ORIGINAL ARTICLE

Elevated C-Reactive Protein Levels, Psychological Distress, and Depression in 73 131 Individuals

Marie Kim Wium-Andersen, MD; David Dynnes Ørsted, MD; Sune Fallgaard Nielsen, MScEE, PhD; Børge Grønne Nordestgaard, MD, DMSc

Context: The pathogenesis of depression is not fully understood, but studies suggest that low-grade systemic inflammation contributes to the development of depression.

Objective: To test whether elevated plasma levels of C-reactive protein (CRP) are associated with psychological distress and depression.

Design: We performed cross-sectional and prospective analyses of CRP levels in 4 clinically relevant categories using data from 2 general population studies.

Setting: The Copenhagen General Population and the Copenhagen City Heart studies.

Participants: We examined 73 131 men and women aged 20 to 100 years.

Main Outcome Measures: We ascertained psychological distress with 2 single-item self-reports and depression using self-reported antidepressant use, register-based prescription of antidepressants, and register-based hospitalization with depression.

Results: In cross-sectional analyses, increasing CRP levels were associated with increasing risk for psychological distress and depression ($P=3\times10^{-8}$ to $P=4\times10^{-105}$ for trend). For self-reported use of antidepressants, the odds ratio was 1.38 (95% CI, 1.23-1.55) for CRP levels of 1.01 to 3.00 mg/L, 2.02 (1.77-2.30) for 3.01 to 10.00 mg/L, and 2.70 (2.25-3.25) for greater than 10.00 mg/L compared with 0.01 to 1.00 mg/L. For prescription of antidepressants, the corresponding odds ratios were 1.08 (95% CI, 0.99-1.17), 1.47 (1.33-1.62), and 1.77 (1.52-2.05), respectively; for hospitalization with depression, 1.30 (1.01-1.67), 1.84 (1.39-2.43), and 2.27 (1.54-3.32), respectively. In prospective analyses, increasing CRP levels were also associated with increasing risk for hospitalization with depression ($P=4\times10^{-8}$ for trend).

Conclusions: Elevated levels of CRP are associated with increased risk for psychological distress and depression in the general population.

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Author Affiliations:
Department of Clinical Biochemistry and Copenhagen General Population Study, Herlev Hospital (Drs Wium-Andersen, Ørsted, Nielsen, and Nordestgaard), and Copenhagen City Heart Study, Bispebjerg Hospital (Dr Nordestgaard), Copenhagen University Hospital, and Faculty of Health and Medical Sciences, University of Copenhagen (Drs Wium-Andersen, Ørsted, Nielsen, and Nordestgaard), Copenhagen, Denmark.

DEPRESSION IS ONE OF THE leading contributors to the global burden of disease and the leading cause of disability measured by years lived with disability.[1] Although the pathogenesis still is not fully understood, previous studies suggest that low-grade systemic inflammation may contribute to the development of depression.[2,3]

C-reactive protein (CRP) is a commonly used marker of inflammatory disease when CRP levels exceed 10 mg/L.[4,5] When used to study low-grade inflammation and future risk for disease, CRP levels are measured with a high-sensitivity assay. Elevated CRP levels have been associated with psychological distress and depression,[6,7] but results are conflicting.[8-11] Cross-sectional population studies with 5000 to 7000 participants have reported an association between CRP levels and depression.[12-14] However, in a cross-sectional population-based study including 9300 participants, the association disappeared when estimates were adjusted for confounding factors, such as chronic illness and body mass index (BMI).[15] This finding is supported by other studies,[9,11] including a population-based study with 5500 participants.[8] In longitudinal studies, a positive association between CRP and depression has been reported by some[6,16] but not all[10,17] studies. One population-based study with 8100 individuals showed an association between self-reported use of antidepressants and elevated CRP levels.[18] Thus, researchers are unclear whether and to what extent elevated CRP levels are associated with psychological distress and depression in the general population.

We tested the hypothesis that elevated CRP levels are associated with symptoms of psychological distress and depression in the general population. For this purpose, we measured CRP levels in 73 131 individuals from 2 independent general population studies and examined the association between CRP levels stratified into 4 clinically relevant categories and symptoms of psychological distress and 3 categories of depression, correcting results for regression dilution bias. To reduce the influence from confounding, we adjusted our analyses for age, sex, alcohol intake, smoking, physical activity, annual income, educational level, BMI, and register-based chronic disease.

METHODS

PARTICIPANTS

We combined 2 independent prospective population-based studies, the Copenhagen General Population Study and the Copenhagen City Heart Study. Participants in both studies were randomly selected from the Danish Central Person Register to represent the general population. From the Copenhagen General Population Study, an ongoing study started in 2003, we included the first 63 083 individuals, that is, all with a CRP value available at the time of the present study.[19] From the Copenhagen City Heart Study, we included 10 048 individuals from the examinations from 1991 through 1994 and 2001 through 2003,[19,20] that is, all individuals with a CRP value available. All participants were aged 20 to 100 years, white, and of Danish descent (ie, the Danish Central Person Register showed that the participant and both parents were born in Denmark and were all Danish citizens) to ensure homogeneity of the study population. For participants in more than 1 study, we included only CRP values and questionnaire information from the first visit. On the day of attendance, participants completed a questionnaire, underwent a physical examination, and had blood samples drawn for biochemical analysis. The study was approved by Herlev Hospital and a Danish ethical committee (100.2039/91 and H-KF-01-144/01). Written consent was obtained from all participants.

MEASUREMENT OF CRP LEVELS

Plasma levels of CRP were measured at the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, with a high-sensitivity assay using latex-enhanced turbidimetry (DAKO) with a biochemical analyzer (Konelab 60i; Thermo Scientific) or latex-enhanced nephelometry on a protein analyzer (BN II; Dade Behring). Measurements of CRP were included in daily internal quality-control programs for assessment of imprecision (the coefficient of variation was 6%-7% at a level of 2.00 mg/L) and a monthly external quality-control program for assessment of accuracy using an external control (UK NEQAS).

PSYCHOLOGICAL DISTRESS

We used the following 2 questions to elicit symptoms of psychological distress possibly related to depression: "Do you have the feeling that you have not accomplished very much recently?" (yes or no) and "Do you feel like giving up?" (yes or no). We included the following parallel question less likely to be related to depression as a possible negative control: "Do you often feel nervous or stressed?" (yes or no). These questions were the only such measures available for all participants and were not part of a diagnostic scoring scale.

DEPRESSION

We ascertained depression using 3 methods. First, we used self-reported use of antidepressants as a confirmative answer to the question, "Do you daily (or most days) use antidepressants, sedatives, or relaxing pills?" (not including sleeping pills or pain-relieving medication).

Second, we obtained information on antidepressant prescriptions from the Danish Register of Medicinal Product Statistics, covering every prescription of antidepressants from all Danish pharmacies claimed by study participants from 1994 through 2009; in Denmark, antidepressants can be obtained by prescription only. We used Anatomical Therapeutic Chemical codes[21] for selective serotonin reuptake inhibitors (SSRIs; N06AB), tricyclic antidepressants (TCAs; N06AA), and a single category that included noradrenaline reuptake inhibitors (NARIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs; N06AX). We chose to include only the participants who at some point in their life had purchased prescription antidepressants for a period of at least 6 months, with an average daily dose of at least 0.75 of a standard World Health Organization–defined daily dose.[21]

Third, we obtained information from the Danish Patient Registry on hospital discharge diagnoses of depression on all participants. Depression was classified according to codes 296.0, 296.2, 298.0, and 300.4 from the *International Classification of Diseases, Eighth Revision,*[22] until 1994 and codes F32 and F33 from the *International Statistical Classification of Diseases, 10th Revision*,[23] from 1994 through 2010.

COVARIATES

All participants in both studies completed a questionnaire, which was reviewed by an investigator on the day of attendance.[24] Covariates were categorized for statistical adjustment on alcohol consumption (0, 0-84, 84-168, and >168 g/wk), leisure-time physical activity (0-2 h/wk of moderate activity, 2-4 h/wk of moderate activity, >4 h/wk of moderate or 2-4 h/wk of vigorous activity, or >4 h/wk of vigorous activity), income (low, middle, or high), level of education (no education, education of less than 13 years, basic vocational training of 1-3 years, higher education of ≤3 years, or university education), and self-reported chronic disease (yes or no). Body mass index was measured as weight in kilograms divided by height in meters squared (categorized as <18.5, 18.5-24.9, 25-29.9, or ≥30.0). Smoking was measured on a continuous scale as the number of cigarettes per day. Register-based chronic disease was ascertained by collecting information from the Danish Patient Registry on ischemic heart disease, myocardial infarction, stroke, diabetes mellitus, cancer, pneumonia, chronic obstructive pulmonary disease, asthma, deep venous thrombosis, and pulmonary embolism.

STUDY DESIGN AND STATISTICAL ANALYSIS

We performed all analyses using commercially available software (STATA, version 11.1; StataCorp).We stratified CRP levels a priori into 4 clinically relevant categories (≤1.00, 1.01-3.00, 3.01-10.00, and >10.00 mg/L)[25]; for trend tests, these categories were assigned the values of 1, 2, 3, and 4, respectively. When median values of each category were used for trend tests, results were similar.

First, we tested the association between elevated CRP levels using the clinical categories and end points of psychologi-

cal distress (feeling of not accomplishing much and wanting to give up) and depression (self-reported antidepressant use, prescription for antidepressants, and hospitalization with depression) cross-sectionally in the entire study population. We used multifactorially adjusted logistic regression models to calculate odds ratios (ORs) with 95% confidence intervals and used 3 different models of adjustment. In model 1 (baseline), we adjusted for age and sex. In model 2, we adjusted for age, sex, alcohol consumption, cigarette smoking, income, level of education, and leisure-time physical activity (multiple factors) because these factors are well-known risk factors for psychological distress and depression and/or may influence CRP levels. In model 3, we adjusted for age and sex with the covariates that previously were shown to confound the association between elevated CRP levels and depression, that is, BMI and register-based chronic disease.[8,9]

Second, we tested the association between elevated CRP levels using clinical categories and hospitalization with depression prospectively in the entire study population. We used a Cox proportional hazards regression model with age as the underlying time scale to calculate hazard ratios with 95% confidence intervals. Participants with previous or current depression at baseline were excluded. Follow-up began at blood sampling, and participants were censored at hospitalization with depression (n=610), death (n=5728), emigration (n=339), or the end of follow-up in August 2010, whichever came first. Multifactorial Cox models were adjusted similarly to the logistic regression models. We tested the assumption of proportional hazards graphically by plotting −log(−log[survival]) vs log (age). Suspicion of nonparallel lines was tested using Schoenfeld residuals. We detected no major violations of the proportional hazards assumption. Furthermore, we calculated Kaplan-Meier cumulative incidence of hospitalization with depression as a function of age and used log-rank tests for trend to examine whether an increase in CRP category was associated with increased cumulative incidence of depression.

Third, we used logarithmically transformed CRP values on a continuous scale to examine the association between a doubling of CRP levels and each of the end points, including not accomplishing much, wanting to give up, feeling nervous or stressed, self-reported antidepressant use, prescription for antidepressants (all, SSRIs, TCAs, and a remainder group combining SNRIs, NARIs, and NaSSAs), and hospitalization with depression.

Fourth, in sensitivity analyses, we stratified for use of antidepressants (self-reported and/or prescription) and then repeated the analyses. In further sensitivity analyses, we examined the association between CRP levels and hospitalization with depression only in a psychiatric hospital. In additional sensitivity analyses, we adjusted for self-reported chronic disease and repeated the analyses. Also, we examined cross-sectional associations between CRP levels and SSRIs, TCAs, and the combined group of SNRIs, NARIs, and NaSSAs. We adjusted for the combined symptoms of psychological distress and further repeated the cross-sectional analyses of the 3 depression end points. Finally, we used logarithmically transformed CRP values on a continuous scale to examine the association between elevated CRP levels and the following 3 different groups of end points aimed at maximizing statistical power: (1) responses to questions of wanting to give up and not accomplishing much, (2) use of antidepressants (self-reported and/or prescription) and hospitalization with depression, and (3) a combination of all these end points. For these analyses, we calculated ORs for a doubling of CRP levels stratified on potential confounding variables. Each stratum was adjusted for all other variables than the one stratified. We tested for interaction using a likelihood ratio test by introducing a 2-factor interaction term (CRP level × stratifying covariate) in the model including all covariates except the one stratified.

Because 4317 individuals had participated in the 1991-1994 and 2001-2003 examinations of the Copenhagen City Heart Study and had CRP levels measured 10 years apart, we were able to calculate a regression dilution ratio of 0.82 using a nonparametric method (eTable; http://www.jamapsych.com). This ratio was used to correct ORs and 95% confidence intervals for regression dilution bias to reduce the effect of regression toward the mean, which might otherwise have led to an underestimation of risk estimates. Regression dilution bias is a measurement bias caused by the dilution/attenuation of the regression coefficient that occurs when a single measured value of a covariate is used rather than the average value from a series of measurements.[26]

We had 98% complete data on alcohol consumption, smoking status, leisure-time physical activity, annual income, level of education, and BMI. All missing values were imputed on the basis of age and sex before multivariable adjustment using multivariable regression for continuous variables and ordered logistic regression for ordinal variables.[27]

RESULTS

Baseline characteristics of the 73 131 participants from the combined studies by plasma levels of CRP are listed in the **Table**.[28] For the end points of psychological distress, 15 466 participants (21.15%) felt that they had not accomplished much recently and 4714 (6.45%) wanted to give up; we used the 16 118 participants (22.04%) who often felt nervous or stressed as a negative control. For the depression end points, 4818 participants (6.59%) reported daily or almost daily use of antidepressants, sedatives, or pills to relax (not including sleeping pills or analgesics), 8326 (11.39%) had purchased prescription antidepressants for a period of at least 6 months, and 1015 (1.39%) had at least 1 hospitalization with depression. Overlap between the different end points is shown in eFigure 1. For the prospective analysis, we had 19 and 5 years of maximal and average follow-up, respectively, and a total of 354 191 person-years. The mean time from baseline to a diagnosis of depression was 6.7 (range, 0.03-18.0) years.

PSYCHOLOGICAL DISTRESS

In cross-sectional analyses, increasing CRP levels were associated with increasing risk for the self-reported symptoms of psychological distress of not accomplishing much ($P = 4 \times 10^{-105}$ for trend) and wanting to give up ($P = 7 \times 10^{-37}$ for trend) but not for feeling nervous or stressed ($P = .51$ for trend) (**Figure 1**).

For not accomplishing much, the age- and sex-adjusted ORs were 1.11 (95% CI, 1.04-1.18) for a plasma CRP level of 1.01 to 3.00 mg/L, 1.80 (1.67-1.94) for 3.01 to 10.00 mg/L, and 2.61 (2.33-2.93) for greater than 10.00 mg/L compared with 0.01 to 1.00 mg/L (Figure 1). Similarly, for wanting to give up, the corresponding ORs were 1.14 (95% CI, 1.02-1.26), 1.79 (1.59-2.02), and 2.30 (1.92-2.74), respectively. Conversely, the corresponding ORs for feeling nervous or stressed were 0.90 (95% CI, 0.85-0.96), 1.00 (0.93-1.08), and 1.02 (0.90-1.17), respectively. Risk estimates for not accomplishing much or for wanting to give up were slightly attenuated when adjusted for multiple factors or for BMI and register-based chronic disease (Figure 1).

Table. Baseline Characteristics of 73 131 Individuals From the General Population

	CRP Level, mg/L[a]					
	≤1.00 (n = 12 098)	1.01-3.00 (n = 45 947)	3.01-10.00 (n = 12 446)	>10.00 (n = 2640)	*P* Value for Trend[b]	z Value
Mean age, y	53	57	60	61	$<1 \times 10^{-300}$	40.2
Female sex	6436 (53.20)	25 423 (55.33)	7253 (58.28)	1497 (56.70)	1×10^{-13}	7.4
Alcohol consumption >84 g/wk	4140 (34.22)	16 532 (35.98)	3898 (31.32)	822 (31.14)	9×10^{-13}	7.2
Smoking, mean No. of cigarettes/d	2.8	3.2	5.3	5.3	3×10^{-141}	25.3
Educational level <13 y	6853 (56.65)	26 278 (57.19)	8870 (71.27)	1880 (71.21)	5×10^{-163}	27.2
Low income	1810 (14.96)	7340 (15.97)	3407 (27.37)	866 (32.80)	2×10^{-226}	32.1
Low leisure-time physical activity level[c]	5579 (46.12)	23 210 (50.51)	7836 (62.96)	1758 (66.59)	3×10^{-213}	31.2
BMI >25.0	4525 (37.40)	25 191 (54.83)	8951 (71.92)	1815 (68.75)	$<1 \times 10^{-300}$	53.4
Register-based chronic disease	3225 (26.66)	14 272 (31.06)	5353 (43.01)	1353 (51.25)	5×10^{-252}	33.0

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein.
[a] Indicates baseline characteristics for participants in the Copenhagen General Population and the Copenhagen City Heart studies. Unless otherwise indicated, data are expressed as number (percentage) of patients.
[b] Calculated by Cuzick's extension of the Wilcoxon rank sum test.[28]
[c] Indicates inactive or less than 2 to 4 h/wk of moderate physical activity.

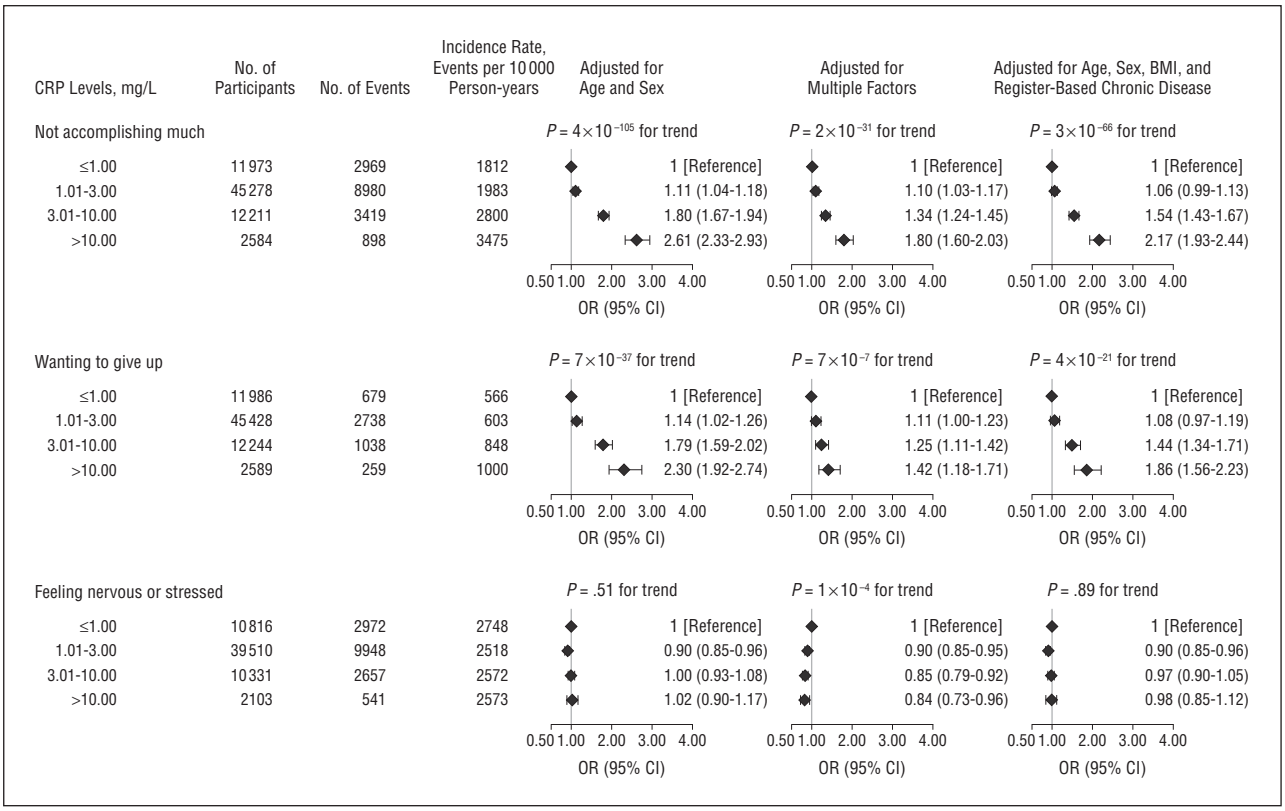

Figure 1. Cross-sectional analyses of the association between self-reported symptoms of psychological distress and levels of C-reactive protein (CRP) in the general population. Findings are based on 73 131 participants from the Copenhagen General Population and Copenhagen City Heart studies combined. Not all participants answered questions concerning psychological distress; therefore, numbers may vary slightly. The question of feeling nervous or stressed was available only for the participants in the Copenhagen General Population Study and was used as a negative control. Multiple factors included age, sex, smoking, alcohol consumption, physical activity, educational level, and annual income. BMI indicates body mass index; OR, odds ratio.

USE OF ANTIDEPRESSANTS

In cross-sectional analyses, increasing CRP levels were associated with increasing risk for self-reported use of antidepressants ($P = 6 \times 10^{-42}$ for trend) and for use of prescription antidepressants for at least 6 months ($P = 2 \times 10^{-25}$ for trend) (**Figure 2**).

For self-reported use of antidepressants, the age- and sex-adjusted ORs were 1.38 (95% CI, 1.23-1.55) for a plasma CRP level of 1.01 to 3.00 mg/L, 2.02 (1.77-2.30) for 3.01 to 10.00 mg/L, and 2.70 (2.25-3.25) for greater than 10.00 mg/L compared with 0.01 to 1.00 mg/L (Figure 2). For use of prescription antidepressants, the corresponding ORs were 1.08 (95% CI, 0.99-1.17), 1.47

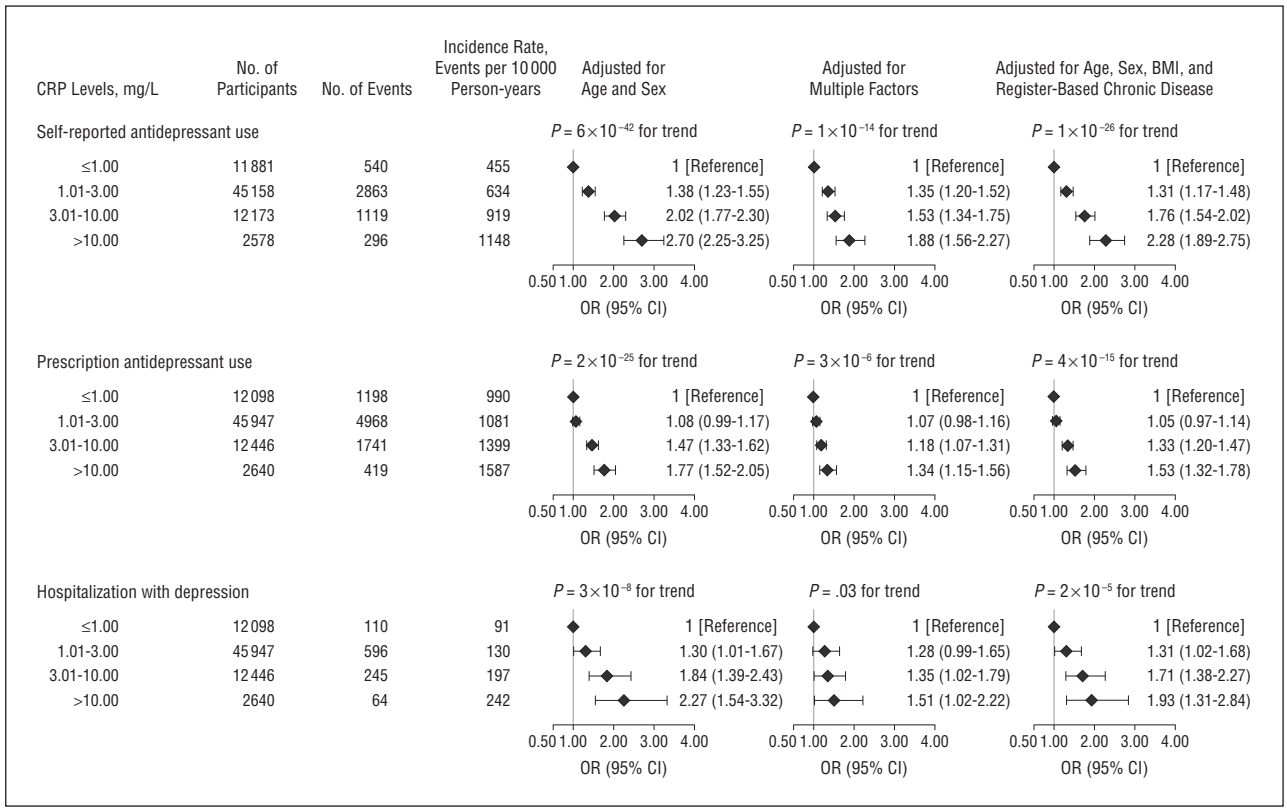

Figure 2. Cross-sectional analyses of the associations between self-reported use of antidepressants, prescription of antidepressants, and hospitalization with depression and C-reactive protein (CRP) levels in the general population. Findings are based on 73 131 participants from the Copenhagen General Population and Copenhagen City Heart studies combined. Not all participants answered questions concerning self-reported use of antidepressants; therefore, numbers may vary slightly. Multiple factors included age, sex, smoking, alcohol consumption, physical activity, educational level, and income. BMI indicates body mass index; OR, odds ratio.

(1.33-1.62), and 1.77 (1.52-2.05), respectively. These risk estimates were slightly attenuated when adjusted for multiple factors or for BMI and register-based chronic disease (Figure 2).

HOSPITALIZATION WITH DEPRESSION

In cross-sectional analyses, increasing CRP levels were associated with an increasing risk for hospitalization with depression ($P = 3 \times 10^{-8}$ for trend) (Figure 2). The ORs were 1.30 (95% CI, 1.01-1.67) for a plasma CRP level of 1.01 to 3.00 mg/L, 1.84 (1.39-2.43) for 3.01 to 10.00 mg/L, and 2.27 (1.54-3.32) for greater than 10.00 mg/L compared with 0.01 to 1.00 mg/L. These risk estimates were slightly attenuated when adjusted for multiple factors or for BMI and register-based chronic disease (Figure 2).

In prospective analyses, the cumulative incidence of hospitalization with depression increased with an increase in CRP levels (log-rank $P = 4 \times 10^{-8}$ for trend) (**Figure 3**). The age- and sex-adjusted hazard ratios were 1.04 (95% CI, 0.76-1.43) for a plasma CRP level of 1.01 to 3.00 mg/L, 1.34 (0.94-1.90) for 3.01 to 10.00 mg/L, and 1.51 (0.92-2.48) for greater than 10.00 mg/L compared with 0.01 to 1.00 mg/L. These risk estimates were slightly attenuated when adjusted for the multiple factors or for BMI and register-based chronic disease.

CRP ON A CONTINUOUS SCALE

When CRP levels were on a continuous scale, a doubling in CRP level was associated with ORs of 1.13 (95% CI, 1.11-1.15) for not accomplishing much, 1.08 (1.05-1.12) for wanting to give up, and 0.98 (0.96-1.00) for feeling nervous or stressed, after adjusting for all covariates (**Figure 4**). Corresponding ORs were 1.13 (95% CI, 1.10-1.17) for self-reported antidepressant use, 1.06 (1.04-1.08) for prescription antidepressant use, 1.05 (1.02-1.08) for use of SSRIs, 1.17 (1.06-1.29) for use of TCAs, 1.06 (0.98-1.15) for use of SNRIs, NARIs, or NaSSAs, and 1.07 (1.01-1.14) for hospitalization with depression.

SENSITIVITY ANALYSIS

Stratifying for use of antidepressants (self-reported and prescription combined), we found an increased risk for the end points of not accomplishing much and wanting to give up and of hospitalization with depression in participants with and without use of antidepressants (eFigure 2).

Effect sizes of hospitalization with depression only in a psychiatric hospital (eFigure 3) were similar to effect sizes of hospitalization with depression using discharge diagnoses from somatic and psychiatric hospitals (Figure 2). Also, when adjusting for self-reported chronic disease (eFigure 4), results were similar to analyses using register-based chronic disease (Figures 1 and 2).

When use of prescription antidepressants was stratified on the type of antidepressant used, increasing CRP levels were associated with increasing risk for use of SSRIs ($P = 2 \times 10^{-19}$ for trend), TCAs ($P = 2 \times 10^{-8}$ for trend), and the combined category of SNRIs, NaSSAs, and NARIs ($P = .05$ for trend) (eFigure 5). For use of SSRIs, the age- and sex-adjusted ORs were 1.09 (95% CI, 0.99-1.21) for a plasma CRP level of 1.01 to 3.00 mg/L, 1.50 (1.34-1.69) for 3.01 to 10.00 mg/L, and 1.64 (1.37-1.97) for greater than 10.00 mg/L compared with 0.01-1.00 mg/L. For use of TCAs, the corresponding ORs were 1.57 (95% CI, 0.97-2.52), 2.25 (1.33-3.83), and 3.12 (1.54-6.33), respectively; for use of SNRIs, NaSSAs, and NARIs, 1.10 (0.82-1.47), 1.11 (0.78-1.58), and 1.67 (1.01-2.78), respectively. Risk estimates were slightly attenuated when adjusted for multiple factors or for BMI and register-based chronic disease.

Odds ratios for risk for depression (self-reported antidepressant use, prescription antidepressant use, and hospitalization with depression) were slightly attenuated when adjusted for psychological distress (eFigure 6 compared with Figure 2).

For CRP levels on a continuous scale, a doubling in CRP level was associated with an increased OR for not accomplishing much or wanting to give up pooled together, for use of antidepressants and/or hospitalization with depression combined, and for all end points combined (eFigure 7). This finding was true for all strata of potential confounders examined.

We did not exclude participants with a CRP level of greater than 10 mg/L potentially caused by an infection or chronic disease; instead, by using clinically relevant categories of CRP, these participants were in a separate group. Furthermore, if this group was excluded, the association between CRP and all end points remained (Figures 1 and 2).

	HR (95% CI)		
CRP, mg/L	Model 1	Model 2	Model 3
≤1.00	1 [Reference]	1 [Reference]	1 [Reference]
1.01-3.00	1.04 (0.76-1.46)	1.09 (0.79-1.49)	1.14 (0.83-1.56)
3.01-10.00	1.34 (0.94-1.90)	1.15 (0.81-1.64)	1.31 (0.92-1.87)
>10.00	1.51 (0.92-2.48)	1.21 (0.73-2.00)	1.36 (0.83-2.25)
P value for trend	.02	.36	.09

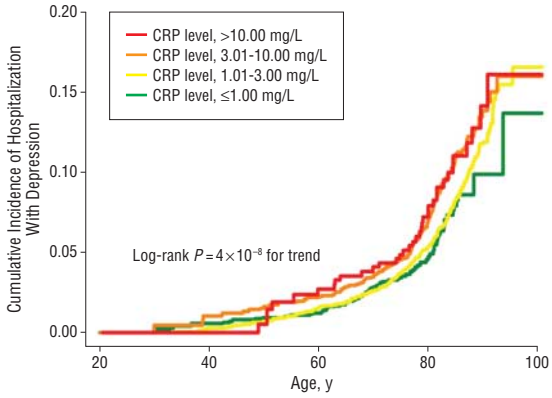

Figure 3. Prospective analyses of the cumulative incidence of hospitalization with depression as a function of age by levels of C-reactive protein (CRP) using Kaplan-Meier estimates. Findings are based on 72 700 participants from the Copenhagen General Population and the Copenhagen City Heart studies combined with CRP levels measured at baseline and observed for as long as 20 years. We excluded 431 participants with a hospitalization with depression before measurements of CRP levels. Hazard ratios (HRs) in model 1 were adjusted for age and sex; in model 2, for multiple factors including age, sex, smoking, alcohol consumption, physical activity, educational level, and income; and in model 3, for age, sex, body mass index, and register-based chronic disease.

COMMENT

The main finding of this study consisted of an association of elevated CRP levels with an increased risk for psychological distress and depression in the general population. This association was observed in 73 131 individuals in cross-sectional analyses and in prospective analyses for hospitalization with depression.

Our results are consistent with previous findings linking psychological distress and depression to elevated CRP levels.[6,7,13,14,29] Contrary to previous studies,[8,9,11,15] however, we did not find that the association disappeared when adjusting for BMI and chronic disease, a discrepancy that merits discussion. First, characteristics of previous cohorts[8,11] differ somewhat from those of the present study. Of equal importance, the ascertainment of depression has been different in all studies; for example, some studies have a proportion of cases up to 10% compared with 1.4% who were hospitalized with depression in our study. For both factors, a differential influence of confounding may contribute to the contradictory findings. In addition, some previous studies[8,9,11] had a smaller number of participants with depression compared with this one, which may have led to an underestimation of the association due to lack of statistical power. Conversely, other studies include a large number of participants with depression and have an age distribution similar to our study.[15] We cannot explain the differences in these studies compared with our findings. However, owing to the large number of participants and well-determined confounders, our results are unlikely to be chance findings.

The underlying mechanism between inflammation and depression is not fully understood. Systemic inflammation and psychological factors interact through complex pathophysiological and behavioral mechanisms. First, inflammation may lead to depression. Some studies indicate that proinflammatory cytokines might contribute to the development of depression by activation of the enzyme indoleamine-2,3-dioxygenase, an activation that leads to decreased production of serotonin and increased production of kynurenic and quinolinic acids.[2,3,30,31] In accordance, decreased serotonin levels are an important factor in the pathogenesis of depression, as observed in the effect of SSRIs in treating depressive symptoms. Also, increased production of kynurenic and quinolinic acids leads to increased release of glutamate and thereby to decreased production of trophic factors, including brain-derived neurotrophic factor, a factor associated with depression.[30,32] We measured only CRP levels, a marker of systemic inflammation that cannot cross

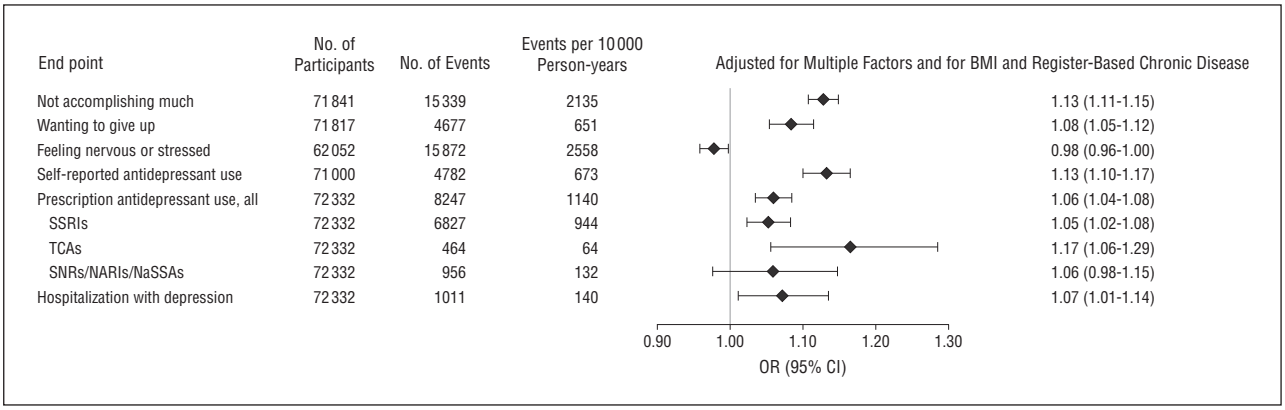

Figure 4. Cross-sectional analyses of the association between end points of psychological distress, hospitalization with depression, self-reported and prescription antidepressant use, and different types of antidepressants and doubled levels of C-reactive protein (CRP). Findings are based on 73 131 participants from the Copenhagen General Population and the Copenhagen City Heart studies combined. Multiple factors include age, sex, smoking, alcohol consumption, physical activity, educational level, income, body mass index (BMI), and register-based chronic disease. NARIs indicates noradrenaline reuptake inhibitors; NaSSAs, noradrenergic and specific serotonergic antidepressants; OR, odds ratio; SNRIs, serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; and TCAs, tricyclic antidepressants.

the blood-brain barrier; however, elevated CRP levels probably indicate elevated levels of cytokines, which can cross the blood-brain barrier.

Second, depression may also lead to inflammation. Psychological stress activates the hypothalamic-pituitary-adrenocortical axis and sympathetic nervous system, which releases stress hormones.[33] These hormones, together with cytokine release induced by stress, initiate the acute-phase response triggering inflammation. Furthermore, depression might lead to inflammation mediated by weight gain.[34] Expansion of adipose tissue increases synthesis of leptin, which in turn increases levels of the proinflammatory cytokine interleukin 6, stimulating the production of acute-phase proteins, including CRP.[35] Finally, the association might also be due to confounding; that is, elevated CRP levels and depression are caused by a third factor.

Levels of CRP ranging from 3.00 to 10.00 mg/L can be caused by chronic diseases, such as cardiovascular disease, metabolic syndrome, and cancer,[20,36] but minor increases in CRP levels have been associated with physical activity and other lifestyle factors, such as smoking.[36,37] In this study, we adjusted for chronic disease, including cardiovascular disease, diabetes mellitus, cancer, and lung diseases; for lifestyle covariates, including smoking; and for covariates for socioeconomic status. However, we cannot exclude the possibility of residual confounding completely. Our study did not assess acute infections at the time of the blood draw specifically because such infections can have a large influence on CRP levels. However, the participants of the present studies were from the general population and decided individually exactly which day they wished to attend the study and were thus unlikely to have major acute infections on the day of attendance.

Among the important strengths of our study, first is our evaluation of 73 131 individuals from the general population, whereas previous studies included 70 to 9300 participants.[6,15,38] Second, we had as long as 20 years of follow-up, whereas previous studies have no more than 12 years of follow-up.[6] Third, using the Danish Patient Registry and Danish Register of Medical Product Statistics, we had 100% complete data on all participants concerning hospitalization with depression and prescription antidepressant use. Fourth, the present study is the first to examine the association between CRP levels and use of antidepressants using very reliable register data; we had information on all prescriptions of antidepressants, including type, dosage, and duration, which allowed us to select patients with a continuous use of antidepressants for at least 6 months and to examine different antidepressants separately. Finally, we had CRP data from 1991 through 1994 and 2001 through 2003 on 4317 individuals, which meant we were able to correct our results for regression dilution bias, a feat not performed in any previous study; this process reduces the effect of regression toward the mean, which might otherwise have led to an underestimation of risk estimates.

Potential limitations of this study include that we did not have a validated diagnostic scoring scale for psychological distress and depression. Another potential limitation is that the questionnaire end points of psychological distress may not reflect depression in participants. Nonetheless, we did not find an association between CRP levels and the end point of feeling nervous or stressed, emotions not generally included among depressive symptoms. This negative finding adds credibility to the positive findings for psychological distress and depression. Furthermore, adjusting for psychological distress in sensitivity analyses did not eliminate the association between CRP and depression, which suggests that psychological distress cannot explain the association. For hospitalization with depression, potential limitations should also be considered. First, we did not have information on severity of depression because we included discharge diagnoses from somatic and psychiatric hospitals. However, hospital diagnoses of depression are clinical diagnoses made by physicians on the basis of standard criteria[22,23] and therefore are likely to be more valid than our questionnaire information. Second, hospitalization with depression is more likely to occur in participants who are smokers and/or have comorbidities. However, when we adjusted for chronic disease and smoking, risk estimates were only slightly attenuated. Finally, be-

cause most people with depression in Denmark are treated in general practice or by private psychiatrists,[39] our use of hospital discharge diagnoses might have underestimated the number of individuals with depression. As a consequence, we examined self-reported and prescription antidepressant use in an attempt to include these patients. Register data on prescription antidepressants may tend to overestimate the number of depressed individuals because antidepressants are used to treat patients with anxiety disorder, obsessive-compulsive disorder, and certain types of pain disorders. Previous studies suggest that some of these disorders may be associated with elevated CRP levels.[40,41] In addition, a large number of patients who begin therapy with antidepressants do not continue the treatment for the recommended 6 months.[42] Accordingly, in an attempt to exclude patients with symptoms that were not severe enough to reach the criteria for a diagnosis of depression or patients treated for conditions other than depression, we chose to include only patients who had purchased antidepressants for at least 6 months (ie, the recommended duration of continued treatment after clinical recovery).[43] Furthermore, for the register data on prescription antidepressants, we had information on the Anatomical Therapeutic Chemical codes for each antidepressant, and we found separate associations with CRP levels for SSRIs, TCAs, and a group combining SNRIs, NARIs, and NaSSAs. Nonetheless, including participants with any prescription of antidepressants showed similar results for participants with at least 6 months of use (data not shown). For self-reported use of antidepressants, this question also included sedatives and/or pills used to relax but not sleeping pills. Thus, someone affirming this item could be responding to something having little (or nothing) to do with the presence of depression. However, risk estimates were similar to risk estimates for use of prescription antidepressants. Another potential limitation of our study is that we limited our study to white participants; therefore, our results may not apply to other races. Finally, a potential limitation may be that this study is based mainly on cross-sectional analyses and, thus, cannot determine a causal association. However, the prospective analyses seemed to indicate that inflammation might increase the risk of future depression, even though risk estimates were not significant individually. Although each of our end points had potential limitations individually, these limitations varied from end point to end point and therefore are unlikely to explain our findings.

More research is needed to establish the direction of the association between CRP and depression because this study and others are primarily cross-sectional. The results also support the initiation of intervention studies to examine whether adding anti-inflammatory drugs to antidepressants for treatment of depression will improve outcome.

In conclusion, in 73 131 individuals from the general population, elevated levels of CRP were associated with an increased risk for psychological distress and depression in cross-sectional analyses and for hospitalization with depression in prospective analyses. For psychological distress, we found an association between CRP levels and the feeling of not having accomplished much and wanting to give up but not with feeling nervous or stressed. For depression, we found an association between register-based hospitalization with depression and self-reported and register-based use of antidepressants. Contrary to previous studies, these associations did not disappear when we adjusted for BMI or chronic disease.

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Correspondence: Børge Grønne Nordestgaard, MD, DMSc, Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark (Boerge.Nordestgaard@regionh.dk).
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