Wake Up and Smell the Coffee

Coffee may indeed be able to forestall some cognitive decline — though overindulgence might not be “good to the last drop” for one’s health.

OK, I admit it: I am addicted to coffee. Of course, I am in good historical company with this involuntary obsession. William Harvey, the 17th century English physician often credited with “discovering” the circulation of the blood, is said to have proclaimed that the coffee bean was the source of “all happiness and wit.” Upon his death, he bequeathed his enormous personal stock, more than 50 pounds of coffee beans, to the Royal College of Physicians.

I am not alone in my addiction. Caffeine is frequently cited as “the most commonly-used psychoactive substance” on earth. On those days when I’ve teetered between the opposing caffeine-related headlines of too much and not enough, I’ve sometimes considered that this stuff really can’t be good for me. It’s practically become a hobby of mine to peruse every article I hear about that addresses the variously purported health risks and benefits of coffee, just to see if I’m really harming myself. Lately, at least as it pertains to cognition in aging, the news is mostly good.

Stimulating News

Two reports came out this year that address the effects of caffeine intake in European samples. One prospective study explored the effects of caffeine consumption on 10-year cognitive decline among older men in Finland, Italy, and the Netherlands; women’s coffee-drinking habits were not addressed. The investigators found that coffee drinkers had 1.4 points less decline on the MMSE than nondrinkers. In a bit of good news for me, there was a dose-related effect, with the most benefit seen at three cups per day. The bad news: a “cup” was defined as only 125ml; my trusty stainless-steel thermal mug holds about 375ml. (So rarely am I without that mug that a colleague once asked me if I’d had it surgically attached to my hand!) In a triumph of wishful thinking, I guess I’ll just believe that European coffee is stronger than what we drink on this side of the pond.

The second study, from a different research group, focused on caffeine intake in three French cities. Over four years of follow-up, women who were heavy coffee drinkers (three or more 100mg caffeine servings per day) showed less decline in verbal and visuospatial memory than low-rate consumers (one serving per day or less). No effect was seen for men, and there was no impact of caffeine consumption on the emergence of dementia.

The absence of a signal regarding dementia risk is a little problematic, because it means that these convergent results might simply represent the well-known (and commonly sought) direct psychostimulant and cognitive enhancement effects of caffeine. The legend of mankind’s discovery of coffee’s stimulant effects is based on what we’d now call an observational study in an animal model. The story goes like this: sometime around the year 600, an Ethiopian goatherd found some of his flock possessed of an unnatural energy after they consumed fruit of a mountainside shrub. He discovered the same effects in himself after eating the berries and passed the knowledge on to a local monastery, from which the news, and then the cultivation of the coffee plant, spread quickly.

Unlike these mythical origins of coffee consumption for mankind as a whole, I can trace the roots of my addiction to some pretty specific circumstances. I was first introduced to the wonderful poison as a freshman in college. My introductory chemistry section met at 8am every Tuesday and Thursday. A classmate, already experienced with the dark brew, explained how it helped her stay awake through the professor’s droning lectures in a hot, overcrowded auditorium filled with more than a hundred dozing 18-year-olds. Like many of us, my addiction rose to full bloom as a house officer in the days before the current era of residency work rules. Toward the end of a 36-hour shift, no sludge in the bottom of those classic spherical glass pots was too thick or too bitter to be considered undrinkable.

The negative findings on AD risk in the French study are also surprising because earlier research suggested that caffeine might protect against the development of AD. When investigators from Portugal retrospectively explored caffeine intake over the 20 years preceding a diagnosis of AD, they found that AD patients had consumed less than half the daily caffeine dose than cognitively normal controls, 199mg vs. 74mg per day. In that study, low caffeine intake was also associated with a greater risk for AD than many of the usual suspects, including low education and positive family history.

Coffee Talk

There are several reasons why these findings on dementia risk might differ from the more recent study. The investigation in France was a prospective design. This suggests that their caffeine intake estimates are likely to be more accurate since they aren’t based on remote recollections. On the other hand, the study examined a much shorter period of exposure, which might be too brief to show an effect. If the Portuguese case-control data represent the true story, I lean toward the briefer expo-
sures considered by the French study as the main reason for the discrepancy. We have already seen a similar effect of exposure duration for nonsteroidal anti-inflammatory drugs (NSAIDs) and AD. Population-based and other epidemiologic studies have pretty consistently supported a role for NSAIDs in protecting against the development of AD, but prospective clinical trials have generally failed to find an effect. So for both caffeine and NSAIDs, it might be that a small cumulative effect only becomes discernable over the course of long term treatment and careful follow-up after a protracted interval.

There are several theoretical reasons to suspect that caffeine might affect dementia risk and expression. Though it has many mechanisms of action, caffeine exerts its stimulant effects primarily by antagonism of neuronal adenosine receptors. There is evidence that caffeine’s antagonism of the A2A class of adenosine receptors may be neuroprotective, perhaps by blocking toxic effects of β-amyloid, though the details of exactly how this occurs remain unclear. Mechanisms unrelated to amyloid might also contribute.

Besides its well-known effect on alertness, caffeine reduces the adverse cognitive consequences of anticholinergic drugs like scopolamine. Other studies suggest augmenting cholinergic transmission might help maintain hippocampal volume in patients with AD, an effect that correlates with improved cognition. Additional subtle mechanisms might also play a role in reducing cumulative AD risk among coffee drinkers. For instance, emerging evidence suggests that caffeine suppresses production of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α). TNF-α mediates inflammatory neurotoxicity in in vitro models of AD. Promising preliminary results have led to proposals for large scale clinical trials to determine if drugs that inhibit TNF-α activity improve cognition or reduce progression in AD patients.

So, should we be suggesting that our patients and those at risk for AD join me in line at the local coffee shop? Certainly that’s premature. Caffeine has other health effects that may offset its potential for cognitive benefits. Those headaches I mentioned, and the occasional bouts of gastritis I recall from my time in training are just the tip of the iceberg. Hypertensive patients, for instance, show all sorts of downstream risks from caffeine intake that may lead to significant increases in cardiac and stroke-related morbidity.

Another observation that raises questions about the clinical meaningfulness of the caffeine effects on dementia risk is the fact that Americans don’t (on average) consume anywhere nearly as much dietary caffeine as our friends in the Nordic countries. Our meager consumption of about 170mg/day pales in comparison to the 400 or so mg/day in Norway, Sweden, Denmark and Finland; residents of the Netherlands are the world’s top consumers of caffeine, at 414mg/day. These figures are important because they place average US consumption in the range suggested to be protective in the Portuguese case-control study on dementia risk, and because incidence and prevalence of AD in those high-consumption countries aren’t clearly different than in low-consumption areas.

Still, the ideas about caffeine’s receptor-based mediation of amyloid neurotoxicity and possible inhibitory effects on the inflammatory cascade warrant careful consideration. That makes me want to grab a cup of coffee and sit down to think this through...