



Gender and ethnicity modify the association between the *CYP1A2* rs762551 polymorphism and habitual coffee intake: evidence from a meta-analysis

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ABSTRACT. The association between the single nucleotide polymorphism rs762551 in the cytochrome P450 family 1, subfamily A2 gene (*CYP1A2*) and caffeine consumption remains controversial. We conducted a meta-analysis to clarify this potential association. Twelve studies were selected from articles retrieved from the and Google Scholar databases, and the data were analyzed to determine the odds ratio (OR) of genotypes AA (conferring fast caffeine metabolism) vs AC + CC (conferring slow caffeine metabolism). Comparisons were made between 6161 high caffeine consumers and 3219 low caffeine consumers. The overall analysis showed a significant association between genotype AA and coffee intake

[OR = 1.13, 95% confidence interval (CI) = 1.03-1.24; $Q = 19.23$, $P = 0.06$; $I^2 = 43\%$]. In subgroup analyses, the association was also found within male, younger, and Caucasian subjects (OR = 1.21, 95%CI = 1.08-1.35; OR = 1.71, 95%CI = 1.18-2.48; OR = 1.29, 95%CI = 1.12-1.49, respectively) but not in female, older, and Asian subjects (OR = 0.98, 95%CI = 0.83-1.15; OR = 0.83, 95%CI = 0.56-1.22; OR = 0.91, 95%CI = 0.71-1.17, respectively). Therefore, the rs762551 AA genotype may lead to higher coffee intake, especially in males, younger age groups, and individuals of Caucasian ethnicity. Our data highlight the need to test other *CYP1A2* polymorphisms showing significance in genome-wide association studies to clarify the association with caffeine intake in the Asian population.

Key words: CYP1A2; rs762551 SNP; Coffee intake; Meta-analysis; Ethnicity

INTRODUCTION

Coffee consumption has become a growing concern for the general public since epidemiological studies have suggested an association between caffeine intake and several pathologies. In fact, long-term caffeine intake has been associated with an increased risk of myocardial infarction and recurrent pregnancy loss but with a decreased risk of type 2 diabetes and Parkinson's disease. Studies on the association between caffeine and cancer showed an increasing risk for ovarian, bladder, and lung cancers but a protective effect of high coffee consumption against breast, colon, prostate, and liver cancers. Environmental, demographic, and social factors may explain the observed inter-individual variability in caffeine intake. However, twin studies have provided evidence of heritability determinants of caffeine intake, suggesting that individual differences in caffeine consumption may be related to genetic factors (Vink et al., 2009). Genome-wide association studies (GWAS) of habitual coffee intake showed significant associations of different gene sequence variants with increased coffee intake, mainly cytochrome P450 family 1, subfamily A1-A2 (*CYP1A1-CYP1A2*), aryl hydrocarbon receptor (*AHR*; Cornelis et al., 2011), neuronal cell adhesion molecule (*NRCAM*; Amin et al., 2012) and taste receptor type 2, family member 43 (*TAS2R43*; Pirastu et al., 2014) loci. These genes have been implicated in caffeine metabolism, regulation of metabolism-related genes, vulnerability to addiction, and coffee taste preferences, respectively.

Caffeine is primarily metabolized by CYP1A2, and genetic variations altering the expression of the enzyme represent a major determinant of enzyme activity. A single nucleotide polymorphism (SNP) in the *CYP1A2* gene (-163A→C, rs762551) was found to be correlated with altered enzyme activity, as C allele carriers showed decreased activity of the enzyme (Sachse et al., 1999). However, the relationship between the rs762551 SNP and coffee consumption remains controversial, owing to conflicting data obtained from GWAS and single-marker association studies. In order to provide further information about the association between the rs762551 SNP and coffee drinking, we conducted a meta-analysis using new data extracted from published studies evaluating the distribution of rs762551 genotypes among subjects stratified according to coffee intake.

MATERIAL AND METHODS

Study selection and inclusion criteria

We searched the and Google Scholar databases for published papers by using combinations of the following terms: “cyp1A2”, “cyp1A2 polymorphism”, “caffeine”, “coffee”, “rs762551”. The search was conducted up until June 4, 2015. GWAS on the association of the rs762551 SNP with caffeine intake were not included. In addition, we avoided using data from patients as they may show differences in terms of the distribution of the rs762551 genotypes and coffee consumption compared to healthy subjects. All studies that evaluated the interaction of the rs762551 SNP with coffee intake in disease susceptibility, or showing the distribution of rs762551 genotypes according to coffee intake strata in relation to a particular phenotype were screened. Data on ethnic origin, mean age, gender ratio, smoking status (never-smoking, current smoker), and rs762551 genotype counts among coffee consumption groups were extracted from the control group data sets. Several studies provided combined AC + CC genotype frequency counts in order to assess the associations between fast caffeine metabolizers (AA genotype) vs low caffeine metabolizers (AC + CC genotypes). We consequently used the dominant CYP1A2 C allele model for this meta-analysis. Hardy Weinberg equilibrium (HWE) conformation was assessed in studies reporting separate CA and CC genotype counts.

Data analysis

For each study, individuals were stratified according to coffee consumption based on the number of cups of coffee consumed per day, amount of caffeine intake per day, never vs ever coffee drinkers, null vs weekly vs daily coffee drinkers, no/low consumers vs moderate consumers vs high consumers, non-heavy coffee consumers vs heavy coffee consumers, or low vs high intake. We examined the association of the CYP1A2 rs762551 SNP with coffee intake by comparing the AA and AC + CC genotype distributions among the coffee consumption categories. In particular, the following groups were compared in the meta-analysis: the highest coffee consumption group (≥2 coffee cups consumed per day, ≥200 mg/day caffeine intake, ever drinkers, daily drinkers, high consumers, heavy coffee consumers, or high intake) vs the lowest coffee consumption group (reference group).

Statistical analysis

We checked the conformation of genotype frequencies to HWE using the HWE web tool (<http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>). Meta-analysis statistics were derived using the Review Manager Program version 5.3 (Cochrane Collaboration, Oxford, UK). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated for each study. Cochran's Q (or c^2) and I^2 values were used to assess heterogeneity among studies. Either fixed- or random-effect models were chosen according to heterogeneity between studies. The random-effect model was used when a significant Q value ($P < 0.05$) was calculated. There was no need to examine the influence of publication bias since data for genotype distributions and coffee intake were derived from separate, independent studies and none directly examined the association between the rs762551 AA genotype and coffee intake. To investigate evidence for any confounding variable that may modify the effect of the

rs762551 AA genotype, we further conducted sub-analyses by stratifying the data according to gender, age, smoking status, and ethnicity. For example, if smoking modifies the genetic effect on caffeine intake, the OR of the AA genotype in the comparison of high vs low caffeine consumers would differ between never-smokers and current smokers. The Cochran test given a statistically significant result ($P < 0.05$) indicates the OR difference across the stratified data and indicates the existence of an effect modification.

RESULTS

Studies included in the meta-analysis

Thirty-three studies were assessed for eligibility. The following papers were excluded: four GWAS (Cornelis et al., 2011; Sulem et al., 2011; Amin et al., 2012; Rodenburg et al., 2012); four studies lacking coffee intake analysis (Sachse et al., 1999; Basvi et al., 2007; Ghotbi et al., 2007; Gunes et al., 2009); eight studies not providing coffee intake data according to rs762551 genotypes (Goodman et al., 2003; Kotsopoulos et al., 2009; Hallström et al., 2010; Schmidt et al., 2010; Guessous et al., 2012; Josse et al., 2012; Palatini et al., 2015; Yamamoto et al., 2015); two studies providing CC and combined AC + AA genotypes counts instead of AA and AC + CC genotype counts (Palatini et al., 2009; Pavanello et al., 2010); two studies using patient samples (Cornelis et al., 2007; Bågeman et al., 2008); and one study with a small sample size (Santos et al., 2015). Finally, 12 studies were included in the meta-analysis (Nordmark et al., 2002; Sata et al., 2005; Cornelis et al., 2006; Kotsopoulos et al., 2007; Tan et al., 2007; Jernström et al., 2008; Djordjevic et al., 2010; Popat et al., 2011; Kohno et al., 2013; Lowcock et al., 2013; Tian et al., 2013; Dik et al., 2014) (Figure 1). The study characteristics are shown in Table 1. Samples showing deviations from HWE ($P < 0.05$) were not included. In total, comparisons were made between 6161 high caffeine consumers and 3219 low caffeine consumers.

Table 1. Characteristics of studies included in the meta-analysis.

References	Location	Ethnicity	Mean age (years)	Gender ratio Male/Female	Coffee intake ascertainment		rs762551 (AA) genotype (N)		rs762551 (AC+CC) genotypes (N)		rs762551 A allele frequency	HWE P
					High intake	Low intake ^b	High intake	Low intake	High intake	Low intake		
Cornelis et al. (2006)	Canada	Hispanic American ^a	58.1	73.8/26.2	≥2 cups/day	<1 cup/day	681	113	746	156	0.73	NA
Dik et al. (2014)	Netherlands	Caucasian	51.2	29.8/70.2	High consumers	Non/low consumers	387	293	329	307	0.75	NA
Djordjevic et al. (2010)	Sweden	Caucasian	26	41.2/58.8	Heavy consumers	Non-heavy consumers	21	25	21	47	0.70	0.002*
	Serbia	Caucasian	27	47.6/53.4	Heavy consumers	Non-heavy consumers	10	12	7	35	0.67	0.75
Sata et al. (2005)	Japan	Asian	19.44	0/100	>300 mg/day	<100 mg/day	6	34	11	31	0.74	0.45
Jernstrom et al. (2008)	Sweden	Caucasian	29	0/100	≥2 cups/day	<1 cup/day	79	43	78	43	0.75	NA
Kohno et al. (2013)	Japan	Asian	52.4	100/0	Daily use	Null use	450	86	579	98	0.72	NA
Kotsopoulos et al. (2007)	Canada	Caucasian	43.1	0/100	Ever use	Never use	81	41	89	30	0.75	NA
Lowcock et al. (2013)	Canada	Caucasian	25.74	0/100	≥2 cups/d	Never use	376	146	365	161	0.75	0.37
Nordmark et al. (2002)	Sweden	Caucasian	28.4	0/100	High intake	Low intake	195	259	199	251	0.75	0.93
Popat et al. (2011)	USA	Caucasian	68.4	65.4/34.6	Ever use	Never use	523	128	475	160	0.75	0.65
Tan et al. (2007)	Singapore	Asian	63.6	51.5/48.5	>200 mg/day	<200 mg/day	161	67	162	65	0.75	0.14
Tian et al. (2013)	Canada	Caucasian/Asian	22.7	29/71	>200 mg/day	<100 mg/day	102	303	90	359	0.73	NA

^aHispanic Americans were treated as Caucasians. ^bReference group; HWE = Hardy-Weinberg equilibrium; NA = not applicable; *HWE $P < 0.05$ (the sample was excluded).

Overall analysis

Data from the 12 included studies were analyzed to obtain the OR of the AA genotype (fast caffeine metabolizer) vs AC + CC genotypes (slow caffeine metabolizer) in relation to coffee intake. Figure 2 shows the individual ORs for each study, as well as the total OR. The fixed-effect model

was used given the overall low level of heterogeneity ($Q = 19.23$, $P = 0.06$; $I^2 = 43\%$). Overall, there was a significant association between AA genotype and coffee intake ($OR = 1.13$, $95\%CI = 1.03-1.24$).

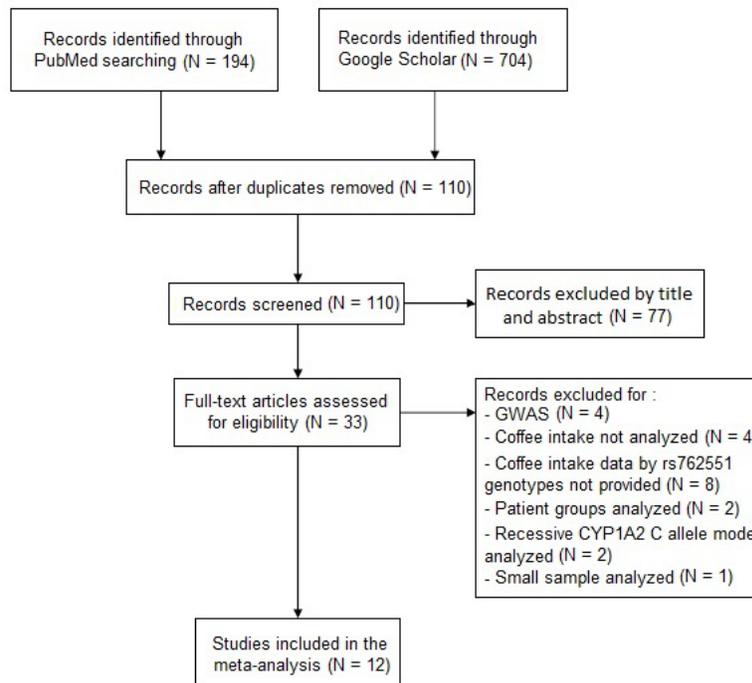


Figure 1. Flow chart for study selection. For Google Scholar records, only the first 200 articles of each search were assessed for eligibility.

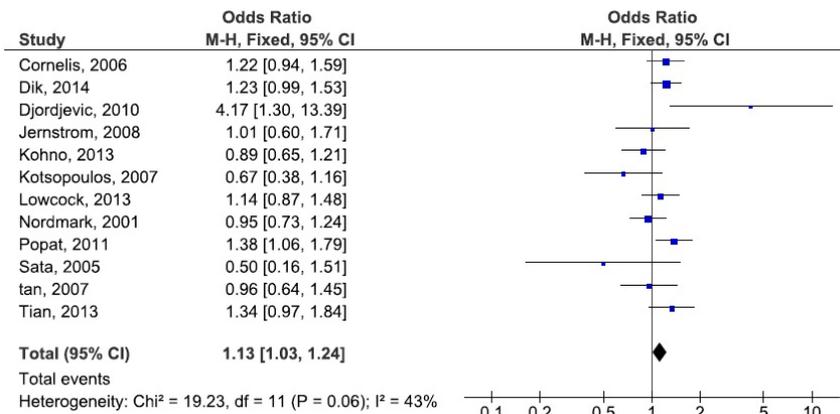


Figure 2. Forest plot of the odds ratios of individual studies and overall odds ratio for the association of coffee intake with the rs762551 AA genotype with (AC + CC) genotypes.

Subgroup analyses

Stratification of the data by gender was not possible within studies. However, inter-study differences between the genders evaluated and gender ratios were evident. Indeed, there were studies including only one gender in the control group, in order to match cases for gender (e.g., association studies on breast cancer risk used fertile women as a control group). Therefore, a subgroup analysis was performed within the 5 studies (N = 2518) comprising only female subjects (F subgroup) and within the 7 remaining studies (N = 6862) with an overall male/female gender ratio of 57.8/42.2 (MF subgroup). This meta-analysis showed that the rs762551 AA genotype was associated with coffee intake in the MF subgroup (fixed-effects model OR = 1.21, 95%CI = 1.08-1.35; $Q = 10.94$, $P = 0.09$; $I^2 = 45\%$) but not in the F subgroup (fixed-effect model OR = 0.98, 95%CI = 0.83-1.15; $Q = 4.53$, $P = 0.34$; $I^2 = 12\%$), with evidence for an effect modification (P value for heterogeneity = 0.04) (Figure 3).

A subgroup analysis according to smoking was also performed using data extracted from studies that analyzed the rs762551 genotype distribution according to both coffee consumption and smoking status. A total of 2633 never-smoker subjects were compared to 1155 current smokers. We found that the rs762551 AA genotype was not associated with coffee intake in either the never smokers (fixed-effect model OR = 1.04, 95%CI = 0.87-1.25; $Q = 2.94$, $P = 0.23$; $I^2 = 32\%$) or current smokers (fixed-effect model OR = 1.09, 95%CI = 0.75-1.58; $Q = 0.28$, $P = 0.87$; $I^2 = 0\%$), with no evidence of any effect modification by smoking (P value for heterogeneity = 0.83) (Figure 3).

Furthermore, data on rs762551 genotypes stratified by both coffee consumption and age were available in only one study; 831 subjects younger than 59 years and 845 subjects 59 years of age or older were assessed. We found that the rs762551 AA genotype was associated with coffee intake in subjects younger than 59 years (OR = 1.71, 95%CI = 1.18-2.48), whereas no association was detected in those aged 59 years or older (OR = 0.83, 95%CI = 0.56-1.22). In this case, the effect modification by age was significant ($P = 0.008$) (Figure 3).

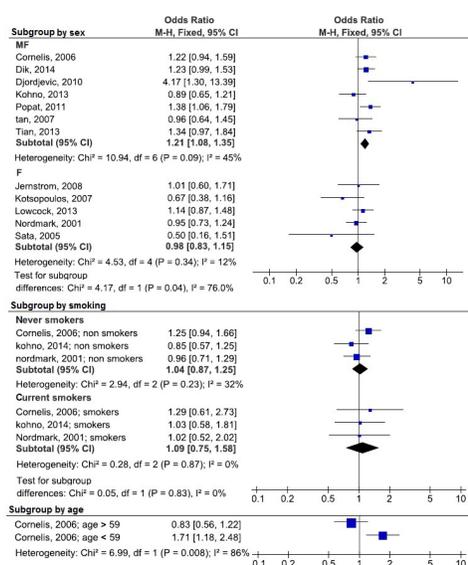


Figure 3. Forest plot of the odds ratios of individual studies and total odds ratio for the association of coffee intake with the rs762551 SNP, pooled by sex, smoking, and age. F: female only; MF: male/female ratio of 57.8/42.2.

Finally, an ethnicity-specific meta-analysis was conducted. Seven studies (N = 6778) included subjects of Caucasian ethnicity and 3 studies (N = 1750) used individuals of Asian ethnicity. One study was excluded since the analyzed sample was ethnically heterogeneous (Caucasians, 47%; Asians, 46%; others, 8%). As a result, the Caucasians subgroup showed a significant relationship between AA genotype and coffee intake (fixed-effect model OR = 1.16, 95%CI = 1.04-1.29; Q = 12.97, P = 0.07; I² = 46%), whereas Asians did not show any association (fixed-effect model OR = 0.89, 95%CI = 0.70-1.13; Q = 1.21, P = 0.55; I² = 0%). However, the test for subgroup differences did not reach significance (P = 0.05), although when we tested the relationship within the MF subgroup, the effect modification was significant (P = 0.02). The OR of the association between AA genotype and coffee intake in Caucasian subjects from the MF subgroup (N = 4342) was 1.29 (95%CI = 1.12-1.49; Q = 4.43, P = 0.22; I² = 32%), whereas Asians from the MF subgroup (N = 1668) did not show any significance (OR = 0.91, 95%CI = 0.71-1.17; Q = 0.11, P = 0.75; I² = 0%) (Figure 4).

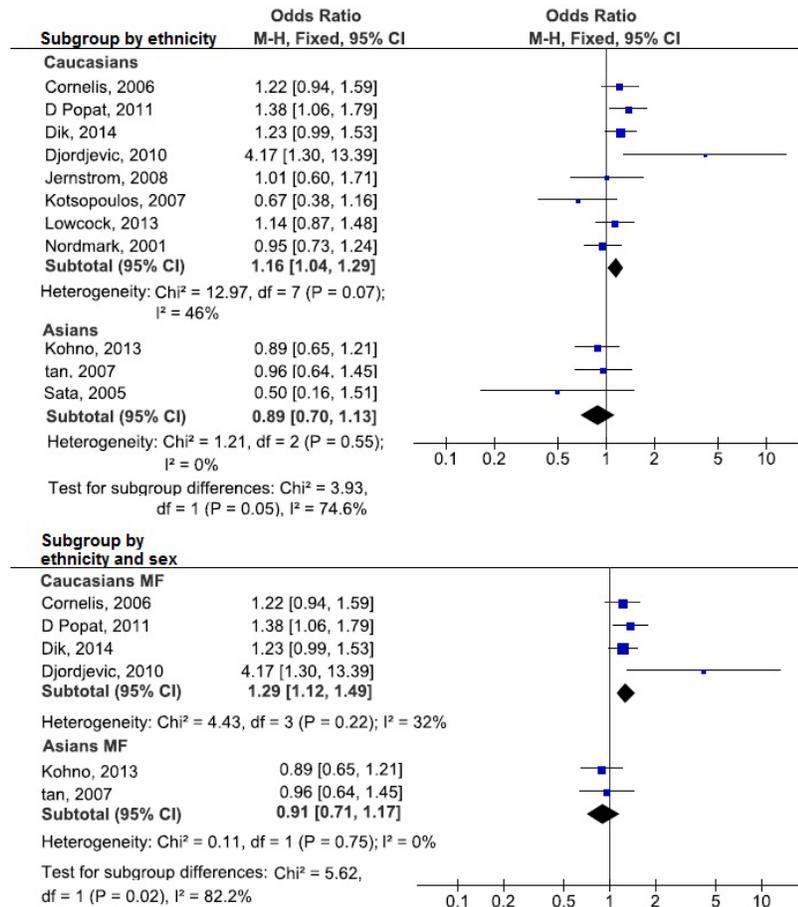


Figure 4. Forest plot of the odds ratios of individual studies and total odds ratio for the association of coffee intake with the rs762551 SNP, pooled by ethnicity and ethnicity + sex. MF: male/female ratio of 57.8/42.2.

Interaction of coffee intake with smoking, gender, age, and ethnicity

The genotype distribution in relation to coffee consumption status (high coffee intake vs low intake) among subgroups was assessed by using the Pearson χ^2 test. Coffee intake was significantly increased by smoking (OR = 3.53, 95%CI = 2.90-4.31, $P < 0.00001$) and male gender (OR = 1.5, 95%CI = 1.36-1.64, $P < 0.00001$). Individuals below 59 years of age showed a non-significant increase in coffee consumption (OR = 1.30, 95%CI = 1.00-1.68, $P = 0.051$). With regards to ethnicity, Asians showed a significantly increased coffee intake compared to Caucasians (OR = 1.70, 95%CI = 1.50-1.93, $P < 0.00001$).

DISCUSSION

Our results of significant associations of male gender and smoking with higher coffee intake are in line with previous studies, suggesting lower CYP1A2 activity in women (Gunes and Dahl, 2008) and that smoking increases CYP1A2 enzyme activity (Backman et al., 2008). There was no significant association observed for age, which is also consistent with previous finding that smoking and gender are the main modifiers of CYP1A2 enzyme activity (24 and 10%, respectively), whereas age explained only 1% of the variation in enzyme activity (Gunes et al., 2009). The first report on the CYP1A2 rs762551 SNP showed a significant correlation with high enzyme inducibility among smokers, while no correlation was observed for non-smokers (Sachse et al., 1999). Consequently, carriers of the C variant allele were considered to be slow caffeine metabolizers, whereas AA homozygous individuals were considered to be fast caffeine metabolizers. The association between the rs762551 SNP and coffee consumption was first assessed in a study conducted with Costa Rican subjects, and no significant association was found (Cornelis et al., 2007). Population-based GWAS for habitual coffee drinking also tested the association with the rs762551 SNP. Amin et al. (2012) conducted a GWAS and found nominal significance for the rs762551 SNP ($P = 0.003$). Sulem et al. (2011) conducted a GWAS, and found that the rs762551 AA genotype was also nominally associated with increased coffee consumption ($P = 0.008$), but the significance disappeared after adjusting for another CYP1A1-CYP1A2 SNP (rs2472297), achieving genome-wide significance ($P = 5.4 \times 10^{-14}$). However, Rodenburg et al. (2012) showed that the A allele of the rs762551 SNP was linked to the G allele of the rs2472299 SNP (complete linkage disequilibrium), and the rs2472299 GG genotype significantly contributed to coffee intake ($P < 0.0002$), even after adjusting for the rs2472297 SNP. Based on these 12 studies, we conducted a meta-analysis including 6161 high consumers and 3219 low consumers. We found that the rs762551 AA genotype was associated with higher coffee intake. These data were then subjected to stratification by gender, age, smoking status, and ethnicity. The rs762551 AA genotype was associated with coffee intake in the subgroup containing both sexes (MF) but no significant association was observed in the female-only (F) subgroup, with evidence for effect modification ($P = 0.04$). With regards to smoking, no association was found in either the never smokers or current smokers subgroups, with no evidence of effect modification ($P = 0.83$). For the interaction with age, we found that the rs762551 AA genotype increased coffee intake in subjects younger than 59 years old but not in those 59 years of age or older, and a significant genotype effect modification was observed ($P = 0.008$). These data are in line with those of Rodenburg et al. (2012), who investigated the modifying effect of gender, age, and smoking on the relationship of the rs762551 SNP with coffee intake in 6288 participants from the Rotterdam cohort. The authors reported a significant

interaction with gender ($P = 0.049$) but not with smoking ($P = 0.79$). However, they did not find any interaction with age ($P = 0.16$). However, our finding of a significant effect modification from age is limited by the small size of the sample analyzed for age interaction ($N = 1676$). The modifying effect of smoking was also evaluated by Guessous et al. (2012), but inconsistent results were obtained. Furthermore, a significant association of the *CYP1A2* rs762551 AA genotype with high caffeine intake, assessed in 5452 subjects from the CoLaus study, was found among non-smokers ($N = 4017$; OR = 1.83, 95%CI = 1.38-2.45, $P < 0.0001$) but not in smokers ($N = 1435$; OR = 1.15, 95%CI = 0.79-1.67, $P = 0.77$) with evidence for a significant effect modification. Another *CYP1A1-CYP1A2* SNP (rs2472297), which showed GWAS significance in relation to coffee intake, was also tested for interactions with putative modifiers (Sulem et al., 2011). Stratification by smoking showed an association with coffee intake in both smokers ($P = 1.9 \times 10^{-6}$) and non-smokers ($P = 0.00089$), with no evidence for an effect modification ($P = 0.83$). However, no interaction effect was observed with gender ($P = 0.47$).

In the present meta-analysis, we further compared the data obtained from 7 studies including subjects of Caucasian origin and in 3 studies performed with subjects of Asian origin. Although Asians showed an overall increased coffee intake compared to Caucasians, a significant association between the AA genotype and coffee intake was only found in the Caucasians subgroup and not in Asians. A significant effect modification was also detected when comparing the association within the MF subgroup ($P = 0.02$). A similar finding, of a modification effect of ethnicity on the risk of rs762551 for cancer was previously reported (Wang et al., 2012). However, this is the first study to assess the relationship of rs762551 with coffee intake in the Asian population, since previous studies have only examined this association in European subjects. Ethnicity was suggested as a putative modifier factor for *CYP1A2* enzymatic activity. Indeed, Ghotbi et al. (2007) reported that *CYP1A2* activity was 1.54-fold higher in Swedes than in Koreans, independent of *CYP1A2* rs762551 genotype. Perera et al. (2012) also showed significantly lower *CYP1A2* activity in South Asian participants as compared to European participants. This reduced *CYP1A2* activity in Asians carrying the rs762551 AA genotype could explain the lack of association with higher coffee intake in this population, suggesting that other genetic factors may be involved in the higher caffeine consumption observed in Asians. Our data highlight the need to test other *CYP1A2* SNPs showing GWAS significance to determine the cause of the overall higher coffee intake in the Asian population.

There are some potential limitations to the current study. The coffee intake strata were assessed across studies. Furthermore, in the subgroup analysis by gender the comparison was made between male + female vs female instead of simply male vs female. Finally, only one study included in the meta-analysis analyzed the genotype interaction with age. Dealing with these concerns may provide a more accurate estimation of the association.

In conclusion, this meta-analysis showed that the *CYP1A2* rs762551 AA genotype may lead to a higher coffee intake, particularly with male sex, younger age, and Caucasian ethnicity, but independent of smoking status. No association was found in people of Asian ethnicity. These data suggest that the genetic background leading to a higher coffee consumption may differ between ethnicities.

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