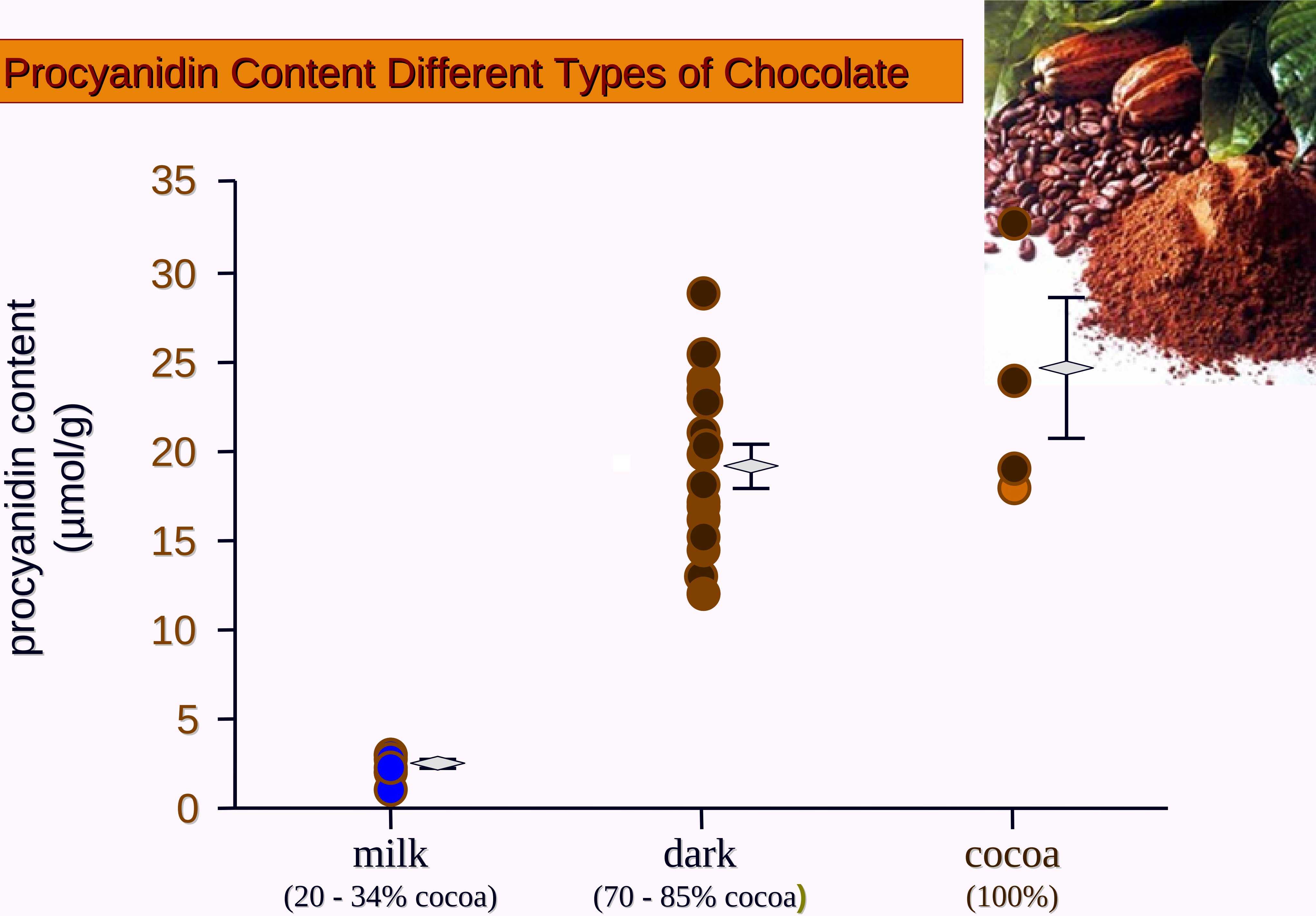
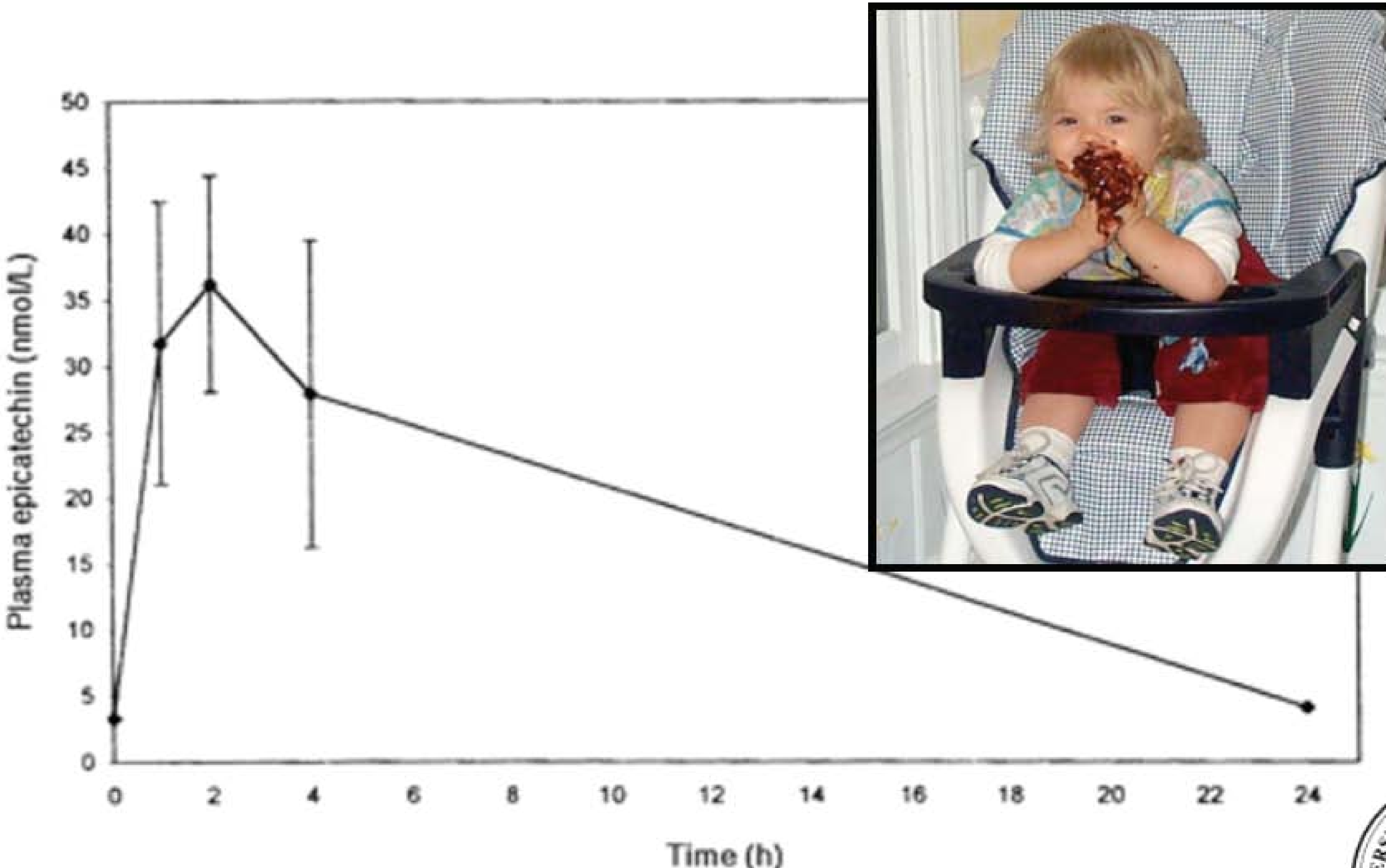
Procyanidin Content Different Types of Chocolate



Plasma concentration of catechins after ingestion of dark chocolate



Ying Wan et al. *Am J Clin Nutr* 2001

University Hospital Zurich

EVIDENZE IN VIVO

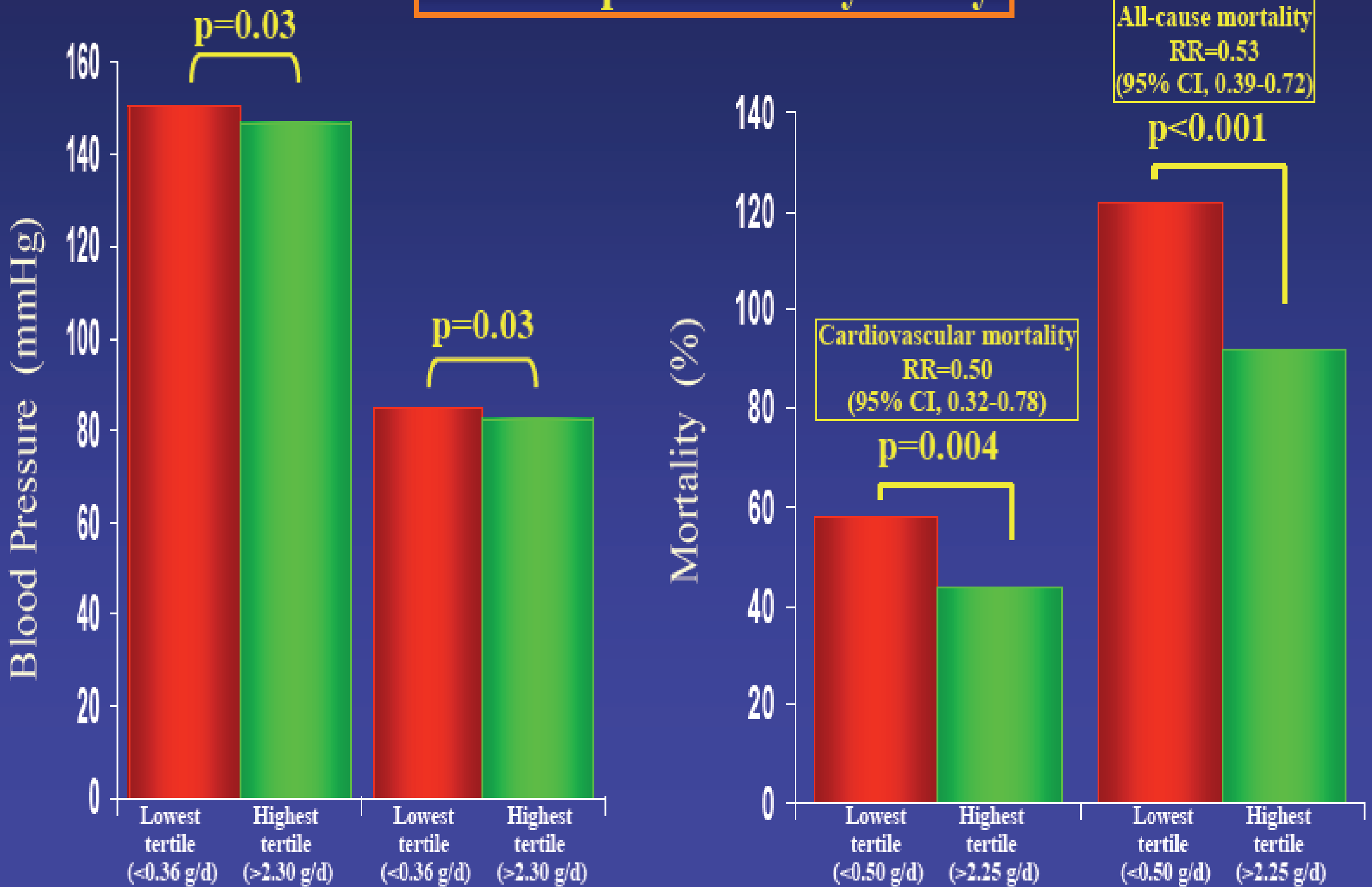
Table 1. Effects of Cocoa and Chocolate on Oxidation

Reference	Type	Subjects	Antioxidant Effect
Wang et al., 2000[29]	Dark chocolate, single dose (27 g, 53 g, or 80 g)	Healthy adults (N = 20)	Weak +
Rein et al., 2000[52]	Dark chocolate, single dose (80 g)	Healthy adults (N = 10)	+
Wan et al., 2001[26]	Cocoa powder (22 g) plus dark chocolate (16 g/d) for 4 weeks	Healthy adults (N = 23)	+
Osakabe et al., 2001[25]	Cocoa powder (36 g/d) for 2 weeks	Healthy adults (N = 15)	+
Mathur et al., 2002[27]	Dark chocolate (36 g/d) plus Cocoa powder (30 g/d) for 6 weeks	Healthy adults (N = 25)	+ LDL oxidizability, − ORAC antioxidant capacity, − urinary F_2 Isoprostanes
Steinberg et al., 2002[24]	Cocoa powder, single dose (37.5 g)	Healthy adults (N = 6)	+
Serafini et al., 2003[35]	Dark chocolate, single dose (100 g, 100 g with 200 mL milk, or 200 g milk chocolate)	Healthy adults (N = 12)	+, −, −
Wiswedel et al., 2004[66]	Cocoa drink, single dose (100 mL)	Healthy adults (N = 20)	+
Kurosawa et al., 2005[67]	Cacao liquor-supplemented diet 1% (w/w), 1–4 months	Hypercholesterolemic Rabbits (N = 15)	+
Fraga et al., 2005[68]	Flavanol-containing milk chocolate (105 g) for 2 weeks	Healthy adults (N = 28)	+
Vlachopoulos et al., 2005[69]	Dark chocolate, single dose (100 g)	Healthy adults (N = 17)	+

PROTEZIONE CARDIOVASCOLARE

Cocoa intake is inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality

The Zutphen Elderly Study



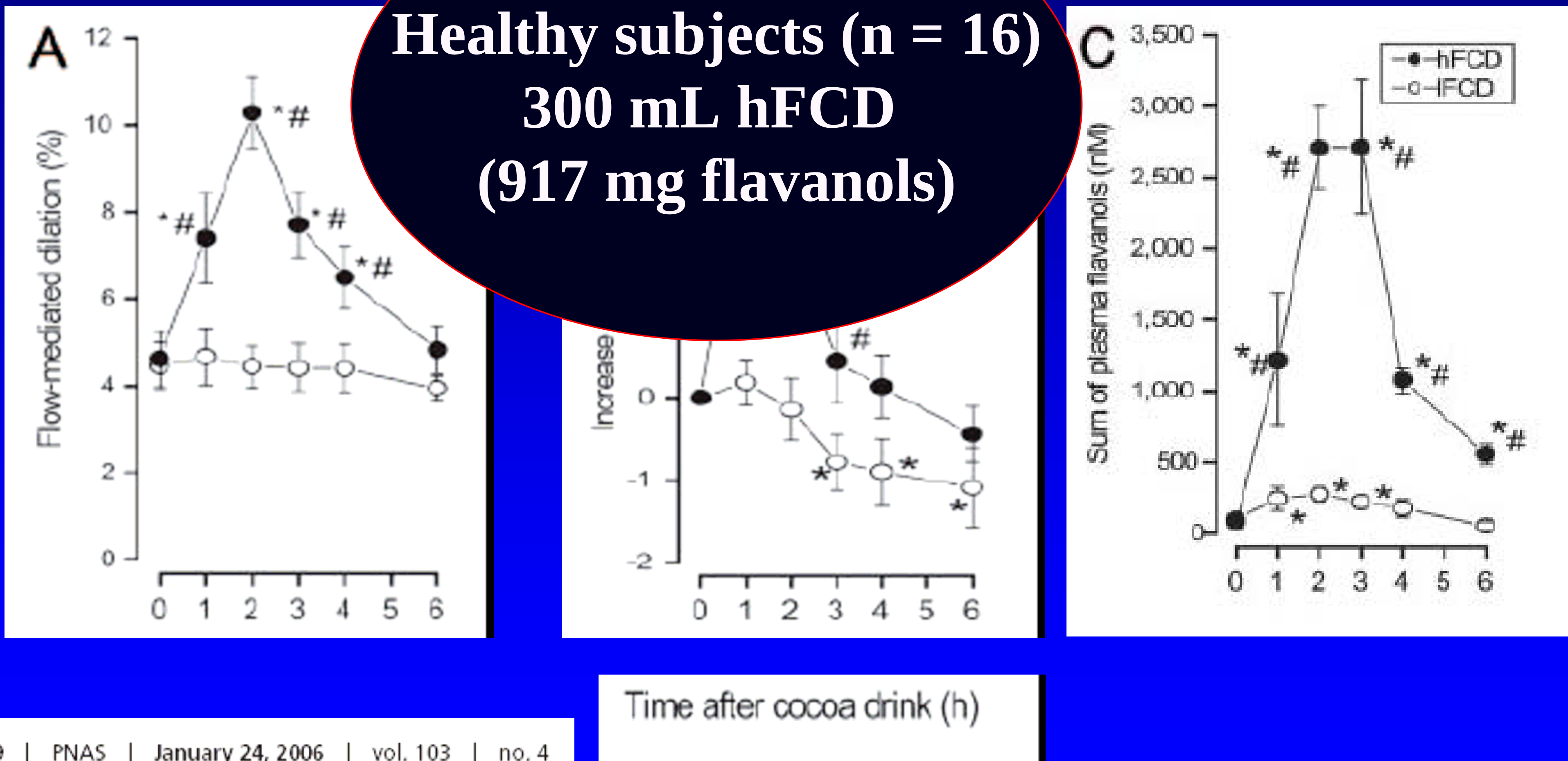
Buijsse B et al, Arch Intern Med. 2006, 166:411-17

(−)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans

Hagen Schroeter*[††], Christian Heiss[†§¶||], Jan Balzer[§], Petra Kleinbongard[§], Carl L. Keen*, Norman K. Hollenberg, Helmut Sies[¶], Catherine Kwik-Uribe[††], Harold H. Schmitz[††], and Malte Kelm[§]**

*Department of Nutrition, University of California, One Shields Avenue, 3150E Meyer Hall, Davis, CA 95616; [§]Division of Cardiology, Pulmonology, and Vascular Medicine, Heinrich-Heine University, Moorenstrasse 5, 40225 Duesseldorf, Germany; [¶]Institute of Biochemistry and Molecular Biology, Heinrich-Heine University, Universitaetsstrasse 1, 40225 Duesseldorf, Germany; **Departments of Medicine and Radiology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115; and [††]A... ...rs Incorporated, 800 High Street, Hackettstown, NJ 07840

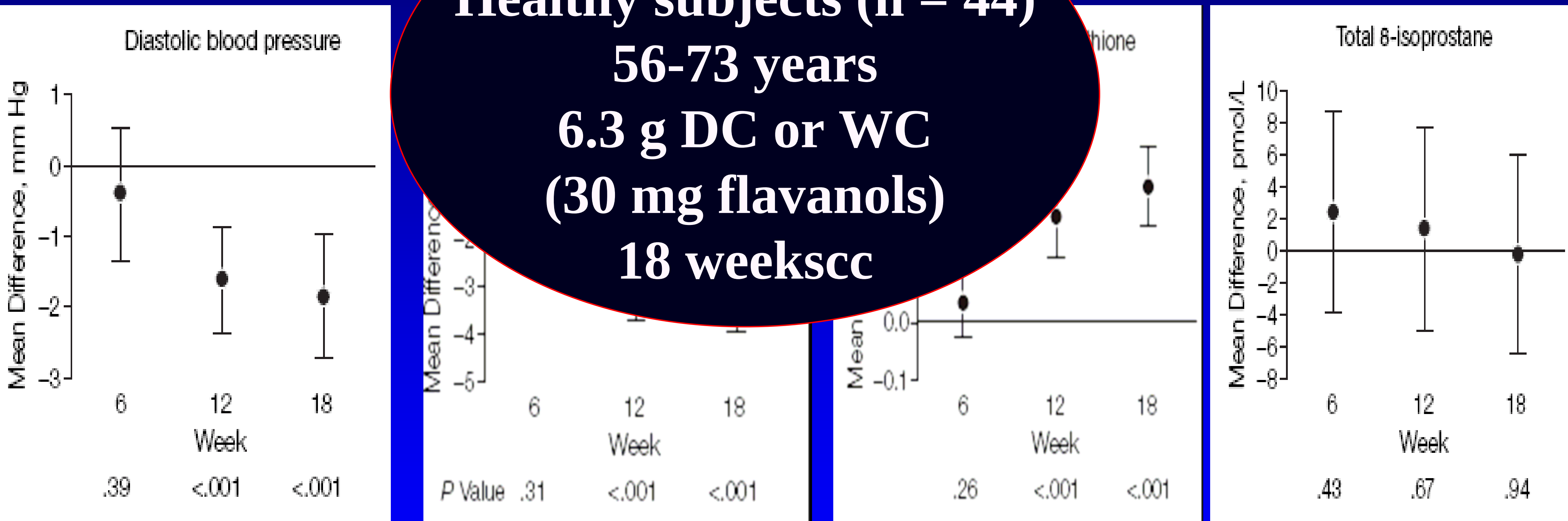
Healthy subjects (n = 16)
300 mL hFCD
(917 mg flavanols)



1024–1029 | PNAS | January 24, 2006 | vol. 103 | no. 4

Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide

A Randomized Controlled Trial



Healthy subjects (n = 44)
56-73 years
6.3 g DC or WC
(30 mg flavanols)
18 weekscc

Taubert et al. JAMA 2007

Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide

A Randomized Controlled Trial

Table 6. Pharmacokinetic Parameters of Cocoa Phenols Derived From a 6.3-g Dose of Dark Chocolate on Day 1 and After 18 Weeks of Intervention[a]

	Mean (SD)		
	Day 1 of Intervention	18 Weeks of Intervention	*P* Value[b]
Epicatechin			
AUC∞, ng/mL × min	761 (210)	774 (253)	.82
C_{max}, ng/mL	3.63 (1.02)	3.58 (0.92)	.78
T_{max}, min	77 (4)	81 (6)	.70
$T_{1/2el}$, min	54 (3)	56 (5)	.79
Catechin			
AUC∞, ng/mL x min	234 (61)	228 (56)	.77
C_{max}, ng/mL	1.12 (0.31)	1.01 (0.26)	.58
T_{max}, min	78 (9)	82 (6)	.69
$T_{1/2el}$, min	54 (6)	58 (7)	.68
Procyanidin B2			
AUC∞, ng/mL x min	99 (30)	102 (32)	.90
C_{max}, ng/mL	0.45 (0.15)	0.43 (0.14)	.94
T_{max}, min	81 (8)	86 (9)	.62
$T_{1/2el}$ min	56 (6)	57 (5)	.91
Procyanidin B2 gallate			
AUC∞, ng/mL x min	33 (14)	33 (13)	.91
C_{max}, ng/mL	0.14 (0.06)	0.14 (0.06)	.98
T_{max}, min	89 (10)	85 (8)	.72
$T_{1/2el}$ min	62 (7)	59 (6)	.76

Abbreviations: AUC∞, total area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to reach the maximum plasma concentration; $T_{1/2el}$, elimination half-life.

[a] Values were obtained for the 22 subjects assigned to dark chocolate by fitting the individual data by a linear 1-compartment model. Data are normally distributed.

[b] *P* values are calculated by paired 2-tailed *t* test. $P < .05$ is considered a statistically significant difference.

Taubert et al. JAMA 2007

EFFETTO SULLA VASODILATAZIONE ENDOTELIALE

Table 2. Effects of Cocoa and Chocolate on Vasodilation

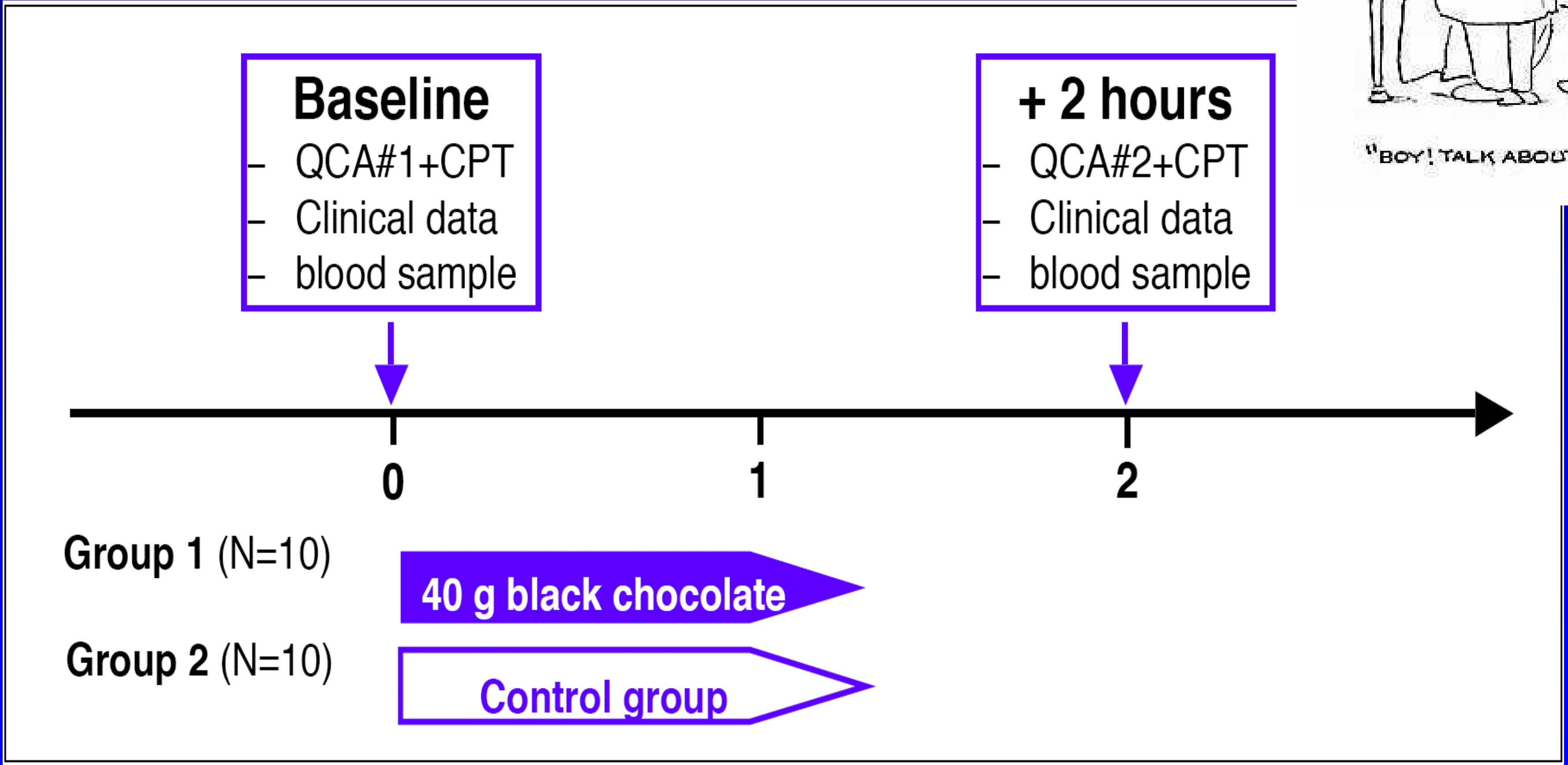
Reference	Type	Cocoa Flavanoids Amount	Model	Endothelium-Dependent Relaxation
Karim et al., 2000[27]	Cocoa extracts (10^{-7} to 10^{-5} mol/L)	—	Isolated rabbit aorta	+
Fisher et al., 2003[39]	Cocoa beverage (230 mL/d) for 4 days	821 mg/d	Healthy adults ($N = 27$) fingertip peripheral artery tonometry	+
Heiss et al., 2003[41]	Cocoa beverage (100 mL/d) for 2 days	176 mg/d	Adults with one cardiovascular risk factor or history of CAD ($N = 26$) brachial artery	+
Engler et al., 2003[31] and Engler et al., 2004[32]	Dark chocolate bars (46 g/d) for 2 weeks	259 mg/d	Healthy adults ($N = 21$) brachial artery	+
Vlachopoulas et al., 2005[66]	Dark chocolate, single dose (100 g)	2.62 g	Healthy adults ($N = 17$) brachial artery	+
Grassi et al., 2005[42]	Dark chocolate bars (100 g) for 15 days	88 mg/d	Hypertensive adults ($N = 20$) brachial artery	+

EFFETTO SULL'AGGREGAZIONE PIASTRINICA

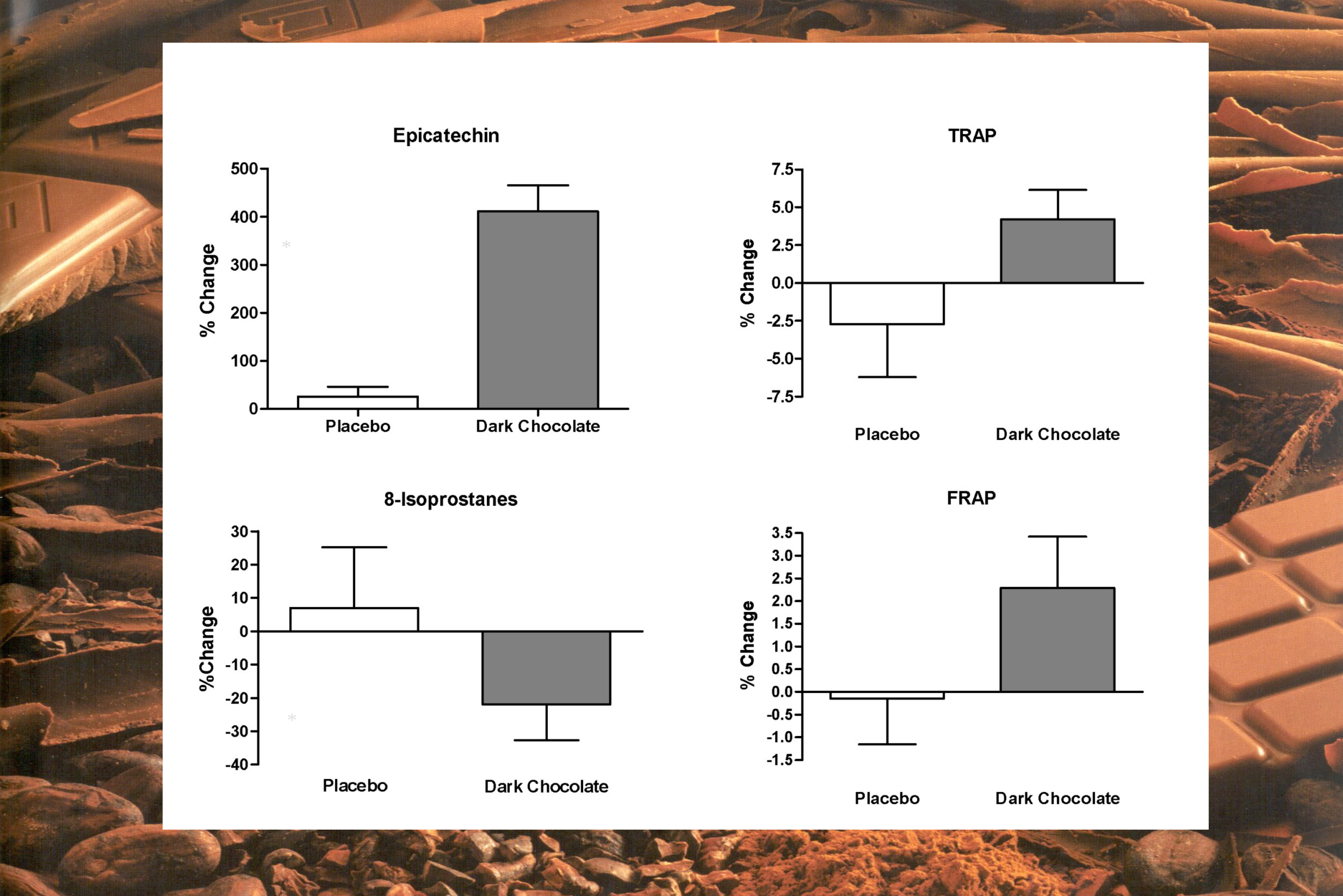
Table 3. Effects of Cocoa and Chocolate on Platelet Function

Reference	Type	Cocoa Flavonoids Amount	Subjects	Platelet Function
Rein et al., 2000[52]	Cocoa beverage, single dose (300 mL)	897 mg	Healthy adults (N = 10)	
Rein et al., 2000[53]	Cocoa beverage, single dose (300 mL)	897 mg	Healthy adults (N = 30)	
Pearson et al., 2002[50]	Cocoa beverage, single dose (300 mL)	897 mg	Healthy adults (N = 16)	
Holt et al., 2002[51]	Semisweet chocolate chips, single dose (25 g)	220 mg	Healthy adults (N = 18)	
Murphy et al., 2003[49]	Cocoa tablets (6/d) for 28 days	234 mg	Healthy adults (N = 32)	
Innes et al., 2003[70]	Dark chocolate, single dose (100 g)	—	Healthy adults (N = 30)	

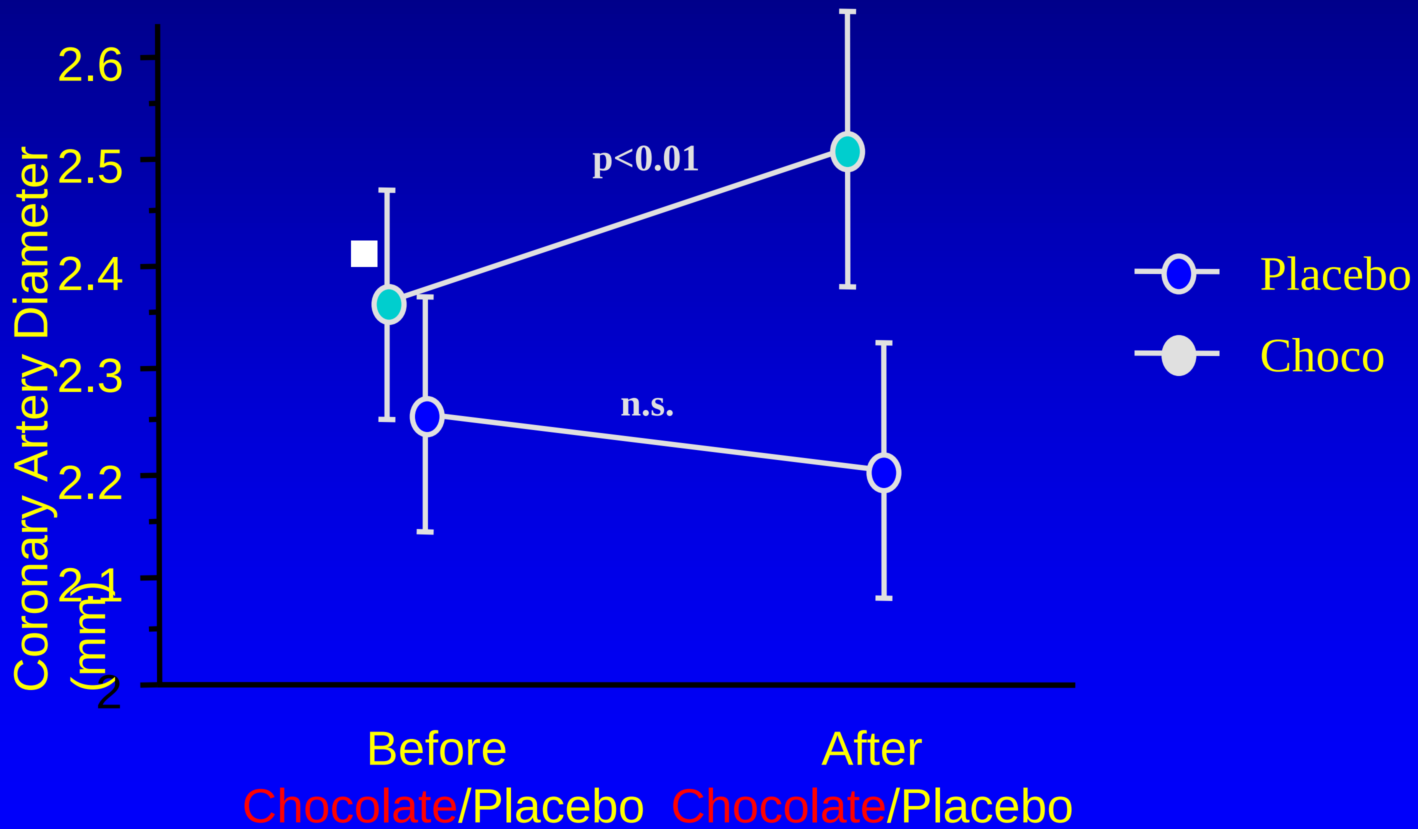
STUDY DESIGN



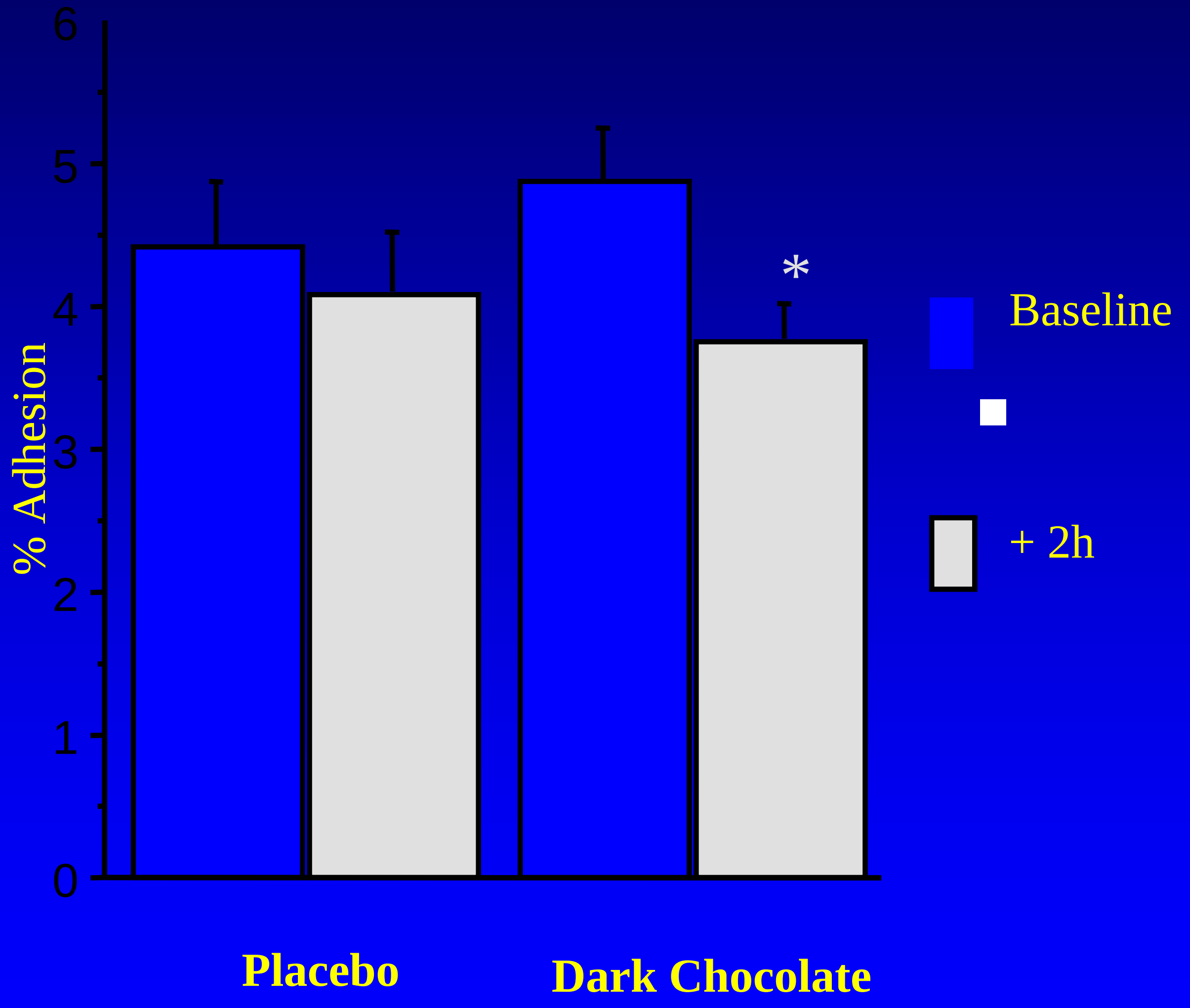
Flammer et al. Circulation 2007


Epicatechin
% Change
500
400
300
200
100
0
Placebo
Dark Chocolate
TRAP
% Change
7.5
5.0
2.5
0.0
-2.5
-5.0
-7.5
Placebo
Dark Chocolate
8-Isoprostanes
%Change
30
20
10
0
-10
-20
-30
-40
Placebo
Dark Chocolate
FRAP
% Change
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Placebo
Dark Chocolate

Coronary Artery Diameter before and 2 hours after chocolate ingestion



Platelet aggregation before and 2 hours after chocolate ingestion



Consumer Awareness

FIRSTLIGHT FOOD

All-Star Foods That Fight for Health

Strawberries and blackberries contain some of the highest antioxidant levels of foods measured by the USDA.

It's no secret that an apple a day—along with other fruits, vegetables, and nuts—will help keep the doctor away. These foods are loaded with antioxidants, substances that fight free radicals, disease-causing compounds that have been linked to heart disease, cancer, and Alzhei But just how many antioxidants these food tain has been a mystery—until now. The Department of Agriculture (USDA) recentl lyzed the antioxidant content of more tha foods, including fruits, vegetables, nuts, fruits, spices, and cereals.

The big surprise: Even though tl consumed in small amounts, herb spices, such as oregano, cinnamor cloves, showed higher amounts tioxidants than researchers had ously thought.

A high antioxidant level doesn't equate to a superfood, however. "There's still a lot we don't understand about how the body uses antioxidants," says Ronald L. Prior, Ph.D., nutritionist and research chemist with the USDA. The body absorbs some antioxidants better than others, he notes, and cooking may also alter the content. But most antioxidant-rich foods also have other benefits, such as low fat and calorie levels, and helpful vitamins and minerals. For optimal health, aim for at least five to nine servings of fruits and vegetables a day. —*Karen Asp*

Many sp and herl like cinr and ore pack a t antioxid punch.

Find easy ways to add power foods to your diet at CookingLight.com /features.

Antioxidant Breakdown

The U.S. Department of Agriculture ranked the following foods among the highest in antioxidant content. The number after each food denotes its **total antioxidant capacity (TAC)**. Foods with TACs of 2,000 or higher, like these, are considered high in antioxidants.

FRUITS one-cup serving
Dried Plums: 14,582
Cultivated blueberries: 9,019
Blackberries: 7,701

VEGETABLES one-cup serving, cooked
Artichoke hearts: 7,904
Red cabbage: 4,718
Russet potato: 4,649

NUTS one-ounce serving
Pecans: 5,095
Walnuts: 3,846
Hazelnuts: 2,739

Sweet cherries (left) clock in with a TAC of 4,873 per cup.

High-ORAC Foods May Slow Aging

[ORAC Research Findings | ORAC Research]
[Recommendations for ORAC Consumption]
[High-ORAC Fruits and Vegetables]

Research results suggest that eating plenty of high-ORAC fruits and vegetables -- such as spinach and blueberries -- may help slow the processes associated with aging in both body and brain.

Foods that score high in an antioxidant analysis called ORAC may protect cells and their components from oxidative damage, according to ORAC studies of animals and human blood at the USDA Agricultural Research Service's Human Nutrition Research Center on Aging at Tufts University in Boston. ARS is the chief scientific agency of the U.S. Department of Agriculture.

ORAC, short for Oxygen Radical Absorbance Capacity, is a test tube analysis that measures the total antioxidant power of foods and other chemical substances.

"If these ORAC findings are borne out in further research, young and middle-aged people may be able to reduce risk of diseases of aging -- including senility -- simply by adding high-ORAC foods to their diets," said ARS Administrator Floyd P. Horn. By the year 2050, nearly one-third of the U.S. population is expected to be over age 65. If further research supports these early findings, millions of aging people may be able to guard against diseases or dementia simply by adding high-ORAC foods to their diets.

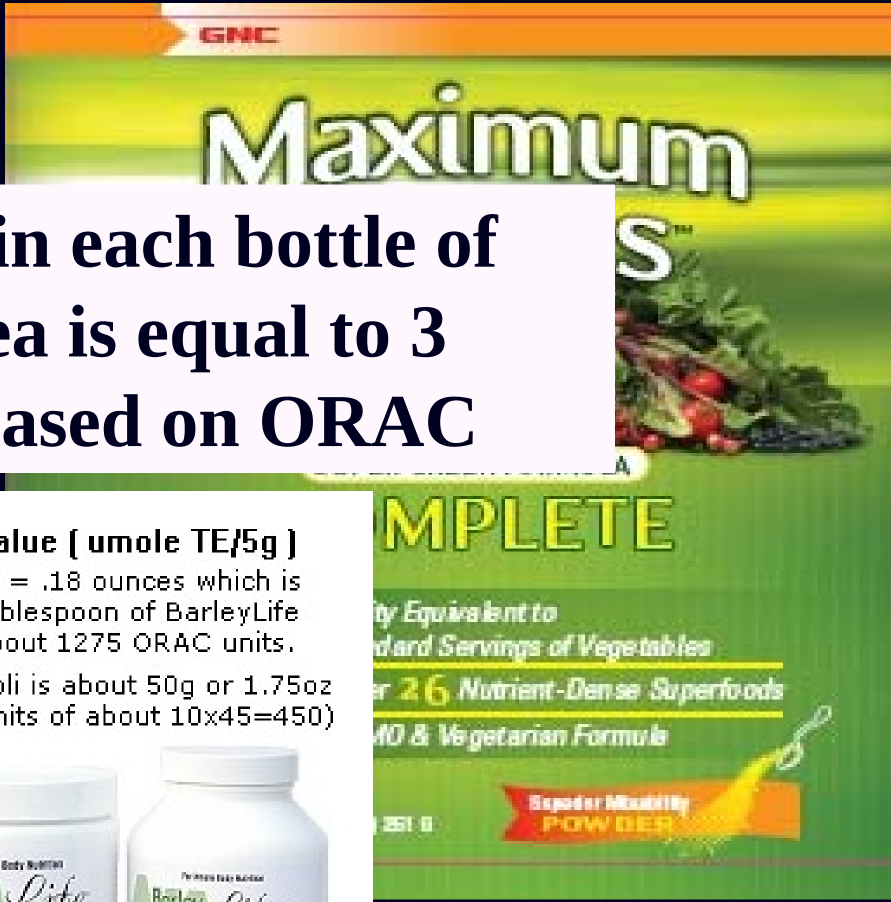
back to top

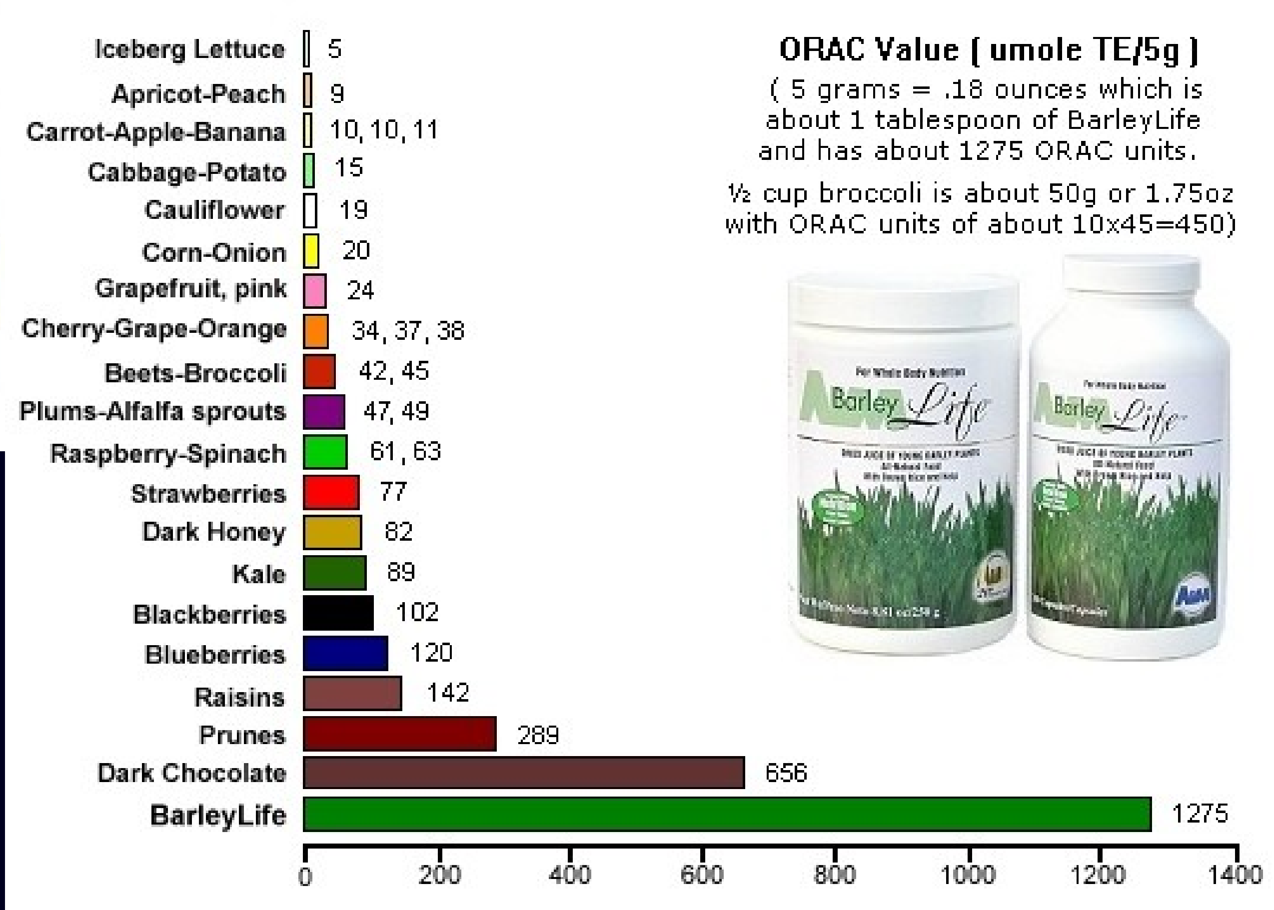
ORAC Research Findings

- High-ORAC foods raised the antioxidant power of human blood 10 to 25 percent.
- High-ORAC foods prevented some loss of long-term memory and learning ability in middle-aged rats.
- High-ORAC foods maintained the ability of brain cells in middle-aged rats to respond to a chemical stimulus--a function that normally decreases with age.
- High-ORAC foods protected rats' tiny blood vessels--capillaries--against oxygen damage.

Nutritionist Ronald L. Prior contends, "If we can show some relationship between ORAC intake and health outcome in people, I think we may reach a point where the ORAC value will become a new standard for good antioxidant protection." (See table at end for ORAC values of fruits and vegetables.)

“The antioxidant capacity in each bottle of FUZE White and Green Tea is equal to 3 servings of vegetables…” based on ORAC





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Acai ORAC - Value

What is ORAC and what does it stand for?

ORAC = Oxygen Radical Absorption Capacity

What is the ORAC Assay?

The Oxygen Radical Absorption Capacity (ORAC) assay is a method for measuring the total antioxidant activity of a biological sample. It measures the antioxidant activities of human, agricultural products, food products, food ingredients and pharmaceutical products.

The assay measures the effectiveness of various natural antioxidants, present in the sample, in preventing the loss in the fluorescence intensity of the fluorescent marker protein, Beta-pycoerythrin (beta-PE), during peroxy radical induced free radical damage. Each reaction is calibrated using known standards of Trolox®, a water soluble vitamin E analog. The results of the assay are reported on the basis of 1 ORAC unit = 1 micro-M Trolox®. 1

What is a normal ORAC for daily consumption?

For the average person they need 1670 ORAC per day. To give this perspective 80% - 90% of people in the world do not consume even half of the daily required ORAC's.

What is the level in Life Dynamics ACAI?

Life Dynamics Acai 4:1will give you a **ORAC level of 3871**. This is based on a dosage leve of 2 capsules of 1 gram (1000 mg).

Life Dynamics Acai Lite 1:1 w/Acerola will give you a **ORAC level of 2100+**. This is based on a dosage level of 6 capsules of 3 gram (3000 mg).

GREEN TEA
DOSE-RESPONSE STUDY

SUBJECTS

- ✓ Fifteen healthy volunteers

  (25.8 ± 4.8 y, 7 M 8 W)
- ✓ Non-smokers, normolipidemic
- ✓ No drug or vitamin supplements

STUDY DESIGN

GTFT 1.4 g/L (500 mL) — Group A (n = 4)

GTFT 1.6 g/L (500 mL) — Group B (n = 4)

GTFT 1.8 g/L (500 mL) — Group C (n = 4)

GTFT 2.0 g/L (500 mL) — Group D (n = 3)

Blood sampling (0, 0.5, 1, 2 and 4 h)

14 Days wash-out

Phases 4

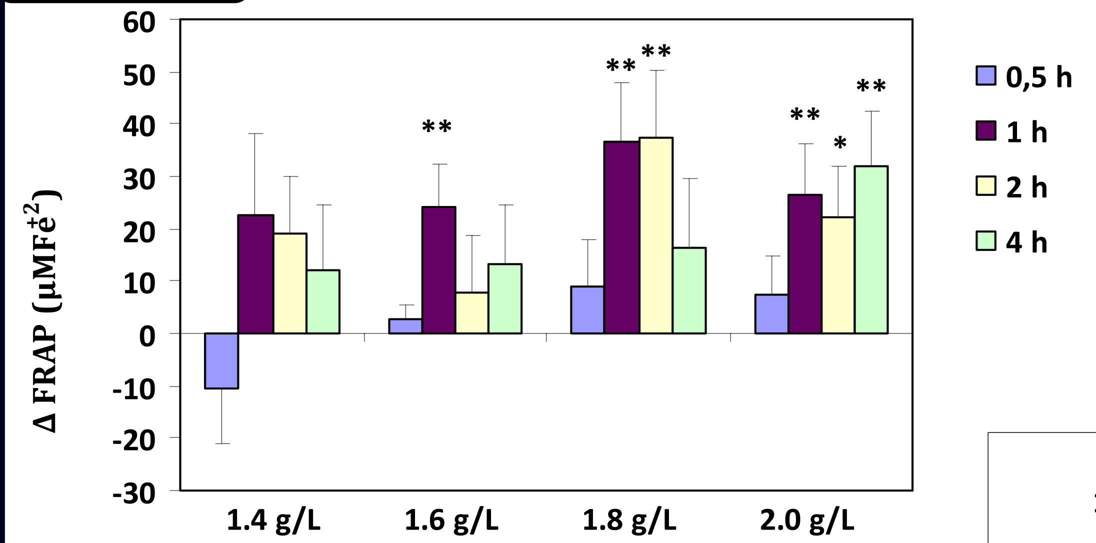
Antioxidant composition (mg/L) of green tea (GTFT) with different amount of tea solids

	1.4 g/L	1.6 g/L	1.8 g/L	2.0 g/L
Vitamin C	213	207	211	201
Gallic acid	0.6	0.7	0.8	0.9
5-Galloylquinic acid	12.9	14.9	17	19.2
Gallocatechin	21.3	24.8	27.9	31.5
Epigallocatechin	129.7	151	171.3	196.9
Epicatechin	31.9	36.9	43.2	47.7
Epigallocatechin-3-gallate	236.1	274.5	312.5	353.9
Catechin gallate	0.7	0.8	0.9	1.1
Epicatechin-3-gallate	42.5	49.5	57.3	65.1
Gallocatechin gallate	2.0	2.1	2.4	2.7
5-Caffeoylquinic acid	2.4	2.8	3.3	3.8
Quercetin rhamnosyl galactoside	2.0	2.3	2.5	3.0
Quercetin-3-rutinoside	3.3	3.7	4.2	4.8
Quercetin-3-galactoside	2.2	2.5	2.9	3.2
Quercetin-hexose-rhamnose- rhamnose	1.7	1.7	2.0	2.4
Kaempferol- rhamnose-hexose- rhamnose	3.8	3.8	4.5	5.6
Kaempferol-Galactoside and Kaempferol-3-rutinoside	2.8	3.1	3.7	4.0
Kaempferol-3-glucoside	2.0	1.5	1.6	1.9
Theaflavin	0.8	0.9	1.0	1.3

* mmol/L
** mmol Fe^{2+}/L

Effects of green teas (GTFT) ingestion on markers of plasma antioxidant status

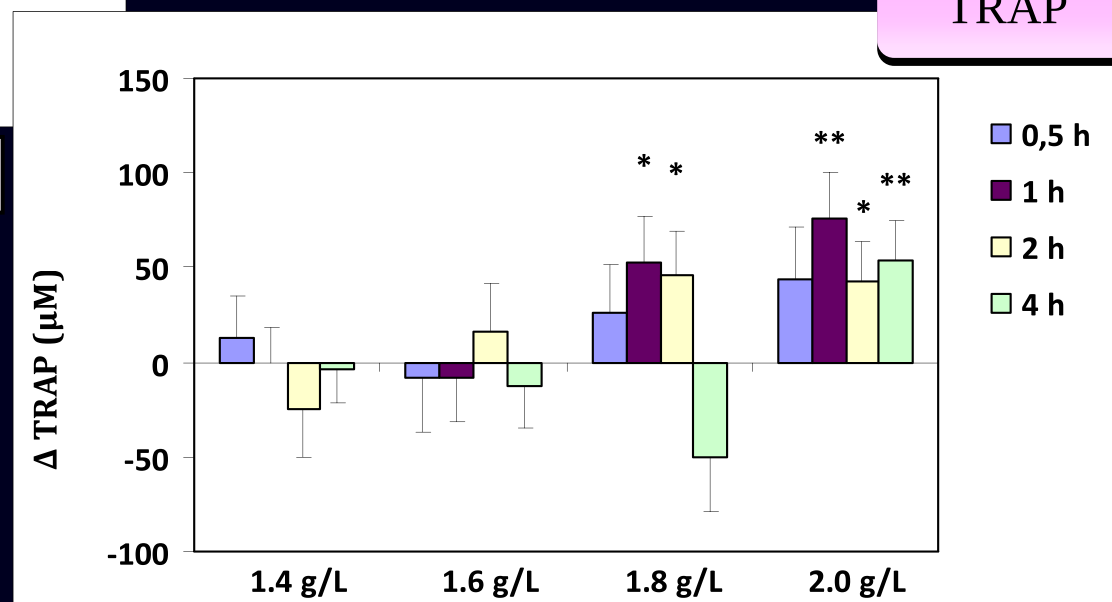
FRAP



* p<0.05; ** p<0.01 compared with baseline (paired t-test)

R = 0.78

TRAP



Acute supplementation studies

Tea (Sung et al. Eur J Clin Nutr 2000)

Wine (Maxwell et al. Lancet 1994)

Alcohol-free wine (Serafini et al. J Nutr 1998)

Chocolate (Richelle et al. Eur J Clin Nutr 1998)

Onion (Mc Anlis et al. Eur J Clin Nutr 1999)

Beer (Ghiselli et al. J Nutr Biochem 2000)

Whisky (Duthie et al. Eur J Clin Nutr 1998)

Grape juice (Day et al. Ann Nutr Metab 1997)

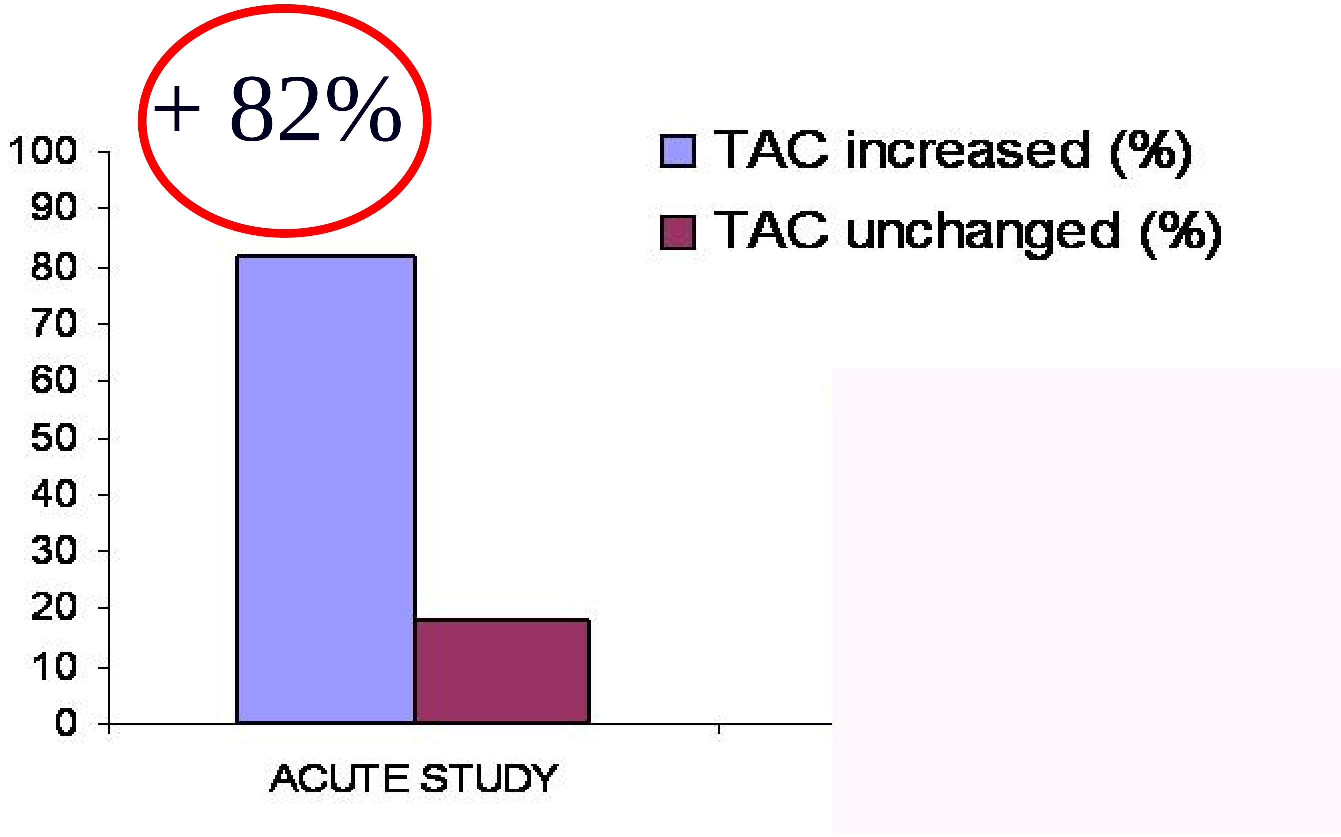
Blueberry (Pedersen et al. Eur J Clin Nutr 2000)

Table 2. Overview of Chronic Human Intervention Studies on Diet and Plasma TAC[a]

Study (Ref.)	Design	Results[b] TAC	Method
Cao et al., 1998 (29)	Volunteers: 36 healthy subjects Duration: 2 wk Diet: 10 servings fruits and vegetables per day	↑	ORAC
Leighton et al., 1999 (30)	Volunteers: 21 healthy subjects Duration: 1 mo Diet: Mediterranean diet	↑	Luminol
Young et al., 1999 (31)	Volunteers: 5 healthy subjects Duration: 1 wk Diet: Fruit juice (up to 1500 mL)	=	TEAC FRAP
Bub et al., 2000 (32)	Volunteers: 23 healthy subjects Duration: 8 wk Diet: vegetable juice 330mL, spinach (10 g)	=	FRAP
Lee et al., 2000 (33)	Volunteers: 6 healthy subjects Duration: 5 wk Diet: tomato products (430 g)	↑	FRAP
Record et al., 2001 (34)	Volunteers: 25 healthy subjects Duration: 2 wk Diet: 5–7 servings of furits and vegetables per day	=	TEAC
Van den Berg et al., 2001 (35)	Volunteers: 22 healthy smokers Duration:3 wk Diet: vegetable burger, fruit drink	↑	TEAC
Roberts et al., 2003 (36)	Volunteers: 18 healthy smoking subjects Duration: 3 wk Diet: 5 servings of furits and vegetables per day	↑	ORAC
Dragsted et al., 2004 (37)	Volunteers: 43 healthy subjects Duration: 25 days Diet: 600 g furits and vegetables per day	=	TEAC FRAP
Pitsavos et al., 2005 (38)	Volunteers: 3,042 Duration: 1 yr Diet: Mediterranean diet	↑	ImAnOx kit

a: Abbreviations are as follows: TAC, total antioxidant capacity; TEAC, Trolox equivalent antioxidant capacity; FRAP, ferric reducing antioxidant power; ORAC, oxygen radical antioxidant capacity; ImAnOx, Immunodiagnostik AG, Bensheim, Germany.
b: Significant increments (↑) or no change (=) in plasma TAC.

Antioxidant efficiency: acute and chronic studies



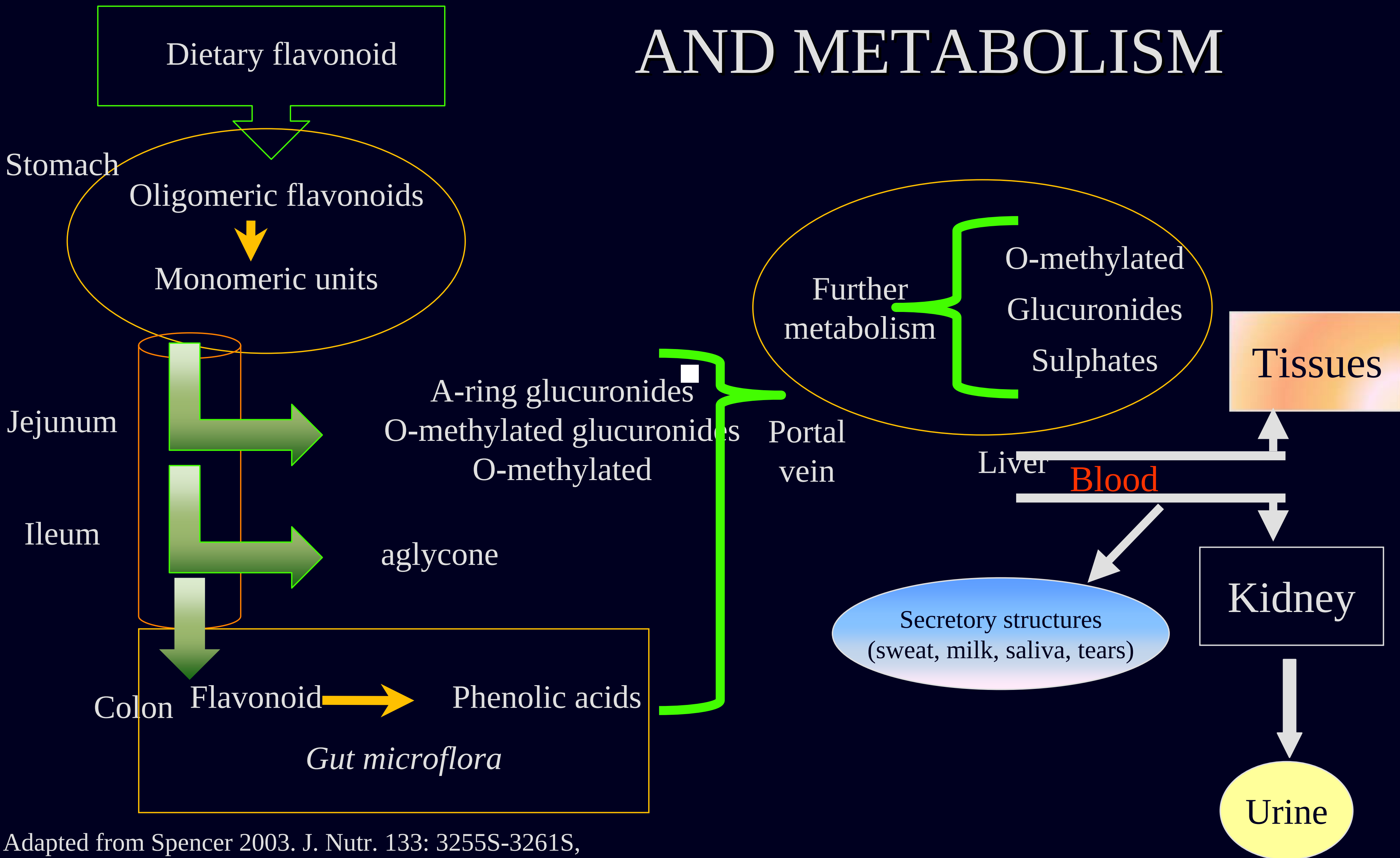
Overview of human intervention studies (1): tea

	days	N°	TAC	PP levels	Ref
BT	28	50	↑	↑	Duffy 2001
[redacted]					
BT	28	10	↔		McAnlis 1998
BT	28	44	↔	↑	Widlansky 2005
[redacted]					
GT	45	100	↑		Bertipaglia de Santana 2008
GT	24	42	↑	↔	Erba 2005
GT	7	14	↑	↑	Panza 2008
[redacted]					

Overview of human intervention studies (2): wine

	days	N°	TAC	PP levels	Ref
[redacted]					
RW	7	8	↑	↔	Otaolaurruchi 2007
RW	21	11	↔		Van der Gaag 2000
[redacted]					
RW, DRW	42	50	↔		Arendt 2005

BIOAVAILABILITY AND METABOLISM



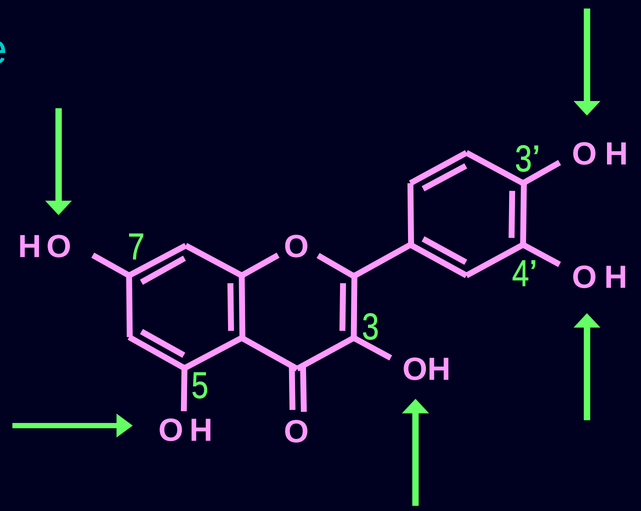
Adapted from Spencer 2003. J. Nutr. 133: 3255S-3261S,

Nature of the circulating metabolites

- ✓ No intact glycosides in plasma, except for anthocyanins/EGCG
- ✓ Exact nature of the major circulating metabolites

Quercetin
Day et al. 2001

3-O-glucuronide
3 ’-O-methylquercetin 3-O-glucuronide
3 ’-O-sulfate
diglucuronide



Daidzein
Genistein
Doerge et al., 2000

7-O-glucuronides
4 ’-O-glucuronides ■

Epicatechin
Natsume et al. 2003

3’-O-glucuronide
4 ’-O-methylepicatechin-O-glucuronide
4 ’-O-methylepicatechin 3 ’-O-glucuronide
aglycones

Anthocyanins

From strawberry
Felgines et al., J. Nutr. 2003

Pelargonidin 3-O-glucoside
Pelargonidin-glucuronides

From blackberry
Felgines et al., 2005 (submitted)

Cyanidin 3-O-glucoside
Cyanidin 3-O-xyloside
Peonidin 3-O-glucoside
Peonidin 3-O-xyloside

Effect of plasma metabolites of (+)-catechin and quercetin on monocyte adhesion to human aortic endothelial cells[1–4]

Takuro Koga and Mohsen Meydani

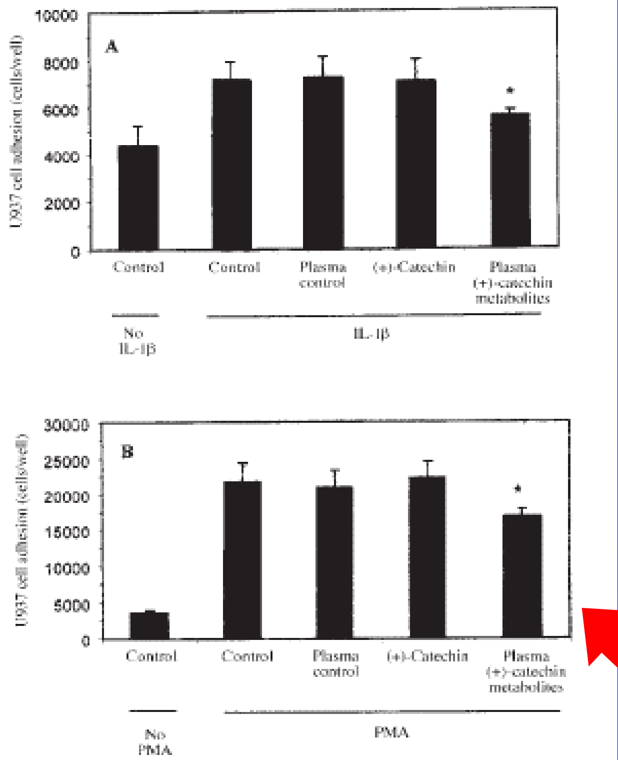


FIGURE 3. Effect of (+)-catechin metabolites on U937 cell adhesion to human aortic endothelial cells (HAEC). HAEC (A) or U937 cells (B) were incubated without catechin or plasma extracts (control), with the plasma extract from control rats (plasma control), with 10 µmol (+)-catechin /L, or with the plasma extract from (+)-catechin–treated rats for 20 h. HAEC were stimulated with interleukin 1β (IL-1β; 10 µg/L) for 6 h and U937 cells were stimulated with phorbol myristyl acetate (PMA; 100 µg/L) for 2 h. The adhesion assay was performed as described in the Methods. Data are the mean (±SD) of 3 experiments, each performed in quadruplicate. *Significantly different from the other treatments, $P < 0.05$.

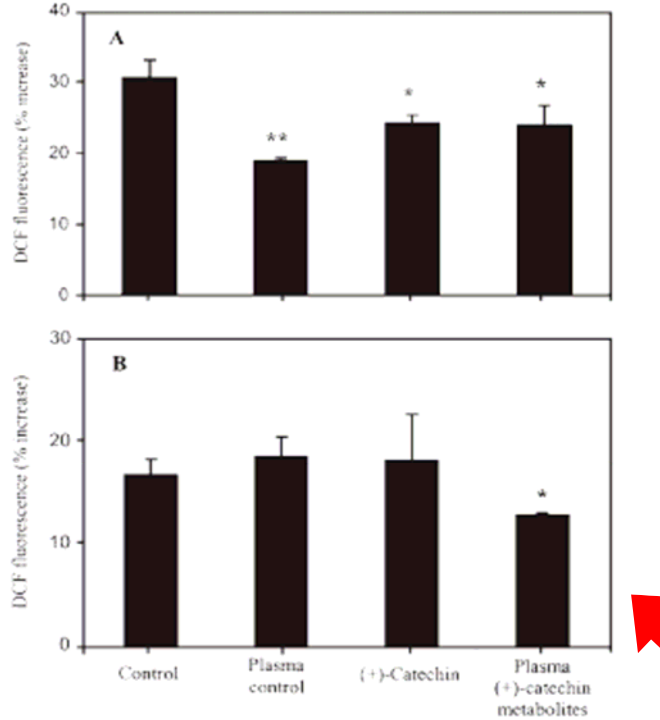
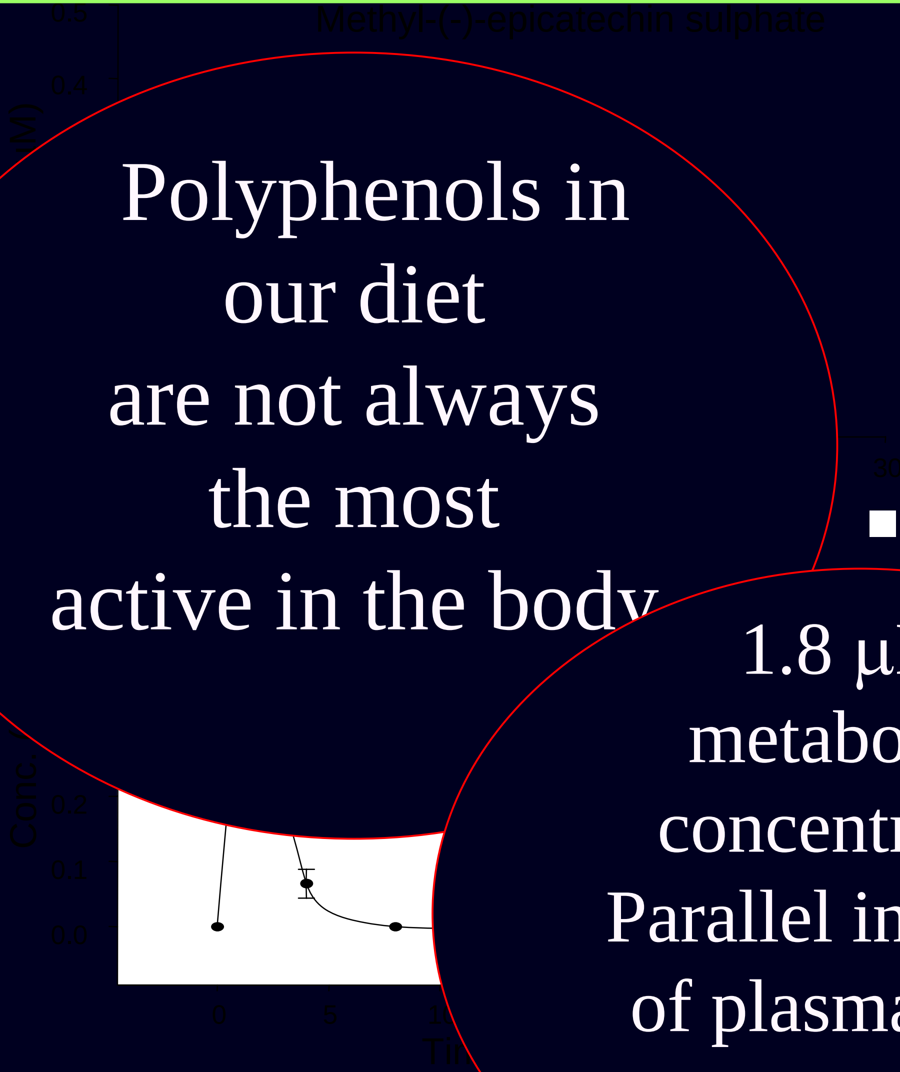
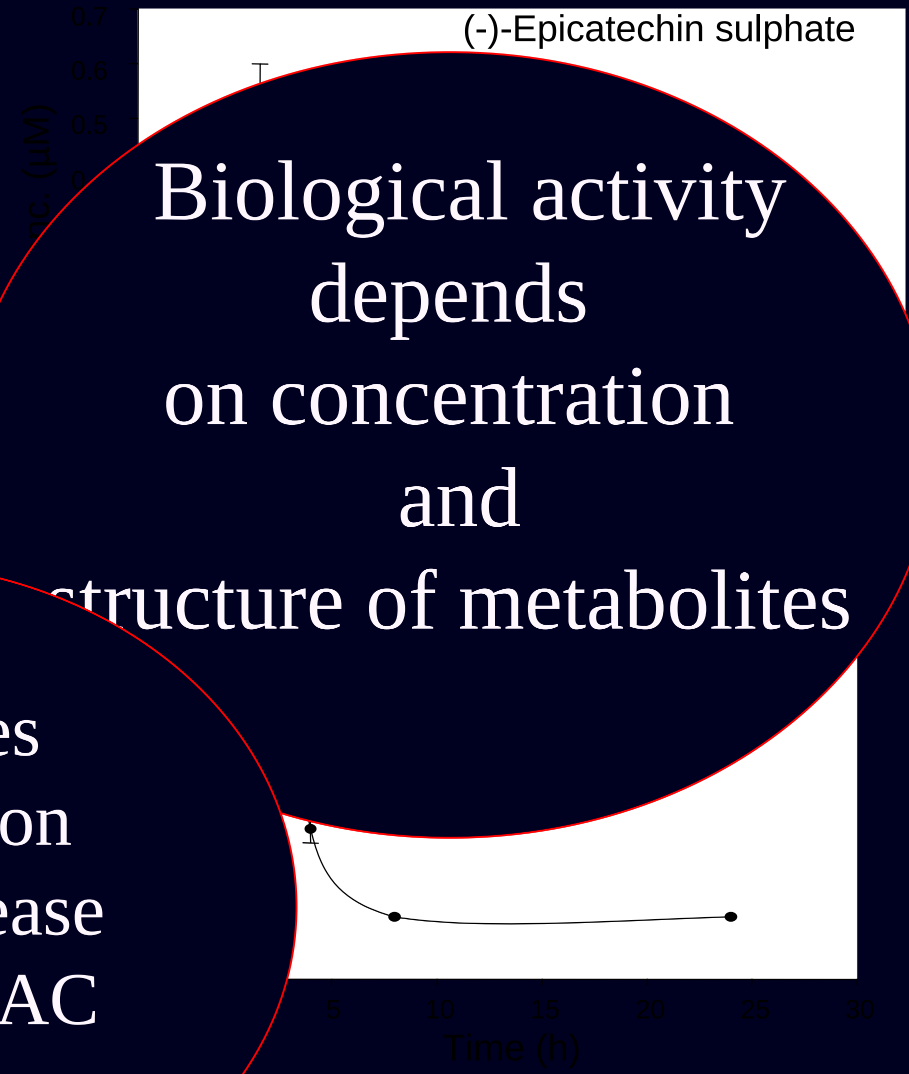


FIGURE 4. Effect of (+)-catechin metabolites on the generation of reactive oxygen species in human aortic endothelial cells (HAEC). HAEC were incubated without catechin or plasma extracts (control), with the plasma extract from control rats (plasma control), with 10 µmol (+)-catechin/L, or with the extract from (+)-catechin–treated rats for 20 h, loaded with 50 µmol 2′,7′-dichlorodihydrofluorescein diacetate/L for 30 min, and stimulated by 20 µmol H_2O_2/L (A) or 10 µg interleukin 1β/L (B). 2′,7′-Dichlorofluorescein (DCF) fluorescence was monitored 45 min after stimulation. Data are presented as the percentage increase in DCF fluorescence compared with unstimulated cells and are the mean (±SD) of 2 experiments, each performed in quadruplicate. *,**Significantly different from control: *$P < 0.05$, **$P < 0.01$.

Koga et al. AJCN 2001

Active metabolites





Polyphenols in
our diet
are not always
the most
active in the body

Biological activity
depends
on concentration
and
structure of metabolites

1.8 μM
metabolites
concentration
Parallel increase
of plasma TAC
~ 31 μM

In Vitro values	% of absorption in vivo
Cumaric acid 7300 μg/250 g	1.1 %
Caffeic acid 31700 μg/250 g	0.2 %
Quercetin 12700 μg/250 g	0.5%
Vitamin C 26.7 mg/250 g	49 %

From: Serafini et al. BJN 2003

TAC in Vitro	TAC Ingested	in Vivo increase
	18.200 μmol TAC (100 g)	+ 20%
	3.930 μmol TAC (200 g)	+ 12%
	1.150 μmol TAC (250 g)	+ 50%
	690 μmol TAC (80 g)	No changes

IS THE ANTIOXIDANT NETWORK REGULATED?

Are antioxidants mobilized in response to oxidative stress?

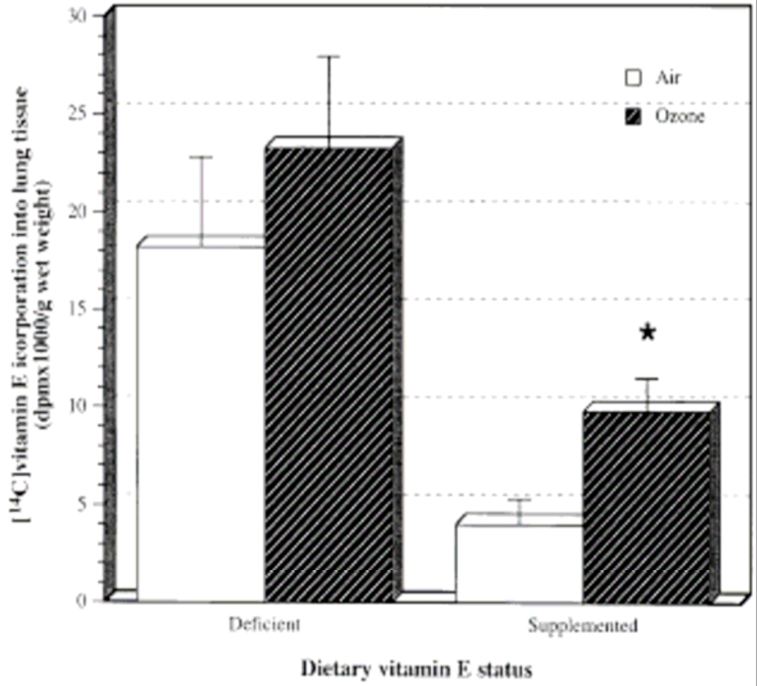
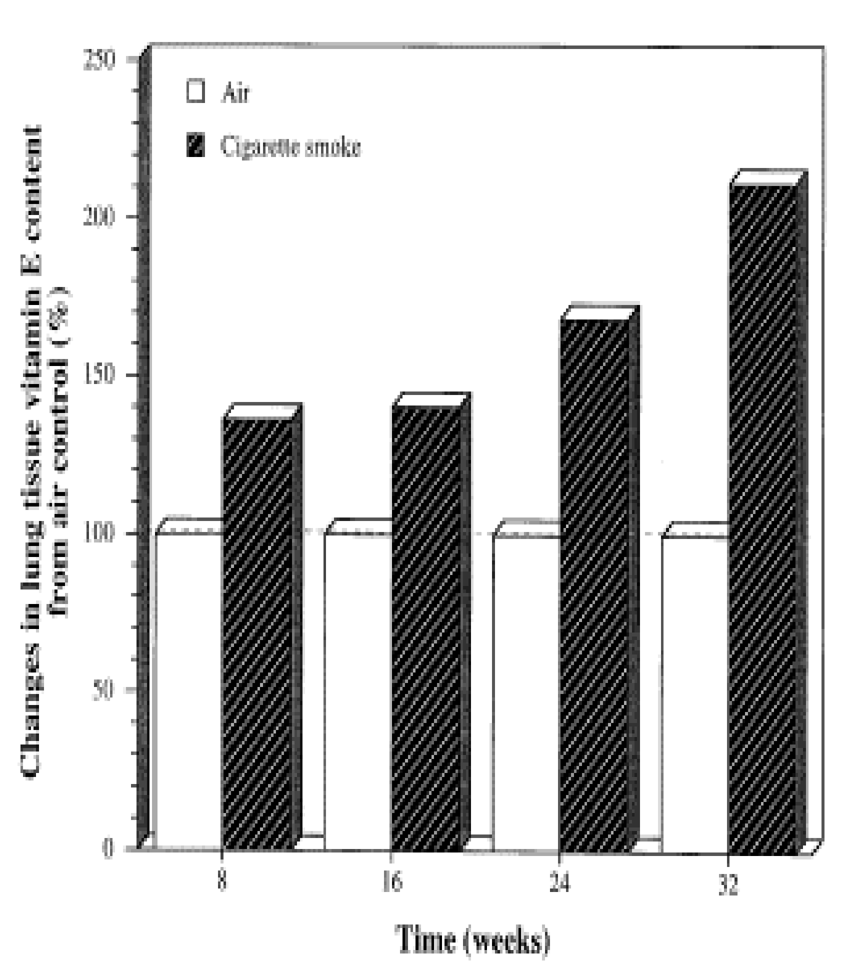


FIG. 3. Changes in [^{14}C] vitamin E incorporation into lung tissue of deficient and supplemented rats after exposure to 0.5 ppm O_3, 24 h/d, 5 d.[3] All rats were fed a deficient diet (0 mg of vitamin E/kg of diet) for 8 wk, and then one group was supplemented with 1000 mg/dL of α-tocopheryl acetate per kilogram of diet for 2 wk. All rats were injected intraperitoneally with 10 μC of [^{14}C]dl α-tocopheryl acetate per rat dissolved in 0.1 mL of vitamin E dissolved in ethanol. [^{14}C] vitamin E was a gift from Larry Machlin.

▪



Elsayed Nutrition, 2001

Risk of gastric cancer among smokers and never smokers in relation to TAC of consumed fruit and vegetables

TRAP	Smokers > 30 yrs		Never-smokers	
(µMTE)	Cases	OR (95% CI)	Cases	OR (95% CI)
49–819	94	1.0 (Ref.)	45	0.56 (0.35-0.90)
820–1015	68	0.68 (0.45-1.02)	45	0.48 (0.30-0.76)
1016-1327	51	0.56 (0.36-0.86)	42	0.46 (0.29-0.73)
1328-3413	55	0.52 (0.34-0.80)	40	0.44 (0.27-0.71)

P value for trend 0.000.
OR and 95% CI adjusted for age, sex, BMI, salt intake, total calories and number of meals per day.

From: Serafini et al. Gastroenterology 2002

Crude and adjusted odds ratios (OR) for risk of breast cancer associated with serum TAC

TAC (mmol/L)	Cases n	Controls n	Crude OR OR (95% CI)	Adjusted OR[1] OR (95% CI)
≤ 1.17	45	24	1.00	1.00
1.17 - 1.24	36	32	0.60 (0.30-1.16)	0.52 (0.26-1.03)
1.24 – 1.31	36	40	0.48 (0.24-0.93)	0.41 (0.20-0.82)
≥ 1.31	33	47	0.45 (0.23-0.88)	0.47 (0.24-0.94)
Test for trend				P = 0.030

[1]OR and 95% CI adjusted for age at menarche, parity, alcohol intake and total fat intake.

From: Ching et al. J Nutr 2002

Contents lists available at ScienceDirect

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Original Contribution

The effect of vitamins C and E on biomarkers of oxidative stress depends on baseline level

Gladys Block [a,*], Christopher D. Jensen [a], Jason D. Morrow [b], Nina Holland [a], Edward P. Norkus [c], Ginger L. Milne [b], Mark Hudes [a], Tapashi B. Dal... Crawford [a], Ellen B. Fung [d], Laurie Schumacher [d], Paul Harmatz [d]

All Subjects	Placebo (n=124)	Vitamin C (n=115)	Vitamin E (n=117)
Before intervention, µg/mL, mean (SD)	54.84 (26.67)	60.67 (30.98)	51.04 (23.99)
After intervention, µg/mL, mean (SD)	58.73 (32.17)	52.31 (24.94)	50.60 (28.99)
Change (µg/mL)	+3.90 (26.11)	-8.37 (28.12)	-0.44 (23.38)
Change (%)	+7.11	-13.80	-0.86

for two months

Subjects with baseline F_2-isoprostanes≤50 µg/mL

	Placebo (n=75)	Vitamin C (n=60)	Vitamin E (n=71)
Before intervention, µg/mL, mean (SD)	38.80 (8.12)	37.97 (8.17)	37.14 (8.30)
After intervention, µg/mL, mean (SD)	47.68 (19.57)	41.82 (16.85)	40.11 (18.91)
Change (µg/mL)	+8.88 (18.38)	+3.85 (17.25)	+2.97 (17.60)
Change (%)	+22.89	+10.14	+8.00
P (change)	<0.0001	0.09	0.16

Subjects with baseline F_2-isoprostanes>50 µg/mL

	Placebo (n=49)	Vitamin C (n=55)	Vitamin E (n=46)
Before intervention, µg/mL, mean (SD)	79.39 (26.52)	85.44 (27.49)	72.50 (24.51)
After intervention, µg/mL, mean (SD)	75.65 (39.74)	63.76 (27.32)	66.78 (34.19)
Change (µg/mL)	-3.73 (33.59)	-21.67 (31.59)	-5.72 (29.67)
Change (%)	-4.70	-25.36	-7.89
P (change)	0.44	<0.0001	0.20

PREDIMED STUDY

EFECTS OF MEDITERRANEAN DIET IN THE PRIMARY PREVENTION OF THE CARDIOVASCULAR DISEASE

STUDY TYPE:

- Large
- Multicenter
- Randomized
- Controlled

PREDIMED STUDY

N=3000
Mediterranean diet
+ virgin olive oil
(1L/week)

N=3000
Mediterranean diet
+ nuts (30g/d)

N=3000
American Heart
Association guidelines

4 years

PREDIMED STUDY

INCLUSION CRITERIA

- ♂ 55-80 years
- ♀ 60-80 years

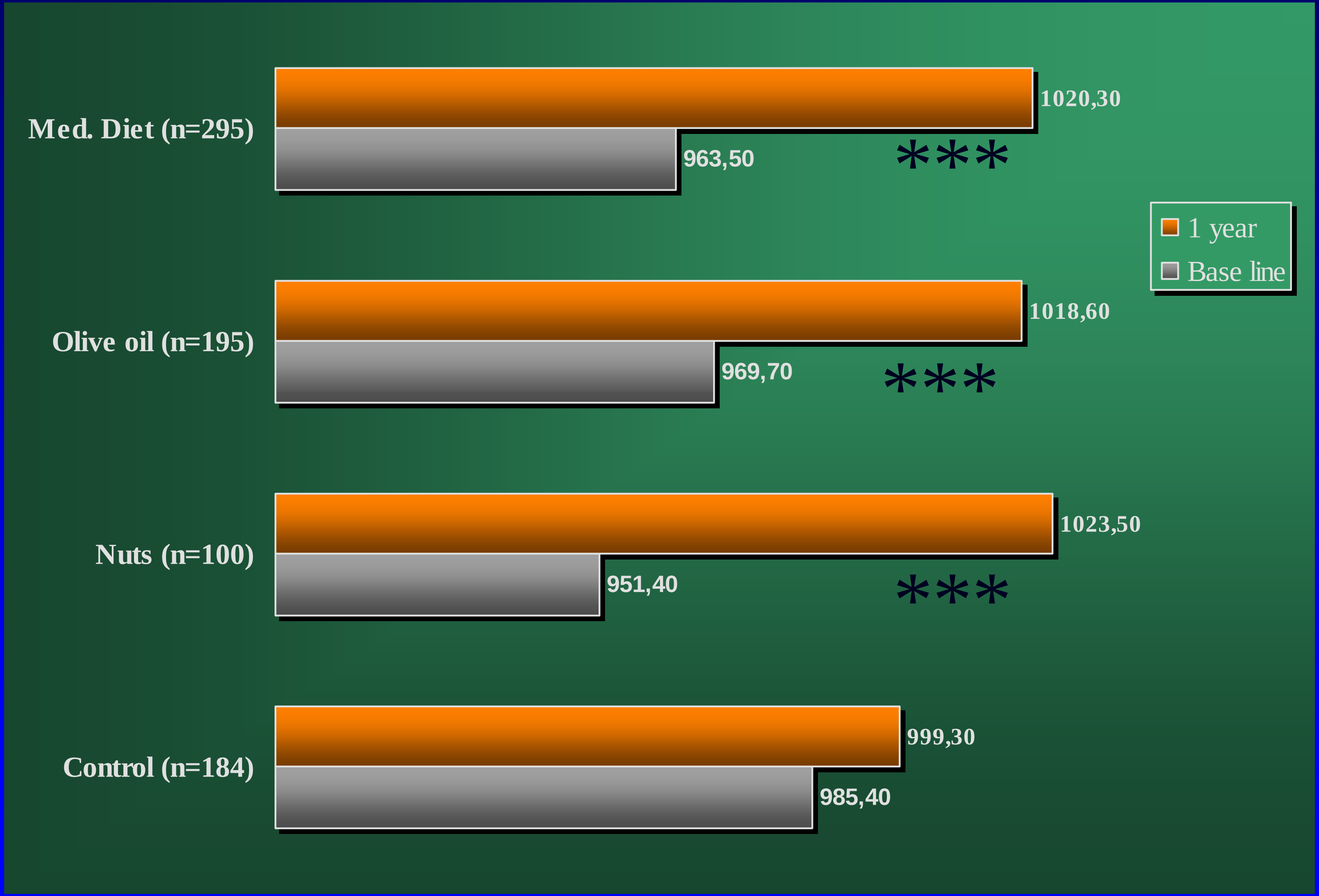
3 risk factors:

- Diabetes type II
- Current smoking
- Hypertension
- BMI >25
- High LDL, cholesterol,...
- Family history of premature CHD

EXCLUSION CRITERIA

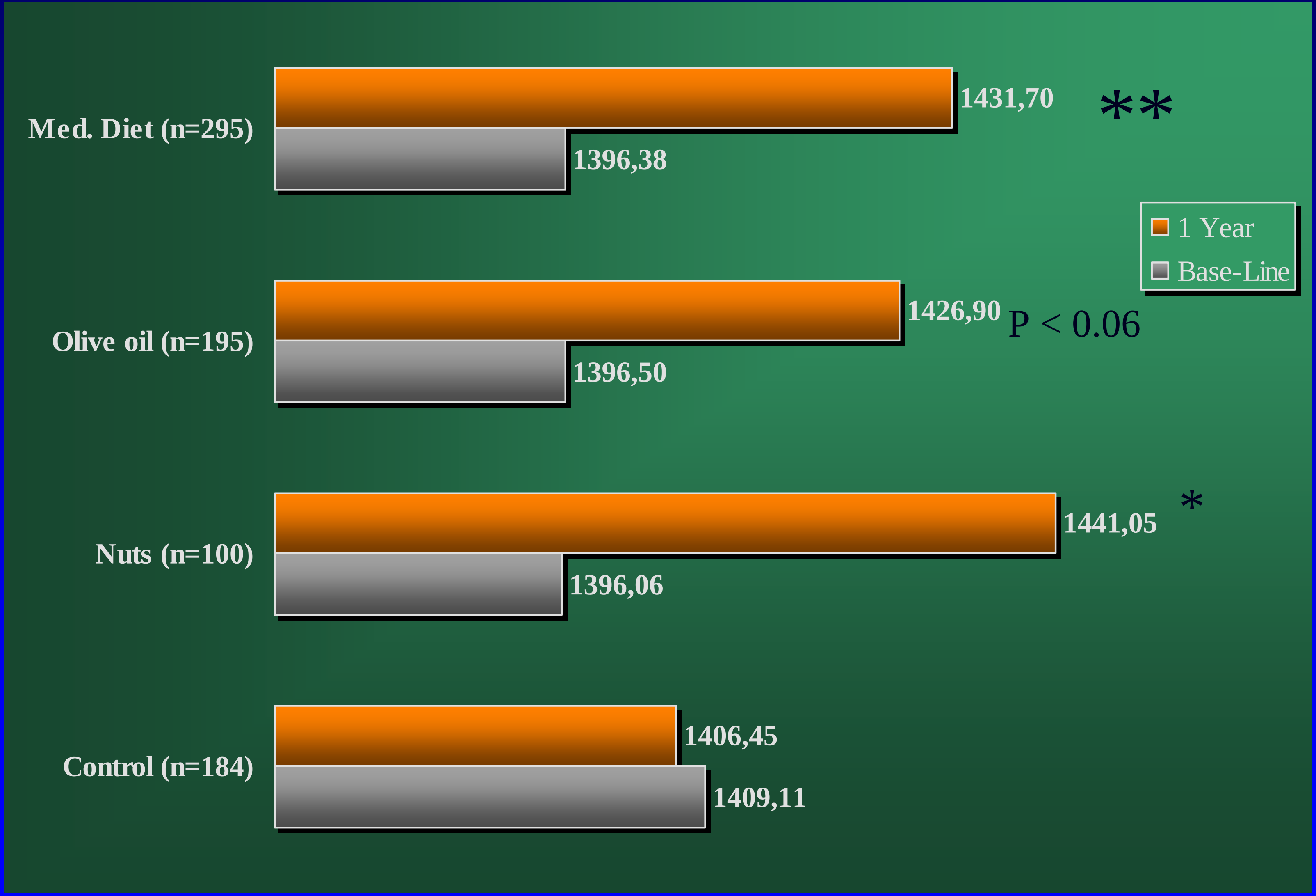
- Any severe chronic illness
- AIDS
- Drug or alcohol addiction
- Allergy or intolerances to nuts or oil

FRAP (μmol/L)



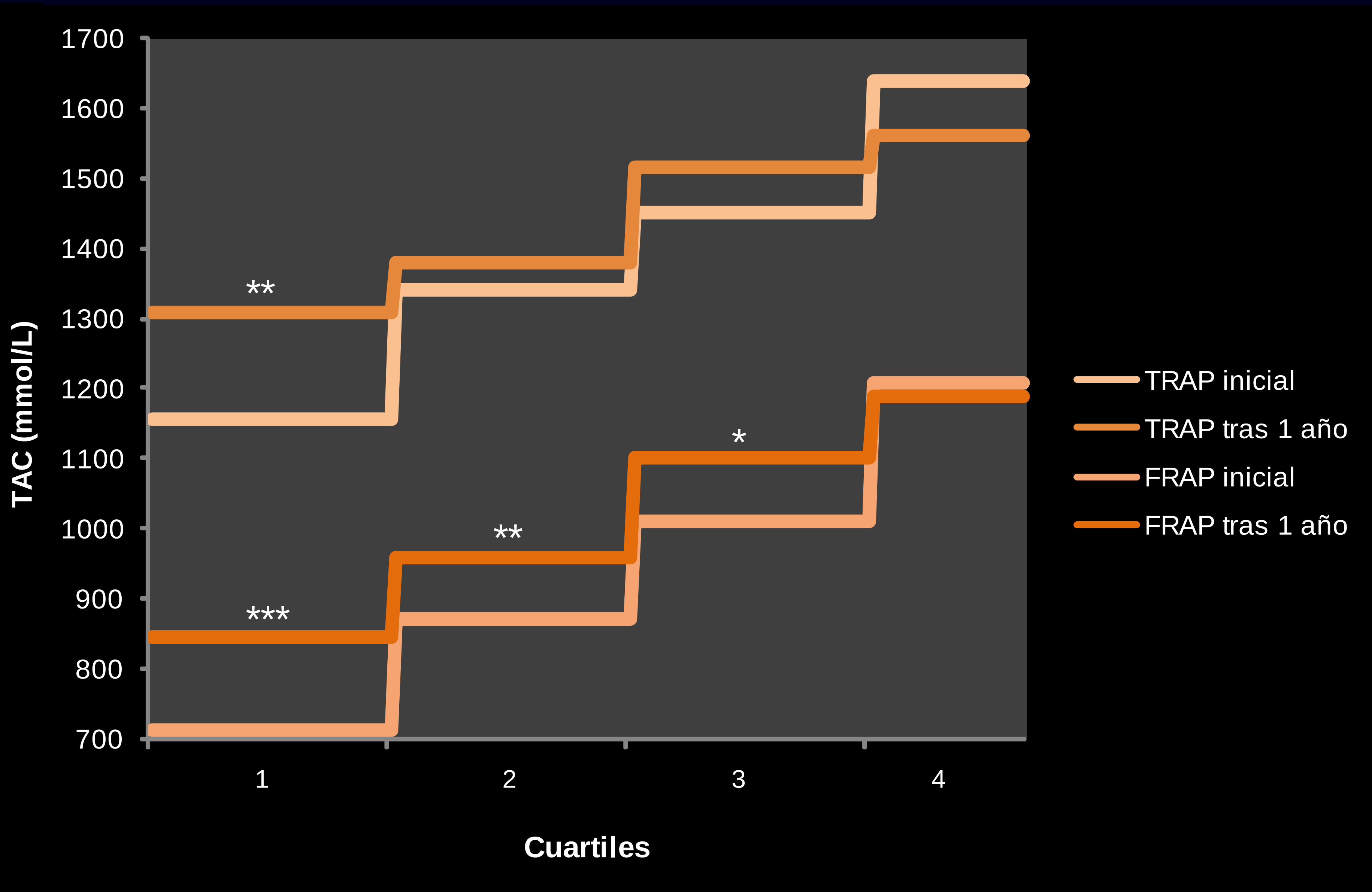
Med. Diet (n=295)
1020,30
963,50
***
Olive oil (n=195)
1018,60
969,70
***
Nuts (n=100)
1023,50
951,40
***
Control (n=184)
999,30
985,40
1 year
Base line

TRAP (μmol/L)



Med. Diet (n=295)
1431,70
**
1396,38
1 Year
Base-Line
Olive oil (n=195)
1426,90
P < 0.06
1396,50
Nuts (n=100)
1441,05
*
1396,06
Control (n=184)
1406,45
1409,11

Changes in plasma TAC according to different quartiles of baseline levels



Uric acid: friend or foe?

Table 1. Cardiovascular Conditions and Risk Factors Associated with Elevated Uric Acid.

Hypertension and prehypertension
Renal disease (including reduced glomerular filtration rate and microalbuminuria)
Metabolic syndrome (including abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein cholesterol, insulin resistance, impaired glucose tolerance, elevated leptin level)
Obstructive sleep apnea
Vascular disease (carotid, peripheral, coronary artery)
Stroke and vascular dementia
Preeclampsia
Inflammation markers (C-reactive protein, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule type 1)
Endothelial dysfunction
Oxidative stress
Sex and race (postmenopausal women, blacks)
Demographic (movement from rural to urban communities, Westernization, immigration to Western cultures)

N Engl J Med 2008;359:1811-21.

Molecular identification of a danger signal that alerts the immune system to dying cells

Yan Shi[1], James E. Evans[2] & Kenneth L. Rock[1]

[1]*Department of Pathology, and* [2]*Proteomics and Mass Spectrometry Facility, Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts 01655, USA*

In infections, microbial components provide signals that alert the immune system to danger and promote the generation of immunity[1,2]. In the absence of such signals, there is often no immune response or tolerance may develop. This has led to the concept that the immune system responds only to antigens perceived to be associated with a dangerous situation such as infection[3,4]. Danger signals are thought to act by stimulating dendritic cells to mature so that they can present foreign antigens and stimulate T lymphocytes[2,5–7]. Dying mammalian cells have also been found to release danger signals of unknown identity[8–11]. Here we show that uric acid is a principal endogenous danger signal released from injured cells. Uric acid stimulates dendritic cell maturation and, when co-injected with antigen *in vivo*, significantly enhances the generation of responses from $CD8^+$ T cells. Eliminating uric acid *in vivo* inhibits the immune response to antigens associated with injured cells, but not to

Immunology

Dangerous liaisons

William R. Heath and Francis R. Carbone

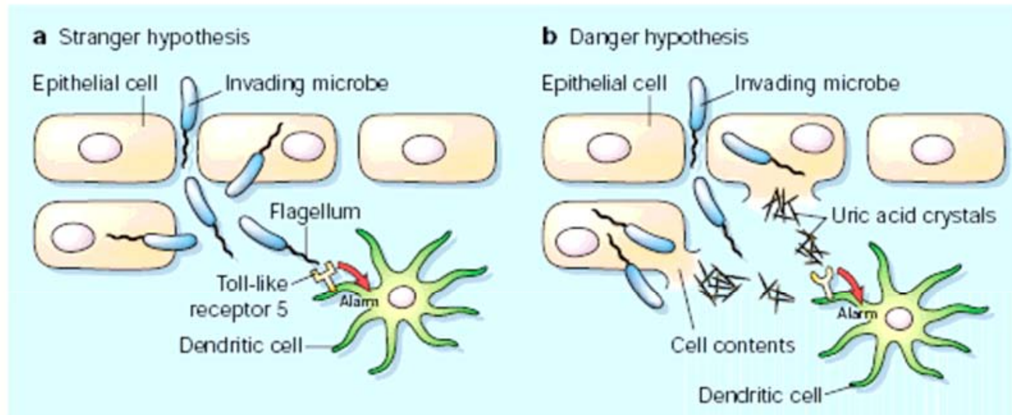


Figure 1 Strangers and danger. Two different theories describe how the immune system is alerted to respond to microbial attack. a, In the 'stranger' model[2,3], microdetectors on the surface of immune cells recognize common molecular patterns on the surface of microbes. For example, Toll-like receptor 5 on the surface of dendritic cells signals an alarm when it recognizes a protein component of the flagella of some bacteria[4]. b, Alternatively, the 'danger' hypothesis[5,6] proposes that the immune system is alerted to the tissue damage associated with microbial infection. Shi *et al.*[1] provide evidence for this second view, showing that damaged cells release uric acid that forms crystals capable of activating dendritic cells. The now-compelling evidence for both hypotheses suggests that the immune system scans for signs of both danger and strangers.

Shi et al. Nature 425, 2003

Heath et al. Nature 425, 2003

URIC ACID AND HEALTH: AN ONGOING DEBATE

"We need a … understand … biologic role … although … proinflammato… it can also functio… antioxidants"

"it remains possible that uric acid may have a variety of as yet incompletely defined actions in cardiovascular disease"

Danie…

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N ENGL J … JANUARY 29, 2009

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TAC AND DISEASE PREVENTION

TAC and disease (1)

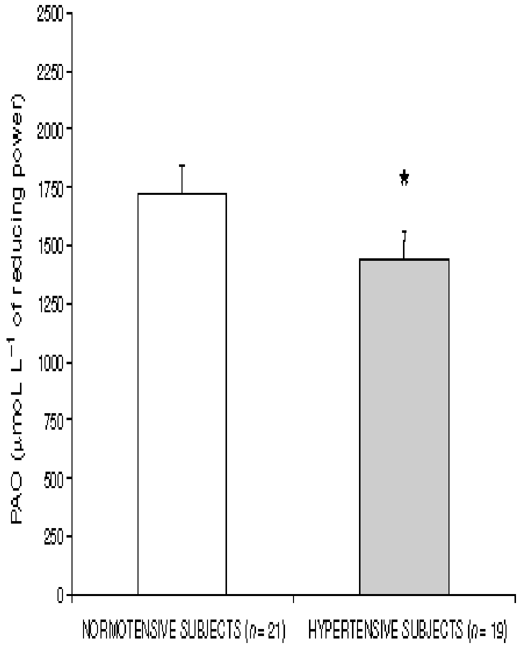


Fig. 3 PAO levels in patients with and without hypertension. $^{*}P < 0.05$.

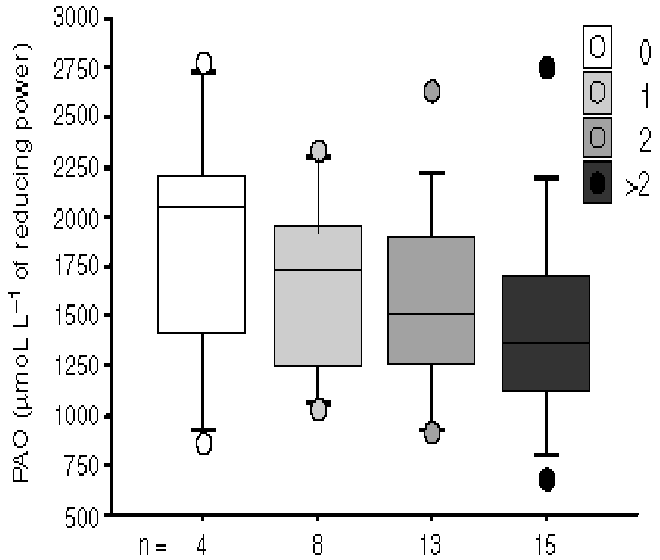
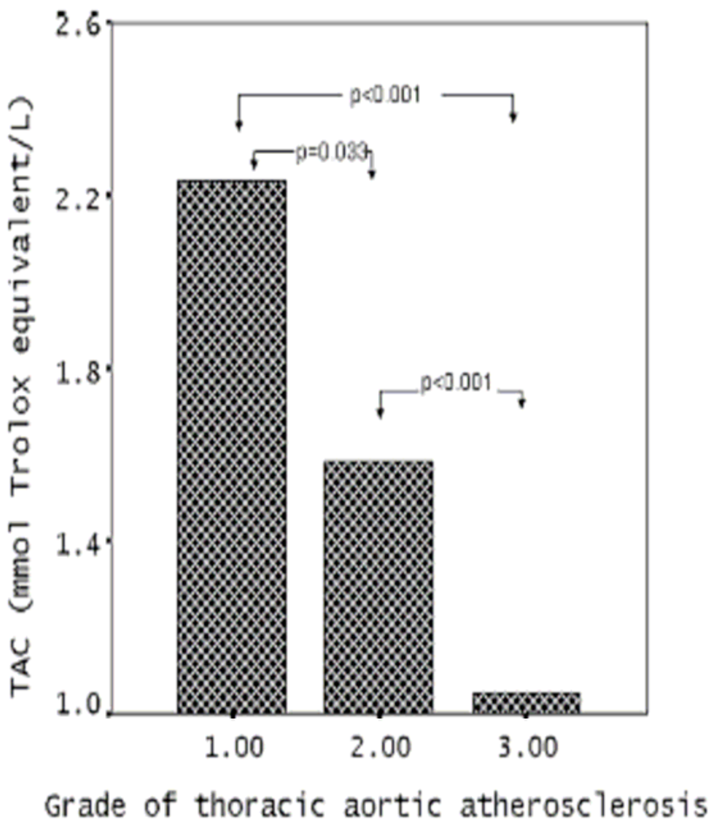


Fig. 4 PAO levels and risk factors for CAD. Risk factors are gender, diabetes mellitus, hypercholesterolaemia, hypertension and smoking habits. Median, interquartile, outliers and extremes of PAO levels are given. $P = 0.07$ for trend.



Vassalle et al. J Int Med 2004

Demirbag et al. 2006

TAC and disease (2)

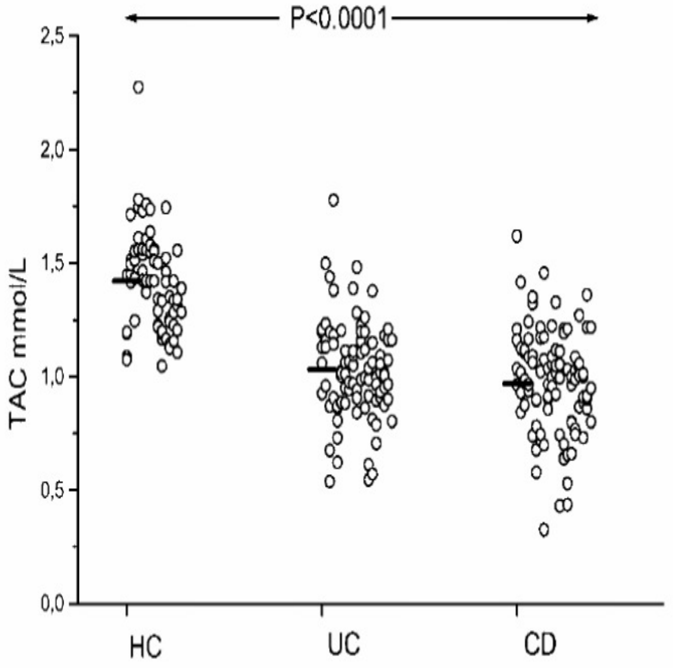


Fig 1. Distribution of total antioxidant capacity (TAC) in healthy controls (HC; $n = 72$), ulcerative colitis patients (UC; $n = 94$), and Crohn's disease patients (CD; $n = 97$). Each individual patient or control is shown as a circle; bold horizontal lines are the mean values.

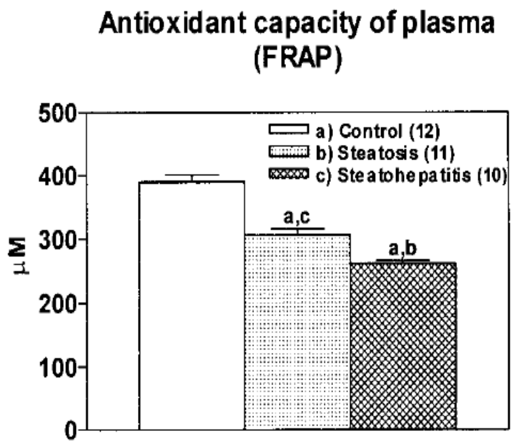


Figure 4 Total antioxidant capacity of plasma in control subjects and in patients with non-alcoholic fatty liver disease with different degrees of liver injury, measured as the FRAP

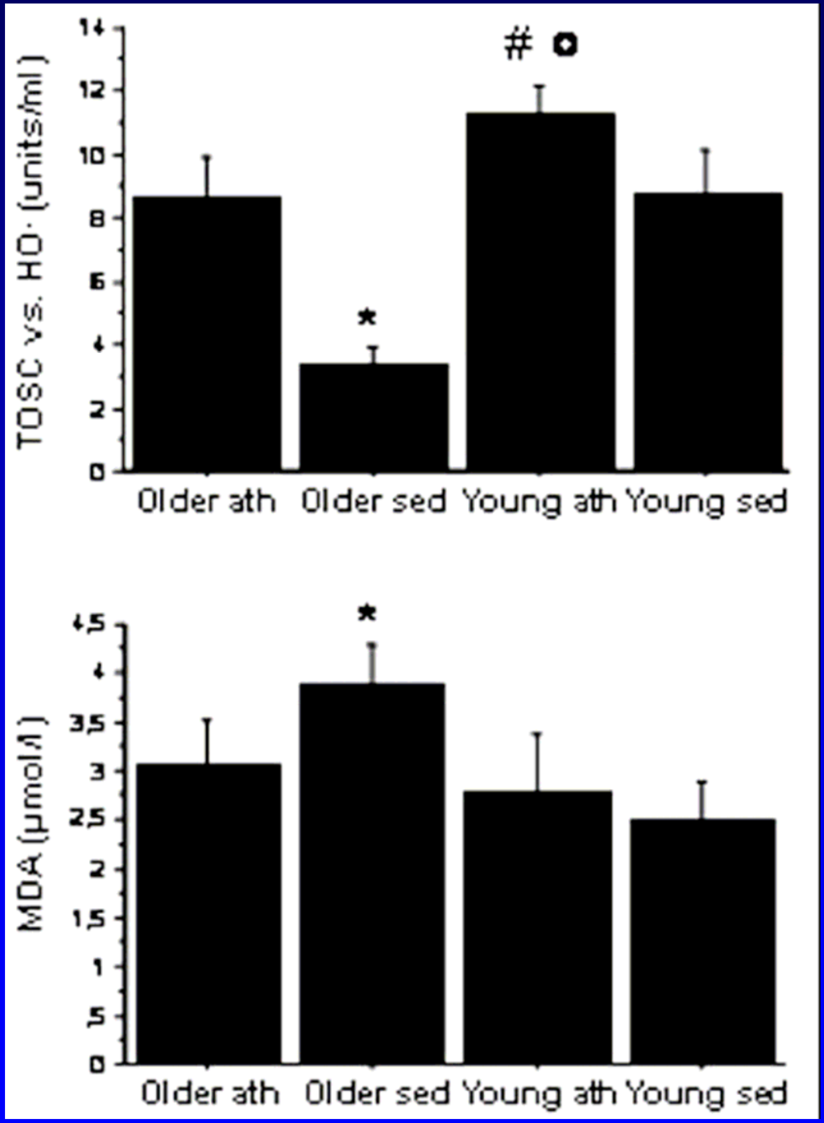
Values represent means ± S.E.M. for the number of subjects indicated in parentheses. The significance between mean values was assessed by one-way ANOVA and Bonferroni's multiple comparison test, and is shown by the letters identifying each group of patients ($P < 0.05$).

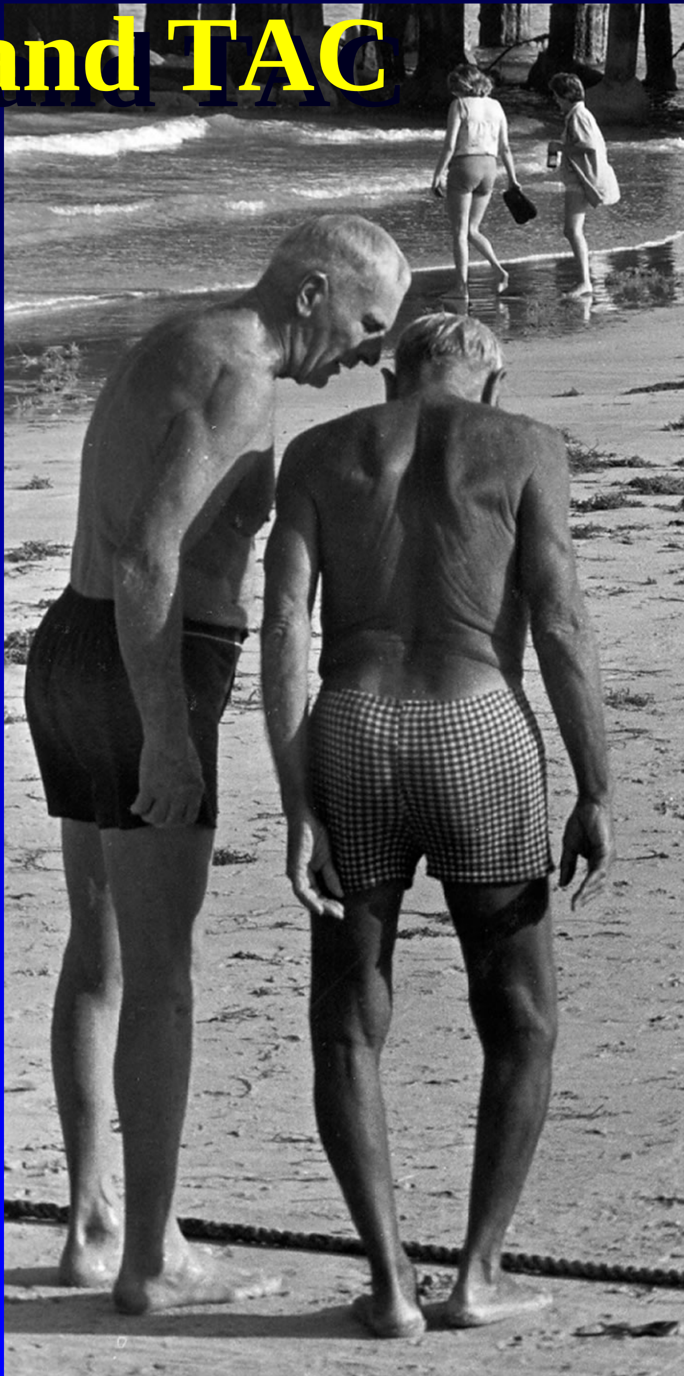
Koutroubakis et al. 2004

Videla et al. 2004

Reference	Biological fluid	TAC Method	Type of cancer	Cancer patients	Healthy subjects	p
Erhola et al, 1997	Plasma	TRAP (µmol/L)	Lung	1143 ± 181 (n = 57)	1273 ± 199 (n = 76)	<0.01
Di Giacomo et al, 2003	Plasma	NPAC (%)	Colon	55 (n = 54)	90 (n = 20)	<0.001
Erten Sener et al, 2006	Serum	TEAC (mmol/L)	Breast	2.01 ± 0.01 (n = 56)	2.07 ± 0.03 (n = 18)	< 0.05
Lee et al, 2005	Plasma	TEAC (mmol/L)	CIN	1.15 ± 0.17 (n = 58)	1.25 ± 0.15 (n = 86)	< 0.05
Ching et al, 2002	Serum	TEAC (mmol/L)	Breast	OR 0.47 (II°Q TAC) (n = 153)	(n = 151)	< 0.05
Liu et al, 2003	Plasma	TAC (U/mL)	Lung Breast Thyroid	8.41 ± 1.78 (n = 28)	10.52 ± 1.64 (n = 33)	< 0.001
Mantovani et al, 2002	Serum	TEAC (mmol/L)	Tumors at different sites	1.30 ± 0.03 (n = 82)	1.10 ± 0.08 (n = 36)	n.s.

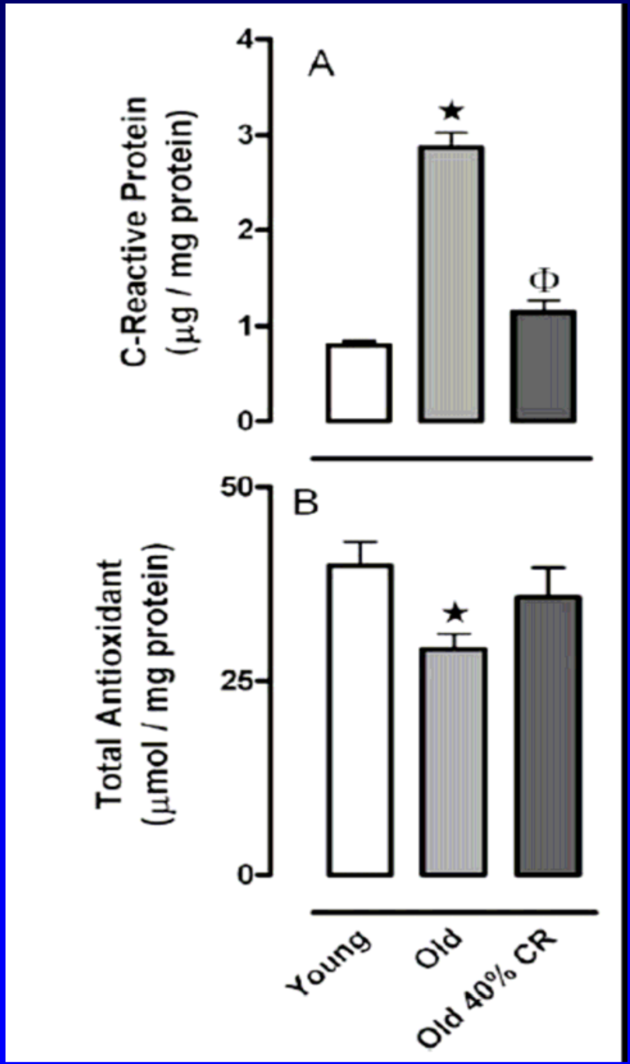
Ageing, physical exercise and TAC

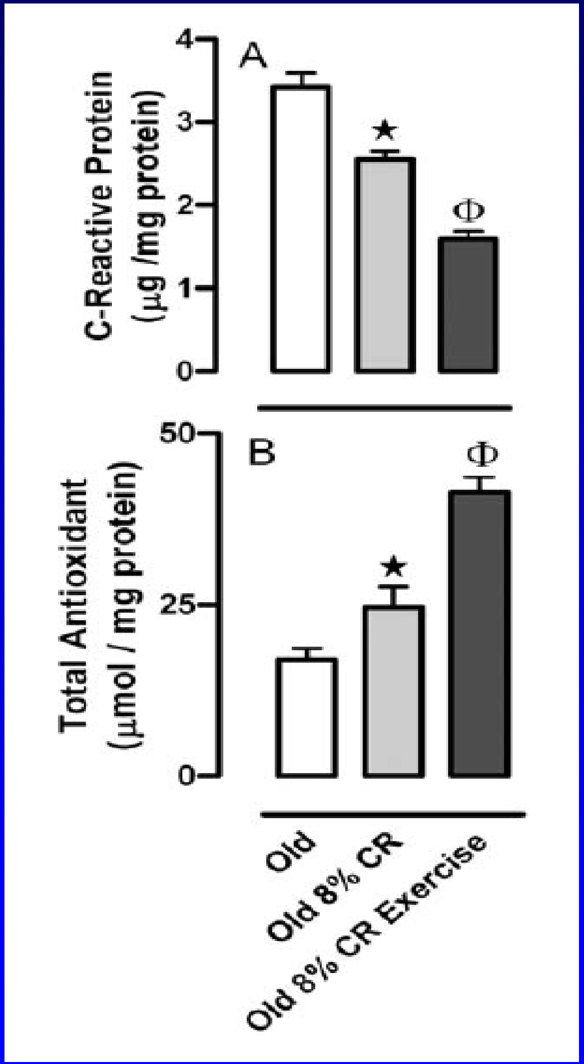




Franzoni et al. 2005

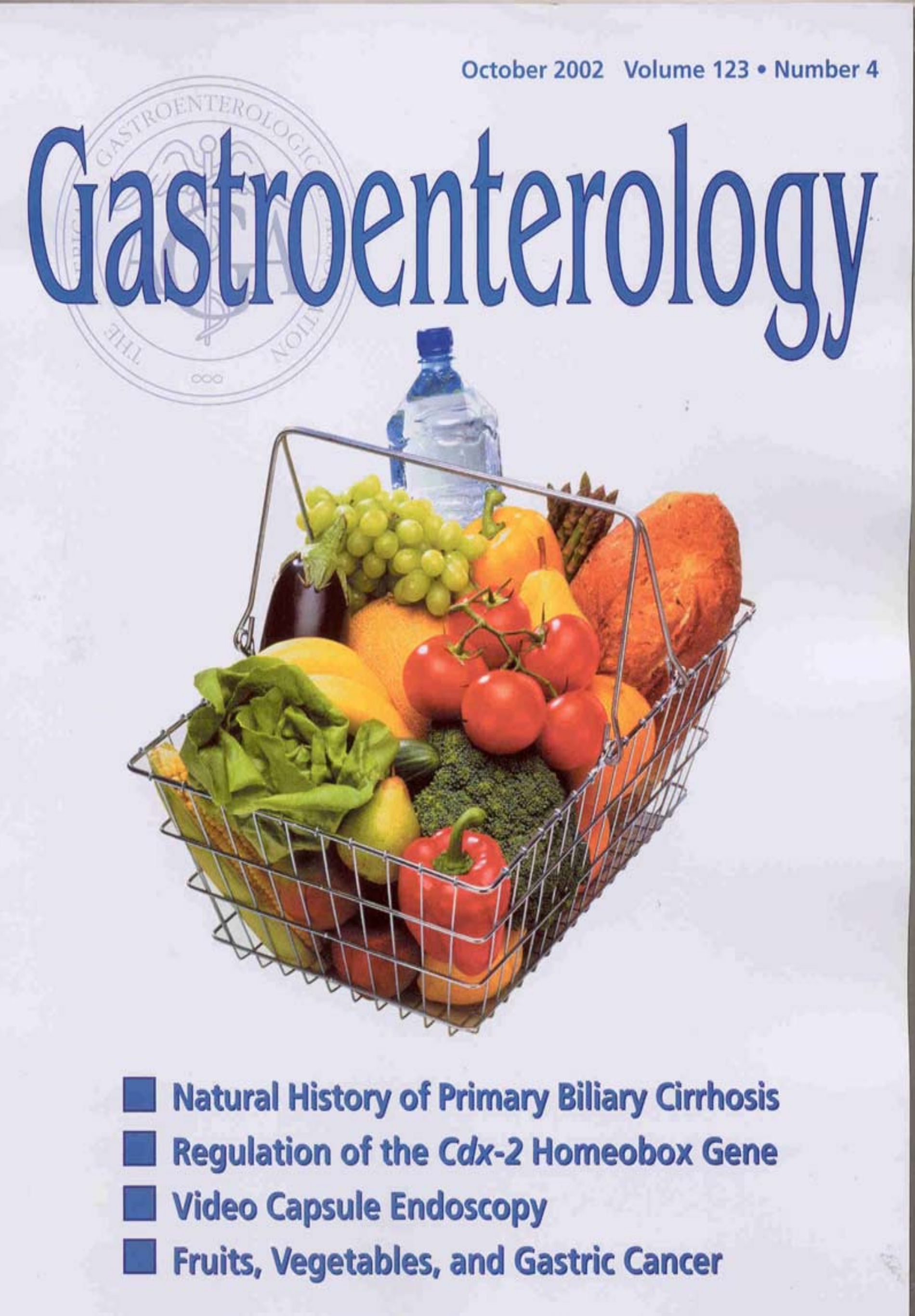
Caloric restriction





Kalani et al. 2006

Gastric cancer risk and dietary TAC.



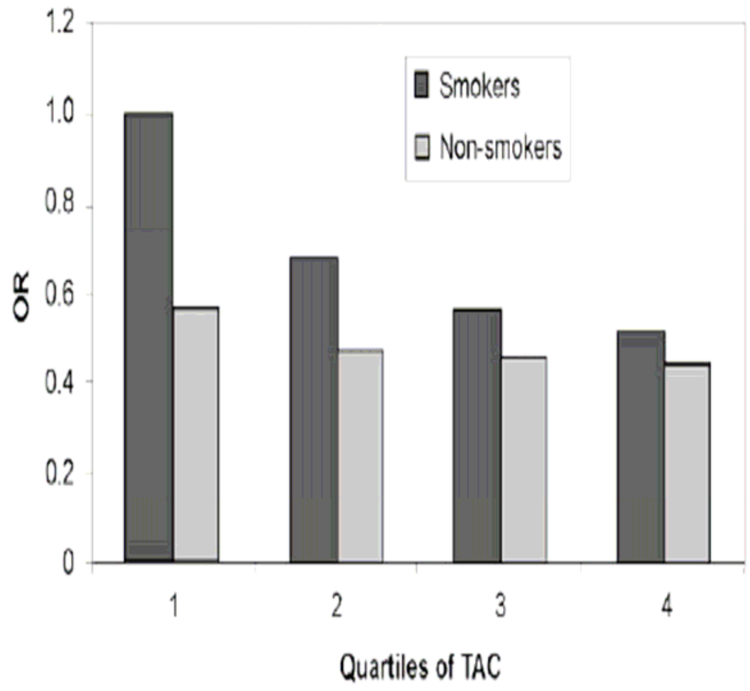


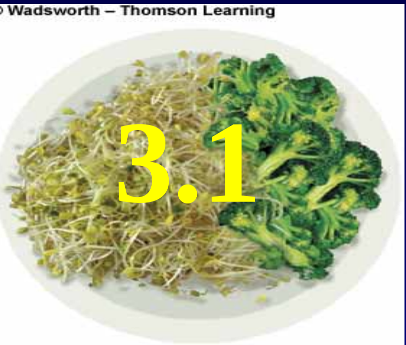
Fig. 2. Odds ratios (OR) for gastric cancer among quartiles of total antioxidant capacity (TAC) of consumed fruit and vegetables in smokers and non-smokers. Quartiles are 1:49–819; 2:820–1015; 3:1016–1327; 4:1328–3413 mmmmoles of Trolox equivalents. Data reproduced from Serafini *et al.*[56] with permission.

Serafini et al. 2002

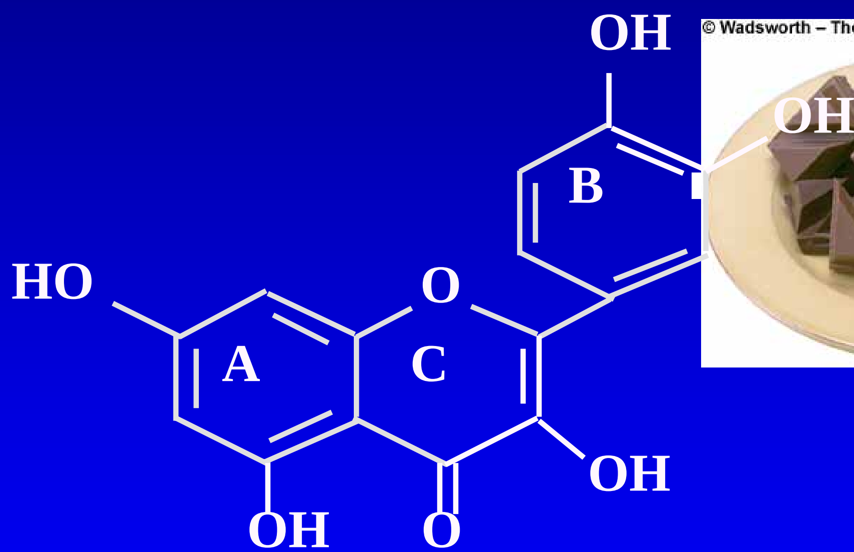
How we can assess dietary intake of total antioxidant capacity in human?

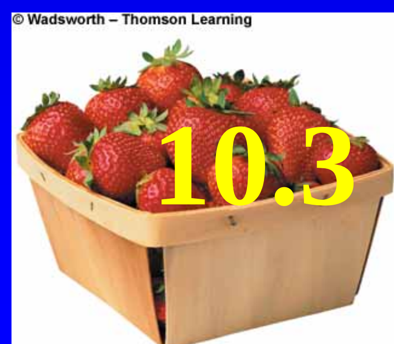
- ✓ 34 vegetables (V), 30 fruits (F), 34 beverages (B), 11 spices (S), 11 nuts and fruit dried (NF) 5 pulses (P) 16 cereals (C) and 6 vegetables oils (VO) have been analyzed using 3 assays: TRAP, FRAP and TEAC in order to take in account different antioxidant mechanisms

Pellegrini et al. J. Nutrition 2003



Redox ingredients





Serafini et al. Nutr & Cancer 2007

Fruit and vegetable intakes, dietary antioxidant nutrients, and total mortality in Spanish adults: findings from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain)[1–3]

Antonio Agudo, Laia Cabrera, Pilar Amiano, Eva Ardanaz, Aurelio Barricarte, Toni Berenguer, María D Chirlaque, Miren Dorronsoro, Paula Jakszyn, Nerea Larrañaga, Carmen Martínez, Carmen Navarro, Jose R Quirós, María J Sánchez, María J Tormo, and Carlos A González

41.358 subjects,
6.5 years follow-up
Age: 30-69 years

TABLE 4
Association between mortality and the consumption of vitamins and carotenoids and total antioxidant capacity of fruit and vegetables in the EPIC-Spain cohort[1]

Nutrients and total antioxidant capacity	HR (95% CI) by quartile[2] Q2	Q3	Q4	*P* for trend	HR (95% CI) (continuous)[2] ($\log_2$)
Vitamin C	0.72 (0.57, 0.91)	0.65 (0.51, 0.83)	0.74 (0.58, 0.94)	0.009	0.87 (0.78, 0.96)
Vitamin E	0.95 (0.75, 1.20)	0.83 (0.65, 1.08)	0.83 (0.64, 1.08)	0.12	0.90 (0.79, 1.02)
β-Carotene	0.76 (0.60, 0.96)	0.72 (0.56, 0.92)	0.74 (0.58, 0.95)	0.022	0.89 (0.80, 0.98)
α-Carotene	0.86 (0.68, 1.08)	0.84 (0.67, 1.06)	0.75 (0.59, 0.96)	0.023	0.95 (0.91, 1.00)
β-Cryptoxanthin	0.73 (0.57, 0.92)	0.77 (0.61, 0.98)	0.75 (0.59, 0.95)	0.034	0.94 (0.90, 0.99)
Provitamin A[3]	0.66 (0.52, 0.83)	0.70 (0.55, 0.89)	0.68 (0.53, 0.87)	0.006	0.88 (0.80, 0.97)
Lutein	0.76 (0.60, 0.98)	0.86 (0.68, 1.09)	0.83 (0.65, 1.05)	0.23	0.97 (0.90, 1.03)
Zeaxanthin	0.78 (0.61, 1.00)	0.75 (0.59, 0.96)	0.91 (0.72, 1.16)	0.48	0.96 (0.89, 1.04)
Lycopene	0.79 (0.63, 0.99)	0.76 (0.60, 0.96)	0.65 (0.51, 0.84)	0.001	0.93 (0.89, 0.97)
Total carotenoids	0.74 (0.59, 0.93)	0.70 (0.55, 0.89)	0.69 (0.55, 0.88)	0.003	0.85 (0.76, 0.94)

British Journal of Nutrition (2005), **93**, 619–625
DOI: 10.1079/BJN20051400

Total antioxidant capacity of the diet is inversely and independently related to plasma concentration of high-sensitivity C-reactive protein in adult Italian subjects

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Inflammation, a risk factor for cardiovascular disease, is associated with low plasma levels of antioxidant vitamins. In addition to vitamins, other antioxidants modulate the synthesis of inflammatory markers *in vitro* and contribute to the total antioxidant capacity (TAC) of a diet. However, the relationship between dietary TAC and markers of inflammation has never been evaluated *in vivo*. We investigated the relationship between dietary TAC and markers of systemic (high-sensitivity C-reactive protein (hs-CRP), leucocytes) and vascular (soluble intercellular cell adhesion molecule-1) inflammation in 243 non-diabetic subjects. General Linear Model (GLM) analysis showed a significant ($P=0.005$) inverse relationship between hs-CRP and quartiles of energy-adjusted dietary TAC, even when recognized modulating factors of inflammation, namely alcohol, fibre, vitamin C, α-tocopherol, β-carotene, BMI, waist circumference, HDL-cholesterol, hypertension, insulin sensitivity and plasma β-carotene, were included in the model as covariates ($P=0.004$). The relationship was stronger for subjects with hypertension ($P=0.013$ *v.* $P=0.109$ for normotensive individuals). Among dietary factors, TAC was significantly higher (5·3 (SD 3·0) *v.* 4·9 (SD 2·7) mmol Trolox/d; $P=0.026$) in subjects with low plasma hs-CRP (range: 0·0–4·1 mg/l) than in subjects with high plasma hs-CRP (range: 4·2–27·8 mg/l). We conclude that dietary TAC is inversely and independently correlated with plasma concentrations of hs-CRP and this could be one of the mechanisms explaining the protective effects against CVD of antioxidant-rich foods such as fruits, whole cereals and red wine. This could be of particular significance for subjects with high blood pressure.

Inflammation: Antioxidants: Hypertension: High-sensitivity C-reactive protein

Inflammation and oxidative stress are involved in the pathogenesis of cardiovascular disease (Wattanapitayakul & Bauer, 2001; Lind, 2003). Oxidative damage of the arterial wall by free radicals and the direct stimulation of endothelial cells by the acute-phase C-reactive protein (CRP) promote the expression of cellular adhesion molecules (CAM), which facilitate the adhesion of monocytes and T cells to the arterial wall in the first steps of the atherogenic process (Parhami *et al.* 1993). Oxidative stress appears also responsible for the oxidation of low-density lipoproteins incorporated to the plaque (Parhami *et al.* 1993).

These *in vitro* observations are confirmed by clinical data. In addition to the already established risk factors, the total leukocyte count is an independent predictor of coronary heart disease and myocardial infarction (Danesh *et al.* 1998), the intercellular adhesion molecule-1 (ICAM-1) is consistently elevated in individuals at high risk for atherosclerosis (Demerath *et al.* 2001) and, though to an extent still under debate (Tall, 2004), high plasma concentrations of CRP significantly increase the risk of cardiovascular events (myocardial infarction, stroke, sudden cardiac death and peripheral vascular disease) even among apparently healthy adults (Willerson & Ridker, 2004). Whether these factors of increased risk for CVD are directly modifiable through the diet is an intense area of research. An inverse relationship between plasma levels of certain vitamins (namely vitamin C, carotenoids and α-tocopherol) and markers of inflammation in healthy adults and in patients with myocardial infarction or stroke has been recently observed (Kritchevsky *et al.* 2000; Ford *et al.* 2003; Sanchez-Moreno *et al.* 2004). However, despite the multiple mechanisms by which these vitamins act as anti-inflammatory agents *in vitro* (Calfee-Mason *et al.* 2002; Carcamo *et al.* 2002), supplementation studies show inconsistent results regarding their ability to reduce systemic and vascular inflammation *in vivo*, especially when dietary rather than pharmacological amounts are used (Sanchez-Moreno *et al.* 2003; Van Dam

Abbreviations: CAM, cellular adhesion molecular; CRP, C-reactive protein; GLM, General Linear Model; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; OGTT, oral glucose tolerance test; ISI, insulin sensitivity index; PA, physical activity; sICAM-1, soluble intercellular adhesion molecule-1; TAC, total antioxidant capacity.

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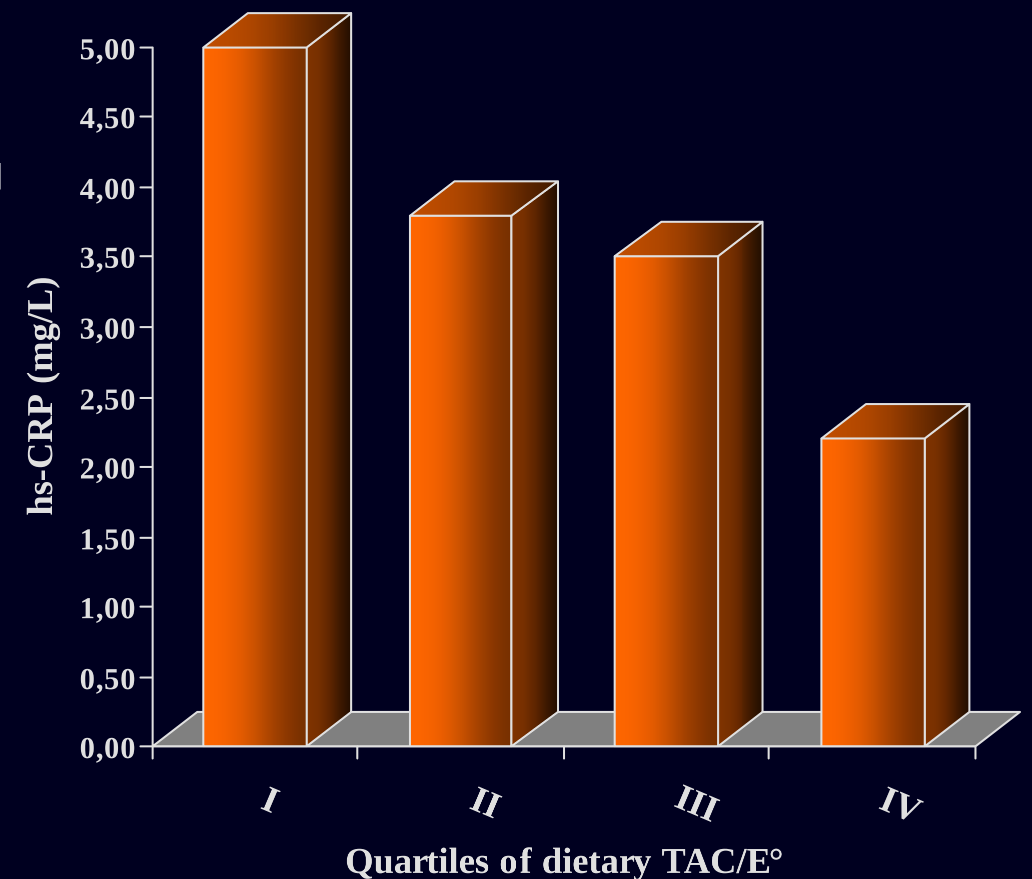
243 healthy subjects;
35-88 yrs
BMI 27.1 Kg/m2
19% smokers



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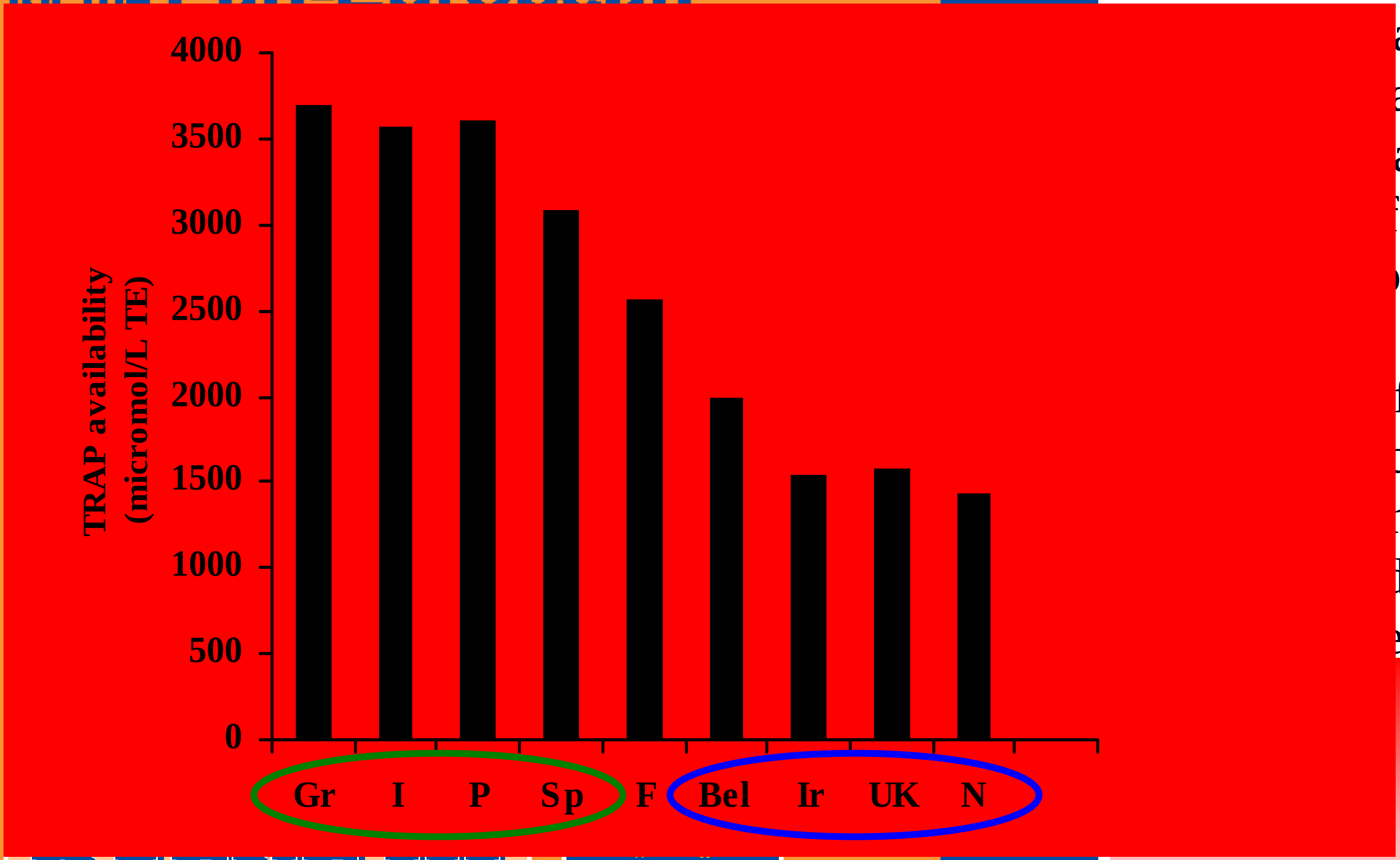

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Data Food Networking

Mediterranean diet and plasma TAC (ATTICA study)

TABLE 1
Lifestyle, clinical, and biochemical characteristics of the part[illegible] Mediterranean diet score[1]

TAC was positively correlated with the intake of fruit, vegetables, olive oils

Characteristic	[illegible]	[illegible]	[illegible]	[illegible]	Women (n = 1528) 2nd (21–35) (n = 509)	3rd (36–55) (n = 510)	P[2]
Age (y)	[illegible]	[illegible]	[illegible]	[illegible]	45 ± 7[5]	47 ± 6[4]	0.01
Duration of education (y)	[illegible]	[illegible]	[illegible]	[illegible]	10 ± 4	13 ± 3	0.001
Current smoking (%)	[illegible]	[illegible]	[illegible]	[illegible]	39	38	0.21
Sedentary life (%)	[illegible]	[illegible]	[illegible]	[illegible]	57[4]	64[4]	0.001
BMI (kg/m^2)	[illegible]	[illegible]	[illegible]	[illegible]	24 ± 4[5]	24 ± 3[5]	0.04
SBP (mm Hg)	129 ± [illegible]	[illegible]	[illegible]	[illegible] ± 18	120 ± 18[4]	120 ± 19[4]	0.003
DBP (mm Hg)	83 ± 11	[illegible]	[illegible]	80 ± 11	75 ± 12	75 ± 10	0.25
Hypertension (%)	51	[illegible]	[illegible]	50	36[4]	10[4]	0.001
Total cholesterol (mg/dL)	197 ± 43	194 ± 41	194 ± 43	196 ± 40	190 ± 42	188 ± 47	0.14
LDL cholesterol (mg/dL)	134 ± 43	124 ± 38	124 ± 42	126 ± 39	120 ± 37	120 ± 41	0.07
Hypercholesterolemia (%)	45	39	36	51	47	25	0.08
Oxidized LDL cholesterol (U/L)	62 ± 21	56 ± 18[4]	51 ± 17[4]	63 ± 22	52 ± 25[4]	51 ± 23[4]	0.03
Blood glucose (mg/dL)	98 ± 25	95 ± 25	95 ± 30	98 ± 25	95 ± 25	95 ± 30	0.35
Diabetes mellitus (%)	10	8	6	11	6	2	0.15

[1] TAC, total antioxidant capacity; SBP, systolic blood pressure; DBP, diastolic blood pressure. No significant interactions were observed between tertile of diet score and sex.

[2] Derived from ANOVA. Reflect the association between tertiles of diet score and the investigated variables, after adjustment for sex.

[3] $\bar{x} \pm$ SD (all such values).

[4,5] Significantly different from 1st tertile (Bonferroni correction for multiple comparisons): [4] $P < 0.01$, [5] $P < 0.05$.

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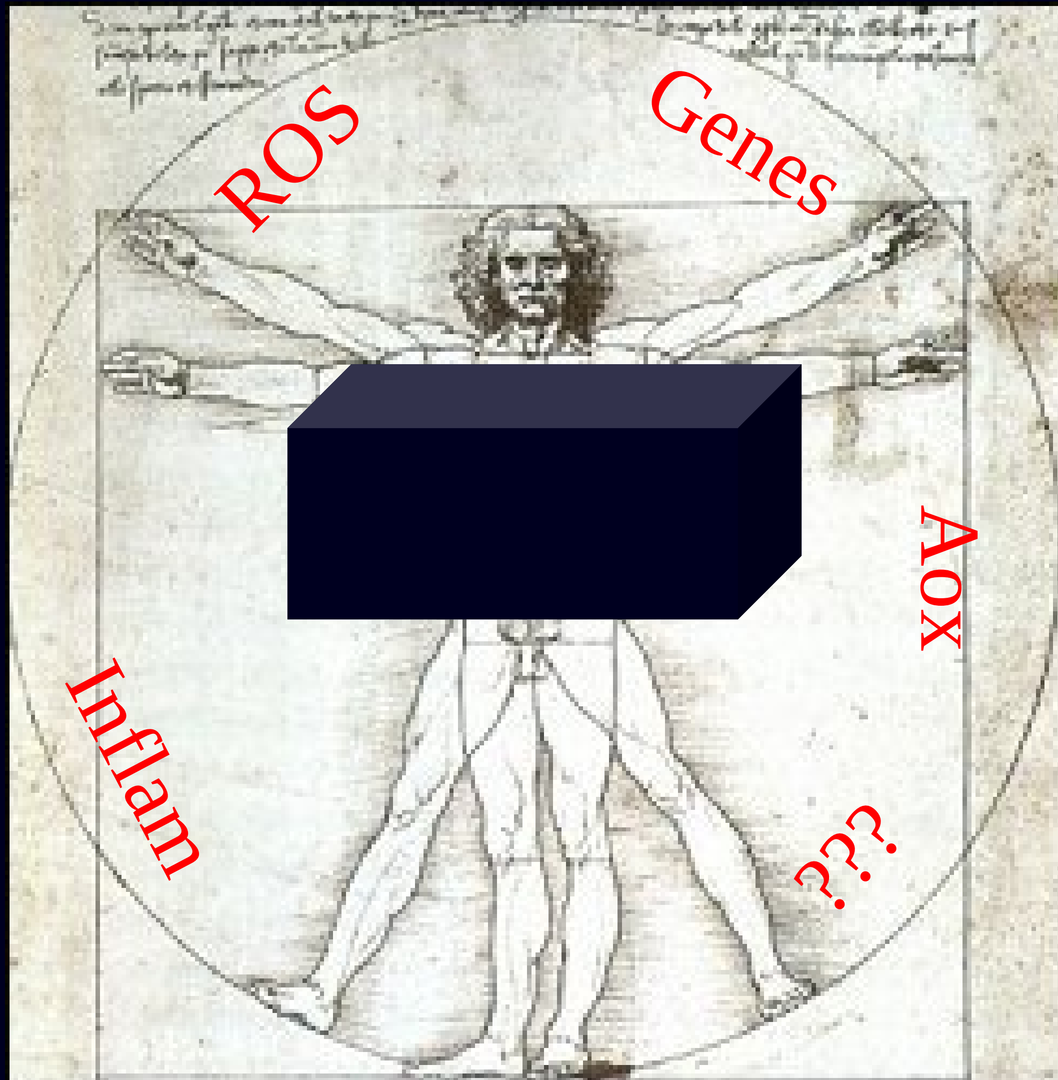
UNDERSTANDING THE “REDOX MAN”

Dietary factors

Life-style



Ageing

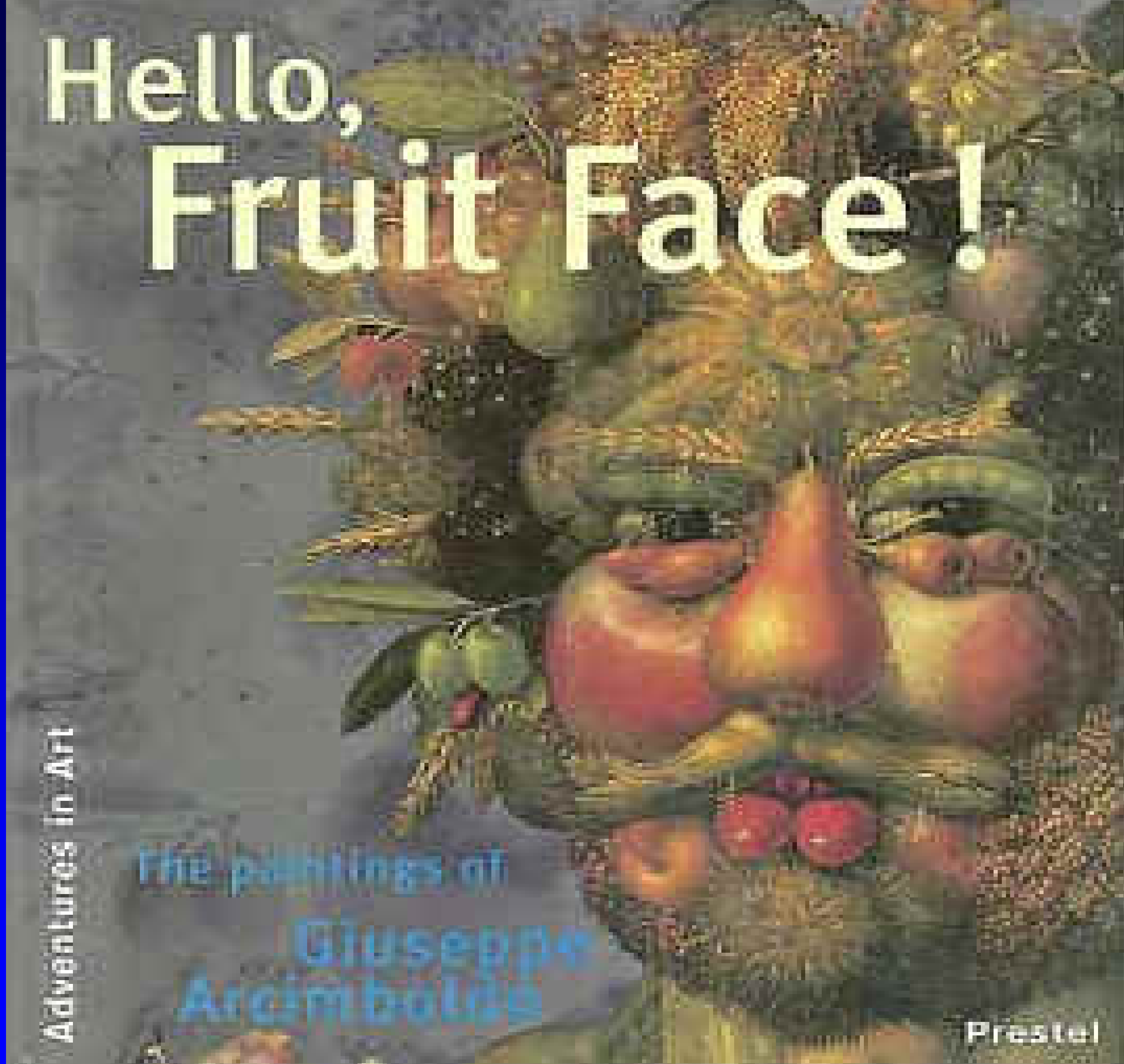
Hormones

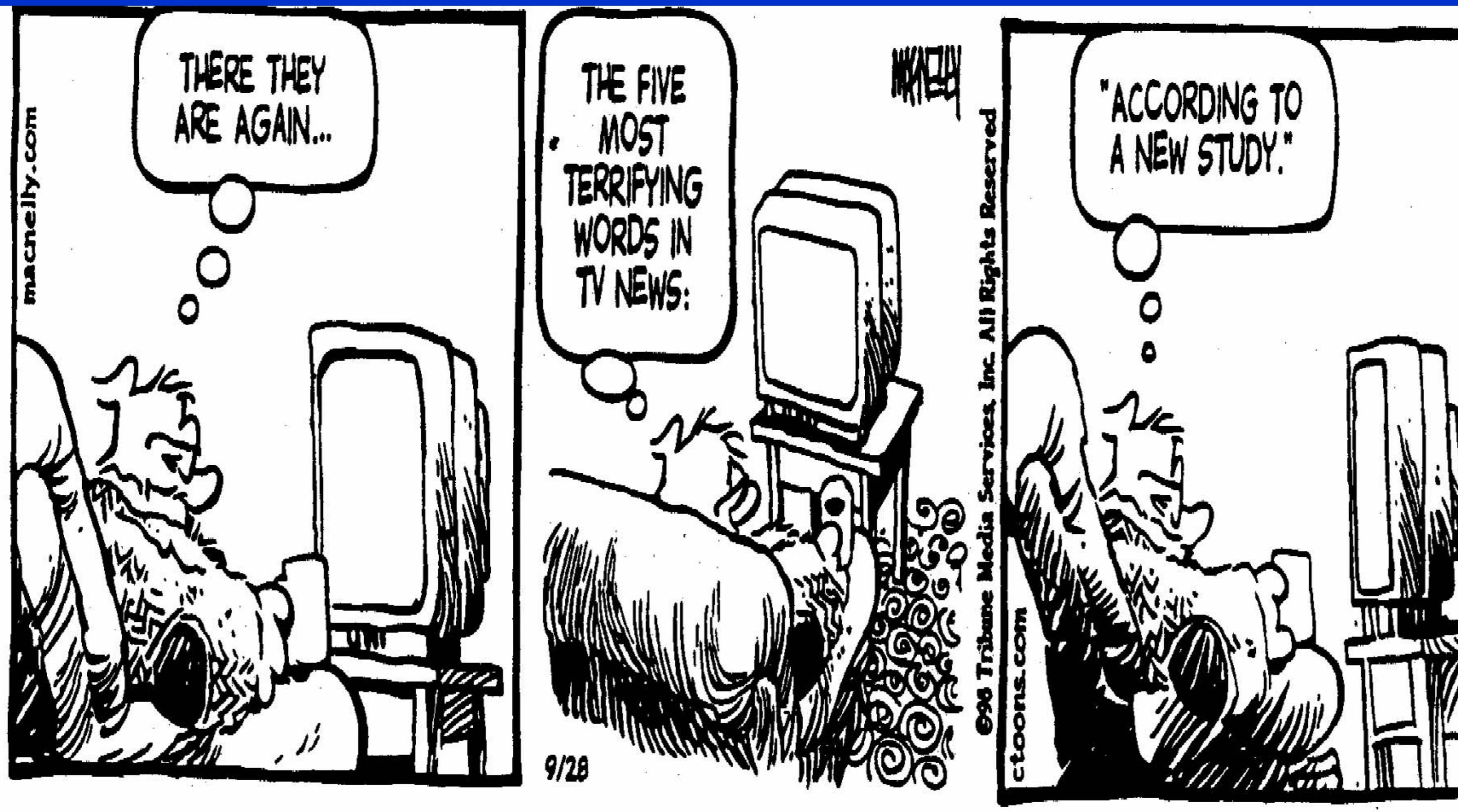
Environment

Stress

Physical activity


Oxidation
Antioxidation


Hello,
Fruit Face!
The paintings of
Giuseppe
Arcimboldo
Adventures in Art
Prestel



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