


Article

Genetic and Non-Genetic Factor-Adjusted Association between Coffee Drinking and High-Density Lipoprotein Cholesterol in Taiwanese Adults: Stratification by Sex

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Abstract: Low high-density lipoprotein cholesterol (HDL-C) is a major risk factor for cardiovascular diseases (CVDs), the leading cause of global mortality. We aimed to determine the effect of coffee drinking and sex and their interaction, as well as rs1800588 and rs1800775 polymorphisms on HDL-C levels in Taiwanese adults. Data of 4262 men and 4813 women, aged 30–70 years, were retrieved from Taiwan Biobank. The interaction between sex and coffee drinking on HDL-C was significant ($p = 0.0452$). Coffee consumption was significantly associated with higher HDL-C levels in only women ($\beta = 0.81679$; $p = 0.0246$). However, rs1800588 and rs1800775 variants were significantly associated with HDL-C in both sexes. In women, β -values were 0.99080; $p = 0.0059$ and 3.16277; $p < 0.0001$ for rs1800588 CT and TT genotypes, respectively and -1.80954 ; $p < 0.0001$ and -2.81512 ; $p < 0.0001$ for rs1800775 AC and CC genotypes, respectively. In men, β -values were 1.32430; $p < 0.0001$ and 3.24976; $p < 0.0001$ for rs1800775 CT and TT genotypes, respectively and -1.96232 ; $p < 0.0001$ and -2.71536 , $p < 0.0001$ for the AC and CC genotypes, respectively. In conclusion, coffee drinking was significantly associated with higher high-density lipoprotein (HDL) levels in women but not men after adjusting for confounders including rs1800588 (LIPC) and rs1800775 (CETP) variants.

Keywords: HDL-C; coffee drinking; sex; Taiwan Biobank; rs1800588; rs180077

1. Introduction

Cardiovascular diseases (CVDs) are among the leading causes of global mortality [1–3]. High-density lipoprotein cholesterol (HDL-C) levels play several clinically relevant roles in cardiovascular health. Lower levels of HDL-C are associated with cardiovascular disease morbidity and mortality [1,4,5]. However, higher levels protect against atherosclerosis and other CVDs [6,7]. It has been projected that a unit increase in HDL-C is associated with 1.9–2.3% and 3.2% reduction in the risk of CVDs in men and women, respectively [8]. The anti-atherosclerotic property of HDL-C is attributed to its ability to enhance the reverse cholesterol transport (RCT) pathway [6,7,9]. RCT is the

removal of excess cholesterol from macrophages to the liver for excretion or redistribution to other tissues [6,10]. Other clinical benefits of HDL-C include the protection against apoptosis, inflammation, infections, thrombosis and oxidation [9,10].

Both genetic and non-genetic factors account for individual variability in high-density lipoprotein (HDL) levels.

About 40–60% of this variability is of genetic origin [11]. In general, HDL-C levels in women are higher than in men [12–14]. The minimal threshold levels are <40 mg/dL in men and <50 mg/dL in women [15,16]. The hepatic lipase (LIPC) and cholesterol ester transfer protein (CETP) genes are well established genetic factors that influence HDL-C levels and metabolism, as well as atherosclerosis [17]. The variants rs1800588 (LIPC) and rs100775 (CETP) have been respectively associated with higher and lower HDL-C levels [17–20]. The cardio-protective property of the LIPC gene is due to its potential to stimulate reverse cholesterol transport and clearance of intermediate-density lipoprotein (IDL) from circulation [21,22]. However, deficiency in LIPC favors the accumulation and circulation of cholesterol-rich atherogenic particles [17]. CETP promotes the transfer of cholesteryl ester from HDL-C to very low-density lipoprotein (VLDL), which is rich in triglycerides [22–24]. Its deficiency is thought to be a major reason for high levels of HDL-C in Asians [23].

Non-genetic factors including, age, exercise, diet, smoking, BMI, alcohol and coffee drinking play pivotal roles in modifying HDL-C levels and managing cardiovascular disease risk [1,14,25]. Coffee, a modifiable lifestyle factor is the second leading non-alcoholic beverage that is consumed worldwide [1]. So far, its association with HDL-C and CVDs is inconsistent. Hence, its role in cardiovascular health is still controversial [1,26]. For instance, coffee has been positively associated with HDL-C [27,28], implying that it might protect against CVDs. The antiatherogenic properties are ascribed to its antioxidant-rich phenolic compounds [7,27], which enhance HDL-C-mediated cholesterol efflux from macrophages [7]. However, some studies reported that coffee drinking and HDL-C are negatively related [26] while others reported no significant associations [29,30]. The association between coffee consumption and HDL-C appears to vary by sex. For instance, significant associations between coffee drinking and HDL-C were observed in women but not men [1]. Furthermore, drinking coffee was inversely associated with coronary calcification especially in women [1].

In most previously conducted studies, adjustments were not made for potential confounders like single nucleotide polymorphisms (SNPs), smoking, tea and alcohol drinking and diet, among others. Since the association between coffee drinking and HDL-C is inconsistent, there is a need for more investigations. Hence, this study was undertaken to explore the effect of coffee drinking and sex and their interaction on HDL-C in Taiwanese adults with rs1800588 (LIPC) and rs1800775 (CEPT) single nucleotide polymorphisms.

2. Methods

Genetic and non-genetic data of 9075 adult Taiwanese comprising 4262 men and 4813 women, aged 30–70 years, were obtained from the Taiwan Biobank, a national health resource, which possesses genetic information of over 200,000 ethnic Taiwanese inhabitants. All the biobank enrollees usually sign informed consent forms prior to the collection of data. Data on coffee, tea and alcohol consumption, age, sex, diet, exercise, smoking, second-hand smoke and disease history (diabetes and hypertension) were collected through questionnaires. The body mass index (BMI) and waist-hip ratio (WHR) were determined through physical examinations while high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and rs1800588 (LIPC) and rs180077 (CEPT) single nucleotide polymorphisms (SNPs) were determined through biochemical examinations.

Participants were classified as coffee drinkers if they drank coffee three or more times in a week. The mean menopausal age was 49.10 years. Hence, age was stratified into two as <49.10 and ≥49.10 years. Tea drinkers were those who drank tea at least once a day. Vegetarians included those who maintained a vegetarian diet at least six months before the data collection date. Those who did exercise for more than 150 min per week were categorized under the regular exercise group.

BMI categories included underweight (BMI < 18.5 kg/m²), normal (18.5 ≤ BMI < 24 kg/m²), overweight (24 ≤ BMI < 27 kg/m²) and obesity (BMI ≥ 27 kg/m²). Non-smokers included those who never smoked or did not continuously smoke for six months or more. Former smokers were those who continuously smoked for a minimum of six months but were not smoking at the time that data were collected, while current smokers included those who ceaselessly smoked for six months or more and were still smoking. Exposure to second-hand smoke was defined as being exposed for at least 5 min per hour. Alcohol consumption categories comprised non-drinkers; those who did not drink alcohol or drank <150 cc per week for six months, former drinkers; those who quit alcohol drinking for more than six months and current drinkers; those whose weekly alcohol drinking for six consecutive months was at least 150 cc [31]. Ethical approval for this study was obtained from the institutional review board (IRB) of Chung Shan Medical University (CS2-16114).

Statistical Analyses

HDL-levels in men and women were compared using the t-test and presented as means ± standard errors (SEs). Categorical variables, e.g., coffee drinking in male and female participants were compared using the chi-square test and presented as percentages. The association between coffee drinking and HDL-C was determined using multivariate linear regression models. Adjustments were made for rs1800588 and rs180077 genotypes, age, vegetarian diet, exercise, BMI, smoking, second-hand smoke, alcohol and tea drinking, WHR, LDL-C, TG and history of diabetes and hypertension. All the above statistical analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC, USA).

3. Results

The basic characteristics of the male and female participants are shown in Table 1. The mean (±SE) HDL-C levels in men (48.585 ± 0.191 mg/dL) and women (58.467 ± 0.171 mg/dL) were significantly different ($p < 0.001$). Among men, 1339 (31.42%) were coffee drinkers while 2923 (68.58%) were non-drinkers. Among women, 1661 (34.51%) were coffee drinkers and 3152 (65.49%) were non-drinkers. The association between coffee drinking and HDL-C in all participants is shown in Table 2. The male sex was significantly associated with lower levels of HDL-C compared to the female sex ($\beta = -6.33560$; $p < 0.001$) while coffee drinking was not significantly associated with HDL-C. However, there was a significant interaction between sex and coffee drinking ($p = 0.0399$). Variants of LIPC (rs1800588) and CETP (rs1800775) were significantly associated with higher and lower levels of HDL-C, respectively (Table 2). For rs1800588, the beta coefficients (β) were 1.14306 ($p < 0.0001$) and 3.24816 ($p < 0.0001$) for the CT and TT genotypes, respectively. For rs1800775, β -values were -1.79140 ($p < 0.0001$) and -2.71185 ($p < 0.0001$) for the AC and CC genotypes, respectively (Table 2). After stratification by sex, there was no significant association between coffee consumption and HDL-C in men (Table 3). However, the rs1800588 genotypes remained significantly associated with higher HDL-C levels in men ($\beta = 1.32430$; $p < 0.0001$ for CT and $\beta = 3.24976$; $p < 0.0001$ for TT) while the rs1800775 genotypes remained significantly associated with lower levels of HDL-C ($\beta = -1.80954$; $p < 0.0001$ and $\beta = -2.81512$, $p < 0.0001$) for the AC and CC genotypes, respectively (Table 3). In women, coffee consumption and the rs1800588 genotypes were significantly associated with higher levels of HDL-C while the rs1800775 genotypes were significantly associated with lower levels of HDL-C (Table 3). The β -values were 0.81679; $p = 0.0246$ for coffee drinking, 0.99080; $p = 0.0059$ for the rs1800588 CT genotype, 3.16277; $p < 0.0001$ for the rs1800588 TT genotype, -1.80954 ; $p < 0.0001$ for the rs1800775 AC genotype and -2.81512 ; $p < 0.0001$ for the rs1800775 CC genotype (Table 3). Exercise, underweight and alcohol drinking were significantly ($p < 0.001$) associated with higher HDL-C levels (Tables 2 and 3). However, vegetarian diet, overweight, obesity, smoking, second-hand smoke, WHR, TG and diabetes were significantly ($p < 0.001$) associated with lower levels of HDL-C (Tables 2 and 3). After stratification by menopausal status, coffee drinking was significantly associated with higher HDL-C ($\beta = 1.36554$; $p = 0.0057$) only in non-menopausal women (Table 4).

Table 1. Basic characteristics of male and female participants.

Variables	Men (n = 4262)	Women (n = 4813)	p-Value
HDL-C (mg/dL)	48.5852 ± 0.171	58.4673 ± 0.191	<0.0001
Coffee drinking			0.0018
No	2923 (68.58%)	3152 (65.49%)	
Yes	1339 (31.42%)	1661 (34.51%)	
rs1800588			0.1561
CC	1764 (41.39%)	1967 (40.87%)	
CT	1981 (46.48%)	2197 (45.65%)	
TT	517 (12.13%)	649 (13.48%)	
rs1800775			0.5161
AA	1034 (24.26%)	1217 (25.29%)	
AC	2194 (51.48%)	2435 (50.59%)	
CC	1034 (24.26%)	1161 (24.12%)	
Age (years)			0.6949
<49.10	2136 (50.12%)	2432 (50.53%)	
≥49.10	2126 (49.88%)	2381 (49.47%)	
Tea drinking			<0.0001
No	2352 (55.19%)	3362 (69.85%)	
Yes	1910 (44.81%)	1451 (30.15%)	
Vegetarian diet			<0.0001
No	4099 (96.18%)	4524 (94.00%)	
Yes	163 (3.82%)	289 (6.00%)	
Exercise			0.0314
No	2400 (56.31%)	2818 (58.55%)	
Yes	1862 (43.69%)	1995 (41.45%)	
BMI (kg/m ²)			<0.0001
Underweight (BMI < 18.5)	1548 (36.32%)	2789 (57.95%)	
Normal (18.5 ≤ BMI < 24)	53 (1.24%)	181 (3.76%)	
Overweight (24 ≤ BMI < 27)	1589 (37.28%)	1140 (23.69%)	
Obesity (BMI ≥ 27)	1072 (25.15%)	703 (14.61%)	
Smoking			<0.0001
No	2422 (56.83%)	4597 (95.51%)	
Former	971 (22.78%)	101 (2.10%)	
Current	869 (20.39%)	115 (2.39%)	
Second hand smoke			<0.0001
No	3606 (84.61%)	4277 (88.86%)	
Yes	656 (15.39%)	536 (11.14%)	
Alcohol drinking			<0.0001
No	3413 (80.08%)	4713 (97.92%)	
Former	233 (5.47%)	33 (0.69%)	
Current	616 (14.45%)	67 (1.39%)	
Waist-hip ratio	0.8971 ± 0.001	0.8468 ± 0.001	<0.0001
LDL-C (mg/dL)	123.40 ± 0.488	120.30 ± 0.461	<0.0001
TG (mg/dL)	135.60 ± 1.537	101.80 ± 1.059	<0.0001
Diabetes			<0.0001
No	3718 (87.24%)	4423 (91.90%)	
Yes	544 (12.76%)	390 (8.10%)	
Hypertension			<0.0001
No	3211 (75.34%)	4110 (85.39%)	
Yes	1051 (24.66%)	703 (14.61%)	

Continuous variables are presented as means ± standard errors (SEs) while categorical variables are presented as percentages (%). $p < 0.05$ —Significant; HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol and TG—triglyceride.

Table 2. Multiple linear regression showing the association between coffee drinking and high density lipoprotein cholesterol (HDL-C) in all participants.

Variables	β	<i>p</i> -Value
Sex (ref: Women)		
Men	−6.33560	<0.0001
Coffee drinking (ref: No)		
Yes	0.38920	0.1100
rs1800588 (ref: CC)		
CT	1.14306	<0.0001
TT	3.24816	<0.0001
rs1800775 (ref: AA)		
AC	−1.79140	<0.0001
CC	−2.71185	<0.0001
Age (ref: <49.10 years)		
≥49.10 years	1.36332	<0.0001
Tea drinking (ref: No)		
Yes	0.44026	0.0675
Vegetarian diet (ref: No)		
Yes	−5.33153	<0.0001
Exercise (ref: No)		
Yes	1.46267	<0.0001
BMI (ref: Normal)		
Underweight	5.47862	<0.0001
Overweight	−3.46621	<0.0001
Obesity	−5.09464	<0.0001
Smoking (ref: No)		
Former	−0.44759	0.2484
Current	−1.94760	<0.0001
Second hand smoke (ref: No)		
Yes	−0.36246	0.2863
Alcohol drinking (ref: No)		
Former	−0.29083	0.6731
Current	4.74316	<0.0001
Waist hip ratio	−23.34675	<0.0001
LDL-C	0.01325	0.0003
TG	−0.04312	<0.0001
Diabetes (ref: No)		
Yes	−2.02392	<0.0001
Hypertension (ref: No)		
Yes	−0.21625	0.4792

Interaction between sex and coffee *p*-value = 0.0452. *p* < 0.05—significant; HDL-C—high-density lipoprotein cholesterol; ref—reference; β —beta coefficient; LDL-C—low-density lipoprotein cholesterol and TG—triglyceride.

In the present study, the interaction between sex and coffee drinking on HDL-C was significant. After stratification by sex, coffee drinking was significantly associated with higher levels of HDL-C levels in women but not men. Moreover, after stratification by menopausal status, coffee drinking was significantly associated with higher levels of HDL-C levels in non-menopausal women but not menopausal women. To our knowledge, this is one of the first studies with a relatively larger sample size to assess the association between coffee drinking and HDL-C. Several potential confounders were adjusted including rs1800588 and rs1800775 variants, age, diet, exercise, BMI, smoking, tea and alcohol drinking, among others.

High-density lipoprotein cholesterol (HDL-C) is inversely associated with cardiovascular disease morbidity and mortality [1,4,5]. The positive association between coffee drinking and HDL-C that was observed in the present study implies that coffee might protect against atherosclerosis and other heart diseases. These results are in conformity with previous findings [27,28,32–34]. In addition, they somewhat conform to a study that demonstrated the anti-atherogenic property of coffee, where it

enhanced HDL-mediated reverse cholesterol transport [7]. Reverse cholesterol transport is the main mechanism that helps in the removal of cholesterol from peripheral tissues and subsequent transport to the liver where it is reused or excreted as bile salts. By so doing, the cholesterol does not develop into foam cells, which are precursors of atherosclerotic plaques [6].

The antiatherogenicity of coffee is due to its possession of antioxidative phenolic compounds including quinides, chlorogenic and ferulic acids [7,35]. Moreover, coffee consumption has also been associated with markers of inflammation, which are well established predictors of heart disease risk [27,36,37].

Table 3. Multiple linear regression showing the association between coffee drinking and HDL-C stratified by sex.

Variables	Men		Women	
	β	<i>p</i> -Value	β	<i>p</i> -Value
Coffee drinking (ref: No)				
Yes	−0.06663	0.8340	0.81679	0.0246
rs1800588 (ref: CC)				
CT	1.32430	<0.0001	0.99080	0.0059
TT	3.24976	<0.0001	3.16277	<0.0001
rs1800775 (ref: AA)				
AC	−1.96232	<0.0001	−1.80954	<0.0001
CC	−2.71536	<0.0001	−2.81512	<0.0001
Age (ref: <49.10 years)			0.0268	0.0371
≥49.10 years	0.54472	0.0991	2.47290	<0.0001
Tea drinking (ref: No)				
Yes	0.36651	0.2195	0.48684	0.1964
Vegetarian diet (ref: No)				
Yes	−4.75567	<0.0001	−5.50703	<0.0001
Exercise (ref: No)				
Yes	1.38414	<0.0001	1.63617	<0.0001
BMI (ref: Normal)			−4.6498	<0.0001
Underweight	7.72243	<0.0001	4.66897	<0.0001
Overweight	−3.68345	<0.0001	−3.06323	<0.0001
Obesity	−5.04663	<0.0001	−5.23881	<0.0001
Smoking (ref: No)				
Former	−0.21607	0.5638	−1.37464	0.2436
Current	−2.14450	<0.0001	−2.19635	0.0508
Second hand smoke (ref: No)				
Yes	−0.65050	0.1155	−0.06277	0.9076
Alcohol drinking (ref: No)				
Former	−0.45523	0.4916	0.73876	0.7186
Current	4.56251	<0.0001	5.19190	0.0003
Waist hip ratio	−23.64856	<0.0001	−23.21757	<0.0001
LDL-C	0.02023	<0.0001	0.00779	0.1591
TG	−0.03421	<0.0001	−0.05936	<0.0001
Diabetes (ref: No)				
Yes	−1.39585	0.0026	−2.21996	0.0007
Hypertension (ref: No)				
Yes	−0.43542	0.2256	0.34212	0.4998

Interaction between mean menopausal age and coffee *p*-value = 0.0399. *p* < 0.05—significant; HDL-C—high-density lipoprotein cholesterol; ref—reference; β —beta coefficient; LDL-C—low-density lipoprotein cholesterol and TG—triglyceride.

The underlying mechanism for the presence of a significant association between coffee and HDL-C only in women especially non-menopausal women in the current study cannot be clearly stated. This could be due to hormonal differences between men and women as well as between menopausal

and non-menopausal women [38]. For instance, the higher levels of HDL-C in non-menopausal women might be partly due to higher endogenous estrogen [12,39]. Coffee consumption and other caffeinated beverages have been reported to be beneficial to plasma levels of estrogen, sex hormone-binding globulin and estradiol in women [38,40]. Sex disparities in HDL-levels could also be due to physiological, physical and other lifestyle differences between men and women [38].

Table 4. Linear regression showing the association between coffee drinking and HDL-C in women stratified by menopausal status.

Variables	<49.10 Years		≥49.10 Years	
	β	p-Value	β	p-Value
Coffee drinking (ref: No)				
Yes	1.36554	0.0057	0.06686	0.9013
rs1800588 (ref: CC)				
CT	1.25492	0.0127	0.78076	0.1307
TT	3.03425	<0.0001	3.37945	<0.0001
rs1800775 (ref: AA)				
AC	−2.65814	<0.0001	−0.99205	0.0902
CC	−3.54764	<0.0001	−2.08574	0.0023
Tea drinking (ref: No)				
Yes	0.65338	0.1930	0.23893	0.6762
Vegetarian diet (ref: No)				
Yes	−5.35759	<0.0001	−5.54455	<0.0001
Exercise (ref: No)				
Yes	1.27759	0.0174	1.91579	<0.0001
BMI (ref: Normal)				
Underweight	3.02720	0.0052	8.31494	<0.0001
Overweight	−2.64081	<0.0001	−3.18604	<0.0001
Obesity	−5.71688	<0.0001	−4.58444	<0.0001
Smoking (ref: No)				
Former	−1.17161	0.4078	2.22341	0.2972
Current	−2.36302	0.0801	−1.41338	0.4893
Second hand smoke (ref: No)				
Yes	−0.11632	0.8641	0.07856	0.9301
Alcohol drinking (ref: No)				
Former	3.19330	0.3045	−0.94144	0.7330
Current	4.22680	0.0132	7.76976	0.0044
Waist hip ratio	−24.43827	<0.0001	−21.90699	<0.0001
LDL-C	0.00799	0.3393	0.01063	0.1594
TG	−0.06725	<0.0001	−0.05527	<0.0001
Diabetes (ref: No)				
Yes	−1.14892	0.4213	−2.50564	0.0008
Hypertension (ref: No)				
Yes	0.62290	0.5663	0.22589	0.6969

$p < 0.05$ —significant; HDL-C—high-density lipoprotein cholesterol; ref—reference; β—beta coefficient; LDL-C—low-density lipoprotein cholesterol and TG—triglyceride.

Our findings are not in line with those of some studies. For instance, an inverse association between coffee and HDL was reported [41]. In addition, even though coffee drinking was positively associated with HDL, an inverse association was observed in women after participants were stratified by sex [42]. In several other studies, coffee drinking was associated with lower HDL levels in women but not men [14,26]. Furthermore, several studies found no significant association between coffee drinking and HDL [29,30,43–46]. The inconsistent findings between the current study and those previously conducted could be due to different study populations, stratification of participants as drinkers or non-drinkers of coffee, sample sizes and the adjusted confounders. Comparatively, our study had a larger sample size and adjustments were simultaneously made for many potential confounders

including rs1800588 and rs180077 genotypes, age, vegetarian diet, exercise, BMI, smoking, second-hand smoke, tea and alcohol drinking, WHR, LDL-C, TG and history of diabetes and hypertension.

The rs1800588 (LIPC) variant was associated with higher HDL-C levels in the present study. These findings are in line with others [17,19]. The LIPC gene possesses anti-atherogenic properties and the underlying mechanism is its ability to stimulate reverse cholesterol transport and remove intermediate-density lipoprotein (IDL) from circulation [21]. The rs100775 (CETP) variant was associated with lower levels of HDL-C levels in our study and other studies [17,18,20]. CETP is proatherogenic and promotes the transfer of cholesteryl ester from HDL-C to very low-density lipoprotein (VLDL) rich in triglycerides [22–24,47].

In a study conducted using the Taiwan biobank data, HDL was positively associated with age, exercise, underweight and current alcohol drinking and negatively associated with overweight, obesity, smoking, former alcohol drinking, WHR and vegetarian diet [34]. This is consistent with the findings of the present study. Similar associations of HDL with age, underweight, overweight, obesity, WHR, smoking, drinking and vegetarian diet have been previously reported [14,25,26].

The limitation of our study is that, the information on the type of coffee consumed by both men and women was not available in the Taiwan Biobank database. Therefore, we could not stratify the study participants based on the coffee type or drinking style.

4. Conclusions

Summarily, coffee drinking was significantly associated with higher HDL in women but not men after adjustments were made for confounders including rs1800588 (LIPC) and rs1800775 (CETP) single nucleotide polymorphisms. Therefore, coffee drinking might be cardioprotective especially in women.

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References

1. Butt, M.S.; Sultan, M.T. Coffee and its consumption: Benefits and risks. *Crit. Rev. Food Sci. Nutr.* **2011**, *51*, 363–373. [[CrossRef](#)] [[PubMed](#)]
2. Roth, G.A.; Huffman, M.D.; Moran, A.E.; Feigin, V.; Mensah, G.A.; Naghavi, M.; Murray, C.J. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation* **2015**, *132*, 1667–1678. [[CrossRef](#)] [[PubMed](#)]
3. Roth, G.A.; Johnson, C.; Abajobir, A.; Abd-Allah, F.; Abera, S.F.; Abyu, G.; Ahmed, M.; Aksut, B.; Alam, T.; Alam, K. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J. Am. Coll. Cardiol.* **2017**, *70*, 1–25. [[CrossRef](#)]
4. Libby, P.; Ridker, P.M.; Hansson, G.K. Progress and challenges in translating the biology of atherosclerosis. *Nature* **2011**, *473*, 317. [[CrossRef](#)] [[PubMed](#)]
5. Navab, M.; Reddy, S.T.; Van Lenten, B.J.; Fogelman, A.M. HDL and cardiovascular disease: Atherogenic and atheroprotective mechanisms. *Nat. Rev. Cardiol.* **2011**, *8*, 222. [[CrossRef](#)]
6. Rye, K.-A.; Bursill, C.A.; Lambert, G.; Tabet, F.; Barter, P.J. The metabolism and anti-atherogenic properties of HDL. *J. Lipid Res.* **2009**, *50*, S195–S200. [[CrossRef](#)]
7. Uto-Kondo, H.; Ayaori, M.; Ogura, M.; Nakaya, K.; Ito, M.; Suzuki, A.; Takiguchi, S.; Yakushiji, E.; Terao, Y.; Ozasa, H.; et al. Coffee consumption enhances high-density lipoprotein-mediated cholesterol efflux in macrophages. *Circ. Res.* **2010**, *106*, 779. [[CrossRef](#)]

8. Gordon, D.J.; Probstfield, J.L.; Garrison, R.J.; Neaton, J.D.; Castelli, W.P.; Knoke, J.D.; Jacobs, D.R., Jr.; Bangdiwala, S.; Tyroler, H.A. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* **1989**, *79*, 8–15. [[CrossRef](#)]
9. Karathanasis, S.K.; Freeman, L.A.; Gordon, S.M.; Remaley, A.T. The changing face of HDL and the best way to measure it. *Clin. Chem.* **2017**, *63*, 196–210. [[CrossRef](#)]
10. Marques, L.R.; Diniz, T.A.; Antunes, B.M.; Rossi, F.E.; Caperuto, E.C.; Lira, F.S.; Gonçalves, D.C. Reverse cholesterol transport: Molecular mechanisms and the non-medical approach to enhance HDL cholesterol. *Front. Physiol.* **2018**, *9*, 526. [[CrossRef](#)] [[PubMed](#)]
11. Wang, X.; Paigen, B. Genetics of variation in HDL cholesterol in humans and mice. *Circ. Res.* **2005**, *96*, 27–42. [[CrossRef](#)]
12. Kim, H.J.; Park, H.A.; Cho, Y.G.; Kang, J.H.; Kim, K.W.; Kang, J.H.; Kim, N.-R.; Chung, W.-C.; Kim, C.H.; Whang, D.H. Gender difference in the level of HDL cholesterol in Korean adults. *Kor. J. Fam. Med.* **2011**, *32*, 173. [[CrossRef](#)] [[PubMed](#)]
13. Carroll, M.D.; Lacher, D.A.; Sorlie, P.D.; Cleeman, J.I.; Gordon, D.J.; Wolz, M.; Grundy, S.M.; Johnson, C.L. Trends in serum lipids and lipoproteins of adults, 1960–2002. *JAMA* **2005**, *294*, 1773–1781. [[CrossRef](#)] [[PubMed](#)]
14. Chang, H.-C.; Hsieh, C.-F.; Tantoh, D.M.; Ko, P.-C.; Kung, Y.-Y.; Lin, M.-C.; Liaw, Y.-C.; Liaw, Y.-P. HDL and associated factors stratified by sex and menopausal status: Results from a community-based survey in Taiwan. *Oncotarget* **2018**, *9*, 16354. [[CrossRef](#)] [[PubMed](#)]
15. Quispe, R.; Manalac, R.J.; Faridi, K.F.; Blaha, M.J.; Toth, P.P.; Kulkarni, K.R.; Nasir, K.; Virani, S.S.; Banach, M.; Blumenthal, R.S. Relationship of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to the remainder of the lipid profile: The Very Large Database of Lipids-4 (VLDL-4) study. *Atherosclerosis* **2015**, *242*, 243–250. [[CrossRef](#)] [[PubMed](#)]
16. Ouyang, F.; Kumar, R.; Pongracic, J.; Story, R.E.; Liu, X.; Wang, B.; Xing, H.; Liu, X.; Li, Z.; Zhang, W. Adiposity, serum lipid levels, and allergic sensitization in Chinese men and women. *J. All. Clin. Immunol.* **2009**, *123*, 940–948. [[CrossRef](#)]
17. Soyul, S.M.; Sandhofer, A.; Hahne, P.; Oberkofler, H.; Felder, T.; Iglseder, B.; Miller, K.; Krempler, F.; Patsch, J.R.; Paulweber, B. Cholesteryl ester transfer protein and hepatic lipase gene polymorphisms: Effects on hepatic mRNA levels, plasma lipids and carotid atherosclerosis. *Atherosclerosis* **2011**, *216*, 374–380. [[CrossRef](#)] [[PubMed](#)]
18. Wang, J.; Wang, L.J.; Zhong, Y.; Gu, P.; Shao, J.Q.; Jiang, S.S.; Gong, J.B. CETP gene polymorphisms and risk of coronary atherosclerosis in a Chinese population. *Lipids Health Dis.* **2013**, *12*, 176. [[CrossRef](#)]
19. Hodoğlugil, U.; Williamson, D.W.; Mahley, R.W. Polymorphisms in the hepatic lipase gene affect plasma HDL-cholesterol levels in a Turkish population. *J. Lipid Res.* **2010**, *51*, 422–430. [[CrossRef](#)]
20. Sull, J.W.; Lee, J.-E.; Lee, M.; Jee, S.H. Cholesterol ester transfer protein gene is associated with high-density lipoprotein cholesterol levels in Korean population. *Genes Genom.* **2012**, *34*, 231–235. [[CrossRef](#)]
21. Zhang, C.; Lopez-Ridaura, R.; Rimm, E.; Li, T.; Hunter, D.; Hu, F. Genetic variation in the hepatic lipase gene and the risk of coronary heart disease among US diabetic men: Potential interaction with obesity. *Diabetologia* **2006**, *49*, 1552–1559. [[CrossRef](#)] [[PubMed](#)]
22. Todur, S.P.; Ashavaid, T.F. Association of CETP and LIPC gene polymorphisms with HDL and LDL sub-fraction levels in a Group of Indian Subjects: A cross-sectional study. *Ind. J. Clin. Biochem.* **2013**, *28*, 116–123. [[CrossRef](#)] [[PubMed](#)]
23. De Grooth, G.J.; Klerkx, A.H.; Stroes, E.S.; Stalenhoef, A.F.; Kastelein, J.J.; Kuivenhoven, J.A. A review of CETP and its relation to atherosclerosis. *J. Lipid Res.* **2004**, *45*, 1967–1974. [[CrossRef](#)] [[PubMed](#)]
24. Zende, P.D.; Bankar, M.P.; Momin, A.R.A.; Kamble, P.S. Study of Cholesteryl Ester Transfer Protein (CETP) I405v Genotype and its association with lipid fractions in myocardial infarction patients: A case control study. *JCDR* **2014**, *8*, CC01. [[CrossRef](#)]
25. Jan, C.-F.; Chang, H.-C.; Tantoh, D.M.; Chen, P.-H.; Liu, W.-H.; Huang, J.-Y.; Wu, M.-C.; Liaw, Y.-P. Duration-response association between exercise and HDL in both male and female Taiwanese adults aged 40 years and above. *Oncotarget* **2018**, *9*, 2120. [[CrossRef](#)] [[PubMed](#)]
26. Balk, L.; Hoekstra, T.; Twisk, J. Relationship between long-term coffee consumption and components of the metabolic syndrome: The Amsterdam Growth and Health Longitudinal Study. *Eur. J. Epidemiol.* **2009**, *24*, 203–209. [[CrossRef](#)] [[PubMed](#)]

27. Kempf, K.; Herder, C.; Erlund, I.; Kolb, H.; Martin, S.; Carstensen, M.; Koenig, W.; Sundvall, J.; Bidel, S.; Kuha, S. Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: A clinical trial. *Am. J. Clin. Nutr.* **2010**, *91*, 950–957. [[CrossRef](#)] [[PubMed](#)]
28. Fried, R.E.; Levine, D.M.; Kwiterovich, P.O.; Diamond, E.L.; Wilder, L.B.; Moy, T.F.; Pearson, T.A. The effect of filtered-coffee consumption on plasma lipid levels: Results of a randomized clinical trial. *JAMA* **1992**, *267*, 811–815. [[CrossRef](#)]
29. 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*, 872. [[CrossRef](#)] [[PubMed](#)]
30. Jee, S.H.; He, J.; Appel, L.J.; Whelton, P.K.; Suh, I.; Klag, M.J. Coffee consumption and serum lipids: A meta-analysis of randomized controlled clinical trials. *Am. J. Epidemiol.* **2001**, *153*, 353–362. [[CrossRef](#)]
31. Tantoh, D.M.; Wu, M.-F.; Ho, C.-C.; Lung, C.-C.; Lee, K.-J.; Nfor, O.N.; Liaw, Y.-C.; Hsu, S.-Y.; Chen, P.-H.; Lin, C.; et al. SOX2 promoter hypermethylation in non-smoking Taiwanese adults residing in air pollution areas. *Clin. Epigenet.* **2019**, *11*, 46. [[CrossRef](#)] [[PubMed](#)]
32. Zargar, A.; Auttapibarn, C.; Hong, S.H.; Larson, T.J.; Hayworth, K.H.; Ito, M.K. The effect of acute café latte ingestion on fasting serum lipid levels in healthy individuals. *J. Clin. Lipidol.* **2013**, *7*, 165–168. [[CrossRef](#)]
33. Suliga, E.; Koziel, D.; Cieśla, E.; Rębak, D.; Głuszek, S. Coffee consumption and the occurrence and intensity of metabolic syndrome: A cross-sectional study. *Int. J. Food Sci. Nutr.* **2017**, *68*, 507–513. [[CrossRef](#)] [[PubMed](#)]
34. Nassef, Y.; Lee, K.-J.; Nfor, O.N.; Tantoh, D.M.; Chou, M.-C.; Liaw, Y.-P. The Impact of Aerobic Exercise and Badminton on HDL Cholesterol Levels in Adult Taiwanese. *Nutrients* **2019**, *11*, 515. [[CrossRef](#)] [[PubMed](#)]
35. Bonita, J.S.; Mandarano, M.; Shuta, D.; Vinson, J. Coffee and cardiovascular disease: In vitro, cellular, animal, and human studies. *Pharmacol. Res.* **2007**, *55*, 187–198. [[CrossRef](#)] [[PubMed](#)]
36. Lopez-Garcia, E.; van Dam, R.M.; Qi, L.; Hu, F.B. Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. *Am. J. Clin. Nutr.* **2006**, *84*, 888–893. [[CrossRef](#)] [[PubMed](#)]
37. Blake, G.J.; Ridker, P.M. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. *J. Am. Coll. Cardiol.* **2003**, *41*, S37–S42. [[CrossRef](#)]
38. Lee, J.; Lee, J.-E.; Kim, Y. Relationship between coffee consumption and stroke risk in Korean population: The Health Examinees (HEXA) Study. *Nutr. J.* **2017**, *16*, 7. [[CrossRef](#)]
39. Rossouw, J.E. Hormones, genetic factors, and gender differences in cardiovascular disease. *Cardiovasc. Res.* **2002**, *53*, 550–557. [[CrossRef](#)]
40. Nagata, C.; Kabuto, M.; Shimizu, H. Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. *Nutr. Cancer* **1998**, *30*, 21–24. [[CrossRef](#)]
41. Kim, H.-J.; Cho, S.; Jacobs, D.R., Jr.; Park, K. Instant coffee consumption may be associated with higher risk of metabolic syndrome in Korean adults. *Diabetes Res. Clin. Pract.* **2014**, *106*, 145–153. [[CrossRef](#)] [[PubMed](#)]
42. Grosso, G.; Stepaniak, U.; Micek, A.; Topor-Mądry, R.; Pikhart, H.; Szafraniec, K.; Pająk, A. Association of daily coffee and tea consumption and metabolic syndrome: Results from the Polish arm of the HAPIEE study. *Eur. J. Nutr.* **2015**, *54*, 1129–1137. [[CrossRef](#)]
43. Grioni, S.; Agnoli, C.; Sieri, S.; Pala, V.; Ricceri, F.; Masala, G.; Saieva, C.; Panico, S.; Mattiello, A.; Chiodini, P. Espresso coffee consumption and risk of coronary heart disease in a large Italian cohort. *PLoS ONE* **2015**, *10*, e0126550. [[CrossRef](#)] [[PubMed](#)]
44. Karabudak, E.; Türközü, D.; Köksal, E. Association between coffee consumption and serum lipid profile. *Exp. Therap. Med.* **2015**, *9*, 1841–1846. [[CrossRef](#)] [[PubMed](#)]
45. Yukawa, G.; Mune, M.; Otani, H.; Tone, Y.; Liang, X.-M.; Iwahashi, H.; Sakamoto, W. Effects of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. *Biochemistry* **2004**, *69*, 70–74. [[CrossRef](#)] [[PubMed](#)]
46. Martínez-López, S.; Sarriá, B.; Mateos, R.; Bravo-Clemente, L. Moderate consumption of a soluble green/roasted coffee rich in caffeoylquinic acids reduces cardiovascular risk markers: Results from a randomized, cross-over, controlled trial in healthy and hypercholesterolemic subjects. *Eur. J. Nutr.* **2018**, *58*, 865–878. [[CrossRef](#)]
47. Barter, P.J.; Brewer, H.B., Jr.; Chapman, M.J.; Hennekens, C.H.; Rader, D.J.; Tall, A.R. Cholesteryl ester transfer protein: A novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 160–167. [[CrossRef](#)] [[PubMed](#)]



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