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Effect of diet on dyslipidemia and CVD

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Disclosures

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  AstraZeneca, Sanofi, Pfizer

- Advisory Boards: Sanofi, Aegerion, AstraZeneca

- Research Funding: Sanofi
Relationship Between Diet and CV Disease

Diet → Intermediary Biological Mechanisms* → Risk of Coronary Heart Disease

*Includes lipid levels [LDL-C, HDL-C, triglycerides, Lp(a), blood pressure, thrombotic tendency, cardiac rhythm, endothelial function, systemic inflammation, insulin sensitivity, oxidative stress, homocysteine level

Source: Hu FB et al. JAMA. 2002;288:2569-2578
Dietary fatty acids

Saturated fatty acids (no double bond)

\[
\text{CH}_3 - \text{COOH}
\]

Mono-unsaturated fatty acids (one double bond)

\[
\text{CH}_3 - \underbrace{\text{C}}_{\text{double bond}} - \text{COOH}
\]

Polyunsaturated fatty acids (two or more double bonds)

\[
\text{CH}_3 - \underbrace{\text{C}}_{\text{double bond}} - \underbrace{\text{C}}_{\text{double bond}} - \text{COOH}
\]
# Structures of Fatty Acids

<table>
<thead>
<tr>
<th>ω-characteristics</th>
<th>Methyl end</th>
<th>Carboxyl end</th>
<th>Saturation</th>
<th>Δ-characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stearic 18:0</td>
<td></td>
<td>COOH</td>
<td>Saturate</td>
<td>18:0</td>
</tr>
<tr>
<td>Oleic 18:1, ω-9</td>
<td></td>
<td>COOH</td>
<td>Monoene</td>
<td>18:1 Δ9</td>
</tr>
<tr>
<td>Linoleic 18:2, ω-6</td>
<td></td>
<td>COOH</td>
<td>Polyene</td>
<td>18:2 Δ9,12</td>
</tr>
<tr>
<td>α-Linolenic 18:3, ω-3</td>
<td></td>
<td>COOH</td>
<td>Polyene</td>
<td>18:3 Δ9,12,15</td>
</tr>
<tr>
<td>EPA 20:5, ω-3</td>
<td></td>
<td>COOH</td>
<td>Polyene</td>
<td>20:5 Δ5,8,11,14,17</td>
</tr>
<tr>
<td>DHA 22:6, ω-3</td>
<td></td>
<td>COOH</td>
<td>Polyene</td>
<td>20:6 Δ4,7,10,13,16,19</td>
</tr>
</tbody>
</table>
Quality of Fats in Modern Nutrition

- Saturated fats (C12:0, C14:0, C16:0, C18:0)
- Trans fatty acids (hydrogenated fats)
- Monounsaturated fatty acids (18:1)
- Sats/MUFA/PUFA
- Cholesterol

- Essential fatty acids w-3 and w-6
- Long Chain PUFAs (AA, EPA, DHA)

- Energy Density of diet (fats and carbohydrates)
Diet and Fats Influence Risk of Coronary Heart Disease

- Effects on Lipoprotein and Cholesterol metabolism receptor systems, gene expression and regulation (LDL, HDL, Lp(a), TG) : **TRANS FATS, SATS, PUFAs n-3 and n-6**, 
- Prostanoids: (Eicosanoids and Docosanoids) related functions Inflammation/cytokines depend on: **PUFAs n-3 & n-6**, 
- Blood pressure. SODIUM POTASSIUM & **PUFAs n-3 & n-6**, 
- Thrombosis and thrombolytic mechanisms **PUFAs n-3 & n-6** 
- Oxidative stress and re-perfusion injury **PUFAs n-3 & n-6** 
- Endothelial function & adhesion molecules **PUFAs n-3 & n-6** 
- Cardiac Rhythm (arrhythmias) **PUFAs n-3** 
- Insulin Sensitivity **PUFAs n-3 & n-6; Trans**
Effects of dietary fat and carbohydrates on LDL-C
A systematic review and meta-regression analysis evaluated 84 randomized controlled trials including 2353 participants

Results demonstrate for each 1% of dietary energy as SFA replaced with an equivalent amount of cis–PUFA or CHO

Effects of dietary fat and carbohydrates on TG
A systematic review and meta-regression analysis evaluated 84 randomized controlled trials including 2353 participants

Effects of dietary fat and carbohydrates on HDL-C
A systematic review and meta-regression analysis evaluated 84 randomized controlled trials including 2353 participants.

<table>
<thead>
<tr>
<th>Lipid or lipoprotein</th>
<th>Unit</th>
<th>Change per 1% of energy replaced</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Carb → SFA</td>
<td>Carb → MUFA</td>
</tr>
<tr>
<td>ΔTotal cholesterol</td>
<td>mmol/L</td>
<td>0.045</td>
<td>-0.004</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.038 to 0.051</td>
<td>-0.010 to 0.001</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>0.097</td>
</tr>
<tr>
<td>ΔLDL cholesterol</td>
<td>mmol/L</td>
<td>0.036</td>
<td>-0.009</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.4 mg/dl</td>
<td>0.030 to 0.043</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔHDL cholesterol</td>
<td>mmol/L</td>
<td>0.011</td>
<td>0.008</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.010 to 0.013</td>
<td>0.007 to 0.010</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔTriglyceride</td>
<td>mmol/L</td>
<td>-0.012</td>
<td>-0.015</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>-0.015 to -0.008</td>
<td>-0.018 to -0.011</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔTotal to HDL cholesterol</td>
<td></td>
<td>-0.002</td>
<td>-0.029</td>
</tr>
</tbody>
</table>

Trans Fat

In controlled feeding trials among adults, for every 1% of energy from \textit{trans} monounsaturated fatty acids replaced with 1% of energy from:

- MUFA or PUFA, LDL–C is lowered by 1.5 mg/dL and 2.0 mg/dL, respectively.
- SFA, MUFA, or PUFA, HDL–C is increased by an estimated 0.5, 0.4 and 0.5 mg/dL, respectively. MUFA or PUFA, TG is decreased by an estimated 1.2 and 1.3 mg/dL.

The effect of diet on LDL particle size

- The relationship between LDL particle size and CVD is controversial.
- Many studies are very short, typically 3-4 weeks.
- Replacing carbohydrates with fat seems to increase LDL particle size.
- There is conflicting and limited evidence on the effects of fatty acid classes (MUFA/PUFA vs SFA) on LDL particle size and LDL-P.
- Trans fat seems to decrease LDL particle size.
- Mediterranean diet improved LDL particle size in Predimed study when enriched with nuts (high in MUFA and PUFA).
- Hard end point RCTs are needed to evaluate if changes LDL-particle size translate into real clinical benefits.
Epidemiologic Studies*

• Populations on diets high in total fat, saturated and trans fats, cholesterol, and sugar have high age-adjusted CHD death rates as well as more obesity, hyperlipidemia, and diabetes

• The converse is also true

*Results from Seven Countries, 18 countries, 20 countries, 40 countries, and Ni-Hon-San Studies
Type of Fat Consumed on Bread in North Karelia, 1972–2000 (25–59-year-old)
Population dietary changes explain much of the reduction in heart disease mortality in Finland.

Vartiainen, Puska et al BMJ 1995
22,043 adults in Greece evaluated for adherence to a Mediterranean diet, with points given for high consumption of vegetables, legumes, fruits, nuts, cereal, and fish and points subtracted for high consumption of meat, poultry, and dairy.

<table>
<thead>
<tr>
<th>Variable</th>
<th># of Deaths/ # of Participants</th>
<th>Fully Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>275/22,043</td>
<td>0.75 (0.64-0.87)</td>
</tr>
<tr>
<td>Death from CHD</td>
<td>54/22,043</td>
<td>0.67 (0.47-0.94)</td>
</tr>
<tr>
<td>Death from cancer</td>
<td>97/22,043</td>
<td>0.76 (0.59-0.98)</td>
</tr>
</tbody>
</table>

High adherence to a Mediterranean diet is associated with a reduction in death.

CHD=Coronary heart disease

Source: Trichopoulou A et al. NEJM 2003;348:2599-2608
The PREDIMED trial (Prevencion con Dieta Mediterranea)

A multicenter trial in Spain

7447 participants at high CVD risk but no prior CVD events

three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet

Lyon Diet Heart Study

605 patients following a myocardial infarction randomized to a Mediterranean* or Western** diet for 4 years

A Mediterranean diet reduces cardiovascular events

*High in polyunsaturated fat and fiber,
**High in saturated fat and low in fiber

65% lower CHD death rate in the treatment group

Oslo Diet Heart Study

- 412 men with CHD, 5 year study
- Treatment group randomized to low saturated fat (8.4% of calories), low cholesterol (264 mg/day), high polyunsaturated fat (15.5%) diet
- Serum cholesterol reduced 14%
- 33% reduction in MI, 26% decrease in CHD mortality

Los Angeles VA study

- 846 men in Veterans Home, 5-8 years
- Groups randomized to diets in which 2/3 of fat given either as vegetable oil (corn, cottonseed, safflower, soybean) or animal fat
- Saturated fat 11% vs. 18%, polyunsaturated fat 16% vs. 5% of calories
- 31% decrease in CVD endpoints

## Adult Treatment Panel (ATP) III Dietary Recommendations

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat*</td>
<td>&lt;7% of total calories</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Up to 10% of total calories</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Up to 20% of total calories</td>
</tr>
<tr>
<td>Total fat</td>
<td>25%–35% of total calories</td>
</tr>
<tr>
<td>Carbohydrate (esp. complex carbs)</td>
<td>50%–60% of total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>20–30 g/d</td>
</tr>
<tr>
<td>Protein</td>
<td>~15% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/d</td>
</tr>
</tbody>
</table>

*Trans fatty acids also raise LDL-C and should be kept at a low intake

Note: Regarding total calories, balance energy intake and expenditure to maintain desirable body weight

LDL-C=Low density lipoprotein cholesterol

Recommendations for Cardiovascular Disease Risk Reduction

- Balance calorie intake and physical activity to achieve or maintain a healthy body weight
- Consume a diet rich in fruits and vegetables
- Consume whole-grain, high-fiber foods
- Consume fish, especially oily fish, at least twice a week
- Limit intake of saturated fat to <7%, trans fat to <1% of energy, and cholesterol <300 mg/day by:
  - Choosing lean mean and vegetable alternatives
  - Choosing fat free (skim), 1% fat, and low-fat dairy products,
  - Minimizing intake of partially hydrogenated fats
- Minimize intake of beverages and foods with added sugar
- Choose and prepare foods with little or no salt
- If alcohol is consumed, do so in moderation
Total Fat and CHD - Cohort Evidence

Quintiles of Total Fat Consumption

Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease

21 studies
5–23 y of follow-up of 347,747 subjects
11,006 developed CHD or stroke

Meta-analysis of core trials on replacing saturated with polyunsaturated fat

<table>
<thead>
<tr>
<th>Sub-Groups</th>
<th>Cases (n)</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dayton</td>
<td>117</td>
<td>0.80 (0.57, 1.12)</td>
<td>15.93</td>
</tr>
<tr>
<td>Oslo</td>
<td>154</td>
<td>0.71 (0.55, 0.92)</td>
<td>27.95</td>
</tr>
<tr>
<td>MRC</td>
<td>136</td>
<td>0.82 (0.62, 1.07)</td>
<td>24.46</td>
</tr>
<tr>
<td>Finnish</td>
<td>312</td>
<td>0.59 (0.46, 0.75)</td>
<td>31.66</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.71 (0.62, 0.81)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

$\text{I}^2=20.3\%, P=0.29$

Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies

Marianne U Jakobsen, Eilis J O’Reilly, Berit L Heitmann, Mark A Pereira, Katarina Bälter, Gary E Fraser, Uri Goldbourt, Göran Hallmans, Paul Knekta, Simin Liu, Pirjo Pietinen, Donna Spiegelman, June Stevens, Jarmo Virtamo, Walter C Willett, and Alberto Ascherio

Design: a follow-up study of 11 pooled American and European cohort studies including 344,696 persons; outcome CHD over a 4–10 yr FU, 5249 coronary events and 2155 coronary deaths occurred.

Results: For a 5% lower energy intake from SFAs and a concomitant higher energy intake from PUFAs risk of coronary events HR: 0.87 (95% CI: 0.77-0.97); HR for coronary deaths 0.74 (0.61-0.89).

For a 5% lower energy intake from SFAs and a concomitant higher energy intake from CHO there was a significant association with coronary events (HR 1.07; (CI: 1.01-1.14); for coronary deaths 0.96 (0.82-1.13).

MUFA intake was not associated with CHD.

Coronary events

Coronary deaths

CHs for SFAs (per 5 E% increments)

Hazard ratio

Combined

1.07 (1.01-1.14)

0.96 (0.82-1.13)

Jakobsen et al Am J Clin Nutr 89:1–8, 2009
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
Meta-analysis of substituting each 5% energy from linoleic acid for 5% energy from carbohydrates relative risk of total coronary heart disease events

Circulation. 2014;130:1568-1578
Meta-analysis of substituting each 5% energy from linoleic acid for 5% energy from carbohydrates and relative risk of coronary heart disease deaths

![Graph showing the results of the meta-analysis.](image)

Circulation. 2014;130:1568-1578
Aim: to investigate the risk of myocardial infarction (MI) associated with a higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs. Carbohydrates with different glycemic index (GI) values were also investigated.

Design: Our prospective cohort study included 53,644 women and men free of MI at baseline with median of 12 years follow up.

Conclusion: This study suggests that replacing SFAs with carbohydrates with low-GI values is associated with a lower risk of MI, whereas replacing SFAs with carbohydrates with high-GI values is associated with a higher risk of MI.

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

Jakobsen et al, AJCN 2010
Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease
Nurses’ Health Study 84,628 women (1980-2010)
Health Professionals Follow-Up Study 42,908 men (1986-2010)
Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease

Nurses’ Health Study 84,628 women (1980-2010)
Health Professionals Follow-Up Study 42,908 men (1986-2010)
Total mortality
- MUFAs, 5% of energy
- PUFAs, 5% of energy
- trans fat, 2% of energy

Cardiovascular disease mortality
- MUFAs, 5% of energy
- PUFAs, 5% of energy
- trans fat, 2% of energy

Cancer mortality
- MUFAs, 5% of energy
- PUFAs, 5% of energy
- trans fat, 2% of energy

Neurodegenerative disease mortality
- MUFAs, 5% of energy
- PUFAs, 5% of energy
- trans fat, 2% of energy

Respiratory disease mortality
- MUFAs, 5% of energy
- PUFAs, 5% of energy
- trans fat, 2% of energy
Benefits of fish oil supplementation

• In the Diet and Reinfarction Trial (DART) in 2033 men with CHD increased intake of fish or use of 2 fish oil caps/day reduced CHD mortality 29% over 2 years

• In GISSI 11324 men and woman with CHD use of 1 gr. of n-3 PUFA decreased CVD events including mortality 15%

Nuts, Soy, Phytosterols, Garlic

• Nurses’ Health Study: five 1oz servings of nuts per week associated with 40% lower risk of CHD events

• Metaanalysis of 38 trials of soy protein showed 47g intake lowered total, LDL-C, and trigs 9%, 13%, and 11%

• Phytosterol-supplemented foods (e.g., stanol ester margarine) lowers LDL-C avg. 10%

• Meta-analysis of garlic studies showed 9% total cholesterol reduction (1/2-1 clove daily for 6 months).
Adverse effects of trans FAs on blood cholesterol

Change in (mmol/L) vs. % of energy as trans fatty acids (C18:1 trans)

Zock et al  Am J Clin Nutr, 1995
Reduction in the Consumption of Trans Fatty Acids and the Risk of CHD in The Netherlands-Zutphen

↓ TFA 2.4%

↓ CHD 23%

Nurses’ Health Study: changes in risk of coronary heart disease associated with iso-energetic diet substititions

Source: Hu et al, JAMA, 2002

- Sat--->Carbo (5% Energy)
- Mono--->Carbo (5% Energy)
- Poly--->Carbo (5% Energy)
- Sat--->Mono (5% Energy)
- Sat--->Poly (5% Energy)
- Sat--->Unsat (5% Energy)
- Trans--->Mono (2% Energy)
- Trans--->Poly (2% Energy)
- Trans--->Unsat (2% Energy)
Dietary fat and cardiovascular risk in children

• Evidence for dietary fat and cardiovascular risk in children is limited.

• The Bogalusa Heart Study found that in children intake of animal fat, the major source of dietary saturated fat, was associated with higher body weight.

• The Cardiovascular Risk in Young Finns study (Young Finns) was a multicenter longitudinal cohort study of 3956 individuals 3 to 18 years of age in 1980 who had ongoing follow-up assessment of diet and blood lipids over 21 years. At the end of follow up those who were on traditional dietary pattern had a higher LDL-C and increased CIMT compared to those on health-conscious pattern diet.

• The STRIP trial is a randomized study with >20 years of follow-up compared the effects of reduction in saturated fat starting in infancy compared with usual dietary intake and lifestyle among normal children from infancy through adolescence. LDL-C cholesterol levels were lower in the intervention compared with the control group.
Key Recommendations:

Consume a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level.

A healthy eating pattern includes:

- A variety of vegetables from all of the subgroups—dark green, red and orange, legumes (beans and peas), starchy, and other
- Fruits, especially whole fruits
- Grains, at least half of which are whole grains
- Fat-free or low-fat dairy, including milk, yogurt, cheese, and/or fortified soy beverages
- A variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products
- Oils

A healthy eating pattern limits:

- Saturated fats and trans fats, added sugars, and sodium

Key Recommendations that are quantitative are provided for several components of the diet that should be limited. These components are of particular public health concern in the United States, and the specified limits can help individuals achieve healthy eating patterns within calorie limits:

- Consume less than 10 percent of calories per day from added sugars
- Consume less than 10 percent of calories per day from saturated fats
- Consume less than 2,300 milligrams (mg) per day of sodium
- If alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and up to two drinks per day for men—and only by adults of legal drinking age

In tandem with the recommendations above, Americans of all ages—children, adolescents, adults, and older adults—should meet the Physical Activity Guidelines for Americans to help promote health and reduce the risk of chronic disease. Americans should aim to achieve and maintain a healthy body weight. The relationship between diet and physical activity contributes to calorie balance and managing body weight. As such, the Dietary Guidelines includes a Key Recommendation to:

- Meet the Physical Activity Guidelines for Americans
### 2013 AHA/American College of Cardiology lifestyle guidelines

**LDL-C - Advise adults who would benefit from LDL-C lowering**

| 1. Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red meats. |
|---|---|---|
| a. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus). |
| b. Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet. |
| **A (Strong)** CQ1: ES4 (high), ES6 (low), ES8 (moderate), ES9 (moderate) |
| **I** | **A** |

| 2. Aim for a dietary pattern that achieves 5% to 6% of calories from saturated fat. |
|---|---|---|
| **A (Strong)** CQ1: ES11 (high) |
| **I** | **A** |

| 3. Reduce percent of calories from saturated fat. |
|---|---|---|
| **A (Strong)** CQ1: ES11 (high), ES12 (moderate), ES13 (moderate) |
| **I** | **A** |

| 4. Reduce percent of calories from trans-fat. |
|---|---|---|
| **A (Strong)** CQ1: ES14 (moderate), ES15 (moderate) |
| **I** | **A** |
There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL–C

Conclusion

- Saturated fat increases LDL-C, a major cause of atherosclerosis and CVD, and replacing it with polyunsaturated or monounsaturated fat decreases LDL-C.

- Randomized clinical trials showed that polyunsaturated fat from vegetable oils replacing saturated fats from dairy and meat lowers CVD.

- Prospective observational studies in many populations showed that lower intake of saturated fat coupled with higher intake of polyunsaturated and monounsaturated fat is associated with lower rates of CVD and all-cause mortality.

- A dietary strategy of reducing intake of total dietary fat, including saturated fat, and replacing the fats mainly with unspecified carbohydrates does not prevent CHD.

- The robust association of higher trans fatty acid intake with elevated CHD risk in observational studies provides the impetus for current policy actions of many local and national jurisdictions to reduce industrial trans fatty acids in the food supply.