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Coffee, CYP1A2 Genotype, and Risk of Myocardial Infarction

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EPIDEMIOLOGIC STUDIES EXAMINING the association between coffee consumption and risk of myocardial infarction (MI) have been inconclusive.¹⁻¹⁴ Coffee is a major source of caffeine (1,3,7-trimethylxanthine), which is the most widely consumed stimulant in the world and has been implicated in the development of cardiovascular diseases such as acute MI.¹⁵⁻¹⁷ However, coffee contains a number of other chemicals that have variable effects on the cardiovascular system.¹⁸ Because of the strong collinearity between caffeine intake and coffee consumption in many populations, it is not clear whether caffeine alone affects the risk of MI or whether other chemicals found in coffee may be responsible. Furthermore, the association between coffee consumption and unhealthy lifestyle factors suggests that previous associations might have been due to residual confounding.¹⁹

Caffeine is metabolized primarily by cytochrome P450 1A2 (CYP1A2) in the liver through an initial N³-demethylation.^{20,21} CYP1A2 accounts for approximately 95% of caffeine metabolism and demonstrates wide variability in enzyme activity between individuals.²¹⁻²³ An A→C substitution at position 734 (CYP1A2*1F) in the CYP1A2 gene decreases enzyme inducibility as measured by the ratio of plasma or urinary caffeine to caffeine metabolites after a dose of caffeine, resulting in impaired caffeine metabolism.²⁴⁻²⁶ Carriers of the

Context The association between coffee intake and risk of myocardial infarction (MI) remains controversial. Coffee is a major source of caffeine, which is metabolized by the polymorphic cytochrome P450 1A2 (CYP1A2) enzyme. Individuals who are homozygous for the CYP1A2*1A allele are "rapid" caffeine metabolizers, whereas carriers of the variant CYP1A2*1F are "slow" caffeine metabolizers.

Objective To determine whether CYP1A2 genotype modifies the association between coffee consumption and risk of acute nonfatal MI.

Design, Setting, and Participants Cases (n=2014) with a first acute nonfatal MI and population-based controls (n=2014) living in Costa Rica between 1994 and 2004, matched for age, sex, and area of residence, were genotyped by restriction fragment-length polymorphism polymerase chain reaction. A food frequency questionnaire was used to assess the intake of caffeinated coffee.

Main Outcome Measure Relative risk of nonfatal MI associated with coffee intake, calculated using unconditional logistic regression.

Results Fifty-five percent of cases (n=1114) and 54% of controls (n=1082) were carriers of the slow *1F allele. For carriers of the slow *1F allele, the multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of nonfatal MI associated with consuming less than 1, 1, 2 to 3, and 4 or more cups of coffee per day were 1.00 (reference), 0.99 (0.69-1.44), 1.36 (1.01-1.83), and 1.64 (1.14-2.34), respectively. Corresponding ORs (95% CIs) for individuals with the rapid *1A/*1A genotype were 1.00, 0.75 (0.51-1.12), 0.78 (0.56-1.09), and 0.99 (0.66-1.48) (P=.04 for gene × coffee interaction). For individuals younger than the median age of 59 years, the ORs (95% CIs) associated with consuming less than 1, 1, 2 to 3, or 4 or more cups of coffee per day were 1.00, 1.24 (0.71-2.18), 1.67 (1.08-2.60), and 2.33 (1.39-3.89), respectively, among carriers of the *1F allele. The corresponding ORs (95% CIs) for those with the *1A/*1A genotype were 1.00, 0.48 (0.26-0.87), 0.57 (0.35-0.95), and 0.83 (0.46-1.51).

Conclusion Intake of coffee was associated with an increased risk of nonfatal MI only among individuals with slow caffeine metabolism, suggesting that caffeine plays a role in this association.

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variant CYP1A2*1F allele are "slow" caffeine metabolizers, whereas individuals who are homozygous for the CYP1A2*1A allele are "rapid" caffeine metabolizers.²⁴⁻²⁶ The purpose of this study was to determine whether CYP1A2 genotype modifies the association between intake of caffeinated coffee and risk of nonfatal MI.

METHODS

Study Design and Participants

The catchment area for this study comprised 7071 km² and 2 057 000 indi-

viduals living in Costa Rica who are self-described Hispanic Americans.²⁷ This area included 36 counties in the Central Valley of Costa Rica representing a full range of socioeconomic levels, as

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well as urban, periurban, and rural lifestyles. Medical services in this area were covered by 6 large hospitals, which are part of the National Social Security System. Eligible case participants were men and women who were survivors of a first acute MI as diagnosed by a cardiologist at any of the 6 recruiting hospitals in the catchment area between 1994 and 2004. To achieve 100% ascertainment, the hospitals were visited daily by the study fieldworkers. All cases were confirmed by 2 independent cardiologists according to the World Health Organization criteria for MI, which require typical symptoms plus either elevation in cardiac enzyme levels or diagnostic change in electrocardiogram tracings.²⁸ Enrollment was carried out while cases were in the hospital's step-down unit. Case participants were ineligible if they died during hospitalization, were 75 years or older on the day of their first MI, were physically or mentally unable to answer the questionnaire, or had a previous hospital admission related to cardiovascular disease.

One control participant for each case, matched for age (± 5 years), sex, and area of residence (county), was randomly selected using information available at the National Census and Statistics Bureau of Costa Rica. Eligible controls were identified within 1 week of the case selection. On average, it took 27 days to complete data collection for cases and 31 days for controls. Because of the comprehensive social services provided in Costa Rica, all persons living in the catchment areas had access to medical care without regard to income. Therefore, control participants came from the source population that gave rise to the cases and are not likely to have had cardiovascular disease that was not diagnosed because of poor access to medical care. Controls were ineligible if they were physically or mentally unable to answer the questionnaires or if they had had a previous hospital admission related to MI or other cardiovascular disease.

Participation for eligible cases and controls was 98% and 88%, respec-

tively. All participants were visited at their homes for collection of biological specimens and information on diet, medical history, and anthropometric measurements. Cases and controls gave written informed consent and the study was approved by the ethics committees of the Harvard School of Public Health and the University of Costa Rica, the Office for the Protection from Research Risks at the National Institutes of Health, and the ethics review committee at the University of Toronto.

All data were collected by trained fieldworkers during an interview using 2 questionnaires consisting of closed-ended questions regarding smoking, sociodemographic characteristics, socioeconomic status, physical activity, diet, and medical history including use of medication and personal history of diabetes and hypertension. Information on dietary intake was collected using a 135-item semiquantitative food frequency questionnaire (FFQ) specifically developed and validated to assess dietary intake during the past year in the Costa Rican population.²⁹ For cases, average intake represented the year preceding their MI. Intakes of nutrients were calculated using the US Department of Agriculture food composition data file. Included in the FFQ were questions related to the consumption of caffeinated coffee, tea, cola beverages, and chocolate. The standard portion size for coffee in the FFQ was fixed as 1 cup equivalent to 250 mL, based on the habitual portion size for coffee-drinking habits established in this population during methods development.²⁹ Participants were asked to specify 1 of 9 categories of coffee intake: none or less than 1 cup/mo, 1 to 3 cups/mo, 1 cup/wk, 2 to 4 cups/wk, 5 to 6 cups/wk, 1 cup/d, 2 to 3 cups/d, 4 to 5 cups/d, or 6 cups/d or more. The correlation coefficient for caffeine intake between seven 24-hour recalls and the average of 2 FFQ interviews was 0.83, and the correlation coefficient between both FFQs was 0.77.²⁹ These results indicate high validity and reliability for the usual intake of coffee. Method of coffee preparation was ascertained for coffee

drinkers. Approximately 90% of coffee consumed in Costa Rica is filtered. Participants were categorized into 4 groups with reported coffee intakes of less than 1, 1, 2 to 3, or 4 or more 250-mL cups per day.

CYP1A2 Genotyping

Blood samples were collected in the morning at the participant's home after an overnight fast and were centrifuged to separate the plasma and leukocytes for DNA isolation by standard procedures. The *CYP1A2*1F* (rs762551) polymorphism was detected by restriction fragment-length polymorphism polymerase chain reaction as previously described,³⁰ without knowledge of case-control status. The genotype distribution among controls did not deviate from Hardy-Weinberg equilibrium according to a Pearson χ^2 test with 1 *df*.

Statistical Analyses

All data were analyzed using SAS version 8.2 (SAS Institute Inc, Cary, NC); $P < .05$ was considered statistically significant. DNA was available from 4369 participants (2113 cases and 2256 controls). A total of 341 participants were excluded because they were missing data on confounders (33 cases, 26 controls), could not be genotyped (63 cases, 73 controls), or became unmatched because of missing data (3 cases, 143 controls), leaving 2014 matched case-control pairs for the final analysis. Individual nutrient intakes were adjusted for total energy as described elsewhere.^{29,31} Because of the matched design, significant differences in the distribution of variables between cases and controls were tested using the McNemar test (categorical variables) and either paired *t* tests or Wilcoxon signed rank tests (continuous variables). Categorical and continuous non-dietary and energy-adjusted dietary variables were assessed for potential confounding by measuring their effect on the model parameter estimates using the likelihood ratio test. Odds ratios (ORs) and Wald 95% confidence intervals (95% CIs) were estimated by conditional logistic regression to de-

termine the effect of coffee intake on the risk of MI, with the lowest level of coffee intake (<1 cup/d) as the reference group. Confounders included in the final models were smoking (never, past, 1-19 cigarettes/d, and ≥ 20 cigarettes/d); alcohol consumption (never, past, and tertiles of intake among current drinkers); history of diabetes (yes/no), history of hypertension (yes/no); quintiles of the continuous variables waist-hip ratio, physical activity, and income; and energy-adjusted intakes of sucrose, saturated fat, polyunsaturated fat, and *trans* fat. We evaluated potential gene \times coffee interactions by determining the relation between coffee intake and the risk of MI for each genotype using conditional and unconditional logistic regression (with match-

ing variables in the model) and by comparing $-2 \log$ (likelihood) ratios from a model with coffee and gene main effects only and from another that included their interaction term. Because results for conditional and unconditional regressions were similar, we report only the data from unconditional analyses to maximize the number of participants. Results are presented using a dominant **1F* allele model with **1A/*1F* and **1F/*1F* genotypes combined, because both groups have a similar rate of caffeine metabolism.²⁴⁻²⁶ We also investigated whether smoking status (nonsmoker, current smoker) or age (below/above median) modified the relationship between *CYP1A2* genotype and MI associated with coffee intake, by performing stratified analyses and

evaluating the gene \times coffee interaction separately for each subgroup.

RESULTS

Demographic and risk factor characteristics of participants based on case-control status and coffee intake among controls are presented in TABLE 1. The proportion of **1F* carriers did not differ between cases and controls or between different categories of coffee intake. TABLE 2 shows the risk of MI associated with coffee intake for all participants and by *CYP1A2* genotype. Compared with individuals consuming less than 1 cup/d, the multivariate-adjusted OR (95% CI) of MI associated with consuming 4 cups/day or more was 1.40 (1.05-1.87). When participants were stratified by *CYP1A2*

Table 1. Demographic and Risk Factor Characteristics by Case-Control Status and by Coffee Intake Among Controls

Characteristic	No. (%)		P Value, Cases vs Controls	Controls Coffee Intake, No. (%)			
	Cases (n = 2014)	Controls (n = 2014)		<1 Cup/d (n = 269)	1 Cup/d (n = 338)	2-3 Cups/d (n = 1133)	≥ 4 Cups/d (n = 274)
<i>CYP1A2</i> *1A/*1F + *1F/*F, No. (%)	1114 (55)	1082 (54)	.31	156 (58)	180 (53)	595 (53)	151 (55)
Age, mean (SD), y*	58.4 (11.0)	58.1 (11.3)		56.7 (12.4)	58.4 (11.9)	58.7 (11.1)	56.7 (10.2)
Men, No. (%)*	1488 (74)	1488 (74)		190 (71)	243 (72)	818 (72)	237 (86)
Urban residence, No. (%)*	1482 (74)	1482 (74)		209 (78)	273 (81)	801 (71)	198 (72)
Secondary education or higher, No. (%)	733 (36)	806 (40)	.007	148 (55)	163 (48)	392 (35)	103 (38)
Household income, mean (SD), US \$/mo	499 (388)	571 (425)	<.001	735 (492)	632 (456)	522 (381)	543 (441)
Waist-hip ratio, mean (SD)	0.97 (0.07)	0.95 (0.07)	<.001	0.94 (0.08)	0.95 (0.08)	0.95 (0.08)	0.96 (0.06)
Physical activity, mean (SD), METs	1.51 (0.69)	1.57 (0.70)	.01	1.46 (0.48)	1.50 (0.68)	1.56 (0.69)	1.76 (0.87)
Medical history, No. (%)							
History of hypertension†	779 (39)	596 (30)	<.001	78 (29)	113 (33)	341 (30)	64 (23)
History of diabetes†	492 (24)	285 (14)	<.001	29 (11)	48 (14)	179 (16)	29 (11)
Current smoking‡	805 (40)	425 (21)	<.001	32 (12)	45 (13)	230 (20)	118 (43)
Current alcohol consumption†	984 (49)	1059 (53)	.01	138 (51)	200 (59)	576 (51)	145 (53)
Nutrient intakes, mean (SD)							
Total energy, kcal	2714 (946)	2457 (764)	<.001	2461 (759)	2340 (674)	2445 (748)	2648 (894)
Carbohydrate, % energy	54.3 (7.6)	55.4 (7.3)	<.001	54.9 (7.9)	53.7 (7.5)	55.9 (6.8)	55.8 (8.1)
Protein, % energy	13.2 (2.2)	12.9 (2.1)	<.001	12.9 (2.3)	13.2 (2.2)	13.0 (2.0)	12.7 (2.2)
Fat, % energy	32.4 (5.9)	31.9 (5.9)	.008	32.6 (6.6)	32.9 (6.4)	31.6 (5.3)	31.3 (6.4)
Saturated fat, % energy	12.4 (3.1)	11.7 (2.9)	<.001	11.4 (3.0)	11.8 (2.9)	11.7 (2.8)	12.0 (3.2)
Polyunsaturated fat, % energy	6.9 (2.3)	7.1 (2.3)	<.001	7.2 (2.0)	7.3 (2.4)	7.1 (2.4)	6.6 (2.4)
Monounsaturated fat, % energy	11.1 (3.5)	11.2 (4.1)	.70	12.2 (5.2)	11.9 (4.8)	10.9 (3.4)	11.0 (4.1)
<i>Trans</i> fat, % energy	1.3 (0.6)	1.3 (0.6)	.06	1.2 (0.6)	1.2 (0.6)	1.3 (0.7)	1.3 (0.6)
Cholesterol, mg/1000 kcal	127 (59)	118 (52)	<.001	120 (48)	113 (50)	119 (53)	117 (57)
Sucrose, g/d	80.1 (50.8)	75.2 (43.2)	<.001	74.3 (40.1)	63.6 (33.0)	73.9 (39.0)	95.8 (62.7)
Fiber, g/1000 kcal	9.5 (2.4)	10.0 (2.5)	<.001	10.1 (2.7)	9.9 (2.5)	10.1 (2.4)	9.3 (2.3)
Folate, μ g/1000 kcal	170 (46)	175 (47)	<.001	183 (50)	174 (46)	177 (46)	162 (43)

Abbreviation: METs, metabolic equivalent tasks.

*Matching variable.

†See "Methods" for definition.

‡One or more cigarettes per day.

Table 2. Coffee Intake and Relative Risk of Myocardial Infarction by CYP1A2 Genotype

Coffee Intake, Cups/d	No. (%)		OR (95% CI)	
	Cases	Controls	Model 1	Model 2
Total population	n = 2014	n = 2014		
<1	202 (10)	269 (13)	1.00*	1.00†
1	234 (12)	338 (17)	0.92 (0.71-1.18)	0.91 (0.68-1.21)
2-3	1146 (57)	1133 (56)	1.33 (1.09-1.63)	1.13 (0.89-1.42)
≥4	432 (21)	274 (14)	2.11 (1.66-2.69)	1.40 (1.05-1.87)
*1A/*1A	n = 900	n = 932		
<1	94 (10)	113 (12)	1.00‡	1.00§
1	117 (13)	158 (17)	0.89 (0.62-1.28)	0.75 (0.51-1.12)
2-3	510 (57)	538 (58)	1.14 (0.85-1.54)	0.78 (0.56-1.09)
≥4	179 (10)	123 (13)	1.76 (1.23-2.52)	0.99 (0.66-1.48)
*1A/*1F + *1F/*1F	n = 1114	n = 1082		
<1	108 (9)	156 (14)	1.00‡	1.00§
1	117 (11)	180 (17)	0.91 (0.65-1.28)	0.99 (0.69-1.44)
2-3	636 (57)	595 (55)	1.51 (1.15-1.98)	1.36 (1.01-1.83)
≥4	253 (23)	151 (14)	2.43 (1.77-3.35)	1.64 (1.14-2.34)

Abbreviations: CI, confidence interval; OR, odds ratio.

*Conditional logistic regression model (unadjusted).

†Conditional logistic regression model adjusted for smoking (never, past, 1-19 cigarettes/d, ≥20 cigarettes/d); waist-hip ratio; income; physical activity; history of diabetes; history of hypertension; and intakes of alcohol, total energy, and energy-adjusted saturated fat, polyunsaturated fat, *trans* fat, folate, and sucrose (see "Methods").

‡Unconditional logistic regression model that included matching variables (age, sex, and area of residence).

§Results from unconditional logistic regression that included matching variables and the confounders listed above for model 2. Gene × coffee interaction, $P = .04$.

genotype, the increased risk of MI associated with coffee intake was observed only among carriers of the slow *1F allele ($P = .04$ for gene × coffee interaction). In this group, the OR (95% CI) of MI was 1.64 (1.14-2.34) for 4 cups/d or more, as compared with less than 1 cup/d. The corresponding OR (95% CI) among those who were homozygous for the rapid *1A allele was 0.99 (0.66-1.48). Similar results were observed when men and women were examined separately. Compared with less than 1 cup/d, the ORs (95% CIs) of MI for 4 cups/d or more among individuals with the *1A/*1A genotype were 0.86 (0.53-1.36) for men and 1.43 (0.54-3.72) for women. Corresponding ORs (95% CIs) among carriers of the *1F allele were 1.54 (1.03-2.32) for men and 2.83 (1.15-6.99) for women.

Because smoking is associated with coffee consumption and is also a strong inducer of CYP1A2,³² we performed analyses separately for current smokers and nonsmokers (never, past). Although the gene × coffee interaction did not reach significance in either group, the modifying effect of CYP1A2 genotype on risk of MI associated with coffee

consumption was similar for both smokers and nonsmokers (TABLE 3).

It has previously been suggested that coffee may be associated with an increased risk of MI only among younger individuals.^{7,8} To investigate whether age modified the interaction between CYP1A2 and coffee on risk of MI, we assessed risk separately for participants above and below the median age (59 years). A significant gene × coffee interaction ($P = .003$) was observed only among the younger participants (Table 3). For those individuals who were carriers of the *1F allele, the ORs (95% CIs) of MI associated with consuming less than 1, 1, 2 to 3, or 4 or more cups of coffee per day were 1.00 (reference), 1.24 (0.71-2.18), 1.67 (1.08-2.60), and 2.33 (1.39-3.89), respectively. Corresponding ORs (95% CIs) for those with the *1A/*1A genotype were 1.00, 0.48 (0.26-0.87), 0.57 (0.35-0.95), and 0.83 (0.46-1.51). Because of the observed interaction with participants younger than the median age of 59 years, we also analyzed those younger than 50 years (448 cases, 478 controls), as has been previously done.³³ For carriers of the *1F allele, the ORs

(95% CIs) of MI associated with consuming less than 1, 1, 2 to 3, or 4 or more cups of coffee per day were 1.00, 2.12 (0.86-5.24), 2.43 (1.22-4.82), and 4.07 (1.89-8.74), respectively. Corresponding ORs (95% CIs) for those with the *1A/*1A genotype were 1.00, 0.39 (0.15-0.97), 0.35 (0.17-0.76), and 0.81 (0.32-2.05) ($P < .001$ for gene × coffee interaction).

COMMENT

Coffee is a major source of caffeine, which has multiple physiological effects that could increase the risk of MI.¹⁷ Numerous studies have examined the association between coffee consumption and risk of MI, but the findings have been inconclusive.¹⁻¹⁴ Caffeine is detoxified primarily through an initial N³-demethylation that is catalyzed by CYP1A2, an enzyme that displays wide interindividual variability in activity.²¹⁻²³ We investigated whether a common genetic polymorphism (CYP1A2*1F) that results in a "slow" metabolizer phenotype modifies the association between intake of caffeinated coffee and risk of nonfatal MI. Our findings show that coffee consumption increases the risk of MI only among individuals with a slow metabolizer genotype.

Meta-analyses examining the relationship between coffee intake and risk of coronary heart disease have observed a positive association among case-control studies but not among prospective cohort studies.^{1,2} According to the most recent meta-analysis,¹ the pooled case-control data show a 60% increased risk for drinking 5 cups/d. It has been suggested that the positive associations reported in case-control studies may have resulted from recall bias or confounding by factors such as smoking.^{19,34} However, because we observed an association between coffee and risk of MI among carriers of the *1F allele, and not among those homozygous for the *1A allele, the associations between coffee and MI are unlikely due to recall bias or residual confounding. Moreover, when we stratified our population by smoking

status, the results were similar for non-smokers and current smokers (Table 3).

A more likely explanation for the discrepancies between case-control and prospective cohort studies is that coffee drinking has mainly acute effects, which would be misclassified in prospective studies with a long follow-up and no updating of coffee intake.¹⁻³ In a study by LaCroix et al,⁴ the relative risk of coronary heart disease for 5 or more cups per day compared with none increased from 1.89 when intake was assessed 10 or more years previously to 2.49 when intake within the past 5 years was used. Similarly, a strong association between coffee consumption and mortality from coronary heart disease, reported after 6 years of follow-up,⁵ was weakened by 6 more years of follow-up.⁶ The decreased effect of coffee after longer follow-up could also be a result of caffeine having a weaker effect in an older population. Indeed, the *CYP1A2* × coffee interaction we observed among individuals younger than the median age suggests that caffeine has a greater relative effect on younger individuals. Among the slow metabolizers, the risk associated with drinking 4 cups/d or more compared with less than 1 cup/d increased from 2-fold for individuals younger than 59 years to more than 4-fold for those younger than 50 years. A similar effect of age was observed by Palmer et al,⁷ who found a greater risk of MI with caffeinated coffee consumption among women 45 through 59 years of age but not among women 60 years or older.

The absence of an association between coffee and risk of MI in some case-control studies may have been due to a lower frequency of **1F* carriers in the populations that were examined. In the present study, the frequency of carriers of the **1F* allele was 54%, but frequencies have been reported to vary by population.³⁵⁻³⁸ Because cases in the present study experienced nonfatal MI, we cannot exclude the possibility that the observed interaction may affect survival after an acute MI.

Although smokers metabolize caffeine more rapidly than nonsmokers

Table 3. Coffee Intake and Relative Risk of Myocardial Infarction by *CYP1A2* Genotype, Smoking Status, and Age Category

Coffee Intake, Cups/d	No. (%)		OR (95% CI)	
	Cases	Controls	Model 1	Model 2
Smoking Status*				
Nonsmokers				
<i>*1A</i> / <i>*1A</i>	n = 532	n = 745		
<1	75 (14)	101 (14)	1.00	1.00
1	84 (16)	135 (18)	0.84 (0.56-1.25)	0.73 (0.47-1.14)
2-3	312 (59)	436 (58)	0.95 (0.68-1.33)	0.75 (0.52-1.07)
≥4	61 (11)	73 (10)	1.13 (0.71-1.77)	1.02 (0.62-1.67)
<i>*1A</i> / <i>*1F</i> + <i>*1F</i> / <i>*1F</i>	n = 677	n = 844		
<1	85 (13)	136 (16)	1.00	1.00
1	97 (14)	158 (18)	0.96 (0.66-1.40)	1.01 (0.67-1.51)
2-3	399 (59)	467 (55)	1.32 (0.97-1.79)	1.27 (0.91-1.76)
≥4	98 (14)	83 (10)	1.93 (1.29-2.88)	1.72 (1.11-2.67)
Smokers				
<i>*1A</i> / <i>*1A</i>	n = 368	n = 187		
<1	19 (5)	12 (6)	1.00	1.00
1	33 (9)	23 (12)	0.90 (0.36-2.23)	0.87 (0.30-2.51)
2-3	198 (54)	102 (55)	1.23 (0.57-2.64)	1.11 (0.45-2.76)
≥4	118 (32)	50 (27)	1.59 (0.71-3.54)	1.22 (0.47-3.18)
<i>*1A</i> / <i>*1F</i> + <i>*1F</i> / <i>*1F</i>	n = 437	n = 238		
<1	25 (6)	20 (8)	1.00	1.00
1	20 (5)	22 (9)	0.65 (0.27-1.54)	0.90 (0.33-2.50)
2-3	237 (54)	128 (54)	1.42 (0.75-2.70)	1.77 (0.83-3.76)
≥4	155 (35)	68 (29)	1.83 (0.94-3.56)	1.79 (0.80-3.98)
Age Category†				
Age <59 y‡				
<i>*1A</i> / <i>*1A</i>	n = 451	n = 446		
<1	51 (11)	50 (11)	1.00	1.00
1	53 (12)	78 (17)	0.66 (0.39-1.12)	0.48 (0.26-0.87)
2-3	228 (51)	252 (57)	0.89 (0.58-1.37)	0.57 (0.35-0.95)
≥4	119 (26)	66 (15)	1.78 (1.09-2.92)	0.83 (0.46-1.51)
<i>*1A</i> / <i>*1F</i> + <i>*1F</i> / <i>*1F</i>	n = 505	n = 552		
<1	49 (10)	98 (18)	1.00	1.00
1	46 (9)	89 (16)	1.03 (0.63-1.69)	1.24 (0.71-2.18)
2-3	266 (53)	282 (51)	1.87 (1.28-2.75)	1.67 (1.08-2.60)
≥4	144 (29)	83 (15)	3.47 (2.24-5.37)	2.33 (1.39-3.89)
Age ≥59 y				
<i>*1A</i> / <i>*1A</i>	n = 449	n = 486		
<1	43 (10)	63 (13)	1.00	1.00
1	64 (14)	80 (16)	1.17 (0.70-1.94)	1.10 (0.63-1.92)
2-3	282 (63)	286 (59)	1.44 (0.94-2.20)	1.06 (0.67-1.69)
≥4	60 (13)	57 (12)	1.56 (0.92-2.66)	1.06 (0.58-1.94)
<i>*1A</i> / <i>*1F</i> + <i>*1F</i> / <i>*1F</i>	n = 609	n = 530		
<1	59 (10)	58 (11)	1.00	1.00
1	71 (12)	91 (17)	0.78 (0.48-1.25)	0.79 (0.47-1.32)
2-3	370 (61)	313 (59)	1.18 (0.79-1.74)	1.06 (0.69-1.63)
≥4	109 (18)	68 (13)	1.54 (0.95-2.48)	1.09 (0.64-1.86)

Abbreviations: CI, confidence interval; OR, odds ratio.

*Model 1: unconditional logistic regression model adjusted for age, sex, and area of residence. Model 2: unconditional logistic regression model adjusted for age; sex; area of residence; waist-hip ratio; income; physical activity; history of diabetes; history of hypertension; and intakes of alcohol, total energy, and energy-adjusted saturated fat, polyunsaturated fat, *trans* fat, folate and sucrose (see "Methods"). Nonsmokers were further adjusted for never and past smoking, and smokers adjusted for cigarettes smoked per day.

†Model 1: unconditional logistic regression model adjusted for age, sex, area of residence. Model 2: unconditional logistic regression model adjusted for age; sex; area of residence; smoking (never, past, 1-19 cigarettes/d, ≥20 cigarettes/d); waist-hip ratio; income; physical activity; history of diabetes; history of hypertension; and intakes of alcohol, total energy, and energy-adjusted saturated fat, polyunsaturated fat, *trans* fat, folate, and sucrose (see "Methods").

‡P = .003 for gene × coffee interaction.

due to the well-known CYP1A2-inducing effect of smoking,³² the extent of CYP1A2 induction among smokers is lower for carriers of the *1F allele.^{25,26} Thus, smokers with the slow metabolizer genotype may still have an increased risk of MI with increasing coffee consumption. Indeed, for carriers of the *1F allele, a similar pattern of risk associated with coffee was observed among smokers and nonsmokers (Table 3).

Among younger individuals who were rapid caffeine metabolizers, coffee intakes of either 1 cup/d or 2 to 3 cups/d were associated with a lower risk of MI compared with intakes of less than 1 cup/d. This finding is consistent with a number of previous reports of J- or U-shaped associations between coffee and MI,¹¹⁻¹⁴ suggesting a protective effect of moderate coffee consumption. It has been proposed that the higher risk of heart disease among the group with the lowest intake might be due to individuals with underlying diseases who are limiting their coffee intake.^{12,14} However, the absence of an elevated risk in the lowest category of coffee intake among the slow metabolizers in the present study indicates that this is unlikely.

Coffee contains other chemicals that may have adverse effects on the cardiovascular system.¹⁸ Distinguishing between the effects of caffeine and those of these other compounds has been difficult, given the strong collinearity between caffeine and coffee intake in many populations. Diterpenoids that are present in the lipid fraction of boiled coffee have been shown to increase levels of serum cholesterol³⁹⁻⁴¹ and may increase the risk of MI.⁹ However, the levels of diterpenoids are greatly reduced in filtered coffee.⁴² About 10% of coffee drinkers in the current population did not report consuming filtered coffee, and excluding them from our analyses did not materially alter the results (data not shown). Besides caffeine, no other major compound found in filtered coffee is known to be detoxified by CYP1A2. Thus, our findings suggest that caffeine is the major component of fil-

tered coffee that increases risk of nonfatal MI. Although the mechanism by which caffeine increases risk of MI remains unclear, it is known to block the A₁ and A_{2A} adenosine receptors.^{43,44} Adenosine is a potent coronary and systemic vasodilator that may play an important role in the reactivity of inflammatory cells and platelets during periods of myocardial ischemia.^{45,46}

Although the CYP1A2*1F polymorphism is located in a noncoding region of the gene, the polymorphism may result in differential binding of regulatory proteins to the surrounding sequence that may affect CYP1A2 expression levels.²⁵ The regulatory mechanisms of intronic polymorphisms on transcriptional activity have been described for several genes.⁴⁷ Alternatively, the polymorphism may be in linkage disequilibrium with other single nucleotide polymorphisms influencing CYP1A2 inducibility.²⁵ Nevertheless, in vivo studies clearly show marked differences in CYP1A2 activity between carriers of the different CYP1A2 alleles.²⁴⁻²⁶

In summary, consistent with most case-control studies, we found that increased coffee intake is associated with an increased risk of nonfatal MI. The association between coffee and MI was found only among individuals with the slow CYP1A2*1F allele, which impairs caffeine metabolism, suggesting that caffeine plays a role in the association.

Author Contributions: Dr El-Sohehy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Cornelis, El-Sohehy, Campos.

Analysis and interpretation of data: Cornelis, El-Sohehy, Kabagambe, Campos.

Drafting of the manuscript: Cornelis, El-Sohehy.

Critical revision of the manuscript for important intellectual content: Cornelis, El-Sohehy, Kabagambe, Campos.

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Obtained funding: El-Sohehy, Campos.

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Study supervision: El-Sohehy, Campos.

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