Cholesterol is an important risk factor for heart disease and current dietary recommendations do more good than harm

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National Institutes of Health

Disclosures

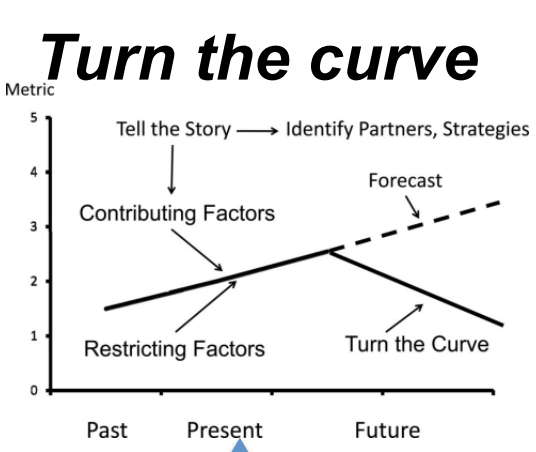
No conflicts of interest

Outline

- Serum Cholesterol as Risk Factor
- The Diet-Heart Hypothesis
- Diet, Obesity, and Diabetes

Serum Cholesterol as Risk Factor

From Research To Impact: High Blood Cholesterol



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Cholesterol "Fractions" Became the Clinical Focus ~50 Years Ago

Total Cholesterol

VLDL Cholesterol + LDL Cholesterol + HDL Cholesterol

"Bad"

High Levels = ↑ Risk

"Good"

High Levels = ↓ Risk

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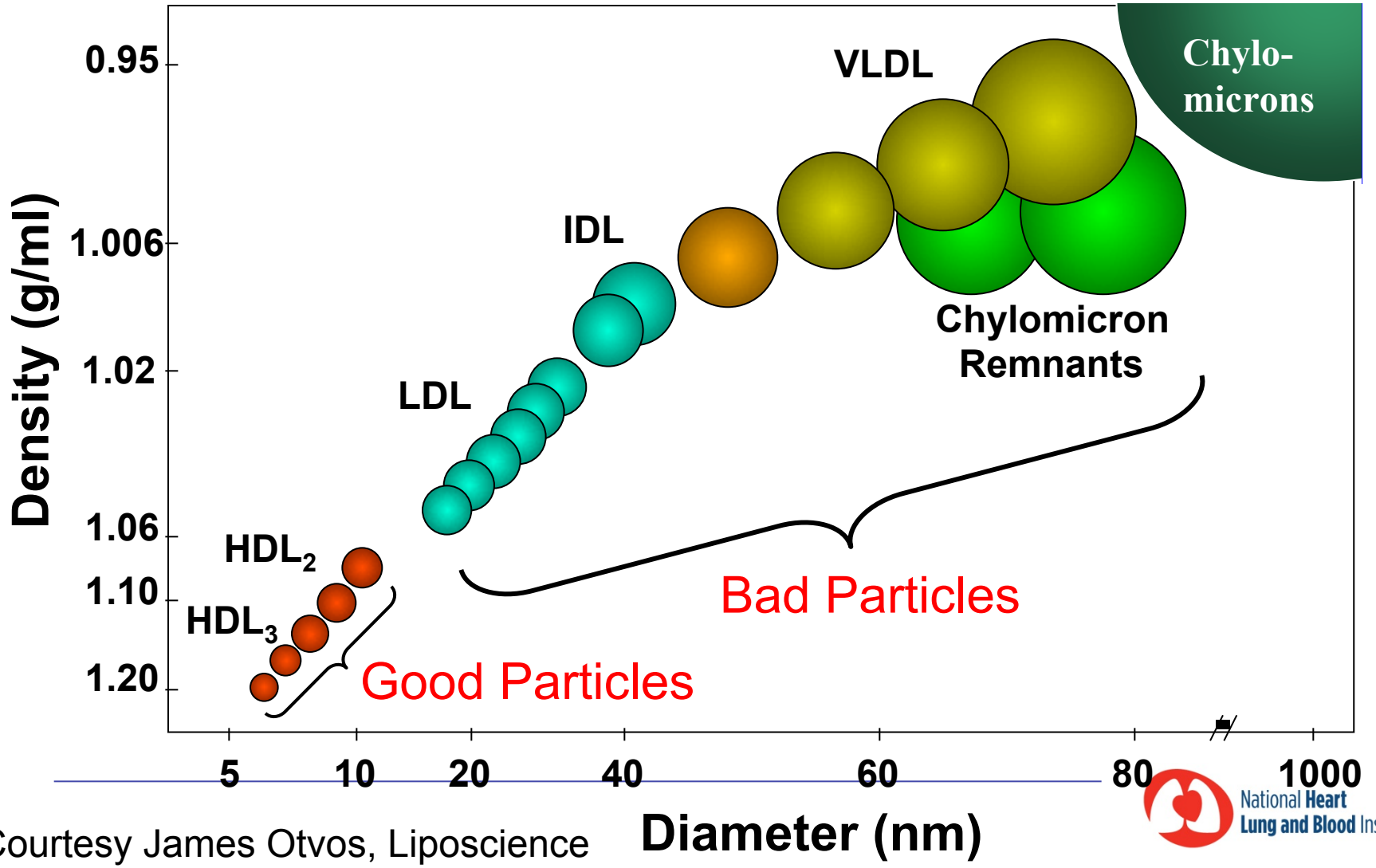
What's Actually "Bad" and "Good" are Different Lipoprotein Particles



Courtesy James Otvos, Liposcience

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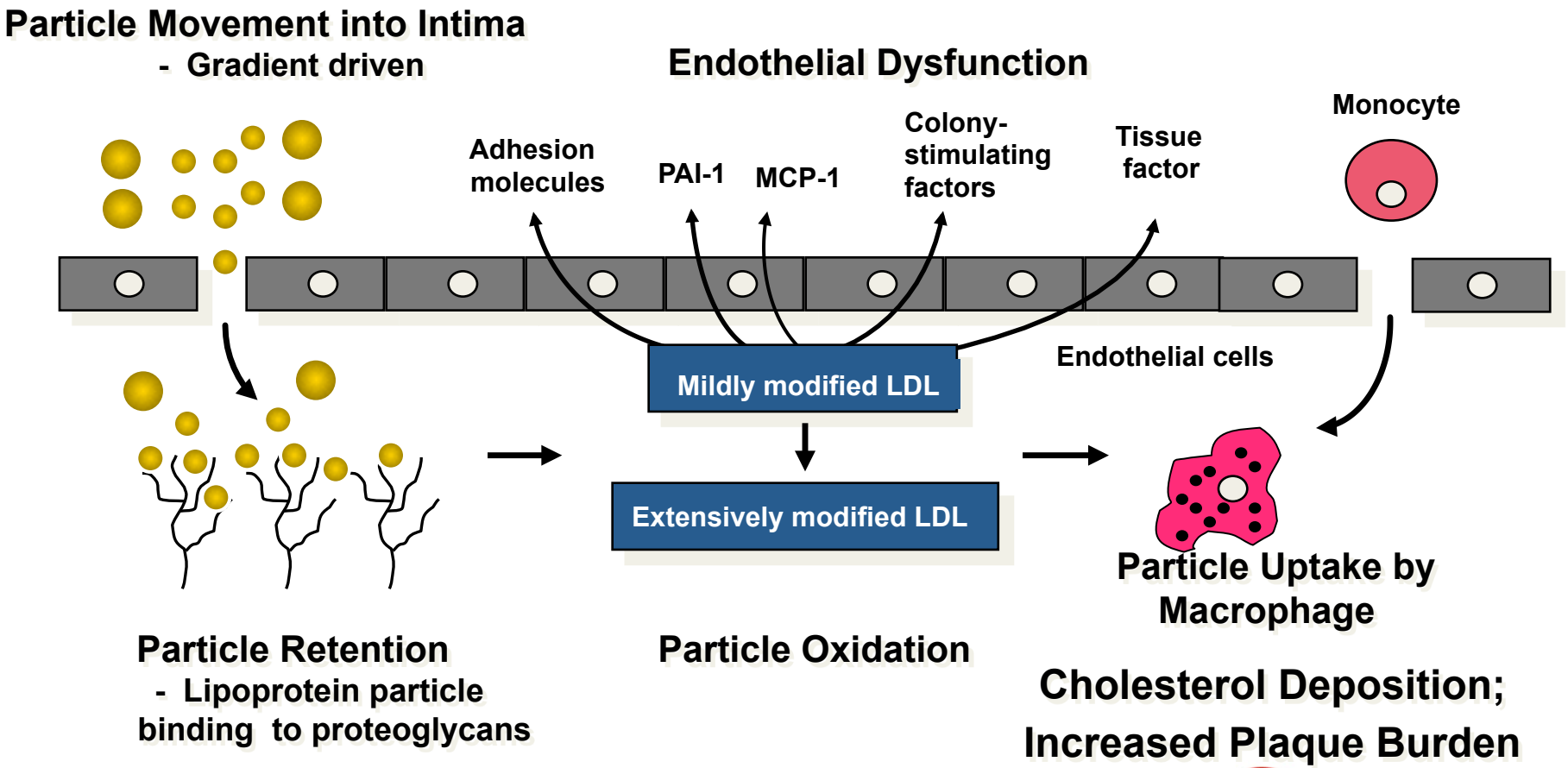
Why LDL Particles are "Bad" They Promote Atherogenesis



Weissberg PL, Rudd JH. Textbook of Cardiovascular Medicine. 2002. p. 6.

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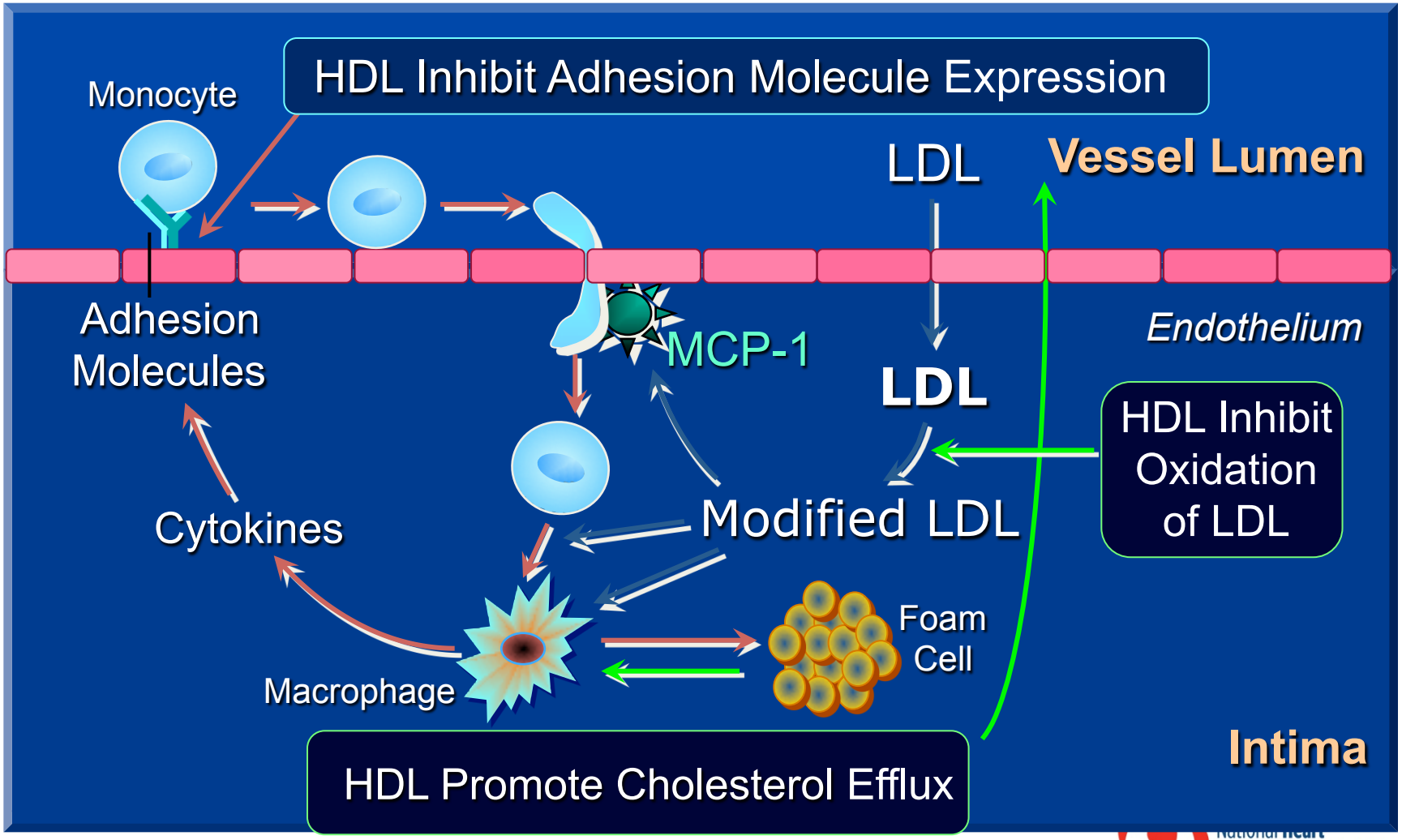
Why HDL Particles are "Good" They Inhibit Atherogenesis



Cockerill GW et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-1994

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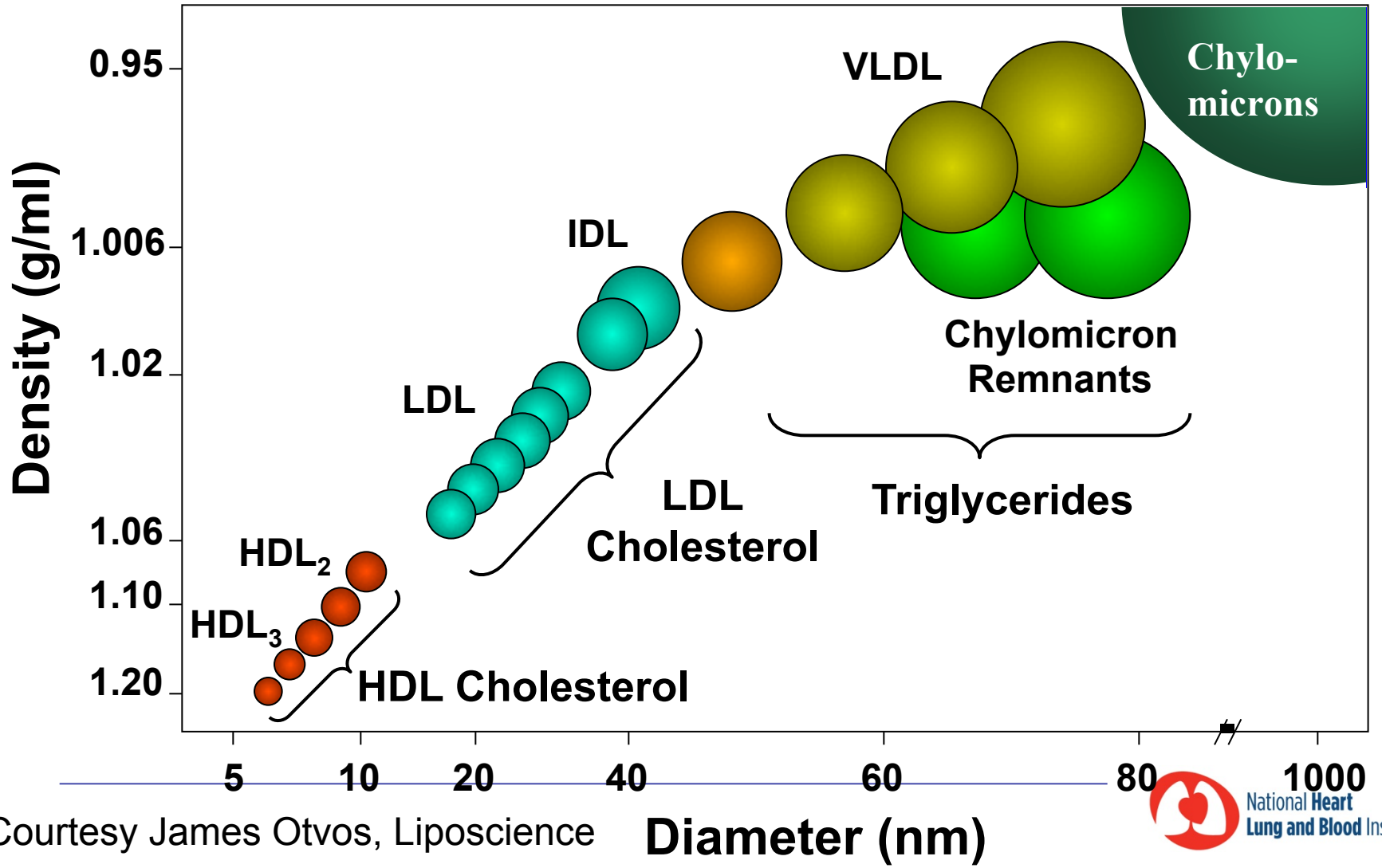
Historically Triglycerides, LDL-C and HDL-C Have Been Used as Biomarkers



Courtesy James Otvos, Liposcience

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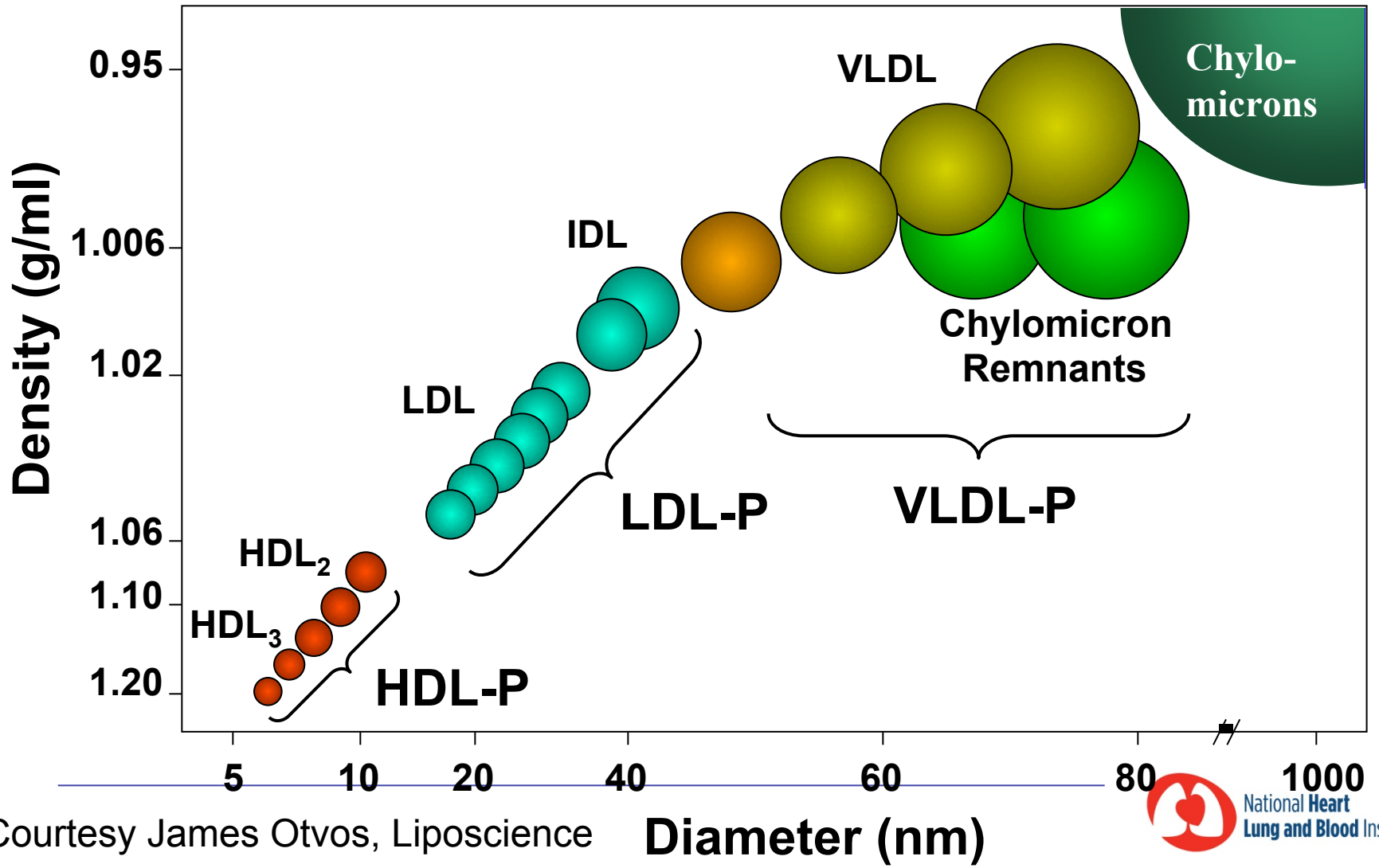
Alternative Lipoprotein Biomarkers Now Exist
Particle Number by NMR



Courtesy James Otvos, Liposcience

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LDL Particles: Number is more important than size

Table 1 Univariate and multivariate analyses on the association of size or number of small, dense LDL particles with cardiovascular diseases

Author	Study design	Univariate	Multivariate	Author	Study design	Univariate	Multivariate
LDL size							
Crouse[22]	CS	Y	N	Skoglund[47]	CS	Y	Y
Austin[23]	CS	Y	N	Zambon[48]	P	Y	Y
Griffin[24]	CS	Y	N	Austin[49]	P	Y	N
Tornvall[25]	CS	Y	–	Hulthe[50]	CS	N	–
Campos[26]	CS	Y	N	Hulthe[51]	CS	Y	–
Coresh[27]	CS	Y	N	Bokemark[52]	CS	Y	N
Griffin[28]	CS	Y	Y	Campos[53]	P	N	N
Campos[29]	CS	N	N	Kamigaki[54]	CS	Y	N
Sherrard[30]	CS	N	–	Rosenson[55]	P	Y	Y
Rajman[31]	CS	N	–	Blake[56]	P	Y	N
Stampfer[32]	P	Y	N	Kuller[57]	P	Y	N
Gardner[33]	P	Y	Y	Liu[58]	CS	Y	Y
Miller[34]	P	Y	N	Koba[59]	CS	Y	Y
Mack[35]	P	Y	N	Vakkilainen[60]	P	Y	N
Lamarche[36]	P	Y	Y	Slowik[61]	CS	Y	–
Gray[37]	CS	N	–	Hallman[62]	CS	Y	–
Wahi[38]	CS	N	–	Watanabe[63]	CS	Y	–
Slyper[39]	CS	N	–	Wallenfeldt[64]	P	Y	–
Freedman[40]	CS	Y	N	Kullo[65]	CS	Y	N
Ruotolo[41]	P	Y	N	van Tits[66]	P	Y	–
O'Neal[42]	CS	Y	Y	Inukai[67]	CS	Y	Y
Landray[43]	CS	Y	N	Mohan[68]	CS	Y	–
Hulthe[44]	CS	Y	–	Yoon[69]	CS	Y	Y
Mykkanen[45]	P	N	N	St Pierre[70]	P	Y	–
Erbey[46]	CS	Y	N	Berneis[71]	CS	Y	Y
LDL number							
Rosenson[55]	P	Y	Y	Kuller[57]	P	Y	Y
Blake[56]	P	Y	Y	Otvos[72]	P	Y	Y

CS, cross-sectional; P, prospective; Y, yes; N, no.

Rizzo M, Berneis K, QJM 2006

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LDL Particles: Number is more important than size
Example from Cardiovascular Health Study

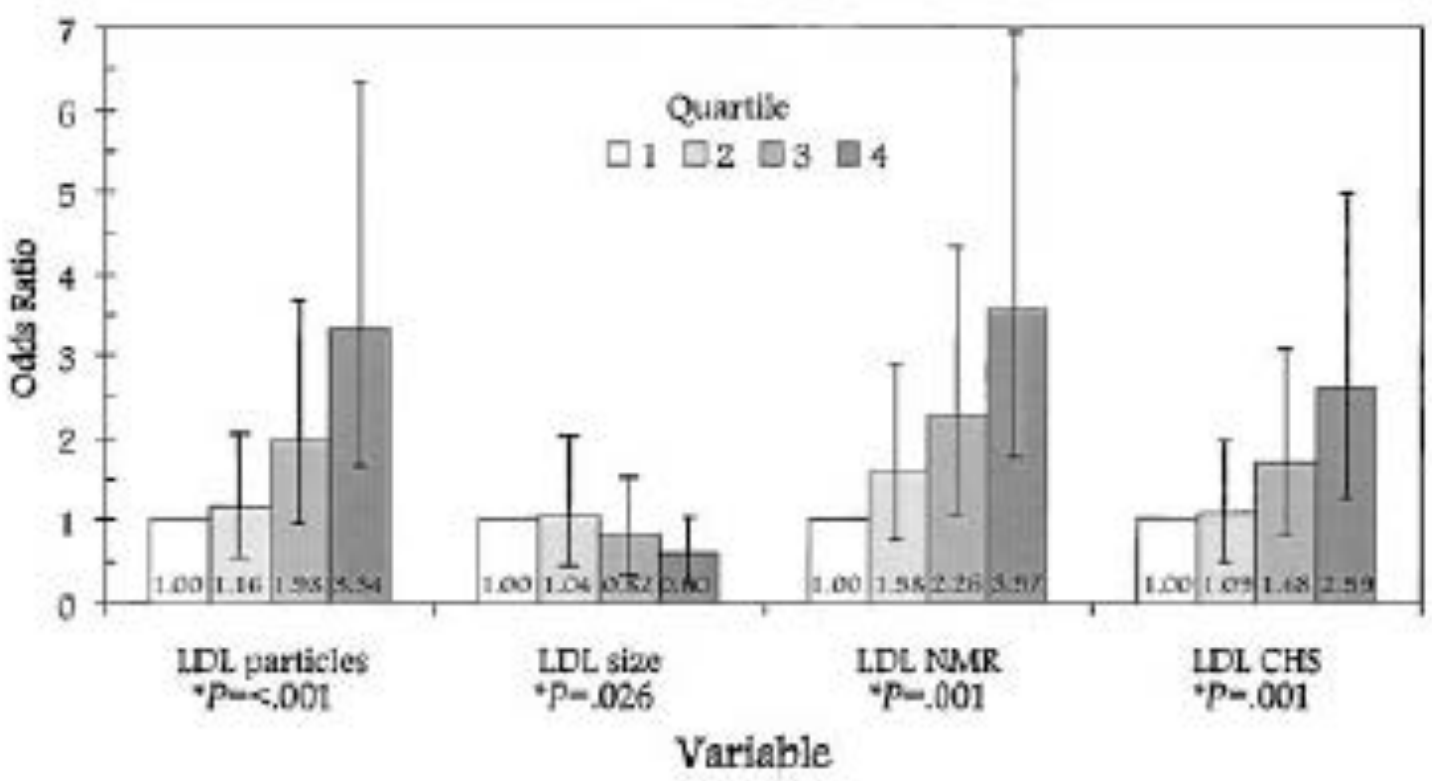

Figure 1. OR for MI and angina by quartiles of LDL, particles, and size compared with healthy CHS women only, adjusted for age and race.

Kuller L et al. ATVB, 2002

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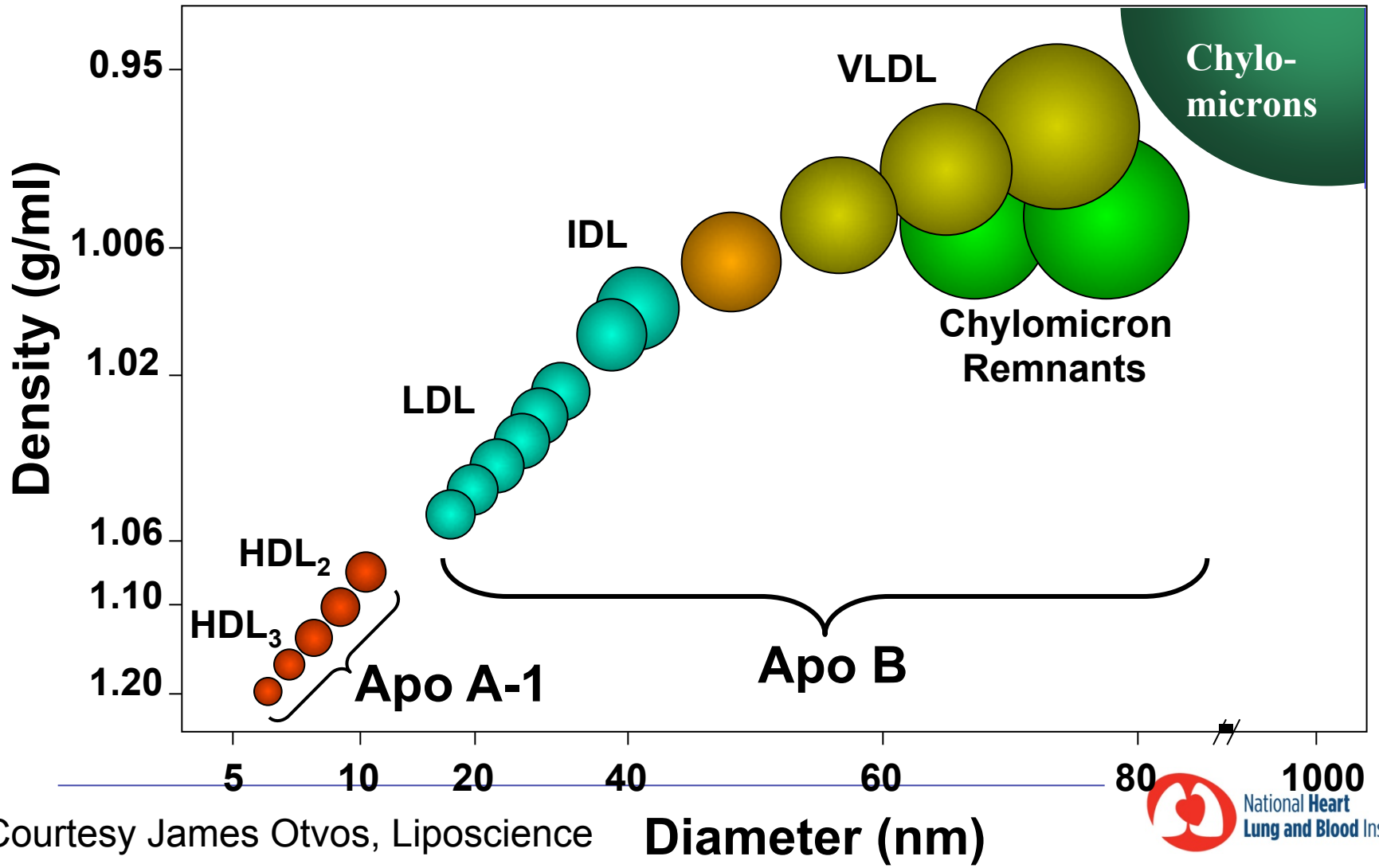
Alternative Lipoprotein Biomarkers Now Exist: Apolipoproteins



Courtesy James Otvos, Liposcience

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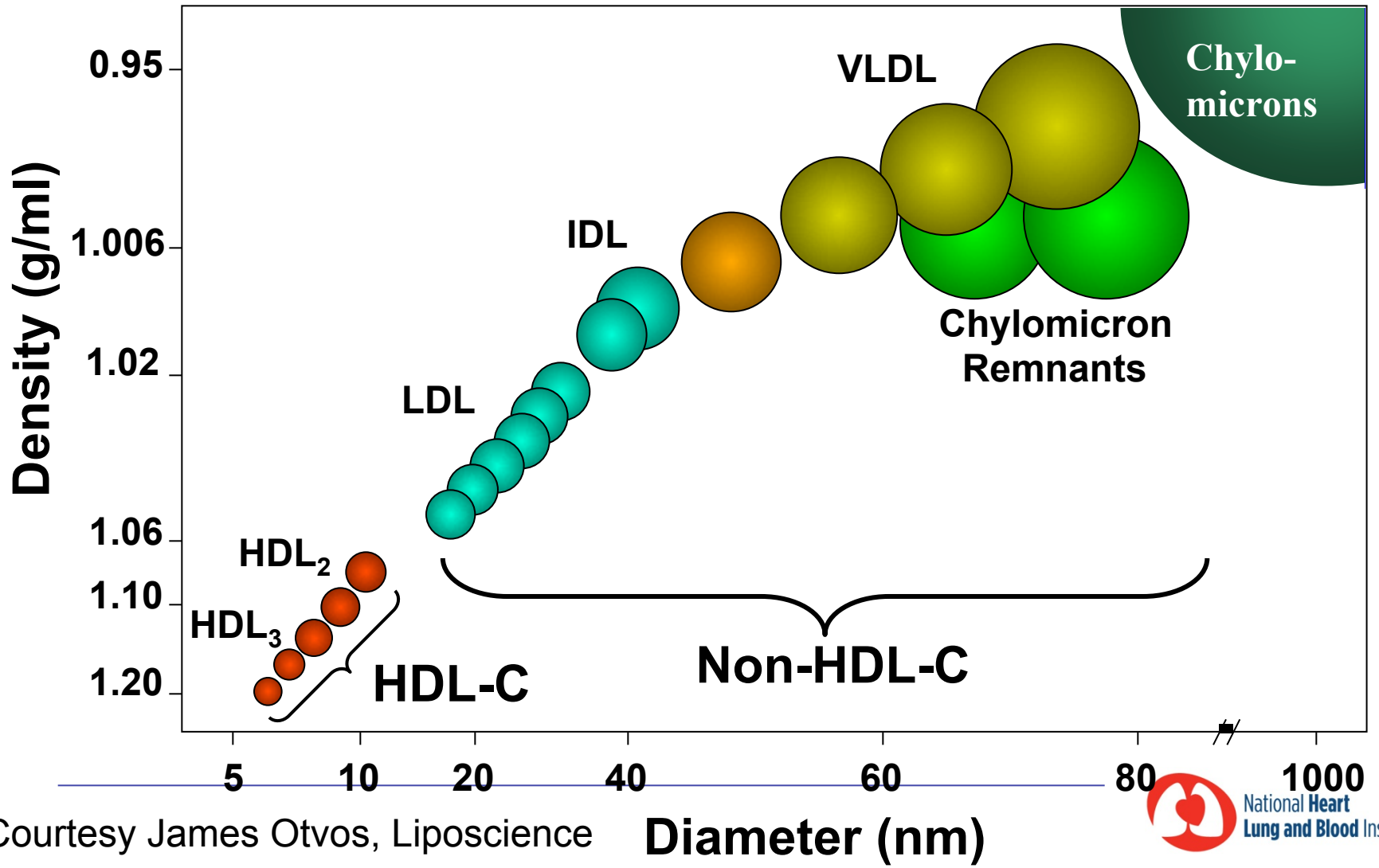
Alternative Lipoprotein Biomarkers Now Exist: Non-HDL-Cholesterol



Courtesy James Otvos, Liposcience

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Non-HDL-C Reflects Atherogenic Lipid Burden

Major Lipids, Apolipoproteins, and Risk of Vascular Disease

The Emerging Risk Factors Collaboration*

RELIABLE ASSESSMENT OF THE separate and joint associations of major blood lipids and apolipoproteins with the risk of vascular disease is important for the de-

Context Associations of major lipids and apolipoproteins with the risk of vascular disease have not been reliably quantified.

Objective To assess major lipids and apolipoproteins in vascular risk.

Design, Setting, and Participants Individual records were supplied on 302 430 people without initial vascular disease from 68 long-term prospective studies, mostly in Europe and North America. During 2.79 million person-years of follow-up, there were 8857 nonfatal myocardial infarctions, 3928 coronary heart disease [CHD] deaths, 2534 ischemic strokes, 513 hemorrhagic strokes, and 2536 unclassified strokes.

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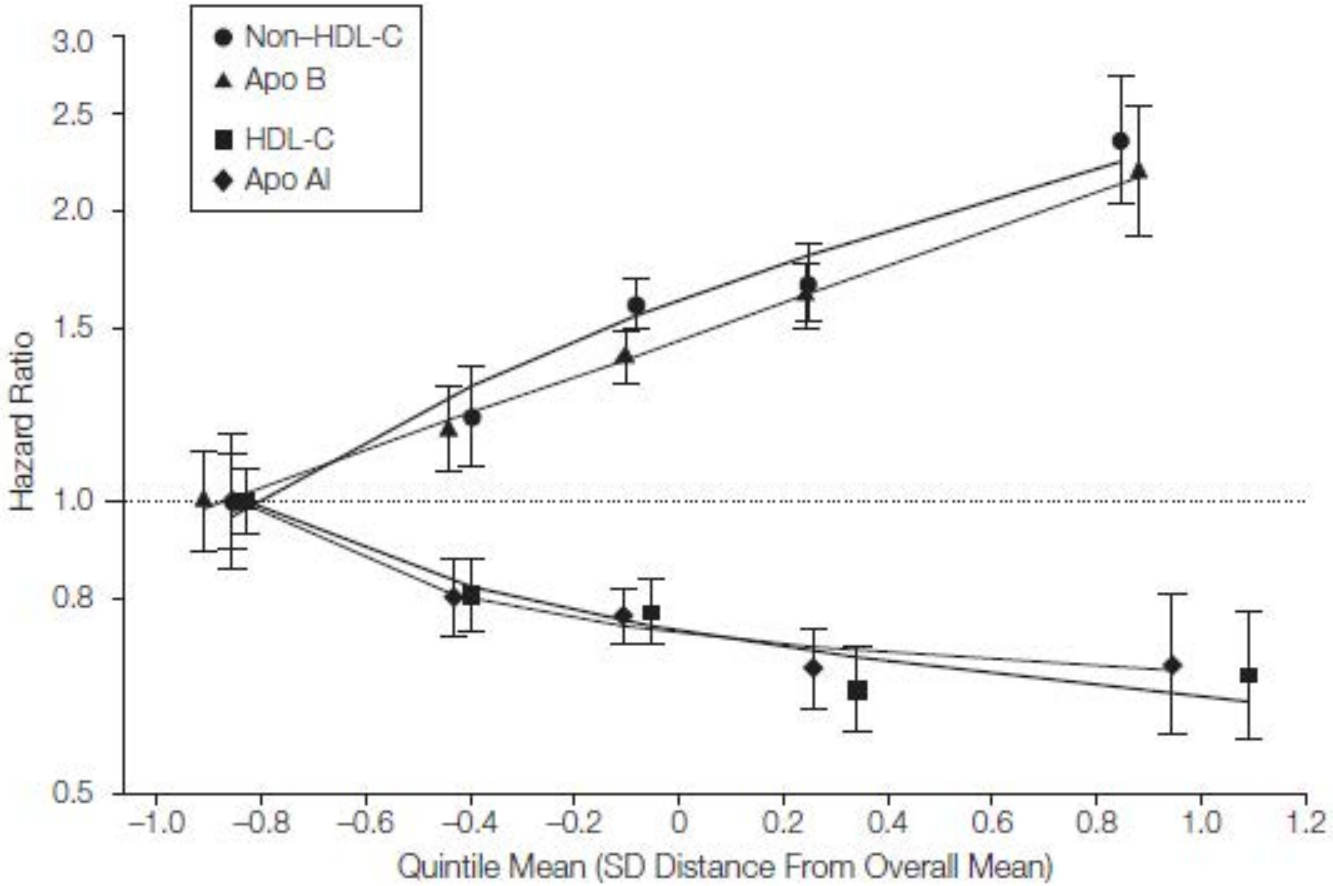
Comparison of Non-HDL-C with Apo B and HDL-C with Apo A1

Figure 3. Hazard Ratios for Coronary Heart Disease Across Fifths of Usual Lipids or Apolipoproteins



The Emerging Risk Factors Collaboration

JAMA. 2009;302(18):1993-2000

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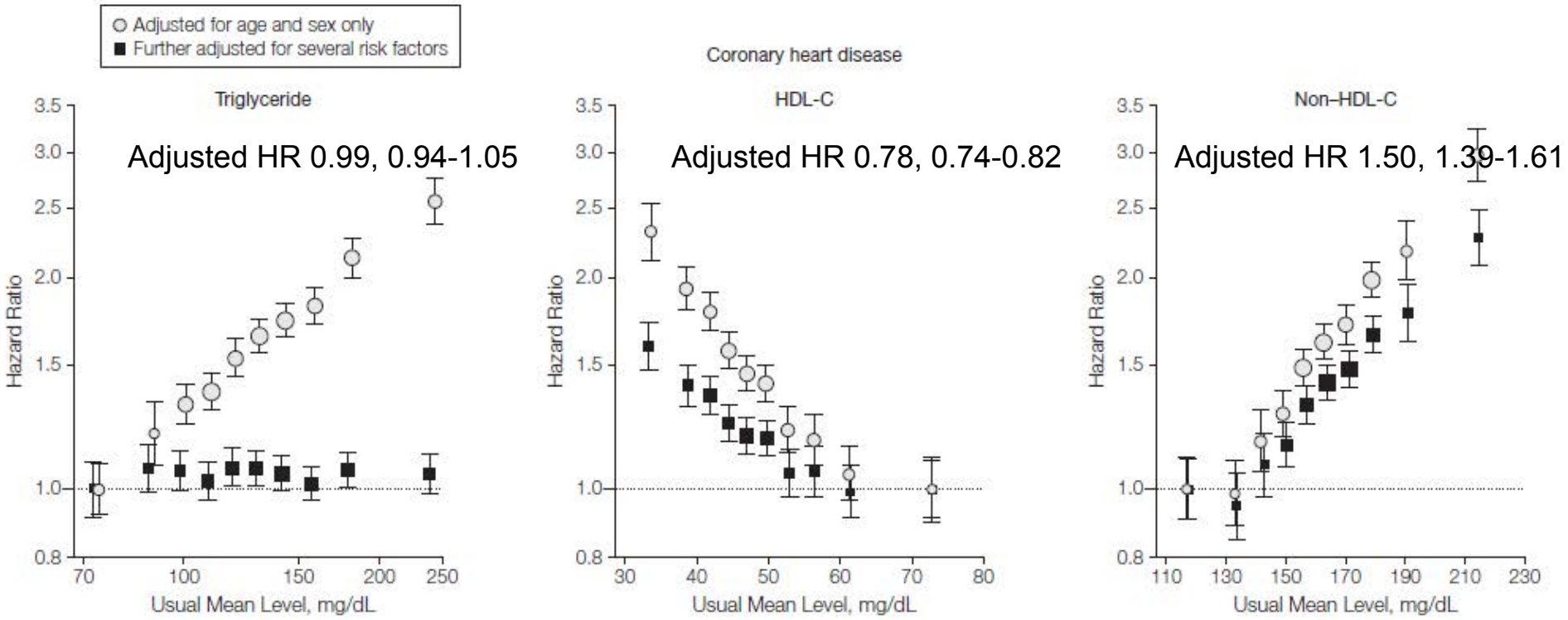
Non-HDL-C and HDL-C are independent risk factors, triglycerides are not

Hazard Ratios for Coronary Heart Disease Across Deciles of Usual Triglyceride, HDL-C, and Non–HDL-C Levels



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JAMA. 2009;302(18):1993-2000

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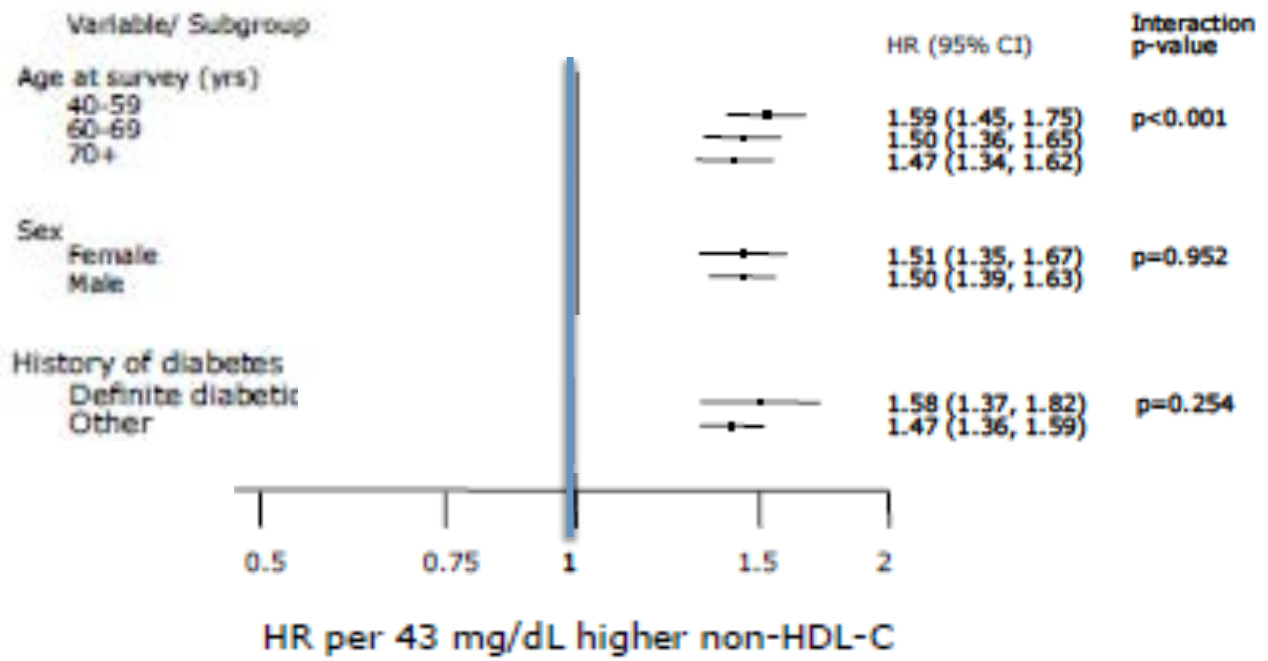
Non-HDL-C is associated with CHD risk in all age groups, men and women, and in diabetics

eFigure 2. Adjusted hazard ratios for coronary heart disease per 1-SD increase in usual triglyceride, HDL-C and non-HDL-C according to various characteristics



In subset of 8 studies:
Overall CHD HR for directly measured LDL-C = 1.38, 1.09-1.73
Overall CHD HR for Non-HDL-C = 1.42, 1.06-1.91

The Emerging Risk Factors Collaboration

JAMA. 2009;302(18):1993-2000

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Major Lipids, Apolipoproteins, and Risk of Vascular Disease

- LDL-C remains a clinically useful marker for CHD risk
- Non-HDL-C is useful in both fasting and non-fasting subjects
  - Proxy for atherogenic particle number
  - Hazard ratios for CHD similar to directly measured LDL-C, Apo B
  - Remains independent risk factor after adjustment for triglycerides and HDL-C
  - Remains risk factor in older subjects, women, diabetics
- HDL-C is an independent (protective) risk factor
  - Hazard ratio similar to Apo A1
- Triglyceride is not an independent risk factor

Causality of low density lipoprotein (LDL) cholesterol

Integral to initiation and progression of coronary heart disease

Estimated heritability: ~40-50%

Rare monogenic conditions leading to very high (*LDLR*, *APOB*, *LDLRAP1*) or low (*MTTP*, *APOB*, *PCSK9*) LDL cholesterol

Key Genetic Variants Affecting LDL Receptor Activity

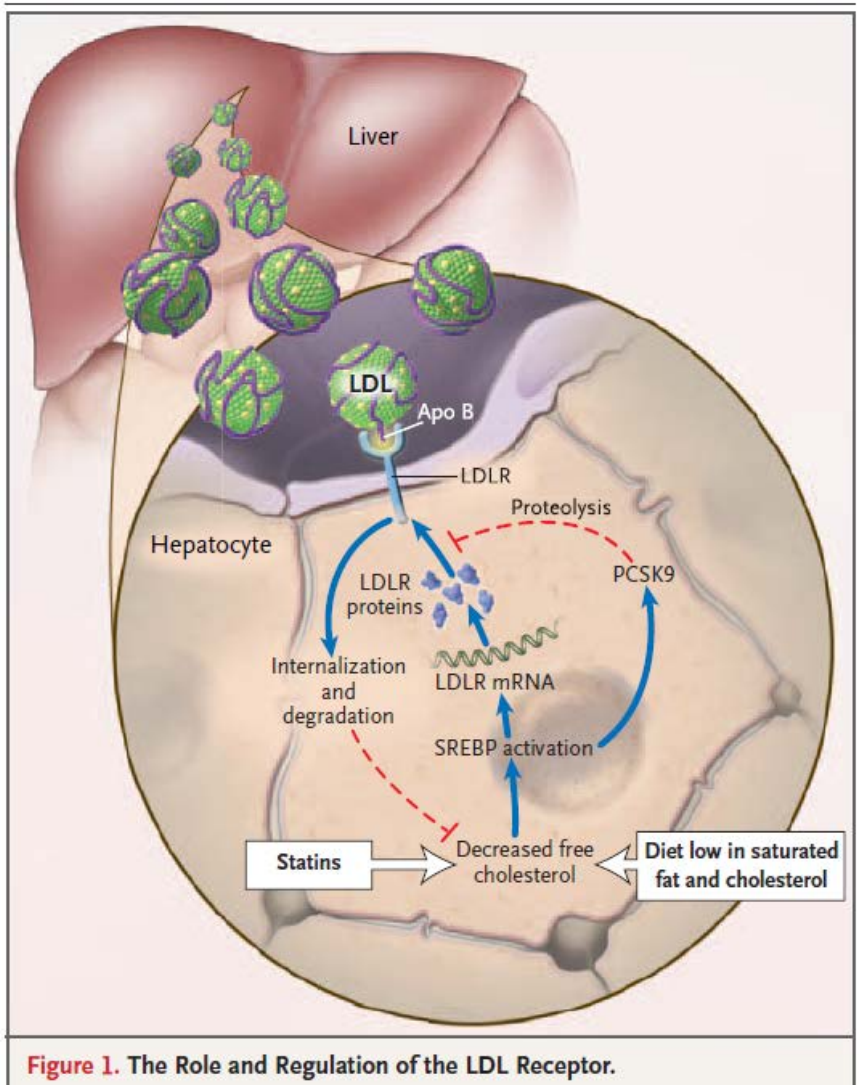

Figure 1. The Role and Regulation of the LDL Receptor.

Tall AR. NEJM 2006

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Development of Coronary Heart Disease in Familial Hypercholesterolemia

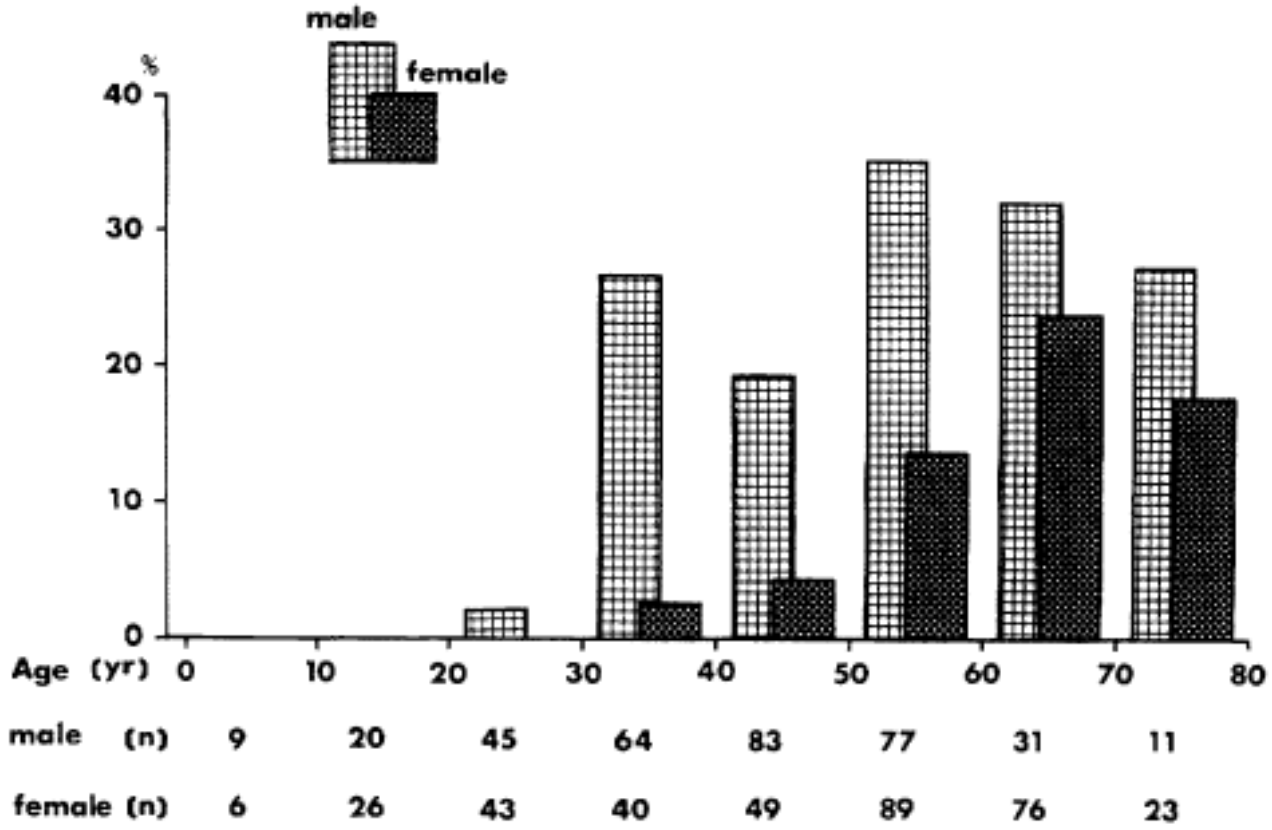

FIGURE 1. *Bar chart of incidence of myocardial infarction by age group in male and female heterozygotes with familial hypercholesterolemia.*

Mabuchi H, et al. Circulation 1989

National Heart Lung and Blood Institute

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

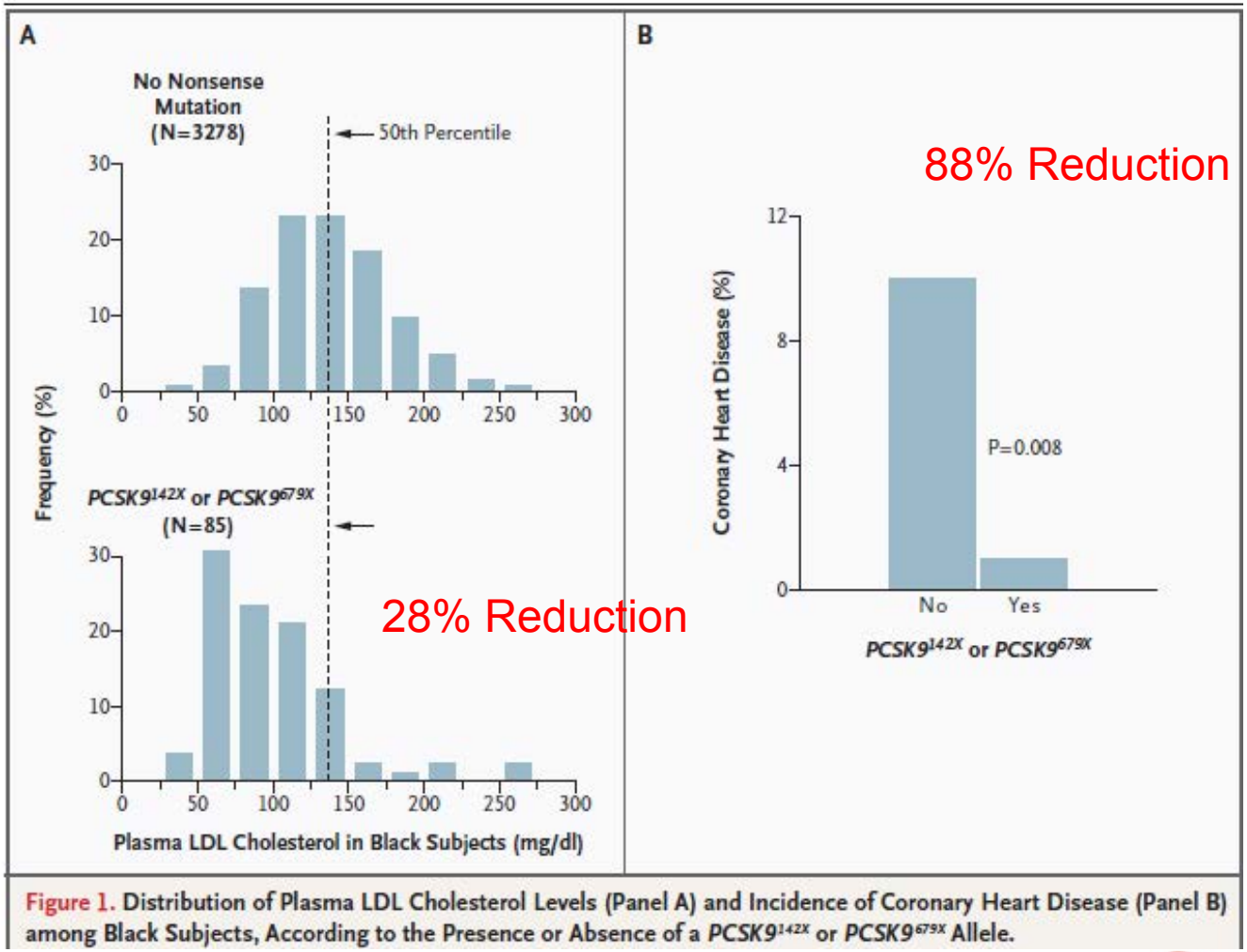

Figure 1. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a *PCSK9*^{142X} or *PCSK9*^{679X} Allele.

NEJM, 2006

National Heart Lung and Blood Institute

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

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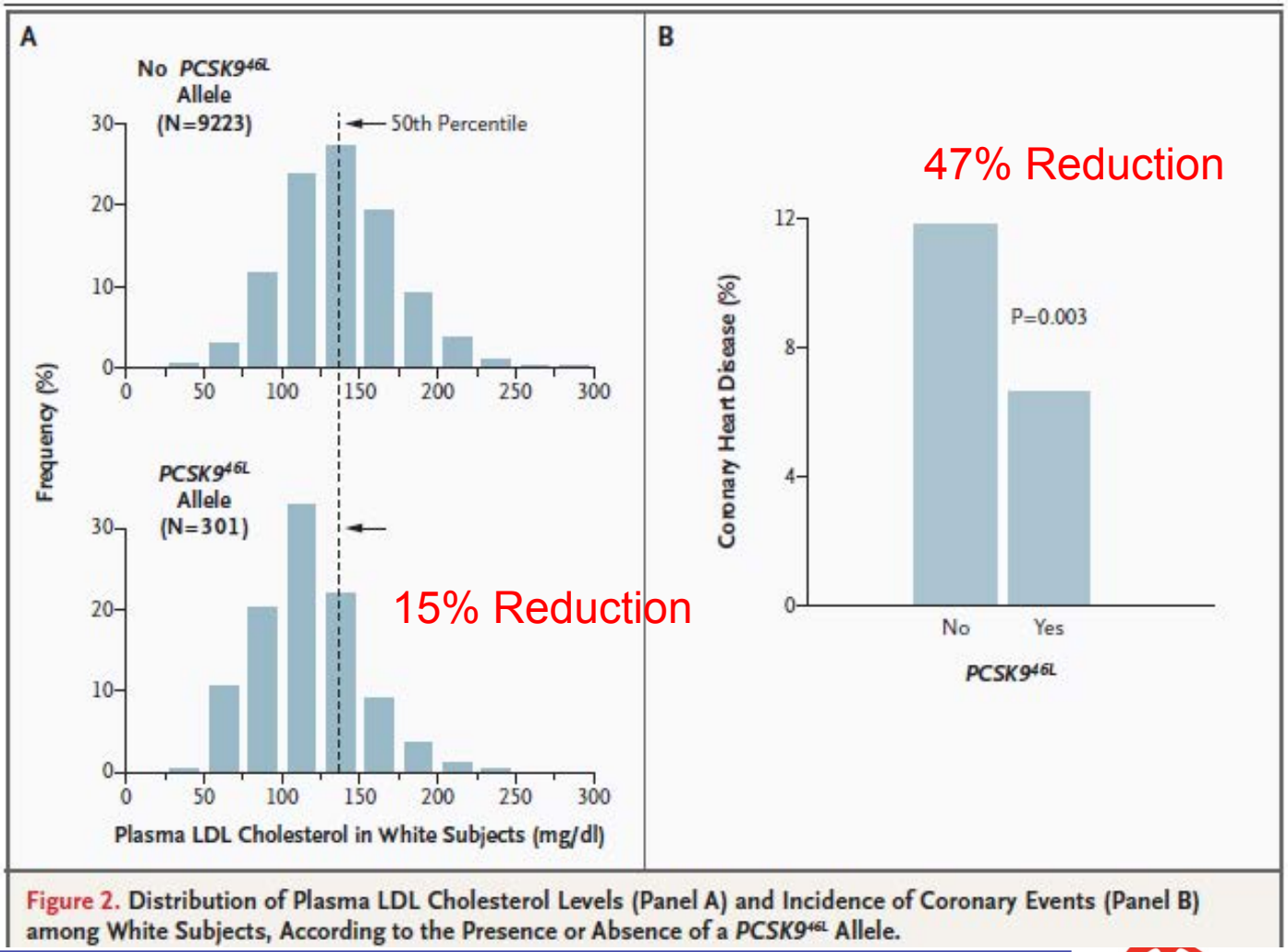

Figure 2. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK9* 46L Allele.

NEJM, 2006

National Heart Lung and Blood Institute

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

CONCLUSIONS

These data indicate that moderate lifelong reduction in the plasma level of LDL cholesterol is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non–lipid-related cardiovascular risk factors.

Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease

A Mendelian Randomization Analysis

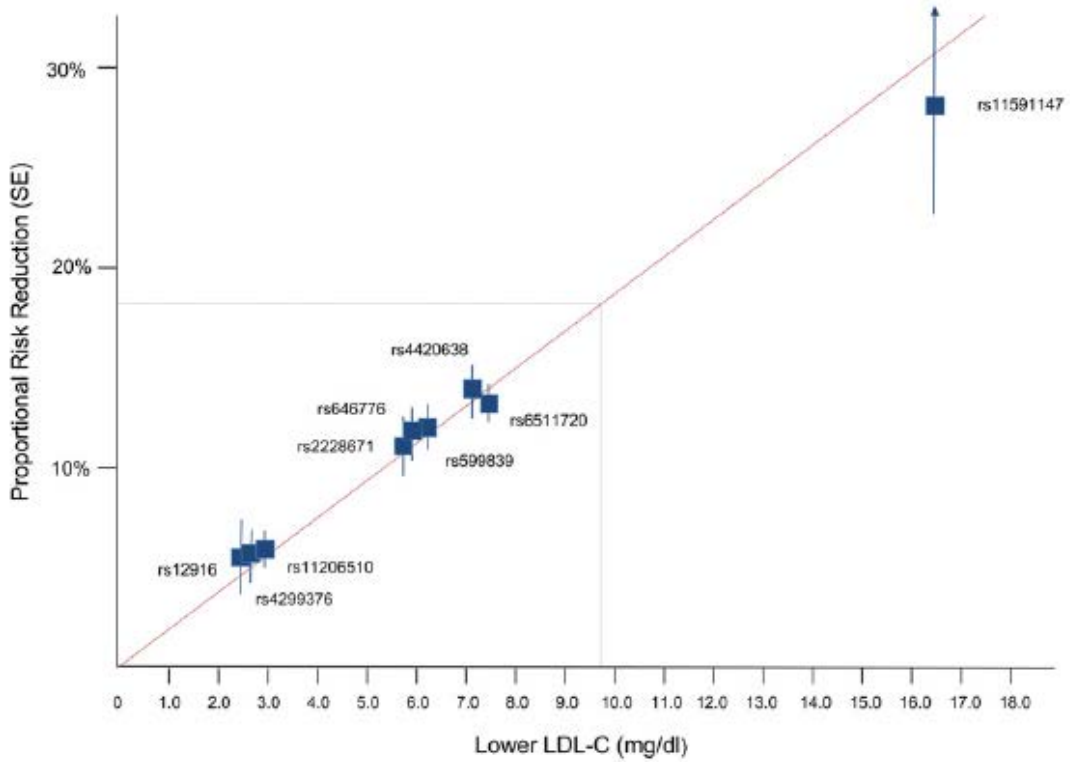

Figure 3 Log-Linear Effect of Each Unit Long-Term Exposure to Lower LDL-C on Risk of CHD

Ference BA et al. JACC 2012

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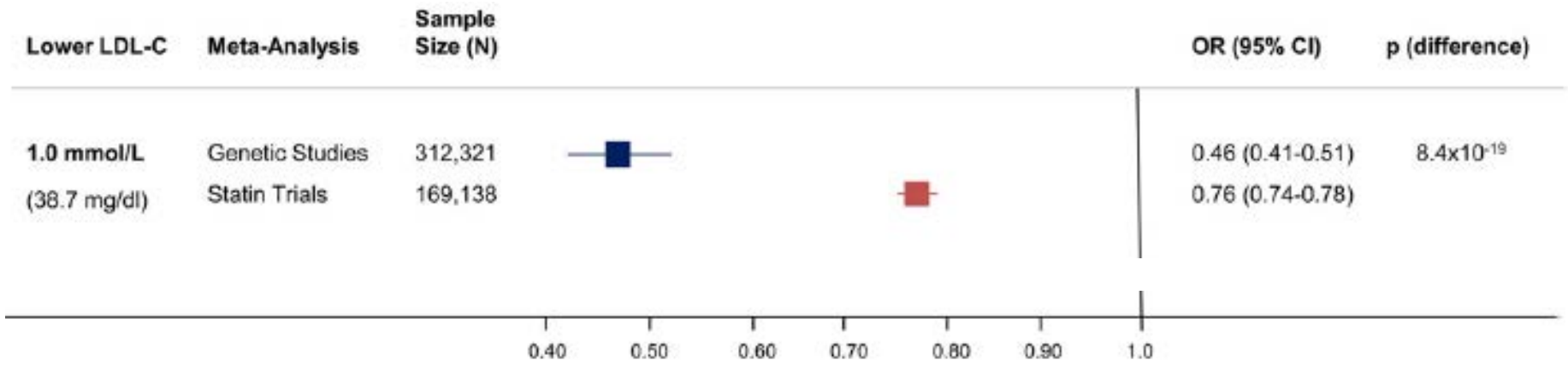
Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease

A Mendelian Randomization Analysis



Comparative CHD Risk Reduction of Earlier and Later LDL-C Lowering

Conclusions Prolonged exposure to lower LDL-C beginning early in life is associated with a substantially greater reduction in the risk of CHD than the current practice of lowering LDL-C beginning later in life. (J Am Coll Cardiol 2012;xx:

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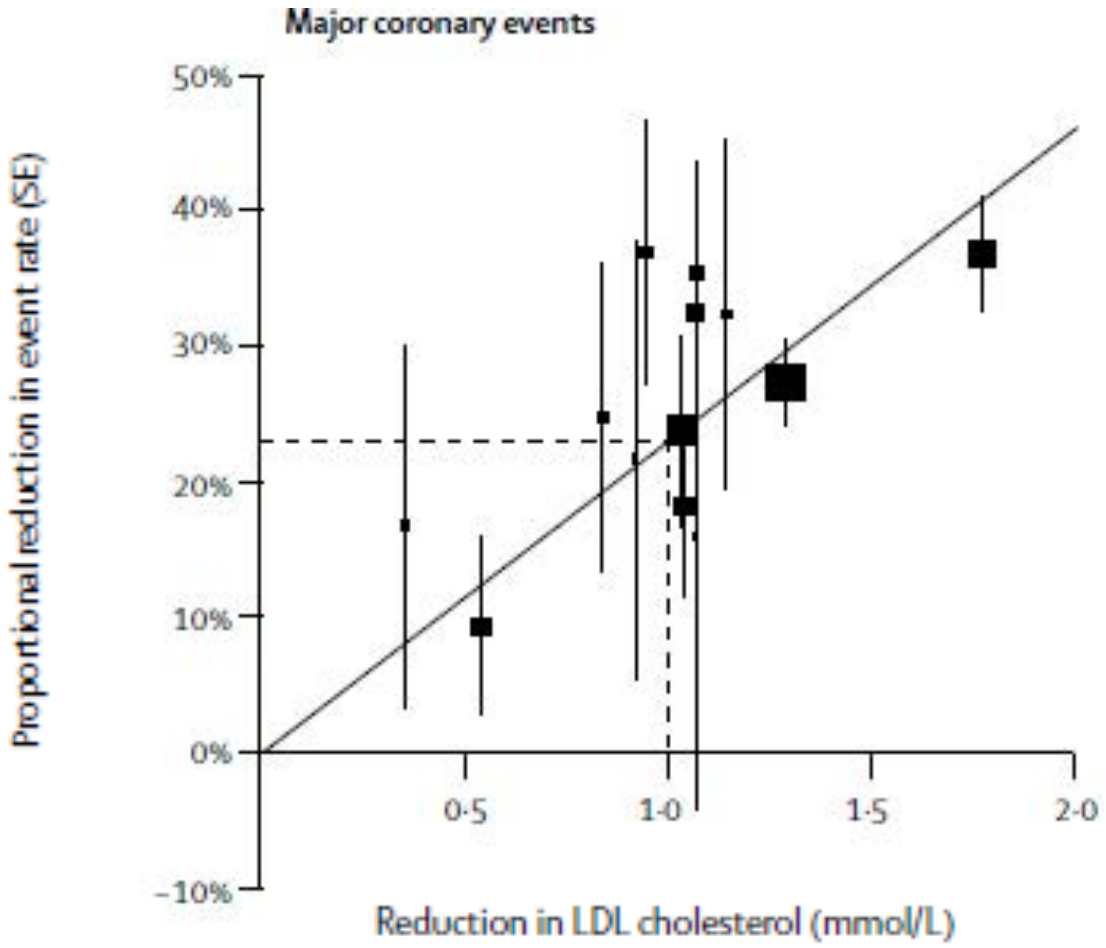
Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins



Cholesterol Treatment Trialists' (CTT) Collaborators
Lancet 2005; 366: 1267–78

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LDL-C is a causal risk factor

Mendelian randomization studies (54% reduction in CHD risk per 1 mmol lower LDL-C over lifetime)

And clinical trials (24% reduction in CHD risk per 1 mmol reduction in LDL-C over 5 years)

Demonstrate that LDL-C is a causal risk factor for CHD

This is not true for triglycerides or HDL-C

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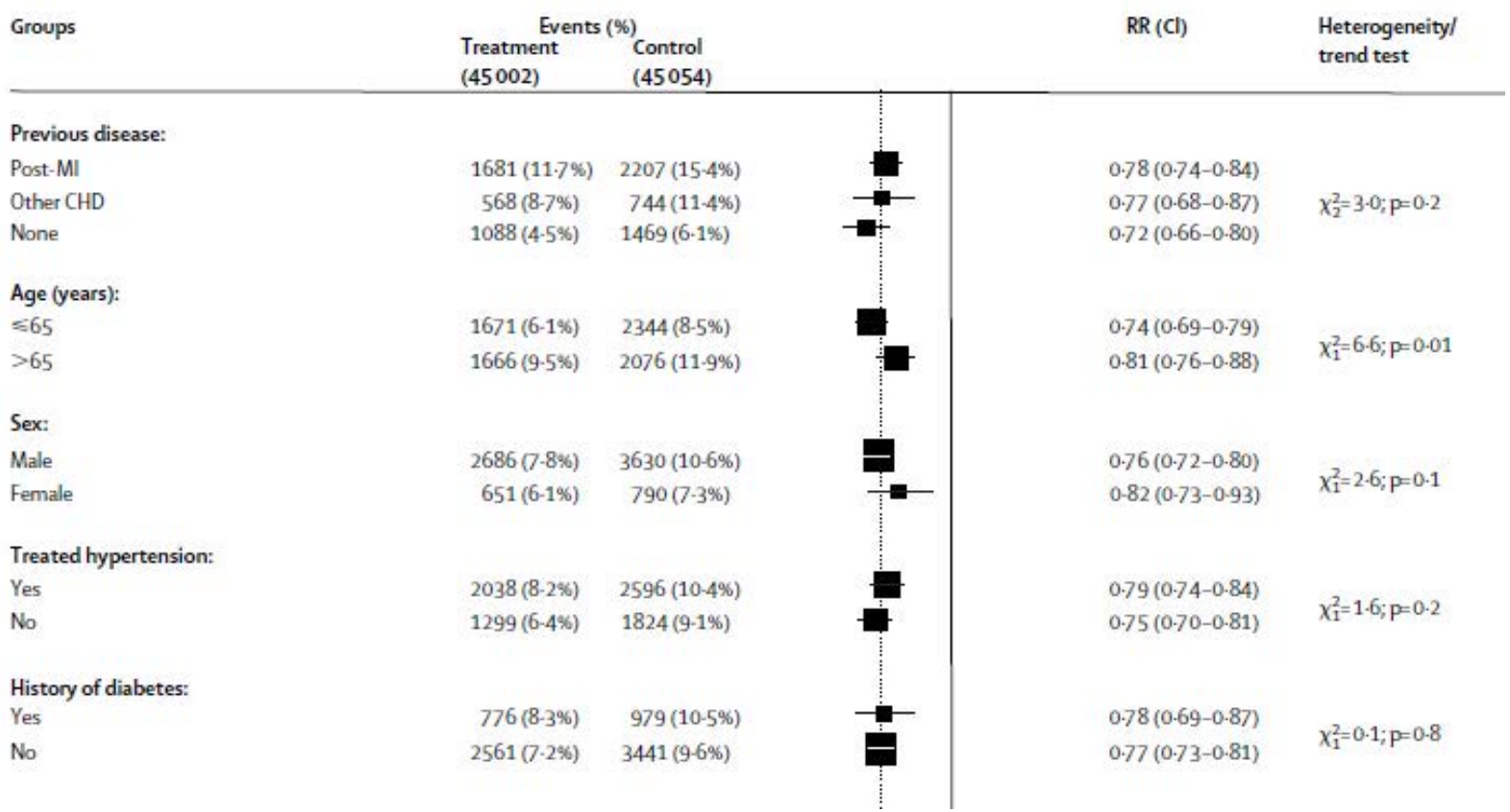
Reducing LDL- C is effective irrespective of prior CHD, age, sex, hypertension, diabetes

Figure 5: Proportional effects on major coronary events per mmol/L LDL cholesterol reduction subdivided by baseline prognostic factors



Groups	Events (%) Treatment (45 002)	Events (%) Control (45 054)	RR (CI)	Heterogeneity/ trend test
Previous disease:				
Post-MI	1681 (11·7%)	2207 (15·4%)	0·78 (0·74–0·84)	
Other CHD	568 (8·7%)	744 (11·4%)	0·77 (0·68–0·87)	χ^2_2= 3·0; p= 0·2
None	1088 (4·5%)	1469 (6·1%)	0·72 (0·66–0·80)	
Age (years):				
≤65	1671 (6·1%)	2344 (8·5%)	0·74 (0·69–0·79)	χ^2_1= 6·6; p= 0·01
>65	1666 (9·5%)	2076 (11·9%)	0·81 (0·76–0·88)	
Sex:				
Male	2686 (7·8%)	3630 (10·6%)	0·76 (0·72–0·80)	χ^2_1= 2·6; p= 0·1
Female	651 (6·1%)	790 (7·3%)	0·82 (0·73–0·93)	
Treated hypertension:				
Yes	2038 (8·2%)	2596 (10·4%)	0·79 (0·74–0·84)	χ^2_1= 1·6; p= 0·2
No	1299 (6·4%)	1824 (9·1%)	0·75 (0·70–0·81)	
History of diabetes:				
Yes	776 (8·3%)	979 (10·5%)	0·78 (0·69–0·87)	χ^2_1= 0·1; p= 0·8
No	2561 (7·2%)	3441 (9·6%)	0·77 (0·73–0·81)	

Cholesterol Treatment Trialists' (CTT) Collaborators

Lancet 2005; 366: 1267–78

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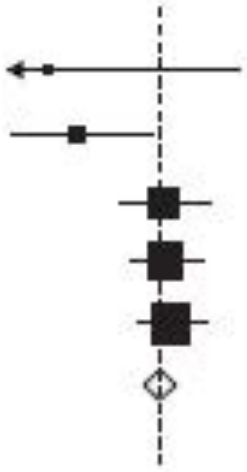
Reducing LDL-C is effective in persons at low baseline risk

Meta-analysis of 134,537 individuals in 27 trials

5-year MVE risk at baseline	Events (% per annum)		RR (CI) per 1·0 mmol/L reduction in LDL cholesterol	Trend test
	Statin/more	Control/less		
Major coronary event				
<5%	50 (0·11)	88 (0·19)	0·57 (0·36–0·89)	
≥5% to <10%	276 (0·50)	435 (0·79)	0·61 (0·50–0·74)	
≥10% to <20%	1644 (1·29)	1973 (1·57)	0·77 (0·69–0·85)	χ^2_1=5·66
≥20% to <30%	1789 (1·93)	2282 (2·49)	0·77 (0·71–0·83)	(p=0·02)
≥30%	1471 (3·73)	1887 (4·86)	0·78 (0·72–0·84)	
Overall	**5230 (1·45)**	**6665 (1·87)**	**0·76 (0·73–0·79) p<0·0001**	



Cholesterol Treatment Trialists' (CTT) Collaborators

Lancet 2012; 380: 581–90

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And the benefits of statins exceed the risks

In low risk subjects with <10% 5-year risk of major vascular events:

Over 5 years for every 1000 individuals each mmol of LDL cholesterol reduction on statin therapy may result in

- 11 fewer MVE
- 5 more diagnoses of diabetes
  - 0.2 fewer MVE avoided
- 0.5 more diagnoses of myopathy
- 0.5 more diagnoses of hemorrhagic strokes
  - i.e. ~twice more benefit than risk

In high risk subjects with 20-30% 5-year risk of MVE:

- 28 fewer MVE
  - i.e. ~five times more benefit than risk

Cholesterol Treatment Trialists' (CTT) Collaborators

Lancet 2012; 380: 581–90

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Thirty-five-year trends in cardiovascular risk factors in Finland

"Finnish men had the highest numbers of CHD mortality at the end of the 1960s, but the decline in coronary mortality among Finnish men since the 1970s has also been the most rapid in the world. About 75% of the observed decline in coronary mortality in middle-aged men can be explained by decline in blood pressure, cholesterol and smoking.

During the past 30 years, the greatest change in health behaviour in Finland has indisputably been the changes in diet, especially in the type and amount of fat and intake of fresh vegetables and fruit. In the early 1970s, Finland was a country with much dairy farming. Butter and milk production was subsidized and all vegetable oil was imported."

Vartainen, E. et al. International Journal of Epidemiology 2010;39:504–518

National Heart Lung and Blood Institute

Thirty-five-year trends in cardiovascular risk factors in Finland

North Karelia Men

	1972	2007	Δ%
Total fat, % en	39	34	-13
SFA, % en	22	13	-41
PUFA, % en	3.5	5.9	+68
Diet cholesterol	617	309	-50
Blood cholesterol	6.92	5.45	-21
BMI	26.0	27.4	+5*
SBP	149	139	-7
DBP	92	83	-10
Smoking, %	52	31	-40

*No BMI increase in women

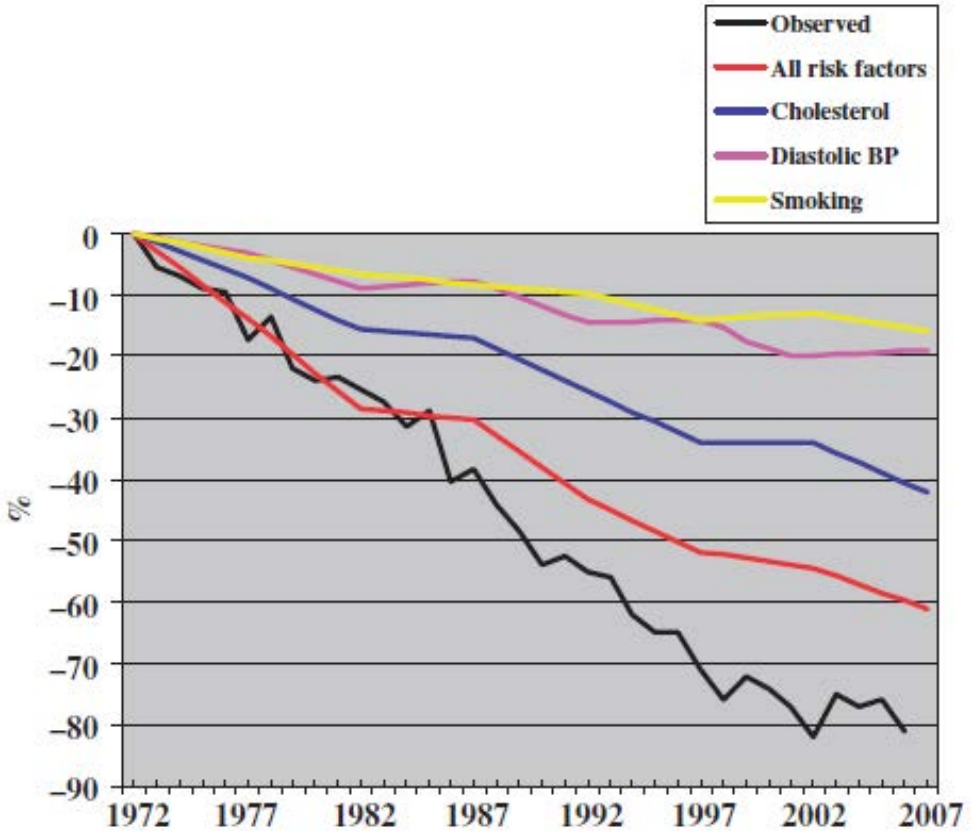

Figure 1 Observed and predicted decline in CHD mortality in men

Vartainen, E. et al. International Journal of Epidemiology 2010;39:504–518

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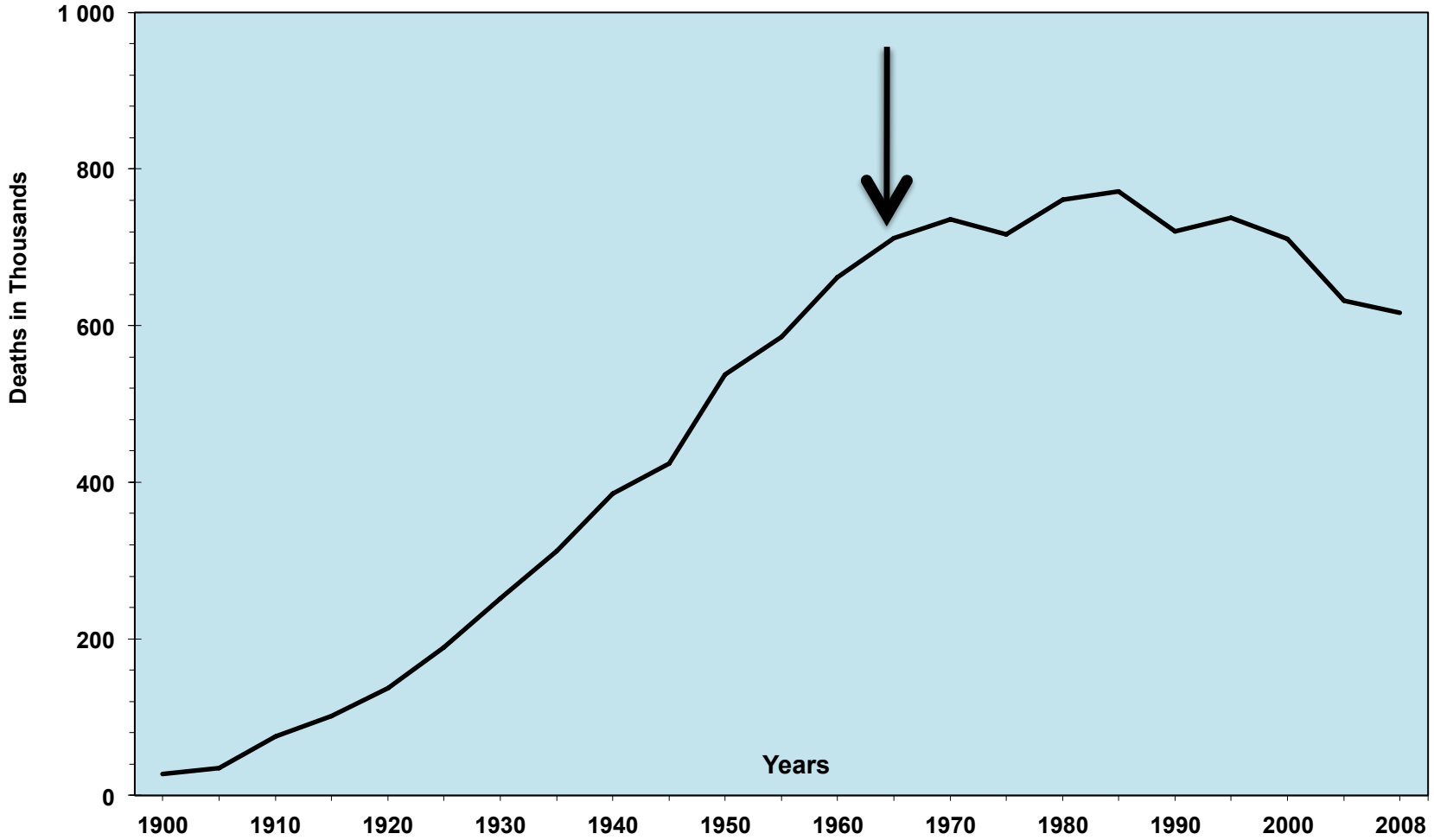
Deaths due to diseases of the heart (United States: 1900–2008

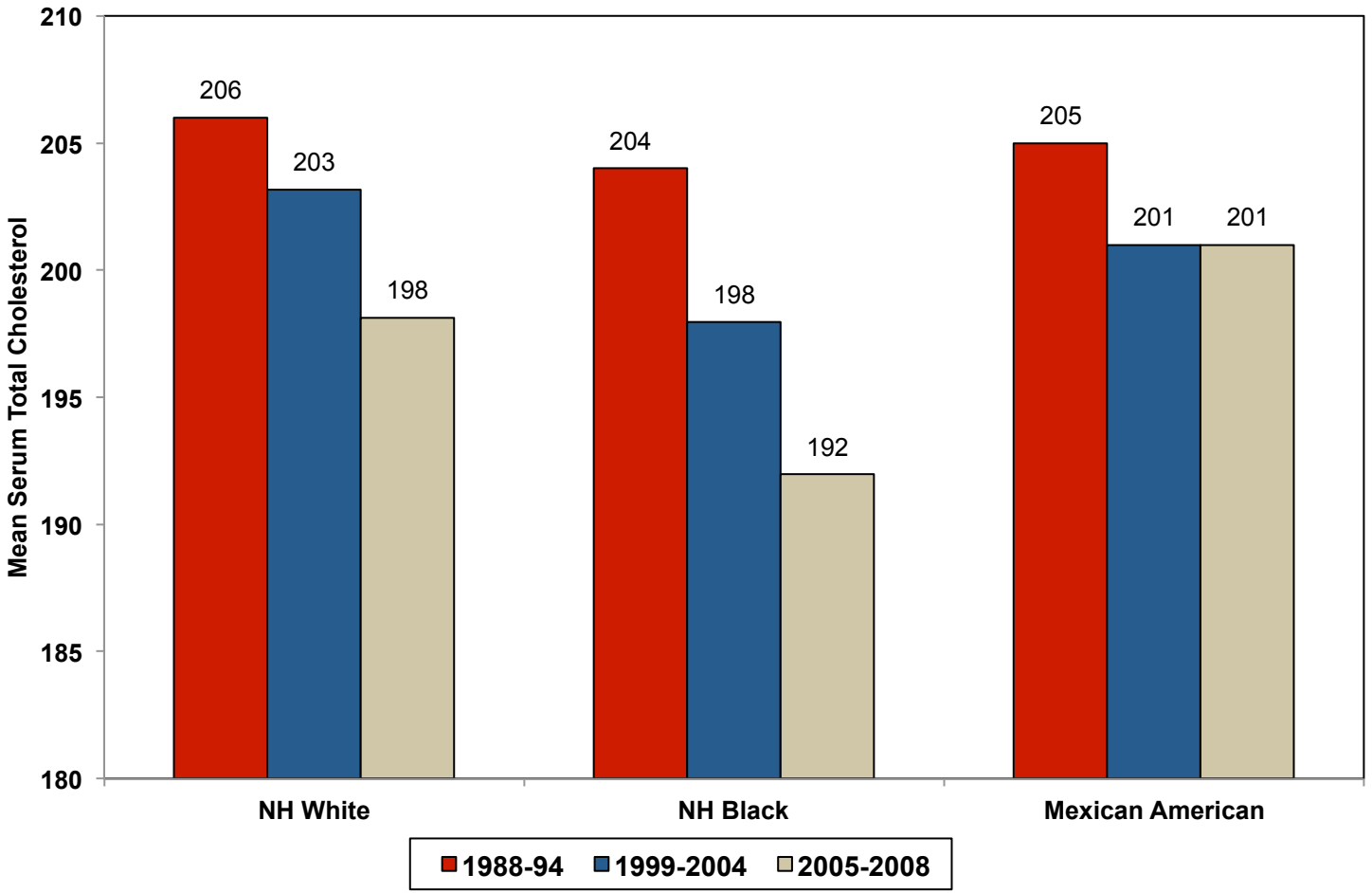


Source: National Center for Health Statistics.

National Heart Lung and Blood Institute

Roger VL et al. Published online in *Circulation* Dec. 15, 2011

Trends in mean total serum cholesterol among adults ages ≥20 by race and survey year, (NHANES: 1988–1994, 1999–2004 and 2005–2008).



Source: NCHS and NHLBI. NH indicates non-Hispanic.

National Heart Lung and Blood Institute

Roger VL et al. Published online in *Circulation* Dec. 15, 2010

Trends in individual fat consumption in US and UK

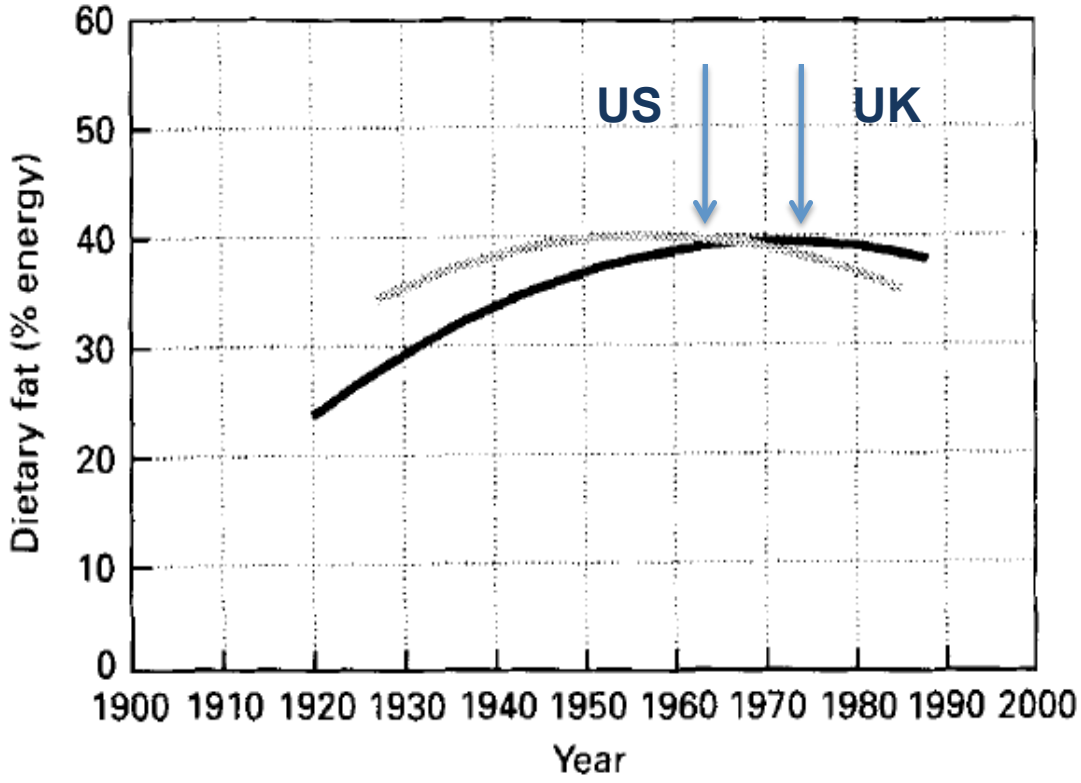


Fig. 2. Quadratic regression lines, weighted by the number of subjects in each study for the UK (▬ ; $P < 0{\cdot}001$, n 97) and the USA (≈≈≈ ; $P < 0{\cdot}001$, n 171). The beginning of the decline in fat intake was approximately 1965 for the USA and 1975 for the UK.

Stephen&Sieber. British J Nutrition, 1994

National Heart Lung and Blood Institute

Trends in CHD death rates in US and UK

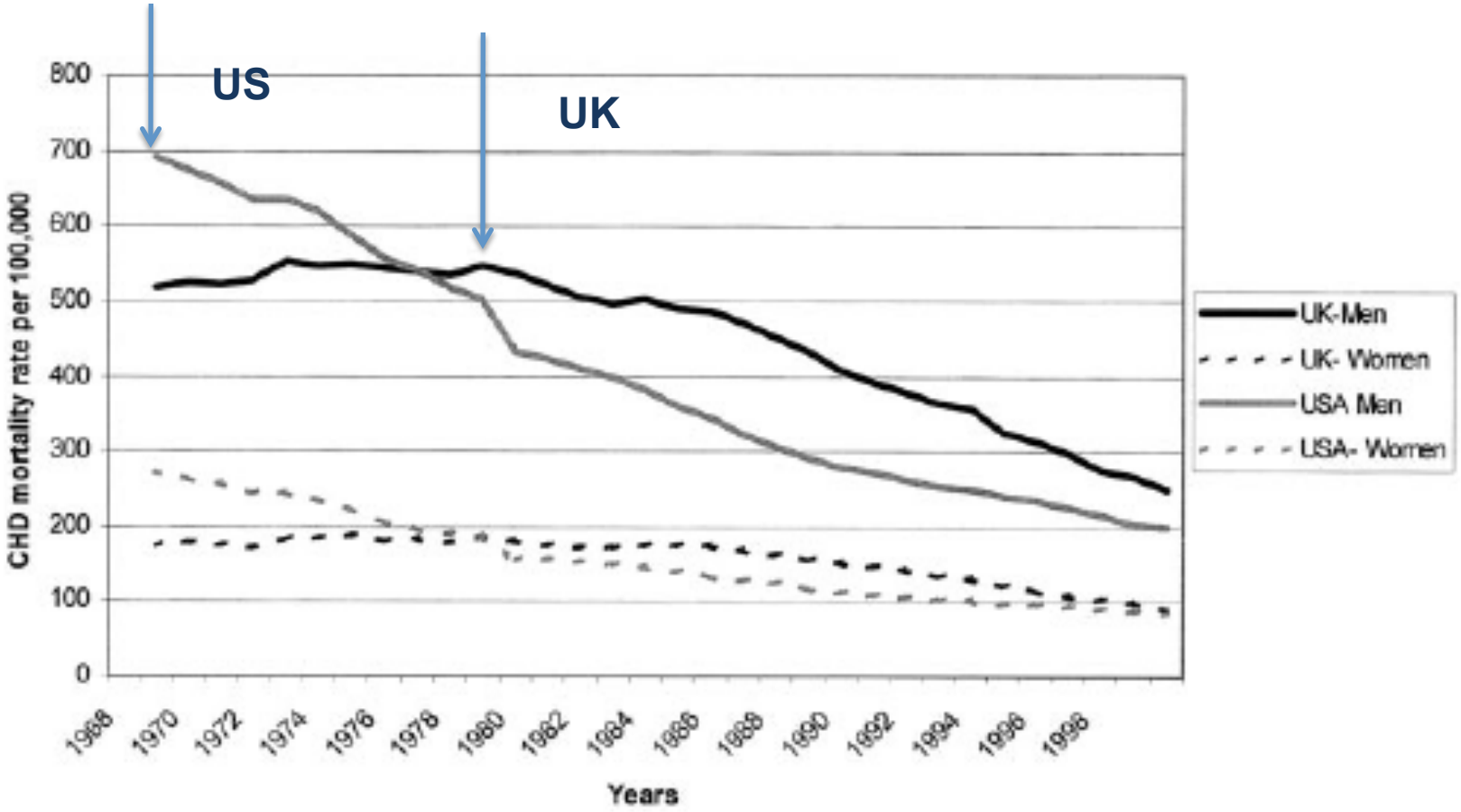


Figure 1. Age-standardized death rates from CHD for men and women in United Kingdom and United States between 1968 and 2000.

Unal, Critchley, Capewell. Circulation 2004

National Heart Lung and Blood Institute

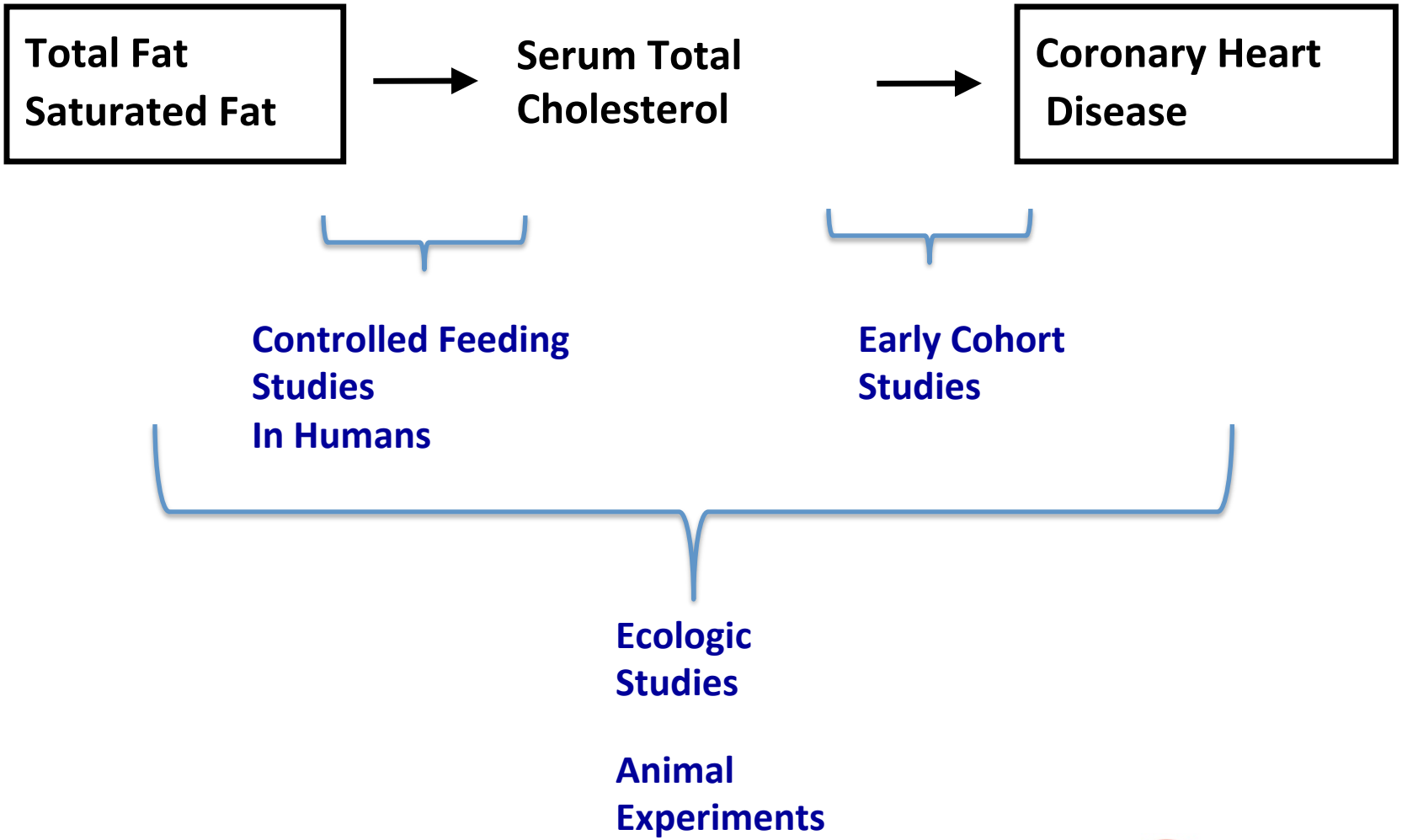
Cholesterol is an important, causal, and modifiable risk factor

In both men and women and at all ages

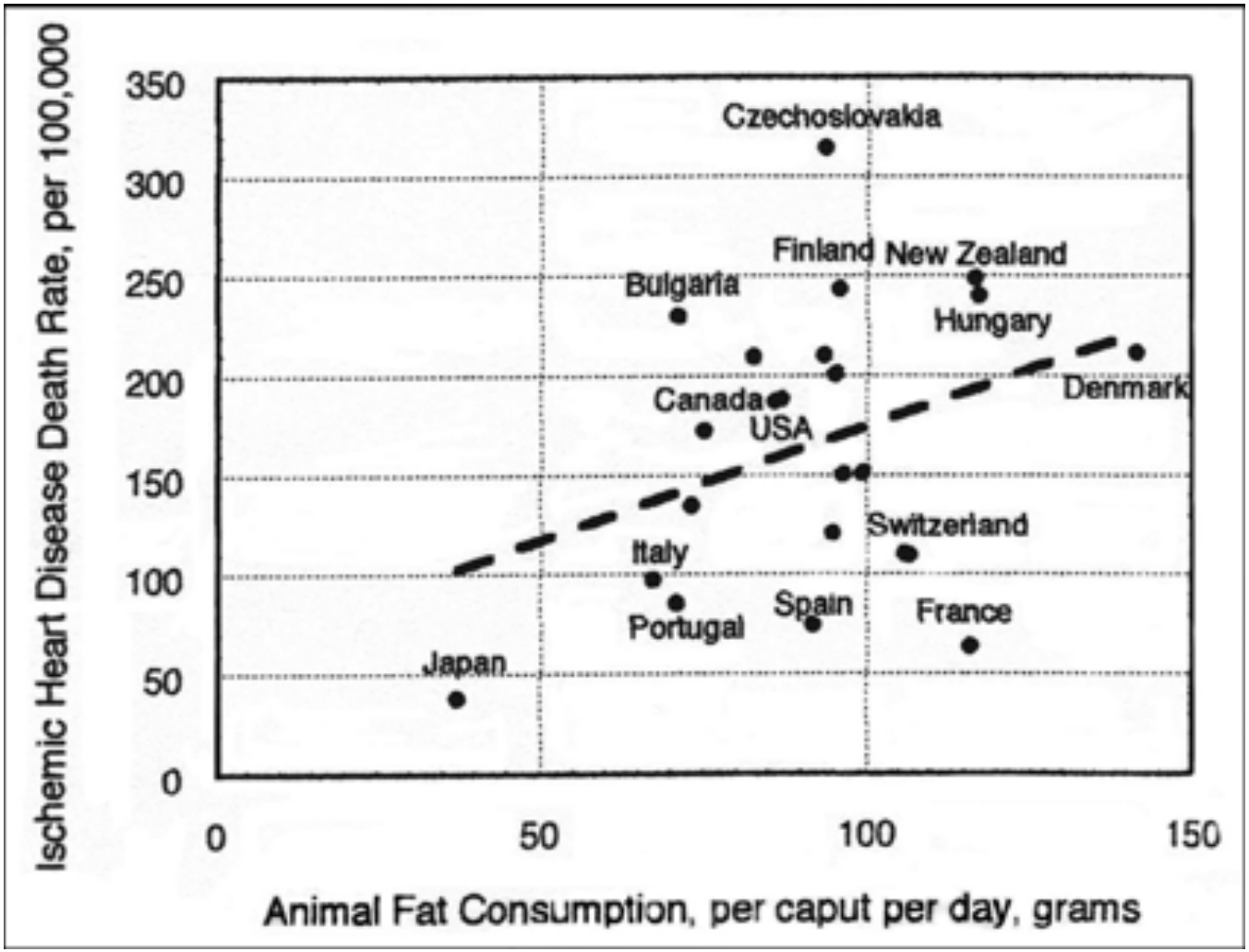
- Cholesterol levels are associated with increased risk of coronary heart disease (even at “normal” levels of cholesterol)
- Biology supports causal role for LDL cholesterol
- Treatment of elevated levels reduces risk in individuals—the ultimate test of causality
- Population risk decreases with adoption of cholesterol-lowering strategies

The Diet-Heart Hypothesis

Diet-Heart Hypothesis--Then



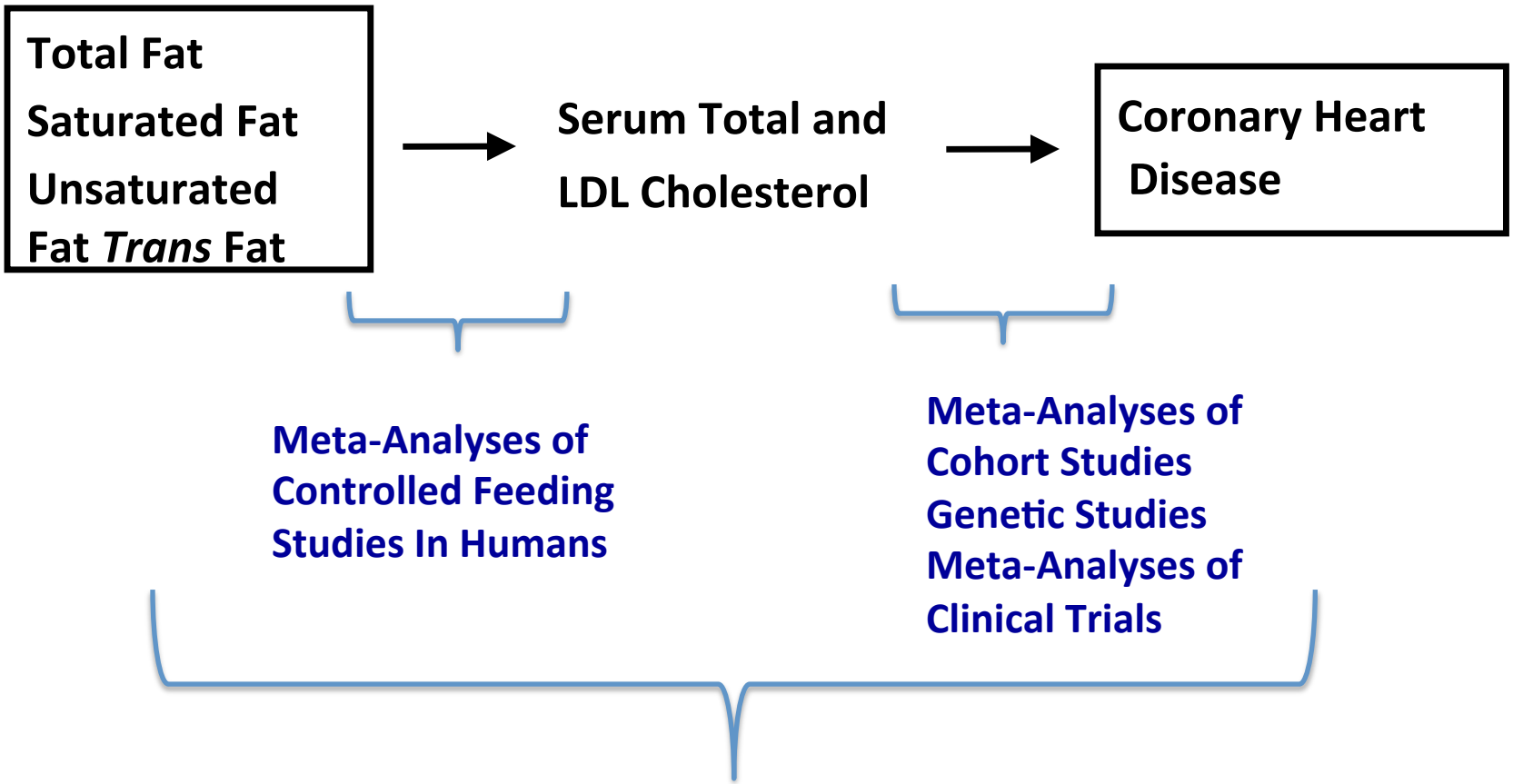
Saturated Fat and CHD - Ecological Evidence



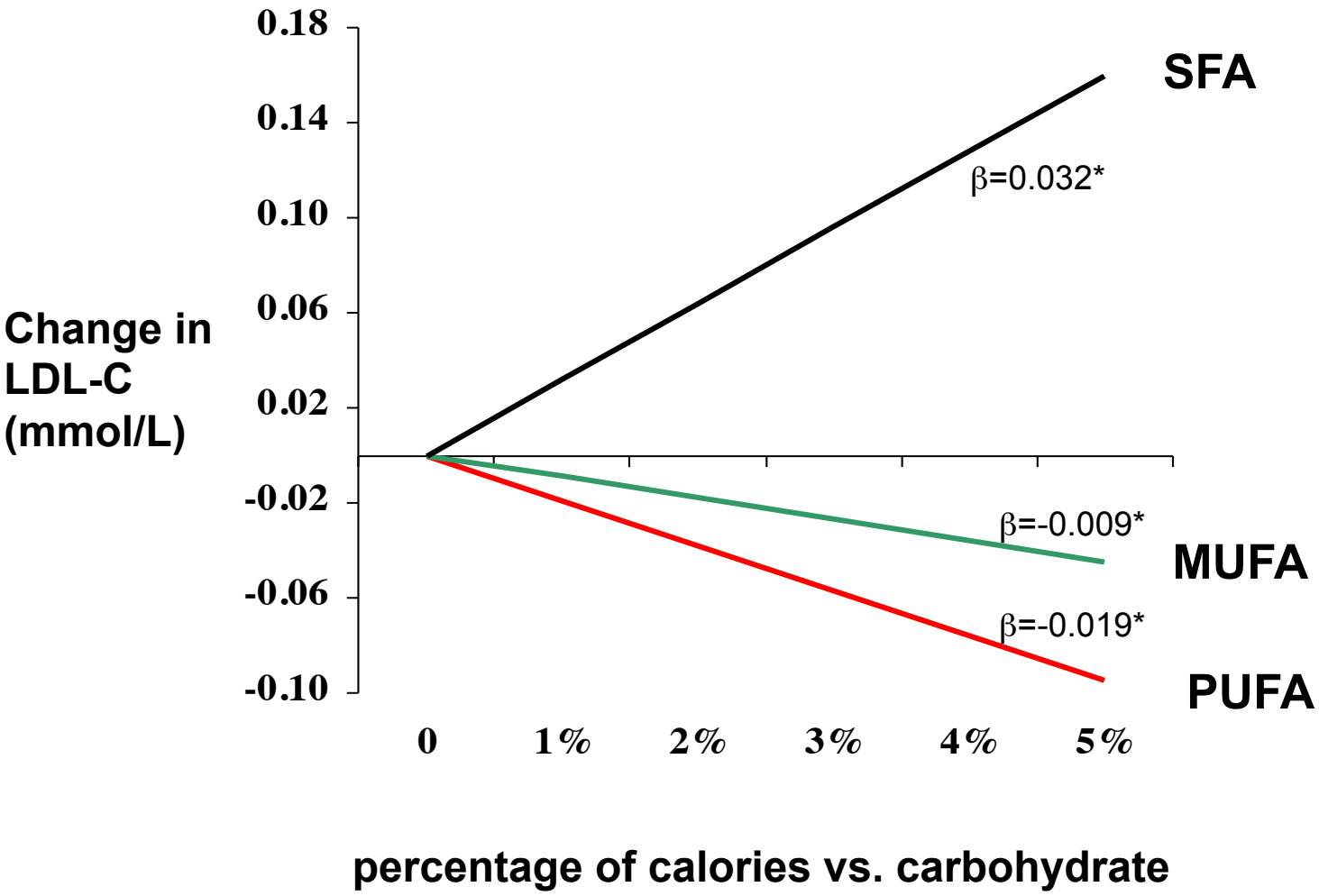
Based on data in 1987-1990

National Heart Lung and Blood Institute

Diet-Heart Hypothesis--Now



Short term feeding studies: LDL-Cholesterol



Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010

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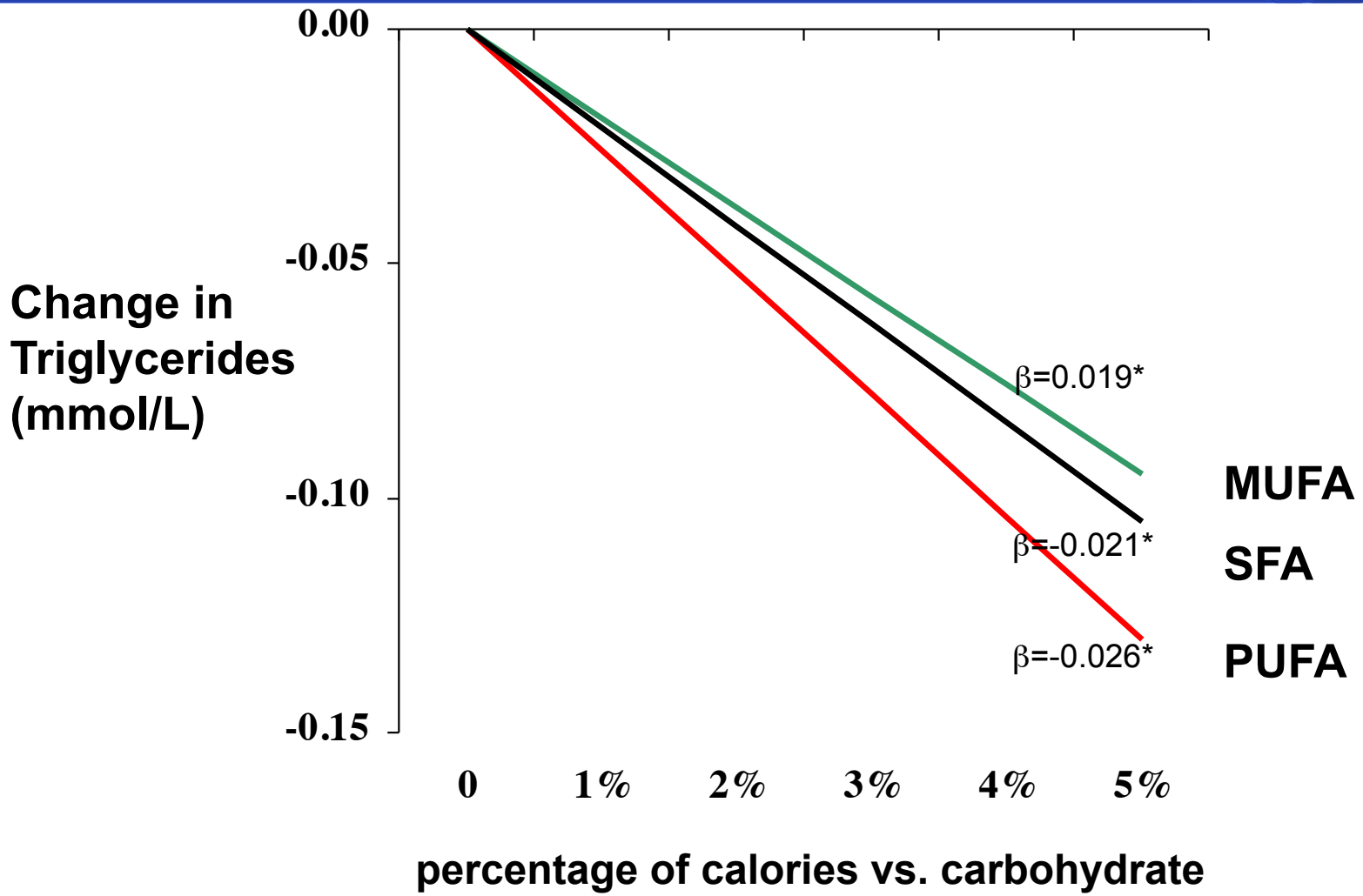
Short term feeding studies: Triglycerides



Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010

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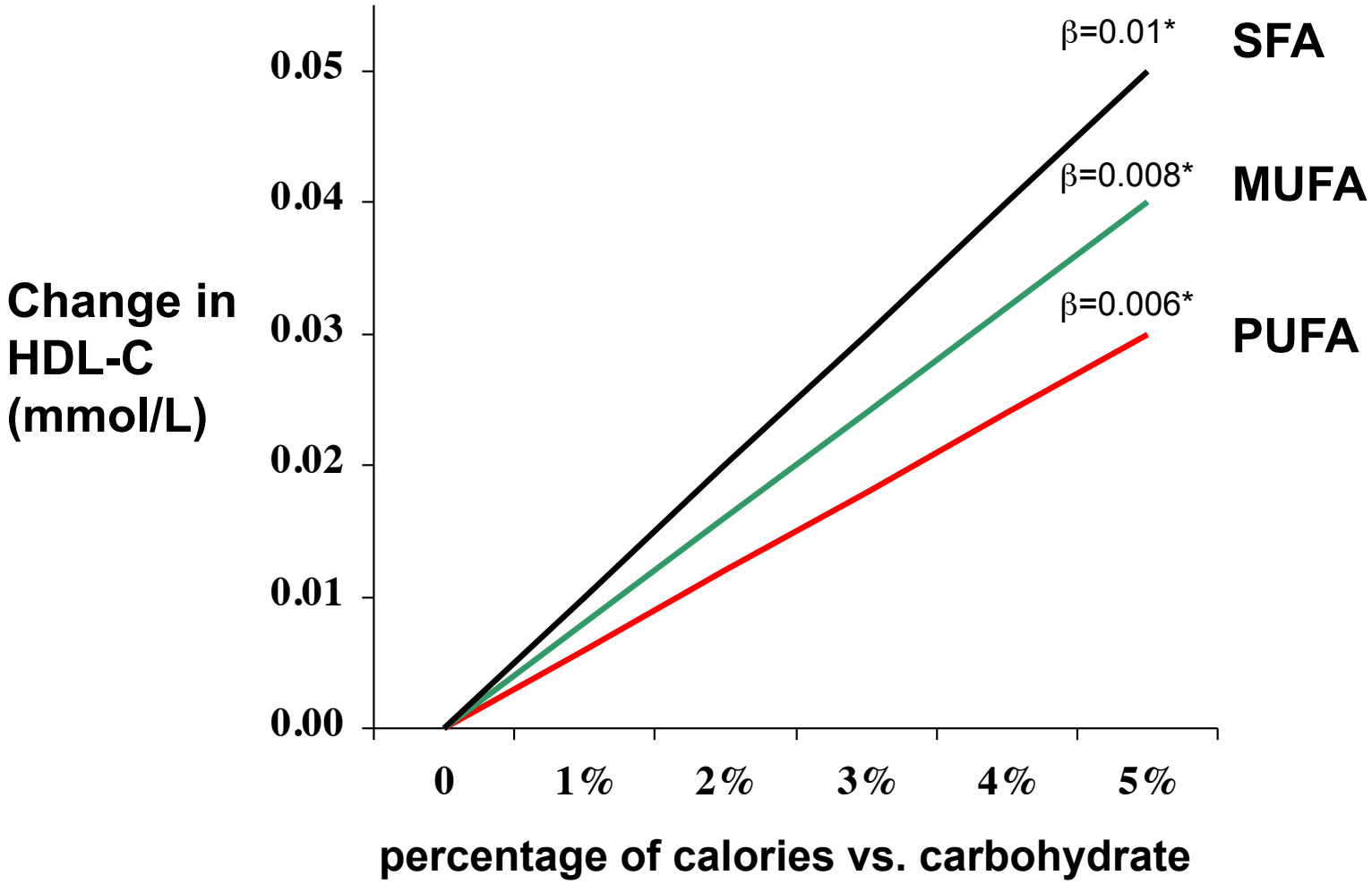
Short term feeding studies: HDL-Cholesterol



Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010

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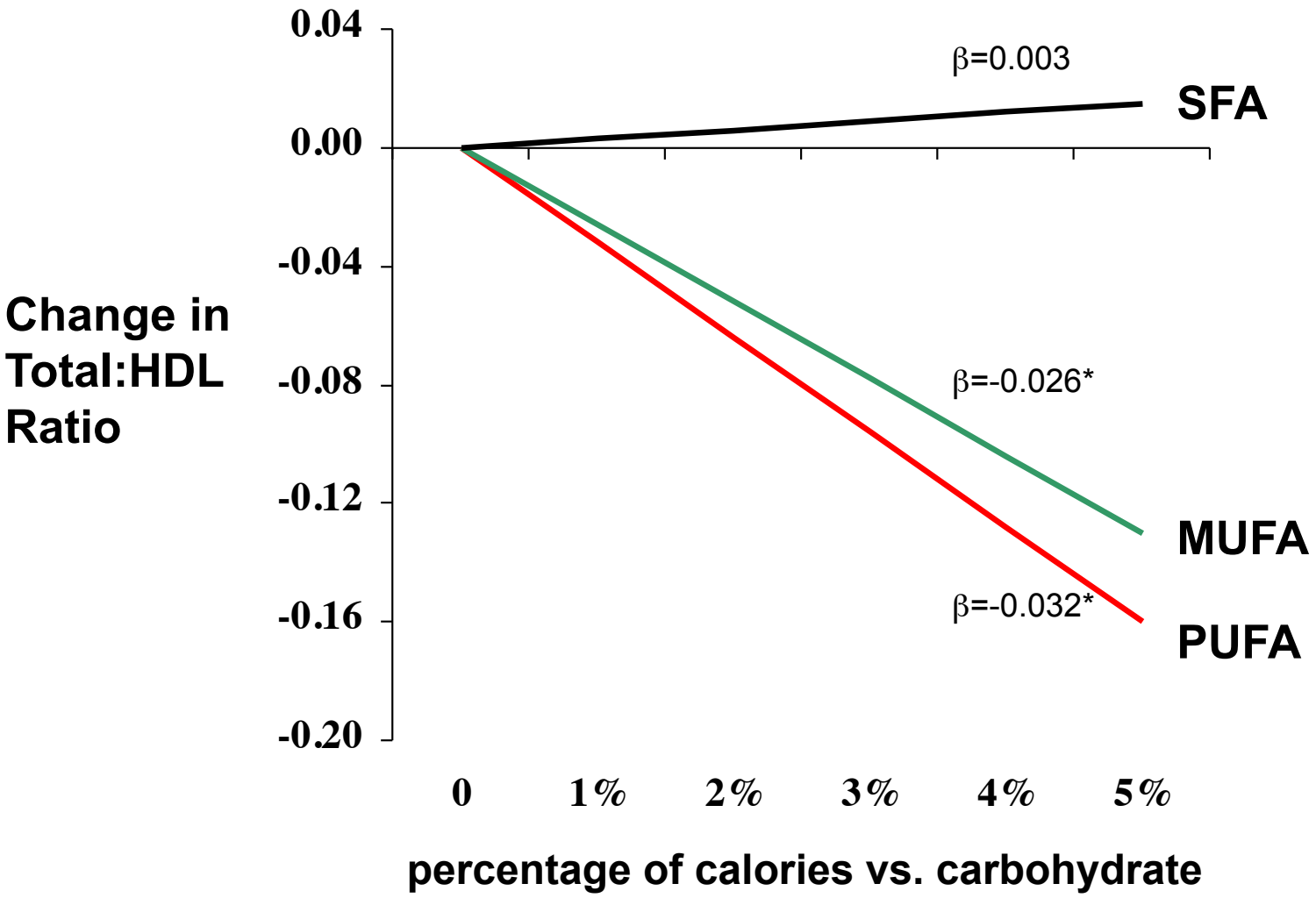
Short term feeding studies: Total:HDL Ratio



Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010

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Short-term Feeding Studies: Lipid Effects of Individual SFAs

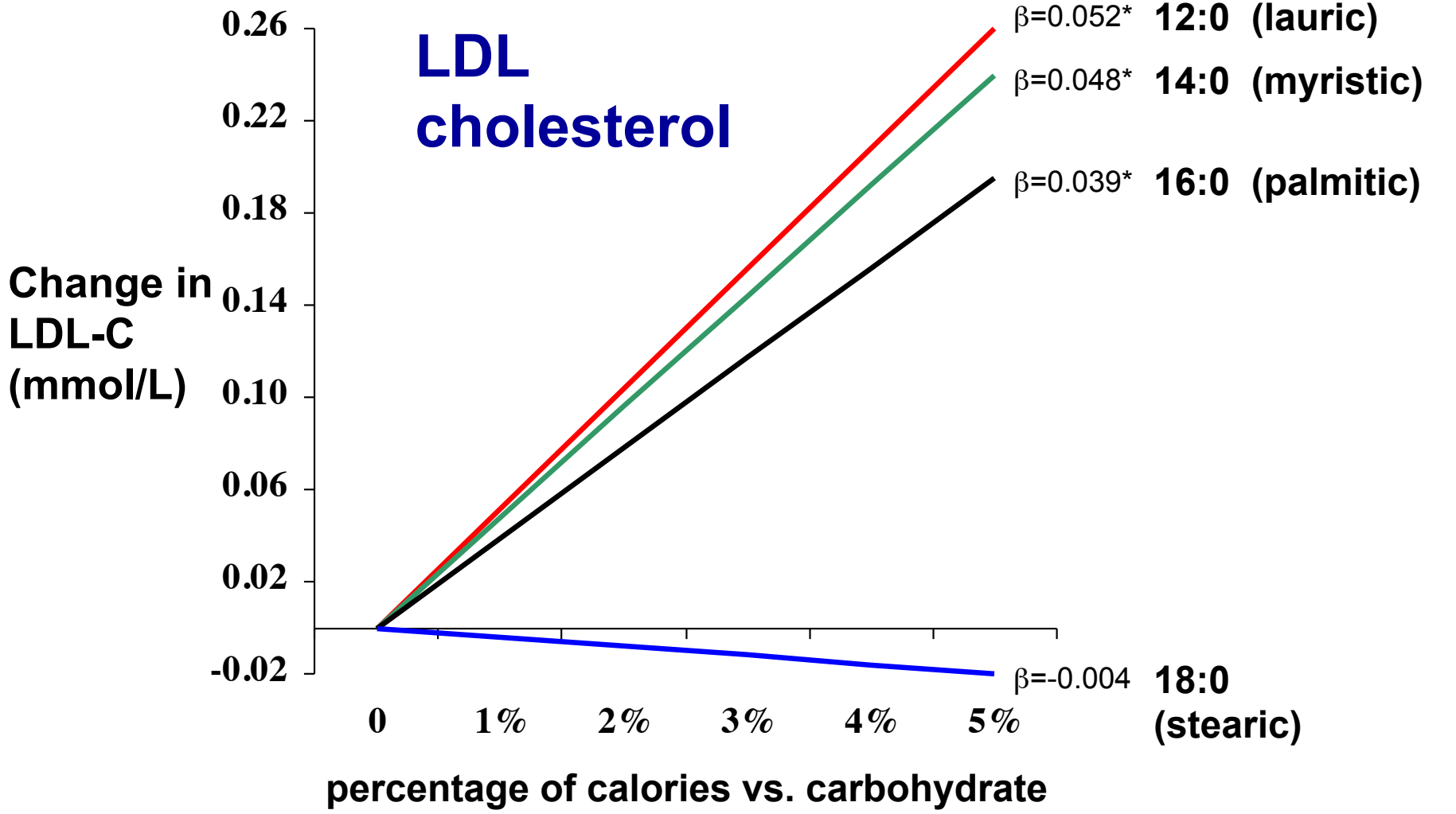

Figure from Micha & Mozaffarian, Lipids 2010. Based on Mensink & Katan 2003.

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Short term feeding studies: Trans Fatty Acids

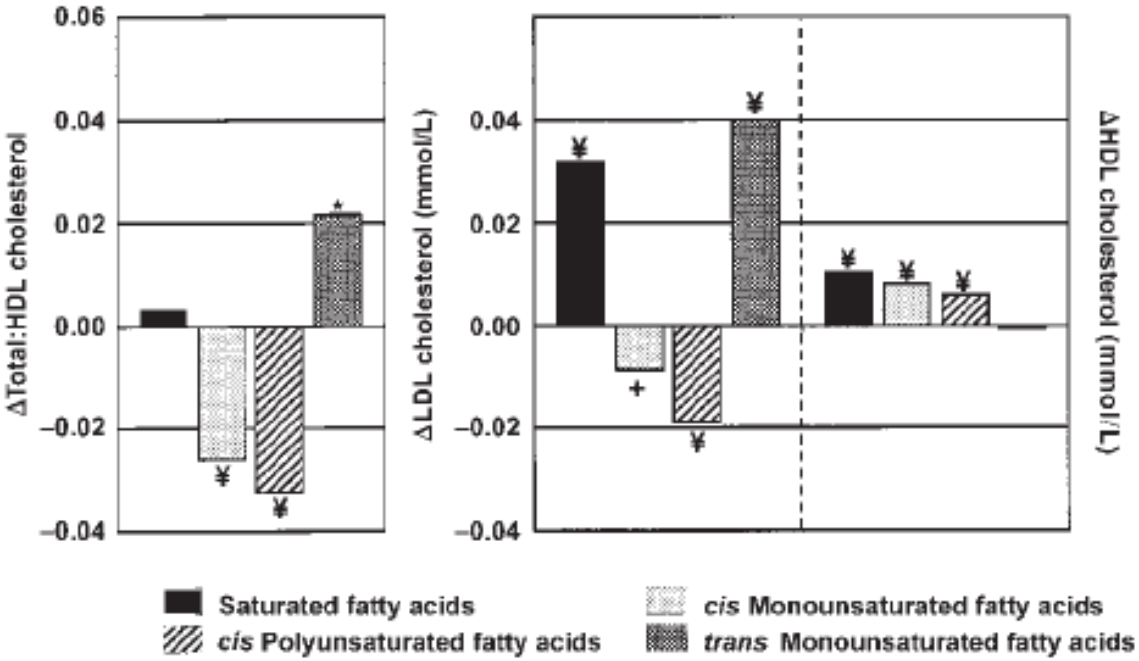
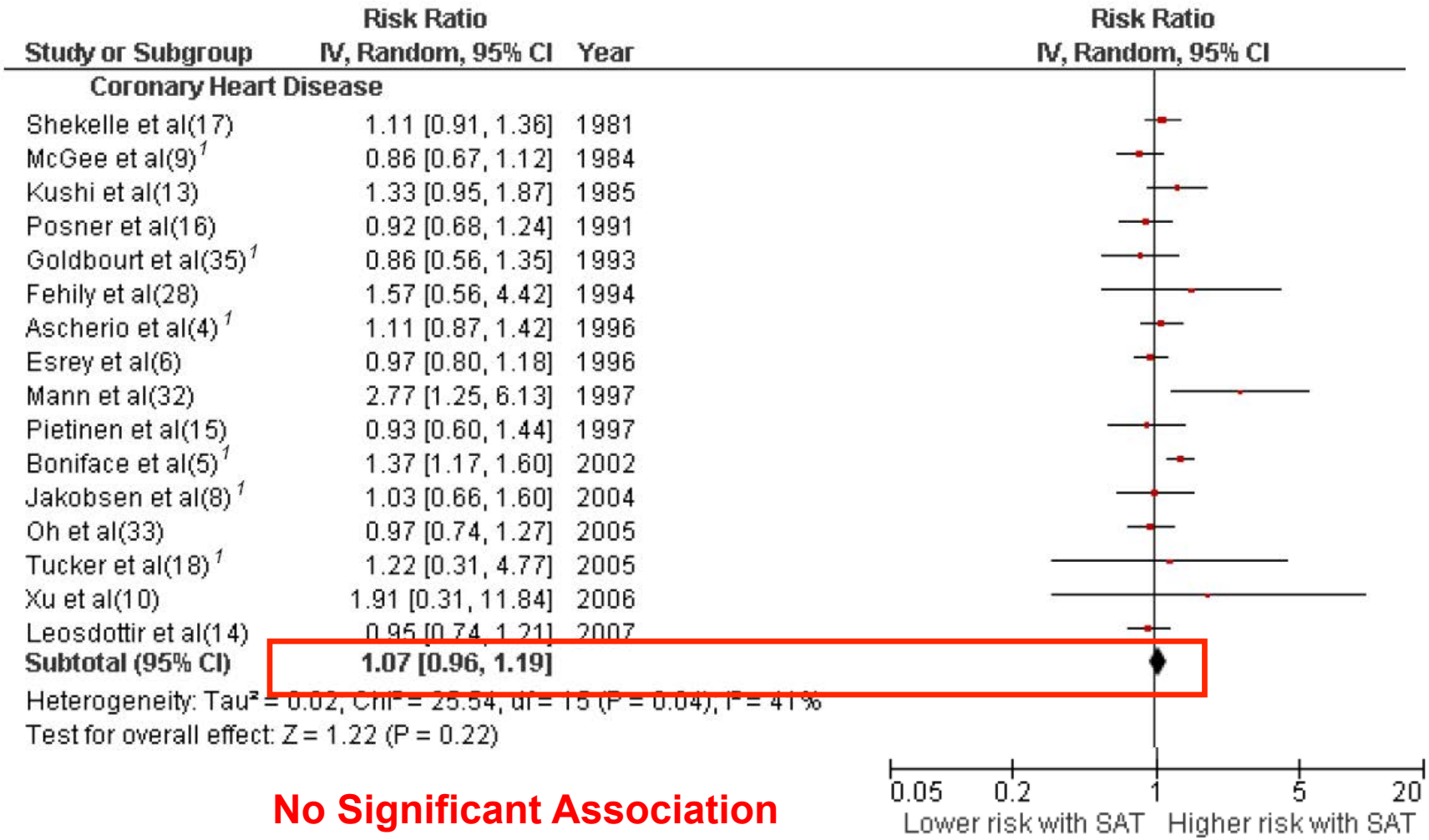


FIGURE 1. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with saturated, *cis* monounsaturated, *cis* polyunsaturated, or *trans* monounsaturated fatty acids. $^{*}P < 0.05$; $^{+}P < 0.01$; $^{¥}P < 0.001$.

Mensink&Katan, AJCN 2003

National Heart Lung and Blood Institute

Saturated Fat and CHD - Prospective Cohorts



No Significant Association

Siri-Tarino et al, AJCN 2010

National Heart Lung and Blood Institute

Saturated Fat and CHD - Prospective Cohorts

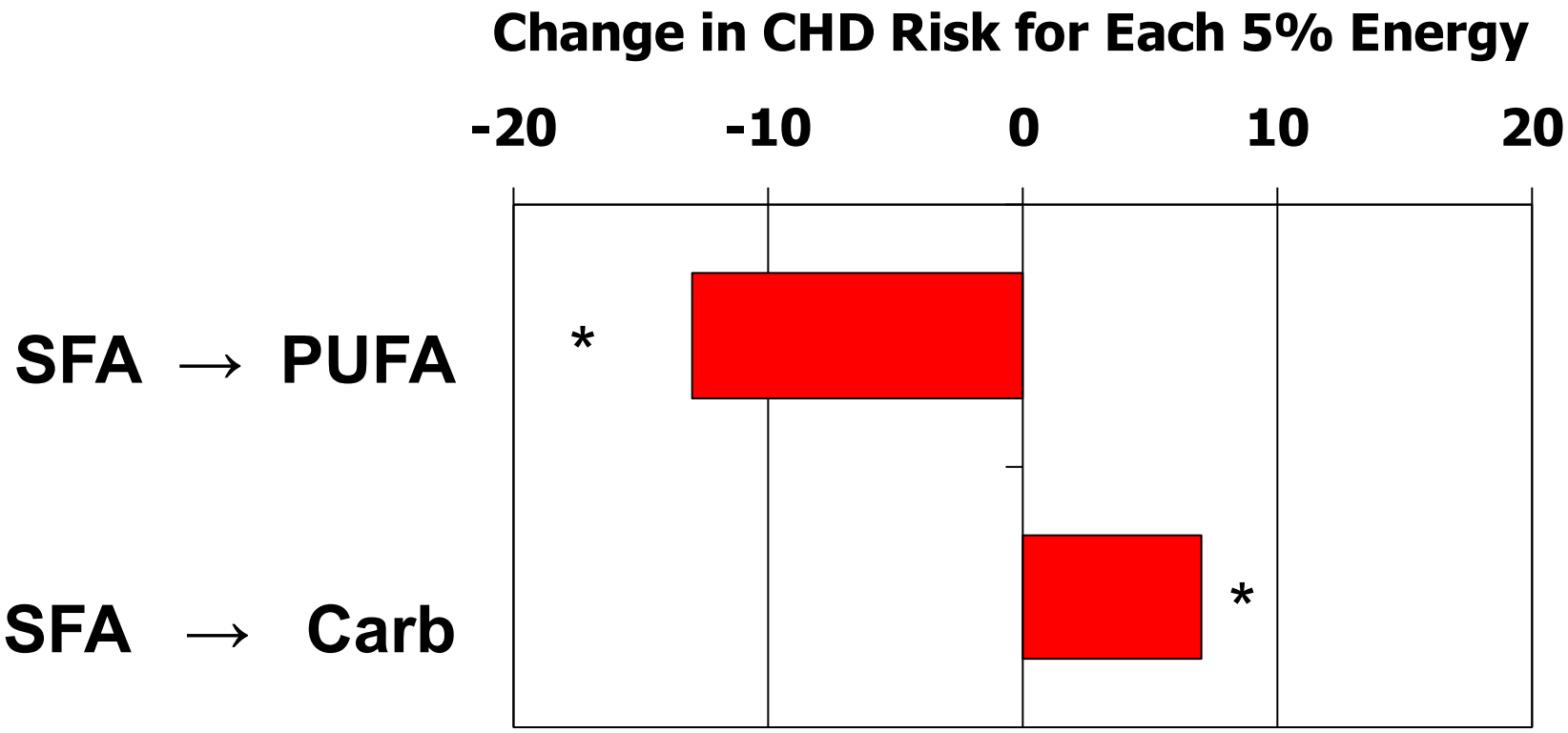
A caveat of this study was its reliance on the accuracy of the dietary assessments of the component studies, which may vary depending on the method used (25). Underreporting of calories has often contributed to the error associated with dietary assessments, particularly in overweight individuals.

Furthermore, there was insufficient statistical power for this meta-analysis to assess the effects on CVD risk of replacing specific amounts of saturated fat with either polyunsaturated fat or carbohydrate. Finally, nutritional epidemiologic studies provide only one category of evidence for evaluating the relation of saturated fat intake to risk for CHD, stroke, and CVD. An overall assessment requires consideration of results of clinical trials as well as information regarding the effects of saturated fat on underlying disease mechanisms, as discussed elsewhere in this issue (46).

Siri-Tarino et al, AJCN 2010

National Heart Lung and Blood Institute

Substitution of SAFA with Polyunsaturated Fat or Carbohydrate: Pooled Analysis of 11 Major Cohort Studies

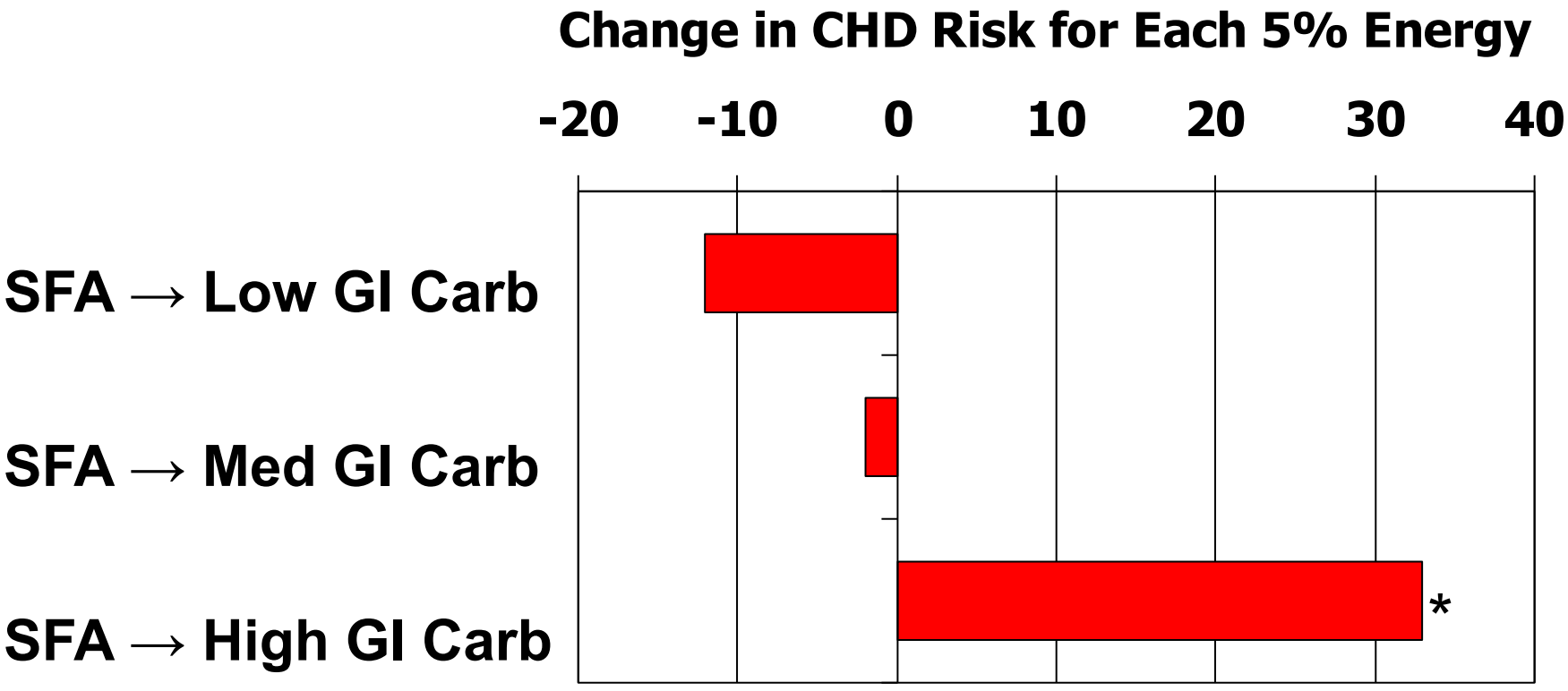


Total of **344,696** individuals with **5,249** CHD events. *p<0.05

Jakobsen et al, AJCN 2009

National Heart Lung and Blood Institute

Substitution of Saturated Fat vs. Carbohydrate Quality

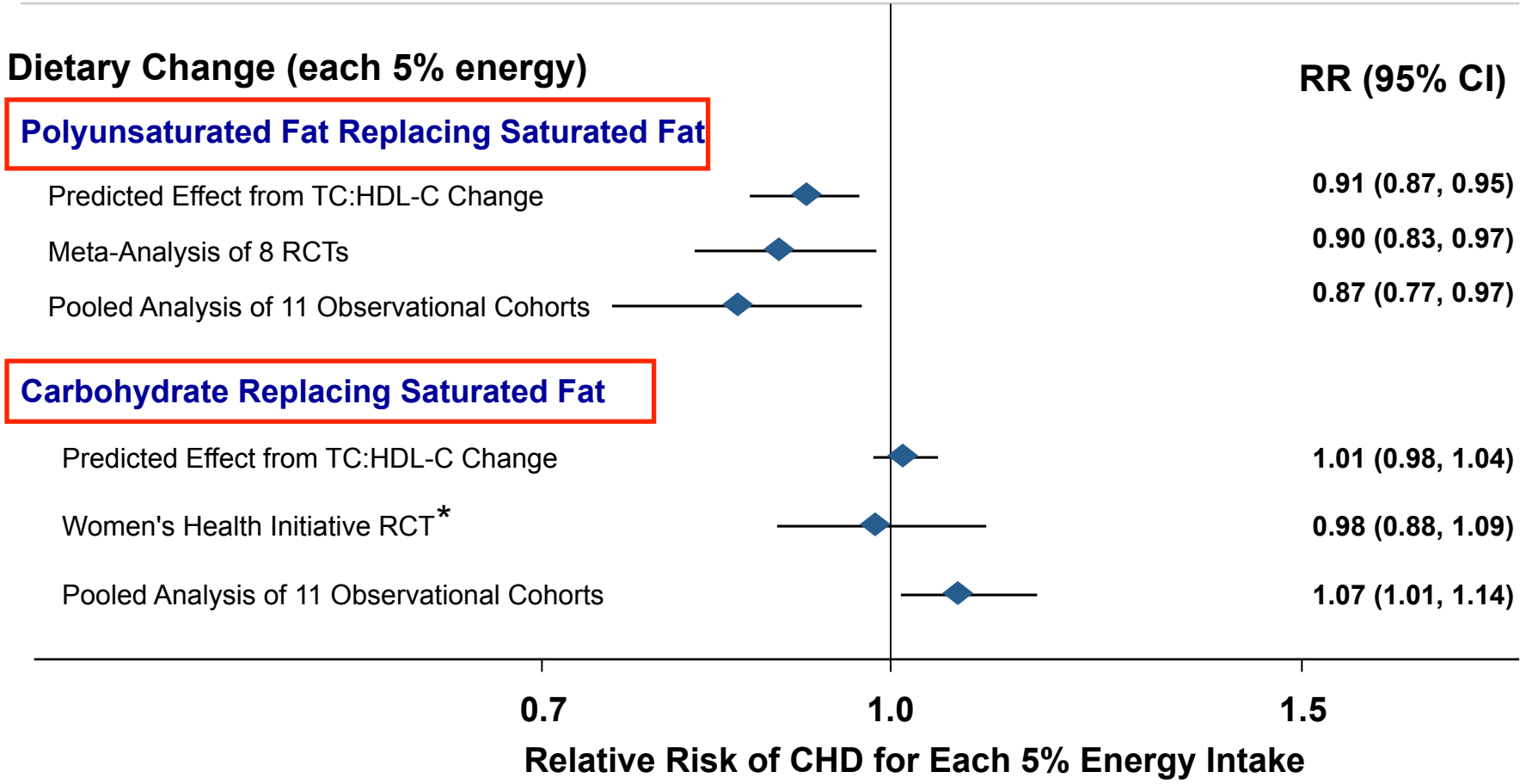


Risk of CHD among 53,644 adults followed for 12 years. *p<0.05

Jakobsen et al, AJCN 2010

National Heart Lung and Blood Institute

SFA and Heart Disease: The Replacement Matters



*WHI trial goal was to reduce total fat; CHD risk was significantly reduced in subsets of women who achieved lowest intakes of saturated fat, trans fat, or highest levels of vegetables and fruits (Howard et al. JAMA , 2006)

Mozaffarian et al., PLoS Med 2010

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The Diet-Heart Hypothesis is Alive and Well

- Elevated LDL-C increases risk of CHD
- Saturated fats increase LDL-C and risk of CHD
  - Type of saturated fat matters—palmitic 16:0 worst
  - Substitution with polyunsaturated fats lowers CHD risk
- Substituting saturated fats with carbohydrates does not increase CHD risk
  - Carbohydrate quality matters—substituting with high GI carbohydrates increases CHD risk

Diet, Obesity, and Diabetes

Weight Management

- Long term excess intake coupled with reduced activity increases weight in many
- Modern lifestyle coupled with physiology geared towards energy conservation is conducive to obesity
- It is much easier to avoid weight gain than to reverse obesity
- Non-surgical reversal of obesity requires moderate but persistent decreases in energy intake
- Decreases in energy intake can be achieved with a variety of dietary patterns

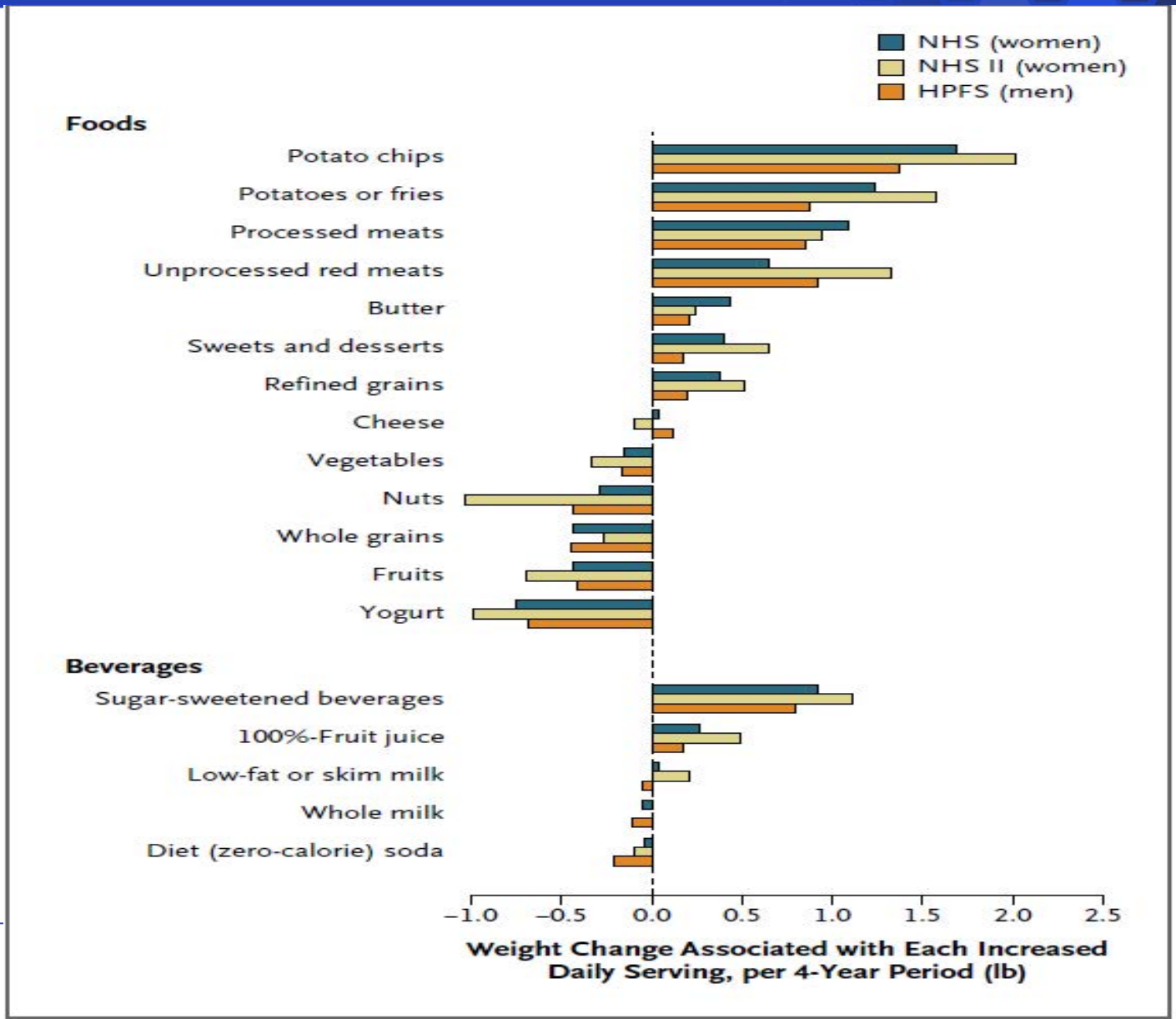
Criticisms of Low Fat, Higher-Carbohydrate Diets

- They stimulate insulin and worsen glucose tolerance
- They raise triglycerides and lower HDL
- They promote weight gain

Do fats or carbohydrates have unique roles in obesity?

- Cannot do experiments in humans to induce obesity
  - Cohort studies
  - Secular trends in human populations
- Can do experiments in obesity prevention or treatment
  - Short term comparisons of calorie-restricted high carbohydrate versus high fat diets
  - Long term RCT of low fat, high carbohydrate diet
  - Surgical calorie restriction

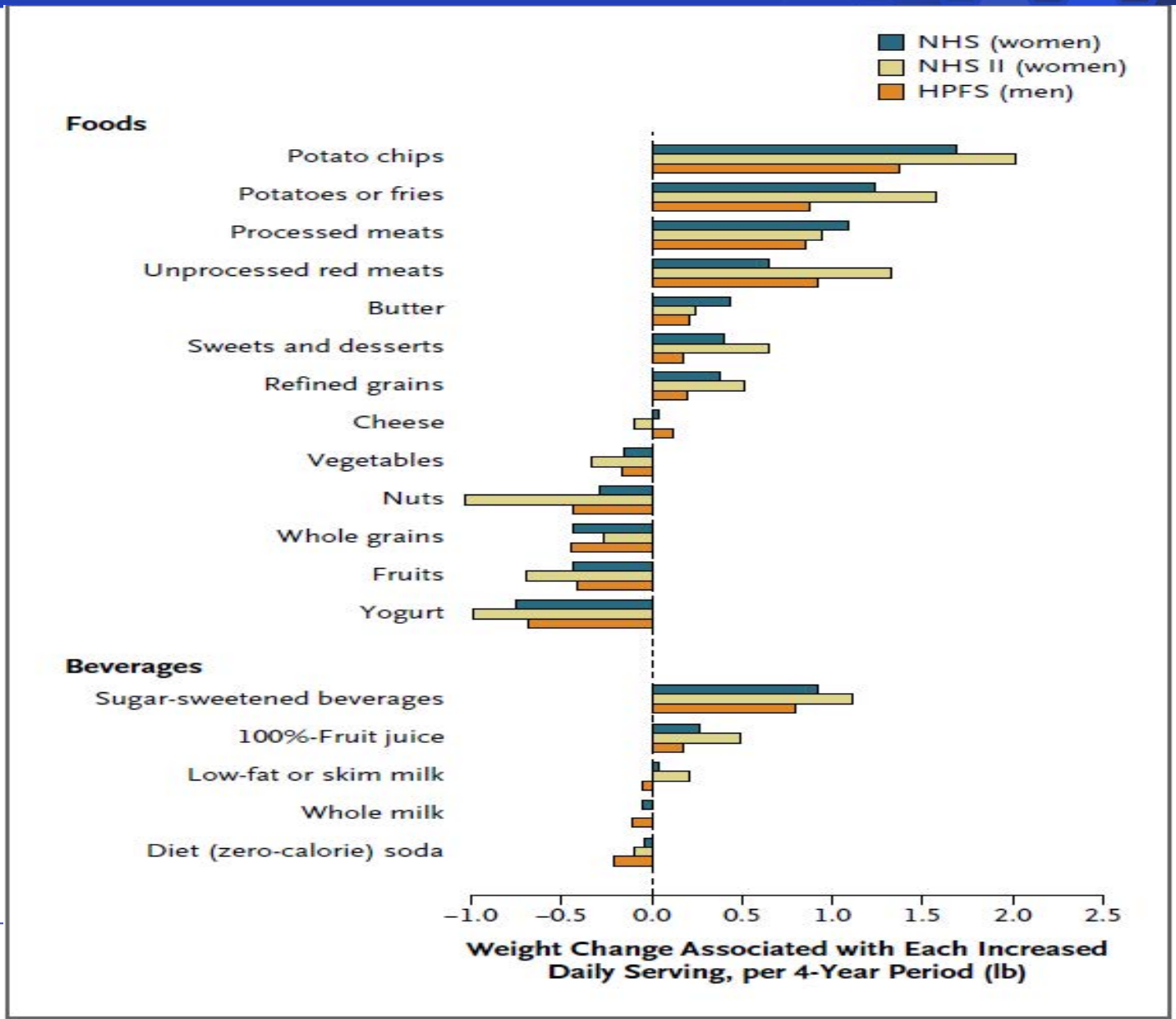
Changes in Diet and Lifestyle and Long-Term Weight Gain in Women and Men



Mozzafarian et al
NEJM, 2011

Changes in Diet and Lifestyle and Long-Term Weight Gain in Women and Men

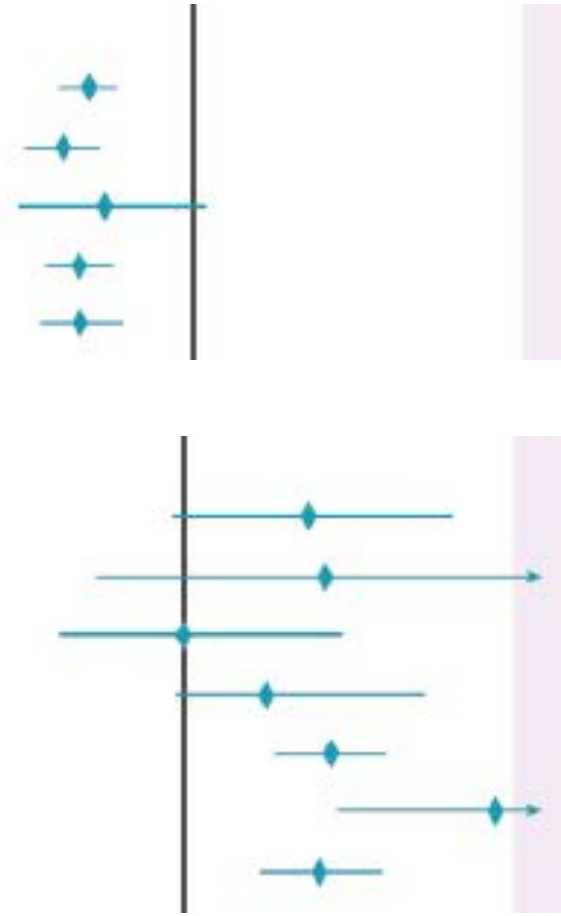
<u>Other lifestyle factors</u>
Physical Activity
Alcohol
Smoking
Sleep
Watching TV



Mozzafarian et al
NEJM, 2011

Whole grains are associated with cardioprotection, meat (and fats) are not

Whole Grains					
	Total CHD	11 PCs	356,070	—	High vs. low quantile
	Total CHD	6 PCs	284,841	4,385	2.5 vs. 0.2 servings/d
	Total stroke	4 PCs	208,143	933	2.5 vs. 0.2 servings/d
	Total CVD	7 PCs	285,376	6,504	2.5 vs. 0.2 servings/d
	Diabetes	6 PCs	286,125	10,944	Each 2 servings/d
Meats					
Total meats	Total CHD	12 PCs	236,414	—	High vs. low quantile
	Diabetes	4 PCs	180,205	5,579	Each serving/d (120 g)
Unprocessed red meats	Total CHD	4 PCs	56,311	1,252	Each serving/d (100 g)
	Diabetes	5 PCs	296,982	7,582	Each serving/d (100 g)
Processed meats	Total CHD	6 PCs	614,062	21,336	Each serving/d (50 g)
	Diabetes	8 PCs	372,205	9,456	Each serving/d (50 g)
	Diabetes	7 PCs	302,725	8,331	Each serving/d (50 g)



Mozzafarian, Appel, Van Horn. Components of a Cardioprotective Diet: New Insights Circulation, 2011

National Heart Lung and Blood Institute

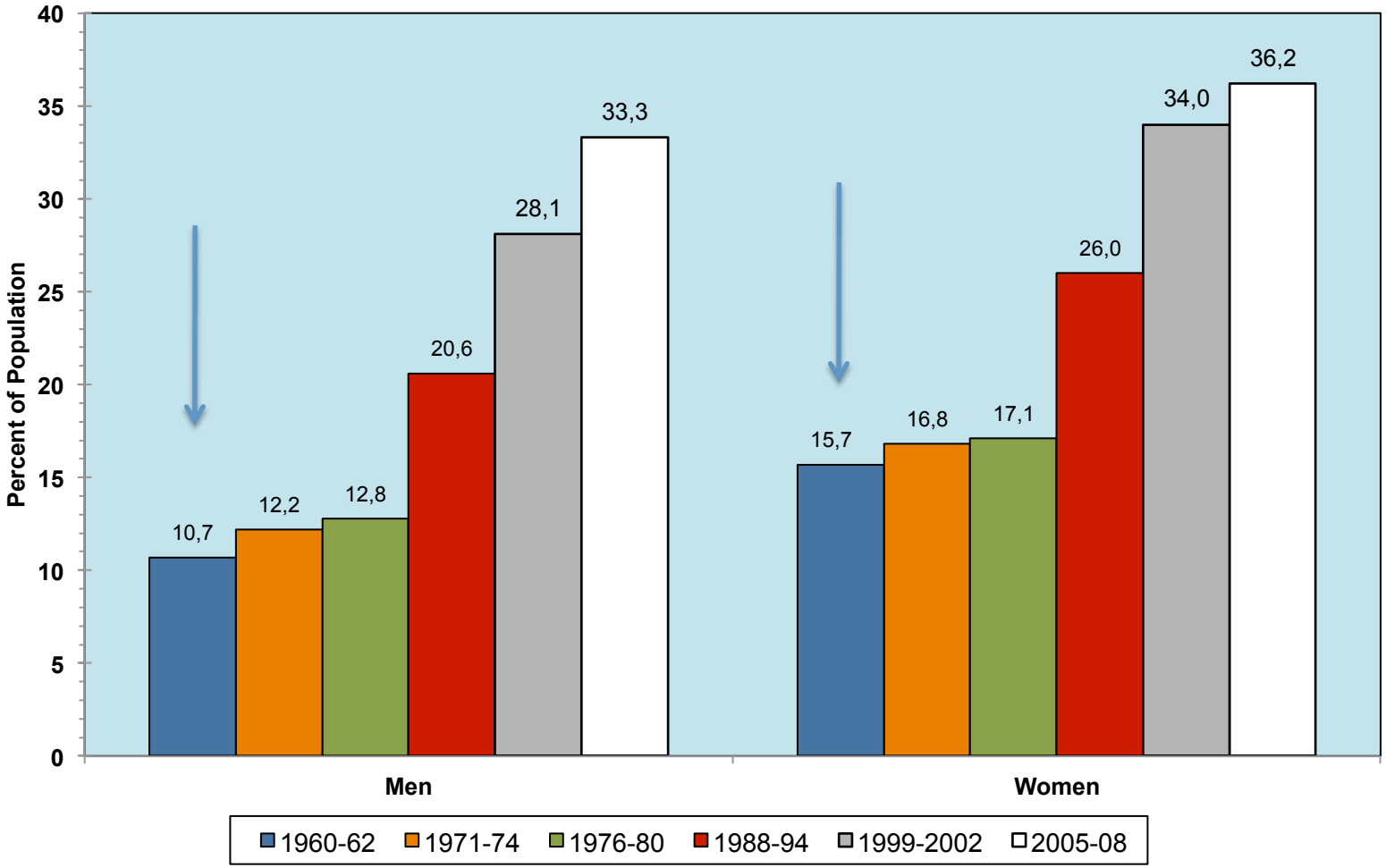
Cohort Studies of Dietary Habits and Obesity

- Methodology challenging
- Well conducted studies indicate that people who gain weight (and likely are overeating) have a poor dietary quality (e.g., potato chips, french fries, processed meats, refined carbohydrates, sugar sweetened drinks)
- Meta-analyses show reduced CHD and diabetes risks associated with whole grains, increased risks with processed meats (high in fat).

Secular Trends in Human Populations

Country	Dietary Fat/SAFA	Serum Cholesterol	CHD Rate	Obesity Rate
Finland	Reduced	Reduced	Reduced	Women no change Men small increase
USA	Reduced	Reduced	Reduced	Increased, but not in parallel
UK	Reduced	Reduced	Reduced	Increased
Poland	Reduced	Reduced	Reduced	Women increased Men no change
Sweden-before 2004	Reduced	Reduced	Reduced	Increased
Sweden-after 2004	Increased	Increased	?	Increased

Age-adjusted prevalence of obesity in adults 20–74 years of age, by sex and survey year (NHES: 1960–62; NHANES: 1971–74, 1976–80, 1988–94, 1999-2002 and 2005-08)



Data derived from *Health, United States, 2010: With Special Feature on Death and Dying.* NCHS, 2011.

National Heart Lung and Blood Institute

Roger VL et al. Published online in *Circulation* Dec. 15, 2011


Green Giant Fresh

Secular Trends in Human Populations

Country	Dietary Fat/SAFA	Serum Cholesterol	CHD Rate	Obesity Rate
Finland	Reduced	Reduced	Reduced	Women no change Men small increase
USA	Reduced	Reduced	Reduced	Increased
UK	Reduced	Reduced	Reduced	Increased
Poland	Reduced	Reduced	Reduced	Women increased Men no change
Sweden-before 2004	Reduced	Reduced	Reduced	Increased
Sweden-after 2004	**Increased**	**Increased**	**?**	**Increased**

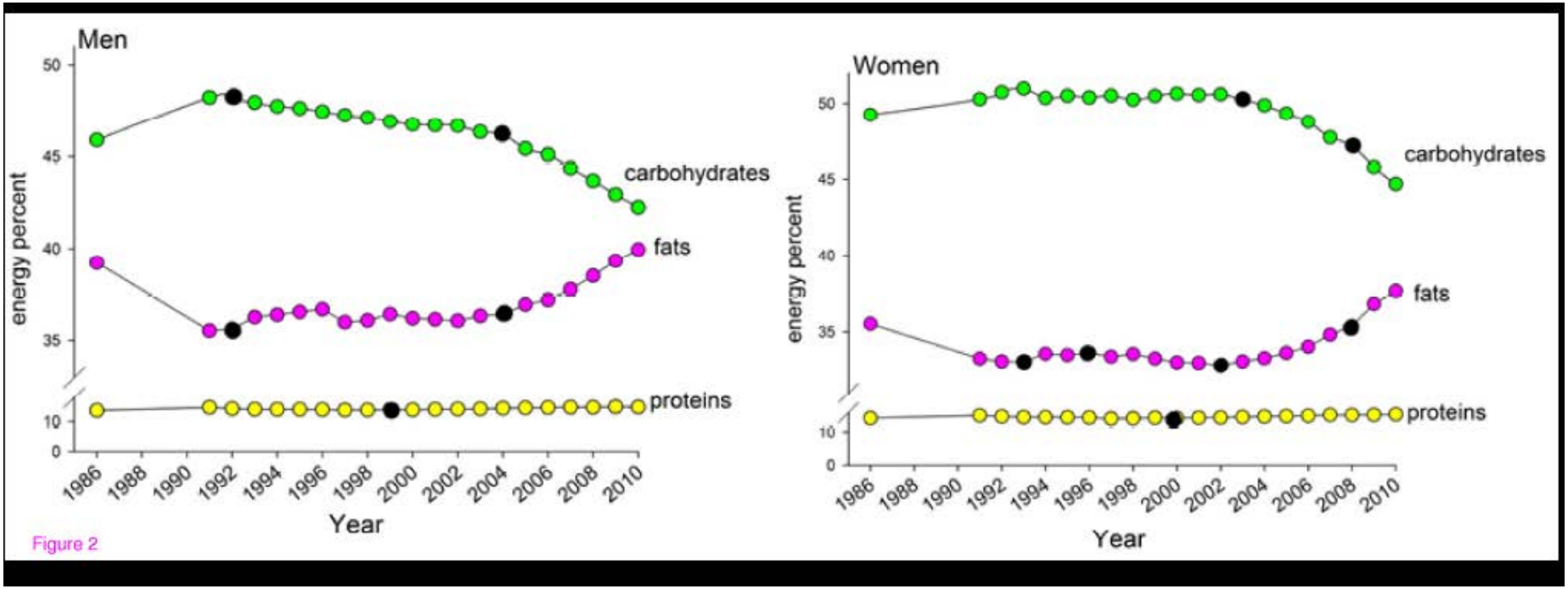
National Heart Lung and Blood Institute

Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden.

- 1970's Northern Sweden among highest CVD rates in world
- 1985 Community intervention program launched
- Central component was intervention on diet
  - "modified Mediterranean diet"
  - i.e. reduction in total fat, shift from saturated to polyunsaturated fatty acids, fewer eggs, more vegetables, fruit, fish, and whole grain bread
- By 2002 CVD rates had declined by 50%

Johansson I, et al. Nutrition Journal 2012;11:40 [epub ahead of print]

Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden.



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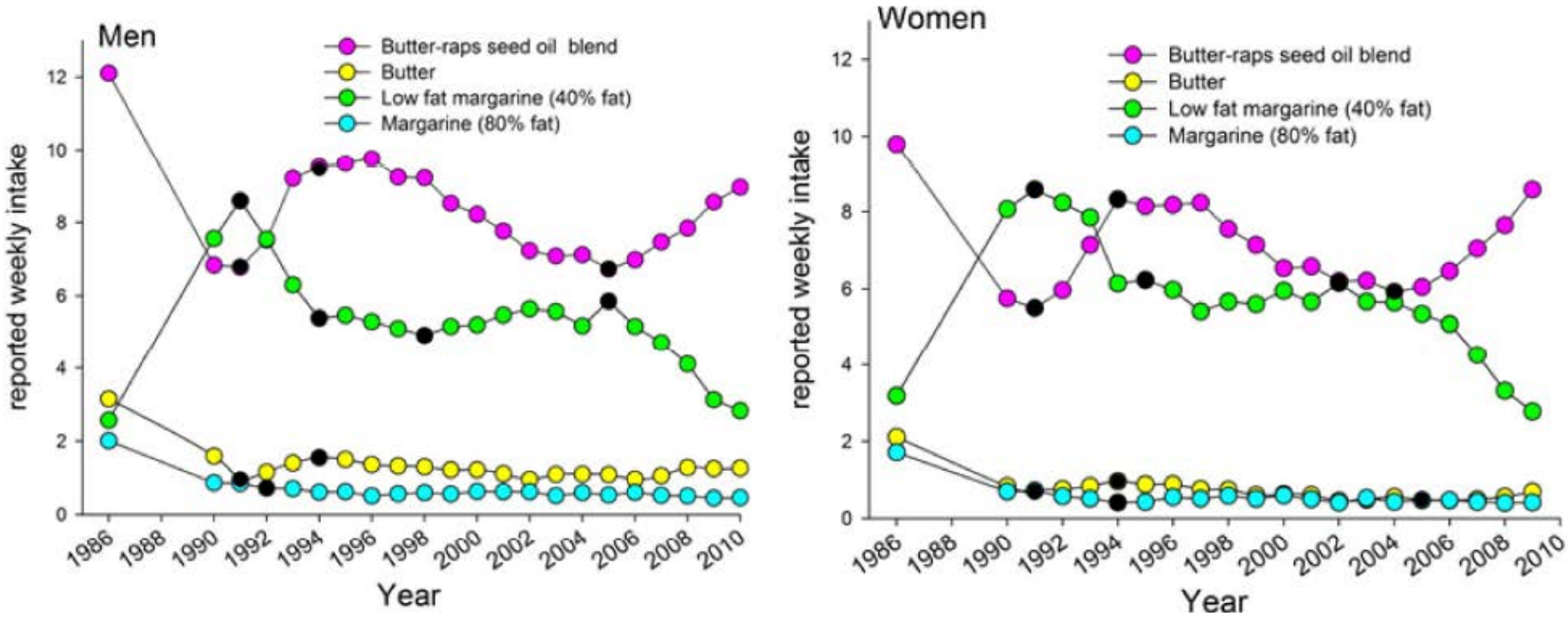

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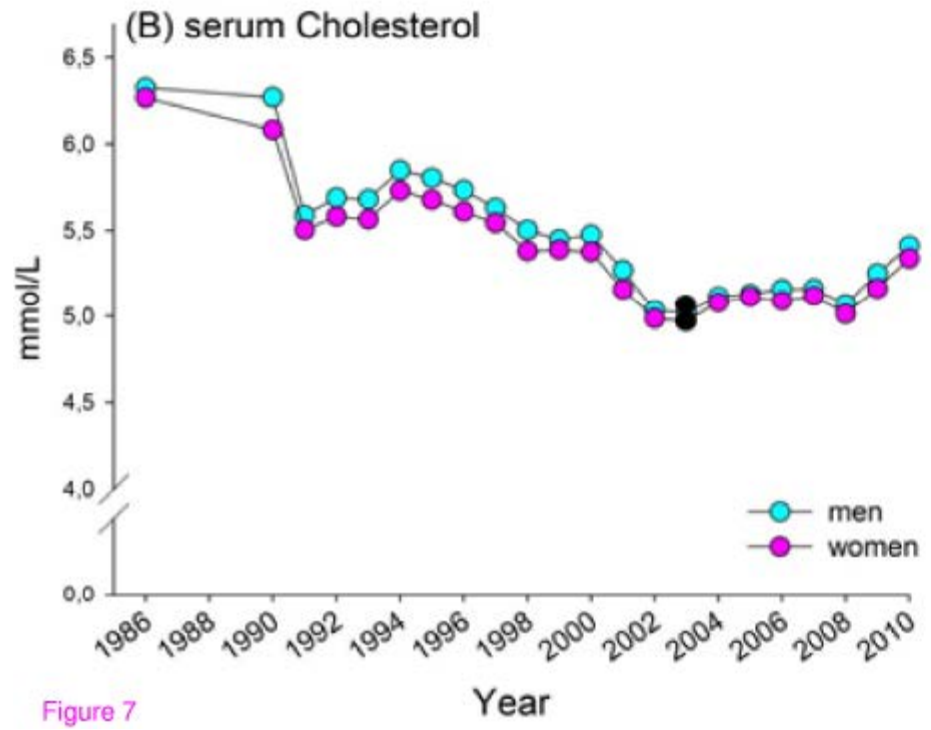
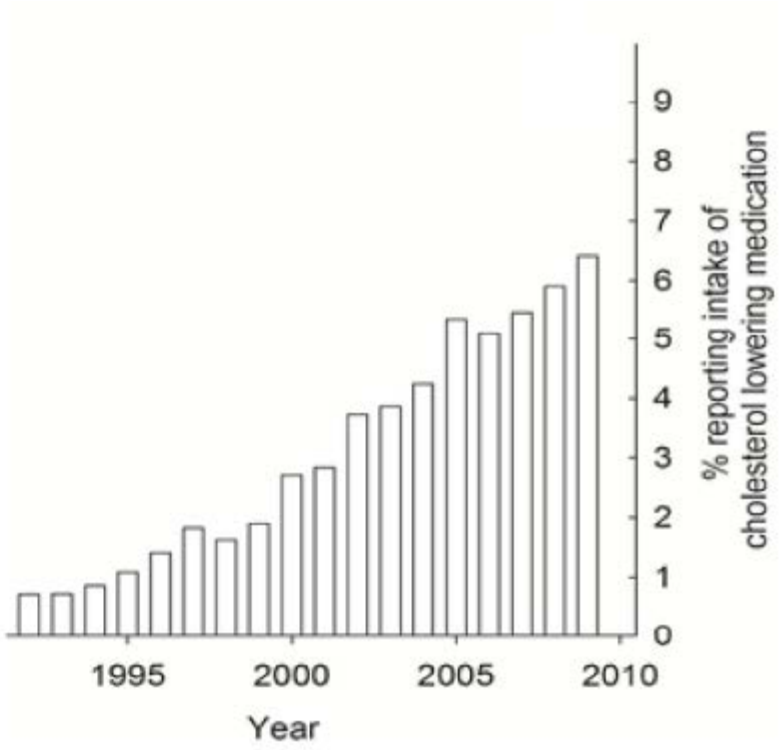


Figure 7



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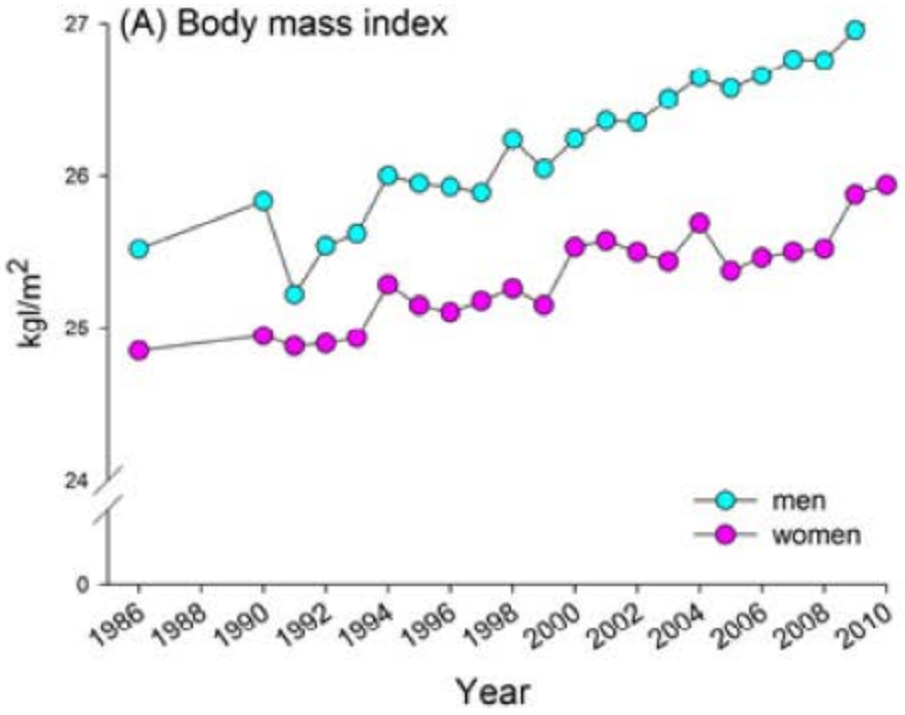
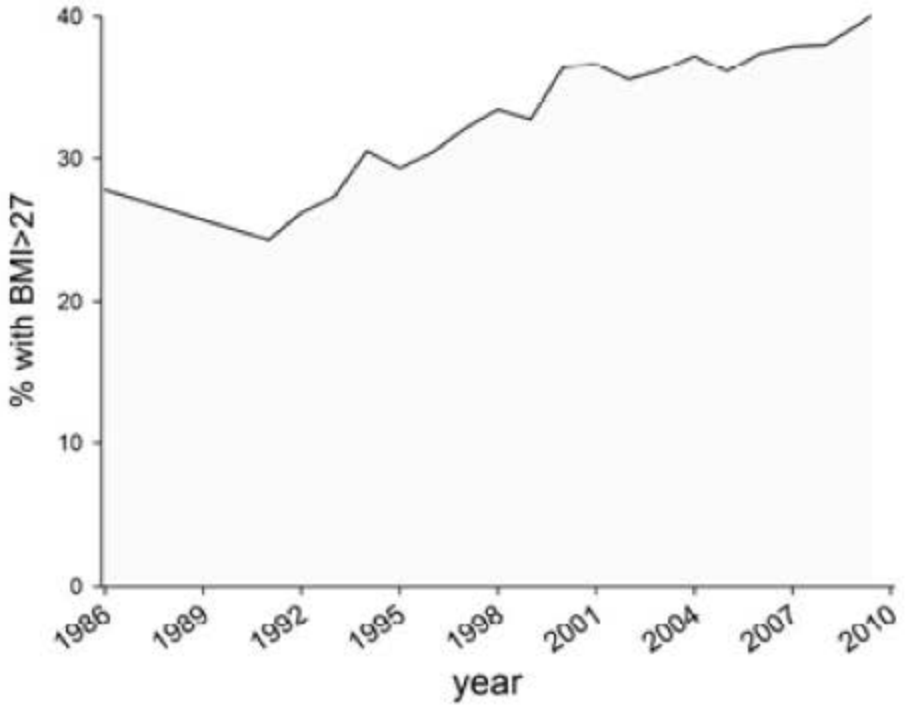
National Heart Lung and Blood Institute

Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden.





Johansson I, et al. Nutrition Journal 2012;11:40 [epub ahead of print]

National Heart Lung and Blood Institute

Low carbohydrate, high protein diets were associated with increased cardiovascular risk in 43, 000 Swedish women followed for 15 years

Table 4| Incidence rate ratios for overall cardiovascular diseases and main diagnostic subcategories, per decreasing tenth of carbohydrate intake, increasing tenth of protein intake, and their addition in Swedish Women's Lifestyle and Health Cohort

	Incidence rate ratios* (95% CI)		
Condition (No of cases)	Low carbohydrate score (per tenth)	High protein score (per tenth)	LCHP score (per 2 units)
All cardiovascular diseases (1268)	1.04 (1.00 to 1.08)	1.04 (1.02 to 1.06)	1.05 (1.02 to 1.08) *
Ischaemic heart disease (701)	1.04 (0.99 to 1.09)	1.03 (1.00 to 1.06)	1.04 (1.00 to 1.08)
Ischaemic stroke (294)	1.05 (0.98 to 1.14)	1.05 (1.01 to 1.10)	1.07 (1.00 to 1.13)
Haemorrhagic stroke (70)	1.00 (0.86 to 1.17)	1.05 (0.96 to 1.14)	1.05 (0.93 to 1.18)
Subarachnoid haemorrhage (121)	1.07 (0.95 to 1.21)	1.05 (0.98 to 1.12)	1.07 (0.97 to 1.17)
Peripheral arterial disease (82)	1.04 (0.90 to 1.21)	1.04 (0.95 to 1.13)	1.04 (0.93 to 1.17)

*Incidence rate ratio comparing highest to lowest quintile = 1.60

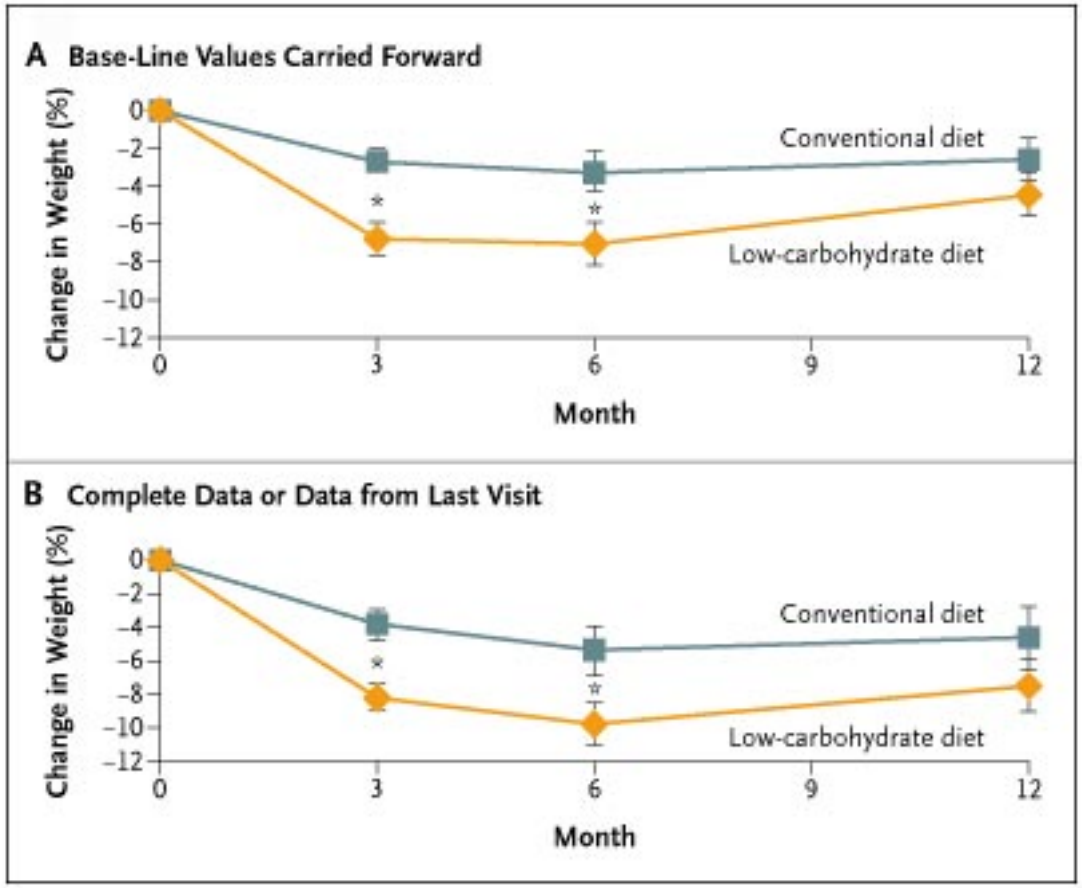
Lagiou et al. BMJ, 2012

National Heart Lung and Blood Institute

Studies of Secular Trends

- The trend towards increasing obesity is not uniquely associated with low fat/higher carbohydrate diets; other factors are responsible
- However, adoption of these diets do result in lower cholesterol levels, CHD risk, total mortality
- Implementation of dietary recommendations has been beneficial
- Reverting to higher fat/lower carbohydrate diets may not reverse a trend towards obesity, but may reverse the cardiovascular benefits

Clinical Trials: Most Widely Cited Evidence – A Small (N=63) 12-month Study

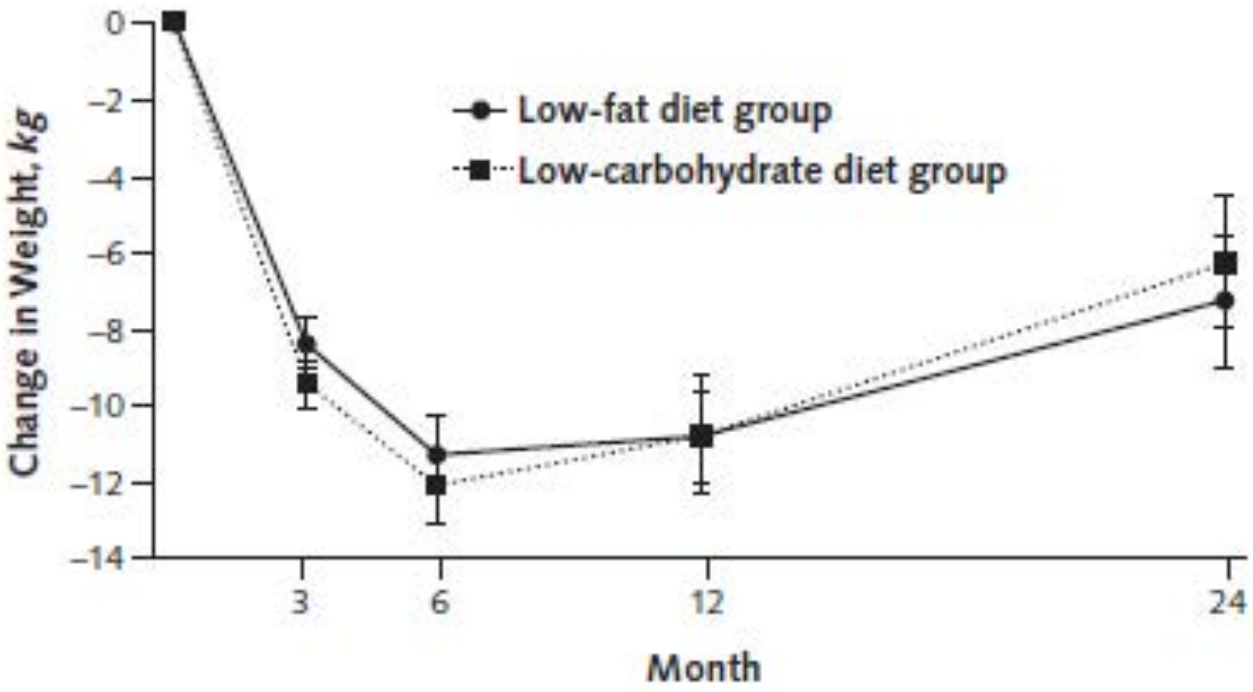


Foster GD, *et al* NEJM, 348:2082, 2003

National Heart Lung and Blood Institute

Better Evidence from same group—2 year trial (N=307)

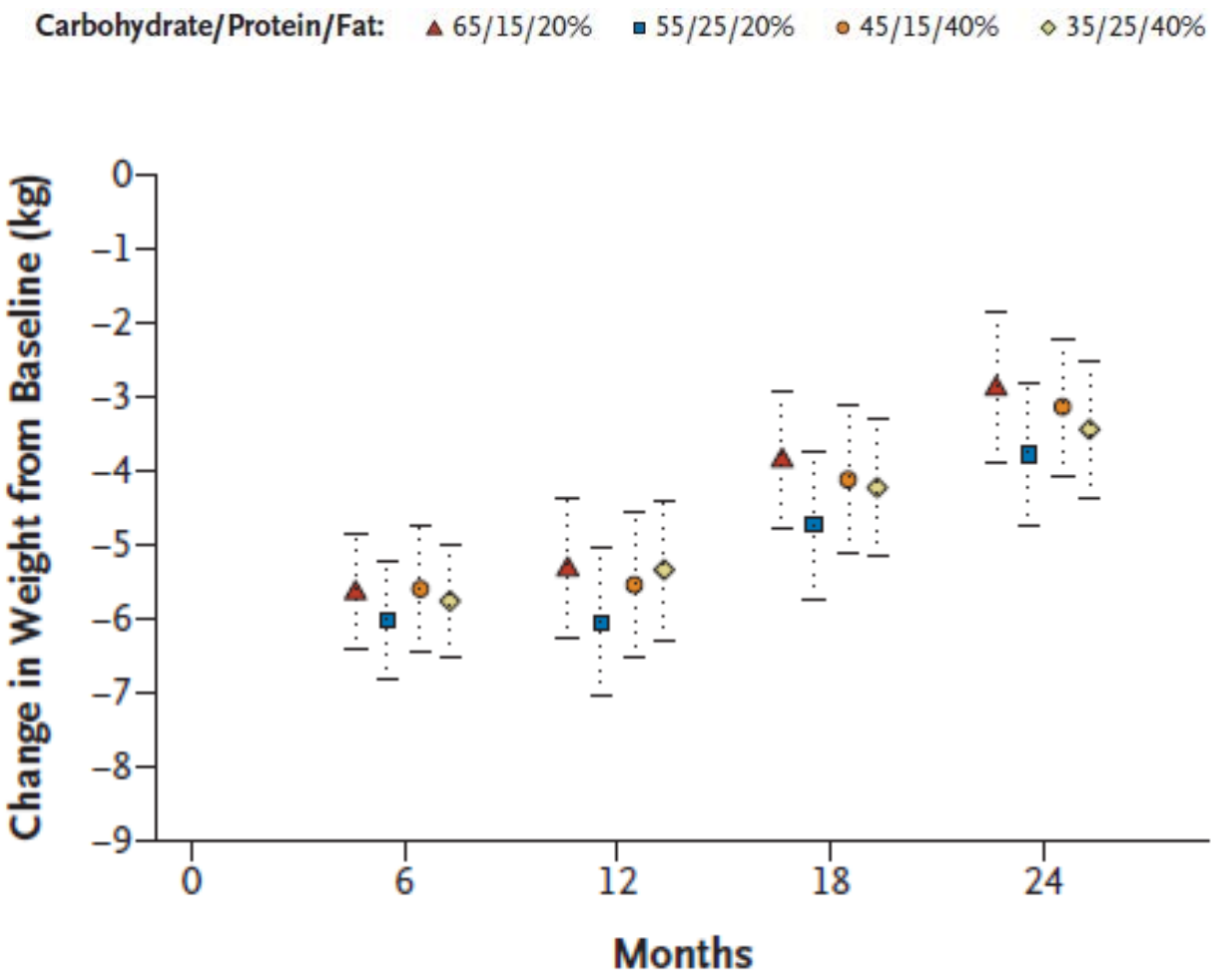
Figure 2. Predicted absolute mean change in body weight for participants in the low-fat and low-carbohydrate diet groups, based on a random-effects linear model.



Foster GD et al. Ann Intern Med, 2010

National Heart Lung and Blood Institute

Better Evidence:
2-year Study Comparing Weight-Loss Diets with Different Compositions of Fat, Carbohydrates, and Protein



Sacks et al. N Engl J Med 2009;360:859-73

National Heart Lung and Blood Institute

Comparison of Weight-Loss Diets with Different Compositions of Fat, Carbohydrates, and Protein

CONCLUSIONS

Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize. (ClinicalTrials.gov number, NCT00072995.)

Sacks et al. N Engl J Med 2009;360:859-73

National Heart Lung and Blood Institute

Comparison of Weight-Loss Diets with Different Compositions of Fat, Carbohydrates, and Protein

	Low Fat, Average Protein		High Fat, High Protein	
	Change from Baseline, %		Change from Baseline, %	
	6-Mo	2-Yr	6-Mo	2-Yr
Cholesterol (mg/dl)				
Total	−5.9	−3.7	−2.3	−0.8
LDL	−6.6	−5.9	−1.1	−1.3
HDL	−0.4	5.6	4.0	8.8
Triglycerides (mg/dl)	−14.2	−11.5	−19.5	−16.7
Glucose (mg/dl)	−3.0	1.1	−1.2	2.8
Insulin (μU/ml)	−16.2	−2.4	−14.4	−9.2
HOMA	−18.7	−1.4	−13.4	−6.3

Sacks et al. N Engl J Med 2009;360:859-73

National Heart Lung and Blood Institute

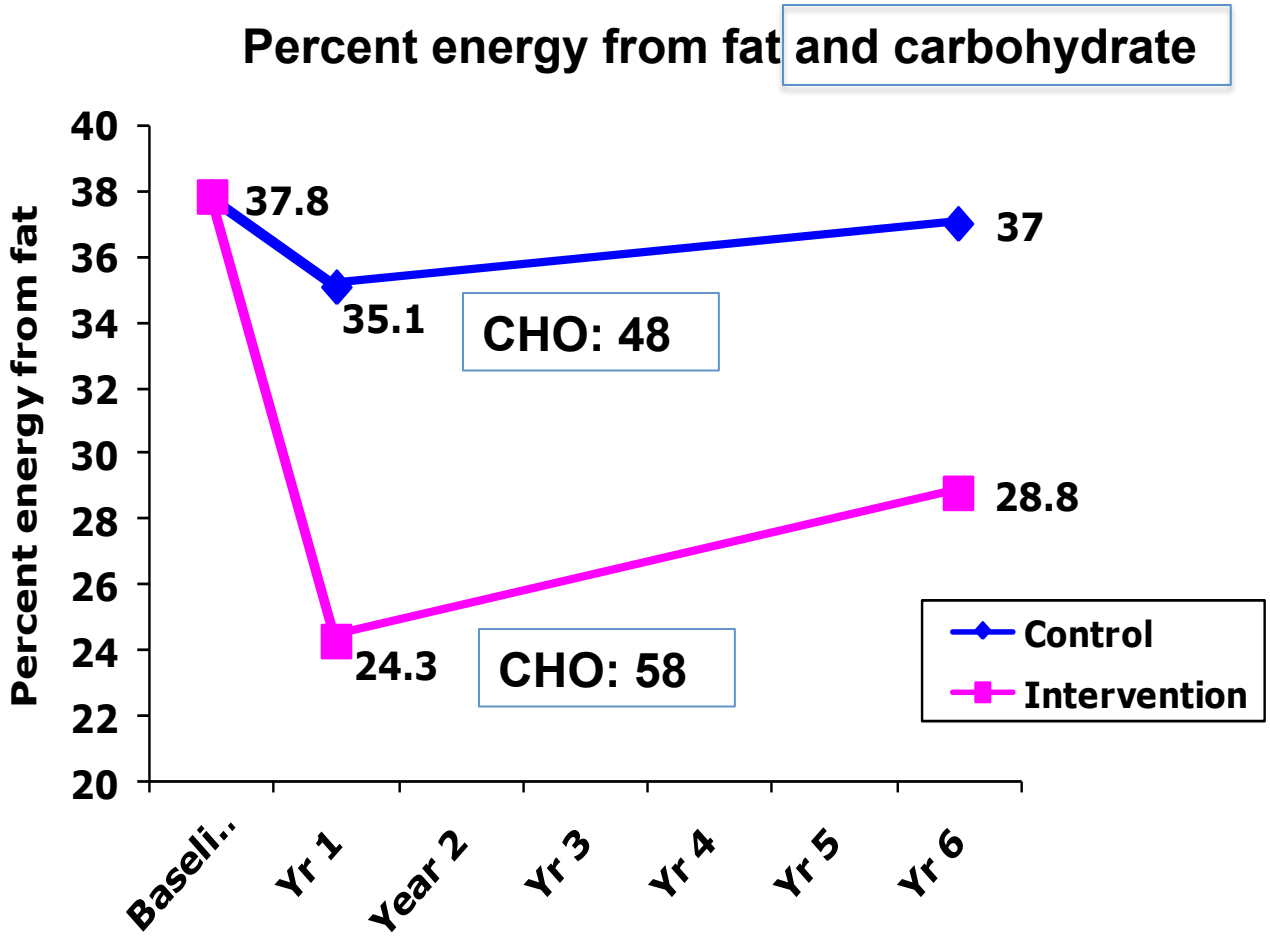
Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates

"In conclusion, diets that are successful in causing weight loss can emphasize a range of fat, protein, and carbohydrate compositions that have beneficial effects on risk factors for cardiovascular disease and diabetes. Such diets can also be tailored to individual patients on the basis of their personal and cultural preferences and may therefore have the best chance for long-term success."

Sacks et al. N Engl J Med 2009;360:859-73

National Heart Lung and Blood Institute

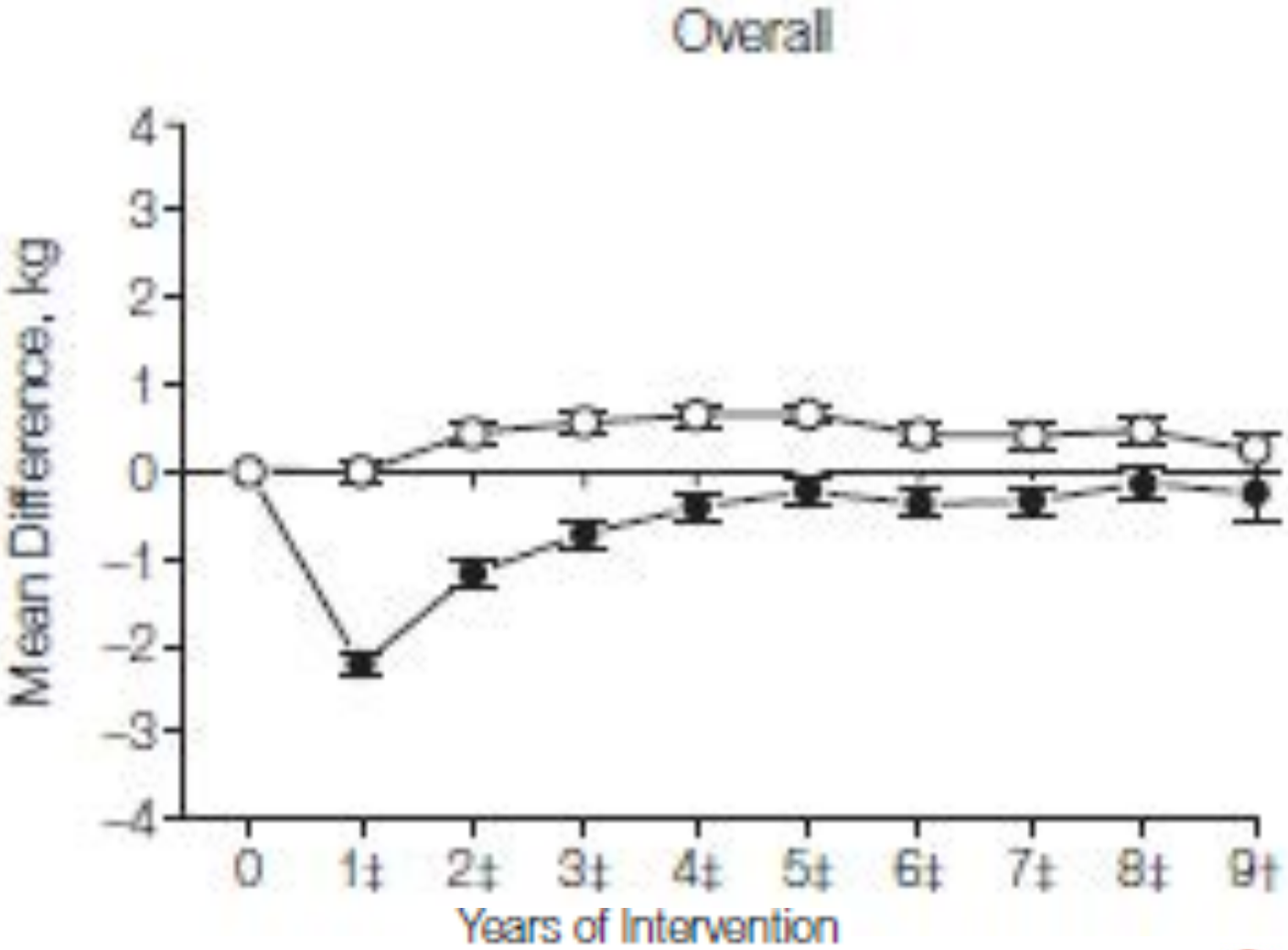
Best Evidence: Large (N~49,000) and Long Term (8-Year) WHI Dietary Modification Trial



Prentice RL et al. JAMA, 2006

National Heart Lung and Blood Institute

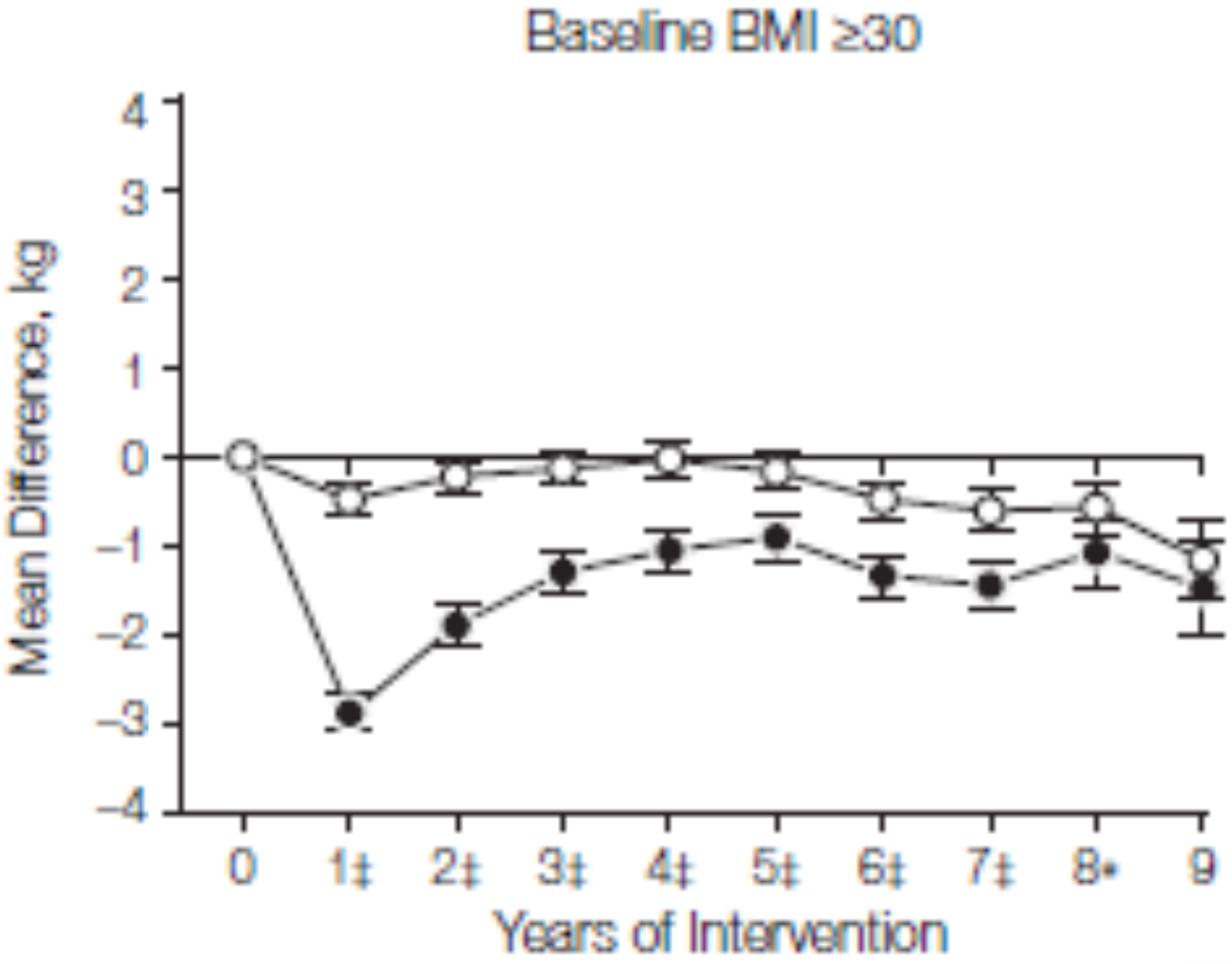
WHI Change in Body Weight by Randomization Group



Howard BV et al. JAMA, 2006

National Heart Lung and Blood Institute

WHI Change in Body Weight in Obese Women



Howard BV et al. JAMA, 2006

National Heart Lung and Blood Institute

WHI DM Trial: Changes in Risk Factors

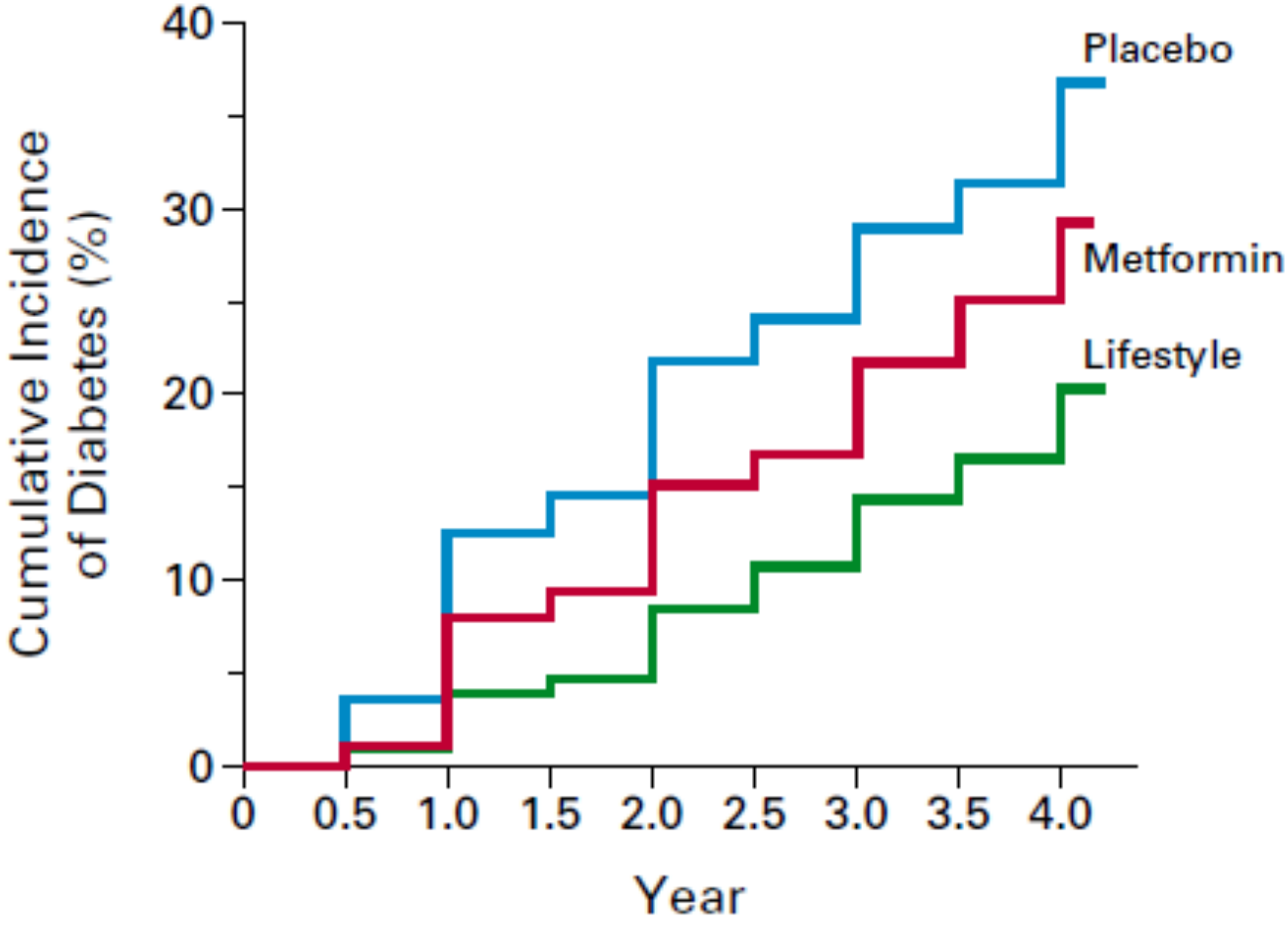
	Risk factor	Baseline	Difference at year 3 (I-C)
IMPROVED	LDL-cholesterol, mg/dL	133	-2.4 *
	Diastolic blood pressure, mmHg	76	-0.4 *
	Factor VIIC, %	131	-3.5 *
NO CHANGE	Triglycerides, mg/dL	139	0
	HDL-cholesterol, mg/dL	60	<1
	Glucose, mg/dL	100	1
	Insulin, µIU/mL	10	0

* Significantly different

Howard BJ et al. JAMA, 2006

National Heart Lung and Blood Institute

Prevention of diabetes in subjects with impaired glucose tolerance with low fat, high carbohydrate NCEP Step 1 Diet as part of lifestyle intervention



Diabetes Prevention Program Research Group. NEJM, 2002

National Heart Lung and Blood Institute

And the change in weight was the best predictor of diabetes

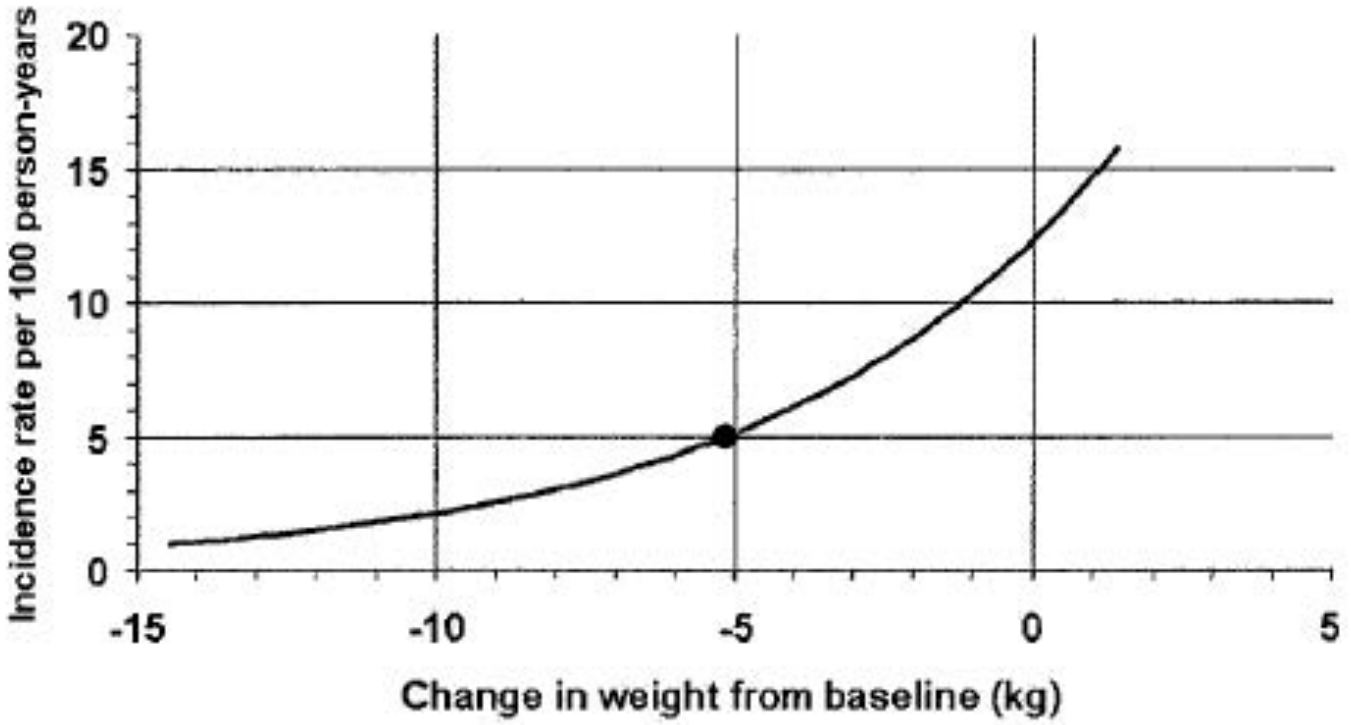
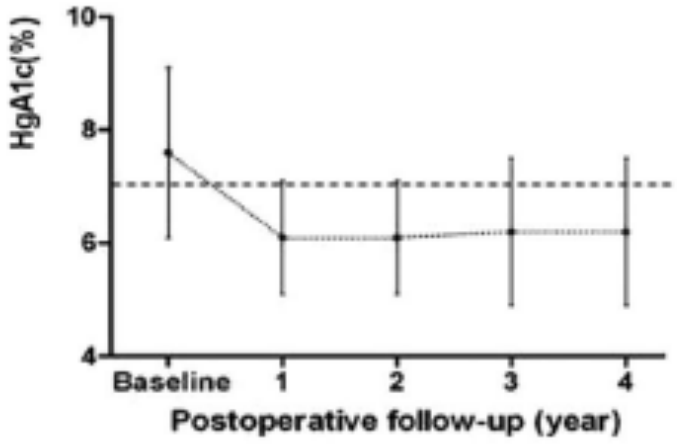


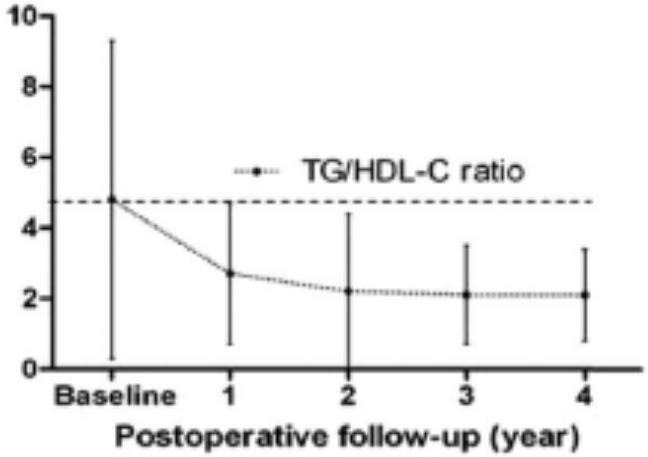
Figure 1—*Diabetes incidence (per 100 person-years) by change in weight after baseline among DPP ILS participants based on the multivariate model in Table 2.* ●, *overall risk in the group at the mean weight loss over an average of 3.2 years of follow-up.*

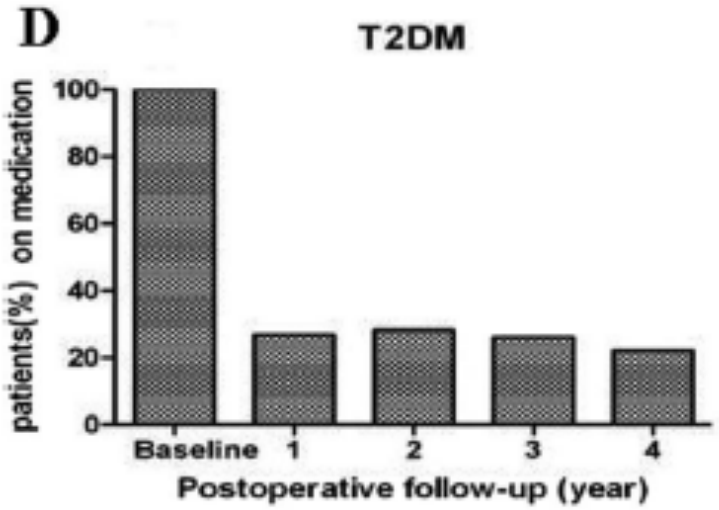
Hamman et al. Diabetes Care, 2006

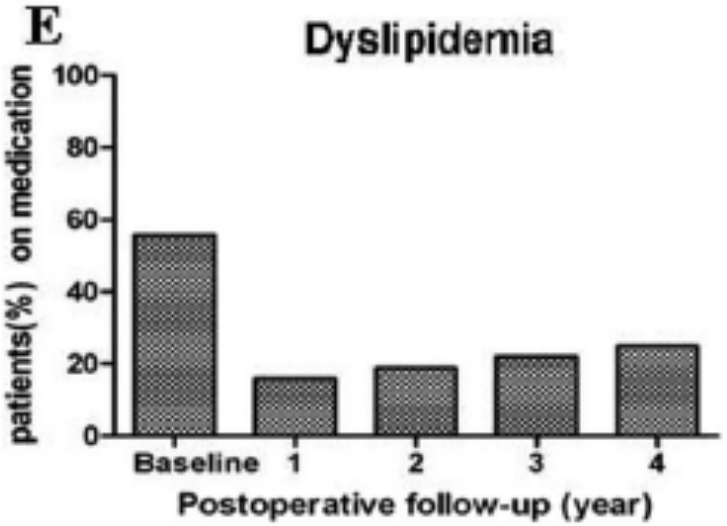
National Heart Lung and Blood Institute

Gastric bypass produces durable remission of diabetes and dyslipidemia









Kim&Richards. Ann Surg, 2010

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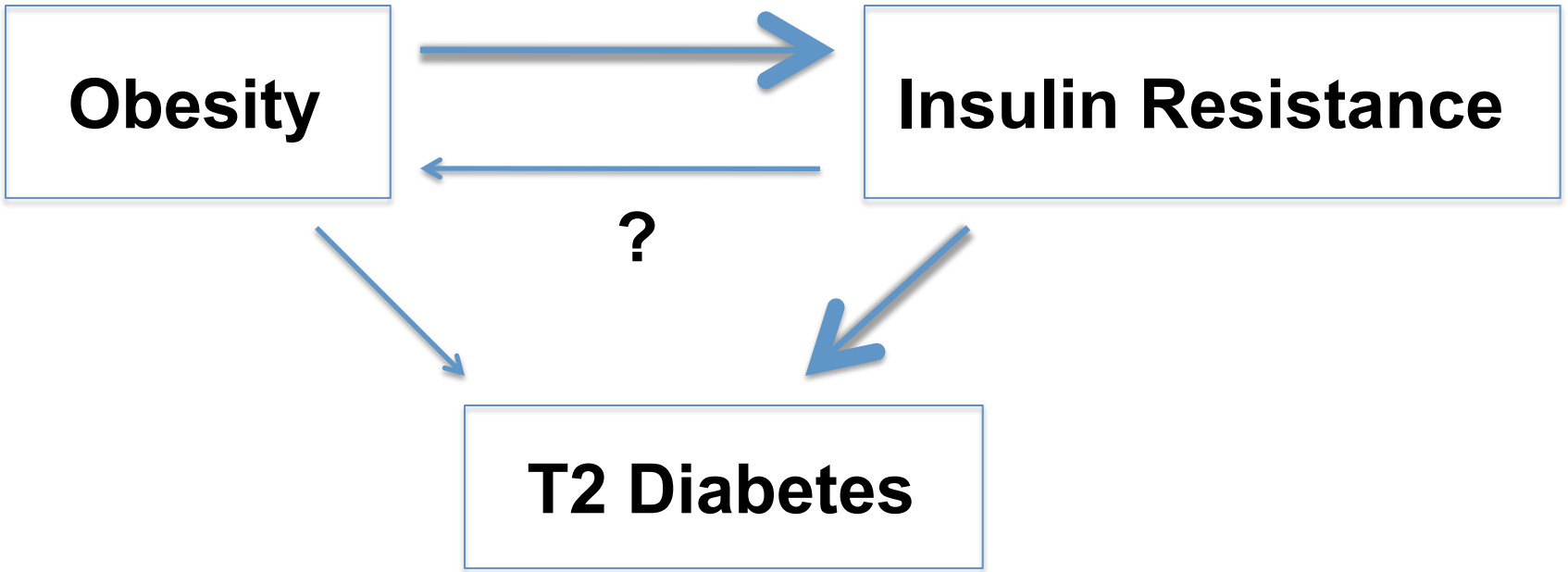
Clinical Trial Evidence: Energy Intake, Dietary Composition, Weight, and Insulin Resistance

- In the longer term, a diet low in fat and high in (good quality) carbohydrates is not associated with weight gain, increase in triglycerides, or insulin resistance
- Any energy restricted diet that reduces weight improves insulin resistance and blood lipids
- Energy restricted low fat, high carbohydrate diets can be used to reduce weight and prevent diabetes in patients with impaired glucose tolerance
- Severe energy restriction by gastric bypass induces weight loss and remission of diabetes
- Obesity is primary driver of T2 Diabetes

Does the chicken or the egg come first?



Prevalence of metabolic syndrome in US adults age 30-74 (NHANES)

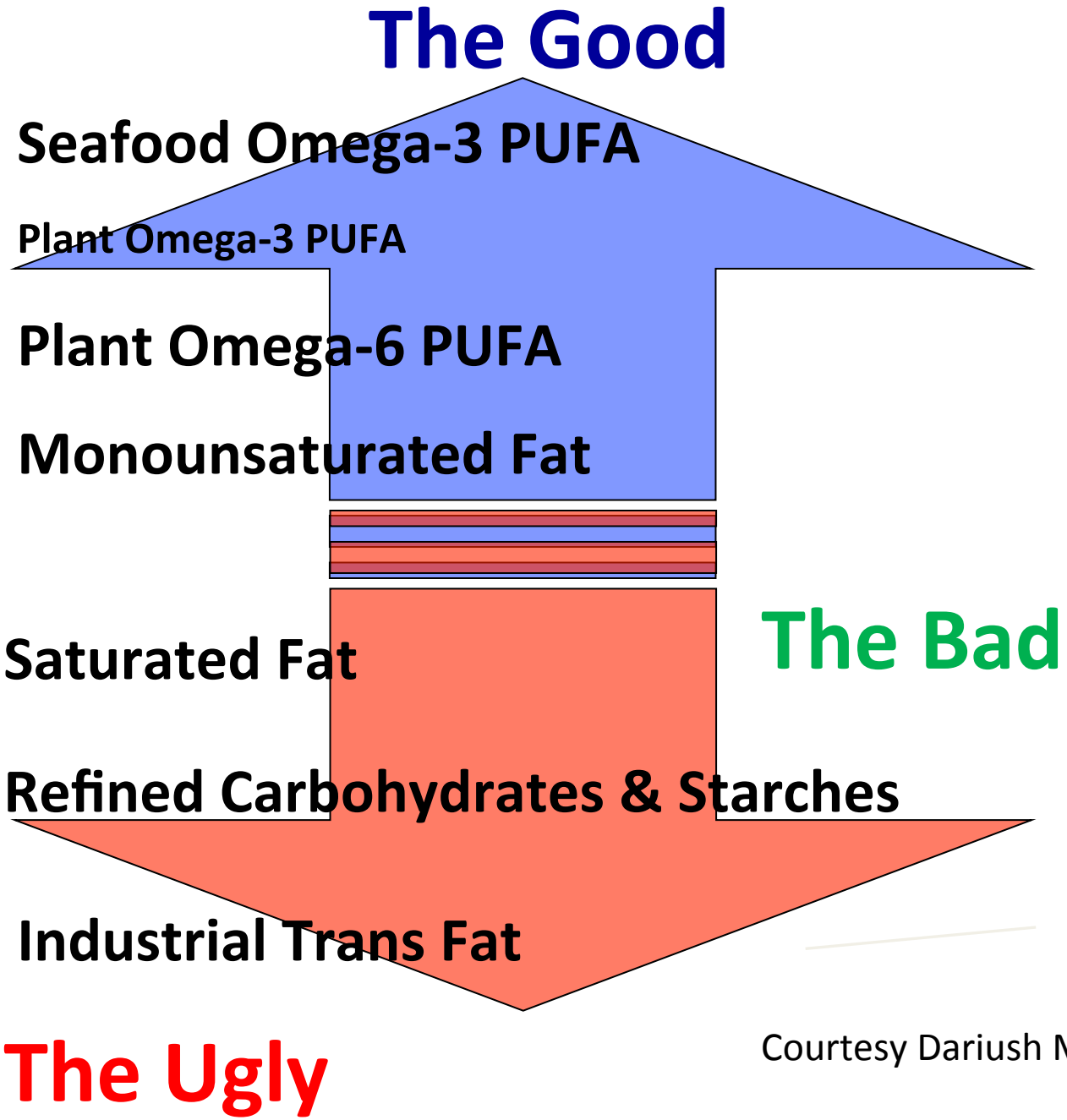
TABLE 1. Prevalence of Individual MetS Abnormalities Among US Adults by Disease Category

Disease	Subjects, n	Weighted No. of Subjects, millions (%)	Disease Condition Categories*				
			Impaired Glucose Tolerance†	Low HDL-C‡	High Triglycerides§	Elevated Blood Pressure‖	Obesity¶
All groups	6255	63.9 (100)	9.0	46.9	21.8	54.8	20.1
No MetS, diabetes, or CVD	2878	34.6 (54.2)	4.6	25.4	9.6	31.5	3.5
MetS (all)	1698	16.6 (26.0)	18.5	85.0	48.2	90.5	56.2
MetS (no diabetes)	1178	12.3 (19.2)	21.0	92.6	52.6	94.9	63.9
Diabetes	520	4.3 (6.8)	100.0#	63.4	35.9	78.0	34.2
CVD (all)	1679	12.6 (19.8)	8.6	59.3	23.3	77.1	20.7
Pre-existing CVD	1398	10.7 (16.9)	8.6	57.3	20.4	74.8	17.8
Diabetes and CVD	281	1.9 (2.9)	100.0#	70.9	40.1	90.0	37.4

*$P<0.0001$ across disease condition categories.
†Glucose 6.1 to 6.94 mmol/L (110 to 125 mg/dL) if fasting or 2-hour postload glucose 7.77 to 11.04 mmol/L (140 to 199 mg/dL).
‡HDL-C <1.04 mmol/L (40 mg/dL) if male or <1.29 mmol/L (50 mg/dL) if female.
§Triglycerides ≥1.69 mmol/L (150 mg/dL) if fasting or ≥4.52 mmol/L if nonfasting (400 mg/dL).
‖Blood pressure ≥130/85 mm Hg or on antihypertensive medication.
¶BMI ≥30 kg/m^2 .
#By definition, all subjects with diabetes mellitus have impaired glucose tolerance, even if on treatment and with normal glucose (only 27.3% of those with diabetes and 19.9% of those with CVD and diabetes had fasting glucose levels of ≥110 mg/dL or 2-hour postload glucose levels of ≥140 mg/dL).

Malik et al, Circulation 2004

National Heart Lung and Blood Institute



Courtesy Dariush Mozzafarian

Essential Dietary Habits for Health

EAT:

- Fish and Seafood
- Whole Grains
- Fruits
- Vegetables
- Nuts
- Vegetable Oils
- Low Fat Dairy

LIMIT:

- Starchy Vegetables, Refined Carbohydrates, Sugars, esp. Sweetened Beverages
- Red Meats, esp. Processed Meats
- Hydrogenated Fats, Oils (Industrial Trans Fat)
- Salt

Mozaffarian , Appel, and Van Horn. Circulation 2011

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Hippocratic Oath

I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.

"Primum non nocere"

Source: Wikipedia

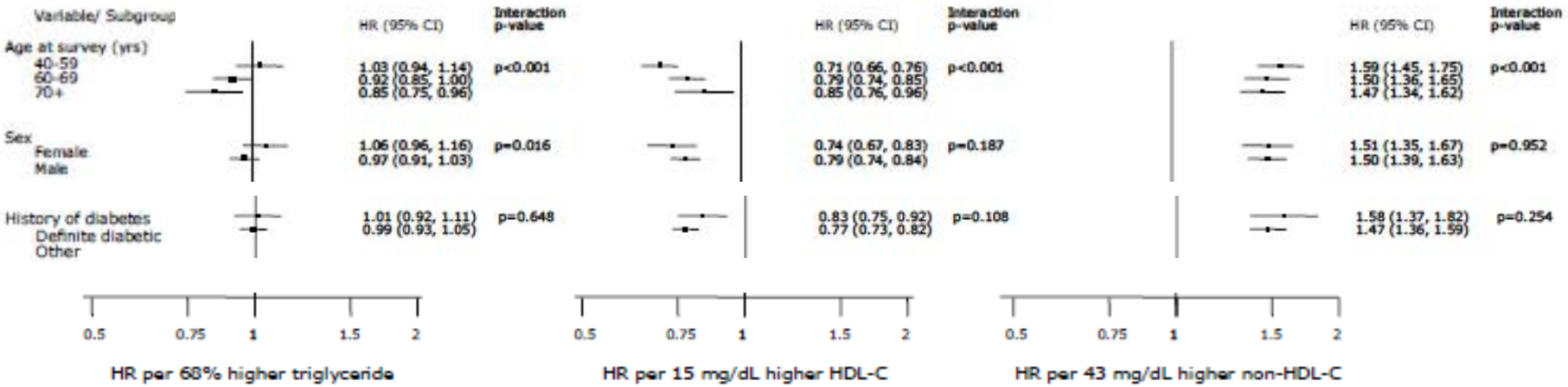
National Heart Lung and Blood Institute

National **Heart**
Lung and Blood Institute
People Science Health

Reserve Slides

Non-HDL-C is associated with CHD risk in all age groups, men and women, and in diabetics

eFigure 2. Adjusted hazard ratios for coronary heart disease per 1-SD increase in usual triglyceride, HDL-C and non-HDL-C according to various characteristics



In subset of 8 studies:
Overall CHD HR for directly measured LDL-C = 1.38, 1.09-1.73
Overall CHD HR for Non-HDL-C = 1.42, 1.06-1.91

The Emerging Risk Factors Collaboration

JAMA. 2009;302(18):1993-2000

National Heart Lung and Blood Institute

The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

Interpretation In individuals with 5-year risk of major vascular events lower than 10%, each 1 mmol/L reduction in LDL cholesterol produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years. This benefit greatly exceeds any known hazards of statin therapy. Under present guidelines, such individuals would not typically be regarded as suitable for LDL-lowering statin therapy. The present report suggests, therefore, that these guidelines might need to be reconsidered.

Cholesterol Treatment Trialists' (CTT) Collaborators

Lancet 2012; 380: 581–90

Short-term Feeding Studies: Lipid Effects of Individual SFAs

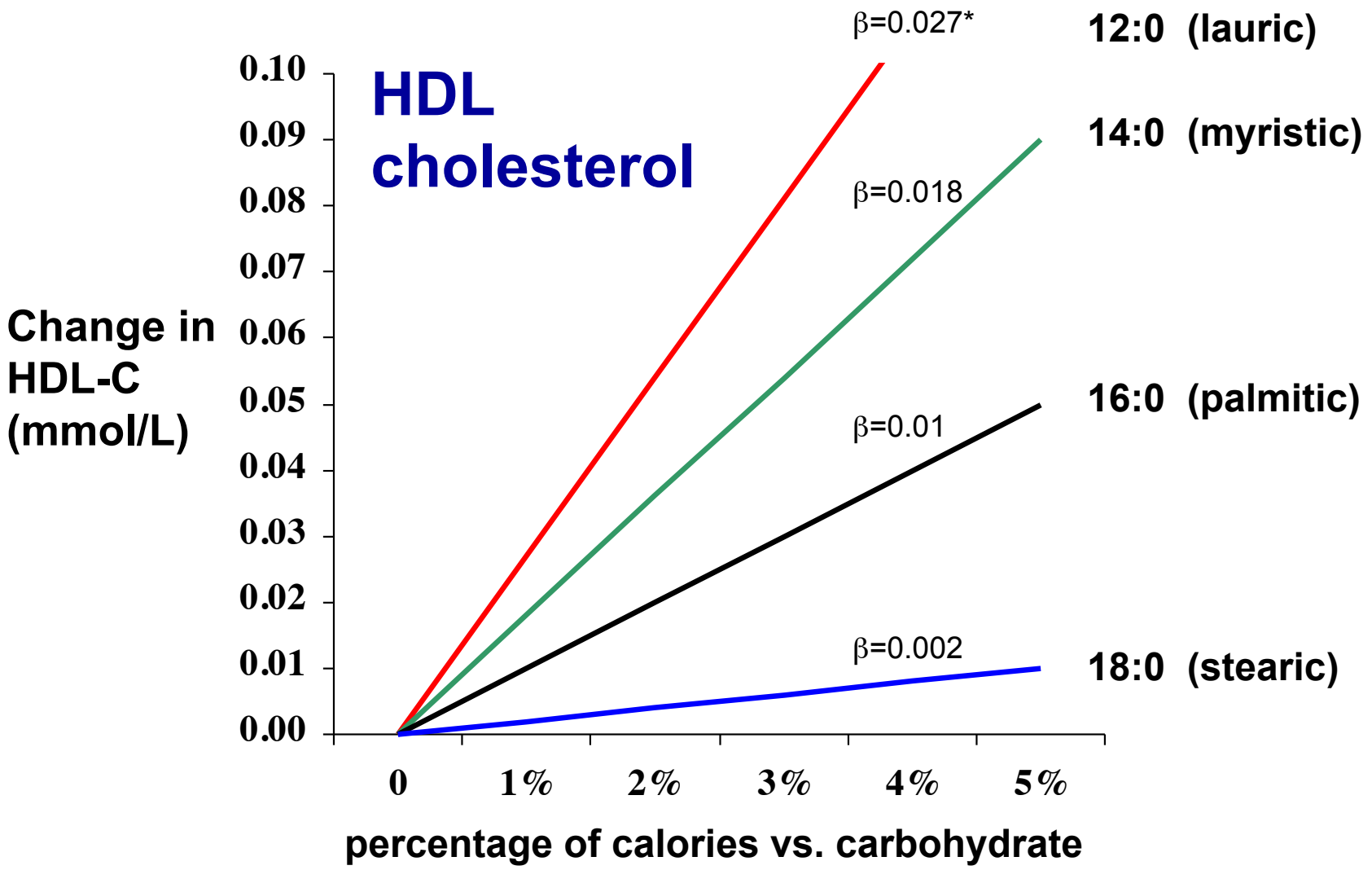


Figure from Micha & Mozaffarian, Lipids 2010. Based on Mensink & Katan 2003.

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Short-term Feeding Studies: Lipid Effects of Individual SFAs

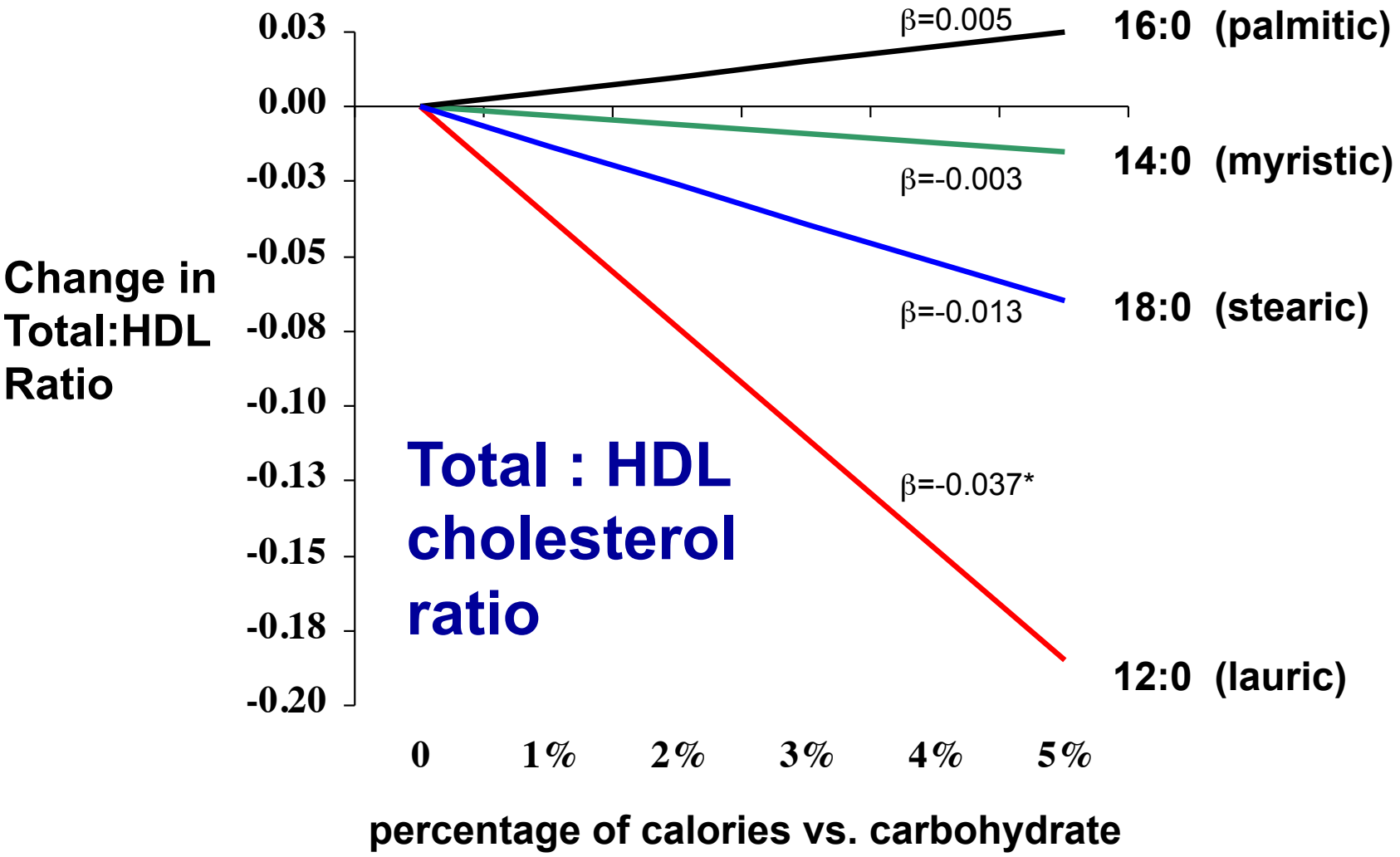

Figure from Micha & Mozaffarian, Lipids 2010. Based on Mensink & Katan 2003.

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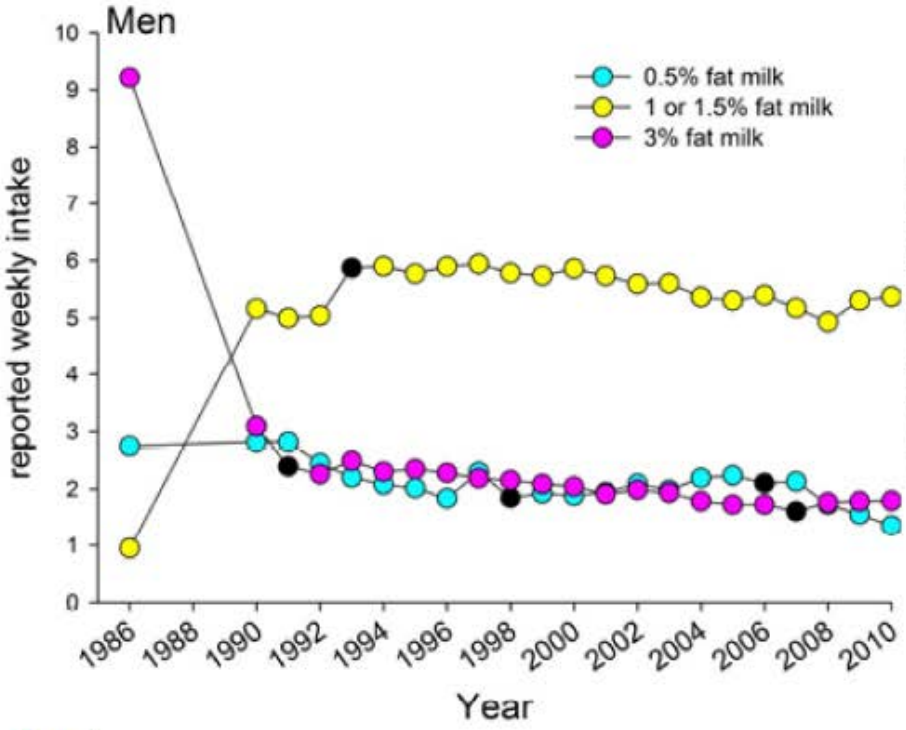
Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden.



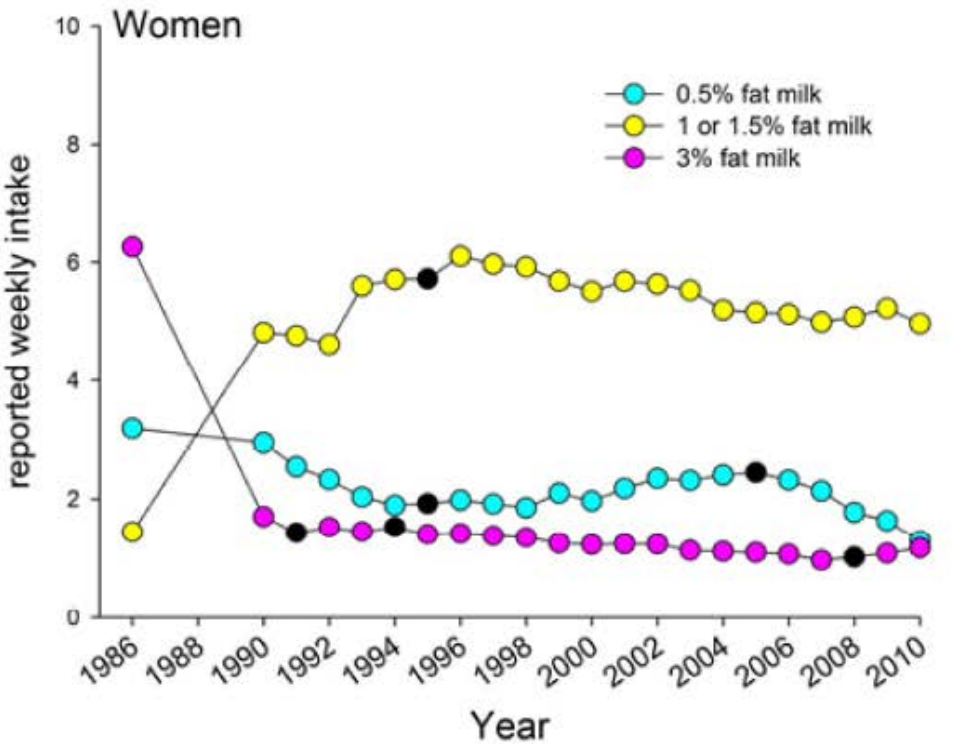


Figure 4

Johansson I, et al. Nutrition Journal 2012;11:40 [epub ahead of print]

National Heart Lung and Blood Institute

Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia

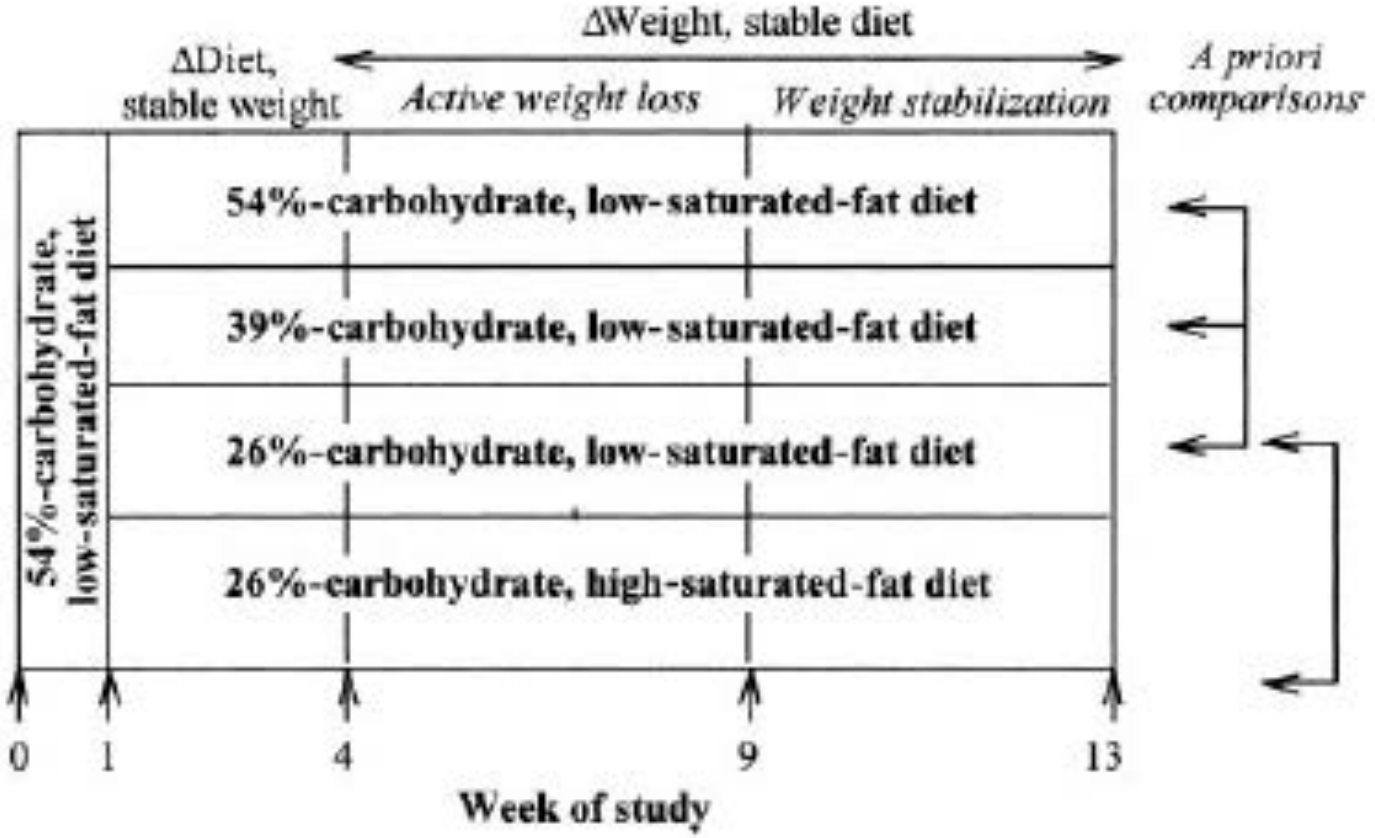


FIGURE 1. Study design. SF, saturated fat.

Ronald M Krauss, et al. Am J Clin Nutr 2006;83:1025–31

National Heart Lung and Blood Institute

Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia

	Low-SF diet (7–9%)		
	54% CHO	39% CHO	26% CHO
LDL cholesterol (mg/dL)			
Baseline	130.1 ± 30.2	125.5 ± 23.1	129.1 ± 25.7
ΔDiet, stable weight	−2.6 ± 3.1	−0.6 ± 3.3	−11.2 ± 2.7
ΔWeight, stable diet	−8.9 ± 2.5	−1.2 ± 2.5	4.3 ± 2.7[4]
Apolipoprotein B (mg/dL)			
Baseline	102.3 ± 21.7	102.6 ± 18.4	100.0 ± 21.2
ΔDiet, stable weight	−4.9 ± 2.0	−9.5 ± 1.8	−15.8 ± 1.9[7]
ΔWeight, stable diet	−6.4 ± 1.8	−0.9 ± 2.4	2.3 ± 1.5[4]
Total:HDL cholesterol			
Baseline	5.03 ± 1.17	5.09 ± 1.25	4.93 ± 1.30
ΔDiet, stable weight	−0.05 ± 0.10	−0.31 ± 0.10	−0.62 ± 0.12[7]
ΔWeight, stable diet	−0.45 ± 0.08	−0.29 ± 0.11	−0.03 ± 0.09[4]

Ronald M Krauss, et al. Am J Clin Nutr 2006;83:1025–31

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Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia

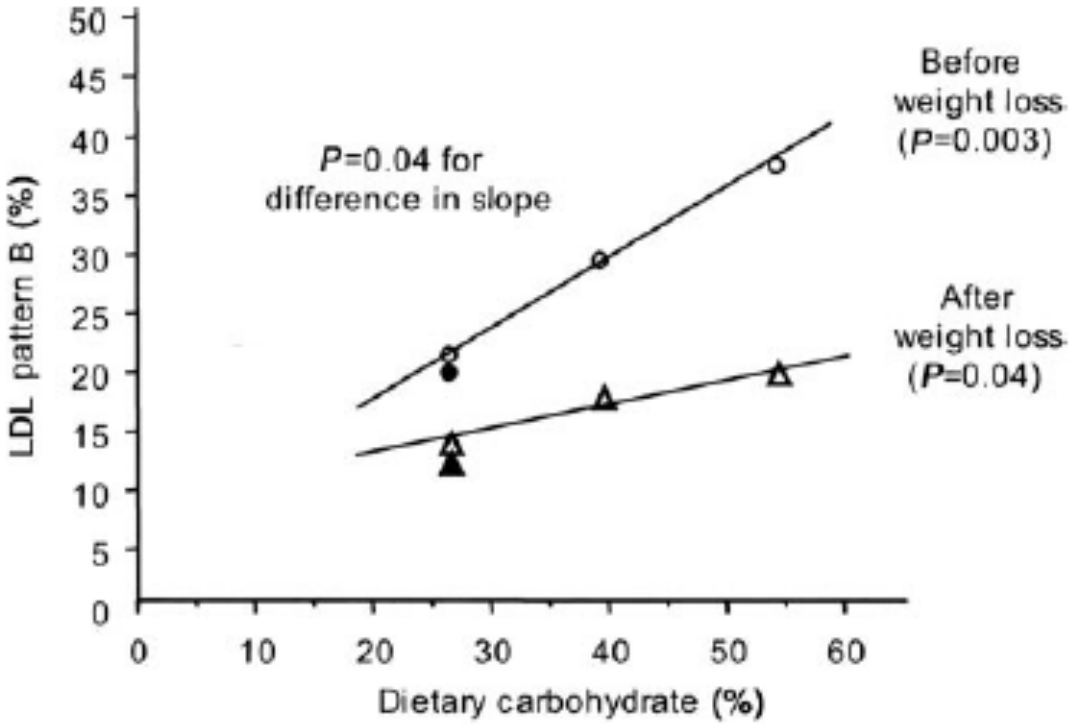


FIGURE 2. Prevalence of LDL subclass pattern B as a function of dietary carbohydrate content for each experimental diet before and after weight loss and stabilization with the diets. Open symbols represent the low-saturated fat diet group (*n49, 42, and 47 for the 54%-, 39%-, and 26%-carbohydrate* diets, respectively), and closed symbols represent the high-saturated-fat diet group (*n 40).*

Ronald M Krauss, et al. Am J Clin Nutr 2006;83:1025–31

National Heart Lung and Blood Institute

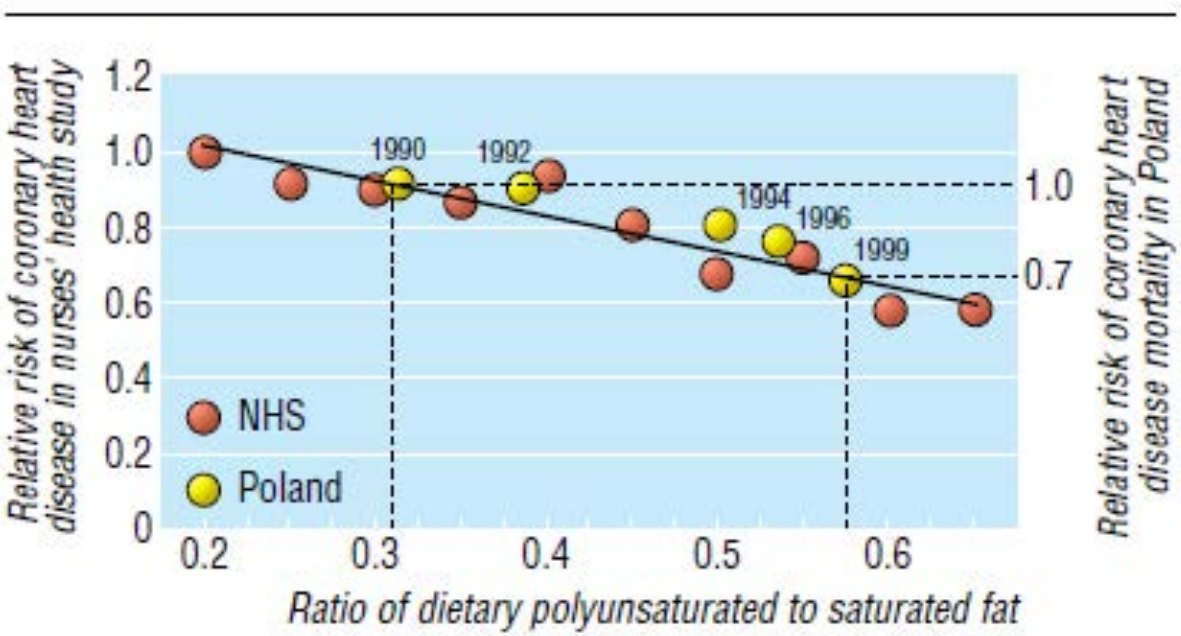
Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia

Conclusions: Moderate carbohydrate restriction and weight loss provide equivalent but nonadditive approaches to improving atherogenic dyslipidemia. Moreover, beneficial lipid changes resulting from a reduced carbohydrate intake were not significant after weight loss. *Am J Clin Nutr* 2006;83:1025–31.

Ronald M Krauss, et al. Am J Clin Nutr 2006;83:1025–31

National Heart Lung and Blood Institute

Changes in dietary fat and declining coronary heart disease in Poland: population based study



Ratio of dietary polyunsaturated to saturated fat and mortality due to coronary heart disease in Poland (relative to rates in 1990), superimposed on the relation between the fat ratio and coronary risk observed in the nurses' health study. Changes in dietary polyunsaturated to saturated fat in Poland between 1990 and 1999 are predicted to result in a 24% drop in coronary mortality, which is similar to the observed decline

Zatonski, Willett. BMJ, 2005

National Heart Lung and Blood Institute