LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

Acute caffeine intake reduces insulin sensitivity in healthy subjects: a systematic review and meta-analysis - Evidence review

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1. ABSTRACT

The analyzed study pooled seven randomized crossover clinical trials, involving a total of 70 healthy adults, to verify whether a single intake of caffeine alters insulin sensitivity, i.e., the efficiency with which insulin promotes glucose entry into cells. The quantitative synthesis indicates an acute reduction in insulin sensitivity compared to placebo, but the studies were small, conducted primarily in young men, and evaluated short-term effects.In section 4.16 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that caffeine can temporarily interfere with the insulin response. Independent evidence confirms that acute caffeine can increase glucose and insulin demand and reduce glucose utilization by muscle. However, a 24-week trial on caffeinated coffee did not find a significant change in insulin sensitivity: acute effects cannot, therefore, be automatically extended to habitual consumption or individual clinical risk.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 22, 2026
Updated: November 22, 2026

DOI 10.5281/zenodo.24436819

MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was simple and clinically relevant: does an acute dose of caffeine, taken by healthy individuals without diabetes, alter insulin sensitivity compared to a placebo? The hypothesis was that caffeine reduces the body's ability to use glucose in response to insulin.The relevance to paragraph 4.16 is precise. The publication subject to the Evidence Review does not demonstrate the entire chain proposed in the book's text, which includes stress, cortisol, insulin signaling, and insulin resistance. Instead, it documents its final and immediate functional segment: after acute caffeine intake, insulin sensitivity is lower in healthy adults.As a meta-analysis of acute studies, the work can estimate the average direction of the short-term effect. It cannot prove that caffeine causes persistent insulin resistance, diabetes, chronic alterations of the stress axis, or greater harm in people predisposed to glucose metabolism disorders.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors searched for studies published up to April 2016 in three bibliographic databases. Randomized clinical trials conducted in healthy humans, with either a parallel or crossover design, were included. In a crossover design, each participant receives both caffeine and a placebo at different times and in a random order; this reduces individual differences between groups.Seven studies were included, with a total of 70 participants. Sample sizes ranged from 7 to 12 people. All studies had a randomized crossover design, either single-blind or double-blind. Six studies included only men; in the remaining one, the distribution between men and women was equal. The participants did not have diabetes or other known metabolic diseases. Most were of normal weight; one study involved men with obesity.Caffeine doses ranged from 3 to 6 mg per kilogram of body weight, with 5 mg/kg being the most frequent dose. Caffeine was administered orally or intravenously. Controls included dextrose, saline solution, water, or decaffeinated coffee. Prior abstinence from caffeine ranged from 48 hours to 7 days in the individual trials reported.Insulin sensitivity was estimated primarily using an oral glucose tolerance test and the Matsuda-DeFronzo index, or with the hyperinsulinemic-euglycemic clamp. The latter is an experimental procedure in which glycemia is kept stable while insulin is infused, measuring how much glucose must be administered to compensate for its action. The authors combined results obtained with different methods using the standardized mean difference, employing a random-effects statistical model.The risk of bias assessment revealed frequent uncertainty regarding allocation concealment and blinding in outcome assessment. This information limits the precision with which the true magnitude of the effect can be estimated.

4. RESULTS

The main result was consistent across the seven included studies: compared to the placebo, acute caffeine Intake reduced the insulin sensitivity index. The combined standardized mean difference was −2.06, with a 95% confidence interval from −2.67 to −1.44. The negative sign indicates that, in the comparison performed by the authors, the value was lower after caffeine than in the control group.Heterogeneity was moderate, with an I^2 of 49%. The I^2 expresses how much of the variability between studies may depend on real differences between protocols, doses, participants, or measurement methods, rather than chance. The P-value for heterogeneity was 0.07. The studies were therefore not identical to each other, but the direction of the effect reported was consistently towards lower insulin sensitivity.The book's paragraph states that the meta-analysis found a reduction in insulin sensitivity of “up to 15%.” The 15% percentage figure is not the combined quantitative result of the meta-analysis, which used a standardized mean difference. In the available material, the 15% figure instead derives from one of the included trials, in which caffeine reduced insulin sensitivity compared to the placebo.The available material does not report an analysis demonstrating a greater effect in subjects predisposed to glucose metabolism disorders. Furthermore, the analyses do not allow for the effect of pure caffeine to be separated with certainty from that of coffee as a beverage in all real-world dietary contexts.

5. INTERPRETATION

In simple terms, after an acute dose of caffeine, the body may require a more intense insulin response to manage the same amount of glucose. This does not necessarily mean that glycemia always increases or that a disease will develop: it describes a lower metabolic efficiency observed in the hours following intake.The segment documented by the publication is therefore: acute caffeine reduced insulin sensitivity. The work does not directly demonstrate that caffeine inhibits the PI3K/AKT pathway in human tissues, nor that cortisol is the predominant mechanism. PI3K/AKT is a sequence of intracellular signals that helps transmit the insulin command and promote glucose utilization. To attribute a causal role to this pathway, direct measurements in tissues and specific experimental studies are needed.A biologically plausible explanation is the activation of counter-regulatory signals, including adrenaline, which can temporarily reduce insulin action. However, plausibility is not equivalent to proof. The greatest strength of the study is the convergence of randomized trials; the main limitations are the very small number of participants, the prevalence of young men, the variety of methods, and the extremely short duration of the observations.

6. INDEPENDENT SUPPORTING EVIDENCE

A subsequent meta-analysis of clinical trials evaluated the acute effects of pure caffeine and caffeinated coffee on glycemic indices. Overall, it found that acute caffeine supplementation increased glucose concentration and reduced the insulin sensitivity index; the effect on glucose was statistically significant, especially at doses of 250 mg or higher. This research directly confirms the passage in the paragraph regarding an acute reduction in insulin sensitivity, while also noting heterogeneity between studies and an important distinction between pure caffeine and coffee containing caffeine [1].A randomized, double-blind, crossover trial conducted on 24 healthy adults, 12 men and 12 women, compared a placebo with caffeine at 1, 3, or 5 mg/kg before an oral glucose tolerance test. As the dose increased, the area under the curve for glucose, insulin, and C-peptide—an indicator of insulin secretion produced by the body—also increased. For every 1 mg/kg increase, the area under the curve for insulin increased by 5.8% and for C-peptide by 8.7%; glucose exposure also increased. This supports the idea that acute impairment can occur in both sexes and follows a dose-dependent relationship. However, it remains a short-term study with a limited sample size and intermediate metabolic outcomes [2].Another randomized crossover study in seven men directly examined skeletal muscle during a hyperinsulinemic-euglycemic clamp. After 5 mg/kg of caffeine, whole-body glucose disposal was lower compared to the placebo: 37.5 ± 3.1 versus 54.1 ± 2.9 micromoles per minute per kilogram. In the muscle, insulin-stimulated glucose uptake was reduced by approximately 50%. This provides a direct mechanistic link to the book's statement regarding glucose entry into target tissues [3].The same study, however, did not observe a reduction in the activation of certain insulin signaling steps measured in the muscle, including the insulin receptor, PI3K, and AKT. Instead, it detected an increase in adrenaline and intramuscular cyclic AMP, a molecule involved in cell signal transmission. Therefore, it confirms reduced muscle glucose uptake, but does not confirm in its specific model that the reduction depends on direct inhibition of the PI3K/AKT pathway [3].

7. CONFLICTING EVIDENCE

A 24-week randomized controlled trial evaluated four cups of regular instant coffee per day compared to a similar-looking placebo beverage in 126 overweight adults with reduced baseline insulin sensitivity. Insulin sensitivity, measured by clamp, did not change significantly compared to the placebo: mean percentage difference 4.0%, 95% confidence interval from –8.3% to 18.0%, P = 0.53. This result does not necessarily contradict the acute effects of pure caffeine, but it shows that prolonged exposure to caffeinated coffee did not produce a measurable worsening in that population [4].The difference in context is substantial. The original study concerns a single administration, often of isolated caffeine, in predominantly young and healthy subjects. The conflicting trial concerns coffee, which contains numerous substances other than caffeine, for 24 weeks, in middle-aged, overweight adults with reduced insulin sensitivity. The absence of a difference in the long term may reflect adaptation,

non-caffeine components of the beverage, or population characteristics. No directly conflicting evidence sufficiently relevant to the acute reduction of insulin sensitivity after pure caffeine has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the acute effect of caffeine studied in the publication that is the subject of the review from independent studies that confirm or define the same narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Systematic review and meta-analysis of seven crossover RCTs	70 healthy adults, predominantly young men	Acute caffeine intake reduced the insulin sensitivity index compared to placebo; standardized mean difference −2.06.	direct confirmation	moderate
[1]	Systematic review and meta-analysis of clinical trials	People with and without diabetes; pure caffeine or caffeinated coffee	Acute caffeine intake increased glucose and reduced the insulin sensitivity index; significant heterogeneity.	direct confirmation	moderate
[2]	Randomized, double-blind crossover RCT	24 healthy adults, 12 men and 12 women	Increasing doses of caffeine increased exposure to glucose, insulin, and C-peptide during the oral test.	direct confirmation	moderate
[3]	Randomized, double-blind crossover RCT	Seven men; skeletal muscle and hyperinsulinemic-eug lycemic clamp	Caffeine reduced insulin-stimulated muscle glucose uptake, without reducing measured PI3K or AKT.	biologically consistent evidence	moderate
[4]	24-week placebo-controlled RCT	126 overweight adults, 35-69 years old, with reduced insulin sensitivity	Four daily cups of caffeinated coffee did not significantly change insulin sensitivity compared to placebo.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the claim that a single intake of caffeine can temporarily reduce insulin sensitivity in healthy adults. This result is confirmed by further trials and an independent meta-analysis, including data showing reduced glucose utilization in muscle.The narrative is therefore moderately supported regarding the acute effect. However, it is not possible to conclude that caffeine causes chronic insulin resistance, that cortisol is always the primary mechanism, or that the effect is necessarily more intense in predisposed individuals. The null result of a prolonged trial on caffeinated coffee requires a strict distinction between isolated acute caffeine and habitual coffee consumption.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

11. RIFERIMENTI BIBLIOGRAFICI

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