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ACE D/I Polymorphism, Migraine, and Cardiovascular Disease in Women

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Abstract

Background—Interrelationships between the *ACE* D/I polymorphism (rs1799752), migraine, and cardiovascular disease (CVD) are biologically plausible but remain controversial.

Methods—Association study among 25,000 white U.S. women, participating in the Women's Health Study, with information on the *ACE* D/I polymorphism. Migraine and migraine aura status were self-reported. Incident CVD events were confirmed after medical record review. We used logistic regression to investigate the genotype-migraine association and proportional hazards models to evaluate the interrelationship between genotype, migraine, and incident CVD.

Results—At baseline, 4,577 (18.3%) women reported history of migraine; 39.5% of the 3,226 women with active migraine indicated aura. During 11.9 years of follow-up, 625 CVD events occurred. We did not find an association of the *ACE* D/I polymorphism with migraine or migraine

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Supplemental data: Table E-1.

M. Schürks (Div. of Preventive Medicine) and R.Y. Zee (Div. of Preventive Medicine) conducted the statistical analysis.

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aura status. There was a lack of association between the *ACE* D/I polymorphism and incident major CVD, including ischemic stroke and myocardial infarction. Migraine with aura doubled the risk for CVD (multivariable-adjusted RR=2.07; 95%CI=1.53-2.79; $p<0.0001$), but only for carriers of the DD/DI genotype. The risk was not significant among carriers of the II genotype (multivariable-adjusted RR=1.47; 95%CI=0.71-3.03), a pattern we observed for myocardial infarction and ischemic stroke.

Conclusions—Data from this large cohort of women do not suggest an association of the *ACE* D/I polymorphism with migraine, migraine aura status, or CVD. The increased risk for CVD among migraineurs with aura was only apparent for carriers of the DD/DI genotype. Due to limited number of outcome events, however, future studies are warranted to further investigate this association.

Keywords

[101] migraine; ACE D/I polymorphism; [2] cardiovascular disease; [54] cohort study

Migraine is a common debilitating headache disorder with a complex etiology, in which heredity plays an important role.[1, 2] Current pathophysiological concepts are based on the 'neurovascular hypothesis'.[3] Vascular dysfunctions are of particular interest since population-based studies have established an increased risk for ischemic stroke and other ischemic vascular events among patients with migraine, in particular migraine with aura.[4-6] In addition, effective treatment of both migraine[7] and cardiovascular disease[8] with drugs inhibiting the angiotensin-converting enzyme (ACE) suggests a link between migraine and cardiovascular disease. Further, the deletion/insertion (D/I) polymorphism (rs1799752) in the ACE gene may be implicated in both migraine and cardiovascular disease (CVD).

Clinic-based case-control studies of limited sample size have associated the *ACE* D/I polymorphism with overall migraine,[9-12] migraine with aura[10, 12, 13] and migraine without aura.[12, 14] However, both the mode of association and whether the risk for migraine is increased or reduced by a certain genotype are unclear.

The relationship between the *ACE* D/I polymorphism and CVD is equally controversial. Meta-analyses of case-control studies found only weak associations of the *ACE* DD genotype with ischemic stroke[15-17] or myocardial infarction.[18] In addition, one cohort study suggested that the *ACE* D/I polymorphism is not a strong risk factor for myocardial infarction.[19]

The Women's Health Study provides the opportunity to investigate whether (1) the *ACE* D/I polymorphism is associated with migraine or migraine aura status; (2) the *ACE* D/I polymorphism is associated with incident CVD; and (3) the previously identified increased risk of CVD among migraineurs with aura is modified according to *ACE* D/I genotype status.

Subjects and Methods

Study population

The WHS was a randomized trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among apparently healthy women. The design, methods, and results have been described in detail previously.[20, 21] Briefly, a total of 39,876 U.S. female health professionals aged ≥45 years at baseline in 1993 without a history of CVD, cancer, or other major illnesses were randomly assigned to active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. All participants provided written informed consent and the Institutional Review Board of Brigham and Women's Hospital approved the WHS. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables.

Blood samples were collected in tubes containing EDTA from 28,345 participating women prior to randomization. After excluding participants with missing information on migraine, *ACE* D/I polymorphism, and with reported CVD or angina prior to receiving the baseline questionnaire, a total of 26,428 women remained in the data set. We further excluded non-Caucasian women (n=1,428) to avoid race-specific genetic interaction, leaving 25,000 Caucasian women for analyses.

Assessment of migraine

Participants were asked on the baseline questionnaire: "Have you ever had migraine headaches?" and "In the past year, have you had migraine headaches?" From this information, we categorized women into "any history of migraine;" "active migraine," which includes women with self-reported migraine during the past year; and "prior migraine," which includes women who reported ever having had a migraine but none in the year prior to completing the baseline questionnaire. In a previous study,[4] we have shown good agreement with 1988 International Headache Society (IHS) criteria for migraine.[22] Participants who reported active migraine were further asked whether they had an "aura or any indication a migraine is coming." Responses were used to classify women who reported active migraine into active migraine with aura and active migraine without aura.

Ascertainment of cardiovascular disease

During follow-up, participants self-reported cardiovascular events. Medical records were obtained for all cardiovascular events and reviewed by an Endpoints Committee of physicians. Nonfatal stroke was confirmed if the participant had a new focal-neurologic deficit of sudden onset that persisted for >24 hours. Based on available clinical and diagnostic information strokes were then classified into major subtypes (ischemic, hemorrhagic, or unknown) with excellent interrater agreement.[23] The occurrence of myocardial infarction was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or abnormal electrocardiograms. Cardiovascular deaths were confirmed by review of autopsy reports, death certificates, medical records, or information obtained from next of kin or family members.

We evaluated the association between migraine and *ACE* D/I genotypes with major CVD, a combined endpoint defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic CVD. We also evaluated the association with any first ischemic stroke and any first myocardial infarction. However, there were too few deaths due to CVD to conduct meaningful analyses.

Genotype determination of the *ACE* D/I polymorphism (rs1799752)

Genotyping was performed in the context of a multi-marker assay using an immobilized probe approach, as previously described (Roche Molecular Systems).[24] In brief, each DNA sample was amplified by polymerase chain reaction (PCR) with biotinylated primers. Each PCR product pool was then hybridized to a panel of sequence-specific oligonucleotide probes immobilized in a linear array. The colorimetric detection method was based on the use of streptavidin-horseradish peroxidase conjugate with hydrogen peroxidase and 3,3′,5,5′-tetramethylbenzidine as substrates. Linear array processing was facilitated by the use of the AutoRELI-Mark II (Dynal Biotech). Genotype assignment was performed using the proprietary Roche Molecular Systems StripScan image processing software. To confirm genotype assignment, scoring was carried out by two independent observers. Discordant results (<1% of all scoring) were resolved by a joint reading, and where necessary, a repeat genotyping.

Statistics

We present baseline characteristics of participants with respect to their *ACE* D/I genotype using descriptive statistics. Genotype and allele frequencies were compared according to migraine and migraine aura status using the chi-square test.

We used logistic regression models to evaluate the association between *ACE* D/I genotypes and migraine. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) from separate models for 1) any history of migraine, 2) active migraine with aura, 3) active migraine without aura, and 4) prior migraine. We built age-adjusted and multivariable-adjusted models. The multivariable-adjusted models included the following covariates: age (continuous), body mass index (continuous), exercise (never, less than once/week, 1-3 times/week, 4 or more times/week), postmenopausal hormone use (never, past, current), history of oral contraceptive use (yes, no, not sure), history of hypertension (yes, no), history of diabetes (yes, no), alcohol consumption (never, 1-3 drinks/month, 1-6 drinks/week, ≥1 drinks/day), smoking (never, past, current <15 cigarettes/day, current ≥15 cigarettes/day), and family history of myocardial infarction (yes, no). Including indicator variables for randomized treatment assignment did not alter the effect estimates for any of the models presented. We incorporated a missing value indicator if the number of women with missing information on covariates was ≥100. For covariates with missing information on <100 women, those were either grouped into the reference category or the past exposure category, if applicable.

We used Cox proportional hazards models to evaluate the association between *ACE* D/I genotypes as well as migraine with incident cardiovascular events. We calculated multivariable-adjusted hazard ratios (HRs) and their 95% CIs including the same covariates as mentioned before.

We tested the proportionality assumption of the Cox proportional hazards models by including an interaction term for the *ACE* D/I polymorphism and migraine status with time, respectively, and found no significant violation.

We built additive models to investigate the association of the *ACE* D/I polymorphism with migraine and incident CVD events. This model assumes that the risk for carriers of the heterozygous DI genotype for developing the outcome is half way between carriers of the homozygous genotypes (DD and II). The advantage of this model is that the strength of genotype-phenotype association is expressed in a single parameter (beta estimate) and statistical tests for detecting a relationship have only one degree of freedom.[25] We checked for deviation from additivity by adding a 'dominance' variable to the model (extended model). This variable was coded as 0 for homozygotes and 1 for heterozygotes.[25] We compared the overall fit of the additive and the extended model using the likelihood ratio test.

We also evaluated the association between migraine and incident CVD stratified by *ACE* D/I genotype status.

All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). All p-values were two-tailed and we considered $p<0.05$ as significant. Since we evaluated biologically plausible associations between only one polymorphism, migraine, and CVD, we did not further adjust p-values.

Results

The baseline characteristics of women according to *ACE* D/I genotype are summarized in Table 1. Age, body mass index, history of diabetes, and history of hypertension were equally distributed among genotypes. Women also did not differ regarding physical activity,

postmenopausal hormone therapy, history of oral contraceptive use, alcohol consumption, smoking habits, and family history of myocardial infarction.

At baseline 4,577 (18.3%) women reported any history of migraine. Active migraine was reported by 3,226 women. Among those, 1,275 (39.5%) indicated migraine aura. The observed genotype distribution for the *ACE* D/I polymorphism deviated from Hardy-Weinberg equilibrium both among women with no history of migraine and among women with migraine (chi-square with 1 degree of freedom: $p<0.0001$). There was no difference in the genotype and allele distribution for *ACE* D/I between women with and without migraine **(Table E-1)**.

Since the results from the age-adjusted and multivariable-adjusted models were almost identical for both the logistic regression analyses and for the Cox proportional hazards analyses we only present the results from the multivariable-adjusted models.

Results from the logistic regression analysis showed no association between *ACE* D/I polymorphism and any history of migraine (Table 2). The multivariable-adjusted OR in the additive mode was 1.00 (95% CI=0.95-1.04; p=0.83). Investigating migraine-specific subgroups did not change this result. We did not find strong evidence for deviation from additivity.

During a mean of 11.9 years of follow-up (296,853 person-years), 625 first major CVD events, 275 ischemic strokes, and 268 myocardial infarctions were confirmed. The *ACE* D/I polymorphism was not associated with increased risk of incident major CVD, including incident ischemic stroke and incident myocardial infarction (Table 3). Again we did not find strong evidence for deviation from additivity.

In Table 4, we summarize the association between migraine status and incident ischemic cardiovascular events. Compared with women without migraine, women with any history of migraine had increased risk for major CVD (multivariable-adjusted HR 1.30; 95% CI 1.06-1.58; $p=0.01$). This elevated risk was only apparent for women with active migraine with aura (multivariable-adjusted HR=2.07; 95% CI=1.53-2.79; $p<0.0001$). This pattern occurred for ischemic stroke (multivariable-adjusted HR=1.90; 95% CI=1.19-3.01; $p=0.007$) and myocardial infarction (multivariable-adjusted HR=2.12; 95% CI=1.36-3.31; $p=0.001$). The stratified analysis shows that the increased risk for major CVD among migraineurs with aura occurred only for carriers of the *ACE* DD/DI genotype, but not for carriers of the II genotype (multivariable-adjusted HR=1.47; 95% CI=0.71-3.03; $p=0.30$). This pattern of lack of association for the II genotype was apparent for both ischemic stroke (multivariable-adjusted HR=1.33; 95% CI=0.41-4.31; $p=0.64$) and myocardial infarction (multivariable-adjusted HR=0.72; 95% CI=0.17-2.98; $p=0.65$).

When we tested whether the association between migraine aura status (i.e., evaluating women with migraine with aura and women with migraine without aura) and incident major CVD was modified by genotype status among the entire cohort, the results were not significant (p for interaction=0.13 assuming an age-adjusted and 0.16 assuming a multivariable-adjusted recessive model).

Discussion

In this large study of Caucasian women, we found no association between the *ACE* D/I polymorphism and migraine or migraine aura status as well as no association between the *ACE* D/I polymorphism and incident major CVD, including myocardial infarction and ischemic stroke. Migraine with aura was associated with a two-fold increased risk of major CVD. This increased risk, however, was only significant among carriers of the *ACE* DD/DI genotype, a pattern appearing for ischemic stroke and myocardial infarction.

Prior studies investigating the association between the *ACE* D/I polymorphism and migraine are contradictory.[9-11, 13, 14] While one study suggested that the *ACE* DD genotype increases the risk for overall migraine, but not for migraine specific subgroups,[9] others showed an increased risk for migraine without aura,[14] migraine with aura,[13] and for overall migraine, with the strongest risk for migraine with aura.[10] Further, one study suggested a protective effect for overall migraine,[11] and findings from a recent one do not indicate an association at all.[12] The different results may be due to targeting different study populations, differences in ethnicity, or small sample size.

Based on available data, the following pathophysiological association may be sketched: *ACE* DD genotype is associated with migraine with aura,[13] because the *ACE* D allele results in higher ACE levels,[26] and higher ACE levels are found in migraineurs with aura.[27] However, our data do not support this association. Reasons for this may include that a pathophysiological association is specific to certain ethnic populations, for example Japanese.[13, 27] In addition, the *ACE* D/I polymorphism accounts for only about 50% of ACE activity variation,[28] and elevated ACE activities may also be attributable to copy number variations of the ACE gene. These copy number variations account for a large amount of genetic heterogeneity and have been associated with various disorders.[29]

The relationship between the *ACE* D/I polymorphism and CVD is equally controversial. A meta-analysis of case-control studies[18] and a prospective population-based study[19] found that the *ACE* DD genotype is not a strong risk factor for myocardial infarction. The results of a case-control study among postmenopausal women indicated that the *ACE* DD genotype may be associated with myocardial infarction/angina, in particular among postmenopausal hormone users.[30] Meta-analyses of case-control studies found only a weak association of the *ACE* DD genotype with ischemic stroke.[15-17] Our results, however, do not suggest that the *ACE* D/I polymorphism alters the risk for incident major CVD, myocardial infarction, or ischemic stroke. The discrepant results may be due to differences in study design and due to population specific gene-gene and gene-environment interactions.[15, 18]

The complex relationship between genetic variants, migraine, and CVD has been the focus of recent studies. Migraine with aura has been shown to increase the risk of CVD by approximately twofold.[4, 5, 31] Further, we have shown that this increased risk was magnified for carriers of the TT genotype of the *MTHFR* 677C>T polymorphism, which was driven by a selective fourfold increased risk of ischemic stroke.[32] These results may suggest in part differential pathophysiological mechanisms in the migraine with aura-ischemic stroke and migraine with aura-myocardial infarction association and are plausible considering the complexity of CVD pathophysiology.[5, 33]

Results from the present study suggest that the increased risk for CVD among women with migraine with aura is only significant for carriers of the *ACE* DD/DI genotype, but not for carriers of the II genotype when contrasted to women without migraine. However, the number of outcome events in subgroups was considerably small and, as a consequence, the CIs are wide, indicating remaining uncertainties. Indeed, when we tested whether the association between migraine aura status and incident major CVD was modified by genotype status, the results were not significant. However, this does not necessarily contradict our findings that a modifying effect is limited to the subgroup of patients with migraine with aura. In addition, a differential association is plausible. For example, higher plasma ACE activities among carriers of the *ACE* DD/DI genotype increase angiotensin II levels, thus boosting RAS activity and mediating the migraine with aura-CVD association. Since elevated angiotensin II levels may also result from non-ACE enzymes like chymase or cathepsins,[34] our results of a differential impact of the RAS on this association may have been further diluted. Unfortunately, we could

not further investigate these hypotheses, since plasma ACE activities or angiotensin II levels were not available.

To further understand the complex interrelationship between migraine and CVD, investigating potential modifying effects of other genetic variants in the RAS and those implicated in migraine or CVD may be promising. In addition, gene-gene and gene-environment interactions need to be considered. Particularly interactions of the *MTHFR* 677C>T and *ACE* D/I polymorphisms seem plausible,[10, 35] but also between genes and underlying vascular risk status.[5]

Our study has several strengths, including the large number of participants with and without migraine and high incidence of confirmed CVD events. Further, information on a large number of potential CVD risk factors was available and the homogenous nature of the cohort, consisting only of white Caucasian women, may reduce confounding. However, several limitations of our study should be considered. First, migraine and aura status were self-reported and were not classified according to strict IHS criteria. Thus, non-differential misclassification is possible. However, the prevalence of migraine (18.3%) and the prevalence of migraine aura among women with active migraine (39.5%) is similar to those seen in other large population-based studies in the U.S.[36] and the Netherlands.[37] The 1-year prevalence of migraine for women was 18.2% in the U.S. and 25% in the Netherlands, while migraine aura was reported by 37% in the U.S.[36] and 31% in the Netherlands.[37] Furthermore, we have previously shown good agreement of our migraine classification with IHS criteria for migraine.[4] Second, the genotype distribution deviated from Hardy-Weinberg Equilibrium. Since genotypes of both women with migraine and women without migraine were in Hardy-Weinberg disequilibrium, this is an unlikely indication for genotype-based differential survival. In addition, genotyping error is unlikely given our stringent genotyping protocol. However, this stringency together with the fact that participants were all white female health professionals age ≥45, not representing all white women, most likely accounts for the deviation from Hardy-Weinberg Equilibrium. Thus generalizability may be limited. Finally, we cannot exclude that examination of a different polymorphism–not in linkage disequilibrium with the variant tested–might lead to a different result. Thus, the *ACE* DD/DI genotype may only be a marker for an increased risk of CVD among patients with migraine with aura.

Future studies need to replicate our findings in other large cohorts with information on migraine and aura status according to IHS criteria. Age and gender specific effects must be considered and gene-gene interactions be explored. Further understanding factors increasing the likelihood of migraine or increasing the risk of CVD among patients with migraine with aura may help to develop preventive strategies.

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Table 1

Baseline characteristics of participants in the Women's Health Study according to *ACE* D/I genotype (N=25,000) *

Characteristic	DD (N=7,327)	DI (N=11,517)	II (N=6,156)
Age, mean (SD), y	54.7 (7.1)	54.6 (7.1)	54.8 (7.1)
Body mass index, mean (SD), kg/m^2	25.9 (5.0)	25.9 (4.9)	25.9 (4.9)
History of diabetes	2.3	2.2	2.1
History of hypertension	25.1	24.3	24.8
Physical activity			
Never	36.8	37.5	36.9
<1/week	19.4	20.0	19.4
1-3/week	32.3	31.3	32.1
≥4/wk	11.5	11.3	11.6
Postmenopausal hormone therapy			
Never	48.1	48.0	48.6
Past	9.2	9.1	8.7
Current	42.7	42.9	42.7
History of oral contraceptive use			
No	30.1	29.9	30.5
Yes	69.5	69.7	69.1
Not sure	0.4	0.4	0.5
Alcohol consumption			
Never	43.1	44.2	42.4
1-3 drinks/month	13.5	13.0	13.3
1-6 drinks/week	32.9	32.3	33.5
≥1 drink/day	10.5	10.5	10.9
Smoking status			
Never	50.4	51.4	51.7
Past	38.0	37.2	37.1
Current <15 cigarettes/day	4.5	4.0	4.0
Current ≥15 cigarettes/day	7.1	7.4	7.3
Family history of MI prior to age 60 yrs			
No	78.6	78.5	77.8
Yes	11.6	11.5	12.2
Unknown	9.7	10.1	10.0

* data are expressed as percentages unless otherwise stated.

Proportions may not add up to 100 due to rounding or missing values.

Table 2

Multivariable-adjusted* odds ratios (OR) and 95% confidence intervals (95% CI) for migraine according to *ACE* D/I polymorphism assuming an additive mode

	OR	95% CI	p-value
No history of migraine (n=20,423) †	1.00	Referent	----
Any history of migraine (n=4,577)	1.00	0.95-1.04	0.83
Migraine with aura (n=1,275)	0.98	0.91-1.06	0.68
Migraine without aura (n=1,951)	0.96	0.90-1.03	0.24
Past migraine (n=1,351)	1.06	0.98-1.14	0.16

*Controlling for: age, body mass index, diabetes, physical activity, postmenopausal hormone use, oral contraceptive use, history of hypertension, alcohol consumption, smoking categories, and family history of myocardial infarction.

†The referent group for each of the analyses remained the same and consisted of women who reported no active or past migraine.

Table 3

Multivariable-adjusted* hazard ratios (HR) and 95% confidence intervals (95% CI) for ischemic vascular events according to *ACE* D/I polymorphism (n=25,000) assuming an additive mode

	HR	95% CI	p-value
No cardiovascular event (n=24,375) †	1.00	Referent	----
Major Cardiovascular Event (n=625)	0.98	0.88-1.09	0.70
Ischemic Stroke (n=275)	1.03	0.88-1.21	0.70
Myocardial Infarction (n=268)	0.87	0.74-1.02	0.09

*Controlling for: age, body mass index, diabetes, physical activity, postmenopausal hormone use, oral contraceptive use, history of hypertension, alcohol consumption, smoking categories, and family history of myocardial infarction.

†The referent group for each of the analyses remained the same and consisted of women without any cardiovascular event during follow-up.

Table 4

Multivariable-adjusted* hazard ratios (HR) and 95% confidence intervals (95%CI) for cardiovascular events according to migraine status, stratified by *ACE* D/I genotype in the Women's Health Study (N=25,000)

Ischemic vascular events	No history of migraine, (n=20,423) Referent	Any history of migraine (n=4,577)	P value	Active migraine with aura (n=1,275)	P value	Active migraine without aura (n=1,951)	P value	Prior migraine (n=1,351)	P value
Major cardiovascular event†	N=504	N=121		N=48		N=32		N=41	
Overall	1.00	1.30 (1.06-1.58)	0.01	2.07 (1.53-2.79)	<0.0001	0.98 (0.68-1.40)	0.90	1.10 (0.80-1.51)	0.56
DD genotype	1.00	1.40 (0.98-2.00)	0.07	2.10 (1.22-3.59)	0.007	1.34 (0.77-2.33)	0.31	0.98 (0.52-1.87)	0.96
DI genotype	1.00	1.41 (1.06-1.88)	0.02	2.31 (1.52-3.51)	<0.0001	0.93 (0.54-1.60)	0.78	1.28 (0.82-1.99)	0.27
II genotype	1.00	0.90 (0.56-1.43)	0.65	1.47 (0.71-3.03)	0.30	0.49 (0.18-1.35)	0.17	0.91 (0.46-1.80)	0.79
Ischemic Stroke	N=228	N=47		N=20		N=14		N=13	
Overall	1.00	1.12 (0.81-1.53)	0.50	1.90 (1.19-3.01)	0.007	0.97 (0.56-1.67)	0.90	0.77 (0.44-1.34)	0.35
DD genotype	1.00	1.22 (0.69-2.16)	0.49	1.97 (0.84-4.59)	0.12	1.04 (0.41-2.62)	0.93	0.90 (0.33-2.49)	0.84
DI genotype	1.00	0.92 (0.56-1.51)	0.74	2.07 (1.10-3.87)	0.02	0.73 (0.30-1.80)	0.49	0.36 (0.11-1.13)	0.08
II genotype	1.00	1.26 (0.68-2.33)	0.46	1.33 (0.41-4.31)	0.64	1.14 (0.41-3.21)	0.80	1.31 (0.56-3.07)	0.53
Myocardial Infarction	N=217	N=51		N=22		N=13		N=16	
Overall	1.00	1.23 (0.90-1.67)	0.19	2.12 (1.36-3.31)	0.001	0.87 (0.50-1.53)	0.64	0.99 (0.60-1.65)	0.98
DD genotype	1.00	1.46 (0.89-2.40)	0.13	2.57 (1.31-5.04)	0.006	1.31 (0.59-2.87)	0.51	0.79 (0.29-2.17)	0.65
DI genotype	1.00	1.58 (1.02-2.47)	0.04	2.49 (1.29-4.83)	0.007	1.00 (0.43-2.30)	0.99	1.56 (0.81-3.01)	0.19
II genotype	1.00	0.35 (0.13-0.97)	0.04	0.72 (0.17-2.98)	0.65	----	0.98	0.43 (0.11-1.78)	0.25

* Controlling for: age, body mass index, diabetes, physical activity, postmenopausal hormone use, oral contraceptive use, history of hypertension, alcohol consumption, smoking categories, and family history of myocardial infarction.

† Defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death due to ischemic cardiovascular cause.