The Effect of Filtered-Coffee Consumption on Plasma Lipid Levels

Results of a Randomized Clinical Trial

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Objective.—To determine the effect of filtered-coffee consumption on plasma lipoprotein cholesterol levels in healthy men.

Design.—Randomized controlled trial with an 8-week washout period followed by an 8-week intervention period during which men were randomly assigned to drink 720 mL/d of caffeinated coffee, 360 mL/d of caffeinated coffee, 720 mL/d of decaffeinated coffee, or no coffee.

Setting.—Outpatient clinical research center in a university medical center.

Participants.—One hundred healthy male volunteers.

Outcome Measure.—Changes in plasma lipoprotein cholesterol levels during the intervention period.

Results.—Men who consumed 720 mL of caffeinated coffee daily had mean increases in plasma levels of total cholesterol (0.24 mmol/L, $P = .001$), low-density lipoprotein cholesterol (0.17 mmol/L, $P = .04$), and high-density lipoprotein cholesterol (0.08 mmol/L, $P = .03$). No significant changes in these plasma lipoprotein levels occurred in the other groups. Compared with the group who drank no coffee, the group who drank 720 mL/d of caffeinated coffee had increases in plasma levels of total cholesterol (0.25 mmol/L, $P = .02$), low-density lipoprotein cholesterol (0.15 mmol/L, $P = .17$), and high-density lipoprotein cholesterol (0.09 mmol/L, $P = .12$) after adjustment for changes in diet.

Conclusion.—Consumption of 720 mL/d of filtered, caffeinated coffee leads to a statistically significant increase in the plasma level of total cholesterol, which appears to be due to increases of both low-density lipoprotein and high-density lipoprotein cholesterol levels.

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DOES DRINKING filtered coffee raise cholesterol levels? Interest in this question was stirred by a report that consumption of boiled coffee raised experimental subjects' cholesterol levels.[1] Most cross-sectional epidemiologic studies have found a positive association between filtered- and boiled-coffee consumption and serum total and low-density lipoprotein cholesterol (LDL-C) levels.[2-32] Randomized trials have helped to clarify whether coffee per se, rather than health behaviors associated with coffee drinking, raises cholesterol levels. Boiled coffee has consistently increased serum total and LDL-C levels compared with tea.[1,33-35] Filtered coffee, however, has not raised cholesterol levels compared with tea[1,34,35] or with abstinence from coffee and tea.[36,37] Limitations of these studies include the use of tea as a comparison beverage, the absence of washout periods, the use of small numbers of subjects, and lack of data about compliance with protocols and about confounding variables (eg, changes in diet and physical activity).

To determine the effect of filtered-coffee consumption on plasma cholesterol levels, we conducted a trial in which 100 healthy men were randomly assigned to drink filtered coffee or no coffee for an 8-week period, preceded by an 8-week washout period.

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METHODS

Subjects

Subjects were recruited from about 350 respondents to publicity about the trial in regional news media. About 200 respondents were informed by telephone about the study protocol, and eligible men were invited to a baseline visit at which informed consent was obtained. Exclusion criteria were age younger than 20 years or older than 60 years, regular consumption of less than 1 or more than 6 cups of coffee daily, plasma total cholesterol level greater than the 90th percentile for age, diabetes mellitus, clinical cardiovascular or cerebrovascular disease, peptic ulcer disease, morbid obesity, use of lipid-lowering agents, thiazide diuretics, β-adrenergic blockers, or methylxanthines, or regular consumption of more than 14 alcoholic beverages per week. Of 116 subjects seen for an initial visit, eight were excluded because of hypercholesterolemia, and six declined to participate. Of the 102 subjects who began the washout period of the study, only two dropped out early in the this period; the remaining 100 subjects completed the study.

Protocol

A washout period of 8 weeks was followed by an 8-week intervention period for which subjects were randomly assigned to one of four groups, receiving 720 mL (24 oz) of caffeinated (ie, regular) coffee daily; 360 mL (12 oz) of caffeinated coffee daily; 720 mL of decaffeinated coffee daily; or no coffee. Each group included 25 subjects. During the washout and intervention periods, subjects abstained from coffee and tea of all types (except for assigned coffee) and from caffeine-containing foods, beverages, and medications. In place of their customary coffee, most subjects reported drinking fruit juice, cold water,

hot water with a twist of lemon, or no beverage. Subjects were requested to make no other changes in their diets and to maintain a constant level of physical activity. Two visits separated by 1 week took place before the washout period and again at the ends of the washout and intervention periods. Study participants received $100 and were reimbursed for travel expenses.

Coffee Preparation

Subjects assigned to drink coffee were supplied with coffee, automatic-drip coffee makers, paper filters, coffee scoops, packets of a sweetener (aspartame), coffee mugs marked at the 180-mL level, and thermoses able to keep one day's allotment of coffee warm for 8 or more hours. Subjects were instructed to prepare coffee once daily, always following the same recipe: 1260 mL of water and 8 level scoops of coffee (64 g of decaffeinated or 72 g of caffeinated coffee to produce a brew strength of 0.73 g of solids per 100 g of brewed coffee). The only coffee additives permitted were aspartame, skim milk, nonfat powdered dry milk, water, and ice.

Lipoprotein Level Analyses

Fasting plasma samples were analyzed for total cholesterol, triglycerides, and lipoprotein cholesterol according to the Lipid Research Clinics procedures,[38] except that cholesterol and triglyceride levels were measured enzymatically with commercially available reagents. High-density lipoprotein cholesterol (HDL-C) levels were measured enzymatically in fresh plasma after precipitation of lipoproteins containing apolipoprotein B with heparin and manganese chloride.[39] The LDL-C levels were calculated using Friedewald's formula.[40] Plasma apolipoproteins A-I and B were measured by radial immunodiffusion in agarose gel.[41,42] All assays were performed in the Lipoprotein Analytical Laboratory at The Johns Hopkins University, Baltimore, Md. This laboratory is standardized for cholesterol, triglyceride, and HDL cholesterol analysis according to Centers for Disease Control–National Heart, Lung, and Blood Institute criteria.[43] Lipid measurements made on paired specimens, obtained 1 week apart at the ends of the washout and intervention periods, were averaged.

Other Measurements

Subjects completed 3-day diet records during the washout and intervention periods. These were coded and analyzed at the Nutrition Coordinating Center of the University of Minnesota, Minneapolis.[44] Mean daily intake of calories, saturated, monounsaturated, and polyunsaturated fats, cholesterol, alcohol, and other nutrients was determined. Height and weight were measured with shoes removed. Subjects were asked how many hours they spent engaged in hard, moderate, and light physical activity, on average, during weekdays and weekend days of the preceding week. Estimates of average daily energy expenditure, in kilojoules, were determined from this information, as described by Sallis and coworkers.[45]

Compliance

Subjects recorded in daily logs their coffee consumption and lapses of compliance with the protocol, and they were contacted by telephone approximately biweekly to assess compliance. Compliance was also assessed by assay of a 24-hour urine specimen for metabolites of caffeine, collected during the washout period, and again during the intervention period. These assays, performed by high-pressure liquid chromatography,[46] could detect caffeine metabolites from as little as 180 mL of coffee intake within 5 days.

Statistical Analyses

To determine the effect of coffee abstention, the change in each subject's plasma lipid levels during the washout period was calculated by subtracting his lipid levels at the start of the washout period from his levels at the end of this period. The mean changes for all subjects were determined and were examined for statistical significance using two-tailed t tests.[47]

The outcomes of primary interest, ie, changes in plasma lipid levels in each group during the intervention period, were calculated by subtracting each subject's lipid levels at the start of the intervention period from his levels at the end of this period, and mean changes for the subjects within each of the four groups were tested for statistical significance using two-tailed t tests.[47] Mean lipid changes during the intervention period were adjusted for changes in diet during the intervention period using linear regression.[48] Adjustment was made for changes in intake of alcohol, cholesterol, eicosapentaenoic acid, energy, fiber, monounsaturated, polyunsaturated, and saturated fats, and protein. The adjusted mean lipid changes in each group were examined for statistical significance and also were compared with changes in other groups using the LSMEANS procedure of the Statistical Analysis System.[48] Comparison of each coffee-drinking group with the no-coffee group yielded "net changes" in plasma lipid levels, which are the adjusted mean changes within the no-coffee group subtracted from these values in other groups. In assessing the effect of coffee consumption on plasma lipid levels, both the net changes and the within-group mean changes have merit. Net changes offer the advantage of having subtracted out any background effects but are statistically underpowered measures of coffee's effects relative to the within-group mean changes since net changes involve comparison of two independent groups. This problem is avoided by examination of the within-group mean changes, a reasonable approach in the absence of background effects. The equality of groups with respect to baseline characteristics and changes in dietary intake and physical activity was tested with analysis of variance.[48]

Distributions were examined for normality and the presence of outliers.[47] Distributions of lipid level changes were approximately normally distributed. One outlier was identified. This subject's plasma total cholesterol level increased by 1.71 mmol/L during the intervention period. The next highest increase in plasma total cholesterol level in any subject was 0.88 mmol/L. He probably had a lipid disorder, with fluctuations in plasma total cholesterol level, not detected at the start of the study because his plasma total cholesterol level was normal then. This is corroborated by his abnormally high plasma total cholesterol level (7.40 mmol/L) at one point in the study. Because means are unreliable summary measures in the presence of outliers and because hypercholesterolemia was an exclusion criterion for study participation, this subject was excluded from analyses.

RESULTS

The participants were predominantly middle-aged with normal plasma lipid concentrations, weight, and blood pressure and consumed 4 to 5 cups of coffee daily prior to the study (Table 1). The baseline characteristics of the participants were similar across treatment groups. Ninety-three subjects were white, five were black, one was Asian, and one was a native of India. Thirteen were cigarette smokers.

During the washout period, plasma total cholesterol levels decreased by 0.15 mmol/L ($P=.005$); plasma LDL-C and HDL-C levels each decreased by 0.08 mmol/L ($P=.08$ and $P<.0001$, respectively). The plasma apolipoprotein A-I level decreased by 9.0 mg/dL ($P<.0001$). Minimal changes occurred in levels of plasma triglycerides (increase of 0.04 mmol/L, $P=.3$) and apolipoprotein B (decrease of 0.7 mg/dL, $P=.7$).

Dietary intake, based on analysis of 3-day diet records, was similar across groups during the intervention period (Table 2). Changes in diet during the intervention period were small relative to the actual levels of intake. Significant

Table 1.—Baseline Characteristics of the Participants* and *P* Values From Test of Equality of Group Means

Characteristics	No Coffee (n=25)	Decaffeinated Coffee, 720 mL/d (n=25)	Caffeinated Coffee, 360 mL/d (n=25)	Caffeinated Coffee, 720 mL/d (n=25)	P
Age, y	44±10	44±11	43±10	44±10	.98
Total cholesterol, mmol/L	5.19±0.76	5.21±0.84	5.21±0.91	5.29±0.82	.97
LDL cholesterol, mmol/L	3.31±0.73	3.35±0.91	3.36±0.80	3.30±0.61	.99
HDL cholesterol, mmol/L	1.33±0.24	1.38±0.28	1.46±0.35	1.41±0.28	.53
Apolipoprotein A-I, mg/dL	130.5±16.4	139.6±25.0	146.4±31.8	139.2±16.2	.16
Apolipoprotein B, mg/dL	121.8±31.1	122.1±38.1	119.1±25.9	125.7±29.6	.90
Triglycerides, mmol/L	1.17±0.68	1.04±0.35	0.88±0.38	1.26±0.76	.11
Weight, kg	79.9±12.8	81.8±8.6	83.5±15.2	85.9±14.9	.43
BMI, kg/m²	26.3±4.3	26.0±2.3	27.4±4.7	26.8±3.5	.58
All coffee, cups/d†	4.6±2.3	5.0±2.7	4.3±2.0	4.6±1.8	.75
Decaffeinated coffee, cups/d†	0.5±1.5	0.5±1.3	0.6±1.5	0.5±1.0	.98
Tea, cups/d†	0.6±1.1	1.3±1.9	0.6±1.0	0.7±1.3	.20
Total caffeine, mg/d	467±248	533±316	413±183	487±202	.37

*Values shown are means±SD and are measurements from immediately prior to the washout period. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and BMI, body mass index.
†One cup of coffee or tea equals 180 mL (6 oz).

Table 2.—Mean Intake of Dietary Constituents in Each Group During the Intervention Period, Mean Changes in Intake From the Washout to the Intervention Periods, and *P* Values From Test of Equality of Group Means

Dietary Constituents	No Coffee (n=25)	Decaffeinated Coffee, 720 mL/d (n=25)	Caffeinated Coffee, 360 mL/d (n=25)	Caffeinated Coffee, 720 mL/d (n=25)	P
Alcohol*					
Intake	3.5	2.4	3.6	3.5	.64
Change	−0.4	0.2	1.1	−1.0	.15
Cholesterol, mg/d					
Intake	323	413	350	434	.13
Change	−62	19	−38	−43	.63
Energy, kJ/d					
Intake	9639	10 466	9198	11 155	.08
Change	−1180	−454	−945	−109	.58
Monounsaturated fat*					
Intake	12	14	13	14	.07
Change	−1	1	0	0	.04
Polyunsaturated fat*					
Intake	6.5	7.7	7.2	7.2	.25
Change	0.2	0.8	−0.1	1.0	.53
Saturated fat*					
Intake	12	13	12	13	.39
Change	−1	1	0	0	.20

*Percentage of total daily calories.

differences between groups were noted only for changes in monounsaturated fat intake, but these differences were minimal and are unlikely to have been of clinical importance. Physical activity levels were similar across groups, and changes in physical activity during the study were minimal in all groups. Mean weight changes during the intervention period were less than 1 kg in each group.

During the intervention period, within-group mean changes in plasma lipoprotein cholesterol levels were minimal and did not differ significantly from zero, except in the group who drank 720 mL/d of caffeinated coffee. This group had mean increases in plasma levels of total cholesterol (0.24 mmol/L, $P=.001$), LDL-C (0.17 mmol/L, $P=.04$), and HDL-C (0.08 mmol/L, $P=.03$). These values were essentially unchanged by adjustment for diet (Figure).

The Figure also shows the results of statistical comparisons between each coffee group and the no-coffee group. Only the group who drank 720 mL/d of caffeinated coffee differed from the group who drank no coffee, with respect to change in total cholesterol levels during the intervention period. The net change in total cholesterol levels in this group (ie, the change in this group minus the change in the no-coffee group) was 0.25 mmol/L ($P=.02$), with net changes in LDL levels of 0.15 mmol/L ($P=.17$) and in HDL levels of 0.09 mmol/L ($P=.12$). There were no significant net changes in plasma triglyceride and apolipoprotein A-I and apolipoprotein B levels in any of the groups.

Other between-group comparisons of changes in total cholesterol levels revealed that the group who drank 720 mL/d of caffeinated coffee differed from the group who drank 360 mL/d of caffeinated coffee ($P=.01$) and from the group who drank decaffeinated coffee ($P=.04$). Analyses adjusting for other variables, ie, changes in physical activity during the intervention period, changes in body weight, initial levels of plasma lipoproteins, and age, did not alter the findings.

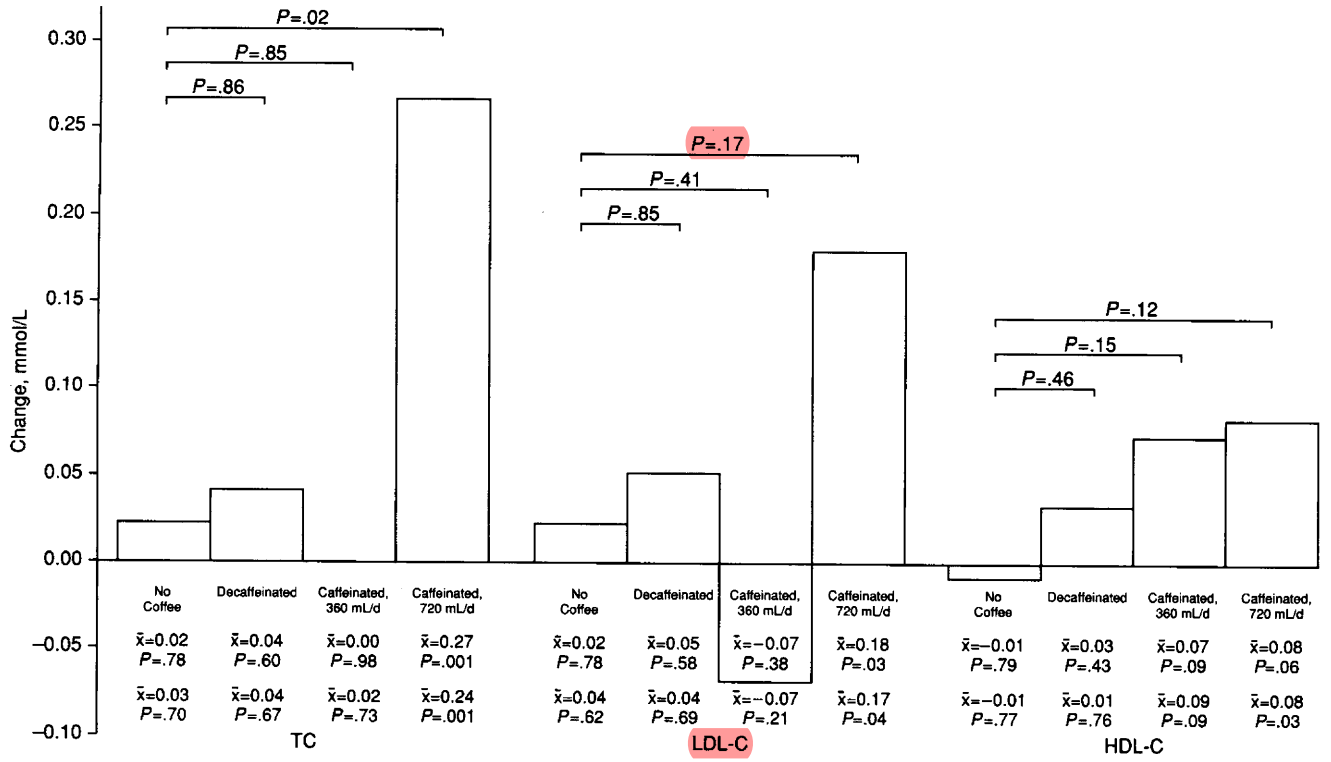
Of the 75 subjects assigned to drink coffee, 71 reported drinking at least 95% of all assigned cups of coffee. Substitution of another brand of coffee for study coffee (eg, due to travel) accounted for more than 10% of all coffee consumed for only five subjects. Of the 25 subjects assigned to the no-coffee group, only one reported drinking, on average, more than 30 mL/d of coffee (of any type). The caffeine content of the caffeinated coffee, as prepared by the subjects, was 460 mg/L and of the decaffeinated coffee, 8 mg/L.

Semiquantitative estimates of daily caffeine intake, based on urine assays, also indicated excellent compliance with the study protocol. Urinary measurements suggested that two members of the no-coffee group, three members of the decaffeinated coffee group, one member of the 360 mL/d caffeinated coffee group, and no members of the 720 mL/d caffeinated coffee group were noncompliant with the study protocol. The study results were unchanged when analyses were restricted to the most compliant subjects, as defined on the basis of self-report or urinary measurements, or both.

COMMENT

The main study finding is that daily consumption of 720 mL of filtered, drip-brewed, caffeinated coffee, as compared with 360 mL/d of caffeinated coffee, 720 mL/d of decaffeinated coffee, and no coffee, leads to a small, statistically significant increase in plasma total cholesterol level. Daily consumption of 720 mL of caffeinated coffee led to a net, diet-adjusted increase in plasma total cholesterol level of 0.25 mmol/L, which was due to net increases in levels of both LDL-C (0.15 mmol/L) and HDL-C (0.09 mmol/L). The amount of coffee consumed by study participants was typical for US coffee drinkers. A survey of coffee consumption found that 73% of caffeinated coffee drinkers in the continental United States drink less than 750 mL/d.[49]

Mean changes in plasma LDL-C and HDL-C levels in the group who drank 720 mL/d of caffeinated coffee were statistically significant, but *net* changes in LDL-C and HDL-C levels in this group (ie, compared with the no-coffee group) were not. Since no background effects were evident, statistically significant net changes would probably have been found with a larger sample size, and the within-



Mean changes in levels of plasma total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol during the intervention period in each group after adjusting for changes in diet. At the top of the figure are *P* values from comparisons of the no-coffee group with each other group. At the bottom of the figure are adjusted (upper row) and unadjusted (lower row) group means with *P* values from tests of their significance.

group mean changes are reasonable measures of coffee's effects.

This was not a double-blind study; almost every subject deduced the identity of his assigned beverage. We have no reason to believe, however, that knowledge of the assigned beverage might have altered the study results. Data on known determinants or predictors of lipoprotein levels remained constant throughout the study (eg, diet, weight, and physical activity), and adjustment for any changes in these factors did not alter the results.

In previous studies, serum total and LDL-C levels increased in subjects with elevated[34,35] and normal[33] serum cholesterol levels after they drank boiled coffee for 4 to 5 weeks, compared with levels after they drank tea. These studies suggest the existence of a cholesterol-raising effect of coffee and/or a cholesterol-lowering effect of tea. Two of these studies also examined filtered coffee. Compared with tea, filtered coffee raised serum total cholesterol levels by 0.26 mmol/L (95% confidence limits [CL], −1.71 and 2.22 mmol/L) in a study of 33 hypercholesterolemic men[34] and by 0.43 mmol/L (95% CL, −0.31 and 1.19 mmol/L) in a study of 42 hypercholesterolemic men and women,[35] which are effect magnitudes similar to those found in our study. In one trial that compared boiled coffee, filtered coffee, and no coffee, subjects in all three groups also drank tea.[1] Boiled coffee (plus tea) led to increases in total and LDL-C levels, compared with filtered coffee (plus tea), and compared with tea alone. Filtered coffee (plus tea), compared with tea alone, led to an increase in plasma total cholesterol levels of 0.07 mmol/L (95% CL, −0.31 and 0.46 mmol/L), an effect magnitude consistent with that found in our study.

Only three randomized trials involving filtered coffee have been reported in which tea was not concurrently consumed by the coffee or no-coffee groups. In one, no effect on serum cholesterol levels was found; however, the sample size (21 subjects) may have been too small to detect significant differences.[36] In the second study, decaffeinated coffee consumption led to increases in plasma LDL-C levels, while caffeinated coffee consumption had no effect.[37] This finding is inconsistent with other studies and may represent a chance result or may be confounded by dietary changes. In the third study, regular coffee had no effect compared with decaffeinated coffee in 22 men and 23 women.[50]

This is the first study to demonstrate an effect of filtered, caffeinated coffee consumption on plasma total and LDL-C levels. The use of a washout period, the proscription of tea consumption, and the relatively large number of subjects may have enabled the detection of effects not found by previous investigators. To our knowledge, this is the first study to find an effect of any type of coffee on HDL-C levels; HDL levels fell during the washout period and rose with caffeinated coffee consumption. If this effect is due to caffeine, it may have escaped detection in other studies in which caffeine was provided in coffee or tea to all subjects. Alternatively, the changes in HDL-C levels may have been chance findings; further work by other investigators is needed to confirm our findings. We did not measure HDL subtypes; therefore, it is possible that the observed change in HDL-C levels was limited to a noncardioprotective subtype of this lipoprotein. The view that cardioprotection is limited to HDL_2 is not well supported,[51] and a prospective study of 14 916 men indicates both HDL_2 and HDL_3 subfractions are cardioprotective.[52]

The mechanism underlying the relationship between coffee drinking and plasma cholesterol levels is unknown.

The observation that boiled coffee has a more potent effect than drip-brewed, filtered coffee has led to speculation that the active substance (or substances) may be removed by adsorption or filtration when a paper filter is used or is better extracted by the higher temperatures used in boiled-coffee preparation.[1] In light of decaffeinated coffee's lack of an effect on lipoprotein cholesterol levels in this study, it may be speculated that the decaffeination process also extracts the active substance(s) or that the coffee beans used to manufacture decaffeinated coffee lack the active substance(s). The active substance does not appear to be caffeine, at least as far as LDL-C is concerned, given the disparate effects of boiled and filtered coffee, which contain similar amounts of caffeine.[1] A putative active substance was recently identified; a filterable, lipid-rich extract from boiled coffee was mixed with custard and fed to 10 volunteers in an amount corresponding to roughly 900 mL/d of boiled coffee (or 100 to 200 times this amount of filtered coffee). The subjects' total and LDL-C levels rose by 23% and 29%, respectively.[53]

The implications for coronary heart disease risk of the coffee-induced increases in LDL-C and HDL-C levels observed in this study appear minimal if these changes are assumed to have the same impact on coronary heart disease risk as has been found in other studies,[54,55] with the caveats noted herein about the changes in HDL levels observed in this study. The 4.7% (ie, 0.15 mmol/L) net increase in LDL-C levels observed after adjustment for dietary changes can be expected to increase the risk of coronary heart disease by 9%.[54] This risk would be countered by the 0.09 mmol/L net increase in HDL-C levels, which can be expected to decrease the risk of coronary heart disease by 7% to 11%.[55]

In summary, daily consumption of 720 mL of drip-brewed, filtered, caffeinated coffee in this study of normocholesterolemic men led to small increases in plasma LDL-C and HDL-C levels, which together should not affect coronary heart disease risk.

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