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# Does Elevated C-Reactive Protein Increase Atrial Fibrillation Risk?

## A Mendelian Randomization of 47,000 Individuals From the General Population

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**Objectives** The purpose of this study was to test whether the association of C-reactive protein (CRP) with increased risk of atrial fibrillation is a robust and perhaps even causal association.

**Background** Elevated levels of CRP previously have been associated with increased risk of atrial fibrillation.

**Methods** We studied 10,276 individuals from the prospective Copenhagen City Heart Study, including 771 individuals who had atrial fibrillation during follow-up, and another 36,600 persons from the cross-sectional Copenhagen General Population Study, including 1,340 cases with atrial fibrillation. Individuals were genotyped for 4 *CRP* gene polymorphisms and had high-sensitivity CRP levels measured.

**Results** A CRP level in the upper versus lower quintile associated with a 2.19-fold (95% confidence interval [CI]: 1.54- to 3.10-fold) increased risk of atrial fibrillation. Risk estimates attenuated slightly after multifactorial adjustment to 1.77 (95% CI: 1.22 to 2.55), and after additional adjustment for heart failure and plasma fibrinogen level to 1.47 (95% CI: 1.02 to 2.13) and 1.63 (95% CI: 1.21 to 2.20), respectively. Genotype combinations of the 4 *CRP* polymorphisms associated with up to a 63% increase in plasma CRP levels ($p < 0.001$), but not with increased risk of atrial fibrillation. The estimated causal odds ratio for atrial fibrillation by instrumental variable analysis for a doubling in genetically elevated CRP levels was lower than the odds ratio for atrial fibrillation observed for a doubling in plasma CRP on logistic regression (0.94 [95% CI: 0.70 to 1.27] vs. 1.36 [95% CI: 1.30 to 1.44]; $p < 0.001$).

**Conclusions** Elevated plasma CRP robustly associated with increased risk of atrial fibrillation; however, genetically elevated CRP levels did not. This suggests that elevated plasma CRP per se does not increase atrial fibrillation risk.
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Elevated levels of C-reactive protein (CRP) have been suggested as a possible contributing factor to the initiation or maintenance of atrial fibrillation. However, whether increased plasma CRP levels are simply a marker for atrial fibrillation or whether elevated CRP actually contributes directly to causing the disorder presently is unknown (1,2). This question has clinical importance because several cardiovascular drugs, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, modulate the inflammatory process in the heart (3,4), and because drugs that specifically lower CRP levels already are being developed for treatment of cardiovascular disease (5).

Cause-and-effect relationships such as the one suggested between plasma CRP levels and risk of atrial fibrillation can be studied using an approach called Mendelian randomization (6). This approach uses genetic variants randomly assorted during gamete formation and associated with levels of plasma CRP to test whether there could be a causal association between elevated plasma CRP levels and increased risk of atrial fibrillation. Thus, genetic variants that

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**Abbreviations and Acronyms**

**CI** = confidence interval
**CRP** = C-reactive protein
**OR** = odds ratio
**LDL** = low-density lipoprotein

specifically increase plasma levels of CRP (7) can be used as instruments to assess the consequences of lifelong high CRP levels independently of other risk factors and not hampered by reverse causation (8).

We tested the hypothesis that there is a robust and potential causal association between elevated CRP levels and increased risk of atrial fibrillation. Robustness was tested by adjustment of risk estimates for age, sex, and statin use; age, sex, statin use, and *CRP* genotype; multifactorially for age, sex, statin use, low-density lipoprotein (LDL) cholesterol, body mass index, smoking, heavy drinking, diabetes mellitus, hypertension, and hyperthyroidism; multifactorially including heart failure, *AGT*-20A→C, *AGT* T174M, and *ACE* insertion or deletion genotypes; or finally, including plasma fibrinogen. Potential causality was tested by examining whether *CRP* genotype combinations associated with an increased risk of atrial fibrillation consistent with their life-long elevation of plasma CRP levels.

## Methods

For full information on study populations, genotyping and biochemical analyses, covariates, and statistical analyses, please refer to Supplementary Methods. The CCHS (Copenhagen City Heart Study) is a prospective study of the Danish general population initiated from 1976 through 1978 with follow-up examinations in 1981 through 1983, 1991 through 1994, and 2001 through 2003 (9). The CGPS (Copenhagen General Population Study) is a cross-sectional study initiated in 2003 with ongoing inclusion. Participants were ascertained exactly as in the CCHS. All participants were white and of Danish

**Table 1** Characteristics of Individuals in the 2 General Population Studies by Plasma CRP Quintiles

| | Quintiles of Plasma CRP | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | p Value |
| Copenhagen City Heart Study | | | | | | |
| CRP (mg/dl) | 1.0 (0.1–1.2) | 1.3 (1.2–1.5) | 1.7 (1.5–2.1) | 2.7 (2.1–3.6) | 9.9 (3.6–103) | <0.001 |
| No. of individuals | 1,656 | 1,657 | 1,654 | 1,654 | 1,655 | |
| Women | 47 | 56 | 58 | 55 | 56 | <0.001 |
| Age (yrs) | 50 (37–63) | 57 (44–68) | 61 (50–70) | 64 (53–72) | 64 (55–72) | <0.001 |
| Statin use | 0.5 | 0.8 | 0.9 | 1.2 | 0.2 | <0.001 |
| LDL cholesterol (mmol/l) | 3.3 (2.7–4.1) | 3.6 (2.9–4.3) | 3.8 (3.1–4.5) | 3.8 (3.1–4.7) | 3.7 (3.0–4.5) | <0.001 |
| Body mass index (kg/m$^2$) | 23 (21–25) | 24 (22–27) | 25 (23–28) | 26 (24–29) | 27 (24–30) | <0.001 |
| Smoking, active and former | 51 | 56 | 60 | 66 | 69 | <0.001 |
| Heavy drinkers | 10 | 10 | 10 | 9 | 10 | 0.52 |
| Diabetes mellitus | 2 | 3 | 3 | 5 | 8 | <0.001 |
| Hypertension | 38 | 48 | 57 | 65 | 65 | <0.001 |
| Hyperthyroidism | 2 | 2 | 2 | 2 | 3 | 0.06 |
| Heart failure | 4 | 7 | 10 | 15 | 19 | <0.001 |
| Fibrinogen (mg/l) | 2.5 (2.1–2.9) | 2.7 (2.3–3.1) | 2.9 (2.5–3.4) | 3.2 (2.8–3.7) | 3.8 (3.2–4.5) | <0.001 |
| *AGT*-29 A→C (AA/AC/CC) | 70/27/3 | 70/27/3 | 72/26/2 | 72/25/3 | 70/28/2 | 0.71 |
| *AGT* T174M (TT/TM/MM) | 77/22/2 | 76/23/2 | 79/19/1 | 77/21/2 | 77/21/1 | 0.29 |
| *ACE* ins/del (dd/id/ii) | 26/50/24 | 26/49/24 | 26/50/24 | 26/48/25 | 25/51/24 | 0.56 |
| Copenhagen General Population Study | | | | | | |
| CRP (mg/dl) | 0.5 (0.01–0.8) | 1.1 (0.8–1.3) | 1.5 (1.3–1.9) | 2.5 (1.9–3.4) | 8.7 (3.4–330) | <0.001 |
| No. of individuals | 7,331 | 7,320 | 7,316 | 7,315 | 7,318 | |
| Women | 53 | 52 | 53 | 52 | 57 | <0.001 |
| Age (yrs) | 53 (45–63) | 58 (48–66) | 59 (49–67) | 60 (50–69) | 62 (51–71) | <0.001 |
| Statin use | 6 | 10 | 11 | 11 | 11 | <0.001 |
| LDL cholesterol (mmol/l) | 3.1 (2.2–3.7) | 3.1 (2.5–3.8) | 3.2 (2.6–3.9) | 3.3 (2.7–4.0) | 3.3 (2.6–3.9) | <0.001 |
| Body mass index (kg/m$^2$) | 24 (24–26) | 25 (23–27) | 26 (23–28) | 27 (24–30) | 28 (25–31) | <0.001 |
| Smoking, active and former | 55 | 45 | 39 | 49 | 58 | 0.12 |
| Heavy drinkers | 2 | 3 | 3 | 3 | 3 | 0.02 |
| Diabetes mellitus | 2 | 3 | 3 | 4 | 6 | <0.001 |
| Hypertension | 55 | 63 | 67 | 72 | 77 | <0.001 |
| Hyperthyroidism | 1 | 1 | 1 | 1 | 2 | 0.02 |
| Heart failure | 1 | 1 | 1 | 2 | 4 | <0.001 |
| Fibrinogen (mg/l) | 1.0 (0.9–1.2) | 1.1 (1.0–1.2) | 1.2 (1.0–1.3) | 1.3 (1.1–1.4) | 1.4 (1.2–1.7) | <0.001 |

Continuous values are summarized as median (interquartile range); p value is for trend among quintiles by a nonparametric test by Cuzick. Categorical values are summarized in percent; p values for trend by Cuzick's extension of a Wilcoxon rank-sum test.
CRP = C-reactive protein; LDL = low-density lipoprotein.

descent. No individuals were included in both populations, and follow-up was 100% complete.

## Results

Characteristics of participants in each study cohort are shown in Table 1 as a function of quintiles of plasma CRP. In each cohort, increasing plasma CRP levels associated with female sex, increasing age, plasma LDL cholesterol, body mass index, and fibrinogen levels and with presence of statin use, smoking, diabetes mellitus, hypertension, and heart failure (all $p < 0.001$ for trend) (Table 1). Levels of plasma CRP did not associate with distribution of *AGT* or *ACE* genotype (Table 1).

**Plasma CRP and risk of atrial fibrillation.** Increasing levels of plasma CRP were associated with increasing risk of atrial fibrillation (Fig. 1). In the CCHS population, CRP in the upper versus lower quintile was associated with a 2.19-fold (95% confidence interval [CI]: 1.54- to 3.10-fold) increased risk of atrial fibrillation after adjustment for age, sex, and statin use. The corresponding hazard ratio after further adjustment for *CRP* genotype was 2.22 (95% CI: 1.55 to 3.16), and that after multifactorial adjustment was 1.77 (95% CI: 1.22 to 2.55). Similar results were seen in the CGPS (Fig. 1).

Heart failure is one of the major risk factors for atrial fibrillation, and including heart failure into the multifactorial model attenuated the risk of atrial fibrillation associated with the plasma CRP level to 1.47 (95% CI: 1.02 to 2.13) for upper versus lower quintile in the CCHS, and similarly in the CGPS (Fig. 2). Adjusting for plasma fibrinogen level, another marker of inflammation, attenuated the corresponding risk of atrial fibrillation to 1.63 (95% CI: 1.21 to 2.20) in the CCHS, and similarly in the CGPS (Fig. 2).

***CRP* genotype and plasma CRP.** In accordance with previous findings (8), the *CRP* polymorphism rs1205 was associated with lower plasma CRP levels, whereas the rs1130864, rs3091244, and rs3093077 polymorphisms were

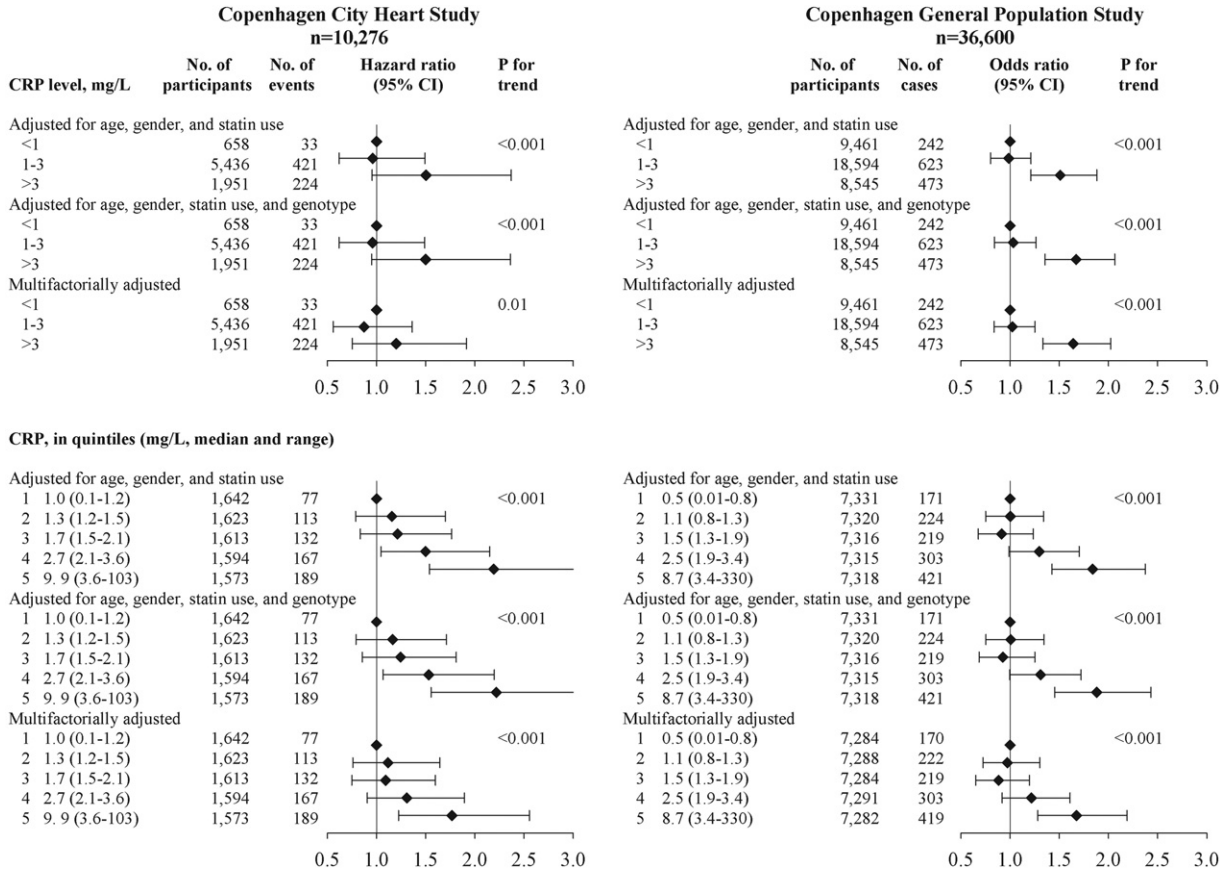


**Figure 1** Risk of Atrial Fibrillation as a Function of Plasma Levels of CRP in the General Population

High-sensitivity plasma C-reactive protein (CRP) levels were measured in 10,276 individuals who participated in the 1991 through 1994 examination of The CCHS (Copenhagen City Heart Study) **(left panels)** and subsequently were followed up for 12 to 15 years with respect to incident atrial fibrillation; individuals with atrial fibrillation before study entry were excluded. Findings were retested in 36,600 individuals from the cross-sectional CGPS (Copenhagen General Population Study) **(right panels)**. Multifactorial adjustment was for age, sex, statin use, low-density lipoprotein cholesterol, body mass index, smoking, heavy drinking, diabetes mellitus, hypertension, hyperthyroidism, and *AGT* and *ACE* genotypes (CCHS only). CI = confidence interval.

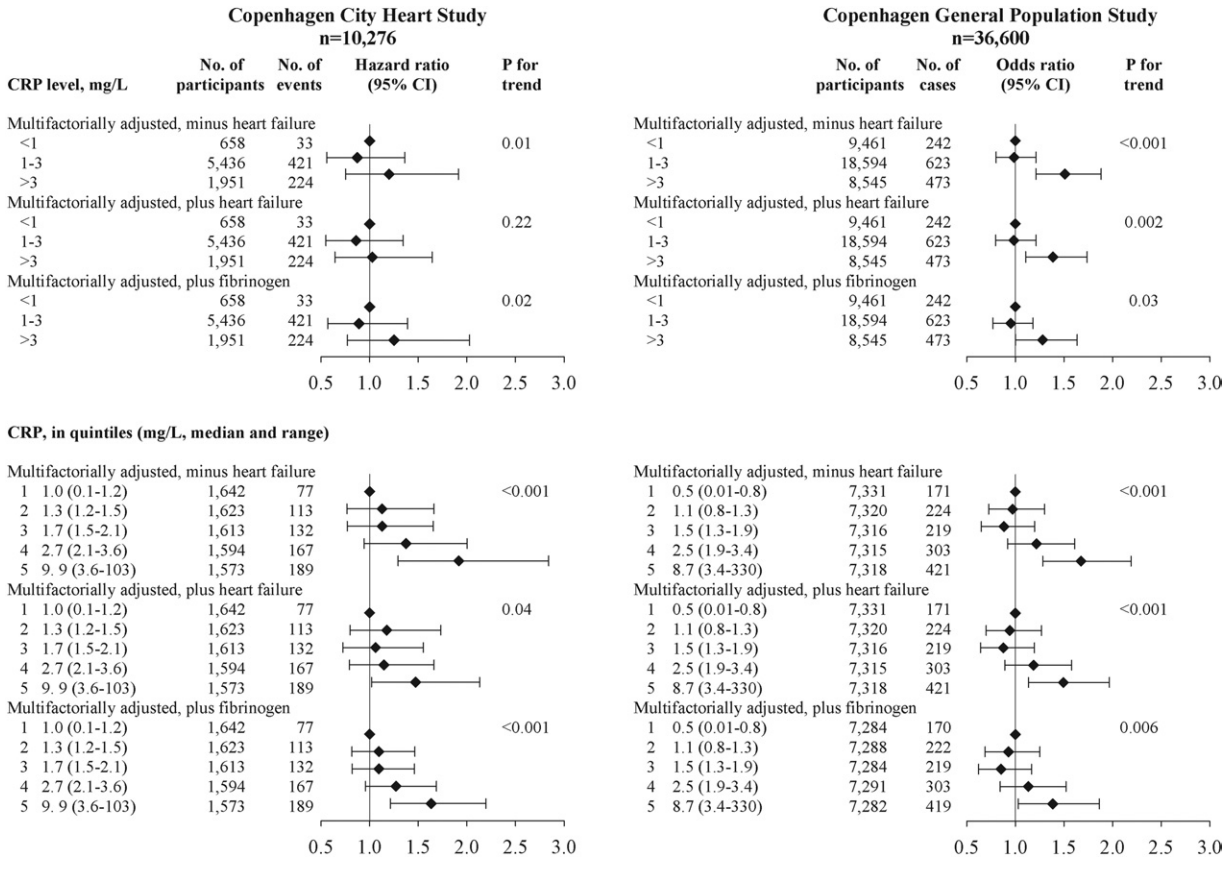


**Figure 2** **Risk of Atrial Fibrillation as a Function of Plasma Levels of CRP in the General Population, Additionally Adjusted for Heart Failure and Plasma Fibrinogen Levels**

Robustness of the association of plasma CRP levels with risk of atrial fibrillation was tested by separately including adjustment of heart failure and plasma fibrinogen levels into the multifactorially adjusted model from Figure 1. This was tested in 10,276 individuals who participated in the 1991 through 1994 examination of the CCHS **(left panels)**, and findings were retested in 36,600 individuals from the cross-sectional CGPS **(right panels)**. Abbreviations as in Figure 1.

associated with higher CRP levels (Fig. 3). Combining the genotypes resulted in up to a 63% difference in plasma CRP levels between the lowest and highest levels among the 9 most common genotype combinations. Contribution of genotype to variation in plasma CRP levels estimated as partial $r^2$ values ranged from 1.3% to 1.5% for the different *CRP* genotypes or genotype combinations. Covariates (age, lipids, body mass index, alcohol consumption, smoking, statin use, hypertension, diabetes, heart failure, and *AGT* and *ACE* genotype) did not differ among the 9 different *CRP* genotypes (Supplementary Table) (8).

***CRP* genotype and risk of atrial fibrillation.** Hazard ratios for atrial fibrillation as a function of genotype in the CCHS did not differ consistently from 1.0 for any of the individual *CRP* polymorphisms, or for genotype combinations ($p = 0.12$ to 0.70 for trend) (Fig. 4). These findings were confirmed in the CGPS ($p = 0.22$ to 0.78 for trend). The various risk factors were distributed equally among the different *CRP* genotype combinations (Supplementary Table) (8). This also was true for each of the 4 genotypes separately and for genotype combinations in each of the studies as previously reported (8).

**Potential causal effect of CRP on the risk of atrial fibrillation.** Assuming that elevations in CRP levels have a causal effect on risk of atrial fibrillation, genetically elevated plasma CRP levels should confer a similar increase in disease risk as that observed for elevated plasma CRP levels encountered in the general populations. Based on this assumption and to obtain maximal statistical power, we estimated, using instrumental variable analysis by generalized least square regression, that a doubling of plasma CRP levels resulting from *CRP* genotype combinations associated with a causal odds ratio (OR) of 0.76 (95% CI: 0.62 to 0.93) in the studies combined, contrasting the observed OR associated with a doubling of plasma CRP levels of 1.12 (95% CI: 1.06 to 1.17) in the 2 studies combined (causal vs. observed OR, $p < 0.001$). Similar results for unadjusted analyses were for plasma CRP 1.36 (95% CI: 1.30 to 1.44) and for genetically elevated CRP 0.94 (95% CI: 0.70 to 1.27) (causal vs. observed OR, $p < 0.001$) (Fig. 5).

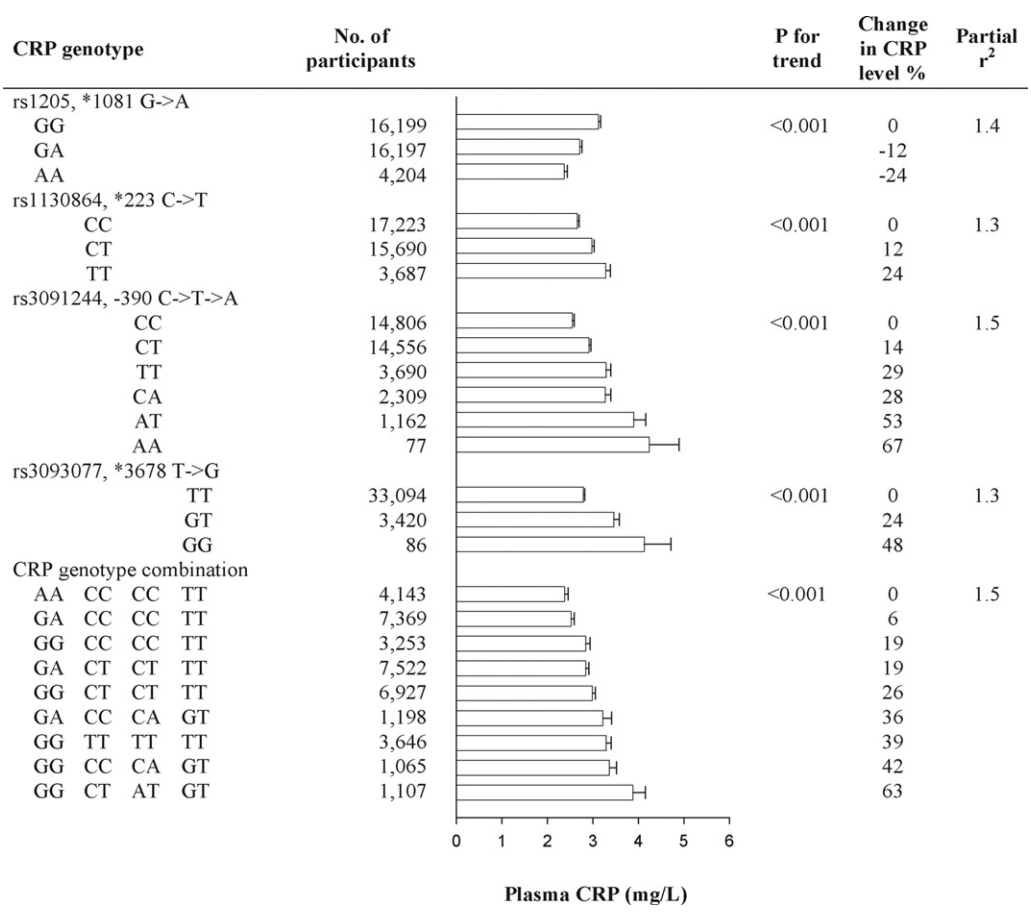


**Figure 3** Plasma Levels of CRP as a Function of *CRP* Genotypes and Genotype Combinations

This was tested in 36,600 individuals from the general population, the CGPS. Partial $r^2$ values were determined after adjustment for variation in plasma CRP levels resulting from age, sex, and statin use. Abbreviations as in Figure 1.

## Discussion

The main findings of this study are that elevated plasma CRP levels are associated robustly with increased risk of atrial fibrillation, but that genetically elevated CRP levels are not. This suggests that elevated plasma CRP levels per se do not increase atrial fibrillation risk.

The finding that increased plasma CRP levels associate with an increased risk of atrial fibrillation is in accordance with a previous prospective study (n = 5,806 including 897 events) (10) and with 3 case-control studies (n = 121, n = 202, and n = 2,796, respectively) (1,11,12). Also, a previous study from the CCHS showed that plasma fibrinogen, another marker of inflammation, associated with risk of atrial fibrillation (13). Importantly, in the present study, we also showed that this association is robust, because estimates only attenuated slightly when adjusting for *CRP* genotype, multifactorially, and multifactorially including heart failure and plasma fibrinogen.

During data analysis, we adjusted estimates of risk associated with plasma CRP levels for potential confounders such as LDL cholesterol, body mass index, smoking, heavy drinking, diabetes mellitus, hypertension, hyperthyroidism, and *ACE* and *AGT* genotypes and observed that the risk estimates largely are not confounded by these factors. Adjusting either for heart failure, a well-known risk factor for atrial fibrillation associated with increased levels of plasma CRP, or for fibrinogen, another marker of inflammation, somewhat attenuated the risk estimates, although they remained significant, also suggesting that plasma CRP levels robustly predict atrial fibrillation risk.

To study a cause-and-effect relationship such as the one suggested between plasma CRP levels and risk of atrial fibrillation, a Mendelian randomization approach can be used to circumvent regression dilution bias, confounding, and reverse causation, although, 3 conditions must be fulfilled (14). First, *CRP* genotype (instrumental variable) must be associated with the exposure variable (plasma CRP). In the present study, CRP genotype combinations contributed 1.5% to the total variation in plasma CRP, but associated with up to a 63% increase in plasma CRP levels.

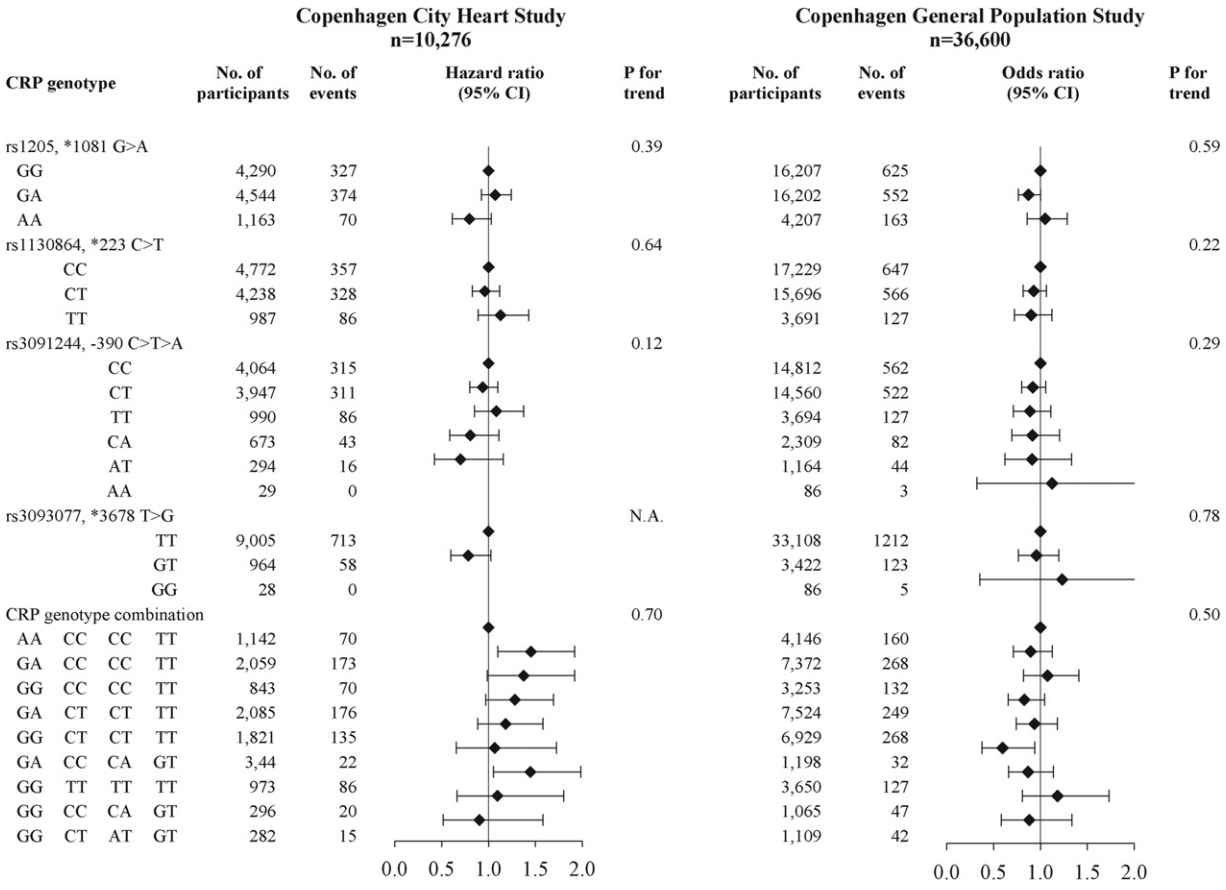


**Figure 4** **Risk of Atrial Fibrillation as a Function of *CRP* Genotype and Genotype Combinations in the General Population**

The hazard and odds ratios were adjusted multifactorially for age, sex, statin use, low-density lipoprotein cholesterol, body mass index, smoking, heavy drinking, diabetes mellitus, hypertension, hyperthyroidism, and AGT and ACE genotype (CCHS only). This was tested in 10,276 individuals who participated in the 1991 through 1994 examination of the CCHS **(left panels)**, and findings were retested in 36,600 individuals from the cross-sectional CGPS **(right panels)**. N.A. = not estimated because of no events in GG genotype group; other abbreviations as in Figure 1.

A similar increase in nongenetic plasma CRP is associated with a 7% increase in risk of atrial fibrillation (OR: 1.07; 95% CI: 1.04 to 1.10) (Fig. 5); thus, genotype combinations associate with a sufficient increase in plasma CRP to serve as instruments in a Mendelian randomization study. Second, *CRP* genotype must be independent of factors confounding the association of plasma CRP levels with risk of atrial fibrillation, clearly fulfilled in the present studies (Supplementary Table) (8). Finally, *CRP* genotype must be independent of the outcome, that is, it must not affect risk of atrial fibrillation by pathways other than plasma CRP, given confounding factors (6,14). Having fulfilled these requirements, comparison of the positive association between plasma CRP levels and the risk of atrial fibrillation (OR per doubling: 1.12 [95% CI: 1.06 to 1.17]; unadjusted OR: 1.36 [95% CI: 1.30 to 1.44]) with the association between genetically elevated CRP levels and risk of atrial fibrillation (OR: 0.76 [95% CI: 0.62 to 0.93]; unadjusted OR: 0.94 [95% CI: 0.70 to 1.27]) showed a significant contrast, not in favor of a causal relationship between elevated plasma CRP levels and increased atrial fibrillation risk. However, because plasma CRP is a marker only of inflammation, our study does not exclude a potential causal association between inflammation and atrial fibrillation.

**Study limitations.** Potential limitations of this study include, as always, selection bias and misclassification of plasma CRP levels, *CRP* genotype, and atrial fibrillation. However, the study populations used were selected using the national Danish Civil Registration system, drawing 2 random samples from the Danish adult general population without knowledge of plasma CRP levels, genotypes, and diagnosis of atrial fibrillation, largely excluding important selection bias. Some misclassification of plasma markers like CRP is well known because of regression dilution bias; however, we were able to correct for this because CRP levels were measured twice in approximately 6,300 individuals. Misclassification of genotype is unlikely in the present study, because genotypes were controlled by sequencing and because overall call rates were more than 99.9% as a result of repeated reruns.

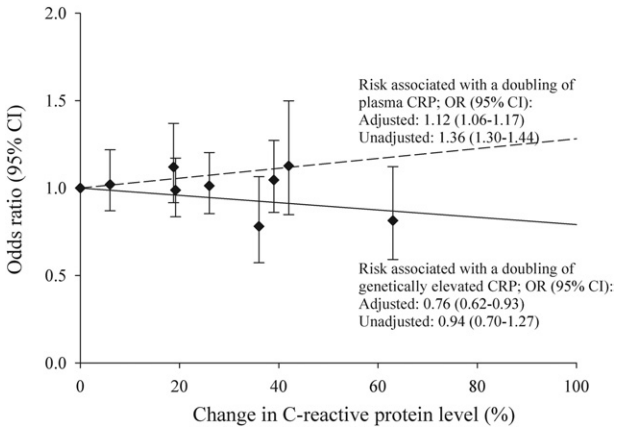


**Figure 5** **Studies Summary of the Causal Effect of CRP on Risk of Atrial Fibrillation in the General Population**

The causal effect of CRP on risk of atrial fibrillation was estimated by the association between genetically elevated CRP levels and risk of atrial fibrillation, using instrumental variable analysis by generalized least square regression **(solid line)**. This risk is compared with the observed risk associated with plasma CRP in the general population **(dashed line)**. For comparison, risk estimates for a doubling (100% increase) in CRP levels are given. Estimates are based on the combined studies with 10,276 individuals from the CCHS and 36,600 individuals from the CGPS. OR = odds ratio; other abbreviations as in Figure 1.

Ascertainment and classification of atrial fibrillation is a potential limitation of the present study because atrial fibrillation may have occurred in some individuals without having been diagnosed, because atrial fibrillation may have been coded incorrectly in the national Danish Patient Registry, or because some individuals might not have had atrial fibrillation at one of the follow-up examinations, that is, if they had paroxystic atrial fibrillation. Misclassification of a diagnosis of atrial fibrillation would result in an underestimation of the risk estimates, and thus more conservative estimates for the association of plasma CRP levels with risk of atrial fibrillation than observed in the present study. Finally, information on medication, that is, treatment with statin and antihypertensive medication, is self-reported and may be inaccurate. Such an inaccuracy tends to make association of plasma CRP levels with risk of atrial fibrillation more conservative, but would not influence the association of *CRP* genotype with risk of atrial fibrillation.

## Conclusions

Elevated plasma CRP was robustly associated with increased risk of atrial fibrillation, although genetically elevated CRP levels were not. This suggests that elevated plasma CRP per se does not increase atrial fibrillation risk.

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**Key Words:** atrial fibrillation ■ C-reactive protein ■ genetics ■ inflammation ■ Mendelian randomization.

**APPENDIX**

**For a supplementary table and method section, please see the online version of this article.**