The background of the slide is a rich, dark brown collage. At the top left, there are green cacao pods on a branch. To the right, more cacao pods are shown, some with yellow and red hues. Below these, a large pile of dark brown cacao beans is visible. In the bottom left corner, there is a variety of chocolate products, including a Hershey's Kisses bar, a Kit Kat bar, and several other chocolate bars and pieces. On the right side, a chocolate fountain is shown with chocolate being poured into a glass, creating ripples in the liquid below.

Health & Nutrition Aspects of Cocoa and Chocolate Polyphenols

**Francene M. Steinberg PhD, RD
Associate Professor
Department of Nutrition
University of California, Davis**

Some Current Nutrition and Health Trends

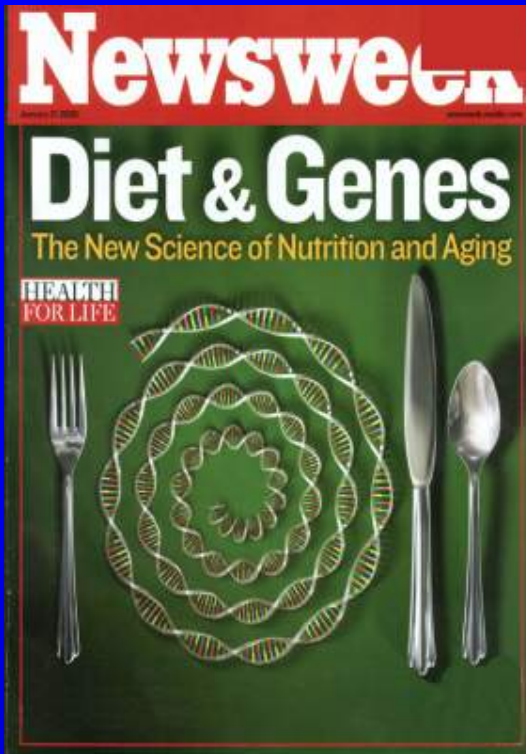
The increasing costs of medical care are crippling the economies of most countries. As a consequence, a new preventive health paradigm has developed that is connecting medicine, health, agriculture and food

Diet is increasingly viewed as a cause/solution for numerous health problems

New sciences and genetic innovation are accelerating the arrival of a new frontier: personalized nutrition

An increasing number of investigators are studying the health effects of “non-essential” nutrients. The science of nutrition is changing at a rapid rate

Consequences



These trends will impact all aspects of health care.

They will alter the fundamental practice of medicine.

In the marketplace, there will be an increasing segmentation of food and agricultural products. There will be significant opportunities for “health promoting” foods.

Disease Pathogenesis: The Modern Paradigm

Polygenic

Major Gene

Environment

Our Changing Expectations of Healthy Foods

Prevention of primary nutritional deficiencies



Reductions in the onset/progression of select cancers



Reduction in the onset/progression of age-related diseases



Improvements in endurance capacity and mental health



Reduction in the occurrence of select birth defects



“Optimal Health”

UC DAVIS

M A G A Z I N E

Number 3
Spring 2005



**TAKE
YOUR
VEGGIES**

Complementing the desire for “optimal health”,

the public is embracing the concept of -- “food as medicine” in response to the evolving health care crisis that is occurring in most developed countries.

Current Drivers: Cost

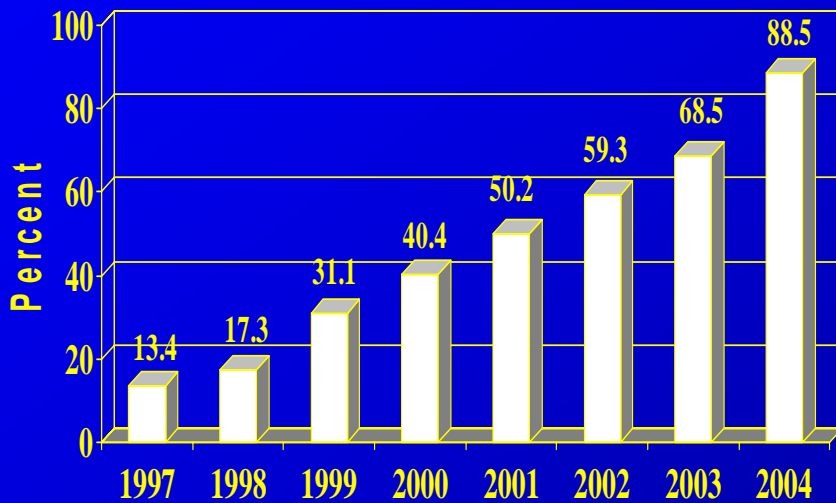
Health Care as total dollars in billions and % of GDP



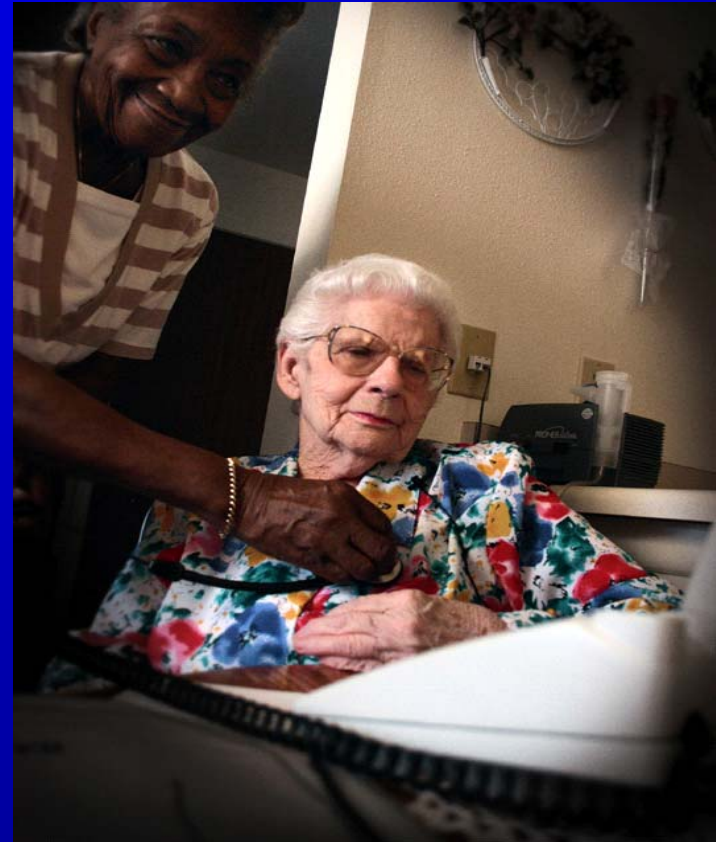
Source: Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group, at <http://www.cms.gov/statistics/nhe/default.asp> (2002 National Health Care Expenditures Data Files for Downloading, file nhegdp02.zip). >2004 projections

Current Drivers: Technology – IT

Percent of on-line adults accessing e-health information



Source: HHN, March 2002



Actual Causes of Death in the United States, 2000

“These analyses show that smoking remains the leading cause of mortality.

However, poor diet and physical inactivity may soon overtake tobacco as the leading cause of death”

Mokdad et al. (2004), *JAMA* 291: 1238-44

Dietary polyphenols have been postulated to modulate the development and progression of several chronic diseases:

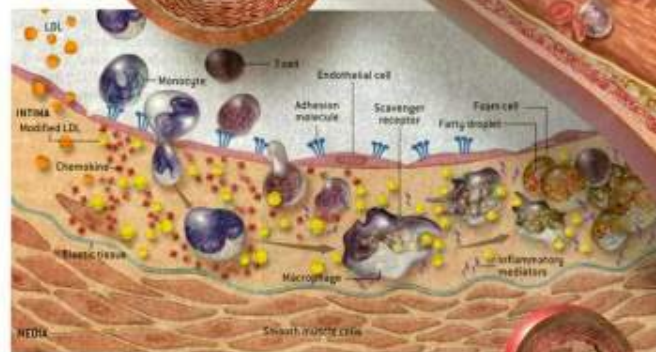
- **Age related vision loss**
- **Cancer**
- **Diabetes**
- **Hypertension**
- **Obesity**
- **Osteoporosis**
- **Cardiovascular disease**

Inflammation's Many Roles

INFLAMMATION—now recognized as a central player in atherosclerosis—occurs when certain white blood cells [those that normally constitute the first line of defense against infection] invade and become active in a tissue. These diagrams depict the growth of an atherosclerotic plaque in a coronary artery; the three close-up views highlight some of the inflammatory processes that can ensue when someone's blood carries too much low-density lipoprotein (LDL).

CROSS SECTION OF HEALTHY CORONARY ARTERY

Blood channel
Intima
Media
Adventitia



BIRTH OF A PLAQUE

1 Excess LDL particles accumulate in the artery wall and undergo chemical alterations. The modified LDLs then stimulate endothelial cells to display adhesion molecules, which latch onto monocytes [central players in inflammation] and T cells [other immune system cells] in the blood. The endothelial cells also secrete "chemokines," which lure the straggled cells into the intima.

2 In the intima, the monocytes mature into active macrophages. The macrophages and T cells produce many inflammatory mediators, including cytokines [best known for carrying signals between immune system cells] and factors that promote cell division. The macrophages also display so-called scavenger receptors, which help them ingest modified LDLs.

3 The macrophages feast on LDLs, becoming filled with fatty droplets. These fatty-looking, fat-laden macrophages [called foam cells] and the T cells constitute the fatty streak, the earliest form of atherosclerotic plaque.

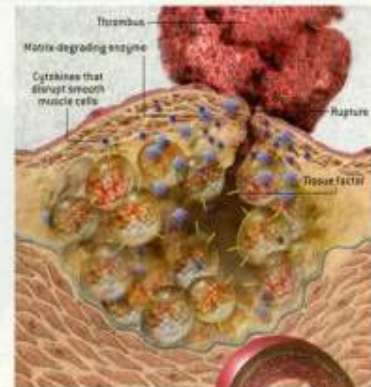
PLAQUE PROGRESSION

4 Inflammatory molecules can promote further growth of the plaque and formation of a fibrous cap over the lipid core. The cap develops when the molecules induce smooth muscle cells of the media to migrate to the top of the intima, multiply and produce a tough, fibrous matrix that glues the cells together. The cap adds to the size of the plaque but also walls it off safely from the blood.



PLAQUE RUPTURE

5 Later, inflammatory substances secreted by foam cells can dangerously weaken the cap by digesting matrix molecules and damaging smooth muscle cells, which then fail to repair the cap. Meanwhile the foam cells may display tissue factor, a potent clot promoter. If the weakened plaque ruptures, tissue factor will interact with clot-promoting elements in the blood, causing a thrombus, or clot, to form. If the clot is big enough, it will halt the flow of blood to the heart, producing a heart attack—the death of cardiac tissue.



CUTAWAY VIEW OF ARTERY AFFECTED BY ATHEROSCLEROSIS

The Global Burden of Cardiovascular Disease

(Lancet 1998;352:1795)

- #1 cause of death worldwide
- #2 cause of death in developing nations
- Leading cause of disability worldwide

Economic Cost of Cardiovascular Disease

In the United States – For 2004 CVD costs are estimated at \$ 368.4 billion

Drugs and Medical Devices are projected to be \$ 43.3 billion for the year.

(Value of entire cocoa crop < \$ 6 billion)

Fruits and Vegetables Decrease Cardiovascular Disease Risk

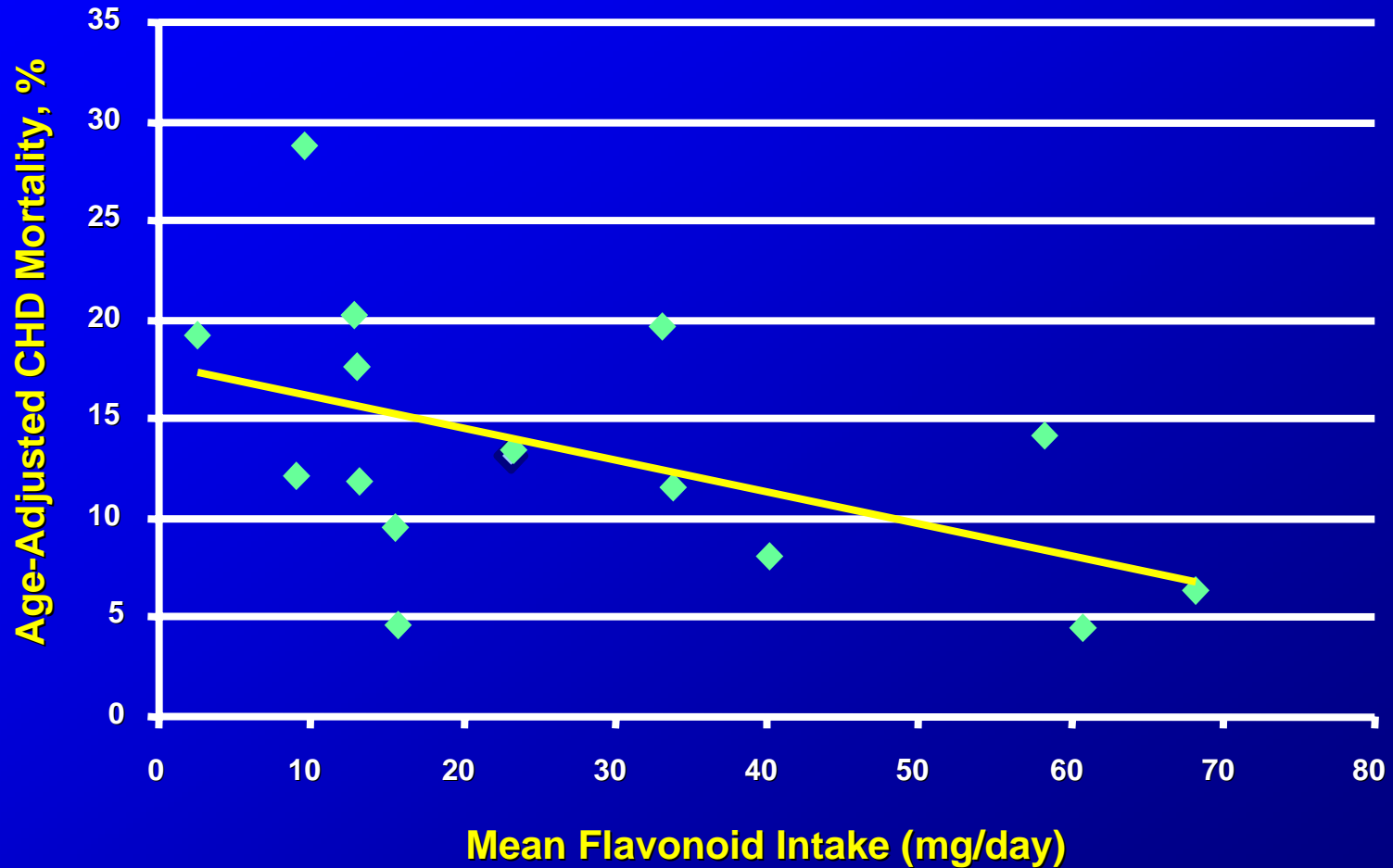


**Multivariate adjusted* RR
for ≥ 3 times/day vs. < 1
time/day**

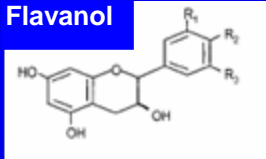
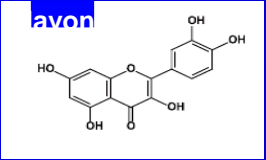
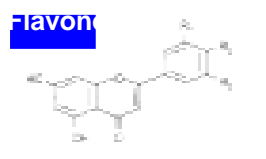
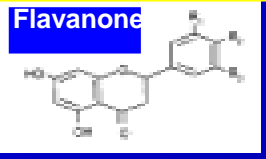
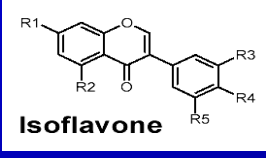
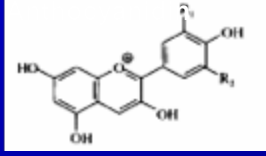
- Ischemic heart disease mortality **RR=0.76**
(95% CI: 0.56, 1.03)
- CVD mortality **RR=0.73**
(95% CI: 0.58, 0.92)
- All cause mortality **RR=0.85** (95% CI:
0.72, 1.00)

*adjusted for age, sex, race, energy, physical activity, alcohol consumption, smoking, plus others
Bazzano et al AJCN 2002; 76, 93-99

Flavonoid Intake and Risk of CHD Mortality



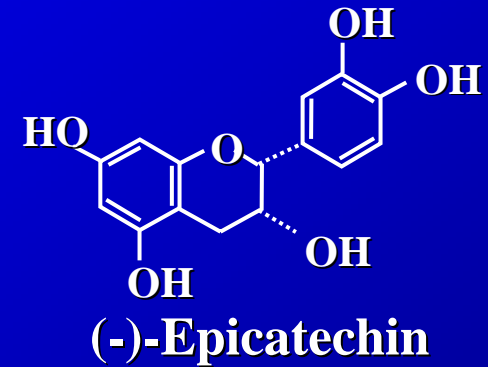
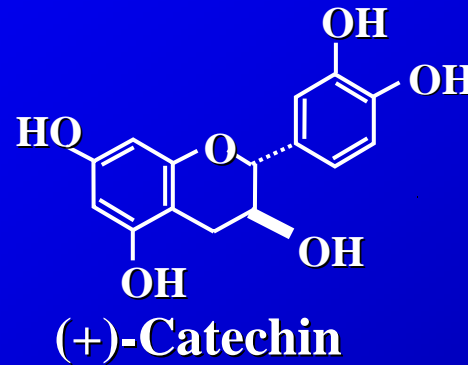
Flavonoids: A Diverse Group

| Class | Structure | Flavonoid | Food |
|----------------|--|-------------|-----------------|
| Flavanols | <p>Flavanol</p>  | Catechin | cocoa-wine-tea |
| Flavonols | <p>Flavonol</p>  | Quercetin | onion-apple-etc |
| Flavones | <p>Flavone</p>  | Apigenin | seed-herb-spice |
| Flavanones | <p>Flavanone</p>  | Naringenin | citrus fruits |
| Isoflavones | <p>Isoflavone</p>  | Genistein | soy products |
| Anthocyanidins |  | Delphinidin | Berries |

FLAVANOL-CONTAINING FOODS



Cocoa Flavanoids: Catechins & Procyanidins



Cocoa Powder

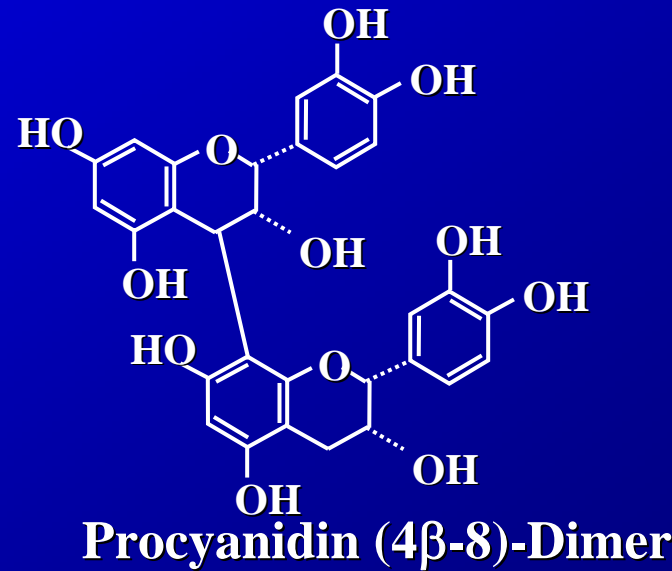
Total Flavonoids: 10%

Fat: 11%

Protein: 22%

Carbohydrate: 45%

Ash: 6%





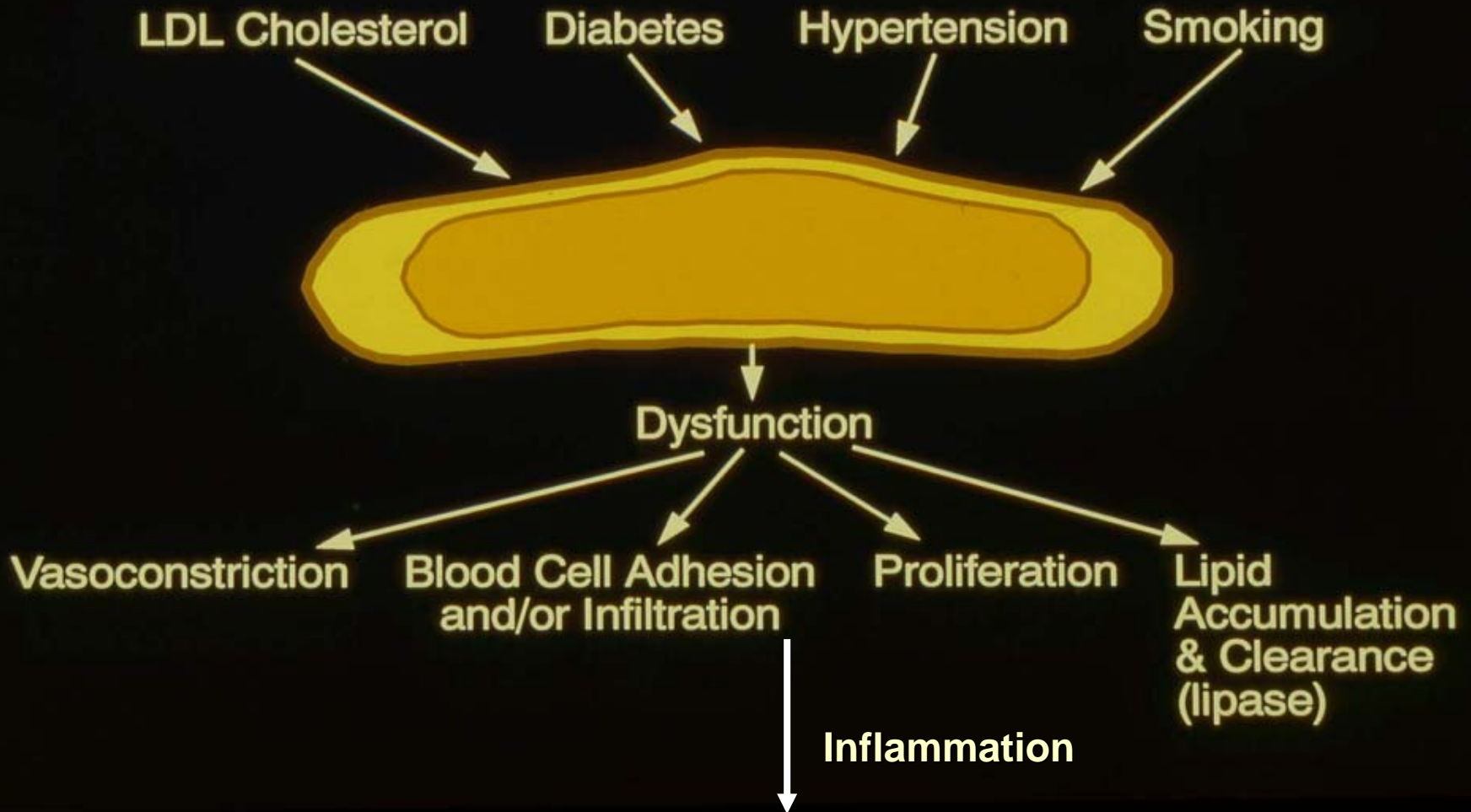
Flavonoids & Vascular Health

Speculation:

The inverse association seen between the consumption of plant food-rich diets and the risk for CVD is due to a number of factors including flavonoid-induced changes in: oxidant defense mechanisms; vascular reactivity; platelet reactivity; and the immune system.

Pathogenesis of Atherothrombotic Disease

Endothelial Cell



Cardiovascular disease and events

Flavanoids and CVD Health

Tea and Vascular Disease-

- **A Meta-Analysis of 10 cohort and 7 case-control studies**
 - Heart Attack incidence reduced by 11% with 3 cup per day increase in tea consumption

Peters et al. *Am J Epidemiol* 2001; 154:495-503

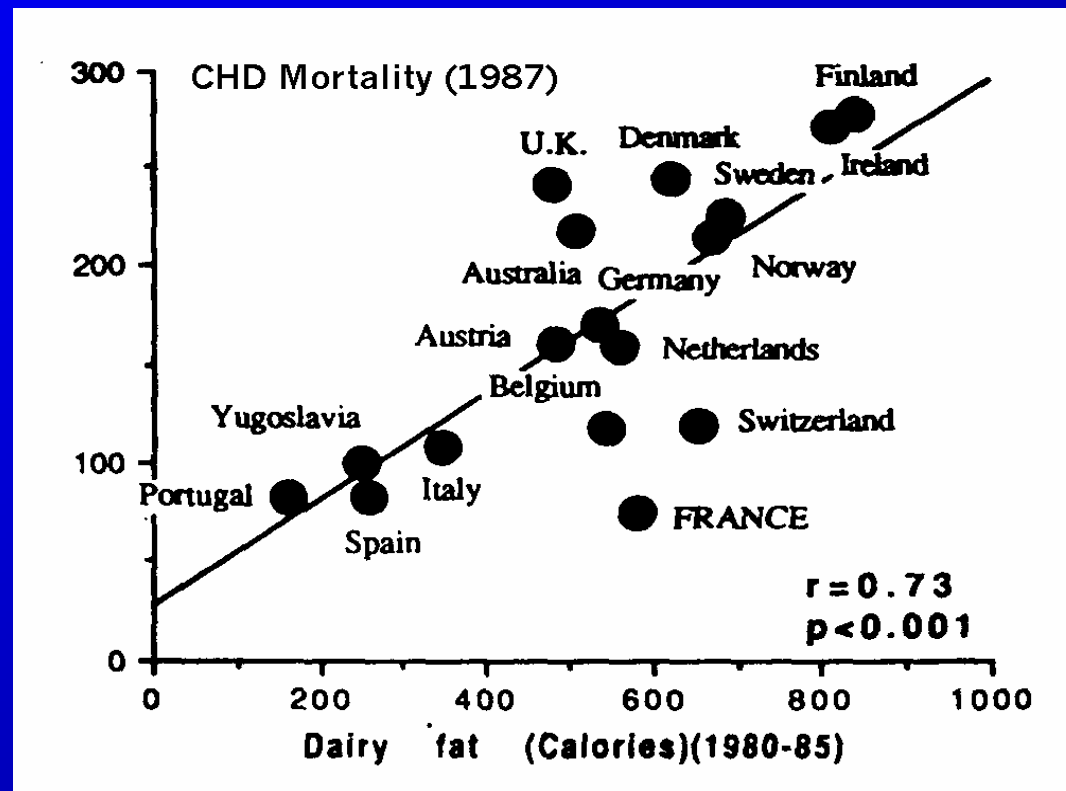
- **Catechin Intake Might Explain the Inverse Relation Between Tea Consumption and Ischemic Heart Disease: the Zutphen Elderly Study**
 - Prospective cohort study of elderly men
 - Determined intake of (+)-catechin, (+)-gallocatechin, (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin gallate, and (-)-epigallocatechin gallate
- **Catechin intake driven by black tea (87%), followed by apples (8%) and chocolate (3%)**
 - 50 mg increase in catechin intake associated with 25% reduction in risk (95% CI: 0.56, 0.99)

Arts, I.C.W. et al. *Am J Clin Nutr* 2001; 74:227-32

Flavanoids and CVD Health: Red Wine

Relationship Between CHD Death Rate and Dairy Fat Consumption

“The French Paradox”



Renaud-S, de Lorgeril, M. *Lancet* 1992; 339:1523-1526

Flavanoids and CVD Health: Red Wine

- Numerous studies demonstrate an inverse association between light to moderate alcohol consumption and reduced risk of CHD
- While several studies find a stronger beneficial effect for wine than other alcoholic beverages, the evidence is not clear whether red wine is truly more beneficial
- Protective effects of red wine have been attributed to polyphenols, in addition to alcohol
- Most abundant polyphenols in wine are gallic acid and the flavanols catechin and epicatechin



The Kuna Amerinds: A New “Paradox”?

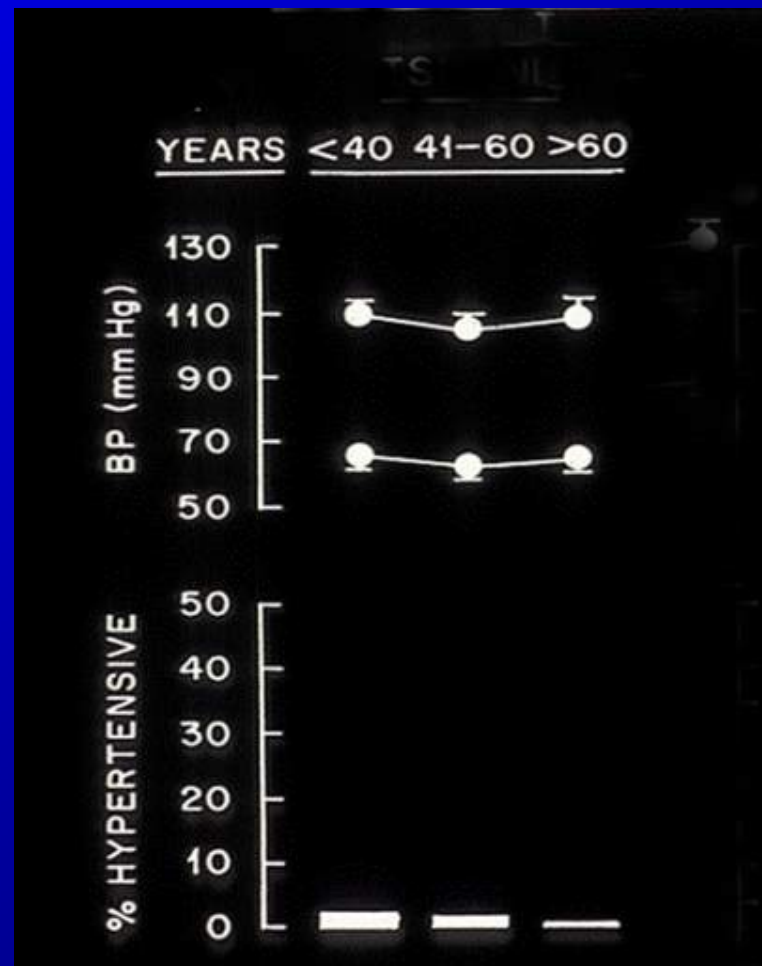
Cross-sectional study of the Kuna Amerinds of Panama

- Isolated island-dwelling Kuna: traditional Kuna lifestyle
- Panama City: minimal traditional Kuna lifestyle
- Kuna Nega on outskirts of Panama City: more traditional Kuna community and lifestyle

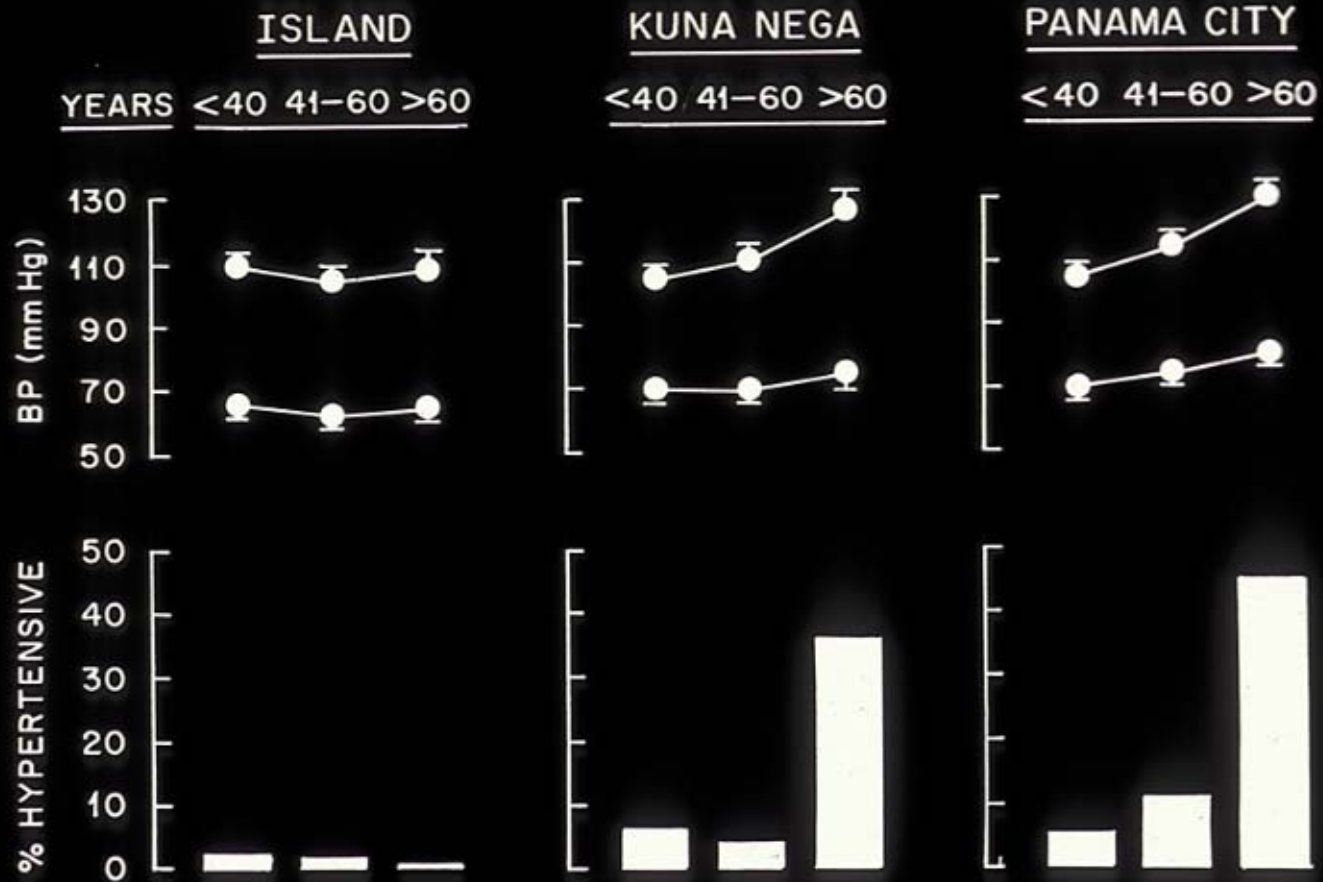
Flavanoids and CVD Health: Cocoa

Island Dwelling Kuna: A New “Paradox”?

Both hypertension and age-related increases in blood pressure are rare in island-dwelling Kuna – despite a substantial intake of salt



MIGRATION, ACCULTURATION and BLOOD PRESSURE



CVD Mortality/ 100,000 inhabitants

San Blas

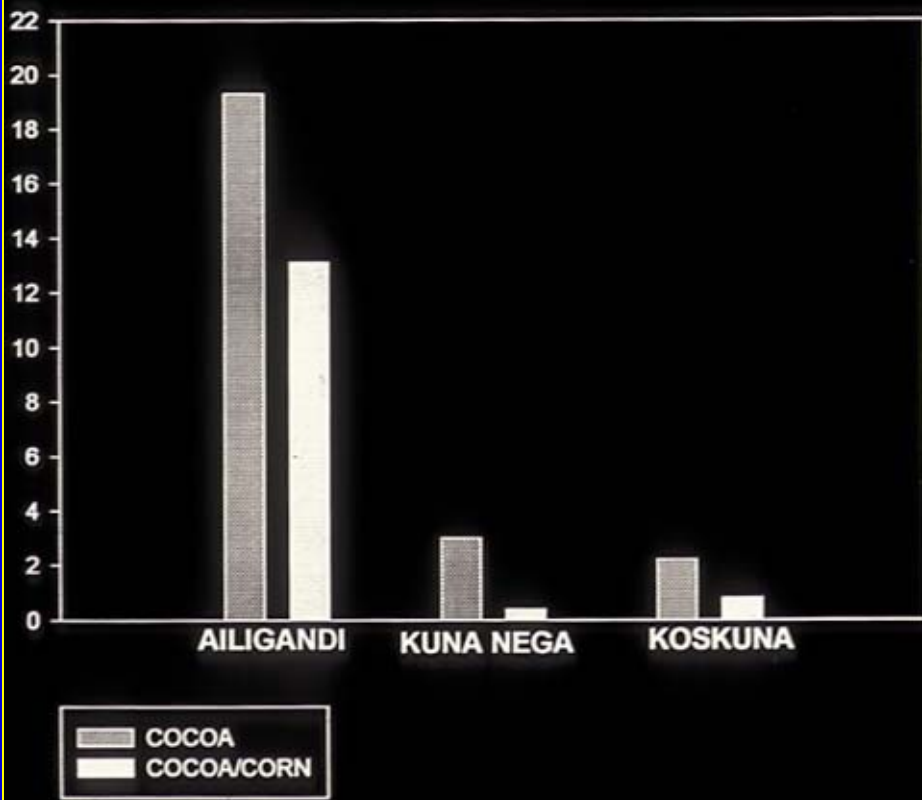
12.33

Mainland Panama

112.48

The Kuna Amerinds

**COCOA INTAKE PER WEEK
KUNA INDIANS**



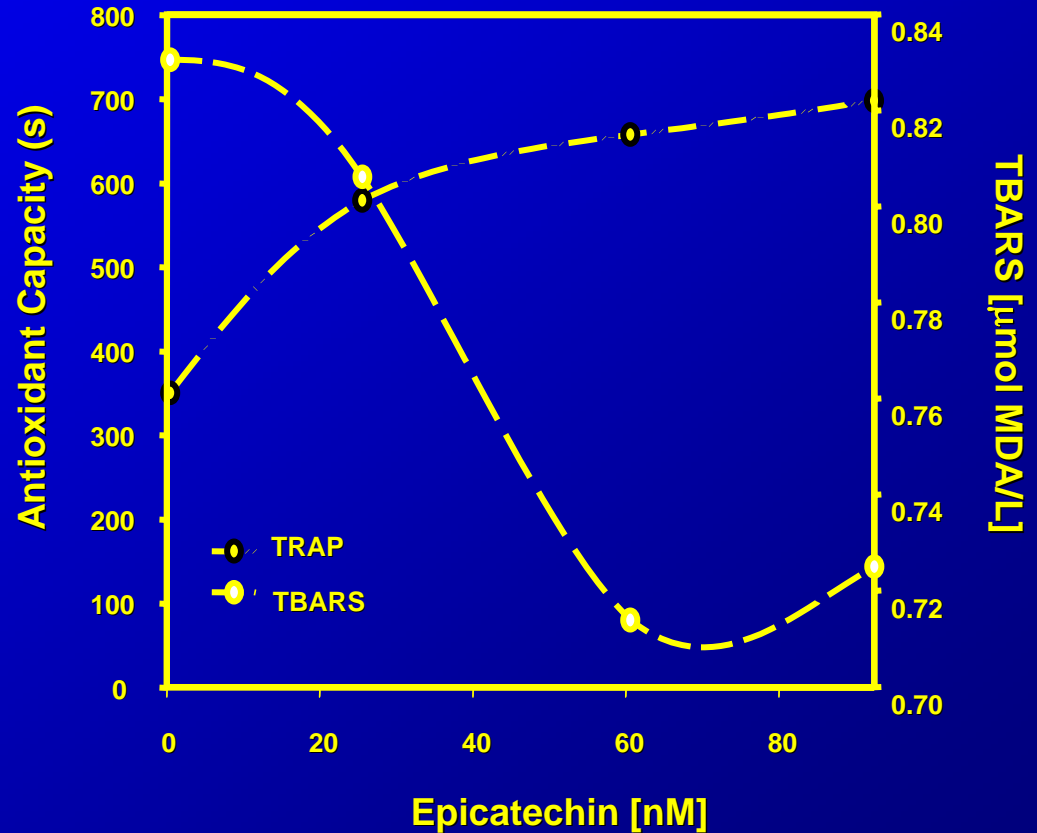
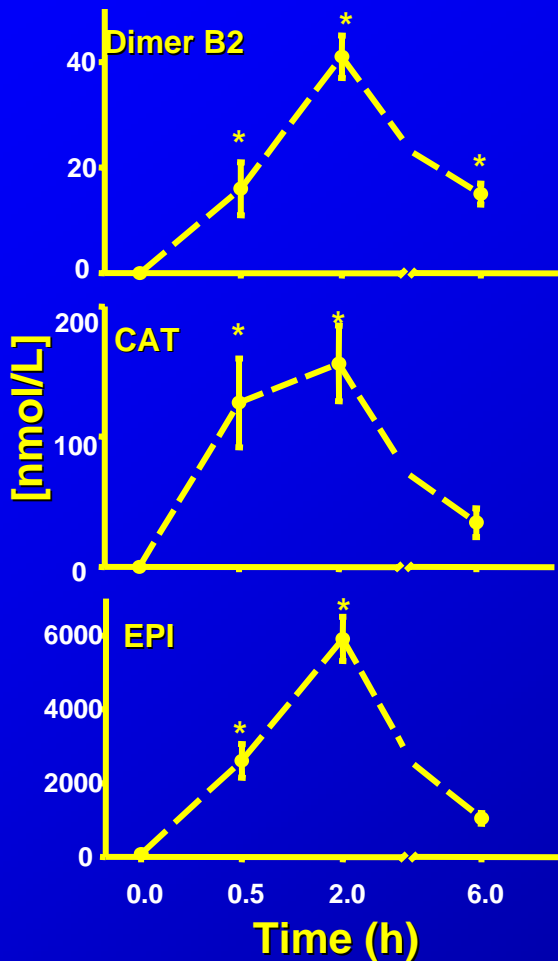
Composition of Foods and Beverages

- Substantial salt intake
- Generally low in fat, high in minerals and contain certain phytochemicals
- Potassium and magnesium at significant levels
- Cocoa-containing beverages frequently consumed – high in flavanols and procyanidins due to specific preparation practices

Can Cocoa Foods Provide Significant Amounts of Flavonoids?

- **Healthy volunteers, 25-56 y.**
- **Asked to refrain from taking supplements, and foods rich in flavonoids for 24 h, and fasted overnight.**
- **Subjects ingested a flavonoid-rich cocoa (0.375 g/kg BW; 12.2, 9.7, 28.2 mg monomers, dimers and higher oligomers respectively)**
- **Blood was drawn at 0 h, 2 h and 6 h**

Plasma concentrations of flavanols and dimers after consuming 0.375 g/kg of cocoa; average flavonoid dose was 1.4 g; approximately half from monomers and dimers



Cocoa and Chocolate Flavanoids: Antioxidant Protection

Effects of coca powder and dark chocolate on LDL oxidative susceptibility and prostaglandin concentrations in humans

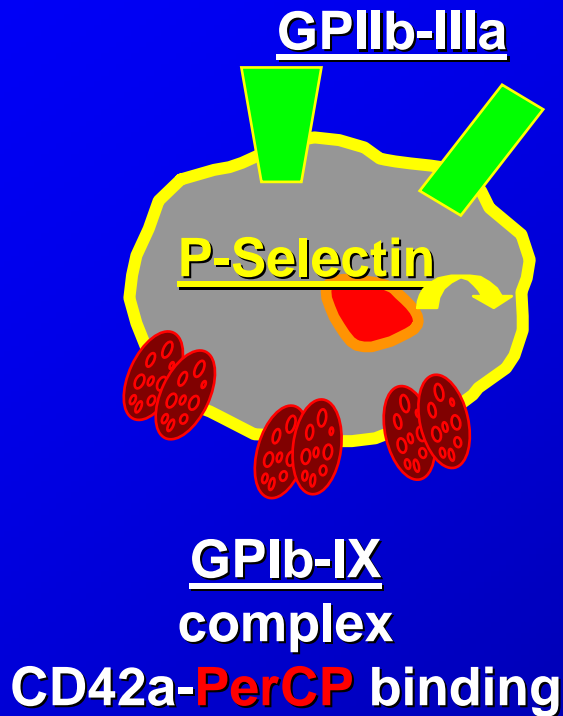
Wan et al, *AJCN* 2001; 74:596-602

Inhibition of AAPH-induced RBC Hemolysis and Antioxidant Capacity after an Intragastric Dose of a Cocoa Extract

Zhu et al, *Expt Biol Med*, 2002;227:321

Platelet Activation and CVD

Resting

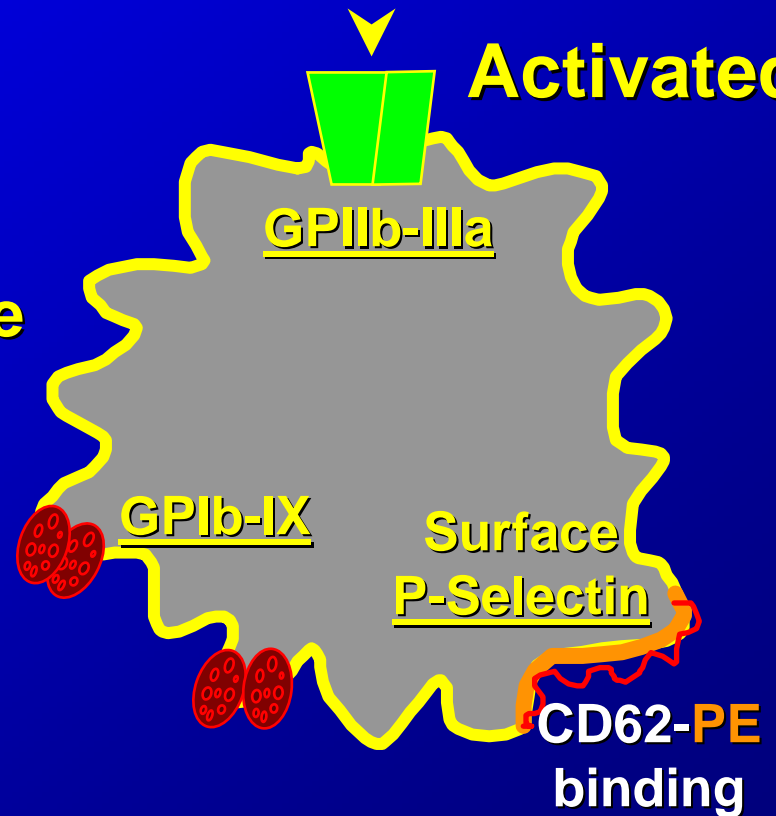


ADP
Epinephrine



Fibrinogen Receptor
PAC1-FITC binding

Activated



Effects of Flavonoid-Rich Beverages on Platelet Activation and Function

Healthy adults

Diet/drug restriction x 4 days

Test products (given in 300ml)

Flavonoid-rich cocoa (897 mg of flavonoids)

Dealcoholized red wine (320 mg of flavonoids)

Caffeine Control

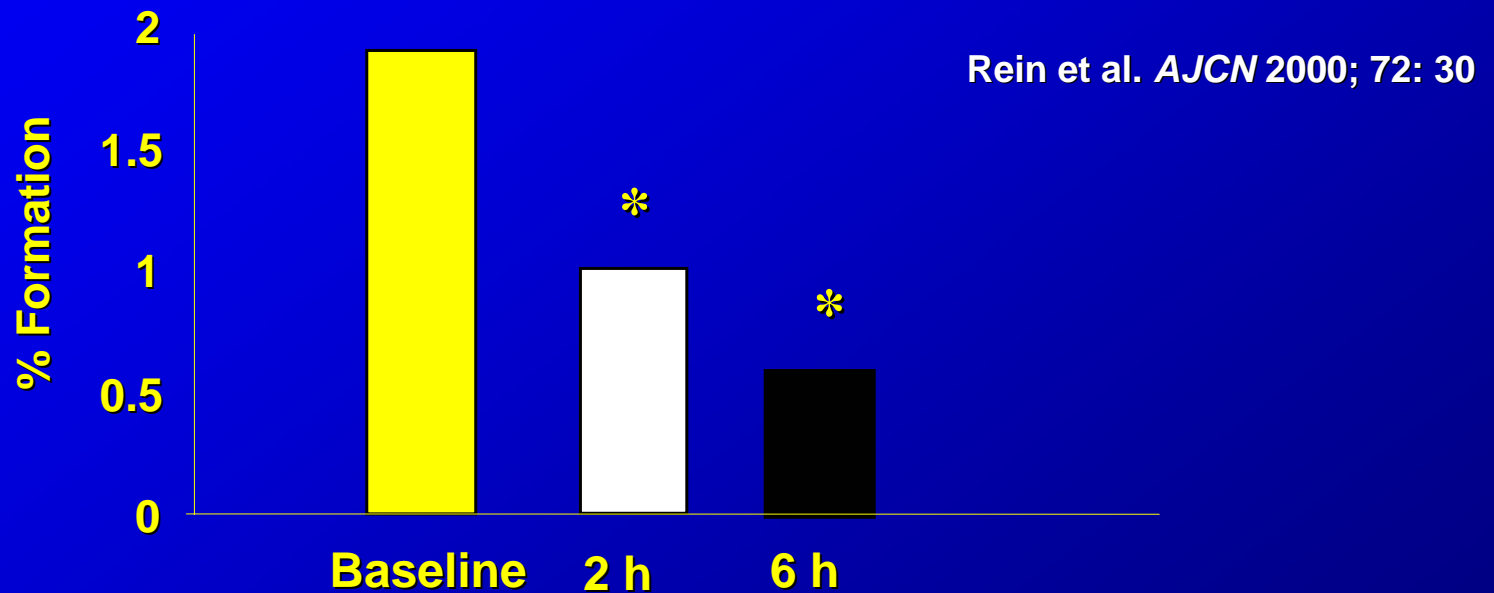
Water Control

Platelet Function Analysis:

Flow cytometry analysis GPIIb/IIIa, P-Selectin, microparticle concentration, PFA

Blood was collected over a 6 h period

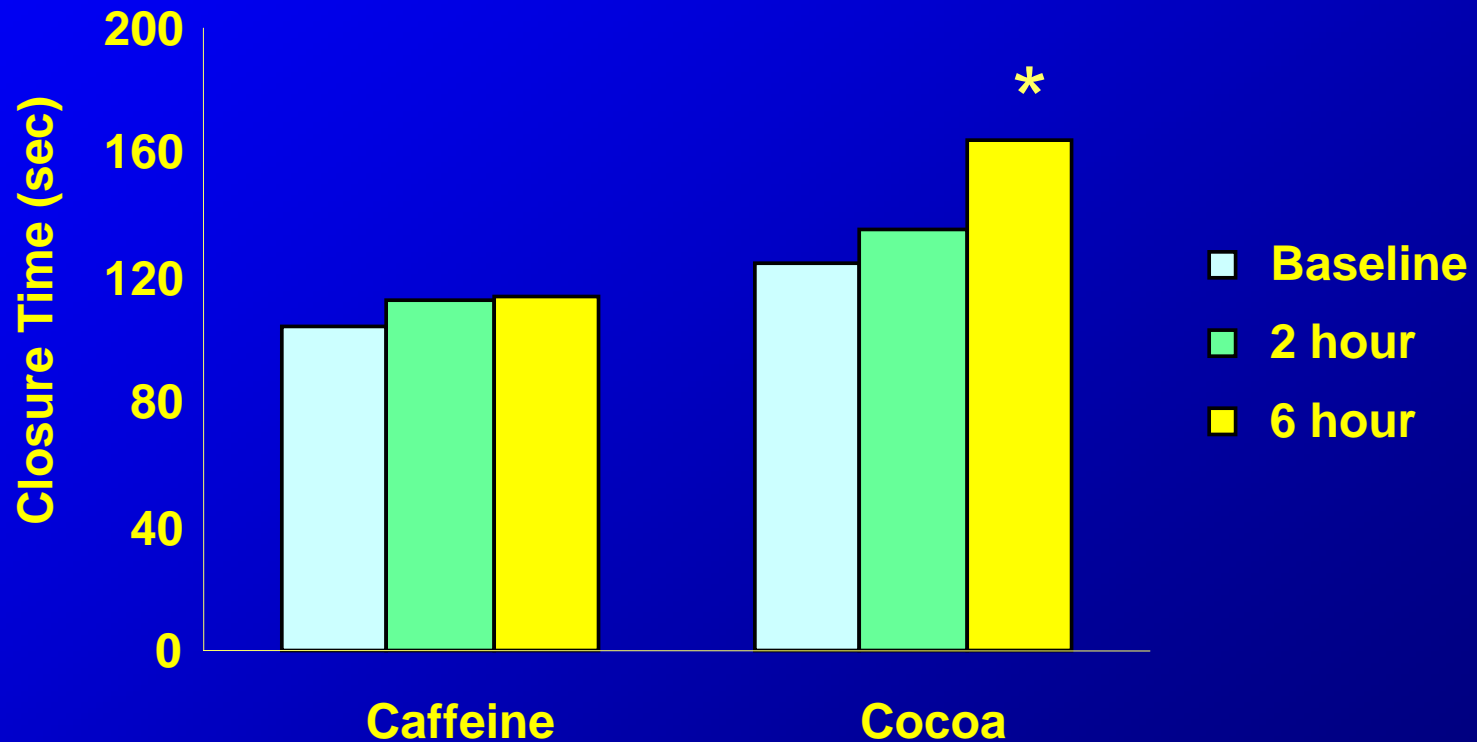
Changes in Platelet Microparticle Formation Following the Consumption of a Flavonoid-Rich Cocoa Beverage



Microparticles are formed during physiologic platelet activation & correlate with thrombotic disorders

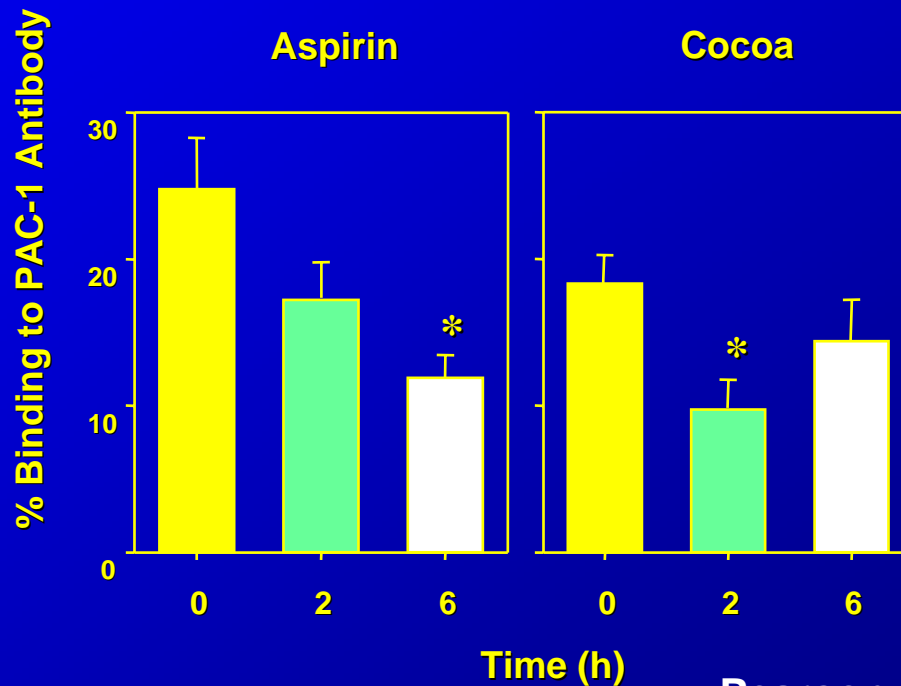
Cocoa Flavonoids: Platelet Reactivity

Consumption of cocoa beverage increases closure time (time to clot); indicating less reactive platelets, and less risk of arterial thrombosis.



How Does the Effect of Cocoa Flavonoids on Platelets Compare to Aspirin?

Influence of Aspirin and Cocoa on Epinephrine-Induced Platelet Surface Activation Marker in Healthy Adults



Pearson et al, *Thromb Res* 2002,

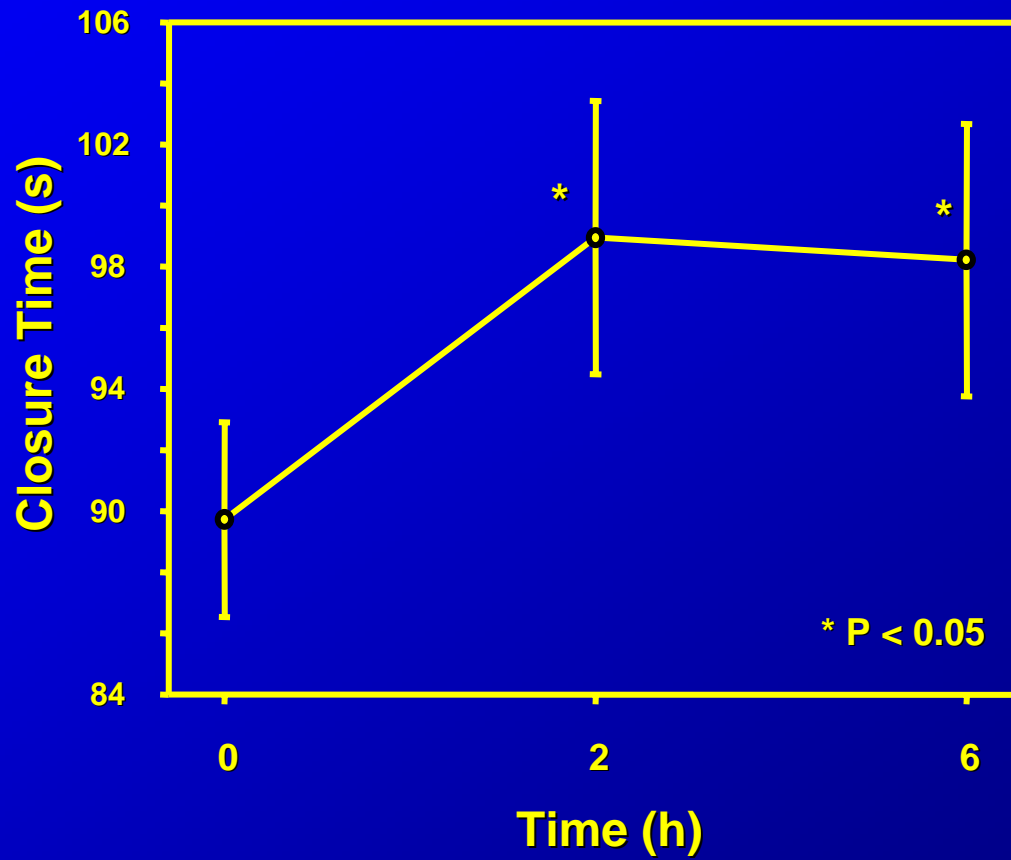
The consumption of flavonoid-rich foods can be associated with a reduction in platelet reactivity.

The flavonoid effect is less robust than that of aspirin, and it is transitory in nature.

Can the platelet effects observed with the flavonoid-rich cocoa be seen with lower flavonoid intakes?

Lower cocoa flavonoid intakes still decrease platelet activation and delay clot formation

ADP-Collagen Induced PFA-100™ Whole Blood Closure Times after Consuming 220 mg of Flavonoids in 25 g of Chocolate (n = 18)



Wine, Grape Products, and Cocoa Reduce Platelet Function



Pignatelli et al., 2002
Demrow et al., 1995
Ceriello et al., 2001

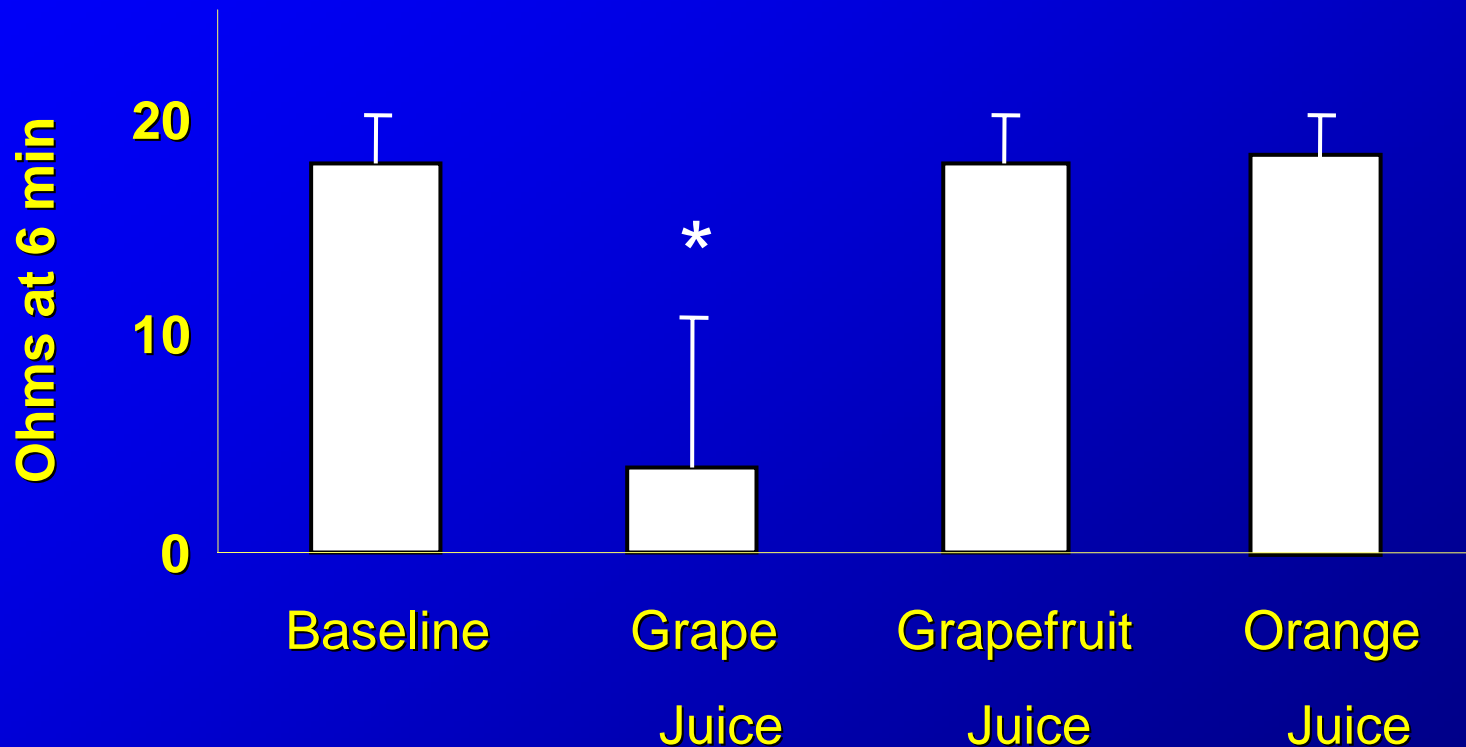


Osman et al., 1998
Keevil et al., 2000
Freedman et al., 2001



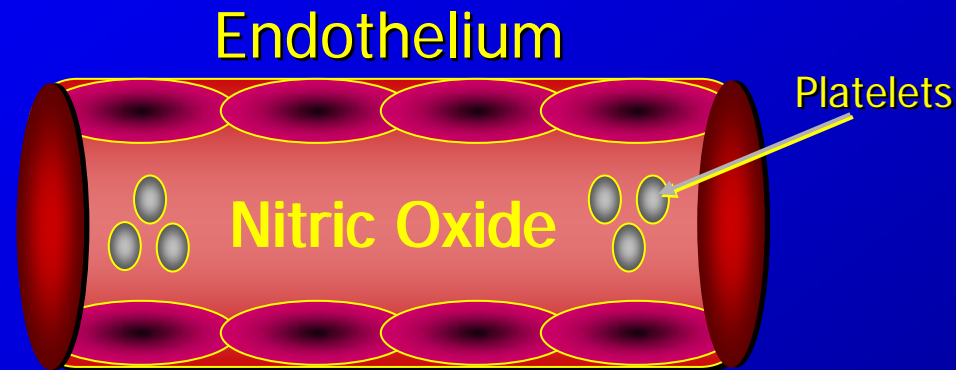
Rein et al., 2000
Pearson et al., 2002
Holt et al., 2002
Murphy et al., 2003
Innes et al., 2003
Hermann et al., 2005

Platelet Aggregation in Healthy Subjects After Consuming 450 mL of Juice / for 7d



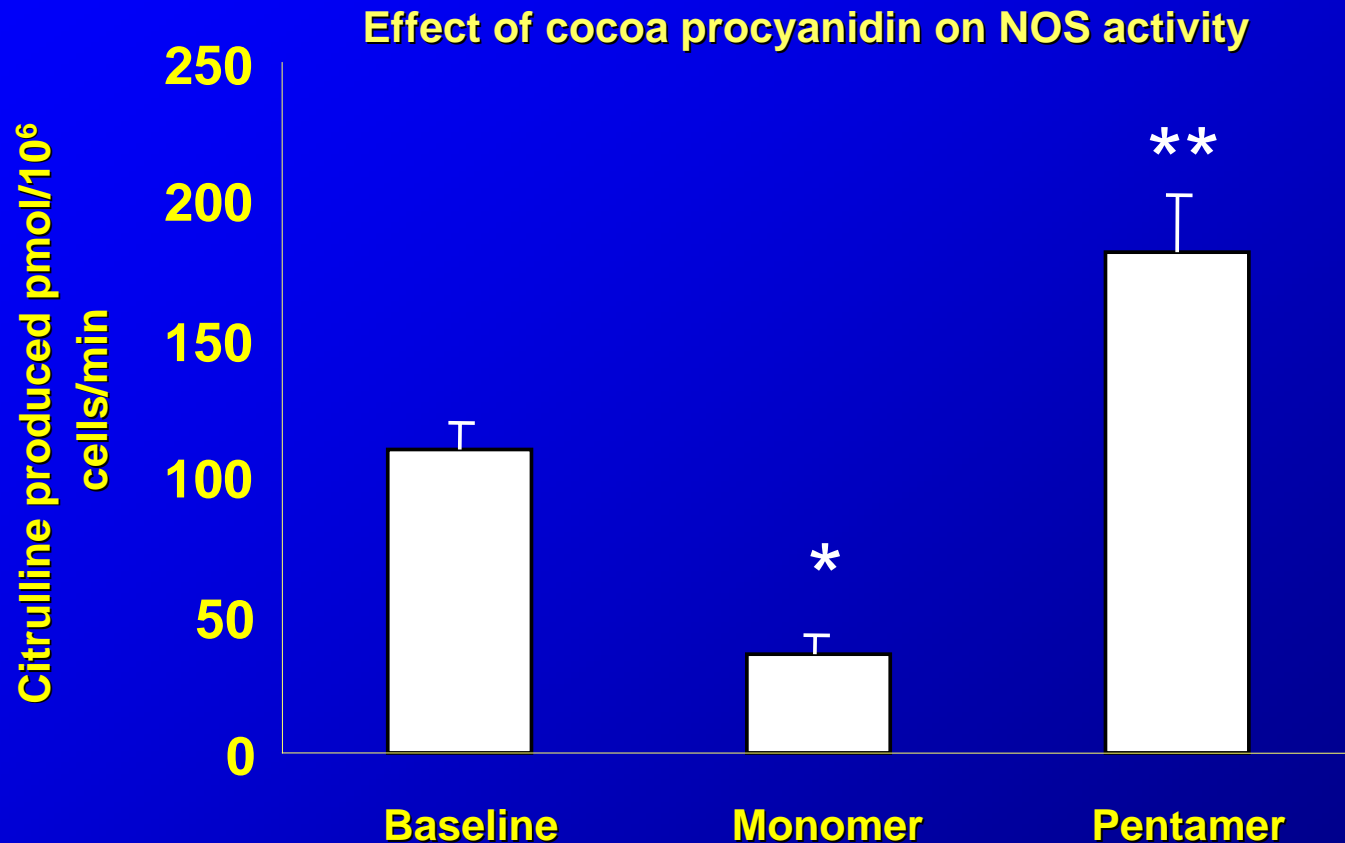
Endothelium Dependent Vasorelaxing Activity of Flavanols

Physiological Effects of Endothelial- and Platelet – Derived Nitric Oxide



- ↑ **Vasodilation**
- ↓ **Platelet activation, adherence and aggregation**
- ↓ **Vascular smooth muscle cell proliferation**
- ↓ **Inflammatory leukocyte recruitment**
- ↓ **Vascular oxidant stress by inactivation of superoxide anion**

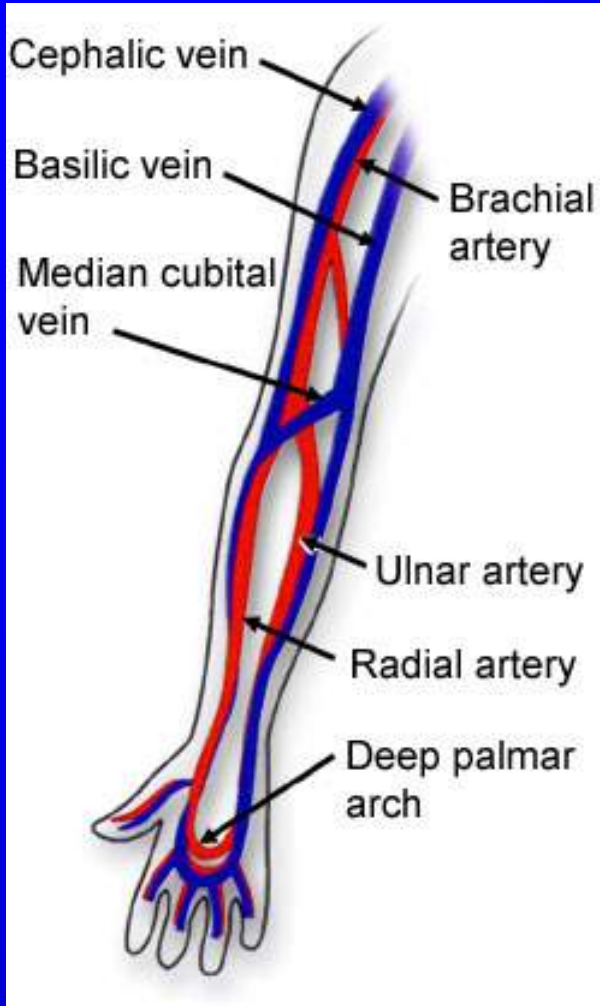
Cocoa Flavonoids: Vascular Endothelial Function



**significantly different from control and monomer, $p < 0.01$

*significantly different from pentamer ($p < 0.01$) and control ($p < 0.05$)

Biological Endpoints - FMD/PAT



Ischemia
(arterial occlusion)

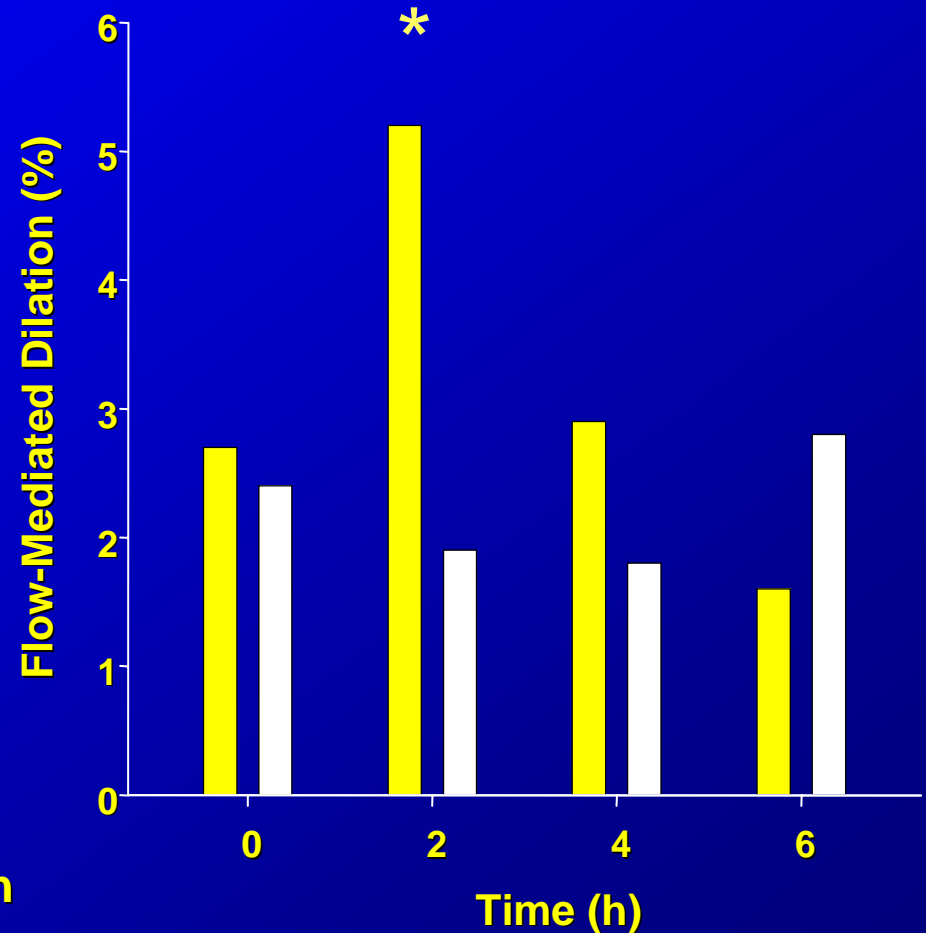
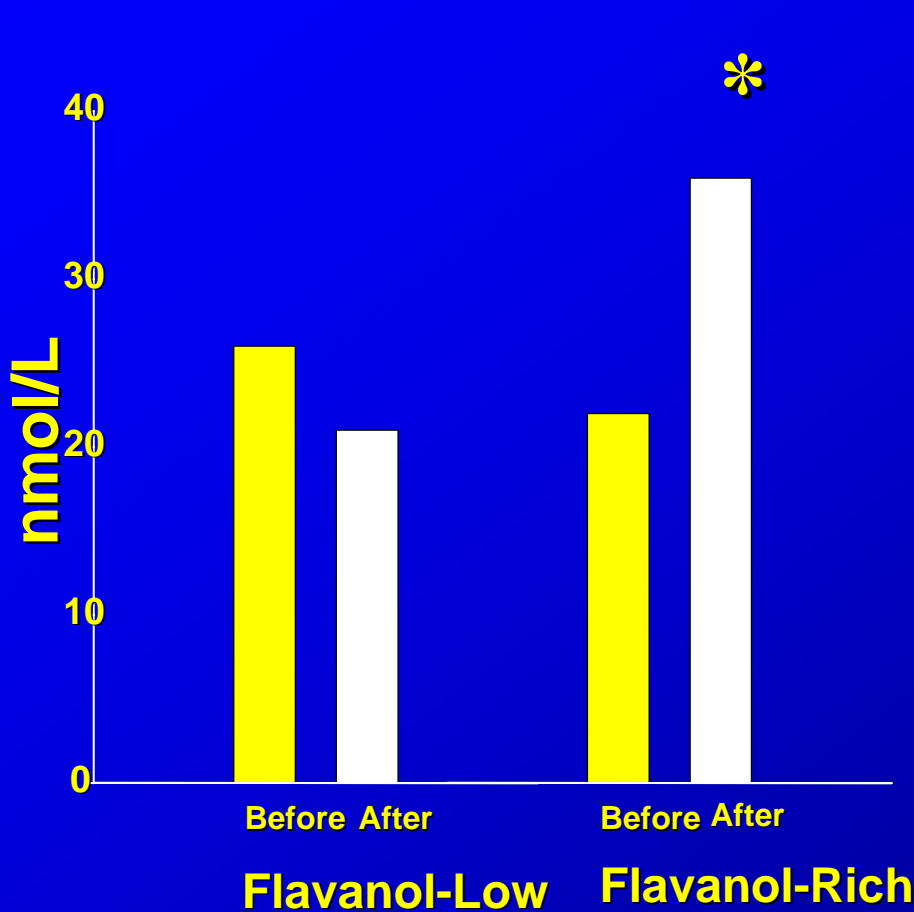
Hyperemia
(transient increase in organ blood flow)

Shear Stress
(arterial occlusion)

NO-Production
(endothelial cells)

Arterial Dilation
(relaxation of smooth muscle)

Flavanol-Rich Cocoa Consumption Results in Improved Endothelial Function by Increasing RNO and FMD

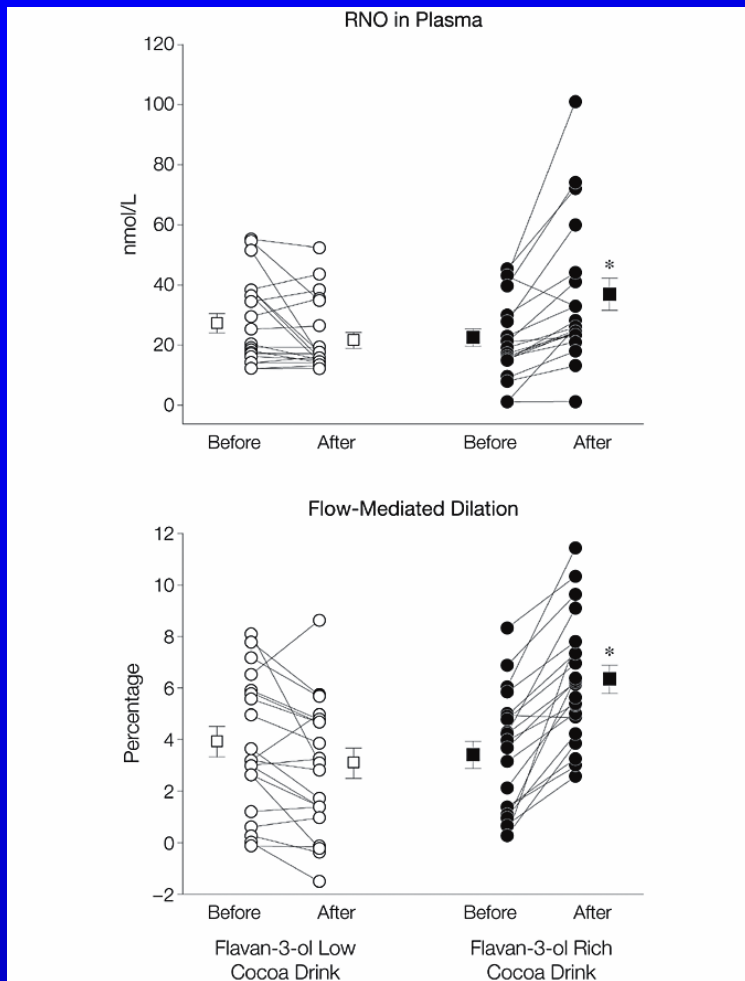


Heiss et al. *JAMA* 2003; 290: 1030

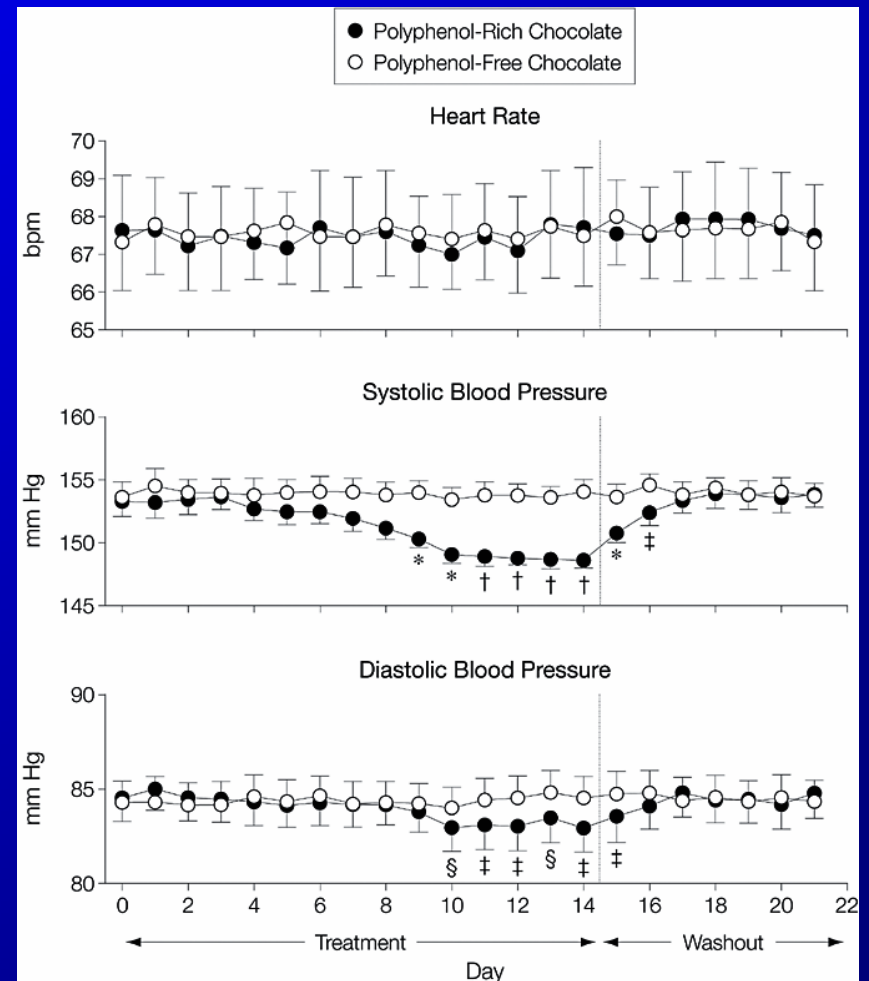
Heiss et al. *J Am Col Cardio* 2005; 46: 1276

Cocoa/Chocolate Dietary Interventions and Cardiovascular Health

Blood Pressure and Vasodilation



Heiss et al. (2003) JAMA, 290, 1031

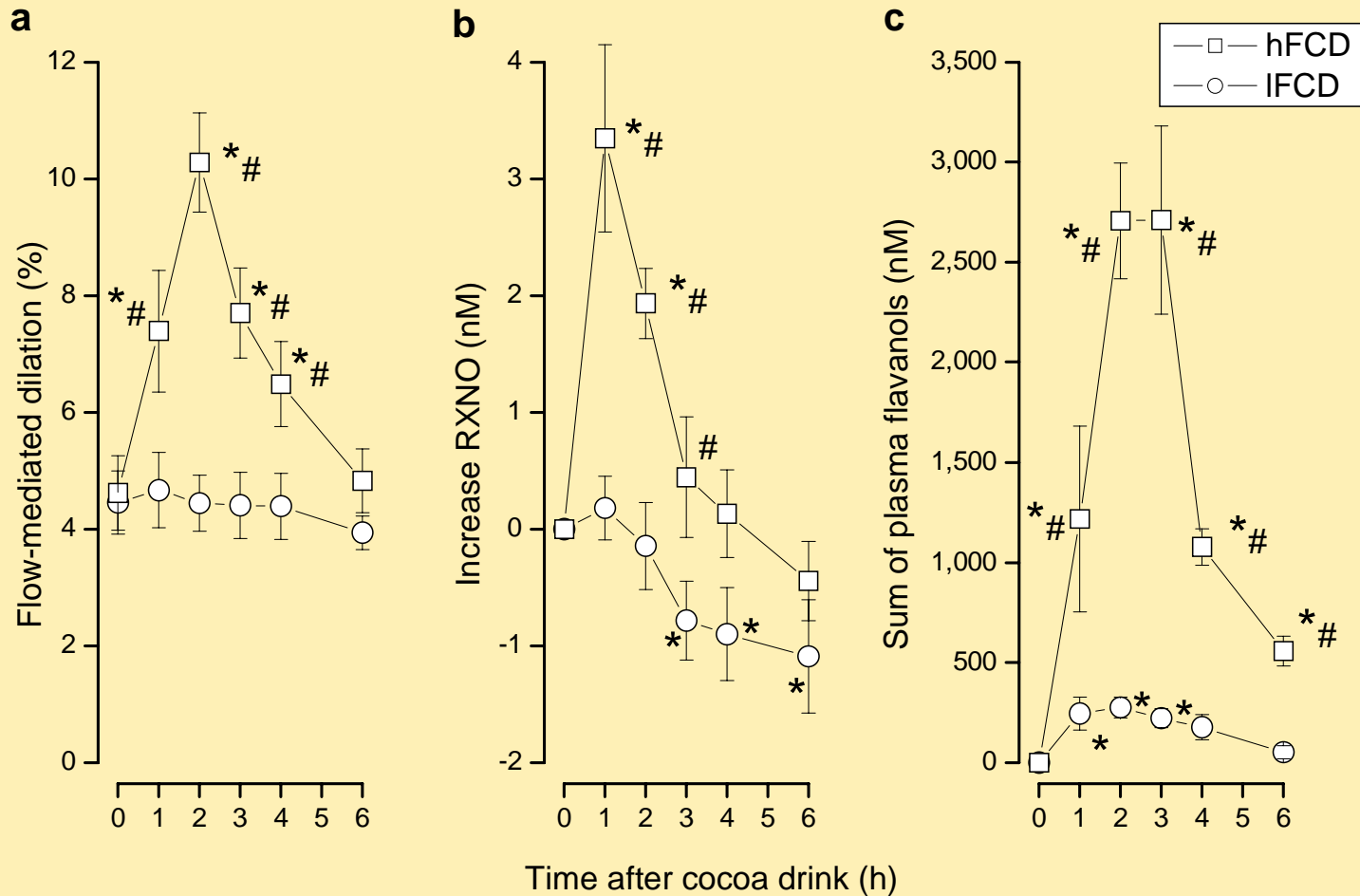


Taubert et al. (2003) JAMA, 290, 1029

What are the effects of the consumption of a purified flavanol on blood flow and platelet reactivity relative to the effects observed with a flavonoid-rich food or beverage ?



Results: Consumption of Purified Cocoa Flavanols Produces the same results as Flavanol-rich Cocoa Foods



Wine, Grape Products, and Cocoa and Chocolate Enhances Endothelial Function *in vitro* and *in vivo*



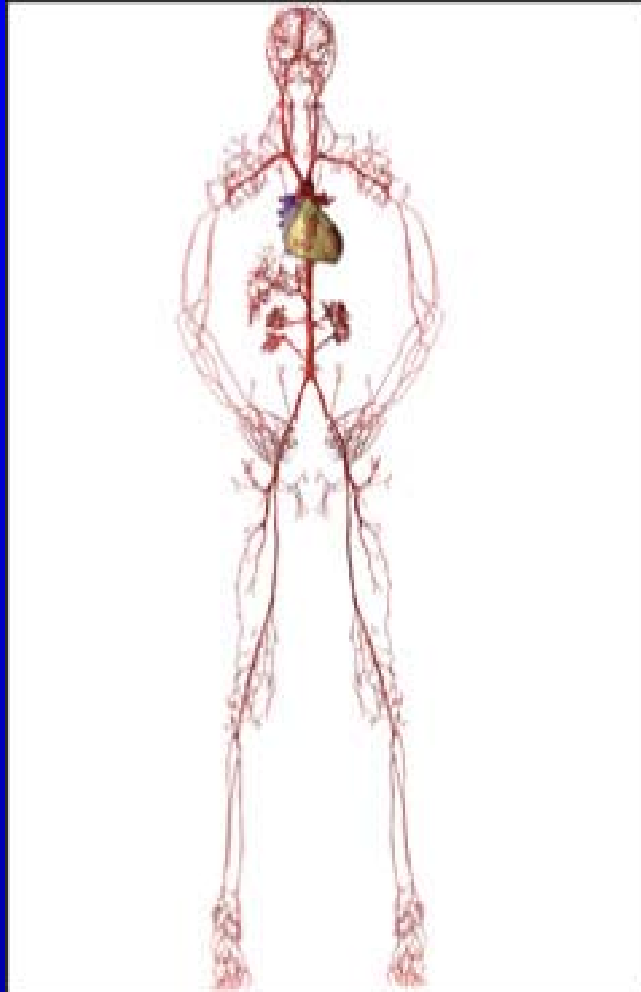
Fitzpatrick et al., 1993, 2000
Cishek et al., 1997
Adriambelosan et al., 1997
Agewall et al., 2000
Hashimoto et al., 2001
Stein et al., 1999
Coimbra, 2005



Karim et al., 2000
Engler et al., 2002, 2004
Rein et al., 2000
Heiss et al., 2003, 2005
Fisher et al., 2003
Grassi et al., 2005
Vlachopoulos, 2005
Hermann et al., 2005

Cocoa flavanols improve endothelial function and decrease platelet reactivity.

Together, these changes support the concept that cocoa flavanols can improve circulatory health



Cocoa Intake, Blood Pressure, and Cardiovascular Mortality

The Zutphen Elderly Study

“ ..to our knowledge, this is the first observational study that found that habitual cocoa intake was inversely associated with blood pressure in cross-sectional analysis and with cardiovascular and all-cause mortality in prospective analysis. Before drawing conclusions, confirmation by other observational and experimental studies is needed.”

Chocolate and Prevention of Cardiovascular Disease: A Systemic Review

“ Multiple lines of evidence from laboratory experiments and randomized trials suggest stearic acid may be neutral; While flavonoids are likely protective against CHD mortality.

The highest priority now is to conduct larger randomized trials to definitively investigate the impact of chocolate consumption on long-term cardiovascular outcomes.”

The Production of Cocoa and Cocoa Products with Improved Nutritional Quality

Factors Affecting Flavanol Content in Cocoa Products and Chocolates:

- Cocoa “Bean” Selection
- Post-Harvest Handling Conditions
- Processing and Manufacturing Conditions



Who Benefits?

- The consumer
- Farmers in the tropics and developing countries
- Food industries that utilize cocoa
- Governments, due to reduced health care costs

