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Contributions of Depressive Mood and Circulating Inflammatory Markers to Coronary Heart Disease in Healthy European Men

The Prospective Epidemiological Study of Myocardial Infarction (PRIME)

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Background—Data on the possible association between depressive disorders and inflammatory markers are scarce and inconsistent. We investigated whether subjects with depressive mood had higher levels of a wide range of inflammatory markers involved in coronary heart disease (CHD) incidence and examined the contribution of these inflammatory markers and depressive mood to CHD outcome.

Methods and Results—We built a nested case-referent study within the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study of healthy middle-aged men from Belfast and France. We considered the baseline plasma sample from 335 future cases (angina pectoris, nonfatal myocardial infarction, coronary death) and 670 matched controls (2 controls per case). Depressive mood characterized men whose baseline depression score (13-item modification of the Welsh depression subscale) was in the fourth quartile (mean score, 5.75; range, 4 to 12). On average, men with depressive mood had 46%, 16%, and 10% higher C-reactive protein, interleukin-6, and intercellular adhesion molecule-1 levels, respectively, independently of case-control status, social characteristics, and classic cardiovascular risk factors; no statistical difference was found for fibrinogen. The odds ratios of depressive mood for CHD were 1.35 (95% CI, 1.05 to 1.73) in univariate analysis and 1.50 (95% CI, 1.04 to 2.15) after adjustment for social characteristics and classic cardiovascular risk factors. The latter odds ratio remained unchanged when each inflammatory marker was added separately, and in this analysis, each inflammatory marker contributed significantly to CHD event risk.

Conclusions—These data support an association of depressive mood with inflammatory markers and suggest that depressive mood is related to CHD even after adjustment for these inflammatory markers. (*Circulation*. 2005;111:2299-2305.)

Key Words: coronary disease ■ depressive disorder ■ epidemiology ■ inflammation ■ risk factors

Several observational studies have reported that negative emotions such as major or clinical depression and depressive symptoms are risk factors for coronary heart disease (CHD) in the general population.¹⁻⁷ However, the mechanisms underlying this association are mostly unknown. The contribution of inflammation to the origin of CHD has been investigated, and prospective studies have shown that levels of interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen,

and adhesion cellular molecule (ICAM-1) are predictive of CHD in healthy populations.⁸⁻¹³ Additionally, some cross-sectional studies have shown that subjects with clinical or major depression, and possibly depressive symptoms, have higher levels of circulating inflammatory markers, including IL-6, CRP, and fibrinogen.¹⁴⁻¹⁸ Thus, the hypothesis was raised that inflammation might partially mediate the relationship between depressive disorders and CHD. Nonetheless,

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*The online-only Data Supplement, which contains a list organizations that contributed to PRIME, can be found with this article at <http://www.circulationaha.org>.

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evidence supporting the association of depressive disorders with inflammatory markers is weak. Although 3 studies on major and clinical depression have reported consistent results,^{14–16} 5 studies on depressive symptoms have provided mixed results.^{17–21} These studies have focused mostly on a single inflammatory marker, and none, including those on clinical and major depression, has investigated the possible association with adhesion cellular molecules such as ICAM-1. This is important because recent data suggest that major depression is associated with endothelial dysfunction.^{22,23} Such studies, however, have all been cross-sectional and thus have been unable to assess prospectively the extent to which inflammatory markers contribute to the association of depressive disorders with CHD.

Using data from the Prospective Epidemiological Study of Myocardial Infarction (PRIME),²⁴ which is prospectively evaluating CHD risk factors in initially healthy middle-aged men in Belfast and France, we sought to explore whether depressive mood assessed by questionnaire is associated with a wide range of circulating inflammatory markers. Then, we estimated the contribution of depressive mood and circulating inflammatory markers to the risk of CHD.

Methods

Study Population

The PRIME Study is a prospective cohort designed to identify risk factors for CHD and to explain the gradient in CHD incidence between Belfast (Northern Ireland) and France.²⁴ Details on recruitment, baseline examination, and follow-up of the PRIME Study have been previously described.²⁵ Overall, 9758 middle-aged men 50 to 59 years of age who were free of CHD at baseline were recruited in Lille, Strasbourg, and Toulouse in France ($n=7399$) and Belfast in Northern Ireland ($n=2359$) between 1991 and 1993 and followed up for ≥ 5 years for occurrence of first CHD events, including coronary death, nonfatal myocardial infarction, and stable and unstable angina pectoris.

Baseline Examination in the Entire Cohort

General Characteristics

Subjects who agreed to take part in the study were given a morning appointment and asked to fast for ≥ 12 hours. A full description of clinical and laboratory measurements has been published elsewhere.^{24,25} Briefly, a self-administered health questionnaire was completed by subjects in their homes and was subsequently checked by trained interviewers at the clinic. It covered a broad range of clinical information, including family and personal clinical histories obtained through the Rose Questionnaire, tobacco consumption, and drug intake. Diabetes mellitus was defined as the current intake of oral hypoglycemic or insulin. Blood pressure was measured twice in subjects in the sitting position with the same automatic device (Spengler SP9). A 12-lead ECG was also recorded. Plasma lipid analyses were centralized (SERLIA INSERM U325, Institut Pasteur de Lille, France).

Assessment of Depressive Mood

Depression was assessed at baseline by questionnaire using a 13-item modification of the Welsh depression subscale derived from the Minnesota Multiphasic Personality Inventory.^{26,27} The items reflect negative perceptions of life (ie, "I feel helpless"). All items were scored as either 0 or 1, giving a score range of 0 to 12 in our samples (no men were scored 1 on each item). Baseline depression score was categorized into quartiles, and we used the fourth quartile of the score to identify men with depressive mood at baseline (mean, 5.75; range, 4 to 12; median, 5) in the absence of predefined cut points. Complete baseline depression scoring was available for 89% of the

cohort; subjects with missing data on some items were significantly ($P<0.05$) older, had higher mean daily alcohol consumption, were more often diabetic and current smokers, and were less frequently married or cohabiting.

Biological Measurements

A subset of biological measurements was performed in the entire cohort at baseline. Total cholesterol and triglycerides were measured by enzymatic methods using commercial kits in an automatic analyzer (Boehringer). HDL cholesterol was determined after precipitation of apolipoprotein B by enzymatic methods (Boehringer). LDL cholesterol was calculated according to the Friedewald formula. Fibrinogen was measured according to the method of Clauss.

Follow-Up and Ascertainment of Cases

During follow-up, subjects were contacted annually by letter and asked to complete a clinical event questionnaire. For all subjects reporting a possible event, clinical information was sought directly from the hospital or general practitioner records. All details of ECGs, hospital admissions, enzymes, surgical intervention, angioplasty, treatments, etc, were collected. Death certificates were checked for supporting clinical and postmortem information on cause of death. Whenever possible, circumstances of death were obtained from the practitioner or the family. A Medical Committee comprising 1 member from each PRIME Centre and the Coordinating Centre and 3 cardiologists (2 from France, 1 from the United Kingdom) was established to provide an independent validation of coronary events. A description of the coronary end point definitions has been published recently.²⁵ Myocardial infarction was defined by one of the following sets of conditions: (1) new diagnostic Q wave or other fresh typical ECG sign of necrosis, (2) typical or atypical pain symptoms and new (or increased) ischemia and myocardial enzyme levels >2 times the upper limit, and (3) postmortem evidence of fresh myocardial infarction or thrombosis. Definite coronary death was defined as death with a documented coronary event. Sudden death was defined as death occurring within 1 hour after symptoms without explanation. However, when significant coronary atheroma was present at autopsy, the death was considered definite coronary death. When a coronary death was suspected with no other documentation or explanation, it was labeled possible coronary death. The 3 death categories were grouped together as coronary deaths. Hard coronary cases were subjects who had ≥ 1 nonfatal myocardial infarction event or who died of coronary disease during follow-up. Angina pectoris was defined by the presence of chest pain at rest and/or on exertion and one of the following criteria: (1) angiographic stenosis $>50\%$, (2) a positive scintigraphy (if no angiographic data), (3) positive exercise stress test (if no angiographic or scintigraphic data), or (4) ECG changes at rest (if no angiographic, scintigraphic, or exercise stress test data) but without myocardial infarction and no evidence of a noncoronary cause in the clinical history. Total coronary cases were defined as all subjects with ≥ 1 of the categories of coronary death, nonfatal myocardial infarction, or angina pectoris. After 5 years of follow-up in France and 6 years in Belfast, there were 335 first total CHD events (138 in Belfast, 197 in France), of which 175 were hard CHD incident cases (69 in Belfast, 106 in France). At the end of follow-up, information on vital status was available for $>98\%$ of the cohort.

Case-Referent Study

A nested case-referent study within the PRIME prospective cohort study was built using the baseline plasma samples from 335 study participants who subsequently developed a first ischemic coronary event during follow-up and from 670 matched controls (2 controls per case). Matched controls were study participants recruited in the same center on the same day (± 3 days) who were of the same age (± 3 years) as the corresponding case and free of CHD at the date of the ischemic event of the case. The inflammatory assays and internal validation of the measures in each laboratory have been previously described.^{11,13} High-sensitivity CRP was measured by immunonephelometry (Dade Behring); IL-6, by ELISA (R&D Systems); and

ICAM-1, with a commercially available ELISA (Immunotech, Beckman Coulter).

Statistical Analysis

Because of skewed distributions, inflammatory markers were log transformed for analyses. We computed Pearson linear correlations between inflammatory markers, cardiovascular risk factors, and baseline depression score. We used general regression models to compare the distribution of baseline characteristics, including inflammatory markers, in men with and without depressive mood. We systematically adjusted for the case-control status in the absence of statistically significant interaction term between each baseline characteristic and case-control status (P for interaction >0.10). The possible confounding effects of alcohol consumption, smoking status, body mass index (BMI), diabetes, systolic blood pressure, and total and HDL cholesterol were also considered. We used conditional logistic regression analysis to estimate the odds ratio (OR) of depressive mood to the development of CHD. In this study, ORs should not be considered relative risk; an increase in the OR is not the same as an increase in relative risk. This analysis was successively adjusted for some social characteristics (university-level education and marital status), traditional cardiovascular risk factors (smoking status, history of diabetes mellitus, systolic blood pressure, and total and HDL cholesterol), and inflammatory markers (fibrinogen, CRP, IL-6, and ICAM-1). We also investigated whether imputation techniques for missing data on depression score modified our results. We replaced missing scores in the cases and controls by the mean value of the score observed in the cases and controls with complete data, respectively, and the results remained similar to those obtained without imputation techniques. All analyses were performed with SAS software 8.2 version (SAS Institute).

Results

Of the 1005 men initially included in this nested case-referent study within the PRIME prospective cohort study, 116 (31 cases, 85 controls) had data missing on some items of the baseline depression score, but they had baseline characteristics similar to those of men without missing data, except fewer had university-level education and more were diabetic. The study thus comprised 889 middle-aged men with complete data on baseline depression score: 304 cases (incident events) and 585 matched controls. The cases included 148 with angina pectoris (stable and unstable) and 161 nonfatal myocardial infarctions and coronary deaths (hard events); 5 cases of angina pectoris occurred before hard events and were included in both sets of cases.

Table 1 presents the baseline characteristics of all cases and matched controls. The mean levels of major cardiovascular risk factors and circulating inflammatory markers were significantly higher in cases than in controls; alcohol intake, however, was higher in controls. The presence of depressive mood, categorized as a baseline depression score in the fourth quartile (mean score in controls, 5.75; range, 4 to 12) was more frequently observed in cases than in controls (28.3% versus 19.7%; $P=0.012$). Stratified analysis by country indicated that depressive mood was also more frequently observed in France than in Belfast (23.4% versus 14.5% in controls).

Linear correlation coefficients between inflammatory markers, other cardiovascular risk factors, and baseline depression score are reported in Table 2. Inflammatory markers were mutually correlated (coefficients correlation range, 0.27 to 0.52); their correlation coefficients with cardiovascular risk factors were moderate. A low (<0.15) but statistically sig-

TABLE 1. Characteristics of Cases and Controls: The PRIME Study

Variables	Controls (n=585)	Cases (n=304)	P^*
Age, y	55.2 (2.7)	55.3 (2.9)	
Depressive mood,† %	19.7	28.3	0.012
University-level education, %	68.9	63.9	0.15
Married/cohabiting, %	88.9	88.5	0.96
Current smoker, %	30.1	38.5	0.013
Diabetes mellitus, %	1.9	6.2	0.007
Family history of CHD, %	13.0	20.3	0.002
Alcohol intake, g/d	35.1 (41.6)	31.9 (40.9)	0.34
SBP, mm Hg	133.5 (18.5)	139.6 (21.9)	0.0001
BMI, kg/m ²	26.6 (3.5)	27.3 (3.7)	0.017
Total cholesterol, mg/dL	222.2 (38.3)	232.2 (38.1)	<0.0001
HDL cholesterol, mg/dL	47.2 (12.7)	44.3 (12.8)	0.0015
Antidepressants, %	1.9	3.6	0.12
Aspirin, %	2.2	1.6	0.55
Antihypertensive treatment, %	11.2	21.7	0.001
Lipid-lowering treatment, %	4.8	9.4	0.03
Statins, %	0.7	3.6	0.001
Fibrinogen, g/L	3.37 (0.96)	3.61 (1.04)	0.0001
hs-CRP, mg/L	2.40 (3.78)	4.41 (11.75)	<0.0001
IL-6, pg/mL	1.82 (2.25)	2.32 (2.61)	<0.0001
ICAM-1, ng/mL	596 (203)	647 (214)	<0.0001

SBP indicates systolic blood pressure; hs-CRP, high-sensitivity CRP. Values are unadjusted mean (SD) when appropriate.

*Conditional logistic regression.

†Fourth quartile of depression score (mean, 5.75; range, 4 to 12).

nificant correlation was observed between depression score and IL-6, CRP, and ICAM-1, but no significant correlation was observed with fibrinogen.

Table 3 compares the baseline characteristics of men with and without depressive mood. Men with depressive mood

TABLE 2. Pearson Correlation Coefficients Between Inflammatory Markers, CHD Risk Factors, and Depression Score in the Total Sample of Cases and Controls: The PRIME Study

	IL-6	hs-CRP	ICAM-1	Fibrinogen
Age	0.06	0.08*	−0.04	0.13‡
Cigarettes per day	−0.15‡	−0.09†	−0.13†	−0.05
BMI	0.09*	0.21‡	0.11*	0.05
WHR	0.11*	0.19‡	0.15‡	0.02
Total cholesterol	−0.02	0.02	0.08*	0.06
HDL cholesterol	−0.15‡	−0.18‡	−0.23‡	−0.13‡
SBP	0.10*	0.12†	0.07*	0.03
Depression score	0.11†	0.10*	0.07*	−0.01
IL-6	...	0.52‡	0.33‡	0.38‡
hs-CRP	...	...	0.35‡	0.52‡
ICAM-1	...	...	...	0.27‡
Fibrinogen	...	...	...	...

hs-CRP indicates high-sensitivity CRP; WHR, waist-to-hip ratio; and SBP, systolic blood pressure. Inflammatory markers were log transformed.

* $P<0.05$; † $P<0.001$; ‡ $P<0.0001$.

TABLE 3. Characteristics of Men With and Without Depressive Mood: The PRIME Study

Variables	Depressive Mood*		P†
	No (n=688)	Yes (n=201)	
Age, y	55.4	55.1	0.38
University-level education, %	67.7	65.2	0.59
Married/cohabiting, %	90.7	82.1	0.0008
Current smokers, %	32.1	36.3	0.39
Diabetes mellitus, %	2.2	7.0	0.004
Family history of CHD, %	15.7	14.9	0.58
Alcohol intake, g/d	35.8	33.6	0.94
SBP, mm Hg	136.5	136.5	0.97
BMI, kg/m ²	26.9	27.2	0.24
Total cholesterol, mg/dL	227.7	226.6	0.71
HDL cholesterol, mg/dL	45.6	46.4	0.44
Antidepressants, %	1.0	7.5	<0.0001
Aspirin, %	1.7	2.5	0.44
Antihypertensive treatment, %	14.1	16.4	0.68
Lipid-lowering treatment, %	5.4	9.0	0.11
Statins, %	1.2	3.5	0.07
Fibrinogen, g/L	3.5	3.48	0.23
hs-CRP, mg/L	3.16	4.13	0.03
IL-6, pg/mL	2.02	2.25	0.08
ICAM-1, ng/mL	614	644	0.07

Abbreviations as in Table 2. Values are unadjusted mean (SD) when appropriate.

*Fourth quartile of depression score (mean, 5.75; range, 4 to 12).

†Logistic regression and general linear regression model adjusted for the case-control status; inflammatory markers were log transformed for analyses.

were less likely to be married or cohabiting but had similar university-level education and comparable mean levels of classic cardiovascular risk factors compared with men without depressive mood. In particular, smoking status, alcohol consumption, and BMI (and waist-to-hip ratio), which are known to modulate the level of inflammatory markers, were

comparable in both groups. However, the proportion of men treated with statins tended to be higher in men with depressive mood ($P=0.07$). Apart from fibrinogen, mean levels of inflammatory markers were higher in subjects with depressive mood: mean levels of CRP, IL-6, and ICAM-1 were 46%, 16% and 10% higher, respectively, independently of the case-control status. These differences were statistically significant for CRP and at the limit of significance for IL-6 and ICAM-1. Further adjustment for alcohol consumption, smoking status, BMI, diabetes, systolic blood pressure, and total and HDL cholesterol did not alter the results (not shown). Only 15 of 889 men were taking statin therapy; thus, the association of depressive mood with inflammatory markers by statin therapy could not be reliably explored.

The CHD incidence rate increased across the quartiles of baseline depression score (P for trend=0.05). Compared with men with baseline depression score in the 3 first quartiles, those men with baseline depression score in the fourth quartile had a 35% increase in the OR of total CHD (95% CI, 1.05 to 1.73) (Table 4). Because we were interested in possible differences by country, we also performed stratified analysis by country. The ORs of depressive mood for CHD were 1.44 (95% CI, 1.06 to 1.95) and 1.18 (95% CI, 0.74 to 1.86) in France and Belfast, respectively (P for interaction=0.50).

Finally, we investigated the contribution of depressive mood and circulating inflammatory markers to risk of CHD; results of this analysis are reported in Table 4. After adjustment for social characteristics, men with depressive mood had a 53% increase in the OR of total CHD. Further adjustment for classic cardiovascular risk factors (smoking status, history of diabetes mellitus, systolic blood pressure, and total and HDL cholesterol) and for lipid-lowering and antihypertensive treatment did not change the results. When inflammatory markers were added separately to the multivariate model (as continuous variables and after log transformation), the association of depressive mood with CHD remained of similar magnitude, and each inflammatory marker contributed significantly to CHD risk. Notably, adjustment for ICAM-1 decreased by 10% the magnitude of the multivariate-adjusted OR of depressive mood for CHD.

TABLE 4. Crude and Multivariate-Adjusted OR of CHD* Associated With Depressive Mood†: The PRIME Study

Adjustment Variables	Depressive Mood	Inflammatory Markers, OR (95% CI)			
		IL-6	hs-CRP	ICAM-1	Fibrinogen
Crude analysis	1.35 (1.05–1.73)	...	...	...	...
+ Social risk factors	1.53 (1.09–2.15)	...	...	...	...
+ Major CV risk factors	1.50 (1.04–2.15)	...	...	...	...
+ IL-6	1.53 (1.05–2.23)	1.39 (1.16–1.66)	...	...	...
+ CRP	1.45 (0.99–2.12)	...	1.30 (1.10–1.54)	...	...
+ ICAM-1	1.39 (0.96–2.01)	...	...	1.22 (1.02–1.46)	...
+ Fibrinogen	1.63 (1.11–2.38)	...	...	...	1.36 (1.14–1.63)

hs-CRP indicates high-sensitivity CRP; CV, cardiovascular. ORs were estimated by conditional logistic regression. Social risk factors include university-level education and marital status; classic cardiovascular risk factors include current smokers, diabetes, BMI, and total and HDL cholesterol. ORs for inflammatory markers are given for a 1-SD increase in the logarithm of each marker.

*Angina pectoris, nonfatal myocardial infarction, and coronary death.

†Fourth quartile of depression score (mean, 5.75; range, 4 to 12).

Discussion

The present data on healthy middle-aged men from Belfast and France suggest that men with depressive mood had higher levels of IL-6, CRP, and ICAM-1 independently of social characteristics and classic cardiovascular risk factors. Men with depressive mood had, on average, a 50% increase in the OR of CHD (including angina pectoris, nonfatal myocardial infarction, and coronary death) after adjustment for these inflammatory markers (taken separately) and other cardiovascular risk factors.

Association Between Depressive Disorders and Inflammatory Markers

We found 8 previous observational studies that investigated the relationship between depressive disorders and inflammatory markers in populations free of CHD.^{14–21} Among these, major depression and clinical depression have consistently been associated with elevated inflammatory markers.^{14–16} In the Rotterdam Study, elderly subjects with major depression had 23% and 44% higher CRP and IL-6 levels, respectively, than controls.¹⁴ Data from the Third National Health and Nutrition Examination Survey showed that a lifetime history of major depression was associated with a 64% increased risk of having elevated CRP levels (OR, 1.64; 95% CI, 1.2 to 2.2), and stratified analysis suggested that the association was present for men but not for women.¹⁵ In a small study ($n=100$), subjects with clinical depression exhibited 41% and 54% higher CRP and IL-6 levels than subjects without clinical depression.¹⁶ In contrast, mixed results have been reported with regard to depressive symptoms and inflammatory markers.^{17–21} In one study that included a small ($n=224$) random sample of middle-aged men and women from the Whitehall Study II, IL-6, CRP, and fibrinogen were not significantly associated with depressive symptoms.²¹

In the present study, the levels of behavioral factors (tobacco and alcohol consumption) and other CHD risk factors (systolic blood pressure, total and HDL cholesterol) were similar in subjects with and without depressive mood, making it less likely that these factors explained the association in question. In fact, the association of depressive mood with inflammatory markers persisted after adjustment for these factors. It should be noted, however, that diabetes was more prevalent in men with depressive mood; nonetheless, adjustment for this risk factor did not change the relationship between depressive mood and inflammatory markers. Adipose tissue has been suggested to be an important source of IL-6 secretion and thereby CRP (hepatic synthesis of CRP is stimulated by IL-6).²⁸ Although anthropometric markers of total (BMI) and intra-abdominal (waist-to-hip ratio) adiposity were related to both inflammatory markers and baseline depression score, adjustment for these anthropometric markers did not alter the relationship between depressive mood and inflammatory markers. Moreover, our population included men free of CHD at baseline and who were, for the most part, still employed. Therefore, this reduced the possibility that preexisting CHD or other severe chronic disease, including cancer, explained the association between depressive mood and inflammatory markers. Statin therapy has been shown to influence the level of inflammatory markers, and in

patients with CAD, major depression has been associated with higher levels of CRP only in patients not taking statin therapy.^{29,30} In the present study, only 15 of 889 men (1.7%) were taking statin therapy at baseline (between 1991 and 1993), so the possible influence of this therapy on the association between depressive mood and inflammatory markers could not be reliably explored. Altogether, the residual confounding effect of unmeasured factors seemed rather small.

We were able to identify, for the first time, an association between cellular adhesion molecules such as ICAM-1 and depressive mood in a healthy population. Higher levels of ICAM-1 have recently been reported in patients with major depression who recovered from an acute coronary syndrome.³⁰ Two other studies have reported impaired brachial artery flow-mediated dilatation in patients with major depression compared with controls free of depressive symptoms.^{22,23} The higher level of ICAM-1 in men with depressive mood who were free of CHD might reflect endothelial dysfunction. Other markers of endothelial function were available in the study, but we restricted our investigation to the most common (VCAM, P and E selectin) to limit the risk of false-positive associations that might have resulted from multiple statistical tests. No significant associations were observed between these 3 markers and depressive mood (not shown). Therefore, the existence of endothelial dysfunction as estimated by increasing levels of specific biomarkers in subjects with depressive mood should be confirmed in other healthy populations.

The cause of the association between depressive disorders and inflammatory markers is largely unknown. The relationship might be reciprocal. For instance, depressive disorders can elevate circulating concentrations of IL-6 through the influence of catecholamine release, which in turn stimulates IL-6 release from adipose tissue. Alternatively, IL-6 might contribute to the development of depressive disorders by stimulating the hypothalamic-pituitary-adrenal axis, which produces hormonal products that might cause depression.^{16,28}

Contribution of Depressive Mood to CHD Occurrence

In the present study of initially healthy men, depressive mood was associated with CHD, which is consistent with previous studies.^{1,4,6} That men from France reported higher rates of depressive mood than men from Belfast was the opposite of what would be expected, given the higher incidence of CHD in Belfast. However, depressive symptoms were self-reported, so the difference may reflect some cultural differences: French men may tend to systematically overreport depressive symptoms compared with men from Belfast, or men in Belfast may underreport depressive symptoms. There was a significant association between depressive mood and CHD occurrence in France but not in Belfast, but there was little indication of a statistically significant interaction with the country (P for heterogeneity=0.50). The pattern of the distribution of cardiovascular risk factors in depressed men was not different between countries in this study. Moreover, previous analyses in the PRIME Study have indicated that the gradient of CHD incidence risk between Belfast and France

was explained only partly by a gradient of major cardiovascular risk factors.²⁴ Therefore, there is no evident argument to suspect that depressive mood would be associated with CHD in France but not in Belfast.

Contribution of Depressive Mood and Inflammatory Markers to CHD

We were able to assess the contribution of depressive mood and inflammatory markers to CHD occurrence, which has not yet been reported. Adjustment for social characteristics, including marital status and university-level education, strengthened the association between depressive mood and CHD, and the association remained stable after further adjustment for circulating inflammatory markers and other cardiovascular risk factors. Thus, inflammation (and other cardiovascular risk factors) might not be primarily responsible for the association between depressive mood and the risk of CHD, at least in healthy European middle-aged men. However, adjustment for ICAM-1 decreased by 10% the magnitude of the OR of depressive mood for CHD. Moreover, the contribution of inflammatory processes may be stronger for more clinically significant depression (major or clinical depression) than it is for depressive symptoms. This is supported by the fact that clinical depression and major depression have been more reliably associated with elevated inflammatory markers^{14–16} and have been more strongly related to incident CHD than depressive symptoms.^{1–7} Thus, the contribution of inflammation to the relation between more clinically significant depression and CHD should be addressed in other studies.

Study Limitations

The present study had some limitations. Protein degradation of inflammatory markers during storage cannot be excluded, even if the plasma samples were kept in liquid nitrogen at very low temperature (–196°C). However, the mean levels of inflammatory markers measured in this study were comparable to those measured in fresh samples from other studies, and analysis of the stability of several risk factors, including CRP and fibrinogen, in plasma kept at –70°C for 5 years has shown no sample degradation over time.³¹ The use of a structured depression interview was not possible given the large, multicenter, and multipurpose design of this study. Thus, we were not able to assess major depression. Whether depressive mood preceded or was the consequence of higher levels of inflammatory markers could not be addressed, given the cross-sectional nature of the association. Because depression score was measured once at baseline, the possible impact of its changing on CHD events could not be assessed. Finally, our results were obtained in white men, so extrapolation to women and to other ethnic backgrounds requires caution.

In conclusion, in healthy European middle-aged men, depressive mood was associated with higher levels of inflammatory markers, including IL-6, CRP, and ICAM-1, independently of social and other cardiovascular risk factors. Depressive mood was also associated with CHD, and this association persisted after adjustment for inflammatory markers. Further studies are needed to elucidate how depressive disorders contribute to CHD.

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