REVIEW ARTICLE

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Coffee, Caffeine, and Health

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Coffee and tea are among the most popular beverages worldwide and contain substantial amounts of caffeine, making caffeine the most widely consumed psychoactive agent.[1] A variety of plants contain caffeine in their seeds, fruits, and leaves. Besides coffee and tea, these plants include cacao beans (an ingredient of chocolate), yerba matte leaves (used to make an herbal tea), and guarana berries (used in various beverages and supplements).[1,2] Caffeine can also be synthesized and is added to foods and beverages, including soft drinks, energy drinks, and energy shots, and to tablets marketed for reducing fatigue.[2] In addition, caffeine is widely used as a treatment for apnea of prematurity in infants,[3] and caffeine and analgesic agents are used together in pain medications.[4]

Coffee and tea have been consumed for hundreds of years and have become an important part of cultural traditions and social life.[5] In addition, people use coffee beverages to increase wakefulness and work productivity. The caffeine content of commonly used sources of caffeine is shown in Table 1. For a typical serving, the caffeine content is highest in coffee, energy drinks, and caffeine tablets; intermediate in tea; and lowest in soft drinks. In the United States, 85% of adults consume caffeine daily,[6] and average caffeine intake is 135 mg per day, which is equivalent to about 1.5 standard cups of coffee (with a standard cup defined as 8 fluid oz [235 ml]).[7] Coffee is the predominant source of caffeine ingested by adults, whereas soft drinks and tea are more important sources of caffeine ingested by adolescents (Fig. 1).

Concerns have long existed that coffee and caffeine may increase the risks of cancer and cardiovascular diseases, but more recently, evidence of health benefits has also emerged.[8] A key issue in research on caffeine and coffee is that coffee contains hundreds of other biologically active phytochemicals, including polyphenols such as chlorogenic acid and lignans, the alkaloid trigonelline, melanoidins formed during roasting, and modest amounts of magnesium, potassium, and vitamin B_3 (niacin).[8] These coffee compounds may reduce oxidative stress,[9] improve the gut microbiome,[10] and modulate glucose and fat metabolism.[11,12] In contrast, the diterpene cafestol, which is present in unfiltered coffee, increases serum cholesterol levels.[13] Thus, research findings for coffee and other dietary sources of caffeine should be interpreted cautiously, since effects may not be due to caffeine itself.

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N Engl J Med 2020;383:369-78.
DOI: 10.1056/NEJMra1816604

METABOLISM, PHYSIOLOGICAL EFFECTS, AND TOXIC EFFECTS

ABSORPTION AND METABOLISM

Chemically, caffeine is a methylxanthine (1,3,7-trimethylxanthine). Caffeine absorption is nearly complete within 45 minutes after ingestion, with caffeine blood

Table 1. Caffeine Content of Commonly Consumed Foods, Beverages, and Over-the-Counter Drugs in the United States.*

Source	Serving Size†	Milligrams of Caffeine
Coffee, brewed, coffee shop	12 fluid oz	235
Americano, coffee shop	12 fluid oz	150
Coffee, brewed	8 fluid oz	92
Coffee, instant	8 fluid oz	63
Espresso	1 fluid oz	63
Decaffeinated coffee	8 fluid oz	2
Black tea, brewed	8 fluid oz	47
Green tea, brewed	8 fluid oz	28
Chamomile or peppermint tea	8 fluid oz	0
Cola soft drink	12 fluid oz	32
Energy drink	8.5 fluid oz	80‡
Energy shot	2 fluid oz	200‡
Dark chocolate	1 oz	24
Milk chocolate	1 oz	6
Over-the-counter drug for alertness	1 tablet	200
Headache medication with caffeine	1 tablet	65

* Information is from FoodData Central.[2]
† To convert fluid ounces to milliliters, multiply by 29.57. To convert ounces of chocolate to grams, multiply by 28.35.
‡ The caffeine content is shown for commonly used versions of energy drinks and shots, but the content may vary, particularly with different brands.

levels peaking after 15 minutes to 2 hours.[14] Caffeine spreads throughout the body and crosses the blood–brain barrier. In the liver, caffeine is metabolized by cytochrome P-450 (CYP) enzymes — in particular, CYP1A2. Caffeine metabolites include paraxanthine and, in smaller amounts, theophylline and theobromine, which are further metabolized to uric acid and eventually excreted with urine. The half-life of caffeine in adults is typically 2.5 to 4.5 hours but is subject to large variation from one person to another.[14] Newborns have a limited capacity to metabolize caffeine, and the half-life is about 80 hours. After 5 to 6 months of age, the capacity for caffeine metabolism per kilogram of body weight does not change much with age. Smoking greatly accelerates caffeine metabolism, reducing the half-life by up to 50%, whereas oral contraceptive use doubles the half-life of caffeine. Pregnancy greatly reduces caffeine metabolism, especially in the third trimester, when the half-life of caffeine can be up to 15 hours.

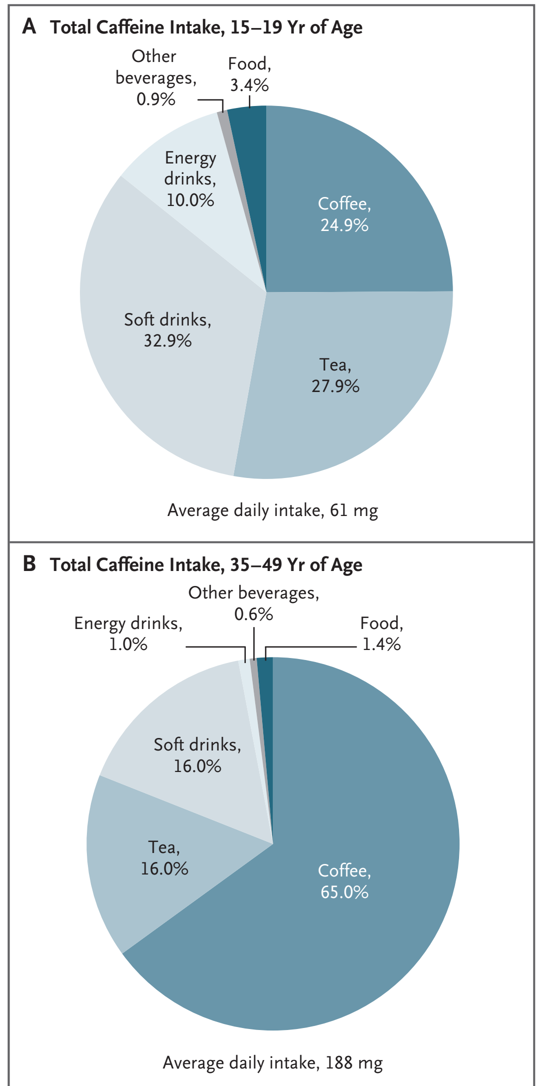

Figure 1. Sources of Caffeine and Average Daily Intake in Adolescents and Middle-Aged Adults in the United States.

Data are from the National Health and Nutrition Examination Surveys, 2011–2012.[7] Panel A shows caffeine sources and daily intake for adolescents, and Panel B shows sources and intake for adults 35 to 49 years of age.

The activity of caffeine-metabolizing enzymes is partly inherited.[15] For example, a variant in the gene encoding CYP1A2 is associated with higher plasma caffeine levels and a lower ratio of paraxanthine to caffeine (which reflects slower caffeine metabolism), as well as with a lower caffeine intake.[16] Persons with genetically determined slower caffeine metabolism tend to com-

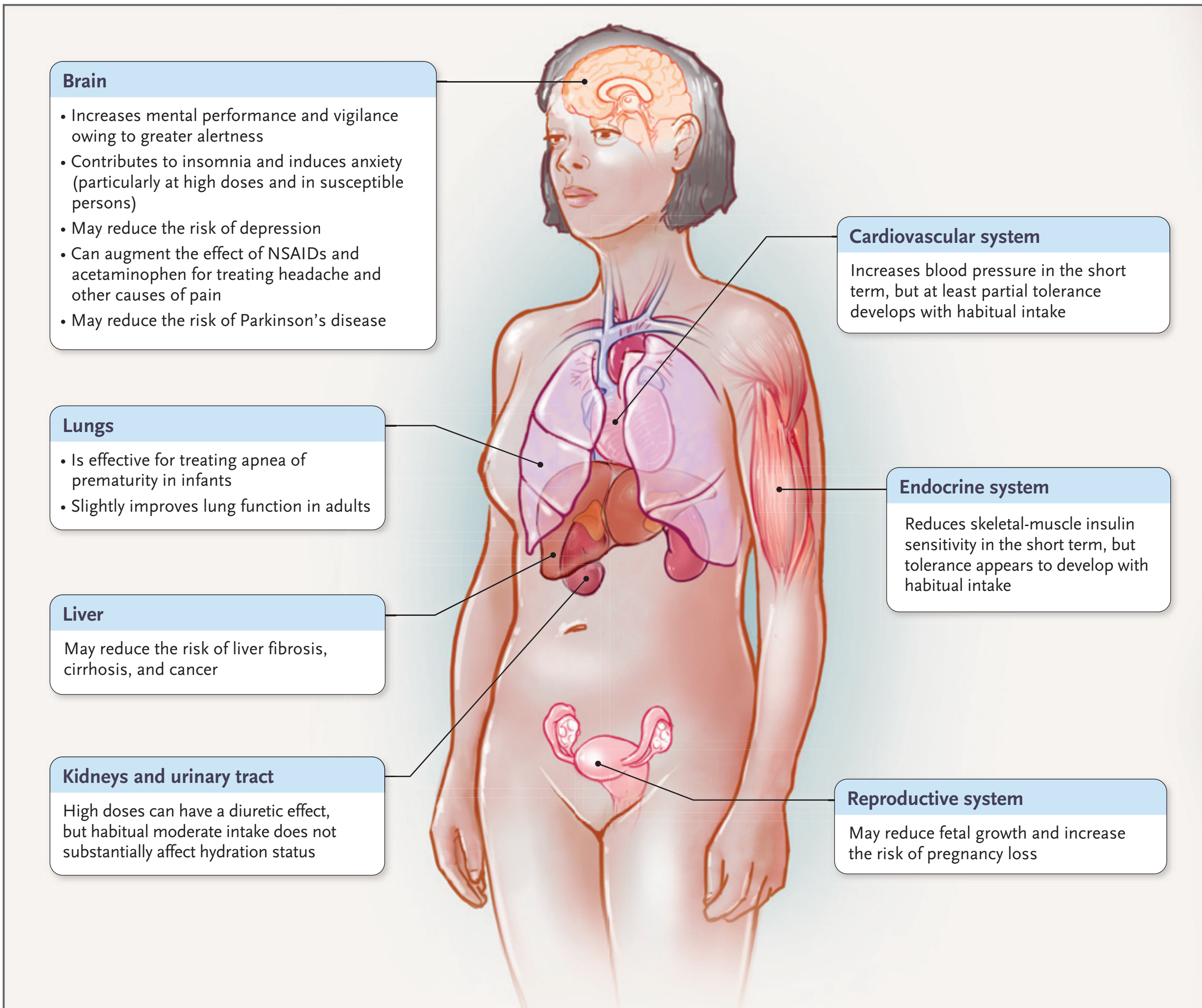

Figure 2. Effects of Caffeine Intake on Health, According to Organ System.

Information is from Schmidt et al.,[3] Derry et al.,[4] McLellan et al.,[18] Clark et al.,[19] Lara,[20] Qi et al.,[21] Kang et al.,[22] Welsh et al.,[23] Kennedy et al.,[24,25] Wijarnpreecha et al.,[26] Chen et al.,[27,28] Armstrong et al.,[29] Robertson et al.,[30] Greer et al.,[31] and Alperet et al.[32] NSAIDs denotes nonsteroidal antiinflammatory drugs.

pensate by having lower habitual caffeine intake than persons without this genetic predisposition.[17] In addition, medications from a range of drug classes (including several quinolone antibiotics, cardiovascular drugs, bronchodilators, and antidepressant agents) can slow caffeine clearance and increase its half-life, generally because they are metabolized by the same liver enzymes.[14] Similarly, caffeine can affect the action of various drugs, and clinicians should consider possible caffeine–drug interactions when prescribing medications.[14]

BENEFICIAL EFFECTS ON COGNITIVE PERFORMANCE AND PAIN

The molecular structure of caffeine is similar to that of adenosine, which allows caffeine to bind to adenosine receptors, block adenosine, and inhibit its effects (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[1] Accumulation of adenosine in the brain inhibits arousal and increases drowsiness. In moderate doses (40 to 300 mg), caffeine can antagonize the effects of adenosine and reduce fatigue, increase alertness, and reduce reaction time (Fig. 2).[19,33]

These effects of caffeine have also been observed in persons who do not habitually consume caffeine and after short periods of abstinence in habitual consumers.[33] Caffeine intake can also improve vigilance during tasks of long duration that provide limited stimulation, such as working on an assembly line, long-distance driving, and flying aircraft.[18] Although these mental benefits are most pronounced in sleep-deprived states,[18,34] caffeine cannot compensate for the decline in performance after long-term sleep deprivation.[35]

Caffeine can contribute to pain relief when added to commonly used analgesic agents. Specifically, a review of 19 studies showed that 100 to 130 mg of caffeine added to an analgesic modestly increased the proportion of patients with successful pain relief.[4]

EFFECTS ON SLEEP, ANXIETY, AND HYDRATION AND WITHDRAWAL SYMPTOMS

As expected from its effects on fatigue, caffeine consumption later in the day can increase sleep latency and reduce the quality of sleep.[19] In addition, caffeine can induce anxiety, particularly at high doses (>200 mg per occasion or >400 mg per day) and in sensitive persons, including those with anxiety or bipolar disorders.[20] Interpersonal differences in the effects of caffeine on sleep and anxiety are large. These differences may reflect variation in the rate of caffeine metabolism and variants in the adenosine receptor gene.[14,36] Caffeine consumers and physicians should be aware of these possible side effects of caffeine, and persons who drink caffeinated beverages should be advised to reduce caffeine intake or avoid intake later in the day, if these effects occur. High caffeine intake can stimulate urine output, but no detrimental effects on hydration status have been found with longer-term intake of moderate doses of caffeine (≤400 mg per day).[29,37]

Quitting caffeine intake after habitual consumption can lead to withdrawal symptoms, including headaches, fatigue, decreased alertness, and depressed mood, as well as influenza-like symptoms in some cases.[38] These symptoms typically peak 1 to 2 days after cessation of caffeine intake, with a total duration of 2 to 9 days, and can be reduced by gradually decreasing the caffeine dose.

TOXIC EFFECTS

Side effects of caffeine at very high levels of intake include anxiety, restlessness, nervousness, dysphoria, insomnia, excitement, psychomotor agitation, and rambling flow of thought and speech.[20] Toxic effects are estimated to occur with intakes of 1.2 g or higher, and a dose of 10 to 14 g is thought to be fatal.[39] A recent review of blood caffeine levels in cases of fatal overdoses showed that the median postmortem blood caffeine level was 180 mg per liter, which corresponds to an estimated intake of 8.8 g of caffeine.[40] Caffeine poisoning from consumption of traditional sources of caffeine such as coffee and tea is rare because a very large amount (75 to 100 standard cups of coffee) would have to be consumed in a short time for the dose to be fatal. Caffeine-related deaths have generally been due to very high doses of caffeine from tablets or supplements in powdered or liquid form, mostly in athletes or patients with psychiatric disorders.[41]

In case reports, high consumption of energy drinks and shots, especially when mixed with alcohol, has also been linked to adverse cardiovascular, psychological, and neurologic events, including fatal events.[42] Caffeine in the form of energy drinks and shots may have more adverse effects than other caffeinated beverages for several reasons: high episodic consumption of these forms of caffeine, which does not allow the development of caffeine tolerance; popularity among children and adolescents, who may be more vulnerable to the effects of caffeine; lack of clarity on the part of consumers about caffeine content; possible synergistic effects with other components of the energy drinks; and combination with alcohol consumption or vigorous exertion. High consumption of energy drinks (approximately 34 fluid oz [1 liter], containing 320 mg of caffeine), but not moderate consumption (≤200 mg of caffeine), resulted in adverse short-term cardiovascular effects (increased blood pressure, prolonged QT interval corrected for heart rate, and palpitations) in several studies.[42] Persons who consume energy drinks should thus be advised to check the caffeine content and avoid high consumption (>200 mg of caffeine per occasion) or consumption in combination with alcohol.

Coffee, Caffeine, and the Risk of Chronic Disease

Methodologic Considerations

Studies of caffeine intake and health outcomes can have several potential limitations. First, observations of the acute effects of caffeine may not reflect long-term effects because tolerance of caffeine effects can develop.[30]

Second, epidemiologic studies of caffeine intake and the risk of chronic disease are potentially confounded by smoking or other unfavorable lifestyle factors, and early studies that did not adequately take this bias into account led to misleading results.[43] Residual confounding remains a concern even for more recent studies with more thorough adjustment for potential confounders. Although longer-term randomized trials are desirable, such studies are often not feasible because of practical and cost considerations. Recently, mendelian randomization studies have used genetic variants as proxy variables for caffeine intake, but limited statistical power and potential pleiotropy of the genetic variants complicate the interpretation of the results.[44] In addition, because variants in caffeine-metabolizing genes can have opposite effects on caffeine intake and circulating caffeine levels,[16,17] these proxy variables (reflecting lower caffeine intake but higher circulating caffeine levels) can be misleading.

Third, measurement error can affect the assessment of caffeine intake. However, self-reports of the frequency of coffee consumption are generally highly accurate and reproducible.[45] Variation in cup size, brew strength, type of coffee bean, and the amounts of sugar and milk or cream added to coffee is generally not captured in epidemiologic studies of coffee consumption, resulting in some exposure misclassification. However, within many populations, variation in cup sizes and brew strength is likely to be modest in comparison with the large variation in frequency of consumption.

Finally, in prospective studies of caffeine intake, coffee and tea have been the predominant sources of caffeine. It is unclear whether the observed outcomes with these caffeinated beverages also apply to other sources of caffeine.

Blood Pressure, Blood Lipids, and Cardiovascular Diseases

In persons who have not previously consumed caffeine, caffeine intake raises epinephrine levels and blood pressure in the short term.[30] Effect tolerance develops within a week[30] but may be incomplete in some persons.[46] Indeed, meta-analyses of trials of longer duration indicate that isolated caffeine intake (i.e., pure caffeine, not in the form of coffee or other beverages) results in a modest increase in systolic and diastolic blood pressure.[47] However, no substantial effect on blood pressure was found in trials of caffeinated coffee,[48] even among persons with hypertension,[49] possibly because other components of coffee, such as chlorogenic acid, counteract the blood-pressure–raising effect of caffeine.[50] Similarly, in prospective cohort studies, coffee consumption was not associated with an increased risk of hypertension.[51]

The concentration of the cholesterol-raising compound cafestol is high in unfiltered coffee such as French press, Turkish, or Scandinavian boiled coffee; intermediate in espresso and coffee made in a Moka pot; and negligible in drip-filtered, instant, and percolator coffee.[13] In randomized trials, high consumption of unfiltered coffee (median, 6 cups per day) increased low-density lipoprotein cholesterol levels by 17.8 mg per deciliter (0.46 mmol per liter), as compared with filtered coffee,[52] predicting an estimated 11% higher risk of major cardiovascular events.[53] In contrast, filtered coffee did not increase serum cholesterol levels.[52] Thus, limiting consumption of unfiltered coffee and moderate consumption of espresso-based coffee may help control serum cholesterol levels.

Experimental studies in humans[54] and cohort studies[55] do not show an association between caffeine intake and atrial fibrillation (Table S1). Many prospective studies have examined coffee and caffeine consumption in relation to the risks of coronary artery disease and stroke.[56] Findings consistently indicate that consumption of up to 6 standard cups of filtered, caffeinated coffee per day, as compared with no coffee consumption, is not associated with an increased risk of these cardiovascular outcomes in the general population or among persons with a history of hypertension, diabetes, or cardiovascular diseases.[56] In fact, coffee consumption was associated with a reduced risk of cardiovascular diseases, with the lowest risk for 3 to 5 cups per day (Table S1).[56] An inverse association has been observed between coffee consumption and coronary artery disease, stroke, and death from cardiovascular causes.[43,56]

Weight Management, Insulin Resistance, and Type 2 Diabetes

Metabolic studies suggest that caffeine may improve energy balance by reducing appetite and increasing the basal metabolic rate and food-induced thermogenesis,[57] possibly through stimulation of the sympathetic nervous system and uncoupling of protein-1 expression in brown adipose tissue.[58] Repeated caffeine intake during the day (6 doses of 100 mg of caffeine) led to a 5% increase in 24-hour energy expenditure.[59] Increases in caffeine intake were associated with slightly less long-term weight gain in cohort studies.[60,61] Limited evidence from randomized trials also supports a modest beneficial effect of caffeine intake on body fatness.[32,62] However, caffeinated beverages that are high in calories, such as soft drinks and energy drinks and coffee or tea with added sugar, may lead to excess weight gain.[63]

Caffeine intake reduces insulin sensitivity in the short term, as assessed with a euglycemic clamp (e.g., a 15% reduction after a dose of 3 mg per kilogram of body weight).[64] This may reflect an inhibitory effect of caffeine on storage of glucose as glycogen in muscle[31] and may partly result from increased epinephrine release.[64] However, consumption of caffeinated coffee (4 to 5 cups per day) for up to 6 months does not affect insulin resistance.[32,62,65] In addition, consumption of both caffeinated and decaffeinated coffee reduces hepatic insulin resistance induced by fructose overfeeding.[12] Furthermore, in cohort studies, habitual coffee consumption has been consistently associated with a reduced risk of type 2 diabetes in a dose–response relationship, with similar associations for caffeinated and decaffeinated coffee (Table S1).[66] Taken together, these findings suggest that tolerance develops for the adverse effect of caffeine on insulin sensitivity or that the adverse effect is offset by longer-term beneficial effects of noncaffeine coffee components on glucose metabolism, possibly in the liver.[12,67]

Cancer and Liver Diseases

The results of many prospective cohort studies provide strong evidence that consumption of coffee and caffeine is not associated with an increased incidence of cancer[68,69] or an increased rate of death from cancer (Table S1).[43] Coffee consumption is associated with a slightly reduced risk of melanoma,[70] nonmelanoma skin cancer,[71] breast cancer,[72] and prostate cancer.[73] Stronger inverse associations have been observed between coffee consumption and the risk of endometrial cancer[74] and hepatocellular carcinoma.[25] For endometrial cancer, the associations are similar with caffeinated and decaffeinated coffee, whereas for hepatocellular carcinoma, the association appears to be stronger with caffeinated coffee (Table S1).

Coffee has also consistently been associated with other aspects of liver health, including lower levels of enzymes reflecting liver damage and a lower risk of liver fibrosis and cirrhosis.[24,26] Caffeine may prevent hepatic fibrosis through adenosine receptor antagonism because adenosine promotes tissue remodeling, including collagen production and fibrinogenesis.[75] In line with this observation, caffeine metabolites reduce collagen deposition in liver cells,[76] caffeine inhibits hepatocarcinogenesis in animal models,[77] and a randomized trial showed that consumption of caffeinated coffee reduces liver collagen levels in patients with hepatitis C.[78] In addition, coffee polyphenols may provide protection against liver steatosis and fibrogenesis by improving fat homeostasis and reducing oxidative stress.[11]

Lithiasis

Coffee consumption has been associated with a reduced risk of gallstones[79] (Table S1) and of gallbladder cancer,[80] with a stronger association for caffeinated coffee than for decaffeinated coffee, suggesting that caffeine may play a protective role. Coffee consumption may prevent cholesterol gallstone formation by inhibiting absorption of gallbladder fluid, increasing cholecystokinin secretion, and stimulating gallbladder contraction.[81,82] In U.S. cohorts, consumption of both caffeinated and decaffeinated coffee was associated with a reduced risk of kidney stones.[83]

Neurologic Diseases

Prospective cohort studies in the United States, Europe, and Asia have shown a strong inverse association between caffeine intake and the risk of Parkinson's disease (Table S1).[21] Consumption of decaffeinated coffee is not associated with Parkinson's disease,[21] suggesting that caffeine, rather than other coffee components, accounts for the inverse association. In addition, caffeine prevents Parkinson's disease in animal models, possibly by inhibiting nigrostriatal dopaminergic neurotoxic effects and neurodegeneration through adenosine A_{2A} receptor antagonism.[84] Coffee and caffeine consumption have also been associated with reduced risks of depression[22] and suicide[85] in several cohorts in the United States and Europe, although these findings may not hold in persons who have very high intakes (≥8 cups per day).[86] Coffee consumption has not been consistently associated with the risk of dementia or Alzheimer's disease.[87]

ALL-CAUSE MORTALITY

Consumption of 2 to 5 standard cups of coffee per day has been associated with reduced mortality in cohort studies across the world[88-90] and in persons of European, African-American, and Asian ancestry[91] (Tables S1 and S2). With consumption of more than 5 cups of coffee per day, the risk of death was lower than or similar to the risk with no coffee consumption in large cohort studies, after adjustment for confounding by smoking status.[88,89] Confounding by baseline health status could be a concern, but coffee consumption was associated with lower mortality in analyses restricted to participants without chronic diseases or poor self-rated health at baseline and after exclusion of the first years of follow-up.[88-91] Consumption of caffeinated coffee and consumption of decaffeinated coffee were similarly associated with a reduced risk of death from any cause.[88,89,91] In line with this observation, the inverse association between coffee consumption and all-cause mortality did not differ according to whether caffeine metabolism was rapid or slow, as defined by the presence or absence of genetic variants related to caffeine metabolism.[88]

EFFECTS OF CAFFEINE INTAKE DURING PREGNANCY

In prospective studies, higher caffeine intake has been associated with lower birth weight[27] and a higher risk of pregnancy loss (Table S1).[28] Caffeine readily passes the placenta, and the slow caffeine metabolism in the mother and fetus can result in high circulating caffeine levels.[14] Caffeine may induce uteroplacental vasoconstriction and hypoxia by increasing blood catecholamine levels in the mother and fetus.[27] Associations with low birth weight have been observed for both coffee and tea (in a predominantly tea-drinking population)[92] and showed a dose–response relationship, without a clear threshold.[27] In contrast, the association between caffeine and pregnancy loss was not significant at lower levels of intake and may have been affected by publication bias.[28]

Residual confounding by smoking or nausea has been suggested as an explanation for the association between caffeine intake and adverse birth outcomes.[28] Nausea during the first trimester is a marker of a lower risk of adverse birth outcomes and may also reduce coffee consumption. However, adjustment for smoking habits or salivary cotinine levels (a biomarker for smoking) and restriction of the analysis to nonsmokers did not appreciably change the association between caffeine intake and pregnancy loss.[28] In addition, prepregnancy coffee consumption, a proxy for caffeine intake during pregnancy that is not confounded by nausea, has been associated with an increased risk of spontaneous abortion.[93] A randomized, controlled trial of caffeine reduction did not significantly affect birth weight, but the caffeine reduction was modest and occurred only in the second half of pregnancy, providing limited power to detect possible effects.[94] Although the evidence for adverse effects of caffeine on fetal health is not conclusive, prudence suggests limiting caffeine consumption during pregnancy to a maximum of 200 mg per day.[37]

CONCLUSIONS

A large body of evidence suggests that consumption of caffeinated coffee, the main source of caffeine intake in adults in the United States, does not increase the risk of cardiovascular diseases and cancers. In fact, consumption of 3 to 5 standard cups of coffee daily has been consistently associated with a reduced risk of several chronic diseases. However, high caffeine intake can have various adverse effects, and limits of 400 mg of caffeine per day for adults who are not pregnant or lactating and 200 mg per day for pregnant and lactating women have been recommended.[37,95] A large majority of adults in the United States adhere to these guidelines,[6] but because of person-to-person variation in metabolism and sensitivity to caffeine, a lower or somewhat higher amount may be appropriate in individual cases. Current evidence does not warrant recommending caffeine or coffee intake for disease prevention but suggests that for adults who are not pregnant or lactating and do not have specific health conditions, moderate consumption of coffee or tea can be part of a healthy lifestyle.

Dr. Hu reports receiving honoraria from Standard Process and consulting fees from Diet Quality Photo Navigation. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Ms. Yvonne Wong for assistance in preparing an earlier version of the manuscript.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: van Dam RM, Hu FB, Willett WC. Coffee, caffeine, and health. N Engl J Med 2020;383:369-78.
DOI: 10.1056/NEJMra1816604

Supplementary Appendix

Coffee, Caffeine and Health

Table of Contents

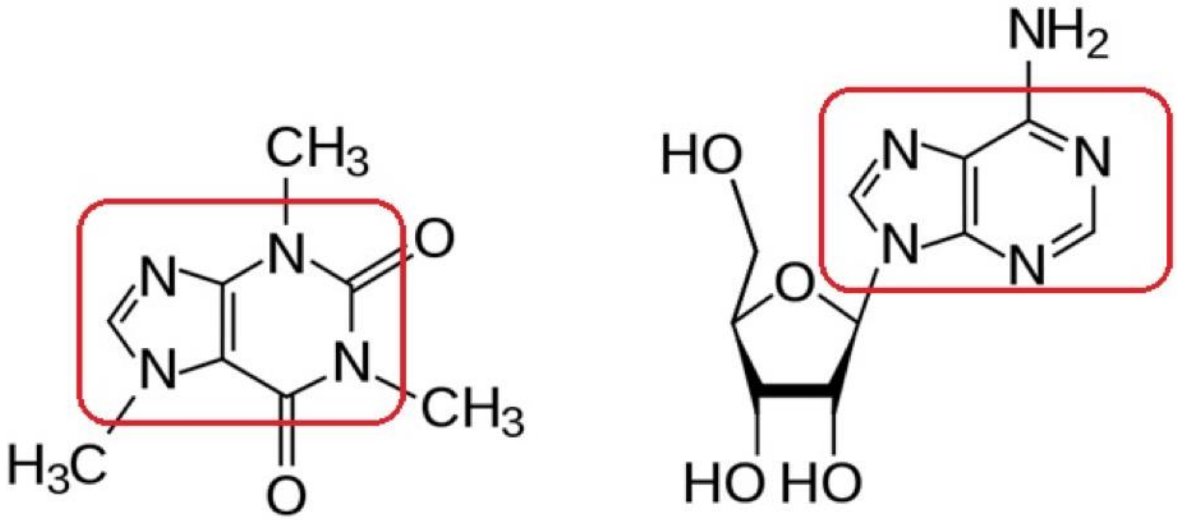

Figure S1. The molecular structure of caffeine and adenosine. The molecular structure of caffeine and adenosine are partly similar allowing caffeine to bind to and block adenosine receptors. As a result, caffeine antagonizes the effects of adenosine. Adenosine modulates the release and action of neurotransmitters such as acetylcholine, adenosine, dopamine, serotonin, norepinephrine, and gamma-aminobutyric acid (GABA).[1] Adenosine accumulates when adenosine triphosphate is used to generate energy during waking hours and its central action results in drowsiness. Adenosine also has peripheral effects and its receptors are present in many tissues including the vascular endothelium, heart, liver, lung, muscle and adipose tissue. Caffeine blockage of adenosine receptors results in greater excitatory neurotransmitter action. Adenosine receptor antagonism (mainly through the A_1 and A_{2A} receptors) is believed to be the main mechanism of action of caffeine at normal levels of caffeine. However, at high or toxic levels caffeine may also act through other mechanisms including elevation of intracellular cyclic adenosine monophosphate (cAMP) concentrations through phosphodiesterase inhibition and the release of intracellular Ca^{2+} through ryanodine-sensitive calcium channels.[1,2]

Table S1. Coffee and caffeine intake and relative risk (RR) of selected health outcomes in meta-analyses of prospective epidemiological studies.*

	Coffee intake				
	N studies (N dose-response)	N cases	RR (95% CI) 3 vs. 0 cups/d†	Evidence for non-linear association	Heterogeneity, coffee type, and publication bias‡
All-cause mortality[3]	36 (28)	323,120	0.85 (0.82-0.89)	Yes (P value < 0.01‡), U-shaped, lowest risk at 3.5-5 cups/d	High heterogeneity (I^2=77%). Similar association for caffeinated [n= 8 cohorts, RR 0.90 (95% CI 0.82-0.99) for high vs. low intake] and decaffeinated [n=11, RR 0.89 (0.85-0.93)] coffee.
Cancer mortality[3]	26 (17)	229,884	0.97 (0.93-1.00)	Yes (P value < 0.01), lowest risk at 2-2.5 cups/d	Moderate heterogeneity (I^2=58%)
Atrial fibrillation[4]	6 (6)	10,406	0.99 (0.91-1.05)	No	Moderate heterogeneity (I^2=66%)
Cardiovascular diseases[5]	36 (29)	36,352	0.89 (0.85-0.93)	Yes (P value <0.01), U-shaped, lowest risk at 3-5 cups/d	Low heterogeneity (P value =0.09). Significant for caffeinated coffee [n=11, RR 0.83 (0.79-0.88) for moderate (median 3.5 cups/d) vs. low intake], but not decaffeinated coffee [n=5, RR 0.98 (0.87-1.10)].
Type 2 diabetes[6]	30 (30)	53,018	0.83 (0.80-0.86)	No	Moderate heterogeneity (I^2=67%). Similar association for caffeinated [n=10, RR=0.80 (0.73-0.88) for 3 vs. 0 cups/d] and decaffeinated [n=10, RR=0.83 (0.73-0.94)] coffee.
Gallstones[7]	5 (3)	11,282	0.85 (0.76-0.94)	Yes (P value=0.01), low risk levels off at >3 cups/d	Moderate heterogeneity (I^2=36%)
Liver cirrhosis[8]	5 (5)	1,364	0.45 (0.26-0.66)	No	High heterogeneity (I^2=91%)
Hepatocellular carcinoma[9]	18 (18)	2,905	0.60 (0.52-0.68)	No	Moderate heterogeneity (I^2=41%). Significant association for caffeinated [n=2, RR=0.62 (0.50-0.78) for 3 vs. 0 cups/d], but not decaffeinated [n=3, RR=0.80 (0.64-1.00)] coffee. Evidence for publication bias (Egger P value <0.01).
Endometrium cancer[10]	10 (9)	10,548	0.85 (0.78-0.92)	No	Moderate heterogeneity (I^2=59%). Similar for caffeinated [n=4, RR=0.65 (0.50-0.85) for high vs. low intake] and decaffeinated [n=4, RR=0.76 (0.62-0.93)] coffee.
Parkinson's Disease[11]	7 (7)	2,414	0.69 (0.61-0.77)	Yes (P value <0.01), low risk levels off at >3 cups/d	Low (I^2=16%). Significant for caffeine intake [n=4, RR=0.78 (0.68-0.90) for 300 vs. 0 mg/d), but not for decaffeinated coffee [n=4, RR=0.94 (0.78-1.12) for high vs. low intake].

	Caffeine intake				
	N studies (N dose-response)	N cases	RR (95% CI) 300 vs. 0 mg/d†	Evidence for non-linear association	Heterogeneity and publication bias
Pregnancy loss[12]	14 (13)	3,429	1.23 (1.09-1.40)	No	High (I^2=81%). Evidence for publication bias (Egger P value <0.01).
Low birth Weight[13]	9 (7)	6,303	1.44 (1.19-1.77)	No	High (I^2=82%).

CI denotes confidence interval

*Selected meta-analyses were based on a reasonably large number of prospective studies and reported on health outcomes relevant for hypotheses on the health effects of coffee and caffeine.

†'Coffee' refers to total coffee consumption. Calculated for a 3 cup per day (for coffee) or 300 mg per day (for caffeine) increment if the association was linear and using cubic spline analyses if the association was non-linear. For the mortality meta-analysis, relative risks are for 3.5 versus 0 cups/day, because results for intake of 3.0 cups/day were not reported.

‡Results for caffeinated and decaffeinated coffee are only provided if available from the meta-analysis. There was no statistical evidence for publication bias unless this is mentioned.

Table S2. Coffee consumption and all-cause mortality in large prospective cohort studies*

Cohort	Country	N	Baseline age (y)	Baseline exclusion	Follow-up (y)	N deaths	Total coffee intake	RR (95% CI) Men	RR (95% CI) Women	Adjustments	Additional analyses
NIH-AARP Diet and Health Study[14]	US	402,260	50-71	Cancer, CAD, stroke	14	52,515	0 cups/d	1.00 (ref)	1.00	Age, ethnicity, education, marital status, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, health status, diabetes.	Similar association for caffeinated and decaffeinated coffee. Inverse associations remained in those with good self-rated health at baseline or after excluding the first 4-9 y of follow-up.
							<1 cup/d	0.99 (0.95-1.04)	1.01 (0.96-1.07)		
							1 cup/d	0.94 (0.90-0.99)	0.95 (0.90-1.01)		
							2-3 cups/d	0.90 (0.86-0.93)	0.87 (0.83-0.92)		
							4-5 cups/d	0.88 (0.84-0.93)	0.84 (0.79-0.90)		
							≥6 cups/d	0.90 (0.85-0.96)	0.85 (0.78-0.93)		
Nurses' Health Studies (NHS, NHSII), Health Professionals Follow-up Study (HPFS)[15]	US	208,501	38-63 (NHS) 27-44 (NHSII) 40-75 (HPFS)	Cancer, CAD, stroke	28 (NHS) 21 (NHSII) 26 (HPFS)	31,956	0 cups/d	1.00 (ref)		Age, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, baseline disease status, PMH use, menopausal status.	Similar association for caffeinated and decaffeinated coffee.
							≤1.0 cup/d	0.95 (0.91-0.99)			
							1.1-3.0 cups/d	0.91 (0.88-0.95)			
							3.1-5.0 cups/d	0.93 (0.89-0.97)			
							>5.0 cups/d	1.02 (0.96-1.07)			
Multiethnic Cohort[16]	US	185,855	45-75	No	16	58,397	0 cups/d	1.00 (ref)		Age, sex, ethnicity, education, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, baseline disease status.	Similar association for caffeinated and decaffeinated coffee and for European, Asian, and African Americans. Inverse association remained in those without chronic diseases at baseline or after excluding the first 5 y of follow-up.
							1-3 cups/mo	1.00 (0.95-1.05)			
							1-6 cups/wk	0.97 (0.93-1.01)			
							1 cup/d	0.88 (0.85-0.91)			
							2-3 cups/d	0.82 (0.79-0.86)			
							≥4 cups/d	0.82 (0.78-0.87)			
European Prospective Investigation into Cancer and Nutrition[17]	10 European countries	521,330	≥35	Cancer, CAD, stroke, diabetes	16	41,693	0 ml/d	1.00 (ref)	1.00 (ref)	Age, center, education, BMI, smoking status and intensity, physical activity, alcohol use, dietary factors, menopausal status, OC and PMH use.	Similar association for caffeinated and decaffeinated coffee. Inverse association remained in those with good self-rated health at baseline and after excluding the first 5-8 y of follow-up.
							Q1 (low)	0.94 (0.87-1.00)	0.94 (0.89-0.99)		
							Q2	0.88 (0.82-0.95)	0.90 (0.85-0.95)		
							Q3	0.84 (0.78-0.90)	0.90 (0.85-0.95)		
							Q4 (high)	0.88 (0.82-0.95)	0.93 (0.87-0.98)		

UK Biobank[18]	UK	387,494	38-73	No	10	14,225	0 cup/d	1.00 (ref)		Age, sex, ethnicity, education, BMI, smoking status and intensity, physical activity, alcohol use, tea intake, health status.	Similar association for caffeinated and decaffeinated coffee and for slow and rapid caffeine metabolizers according to genotypes. Inverse association remained in those without chronic diseases or with good self-rated health at baseline and after excluding first 3 y of follow-up.
							<1 cup/d	0.94 (0.88-1.01)			
							1 cup/d	0.92 (0.87-0.97)			
							2-3 cups/d	0.88 (0.84-0.93)			
							4-5 cups/d	0.88 (0.83-0.93)			
							6-7 cups/d	0.84 (0.77-0.92)			
							≥ 8 cups/d	0.86 (0.77-0.95)			
Japan Collaborative Cohort Study for Evaluation of Cancer Risk[19]	Japan	97,753	40-79	No	16	19,532	<1 cup/d	1.00 (ref)	1.00 (ref)	Age, education, marital status, BMI, smoking status, walking, sleep duration, stress, alcohol use, tea, green leafy vegetables, baseline disease status.	No data on decaffeinated coffee. Inverse association remained in those without chronic diseases at baseline and after excluding the first 2-8 y of follow-up.
							1 cup/d	0.95 (0.89-1.01)	0.82 (0.76-0.89)		
							2-3 cup/d	0.86 (0.81-0.93)	0.83 (0.75-0.91)		
							≥ 4 cups/d	0.80 (0.68-0.95)	0.89 (0.66-1.20)		
Japan Public Health Center-based Prospective Study[20]	Japan	90,914	40-69	Cancer, CAD, stroke	19	12,874	Almost never	1.00 (ref)		Age, sex, center, job status, BMI, smoking status and intensity, physical activity, alcohol use, tea, dietary factors, baseline disease status.	No data on decaffeinated coffee. Inverse associations remained after excluding first 5 y of follow-up.
							<1 cup/d	0.93 (0.88-0.98)			
							1-2 cups/d	0.89 (0.84-0.94)			
							3-4 cups/d	0.81 (0.74-0.89)			
							≥5 cups/d	0.87 (0.75-1.00)			
Three-Prefecture Cohort[21]	Japan	82,809	40-79	No	15	13,680	Never	1.00 (ref)	1.00 (ref)	Age, center, urbanicity, job type, insurance type, BMI, smoking status and intensity, alcohol use, tea, dietary factors, baseline disease status.	No data on decaffeinated coffee.
							<1 cup/d	0.85 (0.80-0.92)	0.91 (0.84-0.98)		
							1-2 cups/d	0.76 (0.71-0.82)	0.82 (0.75-0.90)		
							3-4 cups/d	0.74 (0.67-0.81)	0.73 (0.63-0.86)		
							≥5 cups/d	0.73 (0.64-0.83)	0.83 (0.68-1.02)		

CAD denotes coronary artery disease; BMI denotes Body Mass Index; PMH denotes postmenopausal hormone; OC denotes oral contraceptives. Cups/d, cups/wk, and cups/mo refer to cups per day, week, and month respectively.

*All published cohort analyses of coffee consumption and mortality with >12,000 deaths.

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