58° Congresso Nazionale SIGG
Torino, 27-30 novembre 2013

SIMPOSIO
«IL FENOMENO DELLA REVERSE EPIDEMIOLOGY NELL' ANZIANO»

COLESTEROLO E OBESITA'

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REVERSE EPIDEMIOLOGY

Reverse epidemiology is a term used for a medical hypothesis which holds that High serum Cholesterol and Obesity may (counter intuitively) be protective and associated with greater survival in certain groups of people, such as very-old individuals or those with certain chronic diseases.

It further postulates that normal-low values of BMI or cholesterol may be detrimental and associated with higher mortality in asymptomatic people.

Kalantar-Zadeh et al. *Kidney International* in 2003; *Journal of American College of Cardiology* 2004

“REVERSE” EPIDEMIOLOGY

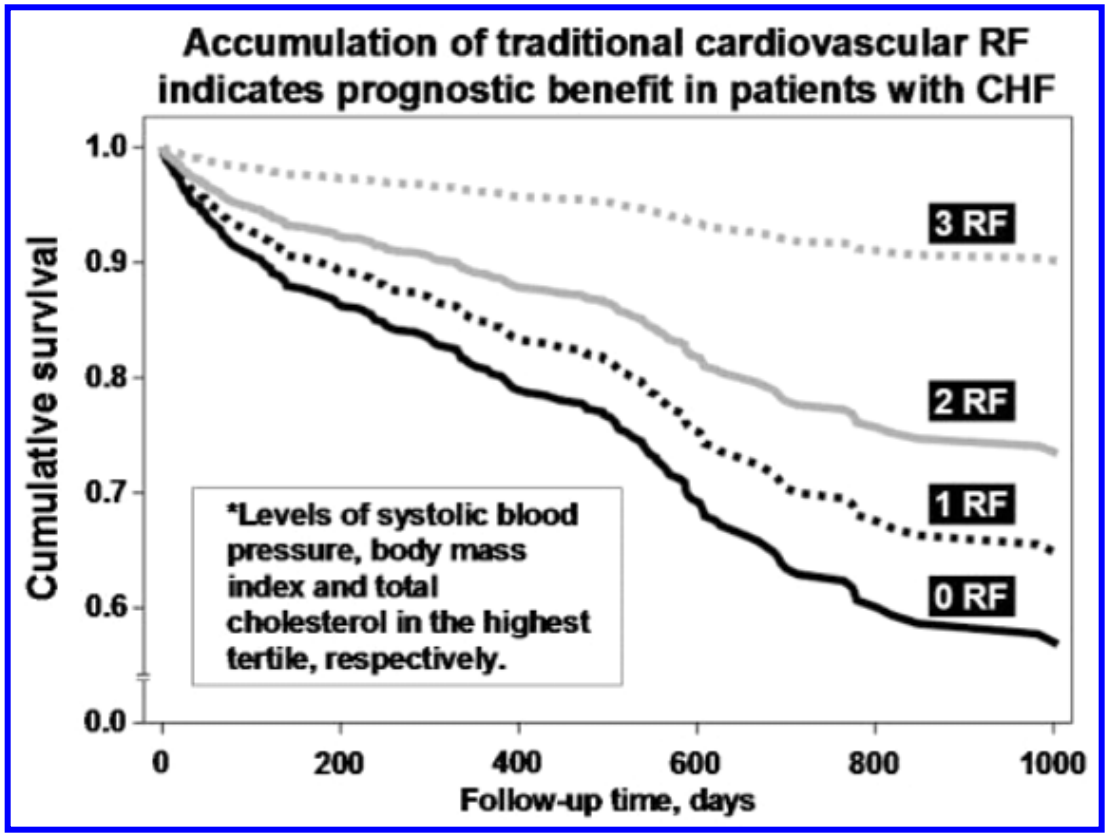
NEVERTHELESS:

- The term “reverse epidemiology” implies either epidemiology or biology might be different in this individuals
- It has NOT been proven that the rules of epidemiology have been reversed in these subjects. Indeed, the complexity of very-old/comorbid populations implies a great attention to distinguish between ***Association*** and ***Causation***, and to consider the importance of ***Confounding*** and ***Bias.***
- In particular, multimorbidity (clinical and sub-clinical) can change associations so drastically that they are dominated by ***Different Causal Pathways*** in this particular population.

Epidemiology and Risk of Heart Failure

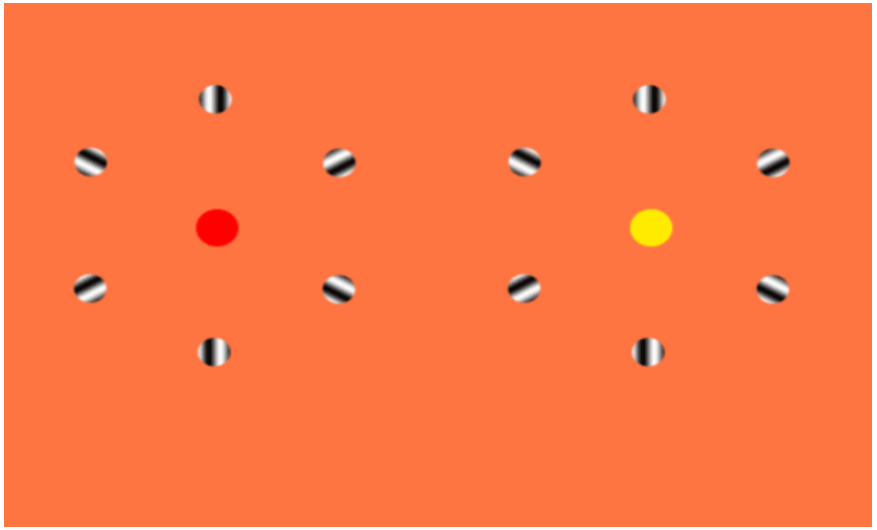
Abstract 3111: Reverse Epidemiology in Chronic Heart Failure: Cumulative Predictive Power of Classical Cardiovascular Risk Factors

Gülmisal Güder ; Stefan Frantz ; Johann Bauersachs ; Bruno Allolio ; Christoph Wanner ; Georg Ertl ; Christiane E Angermann ; Stefan Störk

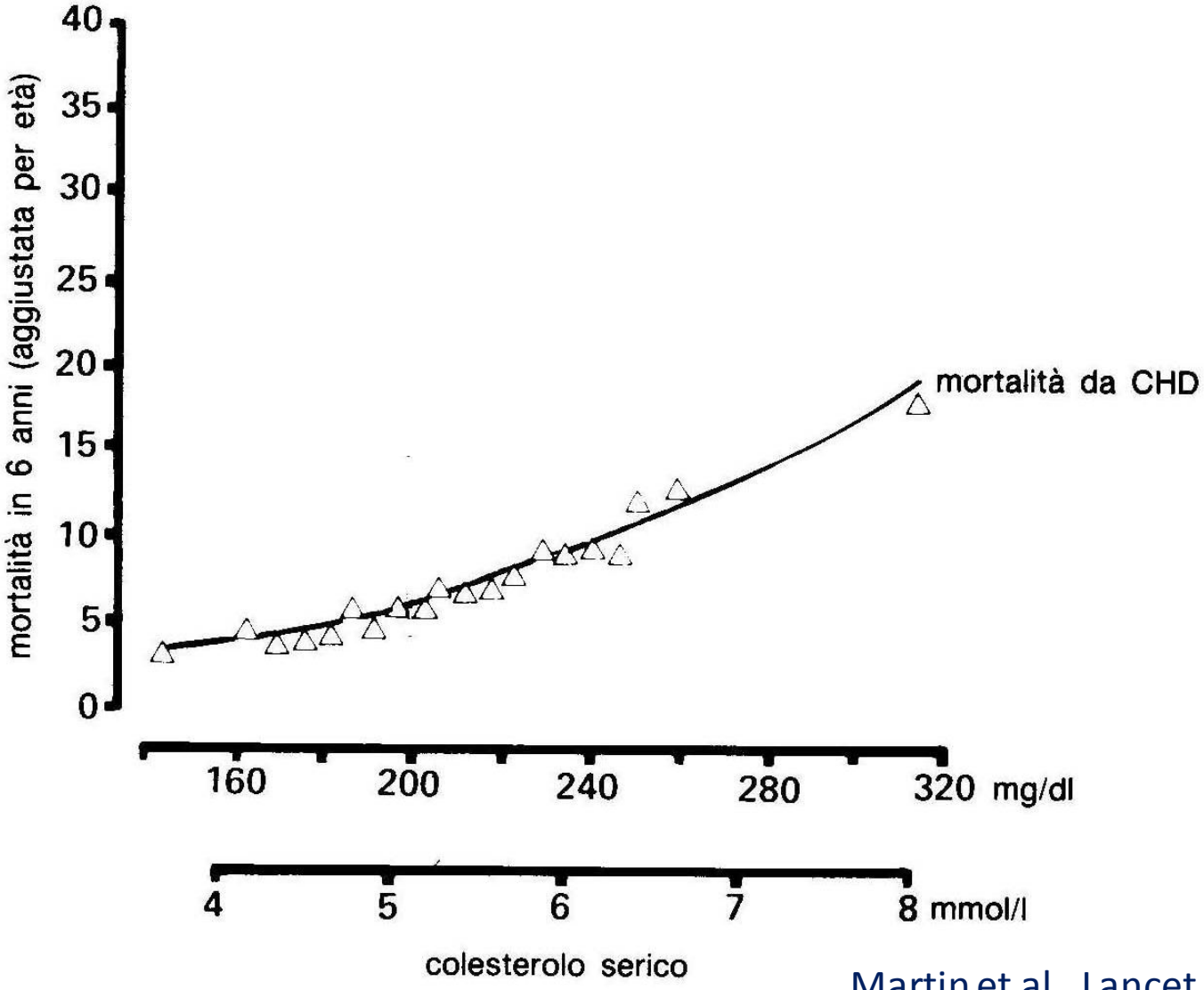


Circulation 2008

1. Serum cholesterol and the reverse epidemiology

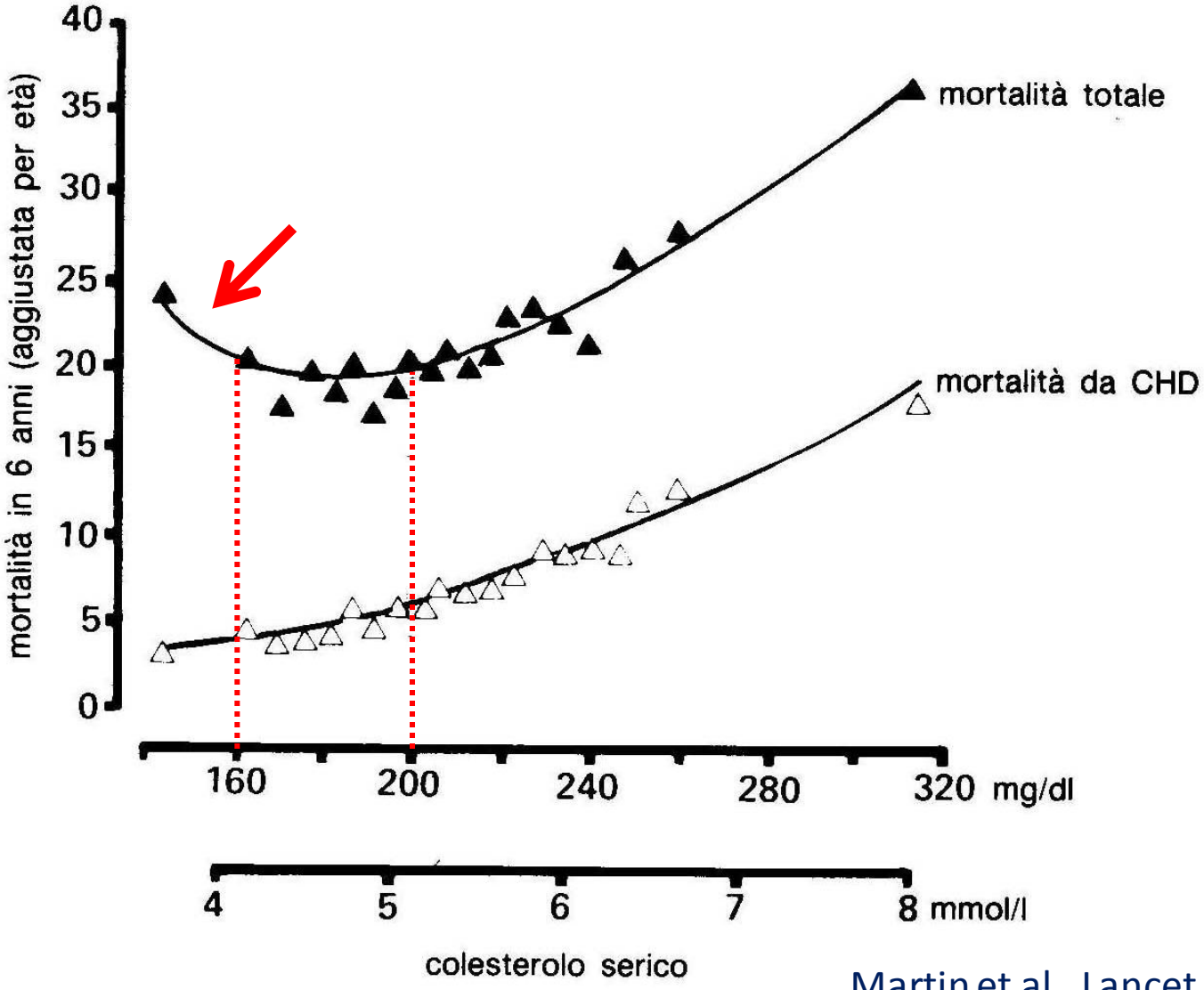


Relationship between total mortality (7 years) and serum total cholesterol in 356.222 men from MRFIT



Martin et al. Lancet 1986

Relationship between total mortality (7 years) and serum total cholesterol in 356.222 men from MRFIT



Martin et al. Lancet 1986

Report of the Conference on Low Blood Cholesterol: Mortality Associations

David Jacobs, PhD; Henry Blackburn, MD; Millicent Higgins, MD; Dwayne Reed, MD, PhD; Hiroyasu Iso, MD; Gardner McMillan, MD, PhD; James Neaton, PhD; James Nelson, MD; John Potter, MD, PhD; Basil Rifkind, MD; Jacques Rossouw, MD; Richard Shekelle, PhD; and Salim Yusuf, DPhil, for Participants in the Conference on Low Cholesterol: Mortality Associations

Background. **A National Heart, Lung, and Blood Institute (NHLBI) Conference was held October 9–10, 1990, to review and discuss existing data on U-shaped relations found between mortality rates and blood total cholesterol levels (TC) in some but not other studies. Presentations were given from 19 cohort studies from the United States, Europe, Israel, and Japan. A representative of each study presented its findings and also submitted tables of proportional hazards regression coefficients for entry TC levels in regard to death, and these were incorporated into a formal statistical overview adjusted for age, diastolic blood pressure, cigarette smoking, body mass index, and alcohol intake, as available.**

Methods and Results. **The U-shape for total mortality in men and the flat relation in women resulted largely from a positive relation of TC with coronary heart disease death and an inverse relation with deaths caused by some cancers (e.g., lung but not colon), respiratory disease, digestive disease, trauma, and residual deaths. Risk for combined noncardiovascular, noncancer causes of death decreased steadily across the range of TC. The conference considered possible explanations for the statistical associations found between low TC levels or active TC lowering and certain causes of death. One is that TC is lowered by some disease conditions themselves, such as wasting in chronic pulmonary disease or reduced production and secretion of cholesterol-bearing lipoproteins with liver disease. In this sort of situation, the TC:mortality association found in observational studies may be due to preexisting disease. This was addressed by excluding early deaths from the analysis, which did not change the results. The conference considered as well the biological function of cholesterol, which, if seriously deranged, might hypothetically cause a wide variety of diseases and dysfunction. The conference also considered the biological functions that might provide plausible mechanisms for the associations found.**

Conclusions. **Definitive interpretation of the associations observed was not possible, although most participants considered it likely that many of the statistical associations of low or lowered TC level are explainable by confounding in one form or another. The conference focused on the apparent existence and nature of these associations and on the need to understand their source rather than on any pertinence of the findings for public health policy. Further research is recommended to explain the observed associations of low TC levels (and TC lowering) with certain noncardiovascular diseases. This includes studies of the time course of TC change in disease, the relation of TC to morbidity, further studies of possible epidemiological confounding, monitoring of population trends in TC and mortality, further studies of the relations in women, auditing of noncardiovascular events in trials, studies of cell membrane, genetic and molecular links to cholesterol metabolism, TC level and disease, studies of disease manifestations in specific lipid disorders, and further study of the proposed causal mechanisms linking low TC and hemorrhagic stroke. (*Circulation* 1992;86:1046–1060)**

523.000 men + 124.000 women; age 35-69; 67.000 deaths; Follow-up 9 to 23 yrs

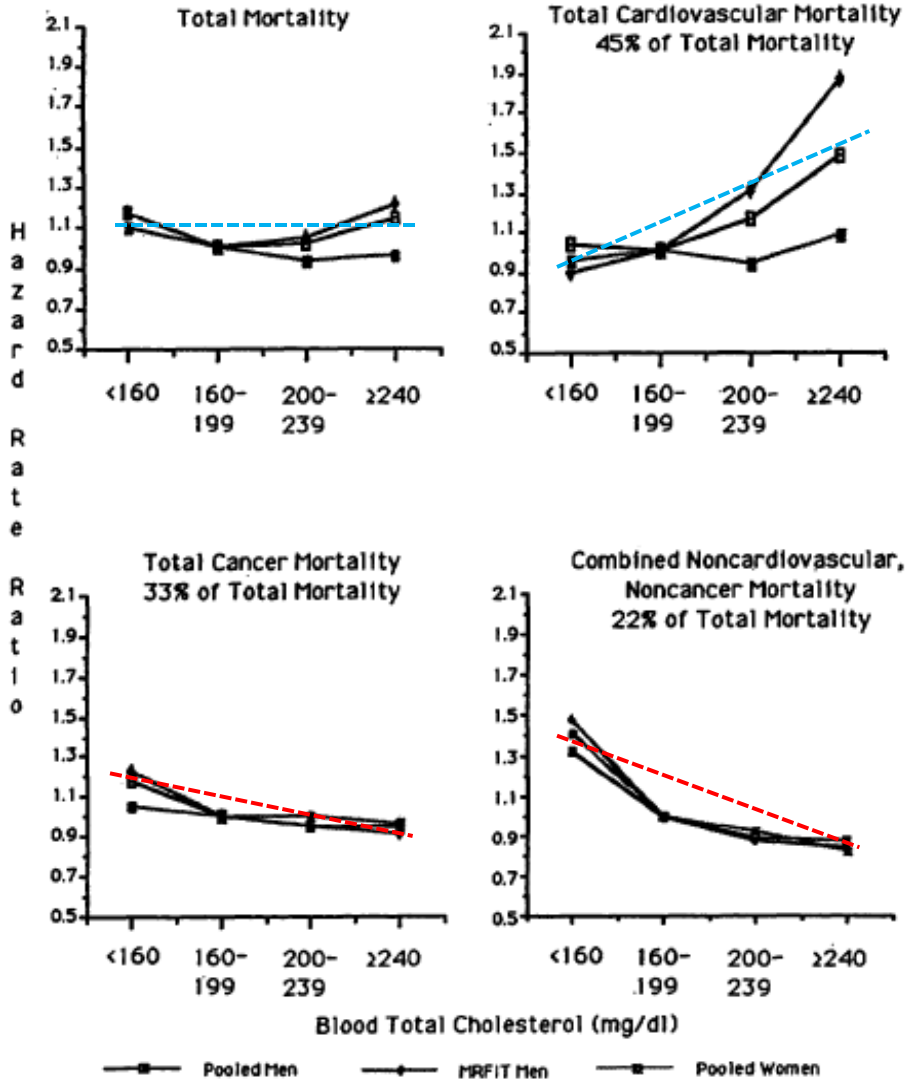


FIGURE 1. *Graphs of pooled and Multiple Risk Factor Intervention Trial (MRFIT) estimates of adjusted hazard rate ratios in deaths occurring at least 5 years after baseline in men and women aged 35–69 years without coronary heart disease at baseline.*

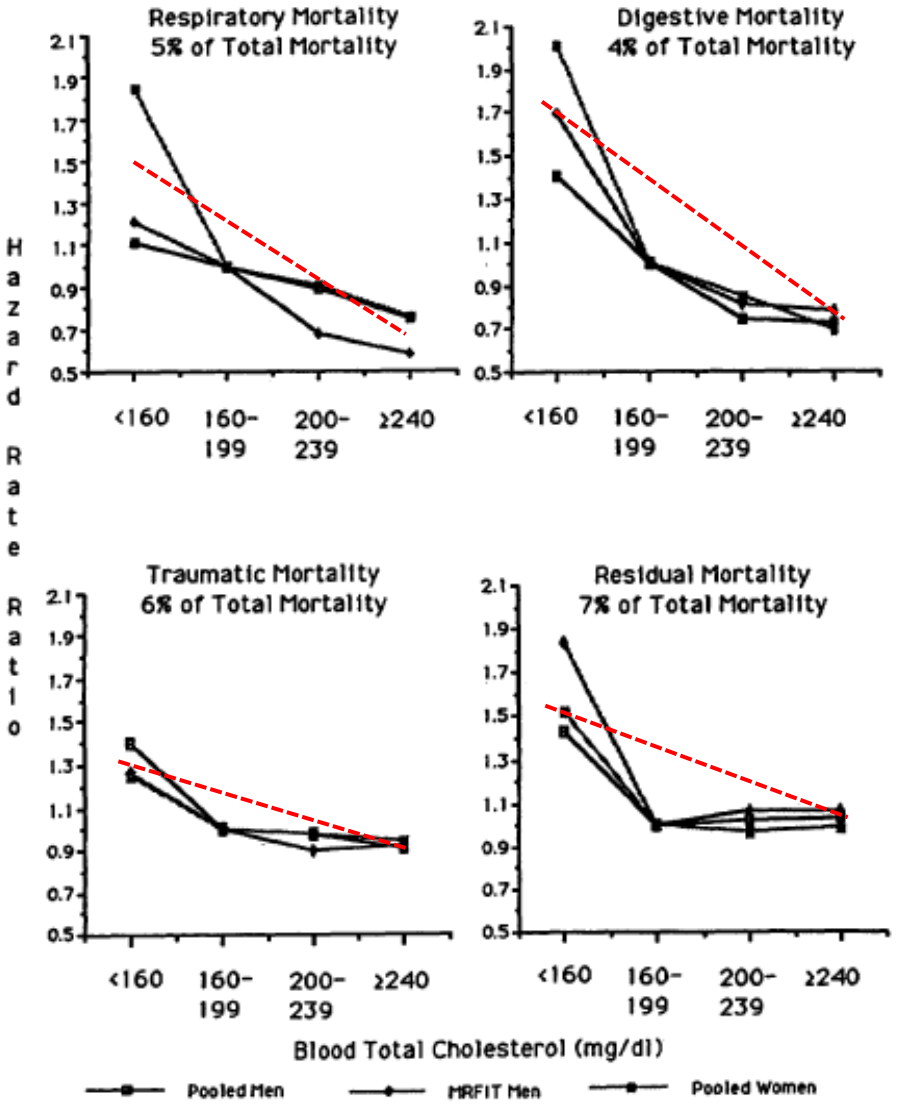
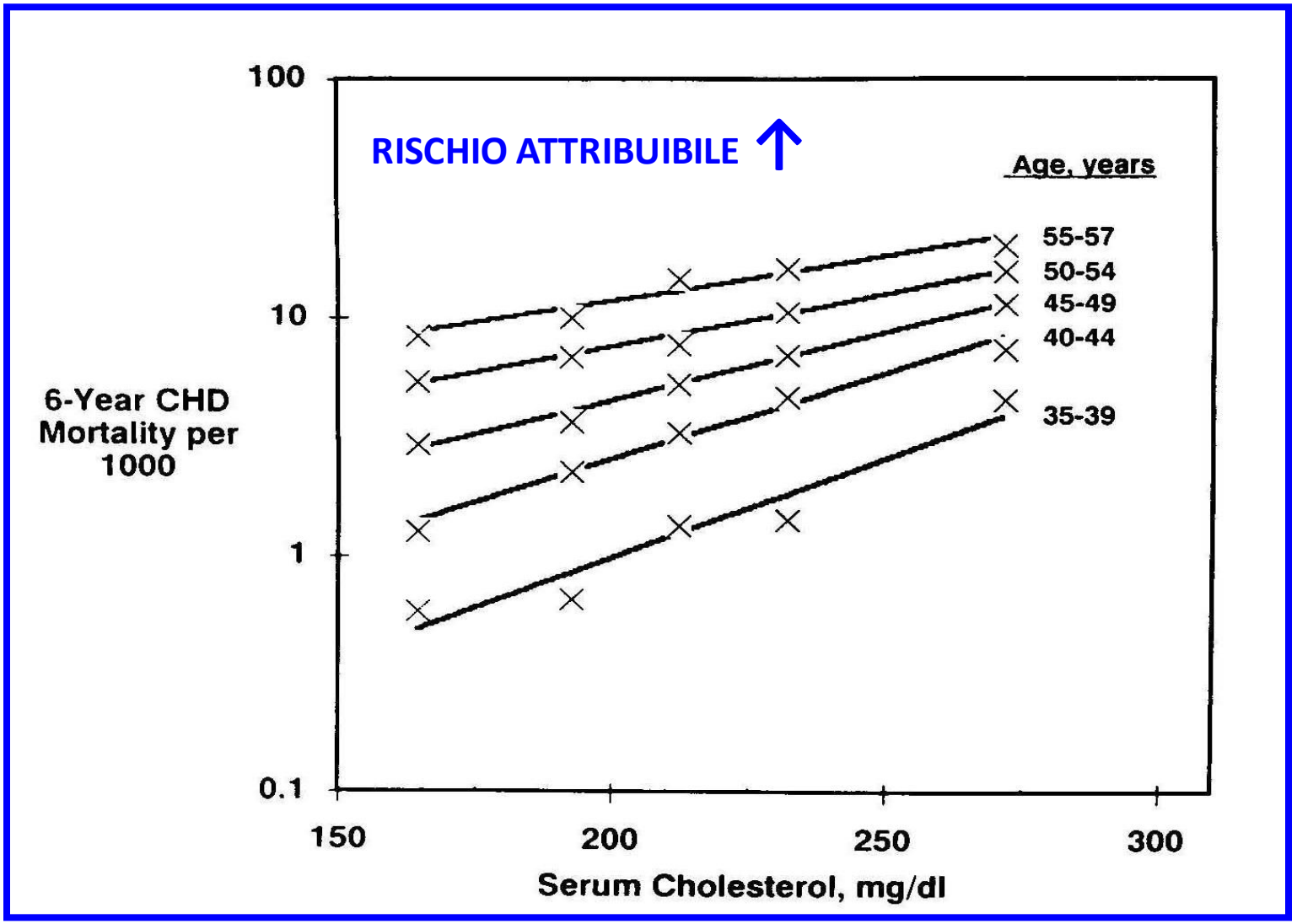


FIGURE 2. *Graphs of pooled and Multiple Risk Factor Intervention Trial (MRFIT) estimates of adjusted hazard rate ratios in deaths occurring at least 5 years after baseline in men and women aged 35–69 years without coronary heart disease at baseline.*

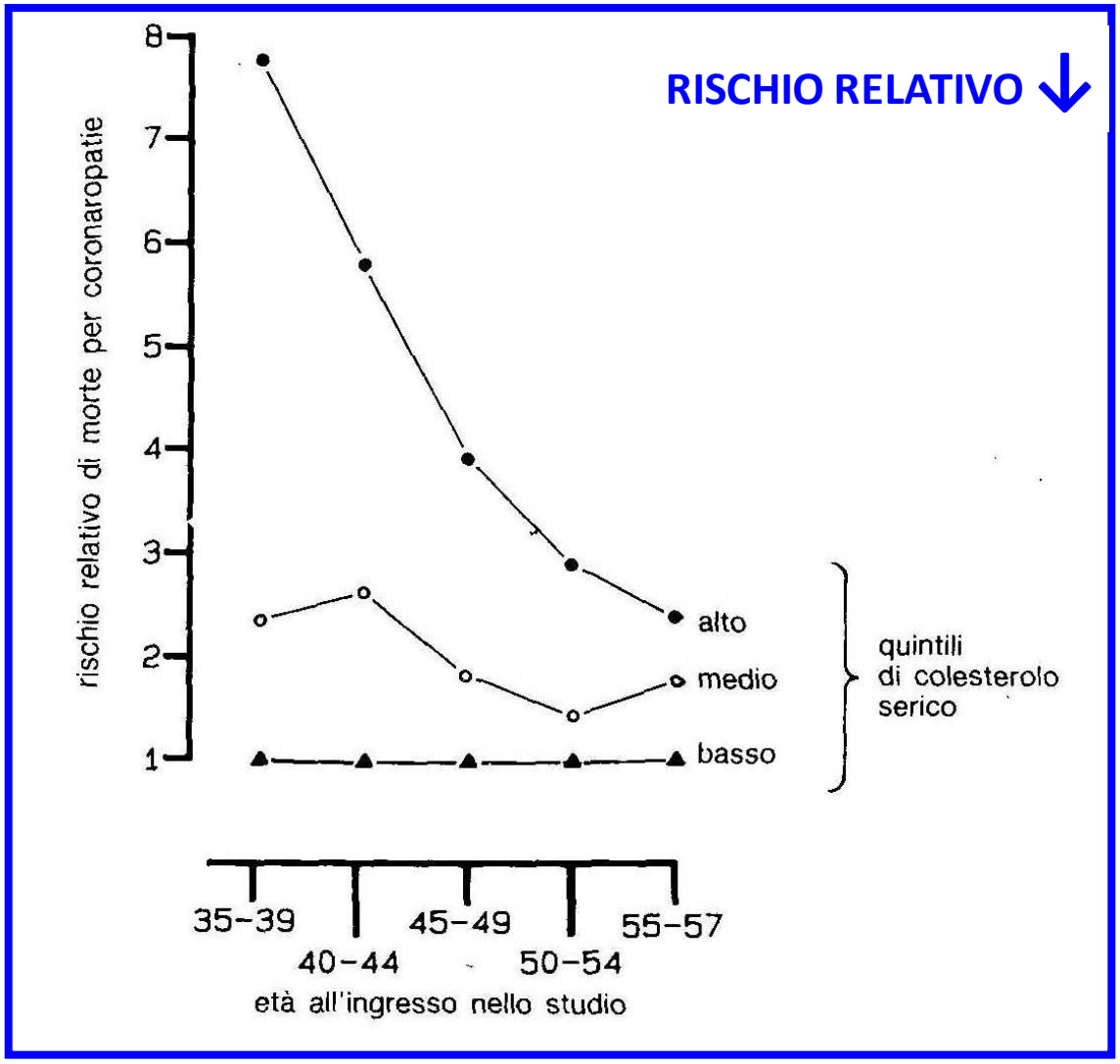
1a. Colesterolo, mortalità cardiovascolare e invecchiamento

Six year CHD mortality by total cholesterol levels and age in 356.222 men from MRFIT



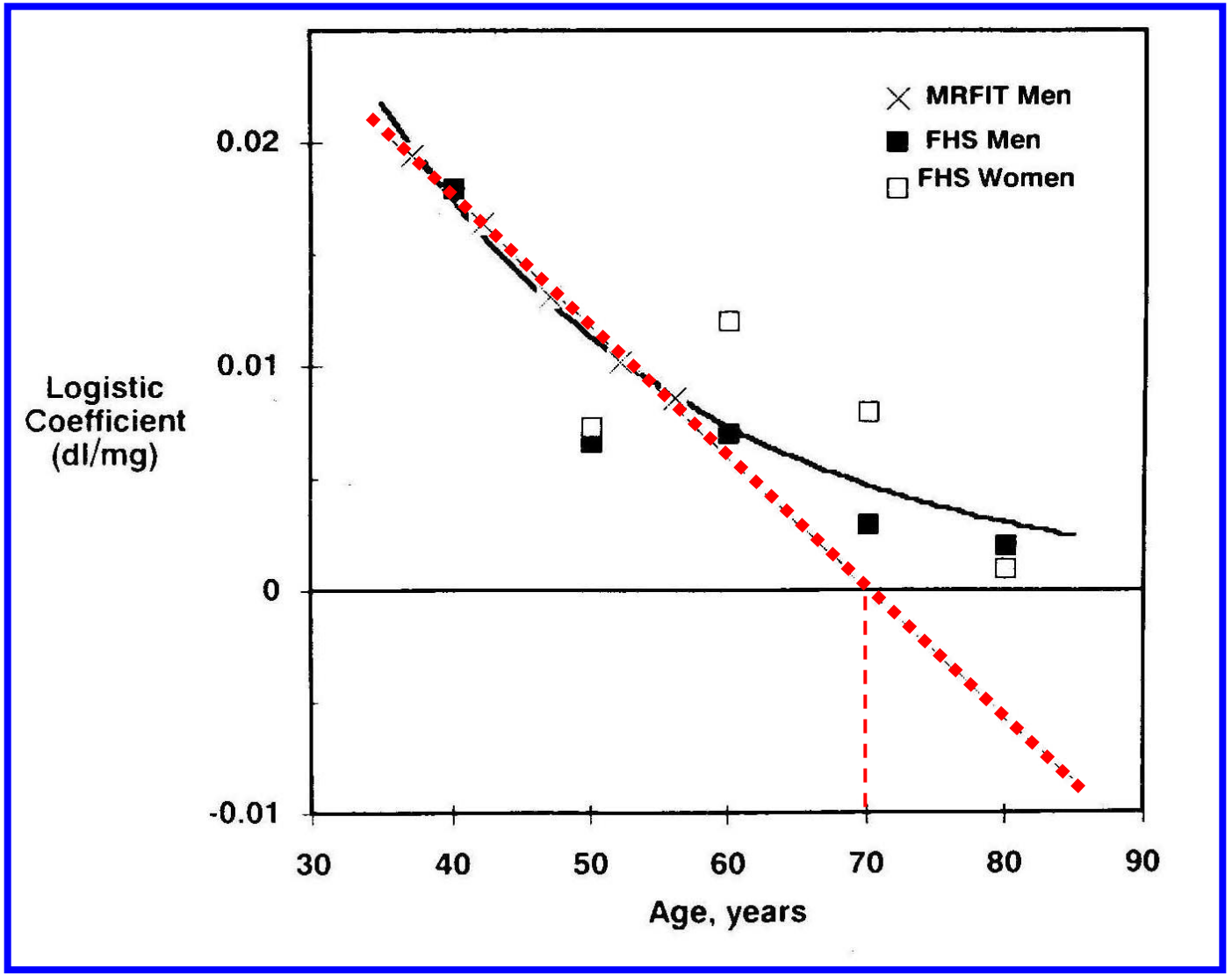
Gordon et al. Am J Card 1989

CHD mortality risk by age in men from MRFIT with high, average, and low total cholesterol levels



Stamler et al . JAMA 1986

Age-specific logistic regression coefficient relating cholesterol levels and CHD mortality in men & women from MRFIT and Framingham Study



Gordon et al. Am J Card 1989

ORIGINAL INVESTIGATION

Cholesterol Fractions and Apolipoproteins as Risk Factors for Heart Disease Mortality in Older Men

Robert Clarke, FRCP; Jonathan R. Emberson, PhD; Sarah Parish, DPhil; Alison Palmer, MSc†; Martin Shipley, MSc; Pamela Linksted, MSc; Paul Sherliker, BSc; Sarah Clark, DPhil; Jane Armitage, FRCP, FFPHM; Astrid Fletcher, PhD; Rory Collins, FRCP

Background: The relevance of blood lipid levels as risk factors for ischemic heart disease (IHD) in older people is uncertain; hence, cholesterol-lowering therapy is not routinely prescribed in older populations.

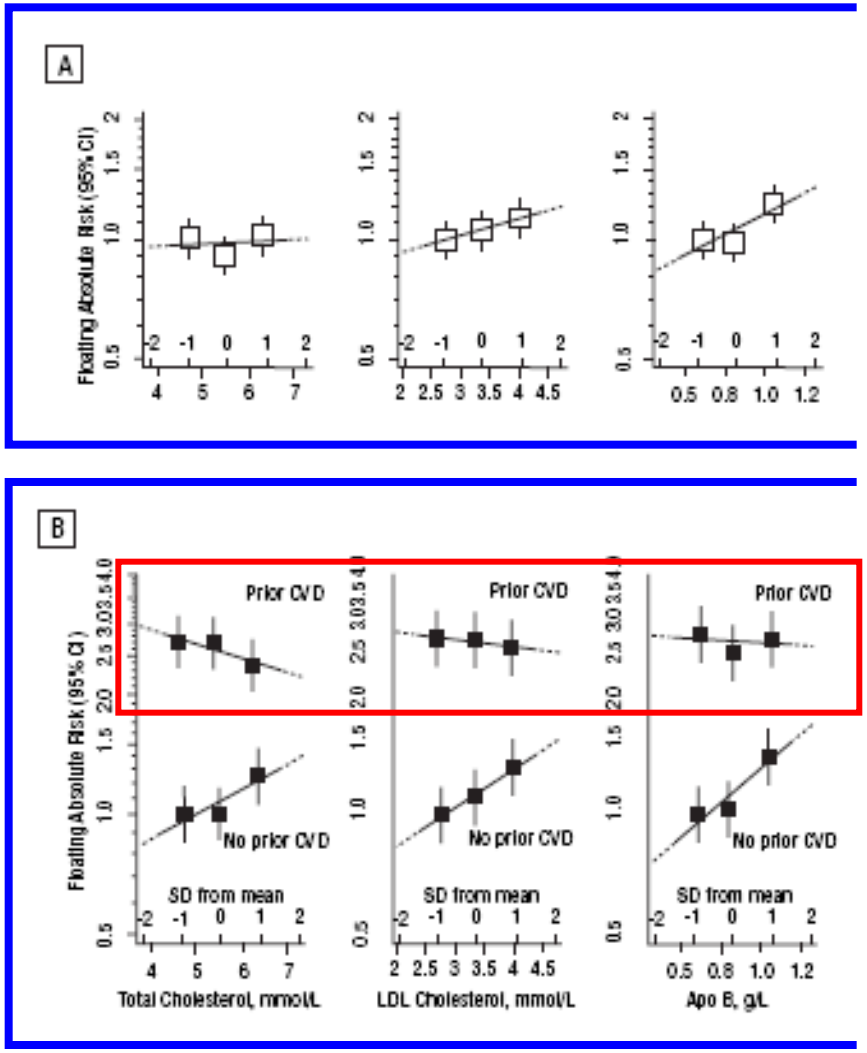
Methods: We assessed IHD mortality associations with plasma levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein B, and apolipoprotein A_1 measured in older men. Ischemic heart disease was assessed in a 7-year follow-up of a cohort of 5344 men (mean age, 76.9 years), including 74.3% without cardiovascular disease (CVD) or statin use and 25.6% with CVD or statin use. Hazard ratios (HRs) for 447 deaths from IHD were estimated for a 2-SD difference in usual plasma lipid levels.

Results: Ischemic heart disease mortality was not significantly associated with total cholesterol levels in all men (HR, 1.05), but a significant positive association in men without CVD and a slight nonsignificant inverse association in men with CVD were observed (HR, 1.47 vs 0.84). The patterns were similar for low-density lipoprotein cholesterol levels (HR, 1.50 vs 0.98) and for apolipoprotein B levels (HR, 1.68 vs 0.93). Ischemic heart disease risks were inversely associated with high-density lipoprotein cholesterol levels and with apolipoprotein A_1 levels in men with and without CVD. Ischemic heart disease risks were strongly associated with total–high-density lipoprotein cholesterol levels (HR, 1.57) and apolipoprotein B–apolipoprotien A_1 levels (HR, 1.54), and remained strongly related at all ages.

Conclusions: Blood lipid levels other than total cholesterol levels were associated with IHD in older men. Differences in lipid levels that are achievable by statin use were associated with about a one-third lower risk of IHD, irrespective of age.

Arch Intern Med. 2007;167(13):1373-1378

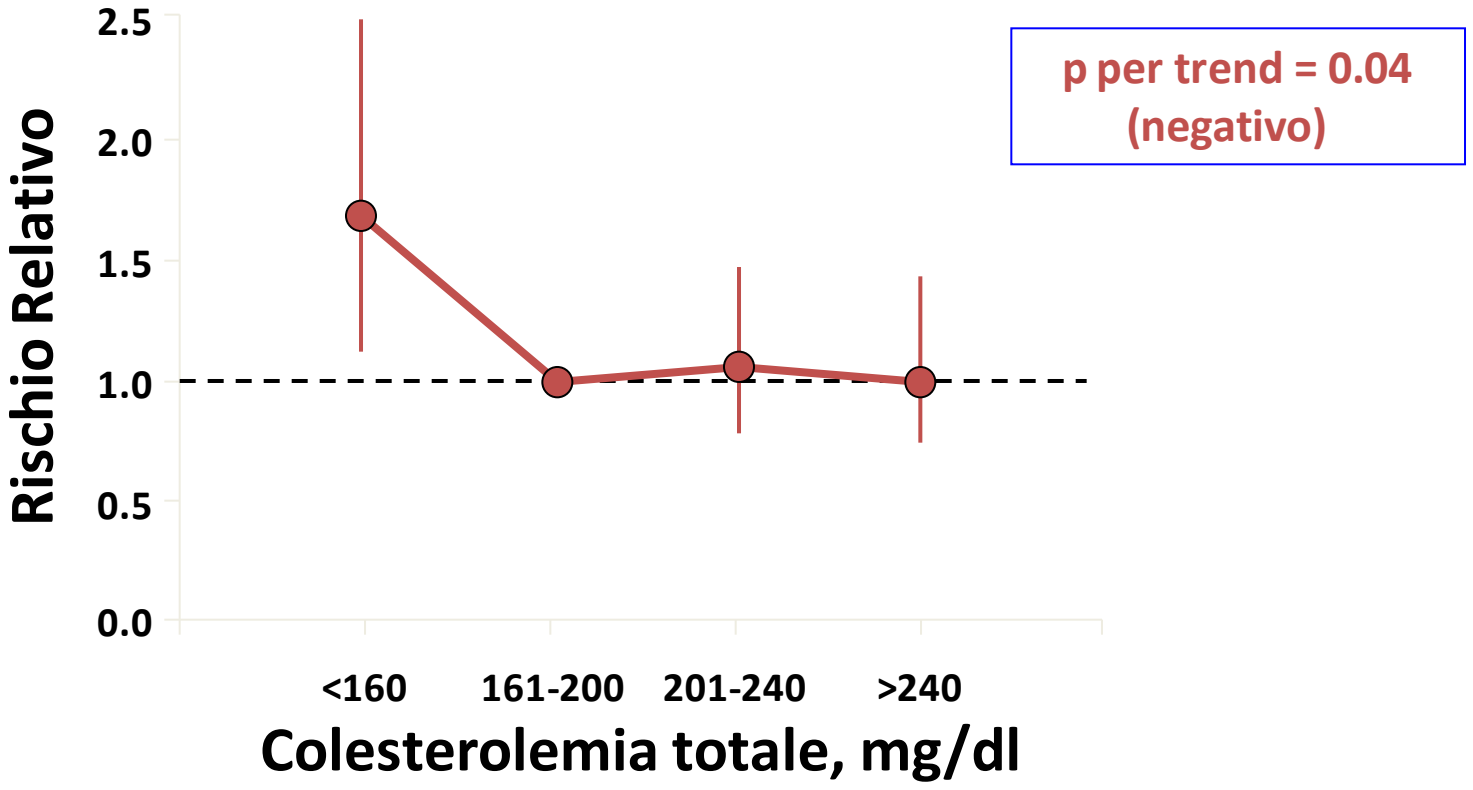
Tot. Chol. **LDL-C** **Apo B**



Clarke et al. Arch Inter Med 2007

Colesterolemia e mortalità coronarica nell'anziano

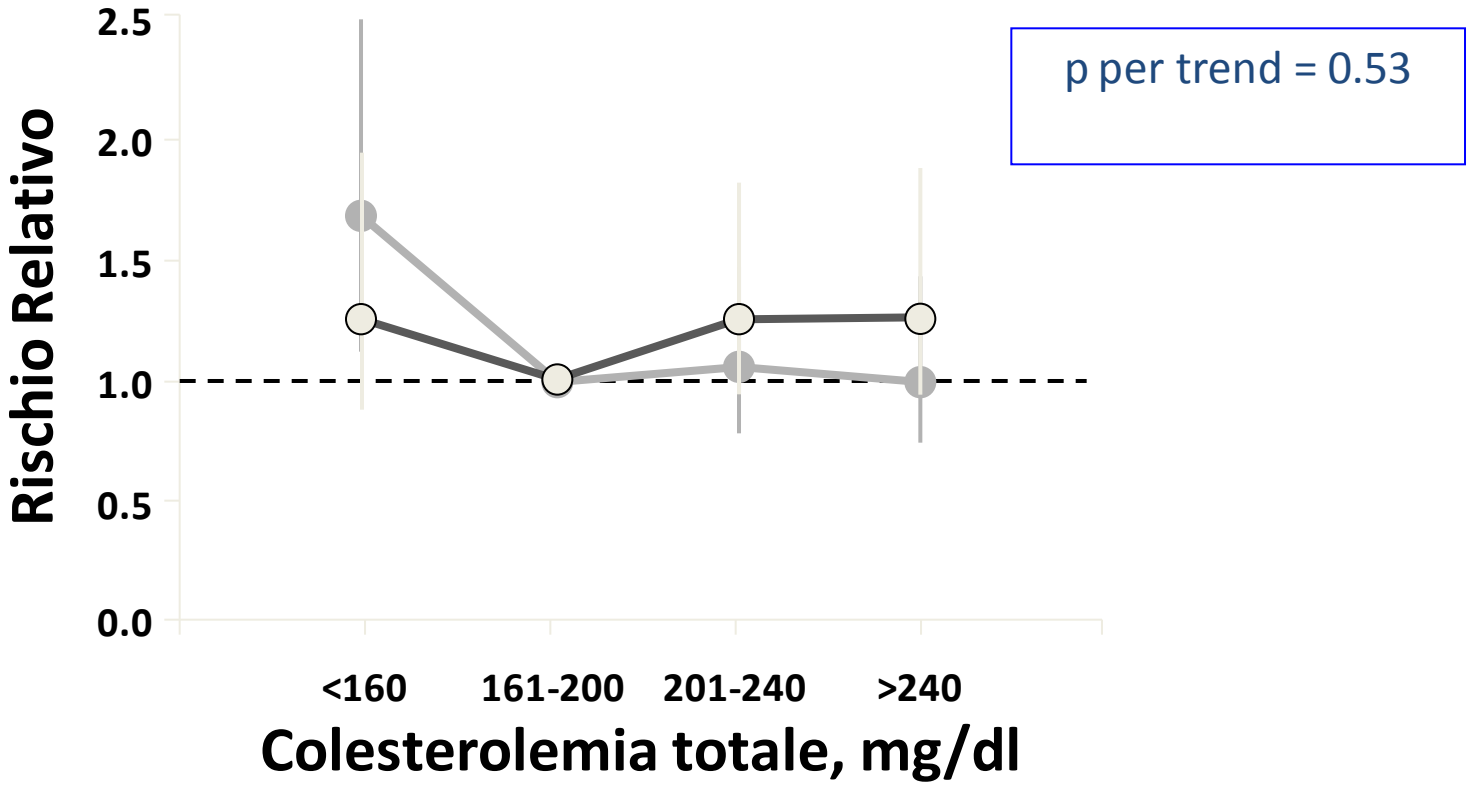
1 = Non aggiustato



Corti et al. Ann Intern Med 1997

Colesterolemia e mortalità coronarica nell'anziano

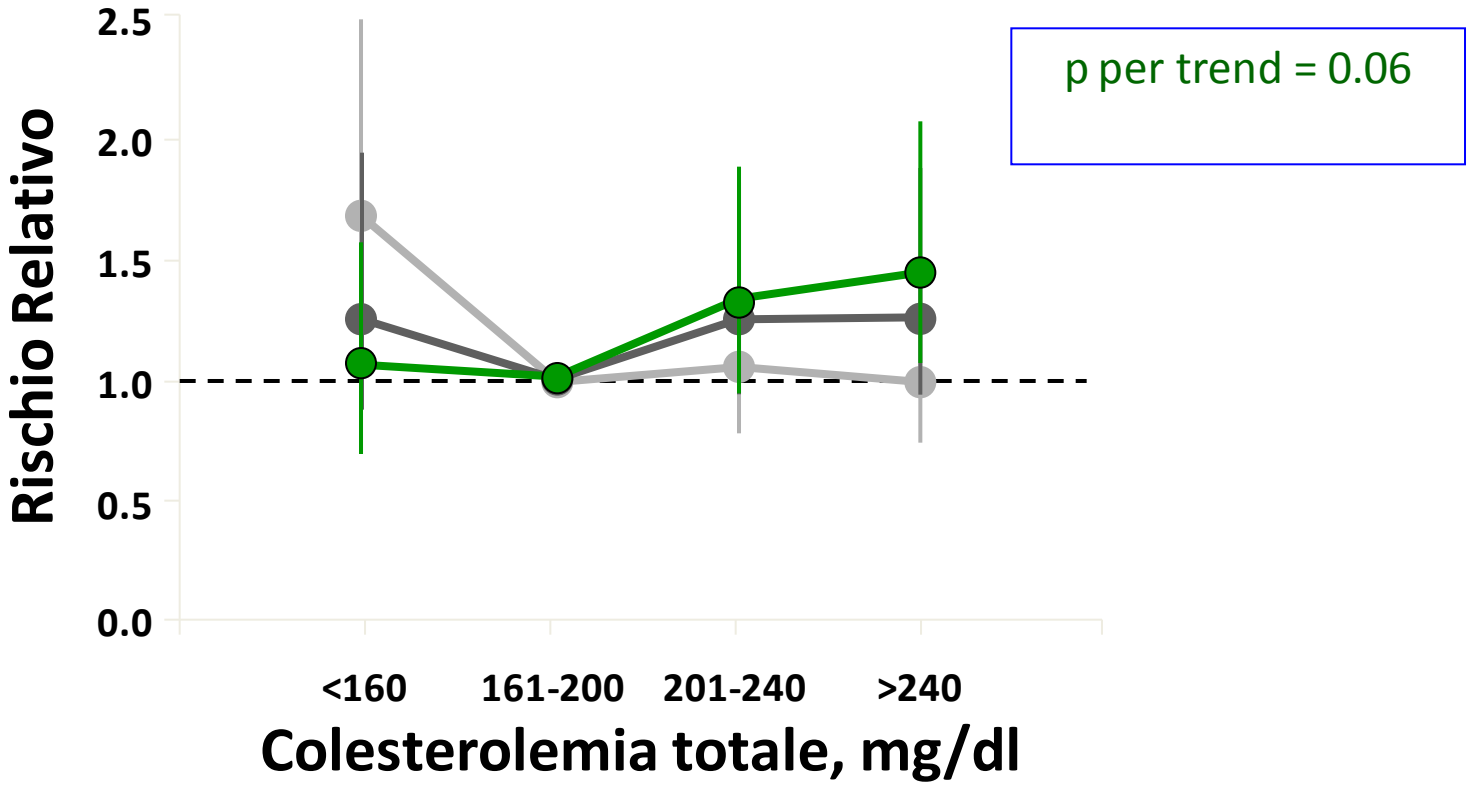
2 = Aggiustato per altri FdR CV



Corti et al. Ann Intern Med 1997

Colesterolemia e mortalità coronarica nell'anziano

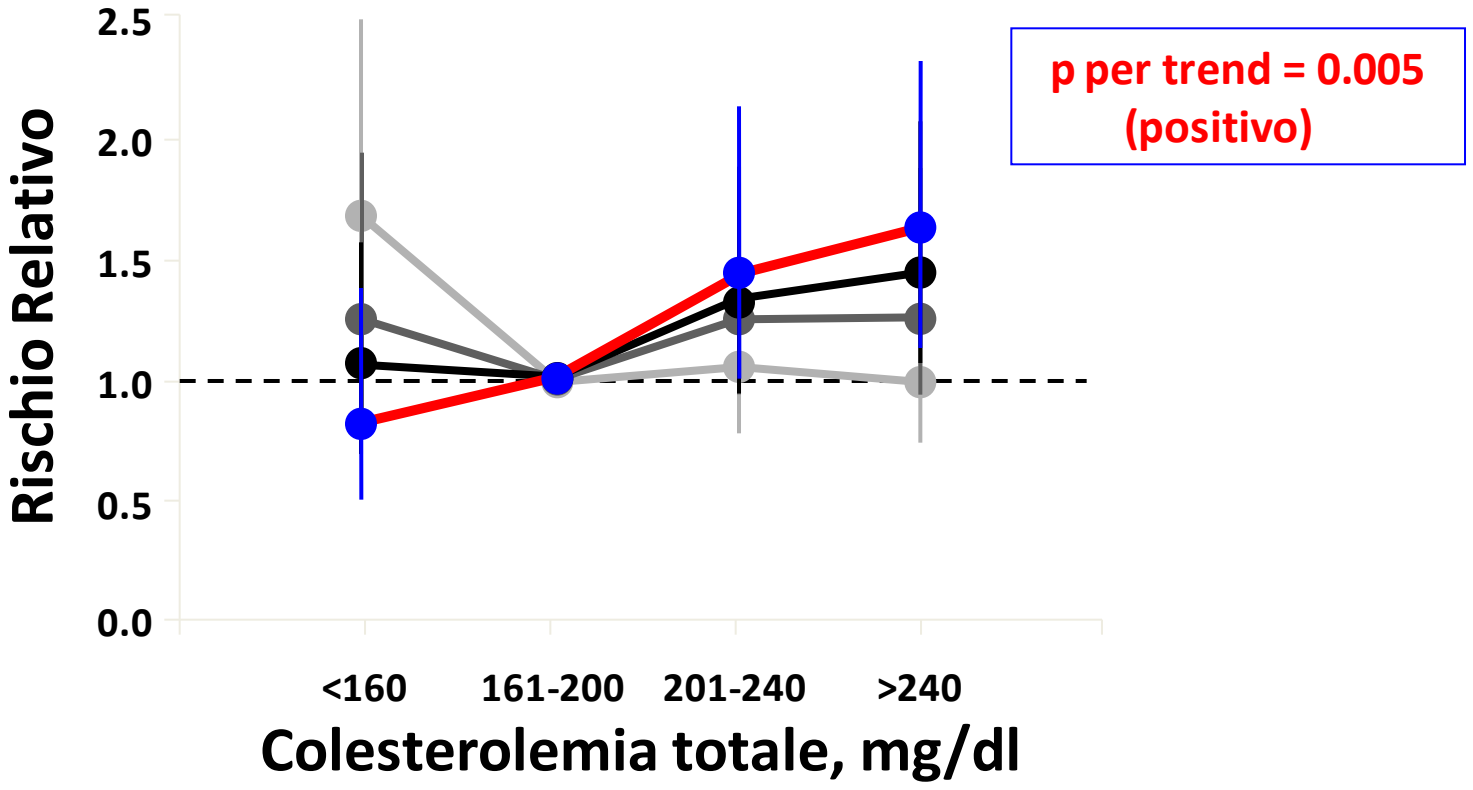
3 = ulteriore agg. per albumina e sideremia



Corti et al. Ann Intern Med 1997

Colesterolemia e mortalità coronarica nell'anziano

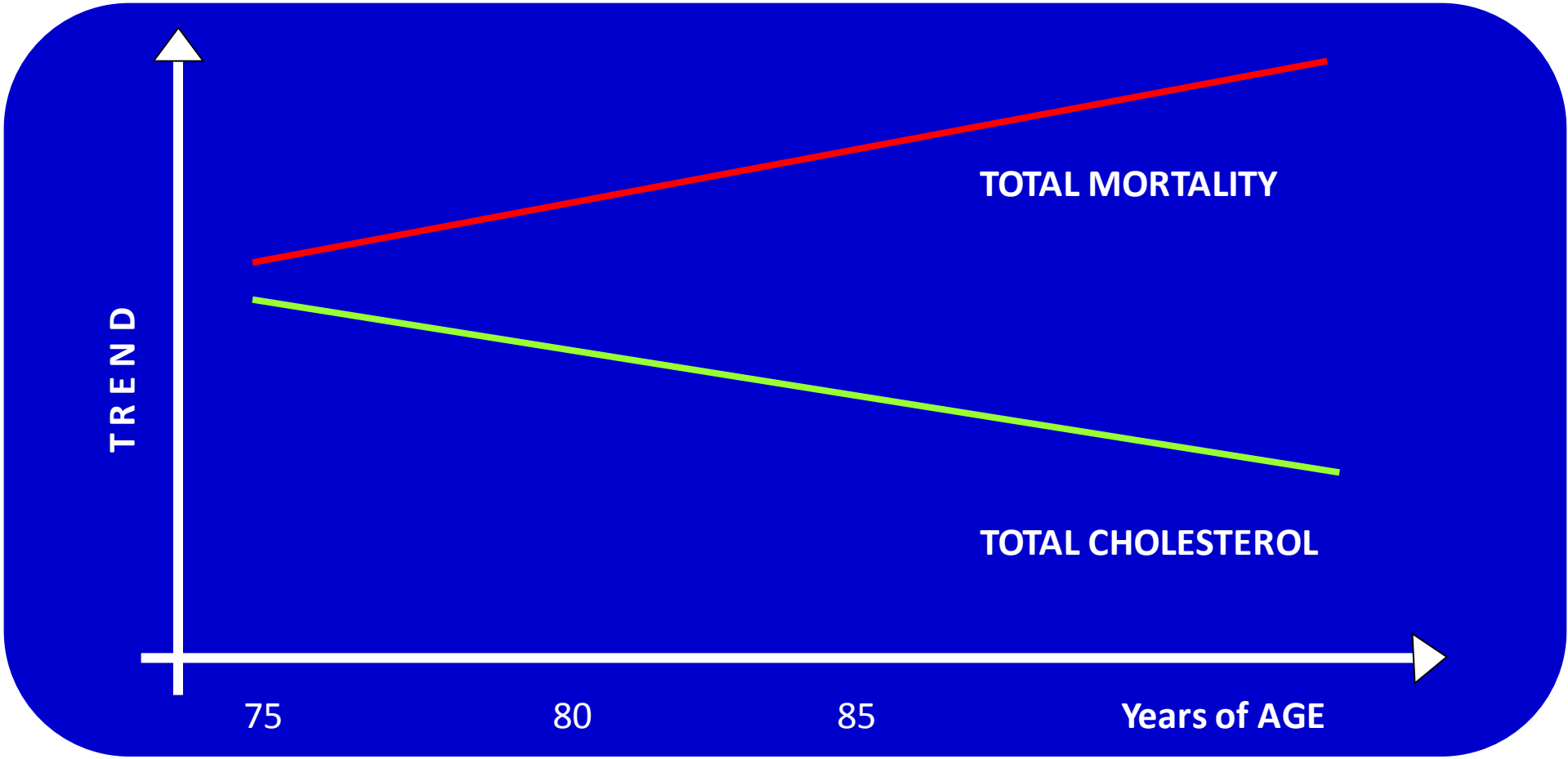
4 = escludendo il primo anno di eventi



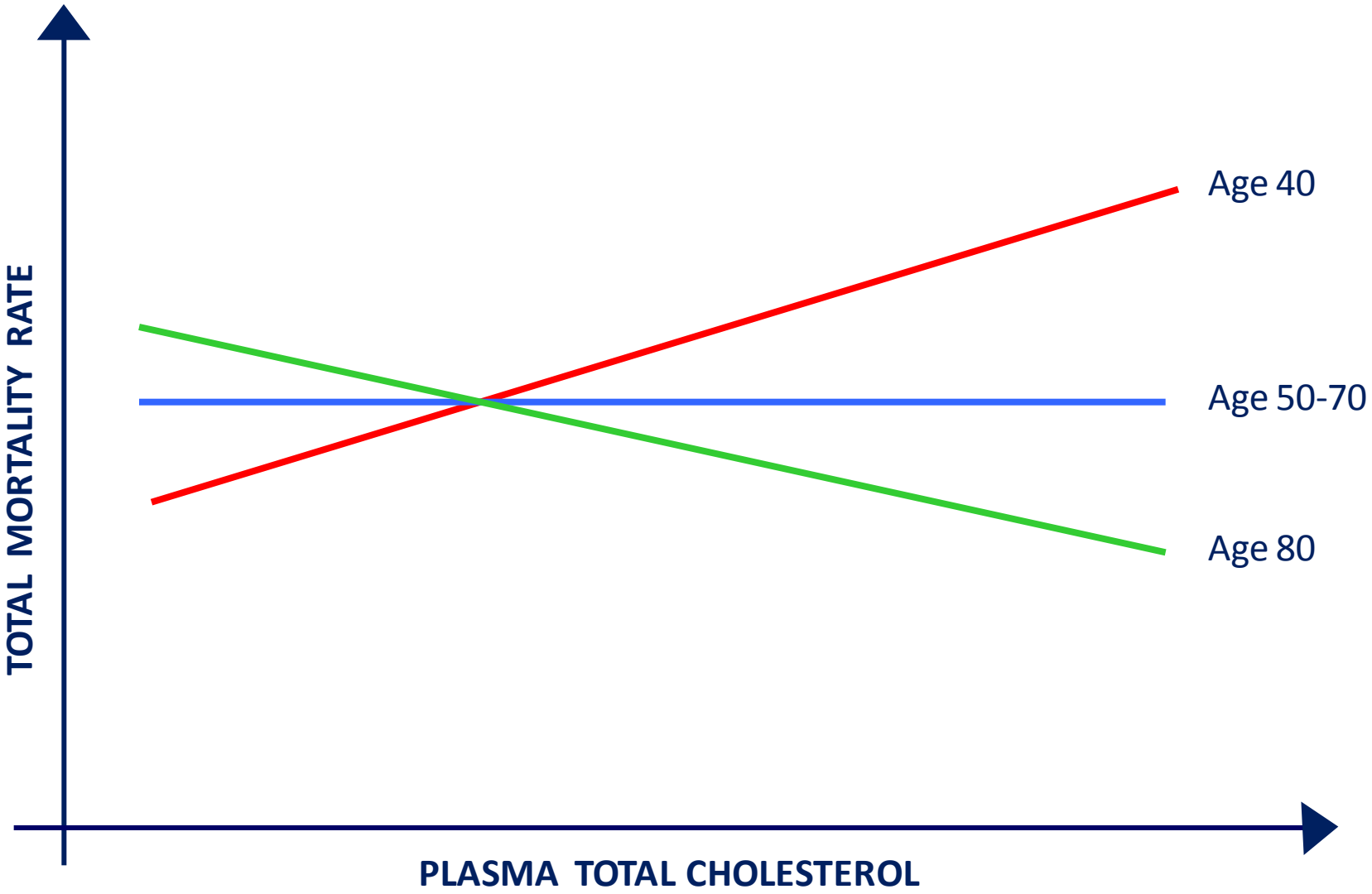
Corti et al. Ann Intern Med 1997

1b. Colesterolo, mortalità totale e invecchiamento

In the elderly total mortality increases in face of a decrease of serum cholesterol levels



Total serum cholesterol and total mortality risk as a function of age. A report based on the Framingham data

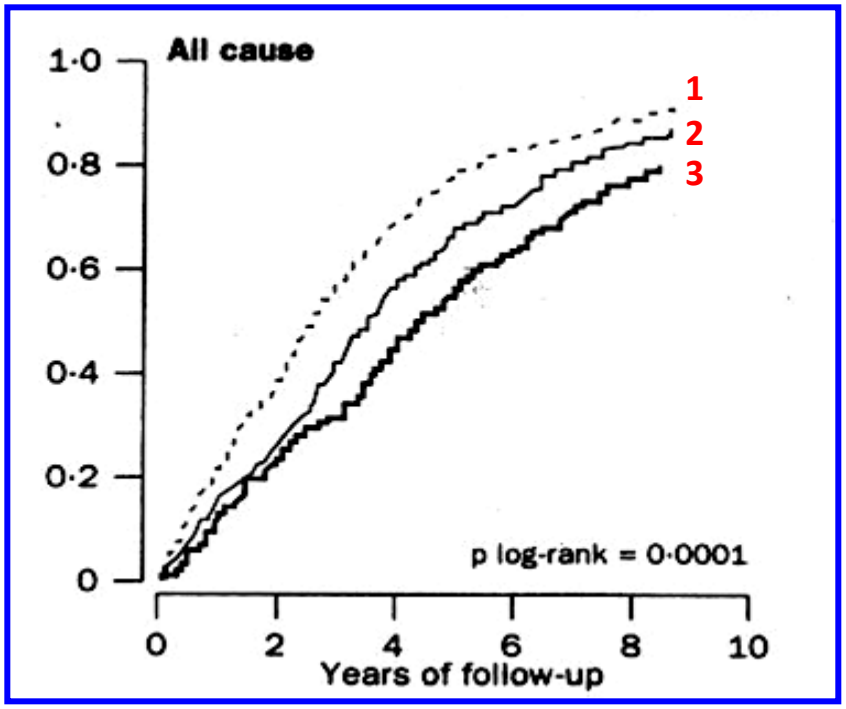


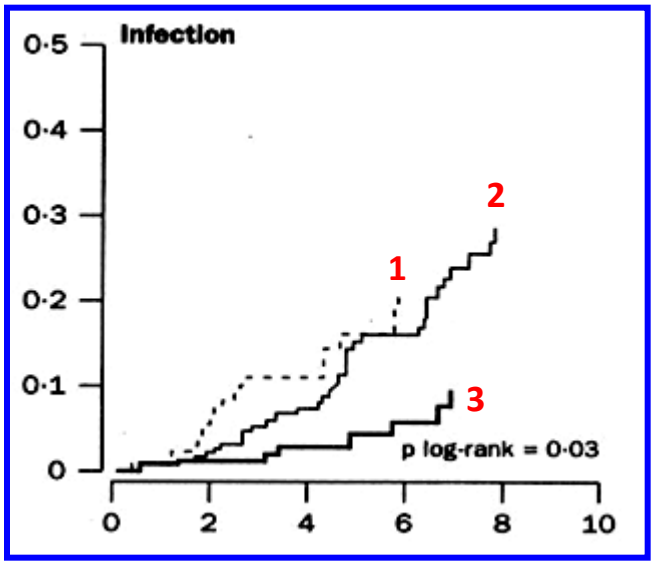
Kronmal et al. Arch Intern Med 1993

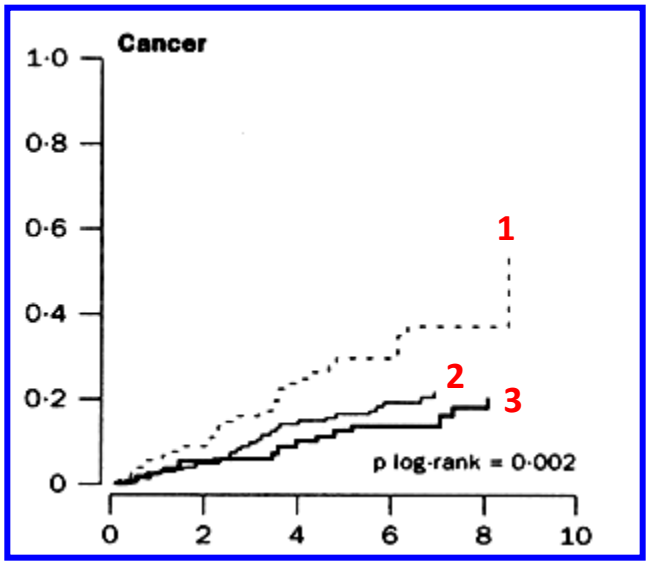
Total cholesterol and risk of mortality in the oldest old

"...In people older than 85 years, high total cholesterol concentrations are associated with longevity owing to a lower mortality from cancer and infections…".

Weverling-Rijnsburger et al. Lancet 1997







Weverling-Rijnsburger et al. Lancet 1997

Relationship Between Plasma Lipids and All-Cause Mortality in Nondemented Elderly

Nicole Schupf, PhD,[*†¶**] *Rosann Costa, MA,*[*] *Jose Luchsinger, MD, MPH,*[*‖]
Ming-Xin Tang, PhD,[*#] *Joseph H. Lee, DrPH,*[*†¶] *and Richard Mayeux, MD, MSc*[*†‡§¶]

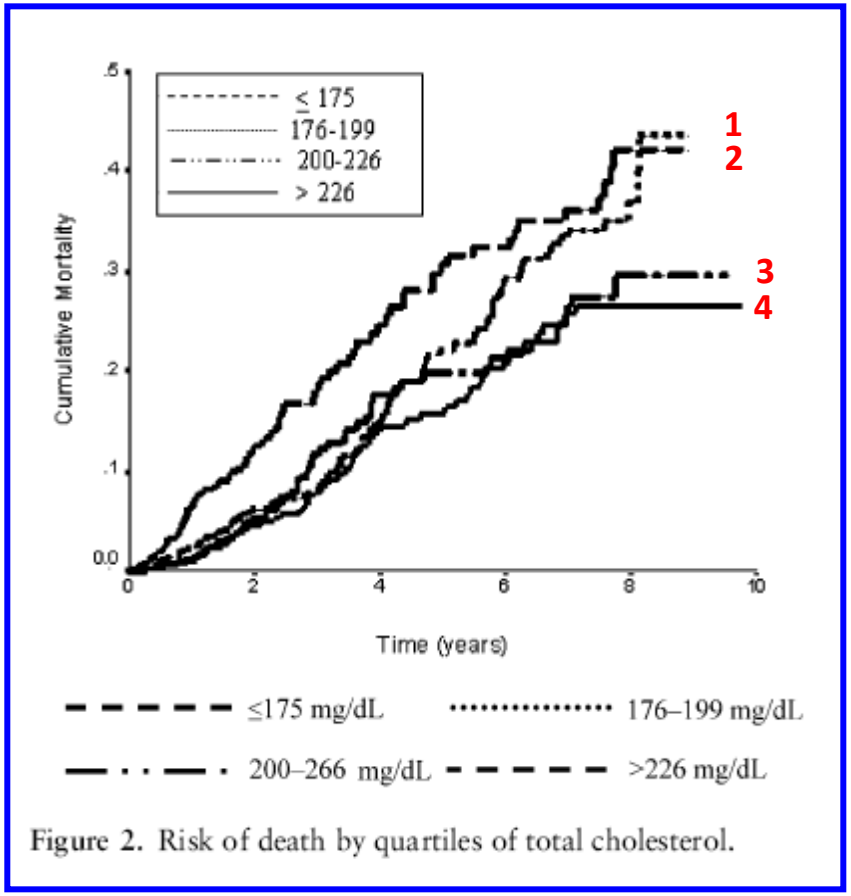


Figure 2. Risk of death by quartiles of total cholesterol.

Schupf et al. JAGS 2005

Low Total Cholesterol and Increased Risk of Dying: Are Low Levels Clinical Warning Signs in the Elderly? Results from the Italian Longitudinal Study on Aging

Sonia Brescianini, MS, Stefania Maggi, MD,† Gino Farchi, MS,* Sergio Mariotti, MS,* Antonio Di Carlo, MD,‡ Marzia Baldereschi, MD,‡ and Domenico Inzitari§ for the ILSA Group*

Table 3. Hazard Ratios by Quartiles of TC and Model Used

	Quartiles of Cholesterol			
	1 (n = 837)	2 (n = 819)	3 (n = 832)	4 (n = 807)
Model	Hazard Ratio (95% Confidence Interval)			
1*	1	0.53 (0.36–0.78)	0.52 (0.34–0.80)	0.59 (0.39–0.91)
2†	1	0.53 (0.35–0.79)	0.52 (0.34–0.80)	0.55 (0.36–0.86)
3‡	1	0.57 (0.38–0.87)	0.56 (0.36–0.88)	0.53 (0.33–0.84)

* Adjusted for age, sex, body mass index (BMI), high-density lipoprotein (HDL), hypertension, diabetes mellitus, fibrinogen, triglycerides, uric acid (UA), Apolipoprotein A-1 (Apo A-1), smoking status, and alcohol intake.

† Adjusted for age, sex, BMI, HDL, hypertension, diabetes mellitus, fibrinogen, triglycerides, UA, Apo A-1, smoking status, alcohol intake, coronary heart disease (CHD), self-reported liver disease, self-reported cancer, and stroke.

‡ Adjusted for age, sex, BMI, HDL, hypertension, diabetes mellitus, fibrinogen, triglycerides, UA, Apo A-1, smoking status, alcohol intake, CHD, self-reported liver disease, self-reported cancer, stroke, weight loss, hemoglobin, disability (the inability to perform at least one activity of daily living), and albumin concentration.

Brescianini et al. JAGS 2003

Regressione logistica multivariata per rischio di presentare disabilità nelle BADL in soggetti 344 anziani istituzionalizzati. *The I.R.A. study*

Gerontology International Journal of Experimental, Clinical and Behavioural Gerontology	β	SE	Odds ratio	IC 95%	p
HDL-C					
III tertile			1.0		
II tertile	0.70	0.33	2.01	1.04–3.91	0.03
I tertile	0.92	0.36	2.52	1.23–5.15	0.01
Total cholesterol					
III tertile			1.0		
II tertile	–0.39	0.33	0.96	0.49–1.86	0.09
I tertile	0.85	0.36	2.35	1.14–4.81	0.01
Blood glucose	–0.012	0.006	0.98	0.97–0.99	0.02
Body mass index	–0.87	0.04	0.91	0.84–0.99	0.04

Nel modello logistico: acido urico, body cell mass, vitamina B-12, acido folico, comorbidità, numero di farmaci, BMI, rapporto vita/fianchi, sesso ed età.

Zuliani et al. Gerontology 1999

CLINICAL INVESTIGATIONS

Increases in Serum Non-High-Density Lipoprotein Cholesterol May Be Beneficial in Some High-Functioning Older Adults: MacArthur Studies of Successful Aging

Arun S. Karlamangla, PhD, MD, Burton H. Singer, PhD,† David B. Reuben, MD,* and Teresa E. Seeman, PhD**

Table 5. Unadjusted and Adjusted Odds Ratios for Each 10 mg/dL Increase in the 1988-to-1991 Change in Non-High-Density Lipoprotein Cholesterol for 1991 to 1995 Events

Model	Mortality	Heart Attack or Stroke	New Activity of Daily Living Disability	Cognitive Decline
	Odds Ratio (95% Confidence Interval)			
Unadjusted	0.92 (0.80–1.06)	1.07 (0.91–1.27)	0.85 (0.74–0.97)†	0.83 (0.72–0.97)†
Adjusted*	0.84 (0.62–1.00)†	1.16 (0.95–1.40)	0.84 (0.71–0.99)†	0.86 (0.73–1.02)

* Adjusted for sex, ethnicity, baseline level of total cholesterol, prevalent cardiovascular disease status at baseline, baseline weight (continuous), and 1988-to-1991 weight loss (continuous and squared term).
† Confidence intervals do not cross 1.

Karlamangla et al. JAGS 2004

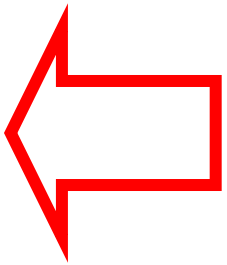
Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study

The Lancet
Volume 358, Issue 9279, August 4, 2001, pp. 351-355

RESULTS

Higher cholesterol concentrations were associated with:

1) Higher body mass index [they were less frail]
2) Higher HDL [good] cholesterol
3) Higher hemoglobin
4) Better hand-grip strength



"Kaplan-Meier survival curves showed lowest survival rates for those with the lowest serum cholesterol concentrations."

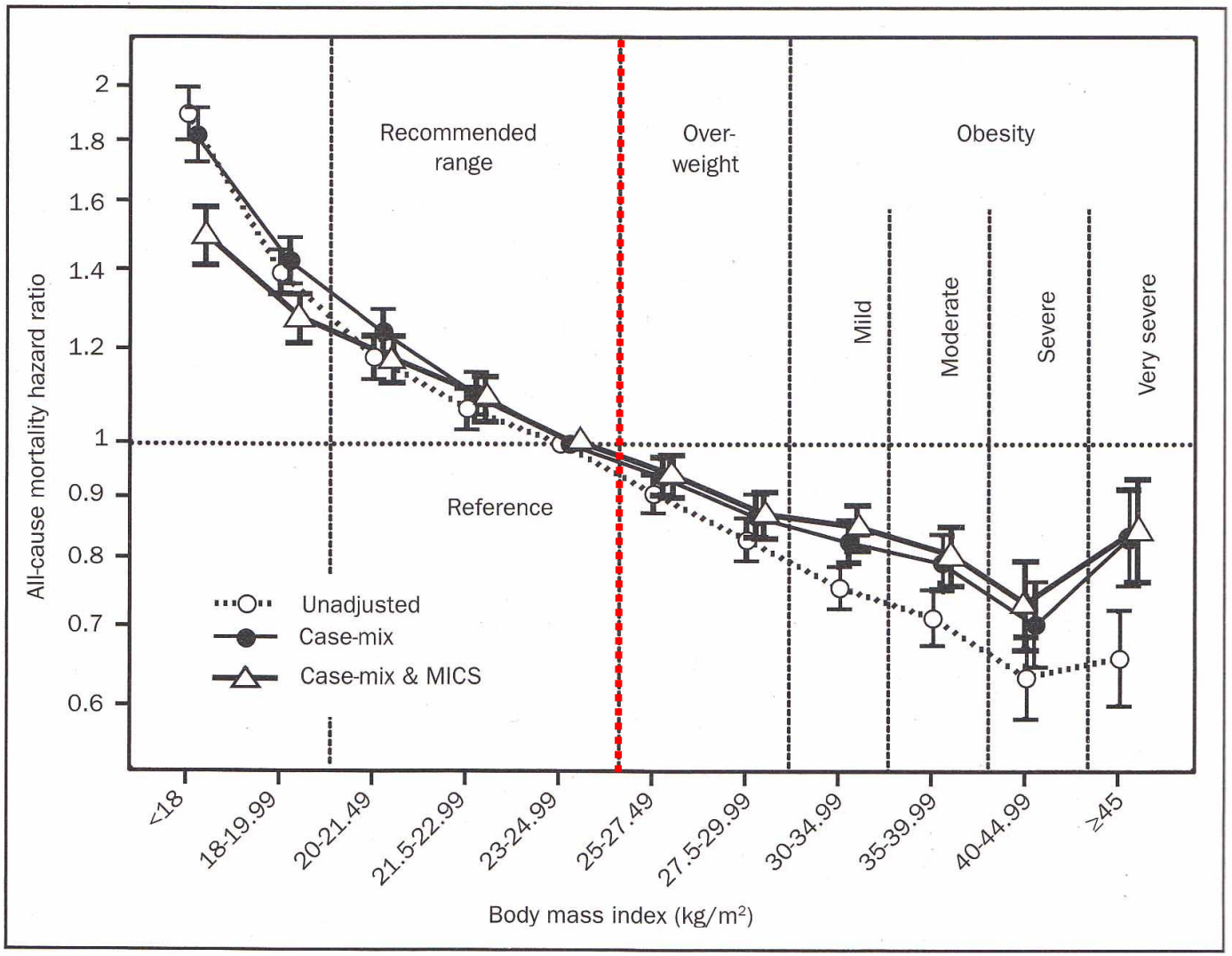
"Low serum cholesterol imparts a poor outlook when compared with higher concentrations of cholesterol in elderly people, our data also suggest that those individuals with a low serum cholesterol maintained over a 20-year period will have the worst outlook for all-cause mortality."

3572 Japanese/American men aged 71-93 years; Follow-up 20 years

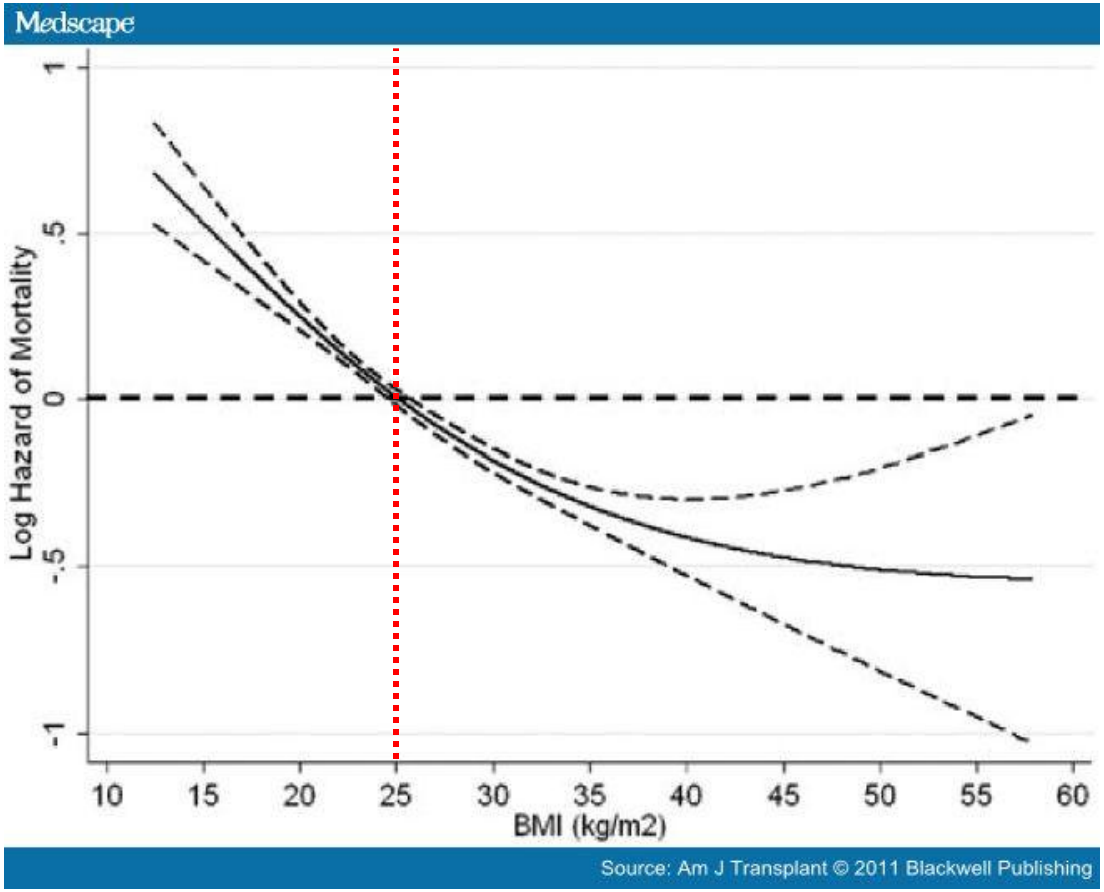
IJ Schats et al. Lancet 2001

2. Obesity and the reverse epidemiology

The Relationship between BMI and total mortality in patients with CKD

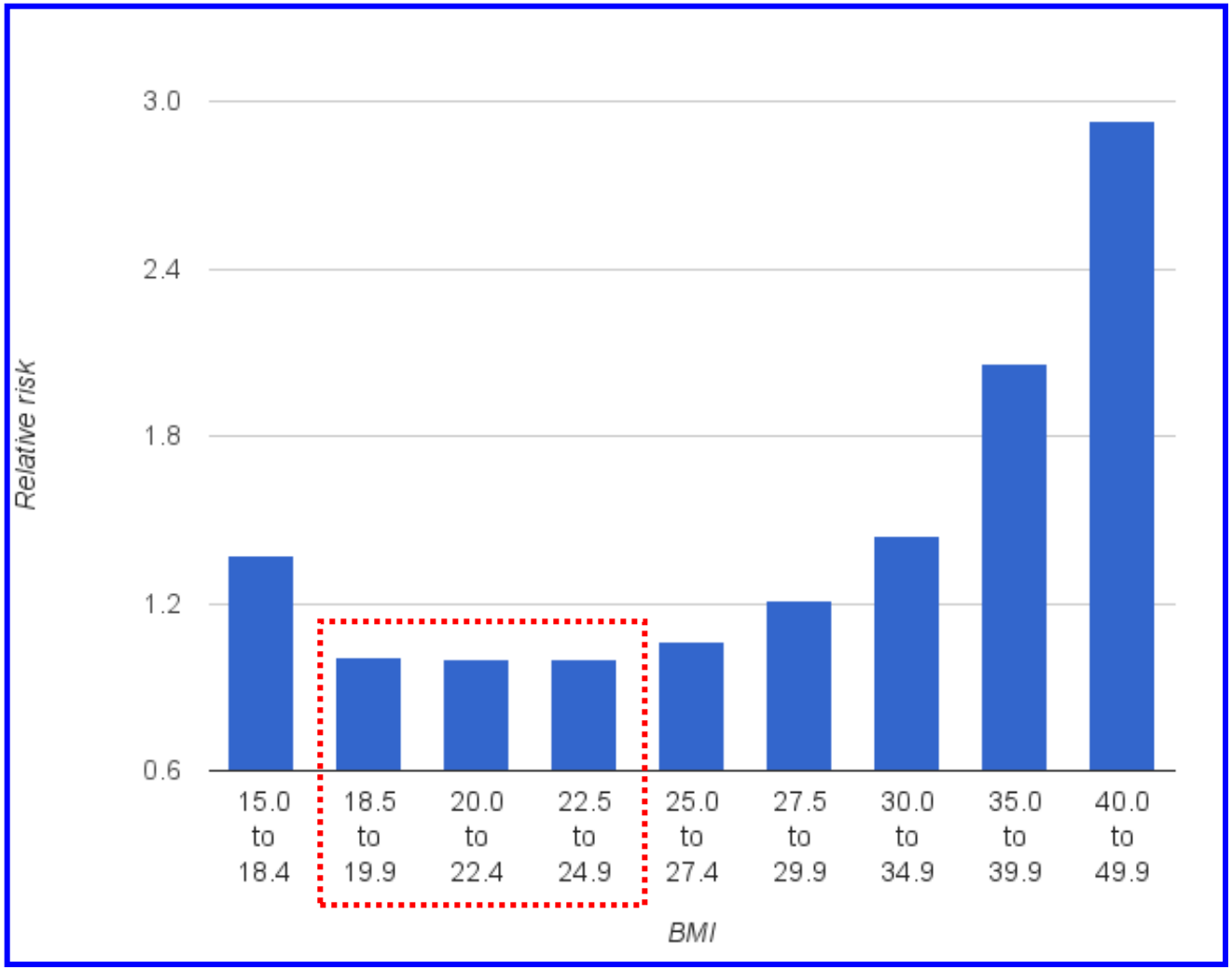


The Relationship between BMI and total mortality in patients with CKD waiting for transplantation



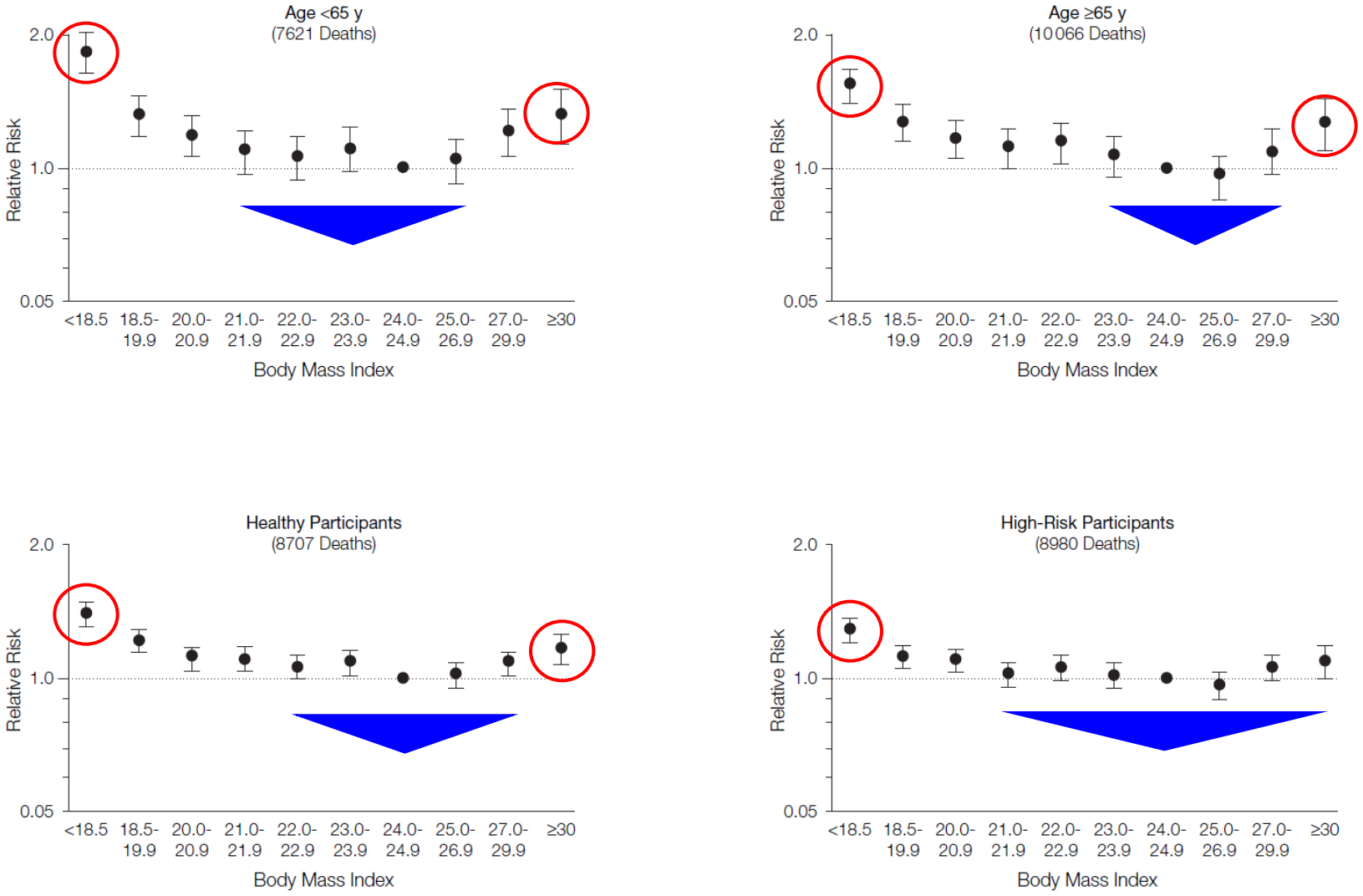
Molnar MZ et al. Am J Transpl 2011

Relative risk of total mortality by BMI levels in white ADULT men from U.S.A.



Adjusted RR for total mortality by BMI and health status

Figure. Multivariate-Adjusted Relative Risks of All-Cause Mortality According to Categories of Body Mass Index by Age and Health Status

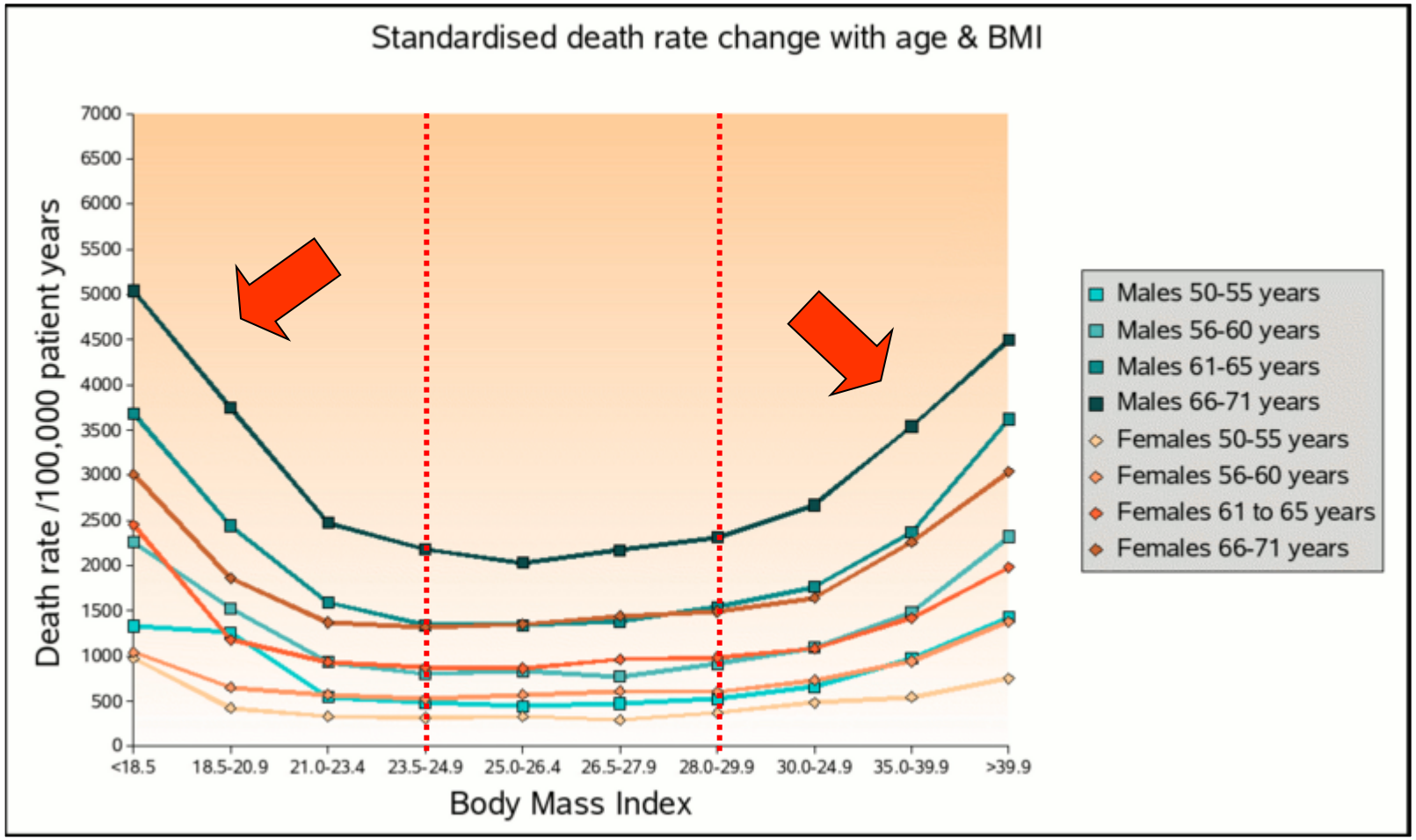


169.871 men & women aged over 40: Follow-up 10 yrs

Dongfeng G et al. JAMA 2006

Overweight, Obesity, and Mortality in a Large Prospective Cohort of Persons 50 to 71 Years Old

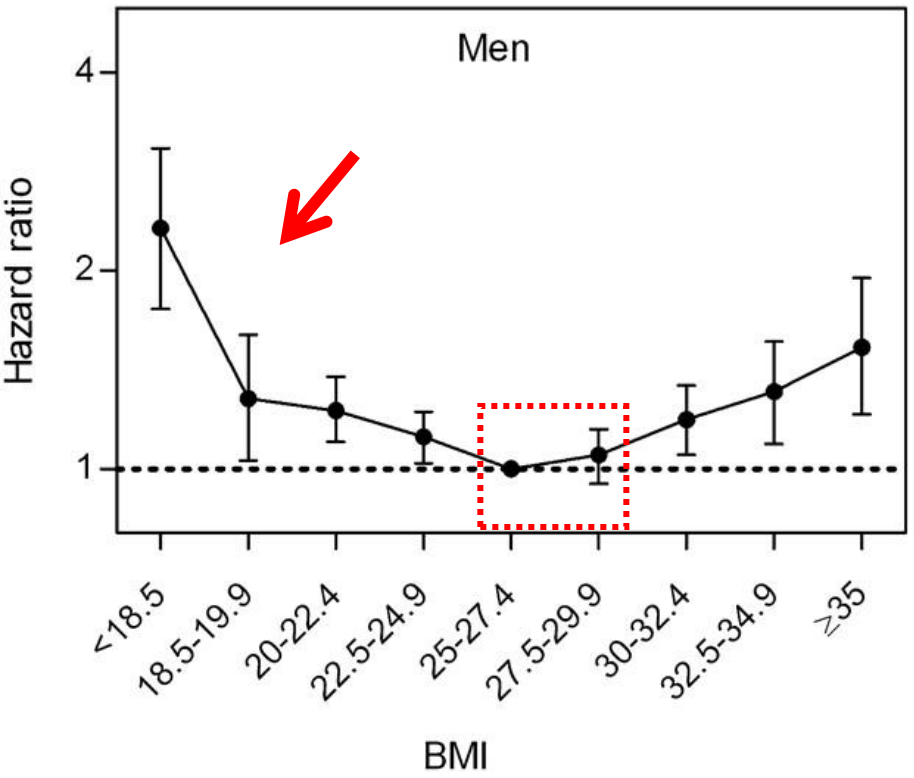
Kenneth F. Adams, Ph.D., Arthur Schatzkin, M.D., Tamara B. Harris, M.D., Victor Kipnis, Ph.D., Traci Mouw, M.P.H., Rachel Ballard-Barbash, M.D., Albert Hollenbeck, Ph.D., and Michael F. Leitzmann, M.D.

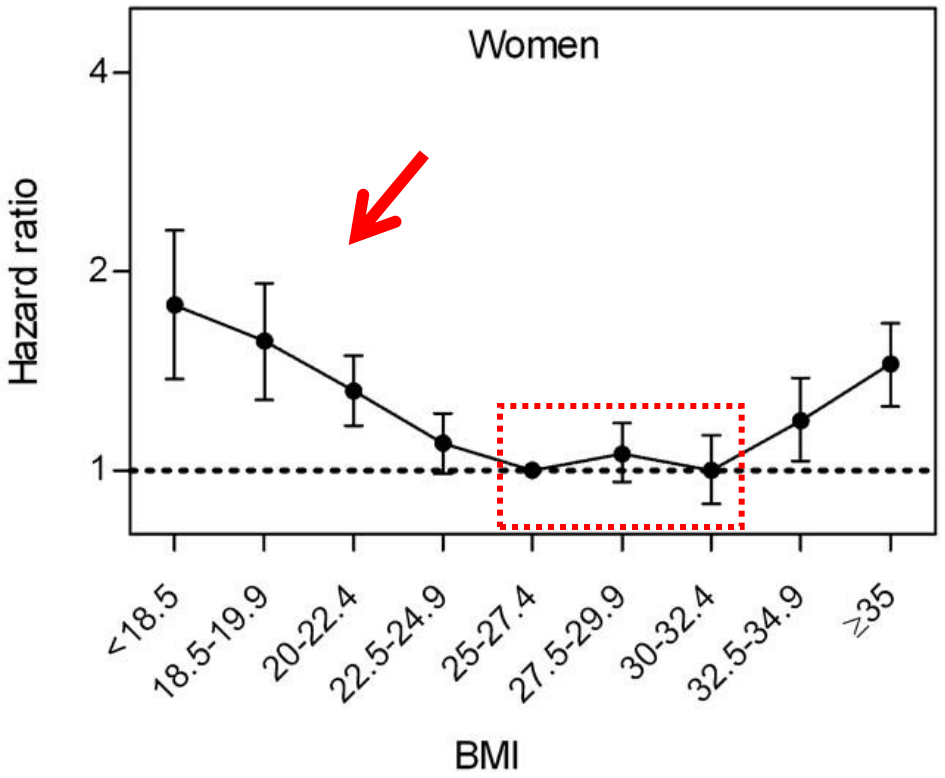


527.265 men and women aged 50 to 71: Follow-up 10 yrs

N Engl J Med 2006

Body mass index and mortality in elderly men and women: the Tromsø and HUNT studies





Kvamme J-M et al. J Epidem Com Health J 2013

Adjusted HR for total mortality for overweight and obesity compared to normal weight

Table 2. Summary Hazard Ratios (HRs) of All-Cause Mortality for Overweight and Obesity Relative to Normal Weight From Studies Considered Adequately Adjusted

	Self-reported or Measured Height and Weight			Height and Weight					
				Measured			Self-reported		
	No. of HRs	Summary HR (95% CI)	I^2, %	No. of HRs	Summary HR (95% CI)	I^2, %	No. of HRs	Summary HR (95% CI)	I^2, %
BMI of 25-<30									
All ages	86	0.94 (0.90-0.97)[a]	87.6	45	0.92 (0.88-0.96)[a]	74.8	41	0.95 (0.90-1.01)[a]	91.0
Mixed ages	68	0.95 (0.91-0.99)[a]	89.3	34	0.93 (0.88-0.98)[a]	79.2	34	0.96 (0.91-1.02)[a]	91.8
Age ≥65 y only	18	0.90 (0.86-0.95)	27.9	11	0.90 (0.84-0.96)	23.4	7	0.91 (0.84-0.98)	42.9
BMI of ≥30									
All ages	42	1.21 (1.12-1.31)[a]	89.3	22	1.11 (1.03-1.20)[a]	67.1	20	1.33 (1.21-1.47)[a]	88.0
Mixed ages	33	1.26 (1.16-1.37)[a]	89.7	16	1.13 (1.04-1.23)[a]	[illegible]	17	1.39 (1.27-1.53)[a]	84.3
Age ≥65 y only	9	1.05 (0.92-1.21)[a]	63.9	6	1.02 (0.81-1.29)[a]	NS	3	1.08 (0.93-1.25)	39.7
BMI of 30-<35									
All ages	42	0.97 (0.90-1.04)[a]	83.8	21	1.00 (0.92-1.09)[a]	64.2	21	0.94 (0.84-1.05)[a]	89.6
Mixed ages	33	0.98 (0.91-1.06)[a]	84.8	16	1.03 (0.94-1.12)[a]	[illegible]	17	0.95 (0.85-1.07)[a]	90.3
Age ≥65 y only	9	0.88 (0.69-1.12)[a]	78.0	5	0.90 (0.70-1.16)[a]	NS	4	0.82 (0.46-1.47)[a]	88.1
BMI of ≥35									
All ages	42	1.34 (1.21-1.47)[a]	81.2	21	1.32 (1.20-1.46)[a]	46.6	21	1.35 (1.16-1.57)[a]	88.7
Mixed ages	33	1.35 (1.22-1.50)[a]	82.2	16	1.37 (1.24-1.52)	40.4	17	1.34 (1.14-1.57)[a]	89.6
Age ≥65 y only	9	1.28 (0.93-1.76)[a]	75.2	5	1.12 (0.89-1.43)	NS	4	1.40 (0.64-3.07)[a]	86.8

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Indicates significant heterogeneity ($P < .05$).

METANALYSIS = 141 studies, 2.88 milion subjects, 270.000 death

Flegal KM et al. JAMA 2013

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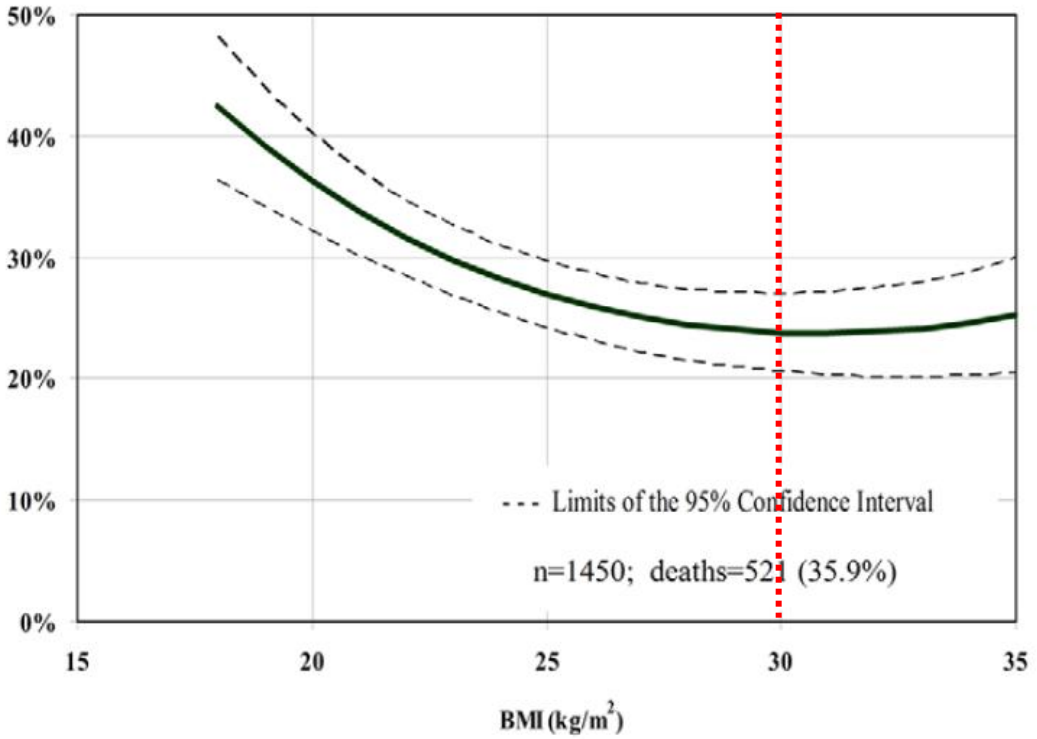
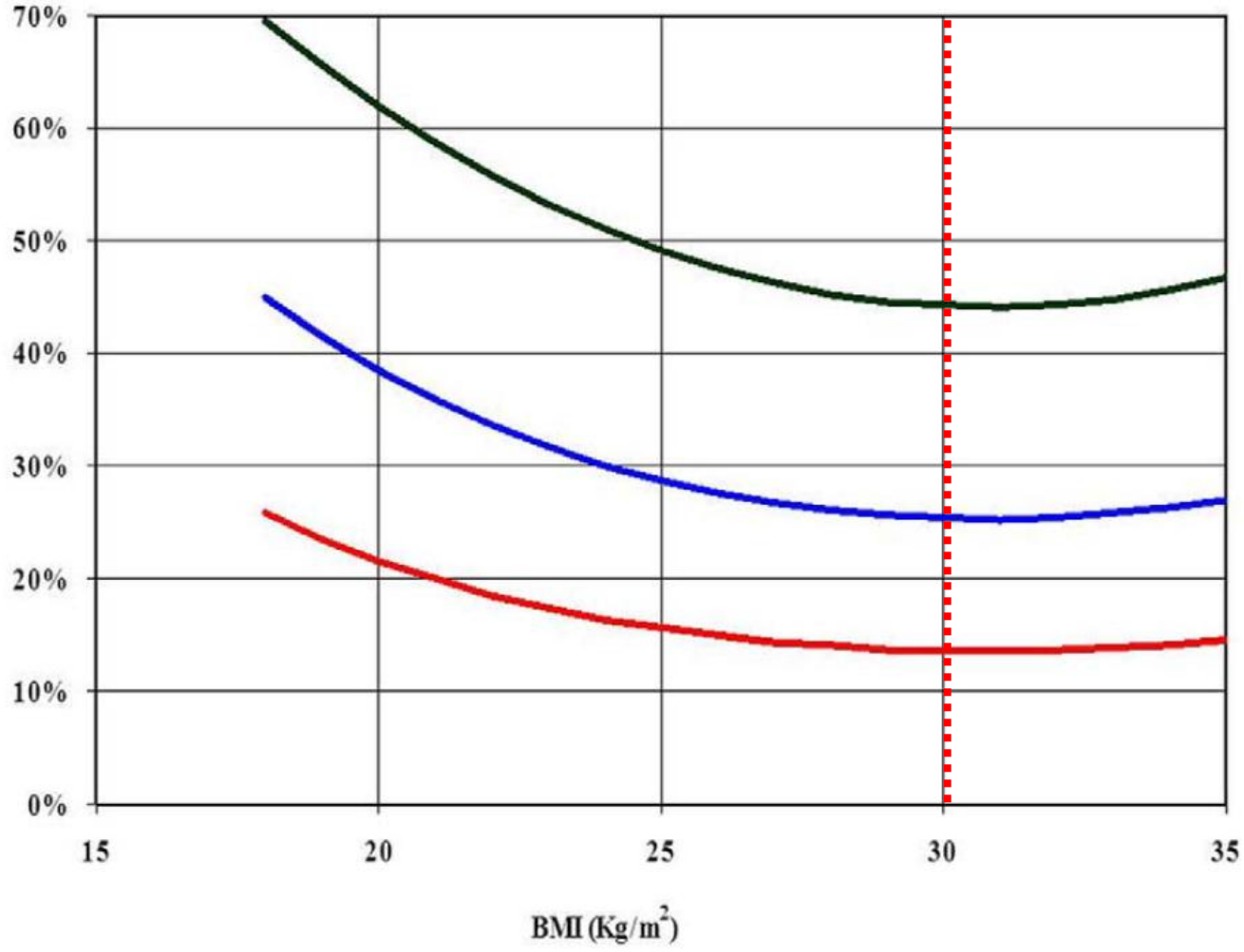
PLOS ONE

Overweight and Class I Obesity Are Associated with Lower 10-Year Risk of Mortality in Brazilian Older Adults: The Bambuí Cohort Study of Ageing

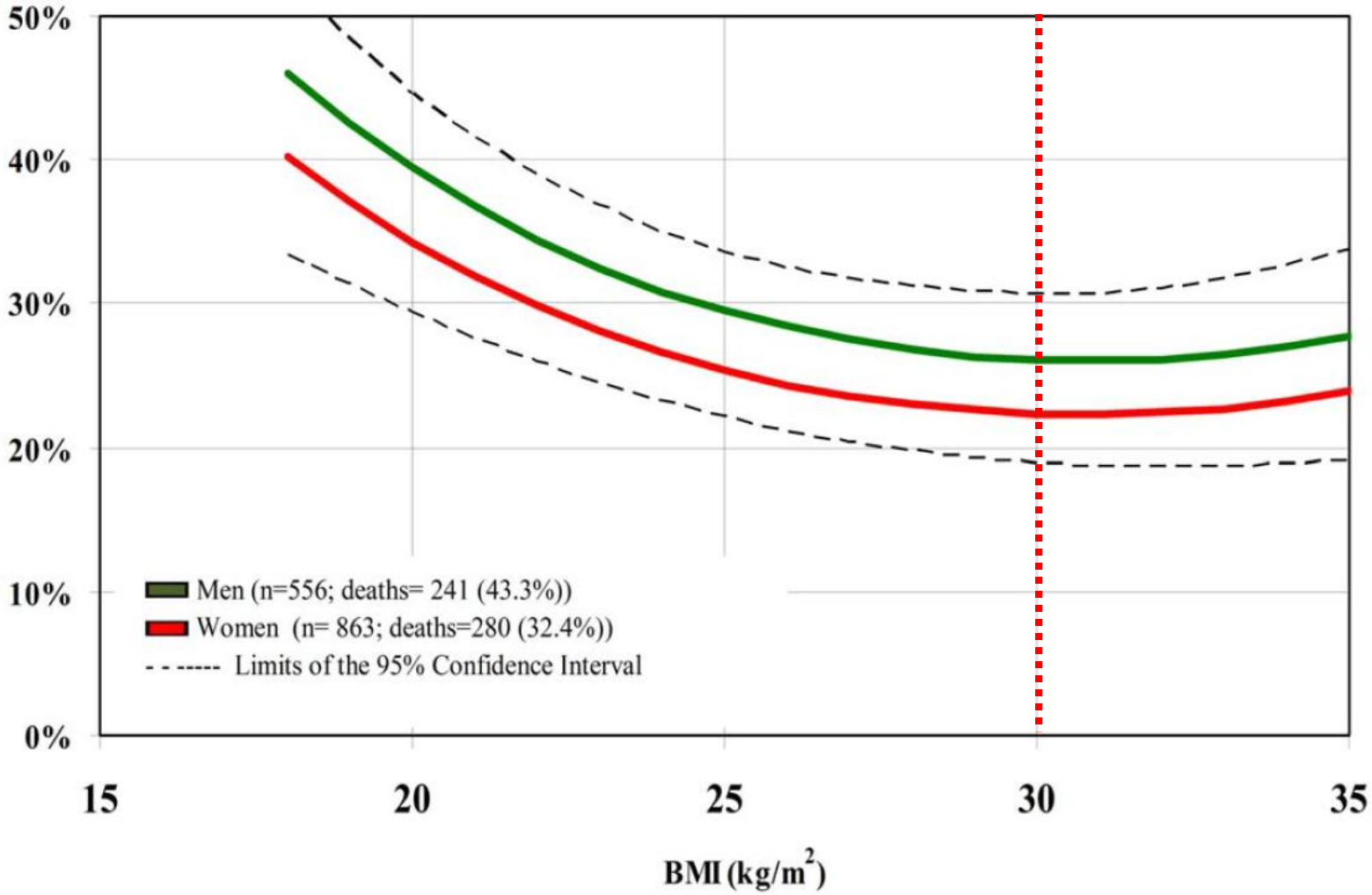
Alline M. Beleigoli[1]*, Eric Boersma[2], Maria de Fátima H. Diniz[1,3], Maria Fernanda Lima-Costa[1,4], Antonio L. Ribeiro[1,3]



1450 men & women aged over 60: Follow-up 10 yrs



Beleigoli AM et al. PLOS One 2012



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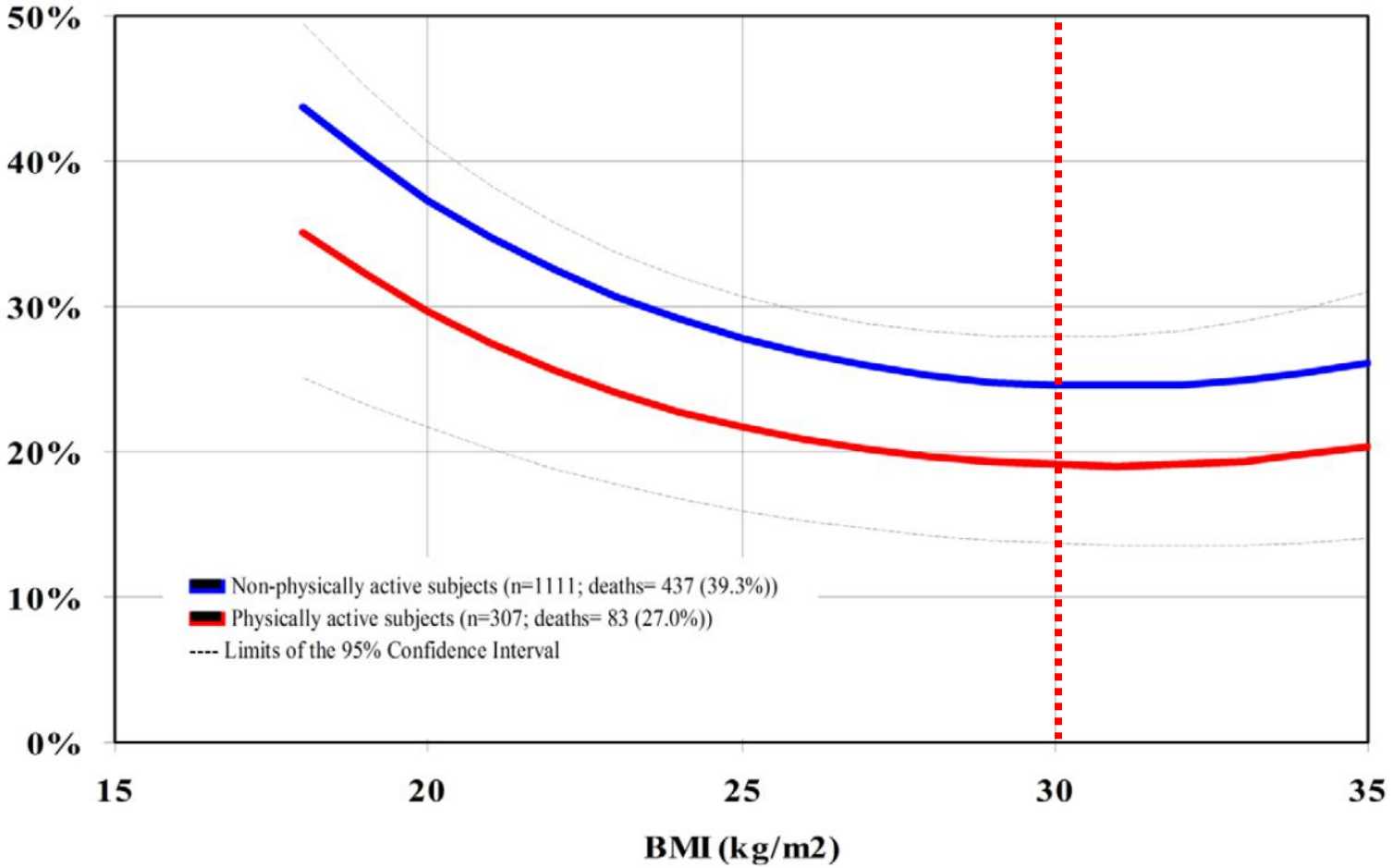


Beleigoli AM et al. PLOS One 2012

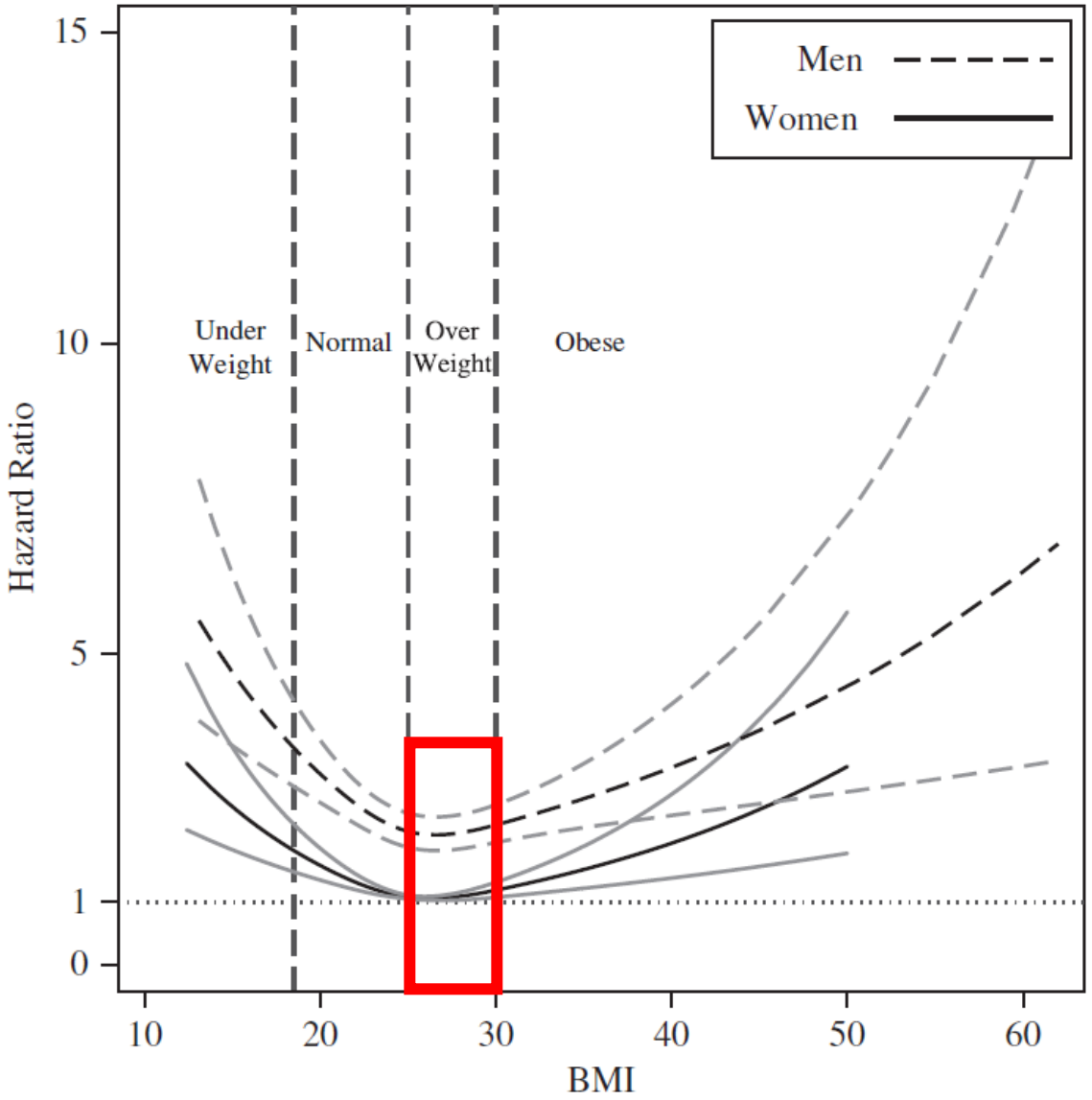


Figure 1. Hazard ratios of all-cause mortality according to body mass index (BMI) in men and women aged 70 to 75 (lines are 95% confidence intervals).

Flicker L et al. JAGS 2010

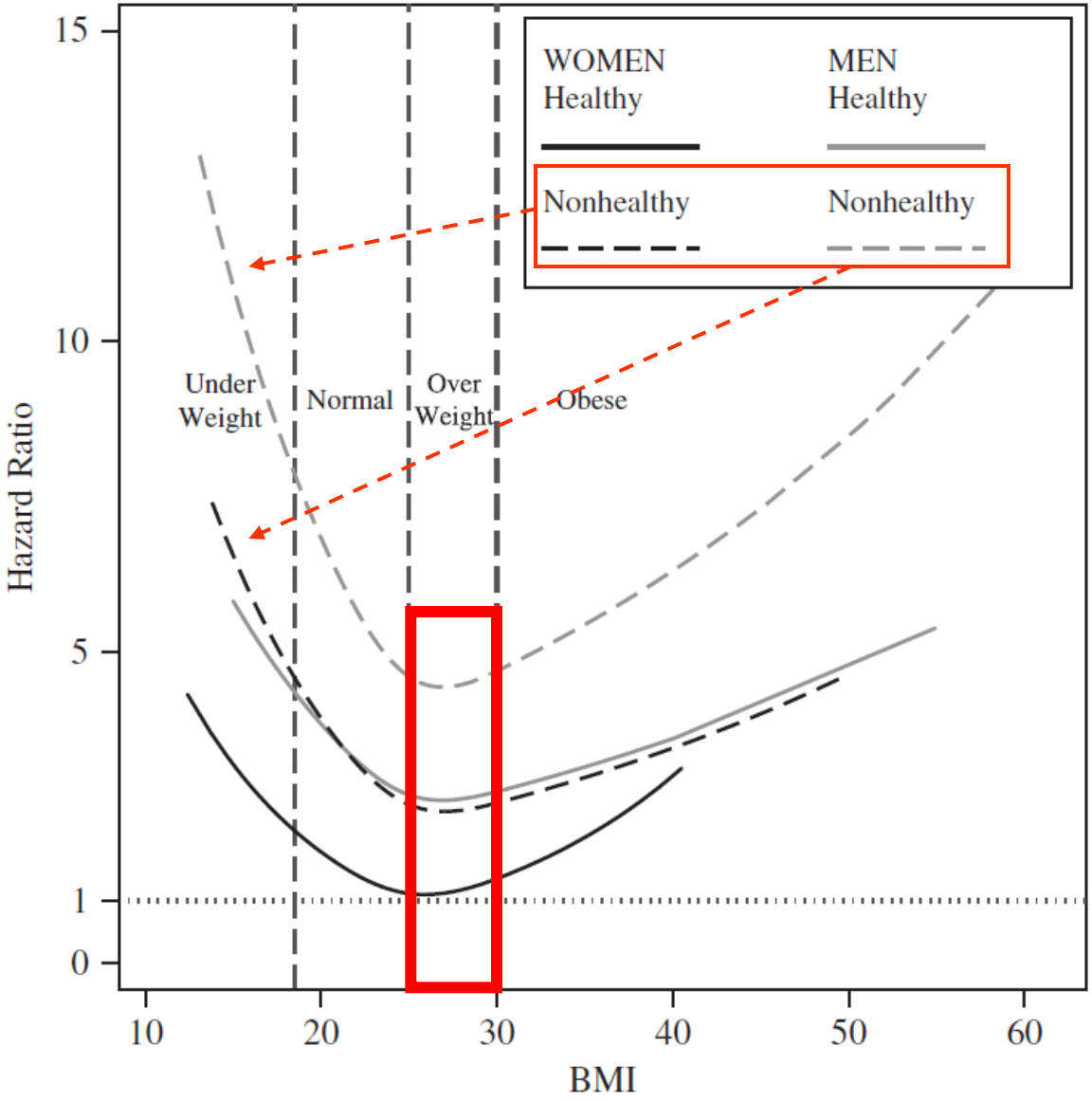
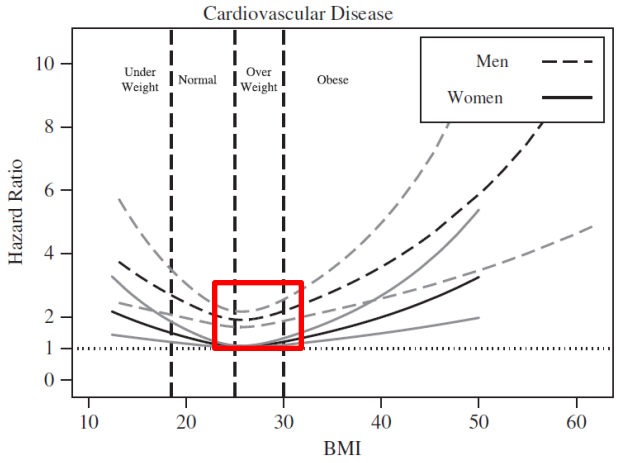
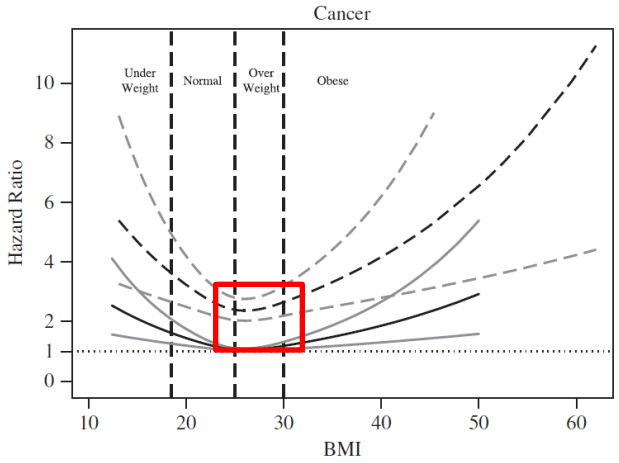
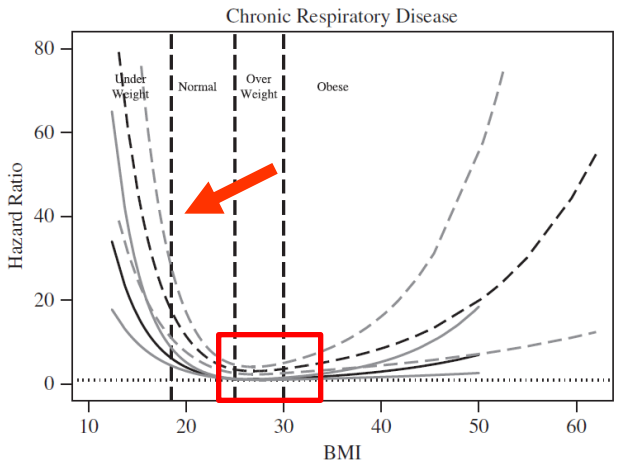


Figure 2. Hazard ratios of all-cause mortality according to body mass index (BMI) in healthy and nonhealthy men and women aged 70 to 75.

Flicker L et al. JAGS 2010







Flicker L et al. JAGS 2010

The effect of middle- and old-age BMI on short-term mortality in older people

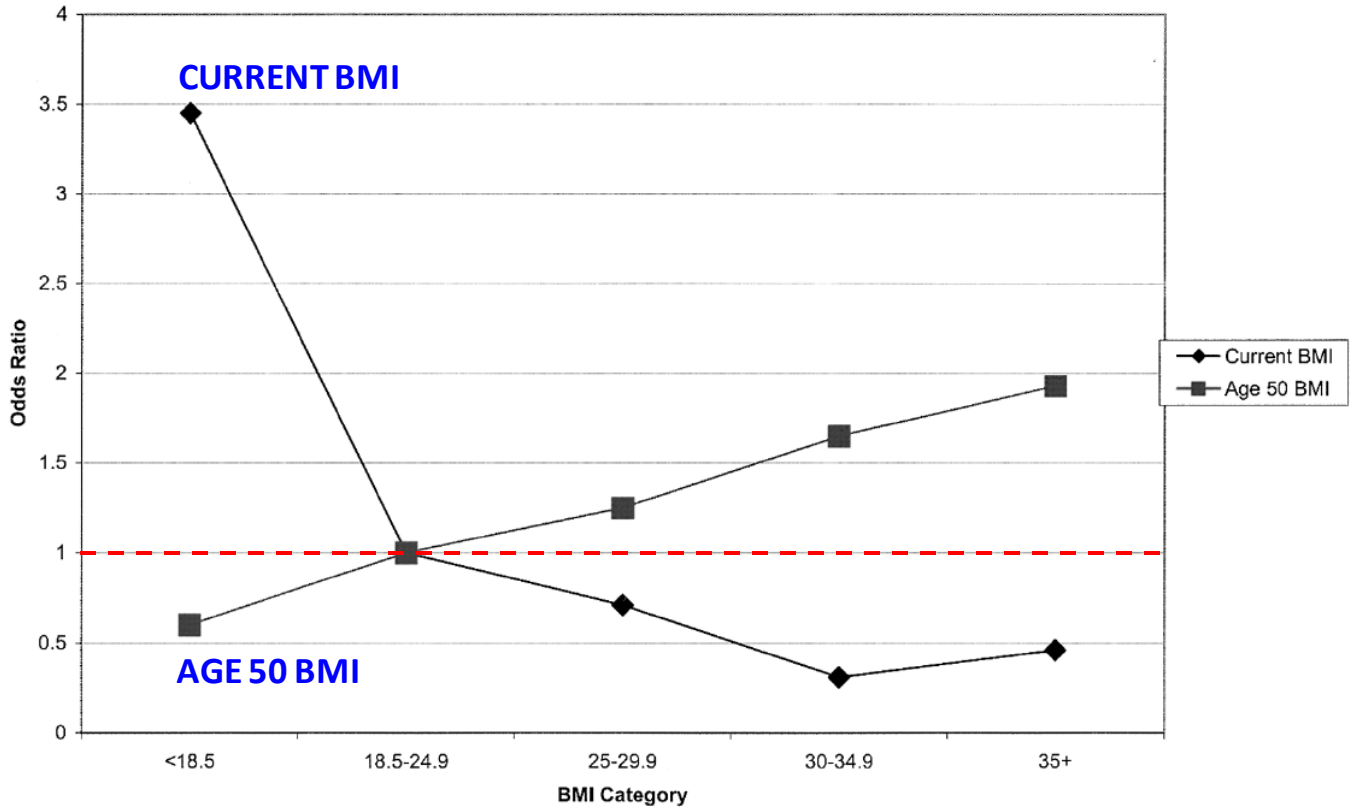


Figure 2. Adjusted odds of mortality by body mass index (BMI) category at age 50 and the 1994 National Long Term Care Survey.

Taylor DH et al. JAGS 2001

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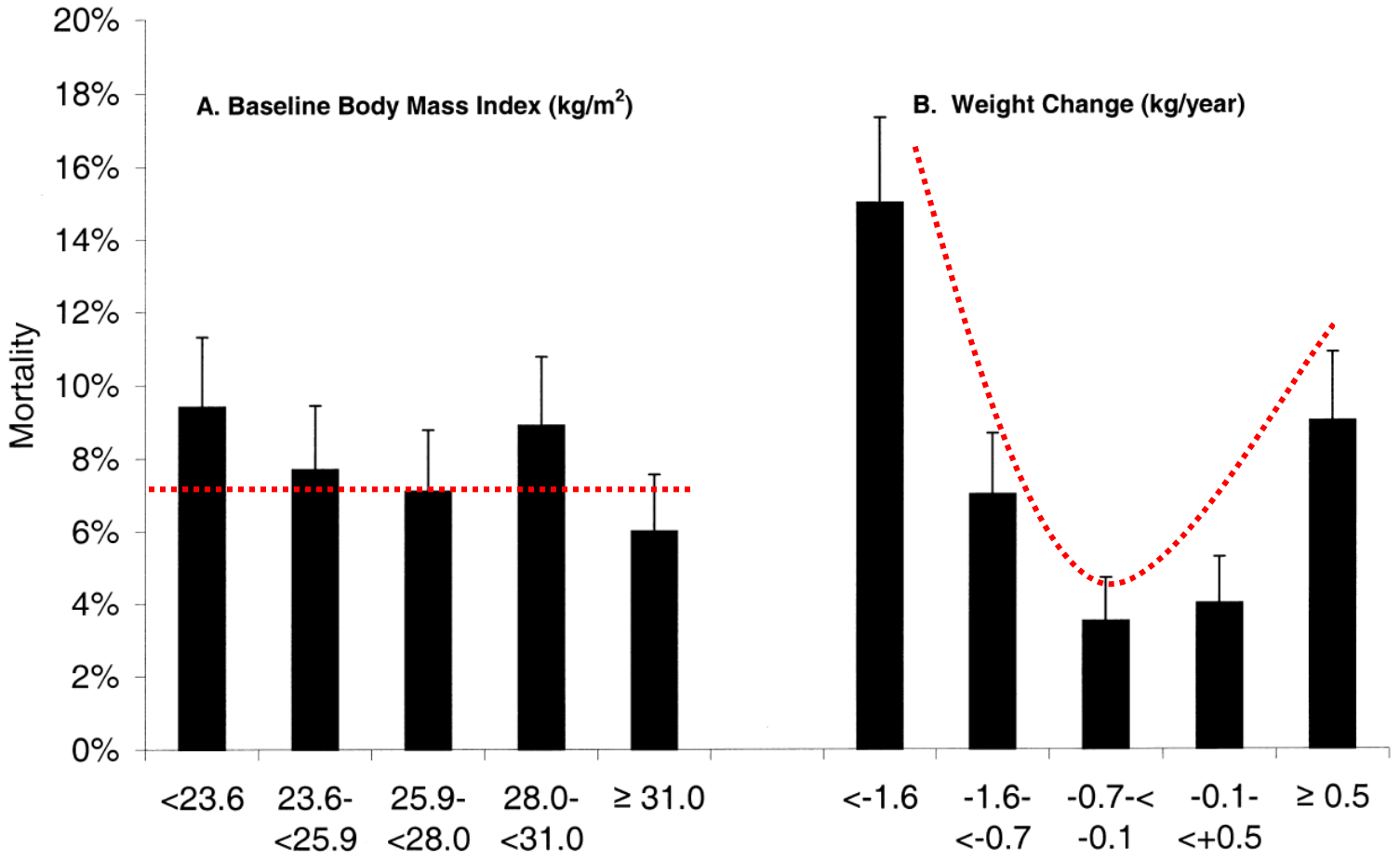
Body Mass Index, Weight Change, and Death in Older Adults

The Systolic Hypertension in the Elderly Program



Somes GW et al. Am J Epidemiol 2002

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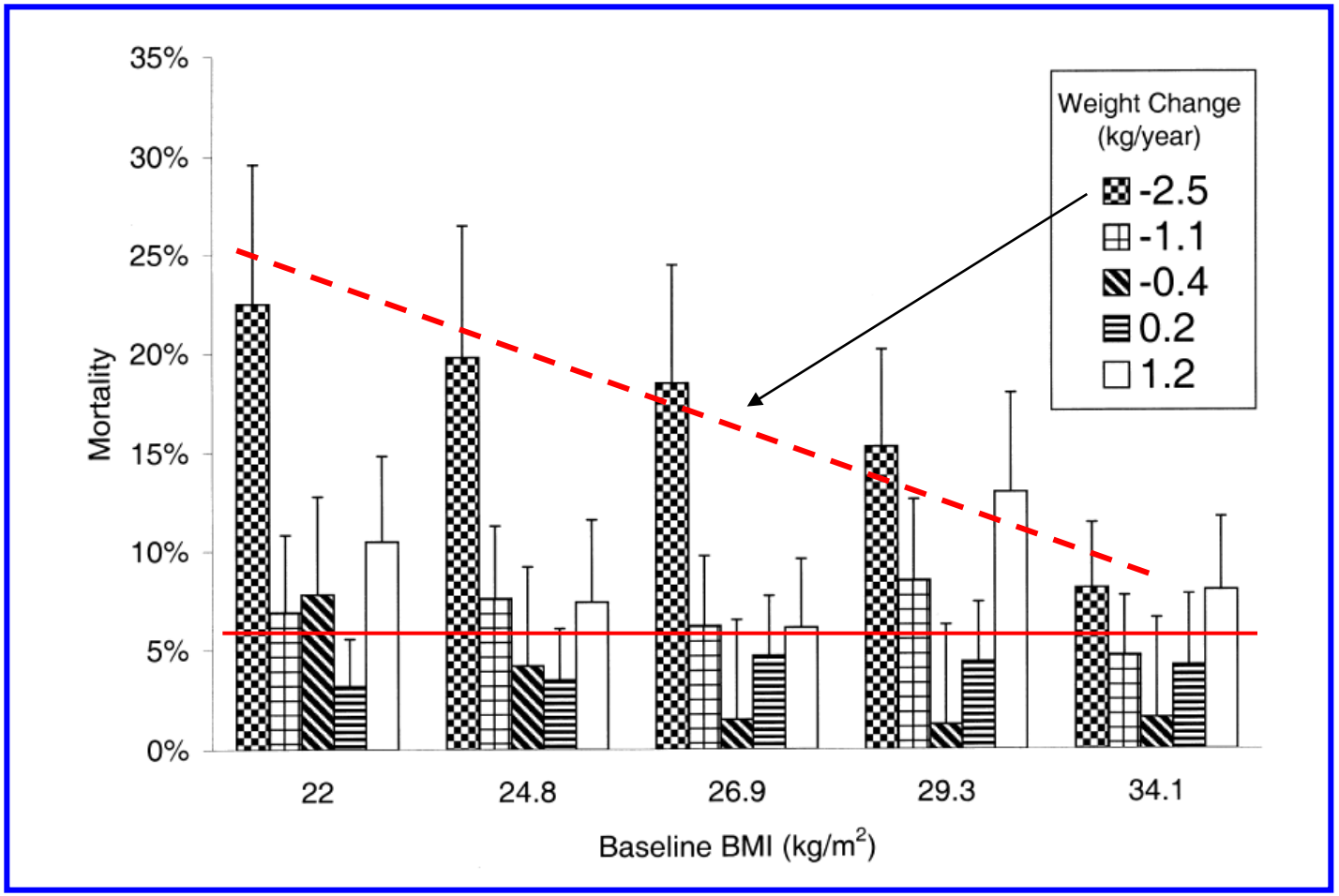
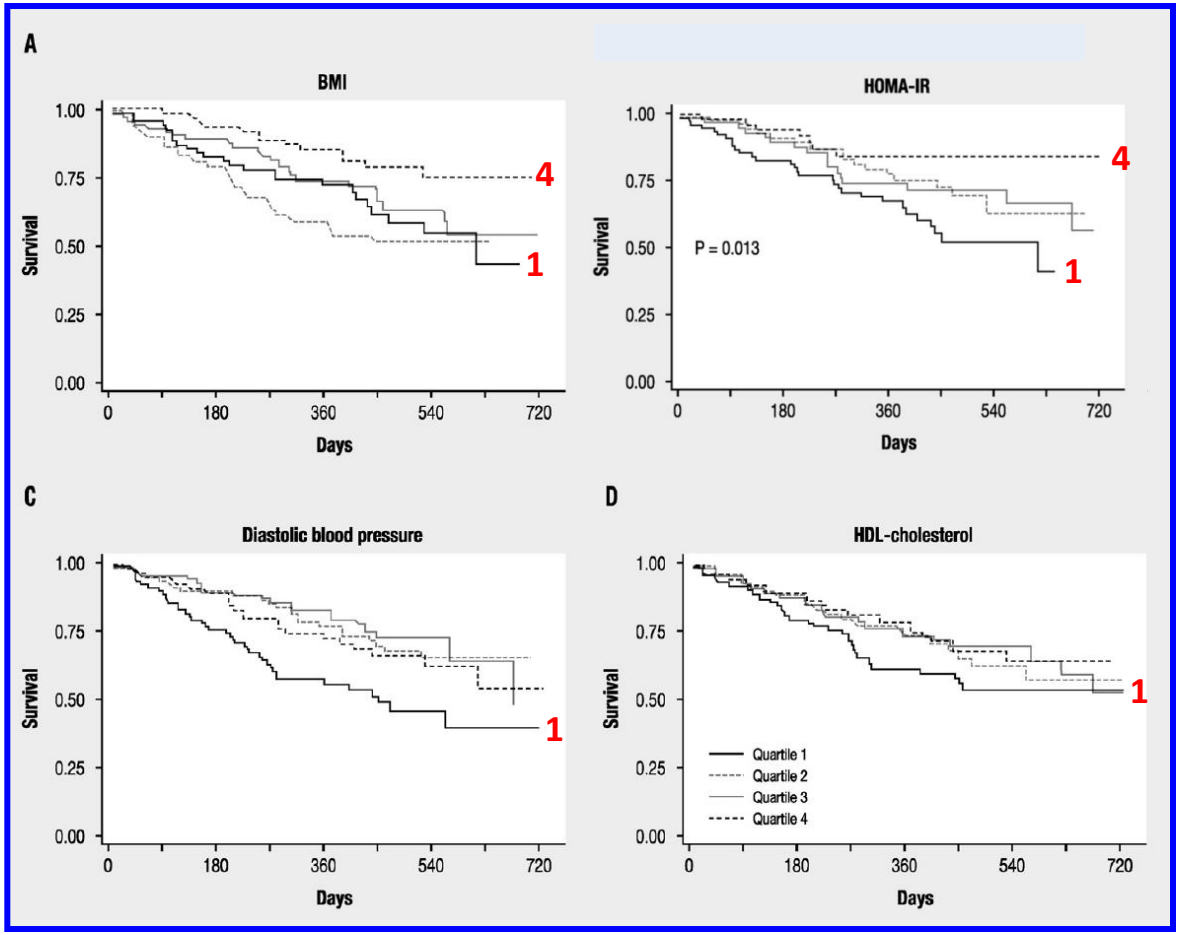


Somes GW et al. Am J Epidemiol 2002

Cardiometabolic determinants of mortality in a geriatric population: Is there a "reverse metabolic syndrome"?

U.M. Vischer [a,*], M.E. Safar [b], H. Safar [b], P. Iaria [b], K. Le Dudal [b], O. Henry [b], F.R. Herrmann [a], P. Ducimetière [c], J. Blacher [b,c]



331 men and women, mean age 85 yrs: follow-up 2 yrs

Vischer UM et al. Diabetes & Metabolism 2009

Cardiometabolic determinants of mortality in a geriatric population: Is there a "reverse metabolic syndrome"?

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*"...**Albumin,** a marker of malnutrition, was associated with blood pressure, total and HDL cholesterol, and HOMA-IR. The inflammation marker **CRP** was associated with low total and HDL cholesterol, and high HOMA-IR..."*

Conclusion: In very old patients, low BMI, low DBP, low total and HDL cholesterol, and high insulin sensitivity predict total mortality, ***indicating a "Reverse Metabolic Syndrome" probably attributable to malnutrition and/or chronic disorders.***

Vischer UM et al. Diabetes & Metabolism 2009

REVERSE EPIDEMIOLOGY

Possible explanations for reverse epidemiology

- "Reverse epidemiology" might be mystifying, since obesity and high serum cholesterol are well-established risk factors for CHD in West Countries.
- There must be prevailing conditions in very-old or comorbid patients which render them ***more susceptible to death when low BMI or low serum cholesterol are present.***
- Alternately, once chronic diseases develops, these factors may actually provide patients with ***protection against disease progression or death***.

1. Survival bias

- Because very-old patients have undergone selection and survival, their characteristics are different from adult population.
- A higher proportion of patients with CVD risk factors do not reach advanced age due to higher mortality, while individuals surviving to advanced age despite CVD risk factors may have other ***Protective Factors*** that negate the adverse effects of risk factors.
- These individuals are ***"Specifically Selected"*** subjects who are not necessarily genetically or phenotypically similar to their predecessors and may not have the survival characteristics and epidemiologic features of their progenitors. A survival bias may heavily influence the epidemiologic constellations in this smaller proportion of cardiovascular survivors .

2. Malnutrition & inflammation

- Very-old patients with low cholesterol levels, hypoalbuminemia, and muscle atrophy (sarcopenia) very often have experimented ***unintentional Weight Loss*** or have ***Frailty Syndrome***.
- In advanced age, ***Weight Loss and Frailty*** are independent predictors of increased mortality.
- An important feature of frailty is the presence of a ***Systemic Inflammation***. Pro-inflammatory cytokines have been reported to be significantly increased in patients with frailty, cachexia, cancer, infections and vascular diseases, and have been associated with low cholesterol levels.

Frailty syndrome

Proposed Nutritional and Metabolic Markers

↓ Albumin levels

↓ **Total cholesterol**

↓ **HDL-C**

↓ Serum Iron

↓ **Body mass index - Body cell mass**

Systemic inflammation

(IL-1β, TNFα, IL-6)

- ↑ CRP
- ↑ Fibrinogen
- ↑ BSR
- ↑ α-2 globulin, γ globulin
- ↓ Albumin, Tranferrin
- ↓ **Cholesterol, ↓ HDL-C**
- ↓ Serum iron

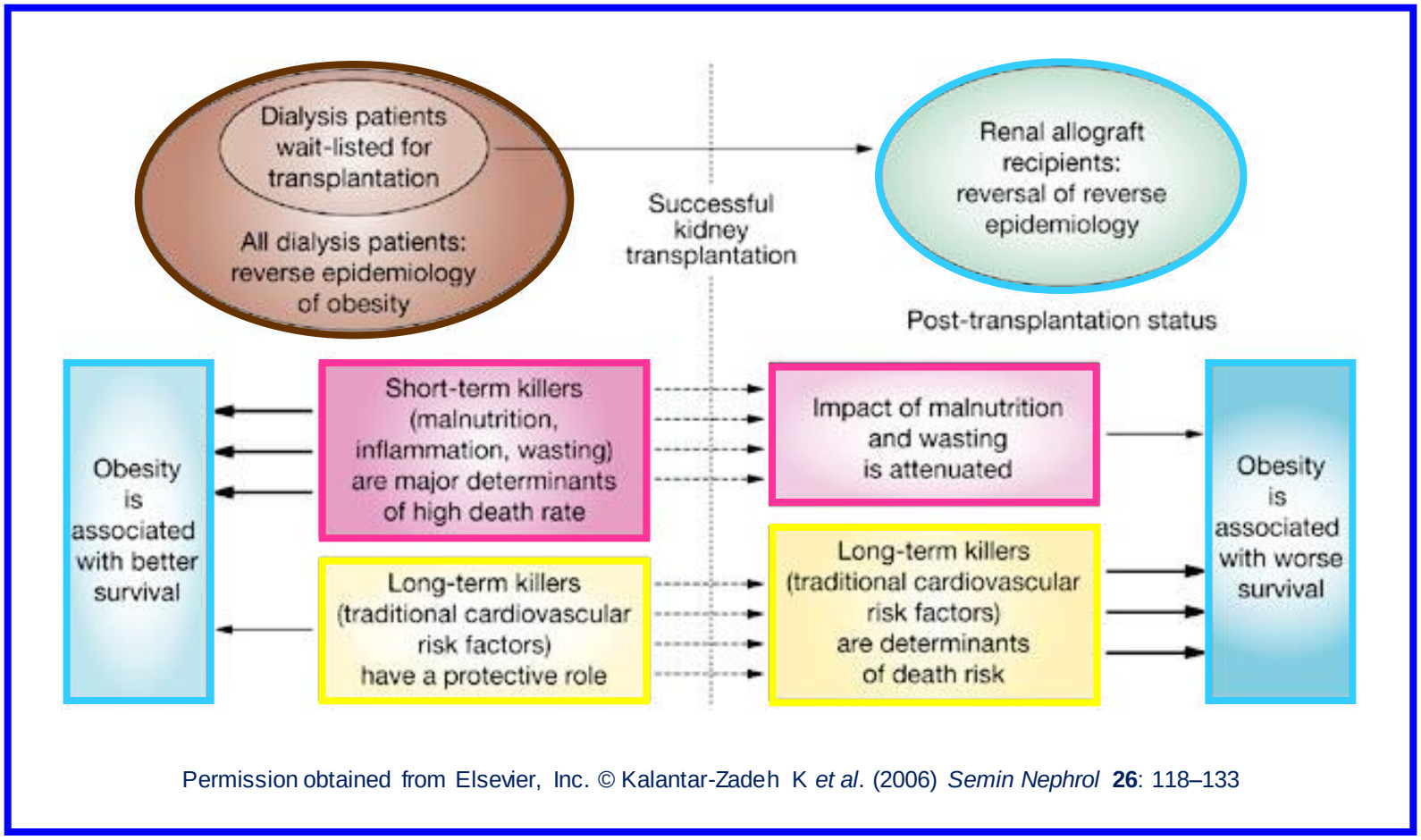
3. Reverse causation

- The direction of causal pathways may be reversed in the paradoxical associations described in very-old/comorbid patients. It may NOT be low cholesterol or BMI that are detrimental, but rather the underlying causes (i.e., chronic diseases, inflammation, malnutrition, frailty).
- This phenomenon **(Reverse Causation)** indicates that low BMI or serum cholesterol are not etiologically linked to a higher mortality rate, they are just ***Markers of a Poor Outcome.***

4. Time discrepancies among competitive risk factors

- In Western Countries, manifestations of over-nutrition such as obesity and hypercholesterolemia are major risk factors for CVD mortality.
- Nevertheless, ***Short-Term Survival Advantages*** might exist in very-old/comorbid individuals with high cholesterol or BMI that might outweigh their harmful effects on CVD in the long-term.
- In very-old/comorbid patients, who have a ***Short Life Expectancy,*** any factor that may improve short-term survival (including obesity or hypercholesterolemia) may exert a desirable effect on longevity.

Reversal of reverse epidemiology after successful kidney transplantation in maintenance dialysis patients



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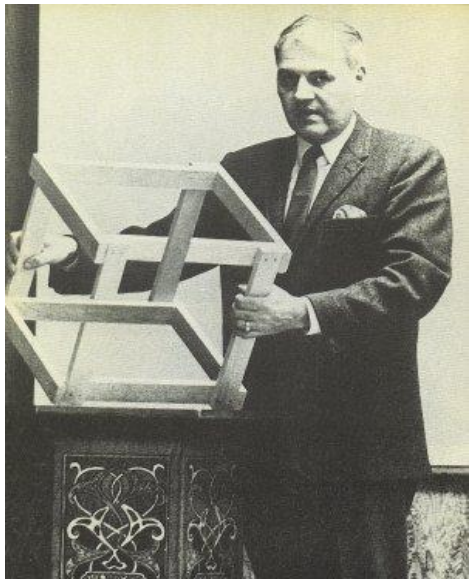
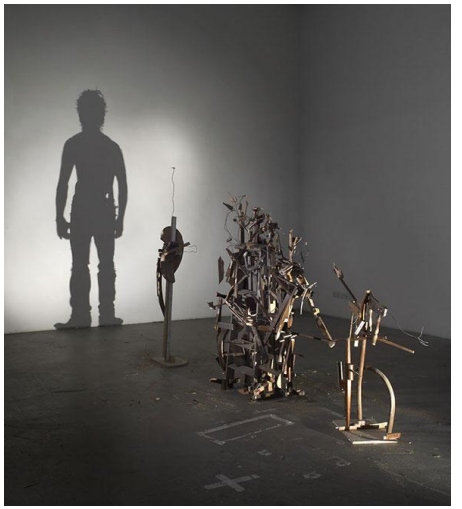
nature CLINICAL PRACTICE NEPHROLOGY

Kalantar-Zadeh K et al. 2007 Nat Clin Pract Nephrol



- ***Survival bias***
- ***Malnutrition***
- ***Inflammation***
- ***Reverse causation***
- ***Time discrepancies among competitive risk factors***

Even if the associations between low Cholesterol and BMI and total mortality are devoid of causation or have a reversed direction, ***the counterfactual inference*** *implies that actions that would avoid lower BMI or cholesterol in very-old/comorbid subjects might be beneficial in their survival.*