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

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Program on Prevention and Population Sciences
Division of Cardiovascular Sciences
National Heart, Lung, and Blood Institute
National Institutes of Health
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

Turn the curve

- Epidemiology
- Efficacy trials
- Basic science
- Effectiveness Trials

Implementation research

Clinical & public health guidelines

National Heart Lung and Blood Institute
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
What’s Actually “Bad” and “Good” are Different Lipoprotein Particles

Courtesy James Otvos, Liposcience
Why LDL Particles are “Bad”

They Promote Atherogenesis

- Increased Plaque Burden;
  - Particle Uptake by Macrophage
- Particle Movement into Intima;
  - Gradient driven
- Particle Oxidation
- Extensively modified LDL
- Mildly modified LDL
- Particle Retention
  - Lipoprotein particle binding to proteoglycans

- Endothelial Dysfunction
  - Adhesion molecules
  - PAI-1
  - MCP-1
  - Colony-stimulating factors
  - Tissue factor

- Endothelial cells
- Monocyte
- Lipoprotein particle

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  - Adhesion molecules
  - PAI-1
  - MCP-1
  - Colony-stimulating factors
  - Tissue factor

- Endothelial cells
- Monocyte
- Lipoprotein particle

Why HDL Particles are “Good”
They inhibit atherogenesis

HDL inhibit adhesion molecule expression

Monocyte

Adhesion molecules

Cytokines

Macrophage

Modified LDL

MCP-1

LDL

Vessel lumen

HDL inhibit oxidation of LDL

HDL promote cholesterol efflux

Intima

Endothelium

Cytokines

Foam cell

HDL inhibit adhesion molecule expression

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

Density (g/ml) vs Diameter (nm) graph showing the distribution of lipoprotein particles:

- **Density (g/ml)** range from 0.95 to 1.06
- **Diameter (nm)** range from 5 to 1000

- **Chylomicrons**
- **VLDL**
- **IDL**
- **LDL**
- **HDL2**
- **HDL3**

Cholesterol and Triglycerides are indicated, with HDL Cholesterol and LDL Cholesterol highlighted.

Courtesy James Otvos, Liposcience

National Heart Lung and Blood Institute
### Alternative Lipoprotein Biomarkers Now Exist

#### Particle Number by NMR

**Courtesy James Otvos, Liposcience**

<table>
<thead>
<tr>
<th>Diameter (nm)</th>
<th>Density (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylo-</td>
<td></td>
</tr>
<tr>
<td>Chylomicrons</td>
<td></td>
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<tr>
<td>HDL-P</td>
<td>1.06</td>
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<tr>
<td>LDL-P</td>
<td>1.02</td>
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<tr>
<td>VLDL-P</td>
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<td>HDL-P</td>
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<tr>
<td>LDL-P</td>
<td>1.02</td>
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<tr>
<td>VLDL-P</td>
<td>0.95</td>
</tr>
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</table>

**Chylomicron Remnants**

Diameter (nm): 5, 10, 20, 40, 60, 80, 1000

Density (g/ml): 0.95, 1.02, 1.06, 1.20

**Graphic Description**

- **Chylo-microns**: Chylomicron Remnants
- **HDL-P**: High-Density Lipoprotein-P
- **LDL-P**: Low-Density Lipoprotein-P
- **VLDL-P**: Very Low-Density Lipoprotein-P
- **IDL**: Intermediate-Density Lipoprotein
### Table 1

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Univariate</th>
<th>Multivariate</th>
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**LDL number**

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<th>Author</th>
<th>Study design</th>
<th>Univariate</th>
<th>Multivariate</th>
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<td>Kuller</td>
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<tr>
<td>Otvos</td>
<td>P</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

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

---

Rizzo M, Berneis K, QJM 2006
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
Alternative Lipoprotein Biomarkers Now Exist: Apolipoproteins

Density (g/ml)

Diameter (nm)

Apo A-1

Apo B

HDL$_2$

HDL$_3$

LDL

IDL

VLDL

Chylomicrons

Chylomicron Remnants

Diameter (nm)

Courtesy James Otvos, Liposcience
Alternative Lipoprotein Biomarkers Now Exist: Non-HDL-Cholesterol

![Graph showing lipoprotein density and diameter](image)

Non-HDL-C  HDL-C

Courtesy James Otvos, Liposcience
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 8,857 nonfatal myocardial infarctions, 3,928 coronary heart disease [CHD] deaths, 2,534 ischemic strokes, 513 hemorrhagic strokes, and 2,536 unclassified strokes.
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

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

The Emerging Risk Factors Collaboration


Adjusted HR 0.99, 0.94-1.05
Adjusted HR 0.78, 0.74-0.82
Adjusted HR 1.50, 1.39-1.61
Non-HDL-C is associated with CHD risk in all age groups, men and women, and in diabetics

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

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

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.

- 28% Reduction
- 88% Reduction
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 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<sup>46L</sup> Allele.

- 15% Reduction
- 47% Reduction

NEJM, 2006
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
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

<table>
<thead>
<tr>
<th>Lower LDL-C</th>
<th>Meta-Analysis</th>
<th>Sample Size (N)</th>
<th>OR (95% CI)</th>
<th>p (difference)</th>
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</thead>
<tbody>
<tr>
<td>1.0 mmol/L</td>
<td>Genetic Studies</td>
<td>312,321</td>
<td>0.46 (0.41-0.51)</td>
<td>8.4x10^{-19}</td>
</tr>
<tr>
<td>(38.7 mg/dl)</td>
<td>Statin Trials</td>
<td>169,138</td>
<td>0.76 (0.74-0.78)</td>
<td></td>
</tr>
</tbody>
</table>

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:
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
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
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

<table>
<thead>
<tr>
<th>Groups</th>
<th>Events (%)</th>
<th>RR (CI)</th>
<th>Heterogeneity/ trend test</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (45 002)</td>
<td>Control (45 054)</td>
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<tr>
<td>Previous disease:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Post-MI</td>
<td>1681 (11.7%)</td>
<td>2207 (15.4%)</td>
<td>0.78 (0.74–0.84)</td>
</tr>
<tr>
<td>Other CHD</td>
<td>568 (8.7%)</td>
<td>744 (11.4%)</td>
<td>0.77 (0.68–0.87)</td>
</tr>
<tr>
<td>None</td>
<td>1088 (4.5%)</td>
<td>1469 (6.1%)</td>
<td>0.72 (0.66–0.80)</td>
</tr>
<tr>
<td>Age (years):</td>
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<td></td>
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<tr>
<td>( \leq 65 )</td>
<td>1671 (6.1%)</td>
<td>2344 (8.5%)</td>
<td>0.74 (0.69–0.79)</td>
</tr>
<tr>
<td>( &gt; 65 )</td>
<td>1666 (9.5%)</td>
<td>2076 (11.9%)</td>
<td>0.81 (0.76–0.88)</td>
</tr>
<tr>
<td>Sex:</td>
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<tr>
<td>Male</td>
<td>2686 (7.8%)</td>
<td>3630 (10.6%)</td>
<td>0.76 (0.72–0.80)</td>
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<tr>
<td>Female</td>
<td>651 (6.1%)</td>
<td>790 (7.3%)</td>
<td>0.82 (0.73–0.93)</td>
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<td>Treated hypertension:</td>
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<td>Yes</td>
<td>2038 (8.2%)</td>
<td>2596 (10.4%)</td>
<td>0.79 (0.74–0.84)</td>
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<tr>
<td>No</td>
<td>1299 (6.4%)</td>
<td>1824 (9.1%)</td>
<td>0.75 (0.70–0.81)</td>
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<tr>
<td>History of diabetes:</td>
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<td>Yes</td>
<td>776 (8.3%)</td>
<td>979 (10.5%)</td>
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<td>No</td>
<td>2561 (7.2%)</td>
<td>3441 (9.6%)</td>
<td>0.77 (0.73–0.81)</td>
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</table>

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

National Heart Lung and Blood Institute
Reducing LDL-C is effective in persons at low baseline risk

Meta-analysis of 134,537 individuals in 27 trials

<table>
<thead>
<tr>
<th>5-year MVE risk at baseline</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1.0 mmol/L reduction in LDL cholesterol</th>
<th>Trend test</th>
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<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
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<tr>
<td>Major coronary event</td>
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<tr>
<td>&lt;5%</td>
<td>50 (0.11)</td>
<td>88 (0.19)</td>
<td>0.57 (0.36-0.89)</td>
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<td>≥5% to &lt;10%</td>
<td>276 (0.50)</td>
<td>435 (0.79)</td>
<td>0.61 (0.50-0.74)</td>
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<td>≥10% to &lt;20%</td>
<td>1644 (1.29)</td>
<td>1973 (1.57)</td>
<td>0.77 (0.69-0.85)</td>
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<td>≥20% to &lt;30%</td>
<td>1789 (1.93)</td>
<td>2282 (2.49)</td>
<td>0.77 (0.71-0.83)</td>
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<td>≥30%</td>
<td>1471 (3.73)</td>
<td>1887 (4.86)</td>
<td>0.78 (0.72-0.84)</td>
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<tr>
<td>Overall</td>
<td>5230 (1.45)</td>
<td>6665 (1.87)</td>
<td>0.76 (0.73-0.79)</td>
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Cholesterol Treatment Trialists’ (CTT) Collaborators

Lancet 2012; 380: 581-90
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
“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.”
Thirty-five-year trends in cardiovascular risk factors in Finland

North Karelia Men

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<th></th>
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<td>34</td>
<td>-13</td>
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<tr>
<td>SFA, % en</td>
<td>22</td>
<td>13</td>
<td>-41</td>
</tr>
<tr>
<td>PUFA, % en</td>
<td>3.5</td>
<td>5.9</td>
<td>+68</td>
</tr>
<tr>
<td>Diet cholesterol</td>
<td>617</td>
<td>309</td>
<td>-50</td>
</tr>
<tr>
<td>Blood cholesterol</td>
<td>6.92</td>
<td>5.45</td>
<td>-21</td>
</tr>
<tr>
<td>BMI</td>
<td>26.0</td>
<td>27.4</td>
<td>+5*</td>
</tr>
<tr>
<td>SBP</td>
<td>149</td>
<td>139</td>
<td>-7</td>
</tr>
<tr>
<td>DBP</td>
<td>92</td>
<td>83</td>
<td>-10</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>52</td>
<td>31</td>
<td>-40</td>
</tr>
</tbody>
</table>

*No BMI increase in women

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

Source: National Center for Health Statistics.

Source: NCHS and NHLBI. NH indicates non-Hispanic.
Fig. 2. Quadratic regression lines, weighted by the number of subjects in each study for the UK (--; $P < 0.001$, $n = 97$) and the USA (--; $P < 0.001$, $n = 171$). The beginning of the decline in fat intake was approximately 1965 for the USA and 1975 for the UK.
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.
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

Controlled Feeding Studies In Humans

Early Cohort Studies

Ecologic Studies

Animal Experiments
Saturated Fat and CHD - Ecological Evidence

Based on data in 1987-1990
Diet-Heart Hypothesis--Now

Total Fat
Saturated Fat
Unsaturated Fat
Trans Fat

→ Serum Total and LDL Cholesterol

→ Coronary Heart Disease

Meta-Analyses of Controlled Feeding Studies In Humans

Meta-Analyses of Cohort Studies of Food Intake
Clinical Trials of Diet
Population Intervention Studies and Secular Trends

Meta-Analyses of Cohort Studies
Genetic Studies
Meta-Analyses of Clinical Trials
Short term feeding studies: LDL-Cholesterol

Change in LDL-C (mmol/L) vs. percentage of calories vs. carbohydrate

- SFA: $\beta = 0.032^*$
- MUFA: $\beta = -0.009^*$
- PUFA: $\beta = -0.019^*$

Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010
Short term feeding studies: Triglycerides

Change in Triglycerides (mmol/L)

0 1% 2% 3% 4% 5%

Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010
Short term feeding studies: HDL-Cholesterol

Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010.
Short term feeding studies: Total:HDL Ratio

Based on Mensink & Katan 2003. Figure from Micha & Mozaffarian, Lipids 2010.
Short-term Feeding Studies: Lipid Effects of Individual SFAs

Figure from Micha & Mozaffarian, Lipids 2010. Based on Mensink & Katan 2003.
FIGURE 1. Predicted changes ($\Delta$) 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
Saturated Fat and CHD - Prospective Cohorts

Siri-Tarino et al, AJCN 2010

### Coronary Heart Disease

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shekelle et al (17)</td>
<td>1.11 [0.91, 1.36]</td>
<td>1981</td>
</tr>
<tr>
<td>McGee et al (9)</td>
<td>0.86 [0.67, 1.12]</td>
<td>1984</td>
</tr>
<tr>
<td>Kushi et al (13)</td>
<td>1.33 [0.95, 1.87]</td>
<td>1985</td>
</tr>
<tr>
<td>Posner et al (16)</td>
<td>0.92 [0.68, 1.24]</td>
<td>1991</td>
</tr>
<tr>
<td>Goldbourt et al (35)</td>
<td>0.86 [0.56, 1.35]</td>
<td>1993</td>
</tr>
<tr>
<td>Fehily et al (28)</td>
<td>1.57 [0.56, 4.42]</td>
<td>1994</td>
</tr>
<tr>
<td>Ascherio et al (4)</td>
<td>1.11 [0.87, 1.42]</td>
<td>1996</td>
</tr>
<tr>
<td>Esrey et al (6)</td>
<td>0.97 [0.80, 1.18]</td>
<td>1996</td>
</tr>
<tr>
<td>Pietinen et al (15)</td>
<td>0.93 [0.60, 1.44]</td>
<td>1997</td>
</tr>
<tr>
<td>Boniface et al (5)</td>
<td>1.37 [1.17, 1.60]</td>
<td>2002</td>
</tr>
<tr>
<td>Jakobsen et al (8)</td>
<td>1.03 [0.66, 1.60]</td>
<td>2004</td>
</tr>
<tr>
<td>Oh et al (33)</td>
<td>0.97 [0.74, 1.27]</td>
<td>2005</td>
</tr>
<tr>
<td>Tucker et al (18)</td>
<td>1.22 [0.31, 4.77]</td>
<td>2005</td>
</tr>
<tr>
<td>Xu et al (10)</td>
<td>1.91 [0.31, 11.84]</td>
<td>2006</td>
</tr>
<tr>
<td>Leosdottir et al (14)</td>
<td>0.95 [0.74, 1.21]</td>
<td>2007</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1.07 [0.96, 1.19]</td>
<td></td>
</tr>
</tbody>
</table>

No Significant Association

Heterogeneity: $\tau^2 = 0.02$, $Chi^2 = 25.34$, df = 13 (P = 0.04), I² = 41%

Test for overall effect: $Z = 1.22$ (P = 0.22)
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).
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
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
SFA and Heart Disease: The Replacement Matters

### Dietary Change (each 5% energy)

**Polyunsaturated Fat Replacing Saturated Fat**
- Predicted Effect from TC:HDL-C Change: 0.91 (0.87, 0.95)
- Meta-Analysis of 8 RCTs: 0.90 (0.83, 0.97)
- Pooled Analysis of 11 Observational Cohorts: 0.87 (0.77, 0.97)

**Carbohydrate Replacing Saturated Fat**
- Predicted Effect from TC:HDL-C Change: 1.01 (0.98, 1.04)
- Women’s Health Initiative RCT*: 0.98 (0.88, 1.09)
- Pooled Analysis of 11 Observational Cohorts: 1.07 (1.01, 1.14)

### Relative Risk of CHD for Each 5% Energy Intake

*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)
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

Other lifestyle factors
Physical Activity
Alcohol
Smoking
Sleep
Watching TV

Mozafarian et al
NEJM, 2011
Whole grains are associated with cardioprotection, meat (and fats) are not.

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

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

Data derived from Health, United States, 2010: With Special Feature on Death and Dying. NCHS, 2011.
# Secular Trends in Human Populations

<table>
<thead>
<tr>
<th>Country</th>
<th>Dietary Fat/SAFA</th>
<th>Serum Cholesterol</th>
<th>CHD Rate</th>
<th>Obesity Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Women no change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Men small increase</td>
</tr>
<tr>
<td>USA</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>UK</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Poland</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Women increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Men no change</td>
</tr>
<tr>
<td>Sweden- before 2004</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Sweden- after 2004</td>
<td><strong>Increased</strong></td>
<td><strong>Increased</strong></td>
<td>?</td>
<td><strong>Increased</strong></td>
</tr>
</tbody>
</table>
• 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%

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

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

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

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

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

*Incidence rate ratio comparing highest to lowest quintile = 1.60

### 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

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

*Lagiou et al. BMJ, 2012*
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

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.*

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

<table>
<thead>
<tr>
<th></th>
<th>Low Fat, Average Protein</th>
<th>High Fat, High Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-Mo</td>
<td>2-Yr</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-5.9</td>
<td>-3.7</td>
</tr>
<tr>
<td>LDL</td>
<td>-6.6</td>
<td>-5.9</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>-14.2</td>
<td>-11.5</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>-3.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>-16.2</td>
<td>-2.4</td>
</tr>
<tr>
<td>HOMA</td>
<td>-18.7</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

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

Percent energy from fat and carbohydrate

Prentice RL et al. JAMA, 2006
WHI Change in Body Weight by Randomization Group

Howard BV et al. JAMA, 2006
WHI Change in Body Weight in Obese Women

Howard BV et al. JAMA, 2006
### WHI DM Trial: Changes in Risk Factors

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

* Significantly different

Howard BJ et al. JAMA, 2006
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
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
Gastric bypass produces durable remission of diabetes and dyslipidemia

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?

Obesity → Insulin Resistance

? → T2 Diabetes
Prevalence of metabolic syndrome in US adults age 30-74 (NHANES)

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

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

*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/m².
#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).
The Good

Seafood Omega-3 PUFA

Plant Omega-3 PUFA

Plant Omega-6 PUFA

Monounsaturated Fat

Saturated Fat

Refined Carbohydrates & Starches

Industrial Trans Fat

The Bad

The Ugly

Courtesy Dariush Mozaffarian
### 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
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”

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

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

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

HDL cholesterol

Change in HDL-C (mmol/L)

percentage of calories vs. carbohydrate

12:0 (lauric)
14:0 (myristic)
16:0 (palmitic)
18:0 (stearic)

β=0.027*
β=0.018
β=0.01
β=0.002

Figure from Micha & Mozaffarian, Lipids 2010. Based on Mensink & Katan 2003.
Short-term Feeding Studies: Lipid Effects of Individual SFAs

![Graph showing lipid effects of individual SFAs](image)

- **12:0** (lauric) with a change in total:HDL cholesterol ratio of $-0.037^*$
- **14:0** (myristic) with a change in total:HDL cholesterol ratio of $-0.013$
- **16:0** (palmitic) with a change in total:HDL cholesterol ratio of $0.005$
- **18:0** (stearic) with a change in total:HDL cholesterol ratio of $-0.003$

**Percentage of calories vs. carbohydrate**

Figure from Micha & Mozaffarian, Lipids 2010. Based on Mensink & Katan 2003.
Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden.

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

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

<table>
<thead>
<tr>
<th></th>
<th>54% CHO</th>
<th>39% CHO</th>
<th>26% CHO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL cholesterol (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>130.1 ± 30.2</td>
<td>125.5 ± 23.1</td>
<td>129.1 ± 25.7</td>
</tr>
<tr>
<td>ΔDiet, stable weight</td>
<td>-2.6 ± 3.1</td>
<td>-0.6 ± 3.3</td>
<td>-11.2 ± 2.7</td>
</tr>
<tr>
<td>ΔWeight, stable diet</td>
<td>-8.9 ± 2.5</td>
<td>-1.2 ± 2.5</td>
<td>4.3 ± 2.7⁴</td>
</tr>
<tr>
<td><strong>Apolipoprotein B (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>102.3 ± 21.7</td>
<td>102.6 ± 18.4</td>
<td>100.0 ± 21.2</td>
</tr>
<tr>
<td>ΔDiet, stable weight</td>
<td>-4.9 ± 2.0</td>
<td>-9.5 ± 1.8</td>
<td>-15.8 ± 1.9⁷</td>
</tr>
<tr>
<td>ΔWeight, stable diet</td>
<td>-6.4 ± 1.8</td>
<td>-0.9 ± 2.4</td>
<td>2.3 ± 1.5⁴</td>
</tr>
<tr>
<td><strong>Total: HDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.03 ± 1.17</td>
<td>5.09 ± 1.25</td>
<td>4.93 ± 1.30</td>
</tr>
<tr>
<td>ΔDiet, stable weight</td>
<td>-0.05 ± 0.10</td>
<td>-0.31 ± 0.10</td>
<td>-0.62 ± 0.12⁷</td>
</tr>
<tr>
<td>ΔWeight, stable diet</td>
<td>-0.45 ± 0.08</td>
<td>-0.29 ± 0.11</td>
<td>-0.03 ± 0.09⁴</td>
</tr>
</tbody>
</table>
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).
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.  

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