Dietary Cholesterol Restriction is Still Important

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Outline

• Dietary cholesterol recommendations

• Evidence to support dietary cholesterol restriction
  • Clinical Studies
  • Epidemiologic Studies (for persons with diabetes)

• Increasing prevalence of diabetes in the U.S.

• Food sources of dietary cholesterol

• Summary
## Recommendations for Dietary Cholesterol

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>The cardioprotective eating pattern should limit cholesterol intake to &lt; 200 mg/day to lower levels of atherogenic cholesterol (LDL-C and non-HDL-C).</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>There are individuals who are hyper-responders to dietary cholesterol because of genetic or other reasons. For known or suspected hyper-responders, further reduction in dietary cholesterol beyond the &lt;200 mg/day that is recommended as part of the cardioprotective eating pattern for the management of dyslipidemia may be considered. Consumption of very low intakes of dietary cholesterol (near 0 mg/day) may be helpful for such individuals.</td>
<td>B</td>
<td>Low</td>
</tr>
</tbody>
</table>
# Recommendations for Dietary Cholesterol

<table>
<thead>
<tr>
<th>Country</th>
<th>Organization</th>
<th>Cholesterol Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Heart Foundation</td>
<td>No cholesterol recommendations or upper limit.</td>
</tr>
<tr>
<td>International</td>
<td>WHO</td>
<td>&lt;300 mg dietary cholesterol/day</td>
</tr>
<tr>
<td>International</td>
<td>International Atherosclerosis Society</td>
<td>&lt;200 mg dietary cholesterol/day</td>
</tr>
<tr>
<td>United States</td>
<td>National Lipid Association</td>
<td>&lt;200 mg dietary cholesterol/day</td>
</tr>
<tr>
<td>United States</td>
<td>American Diabetes Association (2013)</td>
<td>&lt;300 mg dietary cholesterol/day</td>
</tr>
<tr>
<td>United States</td>
<td>2010 Dietary Guidelines for Americans</td>
<td>Consuming &lt; 300 mg/day can help maintain normal blood cholesterol levels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consuming &lt; 200 mg/day can further help individuals at high risk of cardiovascular disease.</td>
</tr>
<tr>
<td>Canada</td>
<td>Heart and Stroke Foundation</td>
<td>Recommendation for healthy individuals is 300 mg of dietary cholesterol/day with &lt;7% of calories from SFA. People with heart disease or diabetes are advised to limit themselves to 200 mg of dietary cholesterol/day with &lt; 7% of calories from SFA.</td>
</tr>
<tr>
<td>Europe</td>
<td>European Society for Cardiology</td>
<td>The cholesterol intake in the diet should ideally be &lt;300 mg/day</td>
</tr>
</tbody>
</table>
Evidence to Support Recommendations to Restrict Dietary Cholesterol

Clinical Studies
↑ Dietary cholesterol → ↑ LDL ≈ 2 mg/dL (0.05 mmol/L)

A Dose-Response Study of the Effects of Dietary Cholesterol on Fasting and Postprandial Lipid and Lipoprotein Metabolism in Healthy Young Men


Arterioscler Thromb
Volume 14:576-586
April 1994

Increases in Dietary Cholesterol Are Associated With Modest Increases in Both LDL and HDL Cholesterol in Healthy Young Women

Henry N. Ginsberg, Wahida Karmally, Maliha Siddiqui, Steve Holleran, Alan R. Tall, William S. Blaner, and Rajasekhar Ramakrishnan

Arterioscler Thromb Vasc Biol
Volume 15:169-178
February 1995
Responses of Plasma Total (Left) and LDL-C (Right) to Increasing Dietary Cholesterol in Men

- 4 period controlled feeding crossover study of 20 healthy men
- Average total-C and LDL-C increased by 1.47 mg/dL and 1.38 mg/dL, respectively, for each 100 mg/day increase in dietary cholesterol.
- HDL-C also increased by 0.29 mg/dL per 100 mg/day of dietary cholesterol

Individual Variability in Dose-Response Relationship for Total-C and LDL-C with Increasing Dietary Cholesterol

- The results indicate that there was a wide range of mostly positive responses to dietary cholesterol.
- However, three subjects actually had negative cholesterol responses to increasing eggs, while several responded at more than twice the mean.

Responses of Plasma Total, LDL-C And HDL-C to Increasing Dietary Cholesterol in Women

- Total fasting cholesterol concentrations increased by 2.81 mg/dL per 100 mg dietary cholesterol added to the diet per day ($P = .001$).
- LDL-C increased by 2.08 mg/dL per 100 mg/d dietary cholesterol ($P = .003$).
- HDL-C concentrations increased by 0.57 mg/dL per 100 mg/d dietary cholesterol ($P < .04$).

Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis

Samantha Berger, Gowri Raman, Rohini Vishwanathan, Paul F Jacques, and Elizabeth J Johnson

Tufts Clinical Evidence Synthesis Center, Tufts Medical Center, Boston, MA, and Jean Mayer USDA Human Nutrition, Research Center on Aging at Tufts University, Boston, MA

- Forty studies (17 cohorts in 19 publications with 361,923 subjects and 19 trials in 21 publications with 632 subjects) published between 1979 and 2013 were included.
- Dietary cholesterol was not significantly associated with coronary artery disease, ischemic stroke or hemorrhagic stroke.
- Dietary cholesterol significantly increased both serum total cholesterol and LDL-C.
- Dietary cholesterol also significantly increased HDL-C and the LDL-C:HDL-C ratio.

Meta-Analysis: Effect of Dietary Cholesterol on LDL-C by Strata of Intervention Dose

Why do Some Studies Show Increased CVD Risk with Egg Consumption and Others do not?

“…most of the included studies were conducted in Western countries that traditionally have a relatively high-cholesterol diet. Thus, it is likely that the background cholesterol concentration among these participants was already high, so that changes in their cholesterol concentrations might not be sensitive to egg consumption.”

Beneficial Effect of Ezetimibe + Simvastatin Compared with Simvastatin Alone on CVD Events in Patients with Diabetes (IMPROVE-IT)

• The median time-weighted average LDL-C level during the study was 53.7 mg/dL in the simvastatin–ezetimibe group, vs. 69.5 mg/dL in the simvastatin alone group (P<0.001).

• The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, vs. 34.7% in the simvastatin alone group.

Summary of Clinical Studies

• Dietary cholesterol increases LDL-C. For every 100 mg/day of dietary cholesterol, LDL-C increases ≈2 mg/dL.

• The increase in LDL-C is related to the baseline cholesterol intake. The lower the intake, the greater the response.

• There is marked variability in the response to dietary cholesterol.

• Small reductions in LDL-C decrease CVD events.
Evidence to Support Recommendations to Restrict Dietary Cholesterol

Epidemiological Studies
Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis

Jang Yel Shin, Pengcheng Xun, Yasuyuki Nakamura, and Ka He

- A total of 22 independent cohorts from 16 studies were identified, including participants ranging in number from 1600 to 90,735 and in follow-up time from 5.8 to 20 years.
- Comparison of the highest category (≥ 1 egg/d) of egg consumption with the lowest (<1 egg/wk or never)

**Conclusion**: egg consumption is not associated with the risk of CVD and cardiac mortality in the general population. However, egg consumption may be associated with an increased incidence of type 2 diabetes among the general population and CVD comorbidity among diabetic patients.

Egg Consumption is not Associated with the Risk of CVD and Cardiac Mortality in the General Population

Pooled HRs and 95% Cis for Incident IHD, Stroke, and Overall CVD

Egg Consumption May be Associated with Increased CVD Comorbidity Among Persons with Diabetes

Patients with diabetes who ate eggs more than once per day had a 69% increased risk of developing CVD than were those who never ate eggs or ate eggs less than once per week.

Two prospective cohort studies, the Health Professionals Follow-up Study (1986-1994) and the Nurses’ Health Study (1980-1994) were evaluated.

In an analysis of subgroups, there was an association between egg consumption and CVD in subjects with diabetes.

- In men with diabetes, greater than 1 egg per day increased relative risk for CHD was **102%**.
- In women, the increase in relative risk was **49%**.

A Higher Intake of Dietary Cholesterol was Related to Increased CVD Risk Among Women (N=5672) with Type 2 Diabetes from The Nurses’ Health Study

Each increase of 200 mg cholesterol/1000 kcal was associated with a **37%** increased risk of CVD, which was a composite of fatal CHD, nonfatal MI, and stroke

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (mg/1000 kcal)</td>
<td>139.6</td>
<td>175.9</td>
<td>203.6</td>
<td>236.5</td>
<td>298.2</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>0.96</td>
<td>1.18</td>
<td>1.24</td>
<td>1.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(0.73, 1.26)</td>
<td>(0.91, 1.53)</td>
<td>(0.96, 1.60)</td>
<td>(1.28, 2.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1.00</td>
<td>0.99</td>
<td>1.19</td>
<td>1.18</td>
<td>1.47</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>(0.74, 1.31)</td>
<td>(0.91, 1.54)</td>
<td>(0.89, 1.57)</td>
<td>(1.10, 1.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for fatty acids**</td>
<td>1.00</td>
<td>0.96</td>
<td>1.16</td>
<td>1.14</td>
<td>1.39</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(0.72, 1.27)</td>
<td>(0.88, 1.54)</td>
<td>(0.85, 1.53)</td>
<td>(1.04, 1.88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, smoking, postmenopausal hormone use, parental history of myocardial infarction before 60 y of age (yes or no), alcohol intake, moderate/vigorous activities, BMI, total caloric intake, protein intake, fiber intake, multivitamin use, vitamin E supplement use, and medication use

** After additional adjustment for trans and monounsaturated fats

Summary of Epidemiological Studies

- Egg consumption is not associated with the risk of CVD and cardiac mortality in the general, healthy population.

- In persons with diabetes, egg consumption and dietary cholesterol significantly increase risk of CVD.
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2013


<table>
<thead>
<tr>
<th>Definitions of prediabetes</th>
<th>NHANES 1988-1994 (n=15,578)</th>
<th>NHANES 1999-2004 (n=12,726)</th>
<th>NHANES 2005-2010 (n=15,135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibrated HbA1c of 5.7% - 6.4%</td>
<td>5.8 ± 0.35</td>
<td>11.9 ± 0.47</td>
<td>12.4 ± 0.42</td>
</tr>
<tr>
<td>Fasting subsample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG level of 5.6-6.9 mmol/L (100-125 mg/dL)</td>
<td>25.2 ± 0.84</td>
<td>26.3 ± 1.14</td>
<td>28.7 ± 0.87</td>
</tr>
<tr>
<td>HbA1c level of 5.7% - 6.4%</td>
<td>6.0 ± 0.40</td>
<td>11.9 ± 0.56</td>
<td>12.4 ± 0.50</td>
</tr>
</tbody>
</table>

In 2012, 86 million Americans age 20 and older had prediabetes; this is up from 79 million in 2010.
Current Intake of Dietary Cholesterol in the US, NHANES 2011-2012

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cholesterol Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males 20+</td>
<td>338 mg/day</td>
</tr>
<tr>
<td>Females 20+</td>
<td>229 mg/day</td>
</tr>
<tr>
<td>Combined</td>
<td>282 mg/day</td>
</tr>
</tbody>
</table>

DATA SOURCE: What We Eat in America, NHANES 2011-2012.
### Top Food Sources of Dietary Cholesterol based on NHANES, 2005-2006

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Contribution to intake (%)</th>
<th>Cumulative Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggs and egg mixed dishes</td>
<td>24.6</td>
<td>24.6</td>
</tr>
<tr>
<td>Chicken and chicken mixed dishes</td>
<td>12.5</td>
<td>37.1</td>
</tr>
<tr>
<td>Beef and beef mixed dishes</td>
<td>6.4</td>
<td>43.6</td>
</tr>
<tr>
<td>Burgers</td>
<td>4.6</td>
<td>48.2</td>
</tr>
<tr>
<td>Regular cheese</td>
<td>4.2</td>
<td>52.4</td>
</tr>
<tr>
<td>Sausage, franks, bacon, and ribs</td>
<td>3.9</td>
<td>56.3</td>
</tr>
<tr>
<td>Other fish and fish mixed dishes</td>
<td>3.4</td>
<td>59.7</td>
</tr>
<tr>
<td>Grain-based desserts</td>
<td>3.3</td>
<td>63.0</td>
</tr>
<tr>
<td>Dairy desserts</td>
<td>3.2</td>
<td>66.3</td>
</tr>
<tr>
<td>Pasta and pasta dishes</td>
<td>3.1</td>
<td>69.3</td>
</tr>
<tr>
<td>Pizza</td>
<td>2.9</td>
<td>72.2</td>
</tr>
<tr>
<td>Mexican mixed dishes</td>
<td>2.9</td>
<td>75.1</td>
</tr>
<tr>
<td>Cold cuts</td>
<td>2.7</td>
<td>77.8</td>
</tr>
</tbody>
</table>

Conclusions

• Scientific evidence supports NLA recommendation for <200 mg/day of dietary cholesterol

• Variability in response to dietary cholesterol makes it difficult to identify hyper-responders

• Even small reductions in LDL-C have CVD benefits

• The growing prevalence of diabetes is a further justification for restriction of dietary cholesterol
Dietary Cholesterol Restriction is Still Important

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Department of Nutritional Sciences
Penn State University
Quiz - Question 1

How much, on average, would an increase in dietary cholesterol of 100 mg/day be expected to affect blood cholesterol levels?

a. 1 mg/dL  
b. 2 mg/dL  
c. 10 mg/dL  
d. 20 mg/dL  
e. None of the above
How much, on average, would an increase in dietary cholesterol of 100 mg/day be expected to affect blood cholesterol levels?

a. 1 mg/dL  

b. **2 mg/dL**  
c. 10 mg/dL  
d. 20 mg/dL  
e. None of the above
Small Decreases in LDL-C Translate to Significant Reductions in CVD Risk

The proportional reductions per 1.0 mmol/L (39 mg/dL) reduction in LDL cholesterol in major vascular events were similar overall for women (rate ratio [RR] 0.84, 99% CI 0.78-0.91) and men (RR 0.78, 99% CI 0.75-0.81).

Quiz - Question 2

A major factor that contributes to the variability in the dietary cholesterol response is:

a. Gender
b. Intake of saturated fat
c. Baseline dietary cholesterol
d. Statins
e. All of the above
Quiz - Question 2

A major factor that contributes to the variability in the dietary cholesterol response is:

a. Gender  
b. Intake of saturated fat  
**c. Baseline dietary cholesterol**  
d. Statins  
e. All of the above
Cholesterol Intake in the U.S.

Men, 20 years and older, 315 mg/day

Men, 40 to 50 years, 371 mg/day

Women, 20 years and older, 221 mg/day

U.S. diet provides 132 mg/1000 Kcal

Calorie intake of U.S. population (10 to 99th %tile) is: 1200-4200 Kcal

Dietary cholesterol for some is \( \approx 550 \text{ mg/day} \)