



DOSSIER · SUBSTANCE

Caffeine

Caffeine is one of the most extensively studied stimulants. Research is broad but unevenly distributed: safety, fatigue and cognition dominate, while skin, gut and inflammation remain niche topics. The most intriguing finding is methodological — a controlled study shows that part of the measured performance enhancement also occurs without caffeine.

719

STUDIES IN
TOTAL

404

IN HUMANS

300

OF WHICH
CONTROLLED

13

IN ANIMALS

2

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Caffeine at a glance

ORIGIN:

Caffeine is a purine alkaloid and acts as a stimulant in the central nervous system; in the studies it appears as an antagonist at adenosine receptors. The material identifies coffee as the most common source of intake, alongside isolated pure substance and as a component of multi-ingredient preparations. Most studies focus on performance and tolerability rather than therapeutic research.

EVIDENCE BASE:

719 evaluated studies · 300 controlled human trials · 104 observational studies · 83 review articles · 13 animal studies · 1 cell culture study

STRONGEST EVIDENCE:

- **Athletic performance:** Numerous controlled trials and review articles, predominantly in trained, sometimes habituated individuals; effects depend on dose, test type, and habituation.
- **Cognition in sport:** A systematic review with meta-analysis demonstrates improvements in sport-related cognitive tasks; observational data support claims for everyday cognition and older adults.
- **Safety and tolerability:** In female team sport athletes, adverse effects were most frequent at 9 mg·kg⁻¹; between 6 and 9 mg·kg⁻¹ no significant differences were observed, with 6 mg·kg⁻¹ recommended.
- **Methodology of effect measurement:** A controlled study on placebo in sports nutrition found that part of the measured performance enhancement also occurs when no caffeine is administered.
- **Genetics and metabolism:** CYP1A2 variants neither altered ergogenic effects nor accompanying symptoms of a moderate caffeine dose; serum caffeine and paraxanthine levels did not differ between genotypes.

LIMITATIONS:

- **Transferability:** Many studies examine young, trained, and often caffeine-habituated individuals under standardised test conditions; observational data show associations, not causation.
- **Genotype hypothesis:** A pilot study found no change in effects due to CYP1A2 variants, while another reports an influence on cognitive but not athletic performance.
- **Skin, gut, and inflammation:** Only individual controlled studies exist in these areas; no conclusions on effects can be drawn.

ASSESSMENT:

Caffeine is a purine alkaloid and adenosine receptor antagonist whose performance-enhancing effects are well-documented, while measurement design and habituation influence the observed effects.

Download this page as PDF · Summary

1. What Caffeine Is

Caffeine is a purine alkaloid that acts as a stimulant in the central nervous system. In the studies it appears as an antagonist at adenosine receptors; the receptor variant ADORA2A and the metabolising enzyme CYP1A2 are investigated as potential modifiers of its effects. The substance features prominently in sports nutrition, cognitive research, and safety assessment. Accordingly, most studies stem from performance and tolerability research rather than therapeutic investigation.

Crucial for evaluating all studies is the form of intake. The material distinguishes between pure substance, caffeine-containing coffee, and multi-ingredient preparations in which caffeine is combined with other substances. Mixture studies cannot establish the effect of the single substance; this also applies to research on pre-workout supplements. Habituation also plays a role: several studies explicitly examine habituated individuals, and one study describes the time course of tolerance to performance effects. Measurements are taken across highly diverse levels — performance tests, cognitive tasks, questionnaires, physiological markers such as muscle oxygenation. These levels are not equivalent: a marker is not a disease course, a test score is not everyday performance.

2. How Robust the Research Is

The research is unevenly distributed. The largest block consists of controlled human trials, alongside foundational and observational studies. By application area, safety and tolerability, fatigue and exhaustion, and cognition lead, while musculoskeletal, metabolic, and cardiovascular topics are less represented. Only individual studies exist on gut, inflammation, and skin. Animal and cell culture studies are marginal; statements on performance are almost exclusively based on human research. The most frequently cited work across the entire material is a position statement by the International Society of Sports Nutrition on caffeine and athletic performance.

Methodologically, the field is exceptionally well-structured: randomised, double-blind crossover designs are standard, and there is a systematic review with meta-analysis on cognition in sport. These works underpin the claims on performance. Transferability is weaker. Many studies examine young, trained, and often caffeine-habituated individuals under standardised test conditions. Observational data, such as the NHANES analysis on coffee and cognition in older adults, show associations, not causation. Individual studies also report that measured effects are influenced by expectation and placebo.

Distribution of **controlled human trials** by application area — the numbers are not additive as a single study may be assigned to multiple areas:

APPLICATION AREA	CONTROLLED TRIALS
Safety and tolerability	90
Fatigue and stress	76
Cognition and psychology	74
Musculoskeletal system	32
Metabolism	29
Cardiovascular system	26
Absorption and bioavailability	15
Gut and microbiome	8

Part of the measured caffeine effect is expectation

A controlled study on placebo in sports nutrition explicitly examined caffeine as a model case and found that part of the measured performance enhancement also occurs when no caffeine is administered. This is not an objection to the substance but to how effects are measured. Knowing that a stimulant has been received changes expectations, and expectations alter performance. Studies reporting only the verum condition thus overestimate the proportion attributable to the substance. For the assessment of individual studies, this means: the design contributes to the size of the observed effect.

The second open question concerns habituation. A frequently cited study describes the time course of tolerance to the performance-enhancing effect; further studies explicitly examine habituated individuals. The widespread assumption that genotype determines benefits and drawbacks is not supported by the available research. A pilot study found no alteration of effects due to CYP1A2 variants, while another study reports an influence on cognitive performance but not on athletic performance. The genotype hypothesis thus remains a testable question rather than a secure basis for individual recommendations.

3. What Is Often Claimed — and What the Data Support

STATEMENT	EVIDENCE BASE
Caffeine enhances athletic performance	Proven: Numerous controlled studies and reviews, predominantly involving trained or habituated individuals. Effects depend on dosage, type of test, and habituation.
Caffeine improves cognition	Proven for cognitive tasks related to sports (meta-analysis). For everyday cognition and older adults, the statement is based on observational data rather than controlled studies.
Coffee protects against cognitive decline in later life	Hypothesis: The most frequently cited work on this topic is a cross-sectional analysis. It demonstrates an association between consumption and test performance.
Caffeine acts on skin, gut and inflammation	Hypothesis: Zu diesen Gebieten liegen einzelne kontrollierte Arbeiten vor. No conclusion about the effect can be drawn from this.

4. Profile: Molecule and Charge

Caffeine is not a single molecule but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; this is the focus of the next section.

5. Charge, Electrons, Radicals

Direct evidence on the electrochemistry of caffeine itself is limited. Radical-scavenging and cytokine-suppressing activity in the same study is attributed to chlorogenic acids and polyphenols rather than caffeine ²⁶. In humans, lactate and potassium concentrations were measured after caffeine intake during acute resistance exercise, depending on the MCT1-A1470T polymorphism ²⁵.

Direct measurements of charge, cation exchange, electron transfer or redox potential in humans are not reported in the evidence statements; research in this area is still pending. A foundational study analysed muscle biopsies before and after exertion for phosphorylation of β 2AR, PKA and MAPK (ERK, JNK, p38) ²⁷; this relates to signal transduction, not electron transfer. The dose-dependent effect on osteoblasts and osteoclasts is noted as a review statement ²⁶. It remains to be clarified whether the measured potassium concentrations ²⁵ are linked to shifts in charge carriers and whether redox markers can be detected in blood under caffeine.

6. Interactions with Other Substances

With which other substances on this platform this substance has been studied or discussed **together** in human trials and reviews — combinations, comparisons or shared pathways. The number indicates studies in which both are present.

SUBSTANCE	SHARED STUDIES	OF WHICH HUMAN-CONTROLLED
High-intensity interval training (HIIT)	111	80
Cognitive behavioural therapy for insomnia (CBT-I)	103	61
Palmitoylethanolamide (PEA)	63	56
Green tea and EGCG	45	13
L-Theanine	44	17
Stress, cortisol and inflammation	40	14
Art therapy	39	13
Creatine	38	8
Chronic inflammation	27	8
Cocoa flavanols	20	8

ESTABLISHED Genetic variants of the CYP1A2 polymorphism (rs762551) did not alter the ergogenic effects or side effects of a moderate caffeine dose in controlled human studies ⁴⁴⁴⁴. One controlled human study reported greater caffeine effects in CYP1A2 'fast' compared to 'slow' metabolisers: reaction time under stress (-18 ± 9 vs. -1.0 ± 11 ms), fastest 10 % of reaction times at rest (-18 ± 11 vs. -3 ± 15 ms), and lapses at rest (-3.8 ± 2.7 vs. $+0.4 \pm 0.9$; $P < 0.05$) ⁷. Serum caffeine and paraxanthine levels did not differ between genotypes ($P > 0.05$) ⁷.

ESTABLISHED Four genotype groups were formed for ADORA2A in combination with CYP1A2 ²⁹. Acute intake of $6.0 \text{ mg} \cdot \text{kg}^{-1}$ caffeine improved several aspects of physical performance, seemingly independent of ADORA2A genotypes alone or in combination with CYP1A2 genotypes ²⁹. Agility (15.8 ± 1.2 s vs. 15.9 ± 1.3 s; $p = 0.070$) and push-ups (26.6 ± 12.0 vs. 25.0 ± 11.0 ; $p = 0.280$) remained unchanged ²⁹. The ergogenic effect of 6 mg/kg may stem from biological actions and expectation, as this dose only outperformed the control condition without differing from placebo ²⁸. It remains unclear how caffeine intake, enzyme activity, and receptor binding interact during drug administration.

7. Overdose, Tolerability, Limits

ESTABLISHED In a controlled human study, 3, 6 and $9 \text{ mg} \cdot \text{kg}^{-1}$ body weight were tested in female team sport athletes with moderate caffeine use ²². Side effects occurred most frequently at $9 \text{ mg} \cdot \text{kg}^{-1}$; no significant differences were found between 6 and $9 \text{ mg} \cdot \text{kg}^{-1}$ across measured parameters ²². The study recommends $6 \text{ mg} \cdot \text{kg}^{-1}$ to limit side effects ²². 31.3 % of C-allele carriers reported increased nervousness after caffeine intake, whereas none of the AA homozygotes reported this side effect ⁴.

ESTABLISHED Further controlled human studies report good tolerability: tested stimulants were well tolerated, with no negative effects on other cognitive domains ⁹; in young, healthy individuals, pre-workout intake was considered well tolerated ¹³. No serious adverse events or severe haemodynamic disturbances were observed after caffeine intake ³⁰. Symptoms were recorded using standardised questionnaires at predefined time points ¹⁶³¹.

Hypothesis: Whether the increased side effects at $9 \text{ mg} \cdot \text{kg}^{-1}$ also occur outside team sport athletes and how individual symptoms are weighted remains unclear; a study using a uniform side effect questionnaire across multiple doses could clarify this.

8. The Most Robust Studies

Ordered by evidence strength, not prominence. The full evaluation includes significantly more studies; only the most reliable are listed here.

Controlled Human Studies

- ¹ Time course of tolerance to the performance benefits of caffeine (2019)
- ² Caffeine and Cognitive Functions in Sports: A Systematic Review and Meta-Analysis (2021)
- ³ The Effects of High Doses of Caffeine on Maximal Strength and Muscular Endurance in Athletes Habituated to Caffeine (2019)
- ⁴ CYP1A2 Genotype Variations Do Not Modify the Benefits and Drawbacks of Caffeine during Exercise: A Pilot Study (2017)
- ⁵ Women Experience the Same Ergogenic Response to Caffeine as Men (2019)
- ⁶ Effects of caffeine on neuromuscular fatigue and performance during high-intensity cycling exercise in moderate hypoxia (2017)
- ⁷ The effect of caffeine on cognitive performance is influenced by CYP1A2 but not ADORA2A genotype, yet neither genotype affects exercise performance ... (2020)
- ⁸ The Effects of 3 Different Doses of Caffeine on Jumping and Throwing Performance: A Randomized, Double-Blind, Crossover Study (2019)
- ⁹ Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine (2021)
- ¹⁰ Acute caffeine intake increases muscle oxygen saturation during a maximal incremental exercise test (2020)
- ¹¹ Effects of Different Doses of Caffeinated Coffee on Muscular Endurance, Cognitive Performance, and Cardiac Autonomic Modulation in Caffeine Naive ... (2020)
- ¹² Acute caffeine intake increases performance in the 15-s Wingate test during the menstrual cycle (2020)
- ¹³ Effects of acute ingestion of a pre-workout dietary supplement with and without p-syneprine on resting energy expenditure, cognitive function and ... (2017)
- ¹⁴ The effects of different doses of caffeine on maximal strength and strength-endurance in women habituated to caffeine (2021)
- ¹⁵ The Effect of Caffeine on the Velocity of Half-Squat Exercise during the Menstrual Cycle: A Randomized Controlled Trial (2019)
- ¹⁶ Short-Term Effects of a Ready-to-Drink Pre-Workout Beverage on Exercise Performance and Recovery (2017)
- ¹⁷ Acute Effects of an "Energy Drink" on Short-Term Maximal Performance, Reaction Times, Psychological and Physiological Parameters: Insights from a ... (2019)
- ¹⁸ Regular Caffeine Intake Delays REM Sleep Promotion and Attenuates Sleep Quality in Healthy Men (2021)
- ¹⁹ The Acute Effect of Various Doses of Caffeine on Power Output and Velocity during the Bench Press Exercise among Athletes Habitually Using Caffeine (2019)
- ²⁰ Combined caffeine and carbohydrate ingestion: effects on nocturnal sleep and exercise performance in athletes (2014)
- ²¹ Acute Caffeine Intake Enhances Mean Power Output and Bar Velocity during the Bench Press Throw in Athletes Habituated to Caffeine (2020)
- ²² Optimizing Short-Term Maximal Exercise Performance: The Superior Efficacy of a 6 mg/kg Caffeine Dose over 3 or 9 mg/kg in Young Female Team-Sports ... (2024)
- ²³ Aspirin, paracetamol (acetaminophen) and caffeine for the treatment of acute migraine attacks: A systematic review and meta-analysis of randomized ... (2022)
- ²⁴ Early absorption sources of caffeine can be a useful strategy for improving female table tennis players-specific performance (2023)

9. Summary

Proven effects on performance: Numerous controlled studies and systematic reviews, predominantly involving trained and sometimes habituated individuals, support these effects. The magnitude of the effects depends on dosage, type of test, and habituation. For sport-related cognitive tasks, a systematic review with meta-analysis supports the claim. Regarding tolerability, a controlled study in female team-sport athletes with moderate caffeine consumption found that side effects occurred most frequently at 9 mg·kg⁻¹. Between 6 and 9 mg·kg⁻¹, no significant differences were observed in the measured parameters, and the study recommends 6 mg·kg⁻¹ to limit side effects. Further controlled studies report good tolerability without serious adverse events.

PLAUSIBLE

Part of the measured effect may be attributable to expectation: a controlled study on placebo in sports nutrition explicitly used caffeine as a model case and found that some performance enhancement also occurs without caffeine. **Hypothesis:** This suggests that studies reporting only the verum condition may overestimate the substance-specific contribution. **Hypothesis:** No effects can be derived from the available studies for skin, gut, and inflammation, or for the relationship between coffee consumption and cognition in older adults.

Outstanding questions include how quickly the performance-enhancing effect diminishes with regular consumption and what duration of abstinence is required. Further questions concern the contribution of caffeine to the effects of multi-ingredient supplements when tested as a whole, and whether CYP1A2 and ADORA2A variants explain the large interindividual differences.

10. Open Questions

- **Genotype:** Do CYP1A2 and ADORA2A variants explain the large interindividual differences, or are previous findings coincidental?
- **Tolerance:** How quickly does the performance-enhancing effect diminish with regular consumption, and what duration of abstinence is required?
- **Multi-ingredient supplements:** What contribution does caffeine make to the effects of multi-ingredient supplements when tested as a whole?

11. Further Paths

Pathways, mechanisms, and networks in which this substance is involved — for those looking beyond the substance itself.

- Interaction network

Frequently Asked Questions

Which doses are investigated in the studies?

The studies use varying doses. Several explicitly compare different doses, while others examine high doses in habitual users. There is no standard reference dose, and results cannot be directly transferred between the dose ranges studied. Anyone interpreting a study must first verify which dose, form of administration and population were examined.

Does the CYP1A2 genotype influence the effects?

Established: The available studies are contradictory. A pilot study found no change in caffeine effects linked to CYP1A2 variants, while another reported an influence on cognitive but not athletic performance. The genotype remains a research approach rather than a confirmed predictor. For individual advice, the study that integrates both findings in a sufficiently powered design is still outstanding.

What does habituation mean for interpreting study results?

Several studies explicitly investigate habitual caffeine consumers, and one describes the time course of tolerance to performance effects. Regular caffeine users often show smaller effects in controlled tests than non-habitual users. Study results therefore apply to the population studied and cannot be assumed to generalise to all consumers. Whether a consumption break restores the effect remains an open question.

Sources

- 1 Time course of tolerance to the performance benefits of caffeine
Lara B, Ruiz-Moreno C, Salinero JJ, Del Coso J · 2019
- 2 Caffeine and Cognitive Functions in Sports: A Systematic Review and Meta-Analysis
Lorenzo Calvo J, Fei X, Dominguez R, Pareja-Galeano H · 2021
- 3 The Effects of High Doses of Caffeine on Maximal Strength and Muscular Endurance in Athletes Habituated to Caffeine
Wilk M, Krzysztofik M, Filip A, Zajac A, Del Coso J · 2019
- 4 CYP1A2 Genotype Variations Do Not Modify the Benefits and Drawbacks of Caffeine during Exercise: A Pilot Study
Salinero JJ, Lara B, Ruiz-Vicente D, Areces F, Puente-Torres C, Gallo-Salazar C et al. · 2017
- 5 Women Experience the Same Ergogenic Response to Caffeine as Men
Skinner TL, Desbrow B, Arapova J, Schaumberg MA, Osborne J, Grant GD et al. · 2019
- 6 Effects of caffeine on neuromuscular fatigue and performance during high-intensity cycling exercise in moderate hypoxia
Smirmaul BP, de Moraes AC, Angius L, Marcora SM · 2017
- 7 The effect of caffeine on cognitive performance is influenced by CYP1A2 but not ADORA2A genotype, yet neither genotype affects exercise performance in healthy adults
Carswell AT, Howland K, Martinez-Gonzalez B, Baron P, Davison G · 2020
- 8 The Effects of 3 Different Doses of Caffeine on Jumping and Throwing Performance: A Randomized, Double-Blind, Crossover Study
Sabol F, Grgic J, Mikulic P · 2019
- 9 Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine
Repantis D, Bovy L, Ohla K, Kühn S, Dresler M · 2021
- 10 Acute caffeine intake increases muscle oxygen saturation during a maximal incremental exercise test
Ruiz-Moreno C, Lara B, Brito de Souza D, Gutiérrez-Hellin J, Romero-Moraleda B, Cuéllar-Rayó A et al. · 2020
- 11 Effects of Different Doses of Caffeinated Coffee on Muscular Endurance, Cognitive Performance, and Cardiac Autonomic Modulation in Caffeine Naive Female Athletes
Karayigit R, Naderi A, Akca F, Cruz CJGD, Sarshin A, Yasli BC et al. · 2020
- 12 Acute caffeine intake increases performance in the 15-s Wingate test during the menstrual cycle
Lara B, Gutiérrez-Hellin J, Ruiz-Moreno C, Romero-Moraleda B, Del Coso J · 2020
- 13 Effects of acute ingestion of a pre-workout dietary supplement with and without p-synephrine on resting energy expenditure, cognitive function and exercise performance
Jung YP, Earnest CP, Koozehchian M, Galvan E, Dalton R, Walker D et al. · 2017
- 14 The effects of different doses of caffeine on maximal strength and strength-endurance in women habituated to caffeine
Filip-Stachnik A, Wilk M, Krzysztofik M, Lulińska E, Tufano JJ, Zajac A et al. · 2021
- 15 The Effect of Caffeine on the Velocity of Half-Squat Exercise during the Menstrual Cycle: A Randomized Controlled Trial
Romero-Moraleda B, Del Coso J, Gutiérrez-Hellin J, Lara B · 2019
- 16 Short-Term Effects of a Ready-to-Drink Pre-Workout Beverage on Exercise Performance and Recovery
Collins PB, Earnest CP, Dalton RL, Sowinski RJ, Grubic TJ, Favot CJ et al. · 2017
- 17 Acute Effects of an "Energy Drink" on Short-Term Maximal Performance, Reaction Times, Psychological and Physiological Parameters: Insights from a Randomized Double-Blind, Placebo-Controlled, Counterbalanced Crossover Trial
Chtourou H, Trabelsi K, Ammar A, Shephard RJ, Bragazzi NL · 2019
- 18 Regular Caffeine Intake Delays REM Sleep Promotion and Attenuates Sleep Quality in Healthy Men
Weibel J, Lin YS, Landolt HP, Berthomier C, Brandewinder M, Kistler J et al. · 2021
- 19 The Acute Effect of Various Doses of Caffeine on Power Output and Velocity during the Bench Press Exercise among Athletes Habitually Using Caffeine
Wilk M, Filip A, Krzysztofik M, Maszczyk A, Zajac A · 2019
- 20 Combined caffeine and carbohydrate ingestion: effects on nocturnal sleep and exercise performance in athletes
Miller B, O'Connor H, Orr R, Ruell P, Cheng HL, Chow CM · 2014
- 21 Acute Caffeine Intake Enhances Mean Power Output and Bar Velocity during the Bench Press Throw in Athletes Habituated to Caffeine
Wilk M, Filip A, Krzysztofik M, Geffert M, Zajac A, Del Coso J · 2020
- 22 Optimizing Short-Term Maximal Exercise Performance: The Superior Efficacy of a 6 mg/kg Caffeine Dose over 3 or 9 mg/kg in Young Female Team-Sports Athletes
Bougrine H, Ammar A, Salem A, Trabelsi K, Jahrami H, Chtourou H et al. · 2024
- 23 Aspirin, paracetamol (acetaminophen) and caffeine for the treatment of acute migraine attacks: A systemic review and meta-analysis of randomized placebo-controlled trials
Diener HC, Gaul C, Lehmacher W, Weiser T · 2022
- 24 Early absorption sources of caffeine can be a useful strategy for improving female table tennis players-specific performance
Pirmohammadi S, Hemmatinavar M, Nemati J, Imanian B, Abdollahi MH · 2023
- 25 Effect of MCT1 A1470T Polymorphism on Lactate and Potassium Concentrations After Caffeine Ingestion During Acute ...
· 2024
- 26 Caffeine can influence osteoblast and osteoclast activity in a dose-dependent manner, while chlorogenic acids (CGA) and ...
· 2025
- 27 Pre- and post-exercise muscle biopsies were analyzed for the phosphorylation (p-) of β 2AR, PKA, and MAPK (ERK)...
· 2023
- 28 However, the ergogenic effect of 6 mg/kg of caffeine may be derived from a combination of biological effects and expecta...
· 2022
- 29 Participants were further divided in four groups (1-TTADORA2A + AACYP1A2; 2-TTADORA2A +...
· 2023
- 30 No major adverse events were reported in relation to caffeine, and no major hemodynamic perturbations were observed with...
· 2021
- 31 Participants then completed side effects and cognitive function tests after 1, 2, 3, 4, 5, and 6 h of treatment ingestio...
· 2021

International Health Research

Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
ih-research.com/en/knowledge/caffeine/ · Last updated 2026-10-15