Long-term effects of caffeine

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Peter Attia April 22, 2025

Source	Caffeine content (mg)	Notes
Drip coffee	90-150	A strong cup (8 oz)
Single espresso shot	60-70	
Black tea	40-70	8 oz
Green tea	30-50	8 oz
Red Bull energy drink	80	250 mL
Soft Drinks		12 oz (~350 mL)
Mountain Dew, Pepsi One	55	
Classic Coke/Pepsi	30-40	
Root beer, lemon/lime	0	
Chocolate	Varies by cocoa content	1 oz (28 gram)
Dark chocolate (70-85% cocoa)	20-60	
Milk chocolate	6-20	
Caffeine pill	100	No-Doz tablet and caffeine-based diuretic pills
Pre-workout supplements	150-400	Per recommended serving size for common pre-workout drinks and powders

Caffeine is woven so thoroughly throughout modern life that we rarely pause to consider its remarkable influence on human physiology and performance. From the morning coffee ritual to the pre-workout supplement, this molecule shapes our daily rhythms in ways both obvious and subtle. Yet despite its ubiquity — or perhaps because of it — many misconceptions persist about caffeine's effects on health and performance.

In this comprehensive review, we'll examine the scientific evidence behind caffeine's impact on the body and mind. Caffeine is widely consumed for its well-known acute effects on mental alertness and mood, its efficacy as an ergogenic aid, and its ability to stave off fatigue, but mounting evidence links caffeine to *long-term* effects on health, too. What role might this ubiquitous compound play in metabolic, cardiovascular, and neurological health? Are there risks associated with its use? Do certain individuals stand to reap greater benefits — or

assume greater risks — with caffeine consumption? We'll examine these questions and more as we explore caffeine's broader implications for health and well-being and attempt to provide practical guidance on its use.

Caffeine's primary mechanism of action

The phrase "Don't talk to me until I've had my coffee" has become such a cultural touchstone that it's easy to forget the array of physiological effects that help to drive that morning boost. After consuming caffeine — whether through coffee, tea, or supplements (see **Table 1**) — absorption occurs rapidly through the gastrointestinal tract, and the concentration of caffeine in the bloodstream quickly rises, peaking within about 30 minutes, though this can vary based on factors like food intake and the specific delivery method.[1] Because it is quite small and is both water- and fat-soluble, caffeine can cross the lipid-based cell membranes of the blood-brain barrier, allowing it to exert its neurological effects.

Caffeine primarily acts by blocking adenosine receptors (particularly the A_{2A} receptor subtype[2]) in the brain, a mechanism that explains both its desired effects and many of its potential drawbacks. Adenosine is widely recognized as a key regulator in sleep homeostasis, driving feelings of drowsiness and increasing sleep pressure as the day wears on.[3] Caffeine's molecular structure allows it to bind to adenosine receptors without activating them, effectively *preventing* adenosine from exerting its calming and sleep-promoting effects and indirectly boosting the release of stimulating neurotransmitters such as dopamine and norepinephrine. While adenosine receptor blockade constitutes the main mechanism through which caffeine exerts its stimulatory effects, other pathways play a role, as caffeine is also known to enhance neurotransmitter activity and alertness by slowing the breakdown of cyclic AMP, a messenger molecule involved in regulating neurotransmitter release, and by suppressing inhibitory signals (GABA) in the brain.[4]

Table 1: Caffeine content found in popular sources

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Individual determinants of caffeine's impact

While caffeine always acts through the same basic mechanisms described above, the intensity and duration of its effects vary dramatically between individuals. This is primarily due to variation in the activity level of CYP1A2, a critical enzyme for caffeine metabolism. Higher levels of CYP1A2 activity lead to faster processing and clearance of caffeine, while lower levels have the opposite effect, resulting in caffeine remaining present in circulation for longer periods of time. But what determines CYP1A2 activity? Genetics certainly plays a key role, but additional variation can be attributed to environmental factors, as well as to habitual patterns of caffeine use and the development of caffeine tolerance.

The CYP1A2 gene, which encodes the CYP1A2 enzyme, exists in different forms (or "alleles") across the population. These different alleles correspond to different levels of enzymatic activity, and individuals who inherit CYP1A2 alleles associated with higher activity ("fast metabolizers") can process caffeine around five times more rapidly than those with the less active variant.[5,6] Thus, one's genotype for the CYP1A2 gene itself has a direct impact on caffeine metabolism rate, though variants in genes involved in *regulating expression* of the CYP1A2 are also likely to contribute to the total impact of genetics on caffeine processing.[7] While debate surrounds the exact contribution of genetics to overall variation in CYP1A2

activity and caffeine metabolism, it is thought to be quite high,[8] so those with “fast metabolizer” gene variants tend to clear caffeine from the body more quickly than those with “slow metabolizer” gene variants.

Certain environmental exposures are also known to impact caffeine metabolism. Tobacco smoking, in particular, has long been recognized for its ability to induce greater CYP1A2 activity and accelerate caffeine clearance by 60-70% relative to nonsmokers.[6,9,10] A handful of dietary elements, including cruciferous vegetables and chargrilled meats, also appear to have the effect of driving CYP1A2 activity, though the precise extent is less clear.[11,12] On the other hand, the use of oral contraceptives has the inverse effect — *reducing* CYP1A2 activity by around 30%.[13] This reduction has been attributed at least in part to the increases in progesterone levels that accompany oral contraceptive use, as women in the luteal phase of the menstrual cycle (when progesterone levels reach their highest point) also show slower rates of caffeine metabolism.[14,15] Other medications, including certain antibiotics, also reduce CYP1A2 activity, while a handful are known to have the opposite effect (see **Table 2**).[10] Thus, even within a given individual, rates of caffeine metabolism may vary from time to time based on diet, hormone fluctuations, and other factors.

Table 2: Environmental exposures influencing rate of caffeine metabolism

CYP1A2 activators	Notes
Tobacco smoke	Activation increases with increasing exposure, from ~20% for 1-5 cigarettes per day to ~70% for a pack or more per day
Chargrilled meat	Variable effect
Cruciferous vegetables	E.g., broccoli, brussel sprouts, kale; variable effect
Heavy caffeine intake	Estimated 45% activation per liter of coffee consumed daily
Modafinil	Stimulant medication used for treatment of narcolepsy & sleep apnea
Omeprazole	Over-the-counter medication for treatment of heartburn
CYP1A2 inhibitors	**Notes**
Oral contraceptives	Estimated ~30% inhibition, but likely to vary by formulation/dose
Pregnancy	Inhibition increases as pregnancy progresses, from ~30% in the first trimester to ~65% in the third trimester[16]
Fluvoxamine	SSRI medication used for treating obsessive-compulsive disorder & anxiety disorders
Select antibiotics	Fluoroquinolones, ciprofloxacin

Another noteworthy contributor to variation in the effects of caffeine is caffeine consumption itself. Heavy caffeine intake has been shown to increase CYP1A2 activity and thus speed up caffeine metabolism,[17] but this is just *one* of the mechanisms through which habitual caffeine intake can attenuate the compound’s effects. Another important mechanism relates to caffeine

tolerance. With daily caffeine exposure, the body attempts to offset the substance's blockade of adenosine by increasing the number of adenosine receptors or making them more responsive. Over time, the nervous system essentially recalibrates so that the user requires caffeine just to achieve what once was a normal baseline of alertness. Missing that morning cup can result in a pronounced slump, as there is suddenly a surplus of adenosine receptors waiting to be activated, leading to heightened feelings of fatigue, headache, or difficulty concentrating. However, not all of the many physiological effects of caffeine are equally impacted by tolerance. We will return to this point throughout our discussion.

Challenges with interpreting caffeine research

To preface our discussion of the many alleged effects of caffeine on health and performance, we must first pause to draw attention to a few key shortcomings with respect to caffeine research.

One issue is a heavy reliance on observational data — a problem we've encountered countless times with research on human nutrition and lifestyle interventions. Observational studies provide insights about how two variables might *correlate* with each other, but they generally cannot be used to make inferences about causal relationships. The fact that variable A and variable B are frequently linked *might* mean that A causes B, or it might mean that B causes A, or it might mean that a third variable C causes *both* A and B — or it might not mean anything at all, and the linkage between A and B is entirely coincidental. Many observational studies attempt to avoid the "third variable problem" (C causes A and B) by using statistical adjustments to control for likely third-variable confounders, such as age or baseline health metrics, but it's never possible to anticipate or correct for *all* variables that might plausibly contribute to an apparent association.

Eliminating the influence of confounding variables is especially tricky for caffeine, which is typically consumed in the context of coffee, tea, energy drinks, chocolate, or other matrices that include myriad other bioactive compounds. Indeed, though nearly 90% of US adults use caffeine on a daily basis, data show that it is rarely consumed in isolation (i.e., caffeine pills).[18] As we've highlighted in a past newsletter, non-caffeine components of coffee or tea can have their own impacts on health which can mask, enhance, or be mistaken for effects from caffeine itself. These additional compounds can even complicate interpretation of intervention studies, as some research on caffeine have involved treatments with coffee or other caffeinated beverages as opposed to caffeine in isolation. Further, it's possible that caffeine exerts some of its effects through *interactions* with other compounds present in caffeinated beverages, such that trials using caffeine alone (e.g., caffeine pills) might miss potential risks or benefits that would be present with caffeine intake under more "natural" conditions.

Finally, an added layer of confusion surrounding caffeine literature arises as a result of uncertainty regarding the direction of any potential "healthy user bias." This bias pops up routinely in our discussions of observational data and essentially refers to the fact that individuals who make healthy choices regarding the variable under study tend to make healthy choices regarding most *other* aspects of their lives as well, which in turn can bias any results related to health outcomes. As an example, assessing the relationship between vegetarianism

and health outcomes is challenging because individuals who adopt a vegetarian diet often do so out of the belief that it is a healthy choice, and thus, these individuals are also likely to engage in other health-promoting behaviors, such as exercising regularly and getting sufficient sleep, and these other factors can impact health outcomes *independently* of diet.

In the vegetarianism example, we can be fairly certain that the individuals who maintain a vegetarian diet will tend to be *more* health-conscious on average than the individuals who do not, so although we can't necessarily know the *magnitude* of the impact of the healthy user bias, we can at least feel confident about its *direction*. This gives us greater power to interpret any results by mentally "correcting" for the bias. For instance, if we can assume that the vegetarian group is healthier on average, then an improvement in a long-term health metric among that group relative to non-vegetarians would need to be quite large to overcome the additional effect of other healthy behaviors. Or to put it another way, we could interpret an *absence* of any between-group differences in long-term health as an indication that vegetarianism actively *compromises* health enough to fully cancel out the benefit from other healthy behaviors.

By contrast, when it comes to observational data on caffeine, we lack any clarity even on the *direction* of any potential healthy user bias. Some individuals who consume caffeine regularly are doing so to get a boost for their daily workouts as part of a healthier-than-average lifestyle. Others who consume caffeine regularly are doing so in order to get by on 2-3 hours of sleep each night as they work or party themselves to death. We generally can't know which of these scenarios is the case when we look at participants in caffeine studies, and in all probability, the overall direction of the healthy user bias will vary between different study populations (Looking at consumers of pre-workout supplements? Probably scenario #1. Looking at college students? Probably scenario #2.) In any case, the uncertainty leaves us at an enormous disadvantage when it comes to interpreting results.

Short-term effects of caffeine

While the bulk of our discussion will focus on potential long-term effects of caffeine on various aspects of health, we would be remiss not to include at least a brief discussion of alleged benefits on shorter timescales. Acute enhancement of focus, reduction of fatigue, and improvements in endurance and power are among the most common motivations for many individuals who consume caffeine regularly. But how strong are these effects? And do they translate to substantially better mental and physical performance?

Before we take a closer look at these questions, we first need to provide a quick refresher on the concept of "standardized mean difference," or SMD, since it comes up so often in caffeine research. SMD is a summary statistic used to quantify the magnitude of the effect caused by a given intervention in pooled data. In essence, SMD provides a common unit to synthesize data from multiple studies investigating the same outcome, and the larger the absolute value of the SMD, the larger the effect of the intervention. Conventionally, an SMD with an absolute value between 0.2 and <0.5 is considered a small effect, between 0.5 and <0.8 is considered a moderate effect, and ≥0.8 is considered a large effect.

Focus and mood

In modern culture, caffeine has become practically synonymous with some of its most popular benefits: a gentle boost in mood, reduced feelings of fatigue, and increased alertness. Research consistently validates these effects for low or moderate caffeine doses (up to ~300 mg, or around 4 mg/kg), with several randomized trials and meta-analyses reporting improvements in both subjective and objective measures of cognitive performance and mood.[19,20] These effects, which include enhancement of reaction time, performance on attention tasks, and self-reported mood and motivation, tend to be small to moderate in magnitude, though larger effects have been reported for attention than for other cognitive and mood metrics. Positive effects can be significant even at doses as low as 60 mg[21] and likely last for 4-5 hours after intake, though this will vary with individual variation in metabolism as described earlier.[1]

Higher doses of caffeine, however, can lead to unpleasant effects, such as heightened anxiety, nervousness, and jitters. A recent meta-analysis reported that caffeine doses of 400 mg or above had very strong effects on increasing anxiety (SMD=2.86; 95% CI: 2.50, 3.22), whereas doses below 400 mg had only low to moderate anxiogenic effects (SMD=0.61; 95% CI: 0.42, 0.79).[22] Thus, given the dose-dependent line between mood- and attention-boosting effects and adverse effects such as anxiety and jitters, individuals aiming for cognitive or mood-related benefits should prioritize moderate caffeine intake while being mindful of personal tolerance and sensitivity to avoid more negative sensations.

Sleep

The same mechanisms through which caffeine enhances alertness also have the potential to disrupt sleep, making it more difficult to fall asleep as well as causing sleep fragmentation (more awakenings throughout the night) and reducing deep sleep. For example, in a small crossover study involving decaffeinated or caffeinated coffee before bed, participants demonstrated an average decrease in total sleep time by two hours (~25% reduction), an increase in sleep latency by 45 minutes (an increase of >200%), and four more nighttime awakenings (a 57% increase) on caffeine nights relative to decaffeinated nights.[23] Sleep stages were also affected, with caffeine resulting in an average 28-minute reduction in deep sleep in the first three hours of sleep.

Both the timing and dose of caffeine intake influence the probability of negative effects on sleep. Caffeine has an average half-life of 5 hours — i.e., it takes ~5 hours to metabolize *half* of the caffeine you've ingested. With low doses, a 50% drop may be sufficient to lower circulating caffeine to a level that won't impact sleep, but the higher the dose, the more time is needed to fall below that threshold. For instance, a 100-mg dose of caffeine has minimal effects on sleep if taken at least *four hours* before bed, but a 400-mg dose affects sleep even when taken *twelve hours* before bed.[24] (Interestingly, this study also found that subjective assessment of caffeine's effects on sleep tend to be poor. Those who *think* caffeine hasn't affected their sleep show the same objective sleep deficits as anyone else.) Based on these data, we can conclude

that any doses *above* 400 mg, regardless when they're consumed, are likely to compromise sleep in an "average" individual. (For someone with slower caffeine metabolism or no built-up tolerance, this threshold dose may be much lower.)

Caffeine-induced sleep disruptions can lead to a vicious cycle — poor sleep may drive greater caffeine consumption the following day to counteract fatigue, but the extra caffeine may then disrupt another night of sleep. Indeed, greater habitual caffeine consumption correlates with worse functional deficits following sleep deprivation, potentially indicating that those who are affected most strongly by sleep deprivation may be more likely to habitually use caffeine (though an alternative explanation may be that habitual caffeine intake leads to greater effects of sleep deprivation).[25] Thus, for patients struggling with insomnia, limiting or avoiding caffeine is often a critical step in breaking the cycle of poor sleep and caffeine intake.

Also contributing to this cycle is the notorious "crash" associated with coming down from caffeine, which drives many to brew another coffee too close to bedtime. Mitigating post-caffeine energy depletion can therefore help to reduce temptation for late-day caffeine and prevent negative effects on sleep. While limited data exist on caffeine crashes, consuming less caffeine, consuming it more slowly, and consuming it with food or on a full stomach will reduce the magnitude of the spike in circulating caffeine levels, which in turn may help to reduce the crash sensation as caffeine's effects wear off. Additionally, the fatigue and brain fog associated with coming down from caffeine can feel worse if it occurs in conjunction with the fatigue and brain fog associated with a drop in blood sugar (as occurs in the hours following a sugar-heavy meal), so overly sweetened coffee or energy drinks are likely to cause a more pronounced crash than caffeine without added sugar.

Ergogenic effects

Caffeine is among the most commonly used ergogenic aids and is an active ingredient in countless pre-workout supplements. It is especially popular for use in endurance sports due to its fatigue-battling effects and has consistently been shown to reduce rate of perceived exertion (RPE) by 4–8% relative to placebo during both endurance tests and short bursts of high-intensity exercise.[26,27] This has contributed to enhanced athletic performance, as several randomized trials and meta-analyses have shown that ~2.5–6 mg/kg caffeine results in small but significant improvements (typically 2–4%) relative to placebo in completion time and mean power output during time trials in running and cycling,[28–30] as well as increasing time-to-exhaustion.[31] These impacts on endurance activities have been observed in cohorts covering a broad range of baseline fitness levels, indicating that they apply to untrained individuals as well as to high-level athletes.[32] Further, although some evidence indicates that benefits may dampen somewhat with habituation to caffeine consumption,[33] they do not disappear entirely.[32,34]

While endurance sports are the most popular use-case for caffeine as an ergogenic aid, the compound may also provide a boost for muscle strength and power, though evidence for these benefits is less compelling.[30] Most trials and meta-analyses point to some positive effect on strength (typically assessed via one-rep maxima or repetitions to failure) and power (e.g., vertical jump tests or peak torque in knee extension), but in virtually all of these reports, results

barely achieve statistical significance, and SMD values generally fall below 0.2, indicating a minuscule effect at best.[35–37] Indeed, many trials report benefits with caffeine in only one or two out of a battery of strength and power tests, which likely reflects the very marginal impact of caffeine on these performance areas as a whole rather than any true differential impact on different muscle groups. Interestingly, caffeine does *not* appear to reduce RPE during strength exercises,[38] nor does it improve performance in most tests of sprinting speed.[39]

Despite widespread agreement that caffeine can yield meaningful enhancements in endurance performance (and possible other areas), neither of the main organizations that establish rules and restrictions around performance-enhancing substances in professional sports — the International Olympic Committee (IOC) and the World Anti-Doping Agency (WADA) — currently prohibit caffeine use among athletes.[30] (Of note, caffeine *is* listed as a banned substance with the National Collegiate Athletic Association, the governing organization for college sports — but only if urinary levels exceed 15 µg/mL, which they estimate would correspond to about 500 mg of caffeine in the 2–3 hours prior to competition.[40] This level exceeds the range that is considered ergogenic and would likely result in adverse effects such as nausea and shaking.) The relatively small magnitude of benefits probably plays some part in the decision to allow caffeine in sports, but in all likelihood, the principal explanation lies in the molecule's sheer ubiquity. Caffeine is found in many unexpected sources such as certain types of breath mints, protein bars, and cereals, making it difficult to avoid altogether, and given that so many people use it regularly for the cognitive benefits discussed above, prohibiting its use altogether might even put athletes at a disadvantage in other aspects of life — for instance, student athletes who might benefit (like many of their fellow students) from taking caffeine to focus during exams.

Overall, caffeine can be a valuable ergogenic aid, particularly for endurance sports, provided dosage and timing are carefully managed to avoid negative effects. Doses of approximately ~2.5–6 mg/kg body weight have shown efficacy in exercise studies, while doses exceeding this recommended range offer no additional performance benefits and may trigger gastrointestinal distress and jitters. Optimal intake within this ~2.5–6 mg/kg range will depend largely on individual metabolic rate and tolerance; for many, 6 mg/kg (the equivalent of 4–5 cups of coffee for a 75-kg individual) will be more than enough to induce negative sensations,[34] so we recommend starting closer to 3–4 mg/kg and titrating up or down based on personal response. Optimal timing will likewise vary across individuals, but improvements in performance have typically been reported with caffeine consumption around 60 minutes before shorter-duration exercise or strategically throughout prolonged events to coincide with expected fatigue.[30]

Most of us who consume caffeine regularly do so for the well-known short-term benefits described above, but what do we know about caffeine's *long-term* health implications? We've seen that this molecule has numerous acute effects on the brain, but the physiological effects of caffeine extend throughout the body as well, from increases in blood pressure to enhanced metabolic rate and higher rates of fluid excretion.

Does less fatigue translate to greater energy expenditure and weight loss? Do acute jolts in mental focus accrue over time into chronic benefits for cognitive function? Let's examine the evidence for these and other potential impacts of caffeine on major health outcomes.

Body weight and fat mass

For decades, caffeine has been included in many over-the-counter pills marketed for weight loss and fat burning. Although such products certainly never proved to be a magic bullet against rising rates of obesity and metabolic syndrome, their failure in that goal doesn't necessarily mean that caffeine itself lacks meaningful impacts in energy balance. Indeed, research indicates that the compound has complex effects on energy expenditure, appetite, and other aspects of metabolism, increasing metabolic rate (i.e., via increased thermogenesis) by ~7% for at least three hours after ingestion (with a 200 mg dose),[41] boosting lipid oxidation (the burning of fats for fuel),[42,43] and potentially suppressing hunger and food intake.[44] But what do these effects mean for *long-term* control of body weight and body composition?

A handful of small randomized trials in humans suggest that caffeine may have marginal benefits in weight loss both alone and in combination with other treatments. A 2018 meta-analysis pooled data from such trials (comprising a total of 606 participants covering a range in baseline BMI from normal to obese), and the authors reported that caffeine interventions drove dose-dependent reductions in body weight, body mass index (BMI), and fat mass, with effect sizes ranging from 0.23 (BMI changes) to 0.36 (fat mass changes).[45] However, most trials included in this analysis combined caffeine with ephedrine, a stimulant known to induce weight loss, and in looking exclusively at trials involving caffeine alone, the effects on these anthropometric metrics appear smaller, even at relatively high doses (~4-5 mg/kg).

Yet some have posited that caffeine may act *synergistically* with other compounds present in common caffeine sources, particularly green tea, to produce positive effects on body weight. In a meta-analysis of trials investigating caffeine with green tea catechins (a class of molecules found in green tea that are thought to have anti-inflammatory and antioxidant properties), results indicated that the combination led to slightly greater weight loss than either catechins without caffeine (a difference of 0.44 kg, or ~1 lb; 95% CI: 0.15, 0.72) or caffeine without catechins (1.38 kg, or ~3 lbs; 95% CI: 1.06, 1.70).[46] These differences in weight loss, though very small, may plausibly accrue over time into clinically relevant impacts on body weight. Further, it's worth noting that catechins alone yielded no weight loss at all compared to placebo, raising the possibility that caffeine may be necessary to potentiate any weight loss effects of catechins, and catechins in turn may enhance weight loss effects of caffeine.

This combination has also been found to be effective in preventing weight regain for at least three months following calorie restriction-induced weight loss, suggesting that regular caffeine intake in the form of green tea may help in *maintenance* of weight loss.[47] (This study used 150 mg caffeine and 270 mg catechins, equivalent to about four cups of green tea per day.) Caffeine alone may also be somewhat beneficial in this regard, as even just 100 mg of caffeine has been shown to increase resting metabolic rate by 3-4% in subjects who have lost weight ("post-obese") — a state that is normally associated with decreased energy expenditure relative to never-obese individuals of the same weight and is thought to contribute to the tendency to regain weight.[48]

While human trials have been small and limited in duration, they have been corroborated by data from animals. Studies in mice and rats have demonstrated that chronic caffeine consumption can help to both prevent excess weight gain in normal-weight animals on high-energy diets and promote weight loss in animals that have already developed obesity (though it's worth noting that animals in such studies were typically exposed to caffeine continuously through food or water, often at higher doses than humans would consume, even after accounting for allometric scaling).[49,50]

In all, caffeine may offer modest support for weight management and fat loss through appetite suppression and increased energy expenditure. However, its effects are likely small — perhaps ~50–150 extra calories burned daily for a couple of cups of coffee. Thus, caffeine may *complement* a more comprehensive weight management strategy, but it should not be relied upon as a primary means of weight control.

Glucose metabolism and diabetes

Beyond effects on body weight, caffeine is also thought to impact metabolic health by altering glucose metabolism and diabetes risk.

In the few hours following caffeine intake, circulating glucose levels tend to rise and insulin sensitivity (e.g., as assessed by hyperinsulinemic euglycemic clamp) tends to fall.[51,52] These effects have been observed in both healthy participants and individuals with type 2 diabetes, yet even in the latter case, we have no evidence that they reach a level that might pose an *acute* threat of ketoacidosis or other dangers caused by excessive blood glucose.

While it's possible that these RCTs were not long enough to detect chronic effects (they ranged in duration from 8–24 weeks), even observational studies with follow-up periods of several years have typically failed to identify significant correlations between caffeine consumption and heightened risk of insulin resistance. In fact, these studies usually report just the opposite — caffeine intake is associated with *lower* risk of diabetes and prediabetes in a dose-dependent manner, at least up to ~6–7 cups of coffee per day (which, according to one meta-analysis, corresponds to a risk reduction of ~40%),[55] and these associations persist after adjustment for BMI.[56,57] Finally, studies in mice and rats consistently demonstrate positive long-term effects of habitual caffeine intake on insulin sensitivity and glycemic control in insulin resistant animals, in some cases fully reversing insulin resistance to the level of healthy controls.[49,50,58] Thus, the congruence between human clinical trials, epidemiology, and animal studies makes a fairly compelling case that caffeine may have significant long-term benefits for glucose metabolism and insulin sensitivity, though the magnitude of these effects remains unclear.

Cardiovascular health

Caffeine has several vascular and metabolic effects which may collectively translate to clinically significant impacts on cardiovascular (CV) health. For instance, it can lead to both vasoconstriction and vasodilation (depending on the area of the body) through direct and indirect actions on vascular muscle and endothelial cells,[59] and as we've just seen, it can boost lipid metabolism. What does this mean for overall heart health?

Caffeine ingestion tends to result in acute increases in blood pressure. As we discussed in a recent premium article, this does not appear to correspond to any *chronic* blood pressure effects or an elevated risk of hypertension, yet this and other acute effects have long been hypothesized to pose a potential danger of cardiac arrhythmias (most notably, atrial fibrillation, or AFib), especially in high-risk individuals with existing hypertension or cardiovascular disease. However, the preponderance of evidence contradicts this possibility. In a randomized trial of 51 patients with heart failure, acute high-dose caffeine administration (500 mg) did not alter the occurrence of arrhythmias relative to placebo, even during tests involving the added strain of exercise on a treadmill.[60] While this study involved just a single treatment with caffeine, multiple meta-analyses of observational data on chronic caffeine consumption habits have likewise reported no association between caffeine intake and AFib in general populations.[61,62] (As we've noted in the past, observational data can be far more telling as an indicator of a *lack* of an effect than for the presence of an effect.) In a study specifically in hypertensive patients, moderate habitual caffeine intake (defined as 2 cups of coffee per day) significantly *increased* the likelihood of recovering a normal heart rhythm during an episode of AFib relative to no intake (OR: 1.5; 95% CI: 0.74–2.01; *P*=0.005).[63] Low (1 cup/day) and high (≥3 cups/day) were reported to modestly reduce likelihood of recovery (by 15% and 10%, respectively), but these figures failed to reach statistical significance. Still, the role of caffeine in cardiac arrhythmias remains somewhat controversial, so individuals with pre-existing concerns related to CV health should be more cautious with their intake. If caffeine consumption leads to noticeable heart palpitations, reducing or avoiding intake is advisable.

The role of caffeine in atherosclerotic cardiovascular disease (ASCVD) is more difficult to ascertain. Observational evidence has long suggested that moderate caffeine consumption, particularly through coffee (up to ~5 cups/day), may modestly reduce ASCVD risk by ~10-15% relative to non-consumption,[64,65] with no added risk in hypertensive individuals.[66] However, epidemiology data are all the more suspect when differences between groups are this small, and as noted earlier, we can't know the direction of potential biases in order to better inform interpretation of such results. Thus, we must turn instead to clues related to the *mechanisms* of atherogenesis.

Longtime readers will recall that elevated low-density lipoprotein (LDL) particle number — commonly estimated through measurement of LDL-cholesterol (LDL-C) — is a key causal element in driving ASCVD, as circulating LDLs are capable of infiltrating artery walls to initiate atherosclerosis. Interventional evidence from humans and animals indicates that caffeine enhances expression of the LDL receptor by the liver and reduces levels of PCSK9 (a protein that, upon binding to the LDL receptor, results in LDL receptor degradation), which together would be predicted to increase clearance of LDL particles from circulation.[67] Indeed, in a randomized trial involving two months of caffeinated coffee intake followed by two months of either continuation of caffeinated coffee or a switch to decaffeinated coffee, those in the decaf group showed significantly increased LDL-C relative to those who continued with caffeine.[68] However, the difference between groups was only ~4.5 mg/dl, and no difference was observed between the caffeinated coffee group and a control group that discontinued coffee consumption altogether at the two-week timepoint. So although LDL reduction through increased clearance

(e.g., via statins) is a proven means of slowing ASCVD progression and preventing adverse CV events, caffeine is very unlikely to move the needle significantly in this regard, though we can interpret these data as indicating that caffeine is also unlikely to *increase* ASCVD risk.

One important caveat to the above point is that, although caffeine itself might pose no increased risk for ASCVD, other compounds present in typical sources of caffeine may be more problematic. A 2012 meta-analysis of human randomized trials found that coffee consumption *increases* serum lipids, including LDL-C (though again, only by a clinically insignificant ~5 mg/dl), yet a closer examination of the included studies reveals that the *method of preparation* is the variable that truly underlies this apparent effect.[69] Specifically, studies involving boiled coffee (i.e., directly boiling coffee grounds in water) without any further filtration were the primary drivers of positive effects on LDL-C, whereas the same studies showed that filtration of boiled coffee (which does not remove caffeine) does not have this effect.[70,71] (Note that, although it is possible to brew coffee through direct boiling, this preparation style is unpopular due to its tendency to extract more bitter-tasting compounds than other methods.)

Neurological health

Given the well-known acute effects of caffeine on cognition described earlier, the possibility that caffeine might also have *chronic* effects on cognition and neurological health has been given considerable attention over the last several decades. Indeed, caffeine consumption has consistently been linked to better performance on cognitive measures in older adults in large-scale epidemiology studies,[72,73] as well as to lower rates of dementia,[7475] and Parkinson's disease (PD).[76] So how well do these associations stand up to closer scrutiny?

Again, we lack long-term intervention studies in humans to substantiate these correlations, but animal studies and mechanistic evidence strongly suggest that caffeine is indeed likely to be somewhat neuroprotective. For instance, an investigation into the effects of chronic low-dose caffeine (5 mg/kg/day, equivalent to 0.8 mg/kg/day for humans) in rats revealed that animals treated with caffeine exhibited significantly fewer age-associated decreases (relative to baseline) in performance on various cognitive tasks compared to rats treated with water only.[77] Further, hippocampal neurons in caffeine-treated rats were found to be healthier than those in water-treated controls in the sense that they showed greater growth and connectivity (e.g., longer and more branched dendrites), which would suggest better cognitive function.

Numerous mechanistic studies have also demonstrated caffeine's ability to mitigate neuroinflammation, a major contributing factor in neurodegeneration. In part, this anti-inflammatory effect appears to result from direct effects of caffeine on inhibiting pro-inflammatory signals, but caffeine can also reduce neuroinflammation through various indirect mechanisms, including the reduction of oxidative stress and neuronal cell death, which would otherwise drive inflammation, as well as contributing independently to neurodegeneration.[78]

While these insights point to overall neuroprotective effects of habitual caffeine consumption, benefits for specific neurodegenerative diseases, such as AD or PD, are less conclusive. Several studies using mouse models of AD and PD have shown positive effects with chronic caffeine treatment — for instance, reducing levels of amyloid beta in AD models or preventing

damage to dopaminergic neurons in PD models.[79,80] However, these models offer little insight as to whether caffeine aids in *preventing* AD or PD, as mice do not develop these diseases spontaneously. Therefore, animal studies can only be designed to test how well caffeine might protect against *progression* of neurodegenerative diseases that have been experimentally induced (typically via genetic mutations and/or introduction of neurotoxic compounds).

This also highlights an additional concern: the degree to which these "artificial" animal models truly recreate the pathology of spontaneous AD and PD in humans is uncertain. Indeed, in contrast to animal data, two small clinical trials on the potential impact of caffeine on PD symptoms have shown very equivocal results at best. Though one of these trials showed modest improvement in motor symptoms and overall disease severity relative to placebo, the larger (n=121) and longer (6-18 months of treatment) of the two reported no improvement in motor symptoms and very slightly worse cognitive and overall disease scores with caffeine versus placebo. (No clinical trials have been conducted with caffeine for AD patients.) These trials, while both very limited in scale, call into question the overwhelmingly positive results from animal models.

Although caffeine is commonly touted as the primary neuroprotective compound in coffee, it's worth noting that some research shows that decaffeinated coffee can provide similar benefits, suggesting that other bioactive substances are at play. This is discussed in greater detail in a previous newsletter, but in brief, several non-caffeine compounds in coffee demonstrate anti-inflammatory and oxidative stress-reducing properties in both in vitro and animal studies, which may help protect against cognitive decline and neurodegenerative diseases.

Taken together, research to date suggests that moderate caffeine intake, particularly through coffee, could play a very small but legitimate role in maintaining brain health and cognition over the long term. If we extrapolate mechanistic insights to the specific pathologies of AD and PD, for which neuroinflammation is considered a risk factor, it seems likely that caffeine might help to prevent these diseases, but the efficacy of this compound in alleviating disease symptoms or slowing disease progression is less clear.

Risks with caffeine consumption

Before we conclude, it's worth addressing a few specific risks — and *misconceptions* about risks — related to caffeine. In particular, these relate to caffeine's alleged dangers related to dehydration, pregnancy, and dependence.

Dehydration

Caffeine is a mild diuretic (increases urine production), and thus, many fear that it can lead to dehydration. Indeed, caffeine is an active ingredient in many diuretic "water pills" (e.g., Diurex), and taken in this way (i.e., as a pill), the compound can certainly have dehydrating effects.

Yet caffeine doesn't necessarily *need* to be dehydrating, especially if you are a habitual consumer. Most people take caffeine with some fluid (e.g., coffee, tea, sodas), which can largely offset the diuretic effect. Further, the tolerance that develops with habitual caffeine intake appears to extend to diuretic effects, such that those who regularly consume caffeine are

less likely to experience significant diuresis than those who are unaccustomed to caffeine.[81] For instance, a trial in habitual coffee drinkers has shown that intake of 800 ml of coffee at a caffeine concentration of around 4 mg/kg did not result in differences in total body water (measured by deuterium oxide) relative to coffee without caffeine.[82] In other words, replacing caffeinated coffee with decaffeinated coffee had no measurable impact on overall hydration status. Thus, individuals who are used to caffeine shouldn't worry much about dehydration, but everyone taking caffeine — especially those who aren't habitual users — should take it with fluids to counteract any dehydrating effect.

Pregnancy

Caffeine is metabolized more slowly by women during pregnancy, especially during the third trimester,[83] and because it can pass through the placental barrier, it has the potential to impact the health and development of the fetus. Observational studies indicate that caffeine consumption is associated with a dose-dependent increase in risk of pregnancy loss, with a 2022 meta-analysis showing a 26% increase in risk for every 100-mg increase in daily caffeine intake across pooled data from case-control studies.[84] While biases in these data are certainly possible (and probable), the notion that caffeine can increase fetal mortality rate has been further validated by research in animals, which have also shown that heavy caffeine intake may impair uterine implantation of fertilized eggs at the start of pregnancy.[85,86]

Further, human epidemiological data also indicate that exposure to caffeine *in utero* can result in chronic health risks among viable offspring. For instance, children of mothers who consumed even as little as 150 mg caffeine per day during pregnancy have been reported to be at increased risk of obesity, impaired cognitive development, and other health concerns during childhood and later in life.[87] In other words, heavy caffeine consumption can threaten the viability of a pregnancy *and* the long-term health of the offspring, and thus, expectant mothers should keep caffeine consumption to a minimum (100 mg/day at most, though complete abstention is ideal).

Dependence & withdrawal

Caffeine isn't as psychoactive as stronger stimulants (e.g., amphetamines, cocaine) and isn't generally labeled severely addictive, yet habitual use does create physiological dependence. Abrupt withdrawal often brings on headaches (usually within 12–24 hours), fatigue, irritability, mild depressive symptoms, and trouble focusing. Recognized by the DSM-5 as a distinct syndrome, caffeine withdrawal typically peaks around day two and fades within a week. Importantly, unlike severe alcohol withdrawal, caffeine withdrawal is not dangerous — though it can certainly be annoying.

If tolerance diminishes caffeine's energizing effect or side effects like poor sleep and anxiety arise, it may be time to cut back. Tapering is often easier than quitting "cold turkey," and reducing intake gradually or substituting decaffeinated options can soften withdrawal. Some people do periodic "resets," abstaining for about a week every couple of months. Others save caffeine for moments that truly demand alertness. The first days can be tough, but occasional mild pain relievers can ease the transition.

Final thoughts: making caffeine work for you

Caffeine is an ever-present companion in modern life, functioning as a social lubricant in coffeehouses, a motivational tool in workplaces, and a focal point of tradition in many cultures. Its popularity stems from a simple truth: it reliably promotes wakefulness and mental sharpness, providing a sense of sustained energy that people value. Whether you are looking to enjoy the lift caffeine brings without sabotaging your sleep, aiming to harness its metabolic and exercise benefits, trying to reduce anxious side effects, or hoping to supplement more comprehensive strategies for long-term metabolic and cognitive health, the key is to develop a thoughtful relationship with caffeine.

For most people, moderate caffeine intake is harmless — even beneficial — if it aligns with personal tolerance and recommended limits. However, anyone prone to insomnia, anxiety, or heart issues should track dosage carefully or opt for lower-caffeine alternatives. If you rely on multiple cups just to function, a gradual taper may help reset your tolerance — many are surprised at the sustained energy and better sleep that follow. And certainly, complete avoidance of caffeine is recommended for anyone who is pregnant.

Pay attention to signals like afternoon headaches or lingering sleeplessness; these may mean you've exceeded your threshold. Adjusting intake, switching to decaf, or setting a cutoff time can restore balance. Meanwhile, recognize that caffeine can mask deeper issues like inadequate rest, nutritional gaps, or chronic stress. If this is the case, it will certainly negate any potential long-term health benefits. Caffeine should complement, not replace, genuine self-care.

There's no one-size-fits-all strategy for caffeine use: complete avoidance works for some, while occasional, strategic boosts suit others. Genetics, lifestyle, and personal preference shape what's ideal for you. By experimenting, listening to your body, and adapting as needed, you can keep caffeine a supportive ally rather than a controlling force.. However, until we have more definitive evidence, the most reliable path to healthy aging remains the consistent application of fundamental lifestyle practices that we know work.

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References

1. Blanchard J, Sawers SJ. The absolute bioavailability of caffeine in man. Eur J Clin Pharmacol. 1983;24(1):93-98. doi:10.1007/bf00613933
2. Huang ZL, Qu WM, Eguchi N, et al. Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. Nat Neurosci. 2005;8(7):858-859. doi:10.1038/nn1491
3. Reichert CF, Deboer T, Landolt HP. Adenosine, caffeine, and sleep-wake regulation: state of the science and perspectives. J Sleep Res. 2022;31(4):e13597. doi:10.1111/jsr.13597
4. Alasmari F. Caffeine induces neurobehavioral effects through modulating neurotransmitters. Saudi Pharm J. 2020;28(4):445-451. doi:10.1016/j.jsps.2020.02.005

5. Tian DD, Natesan S, White JR , Jr, Paine MF. Effects of common CYP1A2 genotypes and other key factors on intraindividual variation in the caffeine metabolic ratio: An exploratory analysis. Clin Transl Sci. 2019;12(1):39-46. doi:10.1111/cts.12598
6. Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: why, how, and when? Basic Clin Pharmacol Toxicol. 2005;97(3):125-134. doi:10.1111/j.1742-7843.2005.pto_973160.x
7. Low JJL, Tan BJW, Yi LX, Zhou ZD, Tan EK. Genetic susceptibility to caffeine intake and metabolism: a systematic review. J Transl Med. 2024;22(1):961. doi:10.1186/s12967-024-05737-z
8. Matthaei J, Tzvetkov MV, Strube J, et al. Heritability of caffeine metabolism: Environmental effects masking genetic effects on CYP1A2 activity but not on NAT2. Clin Pharmacol Ther. 2016;100(6):606-616. doi:10.1002/cpt.444
9. Parsons WD, Neims AH. Effect of smoking on caffeine clearance. Clin Pharmacol Ther. 1978;24(1):40-45. doi:10.1002/cpt197824140
10. Gunes A, Ozbey G, Vural EH, et al. Influence of genetic polymorphisms, smoking, gender and age on CYP1A2 activity in a Turkish population. Pharmacogenomics. 2009;10(5):769-778. doi:10.2217/pgs.09.22
11. Kall MA, Clausen J. Dietary effect on mixed function P450 1A2 activity assayed by estimation of caffeine metabolism in man. Hum Exp Toxicol. 1995;14(10):801-807. doi:10.1177/096032719501401004
12. Vistisen K, Poulsen HE, Loft S. Foreign compound metabolism capacity in man measured from metabolites of dietary caffeine. Carcinogenesis. 1992;13(9):1561-1568. doi:10.1093/carcin/13.9.1561
13. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. Eur J Clin Pharmacol. 1985;28(4):425-428. doi:10.1007/bf00544361
14. Gunes A, Dahl ML. Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. Pharmacogenomics. 2008;9(5):625-637. doi:10.2217/14622416.9.5.625
15. Lane JD, Steege JF, Rupp SL, Kuhn CM. Menstrual cycle effects on caffeine elimination in the human female. Eur J Clin Pharmacol. 1992;43(5):543-546. doi:10.1007/bf02285099
16. Tracy TS, Venkataramanan R, Glover DD, Caritis SN, National Institute for Child Health and Human Development Network of Maternal-Fetal-Medicine Units. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005;192(2):633-639. doi:10.1016/j.ajog.2004.08.030
17. Djordjevic N, Ghotbi R, Bertilsson L, Jankovic S, Aklillu E. Induction of CYP1A2 by heavy coffee consumption in Serbs and Swedes. Eur J Clin Pharmacol. 2008;64(4):381-385. doi:10.1007/s00228-007-0438-6
18. Fulgoni VL 3rd, Keast DR, Lieberman HR. Trends in intake and sources of caffeine in the diets of US adults: 2001-2010. Am J Clin Nutr. 2015;101(5):1081-1087. doi:10.3945/ajcn.113.080077
19. Lorenzo Calvo J, Fei X, Domínguez R, Pareja-Galeano H. Caffeine and cognitive functions in sports: A systematic review and meta-analysis. Nutrients. 2021;13(3):868. doi:10.3390/nu13030868

20. 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. doi:10.1016/j.neubiorev.2016.09.001
21. Wilhelmus MM, Hay JL, Zuiker RG, et al. Effects of a single, oral 60 mg caffeine dose on attention in healthy adult subjects. J Psychopharmacol. 2017;31(2):222-232. doi:10.1177/0269881116668593
22. Liu C, Wang L, Zhang C, et al. Caffeine intake and anxiety: a meta-analysis. Front Psychol. 2024;15:1270246. doi:10.3389/fpsyg.2024.1270246
23. Březinová V. Effect of caffeine on sleep: EEG study in late middle age people. Br J Clin Pharmacol. 1974;1(3):203-208. doi:10.1111/j.1365-2125.1974.tb00237.x
24. Gardiner CL, Weakley J, Burke LM, et al. Dose and timing effects of caffeine on subsequent sleep: A randomised clinical crossover trial. Sleep. Published online October 8, 2024. doi:10.1093/sleep/zsae230
25. Quiquempoix M, Drogou C, Erblang M, et al. Relationship between habitual caffeine consumption, attentional performance, and individual alpha frequency during total sleep deprivation. Int J Environ Res Public Health. 2023;20(6). doi:10.3390/ijerph20064971
26. Glaister M, Gissane C. Caffeine and physiological responses to submaximal exercise: A meta-analysis. Int J Sports Physiol Perform. 2018;13(4):402-411. doi:10.1123/ijspp.2017-0312
27. Doherty M, Smith PM. Effects of caffeine ingestion on rating of perceived exertion during and after exercise: a meta-analysis. Scand J Med Sci Sports. 2005;15(2):69-78. doi:10.1111/j.1600-0838.2005.00445.x
28. Desbrow B, Biddulph C, Devlin B, Grant GD, Anoopkumar-Dukie S, Leveritt MD. The effects of different doses of caffeine on endurance cycling time trial performance. J Sports Sci. 2012;30(2):115-120. doi:10.1080/02640414.2011.632431
29. Southward K, Rutherfurd-Markwick KJ, Ali A. Correction to: The effect of acute caffeine ingestion on endurance performance: A systematic review and meta-analysis. Sports Med. 2018;48(10):2425-2441. doi:10.1007/s40279-018-0967-4
30. Guest NS, VanDusseldorp TA, Nelson MT, et al. International society of sports nutrition position stand: caffeine and exercise performance. J Int Soc Sports Nutr. 2021;18(1):1. doi:10.1186/s12970-020-00383-4
31. Wang Z, Qiu B, Gao J, Del Coso J. Effects of caffeine intake on endurance running performance and time to exhaustion: A systematic review and meta-analysis. Nutrients. 2022;15(1):148. doi:10.3390/nu15010148
32. Carvalho A, Marticorena FM, Grecco BH, Barreto G, Saunders B. Can I have my coffee and drink it? A systematic review and meta-analysis to determine whether habitual caffeine consumption affects the ergogenic effect of caffeine. Sports Med. 2022;52(9):2209-2220. doi:10.1007/s40279-022-01685-0
33. Lara B, Ruiz-Moreno C, Salinero JJ, Del Coso J. Time course of tolerance to the performance benefits of caffeine. PLoS One. 2019;14(1):e0210275. doi:10.1371/journal.pone.0210275
34. Pickering C, Kiely J. What should we do about habitual caffeine use in athletes? Sports Med. 2019;49(6):833-842. doi:10.1007/s40279-018-0980-7

35. Warren GL, Park ND, Maresca RD, McKibans KI, Millard-Stafford ML. Effect of caffeine ingestion on muscular strength and endurance: a meta-analysis. Med Sci Sports Exerc. 2010;42(7):1375-1387. doi:10.1249/MSS.0b013e3181cabbd8
36. Grgic J, Trexler ET, Lazinica B, Pedisic Z. Effects of caffeine intake on muscle strength and power: a systematic review and meta-analysis. J Int Soc Sports Nutr. 2018;15:11. doi:10.1186/s12970-018-0216-0
37. Grgic J, Grgic I, Pickering C, Schoenfeld BJ, Bishop DJ, Pedisic Z. Wake up and smell the coffee: caffeine supplementation and exercise performance-an umbrella review of 21 published meta-analyses. Br J Sports Med. 2020;54(11):681-688. doi:10.1136/bjsports-2018-100278
38. Ferreira TT, da Silva JVF, Bueno NB. Effects of caffeine supplementation on muscle endurance, maximum strength, and perceived exertion in adults submitted to strength training: a systematic review and meta-analyses. Crit Rev Food Sci Nutr. 2021;61(15):2587-2600. doi:10.1080/10408398.2020.1781051
39. Lopes-Silva JP, Choo HC, Franchini E, Abbiss CR. Isolated ingestion of caffeine and sodium bicarbonate on repeated sprint performance: A systematic review and meta-analysis. J Sci Med Sport. 2019;22(8):962-972. doi:10.1016/j.jsams.2019.03.007
40. Collegiate and Professional Sports Dietitians Association. Caffeine and Athletic Performance. National Collegiate Athletic Association; 2014.
41. Koot P, Deurenberg P. Comparison of changes in energy expenditure and body temperatures after caffeine consumption. Ann Nutr Metab. 1995;39(3):135-142. doi:10.1159/000177854
42. Acheson KJ, Zahorska-Markiewicz B, Pittet P, Anantharaman K, Jéquier E. Caffeine and coffee: their influence on metabolic rate and substrate utilization in normal weight and obese individuals. Am J Clin Nutr. 1980;33(5):989-997. doi:10.1093/ajcn/33.5.989
43. Acheson KJ, Gremaud G, Meirim I, et al. Metabolic effects of caffeine in humans: lipid oxidation or futile cycling? Am J Clin Nutr. 2004;79(1):40-46. doi:10.1093/ajcn/79.1.40
44. Gavrieli A, Karfopoulou E, Kardatou E, et al. Effect of different amounts of coffee on dietary intake and appetite of normal-weight and overweight/obese individuals. Obesity (Silver Spring). 2013;21(6):1127-1132. doi:10.1002/oby.20190
45. Tabrizi R, Saneei P, Lankarani KB, et al. The effects of caffeine intake on weight loss: a systematic review and dos-response meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2019;59(16):2688-2696. doi:10.1080/10408398.2018.1507996
46. Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. Am J Clin Nutr. 2010;91(1):73-81. doi:10.3945/ajcn.2009.28157
47. Hursel R, Westerterp-Plantenga MS. Green tea catechin plus caffeine supplementation to a high-protein diet has no additional effect on body weight maintenance after weight loss. Am J Clin Nutr. 2009;89(3):822-830. doi:10.3945/ajcn.2008.27043
48. 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(1):44-50. doi:10.1093/ajcn/49.1.44
49. Panchal SK, Wong WY, Kauter K, Ward LC, Brown L. Caffeine attenuates metabolic syndrome in diet-induced obese rats. Nutrition. 2012;28(10):1055-1062. doi:10.1016/j.nut.2012.02.013

50. Martins BC, Soares AC, Martins FF, et al. Coffee consumption prevents obesity-related comorbidities and attenuates brown adipose tissue whitening in high-fat diet-fed mice. J Nutr Biochem. 2023;117(109336):109336. doi:10.1016/j.jnutbio.2023.109336
51. Whitehead N, White H. Systematic review of randomised controlled trials of the effects of caffeine or caffeinated drinks on blood glucose concentrations and insulin sensitivity in people with diabetes mellitus. J Hum Nutr Diet. 2013;26(2):111-125. doi:10.1111/jhn.12033
52. Shi X, Xue W, Liang S, Zhao J, Zhang X. Acute caffeine ingestion reduces insulin sensitivity in healthy subjects: a systematic review and meta-analysis. Nutr J. 2016;15(1):103. doi:10.1186/s12937-016-0220-7
53. van Dam RM, Pasman WJ, Verhoef P. Effects of coffee consumption on fasting blood glucose and insulin concentrations: randomized controlled trials in healthy volunteers. Diabetes Care. 2004;27(12):2990-2992. doi:10.2337/diacare.27.12.2990
54. Moon SM, Joo MJ, Lee YS, Kim MG. Effects of coffee consumption on insulin resistance and sensitivity: A meta-analysis. Nutrients. 2021;13(11):3976. doi:10.3390/nu13113976
55. Jiang X, Zhang D, Jiang W. Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. Eur J Nutr. 2014;53(1):25-38. doi:10.1007/s00394-013-0603-x
56. Mirmiran P, Carlström M, Bahadoran Z, Azizi F. Long-term effects of coffee and caffeine intake on the risk of pre-diabetes and type 2 diabetes: Findings from a population with low coffee consumption. Nutr Metab Cardiovasc Dis. 2018;28(12):1261-1266. doi:10.1016/j.numecd.2018.09.001
57. Alshahrani SH, Atia YA, Badir RA, et al. Dietary caffeine intake is associated with favorable metabolic profile among apparently healthy overweight and obese individuals. BMC Endocr Disord. 2023;23(1):227. doi:10.1186/s12902-023-01477-1
58. Guarino MP, Ribeiro MJ, Sacramento JF, Conde SV. Chronic caffeine intake reverses age-induced insulin resistance in the rat: effect on skeletal muscle Glut4 transporters and AMPK activity. Age (Dordr). 2013;35(5):1755-1765. doi:10.1007/s11357-012-9475-x
59. Echeverri D, Montes FR, Cabrera M, Galán A, Prieto A. Caffeine's vascular mechanisms of action. Int J Vasc Med. 2010;2010:834060. doi:10.1155/2010/834060
60. Zuchinali P, Souza GC, Pimentel M, et al. Short-term effects of high-dose caffeine on cardiac arrhythmias in patients with heart failure: A randomized clinical trial. JAMA Intern Med. 2016;176(12):1752-1759. doi:10.1001/jamainternmed.2016.6374
61. Caldeira D, Martins C, Alves LB, Pereira H, Ferreira JJ, Costa J. Caffeine does not increase the risk of atrial fibrillation: a systematic review and meta-analysis of observational studies. Heart. 2013;99(19):1383-1389. doi:10.1136/heartjnl-2013-303950
62. Al-Fadhel JA, Al-Sharidi EM, Alashjaee AA, et al. Does excessive caffeine intake increase the risk of atrial fibrillation? A systematic review and meta-analysis of 1176579 subjects. Journal of Advanced Trends in Medical Research. 2024;1(3):870-875. doi:10.4103/atmr.atmr_165_24
63. Mattioli AV, Farinetti A, Miloro C, Pedrazzi P, Mattioli G. Influence of coffee and caffeine consumption on atrial fibrillation in hypertensive patients. Nutr Metab Cardiovasc Dis. 2011;21(6):412-417. doi:10.1016/j.numecd.2009.11.003

64. 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(6):643-659. doi:10.1161/CIRCULATIONAHA.113.005925
65. Rodríguez-Artalejo F, López-García E. Coffee consumption and cardiovascular disease: A condensed review of epidemiological evidence and mechanisms. J Agric Food Chem. 2018;66(21):5257-5263. doi:10.1021/acs.jafc.7b04506
66. 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(4):1113-1126. doi:10.3945/ajcn.111.016667
67. Lebeau PF, Byun JH, Platko K, et al. Caffeine blocks SREBP2-induced hepatic PCSK9 expression to enhance LDLR-mediated cholesterol clearance. Nat Commun. 2022;13(1):770. doi:10.1038/s41467-022-28240-9
68. Superko HR, Bortz W Jr, Williams PT, Albers JJ, Wood PD. Caffeinated and decaffeinated coffee effects on plasma lipoprotein cholesterol, apolipoproteins, and lipase activity: a controlled, randomized trial. Am J Clin Nutr. 1991;54(3):599-605. doi:10.1093/ajcn/54.3.599
69. Cai L, Ma D, Zhang Y, Liu Z, Wang P. The effect of coffee consumption on serum lipids: a meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2012;66(8):872-877. doi:10.1038/ejcn.2012.68
70. Aro A, Tuomilehto J, Kostiainen E, Uusitalo U, Pietinen P. Boiled coffee increases serum low density lipoprotein concentration. Metabolism. 1987;36(11):1027-1030. doi:10.1016/0026-0495(87)90021-7
71. van Dusseldorp M, Katan MB, van Vliet T, Demacker PN, Stalenhoef AF. Cholesterol-raising factor from boiled coffee does not pass a paper filter. Arterioscler Thromb. 1991;11(3):586-593. doi:10.1161/01.atv.11.3.586
72. Dong X, Li S, Sun J, Li Y, Zhang D. Association of coffee, decaffeinated coffee and caffeine intake from coffee with cognitive performance in older adults: National Health and Nutrition Examination Survey (NHANES) 2011-2014. Nutrients. 2020;12(3):840. doi:10.3390/nu12030840
73. van Gelder BM, Buijsse B, Tijhuis M, et al. Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. Eur J Clin Nutr. 2007;61(2):226-232. doi:10.1038/sj.ejcn.1602495
74. Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M. Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. J Alzheimers Dis. 2009;16(1):85-91. doi:10.3233/JAD-2009-0920
75. Barranco Quintana JL, Allam MF, Serrano Del Castillo A, Fernández-Crehuet Navajas R. Alzheimer's disease and coffee: a quantitative review. Neurol Res. 2007;29(1):91-95. doi:10.1179/174313206X152546
76. Costa J, Lunet N, Santos C, Santos J, Vaz-Carneiro A. Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. J Alzheimers Dis. 2010;20 Suppl 1(s1):S221-S238. doi:10.3233/JAD-2010-091525

77. Vila-Luna S, Cabrera-Isidoro S, Vila-Luna L, et al. Chronic caffeine consumption prevents cognitive decline from young to middle age in rats, and is associated with increased length, branching, and spine density of basal dendrites in CA1 hippocampal neurons. Neuroscience. 2012;202:384-395. doi:10.1016/j.neuroscience.2011.11.053
78. Ruggiero M, Calvello R, Porro C, Messina G, Cianciulli A, Panaro MA. Neurodegenerative diseases: Can caffeine be a powerful ally to weaken neuroinflammation? Int J Mol Sci. 2022;23(21):12958. doi:10.3390/ijms232112958
79. Londzin P, Zamora M, Kąkol B, Taborek A, Folwarczna J. Potential of caffeine in Alzheimer's disease-A review of experimental studies. Nutrients. 2021;13(2):537. doi:10.3390/nu13020537
80. Schepici G, Silvestro S, Bramanti P, Mazzon E. Caffeine: An overview of its beneficial effects in experimental models and clinical trials of Parkinson's disease. Int J Mol Sci. 2020;21(13):4766. doi:10.3390/ijms21134766
81. Maughan RJ, Griffin J. Caffeine ingestion and fluid balance: a review. J Hum Nutr Diet. 2003;16(6):411-420. doi:10.1046/j.1365-277x.2003.00477.x
82. Killer SC, Blannin AK, Jeukendrup AE. No evidence of dehydration with moderate daily coffee intake: a counterbalanced cross-over study in a free-living population. PLoS One. 2014;9(1):e84154. doi:10.1371/journal.pone.0084154
83. Yu T, Campbell SC, Stockmann C, et al. Pregnancy-induced changes in the pharmacokinetics of caffeine and its metabolites. J Clin Pharmacol. 2016;56(5):590-596. doi:10.1002/jcph.632
84. Jafari A, Naghshi S, Shahinfar H, et al. Relationship between maternal caffeine and coffee intake and pregnancy loss: A grading of recommendations assessment, development, and evaluation-assessed, dose-response meta-analysis of observational studies. Front Nutr. 2022;9:886224. doi:10.3389/fnut.2022.886224
85. Paula T de MDE, Cardoso LC, Felicioni F, et al. Maternal chronic caffeine intake impairs fertility, placental vascularization and fetal development in mice. Reprod Toxicol. 2023;121(108471):108471. doi:10.1016/j.reprotox.2023.108471
86. Yadegari M, Khazaei M, Anvari M, Eskandari M. Prenatal caffeine exposure impairs pregnancy in rats. Int J Fertil Steril. 2016;9(4):558-562. doi:10.22074/ijfs.2015.4616
87. Qian J, Chen Q, Ward SM, Duan E, Zhang Y. Impacts of caffeine during pregnancy. Trends Endocrinol Metab. 2020;31(3):218-227. doi:10.1016/j.tem.2019.11.004