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File: ■ Coffee (*Coffea arabica*)
■ Caffeine
■ Cognitive Decline
■ Alzheimer's Disease

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RE: Review of Coffee and Caffeine in Delaying or Preventing Cognitive Decline

Carman AJ, Dacks PA, Lane RF, Shineman DW, Fillit HM. Current evidence for the use of coffee and caffeine to prevent age-related cognitive decline and Alzheimer's disease. *J Nutr Health Aging*. 2014;18(4):383-392.

This review evaluated the use of coffee (*Coffea arabica*) and caffeine to delay or prevent age-related cognitive decline and dementia, as well as the influence of coffee and caffeine on aging and age-related diseases. Caffeine and caffeinated coffee have been shown to improve short-term alertness, attention, and memory. No randomized, controlled trials (RCTs) have been conducted and epidemiological studies evaluating the ability of coffee or caffeine to protect against age-related cognitive decline, Alzheimer's disease (AD), or dementia have produced equivocal results. There are numerous factors in addition to methodological and sociodemographic differences that confound the interpretation and meta-analysis of these observational studies such as childhood cognitive ability/IQ, personal and work habits that affect cognitive health, use of unvalidated questionnaires to assess coffee/caffeine intake, potential negative publication bias, and lack of specificity or controls to differentiate the effect of coffee vs. caffeine. However, based on their review of the epidemiological evidence, the authors conclude that there is a trend towards cognitive protection and a positive effect of caffeine in dementia prevention.

There is evidence linking coffee and caffeine to age-related diseases and pathways that influence aging such as cardiovascular health, inflammation, and glucose metabolism. Vascular health plays a role in several cognitive diseases and a number of epidemiological studies have found that people who consume coffee have decreased risk of cardiovascular disease (CVD), death from CVD and stroke, and all-cause mortality. Coffee's effect on inflammation remains equivocal; however, given the important role inflammation plays in AD the authors deem that this area deserves more research. A 2012 systematic review found that coffee consumption was associated with a decreased risk of developing type 2 diabetes mellitus (T2DM); the decreased risk was more strongly correlated with decaffeinated coffee consumption than caffeinated coffee. One study reported that consumption of four to five cups/day of either caffeinated or

decaffeinated coffee decreased the risk of all-cause mortality and mortality from CVD, stroke, and diabetes. These findings suggest that the non-caffeine components of coffee may also convey important health benefits.

Not all coffee studies have produced positive results and dosage may be a key factor, along with coffee chemotype, processing, and preparation. The dosage most frequently associated with decreased risk is one to three cups/day or approximately 350 mg caffeine/day. However, several studies have reported increased mortality associated with consumption of ≥ four cups/day. A meta-analysis concluded that compared to filtered coffee, the major risk factors for CVD (and by extension dementia) were increased by boiled coffee. The protective effect of caffeine from sources other than coffee is unknown. And perhaps most importantly, the duration of coffee consumption required to obtain protective benefits is unclear.

The most well-studied constituent of coffee, caffeine has been shown to act as an adenosine-receptor antagonist that modulates many brain neurotransmitter systems. It may also inhibit gamma-aminobutyric acid receptors and several phosphodiesterases, increase intracellular calcium release, and activate the brain's antioxidant systems. The neuroprotective and cognitive-enhancing effects of caffeine have been demonstrated in a number of animal AD models, most notably by decreasing beta-amyloid production and acutely lowering plasma beta-amyloid levels.

Coffee contains 800-1,000 other constituents in addition to caffeine. Several experimental studies have found crude extracts have greater neuroprotective effects than pure caffeine. The predominant polyphenols in coffee are caffeic acid and derivative chlorogenic acids (CGAs). The total CGA content in one cup of coffee is typically 70-300 mg and the CGA chemical profile depends on the bean chemotype and the type of processing. CGAs have a number of positive effects on pathways influencing the risk of cognitive decline, including hypertension, inflammation signaling, and glucose metabolism. In animals, the antihypertensive effect of CGA was largely negated by the presence of another coffee polyphenol, hydroxyhydroquinone (HHQ), and a validating RCT found that HHQ-free coffee lowered blood pressure in mildly hypertensive subjects. High intakes of CGA or coffee have been correlated with increased levels of homocysteine though, a potential risk factor for dementia and AD. The constituent eicosanoyl-5-hydroxytryptamide acts on a key enzyme that inhibits pathogenesis in AD and has shown neuroprotective effects in mouse models of AD. The authors report that "it will be marketed as a concentrated component of a nutraceutical called CognionTM (Signum Biosciences; www.signumbiosciences.com)." Other bioactive components include diterpenes, lignans, and the antioxidant melanoidins which are formed in coffee beans during roasting.

Individual variables may also influence the effects of coffee and caffeine. Depression is a risk factor for dementia and coffee consumption is correlated with lower rates of depression. Women generally tend to metabolize caffeine more slowly and there is some evidence that coffee has more pronounced effects in women. Polymorphisms in the genes for adenosine receptors and the cytochrome P450 1A2 (CYP1A2) liver enzyme that metabolizes caffeine have been shown to modulate the physiological effects of caffeine. And finally, the adenosine signaling (which caffeine affects) largely regulates the pathways responsible for wakefulness and sleep; poor sleep quality and sleep disruptions are an early indicator and possibly a risk factor for AD.

Although the bulk of safety data is derived from anecdotal and epidemiological reports, moderate coffee (two to three cups/day) or caffeine intake (200-400 mg/day) is generally regarded as safe for healthy adults. People with CVD, high blood pressure, peptic ulcers, and pregnant women are advised to monitor their intake. Coffee/caffeine may affect the absorption and metabolism of some drugs and nutrients, and the acidity of coffee may aggravate peptic ulcers and acid reflux. Excess caffeine intake (>500 mg acute dose) may result in caffeine intoxication and in rare cases, fatal overdoses.

Recommendations for future research include the following: improved blood-based, inflammatory, and neuroimaging biomarkers for clinical research, improved epidemiological studies (increased power of analyses for confounding variables, distinguish between the effects of caffeine and non-caffeine components, and elucidate the optimum coffee/caffeine intake, effective age range, and duration of use required), RCTs (with controls for confounding factors) assessing biomarkers to validate preclinical data, and more research on the non-caffeine constituents of coffee.

The authors conclude that the recommendation of consuming coffee or caffeine to prevent cognitive loss is largely dependent on the individual; namely, their age, genetics, and comorbidities. Well-designed RCTs are needed before recommendations can be made to the general public. According to the authors, "For now, the most that can be said is that the potential health benefits appear to outweigh the potential harms and that coffee and caffeine may represent relatively safe, low-cost components of a broader dementia prevention strategy."

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to include the original article.