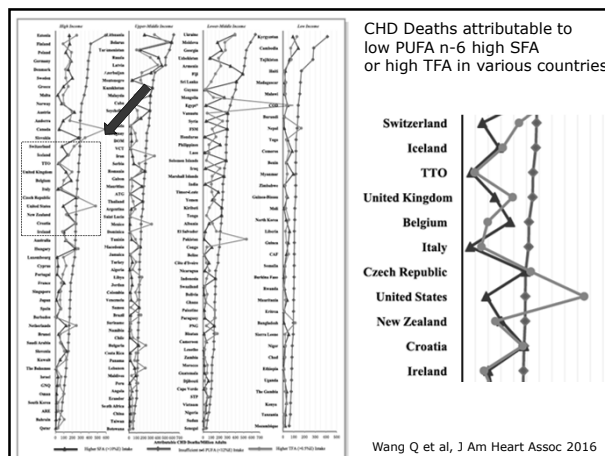
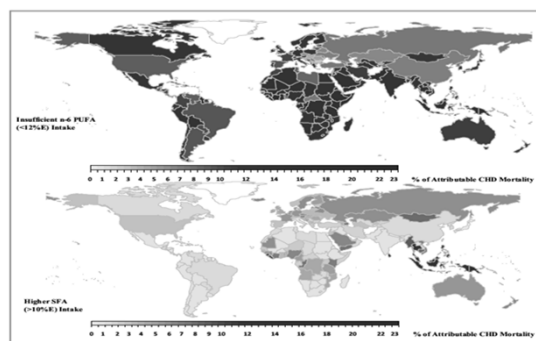
Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of CHD



Li J et al, JACC 2015

Impact of Nonoptimal Intakes of Saturated, Polyunsaturated, and Trans Fat on Global Burdens of Coronary Heart Disease

Qianyi Wang, ScD; Ashkan Afshin, ScD, MD; Mohammad Yawar Yakoob, ScD, MD; Gitanjali M. Singh, PhD; Colin D. Rehm, PhD, MPH; Shahab Khatibzadeh, MD; Renata Micha, PhD; Peilin Shi, PhD; Dariush Mozaffarian, MD, DrPH; on behalf of the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE)*



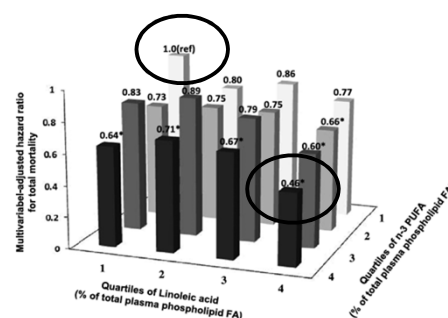
Wang Q et al, J Am Heart Assoc 2016

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		Proportion of CHD Deaths (%) due to (95%UI)		
		Higher SFA (>10%E) Intake†	Insufficient N-6 PUFA (<12%E)intake‡	High TFA (>0.5%E) intake §
Italy				
Age 25-69	36342055	1.7 (1.3, 2.1)	13.9 (12.1, 15.6)	5.2 (4.7, 5.8)
Age 70+	9165930	1.1 (0.6, 1.5)	9.7 (7.6, 11.8)	3.1 (2.6, 3.7)
Female	23795067	1.1 (0.8, 1.5)	9.9 (8.3, 11.5)	3.4 (3, 3.8)
Male	21712918	1.3 (0.9, 1.7)	11.4 (9.6, 13.2)	3.8 (3.3, 4.3)
All	45507985	1.2 (1, 1.5)	10.7 (9.5, 11.8)	3.6 (3.3, 4)

Omega-3, omega-6 in plasma PL and all-cause mortality



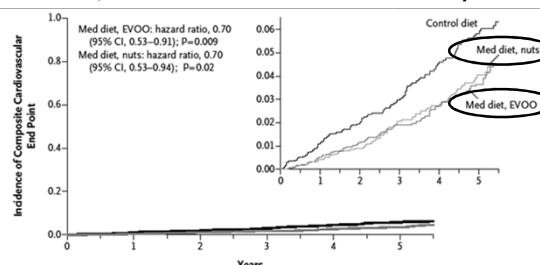
Wu JHY et al, Circulation 2014

Plasma fatty acids in vegans and omnivorous

Fatty acids	Vegans (n = 40)	Soldiers (n = 78)
14:0	0.76 ± 0.64	0.83 ± 0.36
16:0	22.39 ± 1.44	23.21 ± 1.27*
18:0	14.28 ± 1.08	14.38 ± 0.83
18:1trans	0.38 ± 0.25	1.26 ± 0.55*
18:1n9	17.95 ± 1.88	16.16 ± 1.33*
18:2trans	0.51 ± 0.33	0.90 ± 0.18*
18:2n6	18.70 ± 2.68	18.50 ± 1.91
18:3n3	0.49 ± 0.21	0.32 ± 0.13*
20:3n6	2.08 ± 0.42	1.97 ± 0.42
20:4n6	11.95 ± 1.90	12.94 ± 1.65
20:5n3 (EPA)	0.56 ± 0.22	0.40 ± 0.18*
22:4n6	2.44 ± 0.49	2.34 ± 0.44
22:5n3	2.02 ± 0.48	1.51 ± 0.27*
22:6n3 (DHA)	2.28 ± 0.70	2.61 ± 0.65
Omega-3 Index**	3.48 ± 0.81	3.47 ± 0.72

Sarter B et al, Clin Nutr 2014

The PREDIMED Study: incidence of Primary End-Points in the Nuts, EV Olive Oil and in the Control Groups



No. at Risk	Control diet	Med diet, EVOO	Med diet, nuts
2450	2268	2020	1583
2543	2486	2320	1987
2454	2343	2093	1657
			1268
			1687
			1310
			1389
			1031

Estruch R et al, N Engl J Med 2013

Olio di oliva V/EV o "normale"

Risk of cardiovascular events and mortality according to baseline extra-virgin olive oil intake

	Energy-adjusted tertiles of extra-virgin olive oil intake			P for trend	Energy-adjusted extra virgin olive oil intake (10 g/d)
	1 (low) (n = 2,405)	2 (n = 2,406)	3 (high) (n = 2,405)		
Mean extra-virgin olive oil intake	9.1 ± 11.23	19.5 ± 20.0	34.6 ± 27.4		
Major CVD events					
Cardiovascular event, % (n)	4.6 (111)	4.2 (101)	2.7 (65)		3.8 (277)
Multivariable model 1	1 (Ref.)	1.01 (0.77, 1.33)	0.60 (0.43, 0.82)	< 0.01	0.89 (0.84, 0.95)
Multivariable model 2	1 (Ref.)	1.00 (0.76, 1.32)	0.60 (0.44, 0.84)	< 0.01	0.90 (0.85, 0.95)
Multivariable model 3	1 (Ref.)	0.99 (0.75, 1.31)	0.61 (0.44, 0.85)	< 0.01	0.90 (0.85, 0.95)
All-cause mortality					
	1 (low) (n = 2,405)	2 (n = 2,406)	3 (high) (n = 2,405)	P for trend	
All causes of mortality, % (n)	5.2 (125)	4.2 (100)	4.1 (98)		4.5 (323)
Multivariable model 1	1 (Ref.)	0.88 (0.67, 1.15)	0.81 (0.61, 1.07)	0.19	0.95 (0.91, 1.00)
Multivariable model 2	1 (Ref.)	0.84 (0.64, 1.10)	0.80 (0.60, 1.07)	0.20	0.95 (0.90, 1.00)
Multivariable model 3	1 (Ref.)	0.84 (0.64, 1.10)	0.82 (0.61, 1.09)	0.25	0.96 (0.91, 1.01)

Guasch-Ferré M et al, BMC Medicine 2014

Olio di oliva V/EV o "normale"

Risk of cardiovascular events and mortality according to baseline common olive oil intake

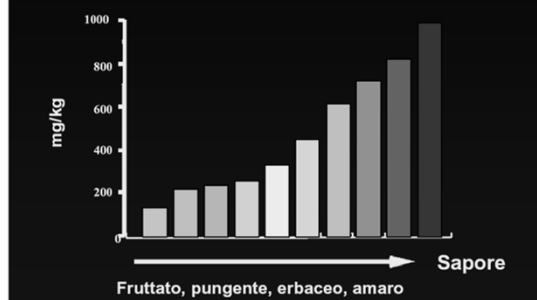
	Energy-adjusted tertiles of common olive oil intake			P for trend	Energy-adjusted common olive oil intake (10 g/d)
	1 (low) (n = 2,405)	2 (n = 2,406)	3 (high) (n = 2,405)		
Mean common olive oil intake	12.1 ± 11.7	18.6 ± 18.5	21.7 ± 25.9		
Major CVD events					
Cardiovascular event, % (n)	3.5 (85)	3.6 (86)	4.4 (106)		3.8 (277)
Multivariable model 1	1 (Ref.)	1.06 (0.78, 1.45)	1.20 (0.88, 1.62)	0.23	1.04 (0.99, 1.10)
Multivariable model 2	1 (Ref.)	1.01 (0.74, 1.38)	1.13 (0.83, 1.54)	0.35	1.04 (0.98, 1.10)
Multivariable model 3	1 (Ref.)	0.99 (0.73, 1.36)	1.11 (0.82, 1.51)	0.40	1.03 (0.98, 1.09)
All-cause mortality					
	1 (low) (n = 2,405)	2 (n = 2,406)	3 (high) (n = 2,405)	P for trend	
All causes of mortality, % (n)	4.2 (101)	4.4 (106)	4.8 (116)		4.5 (323)
Multivariable model 1	1 (Ref.)	1.14 (0.86, 1.51)	1.17 (0.88, 1.51)	0.34	1.01 (0.96, 1.07)
Multivariable model 2	1 (Ref.)	1.10 (0.83, 1.47)	1.16 (0.83, 1.54)	0.37	1.01 (0.96, 1.07)
Multivariable model 3	1 (Ref.)	1.09 (0.82, 1.45)	1.14 (0.85, 1.51)	0.44	1.01 (0.96, 1.07)

Guasch-Ferré M et al, BMC Medicine 2014

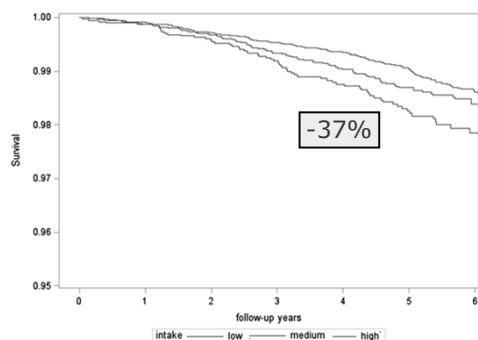
Costituenti dell'olio d'oliva

- Trigliceridi
- Idrocarburi
- Esteri non-glicerici
- Tocoferoli
- **Polifenoli**
- Steroli
- Acidi e alcoli terpenici
- Pigmenti
- Clorofille
- Carotenoidi
- **Polifenoli (50-800 mg/Kg)**
 - Idrossitirosolo
 - Oleuropeina
 - Tirosole
 - Acido caffeico
 - Ligstroside
 - Acido vanillico
 - Esteri di idrossitirosolo
 - Acido sinapico
 - Acido sirigico

Contenuto in polifenoli e gusto dell'olio



Polyphenol intake and all-cause mortality risk: a re-analysis of the PREDIMED trial



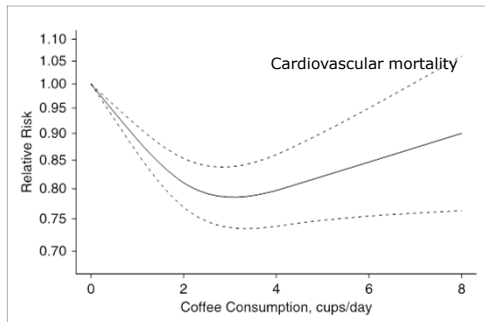
Tresserra-Rimbau A et al, BMC Medicine 2014

Cause specific mortality, according to frequency of nut consumption

Cause of Death and Type of Nut	Women	Men	Pooled	Hazard Ratio (95% CI)
All causes				
Any nut	+	+	+	0.86 (0.82-0.89)
Peanut	+	+	+	0.88 (0.84-0.91)
Tree nut	+	+	+	0.83 (0.79-0.88)
Cancer				
Any nut	+	+	+	0.91 (0.85-0.97)
Peanut	+	+	+	0.94 (0.88-1.02)
Tree nut	+	+	+	0.83 (0.76-0.90)
Heart disease				
Any nut	+	+	+	0.74 (0.68-0.81)
Peanut	+	+	+	0.76 (0.68-0.84)
Tree nut	+	+	+	0.76 (0.67-0.85)
Respiratory disease				
Any nut	+	+	+	0.81 (0.65-1.01)
Peanut	+	+	+	0.84 (0.71-0.99)
Tree nut	+	+	+	0.90 (0.74-1.09)
Neurodegenerative disease				
Any nut	+	+	+	0.98 (0.80-1.22)
Peanut	+	+	+	1.02 (0.84-1.24)
Tree nut	+	+	+	0.95 (0.71-1.26)
Stroke				
Any nut	+	+	+	0.92 (0.79-1.08)
Peanut	+	+	+	0.97 (0.87-1.08)
Tree nut	+	+	+	0.96 (0.78-1.19)

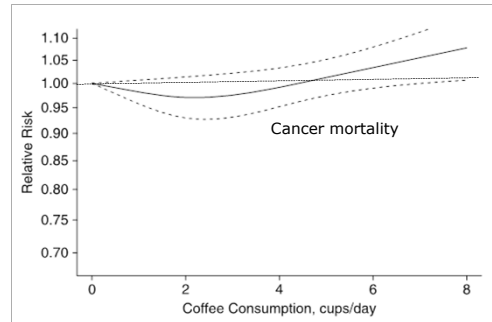
Bao Y et al, N Engl J Med 2013

Coffee Consumption and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Dose-Response Meta-Analysis



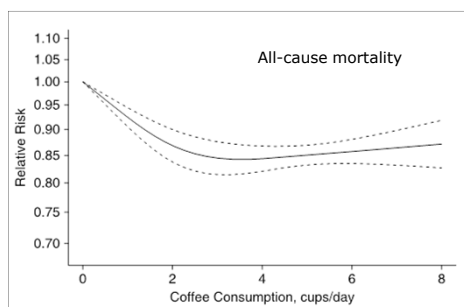
Crippa A et al, Am J Epidemiol 2014

Coffee Consumption and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Dose-Response Meta-Analysis



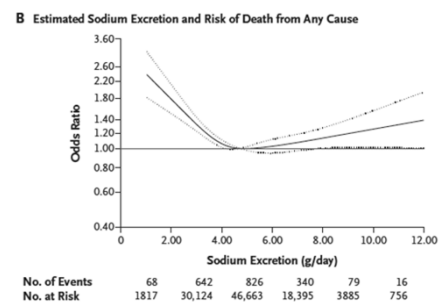
Crippa A et al, Am J Epidemiol 2014

Coffee Consumption and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Dose-Response Meta-Analysis



Crippa A et al, Am J Epidemiol 2014

Sodium, Potassium and all cause mortality: the PURE Study



O'Donnell M et al, N Engl J Med, 2014

Research

Original Investigation

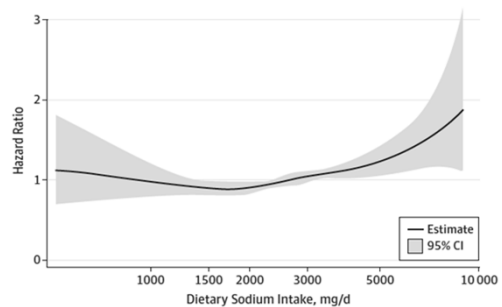
Dietary Sodium Content, Mortality, and Risk for Cardiovascular Events in Older Adults The Health, Aging, and Body Composition (Health ABC) Study

Andreas P. Kalogeropoulos, MD, MPH, PhD; Vasiliki V. Georgopoulos, MD; Rachel A. Murphy, PhD; Anne B. Newman, MD, MPH; Douglas C. Bauer, MD; Tamara B. Harris, MD, MS; Zhou Yang, MPH, PhD; William B. Applegate, MD, MPH; Stephen B. Kritchevsky, PhD

Circa 2500 soggetti di età media 73 anni, di ambo i sessi
Consumo di sale accertato mediante questionari alimentari
CVD all'arruolamento: 25% circa; BMI medio: 27
Follow-up: 10 anni
End-point primario: mortalità per tutte le cause

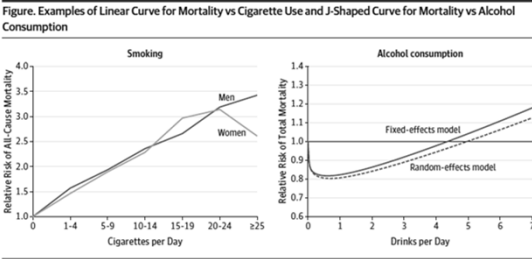
Kalogeropoulos AP et al, JAMA Intern Med 2015

Dietary sodium and mortality in the Health ABC Study



Kalogeropoulos AP et al, JAMA Intern Med 2015

J-Shaped Curves and Public Health



Chokshi DA et al, JAMA 2015

Sensibilità al sale in vari gruppi

TABLE 1 Salt Sensitivity in Various Groups*

Salt Resistant	Salt Sensitive
Young	Aged
Middle-aged	Hypertensive
Normotensive	African American
Caucasian	Chronic kidney disease
	History of pre-eclampsia
	Low birth weight

*Data derived from Weinberger et al. (4), de Bler et al. (9), Koomans et al. (10), Martillotti et al. (11), Weinberger (12,13), and Weinberger et al. (14)

Farquhar WB et al, J Am Coll Cardiol 2015

Healthy eating and mortality in a cohort of CHD patients
whit state-of-the-art drug treatment

The Dutch Healthy Nutrient and Food Score (DHNaFS) included 11 nutrient-dense food groups: vegetables, fruit, whole grains, protein-rich plant foods (mostly legumes), potatoes, lean meat, fish, eggs, low-fat milk and yogurt, oils and soft margarines, and noncaloric drinks.

The Dutch Undesirable Nutrient and Food Score (DUNaFS) included 13 food groups high in solid fats, sodium, and/or added sugar: processed fruit, high-fat meat, processed meat, full-fat milk, cheese; refined grains, butter and hard margarines, soups, spreads, ready-to-eat meals, savory snacks, sweet snacks, and sugar-sweetened beverages.

4,307 CHD pts from the Alpha-Omega Trial, 60-80 yrs at baseline, 10 yrs follow-

Sijstma FPC et al, Am J Clin Nutr, 2015

Healthy eating and mortality in a cohort of CHD patients
whit state-of-the-art drug treatment

Multivariable adjusted HRs for all-cause and CVD mortality across quintiles of the DHNaFS and the DUNaFS ¹							
		Q1	Q2	Q3	Q4	Q5	P-trend
All cause mortality							
DHNaFS							
Model 1	1	0.89 (0.72, 1.10)	0.74 (0.61, 0.90)	0.67 (0.54, 0.84)		0.57 (0.45, 0.71)	<0.0001
Model 2	1	0.97 (0.78, 1.20)	0.81 (0.66, 0.99)	0.78 (0.62, 0.99)		0.72 (0.56, 0.93)	0.0015
Model 3	1	0.95 (0.76, 1.18)	0.77 (0.63, 0.95)	0.76 (0.60, 0.97)		0.70 (0.55, 0.91)	0.0006
DUNaFS							
Model 1	1	1.12 (0.90, 1.39)	1.03 (0.83, 1.27)	1.09 (0.87, 1.36)		0.95 (0.75, 1.20)	0.552
Model 2	1	1.19 (0.94, 1.49)	1.10 (0.87, 1.39)	1.24 (0.95, 1.62)		1.08 (0.79, 1.48)	0.857
Model 3	1	1.22 (0.97, 1.54)	1.14 (0.89, 1.45)	1.28 (0.98, 1.68)		1.15 (0.84, 1.58)	0.702
Cardiovascular mortality							
DHNaFS							
Model 1	1	0.84 (0.60, 1.16)	0.62 (0.46, 0.84)	0.59 (0.41, 0.83)		0.61 (0.44, 0.85)	<0.0001
Model 2	1	0.88 (0.63, 1.23)	0.63 (0.46, 0.87)	0.65 (0.45, 0.94)		0.72 (0.50, 1.03)	0.008
Model 3	1	0.88 (0.63, 1.23)	0.59 (0.43, 0.82)	0.59 (0.41, 0.87)		0.68 (0.47, 0.99)	0.0002
DUNaFS							
Model 1	1	1.17 (0.83, 1.63)	0.90 (0.64, 1.26)	1.14 (0.81, 1.61)		1.05 (0.74, 1.48)	0.99
Model 2	1	1.19 (0.84, 1.68)	0.87 (0.60, 1.27)	1.17 (0.78, 1.76)		1.09 (0.68, 1.74)	0.651
Model 3	1	1.22 (0.86, 1.73)	0.92 (0.63, 1.24)	1.23 (0.82, 1.85)		1.15 (0.72, 1.84)	0.759

4,307 CHD pts from the Alpha-Omega Trial, 60-80 yrs at baseline, 10 yrs follow-

Sijstma FPC et al, Am J Clin Nutr, 2015

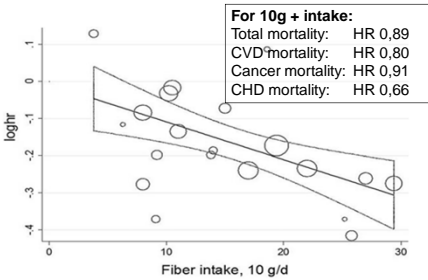
Healthy eating and mortality in a cohort of CHD patients
whit state-of-the-art drug treatment

Multivariable adjusted HRs for all-cause and CVD mortality across quintiles of the DHNaFS and the DUNaFS ¹							
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Model 3	1	1.22 (0.86, 1.73)	0.92 (0.63, 1.34)	1.23 (0.82, 1.85)		1.15 (0.72, 1.84)	0.759

4,307 CHD pts from the Alpha-Omega Trial, 60-80 yrs at baseline, 10 yrs follow-

Sijstma FPC et al, Am J Clin Nutr, 2015

Fiber consumption and all-cause, cardiovascular, and cancer mortalities: A systematic review and meta-analysis of cohort studies



Liu L et al, Mol Nutr Food Res, 2014

