Journal of Agricultural and Food Chemistry 66.21 (2018): 5257-5263

DOI: http://doi.org/10.1021/acs.jafc.7b04506

Coffee consumption and cardiovascular disease: a condensed review of epidemiological evidence and mechanisms

Fernando Rodríguez Artalejo and Esther López García.

Department of Preventive Medicine and Public Health. School of Medicine. Universidad Autónoma de Madrid/IdiPaz, CIBER of Epidemiology and Public Health, and IMDEA-Food Institute, CEI UAM+CSIC, Madrid, Spain.

Address for correspondence:

F. Rodríguez Artalejo, MD, (Fax: +34914975353; Phone: +3491497544; e-mail: fernando.artalejo@uam.es)

or

E. Lopez-Garcia, PhD, (Fax:+34914975353; Phone: +34914972738; e-mail: esther.lopez@uam.es)

Department of Preventive Medicine and Public Health,
School of Medicine
Universidad Autónoma de Madrid
Arzobispo Morcillo, s/n
28029 Madrid, Spain.

ABSTRACT

Coffee is one of the most widely consumed beverages, and some studies have suggested it may be related to cardiovascular disease (CVD), the leading cause of poor health in the world. This manuscript reviews the evidence on the effect of habitual coffee consumption on CVD incidence and mortality. The review is based mostly on observational studies and meta-analyses of the literature. In healthy people, compared to not consuming coffee, habitual consumption of 3-5 cups of coffee per day is associated with a 15% reduction in the risk of CVD, and higher consumption has not been linked to elevated CVD risk. Moreover, in comparison with no coffee intake, usual consumption of 1-5 cups/day is associated with a lower risk of death. In people who have already suffered a CVD event, habitual consumption does not increase the risk of a recurrent CVD or death. However, hypertensive patients with uncontrolled blood pressure should avoid consuming large doses of caffeine. In persons with well-controlled blood pressure, coffee consumption is probably safe, but this hypothesis should be confirmed by further investigations.

KEY Words: Coffee, cardiovascular disease, mortality, cohort studies, experimental studies,

We summarize the evidence on the effects of habitual coffee consumption on cardiovascular disease (CVD) incidence and mortality. This topic is important because coffee is one of the most widely consumed beverages that has been shown to be modulate the risk of non-communicable diseases[1] and because CVD is the leading cause of poor health in the world. In 2015 CVD accounted for 32% of all deaths and 14% of disability-adjusted life years (sum of the years of life lost due to premature mortality and the years lost due to disability).[2]

We begin with a description of the composition of coffee, to understand plausible biological mechanisms derived from its components. Next we present an overview of the designs of studies on the effects of coffee on CVD, which helps to understand their strengths and limitations; we also focus on the main characteristics of coffee consumers among participants in large epidemiologic investigations because some characteristics may confound the relationship between coffee consumption and CVD, and thus should be controlled for in the analyses. Then, we describe the natural history of CVD, because it serves to identify the potential targets of coffee on CVD. The core of this article is a summary of the evidence on the effect of coffee on CVD and its risk factors. We end with some conclusions and a brief research agenda to further increase knowledge on the relationship between coffee and CVD.

For the review of the effect of coffee on CVD and its risk factors we searched PubMed between 1 January 2010 and 31 August 2017; the search terms were “coffee,” “caffeine,” “cardiovascular disease” “cholesterol”, “blood pressure”, “review” and “meta-analysis”. We considered only studies in English or Spanish conducted with humans. We did not focus on individuals investigations, but we have outlined a few of them because they were large studies and seminal articles that have influenced research in the field, or may have

substantially contributed to pooled results in meta-analyses. The final reference list also includes articles retrieved from the identified reviews and was generated because of their relevance to the focus of this paper.

Coffee composition

Coffee has a very complex chemical composition, which includes caffeine, phenolic compounds, diterpenes, magnesium, trigonelline, quinides and lignans, among many others TOC graphic).[3] The relative proportions of these compounds vary with the type of coffee bean, degree of roasting, and method of filtration. It is known that caffeine intake stimulates the release of adrenaline, producing multiple effects on the cardiovascular system such as increase blood pressure and heart rate, endothelial dysfunction, and reduced insulin sensitivity.[4,5] These effects are consistent with the increased risk of suffering a coronary event or a stroke in the hours following coffee consumption.[6,7] Nevertheless, studies in humans and animal models have yielded controversial results about the health effects of caffeine, which can be explained by population, type and dose of caffeine and low statistical power.[8]

By contrast, other components in coffee, such as phenolic compounds (specially chlorogenic acid) magnesium, trigonelline and others, have been found to improve glucose and lipid metabolism, and to exert an antioxidant activity that reduces chronic inflammation and oxidative stress in the atherosclerotic process.[9] Thus, it is plausible that the potentially harmful acute effects of caffeine could be offset by the beneficial effects of these other components in habitual drinkers, who have already developed caffeine tolerance.[9] Accordingly, habitual intake of total caffeine, regular coffee or decaffeinated coffee are not associated with higher risk of sudden cardiac death.[10]

Main study designs on the CVD effects of coffee

The effect of coffee on biological risk factors of CVD is usually assessed with clinical trials, which are experimental studies where individuals are assigned (in most cases, randomly) to coffee or caffeine intake versus no intake. Their main advantage is appropriate control of extraneous variables, so that trials can provide sufficient evidence of the effect of coffee. Unfortunately, these studies have short duration and, thus, may not represent habitual coffee consumption. By contrast, long-term effects of habitual coffee intake are mostly examined with observational studies (e.g., prospective cohort studies) which have a large sample size and continued follow-up. Their main limitations are that they cannot totally exclude reverse causation (e.g., subclinical disease or poor health status leading to change in coffee intake, rather than the contrary) and residual confounding. This is the case where some variables mix their effect with that of coffee. A good example is confounding by tobacco smoking in investigations that have found an increased risk of cancer associated with heavy coffee intake; this resulted from the fact that smoking is a very strong cause of cancer and is correlated with coffee consumption, so the individual effects of tobacco and coffee may not be easily separated in data analyses.

In practice, establishing a causal effect of coffee on CVD requires consistent evidence from clinical trials on cardiovascular risk factors and from observational studies on CVD events, as well as certain biological plausibility: compounds in coffee should show biological effects compatible with the purported effect of coffee on CVD (see next section).[9] Lastly, the dose-response relationship between coffee and CVD should be assessed, because the effect of coffee could vary across levels of consumption, as well as its risk-benefit ratio. This

information is crucial to elaborate coffee consumption guidelines addressed to the general population or to specific subgroups.

Characteristics of coffee drinkers could confound the association between coffee and CVD. Compared to non-coffee drinkers, those with heavier intake of coffee have shown worse health behaviors. For instance, in some studies coffee drinkers have a higher frequency of smoking, greater alcohol intake and worse diet, and they do less physical activity.[11,12] Also, some studies have shown that coffee drinkers have lower educational level and higher body weight than non-drinkers.[12] Thus, statistical analyses in observational studies should attempt to separate the health effects of these variables from those of coffee. This is particularly important for coffee and smoking. Given the strong correlation between coffee and tobacco smoking, and the fact that tobacco smoking is a potent CVD risk factor, multivariate adjustment may not suffice; thus, a better assessment of the effects of coffee may require restricting the analyses to never smokers.[13]

Natural history of cardiovascular disease

This comprises the sequence of events that begins with the initial exposure to the main CVD risk factors, which triggers the disease process, continues with the occurrence and diagnosis of CVD, and ends with its resolution as total recovery, sequelae (e.g., disability), or death (Figure 1).[14] Among CVD risk factors, the most important are genetic and epigenetic factors, family history of premature disease, environmental contaminants (e.g., atmospheric pollution, noise), and health behaviors, such as tobacco smoking, physical activity, sedentariness and diet, which includes both food and beverage intake (e.g., coffee). If these risk factors remain elevated during a sufficient time, atherosclerosis develops and is frequently accompanied by alterations in biological risk factors, including body weight, blood

pressure, lipidemia, serum glucose, endothelial dysfunction, inflammation and thrombosis, among others.[14] Moreover, a substantial fraction of individuals with continuous alteration of these biological factors may subsequently suffer an acute CVD event, such as myocardial infarction or stroke. Some of these events lead to death in a few hours or months but, among survivors, chronic forms of CVD disease (e.g. chronic heart failure) and disability could develop; these individuals may, in turn, suffer recurrent episodes of CVD (Figure 1).

Accordingly, this review examines the associations between coffee and: 1) biological CVD risk factors; 2) atherosclerosis; 3) acute CVD events; 4) all-cause death; and 5) recurrent CVD events (Figure 1).

Cardiovascular effects of coffee consumption

1. Effects of coffee on biological risk factors of cardiovascular disease

As regards habitual coffee consumption and blood lipids, a meta-analysis of 12 trials with 1017 individuals aged 26-49 years followed during a mean of 45 days, found that coffee intake was associated with an average increase of 8.1 mg/dl for total cholesterol (TC), 5.4 mg/dl for low-density lipoprotein cholesterol (LDL-C) and 12.6 mg/dl for triglycerides (TG).[15] The increase in TC was greater in trials using unfiltered coffee and regular coffee; also those who had hyperlipidemia were more sensitive to the cholesterol-raising effect of coffee. Moreover, meta-regression analyses revealed a positive dose-response relationship between coffee intake and TC, LDL-C and TG.[15] Of note is that coffee diterpenes, cafestol and kahweol are the primary hypercholesterolemic agents in boiled coffee, and that their removal by filters significantly reduces the lipid-raising effect of coffee.[16,17] Recent evidence indicates that coffee, which is low in diterpenes and caffeine, does not alter the blood lipid profile.[18]

Also of note is that instant coffee does not have cafestol and kawheol. Finally, more research in needed on the lipemic effect of espresso coffee.

As for blood pressure (BP), a meta-analysis of 10 trials with people aged 25-73 years, followed during a mean of 60 days (enough to have developed tolerance), found no differences in BP by consumption of total, regular or decaffeinated coffee, but there was substantial heterogeneity across studies.[19] It is not clear why the pressor effects of caffeine may be attenuated when administered via coffee, but it has been suggested that polyphenols favorably regulate BP, compensating for the effects of caffeine. Moreover, a dose-response meta-analysis of 7 cohorts, including 205,349 individuals and 44,120 cases of hypertension, found a 1% decreased risk of hypertension for each additional cup of coffee per day. Among subgroups, there were significant inverse associations for females, caffeinated coffee, and studies conducted in the US with longer follow-up. However, smoking-related variables weakened the strength of association between coffee consumption and risk of hypertension.[20] Thus, there is no epidemiological evidence of a detrimental effect of coffee on hypertension risk.

Among hypertensive patients, a review of 5 trials showed that the administration of 200-300 mg caffeine produced a mean increase of 8.1 mm Hg in systolic BP and of 5.7 mm Hg in diastolic BP. The increase in BP was observed in the first hour after caffeine intake and lasted 3 h. Additionally, in 3 studies of the longer-term effect (2 weeks) of regular coffee consumption, no increase in BP was observed when it was compared with a caffeine-free diet or with decaffeinated coffee.[21] However in a recent cross-sectional study of hypertensive older patients, we found that habitual coffee consumption of ≥3 cups/day was associated with uncontrolled BP, as evidenced from 24-h ambulatory BP monitoring.[22]

Therefore, it is prudent that physicians and other health professionals ask hypertensive patients, in particular those with uncontrolled BP, about habitual coffee consumption; and moderating coffee intake may be a simple strategy to maintain or improve BP control among the elderly.

The metabolic syndrome (MS) is a cluster of biological factors, including abdominal obesity, dyslipidemia, high blood pressure and elevated serum glucose, which behaves as an important risk factor for diabetes and CVD. A meta-analysis of 8 studies, published up to March 2015, reported that individuals with the highest coffee consumption were 13% less likely to have the MS. However, there was substantial heterogeneity in results between studies; also, the association of coffee and individual components of MS was not consistent across the studies.[23] There is some evidence that that favorable metabolic effects of caffeine-containing coffee may partly operate through associations with serum concentrations of adiponectin. A protein hormone secreted from adipose tissue that modulates several metabolic processes, including glucose regulation and fatty acid oxidation. Specifically, in women from the Nurses' Health Study, habitual consumption of ≥4 cups/day of caffeine-containing coffee has been associated with 20% higher serum adiponectin concentrations than those associated with habitual consumption of <4 cups of coffee daily;[24] this indicates that increased adiponectin may play a role in the beneficial effects of coffee on insulin sensitivity (an underlying mechanisms of the MS).

Coffee is the main source of polyphenols in the diet of European populations, and it accounts for up to 40% of polyphenol intake, mostly in the form of chlorogenic, ferulic, and p-coumaric acids.[25,26,27] Given that these compounds reduce oxidative stress and chronic inflammation, and that these processes play a key role in the pathogenesis of

atherosclerosis, this could be a biological pathway for the association between coffee and CVD.[28] In a seminal work in the Nurses' Health Study I cohort, no appreciable differences in plasma concentrations of markers of inflammation and endothelial function were found across categories of regular coffee intake in healthy women. In those with type 2 diabetes, higher regular and decaffeinated coffee consumption were associated with lower plasma concentrations of E-selectin and C-reactive protein.[29] Unfortunately, other observational studies[30-33] and clinical trials[34-35] on the effect of coffee on inflammatory markers, such as C-reactive protein and Interleukin-6, have yielded inconsistent results (direct, inverse, and no associations were reported).

2. Coffee consumption and atherosclerosis

Several studies have found inconsistent results on the association between coffee consumption and coronary artery calcium, which is a marker of coronary atherosclerosis; specifically, two cross-sectional studies reported a protective effect of coffee on atherosclerosis[36,37] while two longitudinal studies found no association.[38,39] The Rotterdam Coronary Calcification Study reported an inverse association between coffee consumption and coronary calcification in women, but not in men,[36] and in the Kangbuk Samsung Health Study moderate coffee consumption was associated with a lower prevalence of subclinical coronary atherosclerosis.[37] By contrast, in the CARDIA study no substantial association was observed between coffee or caffeine intake and coronary and carotid atherosclerosis,[38] and in the MESA study regular coffee intake was not statistically linked to coronary artery calcium progression; however, caffeine intake was marginally inversely associated with coronary artery calcium progression.[39]

3. Coffee consumption and cardiovascular disease events

During 14 years of follow-up among men participating in the Health Professionals Follow-up study, regular coffee consumption of up to 6 cups/day was not associated with a higher risk of total, fatal or non-fatal coronary heart disease (CHD). Also, habitual consumption of decaffeinated coffee or tea, and caffeine intake, were not linked to CHD risk. Moreover, in this large study, coffee consumption was not associated with higher levels of blood lipids.[40] Similar results were obtained during a 20-year follow-up of women in the Nurses' Health Study.[40]

As regards stroke, results from women followed during 24 years in the Nurses' Health Study showed that habitually consuming either 2-3 or 4 cups of coffee per day was associated with a 20% lower risk; these results applied to both ischemic and hemorrhagic stroke. The association was stronger among never and past smokers than among current smokers. Other drinks containing caffeine such as tea and caffeinated soft drinks were not associated with stroke. Finally, decaffeinated coffee showed a trend toward lower risk of stroke after adjustment for consumption of regular coffee.[41]

The above-mentioned investigations were also included in a recent meta-analysis of 36 studies, with 1.2 million participants and 36,352 CVD events. The main finding was a nonlinear association between coffee and CVD risk; compared to non-coffee drinkers, the risk of total CVD, of CHD and of stroke was 10-15% lower in moderate drinkers (3-5 cups of coffee/day). Higher consumption of coffee was not associated with elevated CVD disease risk.[42] Results were robust in stratified analyses according to disease endpoints, geographic locations of the studies, type of coffee, and baseline characteristics of the study populations. However, most of the participants' coffee consumption in the reviewed studies was

247 probably in the form of filtered coffee; thus, the results may not apply to unfiltered coffee
248 (e.g., French press, Scandinavian boiled, or Turkish/Greek coffee).[42]

249 The authors of the aforementioned study argued that the nonlinear U-shaped relationship
250 between coffee consumption and risk of CVD might be due to a combination of beneficial
251 and detrimental effects.[42] As commented above, coffee may improve glucose metabolism
252 and reduce inflammation and LDL-oxidation. However, caffeine in coffee may produce short-
253 term elevation of BP and reduce BP control in hypertensive patients. It is possible that the
254 beneficial effects are greater than the adverse effects for moderate coffee consumption,
255 whereas for heavy consumption the detrimental effects may counterbalance beneficial
256 effects.

257 Heart failure is one of the CVD epidemics of the XXI century. Mostofsky et al. have reviewed
258 5 independent prospective studies of coffee consumption and heart failure risk, including
259 6522 heart failure events and 140,220 participants.[43] They found a statistically significant J-
260 shaped relationship between coffee and heart failure. Compared with no consumption, the
261 strongest inverse association was seen for 4 cups/day and a potentially higher risk at higher
262 levels of consumption. Results were not modified by sex or by baseline history of myocardial
263 infarction or diabetes.[43] The inverse association between coffee and heart failure is
264 somewhat expected because CHD is one of the main causes of heart failure and, as
265 commented above, moderate coffee intake has also shown an inverse association with CHD.

266 Lastly, since coffee intake produces a short-term increase in BP, it is of interest to assess the
267 impact of coffee and CVD in hypertensive patients. A systematic review of 7 cohort studies
268 found no evidence of an association between habitual coffee consumption and a higher risk
269 of CVD in these patients.[21]

4. Coffee consumption and all-cause mortality

Among 41,736 men and 86,214 women with no history of CVD or cancer at baseline who were followed during 18 years and 24 years, respectively, we found in a previous study an inverse association between habitual coffee consumption and all-cause death.[44] This association, which was more evident in women than men, was mainly due to a moderately reduced risk for CVD mortality and was independent of caffeine intake. Coffee consumption was not linked to risk for cancer death after adjustment for potential confounders. Lastly, decaffeinated coffee consumption was associated with a small reduction in all-cause and CVD mortality.[44]

A subsequent large analysis of the National Institutes of Health-AARP Diet and Health Study, which included 229,119 men and 173,141 women aged 50-71 years and free of CVD and cancer at baseline, found a significant inverse association between coffee consumption and mortality.[45] The lowest risk was observed for those consuming 4-5 cups/day. Inverse associations were observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections, but not for deaths due to cancer. Results were similar in subgroups, including persons who had never smoked and persons who reported very good-to-excellent health at baseline.[45]

Several subsequent meta-analyses of the literature[46-48] and pooling of individual data[49] have assessed the association between coffee and all-cause death. They reported a modest non-linear inverse association, which probably applies to both regular and decaffeinated coffee.

The most recent meta-analysis has included 31 studies comprising 1,610,543 individuals with 183,991 cases of all-cause, 34,574 of CVD, and 40,991 of cancer deaths.[13] Analyses showed decreased all-cause and CVD mortality associated with coffee consumption in both smokers

and non-smokers. Among non-smokers, an increase of 1 cup/day of coffee yielded a linear decreased risk of death from all-causes (relative risk [RR] = 0.94) and from CVD (RR = 0.94). However, smoking modified the association between coffee and cancer. Whereas in smokers, the risk of cancer increased progressively with coffee consumption, non-smokers showed an inverse continuous association (RR = 0.98 per cup/day). The direct association between coffee intake and cancer risk in smokers was interpreted as a manifestation of confounding by smoking, whereby the protective effect of coffee was attenuated by the increased risk of cancer due to smoking.[13]

The EPIC and MEC studies have examined the association between coffee and mortality across countries and ethnic groups. The EPIC study, a large cohort of over 500.000 individuals from 10 European countries with an average follow-up of 16 years, found an inverse relationship between coffee intake and all-cause or CVD mortality in men and women.[50] The findings were consistent across countries, which increases their generalizability because populations used different coffee preparation methods and had different drinking patterns. The MEC study followed more than 185 000 African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites for an average of 16 years and also found a lower all-cause or CVD mortality associated with coffee drinking in all racial/ethnic groups.[51] This study substantially increases the generalizability of previous findings across the racial/ethnic spectrum.

Mendelian randomization studies have attempted to shed some light on whether the association between coffee and mortality is causal or not. While these investigations have confirmed that, observationally, coffee intake was associated with U-shaped lower CVD disease and all-cause mortality, genetically, caffeine intake was not associated with risk of

316 CVD or all-cause death.[52] Moreover, given that alleles representing intake of caffeine are
317 associated with greater coffee consumption, that coffee is the main source of caffeine, and
318 that results were similar after excluding tea and cola drinkers, these analyses do not support
319 the hypothesis that the association is causal. However, they do not entirely negate the
320 hypothesis because the genetic associations with coffee intake in this study were relatively
321 small compared with observational differences in coffee intake and, thus, it had limited
322 statistical power to rule out a causal association between coffee and mortality.[52] Additional
323 research is clearly needed to establish causation in the association between coffee and
324 mortality.

325 ***5. Coffee consumption and recurrent CVD and mortality in individuals who already***
326 ***suffered a CVD***

327 The few studies conducted on patients with CVD have yielded somewhat inconsistent
328 results. In a population-based case-control study, heavy coffee consumption was associated
329 with higher risk of sudden cardiac death.[53] Another study, in patients hospitalized for acute
330 myocardial infarction, found a strongly protective association between heavy coffee
331 consumption and all-cause mortality after 90 days of follow-up, but not after 4 years of
332 follow-up.[54] Also, cumulative consumption of nonfiltered coffee was not associated with the
333 risk of a second CVD event in another 3-year follow-up study.[55] By contrast, filtered coffee
334 consumption during the year preceding the coronary event has been linked to lower all-
335 cause mortality in a 10-year prospective study of survivors of an acute myocardial
336 infarction.[56] Finally, we examined the association between filtered caffeinated coffee
337 consumption and the risk of all-cause and CVD death in 11,697 women with CVD followed
338 during 24 years in the Nurses' Health Study. The main advantages of this study were the long

follow-up, the large size of the cohort, and the fact that coffee intake was assessed both before and after the CVD event every 4 years. We did not find an association between long-term filtered caffeinated coffee consumption and risk of all-cause or CVD death. Neither was shorter-term coffee consumption associated with mortality in these women.[57] Thus, with the exception of one case-control study, whose small sample size and retrospective design may limit the validity of the results, the available evidence suggests that in survivors of a CVD, coffee intake does not increase, and might even lower, the risk of a recurrent CVD event or death.[58]

We conclude that, in healthy people, habitual consumption of 3-5 cups of coffee/day is associated with a 15% reduction in the risk of CVD, and higher consumption has not been linked to elevated CVD risk. Also, usual intake of 1-5 cups/day is associated with lower risk of all-cause mortality. Finally, in people who have already suffered a CVD event, habitual consumption does not increase the risk of a recurrent CVD or death. Thus, moderate coffee intake can be part of a healthy diet for most people.[59]

However, among hypertensive patients, those with uncontrolled BP should avoid consuming large doses of caffeine. In those with well-controlled BP, coffee consumption is probably safe, but this hypothesis should be confirmed by further investigations.

Despite the substantial amount of evidence indicating that coffee consumption is safe, and even beneficial for cardiovascular health, if physicians are to offer sound medical advice on this subject, more research will be required in the following areas:

a) Better characterization of the effect of coffee in high risk populations, specifically, hypertensive patients with poorly controlled BP and patients with heart failure with and

without atrial fibrillation; this is a frequent comorbidity in heart failure, whose risk could be modified by caffeine.[60-62]

b) Given that most studies have been performed on filtered regular coffee, more research is needed on other types of coffee preparation (boiled-unfiltered, espresso, instant) and on decaffeinated coffee, though it seems that the associated CVD risk is similar to that for regular coffee.

c) The effect of coffee on patient-reported outcomes (e.g., quality of life in the general population or in patients with CHD or heart failure).[63]

d) The effect of genetic polymorphisms, particularly of the cytochrome P450 1A2 (CYP1A2) enzyme, on the pharmacokinetics and pharmacodynamics of caffeine, because those polymorphisms can contribute to can explain inter-individual variability in the amount of coffee consumed[64] as well as in their health effects.[65,66]

REFERENCES

1. Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Annu Rev Nutr. 2017 Aug 21;37:131-156.
2. Institute for Health Metrics and Evaluation. Global Burden of Disease Compare. URL (http: http://vizhub.healthdata.org/gbd-compare/). Access: 23 February, 2017.
3. Farah A. Coffee Constituents. In: Chu YF. Coffee: Emerging Health Effects and Disease Prevention, First Ed. John Wiley & Sons, New Jersey, 2012; pp 21-58.
4. Turnbull D, Rodricks JV, Mariano GF, Chowdhury F. Caffeine and cardiovascular health. Regul Toxicol Pharmacol. 2017 Oct;89:165-185.
5. Wikoff D, Welsh BT, Henderson R, Brorby GP, Britt J, Myers E, Goldberger J, Lieberman HR, O'Brien C, Peck J, Tenenbein M, Weaver C, Harvey S, Urban J, Doepker C. Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children. Food Chem Toxicol. 2017 Nov;109(Pt 1):585-648
6. Baylin A, Hernandez-Diaz S, Kabagambe EK, Siles X, Campos H. Transient exposure to coffee as a trigger of a first nonfatal myocardial infarction. Epidemiology. 2006;17(5):506-511.
7. Mostofsky E, Schlaug G, Mukamal KJ, Rosamond WD, Mittleman MA. Coffee and acute ischemic stroke onset: the Stroke Onset Study. Neurology. 2010;75(18):1583-1588.
8. Zulli A, Smith RM, Kubatka P, Novak J, Uehara Y, Loftus H, Qaradakhi T, Pohanka M, Kobyliak N, Zagatina A, Klimas J, Hayes A, La Rocca G, Soucek M, Kruzliak P. Caffeine and cardiovascular diseases: critical review of current research. Eur J Nutr. 2016 Jun;55(4):1331-1343.
9. Rebello SA, van Dam RM. Coffee consumption and cardiovascular health: getting to the heart of the matter. Curr Cardiol Rep. 2013;15(10):403.
10. Bertoia ML, Triche EW, Michaud DS, Baylin A, Hogan JW, Neuhouser ML, Freiberg MS, Allison MA, Safford MM, Li W, Mossavar-Rahmani Y, Rosal MC, Eaton CB. Long-term alcohol and caffeine intake and risk of sudden cardiac death in women. Am J Clin Nutr. 2013;97(6):1356-1263.
11. Lopez-Garcia E, van Dam RM, Li TY, Rodriguez-Artalejo F, Hu FB. The relationship of coffee consumption with mortality. Ann Intern Med. 2008;148(12):904-914.
12. Lopez-Garcia E, Guallar-Castillon P, Leon-Muñoz L, Graciani A, Rodriguez-Artalejo F. Coffee consumption and health-related quality of life. Clin Nutr. 2014;33(1):143-149.
13. Grosso G, Micek A, Godos J, Sciacca S, Pajak A, Martínez-González MA, Giovannucci EL, Galvano F. Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis. Eur J Epidemiol. 2016;31(12):1191-1205.
14. Labarthe DR. The Causal Complex. In: Labarthe DR. Epidemiology and Prevention of Cardiovascular Diseases. A global Challenge. An Aspen Publication, Gaithersburg, MD, 1998; pp 449-464.

15. Cai L, Ma D, Zhang Y, Liu Z, Wang P. The effect of coffee consumption on serum lipids: a meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2012; 66(8): 872-877.
16. van Rooij J, van der Stegen GH, Schoemaker RC, Kroon C, Burggraaf J, Hollaar L, Vroon TF, Smelt AH, Cohen AF. A placebo-controlled parallel study of the effect of two types of coffee oil on serum lipids and transaminases: identification of chemical substances involved in the cholesterol-raising effect of coffee. Am J Clin Nutr. 1995 Jun;61(6):1277-83.
17. Urgert R, Essed N, van der Weg G, Kosmeijer-Schuil TG, Katan MB. Separate effects of the coffee diterpenes cafestol and kahweol on serum lipids and liver aminotransferases. Am J Clin Nutr. 1997 Feb;65(2):519-24.
18. Agudelo-Ochoa GM, Pulgarín-Zapata IC, Velásquez-Rodriguez CM, Duque-Ramírez M, Naranjo-Cano M, Quintero-Ortiz MM, Lara-Guzmán OJ, Muñoz-Durango K. Coffee Consumption Increases the Antioxidant Capacity of Plasma and Has No Effect on the Lipid Profile or Vascular Function in Healthy Adults in a Randomized Controlled Trial. J Nutr. 2016 Mar;146(3):524-531.
19. Steffen M, Kuhle C, Hensrud D, Erwin PJ, Murad MH. The effect of coffee consumption on blood pressure and the development of hypertension: a systematic review and meta-analysis. J Hypertens. 2012;30(12):2245-2254.
20. Grosso G, Micek A, Godos J, Pajak A, Sciacca S, Bes-Rastrollo M, Galvano F, Martinez-Gonzalez MA. Long-Term Coffee Consumption Is Associated with Decreased Incidence of New-Onset Hypertension: A Dose-Response Meta-Analysis. Nutrients. 2017 Aug 17;9(8).
21. Mesas AE, Leon-Muñoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. Am J Clin Nutr. 2011;94(4):1113-1126
22. Lopez-Garcia E, Orozco-Arbeláez E, Leon-Muñoz LM, Guallar-Castillon P, Graciani A, Banegas JR, Rodríguez-Artalejo F. Habitual coffee consumption and 24-h blood pressure control in older adults with hypertension. Clin Nutr. 2016;35(6):1457-1463.
23. Marventano S, Salomone F, Godos J, Pluchinotta F, Del Rio D, Mistretta A, Grosso G. Coffee and tea consumption in relation with non-alcoholic fatty liver and metabolic syndrome: A systematic review and meta-analysis of observational studies. Clin Nutr. 2016 Dec;35(6):1269-1281.
24. Williams CJ, Fargnoli JL, Hwang JJ, van Dam RM, Blackburn GL, Hu FB, Mantzoros CS. Coffee consumption is associated with higher plasma adiponectin concentrations in women with or without type 2 diabetes: a prospective cohort study. Diabetes Care. 2008 Mar;31(3):504-507.
25. Tresserra-Rimbau A, Medina-Remón A, Pérez-Jiménez J, Martínez-González MA, Covas MI, Corella D, Salas-Salvadó J, Gómez-Gracia E, Lapetra J, Arós F, Fiol M, Ros E, Serra-Majem L, Pintó X, Muñoz MA, Saez GT, Ruiz-Gutiérrez V, Warnberg J, Estruch R, Lamuela-Raventós RM. Dietary intake and major food sources of polyphenols in a

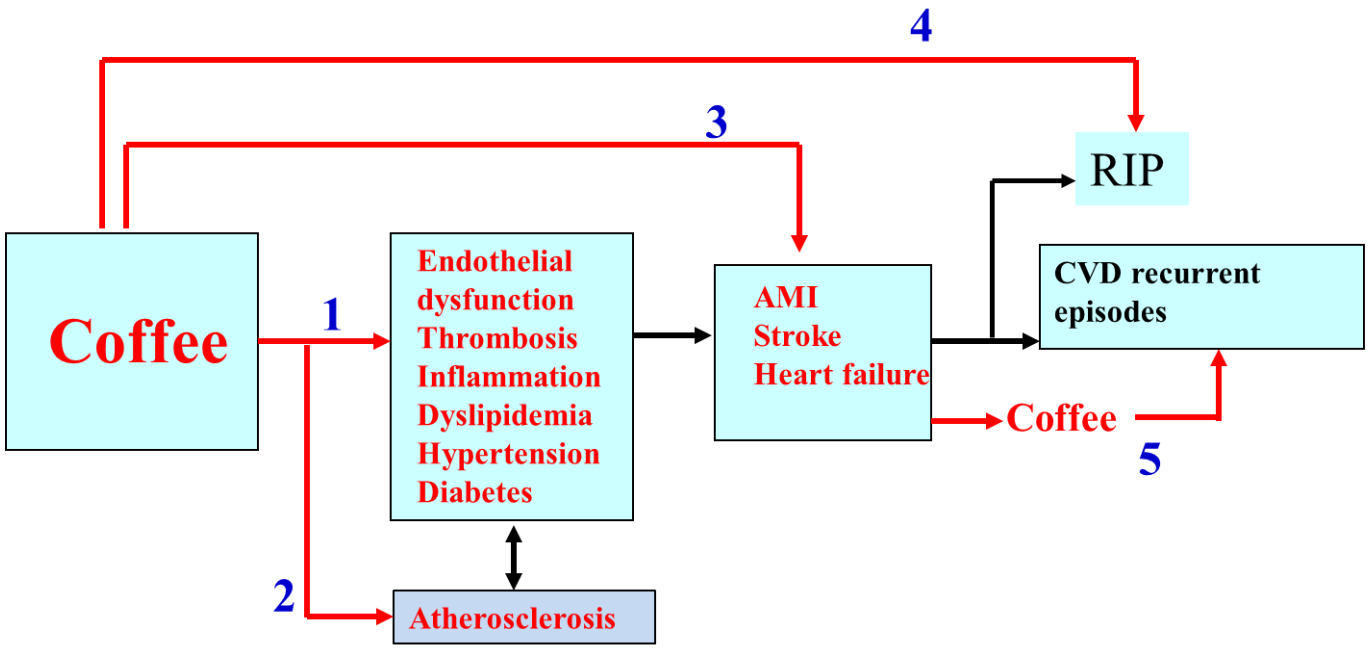
458 Spanish population at high cardiovascular risk: the PREDIMED study. Nutr Metab
459 Cardiovasc Dis. 2013 Oct;23(10):953-959.
460 26. Zamora-Ros R, Knaze V, Rothwell JA, Hémon B, Moskal A, Overvad K, Tjønneland 3,
461 Kyrø C, Fagherazzi G, Boutron-Ruault MC, Touillaud M, Katzke V, Kühn T, Boeing H,
462 Förster J, Trichopoulou A, Valanou E, Peppa E, Palli D, Agnoli C, Ricceri F, Tumino R,
463 de Magistris MS, Peeters PH, Bueno-de-Mesquita HB, Engeset D, Skeie G, Hjartåker A,
464 Menéndez V, Agudo A, Molina-Montes E, Huerta JM, Barricarte A, Amiano P,
465 Sonestedt E, Nilsson LM, Landberg R, Key TJ, Khaw KT, Wareham NJ, Lu Y, Slimani N,
466 Romieu I, Riboli E, Scalbert A. Dietary polyphenol intake in Europe: the European
467 Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Nutr. 2016;
468 55(4):1359-1375.
469 27. Grosso G, Stepaniak U, Topor-Mądry R, Szafraniec K, Pająk A. Estimated dietary
470 intake and major food sources of polyphenols in the Polish arm of the HAPIEE study.
471 Nutrition. 2014 Nov-Dec;30(11-12):1398-403.
472 28. Kishimoto Y, Tani M, Kondo K. Pleiotropic preventive effects of dietary polyphenols in
473 cardiovascular diseases. Eur J Clin Nutr. 2013 May;67(5):532-5.
474 29. Lopez-Garcia E, van Dam RM, Qi L, Hu FB. Coffee consumption and markers of
475 inflammation and endothelial dysfunction in healthy and diabetic women. Am J Clin
476 Nutr. 2006;84(4):888-893.
477 30. Maki T, Pham NM, Yoshida D, Yin G, Ohnaka K, Takayanagi R, Kono S. The relationship
478 of coffee and green tea consumption with high-sensitivity C-reactive protein in
479 Japanese men and women. Clin Chem Lab Med. 2010;48:849-854.
480 31. Rebello SA, Chen CH, Naidoo N, Xu W, Lee J, Chia KS, Tai ES, van Dam RM. Coffee and
481 tea consumption in relation to inflammation and basal glucose metabolism in a
482 multiethnic Asian population: a cross-sectional study. Nutr J. 2011; 10:61.
483 32. Zampelas A, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Associations
484 between coffee consumption and inflammatory markers in healthy persons: the
485 ATTICA study. Am J Clin Nutr. 2004;80:862-867.
486 33. Yamashita K, Yatsuya H, Muramatsu T, Toyoshima H, Murohara T, Tamakoshi K.
487 Association of coffee consumption with serum adiponectin, leptin, inflammation and
488 metabolic markers in Japanese workers: a cross-sectional study. Nutr Diabetes.
489 2012;2:e33.
490 34. Kempf K, Herder C, Erlund I, Kolb H, Martin S, Carstensen M, Koenig W, Sundvall J,
491 Bidel S, Kuha S, Tuomilehto J. Effects of coffee consumption on subclinical
492 inflammation and other risk factors for type 2 diabetes: a clinical trial. Am J Clin Nutr.
493 2010;91:950-957.
494 35. Wedick NM, Brennan AM, Sun Q, Hu FB, Mantzoros CS, van Dam RM. Effects of
495 caffeinated and decaffeinated coffee on biological risk factors for type 2 diabetes: a
496 randomized controlled trial. Nutr J. 2011;10:93.

36. van Woudenbergh GJ, Vliegenthart R, van Rooij FJ, Hofman A, Oudkerk M, Witteman JC, Geleijnse JM. Coffee consumption and coronary calcification: the Rotterdam Coronary Calcification Study. Arterioscler Thromb Vasc Biol 2008;28:1018-1023.
37. Choi Y, Chang Y, Ryu S, Cho J, Rampal S, Zhang Y, Ahn J, Lima JA, Shin H, Guallar E. Coffee consumption and coronary artery calcium in young and middle-aged asymptomatic adults. Heart. 2015;101:686-691.
38. Reis JP, Loria CM, Steffen LM, Zhou X, van Horn L, Siscovick DS, Jacobs DR Jr, Carr JJ. Coffee, decaffeinated coffee, caffeine, and tea consumption in young adulthood and atherosclerosis later in life: the CARDIA study. Arterioscler Thromb Vasc Biol. 2010; 30(10):2059-2066.
39. Miller PE, Zhao D, Frazier-Wood AC, Michos ED, Averill M, Sandfort V, Burke GL, Polak JF, Lima JA, Post WS, Blumenthal RS, Guallar E, Martin SS. Associations of Coffee, Tea, and Caffeine Intake with Coronary Artery Calcification and Cardiovascular Events. Am J Med. 2017;130(2):188-197.
40. Lopez-Garcia E, van Dam RM, Willett WC, Rimm EB, Manson JE, Stampfer MJ, Rexrode KM, Hu FB. Coffee consumption and coronary heart disease in men and women: a prospective cohort study. Circulation. 2006;113(17):2045-2053.
41. Lopez-Garcia E, Rodriguez-Artalejo F, Rexrode KM, Logroscino G, Hu FB, van Dam RM. Coffee consumption and risk of stroke in women. Circulation. 2009;119(8):1116-1123.
42. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014;129(6):643-659.
43. Mostofsky E, Rice MS, Levitan EB, Mittleman MA.Habitual coffee consumption and risk of heart failure: a dose-response meta-analysis. Circ Heart Fail. 2012;5(4):401-405.
44. Lopez-Garcia E, van Dam RM, Li TY, Rodriguez-Artalejo F, Hu FB. The relationship of coffee consumption with mortality. Ann Intern Med. 2008;148(12):904-914.
45. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality. N Engl J Med. 2012;366(20):1891-1904.
46. Malerba S, Turati F, Galeone C, Pelucchi C, Verga F, La Vecchia C, Tavani A. A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. Eur J Epidemiol. 2013;28(7):527-539.
47. Je Y, Giovannucci E. Coffee consumption and total mortality: a meta-analysis of twenty prospective cohort studies. Br J Nutr. 2014;111(7):1162-1173.
48. Crippa A, Discacciati A, Larsson SC, Wolk A, Orsini N. Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis. Am J Epidemiol. 2014;180(8):763-775.

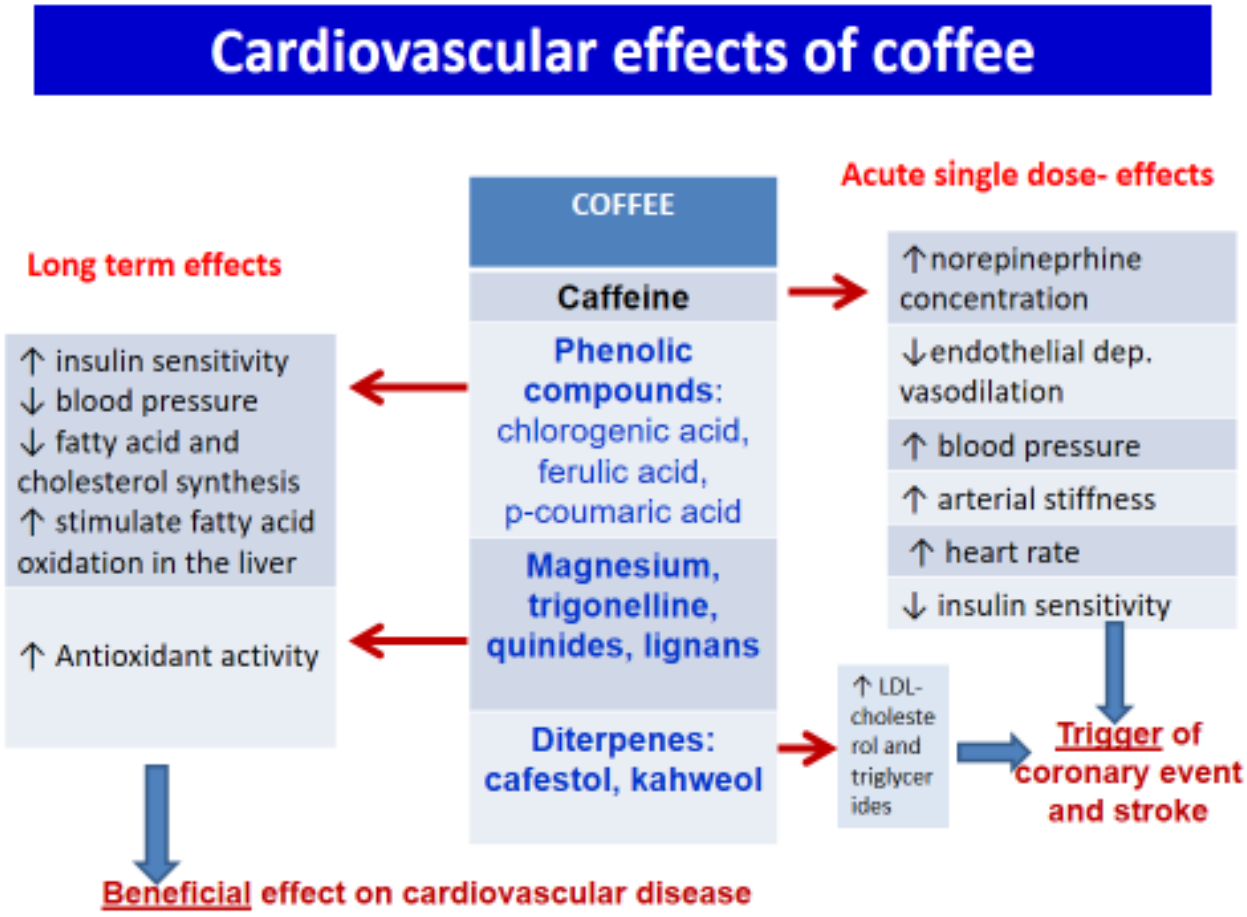
49. Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J, Lopez-Garcia E, Willett W, van Dam RM, Hu FB. Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts. Circulation. 2015;132(24):2305-2315.
50. Gunter MJ, Murphy N, Cross AJ, Dossus L, Dartois L, Fagherazzi G, Kaaks R, Kühn T, Boeing H, Aleksandrova K, Tjønneland A, Olsen A, Overvad K, Larsen SC, Redondo Cornejo ML, Agudo A, Sánchez Pérez MJ, Altzibar JM, Navarro C, Ardanaz E, Khaw KT, Butterworth A, Bradbury KE, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Grioni S, Vineis P, Panico S, Tumino R, Bueno-de-Mesquita B, Siersema P, Leenders M, Beulens JWJ, Uiterwaal CU, Wallström P, Nilsson LM, Landberg R, Weiderpass E, Skeie G, Braaten T, Brennan P, Licaj I, Muller DC, Sinha R, Wareham N, Riboli E. Coffee Drinking and Mortality in 10 European Countries: A Multinational Cohort Study. Ann Intern Med. 2017;167(4):236-247
51. Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW. Association of coffee consumption with total and cause-specific mortality among nonwhite populations. Ann Intern Med. 2017:167(4):228-235.
52. Nordestgaard AT, Nordestgaard BG. Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analyses in 95 000-223 000 individuals. Int J Epidemiol. 2016;45(6):1938-1952.
53. de Vreede-Swagemakers JJ, Gorgels AP, Weijenberg MP, Dubois-Arbouw WI, Golombeck B, van Ree JW, Knottnerus A, Wellens HJ. Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease. J Clin Epidemiol. 1999;52:601-607.
54. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Caffeinated coffee consumption and mortality after acute myocardial infarction. Am Heart J. 2004; 147: 999-1004.
55. Silletta MG, Marfisi R, Levantesi G, Boccanelli A, Chieffo C, Franzosi M, Geraci E, Maggioni AP, Nicolosi G, Schweiger C, Tavazzi L, Tognoni G, Marchioli R. Coffee consumption and risk of cardiovascular events after acute myocardial infarction: results from the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial. Circulation. 2007;116:2944-2951.
56. Mukamal KJ, Hallqvist J, Hammar N, Ljung R, Gémes K, Ahlbom A, Ahnve S, Janszky I. Coffee consumption and mortality after acute myocardial infarction: the Stockholm Heart Epidemiology Program. Am Heart J. 2009;157:495-501.
57. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, Mukamal KJ, Hu FB, van Dam RM. Coffee consumption and mortality in women with cardiovascular disease. Am J Clin Nutr. 2011;94(1):218-224.
58. Brown OI, Allgar V, Wong KY. Coffee reduces the risk of death after acute myocardial infarction: a meta-analysis. Coron Artery Dis. 2016 Nov;27(7):566-572.
59. Guallar E, Blasco-Colmenares E, Arking DE, Zhao D. Moderate Coffee Intake Can Be Part of a Healthy Diet. Ann Intern Med. 2017 Jul 11. [Epub ahead of print]

60. Caldeira D, Martins C, Alves LB, Pereira H, Ferreira JJ, Costa J. Caffeine does not increase the risk of atrial fibrillation: a systematic review and meta-analysis of observational studies. Heart. 2013;99(19):1383-1389.
61. Larsson SC, Drca N, Jensen-Urstad M, Wolk A. Coffee consumption is not associated with increased risk of atrial fibrillation: results from two prospective cohorts and a meta-analysis. BMC Med. 2015 Sep 23;13:207.
62. Mostofsky E, Johansen MB, Lundbye-Christensen S, Tjønneland A, Mittleman MA, Overvad K. Risk of atrial fibrillation associated with coffee intake: Findings from the Danish Diet, Cancer, and Health study. Eur J Prev Cardiol. 2016;23(9):922-930.
63. Lopez-Garcia E, Guallar-Castillon P, Leon-Muñoz L, Graciani A, Rodriguez-Artalejo F. Coffee consumption and health-related quality of life. Clin Nutr. 2014;33(1):143-149.
64. Coffee and Caffeine Genetics Consortium. Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. Mol Psychiatry. 2015 May;20(5):647-656.
65. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. JAMA. 2006 Mar 8;295(10):1135-41.
66. Palatini P, Ceolotto G, Ragazzo F, Dorigatti F, Saladini F, Papparella I, Mos L, Zanata G, Santonastaso M. CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. J Hypertens. 2009 Aug;27(8):1594-601.

Figure 1. Natural history of cardiovascular disease, including the potential targets for the effect of coffee consumption.



TOC GRAPHIC


Cardiovascular effects of coffee
COFFEE
Acute single dose- effects
Long term effects
Caffeine
↑norepineprhine concentration
↓endothelial dep. vasodilation
↑ blood pressure
↑ arterial stiffness
↑ heart rate
↓ insulin sensitivity
Phenolic compounds: chlorogenic acid, ferulic acid, p-coumaric acid
↑ insulin sensitivity
↓ blood pressure
↓ fatty acid and cholesterol synthesis
↑ stimulate fatty acid oxidation in the liver
Magnesium, trigonelline, quinides, lignans
↑ Antioxidant activity
Diterpenes: cafestol, kahweol
↑ LDL-cholesterol and triglycerides
Trigger of coronary event and stroke
Beneficial effect on cardiovascular disease