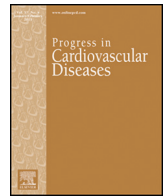




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## Progress in Cardiovascular Diseases

journal homepage: [www.onlinepcd.com](http://www.onlinepcd.com)Coffee for Cardioprotection and Longevity<sup>☆</sup>James H. O'Keefe<sup>a,\*</sup>, James J. DiNicolantonio<sup>a</sup>, Carl J. Lavie<sup>b</sup><sup>a</sup> Saint Luke's Mid America Heart Institute, Kansas City, MO, United States<sup>b</sup> Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, United States

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## ABSTRACT

Coffee, a complex brew containing hundreds of biologically active compounds, exerts potent effects on long-term human health. Recently, a plethora of studies have been published focusing on health outcomes associated with coffee intake. An inverse association between coffee consumption and all-cause mortality has been seen consistently in large prospective studies. Habitual coffee consumption is also associated with lower risks for cardiovascular (CV) death and a variety of adverse CV outcomes, including coronary heart disease (CHD), congestive heart failure (HF), and stroke; coffee's effects on arrhythmias and hypertension are neutral. Coffee consumption is associated with improvements in some CV risk factors, including type 2 diabetes (T2D), depression, and obesity. Chronic coffee consumption also appears to protect against some neurodegenerative diseases, and is associated with improved asthma control, and lower risks for liver disease and cancer. Habitual intake of 3 to 4 cups of coffee appears to be safe and is associated with the most robust beneficial effects. However, most of the studies regarding coffee's health effects are based on observational data, with very few randomized controlled trials. Furthermore, the possible benefits of coffee drinking must be weighed against potential risks, which are generally due to its high caffeine content, including anxiety, insomnia, headaches, tremulousness, and palpitations. Coffee may also increase risk of fracture in women, and when consumed in pregnancy coffee increases risk for low birth weight and preterm labor.

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American adults drink more coffee than any other beverage except water (Fig 1).<sup>1</sup> Coffee is the major source of caffeine intake for adults, though the profound and multifaceted biological effects of chronic

coffee intake go far beyond the actions of caffeine. Consumption of coffee has been generally rising for the past 25 years, and today about 2 out of every 3 American adults drink coffee on a daily basis.<sup>2</sup> The population in the United States (US) consumes over 400 million cups of coffee daily, and has the highest per capita coffee intake of any nation.<sup>3</sup> Because of its widespread habitual consumption even modest health effects of coffee will likely have important public health implications. The purpose of this review is to summarize the emerging data regarding the effects of habitual coffee consumption on long-term health and wellbeing, focusing especially on cardiovascular (CV) health.

**Abbreviations and Acronyms:** BP, blood pressure; CV, cardiovascular; CHD, coronary heart disease; HF, heart failure; HTN, hypertension; T2D, type 2 diabetes; US, United States.

☆ Statement of Conflict of Interest: see page XX.

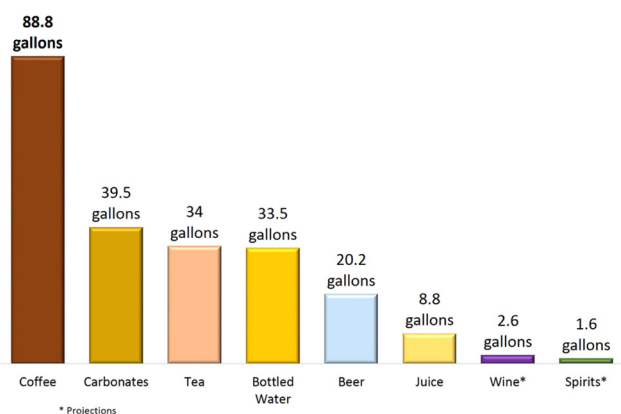
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**Fig 1.** Americans drink more coffee than soda, tea and juice combined. Karl Paul, reporter for MarketWatch: International Coffee Day: Sept 29, 2017.<sup>1</sup>

### Bioactive Compounds in Coffee

Coffee is a complex brew containing over 1000 botanical compounds, many of which are biologically active, including caffeine (a central nervous system stimulant and bronchodilator), diterpenes (which can increase serum cholesterol), chlorogenic acid (which improves glucose metabolism), as well as melanoids, quinides, lignans, and trigonelline—all of which confer antioxidant and anti-inflammatory effects.<sup>4</sup>

Caffeine is largely responsible for the intrinsically habit-forming nature of coffee. The caffeine content of coffee is highly variable, even when the coffee beverage is obtained from the same vendor.<sup>3,5</sup> A typical 8-oz cup of brewed coffee contains from 70 to 165 mg of caffeine. Yet, in the US serving sizes of coffee are often much larger (commonly 10 to 24 oz), often delivering 180 to 300 mg of caffeine per serving.<sup>3,6</sup> Instant coffee contains approximately 30 to 90 mg of caffeine per cup, whereas espresso usually has about 60 mg per shot. Brewed decaffeinated coffee contains only about 3 mg of caffeine per 8 oz.

### Coffee's Effects on Blood Pressure, Coronary Calcium, Erectile Function and Obesity

Coffee drinking can acutely cause modest increases in blood pressure (BP) among caffeine-naïve individuals but exerts insignificant effects on BP levels on habitual coffee drinkers.<sup>7</sup> Meta-analyses consistently report that coffee does not cause clinically important changes in BP, nor does it increase the risk of hypertension (HTN).<sup>7,8</sup> The Nurses' Health Study based on 1.4 million person-years of follow-up found that coffee consumption (up to 6 cups/day) was not associated with an increased risk of developing HTN.<sup>9</sup> However, coffee is high in caffeine, which is metabolized by the cytochrome P450 1A2 (CYP1A2) enzyme. People who are homozygous for the CYP1A2\*1A allele metabolize caffeine rapidly, whereas individuals who carry the variant CYP1A2\*1F allele tend to be relatively slow at metabolizing caffeine. Cross sectional studies suggest that slow caffeine metabolizers may be at higher risk for developing HTN and myocardial infarction.<sup>10,11</sup>

Among 3724 males over the age of 20 who participated in the National Health and Nutrition Examination Survey, the men who consumed the amount of caffeine present in about 2 or 3 cups of coffee daily had a 42% lower occurrence of erectile dysfunction.<sup>12</sup>

Epidemiological studies indicate that coffee consumption may reduce the likelihood of developing obesity. Especially among individuals who are genetically predisposed to develop obesity, higher coffee consumption is associated with lower body mass index.<sup>13</sup> In other words, habitual coffee consumption might attenuate a genetic tendency to become obese.

### Coffee and Diabetes

Although caffeine acutely increases both glucose and insulin levels in short term studies,<sup>14</sup> coffee paradoxically reduces the risk of type 2 diabetes (T2D) in long-term studies. This is likely because coffee contains high concentrations of potent antioxidants, yet has no calories. Notably, intervention trials have established the fact that coffee consumption can improve glucose metabolism and insulin sensitivity. One 16-week randomized trial found that both caffeinated coffee and decaffeinated coffee reduced post-glucose challenge blood sugar levels.<sup>15</sup> Additionally, an 8-week randomized placebo-controlled study showed that coffee improves levels of adiponectin—an insulin-sensitizing cytokine.<sup>14</sup>

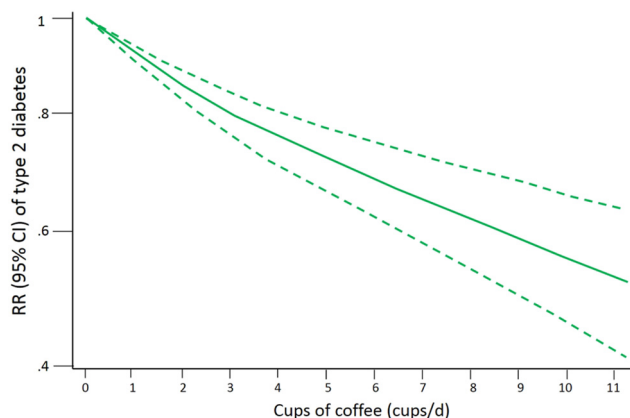
A large meta-analysis of prospective cohort studies show a clear inverse relationship between coffee consumption and the likelihood of developing T2D whereby every additional cup/day conferred an additional 7% risk reduction (Fig 2).<sup>16,17</sup> This study reported that compared to non-coffee drinkers, subjects who consumed 6 or more cups of coffee daily had a significantly lower risk of developing T2D (relative risk [RR]: 0.65; 95% CI: 0.54 to 0.78); subjects who consumed 4 to 6 cups daily also had a significantly lower risk of T2D (RR: 0.72; 95% CI: 0.62 to 0.83).<sup>17</sup>

Recent studies show that changes in one's habitual coffee consumption translate into subsequent changes in risk of T2D. By studying three large prospective cohorts with >1.6 million person-years of follow-up, Ding and colleagues found that individuals who increased their consumption of coffee by one or more cups/day had an 11% lower risk of developing T2D.<sup>18</sup> Conversely, individuals who reduced their coffee intake by 1 cup/day increased their risk of developing T2D by 17%. Importantly, adding sugar or other sweeteners to coffee can diminish its potential benefits on glucose metabolism.<sup>19–21</sup>

### Landmark Epidemiology Studies

Recent large prospective cohort studies using rigorous statistical methodology have consistently found that habitual coffee consumption is associated with a host of health benefits. The cumulative body of data indicates that moderate coffee consumption, about 2 to 5 cups (16 to 40 oz) daily, may be associated with lower all-cause mortality rates, and lower risks for CV death, T2D, liver disease, Parkinson's disease, depression and suicide.

Recently, Poole and colleagues analyzed the totality of higher level evidence regarding the effects of coffee consumption on all studied health outcomes.<sup>22</sup> In the most comprehensive analysis of coffee's health effects published thus far, the researchers concluded that drinking 3 to 4 cups of coffee daily conferred the maximal health benefits, including highly significant risk reductions in all-cause mortality (RR 0.83, CI 0.78 to 0.88), CV mortality (RR 0.81, CI 0.72 to



**Fig 2.** Dose-response analysis of the association between coffee consumption and risk of type 2 diabetes.<sup>16</sup>

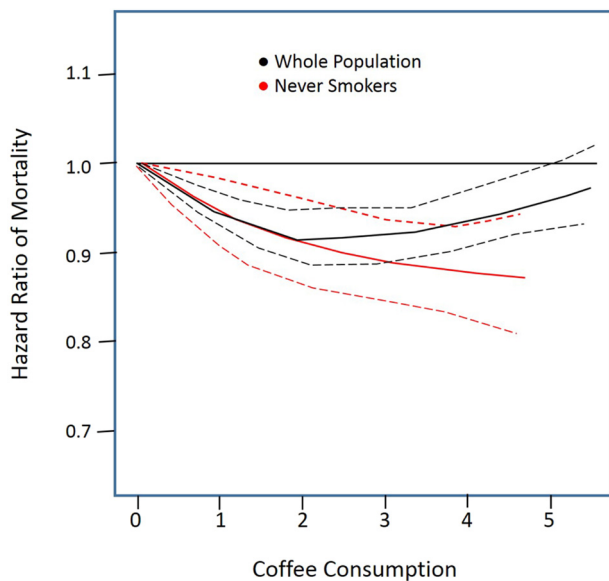


Fig 3. Hazard ratio of mortality with coffee consumption (in cups/day).<sup>31</sup>

0.90), and CV disease (RR0.85, CI 0.80 to 0.90). In this definitive umbrella review of meta-analyses, high versus low coffee intake was also associated with an 18% lower risk of cancer occurrence.<sup>22</sup> Although there is some evidence that drinking >4 cups of coffee per day could have adverse effects in young people,<sup>23</sup> the majority of evidence supports the efficacy and safety of moderate-high coffee doses.

Higher coffee intake was associated with improved life expectancy and reduced risk of CV mortality in EPIC—a multicenter prospective cohort study of 521,330 adults who were recruited from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) and followed for an average of 16 years.<sup>6</sup> This study found that daily coffee drinkers had a 7% to 12% lower risk of dying prematurely compared to non-drinkers; a daily intake of at least 3 cups of coffee per day was associated with a significantly lower risk of all-cause mortality. Moreover, participants who consumed at least 2 cups/day were less likely to die from suicide, and diseases of the circulatory and digestive systems.<sup>6</sup>

Investigators incorporating machine learning in their analysis of data from the Framingham Heart Study recently reported that coffee consumption was associated with a reduced risk for major adverse CV events.<sup>24</sup> Compared to no coffee, every 8-oz cup/day reduced the risk

of heart failure (HF) by 7%, stroke by 8%, and coronary heart disease (CHD) by 5%. A different meta-analysis found a U-shaped association between coffee consumption and the occurrence of HF, wherein 4 cups/day of coffee was linked with the lowest risk.<sup>25</sup> Importantly, caffeine intake at doses up to 500 mg/day (equivalent to 4 or 5 cups of coffee) does not change the frequency, inducibility, or severity of ventricular arrhythmias, as shown in multiple randomized placebo-controlled trials.<sup>26,27</sup> Furthermore, several large prospective epidemiological studies report that consumption of coffee with or without caffeine is not associated with a heightened risk of atrial fibrillation.<sup>28,29</sup>

Another recent cohort study followed 19,896 middle-aged university graduates from Spain.<sup>30</sup> After statistically adjusting for potential confounders, drinking at least two cups of coffee per day was associated with a 22% lower risk of all-cause mortality, with a hazard ratio (HR) = 0.78; 95% confidence interval (CI) = 0.66–0.92. In this cohort the coffee protection was most significant among individuals at least 45-years-old, for whom drinking 2 additional cups of coffee per day was linked with a 30% lower risk of mortality during follow-up (adjusted HR = 0.70; 95% CI = 0.58–0.85).<sup>30</sup>

Harvard researchers followed 208,000 health professionals for about 25 years as part of a prospective cohort study to assess coffee's effects on survival.<sup>31</sup> They reported significant inverse associations for both caffeinated ( $P$  value for trend <0.001) and decaffeinated coffee ( $P$  value for trend = 0.022) and all-cause mortality (Fig 3). Additionally, coffee consumption was significantly inversely associated with CV mortality, and mortality due to neurologic disease.<sup>31</sup> A meta-analysis of 36 prospective cohort studies with 1,279,804 participants found that moderate coffee consumption was associated with lower risks of adverse CV events.<sup>32</sup> Coffee intake of 3 to 5 cups/day was associated with the lowest risk, with less benefit noted at lighter and heavier coffee intakes.<sup>32</sup>

A very recent paper focused on a multi-ethnic prospective cohort study comprised of 185,000 non-white participants including African-Americans, Native Americans, Hawaiians, Japanese-Americans, and Latinos who were followed for a mean of 16 years.<sup>5</sup> This study found that coffee intakes of 1 cup/day and 3 cups/day were associated with 12% and 18% reductions in risk of all-cause mortality, respectively (Fig 4).<sup>5</sup> This study reported that daily coffee consumption was also associated with reduced risks for death due to CV disease, cancer, T2D, respiratory disease and kidney disease.<sup>5</sup>

Coffee consumption is significantly associated with improved asthma control, and reduced risk of some gastrointestinal diseases, including reduced risks for liver disease, hepatic steatosis, and liver cancer.<sup>22</sup> A large meta-analysis comprised of 432,133 participants suggested that increasing coffee consumption might substantially

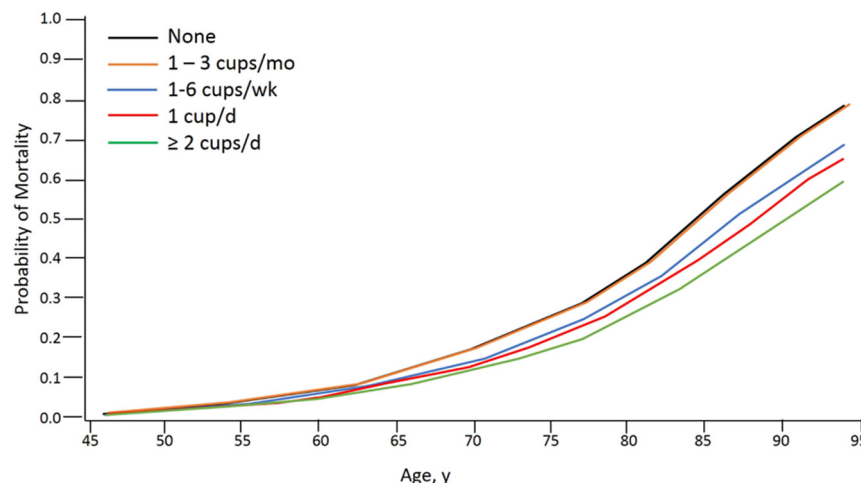


Fig 4. Fully adjusted Cox all-cause mortality curves were generated using the Cox mode. The “None” and “1–3 cups” lines overlap.<sup>5</sup>

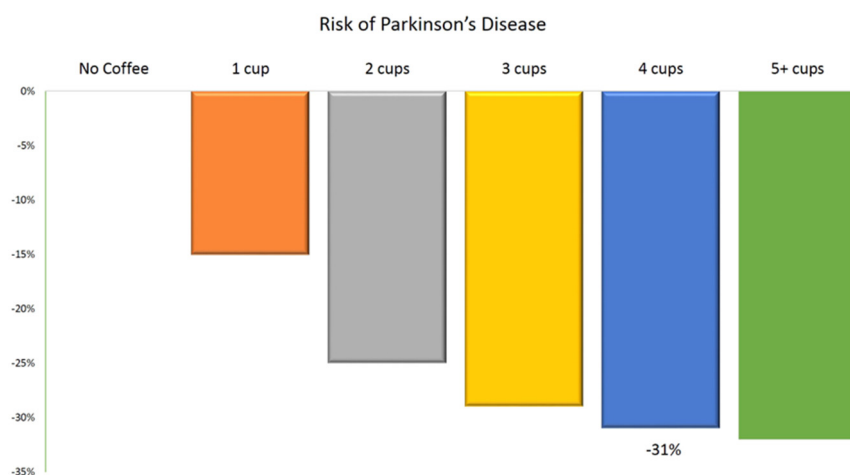


Fig 5. Coffee intake in cups per day and risk of developing Parkinson's disease.<sup>36</sup>

reduce the risk of cirrhosis in a dose-dependent fashion.<sup>33</sup> An increase in coffee consumption of 2 cups/day was linked to a decrease risks for cirrhosis, RR = 0.58 (95% CI 0.41–0.76), and for death from cirrhosis the RR = 0.55 (95% CI 0.35–0.74).

### Coffee and Brain Health

The habitual consumption of coffee daily is also strongly associated with lower risks for neurodegenerative diseases, including Parkinson's disease and Alzheimer's dementia.<sup>34,35</sup> A meta-analysis of 26 studies reported that coffee intake of about 3 cups/day reduced the risk of developing Parkinson's disease by 25% (Fig 5).<sup>36</sup> Additionally, recent reviews concluded that moderate coffee consumption might reduce the risk for Alzheimer's disease, though the precise impact is not yet clear.<sup>34,35</sup> Moreover, coffee intake is associated with lower risks for multiple sclerosis, depression and suicide.<sup>5</sup> Caffeinated coffee (but not decaffeinated coffee) produced a dose-dependent reduced risk of depression and suicide in a group of 208,000 people followed at least 16 years.<sup>37</sup> Four cups of coffee/day reduced risk of suicide by about 50% in both men and women (Fig 6).

### Limitations

The apparent health benefits of coffee are predominantly based on observational data, with a paucity of randomized controlled studies. Association does not prove causation; though the experimental data is

generally confirmatory regarding the epidemiological findings suggesting coffee has beneficial effects on human health. Even so, larger long-term randomized placebo controlled outcome studies with coffee are not feasible for many reasons.

The potential benefits of daily coffee consumption must be balanced against potential risks. The diterpenes in coffee can raise serum cholesterol.<sup>38</sup> In particular, boiled unfiltered coffee can raise cholesterol modestly. However, a standard coffee filter removes diterpenes and thus filtered coffee has largely neutral effects on lipids.<sup>22</sup> Other adverse effects are predominantly due to the high caffeine content of most coffee preparations, which can lead to insomnia, anxiety, palpitations, tremors, in addition to bone loss and the potential for increased fracture risk, especially among women.<sup>3</sup> Additionally, coffee and caffeine consumption during pregnancy can increase risk for low birth weight and preterm birth.<sup>22</sup>

The International Agency for Research on Cancer (IARC), which is the cancer agency of the World Health Organization, recently classified the drinking of very hot beverages (hotter than 149 °F or 65 °C) a probable carcinogen.<sup>39</sup> Hot coffee is typically served at about 65 °C, so coffee should be allowed to cool to less than scalding hot temperatures before drinking. Additionally, roasted coffee contains acrylamide, a potential carcinogen. However, the level of acrylamide in coffee is very low, and the IARC has recently concluded that coffee is associated with decreased risks for liver cancer and endometrial cancer, and is unlikely to cause breast cancer, prostate cancer, or pancreatic cancer.<sup>39</sup>

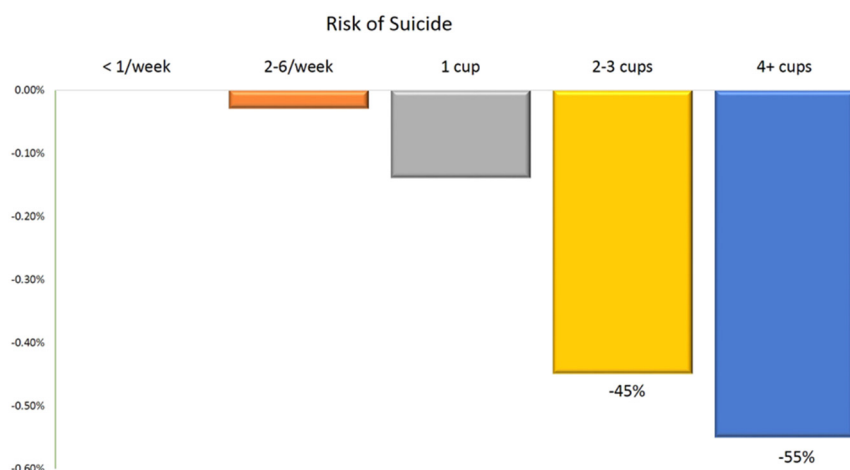


Fig 6. Coffee intake in cups per day and suicide risk.<sup>37</sup>



Finally, regular coffee consumption leads to physical and psychological dependence—another consequence of its high caffeine content. Yet, even this liability can be advantageous in that the predictable withdrawal symptoms of headache, fatigue and lethargy tend to reinforce daily coffee intake—which in fact is the single richest source of antioxidants in the American diet.<sup>3</sup>

## Conclusions

An increasingly impressive and consistent body of data indicates that coffee consumption is associated with dose-dependent reductions in all-cause mortality and CV mortality. Coffee also reduces risks for T2D, liver disease, Parkinson's disease, depression, and suicide. Daily consumption of 2 to 5 cups of coffee (16 to 40 oz) with caffeine intakes up to 400 mg/day appears to be safe and is linked with the strongest beneficial effects for the majority of the studied health outcomes.

## Statement of Conflict of Interest

None of the authors have any conflicts of interests with regard to this publication.

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