Cardiovascular Diseases: from Epidemiology to Nutritional Interventions

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Department of Food Science and Technology
Agricultural University of Athens

Worldwide deaths in 2000 attributable to selected leading risk factors
Source: WHR 2002

All deaths from circulatory disease in Europe; all ages year 2000 or circa

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>4,519,403</td>
<td>4,336,346</td>
</tr>
<tr>
<td>All circulatory</td>
<td>1,963,644</td>
<td>2,307,945</td>
</tr>
<tr>
<td>CHD</td>
<td>967,258</td>
<td>983,229</td>
</tr>
<tr>
<td>Stroke</td>
<td>504,307</td>
<td>775,571</td>
</tr>
<tr>
<td>Rest</td>
<td>492,079</td>
<td>637,405</td>
</tr>
</tbody>
</table>

Source: EHN, Cardiovascular diseases in Europe, 2005

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Levels of evidence

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
</tr>
<tr>
<td>B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies</td>
</tr>
<tr>
<td>C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries</td>
</tr>
</tbody>
</table>

- Total fat
- Fatty acid composition
- Dietary cholesterol intake
- Whole grains
- Dietary pattern
- Alcohol
- Sodium, potassium and other electrolytes
- Fruits and vegetables
- Vitamin supplements
- Plant sterols
- Obesity
- Management
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Low fat dietary pattern and risk of CVD: the Women's Health Initiative randomized controlled modification trial (n=48835)

Differences between the mean changes in cardiovascular disease risk factors from baseline to year 3 in the intervention vs. the comparison group (n=5.8% of the sample)

Percentage of subjects who developed CHD, stroke and CVD after 6 years of dietary intervention
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- Management

Monounsaturated fat

Linear correlation coefficients among simple and combined food-groups and mortality from CHD

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### Odds ratios (OR) (95% CI) of a first myocardial infarction according to olive oil intake

(unchanged for total energy intake)

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Controls/ cases</th>
<th>Median intake (g/day)</th>
<th>Multivariate adjusted OR(^a) (95% CI)</th>
<th>Multivariate adjusted OR(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.17 (0.96-1.40)</td>
<td>0.91 (0.68-1.22)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.93 (0.76-1.15)</td>
<td>0.70 (0.54-0.92)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0.89 (0.74-1.07)</td>
<td>0.70 (0.55-0.90)</td>
</tr>
</tbody>
</table>

Trend test P-value: 0.25

\(^a\) Conditional logistic regression (age-, hospital- and gender-matched pairs), adjusted for smoking, BMI, high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METs-hours/week), marital status, occupation and study level

\(^b\) Additionally adjusted for saturated fat, trans fat and total fibre intake

Fernandez-Jarne E et al., Intern J Epidemiol 2002; 31: 474-80

### Odds ratios (OR) (95% CI) of a first myocardial infarction according to energy adjusted olive oil intake

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Controls/ cases</th>
<th>Median intake (g/day)</th>
<th>Multivariate adjusted OR(^a) (95% CI)</th>
<th>Multivariate adjusted OR(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.39 (0.15-1.00)</td>
<td>0.22 (0.07-0.67)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.40 (0.17-0.93)</td>
<td>0.22 (0.07-0.67)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0.59 (0.23-1.52)</td>
<td>0.22 (0.07-0.67)</td>
</tr>
</tbody>
</table>

Trend test P-value: 0.93

\(^a\) Conditional logistic regression (age-, hospital- and gender-matched pairs), adjusted for smoking, BMI, high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METs-hours/week), marital status, occupation and study level

\(^b\) Additionally adjusted for % energy derived from SFA, % energy derived from trans fat, total fibre consumption, folic acid intake, vitamin C intake, glycaemic load and ethanol intake (adding a quadratic term for non-linearity)

Fernandez-Jarne E et al., Intern J Epidemiol 2002; 31: 474-80

### Diet and coronary heart disease: a case-control study in Athens, Greece

...Major fat components (saturated, monounsaturated, and polyunsaturated) did not appear to have differential risk implications for CHD...

Tzanou A et al., Epidemiology 1993; 4:511-6

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Nutrients Mediterranean diet with olive oil vs. low-fat diet

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Mediterranean diet with olive oil vs. low-fat diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kcal</td>
<td>Mean (95% CI) between-group difference P value</td>
</tr>
<tr>
<td>Protein, %</td>
<td>4.5 (-139.0 to 148.0)</td>
</tr>
<tr>
<td>CHO, %</td>
<td>-0.47 (-1.07 to 0.13)</td>
</tr>
<tr>
<td>Fiber, g/d</td>
<td>0.22 (-1.30 to 1.70)</td>
</tr>
<tr>
<td>Total fat, %</td>
<td>0.49 (-1.90 to 2.90)</td>
</tr>
</tbody>
</table>


Variable Mediterranean diet with olive oil vs. low-fat diet

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mediterranean diet with olive oil vs. low-fat diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>-4.3 (-2.1 to -3.3)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>-1.90 (-3.6 to -0.21)</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>-16.7 (-27.1 to -0.4)</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>-3.5 (-5.5 to 2.5)</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>3.9 (1.7 to 4.0)</td>
</tr>
<tr>
<td>Cholesterol-HDL-C ratio</td>
<td>-0.38 (-4.45 to -3.22)</td>
</tr>
</tbody>
</table>


Changes from baseline in plasma concentrations of the inflammatory biomarkers

Monounsaturated fat

- Epidemiological prospective studies have shown that substitution of SFA by MUFA is associated with lower risk of CAD
- Replacement of SFA with MUFA raises HDL:LDL ratio

Trans fat

Multivariate adjusted relative risk of CHD associated with trans fatty acid intake

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses Health Study, 2005</td>
<td>78,778</td>
<td>1766</td>
</tr>
<tr>
<td>Health Professionals follow-up Study, 2005</td>
<td>36,461</td>
<td>1702</td>
</tr>
<tr>
<td>Alpha-Tocopherol Beta-Carotene Cancer</td>
<td>21,930</td>
<td>1359</td>
</tr>
<tr>
<td>Prevention Study, 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zutphen Elderly Study, 2001</td>
<td>667</td>
<td>98</td>
</tr>
</tbody>
</table>

Pooled prospective studies

EURAMIC, 1995 1,388 671
Costa Rica, 2003 564 482
Australia, 2004 76 44

Pooled prospective and retrospective studies


Multivariate relative risk of CHD with higher trans fatty acid intake 2.5 2.0 1.5 1.0 0.5 0.0
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Changes in total: HDL-C and levels of LDL and HDL cholesterol resulting from the replacement of saturated (1% of total energy intake) or cis unsaturated fatty acids with trans fatty acids


Daily intake of trans fatty acids in the Zutphen Elderly Study (n=667, 64-84 y)

Quote: 'The decrease in trans fatty acid intake of 2.4% of energy ... could have contributed to about 25% less coronary deaths (i.e. about 4600 of 20,000 deaths) in the Netherlands per year'

Oomen et al., Lancet 2001; 357:746-51

Trans fatty acids
- MUFA or PUFA isomers whose conformation has been modified by during the digestion in ruminants or by hydrogenation during industrial processes of foods
- Trans fatty acids increase LDL- and decrease HDL-cholesterol
- Potential studies have found associations between the intake of trans fatty acids and cardiovascular morbidity and mortality in Northern America and in Europe

Saturated fat intake should be <10% of energy
In high risk patients:
Saturated fat intake <7% (inclusive of Trans fat <1%)
Epidemiological studies

- Higher adipose tissue LA is associated with lower CHD mortality
  Rimm et al., Br Med J 1986; 292:1423-7

- Serum LA is negatively associated with to CVD death in post-infarction middle aged men
  Valek et al., Atherosclerosis 1985; 54:111-6

- Low dietary LA intake predisposed to MI

- Dietary PUFA is negatively associated with CHD mortality after adjusting for SFA intake

CHD events, as predicted by linoleic acid, replacing saturated fats

Median Intake (% energy)

% Decrease of risk

-40 -30 -20 -10 0

2.9 4.1 4.3 4.7 4.4

Polyunsaturated fatty acids

- N-6 PUFA decrease LDL- and to a lesser extent decrease HDL-cholesterol
- In prospective epidemiological studies PUFA consumption instead of SFA and trans is inversely correlated with CAD risk
- Clinical studies resulted in lowering of plasma cholesterol and cardiovascular outcomes

n-3 fatty acids

- Alpha-linolenic acid (ALA) is found in vegetables and nuts
- Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) are found in fish and fish oil
- Only 5% of ALA can be transformed into EPA
- Less than 1% of ALA can be transformed into DHA
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Epidemiological studies

- Inverse relationship between adipose tissue ALA and relative risk for myocardial infarction
  Baylin A et al., Circulation 2003; 107:1586-91
- Inverse association between ALA dietary intake and the prevalence of odds ratio for CHD
- Dose-response relationship between ALA dietary intake and relative risk for fatal ischemic heart disease
  Hu FB et al., Am J Clin Nutr 1999; 69:890-7
  Ascherio A et al., BMJ 1996; 313:84-90
- No association between dietary ALA intake and 10-year risk for CAD
  Oomen CM et al., Am J Clin Nutr 2001; 74:457-63

Epidemiological studies (2)

- Observational studies indicate an inverse relationship between fish consumption and risk of CHD
  Rodriguez B et al., Circulation 1996; 94:952-6
  Norell SE et al., BMJ 1986; 293:426
- Moderate consumption once a week has a protective effect but no further reduction in risk is observed in higher fish consumption
  Gilum RF et al., J Clin Epidemiol 2000; 53:237-44
- High risk individuals may benefit more from increasing their fish consumption up to an optimum of 40-60 g/d
- Fish consumption < 150 g/week is associated with 38% lower odds of developing ACS
  Panagiotakos DB et al., Int J Cardiol (in press)

Lyon diet heart study: cumulative survival without cardiac death and nonfatal MI

- Canola oil– based margarine, fiber, low cholesterol, low saturated fat, fruits, vegetables

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N-3 fatty acids from fish and fish oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review

- The data from secondary- and primary-prevention studies support the hypothesis that consumption of very-long-chain FAs from fish and fish-oil supplements reduce all-cause mortality, cardiac and sudden death, and stroke
- The conclusion is not applicable to the population of patients with an implantable cardioverter defibrillator (ICD), in whom 3 recent RCTs found inconsistent anti-arrhythmic effects and no significant overall effect on mortality

Wang C et al., Am J Clin Nutr 2006; 84:5-17

The JELIS trial
Incidence of coronary events
(fatal and non-fatal MI, angina pectoris, cardiac or sudden death and coronary revascularization)

Kaplan Meier estimates of incidence of coronary events in the total study population (A), the primary prevention arm (B) and the secondary prevention arm (C)

Years

Control
EPA

Control
EPA

Control
EPA

Numbers at risk
Control group       9319 8931 8671 8433 8192 7958 7478 7204 7103 6841 6678 6508 1841 1727 1658 1592 1514 1450
Treatment group  9326 8929 8658 8389 8153 7924 7503 7210 7020 6823 6649 6482 1823 1719 1638 1566 1504 1442

Hazard ratio:
0.81(0.69-0.95)
P=0.011

Hazard ratio:
0.81(0.657-0.998)
P=0.048

Hazard ratio:
0.82(0.63-1.06)
P=0.132

Cardiac death in patients with prevalent coronary heart disease in GISSI-Prevezione and JELIS trials of fish supplementation

Rate of cardiac death (per 100 persons)

GISSI
JELIS secondary prevention

Control
Fish oil

Mozaffarian D, Lancet 2007; 369:1062-3

Polyunsaturated fatty acids

- N-3 fatty acids (ALA, EPA and DHA)
- In prospective epidemiological studies a high intake of ALA is associated with a reduction of fatal CV events
- Data from randomized clinical trials on the effects of ALA on CVD events are limited and of poor quality
- The evidence for the benefits of fish oil is stronger in secondary than in primary prevention
- Harmful effects of methyl-mercury exposure?
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- Total fat
- Fatty acid composition
- Dietary cholesterol intake
- Whole grains
- Dietary pattern
- Alcohol
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- Fruits and vegetables
- Vitamin supplements
- Plant sterols
- Obesity
- Management

Dietary cholesterol

150-250mg Cholesterol / yolk

Consensus on effect of dietary cholesterol on serum Cholesterol

Δ Dietary cholesterol
100 mg/day (~0.5 egg yolk)
Clinically...no effect on coronary heart disease risk

Δ Serum cholesterol
< 0.10 mol/l (4-5 mg/dl)
Dietary cholesterol intake

- Little effect
- Reduction of 100 mg dietary cholesterol per day appears to reduce total serum cholesterol by only 0.06 or 0.07 mmol/L (~1%), although this relationship may not be linear.

Total fat
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Whole grains and heart disease risk

- ARIC Study (15,792 men and women) (Steffen et al., 2003)
  3 servings of wholegrain food/d → 28% ↓ risk of CAD

- Iowa Women's Health Study (34,000 women) (Jacobs et al., 1998)
  >1 serving of wholegrain food/d → 30-36% ↓ risk of IHD

- Harvard Nurses' Health Study (75,000 women) (Liu et al., 1999)
  ≥3 servings of wholegrain food/d → 25% ↓ risk of CHD
Prospective cohort studies of CVD and consumption of nuts, fruits and vegetables, or whole grains

Cardiovascular disease
• Whole grains may lower cholesterol levels in part because of high level of soluble (viscous) fiber
• Magnitude of risk reduction 27-37%
• Larger cholesterol level reductions than from reduced cholesterol intake alone

Diabetes
• Consumption of whole grains included in recommendations for diabetes prevention
• 21 – 21% risk reduction by eating 3 servings of whole grain daily
• Whole grain intakes associated with improved insulin sensitivity

Cancer
• Meta-analysis of GI cancers = 21 - 43% lower risk
• Meta-analysis of hormone dependent cancers = 10 - 40% risk reduction

Obesity
• Higher intakes of whole grains
  - lower Body Mass Index
  - lower risk of major weight gain

Total fat
Fatty acid composition
Dietary cholesterol intake
Whole Grains
Dietary pattern
Alcohol
Sodium, potassium and other electrolytes
Fruits and vegetables
Vitamin supplements
Plant sterols
Obesity
Management
A higher adherence to the Mediterranean Diet was associated with a reduction in total mortality; An inverse association with greater adherence to this diet was evident for both death due to CHD and cancer...

Trichopoulou A et al., Arch Intern Med 2005; 165:929-35

It is perhaps naïve to expect a change in one aspect of a diet to lead to a huge decrease in risk of CVD

European society of cardiology - Guidelines for CVD prevention in clinical practice

• Take into consideration the whole dietary pattern
• Cardio-protective:
  – Mediterranean type diet
  – DASH diet

Alcohol

- On a population scale, the relationship between alcohol consumption and total mortality has a U or J shape
- Effect on HDL-cholesterol, glucose intolerance and fibrinogen levels
- Observational and clinical studies have consistently demonstrated a direct, dose-dependent relationship between alcohol intake and BP
- To date no randomized trial has proven that the voluntary intake of a moderate quantity of alcohol is beneficial in terms of morbidity and mortality

Total fat
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Population-based strategy

SBP Distributions

Before intervention

After intervention

Reduction in SBP

% Reduction in mortality

SBP Distributions

Reduction in BP

3

-8

-8

-5

-5

-4

-4

-7

-7

SBP Distributions

Reduction in BP

3

-8

-8

-5

-5

-4

-4

-7

-7

Lifestyle modification

Modification

Approximate SBP reduction (range)

5–20 mmHg/10 kg weight loss

8–14 mmHg

2–8 mmHg

4–9 mmHg

2–4 mmHg

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Sodium, potassium and other electrolytes

- Sodium intake increases blood pressure and potassium intake is associated with reduced blood pressure
- In societies with low salt intake there is no age-related increase in blood pressure
- DASH trial
- A recent Cochrane review (2004) concluded that intensive interventions provide only minimal reductions in blood pressure during long-term trials

Risk of stroke for 3-5 and >5 servings of fruit and vegetables per day compared with <3 servings
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- Pooled estimate of RR and 95% CI of IHD rates for 1 portion increment per day
- Open squares indicate adjusted RR in each study and are inversely related to RRs variance
- Filled diamonds are pooled RR
- Horizontal line represents 95% CI

Health professionals
Nurses' health study
Women's health study
ARIC
NHANES
BLSA

Pooled RRR

Health professionals
Nurses' health study
Women's health study
ATBC
Mobile clinic II (women)
Mobile clinic II (men)

Pooled RRR

Relation between fruit and vegetable intake and RR of CHD
- The circles represent the RR reported in each class of daily servings in each individual study
- The size of the circle is inversely proportional to the logarithm of the RR variance

Effects of fruit and vegetable consumption on blood pressure: a RCT

<table>
<thead>
<tr>
<th>n</th>
<th>Baseline, mean (SD)</th>
<th>Change at 6 months follow up, mean (SD)</th>
<th>Between group difference in change (95% CI)</th>
<th>Adjusted difference in change (95% CI)</th>
<th>P for adjusted difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>320</td>
<td>3.4 (1.7)</td>
<td>1.4 (1.7)</td>
<td>1.1 (1.5 to 1.6)</td>
<td>1.4 (1.2 to 1.6)</td>
</tr>
<tr>
<td>I</td>
<td>344</td>
<td>130.2 (19.7)</td>
<td>-2.0 (13.5)</td>
<td>3.4 (1.3 to 5.5)</td>
<td>4.0 (2.0 to 6.0)</td>
</tr>
<tr>
<td>I</td>
<td>344</td>
<td>76.2 (11.4)</td>
<td>-1.6 (8.7)</td>
<td>1.4 (0.1 to 2.7)</td>
<td>1.5 (0.2 to 2.7)</td>
</tr>
</tbody>
</table>


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Fruits and vegetables

- In a meta-analysis of prospective epidemiological studies, each serving increment of fruit and vegetables intake was associated with a 4% reduction in risk of coronary events and in another one, with 5% reduction in the relative risk of stroke.
- Randomized trials are still necessary.
- Fruits and vegetables, potassium intake and blood pressure.

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Mean total homocysteine levels by treatment group: the VISP study

200 μg pyridoxine, 6 μg cobalamin and 20 μg folic acid

25 mg pyridoxine, 0.4 mg cobalamin and 2.5 mg folic acid

Time after randomization, mo.

Toole JF et al., JAMA 2004; 291:565-71

66
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Probability of stroke, coronary event or death over time by treatment group: the VISP study

Toole JF et al., JAMA 2004; 291:565-71

Homocysteine lowering with folic acid and B vitamins in vascular disease: the HOPE 2 study

The HOPE 2 Investigators, N Engl J Med 2006; 354:1567-77

Effect of folic acid supplementation on risk of CVD: a meta-analysis of RCT's among persons with pre-existing CV or renal disease

Bazzano LA et al., JAMA 2006; 296:2720-6

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The supplementation of vitamins, minerals and antioxidants (SU.VI.MAX) study

- Randomized, double-blind, placebo-controlled primary prevention trial
- 13,017 French adults were included and followed for 7.5 years
- 120 mg ascorbic acid, 30 mg vitamin E, 6 mg beta carotene, 100 μg selenium and 20 mg zinc
- No differences between the groups in total cancer incidence, ischaemic cardiovascular disease incidence or all-cause mortality
- Significant differences in cancer incidence and all cause mortality in men (gender-group interaction)

Herbberg S et al., Arch Intern Med 2004; 164:2335-42

Vitamin supplements

- Vitamin E
- Vitamin A
- Homocysteine, vitamin B12, folic acid and vitamin B6
- Multivitamins

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Overview of cholesterol lowering trials with plant sterols

- Decrease dietary cholesterol absorption; no impact on triglycerides and HDL-cholesterol
- High intakes of > 3.9 g/d have no additional impact
- No randomized nutritional trial to date
- Absorption of fat soluble vitamin?
- Accumulation in atherosclerotic plaque?

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Management

- SFAs, trans fatty acids
- Soluble fiber
- Phytosterols
- N-3 fatty acids from fish
- Potassium
- Motivation (behavior therapy)
- Physical activity

Type of dietary recommendation | Details
--- | ---
Exclusionary | Saturated fatty acids: < 7% total energy
Cholesterol: < 300 mg/d in the general healthy population; < 200 mg/d in those with multiple risk factors or documented disease
Trans fat: should be classified as saturated fat
Salt: < 4 g/d; sodium < 2.4 g/d
Polyunsaturated fatty acids: up to 10% total energy
Total fat: < 30% total energy; 25-30% total energy
Balance total calories to achieve or maintain a desirable body weight
Alcohol: 0-1 drink/d for women and 0-2 drinks/d for men

Intermediate | Saturated fatty acids: < 7% total energy
Cholesterol: < 300 mg/d in the general healthy population; < 200 mg/d in those with multiple risk factors or documented disease
Trans fat: should be classified as saturated fat
Salt: < 6 g/d; sodium < 2.4 g/d
Polyunsaturated fatty acids: up to 10% total energy
Total fat: < 30% total energy; 25-30% total energy
Balance total calories to achieve or maintain a desirable body weight
Alcohol: 0-1 drink/d for women and 0-2 drinks/d for men

Inclusive | Saturated fatty acids: < 7% total energy
Cholesterol: < 300 mg/d in the general healthy population; < 200 mg/d in those with multiple risk factors or documented disease
Trans fat: should be classified as saturated fat
Salt: < 6 g/d; sodium < 2.4 g/d
Polyunsaturated fatty acids: up to 10% total energy
Total fat: < 30% total energy; 25-30% total energy
Balance total calories to achieve or maintain a desirable body weight
Alcohol: 0-1 drink/d for women and 0-2 drinks/d for men

Kris-Etherton PM et al., Curr Opin Lipidol 2002; 13:397-407