Elevated C-Reactive Protein, Depression, Somatic Diseases, and All-Cause Mortality: A Mendelian Randomization Study

Marie Kim Wium-Andersen, David Dynnes Ørsted, and Børge Grønne Nordestgaard

Background: Elevated levels of plasma C-reactive protein (CRP) have been associated with many diseases including depression, but it remains unclear whether this association is causal. We tested the hypothesis that CRP is causally associated with depression, and compared these results to those for cancer, ischemic heart disease, chronic obstructive pulmonary disease, and all-cause mortality.

Methods: We performed prospective and instrumental variable analyses using plasma CRP levels and four CRP genotypes on 78,809 randomly selected 20- to 100-year-old men and women from the Danish general population. End points included hospitalization or death with depression and somatic diseases, prescription antidepressant medication use, and all-cause mortality.

Results: A doubling in plasma CRP yielded an observed odds ratio (OR) of 1.28 (95% confidence interval [CI]: 1.23–1.33) for hospitalization or death with depression, whereas for genetically elevated CRP, the causal OR was .79 (95% CI: .51–1.22; observed vs. causal estimate, p = .03). For prescription antidepressant medication use, corresponding ORs were 1.12 (1.11–1.15) and .98 (1.33–1.15; p = .08). These results were similar to those for risk of cancer (p = .002), ischemic heart disease (p = 4 × 10⁻⁹⁹), chronic obstructive pulmonary disease (p = 6 × 10⁻⁶⁰⁰), and all-cause mortality (p = .001) examined in the same individuals.

Conclusions: Elevated CRP was associated with increased risk of depression in individuals in the general population, but genetically elevated CRP was not. This indicates that CRP per se is not a causal risk factor for depression.

Key Words: All-cause mortality, CRP, depression, genetic variants, inflammation, mendelian randomization, somatic disease

Depression is associated with elevated levels of the inflammatory biomarker C-reactive protein (CRP) (1–6). However, epidemiologic studies are prone to residual confounding, reverse causation, and regression dilution bias (7). Hence, it remains unclear whether the association between CRP and depression is causal.

The Mendelian randomization approach enables testing of causality between an exposure (e.g., plasma CRP) and an outcome (e.g., depression) by using genetic variants (7–11). Mendelian randomization exploits the random allocation of genetic variants during gamete formation, which subsequently results in different phenotypes (i.e., different lifelong CRP levels). As such, a Mendelian randomization study is analogous to a randomized controlled trial in which participants are randomized to either intervention or placebo, and the randomization at baseline ensures equal distribution of confounders and excludes the possibility of reverse causation. Consequently, if CRP is in fact causally related to depression, we would expect individuals with genetic variants resulting in lifelong elevated plasma CRP levels to have a higher risk of depression. If this is not the case, it can be inferred that the association between CRP and depression is not causal but is rather the result of confounding or reverse causation.

In 78,809 men and women from the Danish general population, we tested the hypothesis that elevated plasma CRP is causally associated with depression and psychological distress using a Mendelian randomization design. To this end, we tested the following hypotheses: first, elevated levels of plasma CRP would be associated with depression or psychological distress. Second, four genetic variants in the CRP gene would be associated with plasma CRP levels. We chose four single nucleotide polymorphisms (SNPs) that capture most of the variation in the CRP gene, including the most important 3-allelic promoter SNP (rs3091244) (9,12). All four SNPs cause lifelong elevated but fully functional CRP levels, which have been replicated in independent samples (13–15) and together explain approximately 2% of the variation in plasma CRP levels (9). Third, the CRP polymorphisms would be directly associated with depression or psychological distress. Finally, using instrumental variable analysis, we calculated the causal odds ratio (OR) for depression or psychological distress for a doubling in CRP levels and compared it with the corresponding observed ORs. In addition, we compared the observed and causal association between CRP and depression to those between CRP and ischemic heart disease, cancer, chronic obstructive pulmonary disease, and all-cause mortality, previously reported in smaller samples of our studies (9,16–18).

Methods and Materials

Participants
We used data from two large independent Danish general population studies, the Copenhagen General Population Study 2003–2011 examination (n = 68,779) and the Copenhagen City Heart Study 1991–1994 and/or 2001–2003 examinations (n = 10,030) (19,20). Participants from both studies were aged 20 to 100 years and were randomly selected from the national Danish Civil Registration System (21) to represent the Danish general population.
Psychological Distress was ascertained by two self-reported questions: “Do you have the feeling that you have not accomplished very much recently?” (yes/no) and “Do you feel like giving up?” (yes/no) (20,25). These questions were the only such measures available for all participants and were not part of a diagnostic scoring scale.

Major Somatic Diseases

Diagnoses of somatic diseases and all-cause mortality were ascertained from 1977 through May 2011 as follows. Cancer was ICD-8 140–209 or ICD-10 C00–C97, B21 from the Danish Cancer Registry. Ischemic heart disease including myocardial infarction was ICD-8 410–414 or ICD-10 I20–I25 and chronic obstructive pulmonary disease was ICD-8 491–492 or ICD-10 J41–J44 from the national Danish Patient Registry and the national Danish Causes of Death Registry. Information on all-cause mortality was ascertained from the national Danish Civil Registration System, which records information on death and date of death.

Plasma CRP Measurements and CRP Genotypes

Plasma levels of CRP were measured at the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital. CRP was measured with a high-sensitivity assay using latex-enhanced turbidimetry (Dako, Glostrup, Denmark) or nephelometry (Dade Behring, Deerfield, Illinois); results were similar for the two assays, and therefore all statistical analyses were combined, but with adjustment for assay type and study in all observational analyses. All measurements were performed by laboratory technicians blinded to disease status of participants. CRP measurements were included in daily internal and monthly external routine quality control programs, to ensure precision and accuracy.

We genotyped four polymorphisms in the CRP gene: rs1130864, rs1205, rs3091244, and rs3093077 using TaqMan, ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, California). Each genotyping run included a known noncarrier, a heterozygous, and a homozygous control. Genotyping was verified by Sanger DNA sequencing in more than 30 individuals with each genotype. The call rate was greater than 99.8% after two rounds of reruns. All genotypes were in Hardy-Weinberg equilibrium.

Covariates

Participants reported on smoking status (never, former, current), alcohol intake (0, 1–84, >85 g/week), weekly physical activity (0–2 hours moderate, 2–4 hours moderate; >4 hours moderate activity or 2–4 hours vigorous; >4 hours vigorous), level of education after lower secondary school (no education, shorter education <3 years, basic vocational training 1–3 years; higher education ≥3 years; university education), and level of income (lowest, middle, highest). Women were asked about menopausal status. Body mass index (BMI) was measured weight in kilograms divided by measured height in meters squared (<18.5, 18.5–24.9, 25–29.9, ≥30). Chronic disease was ascertained by collecting information on diagnosis and date of diagnosis from the national Danish Patient Registry, the national Danish Cancer Registry, and the national Danish Causes of Death Registry on ischemic heart disease, myocardial infarction, stroke, diabetes, hypertension, cancer, pneumonia, chronic obstructive pulmonary disease, asthma, deep venous thrombosis, and pulmonary embolism, similar to that described earlier.

Statistical Analyses

Stata version 12.1 (StataCorp, College Station, Texas) was used for all statistical analyses. To achieve maximal statistical power, data from the Copenhagen General Population Study and the Copenhagen City Heart Study was combined. Because levels of CRP were not normally distributed but skewed to the right, logarithmically transformed CRP was used when CRP was used on a continuous scale. All participants were divided into three categories based on their CRP levels: CRP ≤1.00 mg/L, CRP 1.01–3.00 mg/L, and CRP >3.00 mg/L. For trend tests, CRP categories were assigned the values of 1, 2, and 3. We had 98% complete data on alcohol consumption, smoking status, physical activity, income, level of education, and BMI. All missing values were imputed based on age and gender before multivariable adjustment (26). Because 4317 individuals had participated in both the 1991–1994 and 2001–2003 examinations of the Copenhagen City Heart Study and had CRP measured 10 years apart, we were able to calculate a regression dilution ratio of .82 using a nonparametric method (27). This ratio was used to correct ORs and confidence intervals (CIs) for regression dilution bias in

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order to reduce the effect of regression towards the mean, which might otherwise have lead to an underestimation of risk estimates; importantly however, significance levels are not influenced by this correction. In accordance with the design of a Mendelian randomization study, we conducted four different analyses as described below.

First, we tested whether plasma CRP levels were associated with increased risk of depression and psychological distress. To examine associations between CRP categories and all endpoints we used two different logistic regression models to calculate ORs with 95% CIs adjusted for 1) age and gender and 2) age, gender, alcohol consumption, smoking status, level of physical activity, education, income, BMI, and chronic disease.

Second, we tested whether each of the four CRP polymorphisms and the genotype combinations were associated with plasma levels of CRP. Furthermore, we generated all possible genotype combinations and ranked the nine most common combinations based on their CRP levels. For trend tests, we used Cuzick’s extension of the Wilcoxon rank-sum test and ranked genotypes or genotype combinations 1, 2, 3, and so on.

Third, we tested whether the genotype combinations were directly associated with depression and psychological distress. We assumed that the genetically elevated plasma CRP levels theoretically confer the same increase in risk of depression or psychological distress as that observed for elevated plasma CRP in the general population. Thus, the increases in ORs for depression or psychological distress for a 1% increase in plasma CRP were used to calculate theoretically predicted risk associated with the changes in CRP levels for the genotype combinations (9). Theoretically predicted risk was then compared with observed risk.

Fourth, to further test the association between the CRP polymorphisms and depression or psychological distress, we performed instrumental variable analysis with a two-stage regression model using each polymorphism and the genotype combinations as instruments to estimate the causal effect of a doubling in CRP on risk of depression or psychological distress (29). The first stage was a linear regression of each of the CRP polymorphisms on CRP levels. F statistics were used to evaluate the strength of the instruments, with $F > 10$ indicating sufficient strength. The second stage was a logistic regression of values of CRP (generated in the first stage) on depression or psychological distress to calculate causal ORs (29). The unadjusted observed and causal ORs were compared using a Wald test.

Finally, we compared observed and causal ORs (from logistic regression and instrumental variable analysis as described earlier) for the association between a doubling in CRP levels and major somatic diseases (i.e., hospitalization or death with or from cancer, ischemic heart disease, chronic obstructive pulmonary disease), and all-cause mortality with the results for hospitalization or death with depression.

### Results

Baseline characteristics of the 78,809 individuals by plasma levels of CRP are listed in Table 1, and by end points and genotype combinations in Tables S1A, B, and S2 in Supplement 1. All potential confounders were associated with CRP categories and/or endpoints, but not with the genotype combination (for overview, see Table 1). Thus, genotype combination can be used as an unconfounded instrument to assess the causal association between lifelong elevated CRP levels on depression and psychological distress. In total, 1183 (1.4%) individuals had a hospitalization with depression, 8898 (11%) individuals had purchased antidepressant medication for at least 6 continuous months, 5205 (7%) individuals reported use of antidepressant medication, 16,564 (21%) individuals reported not having accomplished much lately, and 5020 (6%) individual reported wanting to give up

### Plasma CRP, Depression, and Psychological Distress: Observed Risk

Increasing CRP levels were associated with increasing risk of hospitalization or death with depression ($p$ trend $= 3 \times 10^{-3}$), prescription antidepressant use ($p$ trend $= 1 \times 10^{-28}$), self-reported antidepressant use ($p$ trend $= 5 \times 10^{-41}$), not accomplishing ($p$ trend $= 2 \times 10^{-94}$), and of wanting to give up ($p$ trend $= 1 \times 10^{-32}$; Figure 1).

For hospitalization or death with depression, age- and gender-adjusted OR were 1.37 (95% CI 1.07–1.75) for individuals with a CRP

### Table 1. Baseline Characteristics of 78,809 Individuals from the General Population

<table>
<thead>
<tr>
<th>C-Reactive Protein (mg/L)</th>
<th>≤1.00</th>
<th>1.01–3.00</th>
<th>&gt;3.00</th>
<th>p Trend CRP</th>
<th>p Value Depression</th>
<th>p Trend Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14,832</td>
<td>48,230</td>
<td>15,747</td>
<td>&lt;1 $\times$ 10^{-30}</td>
<td>2 $\times$ 10^{-90}</td>
<td>.81</td>
</tr>
<tr>
<td>Age, Years, Mean (range)</td>
<td>54 (20–97)</td>
<td>57 (20–97)</td>
<td>60 (20–99)</td>
<td>5 $\times$ 10^{-15}</td>
<td>1 $\times$ 10^{-8}</td>
<td>.60</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>7952 (54)</td>
<td>26,672 (55)</td>
<td>9141 (58)</td>
<td>3 $\times$ 10^{-101}</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Premenopausal, n (%)</td>
<td>3361 (42)</td>
<td>8925 (33)</td>
<td>2443 (27)</td>
<td>.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal, n (%)</td>
<td>4591 (58)</td>
<td>17,747 (67)</td>
<td>6698 (73)</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Consumption &gt;84 g/Week, n (%)</td>
<td>7748 (52)</td>
<td>25,062 (55)</td>
<td>7538 (48)</td>
<td>5 $\times$ 10^{-15}</td>
<td>2 $\times$ 10^{-9}</td>
<td>.81</td>
</tr>
<tr>
<td>Smoking, Current or Former, n (%)</td>
<td>8078 (59)</td>
<td>30,118 (62)</td>
<td>11,031 (70)</td>
<td>6 $\times$ 10^{-24}</td>
<td>3 $\times$ 10^{-29}</td>
<td>.02</td>
</tr>
<tr>
<td>Low Leisure Time Physical Activity: Inactive or &lt;2–4 Hours Light/Day, n (%)</td>
<td>6757 (46)</td>
<td>24,584 (51)</td>
<td>10,126 (64)</td>
<td>.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less Than 3 Years of Education after Lower Secondary School, n (%)</td>
<td>8049 (54)</td>
<td>27,992 (58)</td>
<td>11,437 (72)</td>
<td>5 $\times$ 10^{-24}</td>
<td>9 $\times$ 10^{-34}</td>
<td>.02</td>
</tr>
<tr>
<td>Low Income, n (%)</td>
<td>2047 (14)</td>
<td>7665 (16)</td>
<td>4425 (28)</td>
<td>.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index &gt;25, n (%)</td>
<td>5639 (38)</td>
<td>26,694 (55)</td>
<td>11,365 (72)</td>
<td>&lt;1 $\times$ 10^{-30}</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>Chronic Disease, n (%)</td>
<td>4177 (28)</td>
<td>16,389 (34)</td>
<td>7508 (48)</td>
<td>3 $\times$ 10^{-28}</td>
<td>1 $\times$ 10^{-136}</td>
<td>.22</td>
</tr>
</tbody>
</table>

Baseline characteristics for participants in the Copenhagen General Population Study and the Copenhagen City Heart Study combined. CRP, C-reactive protein.

$p$-value for participants with versus without hospitalization with depression (Table S2B in Supplement 1).

$p$-trend across genotype combination (Table S3 in Supplement 1).

Not significant after Bonferroni correction for multiple tests.
of 1.01 to 3.00 mg/L and 1.77 (95% CI 1.37–2.27) for individuals with a CRP >3.00 mg/L, versus individuals with a CRP ≤1.00 mg/L (Figure 1). The corresponding ORs were 1.17 (95% CI 1.08–1.28) and 1.56 (95% CI 1.42–1.71) for prescription antidepressant use, 1.46 (95% CI 1.30–1.64), 2.17 (95% CI 1.92–2.45) for self-reported antidepressant use, 1.20 (95% CI 1.12–1.28) and 1.97 (95% CI 1.84–2.12) for not accomplishing, and 1.23 (95% CI 1.10–1.38) and 1.91 (1.70–2.14) for wanting to give up. Risk estimates were attenuated when adjusted multifactorially. When we stratified analyses based on gender and menopausal status, results were similar but most pronounced in postmenopausal women (Figures S2–S4 in Supplement 1).

**CRP Polymorphisms and Plasma CRP**

For CRP polymorphism rs1205, the GG versus AA genotype was associated with 29% higher CRP levels (p trend = 2 × 10^{-15}; Figure S5 in Supplement 1). Similarly, the rs3093077 GG versus TT genotype was associated with 36% higher CRP levels (p trend = 5 × 10^{-9}), the rs1130864 TT versus CC genotype was associated with 25% higher CRP levels (p trend = 1 × 10^{-9}), and the rs3091244 AT versus CC genotype was associated with 44% higher CRP levels (p trend = 5 × 10^{-177}). When all genotypes were combined, there was a 54% increase in CRP from the lowest to the highest levels among the nine most common genotype combinations (p trend = 1 × 10^{-208}).

**CRP Polymorphisms, Depression, and Psychological Distress: Theoretically Predicted Versus Observed Risk**

For the genotype combinations resulting in increased CRP, there was an increased theoretically predicted risk of hospitalization or death with depression (Figure 2). For the genotype combination resulting in the highest CRP, there was an age- and gender-adjusted OR of 1.12 (95% CI 1.09–1.15) compared with the genotype combination resulting in the lowest CRP. Corresponding ORs were 1.07 (95% CI 1.06–1.08) for prescription antidepressant use, 1.17 (1.10–1.24) for prescription antidepressant use, 1.56 (1.42–1.71) for self-reported antidepressant use, 2.17 (1.92–2.45) for not accomplishing, 1.91 (1.70–2.14) for wanting to give up, 1.25 (1.05–1.45) for not accomplishing, and 1.31 (1.11–1.55) for wanting to give up.

**Figure 1.** Association between C-reactive protein (CRP) categories and depression and psychological distress in the general population, based on 78,809 participants from the Copenhagen General Population Study and Copenhagen City Heart Study combined. Not all participants answered questions concerning psychological distress or use of antidepressant medication; therefore, numbers vary slightly. Multifactorially adjusted for age, gender, smoking, alcohol consumption, physical activity, education, income, body mass index, and chronic disease. CI, confidence interval; OR, odds ratio.

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1.11 (95% CI 1.09–1.12) for self-reported antidepressant use, 1.11 (95% CI 1.10–1.12) for not accomplishing, and 1.09 (95% CI 1.08–1.11) for wanting to give up.

For hospitalization or death with depression, calculation of observed risk yielded an unadjusted OR of 0.88 (95% CI 0.61–1.30) for the genotype combination resulting in the

![Diagram](image-url)

**Figure 2.** Theoretically predicted versus observed risk of depression and psychological distress as a function of C-reactive protein (CRP) genotype combinations, based on 76,479 participants with the nine most common genotype combinations from the Copenhagen General Population Study and Copenhagen City Heart Study combined. Not all participants answered questions concerning psychological distress or use of antidepressant medication; therefore, numbers vary slightly. Odds ratios (ORs) for theoretically predicted risk of depression and psychological distress were adjusted for age and gender. ORs for observed risk were unadjusted because genotypes do not associate with potential confounders (see Table S2 in Supplement 1). CI, confidence interval.
highest CRP compared with the genotype combination resulting in the lowest CRP (p trend across nine genotype combinations: .55; Figure 2). Correspondingly, ORs were .98 (95% CI 0.84–1.13) for prescription antidepressant use (p trend = .95), 1.01 (95% CI 0.84–1.23) for self-reported antidepressant use (p trend = .12), 1.06 (95% CI 0.95–1.19) for not accomplishing (p trend = .05), and 1.05 (95% CI 0.89–1.25) for wanting to give up (p trend = .55; Figure 2).
trend = .14), and .98 (95% CI .81–1.19) for wanting to give up (p trend = .53).

**CRP Polymorphisms, Depression, and Psychological Distress: Observed Versus Causal Risk**

For hospitalization or death with depression, the instrumental variable analysis yielded a causal OR of .79 (95% CI .51–1.22) for a doubling in CRP estimated from the combined genotype combinations, and the corresponding age- and gender-adjusted OR was 1.19 (95% CI 1.14–1.25; observed vs. causal estimate: p = .03; Figure 3). For prescription antidepressant use, the corresponding ORs were .98 (95% CI .83–1.15) and 1.11 (95% CI 1.09–1.13; p = .08), for self-reported antidepressant use 1.16 (95% CI .95–1.43) and 1.18 (95% CI 1.16–1.21; p = .61), for not accomplishing 1.09 (95% CI .96–1.23) and 1.18 (95% CI 1.16–1.19; p = .10), and for wanting to give up 1.02 (95% CI .83–1.26) and 1.16 (1.14–1.19; p = .28). When analyses were performed separately in men and women, results were similar (data not shown).

**CRP Polymorphisms, Depression, Major Somatic Diseases, and All-Cause Mortality: Observed Versus Causal Risk**

As mentioned earlier, the causal OR was .79 (95% CI .51–1.22) for hospitalization or death with depression, whereas the age- and gender-adjusted observed OR for a doubling in CRP levels was 1.19 (95% CI 1.14–1.25; observed vs. causal estimate: p = .03; Figure 4). For cancer, the corresponding ORs were .94 (95% CI .81–1.08) and 1.06 (1.04–1.08; p = .002), for ischemic heart disease .87 (95% CI .73–1.04) and 1.20 (95% CI 1.18–1.22; p = 4 × 10^{-9}), for chronic obstructive pulmonary disease .87 (95% CI .69–1.11) and 1.40 (95% CI 1.37–1.43; p = 6 × 10^{-86}), and for all-cause mortality 1.08 (95% CI .86–1.34) and 1.41 (95% CI 1.38–1.44; p = .001).

**Discussion**

The main findings of this study of 78,809 individuals from the Danish general population are that elevated plasma CRP is associated with increased risk of depression and psychological distress, whereas genetically elevated CRP is not. This suggests that CRP per se is not causally associated with depression or psychological distress, and underlying inflammation possibly due to other diseases is a more plausible explanation for this association, which could also be explained by depression causing elevated CRP.

Only few other studies have examined the association between CRP polymorphisms and depression, and all results support the hypothesis that CRP is not causally related to depression. Almeida et al. examined the associations between depression and the CRP polymorphisms rs1130864 and rs1205 in 3700 men aged 70 years and older (30). Similar to our study, they found that the TT genotype of rs1130864 was associated with increased CRP levels but not with presence of depression. They even found that participants with the CRP-lowering AA genotype of rs1205 had increased risk of depression, but given the present results, this could simply be a chance finding. In another study, Halder et al. examined the CRP polymorphisms rs1417938, rs1800947, and rs1205 in 868 healthy subjects (31) and generated a three-locus haplotype (T-G-C), which was associated with elevated CRP levels. Similar to our results, neither the polymorphisms nor the TGC-haplotype were associated with depressive symptoms. Compared with our study, these studies did not find an independent significant association between elevated CRP levels and depression after multifactorial adjustment, but both studies included much fewer participants than the present study.

The lack of a causal association between elevated CRP levels and depression in our study suggests that the association might be caused by unresolved confounding or reverse causation, the latter being that depression might increase CRP levels. A possible unmeasured confounder in our study could be elevated pro-inflammatory cytokines, especially interleukin-6 (IL-6), which is the main inducer of hepatic CRP production (32). IL-6 has been associated with depression in both cross-sectional (33) and prospective studies (33), and it is therefore possible that elevated IL-6 may cause both elevated CRP levels and increased risk of depression. However, two prospective studies have shown that depression predicted future elevated IL-6 levels, but not vice versa (34,35). These results therefore suggest that the association between CRP and depression could be due to reverse causation: depression could lead to elevated IL-6, which in turn could lead to elevated CRP. Another possible explanation for the association between elevated CRP and depression and psychological distress not being caused by elevated CRP per se could be underlying inflammation due to other diseases. Thus, many chronic diseases including cancer, ischemic heart disease, and chronic obstructive pulmonary disease, clinically recognized or not, lead to slightly elevated CRP levels (36), like those associated with depression and psychological distress in the present study. In favor of this
idea, we found that for a doubling in CRP were associated with observed risk increases for depression, cancer, ischemic heart disease, chronic obstructive pulmonary disease, and all-cause mortality alike, whereas genetically elevated CRP levels were associated with neither end point.

Another alternative explanation for the current findings is high clinical heterogeneity of depression, which hinders efforts to identify the biological and genetic underpinnings of depression. This means that the link between depression and inflammation may be more relevant for specific groups of people with depression. A growing body of evidence suggests that inflammation appears to be more specific to the atypical depression subtype (37) and a meta-analysis by Howren et al. indicated that although the role of gender differences is not entirely clear, CRP and depression were more strongly related in men than women (6). Furthermore, a study by Liukkonen et al. suggested that in women, the association between CRP and depressive symptoms is only present in postmenopausal women, not in premenopausal women (38). However, when we stratified analyses for gender and menopause status, results were similar. Finally, a recent twin study by Kendler et al. (39) suggested that the underlying genetic variants may differ from for early-life depression (associated with a higher genetic risk of depression in the other twin) versus late-life depression (associated with a higher genetic risk of cardiovascular disease in the other twin); the shared vulnerability between depression and somatic diseases in late life could be due to genes that affect biological pathways such as inflammation.

The strengths of this study should be noted. First, we studied a large sample from the general population. Second, we had no losses to follow-up during up to 20 years of follow-up. Third, we had information on all prescriptions of antidepressant medication including type, dosage, and duration, which allowed us to select participants with a continuous use of antidepressant medication for at least 6 months, the recommended treatment duration of a depressive episode (40). Fourth, we had >99.8% complete data on each of the CRP polymorphisms, and all genotypes were in Hardy-Weinberg equilibrium. This indicates that there is no selective pressure for or against any of the genotypes. Furthermore, all polymorphisms were well qualified as instruments in a Mendelian randomisation analysis (F statistics to evaluate the strength of the instruments were 113–309 for all polymorphisms and genotype combinations, where $F > 10$ indicates sufficient strength) (7). Finally, we also had register-based information on cancer, ischemic heart disease, chronic obstructive pulmonary disease, and all-cause mortality, which meant that we could compare the association between CRP and depression to the association between CRP and these end points within the same individuals.

Potential limitations of this study include that we did not have a validated diagnostic scoring scale for psychological distress and depression. For hospitalization with depression, we included discharge diagnoses from both somatic and psychiatric hospitals. These diagnoses are made by different clinicians throughout Denmark and have a high validity (the diagnosis of a single depressive episode was confirmed in 75.4% of patients) (41,42). However, somatic disease is an important confounder because hospitalization with depression is more likely to occur in individuals with somatic disease and because individuals with somatic disease are more likely to be hospitalized in a somatic hospital and thus receive a diagnosis of depression. Finally, using hospital discharge diagnoses might have underestimated the number of individuals with depression because most people with depression in Denmark are treated in general practice or by private psychiatrists. As a consequence, we used self-reported and prescription antidepressant medication in an attempt to include these participants. Potential limitations for these end points are that antidepressants are being prescribed for a plethora of conditions, including treatment of depression, anxiety and anxiety disorders, pain disorders, obsessive-compulsive disorder, bulimia nervosa, and smoking cessation. A study of 13,835 patients with prescription antidepressant medication showed that 46% received antidepressant medication for depression, and another 17% for anxiety disorders (43). Accordingly, in an attempt to exclude participants with symptoms that were not severe enough to reach the criteria for a diagnosis of depression or participants treated for conditions other than depression, we chose only to include participants who had purchased antidepressants for at least 6 months, the recommended duration of continued treatment after clinical recovery (40). Another potential limitation of our study is that we studied white subjects only, and therefore our results may not necessarily apply to other races; however, we are not aware of data to suggest that results like ours should not be applicable to all races and in most countries. Furthermore, the Mendelian randomization approach has some limitations. Mendelian randomization can be influenced by linkage disequilibrium, pleiotropy of CRP SNPs that influence other biomarkers, gene–gene interactions (false-negative conclusions due to failure to account for a second gene that modifies CRP levels), and canalization (compensatory changes in other systems counterbalance genetic elevations and CRP levels) (7). This means that although the present data are not in favor of a causal association based on the relatively small changes associated with various CRP polymorphisms, it also cannot be completely excluded.

In conclusion, we found that elevated levels of CRP were associated with increased risk of depression and psychological distress in 78,809 individuals from the general population, but genetically elevated CRP levels were not. This indicates that CRP per se is not a causal risk factor for depression and psychological distress. Future studies are needed to determine the direction of the associations among CRP, inflammation, and depression, and whether underlying inflammation possibly due to other diseases is a more plausible explanation for this association. Furthermore, initiation of intervention studies might determine whether adding anti-inflammatory medication to antidepressant medication for treatment of depression will improve outcome.

This study was supported by Herlev Hospital, Copenhagen University Hospital and The Danish Council for Independent Research, Medical Sciences.

We thank the participants and staff of the Copenhagen General Population Study and the Copenhagen City Heart Study for their important contributions.

The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2013.10.009.

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