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Coffee is one of the most popular beverages worldwide. Its effect on health is generally regarded as beneficial in many studies. However, there are growing concerns about the adverse effect of coffee consumption on cardiovascular disease (CVD) due to the potential aggravating impact on the cardiovascular system attributed to various compounds within coffee. This review is focused on deteriorative effects of coffee consumption on CVDs with possible mechanisms. Patients with risk factors of CVDs should prudently consider heavy consumption of coffee as it may exacerbate hypertension, dyslipidemia, and atherosclerosis, and increase the odds of cardiovascular events. J-shaped or U-shaped dose-response graphs of coffee consumption and CVD parameters partially explain the inconsistency of conclusions between coffee studies on CVD, highlighting a moderate intake of coffee. Moreover, there are discrepancies in results from clinical studies elucidating considerable influences of confounding factors including gender and smoking status on outcomes of those conducted to reveal the actual impact of coffee consumption on CVDs. Physical features of subjects including genetic variations and body mass index (BMI) make it difficult to determine moderate intake of coffee for individuals in terms of caffeine metabolism. Further epidemiological studies with consideration about characteristics of the study population are needed to determine the exact effect of coffee consumption on CVD.

Conflicting Effects of Coffee Consumption on Cardiovascular Diseases: Does Coffee Consumption Aggravate Pre-existing Risk Factors?

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Abstract: Coffee is one of the most popular beverages worldwide. Its effect on health is generally regarded as beneficial in many studies. However, there are growing concerns about the adverse effect of coffee consumption on cardiovascular disease (CVD) due to the potential aggravating impact on the cardiovascular system attributed to various compounds within coffee. This review is focused on deteriorative effects of coffee consumption on CVDs with possible mechanisms. Patients with risk factors of CVDs should prudently consider heavy consumption of coffee as it may exacerbate hypertension, dyslipidemia, and atherosclerosis, and increase the odds of cardiovascular events. J-shaped or U-shaped dose-response graphs of coffee consumption and CVD parameters partially explain the inconsistency of conclusions between coffee studies on CVD, highlighting a moderate intake of coffee. Moreover, there are discrepancies in results from clinical studies elucidating considerable influences of confounding factors including gender and smoking status on outcomes of those conducted to reveal the actual impact of coffee consumption on CVDs. Physical features of subjects including genetic variations and body mass index (BMI) make it difficult to determine moderate intake of coffee for individuals in terms of caffeine metabolism. Further epidemiological studies with consideration about characteristics of the study population are needed to determine the exact effect of coffee consumption on CVD.

Keywords: coffee consumption; cardiovascular disease; confounders; dose-response; risk factors

1. Introduction

Coffee is one of the most commonly consumed beverages worldwide [1]. According to a survey, the population number of coffee consumers has increased annually and approximately 65% of adults are taking coffee daily in South Korea [2]. To date, coffee consumption is regarded as beneficial to various health issues. For instance, the extract of coffee has been extensively investigated in various pathophysiological models in vitro and in vivo, showing prominent anti-inflammatory [3], anti-oxidant [4], anti-carcinogenic [5], and other potentials. Based on these findings, it is not very surprising that numerous coffee-related papers report the alleviating effects of coffee consumption on cardiovascular disease (CVD) [6–8] and even lowered all-cause mortality after 18 to 24 years of follow-ups [9]. From a pharmacognostic view, diverse physiological consequences of coffee intake on circulatory system are attributed to caffeine and other various bioactive phenolic compounds [10,11]. Results from a cross sectional study suggested that coffee consumption reduced inflammation and markers of endothelial activation in both healthy and diabetic women, which implies the beneficial

effects of coffee on cardiovascular health [12]. These effects were independent of the presence or absence of caffeine in coffee, which means that the benefits of coffee are not limited by caffeine alone.

Notwithstanding those benefits of coffee as described above, coffee or caffeine intake should be discreetly considered in patients with CVDs since coffee has ambivalent influences on the circulatory system. An increasing number of papers are now reporting conflicting conclusions about the effects of coffee on CVDs. Some researchers have propounded the risk of acute coffee or caffeine consumption in populations with CVD-related risk factors, eminently increasing systolic and diastolic blood pressure [13–15]. In an analysis of a case control study, J-shaped association between coffee consumption and risk of acute coronary syndrome indicated that the amount of coffee intake should be in a consideration [16]. Moreover, coffee drinking turned out to be a significant forecaster of cardiovascular events for hypertensive patients especially in heavy drinkers [17].

The inconsistency over the effects of coffee consumption on cardiovascular health is assumed to be derived from various confounders [18], inadequacy of the study design or statistical analysis [19], and other unidentified reasons. However, what attracts our attention are the cases that coffee consumption aggravated risk factors in stratified group of patients with CVD in epidemiological studies. In these patients with cardiovascular risk factors, coffee consumption tends to aggravate already-existing cardiovascular risk factors [13,20].

Many previous review works have been conducted and present the adverse effects derived from consumption of coffee by analyzing epidemiological studies or randomized controlled trials (RCTs). In this review, we present some papers that considered coffee consumption to be related to the aggravation of CVD. We discuss the detrimental effects of coffee consumption on each risk factor of CVD with probable mechanisms. Then we scrutinize documents to find evidence that coffee consumption worsens preexisting risk factors of CVD in a vulnerable population.

2. Results

2.1. General Effects and Mechanisms of Coffee and Its Compounds on the Circulatory System

The major compound of coffee, caffeine, is a xanthine alkaloid which has structural similarities with adenosine and can act as a competitive inhibitor of adenosine receptor A1, A2a, and A2b [21] which leads to elevated adenosine levels in the plasma. Adenosine acts as a vasodilation factor in coronary arteries and different working modes of adenosine are largely dependent on the localization of adenosine receptor type (mostly A2a type with local vascular vasodilation effect) [22]. Caffeine can elevate intracellular cyclic adenosine monophosphate (cAMP) by inhibiting cAMP phosphodiesterase. Prolonged cAMP is known to accelerate heart function with positive inotropic effects [23]. In addition, caffeine may exert a cardioacceleratory effect and cause vagally-mediated bradycardia via baroreflex activation [24].

Chlorogenic acid is another major compound found in coffee. In addition to its favorable antioxidant properties [25], chlorogenic acid has fundamental influences on the circulatory system by activating the AMP activated protein kinase (AMPK) signaling pathway which is a key modulator of glucose and lipid metabolism [26]. Chlorogenic acid also restores diet-induced cardiovascular changes in vivo and inhibits platelet activation in vitro. Chlorogenic acid inhibits NAD(P)H oxidase activity to reduce superoxide production, and directly scavenges free radicals, and promotes NO production to support normal vascular function, and inhibits the angiotensin-converting enzyme in plasma [27]. Double-blinded randomized controlled crossover study performed with healthy volunteers revealed a decrease of mean systolic blood pressure (SBP) (−2.41 mmHg) and mean diastolic blood pressure (DBP) (−1.53 mmHg) by acute chlorogenic acid treatment [28].

Moreover, ferulic acid, a major metabolite of chlorogenic acid [27], also regulates the effects on blood pressure through inhibiting angiotensin-converting enzyme activity [29]. In a study, ferulic acid even decreased average blood pressure by 29.6% and improved endothelial function in hypertensive

rats by mediating acetylcholine receptors [30]. A summary of coffee compounds and their effects is presented in Table 1.

Table 1. General effects of major compounds derived from coffee on the circulatory system.

Component	Effect on Circulatory System	Mechanisms	Reference
Caffeine	Vasodilation Vasoconstriction (Depending on adenosine receptor)	Increase serum adenosine	[22]
	Increase peripheral resistance	Sympathetic stimulation	[31]
	Inotropic effect	Inhibiting cyclic adenosine monophosphate (cAMP) phosphodiesterase	[22]
	Cardioacceleratory effect	Baroreflex activation	[32]
Chlorogenic acid	Endothelial dysfunction	Increase inflammation (via homocysteine)	[25]
	Vascular protection	NAD(P)H inhibition (Anti-oxidant)	[28]
Ferulic acid	Hypotensive effect	Angiotensin converting enzyme inhibition	[28]
	Hypotensive effect	Angiotensin converting enzyme inhibition	[29]
Cafestol	Cholesterol-increasing effect	CYP7A1 suppression farnesoid-x-receptor (FXR), pregnane-x-receptor (PXR) agonist	[33]

2.2. Epidemiological Studies of CVDs Shed Light on Profound Influence of Coffee Consumption

Investigators have performed clinical studies targeting CVDs by scrutinizing the daily intake of coffee in subjects and recognized that coffee or caffeinated drinks may impact the outcomes of patients with CVDs. Epidemiological studies investigating the influence of undisclosed variates on CVDs have included coffee consumption as a covariate [34] or dietary confounding factor [35], implying its potential influence regardless of whether it is harmful or beneficial. A meta-analysis of 14 coffee consumption trials revealed a relationship between heavy coffee consumption and increased levels of serum cholesterol, triglyceride, and low density lipoprotein (LDL) cholesterol [20]. Results from studies concerning the efficacy of lipid-lowering drugs have also suggested that coffee consumption or caffeine intake may influence the results [36]. In addition, a guideline for hypertensive patients instructed patients to refrain from caffeine before measurement of systolic blood pressure as caffeine is recognized as a potential pressor agent [37]. The summarized result of representative studies investigating the effect of coffee consumption on parameters and risk factors of CVDs is presented in Tables 2 and 3.

Table 2. Major parameters, clinical characteristics, and outcomes from random controlled trials investigating the influence of coffee consumption on cardiovascular disease (CVD) and risk factors reviewed in this work.

Study Model	Subjects	Study Design	Measured Parameters	Significant Outcomes	Reference
Randomized Controlled Trial	Healthy men and women with a family history of hypertension * (n = 52)	0 mg/kg (placebo) or 3.3 mg/kg of anhydrous caffeine single dose	Systolic BP Diastolic BP Heart rate Cortisol CRP	Both sexes showed significant additional increase in systolic BP and cortisol response to the stressor	[38]
Randomized Cross-over trial	Healthy men and women without glucosuria, proteinuria, and current drug administration (n = 11)	Coffee oil (Arabica, Robusta), 2 g per day administered for 3 weeks	Total-C LDL-C HDL-C Triglycerides Thyroid hormones	Average serum cholesterol levels significantly rose by 13% on Arabica oil. Triglycerides levels significantly rose by 71% on Arabica oil and 61% on Robusta oil	[39]
Randomized Controlled Cross-over trial	Healthy men without drug administration (n = 15)	3.3 mg/kg caffeine sodium benzoate 2 days	Systolic BP Diastolic BP Heart rate Stroke volume System vascular resistance	Caffeine increased systolic and diastolic BP and progressively increased systemic vascular resistance	[40]

* Having at least of parents (1) who has hypertension and currently taking or (2) had taken prescription with BP medication. Total-C: total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; BP: blood pressure; CRP: C-reactive protein.

Table 3. Major parameters, clinical characteristics and outcomes from epidemiological studies investigating influence of coffee consumption on cardiovascular disease and its risk factors reviewed in this work.

Study Model	Population	Classification	Variables and Clinical Characteristics	Significant Outcomes	Reference
Prospective Cohort Study	Patients with lone atrial fibrillation cardioverted within 48 h of the onset of arrhythmia (*n* = 116)	Classified with atrial fibrillation and control group with daily coffee intake (0, 1–3, >3 cups per day)	BMI Coffee consumption Stress Type A personality *	Coffee intake (>3 cups of coffee/day) significantly increased risk of atrial fibrillation	[41]
Retrospective Cohort Study	Middle-aged adults Swedish men (*n* = 7495)	Classified all population with daily coffee intake (0, 1–4, ≥5 cups per day)	Age Myocardial infarction in brother and sister Diabetes Chest pain Smoking Alcohol abuse BP BMI	Significantly increased risk of heart failure in subjects who drank 5< cups of coffee per day compared to non-coffee drinkers	[42]
Prospective Cohort Study	Factory employees Italian men and women (*n* = 900)	Classified all subject with daily coffee intake (0, 1–2, 3–4, ≥5 cups per day)	Age BMI Total-C LDL-C Serum Triglycerides HDL-C Alcohol consumption Cigarette smoking	After stratification for smoking status, significant linear trend between coffee consumption and total cholesterol only in smokers	[43]
Cross-sectional Study	Greek men (*n* = 1514) and women (*n* = 1528)	Classified all subject with daily coffee intake (0, <200, 200–400, >400 mL)	Age Education Smoking Physical activity Obese SBP DBP Hypercholesterolemia Diabetes mellitus Family history of CHD	Coffee consumed >200 mL had higher IL-6, CRP, SAA, TNF-a, WBC count (all significant)	[44]

* Following revised Minnesota Multiphasic Personality Inventory (MMPI-2) Type A scale. Total-C: total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; BMI: body mass index; BP: blood pressure; SAA: serum amyloid-A; CRP: C-reactive protein; CHD: coronary heart disease; IL-6: interleukin-6; TNF-αL tumor necrosis factor α; WBC: white blood cell.

2.3. Coffee Consumption Exacerbates Hypertension in People Who Have Risk Factors

As previously studied, adenosine is a potent vasodilator in coronary arteries [45]. However, paraxanthine, a main metabolite of caffeine, has a pressor effect by exerting similar sympathomimetic action to caffeine; therefore it can increase serum epinephrine levels in healthy volunteers [46]. The reason why caffeine increases blood pressure can be explained with increased peripheral resistance, sympathetic tone, catecholamine, and renin secretion [22]. In addition, caffeinated coffee consumption can induce rapid increase in aortic systolic and diastolic pressure compared to decaffeinated coffee consumption in a double-blind study with healthy and young subjects [31]. A noteworthy point in the report is the pulse wave velocity (PWV) result, which increased significantly from 7.2 to 8.0 m/s at the end of 90 min after coffee ingestion, revealing evidences that caffeine intake can increase arterial stiffness.

Age, family history of hypertension, excess potassium or alcohol consumption, and obesity are well-known strong risk factors of hypertension [47]. Fifty-two healthy subjects having normal range blood pressure but with a family history of hypertension showed significant responses to caffeine consumption [38]. In detail, caffeine administration (3.3 mg/kg) caused an additional increase of systolic blood pressure and cortisol response to the stressor. In addition, analysis of controlled clinical and epidemiologic studies revealed that regular coffee ingestion may be harmful to hypertension-prone subjects [13]. Moreover, a cross-sectional study with 843 elderly volunteers aged 60–87 elucidated the positive relation of coffee intake and hypertension, especially in groups using anti-hypertensive drugs [48].

2.4. Lipid Profiles of Coffee Consumers with Underlying Risk Factors can Be Affected by Coffee Brewing Method

Although the doubt about caffeine's property in increasing serum cholesterol level is now almost cleared [20], there are still remaining debates on other compounds of coffee. The effect of coffee drinking on lipid levels of subjects depends on the brewing method of coffee [49]. Cafestol and kahweol are abundant diterpenes in boiled Turkish or French press coffee. It has been reported that cafestol can increase serum cholesterol levels in a dose-dependent manner, with 1 mg/dL increase in cholesterol per 2 mg of cafestol consumption [50,51]. Similar results have been drawn after consumption of coffee oil containing 71.56 mg of cafestol and 52.96 mg of kahweol in daily dose (in Arabica coffee group) [39]. The mechanism of cafestol in increasing serum cholesterol levels includes suppressing both enzyme activity and gene expression of CYP7A1 by discouraging bile acid production, thus increasing hepatic free cholesterol [52]. Moreover, as an agonist ligand for both farnesoid-x-receptor (FXR) and pregnane-x-receptor (PXR), cafestol can modulates cholesterol levels [33]. Coffee consumption may have an inverse correlation with high density lipoprotein in men. The ratio of high density lipoprotein cholesterol to total cholesterol has been found to be lower in male coffee drinkers compared to those in male non-coffee drinkers, implying a deteriorating effect of coffee on lipid profile [53]. In a large cross-sectional study including 14,168 men and 14,859 women in Norway, serum total cholesterol level showed dose-response relation with coffee consumption per day [54]. In this study, investigators observed the strongest cholesterol-increasing effect in groups drinking boiled coffee.

Age, sex, obesity, diabetes sedentary lifestyle, alcohol use, smoking, and genetic factors [55–57] are considered to be related with the occurrence of dyslipidemia. Interestingly, a cross-sectional study carried out in Germany revealed a dose-related increment of serum total cholesterol was found only in young people [58], which is similar to those drawn from an Israeli study [59]. Hypertension and hyperlipidemia are frequently found as comorbidities [60] and the association has been proven in a cohort study [61]. A study investigated a group of 9043 hypertensive adults (during hypertension follow-up program), and found a positive association with coffee intake and serum cholesterol level [62]. Patients with hyperlipidemia tend to have higher cholesterol levels after coffee drinking than healthy subjects demonstrated by a meta-analysis review of 14 randomized clinical trials [20].

2.5. Coffee Consumption Potentially Worsens Vascular Health and Atherosclerosis

Coffee consumption is generally regarded as safe and advantageous to atherosclerosis with anti-oxidant properties because coffee contains phenols that can improve endothelial function [63]. However, there are still unfavorable effects of coffee intake on atherosclerosis progression and vascular health with some explainable mechanisms. Influence of caffeine ingestion on vascular wellness and hemodynamics has been determined by several parameters, including PWV, reflected wave, or carotid artery ultrasound in various studies. Acute or chronic coffee consumption increases arterial stiffness [31,64]. Arterial stiffness measured by carotid-femoral PWV is demonstrated to be positively associated with homocysteine level as an evident factor in atherosclerosis in a Chinese cross-sectional study [65]. It has been found that plasma homocysteine level, an independent risk factor of cardiovascular disease [66], was increased by caffeine (0.4 μmol/L) and coffee intake (0.9 μmol/L) in randomized controlled trials [67]. In addition, chlorogenic acid is known to be responsible for elevated homocysteine level in coffee consumers [68]. Homocysteine can provoke inflammation-driven endothelial dysfunction and generate excessive reactive oxygen species by inducing C-reactive protein which is critical to atherosclerotic progression [69] and can aggravate coronary artery calcium (CAC) [70]. Peripheral vascular resistance is also elevated by caffeine (3.3 mg/kg) [40], implying that coffee might play a role in the progression of atherosclerosis. Moreover, in a randomized, double blinded, cross-over study with 12 hypertensive patients, administration of 250 mg of caffeine showed significantly increased systolic blood pressure and PWV [71]. There is also additional evidence demonstrating relationships between moderate to heavy coffee consumption and increased inflammatory markers including interleukin (IL)-6, C-reactive protein, and serum amyloid-A [44]. Further, heavy coffee drinking of more than 4 cups/day is associated with increased inflammatory markers and impaired thrombosis/fibrinolysis in hypertensive smokers [72].

In a cross-sectional study conducted in Korea including 25,138 asymptomatic men and women, coffee consumption and coronary artery calcium score apparently showed a U-shaped relationship [73]. The authors focused on the point that CAC score ratio is lowest in groups drinking 3–5 cups of coffee/day. However, CAC score ratios of group drinking ≥5 cups of coffee/day showed higher CAC scores than 3–5 cups or even non-drinking groups, suggesting that high doses of coffee have detrimental effects.

2.6. Caffeine may Trigger Arrhythmia and Cardiovascular Events in Certain Populations

Coffee consumption should be considered carefully for patients with arrhythmia. Although many RCT studies concluded that the correlation between the occurrence of arrhythmia and intake of caffeine or coffee is not significant [74,75], there is evidence that coffee or caffeine can be associated with incidents of arrhythmia in populations with certain aggravation factors. Results from large-scale clinical studies have indicated that heavy consumption (more than 9 cups per day) can double the occurrence of premature ventricular complexes [76], particularly in certain subjects with risk factors [77]. By activating ryanodine receptor 2, caffeine may interfere with luminal calcium ion levels responsible for after-potential, thus inducing arrhythmia [78,79]. It has been reported that high coffee consumption increases the incidence of acute lone fibrillation [41].

A cohort study with a huge healthy Italian population revealed the coronary heart disease (CHD) hazard ratio is in direct proportion to the amount of coffee consumption ranging from 0 to 4 cups per day [80]. Meanwhile, an epidemiological study analyzing the etiology and prognosis of heart failure revealed higher odds ratio (OR = 1.11 as compared to non-consuming group) of heart failure in ordinary Swedish people taking more than 5 cups of coffee a day [42]. In another large cohort study conducted in the US, coffee consumption was associated with higher incidence of myocardial infarction with coinciding result of relative risk (RR) [81]. However, a recent meta-analysis demonstrated a J-shaped correlation between heart failure and coffee consumption, showing that the inverse-effect of coffee on relative risk of heart failure rebounded from more than 4 cups of coffee per day [82].

3. Discussion

The present study elucidated on the deteriorating effects of coffee consumption on CVDs with reasonable evidence. To the best of our knowledge, daily ingestion of caffeine less than 400 mg/day has no evident adverse effects in the general and healthy adult population [83]. Moderate coffee consumption itself has more benefits than harms for healthy population as supported by the majority of clinical works. Most published articles have reported that adverse effects of moderate coffee or caffeine consumption on CVDs are not evident in a healthy population without potential risk factors [84–86]. However, as we reviewed in this paper, for certain populations with risk factors, coffee consumption has remarkable deteriorating effects. Discrepancies of study results about coffee consumption can be explained by several reasons.

Consisting of various bioactive compounds, coffee consumption has both risks and benefits on cardiovascular disease due to varying intake amounts. In many papers, the relationship between coffee (or caffeine) intake and cardiovascular parameters showed J-shaped or U-shaped consequences with unfavorable effects on heavy consumers [16,64,73,87–89], implying a non-linear risk–benefit ratio; so it does seem to be a matter of the amount of coffee rather than whether it is consumed or not. "Moderate coffee consumption" whose benefit of consumption outweighs the risk, is often represented as 3–5 cups a day [90]. However, it is not easy to suggest a moderate amount for the entire population concerning individual characteristics. Genetic variation, especially CYP1A2 allele [91], can affect the clearance rate for caffeine among and within individuals and can vary up to 40-fold [92]. Females and non-smokers are reported to have lower activity of CYP1A2 [93], so more attention should be paid to these slow caffeine metabolizers in analyzing epidemiological data. Furthermore, the effect of coffee consumption can be modified by gender and obese status (body mass index, BMI) [94]; obese volunteers exhibited higher absorption rate, lower elimination rate, and longer half-life of caffeine in serum [95].

Confusing variables vary in many coffee studies with modification in criteria that requires delicate interpretation (Table 4). Particularly, as reviewed in many studies, both sex and smoking are two essential confounders in the study of coffee consumption and CVD [96]. Positive correlation between number of cigarettes smoked and amount of caffeine consumed was reported [97], deducing 2.3 times higher amount of coffee consumption in smokers as compared to non-smokers [96]. It has been found that smoking status can change the influence of coffee consumption on serum total cholesterol level [43]. As a significant cause and risk factor of CVD, smoking habits can confuse investigators from deducing appropriate results [98].

The differences in gender responses in cardiovascular parameters to caffeine were importantly considered by numerous studies which attribute the differences to steroid hormones and lifestyle [99–101]. As coffee or caffeine consumption is closely related with sex and smoking status, stratification by gender should be performed to eliminate gender bias. Social status and income levels affect various aspects of the health status of the group members, masking the true effect of coffee consumption on CVD.

To have consistency in clinical investigations, characteristics of subjects in clinical trials should be considered in designing the methodology, including ethnic variations in responsiveness to caffeine and different lifestyles. For instance, results of a Tromsø heart study with a Danish population characterized by highest servings of daily coffee per capita are different from those of an East Asian population in basal serum lipid levels and dose-response to coffee [102,103]. This raises the necessity of clinical investigations for each population according to their lifestyle to determine the precise effect of coffee on CVD. A retrospective investigation using the Framingham risk model determined the influence of coffee consumption on coronary heart disease risk in Korean society [104]. Another study reviewed the association between coffee consumption and stroke risk in a cross-sectional study in Korea [101]. Interestingly, results from both studies indicate that coffee only has beneficial effects in the female population (no significant association in males), attributing the result to lifestyle differences in both sexes. A similar trend was found in a study of Japanese, neighboring Korea, showing a significant inverse correlation of coffee with all mortality and CVD-related mortality only in women [105].

However, beneficial effects of coffee consumption on mortality and coronary morbidity in both sexes have been reported in a Scottish heart study [106] and the Tromsø heart study [102]. Their populations are clearly different from Asian ones.

Therefore, coffee consumption should be prudently considered in patients with high risk factors for cardiovascular events until concrete clinical evidences are established. Dosages of caffeine should be determined in medical context considering the unveiled influence of coffee on risk factors of CVDs and personal lifestyle of the subjects.

Table 4. Suspected confounding factors influencing the effect of coffee consumption on cardiovascular disease-related dependent variables in epidemiological clinical studies:

Independent Variable	Variables (Confounding Factor)	Dependent Variable	Reference
Coffee consumption (instant, brewed)	alcohol, BMI, hospital *, rank **, smoking, tea consumption	Total-C LDL-C HDL-C Triglycerides	[102]
Coffee consumption (Turkish, instant)	age, BMI, daily total energy, food variates (fat, polyunsaturated fat, monounsaturated fat, omega 3, omega 6, carbohydrate and fiber intake, coffee consumption habit), sex, smoking, tea consumption,	Total-C LDL-C HDL-C VLDL-C Triglycerides	[49]
Coffee and tea consumption	age, BMI, education ***, ethnic origin †, saturated fatty acid, season, smoking, sugar, tea consumption	Total-C LDL-C HDL-C	[53]
Coffee and tea consumption	activity at work, age, alcohol, BMI, BP, cotinine, housing tenure ††, leisure activity †††, smoking, occupational social class #, personality score ##, plasma fibrinogen, total-C, HDL-C, triglycerides, vitamin C	Coronary risk factors Coronary disease All-cause mortality	[106]
Coffee consumption	age, alcohol, BMI, education ###, food variates (vegetable, fish, fruit, rice), history of HT, DM, smoking, walking hour,	All-cause mortality CVD mortality Cancer mortality Other causes mortality	[105]
Coffee consumption	age	Total-C LDL-C VLDL-C HDL-C	[107]
	age, BMI, BP, smoking, total-C	CVD events	
Coffee consumption	age, alcohol, BMI, number of cigarettes, smoking, physical activity, time since last meal &	Total-C HDL-C Triglycerides	[102]

* According to three different visited hospitals for their examination; ** rank of subjects in military (low, middle, high); *** categorized as elementary, partial high school, high school, higher education; † according to country of birth (Israel, Europe, Asia, North Africa); †† categorized as owner occupier, renter; ††† categorized as active, average, inactive; # categorized as I~V level; ## according to Bortner score; ### categorized as years of education (~15 years, 16~18 years, 19~ years); & categorized as 5 grades, only in analysis of triglycerides. Total-C: total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; VLDL-C: very-low density lipoprotein cholesterol; BMI: body mass index; BP: blood pressure; HT: hypertension; DM: diabetes mellitus.

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