IFIC REVIEW
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Caffeine & Health: Clarifying The Controversies

Caffeine is one of the most comprehensively studied ingredients in the food supply. Yet, despite our considerable knowledge of caffeine and centuries of safe consumption in foods and beverages, questions and misperceptions about the potential health effects associated with caffeine persist.

This Review provides up-to-date information on caffeine, examines its safety and summarizes the most recent key research conducted on caffeine and health.

EXECUTIVE SUMMARY

Caffeine is added to soft drinks as a flavoring agent; it imparts a bitterness that modifies the flavors of other components, both sour and sweet. Although there has been controversy as to its effectiveness in this role, a review of the literature suggests that caffeine does, in fact, contribute to the sensory appeal of soft drinks. [Drewnowski, 2001]

Moderate intake of 300 mg/day (about three cups of coffee per day) of caffeine does not cause adverse health effects in healthy adults, although some groups, including those with hypertension and the elderly, may be more vulnerable. Also, regular consumers of coffee and other caffeinated beverages may experience some undesirable, but mild, short-lived symptoms if they stop consuming caffeine, particularly if the cessation is abrupt. However, there is little evidence of health risks of caffeine consumption.

In fact, some evidence of health benefits exists for adults who consume moderate amounts of caffeine. Caffeine consumption may help reduce the risk of several chronic diseases, including diabetes, Parkinson's disease, liver disease, and colorectal cancer, as well as improve immune function. Large prospective cohort studies in the Netherlands, Finland, Sweden, and the United States have found caffeine consumption is associated with reduced risk of developing type 2 diabetes, although the mechanisms are unclear. Several other cohort studies have found that caffeine consumption from coffee and other beverages decreases the risk of Parkinson's Disease in men, as well as in women who have never used post-menopausal hormone replacement therapy. Epidemiological studies also suggest that coffee consumption may decrease the risk of liver injury, cirrhosis and hepatocellular carcinoma (liver cancer), although the reasons for these results have not been determined. In addition, coffee consumption appears to reduce the risk of colorectal cancer, but this has not generally been confirmed in prospective cohort studies. An anti-inflammatory effect has also been observed in a number of studies on caffeine's impact on the immune system.

Most studies have found that caffeine consumption does not significantly increase the risk of coronary heart disease (CHD) or stroke. Some randomized controlled trials have found that caffeine consumption increased cardiovascular disease risk factors to some degree, including blood pressure. However, it has been found to have a protective effect in men 65 years and older and women aged 55-69 years who did not previously have severe hypertension. [Greenberg, et al., 2007; Andersen, et al., 2006]

At present, there is little evidence to show consumption of caffeine increases the risk of cancer. Studies have shown no negative association, and possibly some protective effects, between caffeine consumption and several types of cancer.

Most studies have found that caffeine consumption does

CAFFEINE CONSUMPTION

The per capita consumption level of caffeine for all consumers (of all ages) is approximately 120 mg per day, or a mean intake of 1.73 mg/kg body weight/day. [Knight, et al. 2004]

Children consume significantly less caffeine than adults. As of 2004, the average daily intake of caffeine by young children ages 1-5 and 6-9 years from all caffeinated beverages was 14 and 22 mg/day, or 0.82 and 0.85 mg/kg body weight/day, respectively. [Knight, et al. 2004]

For children and young adults, the primary sources of caffeine are soft drinks and teas, while for adults ages 25 and older, it is mostly derived from coffee. [Knight, et al. 2004] However, a growing beverage category, energy drinks, is a popular choice with several age groups, and is a category to monitor for consumption in the coming years.

Evidence from both scientific reviews and specific studies on consumption of caffeine generally concludes that daily consumption of 300 mg/day, or about three cups of coffee, is safe, even for more sensitive segments of the population, such as young children and pregnant women. [Nawrot, et al., 2003]

not reduce bone mineral density in women who consume adequate calcium. However, positive associations between caffeine consumption and hip fracture risk in three studies imply that limiting coffee consumption to three cups per day (about 300 mg/day of caffeine) may help prevent osteoporosis-related fractures in older adults.

Although epidemiological data on the effects of caffeine during pregnancy are conflicting, the evidence suggests that women who are pregnant or are planning to become pregnant, or who are breastfeeding, can safely consume caffeine, but should limit their consumption to three cups of coffee per day, providing no more than 300 mg/day of caffeine.

Based on the data reviewed, it can be concluded that caffeine consumption of 300 mg/day or less does not cause adverse effects on the cardiovascular or reproductive systems, and does not increase risk of cancer or osteoporosis.

BASED ON THE DATA REVIEWED, IT CAN BE CONCLUDED THAT CAFFEINE CONSUMPTION OF 300 MG/DAY OR LESS DOES NOT CAUSE ADVERSE EFFECTS

SOURCES OF CAFFEINE

Caffeine is a naturally occurring substance found in the leaves, seeds and/or fruits of at least 63 plant species worldwide and is part of a group of compounds known as methylxanthines. The most commonly known sources of caffeine are coffee, cocoa beans, kola nuts and tea leaves. [Barone and Roberts, 1996; Frary et al., 2005]

The amount of caffeine in food products varies depending upon the serving size, the type of product, and preparation method. With teas and coffees, the plant variety also affects the caffeine content. An eight-ounce cup of drip-brewed coffee typically has 65-120 mg caffeine; an eight-ounce serving of brewed tea has 20-90 mg; and a 12-ounce canned soft drink has 30-60 mg. [Knight, et al., 2004] Energy drinks can contain 50-160 mg or more per eight-ounce serving, plus caffeine from guarana and other added sources not normally declared as caffeine; and one ounce of solid milk

TABLE 1

CAFFEINE CONTENT CHART		MILLIGRAMS OF CAFFEINE	
ITEM		TYPICAL	RANGE*
Coffee (8 oz. cup)	Brewed, drip method	85	65-120
	Instant	75	60-85
	Decaffeinated	3	2-4
	Espresso (1 oz. cup)	40	30-50
Teas (8 oz. cup)	Brewed, major U.S. brands	40	20-90
	Brewed, imported brands	60	25-110
	Instant	28	24-31
	Iced	25	9-50
Soft drinks (Cola – 12 oz. serving)		40	30-60
Energy drinks (Approx 250 ml. – 8.3 oz. serving)		80	50-160
Cocoa beverage (8 oz. serving)		6	3-32
Chocolate milk beverage (8 oz. serving)		5	2-7
Solid Milk chocolate (1 oz. serving)		6	1-15
Solid Dark chocolate, semi-sweet (1 oz. serving)		20	5-35
Baker's chocolate (1 oz. serving)		26	26
Chocolate flavored syrup (1 oz. serving)		4	4
**Due to brewing method, plant variety, brand, formulation etc.*			

[IFIC Foundation, 1998; Knight, et al., 2004; Mayo Clinic, 2005]

chocolate typically has just six mg caffeine (see Table 1). [American Beverage Association, 2007; Mayo Clinic, 2005]

Other sources of caffeine include over-the-counter pain relievers. Caffeine is an adjuvant—it increases the rate at which the medication is absorbed into the body. It is also present in some stimulant tablets and cold medications. Caffeine can be present in these products ranging from 16-200 mg. [Cleveland Clinic, 2006]

Caffeine and Coffee

Because caffeine is well known as an ingredient in coffee, there is much confusion, even in research literature, between the effects of caffeine and those of coffee. Coffee contains many other constituents that may also carry health benefits; however, this Review will only address the caffeine-related implications of coffee consumption.

Physiological Effects

Caffeine is a pharmacologically active substance and, depending on the amount consumed, can be a mild stimulant to the central nervous system. [Mandel, 2002] Caffeine is not alone in this respect. It is one of several ingredients in foods capable of exerting pharmacological and physiological effects. For example, capsaicin in hot peppers causes the familiar burning sensation that often evokes sweating.

When caffeine is consumed orally, it is rapidly absorbed into body fluids and distributed throughout the body in its "water phase" (i.e. blood, urine etc.). Additionally, it is recognized that caffeine readily passes through the blood-brain barrier, enabling it to exert physiological changes. [Institute of Medicine, 2001] Elimination of caffeine from the body is accomplished mainly through metabolism in the liver in a relatively short time; the average half-life, or time taken for the body to eliminate one-half of the amount consumed, is five hours. [Donovan and DeVane, 2001]

Withdrawal

The American Psychiatric Association's (APA) "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994) cites no evidence for caffeine withdrawal. Some studies suggest that abruptly discontinuing consumption of caffeine can lead to mild symptoms such as headache, insomnia and anxiety, although the intensity of such symptoms varies and it is unclear whether they constitute withdrawal. [Bonnet, et al., 2005] Symptoms may be reduced by gradually decreasing caffeine intake. [Higdon and Frei, 2006] Reported symptoms are generally short-lived and relatively mild in the majority of people affected. [Nawrot, et al., 2003]

A community-based telephone survey followed by a randomized, double-blind, controlled study on 11,169 consumers concluded that when participants were unaware of the caffeine withdrawal focus of the study, both the frequency and severity of caffeine sensitivity was much lower than previous reports. Moreover, clinically significant symptoms may be less common among the general population. [Dews, et al., 1999]

People differ greatly in their sensitivities to caffeine, a fact also acknowledged in DSM IV. A number of factors contribute to effects of caffeine on an individual, including the amount of caffeine ingested, frequency of consumption, individual metabolism, and individual sensitivity. [Dews, 1986]

Caffeine enhances self-rated moods such as vigor, efficiency, energy and clear-headedness.

Mental Performance

It has long been anecdotally reported that caffeine has the ability to improve alertness and aid in concentration. Recent studies in a number of laboratories have consistently demonstrated increases in key aspects of cognitive function related to alertness, even among well-rested volunteers. Additionally, caffeine enhances self-rated moods such as vigor, efficiency, energy and clear-headedness. These effects are present at consumption levels as low as 32 mg (less than an eight-ounce cup of hot tea). [Lieberman, 2001]

Additionally, a study at the French National Institute for Health and Medical Research in Montpellier, France showed that consumption of at least three cups of coffee per day is associated with a slower rate of decline in cognitive abilities in women. Caffeine, which has already been associated with increased mental performance, has been identified as the ingredient most likely contributing to these results. These beneficial effects on cognitive decline in women appear to increase with age. [Ritchie, et al., 2007]

Although there have been reports of caffeine causing anxiety, a number of reviews of the research have shown that only extremely high levels of caffeine bring on anxiety (1,000-2,000 mg caffeine per day), and even this has not been shown to be consistent among reviews. [Smith, 2002; Stern, et al., 1989] Anxiety is rarely seen within the average range of caffeine consumption.

While large amounts of caffeine late in the evening may interfere with the onset of sleep, consumption at least eight hours prior to sleep will not affect sleep onset. [Smith, 2002; Bonnet, et al., 2005] Teenagers tend to stay awake

ADDICTION

In recent years, the term "addiction" has been used colloquially to refer to certain foods of enjoyment, prompting speculation as to whether it is possible to be truly "addicted" to the foods and beverages we consume. [Drewnowski and Bellisle, 2007]

According to the American Psychiatric Association's (APA) "Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV, 1994), there is currently not enough evidence to show that caffeine "dependence" is associated with a significant clinical disorder. However, DSM IV does provide a diagnosis of caffeine intoxication that may occur with consumption in excess of 250 mg, in more sensitive subpopulations. Symptoms may include excitement, restlessness, nervousness, insomnia, diuresis, or gastrointestinal disturbance. Other symptoms of restlessness may occur if consumption exceeds 1,000 mg/day. [FDLJ, 2006]

Although caffeine acts primarily by blocking adenosine receptors, it is unique in that it interacts with the transmission of dopamine (a neurotransmitter released in the brain that travels to dopamine receptors and produces feelings of pleasure), but its mechanism is very different from that of drugs of abuse such as cocaine and

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longer as the school-week progresses, gradually becoming more sleep-deprived, and may consume caffeine to counteract daytime sleepiness. [Pollack and Bright, 2003] In practice, those experiencing sleeplessness learn to moderate caffeine consumption to levels and time of day that are more acceptable to them. [Smith, 2002; Nawrot, et al., 2003] Furthermore, with regular consumption of caffeine, tolerance to some of its effects can result, reducing the severity of those effects. [Bonnet, et al., 2005] Although not well documented, researchers have suggested that the familiar caffeine "morning pick-me-up" may simply be the relief of overnight withdrawal symptoms. [Dews, et al., 2002; British Nutrition Foundation, 2007]

Research has also shown that sleep-deprived individuals consuming caffeine had improved memory and reasoning. [Lieberman, 2001] Alertness and performance also improve at levels of 75-150 mg after acute restriction of sleep, and at intakes of 200-600 mg after one or more nights without sleep. [Bonnet, et al., 2005]

CONSUMPTION OF CAFFEINE PRIOR TO EXERCISE HAS BEEN SHOWN TO IMPROVE ENDURANCE DURING PHYSICAL EXERCISE.

PHYSICAL PERFORMANCE

In addition to its effects on mental performance and mood, evidence has also shown that physical performance may be improved following caffeine consumption. [Magkos and Kavouras, 2004] Also, caffeine in amounts greater than 220 mg has been found to significantly improve performance in simulations of driving and industrial work. [Smith, 2005]

Consuming 6 mg/kg body weight of caffeine, or about five 8-ounce cups of coffee for a 155 lb. male, significantly increased muscle endurance during brief, intense exercise (4–6 min) performed by recreational athletes. [Jackman, et al., 1996] In addition, Bruce et al. (2000) reported that intake of 6 or 9 mg/kg of caffeine, or about five or seven 8-ounce cups of coffee, respectively, produced a significant improvement in performance compared with a placebo for competitive male rowers during a 2,000-meter time trial. Notably, the lower dose of caffeine (6 mg/kg) resulted in the fastest performance times. Caffeine ingestion of 5 mg/kg prior to a maximum effort run resulted in significantly greater anaerobic metabolism and performance among recreational runners. [Doherty, 1998] Similarly, healthy untrained subjects performing a maximal oxygen deficit cycling test had significantly improved endurance following ingestion of 5 mg/kg caffeine. [Bell, et al., 2001] One of the few caffeine studies utilizing female subjects found that 6 or 9 mg/kg caffeine (about four or six 8-ounce cups of coffee for a 132 lb. female, respectively) produced dose-dependent improvements during repeated 2,000-meter time trials among competitive oarswomen. [Anderson, et al., 2000]

In another study on cyclists, moderate levels of caffeine (6 mg/kg) enhanced the performance times during a cycling trial. [Cox, et al., 2002] This result was observed whether caffeine was ingested one hour before exercise or in a series of administrations throughout the trial. The researchers also found support for the observed practice of consuming commercial soft drinks as a replacement for sports drinks during the last part of an endurance event. In a double-blind study, soft drinks produced enhanced performance at the end of the task, with the benefits being largely due to the ingestion of a small amount of caffeine (1.5 mg/kg). Direct comparison of the ingestion of larger amounts of soft drink suggests that all types of caffeinated beverages, including soft drinks and sports drinks, are of equal and worthwhile benefit to the performance of a prolonged cycling task.

Consumption of caffeine prior to exercise has been shown to improve endurance during physical exercise. One suggested explanation for this was that caffeine enhanced fat utilization during exercise, instead of burning muscle; however, Laurent et al. (2000) showed that this was not the case. Rather, caffeine may lower the threshold for exercise-induced ß-endorphin and cortisol release, hormones that produce the so-called "runner's high," which may contribute to the reported caffeine exercise benefits.

Caffeine and Children

Children consume much less caffeine than adults, even in proportion to their smaller size. [Knight, et al., 2004] Research shows that children, including those diagnosed as hyperactive, are no more sensitive to the effects of caffeine than adults, and, except for infants, they metabolize caffeine more quickly than adults. [Dews, 1986; Leviton, 1992] Interestingly, in controlled studies, most adverse effects were reported by "low-consumers" of caffeine, rather than "high-consumers." [Castellanos and Rapoport, 2002]

...EXTENSIVE EPIDEMIOLOGICAL STUDIES HAVE CONFIRMED THAT THERE IS NO LINK BETWEEN COFFEE CONSUMPTION AND HYPERTENSION, HYPERLIPIDEMIA, AND CORONARY ARTERY DISEASE

At low levels of caffeine (2.5 mg/kg), improved performance on attention tests has been noted in children. A study was conducted in which 21 children were administered either a placebo, a low dose of caffeine, or a high dose of caffeine. The authors noted a statistically significant, dose-dependent improvement in performance on an attention test after caffeine administration compared with the placebo group. A significant but non-dose related improvement in hand-eye coordination was also noted. [Bernstein, et al., 1994]

Although there seems to be little hard evidence suggesting that children, whose nervous systems are still developing, are at risk of negative effects from caffeine, Health Canada recommends that daily caffeine intake by children should be limited to 2.5 mg/kg body weight. [Nawrot, et al., 2003] This equates to 37.5 – 45 mg/day for a 1-5 year old (body weight 15-18 kg) and 87.5 - 125 mg/day for a 10-14 year old (body weight 35-50 kg). [NHANES, 1988-94] To put this into perspective, recall from the Caffeine Consumption section of this Review that the average caffeine consumption for children ages 1-5 and 6-9 years is 14 and 22 mg/day, or 0.82 and 0.85 mg/kg body weight per day, respectively, which is lower than these recommendations.

Cancer

Most of the research on possible links between cancer and caffeine has been conducted on coffee and tea. Therefore, it is extremely difficult to isolate the effects of caffeine unless the research specifically focuses on caffeine. Consequently, research on caffeine and its effects on cancer, if any, is sparse. There are however, references in coffee and tea research relating to caffeine that are generally positive.

Caffeine has not been shown in animal or human studies to be carcinogenic. [WHO IARC, 1991] In addition, Nawrot et al. (2003) concluded in his review of the research that caffeine is unlikely to be a human carcinogen at levels below five cups of coffee per day (or less than 500 mg caffeine per day). Furthermore, the overall evidence indicates that caffeine, as present in coffee, does not cause breast or bowel cancer. Moreover, although early case control studies appeared to link caffeine intake to pancreatic, bladder and ovarian cancers, more recent, better designed studies have not supported these conclusions. [Leviton, 1998; Tavani and La Vecchia, 2000; Zeegers, et al., 2004]

A number of case control studies have demonstrated reduced risk of colorectal cancer with coffee consumption. [Tavani and La Vecchia, 2004; Higdon and Frei,

ADDICTION (continued)

amphetamines. The effect of caffeine in nucleus accumbens (a specific portion of the brain involved in addiction) is manifested as a *decrease* in activity of the cells involved, whereas the effects of cocaine and amphetamines are associated with an *increased* activity of the relevant cells. [Fredholm, et al., 1999] Moreover, the term "addiction" implies a compulsive and repeated use of a substance that poses a threat to physical, social, and economic health. Addictive behaviors have been described as both irresponsible and irrational, given the sacrifices the addicts make to procure their drug of choice. This clearly is not the case with caffeine. [Drewnowski and Bellisle, 2007]

HYDRATION

Nearly all the biochemical reactions that occur within the body depend on water and electrolyte balance. These balances are not only vital to maintaining life, but also affect physical and mental performance. Factors affecting hydration are important for everyone, not just for endurance athletes.

People who exercise, especially those who exercise in hot environments, have historically been advised to minimize consumption of caffeine-containing beverages in order to stay hydrated. This is because of caffeine's mild diuretic effect; however, water also has a mild diuretic effect. [Armstrong, 2002] Nonetheless, hydration with respect to caffeinated beverages differs between endurance and at-rest situations. Resting consumption of caffeine results in increased urine flow, whereas consumption during endurance exercise conditions does not. [Wemple, 1997] However, this should not present a problem to the at-rest individual, because the liquid in caffeinated beverages offsets the fluid lost through urination. [Armstrong, 2002; Armstrong, et al., 2005]

Consumption of a caffeinated beverage (max. 250 mg/L) for fluid replacement is effective during moderate to strenuous endurance exercise. [Wemple, et al., 1997]

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2006] In a review, Tavani and La Vecchia (2004) showed that not only was there no risk of colon or colorectal cancer with caffeinated beverages, but there may even be a *protective* effect. A study by Michels et al. (2005) confirmed that there is no association between rectal cancer and consumption of caffeinated beverages.

Cardiovascular Health

The relationship between coffee, caffeine and cardiovascular health markers has been explored, with emphasis on cardiac arrhythmia, heart rate, serum cholesterol and blood pressure. In his review, Nawrot et al. (2003) concluded that moderate caffeine consumption (400 mg or less, or four or fewer cups of coffee per day) does not adversely affect cardiovascular health. Insufficient data exist to be able to draw conclusions about the risk of coronary heart disease (CHD) or mortality associated with consumption of much higher amounts.

In the study by Lopez-Garcia et al. (2006), researchers found that coffee consumption was not associated with an increased risk of coronary heart disease.

Hypertension (high blood pressure) is a recognized risk factor for CHD and stroke. Caffeine can acutely raise heart rate and blood pressure immediately after consumption, although regular caffeine consumers can build up a tolerance to these effects. Although the impact of coffee on blood pressure was first debated nearly thirty years ago, extensive epidemiological studies have confirmed that there is no link between coffee consumption and hypertension, hyperlipidemia, and coronary artery disease (CAD).

One study has linked caffeine intake to abnormal heart rhythms, particularly premature atrial and ventricular contractions of the heart. In this study, caffeine taken in tablet form resulted in blood pressure elevations four times greater than for caffeinated coffee. Thus, although there appears to be no clear evidence for a strong causal relationship between caffeinated coffee and abnormal heart rhythms, it is not as clear when considering caffeine alone or in beverages other than coffee. [Frishman and Sonnenblick, 2002]

Although scientific review author James (2004) suggested there is strong experimental evidence that blood pressure remains reactive to caffeine in the diet, and that overall epidemiological evidence implicates caffeine as a risk factor for hypertension, more recent studies on women have not supported this.

According to the American Heart Association (AHA)'s policy on caffeine, "Whether high caffeine intake increases the risk of coronary heart disease is still under study." [AHA, 2007] However, AHA references two studies of interest —Nurses' Health Studies I and II, carried out on approximately 162,000 nurses over 26 years [Winkelmeyer, et al., 2005], and another long-term study carried out on 128,000 people over 14-20 years in Spain [Lopez-Garcia, et al., 2006] – which offer encouraging results for caffeine.

In the study by Lopez-Garcia et al. (2006), researchers found that coffee consumption was not associated with an increased risk of CHD. In the Nurses' Health Studies I and II, coffee consumption, even at high levels, appeared to have no effect on blood pressure; however, both regular and diet colas caused a modest increase in blood pressure. This apparent contradiction was thought to be due either to an ingredient other than caffeine or by a protective effect of another component of coffee. People already suffering from high blood pressure should consult a physician about their caffeine intake, as they may be more sensitive to the effects of caffeine on blood pressure. [Winkelmeyer, et al., 2005]

Cardiac Arrhythmias

There appears to be no connection between caffeine consumption and cardiac

arrhythmias. Frost and Vestergaard (2005) analyzed the association between the amounts of caffeine consumed daily and the risk of atrial fibrillation (a disorder in which the heart's two upper chambers beat ineffectively, possibly causing clotting and even stroke), or flutter, among 47,949 participants over seven years in a large Danish study. They found no association between caffeine consumption and risk of developing this disorder. [Frost and Vestergaard, 2005] Furthermore, in a study carried out in dogs by Rashid et al. (2006), the presence of caffeine appeared to lead to a reduction in the propensity for atrial fibrillation in both the healthy animals and those with susceptibility for atrial fibrillation.

Stroke

Few studies have specifically reported associations between coffee consumption and stroke, and those that have did not observe significant associations between coffee consumption and the risk of stroke. [Rashid, et al., 2006; Adolfsson, et al., 1977; Grobbee, et al., 1990; Heyden, et al., 1978] One exception was a 25-year study of 499 nonsmoking men with hypertension enrolled in the Honolulu Heart Study. In that high-risk population, the risk of ischemic (clot-induced) stroke in men who consumed at least 24 ounces of coffee per day (about 300 mg caffeine, or three 8-ounce cups) was twice that of men who did not drink coffee. [Hakim and Ross, 1998]

More research is needed to determine whether coffee or caffeine consumption increases the risk of stroke in high-risk groups, such as individuals with hypertension. However, for those having survived a stroke, it would be prudent to seek advice from a physician regarding caffeine intake. [Ragab, et al., 2004]

Heartburn & Gerd

Those affected by gastro-esophageal reflux disease (GERD) and heartburn sometimes complain of discomfort after drinking coffee. However, there is some suggestion that in the elderly, the microsomal enzymatic system (the cleansing function) of the liver may frequently become exhausted, further intensifying GERD and heartburn symptoms, even after consuming small amounts. [Zivkovic, 2000]

Three studies suggested that consuming decaffeinated coffee, but not decaffeinated tea, may reduce the symptoms of GERD. However, tap water with and without added caffeine had no effect on GERD, and reducing the caffeine content of coffee to that of tea still induced symptoms of GERD. Therefore, one can conclude that GERD may be brought on by components of coffee other than caffeine. [Pehl, et al., 1997; Wendl, et al., 1994; Boekema, et al., 1999]

> **"There is insufficient evidence to support the routine recommendation that patients with GERD avoid caffeinated beverages."**

A survey conducted in Australia reported heartburn was aggravated by a number of factors, including spicy foods, greasy or rich foods, stress, alcohol, overeating, smoking, pregnancy, food allergy and coffee. [Bolin, et al., 2000] As these other factors of heartburn do not relate to caffeine, it can be deduced that caffeine in coffee is not the responsible ingredient.

A large, evidence-based review covering research from 1975 to 2004 and 2,039 studies found that the only lifestyle change that favorably impacts those with GERD is sleeping with the head elevated. Removing caffeine from the diet did not improve GERD symptoms, leading the author to conclude that "there is insufficient evidence to support the routine recommendation that patients with GERD avoid caffeinated beverages." [Kaltenbach, et al., 2006]

Hydration (continued)

Research by Armstrong et al. (2005) convincingly shows that during such exercise, caffeine causes no detrimental fluid-electrolyte imbalance. One reason for this may be that exercise reduces glomerular filtration (the filtering and excretory function of the kidney performed by a compact cluster of capillaries in the nephron). This likely is due to the shunting of blood away from the kidneys and other internal organs.

In his review of hydration and caffeinated beverage consumption, Armstrong (2002) concluded that "it is unlikely that athletes and recreational enthusiasts will incur detrimental fluid-electrolyte imbalances if they consume caffeinated beverages in moderation and eat a well-balanced diet. Sedentary members of the general public should be at less risk than athletes because their fluid losses via sweating are smaller."

Contrary to common misperception, these studies show that caffeinated beverages can contribute to hydration. Furthermore, the Institute of Medicine (IOM), in its Dietary Reference Values for Water, Potassium, Sodium, Chloride and Sulfate (IOM, 2004) states that "caffeinated beverages appear to contribute to total daily water intake, similar to non-caffeinated beverages."

With increased attention being paid to nutrition issues, many women, especially those of childbearing age, are concerned about consuming too much caffeine. Women's health issues, such as reproductive effects and osteoporosis, are areas of active research. One confusing aspect of women's health research is that studies of certain women's health issues (such as fertility and birth defects) settle on different levels of caffeine that are considered safe. However, when taken together, the collective research supports moderate consumption of caffeine (approximately 300 mg/day or three cups of coffee per day) as safe for pregnant and post-menopausal women.

Caffeine & Women's Health

Reproductive Health

There are several comprehensive review papers that examine the relationship between caffeine and reproductive health. A review by Leviton and Cowan [2002] specifically examined outcomes such as delayed conception, miscarriage (both chromosomally normal and aberrant), birth defects, premature birth, and low birthweight and found that caffeine does not cause any of these outcomes. The authors concluded that the associations found in the less rigorously analyzed studies could possibly be due to other factors, such as smoking.

Christian and Brent (2001) conducted a very systematic review on the relationship between caffeine consumption by both pregnant women and women of child-bearing age and the occurrence of congenital malformations, fetal growth retardation, small-for-date babies, miscarriages, behavioral effects, maternal infertility and genetic effects. The only statistically significant results were teratogenic (birth defect) effects in rats administered extremely high levels of caffeine intravenously, which do not necessarily translate to humans and also could never be attained merely by drinking beverages containing caffeine.

Fertility

Nawrot et al. (2003) noted in their review of caffeine that most epidemiological studies on caffeine and fertility were affected by methodological issues, including inadequate measurement of caffeine intake, inadequate control for possible confounding factors, recall bias in retrospective studies, lack of data on frequency of unprotected intercourse and, in some studies, inadequate sample size. Despite these limitations, the epidemiological studies generally indicate that consumption of caffeine at levels at or below 300 mg per day, or approximately three cups of coffee per day, did not reduce fertility in otherwise fertile women. [Nawrot, et al., 2003]

A study on the effects of alcohol and caffeine on fertility demonstrated a significant risk when alcohol and caffeine were consumed together; however no effects were observed when caffeine was consumed alone. [Hakim and Gray, 1998] This is important to note, given the combination of energy drinks with alcohol that has been observed in some consumer groups.

Based on the available data from epidemiological studies, Higdon and Frei (2006) suggested that it may be advisable for women who are having difficulty conceiving to limit caffeine consumption to less than 300 mg/day, in addition to eliminating tobacco use and decreasing alcohol consumption. Further studies by Sata et al. (2005) in Japan have suggested that only women having a particular genetic make-up (i.e. possessing homozygous CYP1A21F alleles) are at risk of reduced fertility due to even moderate caffeine consumption (100-299 mg/day).

Miscarriage

There have been numerous epidemiological studies examining the relationship between coffee or caffeine intake by pregnant women and the risk of miscarriage. Some studies have observed significant associations between caffeine intakes greater than 300 mg/day, particularly from coffee, and the risk of miscarriage, whereas other studies have not. [Higdon and Frei, 2006] While individual epidemiological studies cannot prove cause and effect, they can contribute to the wealth of information on potential observed effects. However, they must be taken within the context of the entire body of data. [Nawrot, et al., 2003]

Three reviews were carried out on the effect of coffee and caffeine on miscarriage, but none of them were able to draw concrete conclusions due to methodological issues with the studies reviewed. [Signorello and McLaughlin, 2004; Lawson and LeMasters, 2004; Matijasevich, et al., 2005]

Stein and Susser (1991) hypothesized that the nausea commonly seen in pregnancy may create an erroneous association between caffeine consumption and miscarriage. Nausea is associated with increasing hormone levels during a normal pregnancy and is significantly less common in

pregnancies that end in miscarriage. A more recent study by Lawson et al. (2002) demonstrated that early pregnancy hormone metabolite levels, pregnancy symptoms, and coffee consumption patterns are significantly associated with each other. While higher hormone levels were associated with coffee aversion, lower (unhealthy) levels were not. As a result, caffeine is commonly misperceived to be associated with miscarriage. In fact, nausea due to pregnancy leads to coffee aversion by some women. The authors consider this to be an important variable in investigating any possible relationship between coffee/caffeine consumption and miscarriage, as in many cases nausea is a self-regulating mechanism for reducing caffeine consumption by pregnant women. [Lawson, et al., 2002]

Matijasevich et al. (2006) conducted a case control study to investigate the relationship between caffeine consumption and miscarriage in mothers in Montevideo, Uruguay, and found a positive relationship between high intakes of caffeine (greater than 300mg/day) and miscarriage. This relationship persisted despite accounting for smoking (possibly underreported), prenatal care, nausea/vomiting, both parents' education levels, previous abortions and prenatal deaths, maternal age, and parity. The study did not account for alcohol consumption, and the authors note that there could be another compound in coffee other than caffeine that may affect fetal development.

Cnattingius et al. (2000) conducted a case control study in Sweden to compare the risk of spontaneous first-trimester miscarriage to caffeine intake. They measured plasma cotinine (a metabolite of nicotine) to identify smokers and controlled for fetal karyotype (chromosomal make-up). The results showed that, among smokers, caffeine intake had no effect on first trimester miscarriage. This could be due to the effect of smoking overpowering that of the caffeine, or smoking causing faster metabolism of caffeine. For non-smokers, an effect was only present for those fetuses with normal chromosomal make-up. The authors suggested interpreting the results with caution, as the reason for them is not clear, and under no circumstances recommended smoking.

Methodological issues with these studies have been raised, including limitations in determining caffeine intake and eliminating risk factors for miscarriage, such as nausea and smoking. Although the topic remains controversial, the reviews by Nawrot et al. (2003) and Higdon and Frei (2006) both concluded that maternal consumption of no more than 300 mg/day of caffeine, or approximately three cups of coffee per day, is unlikely to increase the risk of miscarriage.

In early 2008, two studies published on this subject came to significantly different conclusions. Savitz et al. (2008) examined over 2,000 pregnancies and found that caffeine consumption of 200 mg/day during pregnancy is not related to increased miscarriage risk. The median caffeine intake for the women in this study prior to becoming pregnant was 350 mg/day, and they reduced their intake to 200 mg/day during pregnancy. The researchers also noted a possible "recall bias," in which women may inaccurately report prior caffeine consumption after miscarriage. In contrast, in a smaller study of 1,063 pregnancies, Weng et al. (2008) found consumption of 0-200 mg caffeine per day to be associated with increased risk of miscarriage, with a greater risk for intake levels above 200 mg/day. A large percentage of women in the study (59%) miscarried before enrollment, increasing likelihood of "recall bias."

It is notable that the women in the Savitz study reduced their caffeine consumption during pregnancy regardless of whether they had nausea/coffee aversion, demonstrating their previous awareness of advice to pregnant women to reduce their caffeine consumption. Such recommendations are already provided by credible organizations and are generally recognized and accepted by the affected population. For example, the Organization of Teratology Information Specialists (OTIS) [2006] states in informational resources on its Web site for women trying to become pregnant that consuming 300 mg/day of caffeine, or about 3 cups of coffee, should not affect chances of miscarriage. The March of Dimes takes a more conservative approach by recommending that pregnant women limit caffeine consumption to less than 200 mg/day.

Birth Defects (Teratology)

The majority of epidemiological studies have found that maternal caffeine consumption is not associated with increased risk of congenital malformations, or birth defects, in fetuses. [Higdon and Frei, 2006] At present, there is no convincing evidence from epidemiological studies that moderate caffeine consumption by pregnant women ranging from 300–1,000 mg per day throughout the entire pregnancy increases the risk of birth defects. [Nawrot, et al., 2003] However, in light of other women's health issues, such as fertility and miscarriage, pregnant women are advised to keep caffeine consumption at or below 300 mg/day (or approximately three cups of coffee).

Fetal Growth

Grosso et al. (2001) studied the effects of caffeine consumption on Intrauterine Growth Retardation (IUGR) dur-

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Coffee, tea, and other caffeinated beverages appear to lower the risk of Parkinson's Disease (Parkinson's). The mechanism responsible for this reduced risk is thought to be protection of the dopaminergic (DA) cells (neurons in the brain) against neurotoxicity. [Logroscino, 2005] In an article on risk factors of Parkinson's, studies showed coffee drinkers had a 30% lower risk of Parkinson's than non-coffee drinkers. [Hernan, et al., 2003] This protective effect of caffeine has also been seen in previous animal studies. The loss of DA cells due to intentional exposure to a DA neurotoxin was reduced in mice treated with caffeine, but not those that were not exposed to caffeine. [Chen, et al., 2001] Therefore, caffeine may help reduce the loss of DA cells, which in turn lowers the risk of Parkinson's. [Schwartzschild, et al., 2002]

The Honolulu Heart Program, the Nurses' Health Study, and the Health Professionals Follow-Up Study are three long-term studies that showed an association between coffee consumption and a lower risk of development of Parkinson's. [Schwartzschild, et al., 2002; Ross and Petrovitch, 2001] In the Honolulu Heart Program, the incidence of Parkinson's was dose-dependent and decreased with increased coffee consumption. Participants

(continued on p. 11)

ing the first and seventh months of pregnancy. Mothers were interviewed before 16 weeks of gestation and just after birth to determine their caffeine consumption. The babies were weighed within 24 hours of birth and given the Ballard examination (a standard test to determine gestational age). The study found no relationship between caffeine intake and IUGR.

Another study attempted to determine whether a relationship exists between smoking and caffeine intake and the birth weight and size of newborns. All weights and sizes were lower for smokers vs. non-smokers. However, both smoking and non-smoking women with high caffeine intake gave birth to newborns with significantly lower weights compared to women with low caffeine intake. The lengths and head circumferences of the newborns, however, did not change significantly. The authors concluded that smoking was the constant factor in the negative results and should be avoided, and that caffeine intake should be kept at moderate to low (300 mg/day or less) levels during pregnancy. [Balat, et al., 2003] It is important to note that studies on other health conditions (e.g. birth defects) may demonstrate different thresholds for acceptable intake of caffeine. This fact has been reflected in other sections of this Review, concluding that pregnant women should not exceed 300 mg/day (or approximately three cups of coffee).

Bone Health

Given the increased awareness of the incidence of osteoporosis in post-menopausal women, research on the relationship between caffeine intake and bone health has been a particular area of focus.

Consumption of large amounts of caffeine (more than 744 mg/day) has been shown to increase urinary excretion of calcium and magnesium. [Tucker, 2003] However, calcium excretion is complex and is affected by many other dietary constituents such as calcium, potassium, phosphorus, isoflavones, antioxidants, salt, oxalate, phytates, and protein. [Massey, 2003; Atkinson and Ward, 2001]

Studies on caffeine and calcium metabolism and bone deterioration show that, as caffeinated coffee consumption increases, milk consumption decreases. Bone deterioration becomes more pronounced when dietary calcium is inadequate, and less pronounced when dietary calcium intake is adequate. Calcium lost from consuming one cup of coffee per day can be offset by adding just two tablespoons of milk to the coffee. [Ilich and Kerstetter, 2000]

Massey and Whiting (1993) conducted a literature review that examined caffeine intake and bone density, and concluded that moderate caffeine intake did not appear to have negative effects in young adult women. In a more recent review, Massey (1998) concluded that the data support the hypothesis that older women are more sensitive to the effects of caffeine on calcium metabolism, and that caffeine consumption may be a risk factor for bone loss in women over age 50. However, Lloyd et al. (1997) examined the effects of long-term habitual caffeine intake on the bone status of healthy post-menopausal women aged 55-70, who had minimal or no previous exposure to hormone replacement therapy, and found that caffeine intake from 0–1,400 mg/day was not associated with any changes in bone density in this population.

Nawrot et al. (2003) concluded that caffeine's potential to adversely affect calcium balance and bone metabolism is dependent on lifetime caffeine and calcium intakes, and is critical for women. Based on the data reviewed, the authors suggested that caffeine intake of less than 400 mg/day does not have significant effects on bone density, nor on calcium balance in individuals consuming at least 800 mg calcium per day. Higdon and Frei (2006) also suggested that, although most studies have not found coffee or caffeine consumption to reduce 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 three cups of coffee per day (about 300 mg of caffeine per day) may help prevent hip-bone fractures in older adults.

Fibrocystic Breast Disease (FBD)

The debate over whether caffeine has negative effects for breast disease was first raised in the late 1970s. One researcher published several studies suggesting that abstinence from caffeine may alleviate the symptoms of fibrocystic breast disease (FBD), a condition of benign (non-cancerous) fibrous lumps in the breast. Although the studies did not find a link between caffeine and development of the disease, some women with FBD reported feeling less breast tenderness when they eliminated caffeine from their diets. However, no reliable conclusions can be made from the anecdotal reports from these small studies.

The National Cancer Institute (NCI) examined this issue in a case control study involving 3,000 women and found no connection between caffeine and benign breast tumors, FBD, or breast tenderness. [Schairer, et al., 1986] Both the NCI and the American Medical Association (AMA) have concluded that there is no association between caffeine consumption and FBD. [Hogan, et al., 2002]

Benefits of Caffeine

Besides the mental and physical performance benefits of caffeine described above, several areas are emerging in which consumption of caffeine could be beneficial to health. Much of this research has been carried out on coffee, introducing other components of coffee, as well as caffeine, which may be responsible. Such areas include reduced risk of diabetes, reduced risk of Parkinson's Disease (see sidebar on p.10-11), and recovery from liver injury.

Reduced Risk of Diabetes

Caffeine has been shown to improve glucose metabolism in animal studies and short-term human studies. [Keijzers, et al., 2002] However, both caffeinated *and* decaffeinated coffee have also been shown to reduce insulin sensitivity (a potential precursor to diabetes). [van Dam, 2006] Data from epidemiological and cross-sectional studies in Japan, Spain, and Sweden suggest that habitual coffee consumption improves glucose tolerance, and a prospective cohort study of more than 1,100 Dutch men and women found that coffee intake reduced the risk of developing impaired glucose tolerance over the next six years. [Higdon and Frei, 2006; van Dam, et al., 2004]

Large prospective cohort studies in the Netherlands, Finland, Sweden and the United States have found coffee consumption to reduce the risk of developing type 2 diabetes by as much as 55% for men and 79% for women. [Higdon and Frei, 2006; van Dam and Feskens, 2002; Tuomilehto, et al., 2004] Other cohort studies in Finland and Sweden demonstrated a significantly lower risk of developing type 2 diabetes when consuming at least three cups of coffee per day. [Carlsson, et al., 2004; Rosengren, et al., 2004]

The two largest prospective cohort studies to examine the relationship between coffee consumption and type 2 diabetes are the Health Professionals Follow-Up Study (41,934 men) and the Nurses' Health Study (84,276 women). [Salazar-Martinez, et al., 2004] In these studies, men who drank at least six cups of coffee per day had a 54% lower risk of developing type 2 diabetes than men who did not drink coffee at all, and women who drank at least six cups of coffee per day had a 29% lower risk than women who did not drink any coffee. In both cohorts, higher caffeine intakes were associated with significant reductions in diabetes risk. In contrast, tea consumption did not affect type 2 diabetes risk in either study. [van Dam and Feskens, 2002; Salazar-Martinez, et al., 2004] Van Dam and Hu [2005] conducted a systematic review of nine cohort studies, including more than 193,000 men and women, and found a 35% lower risk of type 2 diabetes in those who consumed at least six cups of coffee per day, and a 28% lower risk in those who consumed

REDUCED RISK OF PARKINSON'S DISEASE (continued)

who consumed four 6-ounce cups of coffee per day had more than a five-fold reduction in risk of developing Parkinson's. [Schwartzschild, et al., 2002] In the Nurses' Health Study and the Health Professionals Follow-Up Study, it was reported that regular caffeine consumption was found to be protective against the incidence of Parkinson's. A dose-dependent response was seen in male participants, while women with the lowest risk consumed moderate levels of caffeine (one to three cups of coffee per day, or about 100-300 mg/day). [Ross and Petrovitch, 2001]

Further analysis of the Nurses' Health Study revealed that coffee consumption reduced Parkinson's risk in women who had never used post-menopausal hormone replacement therapy, but a significant increase in Parkinson's risk was observed in women who had used post-menopausal hormone replacement therapy and who drank at least six cups of coffee per day. In the Cancer Prevention Study II cohort, coffee consumption caused a significant reduction in mortality from Parkinson's in women who had never used post-menopausal hormone replacement therapy, but not in those who *had* used it. [Ascherio, et al., 2001]

between four and six cups per day, compared to those who consumed less than two cups per day. In another long-term study of the relationship between caffeinated beverage consumption and incidence of type 2 diabetes, the authors followed more than 41,000 participants over ten years, assessing coffee consumption every two to four years. The results suggest that caffeine intake from coffee and other sources is associated with a significantly lower risk for type 2 diabetes. [Salazar-Martinez, et al., 2004]

Recovery From Liver Injury

Several cross-sectional studies have found coffee intake to reduce serum γ-glutamul transferase (GGT) activity, an indicator of liver injury. [Higdon and Frei, 2006; Dorea and da Costa, 2005] Recently, Ruhl and Everhart (2005) analyzed the data from the U.S. National Health and Nutrition Examination Survey (NHANES) [1988-1994], and found that consumption of either coffee or caffeine decreased the risk of abnormally elevated alanine aminotransferase (ALT) activities. They also conducted a prospective study to examine the relationship between coffee and tea consumption and incidence of chronic liver disease. [Ruhl and Everhart, 2005a] The results showed that individuals who consume more than two cups of coffee or tea per day have less than half the risk of developing chronic liver disease as those who drink less than one cup of coffee per day. Furthermore, several case control studies have demonstrated that coffee consumption reduces the risk of cirrhosis (chronic inflammation of the liver), with four cups per day having the greatest effect. [Corrao, et al., 2001; Gallus, et al., 2002; Higdon and Frei, 2006] Significant inverse associations between consumption of one to three cups of coffee and risk of liver cancer have also been observed in several case control studies in Europe and Japan. [Gallus, et al., 2002a; Wakai, et al., 2007]

Emerging Issues

Science is always evolving into new undiscovered areas. Some of the emerging areas of science that have implications for caffeine and health include improved immune function, genetic susceptibility, and benefits from high intakes of caffeine. These are new areas of research that need more exploration, but they hold promise for prevention and identification of various health conditions in the future.

Improved Immune Function

Horrigan et al. (2006) conducted a critical review of the effects of caffeine on the immune system and the mplications for caffeine consumers. A number of *in-vitro* (in a test-tube or petri-dish) and *in-vivo* (in an animal or human body) studies showed that caffeine can alter various aspects of the immune function. These studies indicate that caffeine is largely anti-inflammatory when consumed at levels of 400-600 mg, or about 4-6 cups of coffee, per day. However, more research is needed to determine the practical implications of caffeine on immunity for a typical coffee consumer.

Genetic Susceptibility

Genetic make-up is becoming an increasing area of interest as it pertains to the effects of caffeine. Initial studies have shown that certain genetic predispositions may exist that could pinpoint someone as part of the sensitive sub-population of caffeine consumers. For example, a study by Sata et al. (2005) referenced in the Women's Health section of this Review suggests that only women possessing homozygous *CYP1A21F* alleles (genetic markers) are at risk of reduced fertility from even low levels of caffeine consumption (100-299 mg/day). Furthermore, a study by Cornelis et al. (2007) suggests that the probability of having the *ADORA2A 1083TT* genotype decreases as habitual caffeine consumption increases, meaning there could be a potential biological basis for caffeine consumption behavior and that individuals with this genotype may be less vulnerable to caffeine's effects.

Benefits of High Intakes of Caffeine

In studies of various health conditions, maximum recommended thresholds for caffeine vary. For example, consumption of 300–1,000 mg caffeine per day has been shown to be acceptable in avoiding birth defects, whereas 300 mg or *less* per day is the threshold for avoiding negative effects on fetal growth.

Athletic performance has also been shown to improve significantly with consumption of moderate and high concentrations of caffeine. As mentioned in the Physical Performance section of this Review, studies showed that consumption of six and eight cups of caffeinated coffee resulted in increased muscle endurance during brief, intense exercise, and improved performance in timed trials, respectively. [Jackman, et al., 1996; Bruce, et al., 2000]

High caffeine intakes for reduced risk of certain health conditions and improvement of athletic performance should be taken in the context of the *overall* health implications. Caffeine levels observed to have beneficial effects for some conditions could have adverse effects for other health conditions, and individuals should consult a physician about safe caffeine intake levels when faced with multiple health concerns.

Summary

Based on the data reviewed, it is evident that caffeine consumption at varying levels may help reduce the risk of several chronic diseases. In addition, most prospective cohort studies have found that caffeine consumption does not significantly increase the risk of coronary heart disease (CHD), stroke, cancer or many women's health issues.

However, sensitive sub-populations, including pregnant women, children and older individuals, and those with a history of heart disease, may experience effects at lower levels of caffeine and should limit their consumption to three cups of coffee per day, or no more than 300 mg/day, to avoid adverse effects. These individuals should consult a physician about caffeine consumption.

For the healthy adult population, moderate caffeine consumption of 300 mg/day is safe and can even have beneficial health implications as part of a healthful diet and physically active lifestyle.

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