Effects of coffee/caffeine on brain health and disease: What should I tell my patients?

Astrid Nehlig

Correspondence to
Dr Astrid Nehlig, INSERM U 1129; Faculty of Medicine; 11 rue Humann, 67085 Strasbourg, France; nehliga@unistra.fr

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ABSTRACT

Over the last decade, Food Regulation Authorities have concluded that coffee/caffeine consumption is not harmful if consumed at levels of 200 mg in one sitting (around 2½ cups of coffee) or 400 mg daily (around 5 cups of coffee). In addition, caffeine has many positive actions on the brain. It can increase alertness and well-being, help concentration, improve mood and limit depression. Caffeine may disturb sleep, but only in sensitive individuals. It may raise anxiety in a small subset of particularly sensitive people. Caffeine does not seem to lead to dependence, although a minority of people experience withdrawal symptoms. Caffeine can potentiate the effect of regular analgesic drugs in headache and migraine. Lifelong coffee/caffeine consumption has been associated with prevention of cognitive decline, and reduced risk of developing stroke, Parkinson's disease and Alzheimer's disease. Its consumption does not seem to influence seizure occurrence. Thus, daily coffee and caffeine intake can be part of a healthy balanced diet; its consumption does not need to be stopped in elderly people.

INTRODUCTION

Coffee is the most frequently consumed drink worldwide after water. It is a very complex drink comprising >1000 compounds, many of which are not yet identified. A main component is caffeine, also found in many other sources (table 1) such as drinks (tea, soft drinks, energy drinks, hot chocolate, mate, guarana), in foods (mainly chocolate)[1] and in medications (painkillers, slimming creams and pills).

The readers will find below a summary of the main effects of caffeine on the brain. However, at this point, the evidence for the benefits and adverse effects of caffeine are derived mostly from observational studies and await confirmation by randomised-controlled studies.

A frequent question: why do I react differently from other people to coffee/caffeine?

In humans, caffeine is rapidly and completely absorbed after oral intake (t_{max} 30–120 min) and freely crosses the blood–brain and placental barriers. The brain/blood ratio is close to 1.0. Caffeine's mean plasma half-life is 2.5–4.5 h. In humans, it is primarily metabolised (70–80%) via N-3 demethylation by liver cytochrome (*CYP*) *1A2* to paraxanthine (84%), theobromine (12%) and theophylline (4%). *CYP1A2* activity accounts for 95% of caffeine clearance.

Individual differences in caffeine metabolism are explained by *CYP1A2* polymorphisms. A single base change of A to C, at position 734 within intron 1 of the *CYP1A2* gene, decreases enzyme inducibility.[2] The homozygote AA genotype is considered 'fast metaboliser' while AC and CC genotypes are considered 'slow metabolisers'. The combined prevalence of the 'slow' CC and AC genotypes is 52–60%, whereas it is 40–48% for the 'fast' AA genotype.[2]

Lifestyle may influence caffeine clearance. The most prominent factors are:

1. Daily coffee consumption, increasing clearance 1.45-fold/L consumed.
2. Smoking, increasing clearance by between 1.22-fold (for 1–5 cigarettes per day) and 1.72-fold (for >20 cigarettes per day).
3. Oral contraceptives, reducing clearance by 0.72-fold.
4. Female sex, reducing clearance by 0.9-fold.[3] During pregnancy, the half-life of caffeine increases: by the end of pregnancy, it is 3–4 times longer than in the non-pregnant state.[4]

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Table 1 Caffeine content of different foods and drinks

	Mean concentration	Range (mg)
Filtered coffee	85 mg/125 mL	60–135
Instant coffee	65 mg/125 mL	35–105
Decaffeinated coffee	3 mg/125 mL	1–5
Espresso	60 mg/30 mL	35–100
Tea (leaves or bag)	32 mg/150 mL	20–45
Iced tea	20 (330 mL)	10–50
Hot chocolate	4 mg/150 mL	2–7
Caffeinated soft drinks	39 mg/330 mL	30–48
Sugar-free soft drinks	41 mg/330 mL	26–57
Energy drinks	80 mg/330 mL	70–120
Chocolate bar	20 (30 g)	5–36
Dark chocolate	60 mg/30 g	20–120
Milk chocolate	6 mg/30 g	1–15

The quantity of caffeine varies a lot for each food or drink. It is related to the brand but also for coffee and tea to the duration of infusion, filtration and mode of preparation.
Data from http://www.coffeeandhealth.org.

How does caffeine act on the brain?

Caffeine acts in the brain as a non-specific potent inhibitor of the actions of A_1 and A_{2A} adenosine receptors. This occurs at low caffeine concentrations, that is, a few μmol/L reached after a single cup of coffee. Caffeine activates the release of mainly excitatory transmitters; these are more strongly inhibited by adenosine than inhibitory neurotransmitters.[5] Based on studies using knockout mice for A_1 and A_{2A} adenosine receptors, it appears that caffeine's blockade of A_{2A} receptors affects on sleep and motor activity, whereas A_1 and A_{2A} blockade influences heart rate, body core temperature and oxygen consumption.[6]

What is a safe daily consumption?

A low dose of caffeine (50–200 mg in one sitting) can have positive effects: increasing alertness and energy, well-being, relaxation, good mood and improved memory. However, high doses of caffeine (400–800 mg in one sitting) may have negative effects: anxiety, nervousness, jitteriness, insomnia, tachycardia and trembling. There is a consensus that the daily ingestion of 300–400 mg caffeine (around 4–5 cups of coffee) does not raise any health concern.[5 7]

Several countries have assessed the safe limits of caffeine consumption. Among the most recent ones, the Belgium Superior Health Council[8] based its recommendations on the assessments conducted previously by the Food Standards of Australia and New Zealand, Health Canada and the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment.[9–11] The Belgium Superior Health Council considered that a caffeine intake of 5.7 mg/kg per day (400 mg/day for a 70 kg adult) was not linked to adverse effects in relation to general toxicity, altered behaviour, decreased male fertility, cardiovascular or cancer risk. The council recommended a maximum daily intake of caffeine of 2.5 mg/kg for children and adolescents, noting an increased risk of anxiety and altered behaviour beyond this dose, and advised to women of childbearing age not to exceed 200–300 mg per day.[12]

The very recent European Food Safety Authority[13] report on the safety of caffeine considered that "single doses of caffeine up to 200 mg (about 3 mg/kg) from all sources have no safety concerns for the general adult population, even if consumed less than two hours before intense physical exercise under normal environmental conditions. Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg) do not raise safety concerns for adults in the general population, except pregnant women". In the latter subgroup, they considered that "caffeine intakes from all sources up to 200 mg per day do not raise safety concerns for the fetus". Finally, "owing to the limited information available for children and adolescents, caffeine intakes derived from acute consumption in adults (3 mg/kg per day) may serve as a basis to derive daily caffeine intakes of no concern".[13]

These data are in line with previous reports from the literature that had reached consensus on dose-dependent effects.

EFFECTS OF CAFFEINE ON A HEALTHY BRAIN

Coffee/caffeine, alertness and sleep

Caffeine ingestion is well known to give a dose-dependent increase in energetic arousal, to improve hedonic tone, and to help concentration, mainly by eliminating distractors. Caffeine (75 mg) can shorten reaction time and improve visual attention and sustained attention mainly in long, demanding tasks.[14 15] It seems particularly effective in improving alertness in situations of reduced arousal, such as the post-lunch attention decline, regular colds, night shift work and driving at night.[16 17]

Caffeine readily affects sleep, and this is the function most sensitive to caffeine. Doses as low as 100 mg (around one single cup of coffee) can prolong sleep latency, shorten total sleep time and prolong light sleep phases while shortening deep sleep. Rapid eye movement (REM) sleep is not much affected.[18]

These effects clearly depend on caffeine being consumed before going to bed, but even caffeine ingested in the morning may detrimentally affect sleep. For example, 200 mg caffeine (around 2–2½ cups of coffee) in the morning reduces total sleep time by about 10 min, sleep efficiency by about 3% and increases the latency to stage 2 sleep. These effects occur in low consumers but not in habitual ones. There is no age-related difference.[18]

However, there are clear differences in individual sensitivity to caffeine effects on sleep. Those may be partly linked to the polymorphism of *CYP1A2*,[2] but more importantly, a polymorphism of the brain

adenosine A_{2A} receptor (*ADORA2A*) modulates the susceptibility to subjective and objective effects of caffeine on sleep. In sensitive individuals, insomnia almost doubles with caffeine consumption compared with no caffeine.[19]

Coffee/caffeine mood and mood disorders

Caffeine in low doses (150–200 mg) has been repeatedly reported to improve mood states. These effects explain why coffee and tea are widely used as breakfast beverages. Its positive effects on mood can be enhanced by the co-consumption of bread and by the presence of blue light (which has positive effects on mood). The effects are more pronounced in the elderly; in addition, non-consumers are influenced by caffeine expectancy (for review, see ref. 20).

Several studies on large cohorts have associated daily coffee drinking with a decreased risk of depression. In the *Nurses' Health Study* concerning 50 730 women followed up for 10 years, the risk of depression was reduced by 15% in those drinking 2–3 cups of coffee daily, and by 20% in those drinking over cups per day. A recent study on a population of 263 923 elderly Americans from the *NIH-AARP Diet and Health Study* showed a 9% reduced risk of depression with the daily intake of ≥4 cups of coffee. Several other studies on young and middle-aged populations confirmed this observation, which also occurs with tea or caffeine alone.[20]

Coffee consumption also appears to be associated with decreased suicide risk. In a cohort of 43 599 men from the *Heath Professionals Follow-up Study* and 73 820 women from the *Nurses' Health Study*, the suicide risk was 45% lower in those consuming 2–3 cups of coffee daily and 53% lower with >4 cups daily.[20]

Coffee/caffeine and anxiety

High doses of caffeine can cause anxiety feelings, though this does not usually occur with low doses.[5] Animal models of anxiety have confirmed caffeine's anxiogenic effect. Two studies in humans reported a caffeine-related increase in self-ratings of anxiety for social threat words (ie, hated and lonely) and negative facial expressions (ie, angry and fearful faces).[21] One study reported that the dose-dependent increase in anxiety after 75–300 mg caffeine occurred in men but not in women.[22]

In a caffeine challenge test (480 mg caffeine given acutely), panic disorder patients and their healthy first-degree relatives were more sensitive than healthy volunteers to panic attack symptoms.[23] This response concords with the finding that a variant of the *ADORA2A* gene modulates caffeine-induced anxiety in people who habitually consume little caffeine. Frequent consumption of caffeine leads to centrally mediated tolerance to its anxiogenic effect, even in genetically susceptible people.[24]

Caffeine and dependence

The possibility of caffeine dependence questions many people. While caffeine in coffee is a mild central nervous system stimulant, preclinical studies showed that caffeine does not stimulate dopaminergic transmission in the shell of the nucleus accumbens, which would be the characteristic and specific feature of drugs of dependence.[25 26] Likewise, human imaging studies show that caffeine does not activate the brain circuit of dependence and reward.[27] Many data suggest that moderate coffee drinkers do not develop a physical dependence to caffeine.

However, the American Psychiatric Association has added caffeine withdrawal to the list of symptoms in Diagnostic and Statistical Manual of Mental Disorders, 5th edn. Some people experience symptoms after abruptly stopping caffeine. Those tend to occur 12–24 h after stopping caffeine and translate mainly into headaches, drowsiness and feeling of fatigue, but usually do not last >48 h. They can be avoided by gradually reducing intake.

Caffeine acts as a reinforcer, meaning it is able to wipe out unpleasant effects due to withdrawal. However, the underlying mechanisms are not clearly understood. The doses of caffeine in tea and coffee appear high enough to act as reinforcers since people look for them in case of withdrawal symptoms, and a dose of 25–50 mg caffeine per cup of coffee already acts as a reinforcer. However, the possible reinforcing effects of coffee unrelated to caffeine—but related to smell, taste and social environment that usually accompany coffee consumption—may be everyday motivators for consumption of caffeine-containing or caffeine-free coffee drinks.[26]

Caffeine and children/adolescents

There are few data on the effects of caffeine in children. About 10% of 12–19 year olds exceed the daily intake of 2.5 mg/kg suggested by Health Canada.[28] However, high caffeine intake in children as young as 12 has consequences on sleep, similar to those in adults. Of particular interest, caffeine gives a dose-dependent decrease in the percentage of time spent in slow-wave or deep sleep and alters the temporal organisation of REM/non-REM sleep. Adolescents consuming caffeine may report morning and daytime sleepiness. Both slow-wave sleep and REM sleep play a prominent role in learning and memory consolidation and daytime sleepiness inversely correlates with academic achievement. High and regular caffeine adolescent users seem to develop a cycle in which disturbed sleep linked to caffeine consumption induces sleepiness, which then leads to increased caffeine intake. High caffeine intake frequently coexists with other behaviours that negatively affect sleep, such as late evening electronic and computer technology use, mostly in adolescents. Some studies also suggest that adolescents may use

caffeine to regulate mood and/or help to alleviate depression.[29]

EFFECTS OF CAFFEINE ON THE DISEASED AND AGEING BRAIN

Coffee/caffeine and headaches/migraines

A recent Cochrane review that included 20 studies (4262 participants) analysed 25 comparisons using a common analgesic (paracetamol, ibuprofen or aspirin) plus caffeine versus the same dose of analgesic alone.[30] Most studies reported the association of acetaminophen or ibuprofen with 100–130 mg caffeine. The proportion of participants with at least 50% of the maximum pain relief after analgesic plus caffeine was 45% compared with 37% after the analgesic alone. The RR for the addition of caffeine was 1.2 and the calculated number needed to treat to benefit from adding caffeine was 13, which is high quality evidence. In migraine, a commonly used effective association is acetaminophen/aspirin/caffeine 500/500/130 mg. Altogether, the addition of at least 100 mg caffeine to commonly used dose(s) of classical analgesic(s) appears to increase the likelihood of achieving a good level of pain relief.[30]

Caffeine is also occasionally used in low-pressure headache, but there are no clinical trial data to determine effective doses and potential combinations with other analgesics.

Caffeine and autonomic failure

At present, only two drugs are approved to treat orthostatic hypotension, the α1-adrenergic agonist midodrine and the noradrenaline prodrug droxidopa. Acute caffeine treatment increases blood pressure.[31] A recent small clinical trial compared midodrine to ergotamine 1 mg with caffeine 100 mg in 12 patients and reported that the drug combination increased seated blood pressure to the same extent as midodrine and was better in improving symptoms of autonomic failure.[32] Unfortunately, there is no information about the use of caffeine alone in the treatment of autonomic failure.

Coffee/caffeine and age-related physiological cognitive decline

Studies suggest that habitual coffee/caffeine consumption may boost the cognitive reserve of older adults, particularly women. Thus, one cup of coffee at breakfast can prevent the decline of performance between morning and afternoon in the elderly. Caffeine (200 mg) also seems to improve reaction time and working memory in the elderly.[20]

In 2010, a meta-analysis including nine studies looking at the effects of coffee/caffeine on different measures of cognitive impairment and/or decline found a reduced risk of cognitive decline across different measures of cognitive impairment (mean RR 0.84) with caffeine intake.[33] For all studies on tea and most of those on coffee, estimates of cognitive decline were lower among consumers but there was no evidence of a dose response. These effects are seen for a daily consumption of 3–4 cups of coffee and are stronger in women than in men.[33] The reason for this gender effect is unclear.

Coffee/caffeine and Alzheimer's disease

Most human epidemiological studies suggest that a lifetime of regular coffee/caffeine consumption reduces the risk of developing Alzheimer's disease, particularly in the elderly. Coffee/caffeine appears particularly helpful during the premorbid phase.

The first meta-analysis of the effects of coffee/caffeine on Alzheimer's disease identified four studies. There was a clear protective effect of coffee consumption (mean RR 0.73) but with much heterogeneity across the studies.[34] A further meta-analysis of the relation between coffee/caffeine intake and the risk of Alzheimer's disease found a summary RR of 0.80–0.83 for Alzheimer's disease after adjusting for smoking and hypertension.[35] A recent study on 124 subjects aged 65–88 years reported that persons evolving from 'moderate cognitive decline' to Alzheimer's disease during the 2–4 years follow-up had 51% lower blood circulating concentrations than those who stayed at the moderate cognitive decline level.[36]

Coffee/caffeine and Parkinson's disease

Caffeine's effects on the development of Parkinson's disease have already been reported in the late 1960s. Many epidemiological studies have reported an inverse, dose–response relationship between coffee/caffeine consumption and the risk of developing Parkinson's disease. Coffee consumption appears to reduce or delay the development of Parkinson's disease, with caffeine as the causal factor.

A meta-analysis including 26 studies appeared to show a mean decrease of 25% in the risk of developing Parkinson's disease among daily caffeine consumers compared with non-consumers. There was a linear dose–response relationship: higher caffeine intake being associated with lower Parkinson's disease risk. Some studies suggested even higher reductions in risk, up to 80% for the intake of >4 cups of caffeinated coffee daily. The overall risk of developing Parkinson's disease seems to fall by 24–32% per 300 mg increase in caffeine intake (about every three cups of coffee).[37] The risk reduction appears similar in fast and slow metabolising individuals. A more recent meta-analysis including 13 studies and 901 764 participants confirmed these results, with an RR of 0.72 for the daily intake of three cups of coffee (figure 1).[38]

In both meta-analyses,[37 38] the risk reduction was not as high in women as in men. The effects of caffeine on Parkinson's disease risk are affected by postmenopausal hormonal treatment. In a study of 86 404

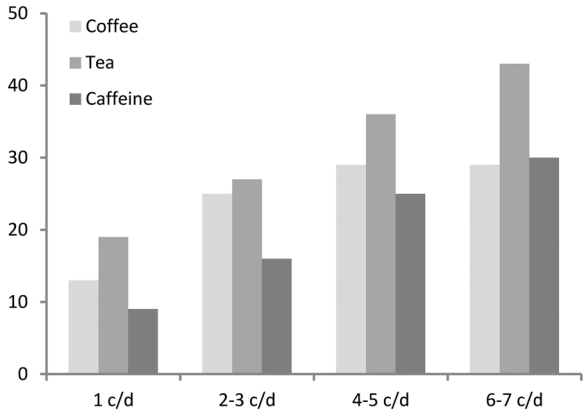

Figure 1 Dose-dependent reduction of the risk of developing Parkinson's disease associated with the lifelong consumption of coffee, tea and caffeine. Data from the meta-analysis by Qi and Li.[38] c/d, cups/day.

men and 97 786 women, the RR for highest daily caffeine consumption (435 mg) versus lowest (5.6 mg) was 0.43 in men and 0.61 in women. Furthermore, the association was stronger in women who were not taking hormone replacement therapy (RR 0.32) compared with those taking hormone replacement therapy (0.81).[39] Only the genetic polymorphism of CYP1A2, associated with reduced enzyme induction by caffeine, marginally increased the risk of Parkinson's disease in women (RR 1.34) but not in men.[40]

A randomised-controlled trial in patients who already had Parkinson's disease reported that caffeine did not change overall quality of life, depression or sleep quality. Caffeine induced only equivocal marginal improvement of excessive somnolence but improved objective motor measures.[41]

In animals, caffeine counteracts the symptoms of Parkinson's disease induced in rats and mice and enhances the effects of L-dopa. Chronic treatment with A2A receptor antagonists such as caffeine on Parkinson's disease motor disability and on motor complications produced by long-term L-dopa treatment suggests that A2A antagonists might be effective in the symptomatic treatment of Parkinson's disease.[42]

Coffee/caffeine and stroke

Several studies reported that moderate coffee consumption may reduce the risk of stroke and limit the deleterious consequences of suffering a stroke.

A meta-analysis including 11 prospective studies and 479 689 participants with 10 003 cases of stroke suggested a 7–14% reduction of the risk of stroke for a coffee consumption ranging from 2 to 8 cups daily. The reduction was found for both ischaemic and haemorrhagic stroke and in both sexes.[43]

In 2014, a large meta-analysis of 36 cohort studies including 1 279 804 individuals with 36 352 cases of cardiovascular diseases including stroke reported a 5% decrease of the relative risk for stroke for a median consumption of 5 cups daily and 15% for 3.5 cups daily compared with a median consumption of zero (figure 2).[44] A recent review of the literature confirmed these figures. Most prospective studies on various ethnic groups and in both sexes support this negative association.[45] Randomised, placebo-controlled trials remain necessary to clarify the relationship between caffeine and stroke.

Caffeine has been tried as a stroke treatment. In one study, 10 patients with a cortical stroke were given a caffeinol mixture injection (8–9 mg/kg caffeine—the equivalent of 5–7 cups of coffee—with 0.3–0.4 g/kg ethanol, or two doses of strong alcohol leading to target caffeine and ethanol circulating levels of 8–10 μg/mL and 0.3–0.5 g/L, respectively). This cocktail was associated with fibrinolysis with tissular plasminogen activator if patients qualified and delivered in the 134 min following the first clinical signs. The efficacy of the cocktail was optimal when administered during the first 95 min. Among the 10 patients treated with caffeinol, 6 (60%) had preserved activities and autonomy, while this was the case in only 26% of the 90 patients treated in a classical manner.[46] A randomised, placebo-controlled trial would be necessary to validate the potential neuroprotective properties of this combination.

Coffee/caffeine and epilepsy

In humans, the potential proepileptic role of caffeine has been debated. Indeed, acute caffeine consumption decreases the seizure threshold in animal models and worsens brain damage induced by seizures.[47] Conversely, chronic caffeine decreases the susceptibility to seizures and limits brain damage consecutive to status epilepticus.

Among young women, moderate–high intake of caffeine is not associated with increased risk of seizures or epilepsy.[48] Likewise, in a recent Norwegian study on 154 cases, there was no influence of caffeine intake 24 h before seizure occurrence compared with consumption on a day without seizures.[49] Only borderline-heavy consumption of caffeine might

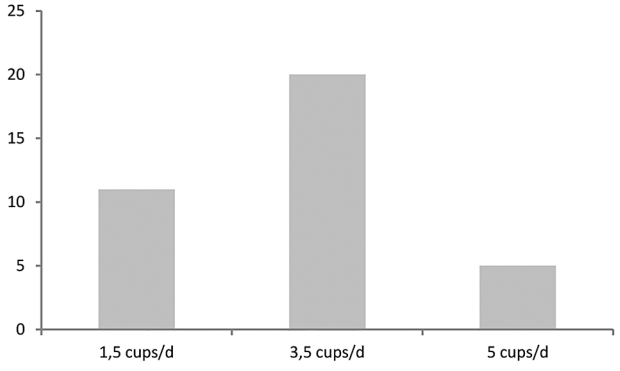

Figure 2 Dose-dependent reduction of the risk of developing stroke associated with the lifelong consumption of coffee. Data from the meta-analysis by Ding *et al*.[44] c/d, cups/day.

aggravate seizure risk, as cited in two single case reports. Thus, there does not seem to be much concern or impact in coffee/caffeine consumption in most patients with seizures. However, several factors act as seizure precipitants in patients with epilepsy. Sleep deprivation is a common one that could clearly be partly linked to the consumption of heavy dosages of caffeine. A few reports on triggering factors for seizures are available, but none has studied the potentially underlying role of caffeine in sleep deprivation in patients with epilepsy.[50] The consumption of caffeine does not appear to induce or aggravate seizures as long as it is drunk in moderation and well distributed throughout the day.

The central target of caffeine in the brain is the adenosine receptor. It appears that the endogenous antiepileptic adenosine plays a central role in seizure expression. Along the whole cycle of adenosine production and degradation, from ATP to reuptake by transporters and phosphorylation by adenosine kinase, changes in the expression and activity of the latter enzyme seem to play a central role. Overexpression of adenosine kinase activity increases central excitability while downregulation leads to resistance to seizures and injury. In the epileptic brain, there is usually overexpression of the kinase and adenosine deficiency. Treatments that increase adenosine levels prevent seizures in animal models and adenosine kinase appears as a target of interest in the prevention of spontaneous seizures (for review, see ref. 51).

CONCLUSIONS

In conclusion, coffee/caffeine consumed at moderate levels (not more than 200 mg caffeine in one setting or 400 mg over the day) does not appear to present any harmful effects for human health. Caffeine increases vigilance and helps concentration but because of that may disturb the quality of sleep. In some people, caffeine also raises the level of anxiety. For migraine and headaches, caffeine potentiates the effect of common analgesic drugs. In non-randomised observational cohort studies, the lifelong consumption of coffee/caffeine is associated with reduced rate of age-related cognitive decline, reduced risk of developing Parkinson's disease or Alzheimer's disease and lower risk of stroke. Its regular consumption does not affect patients with epilepsy. Thus, daily coffee and caffeine intake can be part of a healthy balanced diet and their consumption should not be stopped in elderly people.

Key points

- Coffee/caffeine do not present any harmful effects if consumed at levels of 200 mg in one sitting (2½ cups of coffee) or 400 mg daily (5 cups of coffee).
- Caffeine increases alertness and well-being and helps concentrating.
- Caffeine may disturb sleep.
- Caffeine improves mood and reduces depression.
- Caffeine may raise anxiety in some individuals.
- Caffeine does not lead to dependence.
- Caffeine potentiates the effect of regular analgesic drugs in headache and migraine.
- Lifelong coffee/caffeine consumption prevents cognitive decline.
- Lifelong coffee/caffeine consumption decreases the risk of stroke, Parkinson's disease and Alzheimer's disease.

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