CHAPTER 3.4

Preventive Effect of Coffee Against Cardiovascular Diseases

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3.4.1. Introduction

Coffee is the most widely consumed beverage after water¹, with over 2 billion cups consumed every day mainly in industrialized countries. Annual per capita consumption of coffee has been estimated in over 4 kg in the United States and 5 kg on average in Europe, with consumptions even higher than 10 kg per capita in Nordic countries like Finland, Norway, or Denmark. That can be translated in a daily intake of coffee ranging from 1 to 3 cups on average per person. Any food with such high and widespread consumption may have an important impact on health, either detrimental or positive, and the study of such potential effects becomes an issue of public health interest.

Coffee is mostly consumed for its organoleptic properties, with a unique aroma and taste, and for its stimulatory effects, mostly attributed to its high caffeine content, with important effects on alertness and enhancing performance. Also, in consumers' lifestyle habits, social practices surrounding coffee consumption (at work coffee-break, after-meals coffee, etc.) are important factors in the daily intake of this beverage. However, coffee is also one of the most commonly restrained beverages. It is still very common to limit or totally ban the intake of coffee to patients suffering from hypertension, arrhythmia or other kind of cardiovascular condition, since caffeinated coffee has traditionally been considered harmful. Actually, a scientific report from the American Heart Association (AHA) published in 2008² stated that coffee might increase the risk of heart failure based on the findings from an observational study by Wilhelmsen et al.³ reporting an increased risk of hospitalization or death from heart failure among men consuming 5 or more cups of coffee per day. However, this study did not adjust for potential confounders. Subsequent studies have shown no deleterious effects of coffee consumption⁴⁻⁵ or even a protective action against incidence of heart failure and stroke.⁶⁻⁷ In the most recent guidelines for the management of heart failure released by the AHA⁸ there is no recommendation on coffee

withdrawal. Indeed, the AHA states that moderate coffee drinking does not seem to be harmful, although advising on limiting the amount of caffeine to a cup or two of coffee per day.⁹

This chapter will review evidences from epidemiological and intervention studies on the effect of coffee on cardiovascular diseases, discussing the role and mechanisms of action of the most relevant phytochemicals in coffee with the aim to shed light on the still controversial effects of coffee on cardiovascular health.

3.4.2. Coffee and Cardiovascular Diseases. Findings from Epidemiological Studies

Cardiovascular diseases (CVDs) include a wide spectrum of pathologies affecting the heart and the vascular system, like ischemic heart disease (IHD), coronary heart disease (CHD), cerebrovascular diseases (e.g. stroke), peripheral vascular disease (PVD), hypertension, as well as arrhythmias, cardiomyopathies, heart failure (also known as congestive heart failure), and congenital and rheumatic heart diseases.¹⁰ Atherosclerosis and hypertension are the underlying cause of many of these pathologies; other diseases like diabetes, obesity, metabolic syndrome, chronic inflammation, etc. are important risk factors for the development or progression of cardiovascular pathologies. CVDs are the main chronic or non-communicable diseases (NCDs), and ischemic heart disease and cerebrovascular disease list as the leading causes of death in adults in the world, irrespectively of gender, in both high- and middle/low-income countries.¹¹ Considering the global burden of CVDs and the widespread consumption of coffee, any potential effect of this beverage on cardiovascular health would have a sizable public health impact.

In epidemiological studies, case-control studies have consistently found a positive association between coffee consumption and coronary risk. An early meta-analysis performed in 1993 by Greenland¹² of eight case-control studies on the effect of coffee on myocardial infarction (MI) and coronary death found an increased risk for intake of 5 cups per day compared to no coffee

consumption (geometric mean rate ratio 1.42, 95% confidence interval (CI) 1.30-1.55) (Table 3.4.1). One year later, Kawachi et al.¹³ in a meta-analysis of eight case-control studies on CHD risk reported a pooled odds ratio (OR) for the effect of drinking 5 cups of coffee per day vs. no coffee of 1.63 (see Table 3.4.1 for details), confirming the increased risk of CHD. More recently, a meta-analysis of thirteen case-control studies¹⁴ showed a statistically significant ($P < 0.0001$) association between CHD and high (more than 4 cups/day, OR 1.83) and moderate (3-4 cups/day, OR 1.33) intake of coffee when compared with no coffee consumption, while there was no association with low daily coffee intake (≤ 2 cups/day, OR 1.03; $P=0.45$). Attending to results from case-control studies, the obvious conclusion should be that coffee, even in moderate amounts, increases the risk of cardiovascular pathologies.

[Table 3.4.1. near here]

On the contrary, except for the previously mentioned study by Wilhelmsen et al.³ and few others where confounders like smoking, alcohol intake, etc. had not been corrected for, most prospective cohort studies have systematically shown no association of coffee drinking with CVDs risk, with several observations showing a preventive effect on diverse cardiovascular pathologies. The early studies mentioned above, when performing meta-analysis of long-term follow-up prospective studies, found no association between coffee intake and myocardial infarction or CHD risk,¹²⁻¹⁴ with pooled relative risk (RR) values ranging from 1.05 to 1.16 (Table 3.4.1). An earlier meta-analysis of eleven cohort studies found that coffee intake (1 to 4 cups per day) was not associated with increased CHD occurrence compared with low (≤ 1 cup/day) intake (OR 1.01, 95% CI 0.93-1.11) even in the absence of adjustment for coronary risk factors.¹⁵ Sofi et al.¹⁴ separately examined the effect of decaffeinated coffee in four case-control and three cohort studies and found no increased risk on CHD even with high intakes of decaffeinated coffee (> 4 cups per day) (Table 3.4.1). Furthermore, in a meta-analysis of 21 prospective cohort studies testing for CHD risk, Wu et al.¹⁶ found a pooled RR between 0.96 and 1.07 for moderate

to very heavy consumption of coffee compared to light coffee intake, showing no association of coffee consumption and increased risk of CHD (Table 3.4.1). Interestingly, these authors reported a significantly lower long-term risk of CHD in women consuming moderate amounts of coffee (considered as 1-3 cups/day in US or 3-4 cups/day in Europe, RR 0.82), pointing to a protective effect of this beverage.

There are several reasons that might explain the conflicting findings from case-control and cohort studies. Case-control studies are particularly susceptible to recall bias, especially among the case subjects; while incident cases (i.e. newly diagnosed) are more likely to over-report exposure than healthy controls, prevalent cases (i.e. individuals suffering from the condition under study for certain time) are more prone to report past exposure less accurately. On the other hand, unlike prospective cohort studies, case-control observations do not include fatal events, which is another important source of difference in outcomes from both types of observational epidemiological studies as discussed by Sofi et al.¹⁴

Similarly to CHD, drinking coffee seems to be inversely associated with other CVDs. In a dose-response meta-analysis of prospective studies assessing the association between coffee intake and the risk of heart failure, Mostofsky et al.⁷ reported a statistically significant non-linear association. A “J-shaped” relationship was found, with moderate intakes resulting in smaller RR values than lower or higher consumptions (Table 3.4.1). These authors suggested that moderate intake of coffee (4 cups per day) might protect against heart failure. Similarly, in a large cohort of healthy women participating in the Women’s Health Study, after a median follow-up of 14.4 y, elevated caffeine intake (from coffee, tea, cola, and chocolate) was not associated with an increased risk of atrial fibrillation, with multivariable-adjusted hazard ratios (HR) varying between 1.0 and 0.78 (P for trend = 0.45).¹⁷

In the same way, a “U-shaped” relationship was observed when conducting a dose-response meta-analysis of prospective studies assessing the effect of drinking coffee and the risk of

stroke.¹⁸ The lowest RR (0.83, 95% CI 0.74-0.92) was observed with moderate coffee consumption (3-4 servings per day) (Table 3.4.1). Although weakly, moderate consumption (4 cups per day) also showed to be inversely associated with the risk of stroke in the European population, with a RR of ischemic stroke occurrence of 0.80 (95% CI 0.71-0.90).¹⁹ This protective effect was also seen when analyzing separately women (RR 0.81, 95% CI 0.70-0.93), but not men and women together (RR 1.02, 95% CI 0.83-1.26).¹⁹

Taken together all these findings, cohort studies support an inverse association between moderate coffee intake and the risk of CHD, heart failure and stroke. This was confirmed in a recent systematic review and dose-response meta-analysis of the long-term effect of coffee consumption on CVD risk.²⁰ The analysis of 36 prospective cohort studies including 36 352 CVD cases and 1 279 804 participants showed a statistically significant non-linear relationship of coffee with risk of CVDs (Table 3.4.1). The lowest CVD risk was observed with moderate consumption of 3 to 5 cups of coffee per day (RR 0.85, 95% CI 0.80-0.90), while daily heavy coffee intake (more than 5 servings) was not associated with increased risk. Separately, stratified analysis according to different factors also showed a non-linear association with CHD and stroke risks, and interestingly a slightly lower risk of CVD in elder subjects compared to younger individuals, RR 0.91 (0.59-1.40) for age ≥ 65 y and 0.96 (0.65-1.42) for age < 65 y.²⁰

When looking at the association of coffee intake with mortality, prospective studies have also shown that coffee drinkers, as compared with non-drinkers, had lower HR for overall mortality and for cause-specific mortality due to CVD, CHD, and stroke (Table 3.4.1).²¹⁻²⁴ The lowest HR of death due to CVD was obtained for moderate consumption of 1-3 cups per day in postmenopausal women in the Iowa Women's Health Study (HR 0.76, 95% CI 0.64-0.91),²¹ with similar values for death from heart disease (HR 0.75, 95% CI 0.63-0.90) and stroke (HR 0.77 95% CI 0.54-1.10) for coffee intakes $\geq$ in the cohort study reported by Loftfield et al.²⁴ (Table 3.4.1). These authors reported a low hazard ratio for all-cause mortality with high intakes of coffee (4-

5 cups per day, HR 0.79, 95% CI 0.72-0.86). Outcomes from a meta-analysis of prospective studies on coffee consumption and mortality also found a 12% lower risk (pooled HR 0.88, 95% CI 0.84-0.93) of all-cause death for subjects consuming coffee as compared to non-consumers, with HR for CVD mortality of 0.89 (95% CI 0.77-1.02) and weak inverse association for death from CHD/IHD and stroke in individuals drinking coffee (Table 3.4.1).²³

In summary, observational studies yield conflicting results on the effect of coffee consumption and the risk of CVDs, since case-control studies tend to show an increased risk with coffee intake and contrarily, evidences from prospective cohort studies consistently show no risk of heavy coffee consumption on CVDs. The non-linear relationship seen in cohort studies reveals that long-term consumption of moderate amounts of coffee is associated with a lower risk of CHD, heart failure and stroke. This might easily lead to the conclusion that drinking reasonable amounts of coffee might protect from CVDs. However, this is not the case and we should avoid drawing such (possibly) erroneous conclusions. Observational studies are population-based surveys that provide information on the long-term effect of different doses of exposure (i.e. coffee intake) on selected outcomes, but they do not demonstrate causality. Well-designed and performed epidemiological studies allow for adjustment for confounders like smoking, alcohol intake, etc., and stratification by characteristics like gender, age, race, location, etc. Nonetheless, there are many other factors that cannot be strictly controlled, such as the type of coffee (i.e. Arabica or Robusta), brewing process (boiled, filtered, espresso, etc.), serving size, use of other ingredients or additives (i.e. milk, cream, sugar, sweeteners), etc. which add variability to the results. Also, dietary and lifestyle habits of participants can have an important impact on other CVDs risk factors.

On the other hand, it is also relevant considering possible differences on the effect of coffee on subjects with pre-existing CVDs or other pathologies known to increase CVD risk like diabetes mellitus. Initial studies on the effect of coffee intake in MI patients found no association with

overall long-term post-infarction cardiac mortality rate (adjusted HR 0.88, 95% CI 0.54-1.44)²⁵ and inverse association with total mortality, with HR 0.56 (95% CI 0.37-0.85) for moderate consumption of 1 to 3 cups per day and even lower HR 0.52 (95% CI 0.34-0.83) for higher intakes (5-7 cups per day).²⁶ A lack of association with total and CVD mortality was also reported in a cohort of participants with previous CVDs within 2-year periods of follow-up or even longer [HR varying between 1.01 and 1.18 for total mortality (P for trend = 0.91), and 0.97 and 1.25 for CVD mortality (P for trend = 0.76) depending on the dose],²⁷ as well as in a cohort of patients with recent MI (RR between 0.88-1.02 depending on the dose, P for trend = 0.18), with no association with coronary or cerebrovascular events or sudden death.²⁸ These findings suggest that moderate coffee consumption may be considered of no major health concern for patients with myocardial infarction or other cardiovascular conditions.

Although there are many randomized trials and observational and cross-sectional studies consistently showing a strong association between coffee intake and reduced risk of type 2 diabetes (for review see [chapter XX](#) and ²⁹), knowledge on the effect of coffee on individuals at high risk or with established diabetes are still scarce. In a prospective study in patients with impaired glucose tolerance, the risk of diabetes was much lower in coffee drinkers compared to abstainers (RR 0.36, 95% CI 0.16-0.83), confirming a strong protective effect of caffeinated coffee against incident diabetes.³⁰ Richardson et al.³¹ observed that moderate caffeine intake (equivalent to 2-3 cups of coffee) improved autonomic function and heart rate variability in type 1 diabetic patients, concluding that regular caffeine in doses resembling average coffee intake might potentially reduce the risk for cardiovascular events.

Most studies have been performed in adults from Western countries, and therefore more research is still needed on different populations (elderly, non-Caucasians, patients or individuals at risk of other CVDs, etc.). Meanwhile, in spite of the amounting evidences showing no deleterious effect of coffee intake on CVD risk, care has to be taken when giving

recommendations on the intake of a beverage with such potential impact on the population health, especially for at risk persons. Further information can be found in recent reviews of epidemiological studies on the effect of coffee on CVD risk.³²⁻³⁴

3.4.3. Coffee Phytochemicals and Cardiovascular Risk

To understand the effect of coffee on CVD risk factors it is important bearing in mind the complex composition and variability of this beverage. As already stated in previous chapters, coffee contains a large range of nutrients (mainly micronutrients such as vitamin B3, magnesium, potassium) and phytochemicals. Coffee is the main dietary source of caffeine and hydroxycinnamic acids (chlorogenic acids) and a major contributor of soluble dietary fiber and melanoidins. It also contains minor amounts of other compounds with relevant effects on CVDs, such as diterpenoids cafestol and kahweol, or trigonelline, a precursor of niacin with potential therapeutic effects in diabetes. These phytochemicals are extensively covered in other chapters of this book; here we summarize only the basic aspects of the phytochemicals most influential in relation with CVDs to better understand their mechanisms of action on cardiovascular risk factors.

[Table 3.4.2. near here]

3.4.3.1. Caffeine

Caffeine (1,3,7-trimethylxanthine) is by large considered as the main bioactive compound in coffee, although it is not the most abundant phytochemical in the beverage. Caffeine vary from 0.9 to 1.3% in Arabica beans and 1.5 to 2.5% in Robusta,³⁵ with typical contents between 50 to 100 mg per serving³⁶ although espresso coffees have higher concentrations (between 135-620 mg/100 mL espresso coffee)^{36,37} (Table 3.4.2).

Caffeine is rapidly absorbed from the stomach and small intestine and extensively metabolized mostly in the liver by the cytochrome P450 isoform CYP1A2 to other dimethylxanthines (mostly paraxanthine) and monomethylxanthines and methyluric acids. Caffeine and its metabolites are distributed throughout the body, including the brain. Plasma concentrations of caffeine in the range of 10-12 μM have been reported within 1 h after consumption of a single regular coffee serving.^{38,39}

Pharmacological activities of caffeine include inhibition of cyclic nucleotide phosphodiesterases, 5'-nucleotidase, alkaline phosphatase, release of intracellular calcium, etc. although millimolar concentrations of this xanthine are required to achieve these effects.⁴⁰ At physiological concentrations attained after normal coffee consumption, the main activity of caffeine is related to its binding to adenosine receptors A_1 and A_{2A} .⁴⁰ Adenosine is an endogenous neuromodulator with mostly inhibitory effects, and adenosine receptors are found in most tissues, including the brain, heart, kidney, smooth muscle, skeletal muscle, adipose tissue, etc. Therefore, the antagonizing effect of caffeine on these receptors explains the general stimulatory actions of caffeine in the central nervous system, increasing perception and alertness, but also in other systems increasing metabolic rate, energy expenditure, lipid oxidation, thermogenesis, diuresis, etc.^{36,40,41} Caffeine also acts on the adrenal medulla, increasing circulating levels of catecholamines (nor)epinephrine [(nor)adrenaline] that will activate sympathetic nervous system and elicit vasoconstriction via activation of vascular smooth muscle; in the adrenal cortex, stimulating the release of corticosteroids, that can affect vascular tone among many other effects; in the kidney, decreasing proximal tubular sodium reabsorption and activating the renin-angiotensin-aldosterone system, causing diuresis, natriuresis and vasoconstriction; in the vascular bed, inducing vasoconstriction, etc. All these actions are subjacent to the well-recognized pressor effect of caffeine increasing blood pressure.

However, there are large interindividual variations in the response to caffeine, in part due to genetic polymorphisms in CYP1A2 resulting in different velocities of caffeine metabolism and therefore shorter or longer times of exposure to high circulating levels of caffeine.⁴² Individuals with the *CYP1A2**1F variant (an A→C variant at position 734) are slow metabolizers, while those with the wild *A2**1A allele are fast metabolizers.⁴² It has been reported that the *A2**1A variant protects from hypertension.⁴³ Also, acute vs. long-term effects of caffeine differ,⁴¹ since habitual consumers quickly develop tolerance to the pressor effect of caffeine,⁴⁴ as will be discussed later in this chapter.

3.4.3.2. Polyphenols

Coffee is rich in phenolic compounds, mainly hydroxycinnamic acids (generically known as chlorogenic acids, CGAs), with minor amounts of other polyphenols like tannins, anthocyanins or lignans. Major CGAs in green coffee beans are esters of quinic acid with caffeic acid (mono- and dicaffeoylquinic acids, predominating 5-caffeoylquinic acid or chlorogenic acid) and ferulic acid, and minor quantities of free caffeic and ferulic acids, as well as cinnamoylquinic acids, cinnamic acid and its glycosides and amides.⁴⁵ Polyphenol content is usually higher in Robusta than in Arabica coffees, amounting to up to 10% of the dry weight in the green bean. However, CGAs are drastically lost during roasting, with reductions of over 50% of the initial phenolic content^{35,46,47} (Table 3.4.2). CGAs undergo isomerization and transformation into lactones during roasting,^{46,47} molecules with potentially different biological activities than the precursor CGAs in the green bean. Still, the coffee beverage is the major source of these hydroxycinnamates in the human diet, with nearly 400 mg CGAs in an average 180 mL cup of brewed coffee, varying from 24 to 423 mg in a single serving of espresso coffee.³⁷ It has been estimated that regular coffee intake can provide 1-2 g of CGAs per day.³⁷

Unlike caffeine, polyphenols are in general poorly bioavailable. It has been estimated that only around 30% of the ingested CGAs are absorbed in the upper gastrointestinal tract, being

hydrolyzed by intestinal esterases into free caffeic/ferulic and quinic acids and, together with non-hydrolyzed CGAs, conjugated by phase II metabolizing enzymes into methylated, sulfated and/or glucuronidated metabolites. Maximum plasma concentrations of these metabolites appear between 1-3 h of coffee intake in nM concentrations^{48,49} although μ M levels have also been reported.^{50,51} Polyphenols not absorbed in the small intestine reach the colon, where they are reduced and further metabolized by the intestinal microbiota, absorbed through the colonic epithelium and conjugated by phase II enzymes. These colonic metabolites appear in plasma at longer times after coffee consumption (5-9 h) in higher concentrations, yet also in nM-low μ M range.⁴⁹⁻⁵²

Initially, the biological actions of polyphenols, including CGAs, were mostly associated to their strong antioxidant activity, scoring highest among dietary components in terms of reducing power or free-radical scavenging activities and thus protecting macromolecules from oxidative damage.⁵³ However, polyphenols are highly bioactive compounds that also act modulating many biological processes like gene expression, DNA methylation, cell proliferation, acting through different cell signaling pathways, regulating levels and activity of transcription factors, cell membrane receptors, enzymes levels and activities, expression of cytokines and chemokines, etc.⁵³⁻⁵⁶ Hundreds of studies have been performed on the beneficial effects of phenolic compounds in health, protecting from chronic and degenerative diseases like CVDs, type 2 diabetes mellitus, cancer, obesity, inflammation, neurodegeneration, etc. (for review see⁵³⁻⁶⁰ and references therein).

3.4.3.3. Diterpenes

The diterpenes cafestol and kahweol are minor components of the lipid fraction of the green coffee bean. Estimated contents in coffee brews vary between 0.1-7 mg cafestol/100 mL and 0.1-10 kahweol mg/100 mL⁶¹ (Table 3.4.2). The large variability in diterpene content depends not only on the coffee bean variety, with higher amounts in Arabica beans than in Robusta, but

also on the brewing method. Diterpenes are almost completely removed by filtering and also during instant coffee processing, while boiled, unfiltered coffees like Scandinavian, Turkish or French press beverages retain most cafestol and kahweol.⁶²

These compounds are highly bioavailable in the upper gastrointestinal tract.⁶³ They are mostly considered harmful compounds, since the cholesterol-raising effect of coffee has been associated to their intake in boiled coffee,⁶⁴ increasing the synthesis of cholesterol by decreasing excretion of bile salts and neutral sterols, and modulating the activity of serum enzymes involved in lipoprotein metabolism.⁶⁵ Indeed, two different meta-analysis of randomized clinical trials have reported a positive dose-response relationship between intake of unfiltered coffee and increased levels of total and LDL-cholesterol and triglycerides.^{66,67}

However, recent studies have shown that kahweol possesses important pharmacological properties regulating bone metabolism,⁶⁸ with potential anticarcinogenic activity through its effects inhibiting angiogenesis,⁶⁹ and also exerting multiple anti-inflammatory effects,⁶⁹ regulating the expression of chemokines and cell adhesion molecules by endothelial cells,^{69,70} although its impact on vascular endothelial function in humans has not been determined yet.

3.4.3.4. Other components

During roasting important chemical and structural changes involving carbohydrates, proteins and phenolic compounds take place in the coffee bean, with the formation of polymeric, high molecular weight Maillard reaction products, the melanoidins. **Melanoidins** are absent in the green bean but depending on the degree of roasting they reach high levels in the roasted product, with concentrations between 0.25-0.81 g/100 mL of brewed dark coffee, and estimated consumptions of 0.5-2.0 g per day⁷¹ (Table 3.4.2). The complex structure of these advanced glycation end-products is still largely unknown.⁷² Similarly, although coffee melanoidins seem to be highly resistant to digestion in the gastrointestinal tract, there is no information on their bioavailability due to the complexity and variability of these structures.⁷³

Melanoidins are important contributors to the organoleptic properties of coffee (taste, foam stability, etc.), but recent studies are showing that they are also active phytochemicals, with potent antioxidant, anti-inflammatory, anti-microbial and chemopreventive properties.^{74,75} *In vitro* studies have shown that melanoidins might have anti-hypertensive activity via inhibition of the angiotensin-I converting enzyme,⁷⁴ although this has still to be shown in *in vivo* experiments.

When dealing with the coffee components with potential health effects, dietary fiber is usually overlooked in spite of its high content in brewed coffee. Indeed, coffee is a major contributor of **soluble dietary fiber** (SDF), with contents ranging between 0.14 and 0.75 g/100 mL, depending on the variety, brewing method, etc.^{76,77} Moderate coffee consumption (3-4 cups per day) may provide between 0.4 and 3.0 g of SDF (Table 3.4.2).

Polysaccharides in coffee SDF are mainly galactomannans and type II arabinogalactans.⁷⁷ Like all dietary fibers, the effect of SDF in coffee derives from the physicochemical properties of the non-digestible polysaccharides. Soluble fibers form viscous solutions in the gastrointestinal tract, delaying transit time and hindering the digestion and absorption of food nutrients and the reabsorption of bile salts. This positively affects glucose metabolism, reducing the risk of diabetes, also modulating lipid metabolism, reducing plasma lipid levels, regulating body weight and obesity, reducing chronic inflammation, etc., all of them important CVD risk factors. Besides, SDF is extensively fermented by the colonic microflora, with the formation of short chain fatty acids (acetic, propionic and butyric acids). Propionic acid is known to inhibit cholesterol synthesis, mediating the cholesterol-lowering effect of SDF (reviewed by Satija and Hu⁷⁸).

Evidences from many prospective cohort studies systematically show the benefits of dietary fiber reducing the risk of CVDs, CHD, stroke, etc.,⁷⁸⁻⁸¹ and reducing blood pressure in healthy and hypertensive subjects.⁸² However, to the best of our knowledge, the contribution of coffee to the SDF intake in these studies has not been taken into consideration. Bearing in mind that

coffee is an important source of SDF in our diet (it has been estimated a contribution close to 10% of the total SDF intake in Spain⁷⁶), the potential impact of coffee SDF on cardiovascular health should not be ignored.

Trigonelline (N-methylnicotinic acid) is a minor component in green beans (0.6-1% of the dry weight), with higher amounts in Arabic coffee.⁸³ During roasting it is partly degraded to nicotinic acid and other derivatives like the biologically active N-methylpyridinium. Final contents of trigonelline in the beverage depend on the processing and brewing methods, ranging between 40-110 mg serving^{35,83} (Table 3.4.2). There are no studies on the bioavailability of trigonelline in humans, although it has shown moderate intestinal absorption in animals.⁸³

Trigonelline has been reported to have neuroprotective and chemoprotective properties, as well as antioxidant activity.⁸³ In animal studies, it has shown to lower blood glucose and serum lipids, regulating hepatic lipid metabolism and fat accumulation in adipose tissue,^{83,84} thus modulating different CVD risk factors. In a randomized crossover trial, it showed to significantly reduce glucose and insulin concentrations during an oral glucose tolerance test,⁸⁵ although so far there are no clear evidences on its effect in CVD.

3.4.4. Coffee and Cardiovascular Disease Risk Factors

As mentioned previously, hypertensive and atherosclerotic diseases are intimately associated to increased risk of cardiovascular and cerebrovascular events, being themselves considered as CVDs. Therefore, it is important to study the effect of coffee on these risk factors to gain insight into the overall potential effects of this beverage on CVDs risk and its mechanisms of action. There are other pathologies that increase the risk of suffering from CVDs, such as diabetes mellitus or obesity; these are extensively covered in other chapters of this book, and therefore

this section will focus on the effect of coffee consumption on other risk factors like serum lipids, endothelial function or blood pressure.

3.4.4.1. Effects of coffee consumption on blood lipids

Hyperlipemia is an established risk for CVD. Specifically, the major and independent risk factors for CHD are cigarette smoking, elevated blood pressure, elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), low serum high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, and advancing age.⁸⁶ Therefore, the potential cholesterol-rising effect of coffee could have an important impact on CVD risk.

Early observational epidemiological studies on the effect of coffee consumption on serum cholesterol yielded conflicting results, with some cross-sectional studies showing a positive association of coffee intake with increased cholesterol levels while other studies found no association (reviewed by Ma et al.⁸⁷). Findings from comprehensive revisions of cross-sectional studies published between 1987 and 1990 reported a great variability, and pointed out the importance of the brewing method used in different populations.^{88,89}

Similarly, variability was also found in early randomized controlled trials (RCT). Fried et al.⁹⁰ reported increased TC, LDL-C and HDL-C in subjects consuming filtered caffeinated coffee. However, Superko et al.⁹¹ observed that changing from caffeinated to decaffeinated coffee increased plasma LDL-C and apolipoprotein B concentrations, while cessation of coffee consumption had no effect, concluding that a coffee component different from caffeine was responsible for the cholesterol-rising effect of coffee. In a RCT in healthy subjects, Bak and Grobbee⁹² found that TC and LDL-C were increased in healthy volunteers only when drinking boiled coffee, but not with filtered coffee. In a meta-analysis of fourteen RCT, Jee et al.⁶⁶ found a dose-response relationship between coffee consumption and serum cholesterol, with a net increase of 11.8 mg/dL for TC and 6.5 mg/dL for LDL-C (see Table 3.4.3 for details). In subgroup

analysis, these authors observed that increases in serum lipids were higher in hyperlipidemic patients, as well as in studies with caffeinated coffee, although in trials using a control group drinking decaffeinated coffee there was no effect of consuming regular coffee on serum cholesterol. Also, trials using filtered coffee showed little effect on serum lipids, while those with boiled coffee significantly increased serum cholesterol.⁶⁶ A more recent meta-analysis of twelve RTC also showed a significant contribution of unfiltered coffee to the increase in TC, LDL-C and triglycerides (TG). Drinking coffee was associated with an increase of 8.1, 5.4 and 12.6 mg/dL TC, LDL-C and TG, respectively (Table 3.4.3), with higher increase in studies using unfiltered coffee (TC 12.9 mg/dL, 95% CI 6.8-18.9; LDL-C 11.9 mg/dL, 95% CI 3.2-20.6; TG 18.8 mg/dL, 95% CI 4.8-32.7) compared with those using filtered coffee.⁶⁷ As in the previous meta-analysis, these authors also found higher susceptibility in hyperlipidemic patients and that caffeinated coffee had significant effects on serum lipids, but not decaffeinated coffee.⁶⁷

[Table 3.4.3 near here]

Taking together these findings, there is consistent evidence on the fact that drinking boiled, unfiltered coffee is associated with increased serum cholesterol, although the effect of caffeine seems contradictory. On most cross-sectional epidemiological studies on the effect of caffeine on serum lipids, increased serum cholesterol levels are observed only when caffeine intake comes from coffee but not from other dietary sources like tea or cola drinks,⁸⁷ again pointing to a different coffee component as responsible for the hypercholesterolemic effect. Robusta coffee, richer in polyphenols and with lower diterpene content than Arabica beans (Table 3.4.2), is less favored than Arabica for the superior flavor quality of the latter.⁹³ Therefore, decaffeinated coffees use Robusta beans more extensively and thus they have lower diterpene content.^{61,64}

As seen above, coffee diterpenes can increase the synthesis of cholesterol by decreasing excretion of bile salts and neutral sterols, and modulating the activity levels of enzymes involved

in lipoprotein metabolism.^{64,65} It has been reported that short-term as well as long-term consumption of coffee diterpenes modulates the activity of serum enzymes involved in lipoprotein metabolism, increasing the activity levels of cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP), and decreasing lecithin:cholesterol acyltransferase (LCAT).⁶⁵ Coffee diterpenes are extensively extracted from the coffee grounds during the long times normally used to prepare boiled coffee (up to 10 min.) while methods based on filtration usually require shorter times (less than 2 min.);^{62,64} besides, coffee lipids will be largely retained in paper filter (up to 80%), resulting in much lower concentrations of diterpenes in filtered brews.⁹⁴

To confirm the implication of diterpenes in the cholesterol-increasing effect of boiled coffee, Weusten-Van et al.⁹⁵ carried out a study in volunteers that received the non-TG fraction from coffee oil, a coffee without the non-TG diterpenes or placebo, observing that only the non-TG fraction had a significant effect increasing cholesterol (48 mg/dL relative to placebo). On the other hand, cholesterol levels also increased in volunteers that received cafestol plus kahweol, and when ingesting oil from Robusta coffee beans (that contains cafestol but little kahweol, Table 3.4.2), concluding that cafestol and possible kahweol are responsible for the cholesterol-raising effect of coffee.⁹⁵

In summary, the conflicting results from observational and intervention studies may be explained by the differences in the brewing method used to prepare coffee and point to diterpenes as the compounds responsible for the deleterious effect of coffee on serum cholesterol. Therefore, consuming filtered coffee could be considered as safe, but again generalized recommendations cannot be made. As mentioned above, hyperlipemic subjects seem to be more susceptible to the cholesterol-rising effect of coffee.^{63,67} Also, not all filtering methods are equally effective, and some filtered coffees can have high diterpene concentrations as seen by Strandhagen and Thelle,⁹⁶ and more recently in a study that reported increased

plasma TC, LDL-C and HDL-C, as well as increased levels of endothelial dysfunction-related biomarkers in a randomized clinical trial in healthy volunteers consuming paper-filtered coffee.⁹⁷

On the other hand, the effect of coffee on serum lipids is not limited to the influence of diterpenes on cholesterol levels. In an intervention study in healthy subjects, daily drinking 800 mL of an instant coffee rich in chlorogenic acids for 5 days (1200 mg/d CGAs) significantly reduced the urinary excretion of F2-isoprostane, a biomarker of lipid oxidation, and increased total plasma antioxidant capacity, also slightly reducing plasma levels of oxidized LDL and malondialdehyde, another biomarker of lipid oxidation.⁹⁸ These results were not replicated in a longer intervention, where daily drinking up to 900 mL of filtered coffee for 3 weeks had no effect on plasma lipid oxidation.⁹⁹ However, the amount of CGAs consumed was lower in this trial (728 mg/d), which point to the importance of these phenolic antioxidants on the observed effects of coffee reducing lipid peroxidation. Lower isoprostane urinary levels were also observed in a clinical trial in mild-hypertensive subjects consuming for 8 week a coffee beverage providing 300 mg/d CGAs, but with reduced content of hydroxyhydroquinone (HHQ),¹⁰⁰ a quinone formed during coffee roasting reported to inhibit the effect of CGAs.¹⁰¹

Similarly, a higher resistance of LDL lipoproteins to oxidation has also been reported after acute¹⁰² and short-term (5-7 days)^{98,103} consumption of coffee by healthy volunteers. Natella et al. showed that polyphenols are incorporated into LDL particles after drinking 1 cup of coffee, which could explain the lower susceptibility of LDL to oxidation.¹⁰² Oxidized LDL (oxLDL) play a crucial role in the development of atherosclerosis, since they accumulate in the arterial intima, stimulating endothelial and smooth muscle cells to express cell adhesion molecules [vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1)], growth factors [granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF)], chemoattractants (monocyte chemoattractant protein-1, MCP-1), recruiting monocytes and macrophages. These immune cells phagocyte oxLDL and are

transformed into foam cells, secreting pro-inflammatory cytokines [like interleukin-1 (IL-1), IL-6, tumor necrosis factor- α (TNF α), etc.], enzymes like myeloperoxidase, matrix metalloproteinases (MMPs), reactive oxygen species (ROS), and other mediators like cathepsins, plasminogen activators, etc., thus mediating oxidative stress and inflammation, key processes in the initiation and progression of atherosclerosis.¹⁰⁴

Therefore, coffee could have a role decreasing lipid oxidation and levels of oxLDL, which would be of benefit in the management of CVDs risk. CGAs and coffee polyphenols can also hinder intestinal fat absorption through inhibition of pancreatic lipase,¹⁰⁵ reduce hepatic accumulation of cholesterol and TG,¹⁰⁶ and modulate lipid metabolism through induction/inhibition of the expression and activity of different enzymes involved in lipogenesis and lipid β -oxidation¹⁰⁷⁻¹¹⁰ although these are observations from *in vitro* (cell culture experiments) and animal studies and further studies on healthy and dyslipemic subjects to determine the effect of coffee on serum lipids are necessary.

3.4.4.2. Effects of coffee consumption on endothelial function, inflammation and atherosclerosis. Mechanisms of action

The vascular endothelium is a monolayer of highly metabolically active cells that form a selective barrier between the vascular lumen and the vascular wall, and provides a non-adhesive, non-thrombogenic surface for normal blood flow. Maintaining normal endothelial function is crucial for vascular health, since it regulates vascular tone and controls vascular permeability. The endothelium preserves vascular homeostasis by keeping a balance between vasoconstriction and vasodilation mediated by the secretion of factors like nitric oxide (NO), prostacyclin (PGI₂) or endothelium-derived hyperpolarizing factor (EDHF) with vasodilatory action, or endothelin-1 (ET-1), angiotensin II, thromboxane A₂ and prostaglandin H₂, with vasoconstrictor effects.¹¹¹ NO is considered the most important endothelial-derived factor due to its action maintaining vascular wall homeostasis by inhibiting inflammation, oxidative stress, platelet aggregation,

leukocyte adhesion and vascular smooth muscle cell migration and proliferation. It is also the most potent endogenous vasodilator in the body¹¹¹ (Figure 3.4.1).

[Figure 3.4.1 near here]

NO is synthesized from L-arginine by the action of endothelial nitric oxide synthase (eNOS), an enzyme that plays a central role on the maintenance of endothelial homeostasis.¹¹² Disruption of endothelial function can lead to loss of the crosstalk between the endothelial and vascular smooth muscle cells, which is pivotal in the regulation of vascular tone.¹¹³ Alterations in the vascular tone result in changes in blood pressure, thus linking endothelial dysfunction and hypertension.¹¹⁴

Endothelial dysfunction is associated with inflammation, vasoconstriction, oxidation of lipoproteins, platelet aggregation, and thrombus formation. Disruption of endothelial function generates a proatherogenic environment that facilitates interaction between endothelial cells and blood particles (platelets, immune cells), with the initiation of the atherothrombotic process. Endothelial dysfunction is characterized by decreased NO bioavailability, oxidative stress (increased production of reactive oxygen species, ROS), and induced expression of cell adhesion molecules (ICAM-1, VACM-1, and E-selectin, among others) (Figure 3.4.2). As a consequence of endothelial dysfunction there is loss of endothelium's integrity, recruitment, adhesion and migration of leukocytes that will increase production of pro-inflammatory cytokines, as well as adhesion molecules, chemokines and growth factors; there is also proliferation and migration of smooth muscle cells, with progression of the atherosclerotic plaque.¹¹¹ Plaque disruption will initiate platelet adhesion and aggregation on exposed vascular surfaces, activating the clotting cascade that leads to the formation of thrombus as final steps in the atherothrombotic process.¹¹⁵

[Figure 3.4.2 near here]

Assessment of endothelial function can be measured by different non-invasive methods like flow-mediated dilation (FMD) of the brachial artery, venous occlusion plethysmography, pulse wave velocity, or endothelial peripheral arterial tonometry (Endo-PAT) among others, or by determining circulating levels of markers of endothelial function such as cell adhesion molecules VCAM-1, ICAM-1, E-selectin, inflammatory markers like C-reactive protein (CRP), cytokines and chemokines (IL-1 β , IL-6, TNF α , MCP-1, etc.) and other factors such as tissue plasminogen activator and plasminogen activator-inhibitor 1 (PAI-1), growth factors, etc.¹¹¹

Data on the effect of coffee on endothelial function is limited and yields conflicting results. Several studies have shown negative acute effects of coffee increasing arterial stiffness (increased augmentation index) and arterial wave reflection (measured by applanation tonometry),¹¹⁶⁻¹¹⁸ and decreasing FMD^{119,120} after regular coffee consumption by healthy subjects, but not after decaffeinated coffee. On the contrary, Buscemi et al.¹²¹ showed a significant acute, dose-dependent, favorable effect of decaffeinated coffee increasing FMD, thus attributing the detrimental acute effects of coffee on endothelial function to caffeine. However, acute caffeine administration to healthy volunteers augmented forearm blood flow (measured by plethysmography) in response to the endothelium-dependent vasodilator acetylcholine through an increase in NO production¹²² and improved FMD in subjects with and without coronary artery disease.¹²³ This effect was accompanied by a significant decrease of CRP plasma levels, showing an anti-inflammatory effect.

On the other hand, long-term consumption of green coffee bean polyphenols improved vasoreactivity in healthy subjects, as determined by an enhanced reactive hyperemia ratio as a measure of the vasodilation response.¹²⁴ Similarly, in a randomized, placebo controlled trial in Japanese subjects with mild hypertension and vascular failure, consumption during 8 weeks of a coffee beverage with reduced HHQ contents significantly ameliorated endothelium-dependent flow-mediated vasodilation, also improving systolic blood pressure and reducing

oxidative stress as shown by a lower urinary excretion of isoprostanes.¹⁰⁰ In an pilot study, a polyphenol-rich beverage containing coffee acutely improved several biomarkers related to antioxidant/anti-inflammatory effects, reducing serum concentration of the 8-iso-PGF2 α isoprostane and CRP, and increasing nitric oxide levels in healthy volunteers.¹²⁵ In two acute studies, green coffee bean polyphenols improved peripheral endothelial function after a meal and after a glucose load in healthy adults, ameliorating postprandial endothelial dysfunction.^{126,127} Interestingly, in the study by Ochiai et al.,¹²⁶ the enhanced FMD response was accompanied by increased levels of NO metabolites, suggesting that the improved endothelial function was mediated by an enhanced bioavailability of this potent vasodilator. However, acute administration of pure chlorogenic acid showed no effect on FMD and nitric oxide status in healthy fasting volunteers.¹²⁸

Adding to the conflicting findings on the effect of coffee consumption on endothelial function, Correa et al.⁹⁷ observed increased plasma levels of sVCAM-1, soluble E-selectin, and fibrinogen in healthy subjects after consuming medium and medium-light roasted paper-filtered coffee for 4 weeks, although other inflammation markers were not affected. However, in a cross-sectional study in healthy and diabetic women participating in the Nurses' Health Study I, coffee consumption was associated with lower plasma concentrations of E-selectin and CRP in diabetic women (Table 3.4.3), while in healthy ones these reductions were observed only with decaffeinated coffee.¹²⁹ These results indicated that neither regular nor decaffeinated filtered coffee had a detrimental effect on endothelial function. On the contrary, filtered coffee consumption was inversely associated with markers of inflammation and endothelial dysfunction (lower E-selectin and CRP levels).¹²⁹ Clearly, more intervention studies are necessary to assess the impact of coffee on endothelial dysfunction and the contribution of caffeine and coffee polyphenols.

Caffeic acid is present in coffee, although in lower amounts compared to caffeoylquinic acids, and it is also a circulating metabolite after coffee intake.^{45,49} *Ex vivo* studies have shown that caffeic acid was able to increase NO release by isolated porcine coronary arteries and to induce vasorelaxation of porcine coronary rings.¹³⁰ In an animal study, chlorogenic acid (5-caffeoylquinic acid) was effective improving endothelial function in spontaneously hypertensive rats, with increased urinary excretion of NO metabolites and improved acetylcholine-induced endothelium-dependent vasodilation in the aorta, together with a lower production of ROS in the vasculature.¹³¹ Improved NO bioavailability and reduced oxidative stress are important mechanisms of action of coffee polyphenols protecting endothelial cell function. In cell culture experiments, physiologically relevant concentrations of caffeic acid (100 nM-0.1 μ M) induced NO release in human umbilical vein-derived endothelial cells (HUVEC) by a mechanism independent from eNOS expression and phosphorylation, decreased ROS production, increased cell proliferation and angiogenesis, and inhibited leukocyte adhesion and endothelial cell apoptosis induced by hypoxia¹³² (Figure 3.4.2). Similarly, chlorogenic acid has shown to be highly effective decreasing ROS production in HUVEC cells challenged with pro-inflammatory IL-1 β or the toxic perfluorooctane sulphonate,^{133,134} suppressing the expression of interleukines and cell adhesion molecules (VCAM-1, ICAM-1 and E-selectin), and reducing the adhesion of human monocyte cells to the activated HUVEC cells. Similar effects were also elicited by caffeic acid in HUVEC cells stimulated by the adipokine resistin,¹³⁵ and by ferulic acid, the methylated metabolite of caffeic acid, in gamma-irradiated HUVEC cells¹³⁶ (Figure 3.4.2). These studies show a common mechanism of action of coffee polyphenols, blocking nuclear translocation of the transcription factor NF- κ B, thus suppressing the expression of genes encoding for cell adhesion molecules and proinflammatory cytokines, with the upstream implication of different MAPKs (mitogen-activated protein kinases) depending on the phenolic compound.¹³⁴⁻¹³⁷ Another minor phenolic component of coffee, 3,4-dicaffeoylquinic acid, has shown to protect vascular endothelial cells against oxidative stress and restore impaired endothelium-dependent

vasodilation, inhibiting vascular smooth muscle cell proliferation and migration,¹³⁸ pointing to another potential anti-atherosclerotic mechanism of action of coffee polyphenols. Interestingly, the diterpene kahweol has also shown protective effects on endothelial function (Figure 3.4.2), inhibiting the adhesion of monocytes to TNF α -activated endothelial cells and the TNF α -induced expression of adhesion molecules VCAM-1 and ICAM-1 by ECV304 endothelial cells via down-regulation of the PI3K/Akt-NF- κ B signaling pathway,⁷⁰ showing the anti-inflammatory and anti-atherosclerotic properties of kahweol and its potential contribution against atherosclerosis. More recently, 1,4- and 1,3-dimethylpyridine formed by pyrolysis of trigonelline during coffee roasting have shown to have mild antithrombotic effects in rats through stimulation of prostacyclin release and inhibition of platelet aggregation and reduced fibrin formation,¹³⁹ although their overall contribution would be lesser in view of the low content of these compounds in brewed coffee

Besides the antioxidant, anti-inflammatory and endothelial cell-protective effects of hydroxycinnamic acids and kahweol, coffee has also shown important effects inhibiting platelet aggregation. In a clinical trial in healthy subjects, drinking coffee (containing 180 mg caffeine) inhibited collagen and arachidonic acid induced platelet aggregation, although it had no effect on ADP-induced aggregation.¹⁴⁰ On the contrary, a capsule of caffeine (180 mg) did not affect *ex vivo* platelet aggregation induced by any of the three agonists, demonstrating that the antiplatelet effect of coffee is independent from caffeine. Platelets collected 60 min. after coffee drinking and activated with collagen released significantly less thromboxane B₂ than before drinking, suggesting that coffee affected signal transduction pathways inhibiting enzyme activity upstream of thromboxane B₂ formation.¹⁴⁰ These authors also showed that coffee polyphenols were incorporated into platelets, while caffeine was not detectable. Chlorogenic and caffeic acids have shown to modulate the expression of cyclooxygenase (COX), the enzyme that catalyzes the generation of prostaglandin-H₂ from arachidonic acid, with physiologically relevant doses of chlorogenic acid (0.05 μ M) inhibiting COX-I and COX-II isoforms in mice

platelets, inhibiting P-selectin expression and platelet activation.¹⁴¹ Fuentes et al.¹⁴² observed that chlorogenic acid dose-dependently inhibited human platelet activation and aggregation induced by different agonists (ADP, collagen, arachidonic acid and TRAP-6), reducing platelet adhesion/aggregation and platelet-leukocyte interactions. These antithrombotic effects of chlorogenic acid were concomitant with decreased platelet inflammatory mediators (P-selectin, IL-1 β , sCD40L and CCL5) and increased intraplatelet cAMP/PKA levels, suggesting that the antiplatelet and antithrombotic effects of chlorogenic acid are associated with the A2A adenosine receptor/adenylate cyclase/cAMP/PKA signaling pathway.¹⁴² This is in agreement with the increased levels of aggregation-inhibiting molecules cAMP (cyclic adenosine monophosphate) and cGMP (cyclic guanosine monophosphate) induced by chlorogenic acid and the suppressed production of the aggregation-inducing thromboxane A2 and inhibition of COX-I in platelets concomitant with the potent inhibition by chlorogenic acid of collagen-induced platelet aggregation.¹⁴³

In summary, findings from cell culture assays and animal experiments on the effect of coffee phytochemicals (mostly polyphenols and to a lesser extent the diterpene kahweol and dimethylpyridinium) increasing NO bioavailability, decreasing oxidative stress and inflammation, and inhibiting leukocyte adhesion, vascular smooth muscle cell migration and platelet aggregation, are compatible with the improved vasoreactivity and endothelial function seen in some intervention studies with coffee. However, findings from clinical trials and observational studies are still scarce and contradictory, pointing to the necessity of further research on the effect of coffee on endothelial dysfunction and atherosclerosis.

3.4.4.3. Effects of coffee consumption on plasma homocysteine levels

Homocysteine is considered an independent risk factor for coronary, cerebrovascular and peripheral vascular diseases.¹⁴⁴ In a meta-analysis of homocysteine and CVD, Boushey et al.¹⁴⁵ reported that 10% of all coronary artery disease events may be explained by an elevated

concentration of total plasma homocysteine. In a case-control study of the association of high homocysteine levels and stroke it was found that increasing homocysteine was a strong and independent risk factor for ischemic stroke caused by large-artery atherosclerosis and, to a lesser extent, small-artery atherosclerosis (OR 2.7, 95% CI 1.4-5.1 for an increase in fasting plasma homocysteine from 10 to 15 $\mu\text{mol/L}$).¹⁴⁶ It is believed that hyperhomocysteinemia lead to endothelial dysfunction through inhibition of eNOS, reducing the production and bioavailability of NO (see reviews^{147,148}). It can also increase proliferation of vascular smooth muscle cells and induce synthesis of collagen, playing a role on the arterial wall remodeling resulting in vascular damage and increased arterial stiffness. Homocysteine seem to enhance oxidative stress and promote inflammation by inducing CRP production by vascular smooth muscle cells, also promoting platelet adhesion to endothelial cells¹⁴⁷ (Figure 3.4.2). Hyperhomocysteinemia may also enhance the adverse effects of risk factors like hypertension, smoking or hyperlipemia.

Homocysteine is formed from methionine (Met) as a result of cellular methylation reactions to form S-adenosylmethionine (SAM). Three enzymes are involved in the metabolism of homocysteine: methionine synthase catalyzes remethylation of homocysteine to methionine (with requirement of vitamin B12 and methyl-tetrahydrofolate); cystathionine β -synthase catalyzes trans-sulfuration to cysteine in a reaction that requires vitamin B6; and methionyl-tRNA synthase metabolizes homocysteine to a thioester, homocysteine-thiolactone, which can cause acute protein damage, triggering autoimmune responses, inflammation and atherosclerosis.¹⁴⁹ Elevated plasma levels of homocysteine can be caused by genetic defects in the enzymes involved in homocysteine metabolism or nutritional deficiencies in vitamin B12, vitamin B6 and folate.¹⁴⁸ However, other dietary factors might also affect plasma homocysteine levels, including coffee consumption.

Some observational studies have shown that coffee consumption can significantly increase homocysteine levels. An early study by Nygard et al.¹⁵⁰ found that heavy coffee intake (≥ 9 cups per day) resulted in total plasma homocysteine concentration over 20% higher than in coffee abstainers. Similarly, high consumption (≥ 500 mL/day) of filtered coffee was significantly associated to increased plasma homocysteine in the ATTICA study, but not with lower intakes.¹⁵¹ In contrast, no association between coffee consumption and plasma homocysteine levels was observed in the Atherosclerosis Risk in Communities (ARIC) study.¹⁵² In randomized clinical trials, both unfiltered¹⁵³ and paper-filtered¹⁵⁴ coffee significantly increased plasma homocysteine within a few hours after coffee consumption, but not in a dose-response study performed by Mursu et al.,⁹⁹ in which consuming 3 cups (450 mL) or 6 cups (900 mL) of filtered coffee for 3 weeks did not significantly increase plasma total homocysteine levels, again showing contradictory findings on the effect of coffee as seen previously in other risk factors.

Experiments to determine the components in coffee responsible of this homocysteine-raising effect found that caffeine was partly but not totally responsible, since consumption for two weeks of capsules providing 870 mg caffeine per day resulted in a 5% higher homocysteine fasting concentration compared to the placebo, whilst after consuming 0.9 L of coffee (providing the same amount of caffeine) homocysteine levels were 11% higher.¹⁵⁵ These increments were even higher 4 hours after coffee or capsules intake (4% for caffeine and 19% for coffee) (Table 3.4.3). In another randomized, cross-over, placebo controlled trial, after a 7-d intervention in healthy individuals, a supplement of chlorogenic acid caused a similar increase in total homocysteine than a supplement containing a similar amount of black tea polyphenols (12% and 11% higher homocysteine levels compared to placebo, respectively), but rutin (quercetin-3-rhamnoglucoside) did not affect homocysteine concentrations¹⁵⁶ (Table 3.4.3). These authors concluded that chlorogenic acid could be partly responsible for the higher homocysteine concentrations observed after coffee consumption. Interestingly, they speculated that *O*-methylation reactions catalyzed by the enzyme catechol-*O*-methyl transferase (COMT) of

absorbed polyphenols (both chlorogenic acids and black tea polyphenols) were involved in the homocysteine-raising effects they observed. COMT requires SAM as a methyl donor, which is hydrolyzed to homocysteine. The fact that rutin, a flavanol that is not absorbed in the small intestine, did not affect homocysteine levels, sustained this hypothesis.

Therefore, outcomes from these intervention studies support findings from observational studies, linking high intakes of coffee to increased plasma homocysteine concentrations. In the study by Verhoef et al.¹⁵⁵ volunteers consumed 900 mL of coffee per day, while in the study by Olthof et al.¹⁵⁶ the chlorogenic acid supplement taken daily (2 g) was equivalent to the consumption of 1.5 L of strong coffee per day. However, the study by Mursu et al.⁹⁹ with moderate and high intakes of coffee failed to see a significant effect on homocysteine concentrations, showing the importance of the amount of coffee (polyphenols) consumed, with no effect after moderate intakes. More research is needed to ascertain the effect of coffee on plasma homocysteine levels not only in healthy, but also in other risk populations, and to determine its impact on cardiovascular risk.

3.4.4.4. Effects of coffee consumption on blood pressure

Hypertension is a strong independent risk factor for stroke, CHD and congestive heart failure. It is defined as systolic blood pressure (SBP) greater than 140 mm Hg or diastolic blood pressure (DBP) greater than 90 mm Hg or both. According to the World Health Organization, raised blood pressure is estimated to cause 7.5 million deaths worldwide (about 12.8% of the total of all deaths).¹⁵⁷ Globally, the prevalence of high blood pressure in adults aged 25 and over was around 40%, with a similar prevalence across all income groups of countries (slightly lower for high income countries, 35%). These figures imply that 1 out of every 3 adults has high blood pressure. Data from observational studies have estimated that for every 2 mm Hg reduction in SBP there was a 7% reduction in coronary artery disease risk and 10% lower risk of stroke,¹⁵⁸ and a 2 mm Hg reduction in DBP has been associated with a 7% lower risk of CHD and 10-15%

reduction in heart attack and stroke.¹⁵⁹ Lifestyle factors have an important impact on blood pressure, and general recommendations for hypertensive subjects include following a weight-reducing diet, restriction of salt and alcohol intake, reduce/drop smoking and increase physical activity. Currently, there is no specific recommendation regarding coffee or caffeine intake in hypertension guidelines.^{9,160,161}

Over the last decades, enormous research effort has focused on studying the effect of coffee and caffeine on blood pressure. However, controversy is a common denominator as seen previously with other risk factors. In a comprehensive review of the literature performed by Nurminen et al. in 1999,¹⁶² acute effects of coffee or caffeine intake (in amounts varying between 200-400 mg caffeine) resulted in increased SBP (ranging between 2-14 mm Hg in normotensive, and 8-13 mm Hg in hypertensive subjects) and increased DBP (ranging 3-13 and 6-11 mm Hg in normotensive and hypertensive individuals, respectively), showing that the pressor effect of caffeine was more pronounced in hypertensive patients. The maximal increases took place 60-120 min after intake and lasted 2-4 h. Studies on decaffeinated coffee referred no effect on blood pressure. When reviewing studies on the effect of chronic consumption, some studies did show that caffeine induced persistent pressor effects (increasing blood pressure by 3-6 mm Hg) in habitual coffee consumers, with slight falls of blood pressure when changing from regular to decaffeinated coffee or abstinence from coffee. However, other studies failed to observe any effect on blood pressure for chronic coffee intake or after coffee withdrawal.¹⁶² Similar outcomes were obtained in meta-analysis of controlled clinical trials. In an early study by Jee et al.¹⁶³ assessing the effect of coffee drinking on blood pressure, increased systolic (2.4 mm Hg) and diastolic (1.2 mm Hg) blood pressure were observed with coffee treatment compared to control (Table 3.4.3).¹⁶³ This effect was greater in younger participants. These authors found an independent positive relationship between cups of coffee consumed and subsequent change in blood pressure; for every cup of coffee consumed, SBP increased 0.8 mm Hg and DBP increased by 0.5 mm Hg. Klag et al.¹⁶⁴ observed lower increases, reporting that 1 cup of coffee a

day increased SBP 0.19 mm Hg (95% CI 0.02-0.35) and DBP 0.27 mm Hg (95% CI 0.15-0.39), although these authors did not find association between coffee consumption with incident hypertension. Later, Noordzij et al.¹⁶⁵ in a meta-analysis of sixteen randomized controlled trials on the effect of coffee and caffeine on blood pressure found a comparable significant increase of SBP and DBP (2.04 and 0.73 mm Hg, respectively) after pooling coffee and caffeine trials. When analyzing trials separately, caffeine showed to have a higher effect increasing blood pressure; interestingly, the pressor effect was small if caffeine was consumed through coffee (Table 3.4.3). These authors suggested that differences could be due to different bioavailability of caffeine when taken in capsules as compared to coffee, the lack of favorable “side effects” of coffee (i.e. physical and mental relaxation), and the lack in caffeine tablets of substances that could exert a beneficial effect in the cardiovascular system.

Two more recent systematic reviews and meta-analyses of randomized clinical trials did not support an association between habitual coffee consumption and increased blood pressure or increased risk of hypertension or CVD. Mestas et al.¹⁶⁶ in a meta-analysis of randomized trials in hypertensive individuals observed that administration of caffeine (200-300 mg) caused a mean increase of 8.1 mm Hg in SBP and 5.7 mm Hg increase in DBP (Table 3.4.3) in the first hour after administration, an acute effect that lasted ≥ 3 h. However, longer-time interventions showed no increased blood pressure after coffee intake compared to decaffeinated coffee or a caffeine-free diet. The review of seven cohort studies showed no evidences of association between habitual coffee consumption by hypertensive subjects and a higher risk of CVD.¹⁶⁶ Likewise, in a meta-analysis of ten randomized clinical trials and five cohort studies on the effect of coffee consumption on blood pressure and the development of hypertension, Steffen et al.¹⁶⁷ obtained negative values for pooled weighted differences in the mean change in SBP and DBP (-0.55 and -0.45 mm Hg, respectively) and no association between coffee intake and pooled risk ratio for developing hypertension (RR 1.03, 95% CI 0.98-1.08) (Table 3.4.3). The assumption that regular coffee intake is not a risk factor for developing hypertension was also concluded in a recent

prospective study in 29,985 postmenopausal, normotensive women in the Women's Health Initiative Observational Study.¹⁶⁸ Findings from this study showed that neither caffeinated coffee nor caffeine intake were associated with mean SBP or DBP; only decaffeinated coffee intake was associated with a small decrease in mean DBP, a change that was considered clinically irrelevant by the authors of the study. Intakes of caffeinated coffee, caffeine and decaffeinated coffee were not associated with the risk of incident hypertension (P for trend > 0.05). Finally, a dose-response meta-analysis of six prospective observational studies showed a "J-shaped" relationship (Table 3.4.3), with slightly elevated risk of hypertension associated with light-to-moderate consumption (1 to 3 cups/d) and no increased risk for habitual coffee consumption > 3 cups per day.¹⁶⁹

The analysis of all the evidences from clinical trials and observational studies summarized above show three important dissimilarities to be taken into consideration: i) acute vs. long-term effects differ, ii) differences of caffeine vs. coffee, and iii) unlike responses to coffee/caffeine in habitual vs. non-habitual coffee drinkers. Acutely, caffeine at dietary doses increases blood pressure. The pressor effect of pure caffeine (given as capsules, 200-300 mg) does not greatly differ between normotensive and hypertensive subjects, although it seems slightly higher in the latter (Table 3.4.4).^{122,123,162,170} With caffeinated coffee, blood pressure increases are milder in normotensive than in hypertensive individuals (Table 3.4.4).^{116,118-120,162} Caffeine increases blood pressure in habitual drinkers more than coffee.^{171,172} In non-habitual drinkers, however, acute effects of coffee raising blood pressure are substantial¹⁷² (Table 3.4.4). On the other hand, as could be expected, decaffeinated coffee has no relevant acute effect on blood pressure.^{121,162} As for long-term effects, consumption of caffeinated coffee is not associated with increases in blood pressure or incident hypertension (Table 3.4.3), although changing from decaffeinated coffee or discontinuation of coffee intake caused a significant reduction on blood pressure in normotensive subjects.¹⁷³

[Table 3.4.4 near here]

As mentioned before, caffeine has a potent pressor effect, elicited through different mechanisms. Antagonism of adenosine A₁ and A_{2A} receptors is probably the most relevant, since inhibition constants for these receptors are in the micromolar range (44 and 40 $\mu\text{mol/L}$, respectively⁹³), concentrations that are likely to be attained upon habitual coffee intake. Adenosine is a neurotransmitter with mostly inhibitory effects in the central nervous system and vasodilatory effects in vascular beds;^{41,93,162} therefore, non-specific binding of caffeine to A₁/A_{2A} receptors will result in vasoconstriction and acute increase in blood pressure, as well as increased systemic vascular resistance.⁴¹ Tolerance to the acute humoral and hemodynamic effects of caffeine develops after a few days of coffee consumption,¹⁷⁴ which explains the mild pressor effect in habitual coffee drinkers compared to non-consumers. Development of tolerance is potentially mediated by increases in the number of adenosine receptors,¹⁷⁵ although tolerance can also be lost relatively quickly after cessation of coffee consumption.¹⁷⁴ On the other hand, not all subjects develop tolerance equally. It has been observed that differences in the half-life of caffeine could account for the interindividual variations in the development of tolerance to the acute effects of caffeine.¹⁷⁶

Plasmatic maximum concentrations and half-life of caffeine depend on the metabolism of this trimethylxanthine by CYP1A2. As mentioned before, genetic polymorphisms in this cytochrome P450 isoform affect the rate of caffeine metabolism to dimethylxanthines. Impaired enzyme activity in subjects with the *CYP1A2**1F variant implies a slower metabolism,⁴² and increased risk of hypertension as seen in a recent cohort study.¹⁷⁷ Other factors like metabolic induction or inhibition of cytochrome P450, presence of hepatic diseases or individual factors (i.e. weight, sex) can also affect caffeine metabolism.⁹³ Interindividual variations in the susceptibility to caffeine may be associated to polymorphisms in other genes, such as α - and β -adrenergic receptors, since caffeine increases circulating levels of catecholamines (epinephrine,

norepinephrine), with vasoconstrictor properties. Acute blood pressure responses to coffee were related to polymorphism in the $\alpha 2$ -adrenergic receptor (*ADRA2B**I variant).¹⁷⁸ Also, increased risk of hypertension associated to coffee intake has been related to polymorphism in the NADH dehydrogenase subunit-2 (*ND2-237*).¹⁷⁹

Finally, it is important considering the effects of smoking on the response to coffee and caffeine intake, as it has been shown that combination of smoking and caffeine intake elicits a synergistic detrimental effect increasing blood pressure and aortic stiffness and impairing endothelial function.¹¹⁷

Although caffeine plays a crucial role in the hemodynamic effect of coffee, the fact that acute responses to coffee are milder than to similar doses of caffeine point to other components in coffee counteracting the pressor effects of caffeine. Interestingly, in an acute study, chlorogenic acid (400 mg, equivalent to 2 cups of coffee) showed to significantly decrease blood pressure, with reductions relative to control of -2.41 mm Hg for SBP (95% CI -0.03, -4.78; $P=0.05$) and -1.53 mm Hg (95% CI -0.05, -3.01; $P=0.04$) for DBP.¹⁸⁰ Similarly, in another clinical trial in healthy subjects, drinking caffeinated green coffee, rich in chlorogenic acids, for two weeks showed a positive effect reducing SBP (-3.4 mm Hg, $P=0.018$).¹⁸¹ Likewise, consumption of a green coffee bean extract for 3-4 months also decreased blood pressure in healthy¹²⁴ and mildly hypertensive subjects,¹⁸² with reductions of up to -10/-7 mm Hg in SBP/DBP in the latter. This clearly points to hydroxycinnamic acids in coffee as the components counteracting the effect of caffeine. In line with these findings, two studies on the effect of regular caffeinated coffee and caffeinated coffee free of hydroxyhydroquinone (HHQ), which is known to inhibit the effect of CGAs,¹⁰¹ showed that intake of the regular coffee for 4 or 8 weeks had no effect on blood pressure; in contrast, the HHQ-free coffee was effective reducing blood pressure in subjects with mild hypertension.^{100,182}

In summary, habitual consumption of coffee leads to development of tolerance to the pressor effect of caffeine, resulting in no increased risk or incidence of hypertension in the general population. Although buffered by chronic intake, caffeine maintains its acute effect transiently increasing blood pressure, which has been suggested to pose a potential risk of cardiovascular events in the hours after drinking coffee. This risk could be higher for at risk subjects, especially if combined with cigarette smoking, and perhaps for non-habitual consumers, although interindividual responses to caffeine intake associated to several gene polymorphisms may modulate the overall effects of this xanthine. In turn, since other components in coffee like chlorogenic acids seem to counteract the pressor effect of caffeine, drinking coffee with higher contents of chlorogenic acids might be a healthier alternative.

3.4.5. Concluding remarks

When balancing the divergent results from observational and intervention studies, amounting evidences from prospective cohort studies and many randomized clinical trials support a lack of detrimental effect of moderate coffee consumption on CVDs risk, pointing to a protective effect of moderate intake (around 3-4 cups per day) of coffee, particularly filtered, green or low roasted, reducing the risk of coronary and cerebrovascular heart diseases and heart failure, with no negative impact on the risk of hypertension.

The complex nature of coffee, with many different phytochemical bioactive molecules which content in the final beverage depends on the coffee bean variety, type of processing (e.g. degree of roasting), or brewing method (i.e. filtered vs. unfiltered), as well as the doses consumed in the short-term (acute) or habitually, add to the intrinsic influence of the individual consumer, who will respond differently depending on his/her genetic imprint, lifestyle habits or health status. Therefore, no overall recommendation on coffee intake can be posed, although it could

be time to stop thinking of coffee as a potentially harmful beverage for the general population, who could calmly enjoy their cup of coffee.

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Figure Captions

Figure 3.4.1. Main vascular effects of nitric oxide (NO). NO is synthesized in endothelial cells from L-arginine (L-Arg) by the action of the enzyme endothelial nitric oxide synthase (eNOS), playing a key role in the maintenance of normal endothelial function. VSMC: vascular smooth muscle cells.

Figure 3.4.2. Endothelial dysfunction and atherothrombotic process. Loss of normal endothelial function leads to decreased NO formation and increased ROS production, causing vasoconstriction and oxidative stress, with loss of endothelial integrity, recruitment, adhesion and migration of monocytes to the subendothelial space, stimulating the production of cytokines, chemokines, adhesion molecules and growth factors by endothelial, smooth muscle and immune cells, and stimulating the proliferation and migration of vascular smooth muscle cells. When the atherosclerotic plaque is formed, progression of atherosclerosis would lead to plaque disruption, exposing vascular surfaces, activating platelets that will aggregate and, together with clotting factors, result in the formation of thrombus. Phenolic constituents of coffee and the diterpene kahweol have shown inhibitory effects (truncated arrows) while homocysteine has stimulating effects (open arrows). CA: Caffeic acid; 5CQA: 5-caffeoylquinic acid (chlorogenic acid); 3,4DCQA: 3,4-dicaffeoylquinic acid; FA: ferulic acid; Hcy: homocysteine; NO: nitric oxide; ROS: reactive oxygen species.

Table Captions

Table 3.4.1. Epidemiological studies on the effect of coffee consumption on CVDs

Table 3.4.2. Phytochemical compounds in coffee: chemical structure, effect of processing, content, bioavailability and main health effects*

Table 3.4.3. Evidences from randomized clinical trials, cohort studies and meta-analyses on the effect of coffee consumption on different CVD risk markers*.

Table 3.4.4. Acute blood pressure response to coffee or caffeine intake in normotensive and hypertensive subjects, and in habitual and non-habitual coffee drinkers.*

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Table 3.4.1. Epidemiological studies on the effect of coffee consumption on CVDs

Ref.	Type of study	Participants Follow-up (y)	Endpoint	Outcome* Adjusted OR, RR, HR (95% CI)
Greenland ¹²	Meta-analysis 8 case-control studies	3946 cases	MI, coronary death	Increased risk 1.42 geometric mean rate ratio, 5 vs. 0 cups/d
Kawachi et al. ¹³	Meta-analysis 8 case-control studies	-	CHD	Increased risk OR 1.63 (1.50-1.78) 5 vs. 0 cups/d
Sofi et al. ¹⁴	Meta-analysis 13 case-control studies	9487 cases 27 747 controls	CHD	Increased risk > 4 cups/d, OR 1.83 (1.49-2.24, P<0.0001) 3-4 cups/d, OR 1.33 (1.04-1.71, P<0.0001) ≤ 2 cups/d, OR 1.03 (0.87-1.21, P=0.45)
Greenland ¹²	Meta-analysis 14 cohort studies	5071 cases Participants 2-26 y follow-up	MI, coronary death	No or mild increased risk 0.92-1.27 geometric mean rate ratio
Kawachi et al. ¹³	Meta-analysis 15 cohort studies	-	CHD	No increased risk RR 1.05 (0.99-1.12) 5 vs. 0 cups/d
Sofi et al. ¹⁴	Meta-analysis 10 cohort studies	9440 cases 403 631 participants 3-44 y follow-up	CHD	No increased risk > 4 cups/d, RR 1.16 (0.95-1.41, P=0.14) 3-4 cups/d, RR 1.05 (0.90-1.22, P=0.57) ≤ 2 cups/d, RR 1.04 (0.90-1.19, P=0.60)
Wu et al. ¹⁶	Meta-analysis 21 prospective studies	15 599 cases 407 806 participants 4-32 y follow-up	CHD	No increased risk 1-4 cups/d, RR 0.96 (0.87-1.06) 4-6 cups/d, RR 1.04 (0.92-1.17) ≥ 6-7 cups/d, RR 1.07 (0.87-1.32) Lower CHD risk with moderate intake Women, RR 0.82 (0.73-0.92, P<0.001) Women and men, RR 0.87 (0.80-0.86, P<0.001)

Sofi et al. ¹⁴	Meta-analysis 4 case-control and 3 cohort studies on decaffeinated coffee	-	CHD	No increased risk > 4 cups/d, OR 1.87 (0.96-3.46, P=0.07) ≤ 2 cups/d, OR 1.05 (0.85-1.29, P=0.7) > 4 cups/d, RR 1.10 (0.90-1.34, P=0.33) ≤ 2 cups/d, RR 1.00 (0.93-1.07, P=0.90)
Mostofsky et al. ⁷	Dose-response meta-analysis 5 prospective studies	6522 events 140 200 participants	Heart failure	J-shaped non-linear relationship (P=0.02) 1-2 cups/d, RR 0.93 (0.86-0.99) 3-4 cups/d, RR 0.89 (0.81-0.99) 7-8 cups/d, RR 0.95 (0.87-1.05) 10-11 cups/d, RR 1.01 (0.90-1.14)
Larsson & Orsini ¹⁸	Meta-analysis 11 prospective studies	10 003 events 479 689 participants 2-21 y follow-up	Stroke	U-shaped non-linear association (P=0.005) 2 cups/d, RR 0.86 (0.78-0.94) 3-4 cups/d, RR 0.83 (0.74-0.92) 6 cups/d, RR 0.87 (0.77-0.97) 8 cups/d, RR 0.93 (0.79-1.08)
Kim et al. ¹⁹	Meta-analysis 9 cohort studies	8110 stroke events 206 437 participants 9-24 y follow-up	Stroke	Preventive effect on stroke (≥ 4 cups/d) RR 0.83 (0.76-0.91) Stroke occurrence: RR 0.82 (0.74-0.92) Women: RR 0.81 (0.70-0.93) Ischemic stroke: RR 0.80 (0.71-0.90)
Ding et al. ²⁰	Dose-response meta-analysis 36 prospective cohort studies	36 352 CVD cases 1 279 804 participants 2-32 y follow-up	CVDs (CHD, stroke, heart failure, CVD mortality)	Non-linear relationship for CVD, CHD and stroke risks. 5 cups/d, RR 0.95 (0.87-1.03) 3.5 cups/d, RR 0.85 (0.80-0.90) 1.5 cups/d, RR 0.89 (0.84-0.94)
Anderson et al. ²¹	Prospective cohort study	4265 deaths 27 312 postmenopausal women 15 y follow-up	Deaths from CVD and inflammatory diseases	Decreased risk of CVD and inflammation Mortality from CVD 1-3 cups/d, HR 0.76 (0.64-0.91) 4-5 cups/d, HR 0.81 (0.66-0.99) ≥ 6 cups/d, HR 0.87 (0.69-1.09) Mortality from other inflammatory diseases

				1-3 cups/d, HR 0.72 (0.55-0.93) 4-5 cups/d, HR 0.67 (0.50-0.90) ≥ 6 cups/d, HR 0.68 (0.49-0.94)
Freedman et al. ²²	Prospective cohort study	52 515 deaths 402 260 US adults 14 y follow-up	Total and cause-specific mortality	Inverse association (P<0.001 for trend) Men < 1 cup/d, HR 0.99 (0.95-1.04) 1 cup/d, HR 0.94 (0.90-0.99) 2-3 cups/d, HR 0.90 (0.86-0.93) 4-5 cups/d, HR 0.88 (0.84-0.93) >6 cups/d, HR 0.90 (0.85-0.96) Women < 1 cup/d, HR 1.01 (0.96-1.07) 1 cup/d, HR 0.95 (0.90-1.01) 2-3 cups/d, HR 0.87 (0.83-0.92) 4-5 cups/d, HR 0.84 (0.79-0.90) >6 cups/d, HR 0.85 (0.78-0.93)
Malerba et al. ²³	Meta-analysis 23 cohort studies	9256 deaths 651 323 participants	All-cause and CVD mortality, CHD/IHD, stroke	Inverse relationship with CVD mortality All-cause mortality RR 0.88 (0.84-0.93) CVD mortality RR 0.89 (0.77-1.02) CHD/IHD RR 0.95 (0.78-1.15) Stroke RR 0.95 (0.70-1.29) Cancer RR 1.03 (0.97-1.10)
Loftfield et al. ²⁴	Prospective cohort study	8718 deaths 90 317 US adults 4 y follow-up	Overall and cause-specific mortality	Inverse associations (≥ 4 cups/d) All-cause mortality HR 0.80 (0.74-0.87) Heart disease HR 0.75 (0.63-0.90) Stroke HR 0.77 (0.54-1.10) Similar findings for decaffeinated coffee

*Values in parenthesis are 95% confidence intervals and/or P values. CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; IHD: ischemic heart disease; MI: myocardial infarction; OR: odds ratio; RCT: randomized controlled trials; RR: relative risk.

Table 3.4.2. Phytochemical compounds in coffee: chemical structure, effect of processing, content, bioavailability and main health effects*

Compound	Content in green beans (% dry weight)	Effect of processing	Content in the beverage (daily intake)	Bioavailability and metabolism	Effects on CVD risk factors
Caffeine (1,3,7-trimethylxanthine)	Arabica: 0.9-1.3% Robusta: 1.5-2.5%	Relatively stable to roasting	Normal serving: 50-100 mg Espresso: 135-620 mg/100 mL	High and rapid absorption Metabolism by CYP1A2 C_{max} 10-12 μ M T_{max} 1 h	Acute effects: ↑ Blood pressure ↑ Vasoconstriction ↑ Arterial stiffness ↑ Insulin resistance ↑ (nor)epinephrine ↑ Corticosteroids ↓ Endothelial function Differences: <ul style="list-style-type: none"> • Fast vs. slow metabolizers (CYP1A2 polymorphism) • Acute vs. chronic effects (tolerance)
Hydroxycinnamic acids (5-caffeoylquinic acid)	≈ 10% (Robusta > Arabica)	Drastic reduction during roasting (≈ 50%) Isomerization (lactones)	Normal serving: 220 mg/100 mL Espresso: 80-800 mg/100 mL (1-2 g/d)	Low gastrointestinal absorption (≈ 30%) Extensive colonic metabolism Phase II conjugation (intestinal and colonic metabolites) Biphasic kinetic C_{max} nM, T_{max} 1-3h C_{max} nM- μ M, T_{max} 5-9 h	↑ Antioxidant activity ↓ Lipid levels and oxidability ↓ Inflammation ↑ Endothelial function ↓ Platelet aggregation ↓ Blood pressure ↓ Insulin resistance ↓ Body weight

Diterpenes

Cafestol

Cafestol

Arabica: 0.3-0.7%
Robusta: 0.1-0.3%

Little effect of roasting
Affected by brewing method (removed by filtering)

Cafestol

0.1-7 mg/100 mL

Highly bioavailable

Cafestol

↑ Lipid levels

Kahweol

Kahweol

Arabica: 0.1-0.3%
Robusta: < 0.01%

Kahweol

0.1-10 mg/100 mL

Kahweol

↑ Lipid levels
↓ Inflammation

Melanoidins

0% (in the green bean)
Up to 29% in roasted beans

Formed during roasting

0.25-0.81 g/100 mL
(0.5-2 g/d)

Unknown
(resist gastrointestinal digestion *in vitro*)

↑ Antioxidant activity
↓ Inflammation
Anti-hypertensive

Soluble Dietary Fiber

Galactomannans
Type II arabinogalactans

2.5-20%

Unknown

0.14-0.75 g/100 mL
(0.4-3 g/d)

Non-digestible carbohydrate
Highly fermentable

↓ Lipid levels
↓ Blood pressure
↑ Insulin sensitivity
↓ Inflammation
↓ Body weight

Trigonelline

(N-methylnicotinic acid)

0.6-1%

Degraded to nicotinic acid, N-methylpyridinium

40-110 mg/serving

Unknown
(moderate intestinal absorption in animals)

↓ Glucose levels
↓ Lipid levels

Table 3.4.3. Evidences from randomized clinical trials, cohort studies and meta-analyses on the effect of coffee consumption on different CVD risk markers*.

Ref.	Type of study	Participants/Duration	Endpoint	Outcome (95% CI)
Jee et al. ⁶⁶	Meta-analysis 14 RCT	885 participants 56 d	Serum lipids	Increased serum lipids TC: 11.8 mg/dL (6.8-16.0, P<0.001) LDL-C: 6.5 mg/dL (2.0-11.0, P=0.002)
Cai et al. ⁶⁷	Meta-analysis 12 RCT	1017 participants 45 d	Serum lipids	Increased serum lipids TC: 8.1 mg/dL (4.5-11.6, P<0.001) LDL-C: 5.4 mg/dL (1.4-9.5, P=0.009) TG: 12.6 mg/dL (3.5-12.6, P=0.007)
Lopez-Garcia et al. ¹²⁹	Cross-sectional study	Diabetics Healthy	Endothelial function Inflammation	Higher caffeinated coffee consumption effect (adjusted percentage change per 1 cup/d increment) Healthy women: E-selectin: -2.5% (P=0.08) CRP: -7.9% (P=0.02) Diabetic women: E-selectin: -3.2% (P=0.05) CRP: -10.2% (P>0.001)
Verhoef et al. ¹⁵⁵	RCT	48 subjects 14 d	Homocysteine	Increased fasting Hcy (% vs. placebo) Caffeine (870 mg): 0.4 µmol/L (0.1-0.7, P=0.04), 5% Coffee (~870 mg caffeine): 0.9 µmol/L (0.6-1.2, P=0.0001), 11% Increased Hcy 4 h after intake (vs. placebo) Caffeine: 4% (P=0.09) Coffee: 19% (P=0.0001)
Olthof et al. ¹⁵⁶	RCT	20 healthy subjects 7 d	Homocysteine	Increased fasting Hcy (% vs. placebo) Chlorogenic acid: 0.4 µmol/L (0.0-0.8), 4% Black tea polyphenols: 0.5 µmol/L (0.0-0.9), 5% Rutin: 0.0 µmol/L (-0.4-0.3) Increased plasma Hcy 4-5 h after supplement intake Chlorogenic acid: 1.2 µmol/L (0.6-1.7), 12%

				Black tea polyphenols: 1.1 $\mu\text{mol/L}$ (0.6-1.5), 11% Rutin: 0.3 $\mu\text{mol/L}$ (-0.2-0.7)
Jee et al. ¹⁶³	Meta-analysis 11 RCT	522 participants 56 d	Blood pressure	Increased blood pressure SBP 2.4 (1.0-3.7, $P=0.005$) DBP 1.2 (0.4-2.1, $P=0.015$)
Noordzij et al. ¹⁶⁵	Meta-analysis 16 RCT	1010 participants ≥ 7 d	Blood pressure	Increased blood pressure (pooled coffee & caffeine trials) SBP 2.04 (1.10-2.99, $P=0.005$) DBP 0.73 (0.14-1.31, $P=0.015$) Caffeine trials SBP 4.16 (2.13-6.20)/DBP 2.41 (0.98-3.84) Coffee trials SBP 1.22 (0.52-1.92)/DBP 0.49 (-0.06-1.04)
Mesas et al. ¹⁶⁶	Meta-analysis 5 RCT on acute effects 6 RCT on long-term effects	Hypertensive subjects Acute: 85 Long-term: 364	Blood pressure	Acute Caffeine (200-300 mg): Increased BP (1-3 h) SBP 8.14 mm Hg (5.68-10.61) DBP 5.75 mm Hg (4.09-7.41) Long-term Coffee (2 weeks): No increased BP compared with caffeine-free diet
Steffen et al. ¹⁶⁷	Meta-analysis 10 RCT 5 cohort	-	Blood pressure	RCT (pooled weighted difference in mean changes) SBP -0.55 mm Hg (-2.46-1.36) DBP -0.45 mm Hg (-1.52-0.61) Cohort (pooled RR for developing hypertension) RR 1.03 (0.98-1.08)
Zhang et al. ¹⁶⁹	Dose-response meta-analysis 6 prospective studies	37 153 events 172 567 participants 6-33 y follow-up	Blood pressure	J-shaped inverse association ($P < 0.001$) 3 vs. 0 cups/d, RR 1.07 (0.97-1.20) 6 vs. 0 cups/d, RR 0.99 (0.89-1.10)

*Values in parenthesis are 95% confidence intervals and/or P values. CI: confidence interval; CRP: C-reactive protein; DBP: diastolic blood pressure; Hcy: homocysteine; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RCT: randomized controlled trials; RR: relative risk; SBP: systolic blood pressure; TC: Total cholesterol; TG: triglycerides.

Table 3.4.4. Acute blood pressure response to coffee or caffeine intake in normotensive and hypertensive subjects, and in habitual and non-habitual coffee drinkers.*

	Subjects	ΔSBP (mm Hg)	ΔDBP (mm Hg)
Caffeine [†]	Normotensive	2-14	3-13
	Hypertensive	8-12	6-11
Coffee [†]	Normotensive	3-6	4-11
	Hypertensive	10-13	7-11
Caffeine [‡]	Habitual drinker	5.5	1.3
Coffee ^{‡‡}	Habitual drinker	2.3	0.7
	Non-habitual drinker	12.6	7.1

*DBP: diastolic blood pressure; SBP: systolic blood pressure

[†]Data are ranges of values from clinical trials.

[‡]McMullen et al.¹⁷¹

^{‡‡}Corti et al.¹⁷²