

Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women

The Stockholm Female Coronary Risk Study

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Aims Several studies have reported that women with coronary heart disease have a poorer prognosis than men. Psychosocial factors, including social isolation and depressive symptoms have been suggested as a possible cause. However, little is known about these factors and their independent predictive value in women. Therefore, we investigated the prognostic impact of depression, lack of social integration and their interaction in the Stockholm Female Coronary Risk Study.

Methods and Results Two hundred and ninety-two women patients aged 30 to 65 years and admitted for an acute coronary event between 1991 and 1994, were followed for 5 years from baseline assessments, which were performed between 3 and 6 months after admission. Lack of social integration and depressive symptoms, assessed at baseline by standardized questionnaires, were associated with recurrent events, including cardiovascular mortality, acute myocardial infarction and revascularization procedures (percutaneous transluminal coronary angioplasty and coronary artery bypass grafting). Adjusting for age, diagnosis at index event, symptoms of heart failure, diabetes

mellitus, high density lipoprotein (HDL) cholesterol, history of hypertension, systolic blood pressure, smoking, sedentary lifestyle, body mass index, and severity of angina pectoris symptoms, the hazard ratio associated with low (lowest quartile) as compared to high social integration (upper quartile) was 2.3 (95% CI 1.2–4.5) and the hazard ratio associated with two or more (upper three quartiles) as compared to one or no depressive symptoms was 1.9 (95% CI 1.02–3.6).

Conclusions The presence of two or more depressive symptoms and lack of social integration independently predicted recurrent cardiac events in women with coronary heart disease. Women who were free of both these risk factors, had the best prognosis.

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Introduction

Several studies have reported that women with coronary heart disease have a poorer prognosis than men^[1–7]. Although early reports suggested that the increased mortality after acute myocardial infarction in women as compared to men was due to their older age and unfavourable risk factor profile^[8], incomplete control for these factors made conclusions tentative. However,

recent findings by Marrugat *et al.* show that women have a worse post-acute myocardial infarction prognosis than men even after careful adjustment for age and comorbidity^[7]. Psychosocial factors, including social isolation and depression, have been suggested to play a role in explaining the excess poor prognosis in women coronary heart disease patients^[8,9].

Both socially isolated^[10–14] and depressed^[15–21] coronary heart disease patients have been reported to have an increased risk of recurrent cardiac events including coronary heart disease mortality and non-fatal acute myocardial infarction. Although depression is generally found to be twice as common in women as in men^[22,23], only two studies included enough women to investigate gender-related differences. Neither of these studies reported significant gender differences in terms of the impact of the cardiovascular condition. Barefoot *et al.*, found that elevated scores on the Zung Self-Rating Depression Scale (SDS) were associated with the same increased risk of cardiovascular and total mortality regardless of sex in patients admitted for their first cardiac catheterization, independent of initial disease and treatment^[19]. In a secondary analysis combining post-acute myocardial infarction patients from two separate studies, Frasure-Smith *et al.*^[21] found that elevated scores on the Beck Depression Inventory were associated with similarly increased risk of cardiac mortality for both genders, independent of disease severity and smoking.

In addition, social isolation and depression tend to cluster. Lack of social support during hospitalization has been found to predict subsequent depressive symptoms among coronary artery disease patients^[24], and depression, depressive symptoms and social isolation are known, from psychiatric studies, to be associated^[25–29]. Yet the combined effects of these factors on prognosis in coronary heart disease patients have rarely been examined, especially not in women. The risk for cardiac events may be substantially altered when psychosocial factors occur in combination^[30]. Therefore, it is of clinical interest to investigate whether social isolation and depressive symptoms, when occurring together, predict coronary heart disease prognosis and whether they are independent predictors or interchangeable features. In the Stockholm Female Coronary Risk Study (FemCorRisk study), we had the opportunity to study the prognostic importance of these factors, controlling for clinical cardiac risk factors, in a community-based sample of all women patients, aged 65 years or under, who were admitted for an acute coronary event.

Methods

Study population

Two hundred and ninety-two women, who were admitted between February 1991 and February 1994 for an acute coronary heart disease event and resided in the

greater Stockholm area were asked to participate in the FemCorRisk study. The Swedish health care system provides care to all residents regardless of income, socio-economic or insurance status. Thus we were certain to reach virtually all patients who needed and sought hospital care for an acute coronary heart disease event during this period. The study was approved by the Karolinska Hospital Ethics Committee (No. 91; 119), and all patients gave their written consent.

Patients were included if they had sufficient knowledge of Swedish, were 65 years or under, and met any of the following criteria: (I) definite or suspected acute myocardial infarction, based on the WHO criteria of typical chest pain, typical enzyme patterns and diagnostic electrocardiographic (ECG) changes^[31], classified by the Minnesota code^[32]; (II) unstable angina pectoris defined as the first occurrence of severe angina pectoris that had deteriorated during the 4 weeks before admission, with an increase in pain intensity and pain duration, or with pain at rest or on very low physical exertion^[33]; (III) spasm angina, defined as angina pectoris at rest with pathological ST-changes on the ECG, and with normal coronary arteries on acute clinical coronary angiography. For this report, the diagnosis at the index event was categorized as either angina pectoris or acute myocardial infarction, in all analyses.

During the 3-year inclusion period, 335 women with coronary heart disease were identified in the coronary care units of the 10 cardiology clinics. Forty-three patients (13%) could not be included in the study.

For each patient, the study was carried out during 2 consecutive days, 3–6 months after hospital admission. Patients were asked to continue their usual medications, which were verified upon arrival at the research clinic. A detailed description of the study groups, the response rate, assessments and recruitment is available^[34].

Baseline examinations

Prior to their visit to the research clinic, questionnaires were mailed to subjects to assess their educational level, family history of coronary heart disease, smoking history, exercise habits, and psychosocial characteristics. Each questionnaire was checked by the research nurse for problems and/or missing data. Physical exercise was assessed according to the World Health Organization criteria and dichotomized into: sedentary lifestyle (reading, watching TV or other sedentary leisure activities) or non-sedentary lifestyle (walking, cycling or other heavier forms of physical activity). A family history of coronary heart disease was defined as having at least one close family member (parent or sibling) diagnosed with acute myocardial infarction.

During the first day, the severity of angina pectoris symptoms and a clinical history of diabetes mellitus, hypertension and medication use were assessed during the clinical examination. The severity of heart failure symptoms (Killip classification)^[35] at the time of the index event was abstracted from the medical record and

coded as follows: (I) no signs of left ventricular decompensation, (II) basilar rales, tachypnoea, (III) severe left ventricular decompensation/pulmonary oedema and (IV) cardiogenic shock. The second day included an extensive interview and questionnaire assessments of lifestyle, behavioural and gynaecological characteristics, as well as anthropometric measurements, and a full lipid and routine laboratory profile.

Laboratory analyses

Venous blood samples were drawn from the right arm, between 0800 and 1000h in the morning, with patients fasting from midnight. Serum-separated tubes were centrifuged for 10 min at 3000 g ($\text{rev} \cdot \text{min}^{-1}$). Four ml of plasma were frozen to -70°C . Tubes were sent in batches to the same processing laboratory (CALAB) once per month.

Total cholesterol and triglycerides were determined by enzymatic methods with reagents from Boehringer Mannheim (Germany). High density lipoproteins were determined based on the isolation of LDL and VLDL from serum by precipitation. The cholesterol content of the supernatant, i.e. HDL cholesterol, was measured enzymatically, using an automated Multichannel Analyzer^[36].

Depressive symptoms

Depressive symptoms were measured by means of a nine item questionnaire with yes/no alternatives, derived from Pearlin *et al.*^[37]. The 'yes' answers were summed, with a low score indicating a considerable degree of depression. The scale includes questions on mood, sleeping problems, appetite, energy, interest in normal activities, crying and feelings about the future. Examples of questions are: 'Do you feel bored or do you have little interest in doing things? Do you feel downhearted or blue?' 'Do you feel hopeless about the future?' The scale had an adequate internal consistency (Cronbach's $\alpha=0.85$) and was significantly correlated ($r=0.71$, $P<0.0001$) with the Beck Depression Inventory^[38] in a subsample of the study population ($n=30$)^[39].

Social support

A condensed version of the Interview Schedule for Social Interaction^[40,41] was used to measure social support. This measure has been modified for use in population studies, and examined for reliability and validity in our research laboratory^[40], and found to predict cardiovascular disease in studies of Swedish men^[40,42]. The instrument yields two scales, one describing availability of deep emotional relationships or 'attachment' and the other describing availability of the more peripheral contacts of social networks or 'social integration'.

The 'attachment' scale describes the availability of emotional support, mainly from family and close friends. It consists of six items with a minimum score of zero and a maximum score of six. The 'social integration' scale describes both the quantitative characteristics of the extended network and its function. Functions include a sense of belonging, practical help and support^[42]. It is comprised of six items with a total score range from six to 36.

Ascertainment of recurrent cardiac events

Due to the centralized health care system in Sweden, we were able to obtain complete follow-up information on all patients by matching their unique 10-digit person identification numbers to hospital and death registers^[43,44]. The 292 women were followed from the date of their baseline examination, until 18 August 1997, for cardiovascular and all-cause mortality, acute myocardial infarction, and revascularization procedures (percutaneous transluminal coronary angioplasty [PTCA] and coronary artery bypass grafting [CABG]). The median follow-up period, from baseline assessments, was 4.8 years with a range from 3.2 to 6.2 years.

Mortality was ascertained by linkage to the Swedish National Death Registry, which is maintained for all Swedish residents. All death certificates were collected. Death from cardiovascular causes was considered when the primary cause of death was coded as codes 410–414 (International Classification of Diseases, Ninth Revision, ICD-9).

Recurrent acute myocardial infarction was considered to have occurred on the date of admission for hospitalization with a discharge diagnosis of acute myocardial infarction (ICD-9 code 410) in the hospital register. Swedish hospital registers of acute myocardial infarction have been previously validated with hospital records and found to be highly reliable^[43,44]. Revascularization procedures were considered to have occurred on the date of operation, with International Classification of Operations, Ninth Revision (ICO-9) codes 3105, 3158, 3127 and 3066 for CABG, and 3080 for PTCA. Data on revascularization procedures were further validated using the cardiac procedures register in the respective hospitals.

Data analyses

Baseline characteristics were compared for subjects who developed recurrent events with those who did not, using analyses of variance and chi-square testing for continuous and discrete variables, respectively. The attachment scale was skewed (73% scored the maximum score of 6) and was therefore dichotomized with a cut-off at 5. Kaplan–Meier curves and age-adjusted and multivariate Cox proportional hazard regression models, controlling for potential confounders, were

Table 1 Distribution of the study variables in relation to the presence of recurrent events

Factor	Patients with recurrent events % (n)	Patients without recurrent events % (n)	P*
Educational attainment Mandatory	63 (51)	63 (130)	
High school+college/university	37 (30)	37 (76)	0.98
Menopausal status			
Premenopausal	24 (19)	26 (55)	
Postmenopausal with HRT	6 (5)	15 (31)	
Postmenopausal without HRT	70 (57)	59 (125)	0.09
Cigarette smoking			
Nonsmokers	28 (22)	33 (70)	
Previous smokers	51 (41)	47 (99)	
Current smokers	21 (17)	20 (41)	0.63
Sedentary lifestyle	22 (18)	25 (52)	0.61
History of hypertension	52 (42)	52 (102)	0.99
Diagnosis at index event			
AMI	56 (45)	31 (65)	
Angina pectoris	44 (36)	69 (146)	<0.001
Symptoms of heart failure**	14 (11)	7 (15)	0.08
Family history of CHD	60 (49)	51 (108)	0.16
Diabetes mellitus	17 (14)	9 (19)	0.045
Angina pectoris severity			
No angina	21 (16)	24 (47)	
Mild angina	22 (17)	31 (60)	
Moderately severe angina	40 (31)	34 (67)	
Very severe angina	17 (13)	11 (22)	0.31
	Mean (SD)	Mean (SD)	P†
Age (years)	55.8 (7.5)	56.0 (6.9)	0.98
Systolic blood pressure (mmHg)	121.3 (19.5)	121.5 (16.8)	0.52
BMI (kg.m ²)	26.7 (4.0)	27.2 (4.8)	0.69
Triglycerides (mmol . l ⁻¹)	1.84 (1.50)	1.74 (1.94)	0.45
Cholesterol (mmol . l ⁻¹)	6.57 (1.19)	6.46 (1.25)	0.60
HDL cholesterol (mmol . l ⁻¹)	1.36 (0.38)	1.53 (0.43)	0.003
Depressive symptoms (score)	4.0 (2.5)	3.5 (2.7)	0.12
Social integration (score)	18.8 (6.0)	20.8 (5.8)	0.007
Attachment (score)	5.2 (1.5)	5.5 (1.1)	0.15

HRT=hormone replacement therapy; AMI=acute myocardial infarction, CHD=coronary heart disease; **=Killip class ≥ 2 at the time of the index event; SD=standard deviation; BMI=body mass index; HDL=high density lipoprotein. *=probability value for chi-square test, †=probability value for Wilcoxon signed rank test.

constructed. Hazard ratios from the Cox models, for quartiles of the social support and depressive symptoms scores are presented together with their 95% confidence intervals. The linear trend for the effect of lack of social support and depressive symptoms on recurrent events was assessed by computing the *P*-value for trend^[45]. The outcome was the occurrence of a recurrent event, including cardiovascular death, recurrent acute myocardial infarction or revascularization. Only the first event for each subject was considered, if multiple events occurred during the follow-up period. We used STATA 5.0 (46) for the statistical analyses.

Results

The mean age at entry to the study was 56 years, ranging from 30 to 65 years. Of the 292 patients, 110 (37%) had

an acute myocardial infarction, and 182 (63%) had angina pectoris as the diagnosis at the index event. Distributions of baseline characteristics in patients with and without recurrent events are presented in Table 1.

During the 5-year follow-up period, there were 14 deaths, nine from cardiovascular causes, one from cerebral haemorrhage, three from cancer and one from pulmonary fibrosis; 17 patients with a recurrent acute myocardial infarction, 31 with PTCA, and 37 with CABG were found. A total of 81 patients either died from cardiovascular causes or had recurrent acute myocardial infarction or revascularization procedure, or a combination of these. Prior to the follow-up period, during the 3 to 6 months between hospital admission and examination, two women had a recurrent acute myocardial infarction, one woman underwent CABG and two women underwent PTCA. Analyses of clinical predictors were performed with and without these patients, which did not influence results.

Table 2 Risk for recurrent cardiac event (cardiovascular mortality, recurrent AMI or revascularization) according to social integration and depressive symptoms in women

Social integration scale-scores	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend	P**
N	6–16	17–20	21–24	25–36		
	80	64	74	69		
No. of cardiac events	30	17	16	15		
Hazard ratios*						
Age adjusted	1.9 (1.02–3.5)	1.2 (0.61–2.5)	1.0 (0.50–2.0)	1	0.03	0.02
Multivariate adjusted†	2.3 (1.2–4.5)	1.6 (0.73–3.4)	1.2 (0.56–2.5)	1	0.007	0.01
Attachment scale-scores	Quartile 1	Quartile 2–4			P-trend	P**
	0–5	6				
N	78	208				
No. of cardiac events	26	52				
Hazard ratios*						
Age adjusted	1.4 (0.89–2.3)	1			—	0.14
Depressive symptoms scale-scores	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend	P**
	0–1	2–3	4–5	6–9		
N	81	70	59	80		
No. of cardiac events	14	23	21	23		
Hazard ratios*						
Age adjusted	1	2.2 (1.2–4.4)	2.3 (1.2–4.5)	1.8 (0.92–3.5)	0.12	0.01
Multivariate adjusted†	1	2.2 (1.1–4.4)	1.8 (0.82–3.8)	1.8 (0.86–3.6)	0.22	0.04

AMI=acute myocardial infarction. *Hazard ratios with 95% confidence intervals. **Probability value comparing quartile 1 with the rest. †Adjusted for age, diagnosis at index event, symptoms of heart failure, diabetes mellitus, HDL, severity of angina pectoris symptoms, smoking, sedentary lifestyle, BMI, SBP and history of hypertension.

In relation to baseline characteristics, lack of social integration was statistically significantly associated with smoking ($P=0.04$) and with a history of hypertension ($P=0.05$). Depressive symptoms were associated with diabetes mellitus ($P=0.03$), sedentary lifestyle ($P=0.03$), severity of angina pectoris symptoms ($P=0.0003$), history of hypertension ($P=0.04$), systolic blood pressure ($P=0.02$) and showed a trend with body mass index ($P=0.09$). In addition, depressive symptoms and lack of social integration were closely associated with each other ($\chi^2=22.4$, $P=0.008$).

A comparison across quartiles of scale scores, lack of social integration was associated with an increased risk of recurrent events in a graded fashion (Table 2). The risk was highest in the lowest social integration quartile, and decreased in the second and third quartiles. Depressive symptoms on the other hand, showed a similar degree of elevated risk in each of the three upper quartiles (two or more depressive symptoms). After adjusting for age, diagnosis at the index event, symptoms of heart failure, diabetes mellitus, HDL cholesterol, history of hypertension, systolic blood pressure, smoking, sedentary lifestyle, body mass index, and severity of angina pectoris symptoms, the hazard ratio associated with a low (lowest quartile) as compared to a high social integration score (highest quartile), was 2.3 (95% CI 1.2–4.5) and the hazard ratio associated with two or more (upper three quartiles) as compared to one or no depressive symptoms (lowest quartile) was 1.9 (95% CI 1.02–3.6) (Table 2).

Further adjustment for educational level, menopausal status, total cholesterol, triglycerides, treatment with

beta-blockers, ACE inhibitors and family history of coronary heart disease, did not change the results. Repeating analyses in subgroups of acute myocardial infarction and angina pectoris patients separately resulted in similar but less statistically significant results. Likewise, analyses with separate outcome variables (I) cardiovascular death and recurrent acute myocardial infarction, or (II) revascularization alone, yielded similar but only borderline significant results.

The scale measuring emotional support (attachment) showed no statistically significant association with cardiovascular events. However, among women with a low attachment score (lowest quartile), 33% had at least one cardiovascular recurrent event compared to 25% among women with a high attachment score (upper three quartiles) (HR=1.4; 95% CI 0.89–2.3).

In Fig. 1 the actuarial probability of event free survival is shown, dividing patients into four subgroups, combining low social integration (below median) and depressive symptoms (upper three quartiles). Patients who were both socially integrated and were free from or had just one depressive symptom, had an actuarial probability of 91% (95% CI 79%–97%) of remaining free from recurrent cardiac events, compared to 65% (95% CI 55%–73%) for patients who both lacked social integration and had two or more depressive symptoms (HR=3.7; 95% CI 1.5–9.5). Intermediate figures were found for patients with only one of these two risk factors. When both these risk factors were entered in the model, together with age, diagnosis at the index event, symptoms of heart failure, diabetes mellitus, HDL cholesterol, history of hypertension, systolic blood pressure,

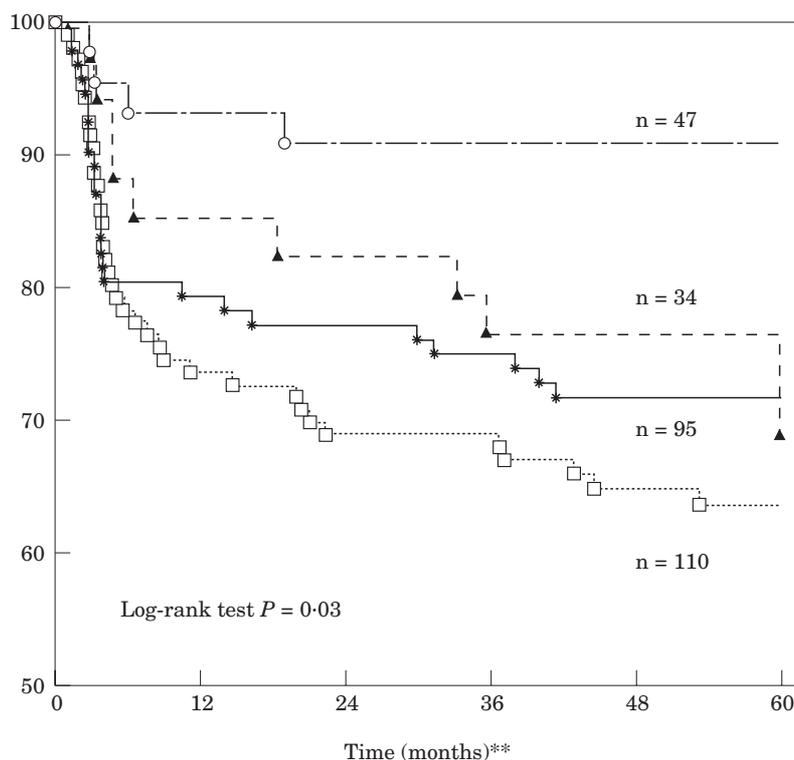


Figure 1 *Hazard ratio (95% CI), adjusted for age, P for trend=0.004. **Time 0 represents start of baseline examination at 3–6 months after hospital admission; ○=social integration and one or no depressive symptom(s). No. events=5^[11]*; ▲=lack of social integration and one or no depressive symptom(s). No. events=9 [2.7 (0.89–7.9)]*; * =social integration and two or more depressive symptoms. No. events=26 [2.9 (1.1–7.6)]*; □=lack of social integration and two or more depressive symptoms. No. events=38 [3.7 (1.5–9.5)]*.

smoking, sedentary lifestyle, body mass index, and severity of anginal symptoms, lack of social integration was statistically significant ($P=0.4$) and depressive symptoms showed a trend ($P=0.07$). A formal interaction test was non-significant ($P=0.23$).

Discussion

These results indicate that among women age 65 or younger, lack of social integration and depressive symptomatology, as assessed between 3 and 6 months following admission for an acute coronary heart disease event, are associated with a poor prognosis during the subsequent 5 years. After 5 years of follow-up, 35% of women who both lacked social integration and had two or more depressive symptoms had a relapse of their coronary disease (cardiovascular death, recurrent acute myocardial infarction or revascularization), as compared to 9% of those who were free of these characteristics. These associations were independent of well established prognostic risk factors including older age, symptoms of heart failure and angina pectoris, diabetes mellitus, post-menopausal status, hypertension,

smoking, obesity, lack of exercise, dyslipidaemia, and treatment with beta-blockers or ACE-inhibitors. When analysing acute myocardial infarction and cardiovascular death as a separate outcome ($n=23$), similar trends were observed but only borderline statistical significance was reached, possibly due to lack of statistical power.

Several previous studies have shown that depressive symptoms^[15–21], social isolation and lack of social support^[10–14] predict poor prognosis in coronary heart disease patients. Few studies^[10,13,16,20,21] have included both factors. Such studies found either social isolation^[10,13] or depressive symptoms^[16,20,21] predictive of poor coronary heart disease prognosis and none of them investigated combinations of these factors. Differences in concepts of social support as well as depressive symptoms further complicate comparisons between studies. Since psychosocial factors, including social isolation and depression tend to cluster^[25–29], and the clustering may further elevate the risk^[30], it is of clinical interest to investigate the effect of social isolation and depressive symptoms occurring in combination. In the present study both depressive symptoms and lack of social integration were associated with a worse prognosis. As their interaction was not statistically significant,

an additive effect of depressive symptoms and lack of social integration on coronary heart disease prognosis in women is suggested.

In our study, the attachment scale describing close emotional relationships mainly provided by spouses or other family members, was not statistically significantly related to recurrent events. Measurement error due to over-reporting of emotional support (attachment), as compared to reporting of social integration, could explain the lack of association. However, the same attachment scale was used in a previous cohort study of Swedish men, and was found to predict coronary heart disease over a 6 year follow-up period, while controlling for standard risk factors^[42]. This suggests a gender difference in the association of close emotional support with health. Besides being a source of support, emotional ties can also comprise a source of stress for women, as they may be associated with both emotional distress and family responsibilities^[47]. Accordingly, it has been reported that perceived primary sources of support differ between men and women. In the Massachusetts studies of healthy men and women, 66% of men as compared to only 26% of women indicated their spouse as their primary source of emotional support^[48]. The results suggest that support from a spouse may be less available or less adequate for women as compared to men^[48–50].

Limitations of the study need to be considered when interpreting these results. The study group included only women coronary heart disease patients under the age of 66, limiting the possibility to generalize the findings to older women or to men. However, women under the age of 66 are often under-represented, particularly in studies of psychosocial factors and coronary heart disease, motivating our attention to this specific group.

Secondly, in order to obtain a comprehensive and reasonably large study group of all younger women with a severe acute coronary syndrome event, both women with acute myocardial infarction, unstable angina pectoris and spasm angina were included. In epidemiological studies, this may be perceived as a limitation. However, in the clinical setting these diagnoses represent different stages of the same underlying coronary disease. Furthermore, the prognostic impact of psychosocial factors did not differ between the diagnostic groups.

Similarly, to obtain a sufficient number of recurrent events after 5 years of follow-up, cardiac deaths, acute myocardial infarctions and revascularizations, were combined into a composite end-point. Revascularizations may be influenced by physician and patient choices, i.e. depressive symptoms could increase angina pectoris symptom reporting^[51], thereby influencing the chance of being detected as a candidate for CABG/PTCA. However, adjusting for patient-reported severity of angina pectoris symptoms did not change the results, indicating that anginal symptoms were probably not responsible for the effects found.

Differential socio-economic access to expensive health care procedures could also produce a bias. This is less likely to be the case in a public health care system with

universal access like the Swedish one, where all patients are admitted for free, and diagnostic and therapeutic criteria are highly standardized. However, differences in care-seeking behaviour cannot be excluded.

Finally, the choice of psychosocial measures may have limited the conclusiveness of the results. We found patients in the upper three quartiles of the depressive symptom distribution to be at increased risk for recurrent events. Using the Beck Depression Inventory, Frasure-Smith *et al.* found an increased risk among the upper half of the women in their study (who had a score between 10 and 63)^[21]. We selected the Pearlin depressive symptom scale, because it was short and convenient. It had an adequate internal consistency and was significantly correlated with the Beck Depression Inventory^[38] in a subsample of the study population^[39]. However, its narrow range of scores from zero to nine, may have attenuated measurement precision and variance, thereby limiting the possibility to detect a graded association between depression and poor prognosis.

Potential mechanisms linking depressive symptoms and lack of social integration with coronary heart disease outcome include adverse lifestyle habits, such as smoking, sedentary lifestyle and poor diet. In our study, smoking, sedentary lifestyle and obesity were associated with psychosocial factors and were therefore included in multivariate models. Although adjusting for self-reported lifestyle-related factors in multivariate analyses may not fully eliminate their confounding effects, the associations with coronary heart disease outcome could not be explained by unhealthy lifestyle alone in the present as well as in other studies^[10–21].

Other potential pathways include the effects of the sympathetic nervous system on atherosclerosis and thrombosis^[30]. Both animal and human studies have demonstrated sympathetic nervous system effects such as elevated blood pressure and heart rates, increased catecholamines and cortisol excretion rates, platelet adhesiveness and hypercoagulability in response to psychosocial influences^[30]. In healthy women from the same population, we found sympathetic nervous system effects, including decreased heart rate variability^[52], haemostatic dysfunction^[53,54] and a higher risk for the metabolic syndrome^[54] in those who lacked social integration. In a cross-sectional analysis of a subgroup of the present women patients, lack of social integration was associated with extent and severity of coronary artery disease, as assessed by quantitative coronary angiography^[55]. The findings were independent of health behaviours, standard risk factors and severity of anginal symptoms therefore, suggesting that psychosocial factors were mediated by sympathetic nervous system activity.

In the present prospective study, both lack of social integration and depressive symptoms had an impact on the risk of recurrent cardiac events in women with established coronary heart disease. When occurring together, the risk was almost four times higher than without these factors, regardless of other clinical prognostic factors. Women who reported no or only one

depressive symptom and were socially integrated had the best prognosis. The implication is that treatment and rehabilitation in women should focus on improving both these factors. Such attempts are ongoing, both in the US and Europe^[56].

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