Perceived Stress and Risk of Ischemic Heart Disease

Causation or Bias?

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Background: It is unclear whether the commonly recognized link between stress and cardiovascular disease is causal or the result of reporting bias. The objective of this study was to address the association between perceived stress and first incidence of ischemic heart disease and to evaluate the suggested reporting bias by addressing subdiagnoses of ischemic heart disease separately.

Methods: The 11,839 men and women who participated in the Copenhagen City Heart Study were at baseline (1981–1983) asked about their stress level. The participants were followed in nationwide registries until the year 2000, and fewer than 0.1% were lost to follow-up. During follow-up, 2316 individuals were diagnosed with ischemic heart disease.

Results: High levels of stress were associated with slightly higher risk of incident ischemic heart disease in both women (hazard ratio = 1.23; 95% confidence interval = 1.01–1.51) and men (1.25; 1.00–1.56). When subdiagnoses of ischemic heart disease were analyzed separately, high stress was associated with markedly higher incidence of angina pectoris for women (1.83; 1.15–2.91) and for men (2.14; 1.32–3.47). There was no association with myocardial infarction for women (0.80; 0.56–1.15) or for men (1.09; 0.79–1.52). All associations attenuated with prolonged follow-up.

Conclusions: It remains uncertain whether perceived stress affects subdiagnoses of ischemic heart disease differently or whether the strong association with angina pectoris was spuriously created by a tendency for stressed individuals to report more cardiovascular symptoms. Future studies on this issue should address subdiagnoses of ischemic heart disease separately and should carefully consider the impact of reporting bias and prolonged follow-up.

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The commonly recognized link between stress and cardiovascular disease (CVD)[1–4] recently has been challenged.[5] It has been questioned whether the observed associations between stress and CVD in observational epidemiologic studies are causal or rather are the result of reporting bias.[5–7] On one hand, individuals who report high levels of stress may have a tendency to also report more symptoms of CVD.[5] This reporting bias will create a spurious association between stress and CVD, especially in studies where the outcome measure is self-reported.[6] On the other hand, a relation between stress and cardiovascular disease is both biologically plausible and empirically supported in a range of observational studies.[1–4,8–10] In a recent large case–control study that included cases and controls from 52 countries, a higher risk of myocardial infarction (MI) was reported among individuals who experienced stress at home or at work, were under severe financial stress, had experienced stressful life events in the past year, or were depressed.[1] Stress seems to activate the sympathetic nervous system, with various metabolic effects: increased blood pressure, pulse rate, and platelet aggregation; reduction in insulin sensitivity; and promotion of endothelial dysfunction.[11] Stress also may lead to changes in smoking, diet, alcohol consumption, and level of physical activity, and thereby indirectly influence the risk of CVD.[11–15]

We examined the association between perceived stress and risk of a first-time diagnosis of ischemic heart disease (IHD) in a large prospective cohort study with 18 years of follow-up. To address the impact and direction of the suggested reporting bias we also conducted separate analyses for the associations between perceived stress and myocardial infarction, angina pectoris, and other IHD.

METHODS

Study Population

The Copenhagen City Heart Study was initiated in 1976.[16] An age-stratified sample of 19,698 men and women were drawn randomly from the Central Population Registry and invited to participate in the study. A physical examination was performed, and participants were asked to fill in a questionnaire regarding various risk factors. In 1981–1983, the study population was supplemented with 500 men and women, and additional study assessments were performed for both new and continuing study participants. The study participants were asked about their stress level only at the second examination; this information is used as baseline for the

present study. The 12,698 women and men participating in the second examination constituted a response proportion of 70%, and most of the participants were white. All participants gave informed consent. We excluded participants with IHD before the second examination (n = 473) or who lacked information on stress (n = 42) or on any of the covariates included in the statistical analysis (n = 344). The analyses were therefore based on 11,839 eligible participants (6543 women and 5296 men). Fewer than 0.1% of these were lost to follow-up. A detailed description of the Copenhagen City Heart Study has previously been published elsewhere.[16]

Perceived Stress

The study participants were asked about stress intensity and stress frequency. In the questionnaire, stress was exemplified as the sensation of tension, nervousness, impatience, anxiety, or sleeplessness, and no time frame was specified for the stress reporting. Stress intensity based on the question, "Do you feel stressed?" was reported in categories of: (0) none, (1) light, (2) moderate, or (3) high. Stress frequency based on the question "How often do you feel stressed?" was reported in categories of: (0) never/hardly ever, (1) monthly, (2) weekly, or (3) daily. The scores of these 2 questions were added and combined into a stress score with 0 as the lowest value (indicating no stress reported) and 6 as the highest value (indicating daily high stress intensity). The stress score was then categorized into low (0–1 points), medium (2–4 points), and high (5–6 points) stress.

Covariates

The following minimum sufficient set of potential confounders was identified according to the methods of causal diagrams developed by Greenland et al[17]: sex, age (continuous), education (less than 8 years, 8–11 years, or 12 or more years), income at baseline (<$1000, $1000–2500, or more than $2500 per month), cohabitation (living with partner or children vs living alone), physical activity in leisure time (none or very little activity; 2–4 hours of light activity per week; more than 4 hours of light activity or 2–4 hours of high level activity; and competitional level or more than 4 hours of hard level activity per week), alcohol consumption (<1, 1–7, 8–14, 15–21, 22+ drinks/wk), body mass index (<18.5, 18.5–30, >30 kg/m^2), tobacco smoking (never-smoker; ex-smoker; smoker of 1–14 g/d, 15–24 g/d, and more than 24 g/d), and parental history of MI (yes/no). Other risk factors for IHD, such as blood pressure, blood glucose, and blood lipids measured nonfasting, were possible intermediates on the pathway between stress and IHD and were therefore not included in the analyses.

Follow-up

Participants were followed from date of the second examination until date of first diagnosis of IHD, death, loss to follow-up, emigration, or end of follow-up (31 December 2000). Thus, it was possible to follow the study population from the second examination for 17 to 19 years for a first-time diagnosis of IHD. Using the civil registry number, which is unique to every Danish citizen, a complete hospital discharge history can be established for each individual, and unambiguous record linkage can be performed. Identification of first-time IHD events was obtained through linkage to the National Patient Registry, which contains data on diagnoses and dates of all hospital discharges in Denmark, and linkage to the Central Death Registry, which contains information on underlying and contributing causes of death. The National Patient Registry and the Central Death Registry have consistently used the International Classification of Disease (ICD) codes version 8 and from 1994 version 10. The following ICD codes were used to identify IHD cases: 410–414 in ICD-8, and I20-I25 in ICD-10. The vital status of the study population was followed in the Central Person Registry.

Statistical Methods

Data were analyzed by means of proportional hazards regression models, with age as the time variable, using SAS/STAT software version 8.2 (SAS Institute, Cary, NC). All included variables met the assumption of proportional hazards. First, we estimated the age-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) of primary IHD associated with stress intensity, stress frequency, and the stress score. Second, a multivariate Cox regression model was fitted to adjust for potential confounding from baseline covariates. By including age as the time variable the estimates were also soundly adjusted for confounding by age. Third, IHD comprises MI, other acute or chronic IHD, angina pectoris, and electrocardiographically diagnosed asymptomatic IHD. By combining the whole range of IHD subdiagnoses from severe cases of MIs to cases of asymptomatic IHD, one may end up combining subsets of the disease with different reporting patterns. For example, the diagnosis of angina pectoris may be more prone to reporting bias than the diagnosis of MI. To address this question, we conducted separate analyses for MI (ICD-codes 410 and I21-I22), angina pectoris (ICD-codes 413 and I20), and other IHD (ICD-codes 411, 412, 414 and I23-I25). Fourth, we conducted the analyses separately for fatal MI (defined as death within 28 days of the event) and nonfatal MI, to address associations with severity of disease. Finally, the associations were assessed in the different intervals of follow-up to estimate the effect of prolonged follow-up and to exclude reverse causality in the first 2 years of follow-up. All analyses were performed separately for men and women. A χ^2-test for goodness of fit was used to test for linear trends.

RESULTS

Baseline Characteristics

The mean age at baseline was 56 years; ages ranged from 21 to 98 years. Forty-four percent of the population reported medium levels of stress, whereas 8% reported high levels of stress (Table 1). Compared with the low-stress group, there were higher proportions of women, individuals with low education and low income, and individuals living alone in the high-stress group. Individuals in the high-stress group also were more likely to be physically inactive, be current smokers, and have higher mean alcohol intake. Systolic and diastolic blood pressure did not vary across stress levels. However, a higher proportion of individuals with high

TABLE 1. Baseline Characteristics of 11,839 Danish Men and Women Participating in the Second Examination of the Copenhagen City Heart Study in 1981–1983 According to the Categorized Stress Score

		Stress Score		
	Study Population (n = 11,839)	**Low (n = 5699)**	**Medium (n = 5161)**	**High (n = 979)**
Age at baseline (year); mean ± SD	56 ± 12	58 ± 13	54 ± 12	58 ± 11
Women; %	55	49	60	66
Education <8 y; %	45	47	41	53
Low income; %	32	32	27	49
Living alone; %	34	33	32	45
None or very little physical activity in leisure time; %	17	15	16	32
Current smoker; %	59	56	60	66
Alcohol intake (drinks/wk); mean ± SD	8.5 ± 13	8.3 ± 12	8.5 ± 12	9.7 ± 19
Body mass index (kg/m^2); mean ± SD	26 ± 4.2	26 ± 4.2	25 ± 4.2	25 ± 4.9
Systolic blood pressure (mm Hg); mean ± SD	140 ± 22	142 ± 22	138 ± 21	140 ± 22
Diastolic blood pressure (mm Hg); mean ± SD	85 ± 12	85 ± 12	85 ± 12	86 ± 12
Antihypertensive treatment; %	16	14	17	24
Blood glucose (mmol/L); mean ± SD	6.2 ± 1.7	6.3 ± 1.7	6.2 ± 1.7	6.2 ± 1.7
Total cholesterol (mmol/L); mean ± SD	5.9 ± 1.2	5.9 ± 1.2	5.9 ± 1.2	5.9 ± 1.2
HDL-cholesterol (mmol/L); mean ± SD	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3

stress received antihypertensive medication compared with individuals with lower levels of stress. There were no differences in mean body mass index, blood glucose, total cholesterol, and high-density lipoprotein cholesterol measured at baseline at the 3 stress levels.

Perceived Stress and Risk of IHD

During follow-up 2316 cases of incident IHD occurred: 1011 among the 6543 eligible women and 1305 among the 5296 eligible men. Of these, 1795 were hospital discharge diagnoses, and 521 were death diagnoses. The mean age at time of first IHD was 74 years for women and 70 years for men.

The age-adjusted hazard ratio of first-time IHD was positively associated with *stress intensity* among both women (test for trend: $P = 0.0005$) and men (test for trend: $P < 0.0001$; Table 2). The association attenuated after control for other covariates, after which high stress intensity was associated with an HR of 1.37 (95% CI = 1.09–1.72) for IHD in women and 1.27 (0.95–1.70) in men compared with those who reported no stress. Higher *frequency of stress* was also associated with a higher age-adjusted risk of primary IHD in a linear manner among both women and men. After adjustment for confounding, daily stress was associated with an HR of 1.19 (0.97–1.45) for primary IHD in women and 1.21 (0.98–1.51) in men. When stress frequency and stress intensity were combined into a *stress score*, the age-adjusted hazard ratio of primary IHD was higher with increasing stress score among both men and women. This trend became less pronounced after controlling for other covariates. High stress compared with low stress was associated with an HR of 1.23 (1.01–1.51) for IHD in women and 1.25 (1.00–1.56) in men.

Perceived Stress and Risk of MI, Angina Pectoris, and Other IHD

Of the 2316 primary cases of IHD that occurred during follow-up, 1001 were the result of MI, 407 were the result of angina pectoris, and the remaining 908 were the result of other IHD. Substantial differences in the associations with stress appeared after dividing IHD into these subcategories (Table 3). There was no association between high stress and risk of MI for women (HR = 0.80; 95% CI = 0.56–1.15) or men (1.09; 0.79–1.52), whereas there was a relatively strong association between high stress and angina pectoris in both women (HR = 1.83; 1.15–2.91) and men (2.14; 1.32–3.47). High stress also was associated with an increased risk of other IHD, especially in women. Addressing fatal and nonfatal MI separately yielded similar results (data not shown).

Influence of Period of Follow-Up

For all subdiagnoses of IHD, the risk estimates attenuated over time (Table 4). Perceived stress appeared to be associated with MI in a dose–response manner in the first period of follow-up, even though the relatively few cases made the effect estimates unstable (P value for trend = 0.12). No association between perceived stress and risk of MI was noted beyond the first 2 years of follow-up. Stress was relatively strongly associated with angina pectoris within all 3 periods of follow-up. High stress also was associated with higher risk of other IHD in the first 2 periods of follow-up, whereas the effect estimates attenuated in the last period of follow-up. The risk estimates for men and women were similar and the analyses were, because of power considerations, not divided by sex, but were instead adjusted for sex.

TABLE 2. Association of 3 Measurements of Stress With Incident Ischemic Heart Disease

	Women					Men				
	No.	No. IHD Cases	Incidence per 100,000 Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR* (95% CI)	No.	No. IHD Cases	Incidence per 100,000 Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR* (95% CI)
Stress intensity										
None†	2181	350	1021	1.00	1.00	2496	633	1914	1.00	1.00
Light	2543	357	857	1.04 (0.90–1.21)	1.03 (0.89–1.20)	1728	389	1557	1.07 (0.94–1.21)	1.08 (0.95–1.23)
Moderate	1357	202	928	1.11 (0.94–1.33)	1.05 (0.88–1.25)	879	228	1874	1.33 (1.14–1.55)	1.29 (1.10–1.51)
High	462	102	1488	1.62 (1.30–2.02)	1.37 (1.09–1.72)	193	55	2580	1.52 (1.16–2.01)	1.27 (0.95–1.70)
P value for trend				0.0005	0.03				<0.0001	0.002
Stress frequency										
Never†	2802	460	1088	1.00	1.00	2920	737	1908	1.00	1.00
Monthly	1970	253	798	1.04 (0.89–1.21)	1.03 (0.88–1.20)	1310	297	1556	1.12 (0.97–1.28)	1.15 (1.00–1.32)
Weekly	1124	168	972	1.14 (0.96–1.37)	1.11 (0.93–1.33)	725	174	1723	1.27 (1.07–1.50)	1.23 (1.04–1.47)
Daily	647	130	1361	1.35 (1.11–1.64)	1.19 (0.97–1.45)	341	97	2385	1.35 (1.09–1.66)	1.21 (0.98–1.51)
P value for trend				0.003	0.07				0.0002	0.005
Stress score										
Low stress (0–1 points)†	2781	447	1050	1.00	1.00	2918	731	1889	1.00	1.00
Medium stress (2–4 points)	3117	435	889	1.08 (0.94–1.23)	1.05 (0.92–1.21)	2044	478	1639	1.17 (1.04–1.32)	1.18 (1.04–1.33)
High stress (5–6 points)	645	129	1357	1.41 (1.16–1.72)	1.23 (1.01–1.51)	334	96	2428	1.45 (1.17–1.79)	1.25 (1.00–1.56)
P value for trend				0.002	0.06				0.0001	0.004

*Adjusted for age, education, income, cohabitation, smoking, alcohol consumption, body mass index, physical activity in leisure-time, and parental history of MI.
†Reference category.

DISCUSSION

We found that high levels of perceived stress was associated with a higher risk of IHD among 11,839 Danish men and women followed for 18 years. After dividing IHD into subdiagnoses, a markedly higher incidence of angina pectoris in particular, as well as other IHD, was found in the high-stress group compared with the low-stress group, whereas an association between perceived stress and risk of MI was virtually nonexistent. These findings contrast with the results from the Interheart Study,[1] in which moderate or

TABLE 3. Association of Perceived Stress With Myocardial Infarction, Angina Pectoris, and Other IHD

	Myocardial Infarction		Angina Pectoris		Other IHD	
	No.	Adjusted HR* (95% CI)	No.	Adjusted HR* (95% CI)	No.	Adjusted HR* (95% CI)
Women						
Low stress†	174	1.00	68	1.00	205	1.00
Medium stress	159	0.91 (0.73–1.13)	98	1.40 (1.02–1.92)	178	1.06 (0.86–1.30)
High stress	37	0.80 (0.56–1.15)	27	1.83 (1.15–2.91)	65	1.46 (1.09–1.95)
P value for trend		0.18		0.005		0.03
Men						
Low stress†	361	1.00	103	1.00	267	1.00
Medium stress	228	1.06 (0.89–1.25)	90	1.41 (1.05–1.89)	160	1.27 (1.03–1.56)
High stress	42	1.09 (0.79–1.52)	21	2.14 (1.32–3.47)	33	1.15 (0.78–1.69)
P value for trend		0.47		0.0007		0.06

*Adjusted for age, education, income, cohabitation, smoking, alcohol consumption, body mass index, physical activity in leisure-time, and parental history of MI.
†Reference category.

TABLE 4. Association of Stress Score With MI, Angina Pectoris, and Other IHD By Follow-Up Period

	Myocardial Infarction		Angina Pectoris		Other IHD	
Time Period of Follow-Up	No.	Adjusted HR* (95% CI)	No.	Adjusted HR* (95% CI)	No.	Adjusted HR* (95% CI)
1981/1982 (baseline) to 1983						
Low stress†	53	1.00	7	1.00	42	1.00
Medium stress	34	1.24 (0.79–1.94)	11	2.47 (0.93–6.61)	21	0.87 (0.50–1.52)
High stress	11	1.68 (0.85–3.29)	2	2.00 (0.40–9.94)	12	1.78 (0.88–3.60)
P value for trend		0.12		0.13		0.32
1984 to 1992						
Low stress†	303	1.00	70	1.00	208	1.00
Medium stress	212	1.06 (0.88–1.27)	71	1.31 (0.93–1.84)	138	1.20 (0.96–1.51)
High stress	40	0.88 (0.63–1.23)	21	2.00 (1.19–3.35)	45	1.59 (1.14–2.22)
P value for trend		0.87		0.009		0.006
1993 to 2000						
Low stress	179	1.00	94	1.00	222	1.00
Medium stress	141	0.97 (0.77–1.22)	106	1.29 (0.97–1.72)	179	1.18 (0.96–1.44)
High stress	28	0.97 (0.64–1.47)	25	1.79 (1.14–2.83)	41	1.14 (0.80–1.62)
P value for trend		0.79		0.008		0.18

*Adjusted for sex, age, education, income, cohabitation, smoking, alcohol consumption, body mass index, physical activity in leisure-time, and parental history of MI.
†Reference category.

severe general stress at work or at home was associated with an odds ratio of 1.55 for a first MI in a case–control study with 11,119 cases and 13,648 controls. Stress reporting may vary by case status, and the differences in results between the Interheart Study and the present prospective cohort study may partly be attributable to recall bias in the case–control design of the Interheart Study. Another explanation is that the effects of high levels of stress are acute in nature and therefore occur shortly after baseline. In this study, perceived stress seemed to be associated with higher risk of MI in the first 2 years of follow-up, whereas no association between perceived stress and risk of MI was noted beyond this period. Thus, a possible relation between stress and MI in the present study may have been diluted by the prolonged follow-up. Two other prospective studies have found a positive association between perceived stress and IHD. Men reporting permanent stress in a Swedish study were found to be at 50% higher risk of nonfatal MI/ fatal coronary artery disease compared with men at the lowest stress level.[2] Also, in a large Japanese population followed for 8 years, women with high levels of stress had a two-fold higher risk of death from coronary heart disease compared with women reporting low levels of stress, whereas the relation was less clear for men.[4] However, neither of the studies conducted separate analyses on first-time MI and angina pectoris, which complicates direct comparisons with the present study.

Strengths and Weaknesses of Our Study

The prospective design of the Copenhagen City Heart Study ensured temporality between self-reported stress and incidence of IHD. The large number of cases made it possible to assess the effect of stress on MI, angina pectoris, and other IHD separately. Linkage of civil registry numbers to nationwide population-based registers enabled identification of virtually all cases of IHD and allowed for nearly complete long-term follow-up.

Stress was defined as an individual state of high arousal and displeasure.[18] We measured stress by asking questions on stress intensity and stress frequency in which we explained the meaning of stress by giving examples of stress reactions such as tension, anxiety, etc. This is similar to the definition of psychologic stress used in the Interheart study and other studies that have addressed the association between perceived stress and cardiovascular disease.[1,2,4] By using a measure of perceived stress we accounted for the fact that each individual has different capacity and ways to cope with stressful situations.[19] A measure of perceived stress will therefore provide a better measure of the actual level of stress experienced by the individual as compared, for example, with a count of potential stressful situations defined by the researcher. However, the health effects of perceived stress may differ from those of acute stress from major life events, and the results can therefore not necessarily be generalized to other kinds of stress. Perceived stress was only assessed at baseline and may have changed over time in a manner that is most likely independent of subsequent IHD. This may have limited our ability to address acute health effects of stress. In another Danish cohort study,[20] which included a question on perceived stress, the majority of the participants (62%) reported the same level of stress in 1994 as in 2000 (Nielsen, unpublished data, 2005). Although this finding indicates that a measure of perceived stress may be relatively stable over time, a large minority changed stress levels over time. Thus,

we cannot exclude the possibility that in our study the relation between stress and risk of IHD may have been partly blurred by nondifferential misclassification from changes in stress levels over time.

Residual confounding from socioeconomic status (SES) may be of concern, because high levels of stress are, in our study population, most prevalent in lower SES groups, and there is a known socioeconomic gradient in IHD incidence.[21] However, the amount of residual confounding is proportional to the amount of confounding originally present, and evaluating the change of the effect estimates after adjustment for SES can provide an idea of the magnitude of distortion.[22] We have in this study used self-reported education and income as proxy-measures for SES. Statistical adjustment for education and income only slightly attenuated the association between perceived stress and risk of MI, angina pectoris, and other IHD (data not shown); residual confounding by SES does therefore not seem to be of great concern in this study.

We assumed that blood pressure, blood glucose, and blood lipids were possible intermediates on the pathway between stress and IHD, and these variables were therefore not included in the statistical analysis. However, it could be argued that these risk factors for IHD may be associated with stress because of unmeasured confounding and therefore should be included in the analysis. Adjustment for blood pressure, blood glucose, and blood lipids did, however, not change any of the risk estimates more than 5% (data not shown).

Causation or Bias?

The subdiagnoses of IHD share pathogenetic pathways to a large extent.[11] Thus, the marked differences in the associations, when IHD was divided into MI, angina pectoris, and other IHD, were unexpected. Individuals with a general tendency toward negative perception of different aspects of life may report both higher levels of stress and more cardiovascular symptoms.[5] This pattern will lead to a higher reporting of cardiovascular symptoms among highly stressed individuals, and thereby spuriously create an association between stress and cardiovascular disease. In a study of Scottish men, Macleod et al[5] found a strong association between self-reported stress and self-reported angina pectoris but no association with hospital admission for coronary heart disease. According to the authors, these contradicting findings indicated substantial bias in the reporting of angina pectoris. The fact, that we in this study find a relatively strong association between perceived stress and risk of angina pectoris but no clear association with MI, supports this concern. However, although Macleod et al studied self-reported angina pectoris, we used hospital discharge with angina pectoris, which is based on a physician's diagnosis, as outcome measure. Our measure of angina pectoris should therefore be less vulnerable to reporting bias, but angina pectoris may still be diagnosed more often in individuals with high levels of stress than among individuals with lower levels of stress.

The lack of a strong association between perceived stress and risk of MI in this study suggests that underlying atherosclerosis may not be a significant pathogenic pathway for stress in initially healthy individuals. This conclusion is supported by the fact that stress was associated with neither blood glucose nor blood lipids in the present study. While atherosclerosis may underlie most cases of angina pectoris, we cannot exclude the possibility that stress may causally affect cases of atypical angina, which is not always accompanied by evidence of atherosclerosis.

The strong association between perceived stress and angina pectoris in the first years after baseline could also be a result of reverse causality. Premonitory signs of IHD such as angina and breathlessness may have led to an increased level of perceived stress. However, preliminary signs of IHD that are strong enough to create a feeling of distress are unlikely go undiagnosed for years, and the possible bias due to reverse causality is expected to be most pronounced in the first years after baseline. The association between perceived stress and angina pectoris was indeed strongest in the first years of follow-up, but it remained noticeable in later periods of follow-up. Another possible explanation for the relatively strong effects of stress on all subdiagnoses of IHD in the first couple of years after baseline is that acute effects of high levels of stress may occur shortly after baseline and that the long follow-up diluted these relations. This may especially be true for MI for which the effect of stress completely disappeared after the first years of follow-up.

In conclusion, perceived stress was associated with higher first-time incidence of angina pectoris, but not with myocardial infarction beyond the first 2 years of follow-up. Although these results are consistent with some degree of reporting bias, they may also point towards different etiologic pathways for subdiagnoses of IHD. Future studies on stress and IHD should therefore address myocardial infarction and angina pectoris separately, use hospital discharge as disease identification, and address the influence of prolonged follow-up, as well as systematic differences in reporting patterns.

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