

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 mate 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 B₃ (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.

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

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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.

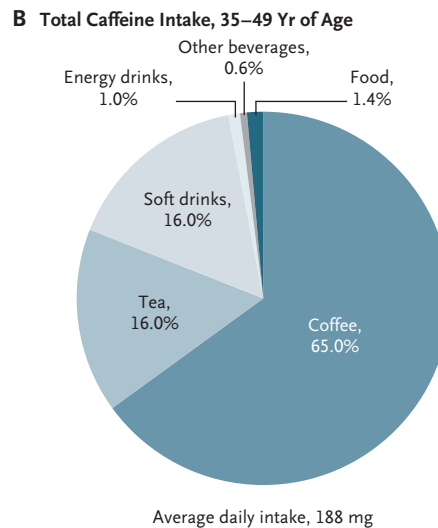
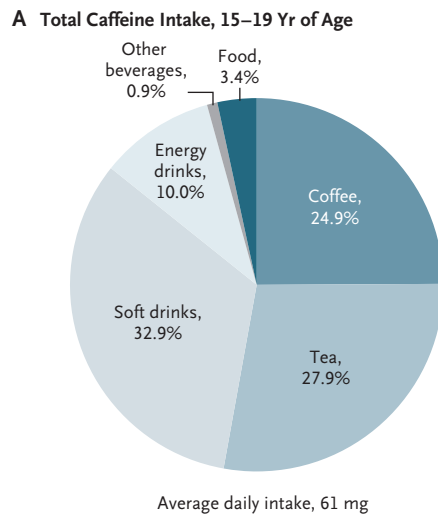
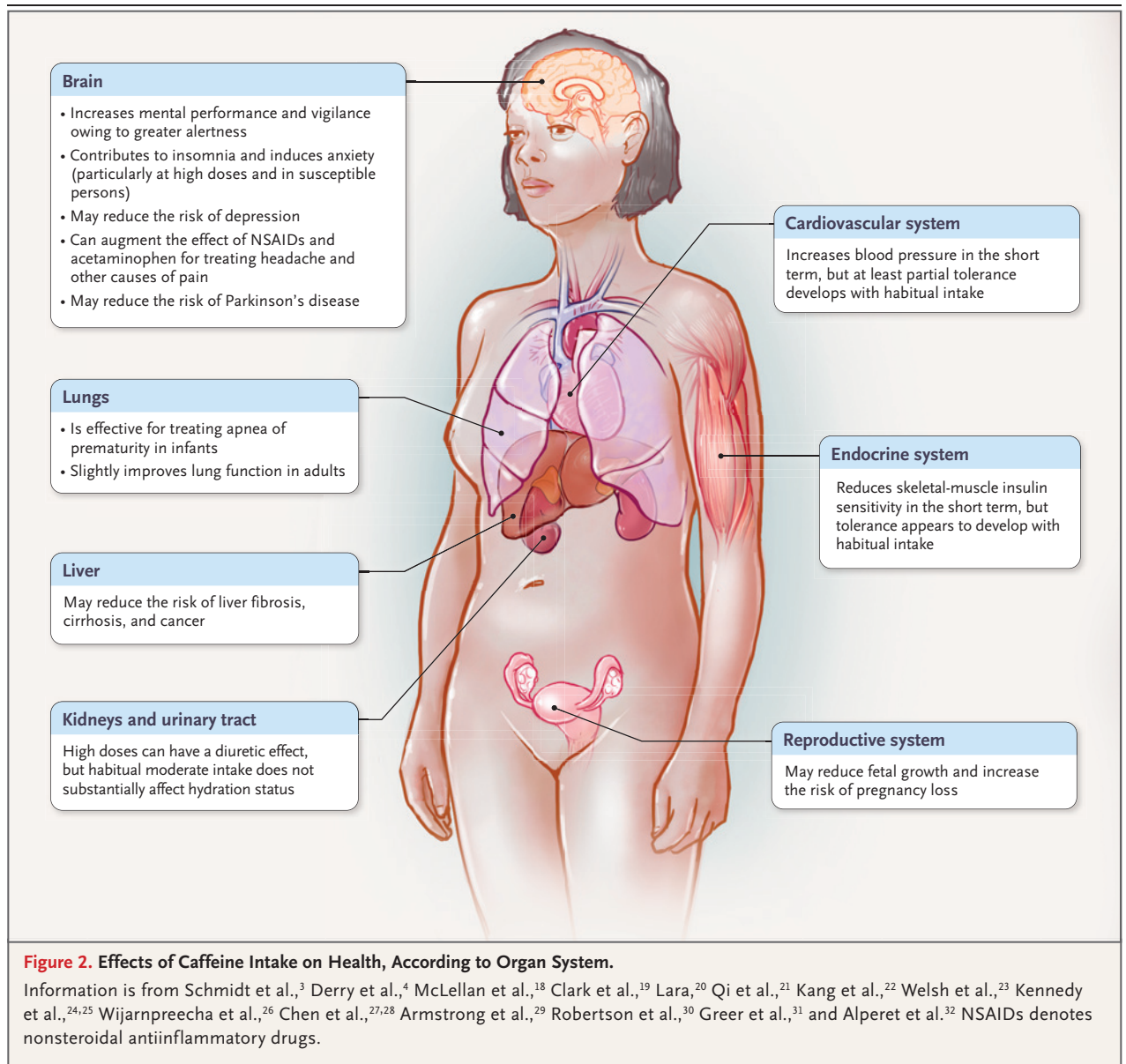


Figure 1. Sources of Caffeine and Average Daily Intake in Adolescents and Middle-Aged Adults in the United States.

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-



compensate 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 week³⁰ 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 humans⁵⁴ and cohort studies⁵⁵ 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 associ-

ated 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 muscle³¹ 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 cancer⁷⁴ 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 gallstones⁷⁹ (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 depression²² and suicide⁸⁵ 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 world⁸⁸⁻⁹⁰ and in persons of European, African-American, and Asian ancestry⁹¹ (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 weight²⁷

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 non-smokers 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.

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

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REFERENCES

1. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 1999;51:83-133.
2. Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. FoodData Central (<https://fdc.nal.usda.gov/>).
3. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;357:1893-902.
4. Derry CJ, Derry S, Moore RA. Caffeine as an analgesic adjuvant for acute pain in adults. *Cochrane Database Syst Rev* 2014;12:CD009281.
5. Pomeranz K, Topik S. The world that trade created: society, culture, and the world economy, 1400 to the present. 2nd ed. New York: Routledge, 2006.
6. Mitchell DC, Knight CA, Hockenberry J, Teplansky R, Hartman TJ. Beverage caffeine intakes in the U.S. *Food Chem Toxicol* 2014;63:136-42.
7. Drewnowski A, Rehm CD. Sources of caffeine in diets of US children and adults: trends by beverage type and purchase location. *Nutrients* 2016;8:154.
8. Ludwig IA, Clifford MN, Lean MEJ, Ashihara H, Crozier A. Coffee: biochemistry and potential impact on health. *Food Funct* 2014;5:1695-717.
9. Corrêa TAF, Monteiro MP, Mendes TMN, et al. Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial. *Plant Foods Hum Nutr* 2012;67:277-82.
10. Jaquet M, Rochat I, Moulin J, Cavin C, Bibiloni R. Impact of coffee consumption on the gut microbiota: a human volunteer study. *Int J Food Microbiol* 2009;130:117-21.
11. Vitaglione P, Morisco F, Mazzone G, et al. Coffee reduces liver damage in a rat model of steatohepatitis: the underlying mechanisms and the role of polyphenols and melanoidins. *Hepatology* 2010;52:1652-61.
12. Lecoultré V, Carrel G, Egli L, et al. Coffee consumption attenuates short-term fructose-induced liver insulin resistance in healthy men. *Am J Clin Nutr* 2014;99:268-75.
13. Urgert R, Katan MB. The cholesterol-raising factor from coffee beans. *Annu Rev Nutr* 1997;17:305-24.
14. Nehlig A. Interindividual differences in caffeine metabolism and factors driving caffeine consumption. *Pharmacol Rev* 2018;70:384-411.
15. Perera V, Gross AS, McLachlan AJ. Influence of environmental and genetic factors on CYP1A2 activity in individuals of South Asian and European ancestry. *Clin Pharmacol Ther* 2012;92:511-9.
16. Cornelis MC, Kacprowski T, Menni C, et al. Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. *Hum Mol Genet* 2016;25:5472-82.
17. Cornelis MC, Byrne EM, Esko T, et al. Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. *Mol Psychiatry* 2015;20:647-56.
18. McLellan TM, Caldwell JA, Lieberman HR. A review of caffeine's effects on cognitive, physical and occupational performance. *Neurosci Biobehav Rev* 2016;71:294-312.
19. Clark I, Landolt HP. Coffee, caffeine, and sleep: a systematic review of epidemiological studies and randomized controlled trials. *Sleep Med Rev* 2017;31:70-8.
20. Lara DR. Caffeine, mental health, and psychiatric disorders. *J Alzheimers Dis* 2010;20:Suppl 1:S239-S248.
21. Qi H, Li S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatr Gerontol Int* 2014;14:430-9.
22. Kang D, Kim Y, Je Y. Non-alcoholic beverage consumption and risk of depression: epidemiological evidence from observational studies. *Eur J Clin Nutr* 2018;72:1506-16.
23. Welsh EJ, Bara A, Barley E, Cates CJ. Caffeine for asthma. *Cochrane Database Syst Rev* 2010;1:CD001112.
24. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. *Aliment Pharmacol Ther* 2016;43:562-74.
25. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. *BMJ Open* 2017;7(5):e013739.
26. Wijarnprecha K, Thongprayoon C, Ungprasert P. Coffee consumption and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2017;29(2):e8-e12.
27. Chen L-W, Wu Y, Neelakantan N, Chong MF-F, Pan A, van Dam RM. Maternal caffeine intake during pregnancy is associated with risk of low birth weight: a systematic review and dose-response meta-analysis. *BMC Med* 2014;12:174.
28. Chen L-W, Wu Y, Neelakantan N, Chong MF-F, Pan A, van Dam RM. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. *Public Health Nutr* 2016;19:1233-44.
29. Armstrong LE, Pumerantz AC, Roti MW, et al. Fluid, electrolyte, and renal indices of hydration during 11 days of controlled caffeine consumption. *Int J Sport Nutr Exerc Metab* 2005;15:252-65.
30. Robertson D, Wade D, Workman R, Woosley RL, Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. *J Clin Invest* 1981;67:1111-7.
31. Greer F, Hudson R, Ross R, Graham T. Caffeine ingestion decreases glucose disposal during a hyperinsulinemic-euglycemic clamp in sedentary humans. *Diabetes* 2001;50:2349-54.
32. Alperet DJ, Rebello SA, Khoo EY-H, et al. The effect of coffee consumption on insulin sensitivity and other biological risk factors for type 2 diabetes: a randomized placebo-controlled trial. *Am J Clin Nutr* 2020;111:448-58.

33. Smith A. Effects of caffeine on human behavior. *Food Chem Toxicol* 2002;40:1243-55.
34. Ker K, Edwards PJ, Felix LM, Blackhall K, Roberts I. Caffeine for the prevention of injuries and errors in shift workers. *Cochrane Database Syst Rev* 2010;5:CD008508.
35. Doty TJ, So CJ, Bergman EM, et al. Limited efficacy of caffeine and recovery costs during and following 5 days of chronic sleep restriction. *Sleep* 2017;40(12).
36. Fulton JL, Dinas PC, Carrillo AE, Edsall JR, Ryan EJ, Ryan EJ. Impact of genetic variability on physiological responses to caffeine in humans: a systematic review. *Nutrients* 2018;10:1373.
37. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on the safety of caffeine. *EFSA J* 2015;13(5):4102.
38. Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology (Berl)* 2004;176:1-29.
39. Center for Food Safety and Applied Nutrition. Highly concentrated caffeine in dietary supplements: guidance for industry. College Park, MD: Food and Drug Administration, April 2018 (<https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM604319.pdf>).
40. Jones AW. Review of caffeine-related fatalities along with postmortem blood concentrations in 51 poisoning deaths. *J Anal Toxicol* 2017;41:167-72.
41. Cappelletti S, Piacentino D, Fineschi V, Frati P, Cipolloni L, Aromataro M. Caffeine-related deaths: manner of deaths and categories at risk. *Nutrients* 2018;10:611.
42. Ehlers A, Marakis G, Lampen A, Hirsch-Ernst KI. Risk assessment of energy drinks with focus on cardiovascular parameters and energy drink consumption in Europe. *Food Chem Toxicol* 2019;130:109-21.
43. Kim Y, Je Y, Giovannucci E. Coffee consumption and all-cause and cause-specific mortality: a meta-analysis by potential modifiers. *Eur J Epidemiol* 2019;34:731-52.
44. Cornelis MC, Munafo MR. Mendelian randomization studies of coffee and caffeine consumption. *Nutrients* 2018;10:1343.
45. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semi-quantitative food frequency questionnaire. *J Am Diet Assoc* 1993;93:790-6.
46. Lovallo WR, Wilson MF, Vincent AS, Sung BH, McKey BS, Whitsett TL. Blood pressure response to caffeine shows incomplete tolerance after short-term regular consumption. *Hypertension* 2004;43:760-5.
47. Noordzij M, Uiterwaal CSPM, Arends LR, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. *J Hypertens* 2005;23:921-8.
48. Steffen M, Kuhle C, Hensrud D, Erwin PJ, Murad MH. The effect of coffee consumption on blood pressure and the development of hypertension: a systematic review and meta-analysis. *J Hypertens* 2012;30:2245-54.
49. Mesas AE, Leon-Muñoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. *Am J Clin Nutr* 2011;94:1113-26.
50. Onakpoya IJ, Spencer EA, Thompson MJ, Heneghan CJ. The effect of chlorogenic acid on blood pressure: a systematic review and meta-analysis of randomized clinical trials. *J Hum Hypertens* 2015;29:77-81.
51. Grosso G, Micek A, Godos J, et al. Long-term coffee consumption is associated with decreased incidence of new-onset hypertension: a dose-response meta-analysis. *Nutrients* 2017;9:890.
52. Jee SH, He J, Appel LJ, Whelton PK, Suh I, Klag MJ. Coffee consumption and serum lipids: a meta-analysis of randomized controlled clinical trials. *Am J Epidemiol* 2001;153:353-62.
53. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;316:1289-97.
54. Zuchinali P, Ribeiro PA, Pimentel M, da Rosa PR, Zimerman LI, Rohde LE. Effect of caffeine on ventricular arrhythmia: a systematic review and meta-analysis of experimental and clinical studies. *Europace* 2016;18:257-66.
55. Larsson SC, Drca N, Jensen-Urstad M, Wolk A. Coffee consumption is not associated with increased risk of atrial fibrillation: results from two prospective cohorts and a meta-analysis. *BMC Med* 2015;13:207.
56. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation* 2014;129:643-59.
57. Harpaz E, Tamir S, Weinstein A, Weinstein Y. The effect of caffeine on energy balance. *J Basic Clin Physiol Pharmacol* 2017;28:1-10.
58. Velickovic K, Wayne D, Leija HAL, et al. Caffeine exposure induces browning features in adipose tissue in vitro and in vivo. *Sci Rep* 2019;9:9104.
59. Dulloo AG, Geissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. *Am J Clin Nutr* 1989;49:44-50.
60. Lopez-Garcia E, van Dam RM, Rajpathak S, Willett WC, Manson JE, Hu FB. Changes in caffeine intake and long-term weight change in men and women. *Am J Clin Nutr* 2006;83:674-80.
61. Larsen SC, Mikkelsen M-L, Frederiksen P, Heitmann BL. Habitual coffee consumption and changes in measures of adiposity: a comprehensive study of longitudinal associations. *Int J Obes (Lond)* 2018;42:880-6.
62. Ohnaka K, Ikeda M, Maki T, et al. Effects of 16-week consumption of caffeinated and decaffeinated instant coffee on glucose metabolism in a randomized controlled trial. *J Nutr Metab* 2012;2012:207426.
63. de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. *N Engl J Med* 2012;367:1397-406.
64. Keijzers GB, De Galan BE, Tack CJ, Smits P. Caffeine can decrease insulin sensitivity in humans. *Diabetes Care* 2002;25:364-9.
65. Wedick NM, Brennan AM, Sun Q, Hu FB, Mantzoros CS, van Dam RM. Effects of caffeinated and decaffeinated coffee on biological risk factors for type 2 diabetes: a randomized controlled trial. *Nutr J* 2011;10:93.
66. Carlström M, Larsson SC. Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis. *Nutr Rev* 2018;76:395-417.
67. Ong KW, Hsu A, Tan BKH. Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by AMPK activation. *Biochem Pharmacol* 2013;85:1341-51.
68. Wang A, Wang S, Zhu C, et al. Coffee and cancer risk: a meta-analysis of prospective observational studies. *Sci Rep* 2016;6:33711.
69. Drinking coffee, mate, and very hot beverages. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 116. Lyon, France: International Agency for Research on Cancer, 2018.
70. Micek A, Godos J, Lafranconi A, Maranzano M, Pajak A. Caffeinated and decaffeinated coffee consumption and melanoma risk: a dose-response meta-analysis of prospective cohort studies. *Int J Food Sci Nutr* 2018;69:417-26.
71. Caini S, Cattaruzza MS, Bendinelli B, et al. Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis. *Eur J Nutr* 2017;56:1-12.
72. Lafranconi A, Micek A, De Paoli P, et al. Coffee intake decreases risk of postmenopausal breast cancer: a dose-response meta-analysis on prospective cohort studies. *Nutrients* 2018;10:112.

73. Xia J, Chen J, Xue J-X, Yang J, Wang Z-J. An up-to-date meta-analysis of coffee consumption and risk of prostate cancer. *Urol J* 2017;14:4079-88.
74. Lafranconi A, Micek A, Galvano F, et al. Coffee decreases the risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. *Nutrients* 2017; 9:1223.
75. Chan ESL, Montesinos MC, Fernandez P, et al. Adenosine A(2A) receptors play a role in the pathogenesis of hepatic cirrhosis. *Br J Pharmacol* 2006;148:1144-55.
76. Klemmer I, Yagi S, Gressner OA. Oral application of 1,7-dimethylxanthine (paraxanthine) attenuates the formation of experimental cholestatic liver fibrosis. *Hepatology* 2011;41:1094-109.
77. Hosaka S, Kawa S, Aoki Y, et al. Hepatocarcinogenesis inhibition by caffeine in ACI rats treated with 2-acetylaminofluorene. *Food Chem Toxicol* 2001;39:557-61.
78. Cardin R, Picocchi M, Martines D, Scribano L, Petracco M, Farinati F. Effects of coffee consumption in chronic hepatitis C: a randomized controlled trial. *Dig Liver Dis* 2013;45:499-504.
79. Zhang Y-P, Li W-Q, Sun Y-L, Zhu R-T, Wang W-J. Systematic review with meta-analysis: coffee consumption and the risk of gallstone disease. *Aliment Pharmacol Ther* 2015;42:637-48.
80. Larsson SC, Giovannucci EL, Wolk A. Coffee consumption and risk of gallbladder cancer in a prospective study. *J Natl Cancer Inst* 2017;109:1-3.
81. Lillemoe KD, Magnuson TH, High RC, Peoples GE, Pitt HA. Caffeine prevents cholesterol gallstone formation. *Surgery* 1989;106:400-7.
82. Douglas BR, Jansen JB, Tham RT, Lamers CB. Coffee stimulation of cholecystokinin release and gallbladder contraction in humans. *Am J Clin Nutr* 1990; 52:553-6.
83. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Soda and other beverages and the risk of kidney stones. *Clin J Am Soc Nephrol* 2013;8:1389-95.
84. Xu K, Di Luca DG, Orrú M, Xu Y, Chen J-F, Schwarzschild MA. Neuroprotection by caffeine in the MPTP model of Parkinson's disease and its dependence on adenosine A2A receptors. *Neuroscience* 2016; 322:129-37.
85. Lucas M, O'Reilly EJ, Pan A, et al. Coffee, caffeine, and risk of completed suicide: results from three prospective cohorts of American adults. *World J Biol Psychiatry* 2014;15:377-86.
86. Tanskanen A, Tuomilehto J, Viinamäki H, Vartiainen E, Lehtonen J, Puska P. Heavy coffee drinking and the risk of suicide. *Eur J Epidemiol* 2000;16:789-91.
87. Larsson SC, Orsini N. Coffee consumption and risk of dementia and Alzheimer's disease: a dose-response meta-analysis of prospective studies. *Nutrients* 2018;10:1501.
88. Loftfield E, Cornelis MC, Caporaso N, Yu K, Sinha R, Freedman N. Association of coffee drinking with mortality by genetic variation in caffeine metabolism: findings from the UK Biobank. *JAMA Intern Med* 2018;178:1086-97.
89. Freedman ND, Park Y, Abnet CC, Holtenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality. *N Engl J Med* 2012;366:1891-904.
90. Tamakoshi A, Lin Y, Kawado M, et al. Effect of coffee consumption on all-cause and total cancer mortality: findings from the JACC study. *Eur J Epidemiol* 2011;26: 285-93.
91. Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW. Association of Coffee Consumption With Total and Cause-Specific Mortality Among Nonwhite Populations. *Ann Intern Med* 2017;167:228-35.
92. Chen L-W, Fitzgerald R, Murrin CM, Mehegan J, Kelleher CC, Phillips CM. Associations of maternal caffeine intake with birth outcomes: results from the Lifeways Cross Generation Cohort Study. *Am J Clin Nutr* 2018;108:1301-8.
93. Gaskins AJ, Rich-Edwards JW, Williams PL, Toth TL, Missmer SA, Chavarro JE. Pre-pregnancy caffeine and caffeinated beverage intake and risk of spontaneous abortion. *Eur J Nutr* 2018;57:107-17.
94. Bech BH, Obel C, Henriksen TB, Olsen J. Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial. *BMJ* 2007; 334:409.
95. Dietary guidelines for Americans, 2015-2020. 8th ed. Washington, DC: Department of Agriculture, December 2015 (https://health.gov/dietaryguidelines/2015/resources/2015-2020_Dietary_Guidelines.pdf).

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