CYP1A2 Genotype and the Health Effects of Coffee: A Genetic Perspective on Caffeine Metabolism and Cardiovascular Risk (Literature Review)

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ABSTRACT

Background:
Coffee is one of the most widely consumed beverages globally and contains numerous biologically active compounds, such as polyphenols, chlorogenic acids, melanoidins, and flavonoids, which are associated with antioxidative, anti-inflammatory, and potential cardioprotective effects (Bakuradze et al., 2010; Cornelis et al., 2006). Moderate coffee consumption has been linked to reduced cardiovascular risk in the general population (Rodríguez-Artalejo & López-García, 2018). However, caffeine — the primary stimulant in coffee — can raise blood pressure and trigger anxiety or cardiovascular risk in susceptible individuals (Palatini et al., 2009; Nehlig, 2018). Its metabolism is primarily regulated by the polymorphic cytochrome P450 1A2 (*CYP1A2*) enzyme, encoded by the *CYP1A2* gene. A common single nucleotide polymorphism (SNP), rs762551, classifies individuals as “fast” or “slow” caffeine metabolizers, potentially modifying the health effects of coffee and explaining inconsistencies in epidemiological findings (Sachse et al., 1999; Nehlig, 2018).

Methods:
This review summarizes evidence from human case–control, cohort, and experimental studies that have assessed the interaction between *CYP1A2* genotype and habitual coffee consumption. Studies examining outcomes such as myocardial infarction, hypertension, and acute blood pressure response were reviewed to evaluate gene – environment interactions and their clinical relevance.

Results:
Approximately 41% of the population are rapid caffeine metabolizers, while the remainder carry one or two non-functional *CYP1A2 *1F* (C allele) variants associated with slower caffeine clearance and prolonged physiological effects (Sachse et al., 1999; Palatini et al., 2009). Epidemiological studies consistently show that heavy coffee consumption increases cardiovascular risk, specifically among slow metabolizers. In a large case–control study, individuals consuming ≥4 cups/day had 64% higher odds of myocardial infarction (MI), whereas no increased MI risk was observed in rapid metabolizers (Cornelis et al., 2006). Similarly, a prospective cohort study found that slow metabolizers consuming >3 cups/day had nearly triple the risk of hypertension, while fast metabolizers showed a protective effect (hazard ratio 0.36, P = 0.026) (Palatini et al., 2009). Guessous et al. (2012) added further evidence: in non-smokers, fast metabolizers not only consumed more caffeine but also demonstrated lower blood pressure and reduced risk of hypertension.Mechanistic studies further support these findings: slow metabolizers exhibit greater acute blood pressure increases and elevated epinephrine levels after caffeine intake, indicating heightened cardiovascular reactivity (Soares et al., 2018; Yoshihara et al., 2019), whereas fast metabolizers appear less susceptible to these effects, particularly with habitual consumption.

Discussion:
These findings indicate that *CYP1A2* genotype plays a significant role in determining individual responses to coffee. While rapid metabolizers can benefit from coffee's antioxidant effects without adverse cardiovascular outcomes, slow metabolizers may be at increased risk when consuming moderate to high amounts of caffeine. The results from Guessous et al. (2012) strengthen this conclusion by showing that, at least in non-smokers, fast metabolizers actually experienced a protective cardiovascular profile linked to higher caffeine intake. Personalized dietary advice based on genetic profiling may be an effective strategy for optimizing health outcomes and preventing caffeine-related risks (Cornelis et al., 2006; Palatini et al., 2009).

Subjects Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Caffeine

INTRODUCTION

Coffee is consumed daily by billions of people and is one of the most complex dietary sources of bioactive compounds. Beyond being a global cultural staple, coffee is also a rich matrix of antioxidants, polyphenols, and diterpenes that have been associated with various health benefits. In observational studies, regular coffee consumption has been linked to lower all-cause mortality and reduced incidence of diseases such as type 2 diabetes, Parkinson's disease, and certain cancers (Bakuradze et al., 2010; Cornelis et al., 2006). However, the beverage's most active compound — caffeine — is also the most controversial, with reported benefits and harms depending on the dose and the individual.

Caffeine is a central nervous system stimulant that acts by antagonizing adenosine receptors, thereby promoting wakefulness and enhancing cognitive performance, but its physiological impact varies significantly across individuals. However, its pharmacological profile includes increasing heart rate and blood pressure, potentially triggering anxiety or insomnia in sensitive individuals (Mendoza et al., 2023). Such effects raise concerns about high coffee intake, particularly in genetically predisposed populations. Genetic polymorphisms, especially in the *CYP1A2* gene, have been increasingly studied to understand the basis of this interindividual variability.

The *CYP1A2* Gene and Caffeine Metabolism

The *CYP1A2* gene encodes the cytochrome P450 1A2 enzyme, a liver enzyme responsible for metabolizing over 90% of ingested caffeine. A common single nucleotide polymorphism (SNP), -163C>A (rs762551), leads to substantial differences in enzymatic activity. Individuals with the AA genotype (*1A/*1A) are considered rapid metabolizers, while those carrying at least one C allele (*1F carriers) are classified as slow metabolizers (Sachse et al., 1999; Nehlig, 2018).

This distinction in metabolism significantly influences how long caffeine remains active in the body. Rapid metabolizers can clear caffeine efficiently, minimizing its adverse physiological effects. In contrast, slow metabolizers experience prolonged caffeine exposure, which may increase the risk of negative outcomes such as insomnia, anxiety, and cardiovascular events. Genotype frequencies vary across populations, but approximately 41% are rapid metabolizers, 43% are intermediate, and 16% are slow metabolizers (Sachse et al., 1999).

The identification of these genotypes allows for more targeted health advice regarding coffee consumption and underscores the potential of nutrigenomics in personalized medicine.

Coffee Consumption and Cardiovascular Risk

Myocardial Infarction Risk

Cornelis et al. conducted a landmark case–control study in Costa Rica involving over 4,000 participants and found a significant interaction between *CYP1A2* genotype and coffee intake (Cornelis et al., 2006).

Among individuals with the slow metabolizer genotype (at least one C allele, approximately 60% of that population), drinking large amounts of coffee was associated with significantly higher odds of having an MI. Specifically, slow metabolizers who drank four or more cups of coffee per day had a 1.64 - fold higher odds of MI compared to those drinking less than one cup per day (OR 1.64) (Cornelis et al., 2006). There was a clear dose-response trend: even 2–3 cups per day carried a moderately elevated risk (OR ~1.36) in slow metabolizers (Cornelis et al., 2006).

In contrast, for individuals with the fast metabolizer genotype (A/A homozygotes), high coffee intake was not associated with increased MI risk. In fact, fast metabolizers showed a trend towards lower MI risk with moderate coffee consumption: for example, 1–3 cups/day in fast metabolizers were associated with an approximately 25–45% reduced risk of MI (Cornelis et al., 2006), suggesting a potential protective effect of coffee in that genotype. These differences were statistically significant, indicating that the impact of coffee on MI risk was dependent on the *CYP1A2* genotype.

These findings suggest that prolonged caffeine exposure in genetically slow metabolizers may counteract the protective effects of coffee's antioxidants, potentially leading to vasoconstriction, increased blood pressure, and elevated sympathetic activity — all known contributors to myocardial infarction.

Hypertension

Hypertension represents another well-documented area of concern for slow metabolizers. In the HARVEST study, Palatini et al. followed young Italian adults over 12 years and found that slow metabolizers who consumed at least three cups of coffee daily had nearly a threefold increased risk of developing hypertension (OR = 2.97) (Palatini et al., 2009). In contrast, rapid metabolizers showed no increased risk; some even had a slightly reduced likelihood of developing high blood pressure. Guessous et al. (2012) confirmed this pattern with nuance: among non-smokers, fast metabolizers consuming more caffeine exhibited significantly lower blood pressure and lower hypertension risk compared to slow metabolizers, while smokers showed no genotype effect. These results underline the importance of considering genetic background in evaluating dietary risk factors and reinforce the role of *CYP1A2* genotype in cardiovascular risk modulation.

Experimental Studies on Caffeine Response

Experimental trials have also shed light on how *CYP1A2* genotype affects physiological responses to caffeine. In a controlled study by Soares et al., participants with slow-metabolizing genotypes exhibited greater elevations in systolic blood pressure following

caffeine ingestion compared to rapid metabolizers (Soares et al., 2018; Yoshihara et al., 2019). Additional studies have shown prolonged heart rate recovery (Thomas et al., 2017) and reduced exercise benefits (Guest et al., 2018) in slow metabolizers.

Interestingly, these effects were moderated by habitual caffeine consumption and physical activity status. Individuals who were physically inactive or non-habitual caffeine users demonstrated the strongest blood pressure responses, reinforcing the complex interplay between genetics, lifestyle, and dietary exposure (Djordjevic et al., 2010).

These findings provide biological plausibility for the epidemiological associations and further support the relevance of *CYP1A2* in modulating cardiovascular outcomes linked to caffeine.

Clinical Implications of Impaired Caffeine Metabolism

Individuals with slow *CYP1A2* activity are at risk of not only cardiovascular events but a wider range of health issues. Prolonged caffeine exposure has been associated with increased risks of anxiety, insomnia, and panic attacks in sensitive individuals (Nehlig, 2018). There is also evidence linking slow caffeine metabolism to reduced bone mineral density, particularly in postmenopausal women, likely due to caffeine's effects on calcium excretion (Bae et al., 2014).

CYP1A2 genotype plays a meaningful role in individual responses to caffeine, particularly in cardiovascular health. Slow metabolizers (*CYP1A2*1F* allele carriers) clear caffeine more slowly and are more likely to experience adverse effects such as increased blood pressure or heightened myocardial infarction risk with high intake (>3–4 cups/day) (Cornelis et al., 2006; Palatini et al., 2009). For these individuals, clinicians may advise limiting caffeine to <200 mg/day and avoiding intake later in the day to support blood pressure control and sleep quality.

Fast metabolizers (*CYP1A2 *1A/*1A*) appear less affected by caffeine's pressor effects and may safely consume moderate to high amounts without increased cardiovascular risk—possibly even gaining protective benefits from coffee's other compounds. Genetic testing may help guide personalized dietary advice (Palatini et al., 2009; Bakuradze et al., 2010; Guessous et al., 2012).

Table 1: Prominent Human Studies on Caffeine Metabolism and *CYP1A2* Genotype

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s) Investigated	Primary Outcome/Key Findings
Cornelis et al., 2006	Case–control	~4,000 total (MI cases + matched controls), Costa Rica	*CYP1A2* rs762551 (−163C>A)	High coffee associated with ↑ MI risk in slow metabolizers; no increase in fast metabolizers (Cornelis, 2006).
Palatini et al., 2009	Prospective cohort	553 young adults with stage-1 HTN risk; ~8y follow-up, Italy	*CYP1A2* rs762551 (−163C>A)	Heavy coffee predicted ↑ incident hypertension in slow metabolizers; neutral/possibly protective in fast metabolizers (Palatini, 2009).

Soares et al., 2018	Experimental trial	Brazil, 37 healthy adults, stratified by physical activity and caffeine use	*CYP1A2* rs762551 (–163C>A)	Slow metabolizers had larger blood pressure increases after caffeine, especially sedentary or low habitual users.
Djordjević et al., 2010	Cross-sectional (enzyme activity)	Healthy non-smokers (Serbia + Sweden)	*CYP1A2* rs762551 (–163C>A)	Coffee-induced *CYP1A2* activity was stronger in AA; C-allele showed weaker inducibility (Djordjević, 2010).
Guessous et al., 2012	Cohorts + Mendelian randomization	4 European cohorts (total n≈16,700), smokers vs non-smokers	*CYP1A2* rs762551 (+ other variants)	In non-smokers, genotype linked to BP/HTN patterns consistent with caffeine–metabolism effects; no clear association in smokers (Guessous, 2012).
Denden et al., 2016	Meta-analysis	12 studies (heavy vs low caffeine consumers)	*CYP1A2* rs762551	AA genotype modestly associated with higher coffee/caffeine consumption (Denden, 2016).
Zhou & Hyppönen, 2019	Prospective cohort	UK Biobank (n≈347,000; ~8,368 CVD cases)	*CYP1A2* rs762551	Coffee intake associated with CVD risk, but no *CYP1A2* × coffee interaction detected for CVD outcomes (Zhou, 2019).
Yoshihara et al., 2019	Double-blind RCT	201 healthy adults, Japan	*CYP1A2* rs762551 (+ ADORA2A)	Caffeine acutely ↑ BP; larger BP rise in slow metabolizers, especially with low habitual intake (Yoshihara, 2019).

CONCLUSION

The relationship between coffee consumption and cardiovascular health is complex and significantly influenced by genetic variation in caffeine metabolism, particularly in the *CYP1A2* gene. Slow metabolizers (*CYP1A2*1F* carriers) experience prolonged caffeine exposure, which increases their risk for adverse outcomes such as hypertension, myocardial infarction, sleep disturbances, and possibly reproductive or skeletal issues — even at moderate intake levels. In contrast, fast metabolizers clear caffeine more efficiently and tend to tolerate it well, often benefiting from coffee's antioxidant and metabolic effects without added cardiovascular risk, even protective effects were shown.

Epidemiological and experimental studies (e.g., Cornelis et al., 2006; Palatini et al., 2009; Soares et al., 2018) consistently show that caffeine's effects are not uniform across the population. This gene–diet interaction helps explain inconsistent findings on coffee and heart health and highlights the need for more personalized guidance.

Understanding one's *CYP1A2* genotype can inform safer caffeine consumption. This emerging field of nutrigenetics holds substantial promises for tailoring everyday nutritional choices to our genetic makeup — turning routine habits like drinking coffee into data-driven, individualized health strategies.

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