

Caffeine and blood pressure: a critical review perspective

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Abstract

The WHO reported that high blood pressure (BP) is one of the primary causes of death worldwide. Hypertension (HPT) is a major risk factor for CVD and related diseases as well as for diseases, leading to a considerable increase in cardiovascular risk. Since BP response could also be influenced by caffeine, which is widely consumed with coffee and other items, it is important to define the possible effects associated with caffeine intake. The most recent findings aimed at clarifying the role of caffeine consumption on BP and HPT risk/incidence are conflicting and difficult to interpret. Therefore, in the present narrative review, we aimed to examine various methodological inaccuracies/aspects and factors that make studies difficult to be compared, in order to obtain a single consensus on the effects of caffeine intake on the risk of BP and HPT. We observed that this heterogeneity in results could be due to the presence of: (i) several variables affecting BP (such as age, sex, genetic and lifestyle aspects); (ii) different caffeine content of food and beverages; and (iii) caffeine metabolism. Moreover, different methodological aspects in the evaluation of daily dietary caffeine intake and in the BP measurement could add some other bias in the interpretation of results. Therefore, it is mandatory to consider all methodological aspects and confounding factors to generate a standardised methodology in order to increase cross-study consistency and minimise confounding effects of different variables on the relationship between BP response and HPT risk/incidence after caffeine intake.

Key words: Hypertension: Blood pressure: Caffeine: Methodology

Background

Hypertension (HPT) is a major risk factor for CVD and related diseases as well as for diseases leading to a marked increase in cardiovascular risk⁽¹⁾.

The WHO reported that high blood pressure (BP) has been listed as the first cause of death worldwide⁽¹⁾ with an age-standardised prevalence of raised BP ranging from 15.2 to 31.7%, as reported by the European Society of Cardiology in 2014⁽²⁾. In particular, it has been reported that BP levels show a continuous linear relationship with the risk of stroke and myocardial infarction⁽²⁾; the INTERHEART study⁽³⁾ estimated that 22% of myocardial infarctions in Europe are related to HPT, which almost doubles the risk compared with individuals with no history of HPT.

The relationship of BP with caffeine and caffeine metabolites is a major interest, given the widespread caffeine intake from food and beverage sources and the public health burden of high BP. Caffeine is the most widely consumed active pharmacological substance in the world and it is found also in common non-essential grocery items such as coffee, tea, cocoa, chocolate and soft drinks⁽⁴⁾.

Caffeine exerts several effects on the autonomic nervous system and blood vessels. The mechanisms by which caffeine exposure affects heart rate and BP levels might include increased catecholamine levels, which might subsequently lead to vasoconstriction^(5,6). Possible mechanisms for the acute cardiovascular effects of caffeine include antagonistic effects on adenosine receptors (particularly, A1 and A2A receptors), activation of the sympathetic nervous system, stimulation of the adrenal cortex (release of corticosteroids), renal effects (diuresis, natriuresis and activation of the renin–angiotensin–aldosterone system) and inhibition of phosphodiesterase⁽⁷⁾.

However, the role of caffeine in the regulation of BP levels is controversial. According to the guidelines for the management of arterial HPT of the European Society of Hypertension⁽⁸⁾ and of the European Society of Cardiology⁽⁸⁾, a firm recommendation or discouragement of coffee consumption cannot be issued due to insufficient quality of most studies⁽⁸⁾.

Recently, the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies reported its

Abbreviations: BP, blood pressure; CYP, cytochrome P450; EFSA, European Food Safety Authority; HPT, hypertension; RCT, randomised controlled trial.

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Scientific Opinion on the safety of caffeine⁽⁷⁾. The effect of caffeine consumption was observed at single doses of caffeine ranging from 80 to 300 mg, inducing a mean increase in systolic BP of about 3–8 mmHg and in diastolic BP of about 4–6 mmHg, with high inter-individual variability. In addition, the available data suggested that BP generally increases 30 min after caffeine consumption, reaches a peak after 60–90 min and returns to baseline after about 2 to 4 h, which is consistent with the pharmacokinetics of caffeine⁽⁷⁾.

However, as well documented⁽⁷⁾, results from prospective cohort studies on the relationship between habitual caffeine intake and long-term changes in BP and on HPT risk are conflicting and difficult to interpret because the data on clinical effects are mixed: equivocal, null and positive.

In the last 10 years, few systematic reviews and meta-analyses^(9–14) have been conducted with the purpose of clarification of the role of caffeine consumption on BP and HPT risk/incidence.

Zhang *et al.*⁽⁹⁾ described an inverse J-shaped relationship between coffee consumption and the incidence of HPT, showing that more than three cups/d habitual coffee consumption, compared with less than one cup/d consumption, was not associated with an increased risk of HPT while a slightly elevated risk appeared to be associated with light to moderate use (i.e. 1–3 cups/d)⁽⁹⁾.

Shah *et al.*⁽¹⁰⁾ assessed the BP and heart rate effects of energy drinks in healthy individuals and described a significant dose-effect increase, where the systolic BP elevation was under 4 mmHg when caffeine consumed was <200 mg and more than 6 mmHg when caffeine consumption was ≥200 mg⁽¹⁰⁾.

On the contrary, Steffen *et al.*⁽¹¹⁾ reported that no strong recommendation or discouragement of coffee consumption related to BP and/or HPT risk could be suggested, revealing that coffee consumption was not associated with any significant change in BP.

D'Elia *et al.*⁽¹²⁾, exploring the relationship between habitual coffee consumption and the risk of HPT in the general population, reported a non-linear inverse dose–response relationship. In fact, consuming one or two cups of coffee/d was not significantly associated with HPT risk while a significant protective effect of coffee consumption was observed when 3–7 cups/d were consumed compared with no coffee consumption⁽¹²⁾.

Mesas *et al.*⁽¹³⁾ reported conflicting results on the influence of caffeine intake on BP distinguishing between acute and long-term effects. Intake of 200 to 300 mg of caffeine/d led to a significant BP increase, observed in the first 60 min post-ingestion up to 180 min, while drinking coffee for 2 weeks (range of caffeine intake/d: 79–300 mg) did not appear to increase BP⁽¹³⁾.

Finally, the most recent meta-analysis of cohort studies, conducted by Xie *et al.*⁽¹⁴⁾, provided quantitative evidence that coffee consumption was inversely associated with the risk of HPT in a dose–response manner. The authors described a reduction of about 2 % per one cup/d increment of coffee consumption⁽¹⁴⁾.

Given the conflicting results described above, in the present narrative review, we provided a critical analysis of the existing literature. From a methodological point of view, summarising various methodological inaccuracies/aspects and confounding factors makes it difficult to compare studies in order to obtain a single consensus on the effects of caffeine intake on BP and HPT risk.

With this purpose, we considered cohort studies and randomised controlled trials (RCT) of the last 10 years (Tables 1 and 2), excluding the systematic reviews and meta-analyses that we mentioned above^(9–14).

Characteristics of the study population

Previous studies^(1,2,15) have reported that the BP response to intake of caffeine is influenced by multiple factors, such as age, sex, genetics^(1,2,16) and lifestyle factors (cigarette smoking, ethanol consumption, weight, Na and K intake)^(1,15), that affect either directly BP response or caffeine metabolism (such as genetic polymorphism).

Age is the factor that most influences BP response to caffeine intake; greater increases in systolic and diastolic BP have been reported in response to caffeine with increasing age⁽¹⁷⁾. In the present review, few cohort studies^(18–28) and only one RCT⁽¹⁷⁾ considered age as a possible confounding factor (Table 1).

Genetics also play a role in caffeine-related BP modulation^(2,15). In humans, caffeine is rapidly and completely absorbed after oral intake and the main route of metabolism is via *N*-3 demethylation to paraxanthine, catalysed by cytochrome P450 (CYP) 1A2 in the liver^(7,16); the activity of CYP1A2 accounts for about 95 % of caffeine clearance⁽⁷⁾. Genetic polymorphism of the CYP1A2 gene has been reported to be a source of variability in the metabolism of caffeine^(7,16).

Moreover, previous genetic studies, conducted on three CYP1A2 alleles (rs762551, rs1133323 and rs1378942)^(29,30), reported that CYP1A2 variants are influenced by cigarette smoking, which increases caffeine metabolism, with caffeine BP response higher in smokers than in non-smokers. Additionally, it has been previously reported that long-term ethanol consumption masks the induction of CYP1A2 activity⁽¹⁵⁾. Therefore, these findings suggest that the interaction between lifestyle factors and genetic assessment may explain a key role in the variability of the cardiovascular effects of caffeine intake.

In the present literature review, only one study⁽³¹⁾ investigated the CYP1A2 polymorphism while other authors considered alcohol intake^(18–20,22–28) and smoking habits^(18–28) as possible confounding factors that directly affect BP response, not considering the genetic aspects (Table 1).

The sex-related effect of caffeine consumption on BP should also be considered⁽⁷⁾. In fact, it has been well recognised that even if BP is generally lower in premenopausal women than in men, postmenopausal women have a higher prevalence of HPT than do men of a similar age⁽²⁷⁾. Moreover, it has been previously reported^(7,16) that CYP1A2 activity is higher in men than in women and lower in women on oral contraceptives. In the present review, only eight studies^(18–24,28) considered sex as a possible confounding factor (Table 1).

Excess body weight, decreased K intake and increased Na consumption with diet are well-recognised risk factors for BP elevation and HPT onset⁽¹⁾. In the present review, eleven studies^(18–28) adjusted their results for weight, seven^(20,22–24,26–28) considered dietary Na intake and only four^(20,24,26,27) dietary K intake (Table 1).

Table 1. Confounding variables affecting blood pressure response or caffeine metabolism

Authors	Study design	Sample age (years)	Adjusted variables								
			Sex	Age	Weight	Alcohol intake	Smoking	Na intake	K intake	Genetics	Stress evaluation
Uiterwaal <i>et al.</i> ⁽¹⁸⁾	Cohort study	30–50	✓	✓	✓	✓	✓				
Palatini <i>et al.</i> ⁽¹⁹⁾	Cohort study	18–45	✓	✓	✓	✓	✓				
Guessous <i>et al.</i> ⁽²⁰⁾	Cohort study	40–65	✓	✓	✓	✓	✓	✓	✓		
Köksal <i>et al.</i> ⁽²¹⁾	Cohort study	20–60	✓	✓	✓	✓	✓				
Lopez-Garcia <i>et al.</i> ⁽²²⁾	Cohort study	≥63	✓	✓	✓	✓	✓	✓			
Chei <i>et al.</i> ⁽²³⁾	Cohort study	45–74	✓	✓	✓	✓	✓	✓			
Grosso <i>et al.</i> ⁽²⁴⁾	Cohort study	45–69	✓	✓	✓	✓	✓	✓		✓	
Bakker <i>et al.</i> ⁽²⁵⁾	Cohort study			✓	✓	✓	✓	✓			
Winkelmayer <i>et al.</i> ⁽²⁶⁾	Cohort study	25–55		✓	✓	✓	✓	✓	✓		
Rhee <i>et al.</i> ⁽²⁷⁾	Cohort study	50–79		✓	✓	✓	✓	✓	✓		
Navarro <i>et al.</i> ⁽²⁸⁾	Cohort study	28–47	✓	✓	✓	✓	✓	✓			
Farag <i>et al.</i> ⁽¹⁷⁾	RCT cross-over	35–64		✓							
Renda <i>et al.</i> ⁽³¹⁾	RCT cross-over	18–40								✓	
Bennett <i>et al.</i> ⁽³⁴⁾	RCT	18–29	✓								✓
Teng <i>et al.</i> ⁽³⁷⁾	RCT	19–26									
Sharbat <i>et al.</i> ⁽⁴⁰⁾	Case–control study	18–35									
Eichelberger <i>et al.</i> ⁽⁴¹⁾	Nested case–control study	23–34									

RCT, randomised controlled trial.

Finally, it has been previously demonstrated that caffeine and stress appear to affect BP more in those with a positive family history of HPT compared with those with no non-contributory history^(32,33); studies reported in the present review did not consider this aspect, excluding Bennett *et al.*⁽³⁴⁾ (Table 1), overshadowing the impact on BP of stress and caffeine combined.

Blood pressure assessment

As well described, BP is characterised by large spontaneous variations both during the day and between days, months and seasons; the diagnosis of HPT should be based on multiple BP measurements, taken on separate occasions over a period of time⁽¹⁾. BP can be measured by a doctor or nurse in the office or clinic (office or clinic BP), by the patient him/herself or by a relative of him/her at home, or automatically over 24 h monitoring (ambulatory BP monitoring)⁽¹⁾. There are different procedures to measure BP, such as mercury sphygmomanometer or other non-invasive devices (auscultatory or oscillometric semi-automatic devices)⁽¹⁾; however, since BP measurements are sensitive, standardised measures are needed⁽³⁵⁾.

Some authors cited in Table 2 registered BP by using automatic techniques^(19–22,25); this could introduce some bias because these are not ‘gold standard’ methods⁽³⁶⁾ and their accuracy should be checked periodically by comparing with mercury sphygmomanometric values⁽¹⁾. Moreover, some studies considered ambulatory BP monitoring^(19,20,22), others isolated BP measurements^(18,24,25,27,37) and others repeated BP measurements^(17,21,31,34).

Therefore, the lack of standardisation to obtain BP measurements has led to values that cannot be compared with each other.

Finally, as far as HPT is concerned (Table 2), some studies^(23,26,28) analysed only the risk of HPT by means of a

self-reported medical diagnosis or through the prescribed HPT medication reported by the patient during a semi-structured interview^(23,26,28).

Caffeine source and daily caffeine intake

The terms caffeine and coffee are often conflated in both the biomedical literature and public perception; however, the terms are not synonymous, and the biological effects of coffee cannot be reduced to the isolated effects of the caffeine that it contains⁽³⁸⁾.

The main sources of caffeine in the diet include coffee, tea, caffeinated soft drinks (including ‘energy drinks’ containing also guarana, taurine and ginseng that may also cause haemodynamic changes) and chocolate⁽¹⁾.

However, a high variability in caffeine levels for different foods and beverages has been noticed within the same product and for the same country⁽⁷⁾. For instance, caffeine concentrations in coffee beverages depend on the manufacturing process, on the type of coffee beans used and on the type of preparation⁽⁷⁾; as reported by Fox *et al.*⁽³⁹⁾ who evaluated twenty-eight varieties of coffee with caffeine concentrations ranging from 10.6 and 19.9 mg/g.

Other food items that might present significant variability in caffeine levels are cocoa-based beverages, depending on the amount and type of cocoa that differ according to the brand⁽¹⁾.

Cohort^(18,19,21–28) and case–control studies⁽⁴⁰⁾, reported in Table 2, evaluated the effects of caffeine on BP and HPT risk; in all these studies coffee was always considered as a source of caffeine, but other sources of caffeine, such as tea^(18,21,23,25–27,40), energy/soft drinks^(21,23,26,27,40) and solid foods^(21,23,26) were also included, increasing the variability of results. Therefore, to better elucidate the variability and effect of caffeine on BP and HPT risk, we should consider the average concentration

Table 2. Methodological aspects influencing the interpretation of results

Authors	Study design	BP measurements						Caffeine dietary intake assessment				Source of caffeine				Type of coffee			
		Manual	Automatic	Self-reported	ABPM	Repeated	Isolated	HPT	Food questionnaires	Number of cups/d and volume	Direct measures	Coffee	Tea	Other caffeinated beverages	Solid foods	Caffeine and amount	R	E	D
Uiterwaal <i>et al.</i> ⁽¹⁸⁾	Cohort study	✓					✓	✓	✓ (125 ml)		✓	✓				✓	✓	✓	
Palatini <i>et al.</i> ⁽¹⁹⁾	Cohort study		✓		✓			✓	✓ (n.s.)		✓						✓		
Guessous <i>et al.</i> ⁽²⁰⁾	Cohort study		✓		✓					✓			n.r.					n.r.	
Köksal <i>et al.</i> ⁽²¹⁾	Cohort study		✓			✓		✓	✓ (n.s.)		✓	✓	✓	✓		✓			
Lopez-Garcia <i>et al.</i> ⁽²²⁾	Cohort study		✓		✓			✓	✓ (75 ml)		✓					✓	✓	✓	
Chei <i>et al.</i> ⁽²³⁾	Cohort study						✓	✓	✓ (237 ml)		✓	✓	✓	✓		✓			
Grosso <i>et al.</i> ⁽²⁴⁾	Cohort study		n.r.				✓	✓	✓ (150 ml)		✓							n.r.	
Bakker <i>et al.</i> ⁽²⁵⁾	Cohort study		✓				✓	✓	✓ (125 ml)		✓	✓				✓	✓		
Winkelmayer <i>et al.</i> ⁽²⁶⁾	Cohort study						✓	✓	✓ (n.s.)		✓	✓	✓	✓		✓	✓		
Rhee <i>et al.</i> ⁽²⁷⁾	Cohort study	✓					✓	✓	✓ (177 ml)		✓	✓	✓			✓	✓	✓	
Navarro <i>et al.</i> ⁽²⁸⁾	Cohort study						✓	✓	✓ (50 ml)		✓					✓	✓		
Farag <i>et al.</i> ⁽¹⁷⁾	RCT cross-over		✓			✓					✓				✓ (240 mg for 6 d and 250 mg for 1 d)				
Renda <i>et al.</i> ⁽³¹⁾	RCT cross-over		✓			✓					✓				✓ (3.0 mg/kg)				
Bennett <i>et al.</i> ⁽³⁴⁾	RCT		✓			✓									✓ (3.3 mg/kg)				
Teng <i>et al.</i> ⁽³⁷⁾	RCT		✓				✓								✓ (1.4 mg/kg)				
Sharbat <i>et al.</i> ⁽⁴⁰⁾	Case-control study				n.r.			✓	✓ (n.s.)		✓	✓	✓					n.r.	
Eichelberger <i>et al.</i> ⁽⁴¹⁾	Nested case-control study				n.r.						✓		n.r.					n.r.	

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; HPT, hypertension; R, regular; E, espresso; D, decaffeinated; n.s., not specified; n.r., not reported; RCT, randomised controlled trial.

of caffeine rather than specific foods or beverages, as already suggested by the EFSA panel⁽⁷⁾.

Finally, we should also take into consideration the direct administration of caffeine in RCT at different timings and concentrations. In humans, 99 % of caffeine is absorbed within 45 min after ingestion, reaching the plasma concentration peak in 30 min; however, caffeine metabolites become higher after 8–10 h from ingestion⁽¹⁶⁾. Moreover, as previously reported, data suggested that BP generally increases 30 min after caffeine consumption, reaches a peak after 60–90 min and returns to baseline after about 2–4 h, which is consistent with the pharmacokinetics of caffeine⁽⁷⁾. Among our selected RCT, only two studies^(31,34) considered a period of abstinence from caffeine from 2 to 4 h. Furthermore, two studies^(17,37) measured BP response within 1 h after caffeine administration and another two^(31,34) within 2 h.

EFSA reported that the effect of caffeine consumption was observed at single doses of caffeine ranging from 80 to 300 mg⁽⁷⁾. RCT showed heterogeneity also in the administered doses of caffeine; in fact, three studies^(31,34,37) administered caffeine in mg/kg body weight, whereas one study⁽¹⁷⁾ administered fixed doses.

Another source of bias is due to the fact that there are different indirect methods to assess daily caffeine consumption, making it difficult to relate caffeine intake to BP and HPT risk results among studies. In fact, most of the studies^(18,19,21–28) estimated caffeine consumption by means of questionnaires or interviews; however, only seven studies^(18,21,23,24,26–28) used a validated FFQ, one study used FFQ together with a photographic food atlas⁽²⁴⁾, and another one⁽²²⁾ used a computerised diet history with photographs, to estimate portion sizes, new dishes and cooking methods and the degree of food processing⁽²²⁾. Other authors^(18,19,21,23–25,27,28) expressed daily caffeine consumption as coffee cups or tea cups with different volumes (Table 2).

Another issue that has been identified relies on the laboratory analytical methodology. It is well known that caffeine is metabolised by the liver CYP1A2 enzyme into paraxanthine (about 80 %), theobromine (about 12 %), and theophylline (about 4 %) and that the urinary excretion of caffeine and caffeine metabolites is a valid measure of caffeine intake⁽²⁰⁾. However, only one study conducted by Guessous *et al.*⁽²⁰⁾ analysed, for the first time, the associations between ABPM with urinary caffeine and caffeine metabolite excretion. Other authors^(17,31,41) evaluated caffeine^(17,31) and its metabolites (paraxanthine)⁽⁴¹⁾ in plasma⁽³¹⁾, serum⁽⁴¹⁾ and salivary samples⁽¹⁷⁾.

Type of coffee

The amount of caffeine in coffee (DM basis of green coffee beans) varies markedly between species and species⁽⁴²⁾. For instance, amounts ranging from 65 to 120 mg of caffeine have been reported to be contained in a normal cup of coffee, whereas Arabica coffee normally contains less caffeine than the Robusta variety⁽⁴²⁾.

Moreover, the content of bioactive compounds is influenced by the extraction mechanism⁽¹⁶⁾.

McCusker *et al.*⁽⁴³⁾ previously evaluated the caffeine content of caffeinated and decaffeinated espresso coffee (EC) and coffee brew purchased ready-to-drink from coffee shops. The caffeine dose (expressed in mg) in caffeinated EC was lower than in caffeinated brewed coffees. However, EC volumes were smaller than regularly brewed coffee and, in terms of caffeine concentration, EC reported higher caffeine concentration than brewed coffees⁽⁴³⁾.

Finally, another study by Fujioka *et al.*⁽⁴⁴⁾ found that the caffeine content in regular coffees ranged from 10.9 to 16.5 mg/g while that of decaffeinated coffees was from 0.34 to 0.47 mg/g.

Studies considered in the present narrative review reported different types of coffee such as regular^(18,21,22,23,25–28), espresso^(19,22,27), decaffeinated^(18,22,25–28) and other⁽¹⁸⁾, even not specified^(24,40).

Conclusion

Coffee consumption has long been a suspected cause of HPT, but the available evidence from the literature is sometimes equivocal, making it difficult to compare studies in order to obtain a single consensus on the effects of caffeine intake on the risk of BP and HPT, as also demonstrated by different systematic reviews and meta-analyses^(9–14) in the last 10 years.

Also worth mentioning in the context of the present review is that Grant *et al.*⁽⁴⁵⁾ also considered the protocols used to control for caffeine's effects on cardiovascular parameters in the extant cardiovascular literature⁽⁴⁵⁾. Grant *et al.*⁽⁴⁵⁾ summarised the widely differing protocols used to identify correctly some primary means to control cardiovascular response after caffeine intakes, such as controlling variables that significantly alter the half-life of caffeine, timing of caffeine administration, and methods of administration. In conclusion, Grant *et al.*⁽⁴⁵⁾ stressed that creating a standard for 'caffeine controls' requires more attention and interest in examining the potentially confounding vascular effect of caffeine. As a result, improvements in methodological controls for caffeine can have significant health consequences. Reliable, methodologically correct cardiovascular research depends on the appropriate control of a myriad of factors that can systematically alter cardiovascular responses⁽⁴⁵⁾.

Similarly, in the present critical narrative review we highlighted how conflicting results could be due to various confounding/different factors such as: (i) variables affecting BP response (age, sex, genetics, smoking habits, alcohol consumption, Na and K intake); (ii) different caffeine content of food and beverages due to different items (coffee, tea, caffeinated beverages or solid foods) and extraction mechanism (espresso, regular or decaffeinated); and (iii) caffeine metabolism. Moreover, different methodological aspects in the evaluation of daily dietary caffeine intake (questionnaires or direct measurements of caffeine's metabolites) and in the BP measurement, concerning instruments (manual or automatic) and timing (ambulatory BP monitoring, isolated or repeated), could add further bias in the interpretation of results.

Therefore, it is mandatory to take into consideration all methodological aspects and confounding factors to generate a

standardised methodology in order to increase cross-study consistency and minimise confounding effects of different variables on the relationship between BP response and HPT risk/incidence after caffeine intake.

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