

Diet and Exercise as Medicine for the  
Whole Body:  
An Uncensored View

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Division of Cardiology, Section of Electrophysiology  
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Conflict Statement

- No conflicts to report.
- Support:
  - AHA National Scientist Development Grant
  - AHA Grant-in-Aid
  - National Institutes of Health: LRP
  - Division of Cardiology, UNMC
  - Department of Internal Medicine, UNMC

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Objectives

- Describe the correlation between diet and inflammatory responses in the body and disease.
- Associate the link between better diets and inflammation on cardiovascular disease.
- Exercise – Detail how it is important.

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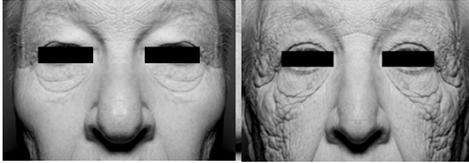
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## How Do We Age?



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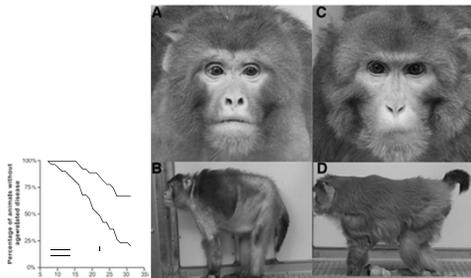
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## How Can I Affect Age?

Calorie Restriction and Calorie Control



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## Diet-Related Chronic Diseases

- Cardiovascular Disease
  - 81 million Americans (37%)
- Hypertension – High Blood Pressure
  - 75 million Americans (34%)
- Diabetes
  - 24 million Americans (11%)
- Pre-diabetic
  - 78 million Americans (35%)
- Cancer
  - One in two Americans
  - Breast (post-menopausal), endometrial, colon, kidney, mouth, pharynx, larynx, and esophagus
- Osteoporosis
  - One in two women

Health.gov

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## Diet: What is the Impact?

- The “Average American” will put on 4 lbs a year
  - And keep it
- About 60 million adults
  - 30 percent of the adult population are obese
- We are eating ourselves to death
  - Easy and cheap access to foods
  - Calorie density and portion size
  - Bad calories

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## Cardiac Risk Factors: The Risk of Having Heart Disease

- Non-modifiable
  - Age
  - Male Gender
  - Family History
- Hyperlipidemia
  - LDL < 70 if disease
    - <70, 70-100, 100-130, >130.
  - HDL >40
- Smoking
- Hypertension
  - SPB < 120 mmHg if disease
- Obesity
- Insulin Resistance and Diabetes
- Sedentary Lifestyle
- Estrogen Status
- Newer Risk Factors
  - Inflammatory Markers

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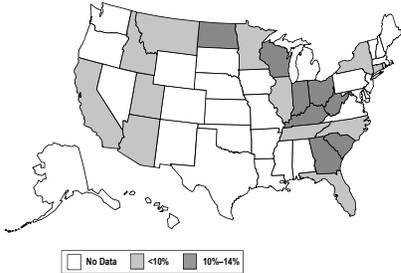
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Obesity Trends\* Among U.S. Adults  
1985  
(\*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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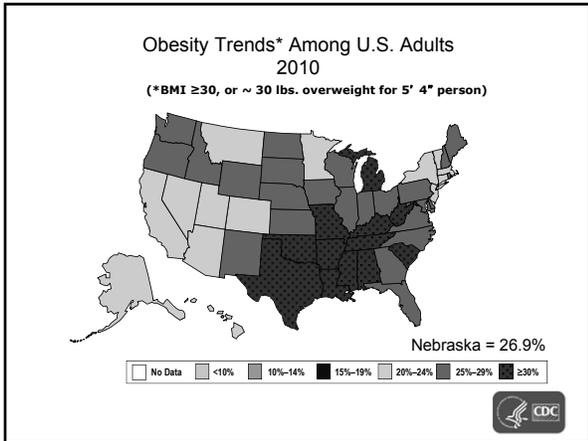
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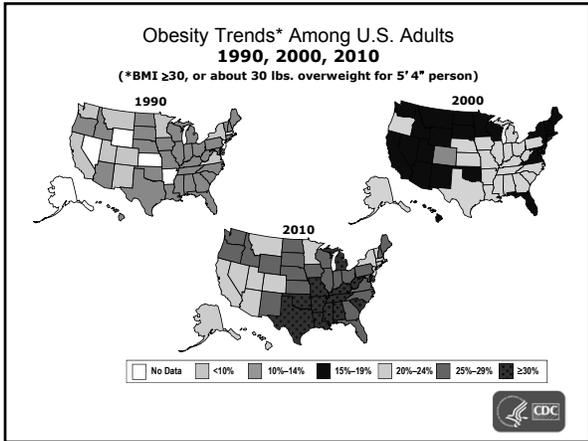
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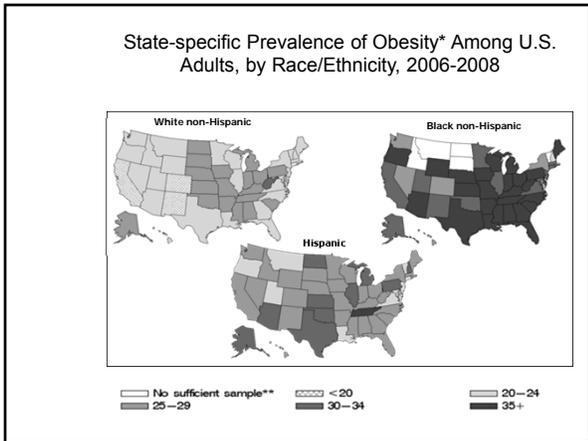
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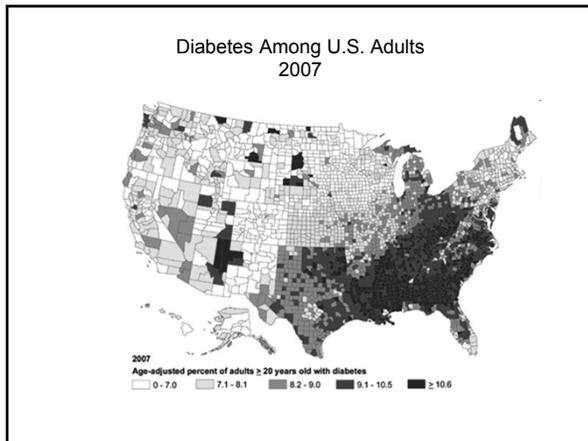
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- ### Cardiac Risk Factors
- Non-modifiable
    - Age
    - Male Gender
    - Family History
  - Hyperlipidemia
    - LDL < 70 if disease
      - <70, 70-100, 100-130, >130.
    - HDL >40
  - Smoking
  - Hypertension
    - SPB < 120 mmHg if disease
  - Obesity
  - Insulin Resistance and Diabetes
  - Sedentary Lifestyle
  - Estrogen Status
  - Newer Risk Factors
    - Inflammatory Markers

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- ### The Whole Picture: It's more than Age, High Blood Pressure, High Cholesterol, Diabetes and Tobacco Use
- Framingham Risk Score (FRS)
    - Clear association to coronary artery disease and coronary heart disease (CHD)
      - Age, HTN, DM, Lipids, gender.
    - Is an underestimation of subclinical disease
      - Intermediate FRS (10-19% 10-year CHD risk)
      - 14% of men and 25% of women had a high atherosclerotic burden
    - Limitations:
      - Under representation
        - Inflammation, family history of CHD, previous CHD, race, obesity, socioeconomic status
    - There is a need for additional tools (i.e. imaging) to further assess individual atherosclerosis risk
    - CAD – An inflammatory disease
- Karim R et al. Am J Cardiol 2008;102: 825-830.  
 Kathiresan S et al. Am J Cardiol 2007;99:310-314.

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## The Inflamed Artery

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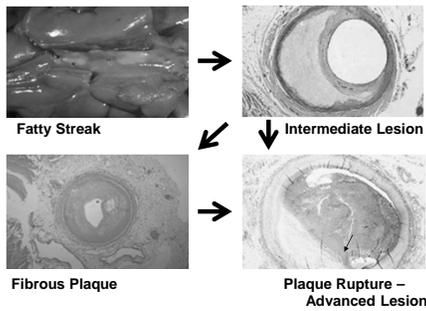
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## Atherosclerotic Lesions: Arterial Disease Progression



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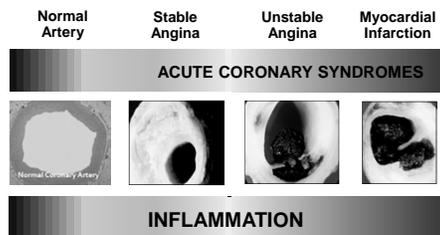
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## Spectrum of Coronary Artery Disease and Heart Attacks



Modified from Davies MJ. Heart 83:361,2000

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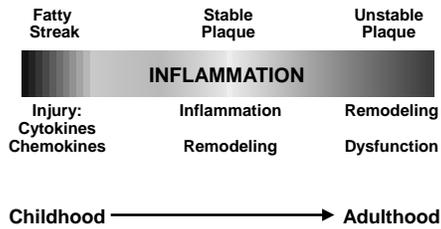
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## Spectrum of Inflammation and the Development of Coronary Artery Disease




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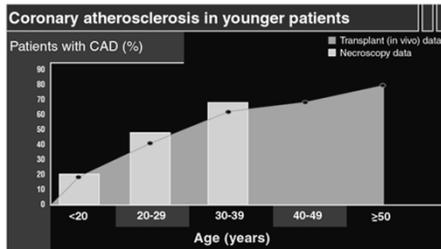
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## Consistent Evidence of Early Atherosclerosis



(Adapted from Berenson et al and Tuzzo et al.)  
Berenson GS et al. *N Engl J Med*. 1998.

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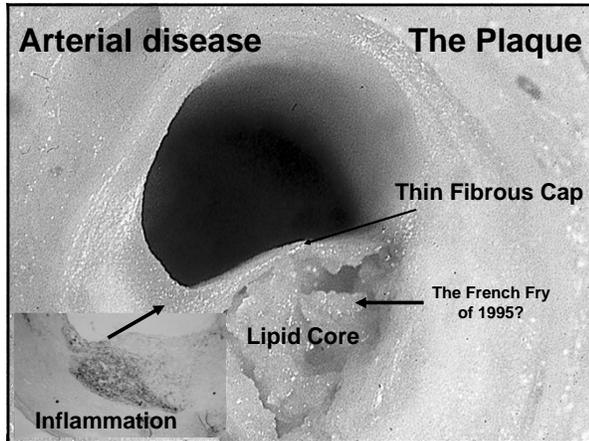
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## Why is Inflammation Important? Does it Impact Coronary Artery Disease?

- Inflammation - Plaque stability
  - Unstable plaques have increased leukocyte infiltrates
  - T cells, macrophages predominate at a rupture site
  - Cytokines and enzymes
    - Stability and degradation of the fibrous cap
- Lipid lowering may reduce plaque inflammation
  - Decreases
    - Macrophage number
    - Collagen degrading enzymes (MMP-1)
    - Lymphocyte receptors (E-selectin)
    - Calcium deposition
  - Increases interstitial collagen

Libby P. *Circulation* 1995;91:2844-2850.  
Ross R. *N Engl J Med* 1999;340:115-126.

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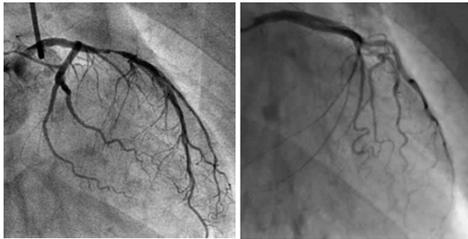
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## Coronary Artery Disease: It is not just one area!




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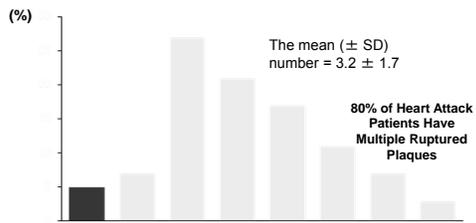
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## The Extent of Plaques in Patients with a Myocardial Infarction



Number of yellow plaques observed in the nonculprit segments.  
A stent or heart bypass does not fix the problem – It is a Band-Aid

Asakura et al. *JACC* 2001; 37:1284-1288

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## New Goals in the Management of Patients with Coronary Artery Disease

- *Stabilizing plaques is an essential treatment goal*

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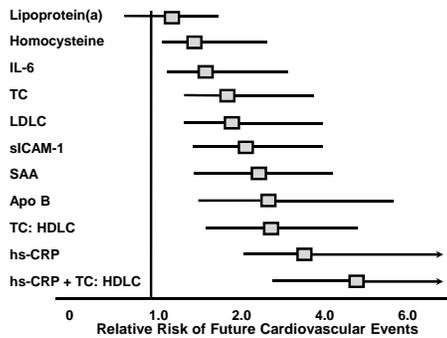


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## Risk Factors for Future Cardiovascular Events




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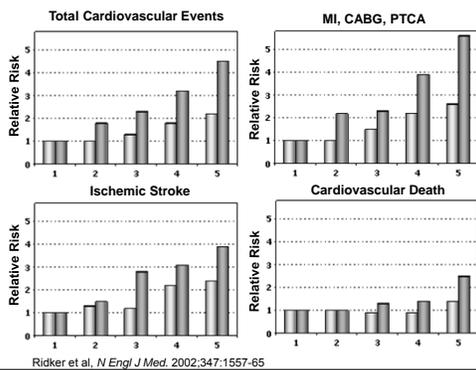


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A Direct Comparison of LDL-C and CRP in the Prediction of First Ever Cardiovascular Events Among 27,939 Women




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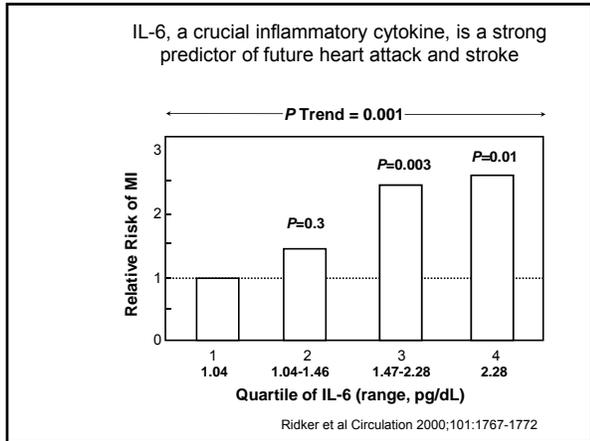
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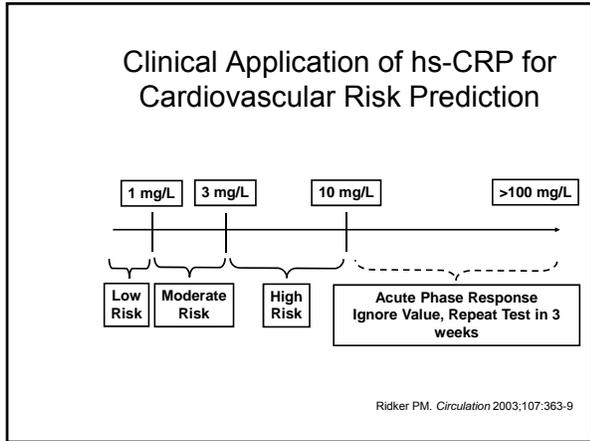
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Inflammation: What Can be Done?

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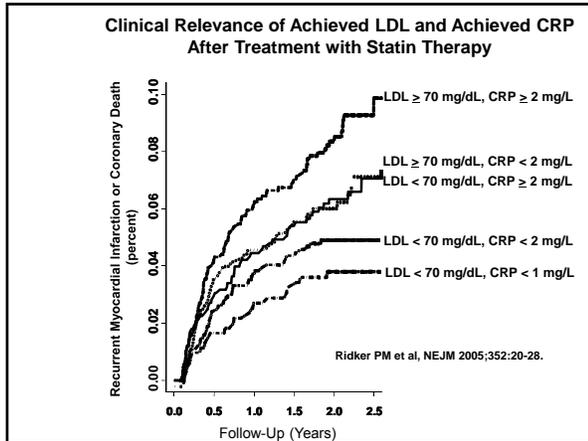
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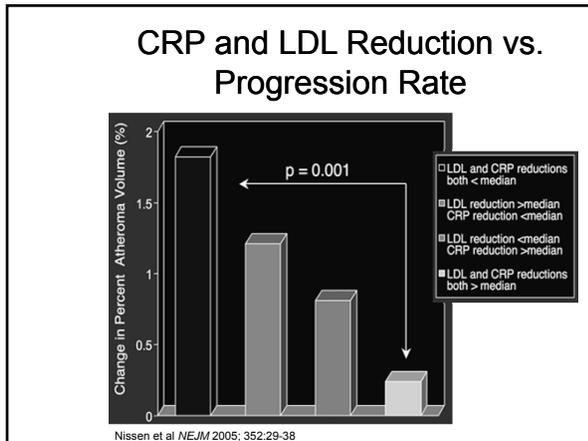
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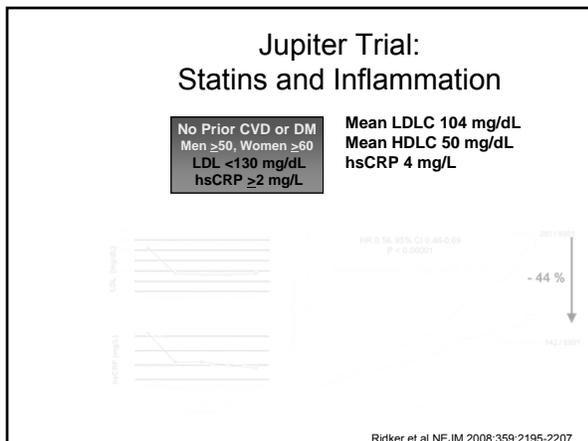
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**What Can We Do??**  
Inflammation, Cellular Dysfunction  
and Disease

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**Inflammation and Risk for CHD**

- Atherosclerosis is a chronic inflammatory disease associated with the accumulation of lipids and fibrous tissue in endothelial cells
- Initiation of inflammation promoted by proinflammatory cytokines, CRP, matrix metalloproteinases, oxidized LDL

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**Inflammation and Risk for CHD**

- There is a positive correlation between plasma biomarkers of inflammation and the consumption of saturated and trans-fatty acids.

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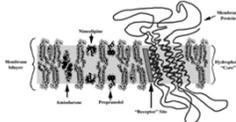
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### Cellular Membranes and Fatty Acids: Macromolecular and Cellular Dysfunction?

- Fatty acids enter the core of the cell membrane as the free molecules or phospholipids
  - Exert remarkable specific effects on the behavior and function of membrane proteins and macromolecular complexes
    - Oxidation, protein quality diseases?
- Trans-fatty acids bind to areas in cell membranes
  - Potential reason for rhythm problems associated with trans-fats
  - Potential reason for beneficial effects of Omega-3 fatty acids
- The good and bad of fat (monounsaturated vs. polyunsaturated vs. saturated vs. trans-fatty acids)
- Membrane fluidity
- Buffer oxidative stress?
- Disease modifiers??



Atherosclerosis Supplements 7, 2006:41-42  
Circulation, 2006;114:209-215.

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### Atherosclerosis and Cellular Membranes: Macromolecular Dysfunction

- The loss of proper 3-dimensional arrangement (unfolding)
  - Impairs protein function
  - Impaired cellular function and viability
- Accumulation of dysfunctional protein due to:
  - Increased production
  - Abnormal processing
  - Decreased elimination ---- protein aggregates
- The effect of protein aggregates
  - Remove amino acids from the recycling pool
  - Tie up clean machinery/mechanisms
  - Causes aggregation of other unrelated proteins
  - Disrupt cellular and tissue functions,
    - A "protein quality disease"

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### Atherosclerosis and Cellular Membranes: Macromolecular Dysfunction

- Precipitates such as amyloid are characteristic late-stage histologic fingerprints of atherosclerotic disease.
- Accumulation of dysfunctional proteins
  - A causal factor?
  - A contributing factor?
  - An epiphenomenon?
  - An increased susceptibility to traditional risk factors?

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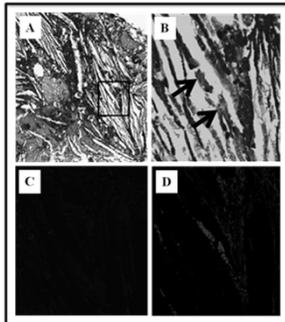
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## Culprit Atheroma: Modified Proteins



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## Diet and Inflammation

- Dietary strategies to prevent coronary heart disease
  - Omega-3 fatty acids from fish or plant sources
  - Fruits, vegetables, nuts, and whole grains
  - Avoid refined grains
  - Substitute non-hydrogenated unsaturated fats for saturated and trans-fats
    - Trans-fats - very atherogenic
      - Most atherogenic macronutrient you consume
      - Not reported if < 0.5 gm per serving
  - High salt diet
    - Promotes endothelial dysfunction and oxidation

Giugliano et al. JACC 2006;48:877-85.  
Kotornik and Mervais. Heart Vessels 2008;23:420-429.

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## Diet and Inflammation

Giugliano et al. JACC 2006;48:877-85

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## Adipose Tissue in Obesity

- Produce proinflammatory proteins
  - TNF- $\alpha$
  - Interleukin 6 (IL-6)
  - Monocyte chemotactic protein 1
  - Inducible nitric oxide synthase
  - Transforming growth factor 1
  - Procoagulant proteins
    - Plasminogen activator inhibitor type 1
    - Tissue factor
    - factor VII

Greenberg and Obin. Am J Clin Nutr 2006;83(suppl):461S-5S.

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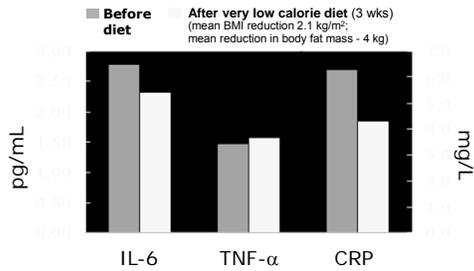
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## Effects of Weight Loss in Obese Women on IL-6, TNF- $\alpha$ , and CRP (Only 3 weeks)



Bastard J-P et al. J Clin Endocrinol Metab 2000;85:3338-3342.

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## Meals Do Make a Difference: Even in the Short Term



- +  = ?
- 680 Calories
  - 42 gms of fat
    - Sat fat 8 gm
    - Trans fat ?
  - 48 g of carbohydrates
  - 1.4 gm sodium

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## Meals: Making a Difference

- 30 healthy volunteers were randomized to a “American diet” (high fat meal) vs. a lower fat meal
- Challenged with:
  - Mental arithmetic
  - Public speaking
  - Arm ischemia response
  - Cold pressor (submerge arm in cold water for 2 minutes)
- Blood pressures and total peripheral resistance improved



A high-fat meal increases cardiovascular reactivity to psychological stress in healthy young adults. Jakulj F, Zernicke K, Bacon SL, van Wieringen LE, Key BL, West SG, Campbell TS. J Nutr. 2007 Apr;137(4):935-9.

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## Diets and Cardiovascular Disease

- Low Carbohydrate (Atkins)
  - 6 month weight loss seen, but no sig difference at one year
  - Weight loss from Caloric Restriction
  - Potentially Atherogenic
  - Renal and hepatic complications
  - Small data demonstrating worse CV outcomes
- Very Low Fat Diets
  - Not palatable
  - Minimal data without exercise bias: some strict vegetarian diets did show atherosclerotic regression when combined with exercise (ornish trial)
- Glycemic Index (South Beach)
  - Allow carbohydrates, but only low glycemic index foods
  - Small trials associated with weight loss
- Mediterranean Diet – The Winner
  - Strong data on cardiovascular mortality
  - Based on Diet of abundance of plant food (fruits, vegetables, breads, cereals, potatoes, beans, nuts and seeds) seasonally fresh, locally grown, with occasional sweets, low amounts red meat, moderate red wine intake, olive oil as main added fat
- DASH
  - Similar to Mediterranean diet
  - Also emphasis's high intake of fruits and vegetables
  - Shown to reduce blood pressure

Diet and Cardiovascular disease: An evidence based Assessment. J Am Coll Cardiol. 2005;45:1379-1387

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## Adipose Tissue, Obesity and Diabetes: Treatment Options

- Exercise (and thiazolidinediones)
  - Decreases
    - IL-6
    - TNF- $\alpha$

Greenberg and Obin. Am J Clin Nutr 2006;83(suppl):461S-5S.

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## Other Mechanisms: Gingivitis and Coronary Artery Disease

- Inflammatory markers of severe gingivitis or periodontitis
  - C-reactive protein (CRP)
  - Fibrinogen
  - Leukocyte
  - Interleukin 1-B
  - Interleukin 6
  - Interleukin 8
- 256 patients evaluated for asymptomatic dental score (ADS)
  - Pericoronitis, retained root remnants, edentulism, dental caries, and gingivitis
- A combination of ADS, CRP, HDL, and fibrinogen offered an risk stratification model that equaled or exceeded that of the Framingham heart score
- Is poor oral health is a predictor of CHD?
  - More studies are needed

Janket et al. *Circulation*. 2004;109:1095-1100.

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## Cardiac Risk Factors: Inflammatory Mediators?

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|---|---|
| <ul style="list-style-type: none"> <li>• Non-modifiable           <ul style="list-style-type: none"> <li>– Age</li> <li>– Male Gender</li> <li>– Family History</li> </ul> </li> <li>• Hyperlipidemia           <ul style="list-style-type: none"> <li>– LDL &lt; 70 if disease               <ul style="list-style-type: none"> <li>• &lt;70, 70-100, 100-130, &gt;130.</li> </ul> </li> <li>– HDL &gt;40</li> </ul> </li> <li>• Smoking</li> <li>• Hypertension           <ul style="list-style-type: none"> <li>– SPB &lt; 120 mmHg if CAD disease</li> </ul> </li> <li>• Obesity</li> </ul> | <ul style="list-style-type: none"> <li>• Insulin Resistance and Diabetes</li> <li>• Sedentary Lifestyle</li> <li>• Estrogen Status</li> <li>• Newer Risk Factors           <ul style="list-style-type: none"> <li>– Inflammatory Markers</li> </ul> </li> </ul> |
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## Recap: Diet

- THE INFLAMMED DIET (AKA the Western Diet)
  - Refined starches, sugar, and saturated and trans-fatty acids
  - Lack of natural antioxidants and fiber from fruits, vegetables, and whole grains
  - High sodium intake
- Inflammation is clearly involved in the progression of vascular disease such as atherosclerosis.
  - We need to develop tools to image and monitor inflammation.
- Life style changes and drug management
  - Decrease inflammation
  - Decreases the progression of vascular disease

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## Your Diet – Your Life

- Decide before you eat!!
  - When you eat
    - Define a time
  - Where you eat
    - Define a place
  - What you eat
    - Make the choice first
- If it is not the time, place or choice
  - DON'T EAT IT!!!
  - ACCOUNTABILITY

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## Exercise

- Begin exercising gradually
  - Brisk walking
  - Don't expect to "get into shape" overnight.
  - Your fitness should start to improve within 3 months, if you are consistent
- Work hard enough to sweat, but not so hard that you cannot carry on a conversation.
- Plan an exercise routine for 20 - 30 minutes at least 3 - 5 days a week.
  - Include stretching before and after your exercise - This will help avoid injury
  - Remember to start slowly and listen to your body
  - If it hurts badly, then you are probably overdoing it
- Aerobic exercises strengthen the heart and lungs and should be part of the fitness routine.
  - Examples of good aerobic exercises include walking, running, jogging, swimming, cross-country skiing, rowing, rope skipping, dancing, racket sports, and cycling.
  - For the biggest benefit, aerobic exercise must be sustained for at least a 10- to 12-minute period.
- Strength and flexibility exercises are important and help you maintain your ability to do daily activities and maintain balance as you grow older.

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## Exercise – Make the Time

- Find an exercise you enjoy!!!
- Find a partner in crime!!!
  
- ACCOUNTABILITY!!!!

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- ***“Awaiting overt signs and symptoms of coronary disease before treatment is no longer justified.”***
- ***“The occurrence of symptoms may be regarded more properly as a medical failure than as the initial indication for treatment.”***

Kannel WB in Atherosclerosis and Coronary Artery Disease, 1996.

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**The Painful Conclusion**

- A refined diet, over consumption, obesity and physical inactivity are major contributors to cardiovascular disease and decline in cardiovascular and general health.
- **ACCOUNTABILITY!!**

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**Thank you!!**

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