ORIGINAL ARTICLE

Genetically Elevated C-Reactive Protein and Ischemic Vascular Disease

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ABSTRACT

BACKGROUND

Elevated levels of C-reactive protein (CRP) are associated with increased risks of ischemic heart disease and ischemic cerebrovascular disease. We tested whether this is a causal association.

METHODS

We studied 10,276 persons from a general population cohort, including 1786 in whom ischemic heart disease developed and 741 in whom ischemic cerebrovascular disease developed. We examined another 31,992 persons from a cross-sectional general population study, of whom 2521 had ischemic heart disease and 1483 had ischemic cerebrovascular disease. Finally, we compared 2238 patients with ischemic heart disease with 4474 control subjects and 612 patients with ischemic cerebrovascular disease with 1224 control subjects. We measured levels of high-sensitivity CRP and conducted genotyping for four CRP polymorphisms and two apolipoprotein E polymorphisms.

RESULTS

The risk of ischemic heart disease and ischemic cerebrovascular disease was increased by a factor of 1.6 and 1.3, respectively, in persons who had CRP levels above 3 mg per liter, as compared with persons who had CRP levels below 1 mg per liter. Genotype combinations of the four CRP polymorphisms were associated with an increase in CRP levels of up to 64%, resulting in a theoretically predicted increased risk of up to 32% for ischemic heart disease and up to 25% for ischemic cerebrovascular disease. However, these genotype combinations were not associated with an increased risk of ischemic vascular disease. In contrast, apolipoprotein E genotypes were associated with both elevated cholesterol levels and an increased risk of ischemic heart disease.

CONCLUSIONS

Polymorphisms in the CRP gene are associated with marked increases in CRP levels and thus with a theoretically predicted increase in the risk of ischemic vascular disease. However, these polymorphisms are not in themselves associated with an increased risk of ischemic vascular disease.

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N Engl J Med 2008;359:1897-908.

Elevated plasma levels of C-reactive protein (CRP) are associated with increased risks of ischemic heart disease and ischemic cerebrovascular disease.[1-5] However, whether CRP is simply a marker for ischemic vascular disease or whether elevated CRP levels actually contribute directly to causing such disorders is presently unknown. This question has clinical importance, since several drugs that specifically lower CRP levels are being developed,[6] with the ultimate aim of preventing ischemic vascular disease.

The random assortment of genes that occurs during gamete formation provides a relatively unbiased method of assessing whether risk factors that have a genetic component are in fact causally related to clinical outcomes.[7] This phenomenon has sometimes been termed "mendelian randomization." Thus, genetic variants that specifically increase plasma levels of CRP[8,9] provide an ideal system to assess the consequences of lifelong high CRP levels, independently of other risk factors.[7]

We examined the hypothesis that genetically elevated CRP levels cause increased risks of ischemic heart disease and ischemic cerebrovascular disease. We tested, first, whether CRP levels were associated with the risks of ischemic heart disease and ischemic cerebrovascular disease; second, whether CRP single-nucleotide polymorphisms were associated with CRP levels; and third, whether CRP polymorphisms were associated with increases in the risks of ischemic heart disease and ischemic cerebrovascular disease that were consistent with their effects on CRP levels.

Methods

We studied four independent cohorts of white people of Danish descent. These groups were defined so that no person appears in more than one of the four analysis groups, thus permitting independent confirmation of the findings in each group. Details about each study cohort are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

The studies were approved by Herlev Hospital and by Danish ethics committees (the Copenhagen and Frederiksberg committee and the Copenhagen County committee) and were conducted according to the standards of the Declaration of Helsinki. Written informed consent was obtained from the participants.

Study Cohorts

The Copenhagen City Heart Study[10,11] is a prospective study of a cohort of persons randomly selected from the population of the city of Copenhagen. Data were available from this study on rates of ischemic heart disease (including fatal or nonfatal myocardial infarction, symptoms of angina pectoris, and revascularization procedures) and rates of ischemic cerebrovascular disease (including fatal or nonfatal ischemic stroke, transient ischemic attack, and amaurosis fugax). We included 10,276 participants from this study in the present analysis, including 1786 in whom ischemic heart disease developed and 741 in whom ischemic cerebrovascular disease developed.

The Copenhagen General Population Study[10,12] is a cross-sectional study of persons selected from the population of the city of Copenhagen. Diagnoses of ischemic heart disease and ischemic cerebrovascular disease were made according to the same criteria as those used in the Copenhagen City Heart Study. We included 37,690 participants in this study in the present analysis. Of these, 31,992 participants (of whom 2521 had ischemic heart disease and 1483 had ischemic cerebrovascular disease) were analyzed as a single cohort for the association of CRP polymorphisms with clinical events; 4474 additional participants were used as controls for the Copenhagen Ischemic Heart Disease Study, and 1224 were used as controls for the Copenhagen Carotid Stroke Study. Of the 37,690 participants, 34,233 who were not receiving statin treatment were included in the analysis of correlation between CRP polymorphisms and plasma CRP levels.

The Copenhagen Ischemic Heart Disease Study[12] was conducted on a cohort of 2238 patients who had been referred for coronary angiography and had documented evidence of ischemic heart disease on the basis of characteristic symptoms of stable angina pectoris, plus at least one of the following: at least one coronary stenosis of more than 50% of vessel diameter or diffuse atherosclerosis according to coronary angiography, a previous myocardial infarction, or a positive result on a bicycle exercise electrocardiography test. These patients were matched according to sex and age (within 1-year strata) with 4474 control subjects without ischemic heart disease from the Copenhagen General Population Study.

The Copenhagen Carotid Stroke Study[13] was conducted on a cohort of 612 patients who had been referred for carotid artery ultrasonography and had documented evidence of ischemic cerebrovascular disease on the basis of ischemic stroke, transient ischemic attack, or amaurosis fugax, together with a stenosis of at least 50% of a carotid artery. Patients with hemorrhage were excluded by means of computed tomography. These patients were matched according to sex and age (within 1-year strata) with 1224 control subjects without ischemic cerebrovascular disease from the Copenhagen General Population Study.

GENOTYPING AND BIOCHEMICAL ANALYSES

An ABI PRISM 7900HT Sequence Detection System (Applied Biosystems) was used to perform genotyping for four single-nucleotide polymorphisms in the CRP gene (rs3091244, rs1130864, rs1205, and rs3093077)[8] and two in the apolipoprotein E gene (rs429358 and rs7412).[14] Genotyping was verified by DNA sequencing in more than 30 persons with each genotype. High-sensitivity CRP was measured by nephelometry or turbidimetry. CRP levels were classified as low (<1.0 mg per liter), average (1.0 to 3.0 mg per liter), or high (>3.0 mg per liter). Levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured with the use of standard hospital assays (Boehringer Mannheim or Konelab). The level of LDL cholesterol was calculated with the use of the Friedewald equation if the triglyceride level was less than 4 mmol per liter (354 mg per deciliter) and was measured directly for higher triglyceride levels.

STATISTICAL ANALYSIS

We used Stata and NCSS-PASS software for all analyses. For trend tests, the groups of subjects classified according to CRP level, genotype, or genotype combination were coded as 1, 2, 3, and so forth, ranked according to increasing CRP levels. From the four CRP polymorphisms, we generated all possible genotype combinations and ranked the nine most common combinations according to increasing plasma CRP levels. Apolipoprotein E genotypes were ranked in a similar fashion according to increasing plasma cholesterol levels.

To investigate our study hypothesis, we first analyzed the relationship between plasma CRP levels and the risks of ischemic heart disease and ischemic cerebrovascular disease in the prospective Copenhagen City Heart Study, with the use of left truncation (or delayed entry) from the results of examinations conducted from 1991 through 1994.[15] Cox regression models with age as the time scale, adjusted for age, sex, and use or nonuse of statins, were used to estimate the hazard ratios for ischemic heart disease and ischemic cerebrovascular disease. Additional regression models that included CRP genotype and multivariable models that included a full set of available risk factors (see Tables 1 and 2 in the Supplementary Appendix) were also developed. Data from the serial examinations of the Copenhagen City Heart Study were used as time-dependent covariates for multivariable adjustment.

Second, we analyzed the relationship between CRP polymorphisms and polymorphism combinations and plasma CRP levels in the cross-sectional Copenhagen General Population Study. Analyses were performed with the use of Kruskal–Wallis analysis of variance.

Third, we analyzed the relationship between CRP polymorphisms and the risks of ischemic heart disease and ischemic cerebrovascular disease in the prospective Copenhagen City Heart Study, with the use of the results of examinations conducted from 1976 through 1978 that involved left truncation (or delayed entry).[15] Cox regression models with age as the time scale, adjusted for age and sex (or adjusted for all covariates), were used to estimate the hazard ratios for ischemic heart disease and ischemic cardiovascular disease. This analysis was retested in the cross-sectional Copenhagen General Population Study; conditional logistic-regression analyses adjusted for age and sex (or for all covariates) were used to estimate the odds ratios for ischemic heart disease and ischemic cerebrovascular disease.

Finally, a third test of the relationship between CRP polymorphisms and the risk of vascular disease was performed, with data from the Copenhagen Ischemic Heart Disease Study used for the ischemic heart disease end point and data from the Copenhagen Carotid Stroke Study used for the ischemic cerebrovascular disease end point. For each of these analyses, patients were matched according to age and sex with control subjects from the Copenhagen General Population Study,

and conditional logistic-regression analyses (either crude or adjusted for all covariates) were used to estimate the odds ratios for ischemic heart disease and ischemic cerebrovascular disease.

The increases in the hazard ratios for ischemic heart disease and ischemic cerebrovascular disease for a 1% increase in CRP level in the Copenhagen City Heart Study were used to predict theoretical hazard ratios for ischemic heart disease and ischemic cerebrovascular disease associated with the changes in CRP levels caused by the combined genotypes. Observed and theoretically predicted hazard ratios as a function of plasma CRP levels were corrected for regression dilution bias[16,17]; similar calculations were performed for apolipoprotein E genotype, plasma cholesterol levels, and the risk of ischemic heart disease. Logistic-regression analysis was used to calculate a combined odds ratio for ischemic heart disease and ischemic cerebrovascular disease as a function of genotype for all studies combined (all patients with ischemic heart disease or ischemic cerebrovascular disease as compared with all control subjects).

RESULTS

Selected clinical characteristics of the participants in each study cohort are shown in Tables 1, 2, and 3 of the Supplementary Appendix. As would be anticipated, persons in both cohorts with vascular disease were older and more likely to be male than those without vascular disease, except for the age- and sex-matched patients and control subjects of the Copenhagen Ischemic Heart Disease Study and the Copenhagen Carotid Stroke Study. Those with vascular disease also tended to have higher levels of total and LDL cholesterol (except for those in the Copenhagen General Population Study, in which persons with vascular disease were more likely to use lipid-lowering therapy) and higher rates of diabetes, cigarette smoking, and use of antihypertensive therapy.

PLASMA CRP AND THE RISK OF VASCULAR DISEASE

The risk of ischemic heart disease was increased by a factor of 2.2 (95% confidence interval [CI], 1.6 to 2.9) and the risk of ischemic cerebrovascular disease by a factor of 1.6 (95% CI, 1.1 to 2.5) in persons with CRP levels above 3 mg per liter, as compared with persons with CRP levels below 1 mg per liter, after adjustment for age, sex, and use or nonuse of statins (Fig. 1). After adjustment for age, sex, use or nonuse of statins, and CRP genotype, the corresponding hazard ratios were 2.2 (95% CI, 1.6 to 2.9) and 1.6 (95% CI, 1.1 to 2.5). After multivariate adjustment, the hazard ratios were 1.6 (95% CI, 1.2 to 2.1) and 1.3 (95% CI, 0.8 to 2.0). P for trend was less than 0.001 in all analyses.

CRP POLYMORPHISMS AND PLASMA CRP

For the CRP polymorphism rs1205, the AA genotype was associated with plasma CRP levels that were 23% lower than those associated with the GG genotype (P for trend, <0.001) (Fig. 2). Significant differences in plasma CRP levels were also associated with the rs1130864 polymorphism (TT vs. CC genotype, 24% increase), the rs3091244 polymorphism (AA vs. CC genotype, 67% increase), and the rs3093077 polymorphism (GG vs. TT genotype, 53% increase) (P for trend for all polymorphisms, <0.001). Combining the genotypes resulted in a difference of up to 64% in plasma CRP levels between the lowest and highest levels among the most common genotype combinations (Fig. 2). Partial r^2 values for the different CRP polymorphisms ranged from 0.4 to 2.0%.

CRP POLYMORPHISMS AND THE RISK OF VASCULAR DISEASE

The various cardiovascular risk factors were equally distributed among the different CRP genotype combinations (see Table 3 in the Supplementary Appendix). This was also true for each of the four genotypes separately and for genotype combinations in each of the individual studies (data not shown).

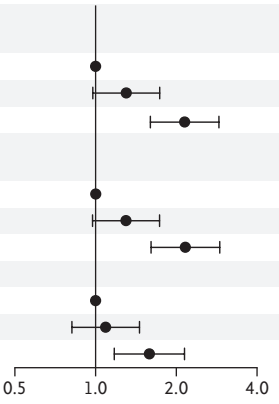
The hazard ratios for ischemic heart disease and ischemic cerebrovascular disease as a function of genotype in the Copenhagen City Heart Study did not differ from 1.0 for any of the individual CRP polymorphisms or for genotype combinations (P for trend, 0.28 to 0.94) (Fig. 3 and 4). These findings were confirmed in the Copenhagen General Population Study (P for trend, 0.13 to 0.95), the Copenhagen Ischemic Heart Disease Study (P for trend, 0.53 to 0.97), and the Copenhagen Carotid Stroke Study (P for trend, 0.79 to 0.99).

PREDICTED VERSUS OBSERVED RISK OF VASCULAR DISEASE

We assumed that if an elevation in CRP level has a causal association with ischemic vascular dis-

A Ischemic Heart Disease

CRP Level	No. of Participants	No. of Events	P for Trend
Adjusted for age, sex, and statin use			<0.001
<1 mg/liter	659	50	
1–3 mg/liter	5370	738	
>3 mg/liter	1905	433	
Adjusted for age, sex, statin use, and genotype			<0.001
<1 mg/liter	659	50	
1–3 mg/liter	5370	738	
>3 mg/liter	1905	433	
Multifactorially adjusted			<0.001
<1 mg/liter	652	50	
1–3 mg/liter	5294	721	
>3 mg/liter	1842	415	



B Ischemic Cerebrovascular Disease

CRP Level	No. of Participants	No. of Events	P for Trend
Adjusted for age, sex, and statin use			<0.001
<1 mg/liter	657	24	
1–3 mg/liter	5451	273	
>3 mg/liter	2003	180	
Adjusted for age, sex, statin use, and genotype			<0.001
<1 mg/liter	657	24	
1–3 mg/liter	5451	273	
>3 mg/liter	2003	180	
Multifactorially adjusted			<0.001
<1 mg/liter	650	24	
1–3 mg/liter	5372	265	
>3 mg/liter	1939	174	

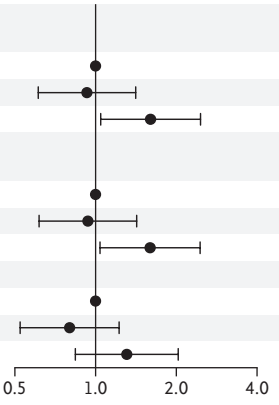


Figure 1. Risk of Ischemic Heart Disease (Panel A) and Ischemic Cerebrovascular Disease (Panel B) as a Function of Plasma Levels of C-Reactive Protein (CRP) in the General Population.

Plasma levels of high-sensitivity CRP were measured in persons who participated in the examination of the Copenhagen City Heart Study conducted from 1991 through 1994 and were subsequently followed for 12 to 15 years for incident ischemic heart disease events (7934 participants) and ischemic cerebrovascular disease events (8111 participants); persons who had ischemic heart disease, ischemic cerebrovascular disease, or both before study entry were excluded. Multifactorial adjustment was performed for all risk factors shown in Tables 1 and 2 in the Supplementary Appendix.

ease, then genetically elevated plasma CRP levels should confer the same increase in disease risk as that observed for elevated plasma CRP levels encountered in the general population. On the basis of this assumption, we estimated that the 64% increment in plasma CRP levels due to CRP genotype combination would predict increased risks of up to 32% (hazard ratio, 1.32; 95% CI, 1.26 to 1.39) for ischemic heart disease and of up to 25% (hazard ratio, 1.25; 95% CI, 1.15 to 1.35) for ischemic cerebrovascular disease (Fig. 5 and 6). However, when the data from all studies of ischemic heart disease and ischemic cerebrovascular disease shown in Figures 3 and 4 were combined to achieve the maximal statistical power, the observed odds ratios for ischemic heart disease and ischemic cerebrovascular disease as a function of genotype combination did not differ significantly from 1.0 (Fig. 5 and 6). Similar observations were made when genotype combinations 3 to 6 or 7 to 9 were pooled and compared with genotype combination 1.

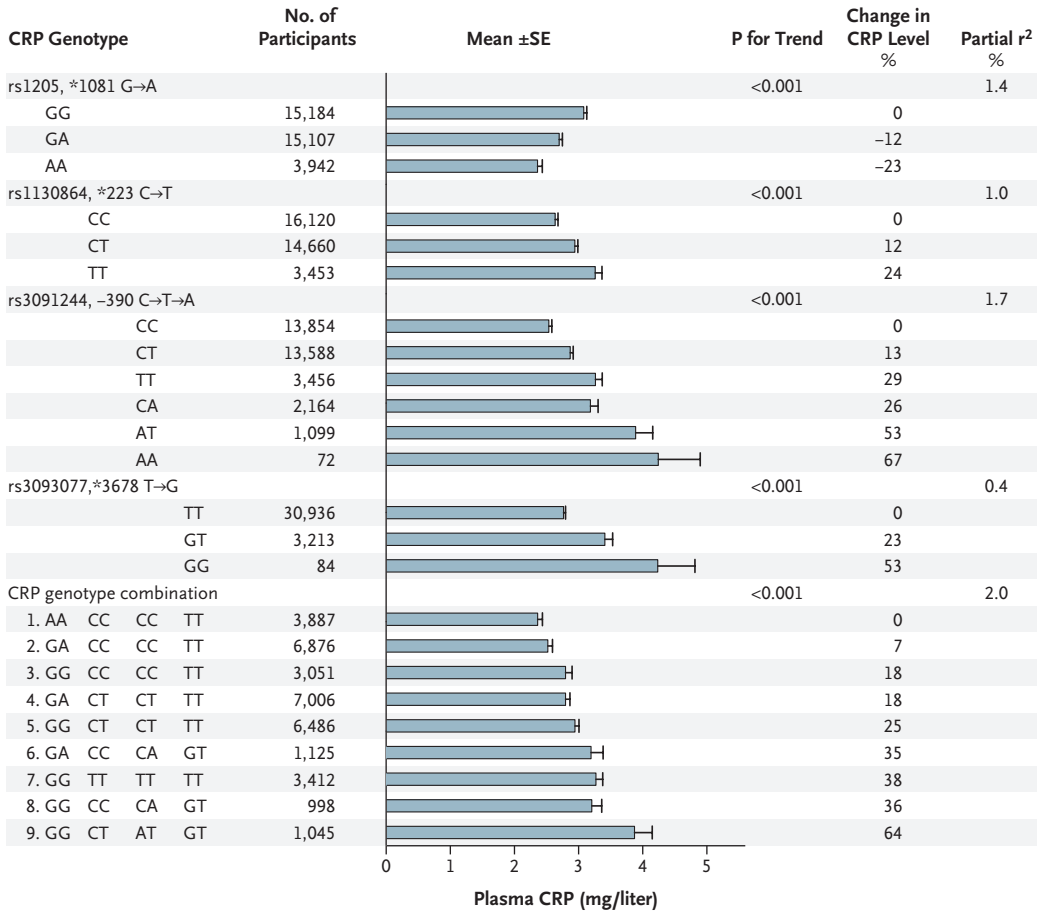


Figure 2. Plasma Levels of C-Reactive Protein (CRP) as a Function of CRP Genotype and Genotype Combination in the General Population.

Plasma levels of high-sensitivity CRP were measured and CRP genotyping was performed in 34,233 persons who were not receiving statin treatment and who were participating in the Copenhagen General Population Study. Partial r^2 values were determined after adjustment for variation in plasma CRP levels due to age, sex, smoking status, and body-mass index. An asterisk indicates a substitution located after the gene, and a minus sign a substitution located in a promoter.

To test the predictive power of our method and to demonstrate that the risk of coronary disease in the study cohorts follows established patterns, we examined the influence of apolipoprotein E genotype on the risk of ischemic heart disease in our study sample. The range of apolipoprotein E genotypes was associated with an increment in plasma cholesterol levels of up to 14%. Given this increment, we predicted hazard ratios for ischemic heart disease of up to 1.12 (95% CI, 1.06 to 1.17) across the range of apolipoprotein E genotypes (Fig. 5). When the data from all studies of ischemic heart disease were combined to achieve the maximal statistical power, the observed odds ratio for ischemic heart disease as a function of apolipoprotein E genotype increased with increasing cholesterol levels to 1.35 (95% CI, 1.12 to 1.61) for the highest-risk genotype. We did not perform a similar analysis for ischemic cerebrovascular disease, since a relationship with apolipoprotein E genotype has not been clearly established for this disorder.

DISCUSSION

The principal finding of this study is that CRP polymorphisms are associated with markedly increased CRP levels but not with an increased risk

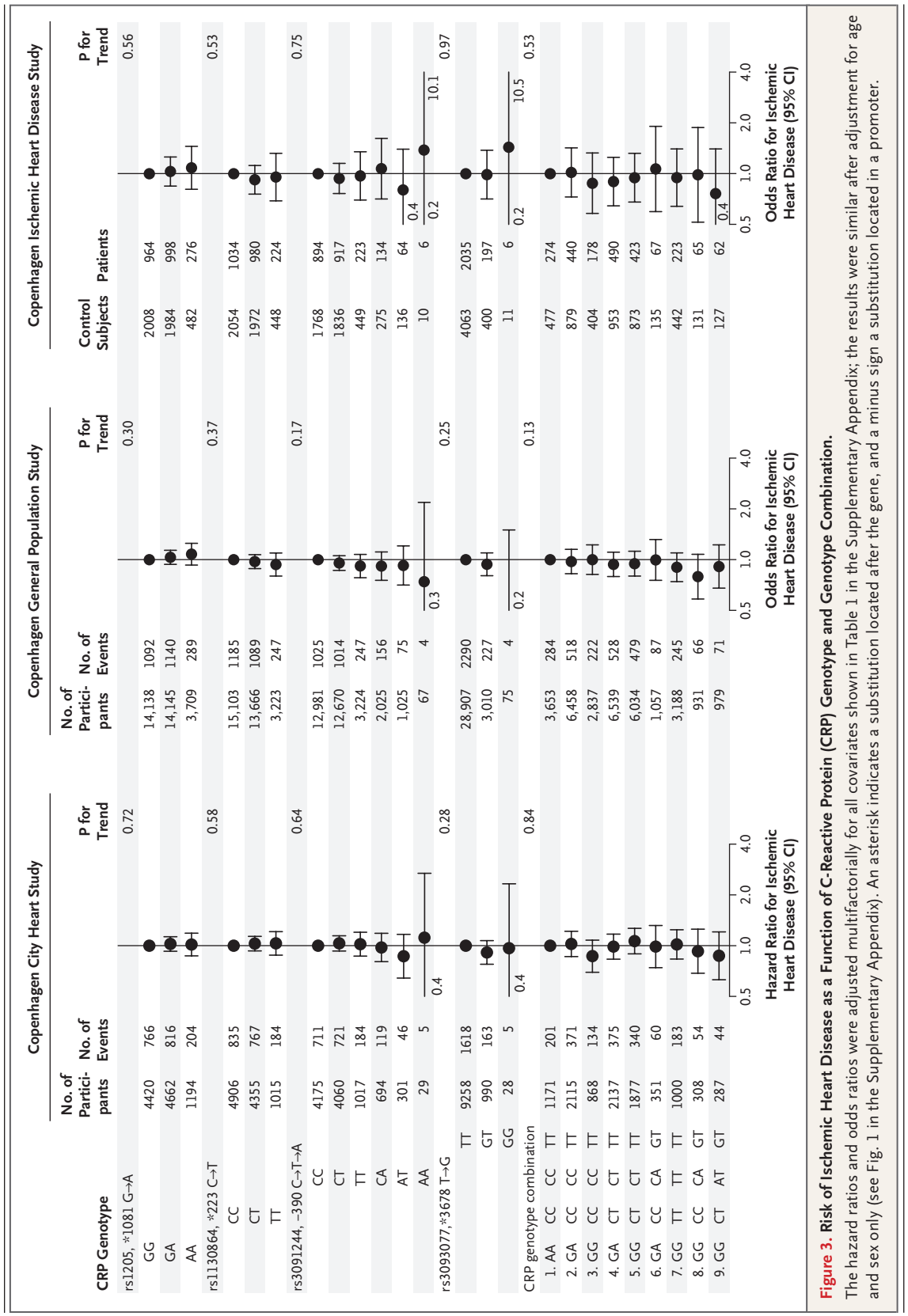


Figure 3. Risk of Ischemic Heart Disease as a Function of C-Reactive Protein (CRP) Genotype and Genotype Combination.

The hazard ratios and odds ratios were adjusted multifactorially for all covariates shown in Table 1 in the Supplementary Appendix; the results were similar after adjustment for age and sex only (see Fig. 1 in the Supplementary Appendix). An asterisk indicates a substitution located after the gene, and a minus sign a substitution located in a promoter.

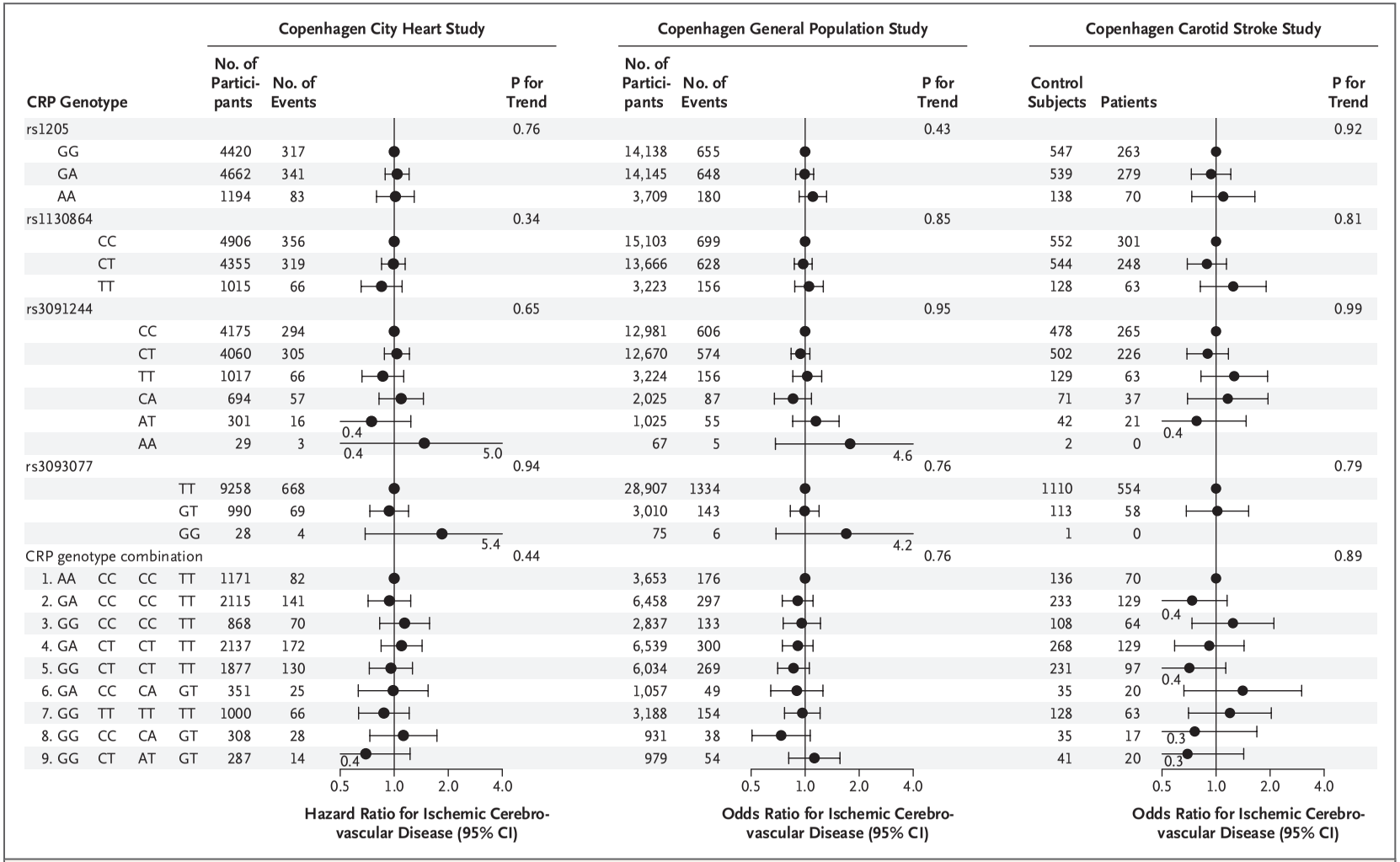


Figure 4. Risk of Ischemic Cerebrovascular Disease as a Function of C-Reactive Protein (CRP) Genotype and Genotype Combination.

The hazard ratios and odds ratios were adjusted multifactorially for all covariates shown in Table 2 in the Supplementary Appendix; the results were similar after adjustment for age and sex only (see Fig. 2 in the Supplementary Appendix).

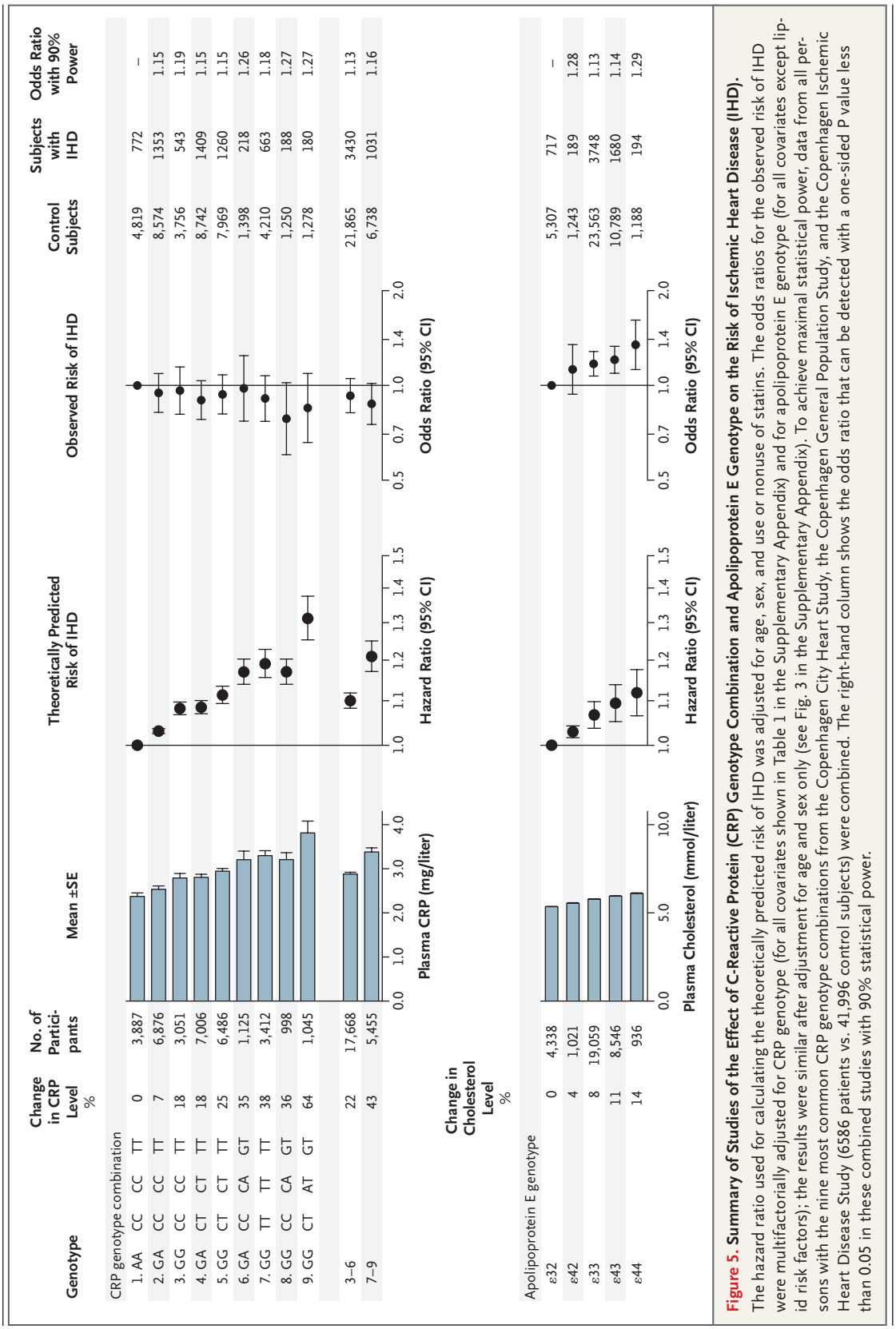


Figure 5. Summary of Studies of the Effect of C-Reactive Protein (CRP) Genotype Combination and Apolipoprotein E Genotype on the Risk of Ischemic Heart Disease (IHD).

The hazard ratio used for calculating the theoretically predicted risk of IHD was adjusted for age, sex, and use or nonuse of statins. The odds ratios for the observed risk of IHD were multifactorially adjusted for CRP genotype (for all covariates shown in Table 1 in the Supplementary Appendix) and for apolipoprotein E genotype (for all covariates except lipid risk factors); the results were similar after adjustment for age and sex only (see Fig. 3 in the Supplementary Appendix). To achieve maximal statistical power, data from all persons with the nine most common CRP genotype combinations from the Copenhagen City Heart Study, the Copenhagen General Population Study, and the Copenhagen Ischemic Heart Disease Study (6586 patients vs. 41,996 control subjects) were combined. The right-hand column shows the odds ratio that can be detected with a one-sided P value less than 0.05 in these combined studies with 90% statistical power.

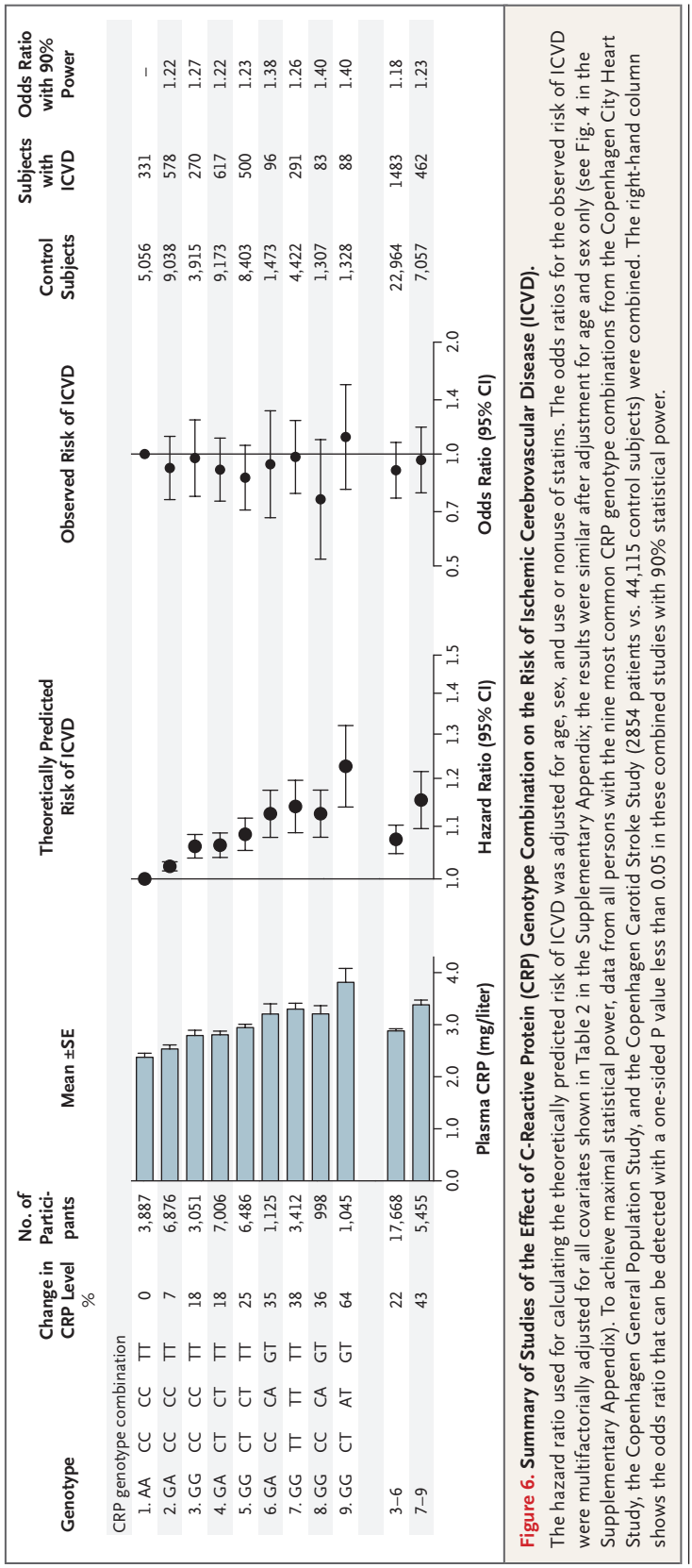


Figure 6. Summary of Studies of the Effect of C-Reactive Protein (CRP) Genotype Combination on the Risk of Ischemic Cerebrovascular Disease (ICVD).

The hazard ratio used for calculating the theoretically predicted risk of ICVD was adjusted for age, sex, and use or nonuse of statins. The odds ratios for the observed risk of ICVD were multifactorially adjusted for all covariates shown in Table 2 in the Supplementary Appendix; the results were similar after adjustment for age and sex only (see Fig. 4 in the Supplementary Appendix). To achieve maximal statistical power, data from all persons with the nine most common CRP genotype combinations from the Copenhagen City Heart Study, the Copenhagen General Population Study, and the Copenhagen Carotid Stroke Study (2854 patients vs. 44,115 control subjects) were combined. The right-hand column shows the odds ratio that can be detected with a one-sided P value less than 0.05 in these combined studies with 90% statistical power.

of ischemic heart disease or ischemic cerebrovascular disease. The absence of an increased risk of ischemic vascular disease associated with genetically elevated CRP levels was consistently observed in four large, independent studies, including a prospective study of the general population, a cross-sectional study of the general population, and two case–control studies.

In epidemiologic studies, elevated plasma CRP levels are consistently associated with increased risks of ischemic heart disease and ischemic cerebrovascular disease,[1-5] as was confirmed in the present study. However, most[8,18-27] but not all[8,28-30] previous studies have shown no association between CRP polymorphisms or haplotypes and the risk of ischemic vascular disease. It has therefore been unclear whether CRP is merely a marker of underlying atherosclerosis or is itself a causal factor for atherosclerosis and ischemic vascular disease. The present study, which is substantially larger than previous studies, was able to exclude small increases in the risk of ischemic vascular disease. For example, in our analysis, we described a genotype combination (7 to 9 vs. 1) associated with a 43% increase in CRP level and thus a theoretically predicted risk of ischemic heart disease of 1.21 (95% CI, 1.17 to 1.25). Instead of this elevated risk, however, we observed a risk of 0.87 (95% CI, 0.75 to 1.02), and our analysis had 90% statistical power to exclude an odds ratio for ischemic heart disease of 1.16, thus effectively excluding the predicted association.

Our CRP results are in contrast to our results for apolipoprotein E genotypes and to emerging genetic data[31,32] that show that nearly all gene variants that increase LDL cholesterol (8 of 11 alleles[32]) are also associated with an increased risk of ischemic heart disease. The finding that apolipoprotein E genotype variants were associated with higher odds ratios for ischemic heart disease in our study than would be theoretically predicted on the basis of elevated cholesterol levels alone may be explained by the fact that these genotypes also cause elevated levels of nonfasting triglycerides,[14] which are known to increase the risk of ischemic heart disease independently of cholesterol levels.[10,33] The CRP genetic data are more like the genetic data for HDL cholesterol. Only a very small fraction of alleles related to HDL cholesterol were associated with the risk of coronary artery disease.[12,32]

Several limitations of our study should be con-

sidered in evaluating our results. It cannot be totally ruled out that the CRP polymorphisms studied are related to higher plasma levels of functionally less active CRP. However, we consider this unlikely, since none of the polymorphisms in our analysis are located in the coding sequence of the CRP gene. The three-allelic CRP promoter polymorphism studied (rs3091244) affects transcription-factor binding and transcriptional activity, which probably leads to increased levels of fully functional CRP.[21,34] In addition, the meaning of theoretically predicted hazard ratios as a function of plasma CRP (as shown in Fig. 5 and 6) may be somewhat difficult to understand. However, presentation of the data in this form offers a simple way of visualizing the study design, and the oversimplification involved in these predictions does not invalidate the conclusions of the study. Furthermore, our four studies have limitations and potential biases that differ from study to study owing to their different designs, although the results of the four studies were similar. Also, we studied only persons of white race, and therefore our results may not apply to other races or ethnic groups.

A potential limitation of our study is lack of statistical power. We cannot exclude a small but measurable increase in risk associated with CRP genotype. For example, the 95% confidence interval for the comparison of genotype combinations 7 to 9 versus combination 1 was 0.75 to 1.02. This suggests that CRP genotypes may be associated with an increase in risk of up to 2%. However, the CRP genotypes clearly were not associated with increases in the risks of ischemic heart disease and ischemic cerebrovascular disease of the magnitudes that were theoretically predicted by the change in CRP levels.

Finally, the limitations of the study design also need to be considered.[35,36] Our study makes use of naturally occurring genetic variation resulting from independent gene assortment, sometimes termed "mendelian randomization," as the basis for our analyses of association. The principal potential limitation to this method is confounding by variation in nearby genes. If variants of another gene related to the risk of ischemic vascular disease are in linkage disequilibrium with the CRP polymorphisms we have studied, this will confound our analysis. Although such confounding is difficult to exclude completely, it is unlikely that it would explain our finding that CRP genetic variation was associated with elevated CRP levels without predicting an increased risk of ischemic vascular disease. For example, one could assume that elevated CRP levels in fact cause ischemic vascular disease but that this relationship is obscured in our analysis by confounding. For this to be true, all CRP variants examined in this study would have to be in linkage disequilibrium with another gene that, independently of plasma CRP levels, decreases the risk of ischemic vascular disease to the same extent that plasma CRP increases the risk. Such a circumstance is unlikely. Furthermore, according to the HapMap database, linkage disequilibrium is not detected between the CRP polymorphisms used in our study and other known nearby genes.

In conclusion, we show that genetic variants that are associated with lifelong increases in plasma CRP levels are not associated with an increased risk of ischemic heart disease or ischemic cerebrovascular disease. This finding suggests that the increase in the risk of ischemic vascular disease associated with higher plasma CRP levels observed in epidemiologic studies may not be causal, but rather that increased CRP levels are simply a marker for atherosclerosis and ischemic vascular disease.

Supported by the Danish Heart Foundation.

Dr. Nordestgaard reports receiving consulting fees from BG Medicine and AstraZeneca and lecture fees from AstraZeneca, Sanofi-Aventis, Merck, Pfizer, and Boehringer Ingelheim; Dr. Sillesen, consulting fees from Merck, Pfizer, BG Medicine, Boehringer Ingelheim, Sanofi-Aventis, and AstraZeneca; Dr. Grande, consulting fees from AstraZeneca; and Dr. Tybjærg-Hansen, lecture fees from Pfizer and Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

We thank Hanne Damm, Dorthe Uldall Andersen, and Dorthe Kjeldgaard Hansen for their assistance with the large-scale genotyping and the staff and participants of the Copenhagen City Heart Study, the Copenhagen General Population Study, the Copenhagen Ischemic Heart Disese Study, and the Copenhagen Carotid Stroke Study for their important contributions to our study.

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