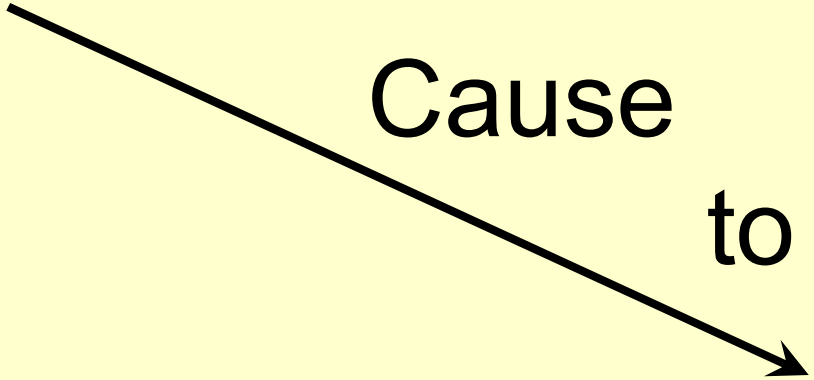
Connecting Cause to Consequence



Bill Lands, College Park, MD
wemlands@att.net

Dec.3, LSRO conference

The Context of Scientific Evidence

Fact= a truth known by actual experience

Oversimplified = Simplified to the point of causing error, misrepresentation, or misconception; = facts out of context

Paradox= an opinion contrary to received opinion;= an apparent self-contradiction that is explained by added truthful information

Fiction= an imaginative narration; =allegation that a fact exists which is known not to exist; = a story invented to deceive

Hypothesis=a fiction not yet proved as fact (i.e. to be disproved)

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Progress in Lipid Research 47 (2008) 77–106

Progress in Lipid Research

www.elsevier.com/locate/plipres

Review

A critique of paradoxes in current advice on dietary lipids

Bill Lands

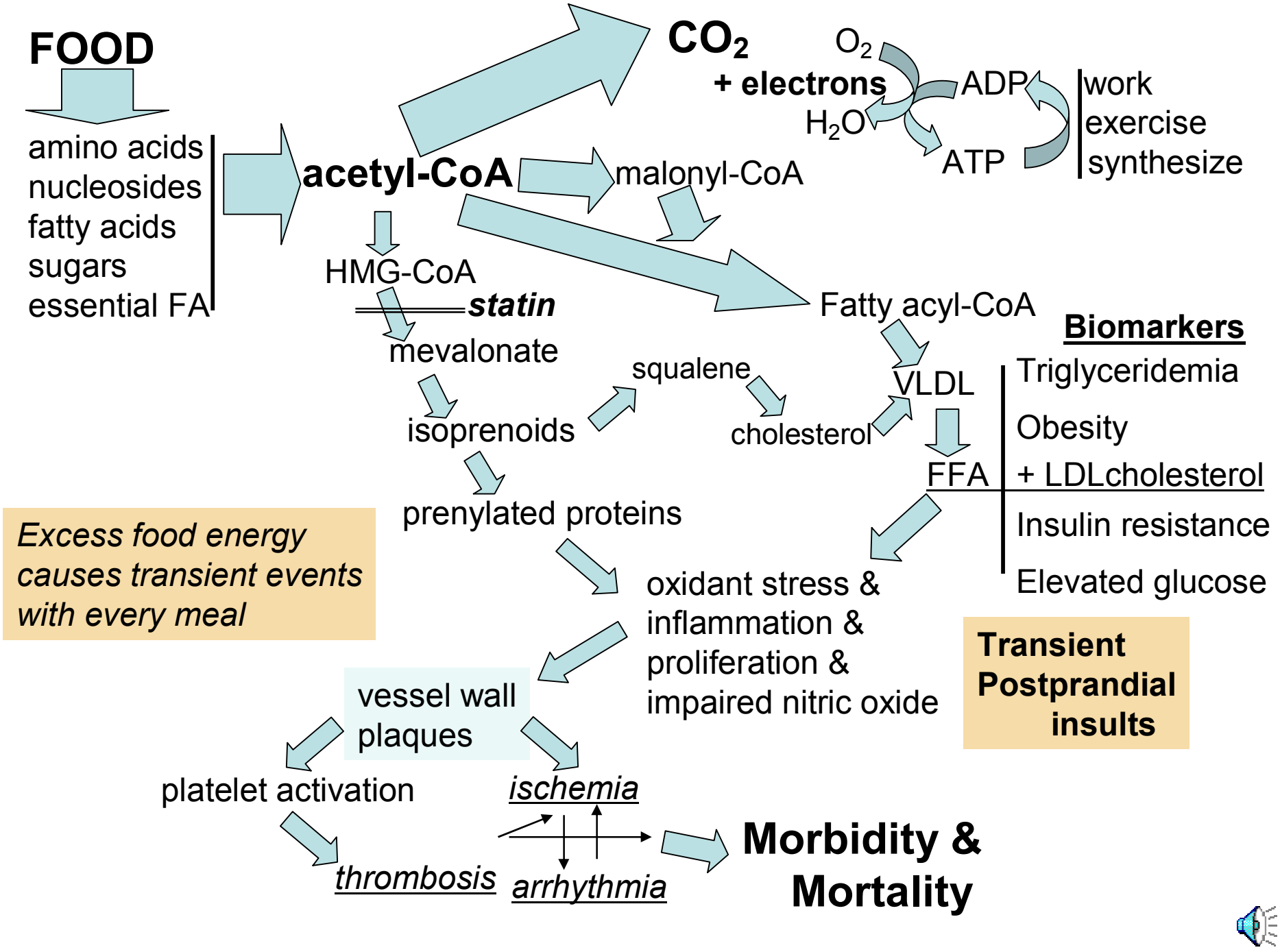
Often-neglected facts cause paradoxes:

An association with disease is not proof of cause.

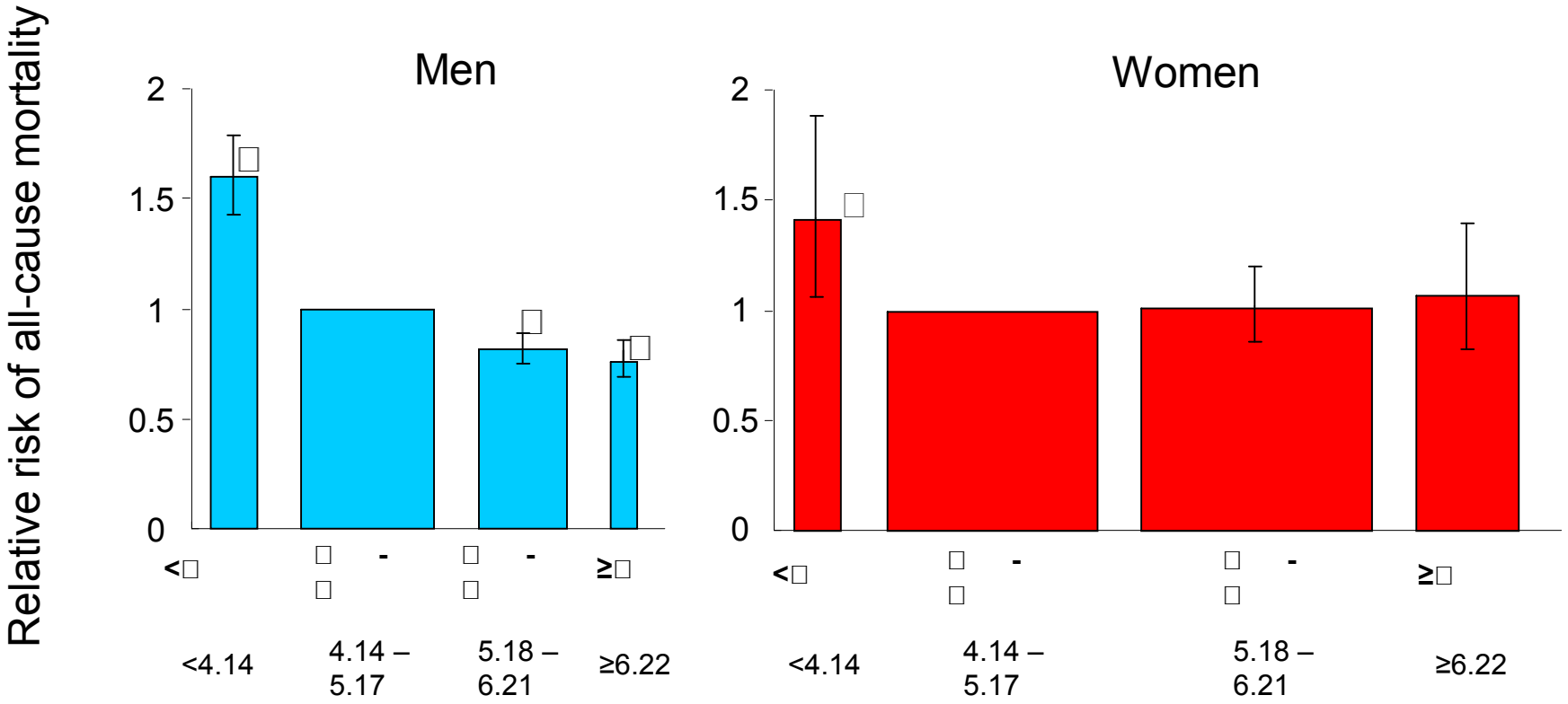
Removing disease signs & symptoms, may not remove the cause.

Lands, B. Prog.Lipid Res. 2008; 47: 77-106.

HOW FOOD HARMS
(1.7 minutes)


FOOD
amino acids
nucleosides
fatty acids
sugars
essential FA
acetyl-CoA
CO2
+ electrons
O2
H2O
ADP
ATP
work
exercise
synthesize
malonyl-CoA
HMG-CoA
statin
mevalonate
Fatty acyl-CoA
squalene
isoprenoids
cholesterol
VLDL
FFA
prenylated proteins
Biomarkers
Triglyceridemia
Obesity
+ LDLcholesterol
Insulin resistance
Elevated glucose
Excess food energy causes transient events with every meal
oxidant stress &
inflammation &
proliferation &
impaired nitric oxide
Transient Postprandial insults
vessel wall plaques
platelet activation
ischemia
thrombosis
arrhythmia
Morbidity & Mortality

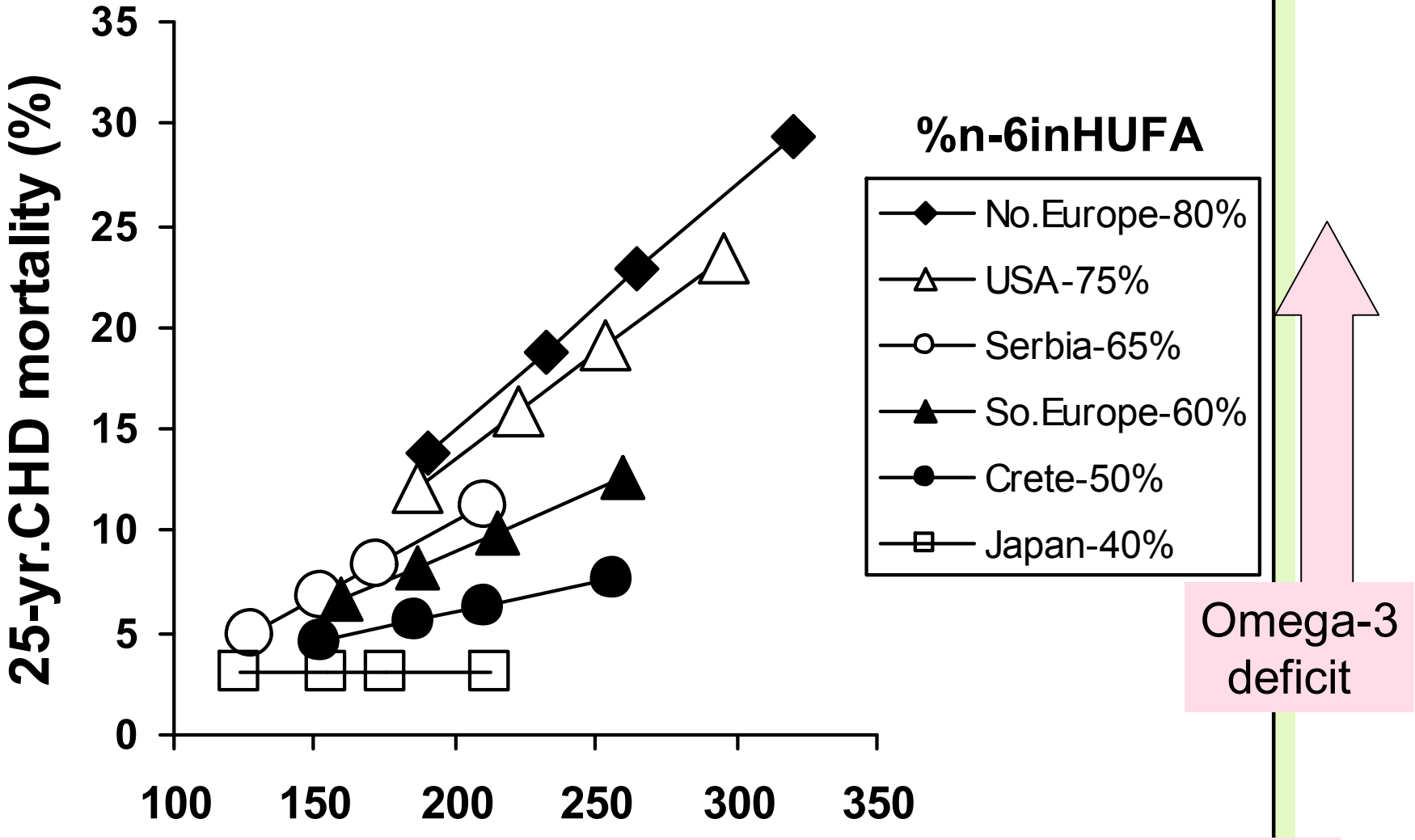
Cholesterol and all-cause mortality in Japan (meta-analysis)



Five reports were included in this metanalysis. Reports excluded were published before 1995, based on a cohort of less than 5000 subjects, or contained no information about the number of deaths in each cholesterol group. The width of each column is proportional to the number of subjects in that group. The total number of subjects: 173,539. *: p=0.02, **: p<0.0001.

Kirihara Y et al. J Lipid Nutr 2008;17:67-78

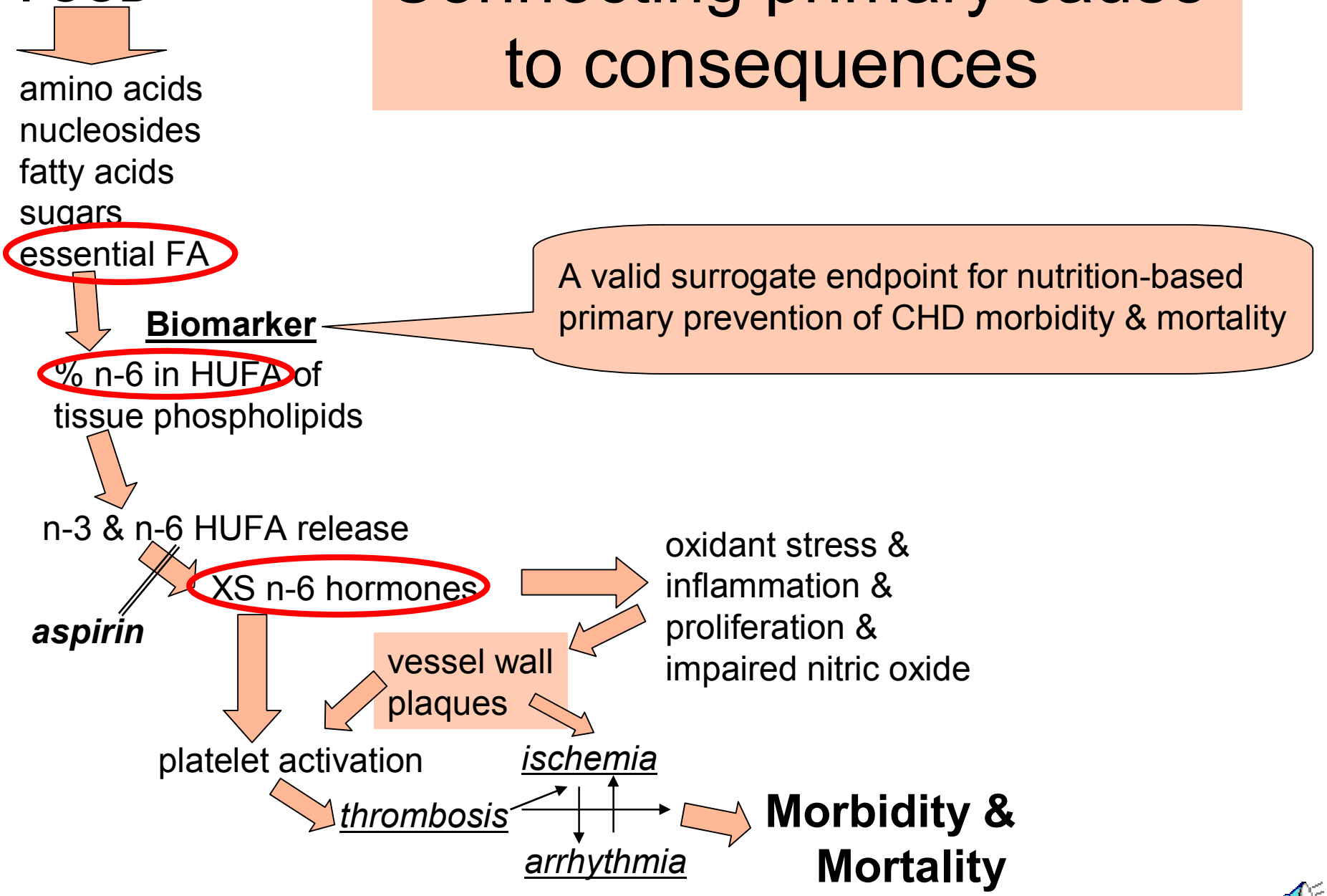
Blood cholesterol is a predictor related to n-3 deficit



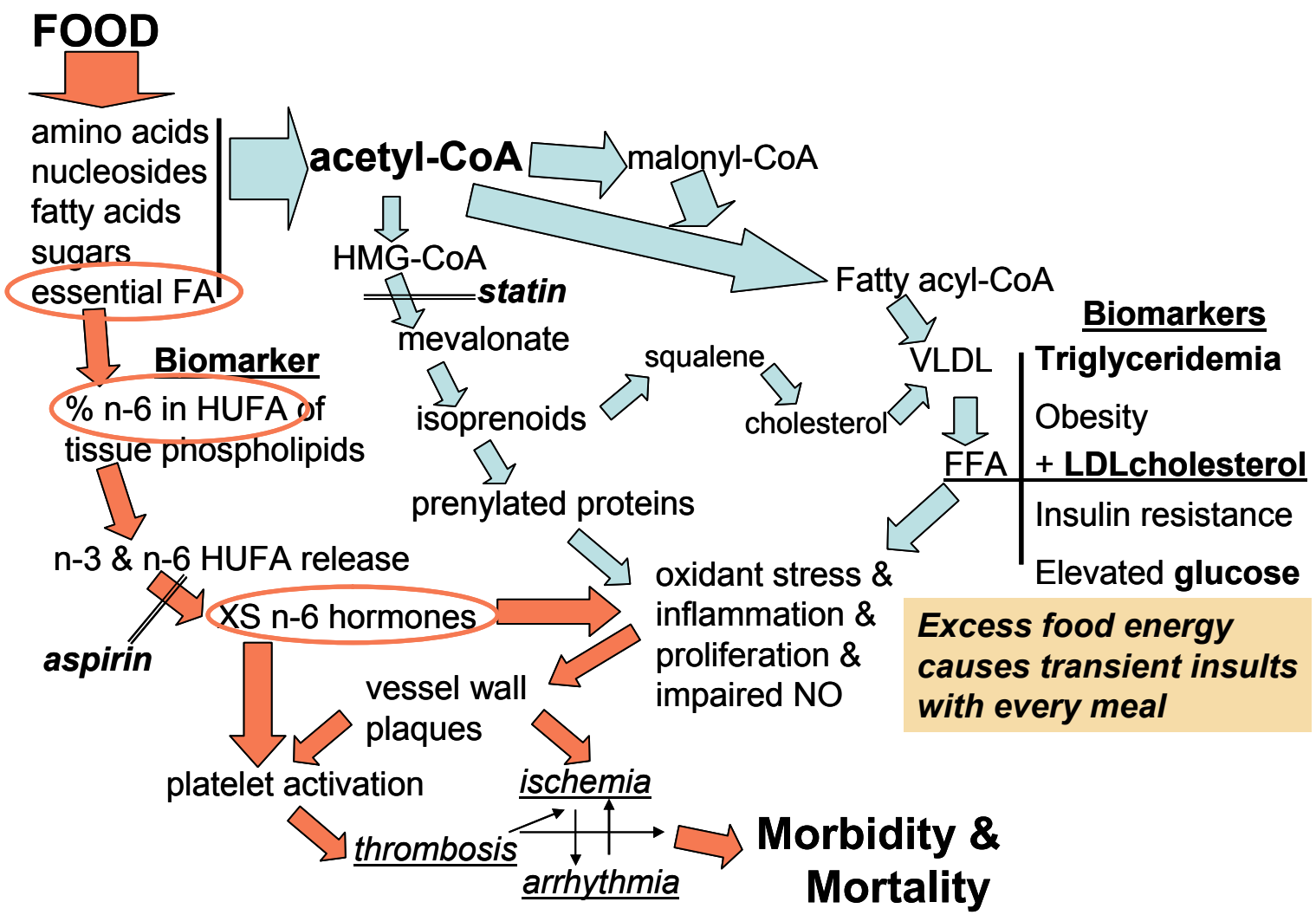
Food energy imbalances which raise blood cholesterol
may be fatal only to the degree that
omega-6 (n-6) EXCEEDS omega-3 (n-3) in tissue HUFA.

HOW OMEGA-6 IN FOOD HARMS
(1.0 minute)

Connecting primary cause to consequences



Food ⇨ tissue insults ⇨ tissue injuries ⇨ disease ⇨ death



High %n-6 in HUFA is a valid surrogate endpoint to prevent.

Choose valid surrogate endpoints for effective prevention.

http://efaeducation.nih.gov/sig/chainofevents.ppt

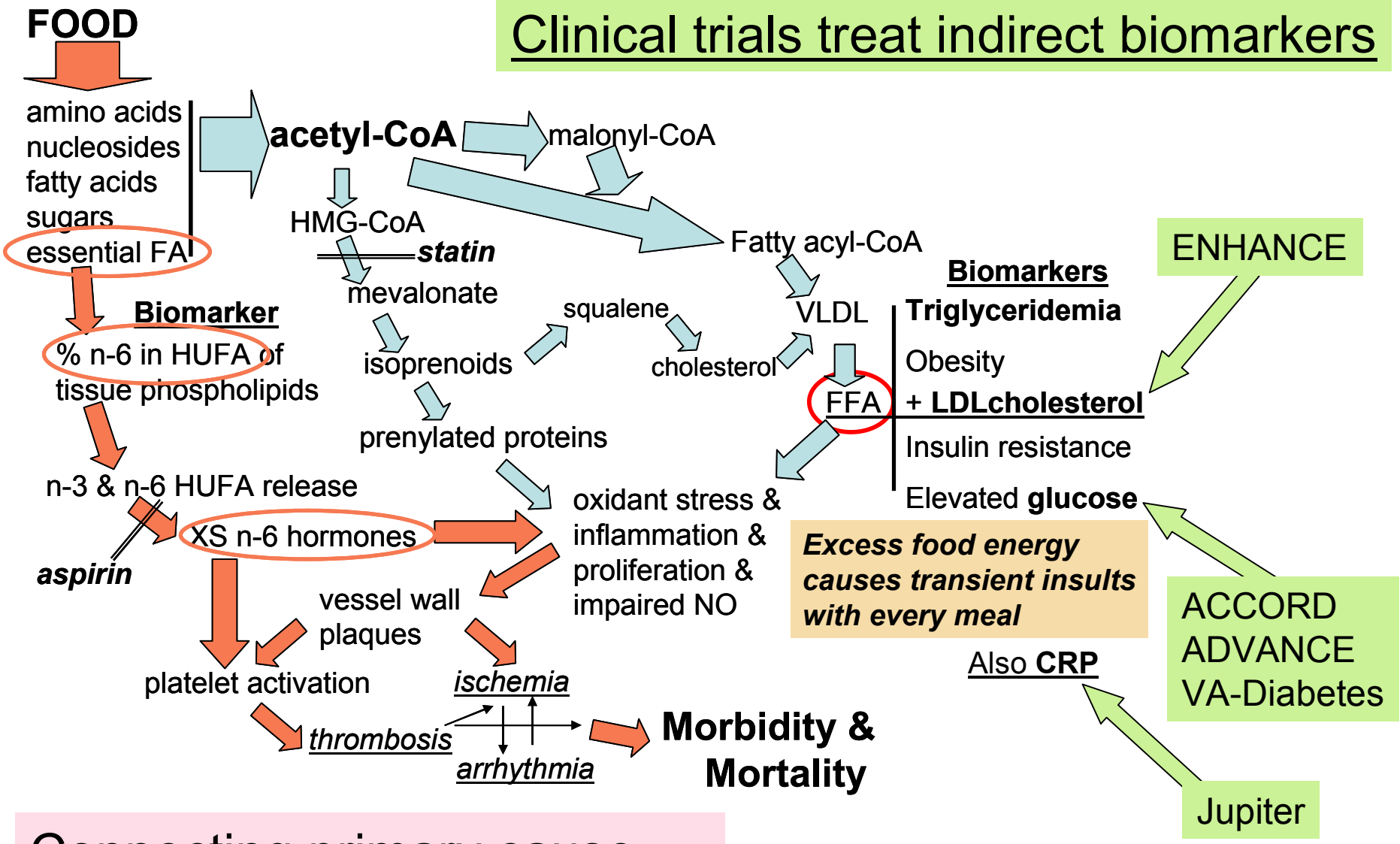
A 1978 European questionnaire had two items:
1.- ‘‘Do you think there is a connection between plasma cholesterol level and the development of coronary heart disease?” (189, yes; 2, no)
2.- ‘‘Do you think that our knowledge about diet and coronary heart disease is sufficient to recommend a moderate change in the diet for the population in an affluent society?” (176, yes; 16, no).

The 1984 NIH Consensus Development Panel regarded CHD as a diet-induced disease caused by imbalanced food energy. It urged that the first step in treatment should be caloric restriction and weight loss, and that ‘‘even when use of drugs seems appropriate, it is important to stress that maximal diet therapy should be continued”.

Nevertheless, the 1984 Panel voted:
1.- ‘‘Is the relationship between blood cholesterol levels and coronary heart disease causal?” (14, yes; 0, no)
2.- ‘‘Should an attempt be made to reduce blood cholesterol levels of the general population?” (14, yes; 0, no)

The Panel report ‘‘figured very large” in the FDA decision to justify approval of cholesterol-lowering therapy without requiring the manufacturers to submit at the time of application clinical trial data demonstrating efficacy

Clinical trials treat indirect biomarkers



Connecting primary cause to consequences

2008 mass media comments on LDL-cholesterol limits in CHD

John Carey, Business Week, Jan., Mar., Apr. 2008
http://www.businessweek.com/print/magazine/content/08_04/b4068052092994.htm
http://www.businessweek.com/print/bwdaily/dnflash/content/mar2008/db20080331_704360.htm
http://www.businessweek.com/print/bwdaily/dnflash/content/apr2008/db20080414_050826.htm

Jennifer Couzin, Science, Oct. 2008
Clinical trials and tribulations.Cholesterol veers off script. Science. 2008; 322: 220-223.

Press release: Oct., 2008 - Pfizer will end early-stage development of cardiovascular treatments in favor of more profitable areas, such as anticancer, anti-inflammatory, psychoses (schizophrenia), pain, Alzheimer's disease, and diabetes candidates.

Bernadine Healy, US News&World Report, Aug. 2008
Test for blood omega-3 levels can be very important in preventing CHD.

Ron Winslow, Wall Street Journal, Nov., 2008
CRP test results may be more useful than cholesterol levels to promote statin use.

Efficacy of Clinical Interventions

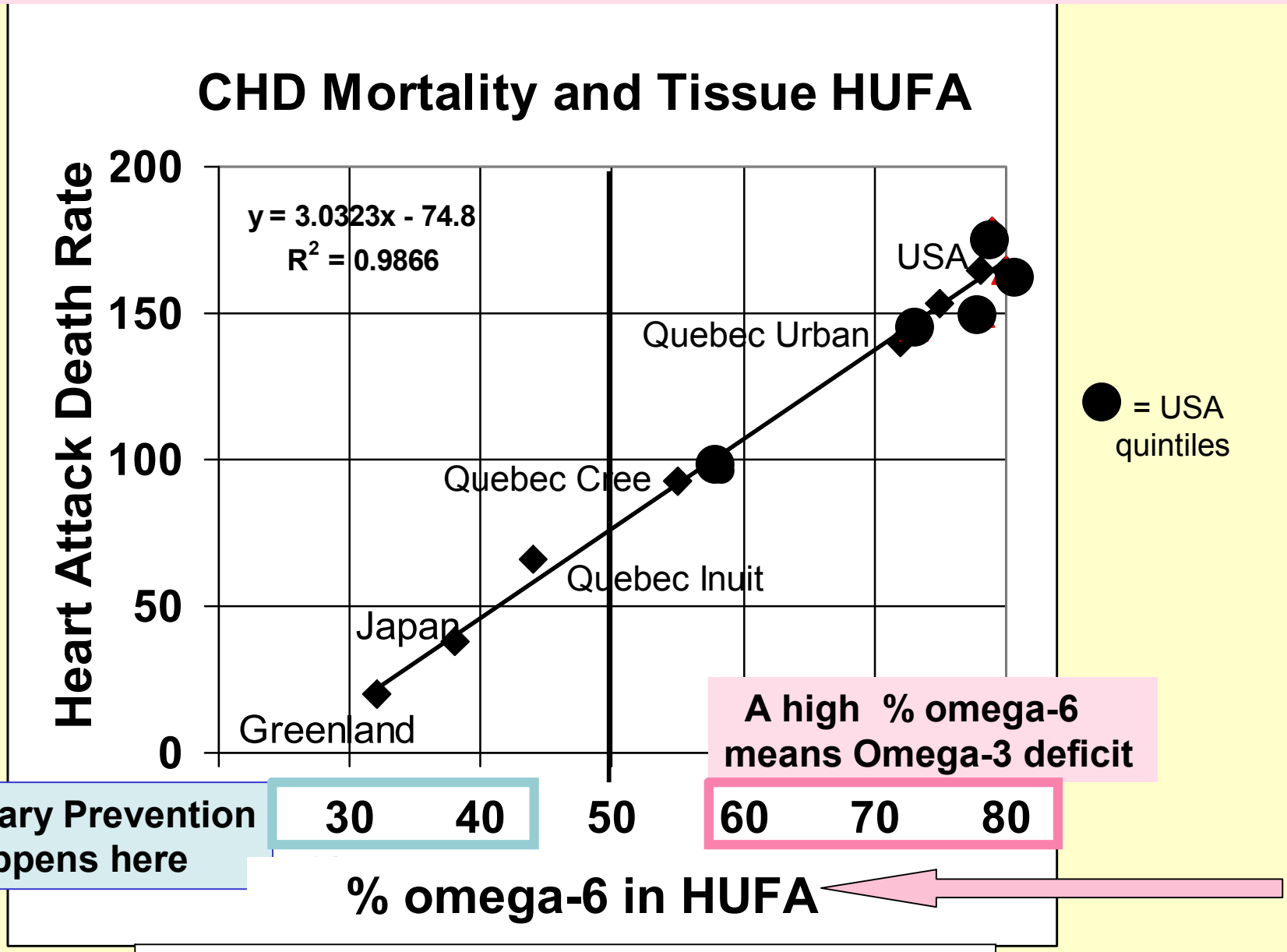
Meta-analysis of 97 randomized controlled trials with
137,140 people in intervention & 138,976 in control groups

Risk Ratios for Overall Mortality

1.00 for fibrates (no better than control)
0.97 for “diet advice”
0.96 for niacin
0.87 for statins
0.84 for resins
0.77 for n-3 fatty acids (less risk than control)

(Studer M, et al. Arch Intern Med. 2005; 165(7): 725-730)

Americans have excessive omega-6 in HUFA & an omega-3 deficit



Lands, Lipids 2003 (Apr.); 38: 317–321
http://efaeducation.nih.gov/sig/personal.html

Adjust Ambient Intakes to Decrease Risk of CHD

	ambient intakes					Raise est. RDA n-3H		Lower est. UL n-6LA		Do both blend both ideas		
	1995 consumption of EFA					fix n-3 HUFA		fix n-6 LA		fix n-3HUFA & n-6LA		
	en% short3	en% short6	en% long3	en% long6	est. %6inH avg	long3	est. %6inH avg	short6	est. %6inH avg	long3	short6	est. %6inH avg
data = Hibbeln et al, AJCN 2006						en%		en%		en%	en%	
Philippine	0.08	0.80	0.26	0.06	**34**	0.17	40	1.11	40	0.17	0.80	40
Iceland	0.33	2.48	0.44	0.10	**50**	0.78	40	1.40	40	0.42	1.40	40
Japan	0.78	4.28	0.37	0.10	**62**	1.30	40	1.40	40	0.40	1.40	40
Denmark	0.33	2.23	0.14	0.09	**64**	0.66	40	0.63	40	0.40	1.40	40
UK	0.77	3.91	0.10	0.07	**70**	0.96	40	0.77	40	0.35	1.60	40
Ireland	0.42	3.57	0.09	0.06	**71**	0.85	40	0.65	40	0.35	1.60	40
Columbia	0.24	3.21	0.05	0.04	**73**	0.70	40	0.49	40	0.32	1.60	40
Australia	0.49	4.71	0.11	0.07	**74**	1.20	40	0.70	40	0.32	1.40	40
Italy	0.51	5.40	0.10	0.06	**75**	1.35	40	0.70	40	0.28	1.40	40
Germany	0.62	5.57	0.08	0.06	**76**	1.35	40	0.70	40	0.30	1.50	40
Netherland	0.28	4.23	0.09	0.08	**77**	1.20	40	0.50	40	0.38	1.40	40
Israel	0.67	7.79	0.12	0.07	**79**	1.95	40	0.77	40	0.30	1.40	40
USA	1.06	8.91	0.10	0.08	**80**	2.27	40	0.80	40	0.28	1.40	40
data = http://efaeducation.nih.gov/sig/dietbalance.html												
USA	0.85	6.82	0.03	0.08	**82**	1.80	40	0.51	40	0.30	1.40	40
Mediterr	0.50	2.30	0.09	0.08	**66**	0.60	40	0.59	40	0.32	1.30	40
Japan	0.76	5.04	0.54	0.08	**57**	1.34	40	2.10	40	0.33	1.40	40

Effective Primary Prevention Needs You

TO UNDERSTAND–

Food energy causes transient tissue insults

Omega-6 hormones amplify insults into inflamed injuries

Omega-3 HUFA diminish inflammatory insults

TO TEACH -

EAT MORE OMEGA-3

EAT LESS OMEGA-6

EAT FEWER CALORIES PER MEAL

Distant learning website for essential fatty acids and eicosanoids

http://efaeducation.nih.gov/

Distant learning website for calculating tissue HUFA balance

http://efaeducation.nih.gov/sig/dietbalance.html

Choose daily foods to balance tissue HUFA using interactive software, KIM-2

http://efaeducation.nih.gov/sig/kim.html