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Coffee and Health: A Review of Recent Human Research JANE V. HIGDON and BALZ FREI

Critical Reviews in Food Science and Nutrition, 46:101–123 (2006)

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ISSN: 1040-8398

DOI: 10.1080/10408390500400009

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Coffee is a complex mixture of chemicals that provides significant amounts of chlorogenic acid and caffeine. Unfiltered coffee is a significant source of cafestol and kahweol, which are diterpenes that have been implicated in the cholesterolraising effects of coffee. The results of epidemiological research suggest that coffee consumption may help prevent several chronic diseases, including type 2 diabetes mellitus, Parkinson's disease and liver disease (cirrhosis and hepatocellular carcinoma). Most prospective cohort studies have not found coffee consumption to be associated with significantly increased cardiovascular disease risk. However, coffee consumption is associated with increases in several cardiovascular disease risk factors, including blood pressure and plasma homocysteine. At present, there is little evidence that coffee consumption increases the risk of cancer. For adults consuming moderate amounts of coffee (3–4 cups/d providing 300–400 mg/d of caffeine), there is little evidence of health risks and some evidence of health benefits. However, some groups, including people with hypertension, children, adolescents, and the elderly, may be more vulnerable to the adverse effects of caffeine.

In addition, currently available evidence suggests that it may be prudent for pregnant women to limit coffee consumption to 3 cups/d providing no more than 300 mg/d of caffeine to exclude any increased probability of spontaneous abortion or impaired fetal growth.

INTRODUCTION

Coffee, an infusion of ground, roasted coffee beans, is reported to be among the most widely consumed beverages in the world. Although coffee is lauded for its aroma and flavor, its caffeine content likely plays a role in its popularity. In fact, coffee is a complex chemical mixture reported to contain more than a thousand different chemicals, including carbohydrates, lipids, nitrogenous compounds, vitamins, minerals, alkaloids and phenolic compounds.¹ The majority of studies on the health effects of coffee consumption in humans are observational. Concerns about potential health risks of coffee and caffeine consumption raised by epidemiological research in the past were likely exacerbated by associations between high intakes of coffee and unhealthy behaviors, such as cigarette smoking and physical inactivity.² More recently, coffee consumption has been associated with reductions in the risk of several chronic diseases.^{3–5}

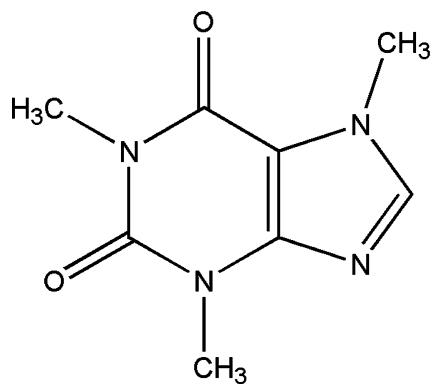
However, in many cases, conflicting findings and concerns about methodological issues have made it difficult for health professionals and the public to interpret the available evidence on coffee consumption and health. The purpose of this article is to review and interpret relatively recent research on the benefits and risks of coffee consumption in humans.

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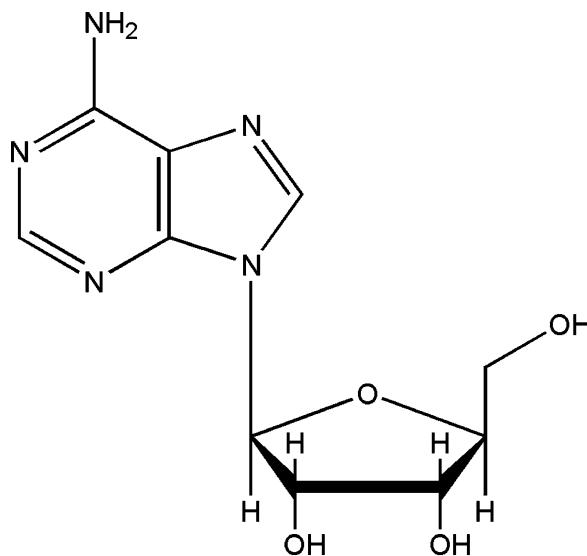
**COMPOUNDS IN COFFEE THAT MAY AFFECT
HUMAN HEALTH**

Caffeine

Caffeine (1,3,7-trimethylxanthine) is a purine alkaloid that occurs naturally in coffee beans (Figure 1). At intake levels associated with coffee consumption, caffeine appears to exert most of its biological effects through the antagonism of the A1 and A2A subtypes of the adenosine receptor.⁶ Adenosine (Figure 1) is an endogenous neuromodulator with mostly inhibitory effects, and adenosine antagonism by caffeine results in effects that are generally stimulatory. Some physiological effects associated with caffeine administration include central nervous system stimulation, acute elevation of blood pressure, increased metabolic rate, and diuresis.⁷ Caffeine is rapidly and almost completely absorbed in the stomach and small intestine and distributed to all tissues, including the brain. Caffeine metabolism occurs primarily in the liver, where the activity of the cytochrome



Caffeine



Adenosine

Figure 1 Chemical structures of caffeine and adenosine.

P450 isoform CYP1A2 accounts for almost 95% of the primary metabolism of caffeine. CYP1A2-catalyzed 3-demethylation of caffeine results in the formation of 1,7-dimethylxanthine (paraxanthine) (Figure 2). Paraxanthine may be demethylated by CYP1A2 to form 1-methylxanthine, which may be oxidized to 1-methyluric acid by xanthine oxidase. Paraxanthine may also be hydroxylated by CYP2A6 to form 1,7-dimethyluric acid, or acetylated by *N*-acetyltransferase 2 (NAT2) to form 5-acetylamino-6-formylamino-3-methyluracil, an unstable compound that may be deacetylated nonenzymatically to form 5-acetylamino-6-amino-3-methyluracil (Figure 2).^{8,9} Caffeine concentrations in coffee beverages can be quite variable.

A standard cup of coffee is often assumed to provide 100 mg of caffeine, but a recent analysis of 14 different specialty coffees purchased at coffee shops in the US found that the amount of caffeine in 8 oz (≈240 ml) of brewed coffee ranged from 72–130 mg.¹⁰ Caffeine in espresso coffees ranged from 58–76 mg in a single shot. Interestingly, the caffeine content of the same type of coffee purchased from the same store on six separate days varied from 130 to 282 mg per 8-oz serving.

Cafestol and Kahweol

Coffee consumption has been associated with higher serum total and LDL cholesterol concentrations in some observational studies but not others.¹¹ The observation that the positive association between coffee consumption and serum cholesterol was more consistent in Scandinavia, where boiled coffee was popular at the time, than in other European countries and the US, where filtered coffee was more popular, led to the hypothesis that the brewing method was critical to the cholesterol-raising effect of coffee.¹² A meta-analysis of 14 randomized controlled trials examining the effect of coffee consumption on serum cholesterol concentrations found that the consumption of boiled coffee dose-dependently increased serum total and LDL cholesterol concentrations, while the consumption of filtered coffee resulted in very little increase in serum cholesterol.¹³

The cholesterol-raising factors, first isolated in coffee oil, were later found to be the diterpenes, cafestol and kahweol (Figure 3).¹² These diterpenes are extracted from ground coffee during brewing, but are mostly removed from coffee by paper filters. Scandinavian boiled coffee, Turkish coffee, and French press (cafetiere) coffee contain relatively high levels of cafestol and kahweol (6–12 mg/cup), while filtered coffee, percolated coffee, and instant coffee contain low levels of cafestol and kahweol (0.2–0.6 mg/cup).^{14,15} Although diterpene concentrations are relatively high in espresso coffee, the small serving size makes it an intermediate source of cafestol and kahweol (4 mg/cup). Studies in ileostomy patients indicate that about 70% of the cafestol and kahweol in unfiltered coffee is absorbed intestinally.¹⁶ The mechanisms for the effects of these diterpenes on lipoprotein metabolism are not yet clear, but consumption of cafestol and kahweol in French press coffee has been found to result in persistent increases in cholesterol ester transfer protein (CETP) activity in humans, which may contribute to increases in LDL cholesterol.¹⁷ CETP transfers cholesterol esters from HDL to the apolipoprotein B-containing lipoproteins, LDL and VLDL.

Chlorogenic Acid

Chlorogenic acids are a family of esters formed between quinic and *trans*-cinnamic acids, which are an important group of dietary phenols (Figure 4).¹⁸ The most common individual chlorogenic acid is 5-O-caffeoquinic acid, which is still often called chlorogenic acid. For those who drink it, coffee represents the richest dietary source of chlorogenic acids and cinnamic acids (caffeic acid). The chlorogenic acid content of a 200 ml (7-oz) cup of coffee has been reported to range from 70–350 mg, which would provide about 35–175 mg of caffeic acid.¹⁸ Studies in colostomy patients indicate that about 33% of ingested chlorogenic acid and 95% of caffeic acid are absorbed intestinally.¹⁹

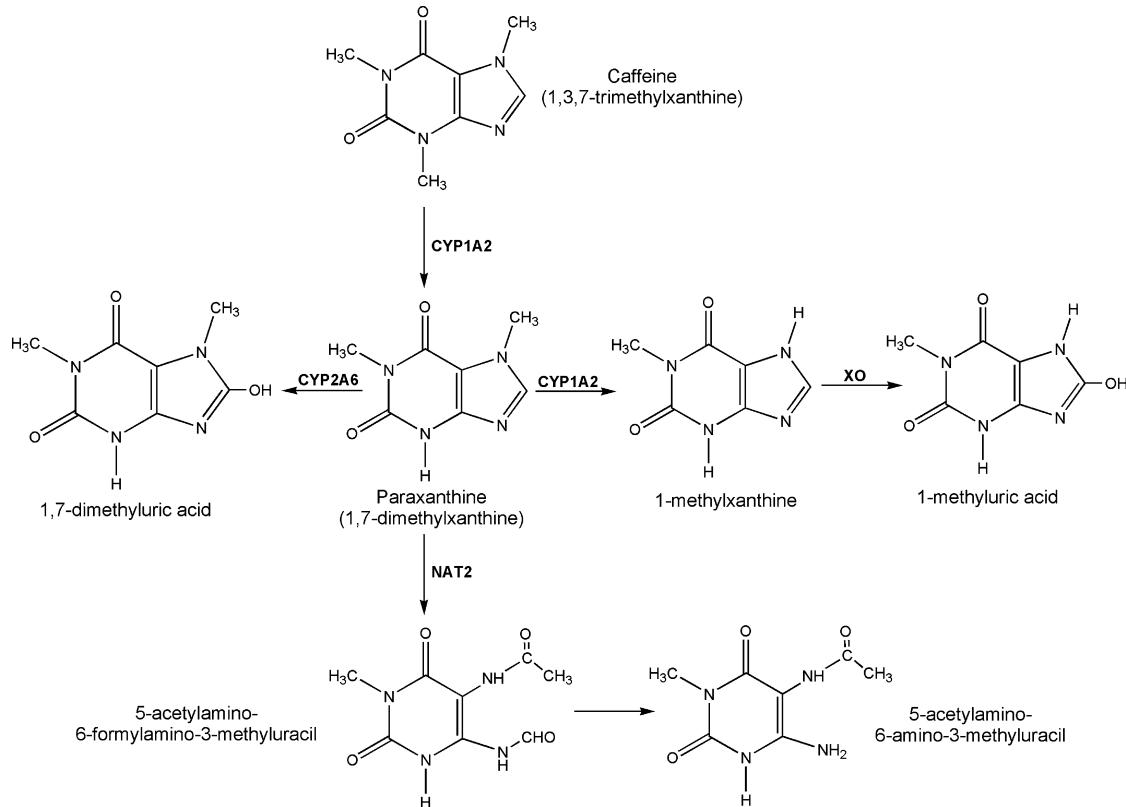


Figure 2 Major pathways in caffeine metabolism. Abbreviations: CYP1A2, cytochrome P450 1A2; CYP2A6, cytochrome P450 2A6; NAT2, *N*-acetyl transferase 2; XO, xanthine oxidase.

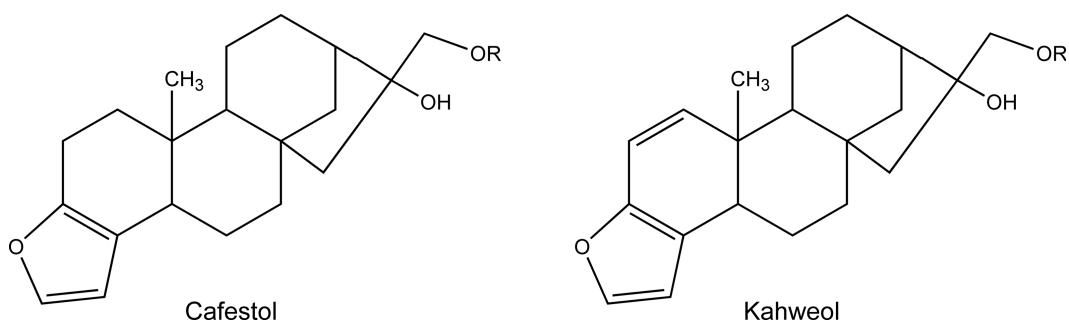
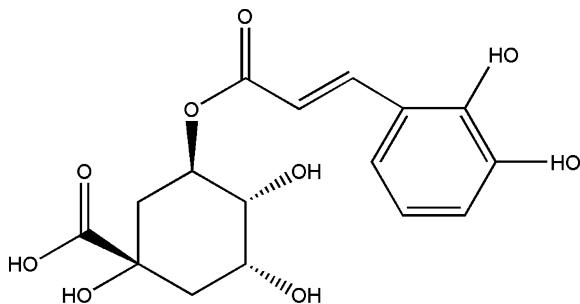


Figure 3 Chemical structures of cafestol and kahweol, diterpenes in coffee with cholesterol-raising effects. R= H: free diterpene; R= fatty acid: diterpene ester.

Thus, about two-thirds of ingested chlorogenic acid reaches the colon where it may be metabolized by the colonic microflora.²⁰

In the colon, chlorogenic acid is likely hydrolyzed to caffeic acid and quinic acid. The presence of bacterial metabolites of chlorogenic acid in the urine suggests that they are absorbed in the colon. Although chlorogenic acid and caffeic acid have antioxidant activity *in vitro*,²¹ it is unclear how much antioxidant activity they contribute *in vivo* because they are extensively metabolized, and the metabolites often have lower antioxidant activity than the parent compounds.



Chlorogenic Acid

Figure 4 Chemical structure of 5-O-cafeoylquinic acid (chlorogenic acid).

Micronutrients

Several micronutrients found in coffee, including magnesium, potassium, niacin, and vitamin E, could contribute to the observed health effects of coffee consumption. According to the USDA Nutrient database, 8 oz (≈240 ml) of brewed coffee provide 7mg of magnesium and 1 oz (≈30 ml) of espresso provides 24 mg of magnesium.²² Thus, one cup of coffee could contribute 1–5% of the recommended dietary allowance (RDA) for magnesium (420 mg/d) in adult men.²³ An 8-oz cup of brewed coffee is reported to provide 116 mg of potassium and a 1-oz shot of espresso 34 mg,²² suggesting that one cup of coffee contributes only 1–2% of the adequate intake (AI) for potassium (4700 mg/d) in adults.²⁴ Trigenolline in coffee beans is demethylated to form nicotinic acid during the roasting process.²⁵ Coffee has been reported to provide 1–3 mg of nicotinic acid per cup.²⁵ Thus, one cup of coffee could contribute 6–18% of the RDA for niacin (16 mg/d) in adult men.²⁶ Coffee does not appear to be an important source of dietary vitamin E since one cup provides about 0.2 mg of α -tocopherol and 0.2 mg of γ -tocopherol,²² about 0.1% of the adult RDA for vitamin E (15 mg/d of *RRR*- α -tocopherol).²⁷

METHODOLOGICAL ISSUES IN EPIDEMIOLOGICAL RESEARCH ON COFFEE

Much of the currently available information on the health effects of coffee is derived from epidemiological research. However, the study of coffee consumption in human populations raises several issues regarding exposure classification and potential confounders that should be considered when interpreting the results of epidemiological studies of coffee consumption.

Exposure Misclassification

Coffee exposure is often assessed using food frequency questionnaires that collect information regarding the number of cups of coffee consumed daily or weekly. However, cup size may vary considerably depending on the population. One study in the US found that cup sizes used by pregnant women ranged from 2–32 oz, with 7-8-oz cups accounting for only 30% of cup sizes used.²⁸

In epidemiological studies, one cup of coffee is often assumed to provide 85–100 mg of caffeine. However, the caffeine content of different coffees can vary considerably (see above), and it is possible that people who drink many cups of coffee on a daily basis consume weaker coffee than people who drink only 1–2 cups daily. Until recently, few epidemiological studies collected information about the brewing process used to prepare coffee.

This information became important when it was discovered that cholesterol-raising compounds in coffee were largely removed by paper filters (see above).¹² Finally, individual variation in the metabolism of compounds in coffee may increase or decrease the exposure of an individual to a bioactive compound in coffee.

For example, NAT2 plays an important role in the metabolism of caffeine.⁷ A genetic polymorphism in the NAT2 gene, which results in “fast acetylators” and “slow acetylators,” is likely to affect individual exposure to caffeine metabolites (see Considerations for Future Research below). Additionally, cigarette smoking increases caffeine clearance by inducing CYP1A2 activity,²⁹ and smokers have been found to have lower plasma levels of caffeine than nonsmokers at the same level of consumption.³⁰

It is not yet known how genetic and lifestyle factors affect individual exposure to other bioactive compounds in coffee.

Confounders

A frequent criticism of epidemiological research on coffee is inadequate adjustment for confounding factors that could influence the relationship between coffee consumption and health outcomes. Cigarette smoking is often cited as a potential confounder because high intakes of coffee are frequently associated with cigarette smoking.³¹ Most analyses are adjusted for the effect of cigarette smoking. However, underreporting of a socially undesirable behavior, such as smoking, while accurately reporting a socially neutral behavior, such as coffee consumption, could lead to inadequate adjustment for the effect of smoking and overestimation of the effect of coffee consumption on a health outcome. This concern may be particularly relevant to studies of pregnant women. Other lifestyle factors may also confound associations between coffee consumption and health outcomes. For example, people who drink coffee in Scotland tend to be younger, have higher incomes, and are generally healthier than people who drink tea.³² This may not be the case in other countries. Health outcomes in consumers of regular coffee are sometimes compared to those in consumers of decaffeinated coffee in order to determine whether a health effect is related to caffeine or other compounds in coffee. However, a study of the traits of decaffeinated coffee consumers in the US found that decaffeinated coffee use was related to a history of illness in some people but to a healthy lifestyle in other people.³³ When evaluating health outcomes in decaffeinated coffee users, most epidemiological studies do not distinguish between former users

of caffeinated coffee, who may have switched to decaffeinated coffee because of a health problem, and never users who may be avoiding caffeine as part of a healthy lifestyle.

POTENTIAL HEALTH BENEFITS OF COFFEECONSUMPTION

Prevention of Type 2 Diabetes Mellitus

Epidemiological Studies

Six out of nine prospective cohort studies have found a significant inverse association between the risk of type 2 diabetes mellitus (DM) and coffee intake (Table 1).^{5,34–37} A prospective study of more than 17,000 Dutch men and women found that the risk of developing type 2 DM was 50% lower in those who consumed at least 7 cups of coffee daily compared to those who drank 2 cups or less.³⁷ In Finland, where coffee consumption is among the highest in the world, a study that followed more than 14,000 men and women for an average of 12 years found that men who drank at least 10 cups of coffee daily had a 55% lower risk of developing type 2DMthan men who drank 2 cups or less, while women who drank at least 10 cups daily had a risk of type 2 DM that was 79% lower.³⁶ In a cohort of more than 10,000 Finnish twins, those who consumed at least 7 cups of coffee daily had a 35% lower risk of type 2 DM than those who consumed 2 cups or less.³⁴ In a smaller cohort of Swedish women followed for 18 years, those who drank at least 3 cups of coffee daily had a risk of type 2 DMthat was about 50% lower than the risk for those who consumed less than 2 cups daily.³⁵ The two largest prospective cohort studies to examine the relationship between coffee consumption and type 2 DM were the Health Professionals Follow-up Study (41,934 men) and the Nurses' Health Study (84,276 women) in the US.⁵ Men who drank at least 6 cups of coffee daily had a 54% lower risk of developing type 2 DM than men who did not drink coffee, and women who drank at least 6 cups of coffee daily had a 29% lower risk than women who did not drink coffee. In both cohorts, higher caffeine intakes were also associated with significant risk reductions. A more modest inverse association between decaffeinated coffee consumption and the risk of type 2 DM was also observed in both men and women, suggesting that compounds other than caffeine may have protective effects. In contrast, tea consumption was not associated with type 2 DM risk in the Dutch³⁷ or American cohorts.⁵

Not all prospective cohort studies have observed significant inverse associations between coffee consumption and type 2DM risk. In an earlier Finnish study that enrolled more than 19,000 men and women between 1973 and 1977, consumption of as much as 7 cups of coffee daily was not associated with the risk of type 2DMafter an average of 14 years of follow-up.³⁸ The investigators hypothesized that the difference in findings between the two Finnish cohorts^{35,37} may have been due to the fact that boiled coffeewas more commonly consumed than filtered coffee at the start of the earlier study. Although the later Finnish study found that consumption of either boiled coffee or filtered coffee was associated with a significant reduction in type 2 DM risk, men who consumed boiled coffee were almost three times as likely to report developing type 2 DM than men who consumed filtered coffee.³⁶ Prospective studies in two smaller cohorts did not observe significant associations between coffee consumption and type 2 DM diagnosed by oral glucose tolerance testing (OGTT) instead of self-report.^{39,40} In a Dutch cohort, coffee consumption as high as 7 cups/d was not associated with a statistically significant reduction in the risk of type 2 DM after 6 years of follow-up, but a significant inverse association between coffee consumption and the risk of impaired glucose tolerance was observed.⁴⁰ A prospective study of Pima Indians in theUSfound no association between coffee consumption and the risk of type 2 DM, despite the large number of cases that developed in this high-risk cohort over the 11-year follow-up period.³⁹

It should be noted that coffee consumption among the Pima Indians was relatively low compared to coffee consumption in cohorts where significant inverse associations were observed. Recently, a systematic review of nine prospective cohort studies, including more than 193,000 men and women, found that the risk of type 2 DM was 35% lower in those who consumed at least 6 cups of coffee daily and 28% lower in those who consumed between 4–6 cups/d compared to those who consumed less than 2 cups/d.⁴¹

Glucose Tolerance and Insulin Sensitivity

Acute caffeine administration has been found to impair glucose tolerance and to decrease insulin sensitivity in a number of controlled clinical trials.^{42–45} Several randomized controlled trials have examined the effect of coffee consumption for 2–4 weeks on serum glucose and insulin levels. When healthy volunteers who usually consumed an average of 560 mg/d of caffeine from coffee or tea consumed only decaffeinated coffee for 14 days, average fasting blood glucose levels decreased significantly.⁴⁶ Interestingly, substituting caffeinated coffee providing 850 mg/d for 20 days did not significantly increase fasting blood glucose compared to decaffeinated coffee. More recently, the effects of coffee consumption on serum glucose and insulin levels were examined in two studies originally designed to assess the effect of coffee consumption on plasma homocysteine concentrations.⁴⁷ In one trial, participants who normally consumed 5–8 cups/d of coffee were assigned in random order to a 4-week period in which they consumed one liter of filtered coffee daily providing 1100 mg/d of caffeine and a 4-week period in which they consumed no coffee. Although fasting glucose levels did not differ between the two treatment periods, serum insulin levels increased during the period that coffee was consumed, suggesting decreased insulin sensitivity.

In a separate crossover trial, participants who normally consumed more than 6 cups of coffee daily consumed 870 mg/d of caffeine, 900 ml/d of coffee providing 870 mg/d of caffeine, and a placebo for 2 weeks each in a randomly assigned order.⁴⁷

Serum insulin levels were nonsignificantly increased during the coffee period compared to placebo, but fasting glucose levels did not differ among the three groups.

Although acute and short-term trials of caffeine and coffee consumption have not demonstrated improvements in glucose tolerance or insulin sensitivity, the results of several epidemiological studies suggest that long-term, habitual coffee consumption may help maintain normal glucose tolerance. Several cross-sectional studies in Japan,⁴⁸ Spain,⁴⁹ and Sweden⁵⁰ have found coffee intake to be inversely associated with the incidence of impaired glucose tolerance after an oral glucose load. Additionally, a prospective cohort study of more than 1100 Dutch men and women found that coffee intake was inversely associated with the risk of developing impaired glucose tolerance over the next 6 years.⁴⁰ Those who drank at least 5 cups of coffee daily had a risk of developing impaired glucose tolerance that was 50% lower than those who drank 2 cups/d or less. Coffee intake was not associated with the risk of impaired fasting glucose, suggesting that habitual coffee consumption affects post-load rather than fasting glucose metabolism.

Potential Mechanisms for Inverse Associations between Coffee and Type 2 Diabetes Mellitus

Inhibition of the Glucose-6-Phosphatase System by Chlorogenic Acid. The hydrolysis of glucose-6-phosphate to glucose and phosphate represents the terminal step of the glucose-producing pathways, gluconeogenesis and glycogenolysis.⁵¹

Glucose-6-phosphate hydrolysis requires the coupled function of glucose-6-phosphatase, a glucose-6-phosphate translocase protein, and a second translocase protein. Chlorogenic acid has been shown to be a specific competitive inhibitor of the glucose-6-phosphate translocase in rat liver microsomes.⁵²

Inhibition of Intestinal Glucose Absorption by Chlorogenic Acid or other Phenolic Compounds in Coffee.

Chlorogenic acid reduced sodium-dependent glucose transport in brush border membrane vesicles isolated from rat small intestine.⁵³ Glucosedeprived insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are intestinal hormones that augment insulin secretion after oral glucose consumption. Consumption of decaffeinated coffee with an oral glucose load decreased plasma concentrations of GIP, which is secreted in the proximal small intestine, and increased plasma concentrations of GLP-1, which is secreted in the distal small intestine, suggesting that compounds in coffee may slow intestinal glucose absorption.⁵⁴

Increased Magnesium Intake. Dietary magnesium intake and serum magnesium concentrations have been inversely associated with the risk of type 2 DM in several large prospective cohort studies.^{55–57} Additionally, several short-term clinical trials have found that magnesium supplementation improves insulin sensitivity in individuals with low serum or erythrocyte magnesium concentrations.^{58–60} However, it is unclear whether coffee represents an important source of dietary magnesium (see above). In the Nurses' Health Study and Health Professionals Follow-up Study cohorts, the statistically significant inverse association between coffee consumption and type 2 DM risk persisted after adjustment for dietary magnesium intake.⁵

Energy Expenditure and Weight Loss. Caffeine has been found to increase the resting metabolic rate in lean as well as obese individuals for up to 24 hours after ingestion.^{61–63} However, controlled trials have not generally found that caffeine alone is effective in promoting weight loss in overweight adults.⁶⁴ Higher coffee consumption was actually associated with higher BMI values in several European cohorts,^{35–37} but coffee intake was not significantly associated with BMI in the Nurses' Health Study or the Health Professionals Follow-up Study in the US.⁵ Recently, a prospective study that followed more than 7000 US adults for an average of 8 years found that the significant inverse association between coffee intake and the risk of type 2 DM observed in the entire cohort applied only to those people ≤60 years of age who had previously lost weight.⁶⁵ Although the significance of this finding requires further clarification, it suggests that weight loss may play a role in the beneficial effect of coffee consumption on the risk of type 2 DM.

Summary: Coffee and Type 2 Diabetes Mellitus

Large prospective cohort studies in the Netherlands, US, Finland, and Sweden have found coffee consumption to be associated with significant dose-dependent reductions in the risk of developing type 2 DM. Although short-term clinical trials have found that caffeine administration impairs glucose tolerance and decreases insulin sensitivity, limited data from epidemiological studies suggest that habitual coffee consumption is inversely associated with impaired glucose tolerance. Until the relationship between long-term coffee consumption and type 2 DM risk is better understood, it is premature to recommend coffee consumption as a means of preventing type 2 DM.^{5,41}

Prevention of Parkinson's Disease

Epidemiological Studies

Overall, the results of case-control studies suggest that coffee and caffeine intakes are inversely associated with the risk of Parkinson's disease.⁶⁶ Several large prospective cohort studies have also found inverse associations between coffee and caffeine intakes and Parkinson's disease risk in

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men (Table 2). A study of more than 8,000 Japanese-American men found that those who did not drink coffee were 3–5 times more likely to develop Parkinson's disease over the next 24–30 years than those who drank at least 28 oz daily.⁶⁷ Caffeine intakes from coffee and other sources were also inversely associated with Parkinson's disease risk. Similarly, in the Health Professionals Follow-up Study, men who regularly consumed at least one cup of coffee daily had a risk of developing Parkinson's disease over the next 10 years that was about half that of men who did not drink coffee.³ The consumption of tea and other caffeinated beverages was also inversely associated with Parkinson's disease risk. In contrast, inverse associations between coffee and caffeine consumption and Parkinson's disease risk over a 16-year period were not observed in the Nurses' Health Study.³ Similarly, in the Cancer Prevention Study (CPS) II cohort of more than 500,000 men and women in the US, coffee consumption was inversely associated with Parkinson's disease mortality in men but not women.⁶⁸ The failure of prospective studies to find an inverse relationship between coffee consumption and Parkinson's disease in women may be due to the modifying effect of estrogen replacement therapy.⁶⁹ Further analysis of the Nurses' Health Study cohort revealed that coffee consumption was inversely associated with Parkinson's disease risk in women who had never used postmenopausal estrogen, but a significant increase in Parkinson's disease risk was observed in postmenopausal estrogen users who drank at least 6 cups of coffee daily.⁷⁰ In the CPS II cohort, a significant inverse association between coffee consumption and Parkinson's disease mortality was also observed in women who had never used postmenopausal estrogen, but not in those who used postmenopausal estrogen.⁶⁸ It is not clear how estrogen use modifies the effect of caffeine on Parkinson's disease risk. However, caffeine is largely metabolized by hepatic CYP1A2, and the use of postmenopausal estrogen replacement therapy has been found to inhibit CYP1A2-mediated caffeine metabolism.⁷¹

Potential Mechanisms for Inverse Associations between Caffeine and Parkinson's Disease

Although the results of epidemiological studies suggest that caffeine consumption decreases the risk of Parkinson's disease, other explanations for the inverse association between caffeine consumption and Parkinson's disease risk have been proposed. For example, subtle changes in mood, sleep patterns, and the sense of smell, which have been proposed as symptoms of preclinical Parkinson's disease, could lead to decreased caffeine consumption.^{69,72} However, this possibility seems unlikely since prospective cohort studies have observed strong inverse associations between Parkinson's disease risk and caffeine consumption more than a decade before diagnosis. Another potential explanation is that a decreased propensity for addictive behavior, e.g., cigarette smoking and caffeine consumption, has the same underlying cause as an increased risk of Parkinson's disease.³ Recent research supports the idea that chronic caffeine consumption could reduce Parkinson's disease risk. Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra.⁷³ Studies in animal models suggest that caffeine consumption decreases the risk of Parkinson's disease by protecting against dopaminergic neurotoxicity.⁷² The effects of caffeine in the central nervous system are related to its activity as an antagonist of the A1 and A2A subtypes of the adenosine receptor.⁷⁴ The expression of A2A-receptors in the brain is restricted almost entirely to the striatum, the target of the dopaminergic neurons that degenerate in Parkinson's disease. Acute toxicity with 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP) can induce Parkinsonism in humans.⁷⁵ A well-established animal model of Parkinson's disease uses MPTP to induce dopaminergic neurotoxicity in mice. Caffeine, at doses comparable to typical human exposures, has been found to attenuate MPTP-induced losses of striatal dopamine and dopamine transporter binding sites in mice.⁷⁶ Specific A2A-receptor antagonists mimicked the effect of caffeine as did the absence of functional

A2A-receptors in A2A receptor knockout mice. At present, it is not known exactly how A2A-receptor blockade reduces dopaminergic neurotoxicity.⁷⁷ Although the results of epidemiological and animal studies suggest that caffeine may reduce the risk of developing Parkinson's disease, it is premature to recommend increasing caffeine consumption to prevent Parkinson's disease, particularly in women taking exogenous estrogens.

Suicide Risk

Two prospective cohort studies in the US found significant inverse associations between coffee consumption and the risk of suicide.^{78,79} A 10-year study of more than 128,000 men and women participating in a California health plan found that the relative risk of suicide decreased by 13% for every cup of coffee consumed daily. Similarly, a 10-year study of more than 86,000 women found that those who drank at least 2 cups of coffee daily had a risk of suicide that was 50% lower than those who did not drink coffee.⁷⁸ Coffee consumption and suicide rates are higher in Finland than in the US. A prospective study that followed more than 43,000 Finnish men and women for an average of 14.6 years found that the relationship between coffee consumption and suicide risk was J-shaped.⁸⁰ Those who consumed at least 8 cups of coffee daily had a risk of suicide that was 58% higher than those with more moderate coffee consumption (0–7 cups/d). The reasons for the inverse association between moderate coffee consumption and the risk of suicide in these cohorts are not known. At present there is not enough evidence to support recommendations for coffee consumption in clinically depressed patients.

Prevention of Colorectal Cancer

Epidemiological Studies

In general, coffee consumption has been inversely associated with the risk of colon cancer in case-control studies, but not in prospective cohort studies.^{81,82} A meta-analysis that combined the results of 12 case-control studies and five prospective cohort studies found that people who drank 4 or more cups of coffee daily had a risk of colorectal cancer that was 24% lower than that of nondrinkers.⁸² However, coffee consumption was not associated with colorectal cancer risk when the results of only the prospective cohort studies were combined. Although case-control studies usually include more cancer cases than prospective cohort studies, they may be subject to recall bias with respect to coffee consumption and selection bias with respect to the control group. Similarly, a more recent review of epidemiological studies found evidence of an inverse association between coffee consumption and colon cancer risk from case-control studies but no evidence of such an association from prospective cohort studies.⁸¹ No overall associations between coffee and rectal cancer emerged in this review. In contrast, the two largest prospective cohort studies to examine the relationship between coffee and colorectal cancer to date found that American men and women who regularly consumed 2 or more cups of decaffeinated coffee daily had a risk of rectal cancer that was 48% lower than those who never consumed caffeinated coffee.⁸³ Consumption of caffeinated coffee, tea, and caffeine were not associated with either colon or rectal cancer risk. Case-control studies have not generally found coffee consumption to be inversely associated with the risk of colorectal adenoma,^{84–86} and coffee consumption was not associated with the risk of recurrent colorectal adenomas over a 4-year period.⁸⁷

Potential Mechanisms for Inverse Associations between Coffee and Colorectal Cancer

Several mechanisms have been proposed to explain the inverse association between coffee consumption and colorectal cancer risk observed in case-control studies. It has been suggested that compounds in coffee, such as diterpenes, could decrease the synthesis and secretion of bile acids, which may promote colon carcinogenesis.⁸¹ However, two human intervention trials do not

support the idea that coffee consumption decreases bile acid synthesis or secretion. Daily consumption of one liter of unfiltered coffee for 2 weeks did not decrease fecal soluble bile acids,⁸⁸ and the daily consumption of coffee oil containing 69 mg of cafestol for 5 weeks did not appear to decrease the activity of cholesterol 7 α -hydroxylase, the rate-limiting enzyme in the classical pathway of bile acid synthesis.⁸⁹ Coffee consumption may increase colonic motility, decreasing the exposure of colonic epithelial cells to potential carcinogens.⁹⁰ However, infrequent bowel movements were not associated with increased risk of colorectal cancer or adenomas in the Nurses' Health Study cohort.^{91,92} In animal studies, diterpenes found in unfiltered coffee have been reported to decrease the formation of DNA-adducts by several genotoxic carcinogens, including 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), a heterocyclic amine found in cooked meat and implicated in colon carcinogenesis.^{93,94} Diterpenes in coffee may promote the elimination of carcinogens and improve antioxidant status by enhancing phase II enzyme activity and glutathione synthesis.^{95,96} Although, consumption of one liter of unfiltered coffee daily for 2 weeks did not increase colorectal glutathione-S-transferase activity in human volunteers, glutathione concentrations significantly increased in colorectal mucosa and plasma by 8% and 15%, respectively.⁸⁸ Despite promising findings in case-control and animal studies, it is unclear whether coffee consumption decreases colon or rectal cancer risk in humans.

Hepatic Injury, Cirrhosis, and Hepatocellular Carcinoma

Liver injury resulting from chronic inflammation may result in cirrhosis. In cirrhosis, the formation of fibrotic scar tissue results in progressive deterioration of liver function and other complications, including hepatocellular carcinoma.⁹⁷ The most common causes of cirrhosis in developed countries are alcohol abuse and viral hepatitis B and C infection.

Coffee and Hepatic Injury

Serum γ -glutamyl transferase (GGT) activity has been widely used as an index of hepatic injury and a marker of alcohol intake.⁹⁸ A number of cross-sectional studies have found coffee consumption to be inversely associated with serum GGT activity.^{99–106} Elevated serum alanine aminotransferase (ALT) activity is a more specific marker of hepatic injury than GGT. An inverse association between coffee consumption and serum ALT activity has been observed in several cross-sectional studies.^{106–108} Recently, a large cross-sectional study in the US found that coffee and caffeine consumption were inversely associated with the risk of having an abnormally elevated serum ALT level (>43 U/L) in almost 6000 adults at high risk of hepatic injury from many different causes, including excessive alcohol consumption, viral hepatitis, iron overload, overweight, or impaired glucose metabolism.¹⁰⁸ Liver damage and cirrhosis have been found to inhibit caffeine metabolism, raising the possibility that people with liver disease consume less coffee because they are more likely to experience adverse effects from caffeine.^{109,110} However, in at least one study, the inverse relationship between coffee consumption and serum ALT did not change when the analysis was limited to those without impaired liver function.¹⁰⁸ The potential for liver disease to impair caffeine clearance highlights the importance of distinguishing between former coffee drinkers and nondrinkers in future epidemiological studies.

Coffee and Cirrhosis

Coffee consumption was inversely associated with the risk of cirrhosis in several case-control studies.^{111–113} and with mortality from alcoholic cirrhosis in two prospective cohort studies.^{114,115} An 8-year study of more than 120,000 US men and women found that the risk of death from alcoholic cirrhosis was 22% lower per cup of coffee consumed daily.⁷⁹ A 17-year study of more than 51,000 men and women in Norway found that those who consumed at least 2 cups of coffee daily had a 40% lower risk of death from cirrhosis than those who never consumed coffee.¹¹⁵

Coffee and Hepatocellular Carcinoma

Several case-control studies in Europe^{116,117} and at least two prospective cohort studies in Japan^{118,119} have observed significant inverse associations between coffee consumption and the risk of hepatocellular carcinoma. A prospective cohort study that followed more than 90,000 Japanese men and women for 10 years found that the risk of hepatocellular carcinoma decreased dose-dependently with increasing coffee consumption.¹¹⁸ Those who consumed at least 5 cups daily had a 76% lower risk of hepatocellular carcinoma than those who never drank coffee. In this study, the strongest inverse association was observed in people infected with the hepatitis C virus. Coffee consumption was not significantly associated with hepatocellular carcinoma risk in people who were not infected with hepatitis B or hepatitis C virus. A pooled analysis of two other prospective cohort studies in Japan that followed more than 50,000 men and women for 7–9 years found no significant association between coffee consumption and the risk of hepatocellular carcinoma in people who did not report a history of liver disease when the study began.¹¹⁹ However, in people with a history of liver disease at baseline, those who consumed at least one cup of coffee daily had a risk of hepatocellular carcinoma that was 48% lower than the risk for those who did not drink coffee.

Potential Mechanisms for Inverse Associations between Coffee and Hepatocellular Carcinoma

It is not clear how coffee consumption could inhibit liver damage or the development of cirrhosis and hepatocellular carcinoma. Consumption of unfiltered coffee and coffee oil containing cafestol and kahweol has been found to increase serum ALT and aspartate transaminase (AST) levels in human clinical trials.^{120,121} In contrast, cafestol and kahweol have been found to induce phase II enzyme activity, enhance hepatic glutathione levels and decrease liver DNA adducts caused by chemical carcinogens in animal models.^{93,95,96} In epidemiological studies, inverse associations between coffee consumption and the risk of cirrhosis and hepatocellular carcinoma have been observed in populations that drink mainly filtered and instant coffee with negligible concentrations of these diterpenes. Although other compounds in coffee, including caffeine and chlorogenic acid, have been found to inhibit chemically induced hepatic carcinogenesis in animal models,^{122,123} more research is needed to determine the nature of the relationship between coffee and caffeine intake and hepatocellular carcinoma in humans.

POTENTIAL HEALTH RISKS OF COFFEE CONSUMPTION

Cardiovascular Disease

Coronary Heart Disease Risk

Several epidemiological studies have examined the relationship between coffee consumption and coronary heart disease (CHD) risk. In general, case-control studies have found high coffee intakes to be associated with significantly increased risk of CHD or myocardial infarction (MI). Two separate meta-analyses that combined the results of eight case-control studies found that CHD risk was 40–60% higher in those who consumed 5 or more cups of coffee daily compared to those who did not drink coffee.^{124,125} Since the publication of the last meta-analysis in 1994, several other case-control studies have found high coffee intakes (5–10 cups daily) to be associated with increased risk of MI,^{126–128} while two case-control studies found that more moderate coffee consumption (3–4 cups daily) was not associated with increased risk of MI.^{129,130} One case-control study in Greece found a J-shaped relationship between coffee intake levels and the risk of developing an acute coronary syndrome (MI or unstable angina).¹³¹ The odds of being diagnosed with an acute coronary syndrome were three times higher in people who drank at least 600 ml of coffee daily than in those who did not drink coffee, but the odds were significantly lower in people who consumed less than 300 ml daily than in those who did not drink coffee.

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Prospective cohort studies have not generally found significant associations between coffee consumption and the risk of CHD. The results of two separate meta-analyses that combined the results of more than 10 prospective cohort studies did not support an association between coffee consumption and CHD risk.^{125,132} Similarly, most of the prospective cohort studies published since the last meta-analysis have not found significant associations between coffee consumption and CHD risk, including studies of large cohorts in the US, Scotland, and Finland.^{2,32,133} Furthermore, a prospective cohort study in Norway that reported that coffee consumption dose-dependently increased the risk of CHD mortality after 6 years of follow-up found that CHD mortality risk was significantly increased only in those who consumed at least 9 cups daily after 12 years of follow-up.¹³⁴

The investigators hypothesized that this may have been due to a decrease in the consumption of boiled coffee and a corresponding increase in the consumption of filtered coffee over time in Norway. Although limited by the potential for selection and recall bias, the results of most case-control studies suggest that people who consume 5 or more cups of coffee daily may be at increased risk of CHD. In contrast, the majority of prospective cohort studies have not found significant associations between coffee intake and CHD risk.

Established Coronary Heart Disease

The effect of coffee or caffeine consumption on people with established CHD has not been well studied. One case-control study found that heavy coffee consumption, defined as more than 10 cups daily, was associated with a significant increase in the risk of sudden cardiac arrest in patients with established coronary artery disease.¹³⁵ However, a multicenter prospective study of 1935 patients who survived a MI found no association between coffee consumption and survival over the next 4 years, even in the heaviest coffee consumers.¹³⁶ It should be noted that few patients reported consuming more than 10 cups of coffee daily in either study.

Cardiac Arrhythmias

Clinical trials have not found coffee or caffeine intake equivalent to 5–6 cups daily to increase the frequency or severity of cardiac arrhythmias in healthy people, CHD patients, or people with preexisting ventricular ectopy.^{137,138} A large prospective study in the US that followed more than 128,000 members of a health plan for 7 years found no association between coffee consumption and sudden cardiac death. More recently, two prospective studies in Scandinavia found no association between coffee consumption and the risk of developing atrial fibrillation, a common supraventricular arrhythmia.^{139,140}

Stroke Risk

Few prospective cohort studies have specifically reported associations between coffee consumption and coffee consumption and the risk of stroke.^{141–143} One exception was a 25-year study of 499 nonsmoking hypertensive men enrolled in the Honolulu Heart Study. In that high-risk population, the risk of thromboembolic (ischemic) stroke in men who consumed at least 24 oz of coffee daily was double that of men who did not drink coffee.¹⁴⁴ More research is needed to determine whether coffee consumption increases the risk of stroke in high-risk groups, such as individuals with hypertension.

Coffee Consumption and Cardiovascular Disease Risk Factors Serum Total and LDL Cholesterol.

A meta-analysis of 14 randomized controlled trials found that the consumption of boiled coffee dose-dependently increased serum total and LDL cholesterol concentrations, while the consumption of filtered coffee resulted in very little change in serum cholesterol.¹³

Overall, the consumption of boiled coffee increased serum total cholesterol by 23 mg/dl and LDL cholesterol by 14 mg/dl, while the consumption of filtered coffee raised total cholesterol by only 3 mg/dl and did not affect LDL cholesterol. The cholesterol-raising factors in unfiltered coffee have been identified as cafestol and kahweol (see above), diterpenes that are removed from coffee by paper filters.¹²

Plasma Total Homocysteine. An elevated plasma total homocysteine (tHcy) concentration is associated with an increased risk for cardiovascular disease, including CHD, stroke and peripheral vascular disease, but it is unclear whether the relationship is causal.¹⁴⁵ Coffee consumption has been positively associated with tHcy concentrations in a dose-dependent manner in numerous cross-sectional studies conducted in Europe,

Scandinavia and the US.^{146–150} Controlled clinical trials have confirmed the homocysteine-raising effect of relatively high intakes of coffee.^{151–153} Consumption of one liter of unfiltered (French press) coffee daily by healthy adults for 2 weeks raised fasting plasma tHcy concentrations by 10%, and consumption of one liter of filtered coffee daily raised fasting plasma tHcy concentrations by about 18%.¹⁵² Abstention from coffee consumption for 6 weeks resulted in an 11% decrease in fasting tHcy concentrations in those who consumed an average of 4 cups of filtered coffee daily.¹⁵¹ The results of controlled clinical trials suggest that caffeine and chlorogenic acid contribute to the homocysteine-raising effect of coffee.^{154,155} In a randomized, placebo-controlled crossover trial, supplementation of healthy men and women with 200 mcg/d of folic acid prevented elevations in plasma tHcy induced by the consumption of 600 ml/d of filtered coffee for 4 weeks.¹⁵⁶ The effect of coffee consumption on plasma tHcy was most pronounced in those who were homozygous for the methionine tetrahydrofolate reductase (MTHFR) C677T polymorphism, but folic acid supplementation also prevented tHcy elevations in this group.¹⁵⁷ Although it is not clear whether elevations in plasma tHcy related to coffee consumption actually increase the risk of cardiovascular disease, this effect may be prevented by adequate folate consumption or folic acid supplementation.

Hypertension. Hypertension is a recognized risk factor for CHD and stroke. It has been well-established that acute consumption of caffeine at dietary levels raises blood pressure in normotensive and hypertensive individuals.⁶ A 200–250-mg dose of caffeine, equivalent to the amount in 2–3 cups of coffee, has been found to increase systolic blood pressure by 3–14 mm Hg and to increase diastolic blood pressure by 4–13 mg Hg in normotensive individuals.¹⁵⁸ This pressor effect of caffeine may be more pronounced in hypertensive individuals.^{158,159} Although habitual consumption has been found to result in a degree of tolerance to the pressor effect of caffeine, the results of several clinical trials suggest that this tolerance is not always complete even in those who consume caffeine daily.^{160–162} Two metaanalyses have examined the results of randomized controlled trials of coffee consumption for more than one week on blood pressure.^{163,164} A meta-analysis that included 11 randomized controlled trials, in which the median duration of coffee consumption was 56 days and the median intake was 5 cups/d, found that coffee consumption significantly increased systolic and diastolic blood pressure by 2.4 and 1.2 mm Hg, respectively.¹⁶³ More recently, a meta-analysis that included 18 randomized controlled trials with a median duration of 43 days and a median intake of 725 ml/d found that coffee consumption significantly increased systolic blood pressure by 1.2 mm Hg, but the increase in diastolic blood pressure of 0.5 mm Hg was not statistically significant.¹⁶⁴ When the same investigators analyzed the results of seven randomized controlled trials of chronic caffeine consumption (median dose 410 mg/d), they found that caffeine significantly increased systolic and diastolic blood pressure by 4.2 and 2.4 mm Hg, respectively. It is not clear why the pressor

response was greater when caffeine was administered in tablets compared to coffee. Overall, caffeine consumption from coffee was not less than from tablets, and caffeine is readily absorbed from coffee. However, it is possible that other compounds in coffee could attenuate the pressor effect of caffeine.

The effects of long-term coffee consumption on blood pressure and the risk of hypertension are less clear. Cross-sectional studies of the relationships between coffee consumption and blood pressure in different populations have reported no association,^{165–167} positive associations^{168–171} and inverse associations.^{172–174} These inconsistent results could be related to measurement issues. For example, one study found that mean systolic and diastolic blood pressure differed significantly by 4 mm Hg and 2 mm Hg, respectively, between those who had consumed caffeine in the last 3 hours and those who had not consumed caffeine in the last nine hours.¹⁷⁵ At the time most of these studies were conducted, people with high blood pressure were often advised to decrease coffee consumption.¹⁷⁶ Thus, inverse associations between coffee and blood pressure could reflect selective reductions in coffee consumption by people with high blood pressure.¹⁷⁷ Few prospective studies have reported on associations between coffee consumption and the risk of hypertension.

A 6-year study of 340 Australian men found that systolic blood pressure decreased significantly in those who reduced their coffee consumption.¹⁷⁸ More recently, a prospective cohort study of 1017 men, who were followed for an average of 33 years, found that consumption of 1 cup of coffee daily raised systolic and diastolic blood pressure by an average of less than 1mmHg. However, men who drank coffee were not more likely than nondrinkers to develop hypertension over the next 33 years, after adjusting for other hypertension risk factors.¹⁷⁷

The acute pressor effects of caffeine have been well-documented, and the results of randomized controlled trials indicate that caffeinated coffee consumption for 1–12 weeks modestly raises systolic blood pressure by about 2 mm Hg. Although such an increase seems small by individual standards, it has been estimated that an average reduction of 2 mm Hg in population systolic blood pressure would result in 10% lower mortality from stroke and 7% lower mortality from CHD.¹⁷⁹ The results of epidemiological studies of long-term coffee consumption are mixed, but generally suggest that any contribution of coffee consumption to the development of hypertension is likely to be small. However, additional prospective cohort studies are needed to clarify the relationships between long-term coffee and caffeine consumption and the risk of hypertension.

Cancer

Numerous epidemiological studies have examined relationships between coffee and caffeine intake and cancer risk in humans. In general, there is little evidence that coffee consumption increases the risk of cancer, especially when the analyses are adjusted for cigarette smoking.¹⁸⁰ Although early case-control studies tended to show positive associations between caffeine intake and pancreatic, bladder and ovarian cancers, more recent and better-designed studies have not supported the hypothesis that coffee consumption contributes significantly to the risk of these cancers.^{181–183} In general, recent prospective cohort studies have not observed significant associations between caffeine or coffee intake and the risk of pancreatic, bladder, ovarian, breast, gastric and prostate cancer.¹⁸²

Osteoporosis and Hip Fracture

The results of controlled calcium balance studies in humans indicate that caffeine consumption leads to a small negative calcium balance in individuals with inadequate calcium intakes.¹⁸⁴ The negative shift in calcium balance has been estimated to be about 4–6 mg of calcium per cup of coffee, and is due to a slight decrease in the efficiency of calcium absorption.^{185,186} The majority of cross-sectional studies have found no association between caffeine consumption and bone mineral density (BMD).¹⁸⁴ Of the six studies that have examined associations between caffeine

consumption and change in BMD over time, four found no effect of caffeine.^{187–190} One found that the consumption of more than 300 mg/d was associated with accelerated loss of BMD,¹⁹¹ and another found that caffeine consumption was associated with accelerated loss of BMD only in women with calcium intakes less than 744 mg/d.¹⁹² Five case-control studies have examined relationships between coffee and caffeine consumption and the risk of hip fracture. None of them found coffee or caffeine consumption to be associated with significantly increased risk of hip fracture.^{193–197} Six prospective cohort studies have examined associations between caffeine (mainly from coffee) or coffee consumption and the risk of hip fracture in women. Two studies, one in Finland¹⁹⁸ and one in Japan,¹⁹⁹ found no association.

Another study in Norway found that women who consumed at least 9 cups of coffee daily tended to have an increased risk of hip fracture, but only 6.8% of women consumed this much coffee.²⁰⁰ However, three prospective cohort studies in the US found that coffee or caffeine consumption was positively associated with the risk of hip fracture in women.^{201–203} In the Framingham cohort, women who consumed more than 2 cups of coffee daily had a 70% higher risk of hip fracture over the next 12 years than women who did not consume caffeinated beverages.²⁰¹ In the Nurses' Health Study cohort, women who consumed 4 or more cups of coffee daily had a risk of hip fracture over the next 6 years that was almost three times the risk of those who did not drink coffee.²⁰² A prospective cohort study of women 65 years of age and older found that a 190 mg increase in caffeine consumption increased the risk of osteoporotic fracture by about 20%.²⁰³ Given the multifactorial etiology of osteoporosis, the impact of coffee or caffeine consumption on the risk of osteoporosis is not clear. However, currently available evidence suggests that ensuring adequate calcium and vitamin D intake and limiting coffee consumption to 3 cups/d (300 mg/d of caffeine) may help reduce the risk of osteoporosis and osteoporotic fractures, particularly in older adults.

Mineral Deficiencies

Impaired Iron Absorption

Polyphenols in coffee can bind nonheme iron and inhibit its intestinal absorption.²⁰⁴ Drinking 150–250 ml of coffee with a test meal has been found to inhibit the absorption of iron by 24–73%.^{205–208} Discontinuing coffee consumption significantly improved the response to iron supplements in Guatemalan toddlers.²⁰⁹ To maximize iron absorption from a meal or iron supplements, concomitant intake of coffee should be avoided.

Impaired Zinc Absorption

Dietary inhibitors of zinc absorption, particularly phytate, increase the risk of zinc deficiency.²¹⁰ Zinc chelating compounds have been identified in coffee,²¹¹ and coffee has been found to inhibit the bioavailability of zinc *in vitro* by 21–32%.²¹² The effect of coffee consumption on human zinc status has not been well studied. Although there is one report that coffee appeared to inhibit zinc absorption in human volunteers,²¹³ discontinuation of coffee for 5 months did not affect plasma zinc levels in Guatemalan toddlers.²⁰⁹

SPECIAL RISK GROUPS

Women of Childbearing Age

Caffeine and Conception

Numerous epidemiological studies have examined the relationship between caffeine consumption and the time to conception (fecundability) in women who are not using contraception.¹⁸⁰ Some

epidemiological studies found no significant delay in time to conception associated with coffee or caffeine intakes.^{214–218} Other studies found that only high intakes of coffee or caffeine ranging from 400–800 mg/d were associated with significant delays in conception.^{219–223} Two studies found significant decreases in the monthly probability of pregnancy in women who consumed at least 300 mg of caffeine daily.^{224,225} Several of these studies have been criticized for failing to adequately control other lifestyle factors related to fertility, particularly cigarette smoking and alcohol consumption.³¹ Based on the available data from epidemiological studies, it may be for women who are having difficulty conceiving to limit caffeine consumption to less than 300 mg/d in addition to tobacco use and decreasing alcohol consumption.

Caffeine and Pregnancy Complications

Spontaneous Abortion. The results of numerous epidemiological studies that have examined the relationship between maternal coffee or caffeine intake and the risk of spontaneous abortion have been conflicting. While some studies have observed significant associations between high caffeine intakes, particularly from coffee, and the risk of spontaneous abortion,^{226–230} other studies have not found significant associations.^{231,232} A number of methodological issues with these studies have been raised, including limitations in determining caffeine intake and confounding by other risk factors for miscarriage, such as nausea and smoking.^{28,31,233} Most studies that observed significant associations between self-reported coffee or caffeine consumption and the risk of spontaneous abortion did so at intake levels of at least 300 mg/d of caffeine.¹⁸⁰ In contrast, one study that assessed caffeine intake by measuring serum concentrations of paraxanthine, a caffeine metabolite, found that the risk of spontaneous abortion was only elevated in women with paraxanthine levels in the 95th percentile, suggesting a caffeine intake of at least 600 mg/d.²³⁴

It has been proposed that an association between caffeine consumption and the risk of spontaneous abortion could be explained by the relationship between nausea and fetal viability.³¹ Nausea is more common in women with viable pregnancies than nonviable pregnancies,²³⁵ suggesting that women with viable pregnancies are more likely to avoid or limit caffeine consumption due to nausea. However, at least one study found that the significant increase in the risk of spontaneous abortion observed in women with caffeine intakes higher than 300 mg/d was independent of nausea in pregnancy,²²⁸ and two other studies found that caffeine consumption was associated with increased risk of spontaneous abortion in women who experienced nausea or aversion to coffee during pregnancy.^{226,230} The authors of recent reviews of epidemiological studies focusing on methodological issues have concluded that a causal association between caffeine consumption and the risk of spontaneous abortion has not been demonstrated.^{31,233} Although the topic remains controversial, the available epidemiological evidence suggests that maternal consumption of less than 300 mg/d of caffeine is unlikely to increase the risk of spontaneous abortion.

Fetal Growth. Epidemiological studies examining the effects of maternal caffeine consumption on fetal growth have assessed mean birth weight, low birth weight (less than 2500 g) and fetal growth retardation (less than the 10th percentile of birth weight for gestational age). Several studies found that maternal caffeine intakes ranging from 200–400 mg/d were associated with decreases in mean birth weight of about 100 g.^{28,236,237} A large prospective study found that caffeine consumption was associated with a small but significant reduction in mean birth weight ($-28 \text{ g}/100 \text{ mg caffeine}$), but the investigators concluded that this decrease was unlikely to be clinically important in women with caffeine intakes of less than 600 mg/d.²³⁸ Results of epidemiological studies examining the effect of maternal caffeine consumption on the risk of low birth weight and fetal growth retardation are conflicting. Maternal caffeine consumption has been positively associated with the risk of low birth weight in some,^{236,237,239–241} but not all epidemiological

studies.^{30,238,242–249} A meta-analysis that combined the results of eight epidemiological studies found that maternal caffeine consumption greater than 150 mg/d increased the risk of low birth weight by approximately 50%.²⁵⁰ However, the investigators were not able to control for the effects of confounders in that meta-analysis. Maternal caffeine and coffee consumption have also been associated with increased risk of fetal growth retardation in some epidemiological studies,^{231,236,240,245,251–253} but not others.^{232,243,254,255} A recent case-control study found that mothers of small for gestational age (SGA) infants had significantly higher caffeine intakes in the third trimester of pregnancy than mothers of non-SGA infants (mean caffeine intake 281 mg/d vs. 212 mg/d).²⁵³ Even after adjusting for other risk factors, such as smoking, high caffeine intakes were still associated with increased risk of delivering an SGA infant, particularly if the infant was a boy. A number of the available epidemiological studies, have been criticized for inadequately controlling for important risk factors for low birth weight and fetal growth retardation,, particularly smoking.³¹ Although the relationship between maternal caffeine consumption and fetal growth requires further clarification, it appears unlikely that caffeine intakes less than 300 mg/d will adversely affect fetal growth in nonsmoking women.

Preterm Delivery. Most epidemiological studies have not found coffee or caffeine consumption to be associated with the risk of preterm delivery.^{218,236,238,244,245,247–249,256}

Birth Defects. Caffeine administration during pregnancy results in congenital malformations in a number of animal species, but usually only at doses that also cause maternal toxicity.²⁵⁷ The majority of epidemiological studies have not found maternal caffeine or coffee consumption to be associated with increased risk of congenital malformations.^{180,257} At present, there is no convincing evidence from epidemiological studies that maternal caffeine consumption ranging from 300– 1000 mg/d increases the risk of congenital malformations in humans.

Lactation

Caffeine is detectable in breast milk within 15 minutes of consumption and peaks at about one hour after consumption.²⁵⁸ After maternal caffeine consumption of up to 335 mg, the amount of caffeine available to the infant through breast milk was estimated to be less than 2 mg over a 24-hour period. Maternal caffeine consumption of 500 mg/d resulted in daily infant caffeine intakes ranging from 0.3–1.0 mg/kg of body weight.²⁵⁹ The American Academy of Pediatrics categorizes caffeine as a maternal medication that is usually compatible with breastfeeding.²⁶⁰ Although high maternal caffeine intakes have been reported to cause irritability and poor sleeping patterns in infants, no adverse effects have been reported with moderate maternal intake of caffeinated beverages equivalent to 2–3 cups of coffee daily.

Children

Research on the effects of caffeine consumption in children is limited, and most studies have focused on behavioral effects.²⁶¹

Despite increasing concern by the public regarding caffeinated beverage intake in children and adolescents,²⁶² there has been little research on the topic in the past decade. A meta-analysis of nine short-term clinical trials of caffeine in children, including four in normal children and five in children with attention deficit hyperactivity disorder (ADHD), found no significant adverse effects on cognition or behavior.²⁶³ In general, caffeine doses less than 3.0 mg/kg of body weight have not resulted in adverse effects in children in controlled clinical trials. However, higher doses have resulted in some behavioral effects, such as increased nervousness or anxiety and sleep disturbances.¹⁸⁰ It is unclear whether caffeine has serious adverse effects in children, but concerns regarding its effects on the developing nervous system have led to recommendations in Canada that daily caffeine intake by children should be limited to 2.5 mg/kg of body weight.²⁶⁴

Older Adults

Coffee is the most common source of caffeine in the elderly.^{265,266} There is limited evidence that older adults are more susceptible to the acute blood pressure-raising effects of caffeine.^{267,268} Because caffeine is distributed mainly through lean mass, and older adults have lower lean mass to adipose ratios than younger adults, a dose of caffeine expressed as mg/kg of body weight has the potential to result in higher plasma and tissue concentrations in older adults.²⁶⁹ Higher plasma caffeine concentrations could increase the risk of drug interactions since older adults are more likely to take one or more medications that interact with caffeine (see Drug Interactions below). The risk of hip fracture increases with age, and the results of several prospective cohort studies suggest that high caffeine intakes may contribute to hip fracture risk, particularly in the presence of calcium and vitamin D insufficiency.²⁷⁰ Overall, there is some evidence to suggest that older adults are more susceptible to some adverse effects of caffeine than younger adults.

ADVERSE EFFECTS OF CAFFEINE

Acute Toxicity and Overdose

Fatal or life-threatening caffeine overdoses generally involve the ingestion of caffeine-containing medications.^{271,272} Oral doses of 5–50 g (mean 10 g) have resulted in fatalities in adults, and the lethal dose is estimated at 100–200 mg/kg of body weight. Ingestion of 15–30 mg/kg has resulted in significant toxicity. Symptoms of caffeine overdose may include agitation, delirium, seizures, dyspnea, cardiac arrhythmia, myoclonus, nausea, vomiting, hyperglycemia and hypokalemia.

Adverse Reactions

Adverse reactions to lower doses of caffeine, such as those that may be achieved through coffee consumption, include tachycardia, palpitations, insomnia, restlessness, nervousness, tremor, headache, abdominal pain, nausea, vomiting, diarrhea and diuresis.^{271,272}

Withdrawal

Caffeine withdrawal symptoms have been documented in a number of case reports and experimental studies.²⁷³ Commonly reported caffeine withdrawal symptoms include headaches, fatigue, drowsiness, irritability, difficulty concentrating and depressed mood. Nausea and myalgia have also been reported.

Significant withdrawal symptoms have been observed at longterm intakes as low as 100 mg/d, although they are more common with higher intakes. Gradual withdrawal from caffeine appears less likely to result in withdrawal symptoms than abrupt withdrawal.²⁷⁴

Drug Interactions

Habitual caffeine consumption increases CYP1A2 activity, which has implications for the metabolism for a number of medications.⁷ Conversely, drugs that inhibit the activity of CYP1A2 interfere with the metabolism and elimination of caffeine, increasing the risk of toxic effects.²⁷⁵

Drugs that Alter Caffeine Metabolism

The following medications may impair the hepatic metabolism of caffeine, decreasing its elimination and potentially increasing the risk of caffeine-related side effects:

cimetidine (Tagamet), disulfiram (Antabuse), estrogens, fluconazole (Diflucan), fluvoxamine (Luvox), mexiletine (Mexitil), quinolone class antibiotics and terbinafine (Lamisil).⁷ Phenytoin (Dilantin) and cigarette smoking increase the hepatic metabolism of caffeine, resulting in increased elimination and decreased plasma caffeine concentrations.²⁷¹

Caffeine Effects on Other Drugs

Caffeine and other methylxanthines may enhance the effects and side effects of β -adrenergic stimulating agents, such as epinephrine and albuterol.⁷ Caffeine could theoretically increase the risk of hypertensive crisis in individuals taking monoamine oxidase inhibitors.²⁷⁶ Caffeine may inhibit the hepatic metabolism of the antipsychotic medication, clozapine, potentially elevating serum clozapine levels and increasing the risk of toxicity. Caffeine consumption can decrease the elimination of theophylline, potentially increasing serum theophylline levels.

Caffeine has been found to decrease the systemic elimination of acetaminophen and to increase the bioavailability of aspirin, which may partially explain its efficacy in enhancing their analgesic effects. Caffeine may decrease serum concentrations of lithium by enhancing its elimination.

CONSIDERATIONS FOR FUTURE RESEARCH

Assessment of the health risks and benefits of coffee and caffeine consumption requires reliable data on exposure to caffeine and other compounds in coffee. The identification of biomarkers that accurately reflect the consumption of bioactive compounds in coffee represents an important tool for studying relationships between coffee consumption and health-related endpoints.²⁷⁷

Serum or urinary measures of caffeine metabolites may be used to assess dietary exposure to caffeine. A study of pregnant women found that the measurement of serum paraxanthine was useful for distinguishing varying caffeine intakes.²⁷⁸

In that study, Pearson correlation coefficients between selfreported caffeine intake and serum paraxanthine concentrations (0.50–0.53) were comparable to reported correlations between cigarette smoking and serum cotinine concentrations. Assessment of urinary caffeine metabolites, such as 1-methylxanthine and 1,7-dimethyluric acid may also be useful for assessing dietary caffeine intake.⁸ Since chlorogenic acid or its metabolites may also contribute to the health effects of coffee, a reliable biomarker for coffee-derived polyphenol intake would be useful. Isoferulic acid has been identified as a specific metabolite of dietary caffeic acid derivatives, such as chlorogenic acid.²⁷⁹

However, in a recent study, less than 7% of the variance in coffee intake was explained by urinary isoferulic acid excretion, suggesting that it has limited usefulness as a biomarker for coffee-derived polyphenol exposure.²⁷⁷

Genetic heterogeneity in a study population may mask associations between dietary exposures and chronic disease risk.²⁸⁰ Epidemiological studies that examine interactions between coffee or caffeine intake and genetic polymorphisms affecting the activity of phase I and phase II biotransformation enzymes could help clarify some of the effects of coffee consumption on human health. CYP1A2 plays a major role in caffeine metabolism (Figure 2), as well as the metabolic activation of potentially carcinogenic heterocyclic amines.²⁸¹ Two genetic polymorphisms (CYP1A2*1C and CYP1A2*1F) have been identified that appear to alter the inducibility of CYP1A2.^{282,283} Recently, a small case-control study of Japanese women found that caffeine intake was not associated with recurrent pregnancy loss when CYP1A2 genotype was not considered.²⁸⁴ However, in women who were homozygous for the CYP1A2*1F polymorphism, a genotype associated with high inducibility of CYP1A2, caffeine intake was positively associated with the risk of recurrent pregnancy loss. CYP2A6 plays a role in caffeine metabolism (Figure 2), as well as nicotine metabolism and the activation of procarcinogenic nitrosamines. A number of distinct polymorphisms of CYP2A6 that affect its activity have been identified, some of which may affect smoking behavior and cancer risk.^{285,286}

Numerous polymorphisms of the gene for NAT2 that affect its acetylation activity have been reported.²⁸¹ Individuals classified as “slow acetylators” are essentially unable to acetylate the primary caffeine metabolite, paraxanthine (Figure 2). Aromatic amines in cigarette smoke and foods are also acetylated by NAT2, and NAT2 polymorphisms have been found to modulate the risk of several cancers in humans, including bladder

and colorectal cancer.²⁸⁷ Caffeic acid, a metabolite of chlorogenic acid, is extensively glucuronidated through the activity of intestinal and hepatic UDP-glucuronosyltransferases (UGT).²⁸⁸ Genetic polymorphisms have been described for 6 of the 16 human *UGT* genes, but functional significance has only been demonstrated for a polymorphism of *UGT1A1*.²⁸⁹ Future epidemiological studies that consider interactions between coffee intake and genetic polymorphisms may identify specific genotypes that are more susceptible to adverse effects of coffee consumption or more likely to experience health benefits related to coffee consumption.

CONCLUSIONS

Coffee is a complex mixture of chemicals that provides significant amounts of chlorogenic acid and caffeine.^{18,265} Unfiltered coffee is a significant source of cafestol and kahweol, which are diterpenes that have been implicated in the cholesterol-raising effects of coffee.¹² The results of epidemiological research suggest that coffee consumption may help prevent several chronic diseases, including type 2 DM,⁴¹ Parkinson's disease⁶⁹ and liver disease.⁴ Large prospective cohort studies in the Netherlands, US, Finland and Sweden have found coffee consumption to be associated with significant dose-dependent reductions in the risk of developing type 2 DM, although the mechanisms are unclear.⁴¹ Several large prospective cohort studies have found that caffeine consumption from coffee and other beverages is inversely associated with the risk of Parkinson's disease in men and women who have never used postmenopausal estrogen.^{3,67,68}

The results of animal studies suggest that the ability of caffeine to block adenosine A2A-receptors in the brain may play a role in this protective effect.⁷⁷ Epidemiological studies also suggest that coffee consumption is associated with decreased risk of hepatic injury, cirrhosis and hepatocellular carcinoma, although the mechanisms are not clear.⁴ Inverse associations between coffee consumption and colorectal cancer risk observed in case-control studies have not generally been confirmed in prospective cohort studies.^{81,82}

Most prospective cohort studies have not found that coffee consumption is associated with significantly increased risk of CHD or stroke.^{81,82} However, randomized controlled trials lasting up to 12 weeks have found that coffee consumption is associated with increases in several cardiovascular disease risk factors, including blood pressure⁶ and plasma tHcy.^{152,153}

At present, there is little evidence that coffee consumption increases the risk of cancer.¹⁸² Although most studies have not found coffee or caffeine consumption to be inversely associated with bone mineral density in women who consume adequate calcium, positive associations between caffeine consumption and hip fracture risk in three prospective cohort studies suggest that limiting coffee consumption to 3 cups/d (300 mg/d of caffeine) may help prevent osteoporotic fractures in older adults.^{201–203} Although epidemiological data on the effects of caffeine during pregnancy are conflicting, they raise concern regarding the potential for high intakes of coffee or caffeine to increase the risk of spontaneous abortion and impair fetal growth.¹⁸⁰ Serious adverse effects from caffeine at the levels consumed from coffee are uncommon, but there is a potential for adverse interactions with a number of medications.⁷ Regular consumers of coffee and other caffeinated beverages may experience withdrawal symptoms, particularly if caffeine cessation is abrupt.²⁷³

Overall, there is little evidence of health risks and some evidence of health benefits for adults consuming moderate amounts of coffee (3–4 cups/d providing 300–400 mg/d of caffeine). A review of the effects of caffeine on human health commissioned by Health Canada also concluded that moderate caffeine intakes up to 400 mg/d are not associated with adverse health effects in healthy adults.¹⁸⁰ However, some groups, including people with hypertension and the elderly, may be more vulnerable to the adverse effects of caffeine.^{6,269} Currently available evidence suggests that it would be prudent for women who are pregnant, lactating, or planning to become pregnant to limit coffee consumption to 3 cups/d providing no more than 300 mg/d of caffeine.¹⁸⁰

Caffeinated soft drinks are the principal source of caffeine in the diets of children and adolescents in the US, although coffee consumption increases somewhat during adolescence.^{265,266} Limited data from short-term clinical trials suggest that daily caffeine intakes of 3 mg/kg of body weight or more may have adverse effects in children and adolescents. These findings are the basis for Health Canada's recommendation that children should not consume more than 2.5 mg/d of caffeine per kg of body weight.^{180,264} Clearly, more research is needed to determine whether long-term caffeine consumption has adverse effects on the health of children and adolescents.

ACKNOWLEDGEMENTS

Funding for this review was provided by Unilever.

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