Evidence for the Numerous Cardiometabolic Benefits of All Dietary Unsaturated Fatty Acids

*With Emphasis on MUFA*

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Outline

• Cardiometabolic disease is a global health problem
• Dietary strategies for decreasing metabolic syndrome (specifically visceral adipose tissue) - benefits of MUFA
  • COMIT Multicentre Intervention Trial
  • PREDIMED
• Health benefits of PUFA
• Summary
  • What is the optimal proportions of MUFA and PUFA
# Criteria for Metabolic Syndrome

<table>
<thead>
<tr>
<th>Required criteria</th>
<th>AHA/NHLBI, 2005</th>
<th>IDF, 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of three or more criteria</td>
<td>MANDATORY presence of increased waist circumference (WC) using ethnicity-specific cutoffs: ≥ 94 cm (Europid men) or ≥ 80 cm (Europid women) PLUS presence of two or more criteria</td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>WC ≥ 102 cm (men) and ≥ 88 cm (women)</td>
<td></td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>≥ 100 mg/dL (5.6 mmol/L) OR drug treatment for this disorder</td>
<td>≥ 100 mg/dL (5.6 mmol/L) OR previously diagnosed type 2 diabetes</td>
</tr>
<tr>
<td>Reduced HDL cholesterol</td>
<td>&lt; 40 mg/dL (1.0 mmol/L) in men, &lt; 50 mg/dL (1.3 mmol/L) in women OR drug treatment for this disorder</td>
<td>&lt; 40 mg/dL (1.0 mmol/L) in men, &lt; 50 mg/dL (1.3 mmol/L) in women OR drug treatment for this disorder</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>≥ 150 mg/dL (1.7 mmol/L) OR drug treatment for this disorder</td>
<td>≥ 150 mg/dL (1.7 mmol/L) OR drug treatment for this disorder</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg OR drug treatment for this disorder</td>
<td>Systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg OR drug treatment for this disorder</td>
</tr>
</tbody>
</table>
## Prevalence of MetS in Selected Countries Worldwide

<table>
<thead>
<tr>
<th>Country</th>
<th>( n )</th>
<th>Age (years)</th>
<th>NCEP:ATPIII</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>11,247</td>
<td>≥25</td>
<td>24.4% male</td>
<td>34.4% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19.9% female</td>
<td>27.4% female</td>
</tr>
<tr>
<td>China</td>
<td>15,540</td>
<td>35–74</td>
<td>9.8% male</td>
<td>N/R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.8% female</td>
<td>N/R</td>
</tr>
<tr>
<td>Denmark</td>
<td>2,493</td>
<td>41–72</td>
<td>18.6% male</td>
<td>23.8% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14.3% female</td>
<td>17.5% female</td>
</tr>
<tr>
<td>India</td>
<td>2,350</td>
<td>&gt;20</td>
<td>17.1% male</td>
<td>N/R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19.4% female</td>
<td>N/R</td>
</tr>
<tr>
<td>Ireland</td>
<td>890</td>
<td>50–69</td>
<td>21.8% male</td>
<td>N/R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21.5% female</td>
<td>N/R</td>
</tr>
<tr>
<td>South Korea</td>
<td>40,698</td>
<td>20–28</td>
<td>5.2% male</td>
<td>N/R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9.1% female</td>
<td>N/R</td>
</tr>
<tr>
<td>United States</td>
<td>3,601</td>
<td>&gt;20</td>
<td>33.7% male</td>
<td>39.9% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35.4% female</td>
<td>38.1% female</td>
</tr>
</tbody>
</table>

Figure Legend:

Age-Specific Prevalence of the Metabolic Syndrome by Sex and Race/Ethnicity, 2003-2012

Error bars indicate 95% confidence intervals. Comparisons of prevalence estimates were performed using χ² tests; patients aged 20-39 years in each group were used as the reference. All comparisons yielded P < .001.
Clinical Significance of MetS and Treatment Recommendations
Abdominal Obesity Increases Risk of MetS and CVD & T2D

Metabolic syndrome

Visceral obesity

Insulin resistance

Additional risk factors

- Low-grade inflammation
- Disturbed adipokine secretion
- Disturbances in hemostasis and fibrinolysis (PAI-1)

Cardiovascular disease
Type 2 diabetes

- Glucose intolerance
- Dyslipidemia
- Hypertension
- Microalbuminuria

Adapted from Van Gaal LF et al. Nature 2006;444:875-80

Source: www.myhealthywaist.org
Intra-Abdominal (Visceral) Adiposity Promotes Insulin Resistance and β-Cell Dysfunction

Intra-abdominal adiposity

Portal circulation

Systemic circulation

Splanchnic & systemic circulation

↑ Hepatic insulin resistance

↑ Hepatic glucose output

↑ Small, dense LDL

Lipolysis

↑ TG-rich VLDL cholesterol

CETP, Lipolysis

Low HDL cholesterol

↓ Glucose utilization

Long-term damage to β-cells by FFA

↓ Insulin resistance

↓ Insulin secretion

CETP: cholesteryl ester transfer protein

FFA: free fatty acids

TG: triglycerides

Adapted from Lam TK et al. Am J Physiol Endocrinol Metab 2003;284:E281-90:
Carr MC et al. J Clin Endocrinol Metab 2004;89:2601-7:
Intra-Abdominal (Visceral) Fat is an Independent Predictor of All-Cause Mortality in Men

The OR for mortality after controlling for age, follow-up time, liver fat, and abdominal SQ fat.

Reproduced with permission from Kuk JL et al. Obesity (Silver Spring) 2006;14:336-41
**Metabolic Syndrome Treatment**

The best way, if overweight, is to lose weight. Also, a healthy diet and physical activity are beneficial.

- Routinely monitor body weight (especially central obesity).
- Monitor blood glucose, lipoproteins and blood pressure.
- Treat individual risk factors (hyperlipidemia, high blood pressure and high blood glucose) according to established guidelines.
- Carefully choose high blood pressure drugs because they affect insulin sensitivity differently.

http://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_300322.pdf
Health Benefits of MUFA on Metabolic Syndrome Criteria

Metabolic Targets

**Blood Lipids**
- Total-C < 200 mg/dL
- LDL-C < 130 mg/dL
- TAG < 150 mg/dL
- HDL-C > 40 mg/dL ♀ or > 50 mg/dL ♂

**Body Composition**
- Waist circumference
  - < 102 cm men or ≥ 88 cm women
  - BMI < 25 kg/m²

**Blood Pressure**
- < 130/85 mmHg

**Glucose & Insulin Sensitivity**
- Glucose < 100 mg/dL

↓ Metabolic Syndrome
↓ Type 2 Diabetes Mellitus
↓ Atherosclerotic Cardiovascular Disease

Dietary MUFA

Adapted from: Gillingham et al., *Lipids* 2011;46:209-28
COMIT: Canola Oil Multi-Centre Intervention Trial

Modification of the fatty acid profile of the diet by the inclusion of novel oil blends that vary in n-6, n-9 and short and long chain n-3 fatty acids will benefit cardiometabolic risk factors

Collaborators

University of Manitoba
Dr. Peter Jones, PI
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Penn State
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Jennifer Fleming
Cindy McCrea

Université Laval
Dr. Benoit Lamarche
Dr. Patrick Couture

University of Toronto
St. Michael's
Dr. David Jenkins
Dr. Phil Connelly

Funding Provided By:

Dow AgroSciences
Canola Council of Canada
Flax Council of Canada
Objectives

1. Examine alterations in plasma lipids, lipoprotein subclasses, and inflammatory cytokines
2. Assess endothelial function in response to treatment oils
3. Examine changes in body composition using DEXA (dual energy x-ray absorptiometry) scanning
4. Examine efficiency of FA conversion to EPA/DHA
5. Investigate association between gene mRNA and protein expression with ALA conversion efficiency to EPA/DHA
6. Investigate association between genetic variants with ALA conversion to EPA/DHA
Eligibility Criteria

Based on International Diabetes Federation Definition of Metabolic Syndrome

- Age: 20-65 y
- BMI: ≥ 22 to ≤ 40 kg/m²
- Waist circumference (WC): Men ≥ 94 cm, Women ≥ 80 cm
- WC + one of the following metabolic syndrome criteria:
  - Glucose: ≥ 5.6 mmol/L (100 mg/dL)
  - HDL-C: men < 1.0 mmol/L (40 mg/dL), women < 1.3 mmol/L (50 mg/dL)
  - TG: ≥ 1.7 mmol/L (150 mg/dL)
  - Blood pressure: >130/85mmHg
Study Design

- Double blind cross-over controlled feeding trial
- Randomized treatment order
- Diets fed as prepared foods

Canola oil

High Oleic Canola oil

High Oleic Canola oil/DHA

Corn/Safflower

Flax/Safflower

Diet period 1

4wk

Diet period 2

4wk

Diet period 3

4wk

Diet period 4

4wk

Diet period 5

4wk

4wk washout

4wk washout

4wk washout

4wk washout

4wk washout
## Nutrient Profile of the Test Diets

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Canola</th>
<th>High Oleic Canola</th>
<th>Canola DHA</th>
<th>Corn/Safflower</th>
<th>Flax/Safflower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>15.6%</td>
<td>15.6%</td>
<td>15.6%</td>
<td>15.6%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50.7%</td>
<td>50.7%</td>
<td>50.7%</td>
<td>50.7%</td>
<td>50.7%</td>
</tr>
<tr>
<td>Fat</td>
<td>35.5%</td>
<td>35.5%</td>
<td>35.5%</td>
<td>35.5%</td>
<td>35.5%</td>
</tr>
<tr>
<td><strong>SFA</strong></td>
<td><strong>6.6%</strong></td>
<td><strong>6.5%</strong></td>
<td><strong>6.9%</strong></td>
<td><strong>6.7%</strong></td>
<td><strong>6.8%</strong></td>
</tr>
<tr>
<td>MUFA</td>
<td>17.6%</td>
<td>19.3%</td>
<td>17.8%</td>
<td>9.5%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Oleic</td>
<td>15.7%</td>
<td>18%</td>
<td>16.5%</td>
<td>8.3%</td>
<td>8.4%</td>
</tr>
<tr>
<td><strong>PUFA</strong></td>
<td><strong>9.1%</strong></td>
<td><strong>6.9%</strong></td>
<td><strong>8.0%</strong></td>
<td><strong>16.3%</strong></td>
<td><strong>16.3%</strong></td>
</tr>
<tr>
<td>Omega-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALA</td>
<td>2.0%</td>
<td>&lt;1.0%</td>
<td>&lt;1.0%</td>
<td>&lt;1.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>DHA</td>
<td></td>
<td></td>
<td></td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Omega-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>6.5%</td>
<td>5.6%</td>
<td>5.2%</td>
<td>15.4%</td>
<td>9.7%</td>
</tr>
</tbody>
</table>
## Fatty Acid Profile of Treatment Oils

<table>
<thead>
<tr>
<th>Treatment Oils</th>
<th>SFA (%)</th>
<th>MUFA (%)</th>
<th>PUFA (%)</th>
<th>Omega-3 (%)</th>
<th>Omega-6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALA</td>
<td>DHA</td>
</tr>
<tr>
<td>Canola</td>
<td>7.2</td>
<td>62.8</td>
<td>29.5</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>High Oleic Canola</td>
<td>6.5</td>
<td>72</td>
<td>17</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>High Oleic Canola + DHA</td>
<td>8.6</td>
<td>63.8</td>
<td>23.3</td>
<td>2.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Corn/Safflower</td>
<td>7.9</td>
<td>17.7</td>
<td>69.6</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Flax/Safflower</td>
<td>8.1</td>
<td>17.9</td>
<td>69.4</td>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>

60 g of oil/day based on 3000 kcal diet; consumed as a “smoothie”
Percentage Change in Lipids After 4-Weeks

a, b, c labels within the same parameter with unlikely superscript letters were significantly different between treatment groups (P<0.05)

# Between-Treatment Comparisons of Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Canola</th>
<th>CanolaDHA</th>
<th>CornSaff</th>
<th>FlaxSaff</th>
<th>CanolaOleic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td>119.32 ± 2.91&lt;sup&gt;a&lt;/sup&gt;&lt;sup,b&lt;/sup&gt;</td>
<td>117.43 ± 2.91&lt;sup&gt;b&lt;/sup&gt;</td>
<td>120.39 ± 2.91&lt;sup&gt;a&lt;/sup&gt;</td>
<td>120.47 ± 2.91&lt;sup&gt;a&lt;/sup&gt;</td>
<td>119.39 ± 2.91&lt;sup&gt;a&lt;/sup&gt;&lt;sup,b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td>77.07 ± 4.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>74.60 ± 4.04&lt;sup&gt;b&lt;/sup&gt;</td>
<td>77.06 ± 4.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77.60 ± 4.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76.75 ± 4.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Mean values within a row with different superscript letters are significantly different between treatments, \( P < 0.05 \) (mixed-model ANOVA and post hoc Tukey’s test).
Framingham 10-year CHD risk score before and after each treatment

Based on age, total cholesterol, HDL-C, systolic blood pressure, & gender

Stars indicate significance at p<0.05 vs before value

Plasma Fatty Acid Composition After Each Experimental Diet (G/100g)

<table>
<thead>
<tr>
<th>Total fatty acid (n=127)</th>
<th>Canola</th>
<th>CanolaDHA</th>
<th>CornSaff</th>
<th>FlaxSaff</th>
<th>CanolaOleic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>∑SFA</td>
<td>41.73a</td>
<td>0.18</td>
<td>43.31b</td>
<td>0.18</td>
<td>42.50cd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.69c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41.95ad</td>
</tr>
<tr>
<td>∑MUFA</td>
<td>18.04a</td>
<td>0.33</td>
<td>16.19b</td>
<td>0.33</td>
<td>14.49c</td>
</tr>
<tr>
<td>c18:1</td>
<td>14.90a</td>
<td>0.26</td>
<td>13.36b</td>
<td>0.26</td>
<td>11.62c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.10c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.51d</td>
</tr>
<tr>
<td>∑PUFA</td>
<td>40.21a</td>
<td>0.32</td>
<td>40.47a</td>
<td>0.33</td>
<td>43.30b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.57b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39.54c</td>
</tr>
<tr>
<td>∑n-6 PUFA</td>
<td>34.67a</td>
<td>0.30</td>
<td>30.91b</td>
<td>0.30</td>
<td>38.78c</td>
</tr>
<tr>
<td>c18:2n6</td>
<td>22.00a</td>
<td>0.23</td>
<td>18.68b</td>
<td>0.23</td>
<td>25.93c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.13d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21.52a</td>
</tr>
<tr>
<td>c20:4n6</td>
<td>9.28a</td>
<td>0.15</td>
<td>9.70b</td>
<td>0.15</td>
<td>9.59ab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.27c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.67b</td>
</tr>
<tr>
<td>∑n-3 PUFA</td>
<td>5.53a</td>
<td>0.09</td>
<td>9.58b</td>
<td>0.09</td>
<td>4.24c</td>
</tr>
<tr>
<td>c18:3n3</td>
<td>0.80a</td>
<td>0.03</td>
<td>0.57bc</td>
<td>0.03</td>
<td>0.49b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.60d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.63c</td>
</tr>
<tr>
<td>c20:5n3</td>
<td>1.09a</td>
<td>0.04</td>
<td>1.53b</td>
<td>0.04</td>
<td>0.49c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.45b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86d</td>
</tr>
<tr>
<td>c22:5n3</td>
<td>0.81a</td>
<td>0.03</td>
<td>0.34b</td>
<td>0.03</td>
<td>0.62c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.97d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.72e</td>
</tr>
<tr>
<td>c22:6n3</td>
<td>2.29a</td>
<td>0.08</td>
<td>7.14b</td>
<td>0.08</td>
<td>2.65a</td>
</tr>
<tr>
<td>n-6:n-3</td>
<td>6.54a</td>
<td>0.13</td>
<td>3.36b</td>
<td>0.13</td>
<td>9.40c</td>
</tr>
</tbody>
</table>

Values are least squares mean ± SEM

Means values with different superscript letters across rows denote significant differences at p<0.05

DEXA used for Visceral Adipose Tissue Mass

• DEXA measures % body fat and divides the body into three compartments: fat mass, bone mass, and lean mass.

• In addition, the DEXA method determines % fat, fat mass, bone mass and lean mass separately for the arms, trunk (android), and legs. (gynoid)

• Android:Gynoid ratio decreases risk factors for CVD

Dr. Xiaoran Liu
Effects of Canola and High-Oleic Acid Canola Oils on Abdominal Fat Mass in Individuals with Central Obesity

**Objective:**
Effect of diets low in saturated fatty acids and high in MUFA or PUFA on body composition in participants at risk for metabolic syndrome (MetS).

**Conclusions:**
Diets high in MUFA (compared with PUFA) reduced central obesity with an accompanying improvement in MetS risk factors. Diets high in MUFA may be beneficial for treating and perhaps preventing MetS.

Liu et al., Obesity, 2016 24:2261-2268
Body Weight Decreased Significantly from Baseline in Participants on All Diets Except the Flax/Safflower Oil Diet (n=54)

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canola</td>
<td>-0.91</td>
</tr>
<tr>
<td>High Oleic Canola</td>
<td>-1.18</td>
</tr>
<tr>
<td>CanolaDHA</td>
<td>-0.96</td>
</tr>
<tr>
<td>Corn/Safflower</td>
<td>-0.79</td>
</tr>
<tr>
<td>Flax/Safflower</td>
<td>-0.47</td>
</tr>
</tbody>
</table>

* Shows difference from baseline, p<0.05

Liu et al., Obesity, 2016 24:2261-2268
Energy Intake was the Same after Each Test Diet

<table>
<thead>
<tr>
<th></th>
<th>Canola</th>
<th>High Oleic Canola</th>
<th>Canola DHA</th>
<th>Corn/Safflower</th>
<th>Flax/Safflower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kcal)</td>
<td>2558 ± 62</td>
<td>2578 ± 55</td>
<td>2572 ± 55</td>
<td>2563 ± 53</td>
<td>2570 ± 60</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SEM
Correlation Between Changes in Abdominal Fat Mass and Changes in Blood Pressure (n=54) Liu et al., Obesity, 2016 24:2261-2268

<table>
<thead>
<tr>
<th>Changes from baseline</th>
<th>Canola</th>
<th>Abdominal fat mass</th>
<th>High Oleic Canola</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
<td>r</td>
</tr>
<tr>
<td>SBP</td>
<td>0.26</td>
<td>0.062</td>
<td>0.39</td>
</tr>
<tr>
<td>DBP</td>
<td>0.38</td>
<td>0.0049</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Correlation Between Changes in Abdominal Fat Mass and Changes in Triglycerides in Response to the High Oleic Canola Diet (n=54)

\[ r = 0.42, p = 0.0017 \]
COMIT Conclusion - Body Composition

• A diet very high in MUFA reduced visceral adipose tissue (i.e., belly fat).
• A decrease in visceral adipose tissue resulted in a decrease in triglycerides and blood pressure.
MUFA consumption & body composition

A meta-analysis of long-term (>6 months) intervention trials: Effect of high-MUFA diets (>12% energy) vs. low-MUFA (≤12% energy) on body weight and fat mass

High-MUFA diet compared with a low-MUFA diet significantly reduced …

BODY WEIGHT by 1.71 kg
(95% CI −3.41 to −0.02), \( P = 0.05 \)

FAT MASS by 1.94 kg
(95% CI −3.72 to 0.17), \( P = 0.03 \)

Schwingshackl et al., Ann Nutr Metab 2011;59:176–186
Substitution of Saturated with Monounsaturated Fat in a 4-week Diet affects Body Weight and Composition in Overweight and Obese Men (N=8)

The men had a lower weight (-2.1 (SE 0.4) kg, P=0.0015) and fat mass (-2.6 (SE 0.6) kg, P=0.0034) at the end of the MUFA-rich diet as compared with values at the end of the SFA-rich diet.

Intake of High-Oleic Peanuts (HOP) Improves Body Composition and in Overweight /Obese Men on a 4 Week Energy-Restricted Diet

HOP = High-oleic peanuts, 56 g/d
CVP = conventional peanuts, 56 g/d
CT = control

- Body weight and composition did not differ between groups.
- However, total body fat (kg) decreased with CVP and HOP compared to baseline, with a significant decrease in body fat percentage in HOP.
- While total lean mass (kg) decreased in CT, total lean mass (%) increased in HOP.
A Lower-Carbohydrate, Higher-Fat Diet Reduces Abdominal and Intermuscular Fat in Adults (n=69) at Risk of Type 2 Diabetes

Low fat diet: 55% CHO, 18% Pro; 27% fat
Low CHO diet: 43% CHO; 18% Pro; 39% fat

• After 8 weeks, loss of intra-abdominal adipose tissue (IAAT) was significantly greater (P < 0.05) in participants who consumed the lower-carbohydrate diet (11%) than in those who consumed the lower-fat diet.

• In the weight loss phase, total fat mass loss was greater in participants who consumed the lower-carbohydrate (4.4%) diet vs. those who consumed the lower-fat diet (P < 0.05)
Low-carbohydrate, higher fat weight loss interventions led to an average 1.15 kg greater long-term weight loss than low-fat weight loss interventions, with minimal between-study heterogeneity.

Beneficial Effect of Low Carbohydrate in Low Calorie Diets on Visceral Fat Reduction in Patients with Type 2 Diabetes (N=22) with Obesity After 4 Weeks

Low carbohydrate (40%E) diet group (●); High carbohydrate (65%E) diet group (○)

- The ratio of visceral fat area to subcutaneous fat area did not change in the high carbohydrate diet group (from 0.70 to 0.68), but it decreased significantly in the low carbohydrate diet group (from 0.69 to 0.47, \( P<0.05 \)).
- These results suggest that a low calorie/low carbohydrate diet might be a more effective treatment for a reduction of visceral fat, than low calorie/high carbohydrate diet in obese subjects with type 2 diabetes mellitus.

What Mechanisms May Account for the Effect of MUFA on Adiposity?
Role for fatty acid ethanolamides in understanding the effects of MUFA on body composition

Dietary Fatty Acids

Fatty Acid Ethanolamide Levels in Plasma

Fatty Acid Composition in Plasma

Fat Oxidation, Energy Expenditure & Appetite
Fatty Acid Ethanolamides

- Series of N-acylethanolamines
- Lipid mediators
- Fatty acid derivatives
- Several types of acyl groups - linked to the nitrogen atom of ethanolamine

<table>
<thead>
<tr>
<th>Fatty Acid Ethanolamide</th>
<th>Abbreviation</th>
<th>Fatty Acid</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleoyl ethanolamide</td>
<td>OEA</td>
<td>Oleic acid</td>
<td>OA</td>
</tr>
<tr>
<td>Arachidonoyl ethanolamide</td>
<td>AEA</td>
<td>Arachidonic acid</td>
<td>AA</td>
</tr>
<tr>
<td>Palmitoyl ethanolamide</td>
<td>PEA</td>
<td>Palmitic acid</td>
<td>PA</td>
</tr>
<tr>
<td>Linoleoyl ethanolamide</td>
<td>LEA</td>
<td>Linoleic acid</td>
<td>LA</td>
</tr>
<tr>
<td>Alpha-linolenoyl ethanolamide</td>
<td>ALEA</td>
<td>Alpha-linolenic acid</td>
<td>ALA</td>
</tr>
<tr>
<td>Docosahexaenoyl ethanolamide</td>
<td>DHEA</td>
<td>Docosahexaenoic acid</td>
<td>DHA</td>
</tr>
</tbody>
</table>
Plasma FAE Levels in Response to COMIT Diets

a,b,c labels within the same FAE with unlikely superscript letters were significantly different between treatment groups. P<0.05.

a,b,c labels within the same FAE with unlikely superscript letters were significantly different between treatment groups. P<0.05.
Android Mass Change Correlates with FAE - OEA levels in COMIT Participants

R = -0.244, P = 0.005

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canola</td>
<td>R = -0.112, P = 0.599</td>
</tr>
<tr>
<td>CanolaDHA</td>
<td>R = -0.016, P = 0.942</td>
</tr>
<tr>
<td>CornSaff</td>
<td>R = -0.433, P = 0.024</td>
</tr>
<tr>
<td>Flaxsaff</td>
<td>R = -0.316, P = 0.115</td>
</tr>
<tr>
<td>CanolaOleic</td>
<td>R = -0.459, P = 0.018</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>R = -0.244, P = 0.005</td>
</tr>
</tbody>
</table>
Mechanism of Action of MUFA in Reducing Abdominal Fat Mass

Bowen et al. Prog Lipid Res 2017

- Oleic acid derived oleoyl ethanol amide (OEA) binds to PPAR-α in liver and muscle to promote fat utilization through increased uptake of fatty acids and fatty acid β-oxidation.
Effect of oleic, linoleic, and alpha-linolenic acid-rich oils on fat oxidation and energy expenditure in healthy men

Energy Expenditure:
Olive > Sunflower > Flaxseed

Jones et al., Metabolism 2008;57:1198-1203
Increased MUFA Intake is Associated with Increased Fat Oxidation and/or Energy Expenditure

- Healthy subjects were given either a high MUFA diet (oleic acid: 31.4%, palmitic acid: 1.7%, n=22) or high SFA diet (oleic acid: 16.4%, palmitic acid: 16.8%, n=21) for 28 days.
- High OA diet increased the rate of FA oxidation in females.
- High OA diet increased daily energy expenditure in males.

Consumption of High MUFA Diets for 3 Weeks Increased Resting Energy Expenditure

- Cohort 1: Healthy subjects (n=18)
- Cohort 2: Obese and non-obese subjects (n=14)
- Subjects were given high MUFA (OA: 28.8%, PA: 2.4%) and high SFA (OA: 16.2%, PA: 16%) for 3 weeks follow by a 1-week washout period.

Effect of dietary fatty acid composition on substrate utilization and body weight maintenance in humans

Sridevi Krishnan · Jamie A. Cooper

DOI 10.1007/s00394-013-0638-z

Received: 17 July 2013/Accepted: 30 November 2013/Published online: 22 December 2013
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Abstract

Background/purpose Dietary fat content is a primary factor associated with the increase in global obesity rates. There is a delay in achieving fat balance following exposure to a high-fat (HF) diet (≥ 40 % of total energy from fat) compared to a low-fat diet (≤ 30 % of total energy from fat). The aim of this study was to compare the effects of saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA) on substrate utilization and body weight maintenance in humans.

Methods In total, 29 healthy male and female volunteers (aged 19–35 years) were randomized to one of three 4-week dietary interventions: SFA, MUFA, or PUFA. They were individually matched for age, sex, body mass index, and physical activity level. They were asked to consume diets containing 50 % of their energy from fat. Dietary fat was divided into 30 % SFA, 10 % MUFA, and 10 % PUFA in the SFA, 10 % SFA, 30 % MUFA, and 10 % PUFA in the MUFA, and 10 % SFA, 10 % MUFA, and 30 % PUFA in the PUFA intervention groups.

Results There were no statistically significant differences in body weight change, body mass index, or substrate utilization among the three diet groups. However, there was a significant increase in the ratio of PYY to ghrelin in the SFA group compared to the MUFA and PUFA groups. The SFA group also had a lower ratio of acetate to propionate than the MUFA and PUFA groups.

Conclusion SFA are likely more obesigenic than MUFA, and PUFA. The unsaturated fats appear to be more metabolically beneficial, specifically MUFA ≥ PUFA > SFA, as evidenced by the higher DIT and FOx following HF meals or diets.
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventós, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*
Modified slide from J. Sabate.

PREDIMED TRIAL: DESIGN

- Men: 55-80 yr
- Women: 60-80 yr
- High CV risk without CVD
  - Type 2 diabetics
  - 3+ risk factors

1. Smoking
2. Hypertension
3. ↑ LDL
4. ↓ HDL
5. Overweight/obese
6. Family history

Random

All free of CVD at baseline

MedDiet + Olive Oil
N=2500

MedDiet + NUTS
N=2500

CONTROL GROUP
n=2500
Difference Between MeDiet + EVOO and MeDiet + Nuts

MeDiet + EVOO

EVOO (1L/week/family = 50 g/day)

MeDiet + Nuts

Walnuts 15 g/d
Almonds 7.5 g/d
Hazelnuts 7.5 g/d

## PREDIMED: Intake of Energy and Nutrients at the End of the Trial by Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>MeDiet + EVOO</th>
<th>MeDiet + Nuts</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kcal</td>
<td>2172</td>
<td>2229</td>
<td>1960</td>
</tr>
<tr>
<td>CHO, % E</td>
<td>40</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>Fat, % E</td>
<td>41</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>SFA, % E</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>MUFA, % E</td>
<td>22</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>PUFA, % E</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Linoleic acid, g/d</td>
<td>12</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>ALA, g/d</td>
<td>1.3</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Marine n-3 FA, g/d</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

PREDIMED Trial: The Incidence of Acute Myocardial Infarction, Stroke, and Death from Cardiovascular Causes by Treatment

Med diet, EVOO: hazard ratio, 0.70 (95% CI, 0.53–0.91); P=0.009
Med diet, nuts: hazard ratio, 0.70 (95% CI, 0.53–0.94); P=0.02

Figure S6. Kaplan-Meier Estimates of Incidence of the Significant Separate Component (Stroke) of the Primary Endpoint

Average bodyweight of PREDIMED participants during follow-up, by intervention group

- Participants in EVOO group had a significant decrease in bodyweight during the trial.
- Average between-group changes were only significant at 3 years ($p=0.026$) and 5 years ($p=0.044$).
- Participants in the nut group showed a non-significant decrease in bodyweight at 3 years and a significant decrease at 5 years compared with baseline, but did not differ from the control group.

Average waist circumference of PREDIMED participants during follow-up, by intervention group

- Changes in waist circumference initially paralleled those of bodyweight.
- However, after 3 years and 5 years, absolute, albeit small, increases in waist circumference were noted.
- Compared to the control group there were significantly lower waist circumference increases at 3 years and 5 years for the EVOO group and at 5 years for the nut group.

What is an Optimal Dietary Fatty Acid Profile?

- **Polyunsaturated Fats**
  - omega-6
  - omega-3

- **Saturated Fats**

- **Monounsaturated Fats**
  - omega-9

- Trans Fat
What is an Optimal Dietary Fatty Acid Profile?

- **Monounsaturated Fats**
  - omega-9

- **Saturated Fats**

- **Polyunsaturated Fats**
  - omega-6
  - omega-3

- **Trans Fat**
What is an Optimal Dietary Fatty Acid Profile?

Monounsaturated Fats

Polyunsaturated Fats

omega-6

Saturated Fats

omega-3

Trans Fat

omega-9

Monounsaturated Fats
DIETARY FATS AND CARDIOVASCULAR DISEASE
A PRESIDENTIAL ADVISORY FROM THE AMERICAN HEART ASSOCIATION

ABSTRACT: Cardiovascular disease (CVD) is the leading global cause of death, accounting for 17.3 million deaths per year. Preventive treatment that reduces CVD by even a small percentage can substantially reduce, nationally and globally, the number of people who develop CVD and the costs of caring for them. This American Heart Association presidential advisory on dietary fats and CVD reviews and discusses the scientific evidence, including the most recent studies, on the effects of dietary saturated fat intake and its replacement by other types of fats and carbohydrates on CVD. In summary, randomized controlled trials that lowered intake of dietary saturated fat and replaced it with polyunsaturated vegetable oil reduced CVD by \( \approx 30\% \), similar to the reduction achieved by statin treatment. 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 of other major causes of death and all-cause mortality. In contrast, replacement of saturated fat with mostly refined carbohydrates and sugars is not associated with lower rates of CVD and did not reduce CVD in clinical trials. Replacement of saturated with unsaturated fats lowers low-density lipoprotein cholesterol, a cause of atherosclerosis, linking biological evidence with incidence of CVD in populations and in clinical trials. Taking into consideration the totality of the scientific evidence, satisfying rigorous criteria for causality, we conclude strongly that lowering intake of saturated fat and replacing it with unsaturated fats, especially polyunsaturated fats, will lower the incidence of CVD. This recommended shift from saturated to unsaturated fats should occur simultaneously in an overall healthful dietary pattern such as DASH (Dietary Approaches to Stop Hypertension) or the Mediterranean diet as emphasized by the 2013 American Heart Association/American College of Cardiology lifestyle guidelines and the 2015 to 2020 Dietary Guidelines for Americans.

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Linda V. Van Horn, PhD, RD, FAHA, Vice Chair
On behalf of the American Heart Association

Cardioprotective Benefits of Linoleic Acid

Dietary LA was associated with a 15% lower risk of CHD events and 21% lower risk of CHD deaths

α-Linolenic Acid and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis

An Pan, Mu Chen, Rajiv Chowdhury, Jason HY Wu, Qi Sun, Hannia Campos, Dariush Mozaffarian, and Frank B Hu

Conclusions: In observational studies, higher ALA exposure is associated with a moderately lower risk of CVD. The results were generally consistent for dietary and biomarker studies but were not statistically significant for biomarker studies. However, the high unexplained heterogeneity highlights the need for additional well-designed observational studies and large randomized clinical trials to evaluate the effects of ALA on CVD.

27 papers included:
16 Diet & CVD
14 Biomarker & CVD
Between 0 and 250 mg/day, mortality risk was decreased by 14.6%; between 250 and 500 mg/day, risk was decreased by 25%.
Fat, Carbohydrates, and Heart Disease: Estimated Percentage of Changes in the Risk of Coronary Heart Disease Associated With Isocaloric Substitutions of 1 Dietary Component for Another
Summary

• With the alarming global epidemic of metabolic syndrome, there is a pressing need to reduce the growing prevalence of this chronic disease.
• A healthy dietary pattern is the cornerstone for the prevention and treatment of metabolic syndrome.
• Weight loss and regular physical activity are important but new treatment options are needed.
• The biological effects of MUFA on fatty acid oxidation, diet-induced thermogenesis and ingestive behavior are promising new strategies for the prevention and treatment of metabolic syndrome.
Thank You!