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ISNN Consensus Article

Moving towards Specific Nutrigenetic Recommendation Algorithms: Caffeine, Genetic Variation and Cardiovascular Risk

Raffaele De Caterina[a] Ahmed El-Sohemy[b]

[a]Institute of Cardiology, 'G. d'Annunzio' University, Chieti, Italy; [b]Department of Nutritional Sciences, University of Toronto, Toronto, Ont., Canada

Key Words
Caffeine · Coffee · Cardiovascular disease · Nutrigenetics · Recommendations

Abstract
Recent research has indicated that part of the interindividual variability in cardiovascular responses to caffeine has a genetic basis. Therefore, knowledge of the individual's genetic constitution may allow an individual tailoring of dietary advice for the use of caffeine-containing beverages, yielding an example of the potential of practical translation of nutrigenetic information. This paper reviews the basis for possible nutrigenetic recommendations on the consumption of caffeine, discussing the current gaps in knowledge but also proposing a mode of action in this research area, which may be transposed to other types of similar recommendations.

Preamble and Aim

Because of the impact on clinical practice, quality criteria for the development of recommendations and guidelines have been gradually established by international societies in order to make all decisions transparent to the user. A systematic approach of this kind has not been undertaken so far in the area of nutrigenetics. In order to formulate and issue tentative consensus recommendations for the first time in this area, in this document we

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Raffaele De Caterina, MD, PhD
Institute of Cardiology, 'G. d'Annunzio' University
c/o Ospedale SS. Annunziata
Via dei Vestini, 30, IT–66013 Chieti (Italy)
E-Mail rdecater@unich.it

Table 1. Classes of recommendations

Classes of recommendations	Definitions	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment[1] or procedure is beneficial, useful, and effective	Is recommended/ is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/ opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful	Is not recommended

[1] By treatment, in this context, one should also refer to a nutritional recommendation.

Table 2. Level of evidence (LOE)

LOE A	Data derived from multiple randomized clinical trials or meta-analyses
LOE B	Data derived from a single randomized clinical trial or large nonrandomized studies
LOE C	Consensus of opinion of the experts and/or small studies, retrospective studies, and registries

have adopted – and propose for future use – the system established by major cardiological societies, and in this case, specifically, by the European Society of Cardiology (ESC) Guidelines Committee, as can be found on the ESC website (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). We feel that the process, rigorously established for diagnostic procedures, drugs, and nonpharmacological interventions in the area of cardiology, can be transferred to the nascent science of nutrigenetics. In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. They perform a critical evaluation of the pertinent literature, including, where possible, an assessment of the risk-benefit ratio. They also include estimates of expected health outcomes for larger population strata, where data exist. Experts weigh the level of evidence (LOE) and the strength (grade) of recommendation of particular options and grade them according to predefined scales, as outlined in tables 1 and 2, with adaptations, so that the term 'clinical trial' should be intended as 'scientific evidence' here. This system allows the comparison of the strength (grade) of recommendations and LOE across disparate recommendations in a quick, practical, and easy-to-use fashion, possibly optimal for practical transferability. The set of conclusions and recommendations is then reviewed by a group of experts, who endorse the conclusions on behalf of the proposing society. In particular, we propose that such a system of analysis of the literature for issuing recommendations should be adopted in future documents of the International Society on Nutrigenetics/Nutrigenomics. This article, therefore, is intended to pave the way for similar attempts in other areas of nutrigenetics by trying to ensure a transparent system for transferring scientific knowledge to practice. This first document is dedicated to cardiovascular health effects of caffeine, not precluding similar attempts in other potential areas of caffeine nutrigenetics besides the cardiovascular system.

Background

Coffee is probably, after water, the most widely used beverage worldwide [1, 2], and its use has been associated with a number of effects on human health (reviewed in [3–5]), including effects on liver health and disease [6, 7], appetite and gastric emptying [8], cognitive decline [9], as well as cardiometabolic diseases (reviewed in [10–12]). The precise mechanisms underlying the actions of coffee on the cardiovascular system are incompletely understood. Many effects have been attributed to caffeine, although coffee is a mixture of hundreds of chemical substances, many of which, such as polyphenols, are pharmacologically active [13]. Besides coffee, caffeine, in significant amounts, is contained in several widely used beverages, including tea and energy drinks.

The main mechanism of action of caffeine is to antagonize adenosine receptors [14]; a secondary effect is the inhibition of phosphodiesterases [14], with the subsequent accumulation of cyclic adenosine monophosphate (cAMP) and an intensification of the effects of catecholamines [15]. Such effects translate, in most people, into a psychoactive response [16] and into a complex cardiovascular response, mainly consisting of an increase in blood pressure (BP) [17] and possible effects on the risk of ischemic heart disease.

Although 'daily caffeine intakes from all sources up to 400 mg per day do not raise safety concerns for adults in the general population, except pregnant women' [18], it is also well known that there is a considerable variability in the cardiovascular and psychoactive responses to coffee drinking. In part, such variability is due to tolerance [19], but there is evidence that some variability may have a genetic basis [20]. Cytochrome P450 1A2 (CYP1A2) accounts for approximately 95% of caffeine metabolism and displays wide interindividual variability in activity [21]. An A>C substitution at position –163 (rs762551) decreases enzyme inducibility, resulting in impaired caffeine metabolism [22], and is therefore potentially associated with cardiovascular risk [23]. Most acute pharmacological effects of caffeine result, however, from the antagonism of adenosine, mostly the adenosine receptor A2A (ADORA2A) [24]. The 1976 C>T genetic variant of the ADORA2A gene has been related to susceptibility to anxiety [25] and sleep disturbances [20]. Moreover, the 34 C>T genetic variant of AMP deaminase (AMPD), catalyzing the deamination of AMP to inositol monophosphate (IMP) and thus reducing enzyme activity [26], may increase adenosine availability for its receptors [27]. Since circulating catecholamines may also be involved in cardiovascular responses to coffee [28], genetic polymorphisms of adrenergic receptors may contribute to the variability of cardiovascular responses to coffee. Polymorphisms of α_1 and α_2 adrenergic receptors (ADRA1A and ADRA2B) [29, 30] and of β_1, β_2, and β_3 adrenergic receptors (ADRB1, ADRB2, and ADRB3) [31–38] influence the cardiovascular response to catecholamines. Also, gene variants affecting enzymes involved in catecholamine metabolism may play a role in cardiovascular effects of caffeine, for example at the level of catechol-o-methyltransferase (COMT), which catalyzes the inactivation of adrenaline and noradrenaline. There are thus several candidate gene variants possibly influencing the cardiovascular effect of caffeine. A list of such variants is presented in table 3.

Few studies until now have examined the effects of gene variants on the cardiovascular effects of caffeine and have been summarized in a review paper by Yang et al. [20]. This review included (1) twin studies comparing the heritability of consumption and of caffeine-related traits, including withdrawal symptoms, caffeine-induced insomnia, and anxiety; (2) association studies linking genetic polymorphisms of metabolic enzymes and target receptors to variations in caffeine response, and (3) case-control and prospective studies examining relationships between polymorphisms associated with variations in caffeine response to risks of Parkinson's disease and cardiovascular diseases in habitual caffeine consumers. Twin studies found the heritability of caffeine-related traits to range from 0.36 to 0.58. Analysis of

Table 3. Gene variants (polymorphisms) suspected to influence cardiovascular effects of caffeine, their known biological effects, corresponding proteins and effectors

Protein	Function	Effector	Genetic variant	rs number	Biological effect of genetic variant
CYP1A2	hepatic metabolism	caffeine demethylation	–163 A>C	rs762551	decreased enzyme inducibility → impaired caffeine metabolism
ADORA2A	mental arousal, psychomotor effect mediated by dopaminergic neurons, vasodilation, platelet aggregation	G protein → adenylate cyclase activation → ↑ cAMP	1976 C>T	rs5751876	susceptibility to anxiety and sleep changes
AMPD1	energy metabolism, vasodilation	AMP hydrolase activity (deamination of AMP to IMP)	C34T	rs17602729	reduced activity of the enzyme → increase in adenosine availability for its receptors
ADRA1A	cardiac positive inotropism, vasoconstriction	G protein → ↑ IP3 and DAG → ↑ intracellular Ca^{++}	Arg347Cys	rs1048101	no information on cardiovascular effects
ADRA2B	inhibition of neurotransmitters delivery	G protein → adenylate cyclase inhibition → ↓ cAMP	Ins+910Del	rs29000568	reduced desensitization → increased vasoconstriction induced by its activation
ADRB1	cardiac positive inotropism and chronotropism → regulation of cardiac output and heart rate	G protein → adenylate cyclase activation → ↑ cAMP	Arg389Gly	rs1801253	greater activity of adenylate cyclase in vitro after stimulation with isoproterenol
ADRB1	cardiac positive inotropism and chronotropism → regulation of cardiac output and heart rate	G protein → adenylate cyclase activation → ↑ cAMP	Ser49Gly	rs1801252	no functional effects identified
ADRB2	smooth muscle relaxation → vasodilation	G protein → adenylate cyclase activation → ↑ cAMP	Arg16Gly	rs1042713	increased downregulation by the agonist, effect on vascular reactivity
ADRB2	smooth muscle relaxation → vasodilation	G protein → adenylate cyclase activation → ↑ cAMP	Glu27Gln	rs1042714	agonist-induced downregulation, effect on vascular reactivity
ADRB2	smooth muscle relaxation → vasodilation	G protein → adenylate cyclase activation → ↑ cAMP	Thr164Ile	rs1800888	decreased ligand affinity and intensity of stimulation
ADRB3	lipolysis activation	G protein → adenylate cyclase activation → ↑ cAMP	Trp64Arg	rs4994	association with essential hypertension
COMT	catecholamine inactivation	inactivation of adrenaline, noradrenaline, and dopamine	Val158Met	rs4680	the lower rates of catabolysis for the Met allele results in higher synaptic dopamine and noradrenaline levels following neurotransmitter release

rs = Reference SNP; ADRA1A = α_{1A} adrenergic receptor; ADRA2B = α_{2B} adrenergic receptor; ADRB1 = β_1 adrenergic receptor; ADRB2 = β_2 adrenergic receptor; ADRB3 = β_3 adrenergic receptor; IP3 = inositol trisphosphate.

polysubstance use shows that the predisposition to caffeine use is highly specific to caffeine itself and has little in common with the use of other substances. Genetic association studies link variations in adenosine and dopamine receptors to caffeine-induced anxiety and sleep disturbances. Polymorphism in the metabolic enzyme CYP1A2 is associated with the risk of myocardial infarction (MI) in caffeine users, which is one of the topics of this review. Subsequent to the review paper by Yang et al. [20], a few other publications have indicated some genetic basis for the effects of caffeine on BP, prompting therefore a revisitation of the topic.

Specifically to cardiovascular responses and cardiovascular risk, it appears useful to distinguish acute cardiovascular responses to coffee (and, presumably, all other caffeine-containing beverages, including tea and energy drinks) from long-term effects on cardiovascular risk.

Acute Effects of Caffeine on BP

Caffeine is known to induce an overall acute hypertensive response [39]. Renda et al. [40], in a randomized placebo-controlled crossover study in 110 male healthy habitual moderate coffee drinkers refraining from coffee for the day preceding the study, found (out of 11 gene polymorphisms analyzed) a relationship between the TT genotype of ADORA2A (rs5751876) and the change (Δ) in peak systolic BP (SBP) as well as between the ADRA2B insertion II variant and the mean and peak ΔSBP within 2 h of 3 mg/kg caffeinated coffee intake. These variants were, therefore, associated with increased SBP responses to caffeine.

This was a small study, conducted only in young male subjects but well controlled and, until now, the only one conducted in a randomized, placebo-controlled design.

Practical Implications

Male subjects with the ADORA2A TT (rs5751876) or the ADRA2B II genotypes are more prone to acute surges in BP in response to caffeine-containing beverages. The amount of caffeine used in that study was 3 mg/kg, meaning 210 mg in a 70-kg average subject; for comparison, one small espresso cup yields about 80 mg of caffeine. In practical terms, drinking a double espresso would yield a sufficient amount of caffeine to differentiate the acute SBP increase in ADORA2A TT or ADRA2B II individuals from that of alternative genotypes. Although there are no data to state that these gene variants are associated with an increased cardiovascular risk, it would appear prudent that such individuals, especially if they are hypertensive, refrain from such amounts of acute coffee drinking (grade IIa, LOE B). No statement can be made for females, although prudent recommendations could be similar (grade IIa, LOE C).

Long-Term Risk of Caffeine on Cardiovascular Events

Happonen et al. [41] hypothesized that the increased risk of cardiovascular disease in heavy drinkers of caffeine-containing coffee is, at least partly, mediated by increased circulating catecholamines. Caffeine is a potent stimulator of plasma renin activity and adrenomedullary secretion; acute ingestion results in substantial increases in plasma concentrations of adrenaline and noradrenaline [15]. Tolerance to these acute humoral effects may develop in the course of 1–4 days of habitual consumption [42] but is not complete [43] and may be lost after abstinence for as little as 12 h [44, 45]. To test this hypothesis, Happonen et al. [41] examined whether the Val108Met (rs4680) polymorphism of the COMT gene, resulting in several-fold differences in the metabolism of circulating and locally released catecholamines, modifies the effect of heavy consumption of caffeine-containing coffee on the risk of acute coronary events in a cohort of 773 Finnish men who were 42–60 years old and initially free from symptomatic coronary heart disease (CHD) in 1984–1989. Seventy-eight participants experienced an acute coronary event during an average follow-up of 13 years. In logistic regression adjusting for age, smoking, family history of CHD, vitamin C deficiency, BP, plasma cholesterol concentration, and diabetes, the odds ratio (OR) (90% confidence interval; CI) comparing heavy coffee drinkers (>814 ml) with the low-activity COMT genotype to those with the high-activity or heterozygotic genotypes was 3.2 (1.2–8.4). Urinary adrenaline excretion increased with increasing coffee intake only in those with the low-activity COMT genotype, being over two-fold in heavy drinkers compared to nondrinkers ($p = 0.008$ for trend). In conclusion, heavy coffee consumption increases the incidence of acute coronary events in men with low, but not high, COMT activity. Further studies are required to determine to which extent circulating catecholamines mediate the relationship between coffee intake and CHD.

This study had a limited sample size to assess outcome events.

Practical Implications

Heavy coffee drinkers (>814 ml) with the low-activity COMT rs4680 AA genotype should be advised to limit their coffee drinking (grade IIb, LOE B).

Cornelis et al. [46] hypothesized that cardiovascular outcome in coffee drinkers may be influenced by the rate of caffeine metabolism. Caffeine is metabolized primarily by CYP1A2 in the liver through an initial N3-demethylation [47, 48]. CYP1A2 accounts for approximately 95% of caffeine metabolism and demonstrates wide variability in enzyme activity between individuals [21, 48, 49]. An A>C substitution at position –163 (rs762551) in the CYP1A2 gene decreases enzyme inducibility as measured by the ratio of plasma or urinary caffeine to caffeine metabolites after a dose of caffeine, resulting in impaired caffeine metabolism [22, 50, 51]. Carriers of the variant C allele are 'slow' caffeine metabolizers, whereas individuals who are AA homozygotes are 'rapid' caffeine metabolizers [22, 50, 51]. The authors investigated whether the CYP1A2 genotype modifies the association between the intake of caffeinated coffee and the risk of nonfatal MI in a case-control study where 2,014 cases with a first acute nonfatal MI were matched with population-based controls (n = 2,014) living in Costa Rica between 1994 and 2004, for age, sex, and area of residence, and genotyped. A food frequency questionnaire was used to assess the intake of caffeinated coffee. Fifty-five percent of cases (n = 1,114) and 54% of controls (n = 1,082) were carriers of the slow C allele. For carriers of the slow C allele, the multivariate-adjusted ORs (95% CI) of nonfatal MI associated with consuming <1, 1, 2–3, and ≥4 cups of coffee per day were 1.00 (reference), 0.99 (0.69–1.44), 1.36 (1.01–1.83), and 1.64 (1.14–2.34), respectively. Corresponding ORs (95% CIs) for individuals with the rapid AA genotype were 1.00, 0.75 (0.51–1.12), 0.78 (0.56–1.09), and 0.99 (0.66–1.48) (p = 0.04 for gene-coffee interaction). For individuals younger than the median age of 59 years, the ORs (95% CIs) associated with consuming <1, 1, 2–3, or ≥4 cups of coffee per day were 1.00, 1.24 (0.71–2.18), 1.67 (1.08–2.60), and 2.33 (1.39–3.89), respectively, among carriers of the C allele. The corresponding ORs (95% CIs) for those with the AA genotype were 1.00, 0.48 (0.26–0.87), 0.57 (0.35–0.95), and 0.83 (0.46–1.51). In conclusion, the intake of coffee was associated with an increased risk of nonfatal MI only among individuals with slow caffeine metabolism, suggesting that caffeine plays a role in this association.

This is the largest study so far relating a genotype affecting caffeine metabolism or effectors of caffeine effects with outcomes.

Practical Implications

Intake of coffee was associated with an increased risk of nonfatal MI only among individuals with slow caffeine metabolism. Findings appear applicable to both male and female, and both to younger and older individuals, perhaps with even greater effects among younger subjects. The risk of nonfatal MI appears to increase selectively in slow caffeine metabolizers already at a level of habitual intake of 2 cups per day. Therefore, slow caffeine metabolizers who are carriers of even one allele with an A>C substitution at position –163 (rs762551) in the CYP1A2 gene should refrain from drinking more than one cup of coffee per day.

The effects of caffeine on cardiovascular outcomes may be related to its effects on BP. However, the evidence of this is equivocal, as no clear association of regular caffeine intake with the incidence of hypertension has been found in large-scale prospective studies [52, 53] or in cross-sectional studies [54–56].

The existence of a relationship appears substantiated by a study by Palatini et al. [57], showing that the risk of hypertension associated with coffee intake varies according to the same CYP1A2 genotype (see above) associated with cardiovascular risk as a function of coffee drinking. This was a prospective study of 553 18- to 45-year-old Northern Italian individuals of both sexes, initiated in 1990, including never treated individuals screened for stage 1

hypertension (SBP between 140 and 159 mm Hg and/or diastolic BP between 90 and 99 mm Hg) and excluding patients with diabetes mellitus, nephropathy, and cardiovascular disease. In this study, carriers of the 'slow-metabolism' C allele appeared to be at increased risk of developing hypertension. Increased risk appeared to be significant for both moderate (1–3 cups/day) and heavy (≥4 cups/day) caffeinated coffee drinkers. In conclusion, carriers of the C allele of young age who drink 1 or more cups/day of caffeinated coffee are at increased risk of sustained hypertension needing antihypertensive treatment and should therefore be advised to abstain from coffee, whereas individuals with the AA genotype can safely drink coffee.

These were prospective observational studies with adjustments for risk factors and reasonable sample sizes. A limitation is that hypertension, not hard events, was chosen as an outcome.

Such conclusions are partially supported by a study by Guessous et al. [58], reporting on the influence of the CYP1A2 gene variants also in relation with the effect of smoking, which is known to induce CYP1A2 [59]. In a combined analysis of 4 observational studies (n = 16,719) and 1 quasi-experimental study (n = 106) including European adults, these authors reported that the mean adjusted SBP and diastolic BP *decreased* with the number of reported caffeinated cups/day in nonsmokers, but this only occurred among fast metabolizers consuming caffeine. Smoking appears, therefore, to blunt the association of caffeine intake with hypertension.

Overall, these findings would suggest that failure to account for the modifying effect of smoking may explain why no clear association of regular caffeine intake with the incidence of hypertension has been found in large-scale prospective studies [52, 53] and in cross-sectional studies [54–56].

Recently, a genome-wide meta-analysis of predominantly regular-type coffee consumption among up to 91,462 coffee consumers of European ancestry with top single-nucleotide polymorphisms (SNPs) was followed up in ~30,062 and 7,964 coffee consumers of European and African-American ancestry, respectively. Studies from both stages were combined in a trans-ethnic meta-analysis. Confirmed loci were examined for putative functional and biological relevance. Eight loci, including 6 novel loci, met genome-wide criteria for significance, with per-allele effect sizes of 0.03–0.14 cups per day. Six are located in or near genes potentially involved in pharmacokinetics (ABCG2, AHR, POR, and CYP1A2) and pharmacodynamics (BDNF and SLC6A4) of caffeine. Two maps to GCKR and MLXIPL genes were related to metabolic traits but were lacking known roles in coffee consumption. Enhancer and promoter histone marks populate the regions of many confirmed loci, and several potential regulatory SNPs are highly correlated with the lead SNP of each. Alleles near GCKR, MLXIPL, BDNF, and CYP1A2 that were associated with higher coffee consumption have previously been associated with smoking initiation, higher adiposity, fasting insulin and glucose, but lower BP and favorable lipid, inflammatory and liver enzyme profiles ($p < 5 \times 10^{-8}$) [60]. These genetic findings among European and African-American adults reinforce the role of caffeine in mediating habitual coffee consumption and may point to additional molecular mechanisms underlying interindividual variability in pharmacological and health effects of coffee.

Final Recommendations

1 The average increase in BP response observed after acute caffeine intake appears conditioned by the genotypes of ADRA2B (rs5751876) and ADORA2A (rs29000568). It would appear prudent that individuals who have the ADORA2A TT and ADRA2B II genotypes, especially if hypertensive, refrain from amounts of acute coffee drinking (grade IIb, LOE B) in the order of a double espresso cup to avoid hypertensive surges. Some interme-

diate-graded risk appears to be present for heterozygotes. No statement can be issued for female individuals, although prudent recommendations could be similar (grade IIb, LOE C).

2 Individuals who are homozygous or heterozygous for the C allele of rs762551 in the CYP1A2 gene appear to be at increased risk of MI. Findings appear applicable to both male and female and both to younger and older individuals, perhaps with even greater effects among younger subjects. An increased risk appears also for heterozygotes. The risk of nonfatal MI appears to increase selectively in slow caffeine metabolizers already at a level of a habitual intake of 2 cups per day (grade IIa, LOE B).

3 Future investigations of the effects of caffeine and caffeine-containing beverages must take into account genetic variation at least in CYP1A2 (rs762551) and ADORA2A (rs5751876) because of the current evidence for an important role of these genes as determinants of the interindividual variability in the response to caffeine. Grant applications and publications without such genetic information and statistical analysis should be considered incomplete.

4 Genome-wide association studies offer new hints to investigate further molecular pathways by which habitual coffee drinking may affect cardiovascular outcomes.

Disclosure Statement

R.D.C. has no conflicts of interest. A.E. holds shares in Nutrigenomix Inc.

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