

Tea, Chocolate and Coffee

Roseanne Schnoll, PhD, RD, CDN
Dept Health and Nutrition Sciences

Polyphenols

- A large family of natural compounds widely distributed in plant foods.
- Polyphenols have specific health-promoting actions, and it is generally recognized that they can reduce the risk factors for many types of chronic diseases.

Polyphenols

- The largest and best studied polyphenols are the flavonoids, which include several thousand compounds, among them the flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids.
- Important dietary sources of polyphenols in Western societies are onions (flavonols); cocoa, tea, apples, and red wine (flavonols and catechins); citrus fruit (flavanones); berries and cherries (anthocyanidins); and soy (isoflavones).

- Drinking a daily cup of tea will surely starve the apothecary

--Chinese Proverb

Proceedings of the Third International Scientific Symposium on Tea and Human Health: Role of Flavonoids in the Diet

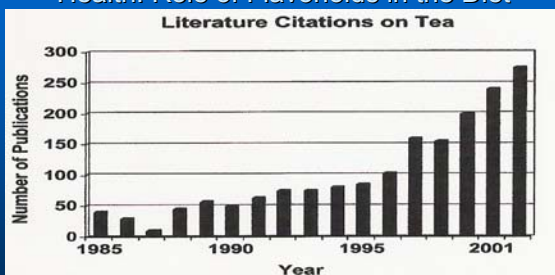


FIGURE 1 Number of peer-reviewed publications (1985–2002) relevant to tea and health.

Blumberg, J. Nutr. 133: 3244S–3246S, 2003

- *Camellia sinensis* is an evergreen plant that grows mainly in tropical climates.
- However, some varieties can also tolerate marine climates and are cultivated as far north as Cornwall on the UK mainland and Seattle in the US.

Processing of tea

- Tea is traditionally classified based on producing technique:
- White tea: Unwilted and unoxidized
- Green tea: Wilted and unoxidized
- Oolong: Wilted, bruised, and partially oxidized
- Black tea: Wilted, crushed, and fully oxidized



Green Tea

- Major polyphenols in green tea are catechins.
- There are 4 major green tea catechins:
 - Epigallocatechin-3-gallate (EGCG)
 - Epicatechin-3-gallate
 - Epigallocatechin
 - Epicatechin
- It's antioxidant activity is reported to be 100X stronger than vitamin C and 25X stronger than vitamin E in protecting DNA from mutations associated with oxidative damage.

Mechanism of action of tea on health

- | | |
|---|--|
| <p><u>Action of tea polyphenols</u></p> <ul style="list-style-type: none"> ■ Potent antioxidant activity ■ Selectively induce Phase I and Phase II metabolic enzymes ■ Inhibit cell proliferation rates ■ Improved composition of intestinal bacterial flora ■ Prevents angiogenesis | <p><u>Consequence</u></p> <ul style="list-style-type: none"> ■ Lower risk of heart disease; ↓ LDL oxidation, ↓ lipid peroxidation, ↓ oxidation of DNA and inhibition of carcinogenesis. ■ Detoxification of carcinogens ■ Decreased growth of abnormal cells and neoplasms ■ Undesirable components of flora replaced by beneficial bacteria. ■ Reduce blood vessel growth (↓ metastasis) |
|---|--|

Catechins / EGCG Green Tea

- Antioxidant (↓ LDL oxidation, ↓ lipid peroxidation, and ↓ DNA oxidation)
- ↓ cholesterol levels
- ↓ platelet aggregation
- ↓ cancer risk in lungs, stomach, breast, colon cancers- detoxification of carcinogens (phase I and phase II)
- ↑ thermogenesis (fat oxidation & energy expenditure)
- Anti-inflammatory (skin disorders, arthritis)



Daily supplements of extracts from green tea (*Camellia sinensis*) was effective for decreasing, in as quickly as 3 weeks, blood pressure, LDL cholesterol, oxidative stress, and a marker of chronic inflammation, all independent cardiovascular risk factors.

Mechanisms by which tea may confer its cardiovascular protective properties

- Inhibition of oxidized LDL cholesterol
- Attenuation of the inflammatory process in atherosclerosis
- Reduction in thrombosis
- Promotion of the normal endothelial function
- Blocking of adhesion molecules
- Reduction in plasma total and LDL cholesterol (LDL-C)

Tea flavonoids gain recognition as powerful weapon against disease

- People who drink five cups of tea daily are not only likely to improve their cholesterol levels but may also protect against damage from smoking

• Journal of Nutrition, (2003) vol 133, no 10

Effect of Increased Tea Consumption on Oxidative DNA Damage among Smokers: A Randomized Controlled Study^{1,2}

Iman A. Hakim,^{1,3} Robin B. Harris,^{4*} Sylvia Brown,^{4†} H-H. Sherry Chow,[†] Sheila Wiseman,^{**} Sanjiv Agarwal[‡] and Wendy Talbot^{*}

¹Mel and Enid Zuckerman Arizona College of Public Health, University of Arizona, Tucson, AZ 85724; ²Arizona Cancer Center, Tucson, AZ 85724; ³Unilever Health Institute, Vlaardingen, The Netherlands; and ⁴Unilever Bestfoods North America, Englewood Cliffs, NJ 07632

ABSTRACT Tea drinking has been associated with decreased occurrence of cancer and heart disease. One potential mechanism for these findings is the strong antioxidant effect of tea polyphenols. A phase II randomized controlled tea intervention trial was designed to study the effect of high consumption (4 cups/d) of decaffeinated green or black tea on oxidative DNA damage as measured by urinary 8-hydroxydeoxyguanosine (8-OHdG) among smokers over a 4-mo period. A total of 143 heavy smokers, aged 18–79 y, were randomized to drink either green or black tea or water. Levels of plasma and urinary catechins and urinary 8-OHdG were measured monthly. A total of 133 of 143 smokers completed the 4-mo intervention. Multiple linear regression models were used to estimate the main effects and interaction effect

of green tea as a confounder. Two groups were revealed (P = 0.002). N that regular diseases or

KEY WORDS

“These data suggest that regular green tea drinking might protect smokers from oxidative damages and could reduce cancer risk or other diseases caused by free radicals associated with smoking.”

J. Nutr. 133: 3303S–3309S, 2003

Foods provide key nutrients that support these detoxification pathways

- Indoles, phytochemicals found in broccoli, cauliflower and other cruciferous vegetables, and **green tea catechins** markedly enhance phase I pathways.
- Dithioalthiones and isothiocyanates; liminoids, phytochemicals in citrus, organosulfuric compounds found in the allium family vegetables (garlic, onions, shallots, and leeks), **green tea catechins** and curcumin increase phase II enzymes, including Glutathione S Transferase which blocks carcinogens from damaging cellular DNA.

SHORT COMMUNICATION
Activation of antioxidant protein kinases by green tea polyphenols: potential signaling pathways in the regulation of antioxidant-responsive element-mediated Phase II enzyme gene expression
 Jieping Yu, Huo Lin, Jian-Lian Chen, Guohong Chen, Guohua Chen, and L. J. Chen (1997)
 Department of Pharmacology and Toxicology, University of California, San Francisco, California, USA
 Green tea polyphenols, a group of flavonoid compounds, have been shown to possess antioxidant and anticarcinogenic activities. In this study, we investigated the mechanism of action of green tea polyphenols in the regulation of Phase II enzyme gene expression. The results showed that green tea polyphenols (100 µg/ml) significantly increased the transcription of Phase II enzyme genes (GSTA1, GSTA2, GSTP1, and GSTT1) in HepG2 cells. This effect was blocked by the antioxidant-responsive element (ARE) inhibitor, N-ethylmaleimide (NEM). The results also showed that green tea polyphenols (100 µg/ml) significantly increased the transcription of Phase II enzyme genes in HepG2 cells transfected with a reporter gene construct containing the ARE. These results suggest that green tea polyphenols may act as antioxidants and anticarcinogens by increasing the transcription of Phase II enzyme genes through the ARE-mediated signaling pathway.

“Green tea polyphenols, major constituents of green tea, are potent chemopreventive agents in a number of experimental models of cancer in animals... This indicates that GTP stimulates the transcription of Phase II detoxifying enzymes through the antioxidant responsive element (ARE).”

Yu R, et al. *Carcinogenesis* 1997;18(2):451-56.



Nakachi (1998) found that the consumption of 5 or more cups of green tea per day was associated with decreased recurrence of stage I and II breast cancer in Japanese women.

Nakachi, et al (as cited in Hasler, 1998).

- Epidemiological studies on Japanese women report that those who drink 2-3 cups or more of green tea a day have a lower incidence of cancer (or develop the disease at a later date).
- The custom of drinking green tea with meals in Japan may be one reason for the low cancer rates. The Japanese smoke nearly twice as many cigarettes as Americans, yet they have approx. half the incidence of lung cancer.
- In vitro showed inhibitory effect on the growth of mammary cell cancer. Prevents angiogenesis (blood vessel growth).

Prospective Cohort Study of Green Tea Consumption and Colorectal Cancer Risk in Women

Gong Yang,¹ Xiao-Ou Shao,² Honglan Li,² Wang Chen³, Bao-Fang Ji³
Xiaohua Zhang⁴, Yu-Tong Cao⁵, and Wei Zhang⁶

¹School of Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong; ²Department of Nutrition, Shandong University School of Public Health, Jinan, Shandong; ³Department of Epidemiology, Shandong University School of Public Health, Jinan, Shandong; ⁴Department of Preventive Medicine, Shandong University School of Public Health, Jinan, Shandong; ⁵Department of Clinical Medicine, Shandong University School of Public Health, Jinan, Shandong; ⁶Department of Preventive Medicine, Shandong University School of Public Health, Jinan, Shandong

Abstract

Tea and its compounds have chemopreventive properties as well as anticancer activity. Epidemiological studies, however, have been inconsistent. We prospectively evaluated the association between green tea consumption and colorectal cancer (CRC) risk in a cohort of 4978 Chinese women aged 40–70 years. Information on tea consumption was assessed through repeated interviews at baseline and mid-study. The average duration of follow-up was 10.2 years. During follow-up, 104 incident CRC cases were identified. After adjusting for age, education, body mass index, alcohol intake, smoking status, family history of CRC, and other factors, we found that regular consumption of green tea (≥ 1 cup per day) was associated with a lower risk of CRC compared with nonconsumption (adjusted hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.47–0.94). This inverse association remained significant after further adjustment for lifestyle factors and other potential confounders. Our findings suggest that regular consumption of green tea may reduce the risk of CRC in Chinese women.

***The results demonstrate a clear inverse correlation between green tea consumption and the risk of CRC—most notably those women who regularly consumed green tea over a longer period of time.**

***With research showing protection against ovarian cancer, breast cancer, as well as a reduction in mortality due to cardiovascular disease in women, it's time for practitioners to begin advising their female patients to start adding green tea to their daily regimen."**

Green Tea Prevents Colorectal Cancer in Women

- **Key Findings:** The multivariate relative risk of colorectal cancer (CRC) was 0.63 (95% confidence interval, 0.45-0.88) for women who reported drinking green tea regularly at baseline compared with non-regular tea drinkers.
- A significant dose-response relationship was found for both the amount of green tea consumed (p trend = 0.001) and the duration in years of lifetime tea consumption (p trend = 0.006).
- Compared with non-drinkers, each 1.67 g increase (approximately equal to the amount of tea in one tea bag) in daily green tea consumption was associated with a 10% reduction in CRC risk (RR, 0.90; CI: 0.80-1.00).
- Additional 5-year consumption of green tea was also associated with a 10% reduction in CRC risk (RR, 0.90; 95% CI: 0.83-0.97) after fully adjusting for potential confounding variables (e.g. cigarette smoking, alcohol consumption, exercise).
- The reduction in risk was most evident for those women who reported to drink tea regularly at both baseline and during follow-up surveys (RR, 0.43; 95% CI: 0.24-0.77).



For a long time, it was believed that these cancer-fighting polyphenols could only be obtained from **GREEN** tea, not **BLACK**. Stoner, G.D. & Mukhtar, H. (1995)

However, recent research has shown that both **GREEN** and **BLACK** tea can inhibit lung cancer in animal experiments.

Yang, et al (1998)

- Recent studies indicate the compounds contained in black tea – theaflavins and thearubigens - do more than contribute to its dark color and distinctive flavor. They also provide health benefits originally attributed solely to green tea.

Tea shown to fight infection

- Drinking tea appears to prime the immune system to fight infection and chronic disease.
- Subjects who drank five to six small cups of black tea daily for two weeks were better able to fight off bacterial infections
- Gamma delta T cells act to prevent and reduce the effects of disease. Previous experiments have shown that exposing these cells to ethylamine, produced when the tea ingredient L-theanine is broken down in the liver, boosted the abilities of the cells to fight infections.
- The researchers also carried out in vivo studies on people who either drank about 20 ounces of tea a day for two weeks, or consumed coffee instead. The tea drinkers' gamma delta T cells produced a wealth of anti-bacterial chemicals when exposed to bacteria.
- In contrast, people who drank coffee during the study produced no disease-fighting proteins in response to bacteria.

Proceedings of the National Academy of Sciences
2003;10. 1073/pnas.1035603100

Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans¹⁻³

Abdel G. Dhalluin, Claudette Dore, Dominique Babin, Lucien Girardin, Nouri Mene, Marc Perle, Philippe Chavoix, and Jacques Thibaut

ABSTRACT Current interest in the role of functional foods in weight control has focused on plant ingredients capable of interacting with the neuroendocrine system.

Objective: To investigate whether a green tea extract, because of its high content of caffeine and catechin polyphenols, could increase 24-h energy expenditure (EE) and fat oxidation in humans.

Design: Twenty-five obese EE, the respiratory quotient (RQ), and the amount (mmol) of energy and catecholamines were measured in a respiratory chamber on 10 healthy men. On 7 separate occasions, subjects were randomly assigned to receive 1 treatment: green tea extract (25 mg caffeine and 70 mg epigallocatechin gallate, caffeine (EGCg), and catechin, which they ingested at breakfast, lunch, and dinner.

Results: Relative to placebo, treatment with the green tea extract resulted in a significant increase in 24-h EE (4%, $P = 0.01$) and a significant decrease in 24-h RQ (from 0.85 to 0.82, $P = 0.001$) without any change in energy intake. Twenty-four-hour urinary catecholamine excretion was higher during treatment with

caffeine, there has been increased interest in the potential thermogenic effects of some compounds extracted from plants (eg, caffeine from coffee and tea, ephedrine from ephedra, and capsaicin from pungent species), largely because of their potential to modulate the distribution of energy and activity (1). For example, capsaicin-rich foods (eg, chili peppers and red peppers) have been shown to stimulate the metabolic and thermogenic response in humans (2, 3), and caffeine is relatively small amounts can promote thermogenesis induced by sympathetic stimuli, whether in response to cold (4) or to exercise (5). In contrast, ephedrine (6) and ephedrine (7) in long-term clinical trials have shown greater losses in both weight and body fat in obese persons treated with a combination of caffeine and ephedrine than in those treated with placebo, caffeine, or ephedrine alone (8).

Because much of our laboratory, in which an in vitro system was used to measure the response rate of brown adipose tissue to catecholamines, suggests that the interaction between caffeine and ephedrine results in a synergistic reduction of energy stores, we tested the effect of a combination of caffeine and ephedrine on energy stores in humans.

"Green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content per se. The green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both."

1580

Am J Clin Nutr 1999; 70:1580-7. Printed in USA. © 1999 American Society for Clinical Nutrition

Green Tea and Skin

Santosh K. Katiyar, PhD; Nihal Ahmad, PhD; Hasan Mukhtar, PhD

Objectives: To discuss the current knowledge of polyphenolic compounds present in green tea as anti-inflammatory, antioxidant, and anticarcinogenic in skin.

Data Sources: References identified from bibliographies of pertinent articles, including our work in related fields.

Study Selection: were selected based on phenolic constitution and cancer-preventive use of green tea derivatives.

Data Synthesis: green tea were to photocarcinogenesis.

phenols were found to afford protection against chemical carcinogenesis as well as photocarcinogenesis in mouse skin. A few experimental studies were conducted in human skin in our laboratory. Analysis of published studies demonstrates that green tea polyphenols have anti-inflammatory and anticarcinogenic properties. These effects appear to correlate with antioxidant properties of green tea polyphenols.

"The outcome of several experimental studies suggests that green tea possess anti-inflammatory and anticarcinogenic potential, which can be exploited against a variety of skin disorders...Supplementation of skin care products with green tea may have a profound impact on various skin disorders in the years to come."

Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea.

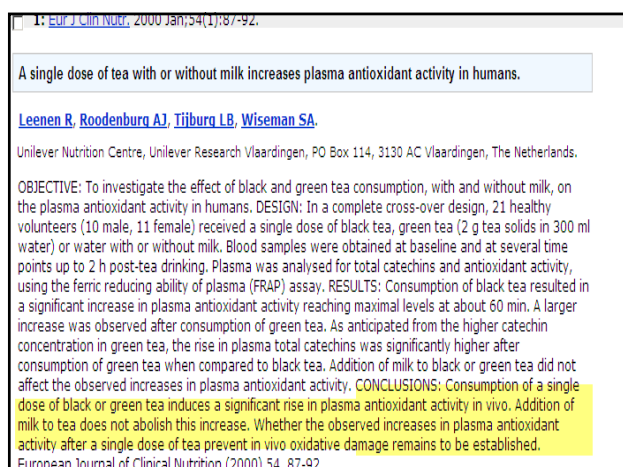
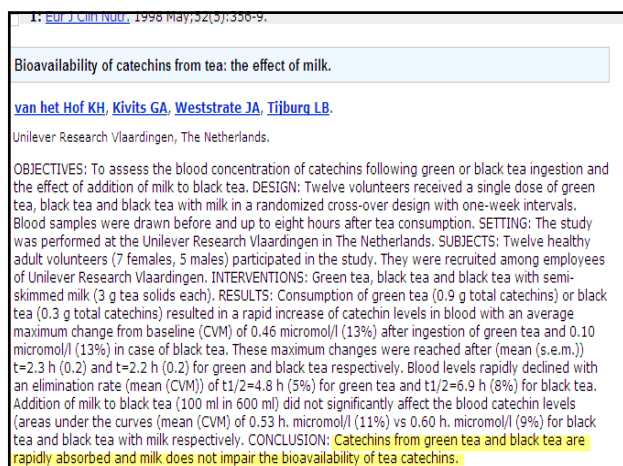
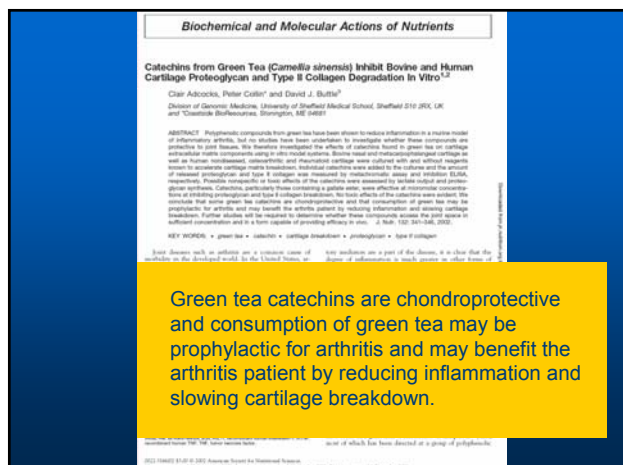
Haqqi TM, Anthony DD, Gupta S, Ahmad N, Lee MS, Kumar GK, Mukhtar H

Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA.

Identified severity fraction anti-infl the effect experim as comp lower in inflamm arthritic GTP-fec alpha-pr joints of arthritic was only collagen studies prevention of onset and severity of arthritis.

- ✓ Antioxidants in green tea may prevent and reduce the severity of rheumatoid arthritis.
- ✓ Polyphenolic action of the green tea can protect the body from oxidative stress that causes arthritis.
- ✓ Researchers chemically induced arthritis in mice: only 44% of mice given green tea developed arthritis (and a less severe form) compared to 94% in the control group.

Proceedings of the National Academy of Science, July 1999



Addition of milk prevents vascular protective effects of tea.

Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stanql K, Stanql V.

Medizinische Klinik mit Schwerpunkt Kardiologie und Angiologie, Charité-Universitätsmedizin Berlin, CCM, Charitéplatz 1, D-10117 Berlin, Germany.

AIMS: Experimental and clinical studies indicate that tea exerts protection against cardiovascular diseases. However, a question of much debate is whether addition of milk modifies the biological activities of tea. We studied the vascular effects of tea, with or without milk, in humans and elucidated the impact of individual milk proteins in cell culture experiments, with isolated rat aortic rings and by HPLC analysis. **METHODS AND RESULTS:** A total of 16 healthy female volunteers consumed either 500 mL of freshly brewed black tea, black tea with 10% skimmed milk, or boiled water as control. Flow-mediated dilation (FMD) was measured by high-resolution vascular ultrasound before and 2 h after consumption. Black tea significantly improved FMD in humans compared with water, whereas addition of milk completely blunted the effects of tea. To support these findings, similar experiments were performed in isolated rat aortic rings and endothelial cells. Tea induced vasorelaxation in rat aortic rings and increased the activity of endothelial nitric oxide synthase by phosphorylation of the enzyme in endothelial cells. All effects were completely inhibited by the addition of milk to tea. Of the various kinds of milk proteins, the caseins accounted for these inhibiting effects of milk, probably by formation of complexes with tea catechins. **CONCLUSION:** Milk counteracts the favourable health effects of tea on vascular function. This finding indicates the need for particular awareness in the interpretation and design of studies comprising nutritional flavonoids.

- Adding milk does not seem to affect antioxidant status of tea, however, it may inhibit nitric oxide synthesis and thereby reduce vascular relaxation.

Cocoa

- A natural antioxidant
- Traditionally used in Mexico and parts of Latin America for medicinal purposes
- Theobroma cacao plant used to make chocolate
- Recent studies find cocoa to be cardioprotective improve blood flow to the heart muscle.

Chocolate Polyphenols



Cocoa is rich in antioxidant flavonoids called flavanols, which include procyanidins, epicatechins, and catechins.

Chocolate Polyphenols



- Antioxidant
- ↓ blood platelet aggregation
- ↑ flexibility of blood vessels and ↑ blood flow (↑ production of nitric oxide).
- ↓ moderately high BP
- ↓ LDL oxidation

- High concentration of polyphenol compounds called flavanols, including epicatechin and catechin.
- Cocoa flavanols improve endothelial function by enhancing nitric oxide bioactivity which helps dilate the blood vessels, increasing blood flow, reducing blood clot formation, and reducing blood pressure. Flavanols can also reduce LDL oxidation which may prevent buildup of atherosclerotic plaque in the artery walls.

Chocolate: Food as Medicine/Medicine as Food

Carl E. Korte, PhD

Department of Nutrition and Food Medicine, University of California at Davis, Davis, California

Key words: chocolate, flavanols, antioxidants, glycosides, epigenetics, cardiovascular disease

Cocoa and chocolate products have been followed by hundreds of years. Their capacity have been recognized as significant sources of phytochemicals with beneficial effects. These foods are among the most consumption sources of the polyphenols flavanols, including dark chocolate. Recent studies have shown that these polyphenols are absorbed from the intestine of humans and humans with epigenetic effects on many genes. These studies show flavanols have potent antioxidant and angiogenic activities following consumption of cocoa or chocolate.

Key findings points:

- Cocoa and chocolate products have the highest concentrations of flavanols among commonly consumed foods.
- The polyphenols flavanols are essential and specific, which are found in various.
- These flavanols have potent antioxidant effects in vivo and in vitro, and potent antioxidant vitamins.
- Cocoa-derived polyphenols also exhibit potent effects.
- Multiple mechanisms are involved in which phytochemicals from cocoa may exert beneficial effects.

Why study chocolate and health? Why study chocolate and cocoa as a source of flavanols? What is the bioavailability of cocoa or chocolate flavanols? What are the effects of cocoa or chocolate on human health? What are the effects of cocoa or chocolate on human health? What are the effects of cocoa or chocolate on human health?

The idea that chocolate or cocoa may have some health benefits is not a new concept. When Cortez first arrived in Central America, one of his first observations was the common use of chocolate, particularly by the high priests. Most surprising was reference to chocolate generally as a medicine. Historical documents on Europe refer to chocolate's medicinal value. By the 18th and 19th, chocolate and cocoa were viewed not just as a beverage with a pleasant taste, but generally as a food to treat a number of disorders, including asthma and heart pain. The concept that cocoa beverages may provide some health benefits was widely accepted as well about the 18th and into the early 19th. Only in the past 10 to 40 years have perceptions of chocolate changed from its being

a medicinal food to a confectionery with no health benefits or possible negative effects on one's health.

The reasons for studying chocolate come from the recognition that chocolate per se is a food rich in flavanols. The current epidemiological studies indicate a strong inverse correlation between cocoa, heart disease and consumption of wine [1], other chocolate beverages [2], and flavanols and other polyphenols in wine, fruits and vegetables [3]. Because cocoa is a polyphenol-rich food containing primarily glycosides, as well as methylxanthines, one can argue that intake of cocoa may also be associated with reduced risk for cardiovascular disease.

Cocoa is one of the richest flavanol-containing foods available. Over 10 percent of the weight of cocoa products, which is used to make beverages, is flavanols [4]. Chocolate also contains a small amount of theobromine (2.7%). Contrary to common belief, chocolate is not a rich source of caffeine. Typically, the cocoa beverage used in most studies contains less caffeine than found in a cup of decaffeinated coffee [5]. Chocolate and cocoa are unique in the type of flavanols

References

Presented at the 10th Nutrition Research Conference on Medical Issues, "Nutrition in Medical and Nutritional Therapy," November 6-8, 2006, San Diego, Florida. Address reprint requests to: Carl E. Korte, PhD, Department of Nutrition, University of California at Davis, 101 Shattuck Hall, Davis, CA 95616-8502 and ckorte@ucdavis.edu.

Journal of the American College of Nutrition, Vol. 20, No. 5, 430S-439S (2001)
Published by the American College of Nutrition

- Preliminary clinical studies, with participants consuming flavanol-rich cocoas and chocolates, have resulted in a number of positive effects relating to cardiovascular health, including decreased blood pressure and improved blood flow through the vessels.
- In fact, a recent clinical study simultaneously compared low-dose aspirin and a flavanol-rich cocoa beverage, and found reductions in platelet "stickiness," which may improve blood flow, with both.

- *In vitro* studies found that the flavanols in chocolate may decrease the oxidation of Low Density Lipoproteins (LDL), or "bad" cholesterol. When LDLs become oxidized, they promote the build up of plaque along the lining of blood vessels, which can reduce blood flow and supports the development of high blood pressure and atherosclerosis.
- Additional *in vitro* studies found that flavanols may reduce platelet aggregation. Platelet aggregation is when blood components become "sticky" and adhere to the lining of the blood vessel. Platelet aggregation may be a risk factor for cardiovascular disease and is thought to lead to high blood pressure and other forms of heart disease.
- A diet containing about an ounce of chocolate a day increases good cholesterol and prevents bad cholesterol from oxidizing.

Table 1. Human intervention trials with cocoa

Intervention	Polyphenol content	Control	Subjects	Main outcomes	Industry-funded	Reference
1 Semi-sweet chocolate baking bits (one dose of 2.7 g b. 53 g c. 60 g)	Total procyanidins (epicatechin) 90 (180 mg) (a) 90 (180 mg) (b) 90 (180 mg) (c) 90 (180 mg)	No chocolate	20 healthy adults (20–56 years)	Dose-dependent increase in plasma epicatechin. Non-significant trend for an increase in plasma antioxidant activity and a decrease in TRAPs	Partially	Wang <i>et al.</i> ¹⁴
2 18.75 mg procyanidin-rich cocoa powder in 300 ml water (one dose)	887 mg epicatechin and total procyanidins	Caffeine and sucrose but drink or water	30 healthy adults (24–50 years), 10 per group	Suppression of platelet activation. Aspirin-like effect on primary hemostasis 6 h after consumption	Authors from industry, not stated	Rees <i>et al.</i> ¹⁵
3 100 g of which 80 g chocolate (semi-sweet baking bits (one dose)	557 mg total procyanidins of which 100 mg epicatechin	Vanilla milk chips (isocaloric)	10 healthy adults (20–49 years) + 3 healthy adults (20–30 years) consuming control	12-fold increase in plasma epicatechin 2 h later; increase in plasma total antioxidant activity and decrease in TRAPs	Partially	Rees <i>et al.</i> ¹⁵
4 12 g cocoa powder × 30 for 2 weeks	2010 mg total polyphenols of which 348 mg epicatechin	Sugar	15 healthy men, 9 in active group (32.5 ± 6.4 years)	Increase in LDL oxidation lag time, no change in plasma lipids or antioxidants. Higher excretion of epicatechin/metabolites in urine	Authors from industry, not stated	Okinaka <i>et al.</i> ¹⁶
5 22 g cocoa powder and 16 g dark chocolate for 4 weeks	486 mg procyanidin of which 111 mg monomers	Average American diet	23 healthy adults (21–62 years)	Increase in LDL oxidation lag time, increase in serum antioxidant capacity, increase in HDL cholesterol	No but industrial authors	Wan <i>et al.</i> ¹⁷
6 18.75 g cocoa powder in 300 ml water with sugar, with and without aspirin (one dose)	887 mg epicatechin and procyanidins	81 mg aspirin	16 healthy adults (22–49 years)	After 6 h, cocoa inhibited aspirin-induced platelet activation and function	Partially	Pearson <i>et al.</i> ¹⁸
7 30 g dark chocolate and 30 g cocoa powder in a drink for 6 weeks	651 mg total procyanidin (chocolate = 168 mg) cocoa = 483 mg)	None	25 healthy adults (20–40 years)	LDL oxidizability was lower, but no effect on inflammation markers, or plasma antioxidant capacity	Partially	Mather <i>et al.</i> ¹⁹
8 25 g semi-sweet chocolate chips (one dose)	220 mg flavanols and procyanidins	None	18 healthy adults	Increase in plasma epicatechin after 2 h with concurrent increase in proinflammatory cytokines and reduction in platelet-related haemostasis	Partially	Hick <i>et al.</i> ²⁰
9 100 g dark chocolate for 14 d	500 mg total polyphenols	90 g white chocolate	13 elderly adults (53–64 years with mild hypertension)	Lower systolic and diastolic blood pressure	No	Taddei <i>et al.</i> ²¹
10 Cocoa flavanol/procyanidin tablets for 28 d	234 mg flavanols and procyanidins (0.3 mg tablet ⁻¹)	Placebo tablets	42 ± 6, 15 healthy adults (control 47.4 years ± 6)	Lower platelet aggregation and P-selectin expression, higher plasma ascorbic acid, no change in inflammation-related status markers, increase in plasma epicatechin and catechins	Partially	Murphy <i>et al.</i> ²²
11 High polyphenol cocoa drink 4 × 250 ml for 4 d	621 mg total flavanols (epicatechin, catechin and related oligomers) 17 mg total (70 mg monomers, 100 mg procyanidins)	Low flavanol cocoa drink	27 healthy adults (19–72 years)	Improved peripheral vasodilation after 4 d, large acute response after 30 min	Partially	Fisher <i>et al.</i> ²³
12 100 ml high cocoa polyphenol drink (one dose)	170 mg total (70 mg monomers, 100 mg procyanidins)	Low flavanol cocoa drink	20 adults (all with 1 CHD risk factor) ± 1 years ± 14 (17% were smokers)	NO bioactivity and arterial FMD increased	Partially	Hales <i>et al.</i> ²⁴

Table 1. Continued

Intervention	Polyphenol content	Control	Subjects	Main outcomes	Industry-funded	Reference
13 100 g dark chocolate (with and without 200 ml milk) (one dose)	Polyphenols not stated but FRAP values were 141.4 and 161.0 g)	200 g milk chocolate (FRAP 78.3 and 100 g)	12 healthy adults (25–35 years)	Dark chocolate increased plasma antioxidant capacity and epicatechin. Consuming milk with it reduced these effects. Milk chocolate had less effect than both these treatments	No	Serdar <i>et al.</i> ²⁵
14 71 g dark chocolate or high phenolic dark chocolate for 3 weeks	Dark = 274 mg (14 mg) epicatechin, catechin and related oligomers. High = 418 mg (170 mg) epicatechin	71 g white chocolate	45 healthy adults (19–49 years)	Both dark chocolates increased HDL cholesterol and lipid peroxidation decreased but also with white chocolate controls. No change in plasma antioxidant capacity	Partially	Murru <i>et al.</i> ²⁶
15 40 g high phenolic dark chocolate for 14 d	210 mg total polyphenols of which 46 mg epicatechin	Low phenolic dark chocolate	21 healthy adults (21–55 years)	Improved endothelium-dependent FMD, no change in blood pressure, oxidative markers or blood lipids	No	Engler <i>et al.</i> ²⁷
16 High polyphenol cocoa drink, 100 ml (one dose)	187 mg total monomers and oligomeric procyanidins	Low phenolic cocoa drink	20 healthy males (20–40 years)	F2 isoprostanes improved 2 and 4 h after exercise	No but industrial involvement	Wilmsdorf <i>et al.</i> ²⁸
17 Dark chocolate, 100 g (one dose)	500 mg total polyphenols	90 g white chocolate	15 healthy adults (24 ± 7.5 years)	Insulin sensitivity higher and insulin resistance lower. Sympathetic pressure lower	No	Gross <i>et al.</i> ²⁹
18 Flavanol-rich drink at 0.25, 0.375, 0.5 g/kg body weight (one dose)	12.2 mg/kg monomers, 9.7 mg/kg oligomers, 88.2 mg/kg procyanidins	Bread and water	8 healthy males (26 ± 2 years)	Reduction in the rate of free radical-induced haemolysis	Partially	Zhu <i>et al.</i> ³⁰
19 100 g milk chocolate for 14 d	168 mg total flavanols of which 38 mg monomers and 130 mg polymers	Cocoa butter chocolate	26 healthy males (19–20 years) under exercise stress	Decrease in diastolic and mean blood pressure, plasma cholesterol, LDL, malondialdehyde, uric acid and lactate dehydrogenase activity, increase in plasma epicatechin and catechins. No change in plasma epicatechin but samples were fasting	No but industrial involvement (no author ship)	Frage <i>et al.</i> ³¹
20 100 g dark chocolate (one dose)	242 g of which 0.54 g monomers and dimer, 0.76 g trimer heptamers	Sham chewing and water	17 healthy adults (24–32 years)	Increase in resting and hypoxemic bronchial artery diameter. Increase in FMD at 60 min. Acute augmentation index decreased. No significant change in malondialdehyde, and total antioxidant capacity and pulse wave velocity	No	Vlachogiannis <i>et al.</i> ³²
21 100 g dark chocolate for 15 d	88 mg total flavanols (22 mg catechins, 66 mg epicatechin)	90 g white chocolate	20 never-treated adults with essential hypertension (44 ± 8 years)	Insulin sensitivity improved, lower systolic and diastolic blood pressure and LDL, and improved FMD	No	Gross <i>et al.</i> ²⁹
22 High polyphenol cocoa drink, 100 ml (one dose)	170–180 mg flavanols (70–74 mg monomers, 20–22 mg epicatechin, 100–111 mg procyanidins)	Low phenolic cocoa drink	17 adult smokers (average 37 years)	Increased circulating NO, FMD, both completed to increases in branched metabolites. Effects were reversed with NO-monomethyl-L-arginine to prove link to NO	Yes	Hales <i>et al.</i> ²⁴

Table 1. Continued

Intervention	Polyphenol content	Control	Subjects	Main outcomes	Industry-funded	Reference
23 300 ml high polyphenol cocoa drink (one dose)	917 mg flavanols (19% epicatechin)	300 ml low polyphenol cocoa drink	16 healthy males (25–32 years)	Acute elevations in levels of circulating NO species, an enhanced FMD response of conduit arteries, and an augmented microcirculation	Partially	Schuster <i>et al.</i> ³³
24 40 g dark chocolate (one dose)	Not stated but same brand as used for Vlachogiannis <i>et al.</i> ³²	White chocolate	20 male smokers (age not given)	Improved FMD after 2 h lasting for 8 h. Reduction in platelet function. Increased plasma total antioxidant status	No	Hermann <i>et al.</i> ³⁴
25 High polyphenol cocoa drink 4 × 250 ml for 4–6 d	Per 100 ml, 9.2 mg epicatechin, 10.7 mg catechin and 68.3 mg flavanol oligomers (88.2 mg)	None	15 young (<30 years) and 10 older (>50 years)	NO synthesis after cocoa was suppressed in older volunteers. FMD was enhanced in both groups but more in older group. Pulse wave amplitude enhanced in both groups, with acute rise with cocoa ingestion, more robustly in older subjects. No change in BP	Partially	Fisher & Hickling ²³
26 22 g cocoa powder and 10 g dark chocolate (in a muffin)	111 mg monomers and 466 mg procyanidins	Cocoa butter equivalent in muffin	4 (30–40 years) normotensive subjects (split trial)	Dark chocolate increased resistance of LDL and VLDL to oxidation whilst cocoa butter alone decreased resistance. Based after normalization of dietary data that chocolate is third highest contributor of antioxidants to the American diet	No	Vinson <i>et al.</i> ³⁵
27 41 g of high polyphenol dark chocolate either with or without almonds 60 g for 6 weeks (plus dietary advice)	Not stated	No intervention except same dietary advice	40 women with cholesterol 4.1–7.8 mmol/l (22–65 years)	Dark chocolate decreased FMD by 21%, 10% when eaten with almonds, 13% with almonds alone and 11% with no intervention. Consuming intracellular adhesion molecule with dark chocolate alone	No, industry supplied chocolate only	Kurlandsky & Sava ³⁶
28 High flavanol cocoa drink 100 ml × 30 for 1 week	Per 100 ml, 51 mg epicatechin, 10.7 mg catechin and 220 mg flavanol oligomers (181 mg procyanidins)	Low phenolic cocoa drink	6 male smokers with smoking-related endothelial dysfunction (11 total (22–32 years)	Daily continued FMD increases at baseline (baseline) and a sustained FMD augmentation at 2 h post-ingestion. A dose-dependent effect also seen with FMD and vitals. Biomarkers for oxidative stress unaffected	Yes	Hales <i>et al.</i> ²⁴

FE, Ferric reductase; FMD, flow-mediated dilation; FRAP, ferric-reducing ability of plasma; TRAP, ferric-reducing ability of plasma or antioxidant capacity; TRAPs, triphenyltetrazolium salt reduces substrates.

Effects of cocoa powder and dark chocolate on LDL oxidative susceptibility and prostaglandin concentrations in humans¹⁻³

Rag Wan, Joe A. Vlietin, Terry D. Edwards, John Pech, Sheryl A. Luzzari, and Penny M. Kite-Edwards

ABSTRACT

Background: Flavonoids are polyphenolic compounds of plant origin with antioxidant effects. Flavonoids inhibit LDL oxidation and reduce thrombotic tendency in vivo. Little is known about how cocoa powder and dark chocolate, rich sources of polyphenols, affect these cardiovascular disease risk factors.

Objective: We evaluated the effects of a diet high in cocoa powder and dark chocolate (CP-DC diet) on LDL oxidative susceptibility, serum total antioxidant capacity, and urinary prostaglandin concentrations.

Design: We conducted a randomized, 2-period, crossover study in 25 healthy subjects but 2 diets: an average American diet (AAD) supplemented with 22 g cocoa powder and 14 g dark chocolate (CP-DC diet), providing ~800 mg procyanidin.

Results: LDL oxidative lag time was significantly greater ($P < 0.01$) after the CP-DC diet than after the AAD. Serum total antioxidant capacity increased by an eightfold absolute increase in the CP-DC group ($P < 0.001$) after the CP-DC diet than after the AAD and was positively correlated with LDL oxidative lag time.

See corresponding editorial on page 603.

reported that dark chocolate contains catechins in a group of flavan-3-ol flavonoid compounds at an average concentration of 0.157 mg/g, 4 times that of tea (0.039 mg/g). In a representative sample of the Dutch population, chocolate contributed 30% of the catechin intake whereas tea contributed 30%. In younger age groups, in which chocolate is probably consumed in tea, and in countries where tea is consumed less, chocolate may be a more important source of catechins and their oligomeric procyanidins. Therefore, cocoa and chocolate can be important dietary sources of flavonoids in addition to tea.

Chocolate modification of LDL was shown to play a key role in the initiation of atherosclerosis (5). Studies have shown that flavonoids prevent LDL oxidation in vitro by scavenging radical species or augmenting metal ion chelation (6). Effects of cocoa powder also significantly inhibit LDL oxidation (Kondo et al (8)) reported that cocoa prolongs the lag time of LDL oxidation in a concentration-dependent manner. Watanabe et al (11) found that at 7 μ mol gallic acid equivalents, cocoa phenolics inhibited LDL oxidation by 70%, whereas wine inhibited LDL ox-

"Cocoa powder and dark chocolate may favorably affect cardiovascular disease risk status by modestly reducing LDL oxidation susceptibility, increasing serum total antioxidant capacity and increasing HDL-cholesterol concentrations, and not adversely affecting prostaglandins.

Am J Clin Nutr 2001 Nov;74(5):596-602

See corresponding editorial on page 603. Accepted for publication June 5, 2001.

596

Am J Clin Nutr 2001;74(5):596-602. Printed in USA. © 2001 American Society for Clinical Nutrition

- **Dark chocolate inhibits platelet aggregation in healthy volunteers.** Innes AJ, Kennedy G, McLaren M, Bancroft AJ, Belch JJ. *Platelets*. 2003 Aug; 14(5): 325-7.

- **Vascular effects of cocoa rich in flavan-3-ols** Heiss C, Dejam A, Kleinbongard P, Schewe T, Sies H, Kelm M. *JAMA*. 2003 Aug 27; 290(8): 1030-1

- **Chocolate and blood pressure in elderly individuals with isolated systolic hypertension** Taubert D, Berkels R, Roesen R, Klaus W. *JAMA*. 2003 Aug 27; 290(8): 1029-30

Dietary flavanols and procyanidin oligomers from cocoa (Theobroma cacao) inhibit platelet function¹⁻³

Karen J. Murphy, Anthony K. Chompey, John Singh, Massimo A. Bazzani, Silvia Moriarty, Marilyn J. Pike, Alan H. Turner, Neil J. Mann, and Andrew J. Sinclair

ABSTRACT

Background: Flavonoids may be partly responsible for some health benefits, including antithrombotic action and a decreased tendency for the blood to clot. An acute dose of flavanols and oligomeric procyanidins from cocoa powder inhibits platelet activation and function over 5 h in humans.

Objective: This study sought to evaluate whether 28 d of supplementation with cocoa flavanols and oligomeric procyanidins would modulate human platelet reactivity and primary hemostasis and reduce oxidative markers in vivo.

Design: Thirty-two healthy subjects were assigned to consume either 224 mg cocoa flavanols and procyanidins or placebo (1:1 mg cocoa flavanols and procyanidins) tablets in a double-blind, parallel, designed study. Platelet function was determined by measuring platelet aggregation, ATP release, and expression of activation-dependent platelet antigens by using flow cytometry. Plasma was analyzed for oxidative markers and antioxidant status.

Results: Plasma concentrations of epicatechin and catechin in the active group increased by 60% and 30%, respectively, during the

study and hemorrhage (15-18), including cocoa and chocolate (19-21). Cocoa contains numerous flavanols (epicatechin and catechin) and oligomeric procyanidins (4). Flavonoids inhibit platelet aggregation and are thought to decrease arterial risk factors for cardiovascular disease (CVD) through a variety of mechanisms, including reduced LDL oxidation (15, 16), improved endothelial-dependent vasodilation (17, 18), and modulation of cytokine involvement involved in the inflammatory response (19-22). Many of the physiologic effects of flavanols and procyanidins, especially those cocoa, may prevent cellular oxidation and atherogenic reactive oxygen species. Platelet aggregation is the critical event occurring during the initiation of coronary thrombosis, and cocoa epicatechin and catechin have been reported to modulate platelet function, thus reducing the risk of atherosclerosis (17-18, 23, 24). The rate and extent of absorption and metabolism of polyphenols are determined largely by the chemical structure and the glycosylation, acylation, conjugation, polymerization, and stability of the compound (25, 26). Monomeric flavanols are absorbed in the small intestine, whereas polymeric procyanidins (epicatechin) may be degraded to monomeric and oligomeric units.

"Researchers found that cocoa flavanol and procyanidin supplementation for 28 d significantly increased plasma epicatechin and catechin concentrations and significantly decreased platelet function. These data support the results of studies that used higher doses of cocoa flavanols and procyanidins." Am J Clin Nutr. 2003 Jun; 77(6): 1466-73

See corresponding editorial on page 603. Accepted for publication November 8, 2002.

1466

Am J Clin Nutr 2003;77(6):1466-73. Printed in USA. © 2003 American Society for Clinical Nutrition

Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide A Randomized Controlled Trial

Dick Taylor, MD, PhD
Barbara Brown, PhD
Chen Lefkowitz, MD
Nancy Ross, MD
Edgar Imhoff, MD

Context: Regular intake of cocoa containing flavanols is linked to lower cardiovascular mortality in observational studies. These study interventions of at least 2 weeks indicate that high doses of cocoa can improve endothelial function and reduce blood pressure (BP) due to the action of the cocoa polyphenols, but the clinical effect of low habitual cocoa intake on BP and the underlying BP-lowering mechanisms are unclear.

Objective: To determine effects of low doses of polyphenol-rich dark chocolate on BP.

Design, Setting, and Participants: Randomized, controlled, investigator-initiated, parallel-group trial involving an adult aged 56 through 79 years (24 women, 20 men) with self-reported average single polyphenol or stage 1 hypertension without concurrent risk factors. The trial was conducted at a primary care clinic in Germany between January 2005 and December 2006.

Intervention: Participants were randomly assigned to receive for 18 weeks either 6 g (30 kcal) per day of dark chocolate containing 80 mg of polyphenols or matching polyphenol-free white chocolate.

Main Outcome Measures: Primary outcome measure was the change in BP after 18 weeks. Secondary outcome measures were changes in plasma markers of endothelial stress, nitric oxide (NO), and oxidative stress (O₂ superoxide), and bioavailability of cocoa polyphenols.

Results: From baseline to 18 weeks, dark chocolate intake induced mean (SD) systolic BP to decrease by 6 mm Hg (P < .001) and diastolic BP by 4 mm Hg (P < .01). The mean (SD) change in pulse wave velocity (PWV) was 0.5 m/s (P < .001) and in carotid-femoral PWV was 0.3 m/s (P < .001). The mean (SD) change in carotid-femoral PWV was 0.3 m/s (P < .001) and in carotid-femoral PWV was 0.3 m/s (P < .001). The mean (SD) change in carotid-femoral PWV was 0.3 m/s (P < .001) and in carotid-femoral PWV was 0.3 m/s (P < .001).

"The inclusion of small amounts of polyphenol-rich dark chocolate as part of a usual diet efficiently reduced BP and improved formation of vasodilative nitric oxide."

© 2007 American Medical Association. All rights reserved.

J Gen Intern Med. 2007;22(10):686-692.

Cocoa Intake, Blood Pressure, and Cardiovascular Mortality The Copenhagen Elderly Study

Brian Borge, MD, PhD; J. M. Folsom, PhD; Frank J. Kok, PhD; Dan Kromhout, PhD

Background: Small doses of cocoa, flavanols, and polyphenols may improve endothelial function and reduce blood pressure. We studied whether habitual cocoa intake was associated with blood pressure and prospectively related with cardiovascular mortality.

Methods: Data from 10,000 elderly men (aged 70-79) participating in the Copenhagen Elderly Study and from 10,000 elderly women (aged 70-79) participating in the Copenhagen Elderly Study were analyzed. Blood pressure was measured at baseline and 5 years later, and cases of death were ascertained during 15 years of follow-up. Habitual cocoa intake was assessed by the cocoa check-list questionnaire in 1985, 1990, and 1995. Cocoa intake was categorized by the consumption of cocoa powder, cocoa beans, and cocoa products.

Results: One third of the men had not consumed cocoa at baseline. The median cocoa intake among men was 2.1 g/d. The median cocoa intake among women was 1.1 g/d.

After adjustment, the mean systolic blood pressure in the highest quintile of cocoa intake was 1.7 mm Hg lower (95% confidence interval [CI], -0.7 to -2.7 mm Hg, P < .01) than in the lowest quintile. The mean diastolic blood pressure was 1.1 mm Hg lower (95% CI, -0.4 to -1.8 mm Hg, P < .01) than in the lowest quintile. During follow-up, 10,000 men died (10,000 deaths) and 10,000 women died (10,000 deaths). The age-adjusted relative risk for mortality in the highest quintile was 0.92 (95% CI, 0.82 to 1.02, P = .08) for men and 0.92 (95% CI, 0.82 to 1.02, P = .08) for women. The age-adjusted relative risk for mortality in the highest quintile was 0.92 (95% CI, 0.82 to 1.02, P = .08) for men and 0.92 (95% CI, 0.82 to 1.02, P = .08) for women.

Conclusion: In a cohort of elderly men, cocoa intake is inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality.

Arch Intern Med. 2006;166:811-817.

"This study suggests that higher cocoa intake is associated with reduced blood pressure and reduced risk of cardiovascular and all-cause mortality in elderly men."

Arch Intern Med. 2006;166:811-817.



Cocoa increases blood flow to brain

- Cocoa flavanols have been directly linked with improved cerebral blood flow.
- Thirteen men and women (avg age 72) consumed flavanol-rich cocoa and a 21 participants consumed a flavonoid-poor cocoa product.
- Ultrasound methods were used to analyze blood flow to the brain.
- The 13 participants who consumed flavanol-rich cocoa for 2 weeks (900 mg flavanols daily) achieved a 10% increase in cerebral blood flow.

Sorond FA, Lipsitz LA, Hollenberg NK, Fisher ND. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. *Neuropsychiatric Disease and Treatment*. 2008; 4: 433-440.



Cocoa increases blood flow to brain

- Harvard researchers report that cocoa flavanols improve brain flow in older adults. It has been speculated that increasing blood flow to the brain could help reduce cognitive decline in aging individuals. The current finding could be helpful in improving cognitive function among individuals suffering from conditions in which brain flow is impaired, such as stroke and dementia.

Sorond FA, Lipsitz LA, Hollenberg NK, Fisher NDL. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. *Neuropsychiatric Disease and Treatment*. 2008; 4: 433-440.

ORIGINAL RESEARCH

Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans

Farzaneh A. Sorond^{1,2}
Lewis A. Lipsitz^{1,2}
Norman K. Hollenberg^{1,3}
Nancy DL Fisher²

¹Department of Neurology, Stroke Disease Institute for Aging Research, Harvard School of Public Health, Boston, MA; ²Department of Medicine, Tufts Medical Center, Boston, MA; ³Department of Physiology, Tufts Medical Center, Boston, MA

Background and Purpose: Cerebral ischemia is a common, cerebral condition accompanied by cognitive decline. Recent reports on the vascular health benefits of flavanol-containing foods suggest a promising approach to the treatment of cerebral ischemia. The study was designed to investigate the effects of flavanol-rich cocoa (FRC) consumption on cerebral blood flow in older healthy volunteers.

Methods: We used transcranial Doppler (TCD) ultrasonography to measure mean blood flow velocity (MBFV) in the middle cerebral artery (MCA) in thirty-four healthy elderly volunteers (72 ± 9 years) in response to the regular intake of FRC or flavanol-poor cocoa (FPC).

Results: In response to two weeks of FRC intake, MBFV increased by 8% ± 4% at one week ($p = 0.01$) and 10% ± 4% ($p = 0.001$) at two weeks. In response to one week of eating, significantly more subjects in the FRC group had an increase in their MBFV ($p = 0.05$).

The researchers tested the effects of beverage containing high amounts of cocoa flavanols on participants between the ages of 59 and 83. The investigators found an 8 percent increase in the participants' brain blood flow following one week of consuming the beverage, and a 10% increase after 2 weeks.

Neuropsychiatric Disease and Treatment, 2008; 4(2), 433-430.

foods and beverages rich in flavanols is associated with a decreased risk of cardiac and cerebrovascular mortality (Kieckhefer et al 1996; Conneally 2000; Gullu 2002; Yessierli 2002). In the context of human cognition, research occurs in neurocognitive research.



Cocoa increases blood flow to brain

Table 2 Nutritional content of the study beverages

	Flavanol-rich cocoa (FRC)	Flavanol-poor cocoa (FPC)
Cocoa flavanols, mg	451.1	18.2
Calories	118.1	117.2
Total fat, g	1.4	1.5
Cholesterol, mg	4.4	4.9
Total carbohydrates, g	17.1	16.5
Dietary fiber, g	3.0	3.9
Sugars, g	9.4	9.2
Protein, g	9.4	9.4
Caffeine, mg	18.3	21.2
Theobromine, mg	336.5	327.4
Sodium, mg	105.1	155.0
Potassium, mg	530.1	644.8
Calcium, mg	243.7	241.2
Iron, mg	1.9	2.9
Phosphorous, mg	280.2	265.4
Magnesium, mg	85.9	78.4
Zinc, mg	1.6	1.6
Copper, mg	0.4	0.4
Manganese, mg	0.6	0.6

Plasma antioxidants from chocolate

Dark chocolate may offer its consumers health benefits the milk variety cannot match.



Figure 1 Stack of benefits? Unlike its milky counterpart, dark chocolate may provide more than just a treat for the taste buds.

Plasma antioxidants from chocolate

Dark chocolate may offer its consumers health benefits the milk variety cannot match.

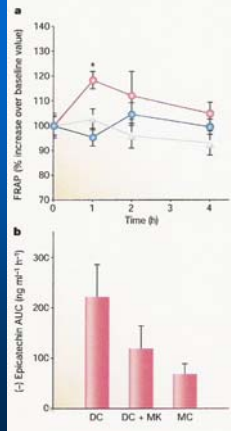
Nature 2003
Aug
28; 424(6952):
1013.
Serafini M, Bugianesi
R, Maiani G, Valtuena
S, De Santis S,
Crozier A.



Figure 1 Stack of benefits? Unlike its milky counterpart, dark chocolate may provide more than just a treat for the taste buds.

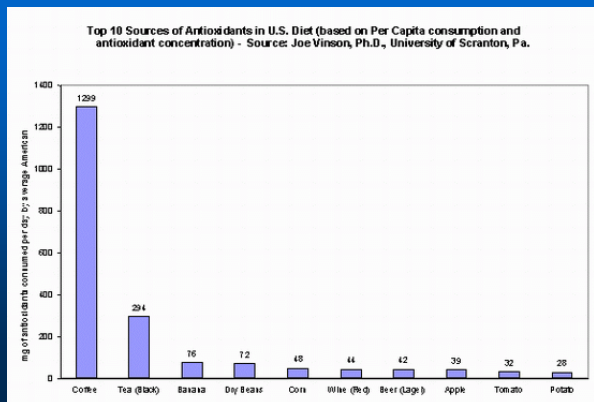
Effects of ingesting 100g dark chocolate (DC), 100 g dark chocolate with 200 ml milk (DC+ MK), or 200 g milk chocolate on total antioxidant capacity and epicatechin content of human plasma.

(red=DC; blue DC+MK; grey=MC. FRAP= ferric-reducing antioxidant potential was used to measure antioxidant capacity. Asterisk = $P < 0.001$)



- **Coffee Is No. 1 Source of Antioxidants** (*Fox News*)
- **That daily cup of coffee can help prevent cancer, researchers find** (*Detroit Free Press*)
- **'Joe' gives free radicals a jolt** (*Newsday*)
- **Grounds for Health** (*San Jose Mercury News*)
- **Study says coffee delivers more health benefits than fruit and veg** (*Scotsman*)
- **What apples? A cup of coffee a day keeps the doctor away** (*Newwindpress.com – India*)
- **Coffee found to be high in health-giving antioxidants** (*The Independent – UK*)

Coffee came out on top, on the combined basis of both antioxidants per serving size and frequency of consumption



- Chlorogenic acid and caffeic acid are strong antioxidants *in vitro*.
- The amount of chlorogenic acid or caffeic acid available to act as an antioxidant *in vivo* will depend on absorption from the gut. It has recently been demonstrated that humans absorb about 33% of ingested chlorogenic acid and about 95% of ingested caffeic acid.
- Coffee beans are one of the richest dietary sources of chlorogenic acid and for many consumers this will be their major dietary source.
- It has been estimated that coffee drinkers might ingest as much as 1 g per day of chlorogenic acid and 500 mg per day of caffeic acid.
- Coffee could supply as much as 70% of the total making it far and away the most important dietary source of this group of antioxidants.

- The roasting of coffee beans dramatically increases their total antioxidant activity. A roasting time of 10 minutes (medium-dark roast) was found to produce coffee with optimal oxygen scavenging and chain breaking activities *in vitro*
- It can be concluded that coffee possesses greater in-vitro antioxidant activity than other beverages, due in part to intrinsic compounds such as chlorogenic acid, in part to compounds formed during roasting such as melanoidins and in part to as yet unidentified compounds.

Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study¹⁻⁴

Lene Frost Andersen, David R Jacobs Jr, Monica H Carlsen, and Børge Blomhoff

ABSTRACT
Background: Coffee is the major source of dietary antioxidants. The association between coffee consumption and risk of death from diseases associated with inflammatory or oxidative stress has not been studied.

Objectives: We studied the relation of coffee drinking with total mortality and mortality attributed to cardiovascular diseases, cancer, and other diseases with a major inflammatory component. Design: A total of 14 174 postmenopausal women aged 55-84 y at baseline were followed for 17 y. After controlling for cardiovascular disease, cancer, diabetes, coffee, and liver alcohol, at baseline, 12 772 participants remained, resulting in 14 125 person-years of follow-up and 1247 deaths. The major outcome measure was disease-specific mortality.

Results: In the fully adjusted model, similar to the relation of coffee intake to total mortality, the hazard ratio for death attributed to cardiovascular disease was 0.76 (95% CI 0.64, 0.91) for consumption of 1-3 cups/d, 0.61 (95% CI 0.46, 0.81) for 4-5 cups/d, and 0.67 (95% CI 0.49, 0.90) for ≥6 cups/d. The hazard ratio for death from other inflammatory diseases was 0.77 (95% CI 0.59, 0.99) for consumption of 1-3 cups/d, 0.67 (95% CI 0.50, 0.90) for 4-5 cups/d, and 0.69 (95% CI 0.49, 0.94) for ≥6 cups/d.

Conclusion: Consumption of coffee, a major source of dietary antioxidants, may reduce inflammation and thereby reduce the risk of cardiovascular and other inflammatory diseases, as previously

mediates the respiratory burst (3, 6). Its primary product, superoxide (O₂⁻), can lead to other reactive oxygen species. Superoxide is also formed by the mitochondrial electron transport chain during inflammation (7). Furthermore, induction of nitric oxide synthase will increase the production of the NO radical and subsequent reactive nitrogen species (8, 9). Antioxidant enzymes (reactive oxygen species or reactive nitrogen species decomposition catalysts or selective antioxidant enzymes) may have been down-regulated or inactivated during inflammation (10, 11).

We recently studied the total antioxidant capacity of several biological fluids (12, 13) and were surprised to learn that in a healthy Norwegian population coffee contributes 10-15% of total dietary antioxidant capacity. In the light of the other analysis of health (14). Several different compounds contribute to coffee's antioxidant capacity: polyphenols (15), polyphenols, including flavonoids (16), volatile organic compounds (16), and heterocyclic compounds, including pyridines, nucleotides, thiazoles, thiophenes, imidazoles, and pyrazoles (16, 17). Many of these are efficiently absorbed, and plasma antioxidant capacity after oral intake (18, 19). Epidemiologic studies have found that coffee is associated with reduced frequency of oxidative stress (20). Additional studies in coffee in relation to inflammatory diseases where chronic coffee and effectively reduce the risk to cause the activation of the transcription factor NF-κB in the

Consumption of coffee, a major source of dietary antioxidants, may inhibit inflammation and thereby reduce the risk of cardiovascular and other inflammatory diseases in postmenopausal women.

Am J Clin Nutr, 2006, 83: 1039-46.

Coffee May Protect Against Colon Cancer

Journal of Agricultural and Food Chemistry, Nov. 5, 2003



Researchers say they've found a highly active anti-cancer compound, called methylpyridinium, in coffee that may prevent colon cancer. In studies with animals, this potent antioxidant compound appears to boost the activity of phase II enzymes, which are believed to protect against colon cancer.

- Espresso-type coffee contains about two to three times more of the anticancer compound than a medium roast coffee.
- Methylpyridinium is found almost exclusively in coffee and coffee products. It's not present in raw coffee beans. It's formed during the roasting process from its chemical precursor, trigonellin.
- The anticancer compound is present in both caffeinated and decaffeinated coffee and is even found in instant coffee.

Journal of Agricultural and Food Chemistry, Nov. 5, 2003

Effects of coffee consumption on glucose tolerance, serum glucose and insulin levels--a cross-sectional analysis

- Coffee consumption showed positive effects on glucose tolerance, and on glucose and insulin levels.
- Coffee consumption was significantly and inversely associated with fasting glucose, two-hour plasma glucose, and fasting insulin, in both men and women.
- Additionally, coffee consumption was significantly and inversely associated with impaired fasting glucose, impaired glucose regulation, and hyperinsulinemia, in both men and women, and inversely associated with isolated impaired glucose tolerance in women.
- Thus, this cross-sectional analysis suggests that the consumption of coffee exerts positive effects on glucose tolerance, and glucose and insulin levels.

Horm Metab Res., 2006; 38(1): 38-43

Coffee consumption and Type 2 Diabetes - An Extensive Review

Samuel Balle^{1,2}, Gang Hu^{1,2}, Jaakko Tuomilehto^{1,2}

¹Department of Health Promotion and Disease Prevention, National Public Health Institute, Helsinki, Finland

²Department of Public Health, University of Helsinki, Helsinki, Finland

³South Metropolitan Central Hospital, Dandenong, Victoria

Received 21 August 2005, Accepted 17 September 2005

Abstract: Coffee is a complex mixture of potentially active chemicals. Numerous biological processes of potential pathogenesis, development and progression of type 2 diabetes have been studied, including insulin resistance, beta cell dysfunction, and insulin sensitivity. Habitual coffee consumption may play a protective role in the development of type 2 diabetes. Despite the fact that the clinical trials of the effect of coffee on decreasing insulin sensitivity, long-term prospective studies revealed that coffee may improve fasting glucose, glucose tolerance and insulin sensitivity, as well as the most recent publications indicate coffee consumption has a lower total and cardiovascular mortality rate among diabetic subjects.

Keywords: Coffee • Type 2 Diabetes • Disease Prevention

1. Introduction

is traditional endogenous diet to a typical western diet.

Long term prospective studies revealed that coffee may improve fasting glucose, glucose tolerance and insulin sensitivity. Habitual coffee drinkers have a lower total and cardiovascular mortality among diabetic subjects.

© 2006 Springer

Springer

Does Coffee Consumption Reduce the Risk of Type 2 Diabetes in Individuals With Impaired Glucose?

De-Ann S. Berry, PhD
University of Wisconsin, Madison, WI
David R. Jacobs Jr, PhD
University of Wisconsin, Madison, WI

OBJECTIVE: The purpose of this study was to investigate the association between coffee consumption and the risk of type 2 diabetes in individuals with impaired glucose tolerance.

RESEARCH DESIGN AND METHODS: In this prospective study, 100 individuals with impaired glucose tolerance were followed for 10 years. Coffee consumption was assessed at baseline and during follow-up. Anthropometric, metabolic, and lifestyle factors were also assessed.

RESULTS: The incidence of type 2 diabetes was 10.5% over 10 years. Coffee consumption was inversely associated with the risk of type 2 diabetes in individuals with impaired glucose tolerance. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of caffeinated coffee on the risk of type 2 diabetes in individuals with impaired glucose tolerance, independent of multiple plausible confounders.

Additionally, we consider coffee consumption in relation to the risk of type 2 diabetes in individuals with normal glucose tolerance. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

RESEARCH DESIGN AND METHODS: In this prospective study, 100 individuals with normal glucose tolerance were followed for 10 years. Coffee consumption was assessed at baseline and during follow-up. Anthropometric, metabolic, and lifestyle factors were also assessed.

RESULTS: The incidence of type 2 diabetes was 10.5% over 10 years. Coffee consumption was inversely associated with the risk of type 2 diabetes in individuals with normal glucose tolerance. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of caffeinated coffee on the risk of type 2 diabetes in individuals with normal glucose tolerance, independent of multiple plausible confounders.

This study confirms a striking protective effect of caffeinated coffee by reducing incidence of diabetes independent of multiple plausible confounders.

Background: Individuals with impaired glucose tolerance are at a higher risk of developing type 2 diabetes. Coffee consumption has been associated with a lower risk of type 2 diabetes in individuals with normal glucose tolerance.

OBJECTIVE: The purpose of this study was to investigate the association between coffee consumption and the risk of type 2 diabetes in individuals with impaired glucose tolerance.

RESEARCH DESIGN AND METHODS: In this prospective study, 100 individuals with impaired glucose tolerance were followed for 10 years. Coffee consumption was assessed at baseline and during follow-up. Anthropometric, metabolic, and lifestyle factors were also assessed.

RESULTS: The incidence of type 2 diabetes was 10.5% over 10 years. Coffee consumption was inversely associated with the risk of type 2 diabetes in individuals with impaired glucose tolerance. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of caffeinated coffee on the risk of type 2 diabetes in individuals with impaired glucose tolerance, independent of multiple plausible confounders.

Background: Individuals with impaired glucose tolerance are at a higher risk of developing type 2 diabetes. Coffee consumption has been associated with a lower risk of type 2 diabetes in individuals with normal glucose tolerance.

OBJECTIVE: The purpose of this study was to investigate the association between coffee consumption and the risk of type 2 diabetes in individuals with impaired glucose tolerance.

RESEARCH DESIGN AND METHODS: In this prospective study, 100 individuals with impaired glucose tolerance were followed for 10 years. Coffee consumption was assessed at baseline and during follow-up. Anthropometric, metabolic, and lifestyle factors were also assessed.

RESULTS: The incidence of type 2 diabetes was 10.5% over 10 years. Coffee consumption was inversely associated with the risk of type 2 diabetes in individuals with impaired glucose tolerance. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of caffeinated coffee on the risk of type 2 diabetes in individuals with impaired glucose tolerance, independent of multiple plausible confounders.

PAPER

Coffee, tea and diabetes: the role of weight loss and caffeine

J.A. Greenberg¹, K.V. Assari², R. Schell³ and C.N. Boushey⁴

¹Department of Health and Nutrition Sciences, Brooklyn College of the City University of New York, Brooklyn, NY, USA; ²Energy Metabolism Core Laboratory, New York University School of Medicine, New York, NY, USA; ³Department of Medicine, Institute of Human Nutrition, Columbia University Medical Center, New York, NY, USA

OBJECTIVE: To assess the effect of weight change on the relationship between coffee and tea consumption and diabetes risk.

DESIGN: Prospective cohort study, using data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (FHS).

RESULTS: In a population of 10,000 subjects aged 40-60 years with no reported history of diabetes, coffee and tea consumption were inversely associated with the risk of developing type 2 diabetes. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of coffee and tea consumption on the risk of type 2 diabetes, independent of multiple plausible confounders.

Prospective cohort study from NHANES I found a negative association between diabetes risk and consumption of ground coffee and regular tea in those under 60y.o. who had lost weight.

Background: Individuals with impaired glucose tolerance are at a higher risk of developing type 2 diabetes. Coffee consumption has been associated with a lower risk of type 2 diabetes in individuals with normal glucose tolerance.

OBJECTIVE: The purpose of this study was to investigate the association between coffee consumption and the risk of type 2 diabetes in individuals with impaired glucose tolerance.

RESEARCH DESIGN AND METHODS: In this prospective study, 100 individuals with impaired glucose tolerance were followed for 10 years. Coffee consumption was assessed at baseline and during follow-up. Anthropometric, metabolic, and lifestyle factors were also assessed.

RESULTS: The incidence of type 2 diabetes was 10.5% over 10 years. Coffee consumption was inversely associated with the risk of type 2 diabetes in individuals with impaired glucose tolerance. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of caffeinated coffee on the risk of type 2 diabetes in individuals with impaired glucose tolerance, independent of multiple plausible confounders.

Caffeinated beverage intake and the risk of heart disease mortality in the elderly: a prospective analysis^{1,2}

James A. Greenberg, Christopher C. Dwyer, Rosemarie Schell, Rosemarie Kukulski, Susan Kukulski, and John Kukulski

¹Department of Health and Nutrition Sciences, Brooklyn College of the City University of New York, Brooklyn, NY, USA; ²Energy Metabolism Core Laboratory, New York University School of Medicine, New York, NY, USA; ³Department of Medicine, Institute of Human Nutrition, Columbia University Medical Center, New York, NY, USA

OBJECTIVE: To assess the effect of weight change on the relationship between coffee and tea consumption and diabetes risk.

DESIGN: Prospective cohort study, using data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (FHS).

RESULTS: In a population of 10,000 subjects aged 40-60 years with no reported history of diabetes, coffee and tea consumption were inversely associated with the risk of developing type 2 diabetes. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of coffee and tea consumption on the risk of type 2 diabetes, independent of multiple plausible confounders.

Higher caffeinated beverage consumption in the elderly (aged 65 years or over) without HBP experienced a lower risk of heart disease mortality than did those who reported a lower intake of caffeinated beverages.

Background: Individuals with impaired glucose tolerance are at a higher risk of developing type 2 diabetes. Coffee consumption has been associated with a lower risk of type 2 diabetes in individuals with normal glucose tolerance.

OBJECTIVE: The purpose of this study was to investigate the association between coffee consumption and the risk of type 2 diabetes in individuals with impaired glucose tolerance.

RESEARCH DESIGN AND METHODS: In this prospective study, 100 individuals with impaired glucose tolerance were followed for 10 years. Coffee consumption was assessed at baseline and during follow-up. Anthropometric, metabolic, and lifestyle factors were also assessed.

RESULTS: The incidence of type 2 diabetes was 10.5% over 10 years. Coffee consumption was inversely associated with the risk of type 2 diabetes in individuals with impaired glucose tolerance. The association remained significant after adjustment for age, sex, BMI, waist circumference, and other factors.

CONCLUSIONS: This study confirms a striking protective effect of caffeinated coffee on the risk of type 2 diabetes in individuals with impaired glucose tolerance, independent of multiple plausible confounders.

Caffeinated Coffee Consumption, Cardiovascular Disease, and Heart Valve Disease in the Elderly (from the Framingham Study)

James A. Gidding, PhD^{1,2}, Grant Chew, MD³, and Rex C. Ziegler, MD⁴

The relation between caffeinated coffee consumption and heart disease morbidity and mortality is of great interest given the extensive use of this beverage. A recent prospective update of the only found a strong protective association to elderly subjects without moderate to severe hypertension in the WHAHE. To test the association in the Framingham Heart Study population, in which cardiovascular risk factors and health behaviors were carefully documented. Cox regression analyses were conducted for 1,034 subjects aged 65 to 94 years at study entry. There were 100 deaths from cardiovascular disease and 110 from coronary heart disease (CHD) during 24.3 years of follow-up. A significant negative association between caffeinated coffee consumption and CHD mortality was observed for subjects with stroke without previous (BP <160 mm Hg and diastolic BP <95 mm Hg). The decrease in risk of CHD mortality for any caffeinated coffee versus none was 45% (95% confidence interval 1 to 94). This decrease did not appear to be related primarily to an inverse prospective relation between caffeinated coffee consumption and the development or progression of heart valve disease. The decrease in risk of heart valve disease for subjects with stroke, BP <160 mm Hg and diastolic BP <95 mm Hg for any caffeinated coffee versus none was 45% (95% confidence interval 4 to 86). In conclusion, caffeinated coffee consumption was associated with lower risk of CHD mortality and heart valve disease development or progression in older Framingham subjects without moderate or severe hypertension. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102:1062-1068).

There is conflicting evidence concerning the relation of caffeinated coffee consumption to the risk of cardiovascular disease (1-5). A meta-analysis of the prospective cohort studies (6,7) found a protective association between coffee consumption and CHD mortality in subjects without moderate or severe hypertension. Physical exercise, smoking, alcohol consumption, and laboratory tests have been conducted every 2 years since 1960. The cohort has also been followed up to 2006.

Caffeinated coffee consumption was associated with lower risk of CHD mortality and heart valve disease development or progression in older Framingham subjects without moderate or severe hypertension.

From the Department of Medicine, Harvard Medical School, Boston, MA (Dr. Gidding); Department of Medicine, Harvard Medical School, Boston, MA (Dr. Chew); Department of Medicine, Harvard Medical School, Boston, MA (Dr. Ziegler); and the Department of Medicine, Harvard Medical School, Boston, MA (Dr. Ziegler). Manuscript received 10/10/07; revised manuscript received 11/10/07; accepted 12/10/07. Address correspondence and reprint requests to Dr. Gidding at the Department of Medicine, Harvard Medical School, Boston, MA 02115.

Caffeine May Provide Protection from Parkinson's Disease

- As part of a long-term study of the Honolulu Heart Program, a team of researchers examined the relationship between coffee intake and the incidence of Parkinson's disease.
- Researchers studied 8,004 Japanese-American men over a 30 year period. Of these men, 102 developed Parkinson's disease.
- The incidence of Parkinson's disease was found to be lower in those who drank coffee. In fact, the men who drank the most coffee were the *least likely* to get Parkinson's disease. Men who did not drink any coffee were five times more likely to exhibit symptoms of Parkinson's disease than men who drank more than 28 ounces of coffee each day. Consumption of caffeine from other sources such as green tea, black tea, chocolate and soda was also associated with a lower risk of Parkinson's disease.
- Caffeine belongs to the **xanthine** chemical group. A naturally occurring xanthine in the brain called adenosine is used as a neurotransmitter at some synapses. When adenosine receptors are blocked, levels of the neurotransmitter dopamine increase. Caffeine may protect against Parkinson's disease by blocking adenosine receptors, thus increasing the amount of dopamine in the brain.