Molecule ID: 59
Keyword: caffein
User Name: user4
Date of Creation: 2024-04-23 23:20:01

PubChem

Compound Name: Caffeine
Molecular Form: C8H10N4O2
Molecular weight:194.19 g/mol
CAS registration: 58-08-2;
ATC code: N - Nervous system / N06 - Psychoanaleptics / N06B - Psychostimulants, agents used for adhd and nootropics / N06BC - Xanthine derivatives / N06BC01 - Caffeine
IUPAC name: 1,3,7-trimethylpurine-2,6-dione
Solubility: 21.6 mg/mL at 25 °C
Physical description: Liquid
Melting point: 238 °C
Decomposition: Decomposition not found
Half life: In an average-sized adult or child above the age of 9, the half-life of caffeine is approximately 5 hours. Various characteristics and conditions can alter caffeine half-life. It can be reduced by up to 50% in smokers. Pregnant women show an increased half-life of 15 hours or higher, especially in the third trimester. The half-life in newborns is prolonged to about 8 hours at full-term and 100 hours in premature infants, likely due to reduced ability to metabolize it. Liver disease or drugs that inhibit CYP1A2 can increase caffeine half-life.
Reactivity: Reactivity not found

PubMed

Pharmacodynamics: URL: http://www.ncbi.nlm.nih.gov/pmc/articles/pmc7777221/ Paragraphs: Along with naturally occurring sources, such as coffee, tea and cocoa, caffeine is also added to many foods, beverages and novelty products, such as jerky, peanut butter, and candy, in both synthetic (e.g. powder) and natural (e.g. guarana, kola nut) forms. Synthetic caffeine is also an ingredient in several over-the-counter and prescription medications, as it is often used in combination with analgesic and diuretic drugs to amplify their pharmacological potency [21].. The results suggest that the rate of drug absorption from the gum formulation was significantly faster. In the groups ingesting 100 and 200 mg, both gum and capsule formulations provide near comparable plasma caffeine concentrations to the systemic circulation. These findings suggest that there may be an earlier onset of pharmacological effects from caffeine delivered through the gum formulation. Further, while no data exist to date, it has been suggested that increasing absorption via the buccal cavity may be preferential over oral delivery if consumed closer to or during exercise, as splanchnic blood flow is often reduced [383], potentially slowing the rate of caffeine absorption.

Overview of Efficacy: URL: http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4636025/ Paragraphs: In this systematic overview, we categorised the efficacy for seven interventions based on information about the effectiveness and safety of betahistine plus thiazide diuretic, caffeine restriction, intratympanic corticosteroids, intratympanic gentamicin, psychological support, salt restriction, and vestibular rehabilitation.

Pharmacodynamics Drug Interaction: URL: http://www.ncbi.nlm.nih.gov/pmc/articles/pmc7777221/ Paragraphs: Significant research on the effects of caffeine on exercise performance with more subjects, different sports, and exploring variables such as the effects between trained and untrained individuals, began and continued through the 1940s [14, 17]. However, it was the series of studies

investigating the benefits of caffeine in endurance sports in the Human Performance Laboratory at Ball State University in the late 1970s, led by David Costill [18, 19] and others [20], that sparked a generation of research on the effects of caffeine in exercise metabolism and sports performance.. Investigations examining the effects of caffeinated chewing gum on caffeine absorption and exercise performance. Caffeine absorption from food and beverages does not seem to be dependent on age, gender, genetics or disease, or the consumption of drugs, alcohol or nicotine. However, the rates of caffeine metabolism and breakdown appear to differ between individuals through both environmental and genetic influences [3, 124, 125].. These three caffeine metabolites undergo further demethylations and oxidation to urates in the liver with about 3–5% remaining in caffeine form when excreted in the urine [129, 130]. While the average half-life (t1/2) of caffeine is generally reported to be between 4 and 6 h, it varies between individuals and even may range from 1.5 to 10 h in adults [120]. The wide range of variability in caffeine metabolism is due to several factors. The rate of caffeine metabolism may be inhibited or decreased with pregnancy or use of hormonal contraceptives. Several studies have also shown that the form of caffeine or its vehicle for entry into the body can modify the pharmacokinetics [58, 81, 119, 122]. One small trial (n = 3) evaluated Tmax for a variety of beverages that all included 160 mg of caffeine but in different volumes of solution, and reported that Tmax occurs at 0.5, 0.5, and 2 h for coffee, tea and cola, respectively [135]. In another study involving seven participants, caffeine plasma concentrations peaked rapidly at 30 min for capsule form, whereas caffeine absorption from cola and chocolate was delayed and produced lower plasma concentrations that peaked at roughly 90–120 min after consumption.. One study [121] compared five conditions that included: slow ingestion (20 min) of hot coffee, and fast (2-min) or slow (20-min) ingestion for both cold coffee and energy drinks. Similar to other caffeine pharmacokinetic studies [122, 135], White et al. [121] reported that although the rate of consumption, temperature, and source (coffee vs. energy drink) may be associated with slight differences in pharmacokinetic activity, these differences are small.. Chewing gum formulations appear to alter pharmacokinetics, as much of the caffeine released from the gum through mastication can be absorbed via the buccal cavity, which is considered faster due to its extensive vascularization, especially for low molecular weight hydrophobic agents [137]. Kamimori et al. [58] compared the rate of absorption and relative caffeine bioavailability from chewing gum compared to a capsule form of caffeine. Although caffeine administered in the chewing gum formulation was absorbed at a significantly faster rate, the overall bioavailability was comparable to the capsuled 100 and 200 mg caffeine dose groups.. These pharmacokinetic findings are useful for military and sport purposes, where there is a requirement for rapid and maintained stimulation over specific periods of time. Chewing gum may also be advantageous due to reduced digestive requirements, where absorption of caffeine in other forms (capsule, coffee etc.) may be hindered by diminished splanchnic blood flow during moderate to intense exercise. Finally, there is a growing prevalence of caffeinated nasal and mouth aerosols administered directly in the mouth, under the tongue or inspired may affect the brain more quickly through several proposed mechanisms [5], although there are only a few studies to date to support this claim.. The administration of caffeine via aerosol into the oral cavity appears to produce a caffeine pharmacokinetic profile comparable to the administration of a caffeinated beverage [81]. Nasal and mouth aerosols will be discussed further in another section.. Although the action of caffeine on the central nervous system (CNS) has been widely accepted as the primary mechanism by which caffeine alters performance, several mechanisms have been proposed to explain the ergogenic effects of caffeine, including increased myofibrillar calcium availability [138, 139], optimized exercise metabolism and substrate availability [45], as well as stimulation of the CNS [140–142]. One of the earlier proposed mechanisms associated with the ergogenic effects of caffeine stemmed from the observed adrenaline (epinephrine)-induced enhanced free-fatty acid (FFA) oxidation after caffeine ingestion and consequent glycogen sparing, resulting in improved endurance performance [18, 45, 143].. However, this substrate-availability hypothesis was challenged and eventually dismissed, where after several performance studies it became clear that the increased levels of FFAs appeared to be higher earlier in exercise when increased demand for fuel via fat oxidation would be expected [141, 144, 145]. Furthermore, this mechanism could not explain the ergogenic effects of caffeine in short duration, high-intensity exercise in which glycogen levels are not a limiting factor. Importantly, several studies employing a variety of exercise modalities and intensities failed to show a decrease in

respiratory exchange ratio (RER) and/or changes in serum FFAs, which would be indicative of enhanced fat metabolism during exercise when only water was ingested [144, 146–148].. A recent meta-analysis reporting on 56 endurance time trials in athletes (79% cycling), found the percent difference between the caffeine and placebo group ranged from – 3.0 to 15.9% [195]. This wide range in performance outcomes highlights the substantial inter-individual variability in the magnitude of caffeine's effects as reported. These inter-individual differences might be due to the methodological differences between the studies, habitual caffeine intake of the participants, and/or partly due to variation in genes that are associated with caffeine metabolism and caffeine response [213].. These inter-individual differences appear to be partly due to variations in genes such as CYP1A2 and possibly ADORA2A, which are associated with caffeine metabolism, sensitivity and response [213]. Over 95% of caffeine is metabolized by the CYP1A2 enzyme, which is encoded by the CYP1A2 gene and is involved in the demethylation of caffeine into the primary metabolites paraxanthine, theophylline and theobromine [127]. The -163A > C (rs762551) single nucleotide polymorphism (SNP) has been shown to alter CYP1A2 enzyme inducibility and activity [132, 134], and has been used to categorize individuals as 'fast' or 'slow' metabolizers of caffeine.. More recently, caffeine gum ingestion enhanced cycling performance when it was administered immediately prior to exercise, but not when administered 1 or 2 h beforehand. This may have been due to the faster absorption with caffeinated gum consumption, and due to the continued increase in plasma caffeine concentrations during the cycling time trial, when athletes may become fatigued (i.e. 30 + minutes into exercise), as the trials also included a 15 min steady-state cycling bout prior to the time trial [60].. The impacts of caffeine on sleep and behavior after sleep deprivation are widely reported [321]. Sleep is recognized as an essential component of physiological and psychological recovery from, and preparation for, high-intensity training in athletes [322, 323]. Chronic mild to moderate sleep deprivation in athletes, potentially attributed to caffeine intakes, may result in negative or altered impacts on glucose metabolism, neuroendocrine function, appetite, food intake and protein synthesis, as well as attention, learning and memory [323].. Caffeine was provided at doses ranging from 600 to 800 mg in the form of chewing gum, owing to its practicality, i.e., rapid absorption and portability [58]. The investigators found that vigilance was either maintained or enhanced under the caffeine conditions (vs. placebo), in addition to improvements in run times and obstacle course completion [329, 330, 334]. Similarly, Lieberman et al. [42] examined the effects of caffeine on cognitive performance during sleep deprivation in U. S. Navy Seals.. Sources other than commonly consumed coffee and caffeine tablets have garnered interest, including caffeinated chewing gum, mouth rinses, aerosols, inspired powders, energy bars, energy gels and chews, among others. While the pharmacokinetics [18, 373–376] and effects of caffeine on performance when consumed in a traditional manner, such as coffee [47, 49, 55, 153, 368, 377, 378] or as a caffeine capsule with fluid [55, 203, 379, 380] are well understood, curiosity in alternate forms of delivery (as outlined in pharmacokinetics section) have emerged due to interest in the speed of delivery [81].. Several investigations have suggested that delivering caffeine in chewing gum form may speed the rate of caffeine delivery to the blood via absorption through the extremely vascular buccal cavity [58, 381]. Therefore, caffeine via chewing gum may be absorbed via two passageways: the buccal mucosa in the oral cavity and/or gut absorption due to the swallowing of caffeine-containing saliva [58, 381, 382]. Kamimori and colleagues [58] compared the rate of absorption and relative caffeine bioavailability from caffeinated chewing gum and caffeine in capsule form.. The results suggest that the rate of drug absorption from the gum formulation was significantly faster. In the groups ingesting 100 and 200 mg, both gum and capsule formulations provide near comparable plasma caffeine concentrations to the systemic circulation. These findings suggest that there may be an earlier onset of pharmacological effects from caffeine delivered through the gum formulation. Further, while no data exist to date, it has been suggested that increasing absorption via the buccal cavity may be preferential over oral delivery if consumed closer to or during exercise, as splanchnic blood flow is often reduced [383], potentially slowing the rate of caffeine absorption.. Similar to caffeinated gels, no studies measured plasma caffeine concentration following caffeinated bar consumption; however, absorption and delivery likely mimic that of coffee or caffeine anhydrous capsule consumption. While caffeinated bars are commonly found in the market, research on caffeinated bars is scarce. To date, only one study [82] (Table 7) has examined the effects of a caffeine bar on exercise performance. Specifically,

participants that consumed a carbohydrate-bar containing 100 mg of caffeine significantly improved their time to exhaustion during cycling compared to a carbohydrate bar and placebo with no differences found in ratings of perceived exertion, average heart rate and relative exercise intensity.. While the majority of training or performing individuals would choose to supplement with caffeine prior to exercise or during competition, interest in caffeine's effect on muscle glycogen repletion during the post-exercise period has garnered interest. Few studies to date have investigated the effect of post-exercise caffeine consumption on glucose metabolism [413, 414]. While the delivery of exogenous carbohydrate can increase muscle glycogen alone, Pedersen et al. [413] report faster glycogen repletion rates in athletes who co-ingested caffeine (8 mg/kg body mass) and carbohydrate (4 g/kg body mass), compared to carbohydrate alone (4 g/kg body mass).

Clinical Studies: URL: http://www.ncbi.nlm.nih.gov/pmc/articles/pmc5696634/ Paragraphs: Design Umbrella review of the evidence across meta-analyses of observational and interventional studies of coffee consumption and any health outcome.. Eligibility criteria for selecting studies Meta-analyses of both observational and interventional studies that examined the associations between coffee consumption and any health outcome in any adult population in all countries and all settings. Studies of genetic polymorphisms for coffee metabolism were excluded.. Results The umbrella review identified 201 meta-analyses of observational research with 67 unique health outcomes and 17 meta-analyses of interventional research with nine unique outcomes. Coffee consumption was more often associated with benefit than harm for a range of health outcomes across exposures including high versus low, any versus none, and one extra cup a day. There was evidence of a non-linear association between consumption and some outcomes, with summary estimates indicating largest relative risk reduction at intakes of three to four cups a day versus none, including all cause mortality (relative risk 0.83, 95% confidence interval 0.83 to 0.88), cardiovascular mortality (0.81, 0.72 to 0.90), and cardiovascular disease (0.85, 0.80 to 0.90).. Existing research has explored the associations between coffee as an exposure and a range of outcomes including all cause mortality, cancer, and diseases of the cardiovascular, metabolic, neurological, musculoskeletal, gastrointestinal, and liver systems, as well as outcomes associated with pregnancy. Most of this research has been observational in design, relying on evidence from cross sectional, case-control, or cohort studies, and often summarised by outcome through systematic review and meta-analysis.. We searched PubMed, Embase, CINAHL, and the Cochrane Database of Systematic Reviews from inception to July 2017 for meta-analyses of observational or interventional studies that investigated the association between coffee consumption and any health outcome. We used the following search strategy: (coffee OR caffeine) AND (systematic review OR meta-analysis) using truncated terms for all fields, and following the SIGN guidance recommended search terms for systematic reviews and meta-analyses.12 Two researchers (RP and OJK) independently screened the titles and abstracts and selected articles for full text review.. Articles were eligible if they were meta-analyses and had been conducted with systematic methods. We included meta-analyses of both observational (cohort, case-control, and cross sectional with binary outcomes) and interventional studies (randomised controlled trials). Meta-analyses were included when they pooled any combination of relative risks, odds ratios, relative rates, or hazard ratios from studies comparing the same exposure with the same health outcome. Articles were included if the coffee exposure was in any adult population of any ethnicity or sex in all countries and all settings.. Additionally, we were interested in coffee, rather than caffeine, as a potential intervention in a future randomised controlled trial. All health outcomes for which coffee consumption had been investigated as the exposure of interest were included, except studies of genetic polymorphisms for coffee metabolism. We included any study with comparisons of coffee exposure, including high versus low, any versus none, and any linear or non-linear dose-responses. If an article presented separate meta-analyses for more than one health outcome, we included each of these separately.. RP and OJK independently extracted data from eligible articles. From each meta-analysis, they extracted the first author, journal, year of publication, outcome(s) of interest, populations, number of studies, study design(s), measure(s) of coffee consumption, method(s) of capture of consumption measurement, consumption type(s), and sources of funding. For each eligible article they also extracted study specific exposure categories as defined by authors, risk estimates and corresponding confidence intervals, number of cases and

controls (case-control studies), events, participant/person years and length of follow-up (cohort studies) or numbers in intervention and control groups (randomised controlled trials), type of risk used for pooling, and type of effect model used in the meta-analysis (fixed or random).. When a meta-analysis considered a dose-response relation and published a P value for non-linearity this was also extracted. Finally, we extracted any estimate of variance between studies ($\tau 2$), estimates of the proportion of variance reflecting true differences in effect size (I2), and any presented measure of publication bias. Any difference in extracted data between the two researchers was resolved by consensus.. We considered the random effects model the most appropriate to be used in pooling estimates because the heterogeneity in study designs, populations, methods of coffee preparation, and cup sizes meant we would not expect a single true effect size common to all studies.. We reanalysed each meta-analysis using the DerSimonian and Laird random effects model, which takes into account variance between and within studies.16 We did this through extraction of exposure and outcome data, as published in each meta-analysis article, when these were available in sufficient detail. We did not review the primary study articles included in each meta-analysis. As is conventional for risk ratios, we computed the summary estimates using the log scale to maintain symmetry in the analysis and took the exponential to return the result to the original metric.. We produced the $\tau 2$ statistic as an estimate of true variation in the summary estimate and the I2 statistic as an estimate of proportion of variance reflecting true differences in effect size. We also calculated an estimate for publication bias with Egger's regression test17 for any reanalyses that included at least 10 studies. A P value <0.1 was considered significant for Egger's test. We did not reanalyse any of the dose-response meta-analyses because of the scarcity of published estimates for number of cases and controls/participants and estimates for each dose of coffee exposure needed for a dose-response analysis.. If two or more studies were published within the same 24 month period for the same category of exposure and same outcome, we selected the one with the highest number of cohort studies. We used a final tier of highest AMSTAR score if two studies published in the same period had the same number of cohort studies. When a meta-analysis included both cohort and case-control studies and when subgroup analysis was published by study design, we selected the cohort design subanalysis for inclusion in the summary forest plots or reanalysed when possible.. This was deemed to represent the higher form of evidence as it was not affected by recall and selection bias and was less likely to be biased by reverse causality that can affect case-control studies. When linear dose-response analyses presented results for two or three extra cups a day we converted this to one extra cup a day by taking the square or cube root respectively (A Crippa, personal communication, 2017). We included heterogeneity, represented by the $\tau 2$ statistic, and publication bias, represented by Egger's test.. This study was informed by feedback from a patient and public involvement focus group and from an independent survey of patients with chronic liver disease in secondary care. This preliminary work showed enthusiasm from patients in participating in a randomised controlled trial involving coffee as an intervention and in finding out more information about the wider benefits and potential harms of increasing coffee intake. Furthermore, the results of this umbrella review were also disseminated during a recent focus group session that had been arranged to gather opinions regarding the acceptability of qualitative research to investigate patterns of coffee drinking in people with non-alcoholic fatty liver disease.. Figure 1 shows the results of the systematic search and selection of eligible studies. The search yielded 201 meta-analyses of observational research in 135 articles with 67 unique outcomes and 17 meta-analyses of randomised-controlled trials in six articles with nine unique outcomes. The median number of meta-analyses per outcome for observational research was two (interquartile range 1-4, range 1-11). Twenty two outcomes had only a single meta-analysis. For meta-analyses of randomised controlled trials, outcomes were limited to systolic and diastolic blood pressure, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, and three outcomes related to pregnancy: preterm birth, small for gestational age, and birth weight.. Fig 1 Flowchart of selection of studies for inclusion in umbrella review on coffee consumption and health. Eight out of 18 studies19 20 21 22 23 24 25 26 27 that tested for non-linearity for the association with one extra cup a day found significant evidence for this.. In the most recent meta-analysis, by Grosso and colleagues, the highest exposure category (seven cups a day) of a non-linear dose-response analysis was associated with a 10% lower risk of all cause mortality (relative risk 0.90, 95% confidence interval 0.85 to 0.96),28 but summary estimates

indicated that the largest reduction in relative risk was associated with the consumption of three cups a day (0.83, 0.83 to 0.88) compared with no consumption. Stratification by sex produced similar results.. A meta-analysis of 40 cohort studies showed a lower incidence of cancer for high versus low coffee consumption (relative risk 0.82, 95% confidence interval 0.74 to 0.89),38 any versus no consumption (0.87, 0.82 to 0.92),38 and one extra cup a day (0.97, 0.96 to 0.98).38 In a separate article, in non-smokers there was a 2% lower risk of mortality from cancer for exposure of one extra cup a day (0.98, 0.96 to 1.00).28 For smokers, the article provided results only from a non-linear analysis, and the risk of mortality from cancer increased at all levels of coffee exposure, reaching significance above four cups a day.. There were consistent harmful associations for coffee consumption with lung cancer for high versus low consumption (odds ratio 1.59, 95% confidence interval 1.26 to 2.00),46 any versus none (relative risk 1.28, 1.12 to 1.47),47 and one extra cup a day (1.04, 1.03 to 1.05).47 The effect was diminished, however, in studies that adjusted for smoking, and the association was not seen in never smokers. In the most recent meta-analysis, any versus no consumption in people who had never smoked was associated with an 8% lower risk of lung cancer (0.92, 0.75 to 1.10),47 and in studies that adjusted for smoking the risk estimate was reduced (1.03, 0.95 to 1.12)47 compared with the overall analysis, and neither reached significance.. In contrast, a meta-analysis of two studies showed that high versus low consumption of decaffeinated coffee was associated with a lower risk of lung cancer.48. A single meta-analysis found an association between any versus no coffee consumption and higher risk of any urinary tract cancer (odds ratio 1.18, 95% confidence interval 1.01 to 1.38).49 In other meta-analyses of cohort studies of bladder cancer and renal cancer separately, however, associations did not reach significance.39. Coffee consumption of any versus none was associated with a lower risk of urinary incontinence68 and chronic kidney disease,69 but neither association reached significance, and the meta-analyses included cross sectional studies.. There was a non-significant association between high versus low consumption and risk of hip fracture in a subgroup analysis of women (relative risk 1.27, 0.94 to 1.72)72 but not men (0.53, 0.38 to 1.00)72 (test of interaction 2.40, 1.35 to 4.24; P<0.01). For consumption of one extra cup a day there was also an association with increased risk of fracture in women (relative risk 1.05, 1.02 to 1.07)71 but a lower risk in men (0.91, 0.87 to 0.95)71 (test of interaction 1.15, 1.10 to 1.21; P<0.001). These results suggest that sex might be a significant effect modifier in the association between coffee and risk of fracture.. Coffee consumption was consistently associated with a lower risk of Parkinson's disease, even after adjustment for smoking, and across all categories of exposure.22 76 77 Decaffeinated coffee was associated with a lower risk of Parkinson's disease, which did not reach significance.22 Consumption had a consistent association with lower risk of depression78 79 and cognitive disorders, especially for Alzheimer's disease (relative risk 0.73, 95% confidence interval 0.55 to 0.97)80 in meta-analyses of cohort studies.. We were able to re-analyse by random effects, 83% of comparisons for high versus low and 79% for any versus none, but none for one extra cup a day. About 40% of the 83 meta-analyses that we re-analysed had significant heterogeneity, and 90% of these had an I2 >50%. The individual studies within each meta-analysis varied by many factors, including the geography and ethnicity of the population of interest, the type of coffee consumed, the method of ascertainment of coffee consumption, the measure of coffee exposure, duration of follow-up, and outcome assessment.. For the 54 that we were unable to re-analyse, 19% had significant heterogeneity, and 27% of meta-analyses did not publish heterogeneity for the studies included in the specific exposure comparison. Only four studies that we were unable to re-analyse used a fixed effects model.. We performed Egger's regression test in only 40% of the meta-analyses in our reanalysis because the remaining 60% contained insufficient numbers of studies. In those that we reanalysed, 20% had statistical evidence of publication bias. This included high versus low comparisons for type 2 diabetes (P=0.049),21 stroke (P=0.09),19 gastro-oesophageal reflux disease (P=0.04),64 bladder cancer (P<0.01),39 endometrial cancer (P=0.03),40 and hip fracture (P=0.02),72 and in the meta-analysis of randomised controlled trials for total cholesterol (P<0.01).. For meta-analyses that we were unable to reanalyse, none reported significant publication bias or they did not conduct or publish a statistical test for publication bias for the specific exposure comparison. This could have been in part because of low number of studies included in the pooling. It is possible, however, that unmeasured publication bias exists in many of the summary estimates we have presented and not assessed.. The median AMSTAR

score achieved across all studies was 5 out of 11 (range 2-9, interquartile range 5-7). Eleven studies were downgraded on method of meta-analysis because they used a fixed, rather than random effects, model. Appendix 3 provides a breakdown of AMSTAR scores for studies representing each outcome. In terms of quality of evidence for each outcome, about 25% were rated as being of “low” and 75% as “very low” quality with the GRADE classification. Even the meta-analyses of randomised controlled trials were graded as low quality of evidence because of risk of bias, inconsistency, or imprecision.. Only outcomes identified as having a significant dose-response effect, or large magnitude of effect, without significant other biases reached a GRADE classification of “low” compared with the majority rating of “very low.” Appendix 4 shows a breakdown of GRADE scores for studies representing each outcome.. There were also harmful associations between consumption and congenital malformations, though these did not reach significance.85 The half life of caffeine is known to double during pregnancy,92 and therefore the relative dose of caffeine from equivalent per cup consumption will be much higher than consumption outside pregnancy. Caffeine is also known to easily cross the placenta,93 and activity of the caffeine metabolising enzyme, CYP1A2, is low in the fetus, resulting in prolonged fetal exposure to caffeine.94 Though we found no significant associations between coffee exposure and neural tube defects,84 for this outcome, all bar one of the included studies were of case-control design and therefore prone to recall bias.. Maternal exposure to coffee had a harmful association with acute leukaemia of childhood,87 88 89 but evidence for this also came from case-control studies.. A recent comprehensive systematic review of the health effects of caffeine, however, concluded, with regard to bone health, that a caffeine intake of 400 mg/day (about four cups of coffee) was not associated with adverse effects on the risk of fracture, falls, bone mineral density, or calcium metabolism.97 There is limited evidence at higher intakes of caffeine to draw firmer conclusions. Notably, many of the studies included in the meta-analyses of coffee consumption and risk of fracture did not adjust for important confounders such as body mass index (BMI), smoking, or intakes of calcium, vitamin D, and alcohol.. Some studies suggest that caffeine consumption is associated only with a lower risk of low bone mineral density in women with inadequate calcium intake,98 and that only a small amount of milk added to coffee would be needed to offset any negative effects on calcium absorption.95 The type of coffee consumed might therefore be an important factor. Coffee and caffeine have also been linked to oestrogen metabolism in premenopausal women99 and increased concentrations of sex hormone binding globulin (SHBG) in observational research of postmenopausal women.100. Firstly, they performed the meta-analysis in those who had never smoked and detected no harmful association. Next, they performed the meta-analysis in only those studies that adjusted for smoking, and the magnitude of the apparent harmful association was reduced and was no longer significant. It is likely that residual confounding by smoking, despite some adjustment, can explain this apparent harmful association. A similar pattern was seen in stratification by smoking for coffee consumption and mortality from cancer in the recent meta-analysis by Grosso and colleagues.28. Studies also suggest, however, that the dose of diterpenes needed to cause hypercholesterolaemia is likely to be much higher than the dose needed for beneficial anticarcinogenic effects.107 For unfiltered coffee, the clinical relevance of such small increases in total cholesterol, low density lipoprotein cholesterol, and triglyceride due to coffee are difficult to extrapolate, especially as coffee consumption does not seem to be associated with adverse cardiovascular outcomes, including mortality after myocardial infarction.30 Changes in the lipid profile associated with coffee also reversed with abstinence.106. AMSTAR has good evidence of validity and reliability.13 The AMSTAR score assisted us in identifying the highest quality of evidence for each outcome. It also allows judgment regarding quality of the meta-analysis presented for each outcome. A high AMSTAR score for a meta-analysis, however, does not equate to high quality of the original studies, and the assessment and use of quality scoring of the original studies accounts for only two of 11 possible AMSTAR points. Additionally, appropriate method of analysis, accounting for one score of quality, can be subjective.. One recurring issue for many of the included meta-analyses was the assumption that summary relative risk could be pooled from a combination of odds ratio, relative rates, and hazard ratios so that they could combine studies with differing measures. Statistically, the odds ratio is similar to the relative risk when the outcome is uncommon114 but will always be more extreme.114 Similarly, for rare events, relative rates and hazard ratios are similar to the relative risk when censoring is uncommon or evenly distributed

between exposed and unexposed groups.114 Many meta-analyses stated their assumption but included insufficient information to allow us to judge the suitability of the pooling.. Most of the studies we included were meta-analyses of observational studies. One strength of the umbrella review was the inclusion only of cohort studies, or subgroup analyses of cohort studies when available, in preference to summary estimates from a combination of study designs. In meta-analyses that we were unable to re-analyse and when subgroup analysis did not allow the disentanglement of study design, the presented results were from the combined estimates of all included studies. Observational research, however, is low quality in the hierarchy of evidence and with GRADE classification most outcomes are recognised as having very low or low quality of evidence where a dose-response relation exists.. A possible limitation of our review was that we did not reanalyse any of the dose-response meta-analyses as the data needed to compute these were not generally available in the articles. We did not review the primary studies included in each of the meta-analyses that would have facilitated this. We decided that reanalysing the dose-response data was unlikely to result in changes to the GRADE classification. In our reanalysis of the comparison of high versus low and any versus no coffee, we used data available in the published meta-analyses and therefore assumed the exposure and estimate data for component studies had been published accurately.. We were able to produce estimates for publication bias using Egger's test for meta-analyses containing 10 or more studies.17 Egger's test is not recommended with fewer studies. We were unable to conduct alternative tests, such as Peters' test,117 which is more appropriate for binary outcomes, because this needed cases and non-cases for each level of exposure and this detail was largely unavailable in the meta-analyses. We did not calculate excess significance tests, which attempt to detect reporting bias by comparing the number of studies that have formally significant results with the number expected, based on the sum of the statistical powers from individual studies, and using an effect size equal to the largest study in the meta-analysis.118 Excess significance tests, however, have not been fully evaluated and are not therefore currently recommended as an alternative to traditional tests of publication bias.119 Further bias in methods could have occurred if the same meta-analysis authors conducted multiple meta-analyses for different health outcomes.. There was also an overlap of health outcomes with data from the same original cohort studies. While the associations for different health outcomes were statistically independent, any methodological issues in design or conduct of the original cohorts could represent repeated bias filtering through the totality of evidence.. The beneficial association between coffee consumption and all cause mortality highlighted in our umbrella review is in agreement with two recently published cohort studies. The first was a large cohort study of 521 330 participants followed for a mean period of 16 years in 10 European countries, during which time there were 41 693 deaths.120 The highest quarter of coffee consumption, when compared with no coffee consumption, was associated with a 12% lower risk of all cause mortality in men (hazard ratio 0.88, 95% confidence interval 0.82 to 0.95) and a 7% lower risk in women (0.93, 0.82 to 0.95).. Many of the associations between coffee consumption and health outcomes, which are largely from cohort studies, could be affected by residual confounding. Smoking, age, BMI, and alcohol consumption are all associated with coffee consumption and a considerable number of health outcomes. These relations might differ in magnitude and even direction between populations. Residual confounding by smoking could reduce a beneficial association or increase a harmful association when smoking is also associated with an outcome.. Coffee could also be a surrogate marker for factors that are associated with beneficial health such as higher income, education, or lower deprivation, which could be confounding the observed beneficial associations. The design of randomised controlled trials can reduce the risk of confounding because the known and unknown confounders are distributed randomly between intervention and control groups. Mendelian randomisation studies can also help to reduce the effects of confounding from random distribution of confounders between genotypes of known function related to the outcome of interest.. The association between coffee consumption and lower risk of type 2 diabetes122 and all cause and cardiovascular mortality123 was found to have no genetic evidence for a causal relation in Mendelian randomisation studies, suggesting residual confounding could result in the observed associations in other studies. The authors point out, however, that the Mendelian randomisation approach relies on the assumption of linearity between all categories of coffee intake and might not capture non-linear differences.. Bias from reverse causality can also occur in observational studies. In case-control studies, symptoms from disease might have led people

to reduce their intake of coffee. When possible, we included meta-analyses of cohort studies or cohort subgroup analyses in our review as they are less prone to this type of bias. Even prospective cohort studies, however, can be affected by reverse causality bias, in which participants who were apparently healthy at recruitment might have reduced their coffee intake because of early symptoms of a disease.. Most meta-analyses produced summary effects from individual studies that measured coffee exposure by number of cups a day. Some individual studies, however, used number of times a day, servings a day, millilitres a day, cups a week, times a week, cups a month, and drinkers versus non-drinkers to measure coffee consumption. There is no universally recognised standard coffee cup size, and the bioactive components of coffee in a single cup will vary depending on the type of bean (such as Arabica or Robusta), degree of roasting, and method of preparation, including the quantity of bean, grind setting, and brew type used.. Therefore, studies that are comparing coffee consumption by cup measures could be comparing ranges of exposures. The range of number of cups a day classified as both high and low consumption from different individual studies varied substantially for inclusion in each meta-analysis. High versus low consumption was the most commonly used measure of exposure. Consistent results across meta-analyses and categories of exposure, however, suggest that measurement of cups a day produces a reasonable differential in exposure.. The inclusion criteria for the umbrella review meant that some systematic reviews were omitted when they did not do any pooled analysis. Meta-analyses in relation to coffee consumption, however, have been done on most health outcomes for which there is also a systematic review, except for respiratory outcomes125 and sleep disturbance.126 There could also be important well conducted studies that have assessed coffee consumption in relation to outcomes for which no investigators have attempted to perform any combined review, whether pooling the estimate or not.. Despite our broad inclusion criteria, we identified only one meta-analysis that focused on a population of people with established disease. This was a meta-analysis of two small cohort studies investigating risk of mortality in people who had experienced a myocardial infarction.30 In contrast, most meta-analyses estimated the association between coffee consumption and outcomes in general population cohorts rather than those selected by pre-existing disease. Our summation of the existing body of evidence should therefore be viewed in this context and suggests that the association of coffee consumption in modifying the natural history of established disease remains unclear.. We extracted details of conflicts of interest and funding declarations from articles selected in the umbrella review. Only one article declared support from an organisation linked to the coffee industry, and a second article stated that their authors contributed to the same organisation. Neither of these articles was selected to represent the respective outcome in the summary figures, and all references for studies not included in the summary tables are available on request. We did not review the primary studies included in each meta-analysis and cannot comment on whether any of these studies were funded by organisations linked to the coffee industry.. Consumption is also beneficially associated with a range of other health outcomes and importantly does not seem to have definitive harmful associations with any outcomes outside of pregnancy. The association between consumption and risk of fracture in women remains uncertain but warrants further investigation. Residual confounding could explain some of the observed associations, and Mendelian randomisation studies could be applied to a range of outcomes, including risk of fracture, to help examine this issue.. Appendix 3: AMSTAR scores for individual studies. Data sharing: References for studies included in the umbrella review but not selected to represent the outcome in the summary figures are available on request.

Overview of Safety: URL: http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4636025/ Paragraphs: In this systematic overview, we categorised the efficacy for seven interventions based on information about the effectiveness and safety of betahistine plus thiazide diuretic, caffeine restriction, intratympanic corticosteroids, intratympanic gentamicin, psychological support, salt restriction, and vestibular rehabilitation.. The subsequent RCT compared two different doses of OTO-104 (a sustained-release dexamethasone formulation) with placebo given as a single injection. Between 13% and 29% of people in the three groups had received intratympanic corticosteroid injections previously. Initially, people were allocated on a 2:1 basis to lower-dose intratympanic dexamethasone (14 people) or placebo (7 people). After a safety evaluation, "the high dose cohort was open to enrolment" and the remaining participants

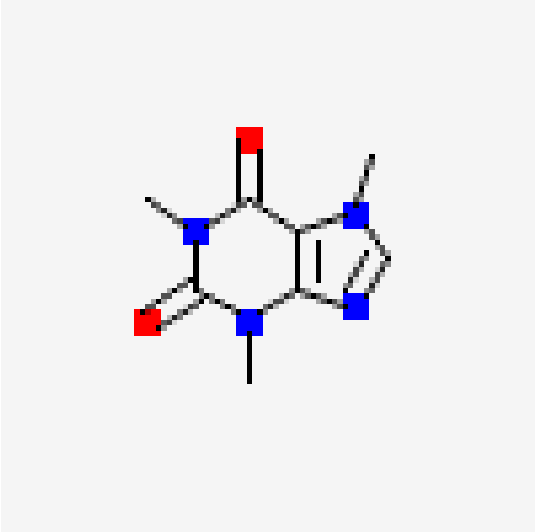
seem to have been allocated to higher-dose dexamethasone or placebo.

Marketing Experience: URL: http://www.ncbi.nlm.nih.gov/pmc/articles/pmc9207555/ Paragraphs: Attempts to enhance human memory and learning ability have a long tradition in science. This topic has recently gained substantial attention because of the increasing percentage of older individuals worldwide and the predicted rise of age-associated cognitive decline in brain functions. Transcranial brain stimulation methods, such as transcranial magnetic (TMS) and transcranial electric (tES) stimulation, have been extensively used in an effort to improve cognitive functions in humans.. Brain stimulation devices marketed for consumer use are distinct from medical devices because they do not make medical claims and are therefore not necessarily subject to the same level of regulation as medical devices (i.e., by government agencies tasked with regulating medical devices). Manufacturers must follow ethical and best practices in marketing tES stimulators, including not misleading users by referencing effects from human trials using devices and protocols not similar to theirs.. Stress and burnout symptoms are indirectly connected with neuroenhancement. Some evidence exists that bilateral tDCS over the DLPFC is efficient in alleviating stress-induced creativity impairment (Wang et al., 2021). In this area, however, frequently popular information is mixed with science. Many companies marketing tDCS directly to use, indicate that devices are not sold for medical conditions but to enhance “wellness”, for example by decreasing general stress level, enhancing focus, or ameliorating burnout symptoms.. TDCS is seen as a potential ergogenic resource to improve muscular strength (Lattari et al., 2016, Lattari et al., 2020), and endurance (Okano et al., 2015, Lattari et al., 2018) in both nonathletes (Okano et al., 2015, Lattari et al., 2016, Lattari et al., 2020, Machado et al., 2019, Angius et al., 2018) and athletes (Sales et al., 2016, Hazime et al., 2017, Vargas et al., 2018).. Using tDCS to improve performance in sport/exercise could be considered a form of “neurodoping” (Davis, 2013, Banissy and Muggleton, 2013, Colzato et al., 2017, Park, 2017), as it associated with physical risks, behavioral and ethical issues. Nevertheless, tDCS has escaped so far the standards of the world anti-doping agency (WADA), which are entirely focused on drugs: https://www.wada-ama.org/sites/default/files/resources/files/2021list_en.pdf. Since there is reasonable evidence that some tES protocols may improve motor performance in normal persons, it may thus be seen as a ‘doping method’, without legal regulations so far.. Further empirical work on media representation of brain stimulation was influenced by the appearance of commercial tDCS devices on the market, and by the specific use of enhancement claims in order to avoid FDA regulation of therapeutic devices. In 2014, Dubljevic and colleagues reported strong and potentially misleading statements about the real-world effects and applicability of tDCS, even in otherwise serious news outlets (e.g., “schoolchildren who struggle to grasp mathematics could benefit from having their brains roused with electricity”. The non-professional or “lay” use of electrical stimulation has a long history dating back several centuries in both Europe and the United States (Kadosh, 2014). In the late nineteenth and early twentieth century, handheld devices known as “medical batteries” that provided either alternating or direct current were sold to both physicians and the public with claims of treating a wide variety of ailments and disorders (Peña, 2003, Currier, 2004, Waits, 2013, Wexler, 2017b). Aside from the marketing of a handful of products in the 1920 s and 1930 s for “rejuvenation” and “reinvigoration,” the notion of the use of electricity for enhancement—cognitive or otherwise—appears to have been largely absent from most historical marketing claims (Wexler, 2017a).. The contemporary movement regarding the lay use of tES for enhancement began in 2011, when lay individuals began to construct tDCS devices in their homes. Since then, dozens of companies, largely based in the U.S., have marketed ready-to-wear tES devices for brain optimization and cognitive enhancement (Wexler, 2015, McCall et al., 2019). To date, three empirical studies have been conducted to better understand users of self-directed home tES devices (Jwa, 2015, Wexler, 2016, Wexler, 2018; for review see Wexler, 2020).. Many scholarly and media articles have portrayed the home use of tES as increasing, although an empirical assessment of the phenomenon in “real-world” scenarios is challenging. It is clear, however, that the home use of tES has not become mainstream at this time, but rather has remained limited to small groups of users. While devices continue to be sold—one online survey of tES devices claims to have sold tens of thousands of products per year to consumers (Waltz, 2019)—the effectiveness of these devices, and the value they provide to consumers, remains an open question..

Still, companies continue to bring new devices to market, in many regions aided by the lack of strict oversight from regulatory bodies regarding products marketed for enhancement or wellness purposes.. Most nations clearly differentiate the regulation of medical devices from that of other instruments and appliances. This distinction stems from the high standards for regulating the marketing of devices for medical diagnosis and treatment. While the regulation of medical devices is often determined by their perceived risk level, whether a device is considered to fall under medical device regulations (MDR) is not governed by risk, but rather by its ability to diagnose or treat a medical condition (e.g., a chainsaw would not be regulated as a medical device despite posing a clear potential health risk).. Neuromodulation devices marketed for wellness and cognitive enhancement without explicit connection to a disease are not considered medical devices in all well-known U.S. jurisdictions. However, in some cases (notably the updated EU MDR) “products without an intended medical purpose” may fall under medical device regulations; in addition practices developed to ensure medical device quality (e.g., risk management) may be adopted through voluntary industry standards (Bikson et al., 2018). In the EU all tES and TMS devices have been treated as Medical Devices since May, 26th 2021; this includes any electrical, magnetic or electro-magnetic stimulation device for cognitive enhancements.. As noted, governments (mainly outside the EU) only rarely restrict sales of non-medical devices to consumers, except for firearms and such. The theoretical potential for a non-medical device to be used by an individual for self-directed medical care has no bearing on how the device is regulated. For neuromodulation devices there may be a potential for both medical (e.g., insomnia) and wellness (e.g., “good night sleep”) uses. This cannot in-itself justify regulation for the latter if there are no further, specific reasons (although we acknowledge that selling such devices without any evidence for the efficacy of the particular device could serve as a reason).. This raises the conundrum that a device, such as a tDCS device marketed for wellness (thus not as a medical device) may be obtained by an individual and used for self-directed treatment.. It is therefore not correct to insinuate that there is no legal guidance for consumer neuromodulation, at least in most of the countries. First, as noted above there is an extensive framework for distinguishing between medical devices and wellness devices. Indeed, in some cases the medical device regulator even provides an explicit mechanism to confirm that a device is not a medical device, and is thus not regulated as such (e.g., the 513 g mechanism for the US FDA). Second, non-medical devices are subject to a range of regulations including those dealing with fair marketing (e.g., the Federal Communications Commission - FCC in the US).. Furthermore, the translation of laboratory findings of selected aspects of cognitive or behavioral enhancement by NIBS to real-life contexts is largely unexplored. For instance, we might observe improved performance in a working memory task after applying a form of NIBS in the laboratory, but there are no data if this would translate to improved performance at work or school when applied in settings outside the laboratory. Additional research on the effects of NIBS is needed, including how use and outcomes may vary in “real world” settings.. To maximize reliability, tES devices marketed for cognitive enhancement should be engineered and manufactured to standards adopting appropriate practices established for medical devices, whether guided by industry standards (Bikson et al., 2018) or national regulators (as the new law in the EU). There will be Common Specifications as mentioned in EU’s rolling plan item #3 in https://ec.europa.eu/health/sites/default/files/md sector/docs/md rolling-plan en.pdf by next year. According to this, manufacturers have to adapt to these regulations within 6 months after publication.

Benefits/Risks: URL: https://doi.org/10.1093/jn/nxy303 Paragraphs: The present study evaluated the effects of a representative commercial ED and its major components on cardiovascular and metabolic parameters in young and healthy individuals. Apart from cardiovascular and metabolic effects, we studied tolerance and safety of 2 volumes (750 mL and 1000 mL) of the ED and other study drinks containing corresponding concentrations of the relevant agents. This amount is regularly reported by consumers, but might bear a health risk. We found that both volumes were reasonably tolerated subjectively.. It has been suggested that EDs are harmful to individuals at higher cardiovascular risk; the increased HR and prolongation of the QTc interval induced by EDs are considered risk indicators for heart rhythm disorders in vulnerable individuals (8). Such changes could be critical in individuals with acquired or congenital history of cardiovascular disease (8), diabetes, or in those taking

medications, such as diuretics, cardiac glycosides, or psychotropic drugs (28, 40, 41). A cardiovascular risk from consumption of EDs could be assumed for patients with hypertension and hypertension-risk groups, such as patients in kidney failure, morbidly obese individuals, patients with valvular heart disease, pregnant women, and especially for those who already suffer from hypertension-related complications or congenital or acquired abnormalities of the vascular system (8, 18, 40, 42).. Not all consumers are aware that they belong to such risk groups. Also CYP1A2 polymorphisms can influence cardiovascular response to EDs. Previous studies noted that carriers of a slow CYP1A2*1F allele have a higher risk for myocardial infarction and hypertension because of impaired caffeine metabolism (43, 44). Therefore, carriers should abstain from caffeinated drinks, including EDs. Along with possible cardiovascular symptoms, the main effects of EDs were identified as gastrointestinal upset or neurological side effects (agitation or tremor), sometimes requiring hospitalization (45).. In the present study, 7 of 38 participants developed notable symptoms, that is, tremor and nausea, after consumption of an ED. The present study provides further evidence of unintended side effects, but is too small to draw final conclusions about safety and side effects.. In conclusion, the present study determined that ED consumption causes significant adverse changes in BP, HR, QTc intervals, and glucose metabolism in young and healthy individuals. The clinical impact of these changes cannot be evaluated definitively within the present study. Although it is likely that caffeine causes increase in MAP, the other cardiovascular and metabolic effects of EDs cannot be attributed easily to the single components caffeine, taurine, or glucuronolactone. The clinical impact of the adverse changes could be of relevance to individuals at risk for cardiovascular or metabolic disease.



Img 1: Molecule structure of caffein (Source: PubChem)