Caffeine and Caffeine Metabolites

Sources and Physiological Functions

Caffeine (1,3,7-trimethylxanthine) is a purine alkaloid naturally found in certain plants. Although hundreds of plant species contain methylxanthines, only a few are significant sources of caffeine. Notable examples include plants from the genera *Coffea* (coffee), *Camellia* (tea), *Theobroma* (cacao), and, to a lesser extent, *Ilex* (mate), *Paullinia* (guarana), and *Cola* (cola) (Lean 2011). Caffeine is introduced into the diet primarily through foods and beverages made from these caffeine-containing plants, with coffee and tea being the major sources (Ahluwalia 2014; Fulgoni 2015). In addition to being a natural food ingredient, caffeine is widely used as a food additive in soft drinks and energy drinks. Caffeine is sometimes found in medications and supplements. Most individuals encounter caffeine daily. In the United States, approximately 70% of children and 90% of adults consume caffeine on any given day (Ahluwalia 2014; Fulgoni 2015; Mitchell 2025).

Caffeine is a widely recognized central nervous system stimulant. Dietary sources such as coffee, tea, soft drinks, and energy drinks contain enough caffeine to produce psychostimulatory effects (Smith 2002). These effects are believed to occur due to caffeine's action on adenosine receptors. Adenosine is a neuromodulator with sedative properties, and caffeine acts as a nonselective, competitive antagonist at adenosine receptors (Fredholm 1999). The psychostimulatory effects from dietary caffeine intake can include positive outcomes like improved cognitive performance and mood, as well as negative effects such as nervousness and impaired fine motor skills (Smith 2002). Caffeine's interaction with adenosine receptors can also lead to other effects beyond psychostimulation. Dietary caffeine intake has been linked to cardiovascular effects (Riksen 2006), such as a slight increase in blood pressure and a slight decrease in heart rate (Nurminen 1999). It can play a role in regulating inflammatory responses (Haskó 2011), affect kidney function as a mild diuretic (increased urine flow) and natriuretic (increased sodium excretion) (Osswald 2010), and affect lung function as a mild bronchodilator (increased air flow) (Becker 1984; Tilley 2011).

The pharmacokinetics and metabolism of caffeine are well understood (Arnaud 2011; Arnaud 2013). When consumed, caffeine is rapidly absorbed and distributed throughout the body (Yesair 1984). Gastrointestinal absorption is typically complete within 45 minutes, with peak circulating concentrations occurring about 30 minutes after ingestion (Blanchard 1983). Once absorbed, caffeine enters the intracellular tissue water and is distributed throughout the body. It can pass

through all biological membranes and is found in all bodily fluids and tissues (Burg 1975). Caffeine also freely crosses the blood-brain barrier and in pregnant women can be transmitted to the fetus and embryo (Wilkinson 1993). Caffeine does not accumulate in organs and tissues (Burg 1975). Instead, it undergoes extensive metabolism by liver enzymes, with urine excretion being the primary route of elimination. Only a small fraction (2%) of caffeine is excreted unmetabolized, as most of it undergoes renal tubular reabsorption (Tang-Liu 1983), leading to recirculation and continued metabolism (Arnaud 2013).

Caffeine metabolism primarily involves two types of reactions: *N*-demethylations and *C*-8 hydroxylations. *N*-demethylations convert caffeine's trimethylxanthine structure into dimethylxanthines (paraxanthine, theophylline, theobromine). *C*-8 hydroxylations produce a series of uric acids (Figure 1). Cytochrome P450 (CYP) enzymes in the liver, particularly the CYP1A2 enzyme, catalyze most of these metabolic transformations (Arnaud 2013). The enzymes involved in caffeine metabolism are crucial for detoxification, drug metabolism, and have implications in chronic disease risk. Since caffeine metabolism relies on these enzyme systems, the relative amounts of caffeine and its metabolites in urine or other bodily fluids can provide insights into an individual's metabolic activity (Hakooz 2009; Tremmel 2024).

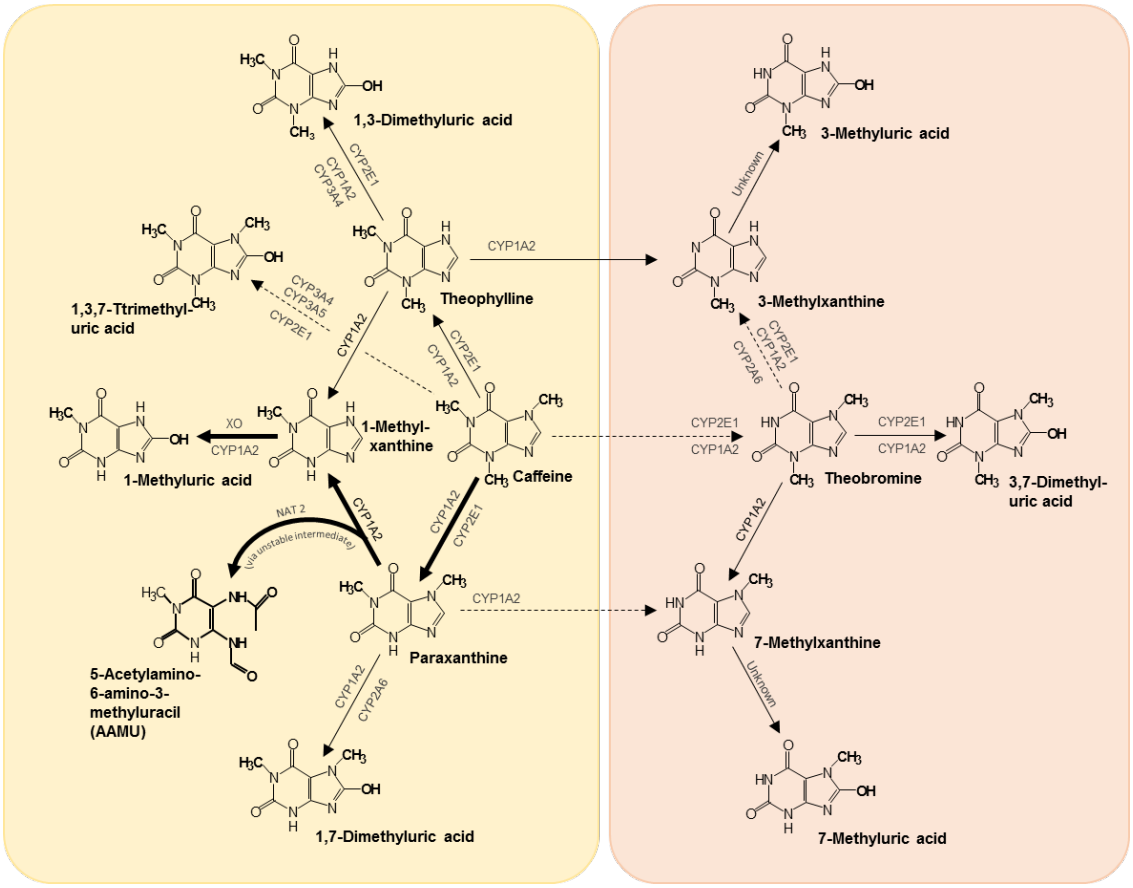


Figure 1. Caffeine metabolism. *Arrows indicate metabolic pathways and enzymes. Weight of arrows indicate relative preference of a given metabolic pathway (Rybak 2015; Pao 2025). Groupings correspond to correlations observed between spot urine caffeine and caffeine metabolite concentrations and 24-hour caffeine intake from foods and supplements in US persons aged ≥6 y, NHANES 2009–2014. Left: Moderate Spearman correlations of ρ = 0.55–0.63 with intake. Right: Weak Spearman correlations of ρ = 0.15–0.25 with intake (Rybak 2015; Pao 2025). Used with permission.*

Health Effects

Caffeine is best viewed as a context-dependent risk factor in health and disease. Moderate regular caffeine use—usually from coffee or tea—is not consistently linked to higher risk of chronic disease and is often linked to lower all-cause mortality. However, the research is mixed and is based mostly on observational studies of coffee and tea, not on clinical trials of pure caffeine (van Dam 2020; Kim 2019). At the same time, people respond very differently to caffeine because metabolism and sensitivity are influenced by genetics, smoking, hormones, liver function, medications, and other individual factors (Low 2024; Nehlig 2018). Coffee studies cannot be equated with caffeine studies. The link between coffee and lower risk of death persists for both regular and decaffeinated coffee, which suggests that other compounds in coffee, not just

caffeine, may provide health benefits (Kim 2019). On the other hand, some negative effects of coffee are unrelated to caffeine: for example, unfiltered coffee contains cafestol and kahweol, substances that can raise blood lipids and certain liver enzymes (aminotransferases) (Urgert 1997a). Caffeine is just one of many bioactive ingredients in coffee, and these compounds as well as the way coffee is brewed can significantly change its health effects (Kim 2019; Urgert 1997b).

The cardiovascular effects of caffeine are mixed but generally positive. In a meta-analysis of randomized trials, caffeine supplements slightly raised blood pressure: systolic by about 1.9 mmHg and diastolic by about 1.7 mmHg, with larger effects at higher doses and with longer use (Abbas-Hashemi 2023). However, large long-term studies do not support avoiding coffee because of concern about heart rhythm problems. In the UK Biobank study, each extra daily cup of coffee was linked to about a 3% lower risk of developing an arrhythmia and generally did not vary by caffeine-metabolism genotype (Kim 2021). Meta-analyses have not shown an increased risk of atrial fibrillation (Caldeira 2013) or an increase in ventricular arrhythmia (Zuchinali 2016) in human studies at usual exposure levels. Overall, current evidence suggests that while caffeine can temporarily raise blood pressure, regular coffee drinking does not seem to increase arrhythmia risk in the general population and may even help lower it (Abbas-Hashemi 2023; Kim 2021). Caffeine in energy drinks, however, is an area of possible concern. A 2024 meta-analysis of 17 randomized trials found that drinking energy drinks caused short-term increases in systolic and diastolic blood pressure, as well as in cardiac output (Gualberto 2024).

Metabolic effects are also mixed. Observational studies suggest that people who drink a moderate amount of coffee (about 2 to 4 cups per day) have lower risks of death from any cause, and from heart disease, lung disease, and diabetes (Kim 2019). A Mendelian randomization study that looked at genetically predicted caffeine levels in the blood found that higher caffeine levels were linked to lower BMI, lower body fat, and a lower risk of type 2 diabetes. However, it did not find strong evidence for lower risk of heart attack, atrial fibrillation, heart failure, or stroke (Larsson 2023).

Liver outcomes associated with caffeine and coffee consumption are encouraging. A recent meta-analysis found that people who drink coffee have a lower risk of NAFLD (nonalcoholic fatty liver disease) and, among those who already have NAFLD, a lower risk of developing liver fibrosis (Hayat 2021).

Cancer evidence is more nuanced. The IARC no longer labels coffee as carcinogenic in humans and has reported lower risks of liver and uterine endometrial cancer in observational studies.

However, it also warns that very hot drinks are a separate issue, because high temperature itself is likely to increase esophageal cancer risk (Loomis 2016). More recently, a Mendelian randomization meta-analysis did not find clear evidence that coffee causes a meaningful reduction in hepatocellular carcinoma risk. This suggests that some of the observed protection in earlier studies may be due to confounding, reverse causation, or to other non-caffeine compounds in coffee (Choi 2026).

Bone health shows important differences between caffeine and coffee consumption. An updated meta-analysis found no clear link between coffee drinking and overall fracture risk. However, higher caffeine intake was linked to a statistically significant increase in fracture risk, with about a 2% higher risk for each additional 100 mg of caffeine per day (Asoudeh 2023).

Pregnancy is the situation where caution with caffeine is likely most warranted. The American College of Obstetricians and Gynecologists reaffirmed in 2023 that consuming less than 200 mg of caffeine per day does not seem to be a major cause of miscarriage or preterm birth, but it notes ongoing uncertainty about effects on fetal growth (American College of Obstetricians and Gynecologists 2010). More recent evidence supports this concern. A dose-response meta-analysis found that every extra 100 mg of caffeine per day in pregnancy was linked to a 12% higher risk of having a low-birth-weight baby (Soltani 2023) and a 2024 integrative review also associated prenatal caffeine exposure with pregnancy loss, low birth weight, certain birth defects, higher body weight in children, and possible effects on neurodevelopment, with some of these signals seen even at intakes below 200 mg per day (Rohweder 2024). At the same time, a separate 2024 systematic review on neurobehavioral disorders judged the evidence to be insufficient and of very low certainty (Santana 2024). Taken together, caffeine consumption during pregnancy should be approached with caution as its effects on fetal growth and brain development are still not clearly settled.

Current evidence suggests that caffeine may help protect against Parkinson disease. A meta-analysis found that regular caffeine use was linked to a lower risk of developing Parkinson disease and to slower progression among people who already had it (Hong 2020). For dementia and Alzheimer disease, however, the data are less clear. A 2024 meta-analysis reported low-certainty evidence of a non-linear link between coffee and dementia, with possible benefits at 1 to 3 cups per day, but estimates for caffeine itself were not clearly protective (Li 2024).

Sleep disruption is likely the most consistent and well-documented harm from caffeine. A meta-analysis of controlled studies found that caffeine cut total sleep time by about 45 minutes, lowered sleep efficiency, made it harder to fall asleep, and caused more waking during the night. In practical terms, a typical cup of coffee may need to be avoided for about 9 hours before bedtime to reduce measurable sleep loss (Gardiner 2023). Anxiety is also a concern. A 2024 meta-analysis in healthy people found that caffeine increased anxiety scores (Liu 2024). Challenge studies in people with panic disorder showed especially strong effects: about half of the participants had a panic attack after taking caffeine, while none did after taking a placebo (Klevebrant 2022).

Intake Recommendations

Caffeine is not a nutrient, and caffeine intake up to 400 mg/day is generally not associated with overt, adverse health effects (Wikoff 2017). Lower intakes are recommended for children (2.5 mg/kg/day), and women who are pregnant, planning to become pregnant, or breastfeeding (300 mg/day) (Wikoff 2017). Organizations such as the March of Dimes and the American College of Obstetricians and Gynecologists suggest that pregnant women further restrict their caffeine intake to 200 mg/day (March of Dimes 2020; American College of Obstetricians and Gynecologists 2010). When consuming caffeinated beverages, it is important to consider the potential health consequences of other ingredients besides caffeine (e.g., calories from added sugars already present in beverages like sodas and energy drinks, or those added based on personal preference, such as adding creamer, sugar, or flavorings to coffee or tea).

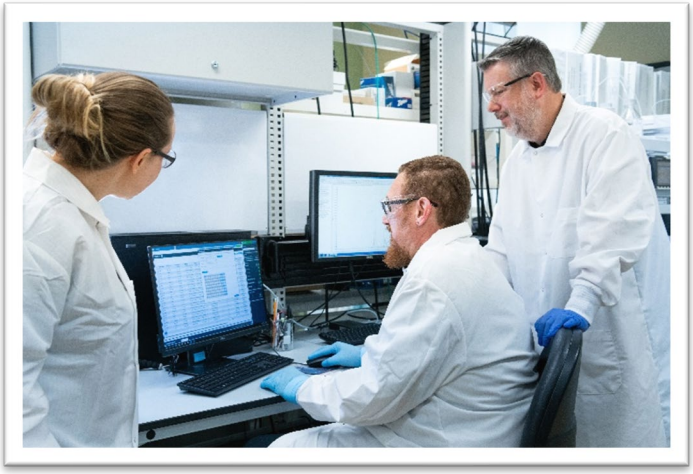
Biochemical Indicators

Before the availability of urine caffeine and caffeine metabolite data in the NHANES, caffeine intake biomarkers were explored in a few small studies (Klebanoff 1998; Crews 2001; Grosso 2008). Analyses of the NHANES 2009–2014 biomarker data found that urine concentrations and excretion rates for caffeine and 8 of its metabolites (theophylline, paraxanthine, 1-methylxanthine, 1-methyluric acid, 1,3-dimethyluric acid, 1,7-dimethyluric acid, 1,3,7-trimethyluric acid, and 5-acetylamino-6-amino-3-methyluracil (AAMU)) were correlated with 24-hour caffeine intake from foods, beverages, and dietary supplements (Spearman ρ = 0.55–0.68, P <0.0001) (Figure 1), supporting their use as caffeine intake biomarkers (Rybak 2015; Pao 2025). Other metabolites (theobromine, 3-methylxanthine, 3-methyluric acid, 7-methylxanthine, 7-methyluric acid) showed low correlation with caffeine intake (ρ = 0.15–0.28, P <0.0001) but moderate correlation with 24-hour theobromine intake from foods and beverages (ρ = 0.36–0.41, P <0.0001) (Pao 2025). A

principal components analysis (PCA) of the same 2009–2014 intake and urine excretion data showed that 1-methylxanthine, 1-methyluric acid, and AAMU may be better biomarkers of caffeine intake than other metabolites based on their higher correlation and covariance in the PCA model (Pao 2025).

Researchers evaluated the reliability of using random spot urine samples to measure caffeine and its metabolites using intraclass correlation coefficients (ICCs). ICCs measure the ratio of variance between individuals to the total variance in repeated samples collected over a specific timeframe. The closer the ICC value is to 1, the more reliable the measurement. For caffeine and most of its metabolites, ICCs are ≥0.8 over 24 hours and ≥0.6 over 6 weeks (Rybak 2025). The urine excretion mechanism of the caffeine metabolite also affects measurement reliability. Caffeine, paraxanthine, theophylline, and theobromine show flow-dependent urine excretion (Tang-Liu 1983). In these cases, and when using unadjusted urine concentrations, spot urine measurements are most reliable (i.e., ICCs are highest) (Rybak 2025). In contrast, methylxanthines, uric acids, and AAMU exhibit flow-independent excretion (Tang-Liu 1982). For these metabolites, expressing concentration as an excretion rate or using an adjusted concentration (e.g., creatinine, specific gravity) provides the most reliable measurements (i.e., the highest ICCs) (Rybak 2025).

Analytical Methods



Caffeine and its metabolites have been measured in biologic matrices using various analytical techniques. Analyses studying the association between dietary caffeine intake and caffeine metabolite concentrations in bodily fluids have used techniques like high-performance liquid chromatography (HPLC) coupled with UV-visible detection (Klebanoff 1998; Crews 2001). More recently, HPLC-tandem mass spectrometry (MS/MS) has been employed (Grosso 2008; Rybak 2014; Rybak 2025). HPLC-MS/MS has also been used to measure caffeine and its metabolites in phenotyping studies (Schneider 2003; Caubet 2004; Stewart 2011; Tremmel 2024).

Findings from NHANES

The National Health and Nutrition Examination Survey (NHANES) is the only source for nationally representative data on urine caffeine and caffeine metabolites for the U.S. population (Pfeiffer 2026). The compounds have been measured in NHANES 2009–2014 (Rybak 2015; Pao 2025) and in surplus urine samples from NHANES 1999–2002.

For more information about caffeine, see the fact sheet from the National Institutes of Health, Office of Dietary Supplements (https://ods.od.nih.gov/factsheets/list-all/).

Data in the 2026 tables

Data presented are from univariate analysis that was not adjusted for demographic variables (e.g., age, sex, race and Hispanic origin) or other blood concentration determinants (e.g., dietary intake, supplement use, smoking, BMI). Data for caffeine and caffeine metabolites were available from NHANES 2009–2014 and are shown for both the urine concentration and for excretion rates. Biomarker data were generated using an HPLC-MS/MS method. This method was specifically designed to comprehensively measure caffeine and its metabolites in population-based settings (NHANES 2009–2010: Rybak 2014; NHANES 2011–2014: Rybak 2025).

Compound	Type
Caffeine	Trimethylxanthine
Paraxanthine	Dimethylxanthine
Theobromine	Dimethylxanthine
Theophylline	Dimethylxanthine
1-Methylxanthine	Methylxanthine
3-Methylxanthine	Methylxanthine
7-Methylxanthine	Methylxanthine
1,3,7-Trimethyluric acid	Trimethyluric acid
1,3-Dimethyluric acid	Dimethyluric acid
1,7-Dimethyluric acid	Dimethyluric acid
3,7-Dimethyluric acid	Dimethyluric acid
1-Methyluric acid	Methyluric acid
3-Methyluric acid	Methyluric acid
7-Methyluric acid	Methyluric acid
5-Acetylamino-6-amino-3-methyluracil (AAMU)	Uracil

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