Gezond ouder worden in een pro-inflammatoire Westerse maatschappij

Frits A.J. Muskiet

Laboratorium Geneeskunde
UMCG
NL: life expectancy and life expectancy without physical limitation increase, but life expectancy without chronic disease falls!
Hunter-gatherer mortality

Causes of death:

- Infectious disease (GI, respiratory)
- Violence
- Famine
- Lack of secondary prevention

Solved by:

- Public health
- Culture
- Agricultural revolution
- Health care

Hill, J Hum Evol 2007
1. **Normal aging**  
   (also known as healthy aging and primary aging)

2. **Pathological aging**  
   (also known as age-related disease and secondary aging)

3. **Premature aging**  
   (also known as segmental progeria)

*Van de Ven, Mech Ageing Dev 2007*
Primary aging

Primary aging is the gradual and inevitable process of body deterioration that takes place throughout life. This aging is genetic. It's the preprogrammed coding that our bodies follow.

Secondary aging

Secondary aging results from disease, lack of physical activity, unhealthy habits (smoking and drinking), poor nutrition and exposure to hazardous materials.
Healthy Aging is the ability to maintain:

1. Low risk of disease or disability
2. High mental & physical function
3. Active engagement with life
Outline

Demographics and aging
Lifestyle may affect aging via telomere length
Role of inflammation and oxidative stress
Our pro-inflammatory lifestyle
  Physical activity
  Diet
    Vegetables/fruits
    Fish fatty acids
Lifestyle intervention
21st Century hunter gatherer
### Some aging hypotheses
(not necessarily mutually exclusive)

<table>
<thead>
<tr>
<th>Theory</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Telomere theory</td>
<td>Accumulative-Waste theory</td>
</tr>
<tr>
<td>Reproductive-Cell Cycle theory</td>
<td>Autoimmune theory</td>
</tr>
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<td>Evolutionary theories</td>
<td>Mitohormesis (calorie restriction)</td>
</tr>
<tr>
<td>Non-infectious chronic inflammation</td>
<td>Insulin resistance</td>
</tr>
</tbody>
</table>
## Factors affecting telomere length

- Age
- Genetic and epigenetic make-up
- Environment
- Socio-economic status
- Exercise
- Body weight,
- Unhealthy diet (fiber, PUFA notably LA)
- Environmental pollution
- Nature of profession
- Stress

## Diseases related to shorter telomere length

- Myocardial infarction
- Coronary heart disease
- Heart failure
- Diabetes
- Genomic instability
- Cancer risk (lung, bladder, renal cell, gastrointestinal, and head and neck cancers)
- Osteoporosis

Telomere length in humans seems to decrease at a rate of 24.8–27.7 base pairs per year.

Shammas, Curr Opin Clin Nutr Metabol Care 2011
The leukocytes derived from athletes had elevated telomerase activity and reduced telomere shortening, relative to nonathletes.

Peripheral blood leukocytes isolated from endurance athletes showed increased telomerase activity, expression of telomere-stabilizing proteins, and downregulation of cell-cycle inhibitors compared with untrained individuals.

Werner, Circulation 2009
Relative telomere length of leukocyte DNA was on average 5.1% longer among daily multivitamin users.
Baseline omega-3 fatty acid levels are associated with changes in leukocyte telomere length over 5 years in a prospective cohort study of outpatients with coronary artery disease. 5 years study; 608 subjects; Baseline EPA+DHA levels in fasting whole blood not related to telomere length. Baseline EPA+DHA levels positively related with 5-year change in telomere length in 5 years.
Telomere length relates positively to Chinese tea consumption in 976, 65+ Chinese men

There are three major types of tea, depending on the level of fermentation: green (unfermented), oolong (partially fermented) and black (fermented) tea. Both green and oolong teas are popular in the Chinese population.

Chan, Br J Nutr 2010
Higher 25(OH)D relates to leukocyte telomere length

1. Leukocyte telomere length (LTL) is a predictor of aging-related disease
2. LTL decreases with each cell cycle and increased inflammation
3. 2,160 women aged 18–79 y (mean age: 49.4)
4. Age: negatively correlated with LTL
5. Serum 25(OH)D: positively associated with LTL
6. Relation persisted after adjustment for age, season of vitamin D measurement, menopausal status, use of hormone replacement therapy, and physical activity
7. Difference in LTL between the highest (124 nmol/L) and lowest (41 nmol/L) tertiles of 25(OH)D was 107 base pairs, which is equivalent to 5.0 y of telomeric aging

Richards, AJCN 2007
Premature aging of skin of vitamin D receptor (VDR) knockout mice (KO) is visible at the age of 8-9 months.

Tuohimaa, Psychoneuroendocrinology 2009
Telomers and the (pleiotropic) statins: Statin users have longer telomers

- Reduction of vascular inflammation
- Reduction of intracellular reactive oxygen species (ROS) generation
- Increase of nitric oxide (NO) bioavailability
- Reduction of platelet aggregation and thrombus deposition
- Stimulation of the angiogenic process
- Immuno-modulatory actions. Recently, the following additional pleiotropic effects of statins have been highlighted:
  - Reduction of cholesterol levels in erythrocyte membranes, considered a marker of clinical instability in patients with coronary artery disease (CAD).
  - Induction of mobilization, proliferation, differentiation, prevention of cellular senescence and reduction of apoptosis of different vascular cell types, including circulating bone marrow-derived endothelial progenitor cells (EPC), mature EC and VSMCs.
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Reactive oxygen species (ROS)
superoxide radical (O2.–), hydroxyl radical (.OH), hydrogen peroxide (H2O2), nitric oxide (NO), peroxynitrite radical (ONOO.)

ROS indispensable in:
- Intracellular messaging
- Cellular differentiation
- Growth arrestment
- Apoptosis
- Immunity
- Defense against microorganisms

ROS-antioxidant imbalance
- Too much ROS generation
- Depression of antioxidant systems
- Causes oxidative stress

Lifestyle origins
- Inappropriate diet
- Physical inactivity
- Smoking, pollution, insufficient sleep, bacteria, etc

Roberts, Life Sci 2009
Inflammation may be useful when controlled, but deadly when it is not

Rogers, J Peridontol 2008
19th Century data: low mortality in a cohort of age 1 predicts higher body length and low mortality in the same cohort at age 70.
Less infection and inflammation at young age contributes to better growth and development and longevity: reduced levels of inflammation will delay aging processes relevant to mortality.
Outline

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More than 95% of our diseases are caused by environment

Our genetic material has a secondary role at most
Environmental influences on major diseases

PARs for lifestyle (here: specific aspects of diet, overweight, inactivity, smoking)

Willett, Science 2002
We bevinden ons in een pro-inflammatoire toestand.
The difference between classical inflammation initiated by a microbial antigen or injury, and metaflammation caused by lifestyle or environmental inducers

A. Classical, acute, infectious response

B. Modern, chronic, Non-infectious response

Egger, Br J Nutr 2009
Inflammation and metabolism are intimately related.

Hotamisligil, Nat Rev Immunol 2008
Huidige leefstijl

Chronische systemische lage graad ontsteking

Insuline resistentie

Metabool syndroom

Metabool syndroom gerelateerde ziektes
Centenarians vs. adults of various ages

- Lower body mass index (BMI)
- Lower body fat
- Lower plasma triglycerides
- Lower oxidative stress levels (higher vitamin E)
- Higher insulin sensitivity (less risk T2D)
- Higher plasma levels of active IGF-1 (IFG-1/IGFBP-3)
- 90% of centenarians living independent at age 90

Barbieri, Horm Res 2009; Paolisso, J Clin Endocrinol Metab 1997
Factoren in onze leefstijl die ons in een pro-inflammatoire toestand hebben gebracht of anti-inflammatoire responsen verhinderen

1. abnormale voedingssamenstelling
2. abnormale microbiëlle flora
3. onvoldoende fysieke activiteit
4. chronische stress
5. slaaptekort
6. milieu verontreiniging (b.v. roken)
Recalled physical activity at 15, 30, and 50 years in a large sample of Swedish men (n=33,466) from 1932-1997

The decline in activity was especially marked at 15 years of age from the 1940s through the 1960s which was due to a reduction in work or occupational activity. At the three ages, the decrease in physical activity over time was due in large part to a reduction in occupational and leisure time activities.
Exercise elicits an anti-inflammatory reaction

In sepsis (A), the cytokine cascade within the first few hours consists of TNF-alpha, IL-1, IL-6, IL-1ra, TNF-R, and IL-10.

The cytokine response to exercise (B) does not include TNF-alpha and IL-1 but does show a marked increase in IL-6, which is followed by IL-1ra, TNF-R, and IL-10. Increased CRP levels do not appear until 8–12 h later.

Petersen, J Appl Physiol 2005
Het belangrijkste effect van fysieke activiteit voor de preventie van leefstijl-geassocieerde ziektes is om de insuline gevoeligheid te verbeteren

Voedingskarakteristieken die we veranderd hebben sinds de landbouw en de industriële revolutie
Gezondheidverlies (incidentie van ziekte, sterfte) veroorzaakt omdat 5 voedingsfactoren (SAFA, transvetzuren, vis, fruit en groente) en lichaamsgewicht (BMI) niet voldoen aan de aanbevelingen.

Van alle sterfgevallen

Ons eten gemeten, RIVM 2004
Fruit & Vegetables

One serving of fruit, or vegetables, is 80 grams (2.8oz). You should eat at least five servings every day to get enough vitamins, minerals and fibre.

USA: 1 serving = 80 g
Advice: 5 servings = 400 g/day
Wat u doet
En wat u denkt dat u doet

De meeste Nederlanders denken dat ze niet alleen lekker maar ook goed eten

Groente: 10% denkt te weinig groente te eten; in werkelijkheid is dat 80%

Fruit: 33% denkt onvoldoende fruit te eten; in werkelijkheid is dat 60%

NHS; Eten naar hartelust, januari 2010
Representative natural dietary bioactive compounds and their sources

Pan, J Agric Food Chem 2009
Antioxidant defence network

Benzie, Eur J Nutr 2000
Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of 12 cohort studies (278,459 subjects, 9,143 events).

<table>
<thead>
<tr>
<th>Author</th>
<th>Servings per day</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu⁸</td>
<td>3-5 serving/d</td>
<td>0.45 (0.24-0.83)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>0.64 (0.46-0.90)</td>
</tr>
<tr>
<td>Hirvonen⁹</td>
<td>3-5 serving/d</td>
<td>0.95 (0.90-1.00)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>Joshipura¹⁰  (Men)</td>
<td>3-5 serving/d</td>
<td>0.98 (0.85-1.13)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>0.94 (0.79-1.13)</td>
</tr>
<tr>
<td>Joshipura¹⁰  (Women)</td>
<td>3-5 serving/d</td>
<td>0.81 (0.73-1.00)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>0.95 (0.78-1.15)</td>
</tr>
<tr>
<td>Liu¹¹</td>
<td>3-5 serving/d</td>
<td>0.79 (0.65-0.98)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>1.11 (0.83-1.48)</td>
</tr>
<tr>
<td>Bazzano¹²</td>
<td>3-5 serving/d</td>
<td>0.88 (0.71-1.10)</td>
</tr>
<tr>
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<td>&gt;5 serving/d</td>
<td>1.12 (0.87-1.46)</td>
</tr>
<tr>
<td>Steffen¹³</td>
<td>3-5 serving/d</td>
<td>0.95 (0.80-1.13)</td>
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<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>1.04 (0.81-1.34)</td>
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<tr>
<td>Dauchet¹⁴</td>
<td>3-5 serving/d</td>
<td>0.85 (0.62-1.21)</td>
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<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>1.04 (0.74-1.47)</td>
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<tr>
<td>Tucker¹⁵</td>
<td>3-5 serving/d</td>
<td>0.88 (0.62-1.31)</td>
</tr>
<tr>
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<td>&gt;5 serving/d</td>
<td>1.07 (0.71-1.63)</td>
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<td>Mann¹⁷</td>
<td>3-5 serving/d</td>
<td>0.85 (0.54-1.34)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>0.90 (0.57-1.42)</td>
</tr>
<tr>
<td>Sahyoun¹⁹</td>
<td>&gt;5 serving/d</td>
<td>0.62 (0.48-0.80)</td>
</tr>
<tr>
<td>Fraser²⁰</td>
<td>3-5 serving/d</td>
<td>1.17 (0.79-1.73)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>1.18 (0.82-1.70)</td>
</tr>
<tr>
<td>Knekt²⁴</td>
<td>3-5 serving/d</td>
<td>0.78 (0.66-0.93)</td>
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<tr>
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<td>&gt;5 serving/d</td>
<td>0.79 (0.70-0.89)</td>
</tr>
<tr>
<td>Pooled RR</td>
<td>3-5 serving/d</td>
<td>0.93 (0.86-1.00)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 serving/d</td>
<td>0.83 (0.77-0.89)</td>
</tr>
</tbody>
</table>

<3 vs. >5 servings/day relates to 17% difference in CHD risk.

He, J Hum Hypertens 2007
Meta-analysis

Prospective studies

He, Lancet 2006

3-5 vs. >5 servings/day:

<3 vs. 3-5 servings/day: 11% difference in stroke risk

<3 vs. >5 relates to 26% stroke difference

Servings per day

<table>
<thead>
<tr>
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<th>Relative risk (95% CI)</th>
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<tr>
<td>&lt;3</td>
<td>0.89 (0.66–1.20)</td>
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<tr>
<td>3–5</td>
<td>0.70 (0.58–0.85)</td>
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<tr>
<td>&gt;5</td>
<td>0.77 (0.49–1.20)</td>
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<tr>
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</tr>
</tbody>
</table>

Hirvonen et al\textsuperscript{7}

Bazzano et al\textsuperscript{8}

Johnsen et al\textsuperscript{9}

Sauvaget et al\textsuperscript{10}

Steffen et al\textsuperscript{11}

Keli et al\textsuperscript{15}

Gillman et al\textsuperscript{16}

Pooled relative risk

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<td>3–5</td>
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<td>&gt;5</td>
<td>0.74 (0.69–0.79)</td>
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WCRF-AICR (1997) and COMA (1998) reports on the possible effect of high fruit and vegetable consumption on cancer risk

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>WCRF-AICR</th>
<th>COMA</th>
</tr>
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<tbody>
<tr>
<td>Mouth and pharynx</td>
<td>Convincing</td>
<td>Weakly consistent for fruit, inconsistent for vegetables</td>
</tr>
<tr>
<td>Larynx</td>
<td>Probably</td>
<td>Moderately consistent, limited data</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Convincing</td>
<td>Strongly consistent</td>
</tr>
<tr>
<td>Lung</td>
<td>Convincing, particularly for green vegetables and carrots</td>
<td>Moderately consistent for fruit, weakly consistent for vegetables</td>
</tr>
<tr>
<td>Stomach</td>
<td>Convincing, in particular for raw vegetables, allium vegetables, and citrus fruit</td>
<td>Moderately consistent</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Probable</td>
<td>Strongly consistent, limited data</td>
</tr>
<tr>
<td>Liver</td>
<td>Possible for vegetables, not fruit</td>
<td>Not included in the review</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>Convincing for vegetables, limited and inconsistent data for fruit</td>
<td>Moderately consistent for vegetables, inconsistent and limited data for fruit</td>
</tr>
<tr>
<td>Breast</td>
<td>Probable, in particular for green vegetables</td>
<td>Moderately consistent for vegetables, weakly consistent for fruit</td>
</tr>
<tr>
<td>Ovary</td>
<td>Possible</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Possible</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Cervix</td>
<td>Possible</td>
<td>Strongly consistent, limited data</td>
</tr>
<tr>
<td>Prostate</td>
<td>Possible for vegetables, inconsistent for fruit</td>
<td>Moderately consistent, especially raw and salad type for vegetables, inconsistent for fruit</td>
</tr>
<tr>
<td>Kidney</td>
<td>Possible for vegetables, limited evidence for fruit</td>
<td>Not included in the review</td>
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<tr>
<td>Thyroid</td>
<td>Possible</td>
<td>Not included in the review</td>
</tr>
<tr>
<td>Bladder</td>
<td>Probable</td>
<td>Moderately consistent, limited data</td>
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1 WCRF-AICR, World Cancer Research Fund–American Institute for Cancer Research; COMA, Chief Medical Officer’s Committee on Medical Aspects of Food and Nutrition Policy of the United Kingdom.

Riboli, AJCN 2003
Fat intake of hominids and *homo sapiens*

Common ancestor with chimpanzee
Switch from vegetarian to hunting-gathering omnivore
-160,000 years: *homo sapiens*

Society
- Hunter-gatherer
- Agricultural
- Industrial

Total fat
Fatty acids
Saturated

Paleolithic diet
Agricultural revolution
Industrial revolution

Simopoulos, AJCN 1999
Low LCPω3 status involved in the (patho)physiology of:

1. (neuro)development
2. coronary artery disease
3. psychiatric disorders
4. pregnancy complications
5. others
GISSI: secondary prevention trial
11,324 MI patients; 1 g n-3/day; 3.5 y NNT at low risk (2.6% annual mortality)=164 patients

Marchioli et al. Circulation 2002

Lavie, J Am Coll Cardiol 2009
EPA >60% is effective in depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>% EPA</th>
<th>% Weight</th>
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<tr>
<td>Peet and Horrobin, 2002</td>
<td></td>
<td>100</td>
<td>9.40</td>
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<td>Nemets et al, 2002</td>
<td></td>
<td>100</td>
<td>5.60</td>
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<td>14.20</td>
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<td>8.30</td>
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<td>Frangou et al, 2006</td>
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<td>13.90</td>
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<tr>
<td>Su et al, 2003</td>
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<td>66.67</td>
<td>6.80</td>
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<td>66.67</td>
<td>5.60</td>
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<tr>
<td>Su et al, 2008</td>
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<td>64.71</td>
<td>9.20</td>
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<tr>
<td>da Silva et al, 2008</td>
<td></td>
<td>60</td>
<td>3.60</td>
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<tr>
<td>da Silva et al, 2008</td>
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<td>60</td>
<td>4.40</td>
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<tr>
<td><strong>Overall EPA ≥ 60%</strong></td>
<td></td>
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<tr>
<td>Freeman et al, 2008</td>
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<td>57.89</td>
<td>9.50</td>
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<tr>
<td>Carney et al, 2009</td>
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<td>55.36</td>
<td>20.70</td>
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<td>Rogers et al, 2008</td>
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<td>42.57</td>
<td>35.50</td>
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<td>Grenyer et al, 2007</td>
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<td>21.43</td>
<td>11.50</td>
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<tr>
<td>Rees et al, 2008</td>
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<td>20.18</td>
<td>4.00</td>
</tr>
<tr>
<td>Silvers et al, 2005</td>
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<td>20</td>
<td>12.70</td>
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<tr>
<td>Marangell et al, 2003</td>
<td></td>
<td>0</td>
<td>6.10</td>
</tr>
<tr>
<td><strong>Overall EPA &lt; 60%</strong></td>
<td></td>
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</tr>
</tbody>
</table>

Effective dose is 200-2,200 EPA in excess of DHA per day, Sublette, J Clin Psychiatry 2011
Reported frequency of fish consumption by the Dutch population aged 7-69 years (DNFCS 2007-2010), weighted for socio-demographic factors and season

<table>
<thead>
<tr>
<th></th>
<th>7-8 years</th>
<th>9-13 years</th>
<th>14-18 years</th>
<th>19-30 years</th>
<th>31-50 years</th>
<th>51-69 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total (n=304) %</td>
<td>male (n=351) %</td>
<td>female (n=352) %</td>
<td>male (n=352) %</td>
<td>female (n=354) %</td>
<td>male (n=356) %</td>
</tr>
<tr>
<td>Twice or more per week (=recommended)</td>
<td>6-28%</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Less than twice per week</td>
<td>82</td>
<td>87</td>
<td>79</td>
<td>80</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td>Less than twice but at least once per week</td>
<td>28-65%</td>
<td>41</td>
<td>36</td>
<td>28</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Never</td>
<td>5-18%</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>11</td>
<td>18</td>
</tr>
</tbody>
</table>
Fish is high in EPA and DHA

Richtlijnen Goede Voeding 2006: 450 mg/dag

NL, VCP-2003:
EPA+DHA:
F  84 mg/day
M  103 mg/day
The historical event immediately preceding the largest increase in apparent consumption of soy oil in the United States was the 1961 American Heart Association (AHA) Central Committee Advisory Statement that advised Americans to replace their saturated fat intake with polyunsaturated fats.

Blasbalg, Ramsden AJCN 2011
Linoleic and alpha-linolenic acid content in mature breast milk of US women from 1945-present

Both milk DHA and AA have declined about 50% in Vancouver from 1988-1998 (Innis, J Pediatr 2003)

In Australia, from 1981-2000, the milk LA content increased while the milk DHA decreased

Ailhaud, Prog Lipid Res 2006
Outline

Demographics and aging
Lifestyle may affect aging via telomere length
Role of inflammation and oxidative stress
Our pro-inflammatory lifestyle
   Physical activity
   Diet
      Vegetables/fruits
      Fish fatty acids
Lifestyle intervention
21st Century hunter gatherer
De trigger en het aanhouden hiervan is abnormaal
NIET de respons
Huidige leefstijl

Chronische systemische lage graad ontsteking

Insuline resistentie

Metabool syndroom

tijd

Metabool syndroom
tijd

gerelateerde ziektes
All cause mortality: Statin vs. Diet

Scandinavian Simvastatin Survival Study (4 S)

- About 2.5% less deaths

Lyon Diet Heart study (Mediterranean type of diet)

- About 12% less deaths

Pedersen, Atheroscler Suppl 2004

De Lorgeril, Lancet 1994
Iso-energetic Paleolithic vs. Usual diet
9 non-obese healthy volunteers, sedentary, BMI 27.8, 3 days usual diet, 3 days ramp-up diet, 10 days Paleolithic diet

<table>
<thead>
<tr>
<th>Diet factors</th>
<th>Usual diet</th>
<th>delta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (Kcal)</td>
<td>2372 ± 886</td>
<td>+ 329 ± 840</td>
<td>NS</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>107 ± 49</td>
<td>+ 91 ± 50</td>
<td>0.0006</td>
</tr>
<tr>
<td>Carbohydrates (g)</td>
<td>254 ± 128</td>
<td>− 5 ± 126</td>
<td>NS</td>
</tr>
<tr>
<td>Total fat (g)</td>
<td>99 ± 56</td>
<td>− 3 ± 53</td>
<td>NS</td>
</tr>
<tr>
<td>Saturated fat (g)</td>
<td>32 ± 22</td>
<td>− 16 ± 21</td>
<td>0.05</td>
</tr>
<tr>
<td>Monounsaturated fat (g)</td>
<td>33 ± 22</td>
<td>+ 13 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>Polyunsaturated fat (g)</td>
<td>10 ± 4</td>
<td>+ 20 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol (mg)</td>
<td>498 ± 290</td>
<td>− 187 ± 275</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium (mmol)</td>
<td>22 ± 10</td>
<td>− 2 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium (mmol)</td>
<td>156 ± 84</td>
<td>− 92 ± 82</td>
<td>0.01</td>
</tr>
<tr>
<td>Potassium (mmol)</td>
<td>81 ± 29</td>
<td>+ 193 ± 42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Phosphate (mmol)</td>
<td>56 ± 21</td>
<td>+ 22 ± 19</td>
<td>0.01</td>
</tr>
<tr>
<td>Magnesium (mmol)</td>
<td>15 ± 4</td>
<td>+ 14 ± 6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Frassetto, Eur J Nutr 2009
## Iso-energetic Paleolithic vs. Usual diet

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Usual diet</th>
<th>Paleolithic diet</th>
<th>% Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipids</strong></td>
<td>Total cholesterol (mmol/l)</td>
<td>4.7 ± 0.9</td>
<td>4.0 ± 0.9</td>
<td>17.0</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>HDL (mmol/l)</td>
<td>1.3 ± 0.2</td>
<td>1.3 ± 0.1</td>
<td>0.00</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LDL (mmol/l)</td>
<td>3.0 ± 0.1</td>
<td>2.9 ± 0.1</td>
<td>0.33</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>VLDL (mmol/l)</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>16.6</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Triglycerides (mmol/l)</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>15.4</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Fasting Insulin and Glucose</strong></td>
<td>Fasting insulin (μU/mL)</td>
<td>71 ± 6</td>
<td>59 ± 4</td>
<td>−21.1</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Fasting insulin (μU/mL)</td>
<td>170 ± 24</td>
<td>120 ± 18</td>
<td>−29.4</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>OGTT</strong></td>
<td></td>
<td>39 ± 12</td>
<td>39 ± 12</td>
<td>-0.00</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Factor</strong></td>
<td>Days 1 to 4 (usual diet)</td>
<td>36 ± 12</td>
<td>−9 ± 6</td>
<td>25.0</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Days 15 to 17 (Paleo diet)</td>
<td>30 ± 12</td>
<td>−12 ± 7</td>
<td>40.0</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Brachial artery diameter at baseline (BAD; mm)</strong></td>
<td>3.97 ± 0.88</td>
<td>3.98 ± 0.85</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brachial artery diameter during hyperemia (pkFMD; mm)</td>
<td>4.25 ± 0.83</td>
<td>4.35 ± 0.73</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absolute difference (pkFMD-BAD; mm)</td>
<td>0.288 ± 0.089</td>
<td>0.371 ± 0.158</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

Frassetto, Eur J Nutr 2009

Improvement of 3/4 symptoms of the metabolic syndrome; the 4th (weight) was deliberately kept constant
Outline

Demographics and aging
Lifestyle may affect aging via telomere length
Role of inflammation and oxidative stress
Our pro-inflammatory lifestyle
  Physical activity
  Diet
    Vegetables/fruits
    Fish fatty acids
Lifestyle intervention
21st Century hunter gatherer
Yakky! Moet ik dit dan weer gaan doen?

Foto: Remko Kuipers en Martine Luxwolda
Moet ik weer knollen gaan graven?
Moderne jager-verzamelaars jagen in de Supermarkt
Die voedingspyramide moet op zijn kop.

Wat overblijft is groente/fruit and dierlijke producten.
Dit is dus okay!
Eet meer groente en pluk de vruchten van het leven
Eicosapentaenoic acid (EPA) c20:5 (n-3)

Docosahexaenoic acid (DHA) c22:6 (n-3)

Mackerel - 1 810 mg
Salmon - 1 800 mg
Tuna - 1 500 mg
Haring - 1 200 mg
Salmon trout - 1 060 mg
Codfish - 240 mg

Fedacko Pathophysiology 2007
Dit is NIET okay
Go jog,
Fatass
Dit is het alternatief
Sometimes it is better to go fishing!
The end
Coronary heart disease (CAD) event rates in primary and secondary prevention trials

**Primary prevention trials**
(4 to 5 years duration)

**Secondary prevention trials**
(PROVE-IT 2 years, all others 5 years duration)

LDL 1.3-1.8 mmol/L

O’Keefe and Cordain, Mayo Clin Proc 2004
LDL-reduction correlates strongly with CRP-reduction in trials of lipid lowering

O'Keefe, Am J Cardiol 2006
Proposed Mechanisms of the Pleiotropic Effects of Statins on the Cardiovascular System

- Upregulation of endothelial nitric oxide synthase and on improved pathophysiologic response, including inhibition of vasoconstriction and promotion of reendothelialization
- Antioxidant effects via the inhibition of nicotinamide adenine dinucleotide phosphate oxidase and thus reactive oxidant species
- Anti-inflammatory properties including reduction in C-reactive protein, interleukin 6, tumor necrosis factor alpha, and nuclear factor-kB levels
- Down-regulation of cytokines and chemokines
- Stabilization of atherosclerotic plaques and inhibition of plaque inflammation
- Decreased activation of the blood coagulation cascade
- Inhibition of platelet aggregation
- Normalization of sympathetic tract outflow
- Increased circulating endothelial progenitor cells and enhancement of function
- Stabilization of myocardial electrical function
- Increased peripheral baroreceptor reflex sensitivity and vasomotor reactivity
JUPITER trial
Primary prevention; 17,802 subjects

‘Normal’ LDL-cholesterol (<3.37 mmol/L)
Increased hsCRP (≥2 mg/L)

Treatment: 20 mg rosuvastatin; median duration 1.9 years

Reductions:
50% LDL-cholesterol
54% MI
47% necessary angioplasty/bypass operation
43% venous thrombosis
37% hsCRP
48% stroke

Subjects with lowering LDL-cholesterol and hsCRP benefitted most

Consider statin treatment at increased hsCRP and normal LDL-cholesterol

Ridker, NEJM 2008
Those who obtain the greatest clinical benefit from statin therapy are those with increased inflammation, irrespective of the LDL-cholesterol concentration.

Ridker, Clin Chem 2010
Genetic support for the role of inflammation in CAD: minor IL6R allele (frequency=39%)

For every copy of Asp358Ala inherited the risk of CAD is reduced by 3.4% (1.8–5.0), independent of other CAD risk factors.

IL6R genotypes and risk of coronary heart disease

IL6R genotypes and circulating concentrations of inflammation markers

US