The J-Shaped Effect of Coffee Consumption on the Risk of Developing Acute Coronary Syndromes: The CARDIO2000 Case-Control Study\textsuperscript{1,2}

Demosthenes B. Panagiotakos,\textsuperscript{1,3} Christos Pitsavos,\textsuperscript{*} Christina Chrysohoou,\textsuperscript{*} Peter Kokkinos,\textsuperscript{†} Pavlos Toutouzas\textsuperscript{*} and Christodoulos Stefanadis\textsuperscript{*}

\textsuperscript{*}Cardiology Clinic, School of Medicine, University of Athens, Athens, Greece and \textsuperscript{†}Cardiology Division, Veterans Affairs Medical Center, George Washington University, Washington, DC

ABSTRACT The effect of coffee consumption on cardiovascular disease has been debated for many years. In this work, we evaluated the association between coffee consumption and the risk of developing acute coronary syndromes, based on a random sample of 848 patients with their first coronary heart disease event and 1078 frequency-matched controls with no cardiovascular disease in their medical history, from the entire country. The multivariate analysis raises a J-shaped association between the risk of developing acute coronary syndromes and the quantity of coffee consumed per day. In particular, the odds ratios for moderate (<300 mL/d), heavy (300–600 mL/d), and very heavy (>600 mL/d) consumption, relative to no consumption, were 0.69 (95% CI, 0.50–0.86), 1.56 (95% CI, 1.10–2.34) and 3.10 (95% CI, 1.82–5.26), respectively, after controlling for the presence of hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary heart disease, physical activity status, smoking habits, BMI, alcohol consumption, triglycerides, consumption of several food items, depression scale score and education status. The suggested J-shaped association between coffee consumption and the risk of developing acute coronary syndromes may partially explain the conflicting results from other studies in the past.


KEY WORDS: coronary risk • coffee • acute coronary syndrome

Conflicting information exists regarding the effect of coffee consumption on the cardiovascular system. Some authors have reported a positive association (1–3) between coffee intake and coronary heart disease, whereas others have reported no relationship (4–6). Moreover, several investigators have suggested that the increase in coronary heart disease risk may be the result of elevated blood pressure and cholesterol levels due to unhealthy diet habits or increased smoking habits associated with coffee consumption (7–13). It seems that an independent association between coffee consumption and the risk of developing coronary heart disease has not yet been established. Furthermore, epidemiologic studies at the population level that examine the association of coffee consumption in various quantities with the risk of developing nonfatal acute coronary syndromes are rather limited in the medical literature.

To evaluate the association between various quantities of coffee consumption and the risk of developing acute coronary syndromes, we studied \textsuperscript{1} 2000 coronary patients and controls from the CARDIO2000 study (14–17). The relationship was adjusted for multiple potential confounding risk factors, including the conventional cardiovascular risk factors, the presence of depression, nutritional habits and the educational level of the participants.

SUBJECTS AND METHODS

Study population. The CARDIO2000 is a multicenter case-control study that explores the association between several demographic, nutritional, psychological, lifestyle and clinical factors with the risk of developing nonfatal acute coronary syndromes. According to the population distribution provided by the National Statistical Services we stratified our sampling into all regions of Greece. For each region, we randomly selected a specific number of patients from the prefectorial or the major private hospitals of each county. The patients were from approximately half of the clinics in Athens and Thessalonica (the two major cities in Greece, covering \textasciitilde 55% of the total population), and from almost all of the clinics of the other counties. The number of participants was determined through power analysis to evaluate a minimum difference of 7% in relative risk between those who do and do not drink coffee with statistical power of 0.80 and \( P < 0.05 \). Thus, from January 2000 to August 2001, 848 of 956 patients (89% response rate) who had been randomly preselected from the hospitals with a first symptom of coronary heart disease (stable angina was excluded from the analysis) in their life agreed to participate in the study (cases). The inclusion criteria for cardiac cases were as follows: 1) diagnosis of first acute myocardial infarction that was defined by two of three features, i.e., electrocardiographic changes, or compatible clinical symptoms of/and specific diagnostic enzyme elevations (49% of the patients had myocardial infarction); or 2) diagnosis of unstable angina (i.e., one or more angina episodes at rest within the preceding 48 h with no abnormal enzyme rise) corresponding to class III of the Braunwald classification.
(51% of the patients had unstable angina). Patients with a previous history of cardiovascular disease, including aortic aneurysm, stroke and peripheral vascular disease, were excluded from this study.

After the selection of the cardiac patients, we randomly selected 1300 controls who were free of cardiovascular disease. One thousand seven hundred and eighty-five controls (83% response rate) agreed to participate. The controls were frequency matched to the patients according to their age distribution (within classes of ≤ 3 y), their gender and the region of Greece (we matched the controls with the patients by region to reduce the potential confounding effect of culture differences among Greek citizens). Controls were mainly individuals (91% of the total number of controls) who visited the outpatient departments of the same hospital during the same time period as the coronary patients for minor surgical operations (e.g., bone fracture) or for routine examinations (e.g., medical examinations for the driving license or other official certificates such as validation of the social security handbooks). We used these types of controls to have more accurate medical information, to eliminate the potential adverse effect of several, unknown, confounders and to increase the likelihood that cases and controls shared the same study base (18). However, in a few country hospitals in which the available number of "hospitalized" controls was not sufficient for the matching procedure, we randomly selected a small proportion of people (9% of the total number of controls) from the municipality rolls. An indicator variable was used for the sensitivity analysis that was applied to explore whether the different "sources" of controls might influence our findings. All controls were people without any clinical symptoms, signs or suspicion of cardiovascular disease in their medical history, including stroke, aortic aneurysm and peripheral vascular disease, as evaluated by a cardiologist.

As mentioned, to reduce the unbalanced distribution of several measured or unmeasured confounders, both patients and controls were randomly selected. The randomization procedure was based on a sequence of binary numbers (i.e., 1, 0, 0, 0, 1, 1... ) that was first applied in the cardiology clinics' admission lists. Thus, the coronary patients assigned the number 1 were selected and asked to participate (this procedure ensured the selection of approximately the half of the cardiac patients that visited each cardiology clinic). The same procedure (i.e., admission listings) was applied for the controls, after taking into account the matching and exclusion criteria. In the case of population controls, the random selection was obtained through the municipal rolls.

Investigated measurements. All participants were asked to describe their usual frequency of consumption of coffee over the last year. Based on the distribution of coffee consumption, we categorized usual coffee consumption as none, up to 300 mL/d (moderate use), or up to 600 mL/d (heavy use) and >600 mL/d (very heavy use). All reported types of coffee (instant coffee, "Greek" type, filtered or "cappuccino") were adjusted for one cup (150 mL) of coffee and a caffeine concentration of 27.5% (19). We did not include the consumption of decaffeinated coffee, tea and caffeine-containing drinks (Coca-Cola) or chocolate. Cessing to drink coffee during the last year (in months of abstinence) was recorded and taken into account as a covariate for the analysis.

We defined current smokers as those who smoked at least 1 cigarette/d. Former smokers were defined as subjects who had stopped smoking for ≥1 y. Individuals who reported that they had never smoked a cigarette were considered to be never smokers. Occasional smokers were excluded from the analysis due the small number in cases (n = 12) and controls (n = 21). Educational level was measured by years of schooling. Clinical symptoms of depression during the previous month were evaluated using the Center of Epidemiological Studies-Depression scale (range 0–60). Values > 15 on this scale indicate significant depressive episodes (20). Physical activity was defined as any type of nonoccupational physical exercise, at least once per week during the past year, and was graded in qualitative terms such as light (expended energy <16 kJ/min, e.g., walking slowly, cycling stationary, light stretching), moderate (expended energy 16–28 kJ/min, e.g., walking briskly, cycling outdoors, swimming with moderate effort) and vigorous (expended energy >28 kJ/min, e.g., walking briskly uphill, long distance running, cycling fast or racing, swimming fast crawl). The rest of the subjects were defined as physically inactive. Also, the duration (in minutes) per session and the years of leisure time physical activity were taken into account as covariates in the multivariate analysis. The evaluation of usual nutritional habits and the classification as those who did or did not follow the Mediterranean diet (characterized by a pattern that is high in fruits, vegetables, bread, cereals, potatoes, poultry, beans, nuts and fish, little red meat and dairy products, and moderate alcohol consumption, and with olive oil as an important source of fat) was based on a questionnaire from the Department of Nutrition of the National School of Public Health (19). Finally, alcohol consumption was measured by daily ethanol intake, in wine glasses of 100 mL, and adjusted for 12% ethanol concentration.

We kept with the original classification criteria used in several epidemiologic studies, subjects who reported that they have been told they had hypertension, were currently taking any antihypertensive medication and whose blood pressure was >140/90 mm Hg were classified as hypertensive (14). Moreover, during the first 12 h of hospitalization for the patients and at the end of the interview for the controls, we measured serum fasting total cholesterol and blood glucose levels. Also, the majority of the controls (86%) and patients (83%) had at least one laboratory measurement in their medical records during the past year. The average values of total cholesterol and blood glucose levels, as well as the patients' medical records and reports assisted us in classifying the participants as hypercholesteroleemics and diabetics. In particular, according to National Cholesterol Education Program Adult Treatment Panel II criteria, hypercholesteroleemics were those who received special hyperlipidemic treatment or had fasting blood measurement of serum total cholesterol > 5.68 mmol/L or > 5.16 mmol/L in the cases of subjects having ≥ 2 other risk factors for coronary heart disease (hypertension, cigarette smoking, diabetes and positive family history for primary coronary heart disease). Diabetics were those with fasting blood glucose ≥ 6.94 mmol/L or who were receiving a special diet or treatment. BMI was calculated in all participants as weight (kg)/height2 (m2). Finally, premature history of myocardial infarction or sudden death in first- or second-degree relatives (< 55 y old for men and ≤ 65 y old for women) led to a classification in the positive family history group.

All participants were informed about the purposes of the study and agreed to participate. The CARDIO2000 study was approved by the Institutional Ethics Committee Further details regarding the design and methodology of the study were published previously (14–17). Statistical analysis. Continuous variables are presented as means ± 1 SD. Qualitative variables are presented as absolute and relative frequencies. Contingency tables with calculation of the χ2 test, as well as application of Student's t-test, evaluated associations between the categorical and normally distributed continuous variables. The estimates of the relative risks of developing acute coronary syndromes were made by calculating odds ratios (OR) and their corresponding 95% CI through conditional logistic regression analysis. First we evaluated all of the interactions between the exposure variables and the main factor of interest (coffee consumption). Then we explored the potential confounding effect of the other exposure variables (by adding and removing each one from the model). Both elimination procedures were based on the Wald statistic. Significant confounders as well as interactions were retained in the model. Deviance residuals were calculated to evaluate the model's goodness-of-fit. A sensitivity analysis was also applied to evaluate the hypothesis tested in various subgroups of participants.

The "link function" (association) between the OR and coffee consumption (none, moderate, and heavy) was evaluated through second-order polynomial interpolation using Lagrange multipliers (21). All reported probability values were based on two-sided tests and compared with a significance level of P = 0.05. STATA 6 software was used for the all the calculations (Stata, College Station, TX).

RESULTS

Of the coronary patients, 700 (83%) were men and 148 (17%) were women, whereas 862 (80%) of the controls were men and 216 (20%) were women (Table 1).
mo of abstinence, respectively). Then we classified education status and depression scale score of the participants.

The benefit of coffee drinking on coronary risk seems to hold only in the moderate group. In particular, the crude (unadjusted) relative risk estimates (OR) for moderate, heavy and very heavy consumption, compared with no consumption, were 0.75 (95% CI, 0.58–0.96), 1.65 (95% CI, 1.18–2.33) and 3.24 (95% CI, 1.90–5.50), respectively. Furthermore, multivariate analysis revealed that the relative risk estimates (OR) for moderate, heavy and very heavy consumption, compared with no consumption, were 0.67, 1.56 and 3.10, respectively (Table 2), after controlling for the presence of hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary heart disease, physical activity status, cigarette smoking, BMI, alcohol consumption, triglyceride levels, nutritional habits, education status and depression scale score. We then stratified our analysis by gender. The J-shaped effect of coffee intake on coronary risk was similar in men and women (OR for moderate, heavy or very heavy consumption vs. no consumption were 0.73, 1.51, 3.74 and 0.64, 1.60, 3.24, respectively). Moreover, the use of the hospitalized or population-based controls did not influence our findings as concluded form the applied sensitivity analysis (P for difference in the OR between “hospitalized” and “population based” controls = 0.98). The duration of abstention from coffee drinking during the last year did not alter our results (OR for acute coronary syndromes per month of not coffee drinking = 0.99, P = 0.91).

When exact quantities of coffee consumption were considered in the analysis, a J-shaped association between the adjusted (after controlling for the previously mentioned potential confounders) odds of developing acute coronary syndromes and the daily quantity of consumed coffee was revealed (Fig. 1).

We further examined the interaction between coffee con-

### TABLE 1

Clinical, demographic and lifestyle characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>700</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59.1 ± 10</td>
<td>65.3 ± 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>862</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58.8 ± 10</td>
<td>64.8 ± 10</td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9 y of schooling, n (%)</td>
<td>406 (58)</td>
<td>114 (77)</td>
<td>0.012</td>
</tr>
<tr>
<td>10–14 y of schooling, n (%)</td>
<td>182 (26)</td>
<td>31 (21)</td>
<td></td>
</tr>
<tr>
<td>&gt;14 y of schooling, n (%)</td>
<td>112 (16)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>525 (75)</td>
<td>44 (30)</td>
<td></td>
</tr>
<tr>
<td>Pack years, y</td>
<td>39.9 ± 14</td>
<td>13.1 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive, n (%)</td>
<td>308 (44)</td>
<td>102 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemic, n (%)</td>
<td>413 (59)</td>
<td>100 (68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic, n (%)</td>
<td>168 (24)</td>
<td>44 (30)</td>
<td>0.012</td>
</tr>
<tr>
<td>Family history of heart disease, n (%)</td>
<td>308 (44)</td>
<td>77 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.4 ± 4</td>
<td>27.1 ± 4</td>
<td>0.120</td>
</tr>
<tr>
<td>Physically inactive, n (%)</td>
<td>448 (64)</td>
<td>111 (75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adopted the Mediterranean diet, n (%)</td>
<td>119 (17)</td>
<td>34 (23)</td>
<td>0.045</td>
</tr>
<tr>
<td>Alcohol consumer (&gt;100 mL/d), n (%)</td>
<td>336 (48)</td>
<td>25 (17)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Experienced depressive episodes, n (%)</td>
<td>161 (23)</td>
<td>46 (31)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

1 Values are means ± SD.
2 P-values are for the differences between patients and controls.

### TABLE 2

Results from the multivariate logistic model for the effect of coffee consumption on the risk of developing acute coronary syndromes in a random sample of patients with their first coronary heart disease event and frequency-matched controls with no cardiovascular disease in their medical history after controlling for several potential confounders.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>848</td>
<td>1078</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with no coffee consumption (reference group)</td>
<td>171</td>
<td>158</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Subjects with moderate (&lt;300 mL/d) coffee consumption</td>
<td>484</td>
<td>773</td>
<td>0.69</td>
<td>0.50–0.86</td>
</tr>
<tr>
<td>Subjects with heavy (300–600 mL/d) coffee consumption</td>
<td>136</td>
<td>97</td>
<td>1.56</td>
<td>1.10–2.34</td>
</tr>
<tr>
<td>Subjects with very heavy (&gt;600 mL/d) coffee consumption</td>
<td>47</td>
<td>20</td>
<td>3.10</td>
<td>1.82–5.26</td>
</tr>
</tbody>
</table>

1 Confounders included age, gender, as well as the effect of hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary heart disease, physical activity status, smoking habits, BMI, alcohol consumption, triglyceride levels, adoption of Mediterranean diet, education status and depression scale score of the participants.
COFFEE CONSUMPTION AND CORONARY RISK

3231

FIGURE 1 Estimations of the odds ratio (OR) and 95% CI of developing acute coronary syndromes in those who drank coffee compared with those who did not in a random sample of 848 patients with their first coronary heart disease event and 1078 frequency-matched controls with no cardiovascular disease in their medical history. The variables adjusted for in the models of the separate OR included age, sex, smoking habits, hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary heart disease, physical inactivity, alcohol consumption, triglyceride levels, nutritional habits, education level, BMI and Center of Epidemiological Studies depression scale.

suggestion and hypertension status, alcohol consumption, triglyceride levels, nutritional habits, cigarette smoking, BMI, physical activity and depression because these factors have been considered to be modifers of the effect of caffeine on coronary risk in previous works (5). No significant interactions were observed between coffee consumption and the presence of hypertension (P = 0.123), alcohol drinking (P = 0.706), triglyceride levels (P = 0.782), cigarette smoking (P = 0.455), BMI (P = 0.770), physical activity status (P = 0.525) and the presence of depressive episodes (P = 0.167).

DISCUSSION

In this study, we demonstrated a J-shaped association between coffee consumption and the risk of developing acute coronary syndromes. In particular, moderate coffee consumption (<300 mL coffee/d) was associated with a lower coronary risk, whereas heavy or very heavy consumption (>300 mL coffee/d) was associated with a significant increase in risk. One may argue that “light” coffee drinking is a marker for healthy people, rather than that the low levels of coffee consumption reduce the risk. However, our findings are independent of the known confounding factors such as hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary heart disease, or physical activity status, nutritional and smoking habits, BMI, alcohol drinking, triglyceride levels, depression and education status.

Although several studies in the past have attempted to assess the role of coffee consumption on cardiovascular disease incidence, the information remains inconsistent. Based on a large sample of coronary patients and cardiovascular disease-free controls, this study is one of the few in the literature that suggests a J-shaped association between coffee consumption and the risk of developing acute coronary syndromes. This finding may explain in part the contradictory results reported by earlier studies (1-7). It is important to mention that different brewing methods alter the concentrations of kahweol and cafestol, the most likely cholesterol-raising factors in unfiltered coffee; this may explain the discrepant results in studies from different parts of the world (22,23). In addition, Marchioli et al. (24) suggested that cohort studies that evaluate the effect of nutritional habits on human health cannot readily account for changes in lifestyle habits that occur during the observation period. Thus, they suggest that negative results of cohort studies could be associated with a modification of lifestyle habits (including stopping drinking coffee and lowering intake in addition to changing the type of coffee consumed) that is due either to aging of the cohort or to a worsening health status during follow-up. Furthermore, Lang et al. (7) investigated the relationships and possible interactions between coffee consumption and several potential confounders, such as tobacco consumption, blood pressure, age, and BMI, in a cross-sectional epidemiologic study. They suggested that the contradictory interactions observed among blood pressure levels, cigarette smoking and coffee drinking might help to explain the conflicting reports concerning the association between coffee consumption and ischemic heart disease. However, the present study revealed the J-shaped association between coffee consumption and coronary risk, independently of the aforementioned confounding factors.

A discussion of the mechanisms responsible for the effect of coffee consumption on the coronary risk is beyond the scope of this study. However, some investigators have reported that an increase in homocysteine levels as a result of coffee consumption could at least partially explain its positive effect on coronary risk (25) and thromboembolic stroke risk in hypertensives (26). Thus, it remains to be investigated whether the observed J-shaped association is explained in part by the association between coffee consumption and homocysteine levels. It has also been reported that a lipid fraction of boiled coffee has been shown to significantly raise cholesterol and LDL levels in a dose-dependent manner, whereas filtered coffee does not contain this lipid-elevating fraction (27). We speculate that the observed J-shaped association between boiled coffee consumption and the risk of developing acute coronary syndromes could be due to this dose-response association between lipid levels and boiled coffee intake. However, the present analysis revealed that the variant effect of coffee consumption on coronary risk was independent of serum total cholesterol and blood glucose levels of the participants; thus the aforementioned potential explanation may not hold. On the other hand, our inability to take into account the method of coffee preparation may limit the value of the previous hypothesis. Moreover, unfiltered coffee, brand by brand, contains lipid-related effects on coronary risk that were not investigated in the present study. Finally, Roginsky and Barsukova (28) reported that the protective effects of coffee on atherosclerosis and other diseases can be attributed to the antioxidant activity of polyphenols. In particular, they observed that the inclusion of soluble coffee and other beverages in the testing system resulted in a pronounced retardation of methyl linoleate oxidation. Unfortunately, the present study could not test the antioxidant activity of polyphenols in the link between coffee and coronary risk, thereby explaining the observed association by this mechanism.

In retrospective case-control studies, two main sources of systematic errors may exist, i.e., the selection and the recall bias. To eliminate selection bias, we tried to set objective criteria for both patients and controls. However, insignificant
miscalssification may exist because a small percentage of asymptomatic coronary patients may be wrongly assigned as controls, even if a cardiologist had evaluated them. The use of “hospitalized” controls instead of a population-based group may increase the accuracy of the biometric evaluation of the participants, but could overestimate the findings because they may differ from the general population by being more health conscious. Also, one of main limitations of case-control studies is their failure to recognize that in the case of myocardial infarction (likely less for unstable angina), a substantial proportion of cases never reach the hospital because they die outside of the hospital setting. Furthermore, in case-control studies, it is usually observed that patients who had a recent adverse event are more likely to place greater emphasis (overestimate) on several factors related to the disease than the control group (recall bias). To reduce this type of bias and analyze accurate information, we made an effort to obtain precise information from the patients as well as from their relatives or accompanying persons and compare their responses with Kendall’s ω-criterion. However, overestimation of the effect of the investigated combination may still exist. For the medical purposes, we tried to avoid recall bias by obtaining accurate and detailed data from the subjects’ medical records. However, over- or underestimation may exist, especially in the measurement of nutritional and smoking habits, and the onset of the investigated cardiovascular risk factors. Moreover, the coronary patients who died at entry or during the first 12 h were not included in the study. This bias could influence our results, but because the proportion of deaths during d 1 was estimated to be between 2 and 4% by the physicians of the study, we believe that the inability to include the fatal events did not significantly alter our findings. Furthermore, the potential effect of uncontrolled/unknown confounders was reduced by using the same study base for both patients and controls.

In conclusion, our findings offer a message for public health, i.e., moderate coffee consumption may be of benefit because it seems to be associated with lower coronary heart disease risk, whereas heavy consumption is associated with a significant increase of the previous risk. The J-shaped association noted in the plasma homocysteine results from the Atherosclerosis Risk in Communities Study. Ann. Epidemiol. 4: 366–374.

REFERENCES


