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Original Contribution

Perceived Stress and Cause-specific Mortality among Men and Women: Results from a Prospective Cohort Study

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The authors assessed the effect of psychological stress on total and cause-specific mortality among men and women. In 1981–1983, the 12,128 Danish participants in the Copenhagen City Heart Study were asked two questions on stress intensity and frequency and were followed in a nationwide registry until 2004, with <0.1% loss to follow-up. Sex differences were found in the relations between stress and mortality ($p = 0.02$). After adjustments, men with high stress versus low stress had higher all-cause mortality (hazard ratio (HR) = 1.32, 95% confidence interval (CI): 1.15, 1.52). This finding was most pronounced for deaths due to respiratory diseases (high vs. low stress: HR = 1.79, 95% CI: 1.10, 2.91), external causes (HR = 3.07, 95% CI: 1.65, 5.71), and suicide (HR = 5.91, 95% CI: 2.47, 14.16). High stress was related to a 2.59 (95% CI: 1.20, 5.61) higher risk of ischemic heart disease mortality for younger, but not older, men. In general, the effects of stress were most pronounced among younger and healthier men. No associations were found between stress and mortality among women, except among younger women with high stress, who experienced lower cancer mortality (HR = 0.51, 95% CI: 0.28, 0.92). Future preventive strategies may be targeted toward stress as a risk factor for premature death among middle-aged, presumably healthy men.

cause of death; mortality; prospective studies; stress, psychological

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-8, *International Classification of Diseases*, Eighth Revision; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision.

Editor's note: *An invited commentary on this article appears on page 000, and the authors' response is published on page 000.*

Acute stressors such as earthquakes or loss of a child may trigger death (1, 2), but there has been less focus on how chronic ''low-key'' stress of everyday life affects mortality in a general population. The human body responds to stress by activating the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, which may in turn affect the cardiovascular, the metabolic, and the immune systems (3). Prolonged activation of these systems may lead to stress-related disease and possibly increase the risk of premature death. Stress may also contribute to a higher frequency of adverse health behaviors, which may affect health. Previous studies have found stress to increase the risk of ischemic heart disease (4) and possibly decrease the risk of some hormone-dependent cancers (5–7), but the combined effect of everyday stress on total and cause-specific mortality remains unknown.

Some studies have suggested that the effects of stress on health outcomes are different for men and women (8–10), which may be explained by sex differences in vulnerability, stress response, or coping strategies. To our knowledge, the

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suggested sex differences remain to be studied in a large community sample. In addition, the stress response may have a different impact on different diseases, making it important to differentiate between causes of deaths. However, previous studies have not had sufficient statistical power to address uncommon causes of death such as those due to respiratory diseases, external causes, and suicide (8, 10–14).

We aimed to address the effects of stress on all-cause and cause-specific mortality as well as possible sex differences in vulnerability to stress in a large, population-based cohort study. Nationwide registries allowed for sound adjustment for baseline morbidity as well as almost complete assessment of long-term mortality.

MATERIALS AND METHODS

Study population

The longitudinal Copenhagen City Heart Study was initiated in Denmark in 1976. An age-stratified, random sample of 19,698 men and women 20–93 years of age were invited to participate in the study. A physical examination was performed, and the participants were asked to complete a questionnaire regarding various risk factors. In 1981–1983, the study population was supplemented with 500 men and women 20–25 years of age, and additional study assessments were performed for both new and continuing participants. Participants were asked about stress at the second examination only; we used this information as baseline for the present study. The 12,698 women and men who participated in the second examination constituted a response proportion of 70 percent, and the vast majority were Caucasian. All participants gave informed consent. A detailed description of the Copenhagen City Heart Study has previously been published (15). Participants for whom information on stress ($n = 42$) or other covariates ($n = 528$) was missing were excluded, leaving 6,700 women and 5,428 men for the analyses.

Perceived stress

Participants were asked about stress in terms of intensity and frequency at baseline in 1981–1983. In the questionnaire, stress was exemplified as the sensation of tension, nervousness, impatience, anxiety, or sleeplessness, and no time frame was specified. To assess *stress intensity*, participants were asked, Do you feel stressed? and the response categories were 0) no, 1) light, 2) moderate, or 3) high. To assess *stress frequency*, participants were asked, How often do you feel stressed? and the response categories were 0) never/hardly ever, 1) monthly, 2) weekly, or 3) daily. To combine the two dimensions of stress intensity and frequency, the two questions were added and combined into a seven-point stress score ranging from 0 (indicating low stress) to 6 (indicating high daily stress). For example, if a woman reported moderate, daily stress, she would be given a stress score of 5 (2 points for moderate at the intensity dimension plus 3 points for daily at the frequency dimension). To gain power for the statistical analyses, the stress score was further categorized into low (0–1 points), medium (2–4 points), and high (5–6 points).

Covariates

The following covariates were included in the analyses: age (continuous), marital status (married, unmarried, divorced/separated, widowed), educational level (<8, 8–10, ≥ 11 years of formal schooling), tobacco smoking (never smoker; former smoker; smoker of 1–14 g/day, 15–24 g/day, >24 g/day), alcohol intake (<1, 1–7, 8–14, 15–21, ≥ 22 drinks/week), physical activity during leisure time (sedentary or very light activity, 2–4 hours of light activity/week; >4 hours of light activity or 2–4 hours of high-level activity, competitional level or >4 hours of hard-level activity/week), body mass index (continuous), systolic blood pressure (continuous), and serum cholesterol (continuous). All covariates were measured at baseline in 1981–1983. Measures of baseline morbidity included having a history of ischemic heart disease, stroke, cancer, or diabetes mellitus at baseline.

Follow-up

Participants were followed from date of the second examination until date of death ($n = 6{,}121$), emigration out of Denmark ($n = 75$), or end of follow-up on March 11, 2004 ($n = 5{,}932$). Thus, fewer than 0.1 percent of participants were lost to follow-up because of emigration. Using the civil registry number, which is unique to every Danish citizen, all-cause and cause-specific mortality was identified through linkage to the Central Person Registry and the Central Death Registry, respectively. The Central Death Registry, which contains information on underlying and contributing causes of death, was updated until only December 31, 2001, and the follow-up period for the cause-specific mortality analyses was therefore stopped at this time point. The Central Death Registry has consistently used *International Classification of Diseases*, Eighth Revision (ICD-8) codes, and, since 1994, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) codes. The following codes were used to identify the different causes of death: cardiovascular diseases (ICD-8: 390–458; ICD-10: I00–I99, G45), ischemic heart disease (ICD-8: 410–414; ICD-10: I20–I25), stroke (ICD-8: 430–438; ICD-10: I60–I69, G45), cancer (ICD-8: 140–209; ICD-10: C00–C97), respiratory diseases (ICD-8: 460–519; ICD-10: J00–J99), external causes (ICD-8: 800–999; ICD-10: V01–Y98), suicide (ICD-8: 950–959; ICD-10: X60–X84), and symptoms or abnormal findings insufficiently defined (ICD-8: 780–796; ICD-10: R00–R99). Only the most common causes of death or causes of death expected to be strongly related to stress, such as suicide, were included in the cause-specific analyses.

Statistical methods

Data were analyzed by means of Cox proportional hazards models with age as the time variable. Initially, we estimated mortality risks and 95 percent confidence intervals

associated with stress. By including age as the time variable, the estimates were soundly adjusted for confounding by age. Second, a multivariate model was fitted to adjust for potential confounding from baseline covariates. Third, a model was fitted to also adjust for baseline morbidity. Fourth, plots of the hazard functions in the different stress strata over age indicated some differences in effects between younger and older participants, so the associations between stress and risk of all-cause, cardiovascular, ischemic heart disease, and cancer mortality were analyzed separately according to age categories at baseline. Because of a lack of statistical power, the age-stratified analyses were performed for only the most common causes of death. Fifth, the associations were assessed in different intervals of follow-up to estimate the effect of prolonged follow-up. Finally, the associations between stress and all-cause mortality were addressed in strata of sociodemographic status, lifestyle factors, and baseline morbidity. All analyses were performed separately for men and women; therefore, the risk estimates for men and women cannot be directly compared.

RESULTS

Baseline characteristics

The mean age at baseline was 56 years and ranged from 21 years to 98 years. Ten percent of the women and 6 percent of the men reported high levels of stress. The distribution of baseline variables is shown in table 1.

TABLE 1. Baseline characteristics* of 12,128 Danish men and women participating in the second examination of the Copenhagen City Heart Study in 1981–1983

	Women ($n = 6,700$)	Men ($n = 5,428$)
Age at baseline (years)	57 (12)	56 (13)
Stress score	2.0 (1.8)	1.5 (1.7)
High stress	10	6
Divorced	14	11
Education: <8 years	46	45
Current smoker	53	64
Alcohol intake >14 drinks/week	7	33
None or very little leisure-time physical activity	18	16
Body mass index (kg/m^2)	25 (5)	26 (4)
Systolic blood pressure (mm Hg)	139 (22)	143 (21)
Total cholesterol (mmol/liter)	6.1 (1.2)	5.7 (1.1)
Ischemic heart disease	2.3	5.0
Stroke	1.4	2.3
Cancer	9.1	4.6
Diabetes mellitus	1.8	3.5

* Values are expressed as mean (standard deviation) or percentage.

All-cause mortality

During 22 years of follow-up, 6,121 deaths occurred: 2,998 among the 6,700 eligible women and 3,123 among the 5,428 eligible men. The mean age at time of death was 76.4 years for women and 73.6 years for men. In an adjusted model, high stress was associated with a hazard ratio of 1.32 (95 percent confidence interval (CI): 1.15, 1.52) for all-cause mortality among men, whereas no association was found between high stress and all-cause mortality among women (hazard ratio (HR) = 1.00, 95 percent CI: 0.89, 1.13) (table 2). In support of a different relative effect of stress on mortality for men and women, the p value for a multiplicative interaction between stress and sex on all-cause mortality was 0.02.

Cardiovascular diseases

A total of 968 women and 1,104 men died from cardiovascular diseases during follow-up. This total included 444 deaths from ischemic heart disease and 226 deaths from stroke among women; the numbers for men were 633 and 185, respectively. Among women, high stress was associated with a higher risk of cardiovascular disease mortality in an age-adjusted model (HR = 1.31, 95 percent CI: 1.08, 1.60), but the association attenuated in an adjusted model (HR = 1.11, 95 percent CI: 0.91, 1.37). A similar pattern was observed for men. When we looked at ischemic heart disease mortality specifically, high stress compared with low stress was associated with a higher risk of ischemic heart disease mortality for both women (HR = 1.22, 95 percent CI: 0.90, 1.65) and men (HR = 1.25, 95 percent CI: 0.91, 1.73), but the risk estimates were unstable because of small numbers. There were no associations between stress and stroke mortality for either women or men.

Cancer

During follow-up, 847 women and 892 men died from cancer. In an adjusted model, women with high stress had a lower risk of dying from cancer compared with women with low stress (HR = 0.73, 95 percent CI: 0.57, 0.93). Stress was not associated with cancer mortality among men.

Respiratory diseases

A total of 255 women and 212 men died from respiratory diseases, such as acute respiratory infections, pneumonia, and chronic respiratory diseases. In an adjusted model, high stress was associated with a higher risk of death from respiratory diseases among men (HR = 1.79, 95 percent CI: 1.10, 2.91) but not among women (HR = 1.27, 95 percent CI: 0.86, 1.87).

External causes

Only 69 women and 86 men died because of external causes (e.g., accidents, intentional self-harm, assault) during follow-up, but high stress was strongly associated with these causes of death for men (table 2). In a fully adjusted model, men with high stress versus low stress had a threefold higher

TABLE 2. All-cause and cause-specific mortality risk associated with perceived stress among Danish participants in the Copenhagen City Heart Study in 1981–1983*

	Women			Men		
	Low stress	Medium stress	High stress	Low stress	Medium stress	High stress
All-cause mortality						
No. of deaths	1,365	1,285	348	1,816	1,074	233
Mortality rate/10,000 years	275	222	308	398	304	530
Age adjusted						
HR†	1 (ref†)	1.03	1.22	1 (ref)	1.08	1.52
95% CI†		0.95, 1.11	1.08, 1.37		1.00, 1.16	1.33, 1.75
Multiple adjusted‡						
HR	1 (ref)	0.99	1.03	1 (ref)	1.08	1.35
95% CI		0.92, 1.07	0.91, 1.16		1.00, 1.17	1.17, 1.55
Further adjusted for baseline morbidity§						
HR	1 (ref)	0.98	1.00	1 (ref)	1.04	1.32
95% CI		0.91, 1.06	0.89, 1.13		0.97, 1.13	1.15, 1.52
Cardiovascular disease mortality						
No. of deaths	466	380	122	655	381	68
Mortality rate/10,000 years	101	71	115	153	116	163
Age adjusted						
HR	1 (ref)	0.98	1.31	1 (ref)	1.13	1.25
95% CI		0.85, 1.12	1.08, 1.60		1.00, 1.29	0.97, 1.60
Multiple adjusted‡						
HR	1 (ref)	0.96	1.17	1 (ref)	1.17	1.15
95% CI		0.84, 1.11	0.96, 1.44		1.03, 1.33	0.89, 1.48
Further adjusted for baseline morbidity§						
HR	1 (ref)	0.95	1.11	1 (ref)	1.08	1.14
95% CI		0.83, 1.09	0.91, 1.37		0.95, 1.24	0.89, 1.47
Ischemic heart disease mortality						
No. of deaths	195	192	57	372	219	42
Mortality rate/10,000 years	42	36	54	87	67	101
Age adjusted						
HR	1 (ref)	1.16	1.45	1 (ref)	1.12	1.34
95% CI		0.95, 1.42	1.08, 1.95		0.95, 1.33	0.98, 1.85
Multiple adjusted‡						
HR	1 (ref)	1.15	1.30	1 (ref)	1.16	1.26
95% CI		0.94, 1.41	0.96, 1.76		0.98, 1.38	0.91, 1.75
Further adjusted for baseline morbidity§						
HR	1 (ref)	1.12	1.22	1 (ref)	1.06	1.25
95% CI		0.92, 1.37	0.90, 1.65		0.90, 1.27	0.91, 1.73
Stroke mortality						
No. of deaths	117	80	29	113	61	11
Mortality rate/10,000 years	25	15	27	26	19	26
Age adjusted						
HR	1 (ref)	0.83	1.26	1 (ref)	1.12	1.19
95% CI		0.62, 1.11	0.84, 1.90		0.82, 1.54	0.64, 2.20
Multiple adjusted‡						
HR	1 (ref)	0.82	1.17	1 (ref)	1.14	1.07
95% CI		0.61, 1.09	0.77, 1.78		0.83, 1.57	0.57, 2.01
Further adjusted for baseline morbidity§						
HR	1 (ref)	0.81	1.14	1 (ref)	1.04	1.06
95% CI		0.61, 1.09	0.75, 1.73		0.76, 1.44	0.56, 1.98
Cancer mortality						
No. of deaths	384	385	78	540	293	59
Mortality rate/10,000 years	83	72	74	126	89	141

Table continues

TABLE 2. Continued

	Women			Men		
	Low stress	Medium stress	High stress	Low stress	Medium stress	High stress
Age adjusted						
HR	1 (ref)	1.00	0.90	1 (ref)	0.96	1.25
95% CI		0.86, 1.15	0.71, 1.15		0.83, 1.11	0.95, 1.64
Multiple adjusted‡						
HR	1 (ref)	0.94	0.75	1 (ref)	0.95	1.13
95% CI		0.81, 1.08	0.58, 0.96		0.82, 1.10	0.86, 1.49
Further adjusted for baseline morbidity§						
HR	1 (ref)	0.93	0.73	1 (ref)	0.96	1.08
95% CI		0.81, 1.08	0.57, 0.93		0.83, 1.11	0.82, 1.43
Respiratory disease mortality						
No. of deaths	96	122	37	120	72	20
Mortality rate/10,000 years	21	23	35	28	22	48
Age adjusted						
HR	1 (ref)	1.42	1.83	1 (ref)	1.24	2.11
95% CI		1.08, 1.86	1.25, 2.68		0.92, 1.66	1.32, 3.40
Multiple adjusted‡						
HR	1 (ref)	1.20	1.27	1 (ref)	1.24	1.73
95% CI		0.92, 1.58	0.86, 1.87		0.92, 1.67	1.07, 2.81
Further adjusted for baseline morbidity§						
HR	1 (ref)	1.20	1.27	1 (ref)	1.25	1.79
95% CI		0.92, 1.58	0.86, 1.87		0.92, 1.69	1.10, 2.91
Death due to external causes						
No. of deaths	31	30	8	42	29	15
Mortality rate/10,000 years	7	6	8	10	9	36
Age adjusted						
HR	1 (ref)	0.99	1.21	1 (ref)	1.01	3.76
95% CI		0.59, 1.64	0.55, 2.63		0.63, 1.64	2.07, 6.84
Multiple adjusted‡						
HR	1 (ref)	0.96	1.03	1 (ref)	0.96	3.02
95% CI		0.57, 1.60	0.46, 2.29		0.59, 1.57	1.63, 5.61
Further adjusted for baseline morbidity§						
HR	1 (ref)	0.95	1.01	1 (ref)	0.96	3.07
95% CI		0.57, 1.60	0.45, 2.26		0.59, 1.57	1.65, 5.71
Death due to symptoms or abnormal findings that were insufficiently defined						
No. of deaths	66	80	24	107	51	20
Mortality rate/10,000 years	14	15	23	25	16	48
Age adjusted						
HR	1 (ref)	1.38	1.79	1 (ref)	0.86	2.15
95% CI		1.00, 1.92	1.12, 2.86		0.61, 1.20	1.33, 3.48
Multiple adjusted‡						
HR	1 (ref)	1.38	1.51	1 (ref)	0.84	1.70
95% CI		0.99, 1.92	0.93, 2.44		0.60, 1.19	1.05, 2.78
Further adjusted for baseline morbidity§						
HR	1 (ref)	1.39	1.51	1 (ref)	0.83	1.70
95% CI		0.99, 1.93	0.94, 2.45		0.59, 1.17	1.04, 2.78

* All covariates were measured at baseline (1981–1983).

† HR, hazard ratio; ref, referent; CI, confidence interval.

‡ Multiple adjusted for age, marital status, educational level, tobacco smoking, alcohol intake, physical activity in leisure time, body mass index, systolic blood pressure, and serum cholesterol.

§ Baseline morbidity: ischemic heart disease, stroke, cancer, and diabetes mellitus.

risk of death due to external causes (HR = 3.07, 95 percent CI: 1.65, 5.71). Suicide accounted for 37 of the deaths among men, and even though the results were rather unstable, high stress was associated with an almost sixfold higher risk of suicide (HR = 5.91, 95 percent CI: 2.47, 14.16) in an adjusted model of men (data not shown). We found no associations between stress and death due to external causes or suicide for women.

Deaths due to symptoms or abnormal findings defined insufficiently

Several deaths (170 women and 178 men) were classified as due to symptoms or abnormal findings that were insufficiently defined, such as, for example, sudden death. High stress was associated with a higher risk of having an insufficiently defined cause of death for both women (HR = 1.51, 95 percent CI: 0.94, 2.45) and men (HR = 1.70, 95 percent CI: 1.04, 2.78).

Subgroup analyses

The associations between stress and all-cause and cause-specific mortality depended on age at baseline (table 3). Hence, the association between stress and risk of all-cause mortality was strongest among men younger than age 55 years at baseline (HR = 1.44, 95 percent CI: 1.06, 1.96), whereas there was no clear association between stress and mortality among men older than age 70 years at baseline (HR = 1.19, 95 percent CI: 0.85, 1.67). High stress was associated with a more than twofold higher risk of ischemic heart disease for younger men (HR = 2.59, 95 percent CI: 1.20, 5.61), while there was no association between stress and ischemic heart disease mortality among older men. The lower cancer mortality observed among stressed women was most pronounced for women younger than age 55 years at baseline (HR = 0.51, 95 percent CI: 0.28, 0.92).

The association between stress and risk of all-cause mortality observed among men was strongest in the first 2–3 years of follow-up, but the association remained in the following 10-year period of follow-up (table 4). Stress was not predictive of death after 12 years of follow-up.

The observed positive association between stress and all-cause mortality among men differed in different strata of sociodemographic status, lifestyle factors, and baseline morbidity (table 5). High stress was associated with a higher mortality risk at all educational levels but was most pronounced among men at the highest level (HR = 1.58, 95 percent CI: 1.02, 2.46). In general, the association between high stress and mortality risk was most pronounced among men with the following characteristics: physically active, never or former smoker, normal weight, and normal systolic blood pressure. High stress was associated with higher risk of death from all causes irrespective of baseline disease. Among healthy men who were free of baseline disease, were nonsmokers, were physically active, had normal blood pressure, and had a body mass index below 30 kg/m^2, high stress compared with low stress was associated with an almost fourfold higher mortality risk (HR = 3.90, 95 percent CI: 1.92, 7.93). Only 11 percent of male participants fulfilled these criteria, and the baseline mortality rate was of course lower among these men (126/10,000 years) than among those not belonging to this category (445/10,000 years). However, the rate differences between high and low stress were higher among the healthy men (189/10,000 years) than among other men (101/10,000 years), supporting a higher risk associated with high stress in healthy men even in absolute terms. As many as 12.5 percent of all deaths could be ascribed to stress among the healthy men compared with only 3.4 percent among all men. The pattern of causes of deaths among the healthy men was similar to that observed among all male participants. No associations were found between stress and all-cause mortality in any of the above-mentioned strata for women (data not shown).

DISCUSSION

In this large prospective study, high stress, measured by a single question on stress intensity and stress frequency, was associated with higher all-cause mortality among men but not among women. For men, this relation was most pronounced for deaths due to respiratory diseases, external causes, and insufficiently defined symptoms/abnormal findings. Men with high stress versus low stress were found to have an almost sixfold higher risk of suicide. High stress was also related to a doubling in the risk of ischemic heart disease mortality among younger but not older men. In general, the detrimental effects of stress were most pronounced among younger and healthier men. No clear associations were found between stress and mortality among women, except that younger women with high stress experienced lower cancer mortality rates.

Previous studies on the association between different measures of stress (including marital dissolution, work-related stressors, and caregiving stress) and mortality have not been as thorough as the present study in addressing cause-specific mortality and vulnerable subgroups. The observed differences in effect according to length of follow-up and in different groups defined by age and lifestyle factors in the present study may explain some of the heterogeneity in the results previously observed in other studies (8–14, 16).

Strengths and weaknesses

The large sample size and the long follow-up of the Copenhagen City Heart Study ensured sufficient statistical power to assess the effects of stress on a broad range of causes of death, including uncommon ones. Inclusion of both men and women allowed for assessment of sex differences in the associations. Linkage of civil registry numbers to a death registry with nationwide coverage enabled identification of virtually all causes of death and allowed for nearly complete long-term follow-up. Information on sociodemographic status, lifestyle factors, and baseline morbidity allowed for thorough adjustment for confounding.

Perceived stress was assessed by combining two questions on stress intensity and stress frequency asked at baseline. Since these two questions were not validated against a more extensive scale, such as the Perceived Stress Scale

TABLE 3. Multiple-adjusted hazard ratios* for all-cause and cause-specific mortality associated with perceived stress, according to age category at baseline, among Danish participants in the Copenhagen City Heart Study in 1981–1983†

	Women			Men		
	Low stress	Medium stress	High stress	Low stress	Medium stress	High stress
All-cause mortality						
<55 years at baseline						
Adjusted HR‡	1 (ref‡)	0.84	0.86	1 (ref)	0.93	1.44
95% CI‡		0.69, 1.03	0.63, 1.18		0.79, 1.11	1.06, 1.96
55–70 years at baseline						
Adjusted HR	1 (ref)	0.98	1.06	1 (ref)	1.05	1.31
95% CI		0.89, 1.09	0.91, 1.24		0.95, 1.16	1.09, 1.56
>70 years at baseline						
Adjusted HR	1 (ref)	1.10	0.99	1 (ref)	1.15	1.19
95% CI		0.93, 1.29	0.77, 1.27		0.94, 1.39	0.85, 1.67
Cardiovascular disease mortality						
<55 years at baseline						
Adjusted HR	1 (ref)	1.00	0.82	1 (ref)	1.00	1.72
95% CI		0.58, 1.71	0.34, 1.99		0.71, 1.42	0.94, 3.15
55–70 years at baseline						
Adjusted HR	1 (ref)	0.94	1.08	1 (ref)	1.09	1.11
95% CI		0.78, 1.13	0.82, 1.44		0.93, 1.29	0.79, 1.56
>70 years at baseline						
Adjusted HR	1 (ref)	1.04	1.23	1 (ref)	1.19	1.00
95% CI		0.82, 1.32	0.89, 1.70		0.91, 1.57	0.59, 1.71
Ischemic heart disease mortality						
<55 years at baseline						
Adjusted HR	1 (ref)	0.89	1.28	1 (ref)	1.10	2.59
95% CI		0.40, 1.99	0.43, 3.86		0.60, 1.76	1.20, 5.61
55–70 years at baseline						
Adjusted HR	1 (ref)	1.19	1.33	1 (ref)	1.05	1.25
95% CI		0.91, 1.56	0.88, 2.00		0.85, 1.31	0.82, 1.92
>70 years at baseline						
Adjusted HR	1 (ref)	1.22	1.16	1 (ref)	1.17	0.84
95% CI		0.86, 1.72	0.69, 1.94		0.81, 1.68	0.41, 1.75
Cancer mortality						
<55 years at baseline						
Adjusted HR	1 (ref)	0.87	0.51	1 (ref)	0.88	0.84
95% CI		0.64, 1.18	0.28, 0.92		0.65, 1.17	0.43, 1.64
55–70 years at baseline						
Adjusted HR	1 (ref)	0.92	0.84	1 (ref)	0.94	1.08
95% CI		0.77, 1.10	0.62, 1.14		0.78, 1.14	0.77, 1.52
>70 years at baseline						
Adjusted HR	1 (ref)	1.15	0.76	1 (ref)	1.03	1.25
95% CI		0.79, 1.69	0.40, 1.47		0.69, 1.53	0.63, 2.49

* Multiple adjusted for age, marital status, educational level, tobacco smoking, alcohol intake, physical activity in leisure time, body mass index, systolic blood pressure, serum cholesterol, and baseline morbidity: ischemic heart disease, stroke, cancer, and diabetes mellitus.

† All covariates were measured at baseline (1981–1983).

‡ HR, hazard ratio; ref, referent; CI, confidence interval.

TABLE 4. Multiple-adjusted hazard ratios* for all-cause mortality associated with perceived stress, according to period of follow-up, among Danish participants in the Copenhagen City Heart Study in 1981–1983†

	Women			Men		
	Low stress	Medium stress	High stress	Low stress	Medium stress	High stress
Baseline (1981–1983) to 1984						
No. of deaths	67	64	21	171	92	39
Adjusted HR‡	1 (ref‡)	1.06	0.99	1 (ref)	1.09	1.94
95% CI‡		0.75, 1.51	0.59, 1.64		0.84, 1.42	1.35, 2.79
1985–1994						
No. of deaths	560	528	130	843	463	108
Adjusted HR	1 (ref)	1.02	0.90	1 (ref)	1.02	1.32
95% CI		0.91, 1.15	0.74, 1.09		0.91, 1.15	1.07, 1.62
1995–2004						
No. of deaths	738	693	197	802	519	86
Adjusted HR	1 (ref)	0.93	1.07	1 (ref)	1.03	1.18
95% CI		0.84, 1.03	0.91, 1.26		0.91, 1.15	0.94, 1.48

* Multiple adjusted for age, marital status, educational level, tobacco smoking, alcohol intake, physical activity in leisure time, body mass index, systolic blood pressure, serum cholesterol, and baseline morbidity: ischemic heart disease, stroke, cancer, and diabetes mellitus.

† All covariates were measured at baseline (1981–1983).

‡ HR, hazard ratio; ref, referent; CI, confidence interval.

(17), we could not fully determine the magnitude of the misclassification. By using only two questions on stress instead of a more extensive scale, an even stronger relation between stress and mortality risk may have been blurred. However, in a recent study, two single-item measures on stress were found to be just as reliable and valid as three fully validated, multi-item measures on perceived stress (18), which may provide some assurance that the single-item measurements used in the present study provided a reasonable measure of stress. In addition, the same measure of stress has been found to be predictive of a range of diseases in the same cohort (5, 19, 20). Stress was assessed at baseline only and may therefore not have fully captured chronic stress, which may explain the diluted effects of stress with prolonged follow-up.

Stress may be merely a marker of baseline physical illness (21). However, we found the relation between stress and mortality to be strongest among healthy men; therefore, we find this explanation unlikely. In addition, if stress was merely an indicator of baseline morbidity, we would not have expected such differential effects of stress on cause-specific mortality as were observed in the present study, especially not on death from external causes. Furthermore, even though the effect of stress was strongest in the first years of follow-up, it still remained in the next 10 years of follow-up.

Residual confounding from socioeconomic status may be of concern. In a Scottish study, in which stress (unlike most other studies) was not associated with social disadvantage, Macleod et al. (22) found no association between stress and all-cause mortality. They argued that previous reports of positive associations between stress and mortality may be due to residual confounding from socioeconomic status (22). We found a relation between stress and mortality among men in all educational strata, and we even found the association to be most pronounced in men with high educational levels, which contradicts the argument of Macleod et al.

Changes in the risk estimates after adjustments may also raise concern about residual confounding. However, the observed threefold higher risk of death due to external causes among stressed men is unlikely to be explained by residual confounding or unmeasured confounding from yet-unknown confounders.

We adjusted the associations for alcohol intake, smoking, cholesterol, and blood pressure, which may have been possible intermediates on the pathway between stress and mortality risk. We cannot exclude the possibility that some of the effect of stress on mortality may have been mediated through these factors and that the reported estimates therefore underestimated the true relations.

Part of the observed sex differences in the effects might be explained by differential reporting. However, although we observed sex differences in the reporting of stress, the differences were relatively small, and we find it unlikely that they fully explain the large sex differences we found in the present study.

Possible causal pathways

The human body is in a state of dynamic equilibrium, also known as allostasis (23). The stress response is initiated

TABLE 5. Multiple-adjusted hazard ratios* for all-cause mortality associated with perceived stress in strata of sociodemographic status, lifestyle factors, and baseline morbidity among Danish men participating in the Copenhagen City Heart Study in 1981–1983†

	Low stress	Medium stress		High stress	
		HR‡	95% CI‡	HR	95% CI
Educational level					
Low	1 (ref‡)	1.11	1.00, 1.24	1.32	1.09, 1.59
Medium	1 (ref)	1.06	0.94, 1.21	1.23	0.96, 1.57
High	1 (ref)	0.80	0.63, 1.02	1.58	1.02, 2.46
Marital status					
Married	1 (ref)	1.05	0.96, 1.15	1.28	1.08, 1.53
Unmarried/divorced/widowed	1 (ref)	1.06	0.91, 1.23	1.44	1.14, 1.82
Physical activity in leisure time					
Inactive	1 (ref)	1.04	0.86, 1.25	1.03	0.79, 1.33
Active	1 (ref)	1.05	0.96, 1.14	1.41	1.19, 1.67
Tobacco smoking					
Never or former smoker	1 (ref)	0.98	0.85, 1.13	1.59	1.23, 2.05
Current smoker	1 (ref)	1.07	0.97, 1.17	1.24	1.05, 1.46
Alcohol intake (drinks/week)					
$\leq$14	1 (ref)	1.06	0.96, 1.17	1.36	1.15, 1.62
>14	1 (ref)	1.00	0.88, 1.14	1.30	1.03, 1.65
Body mass index (kg/m^2)					
<25	1 (ref)	1.09	0.96, 1.23	1.57	1.27, 1.95
25–30	1 (ref)	1.01	0.91, 1.13	1.24	1.01, 1.52
>30	1 (ref)	1.05	0.81, 1.36	0.78	0.51, 1.21
Systolic blood pressure (mm Hg)					
<140	1 (ref)	1.02	0.90, 1.16	1.58	1.27, 1.96
$\geq$140	1 (ref)	1.05	0.95, 1.16	1.15	0.96, 1.38
Total cholesterol (mmol/liter)					
<6.2	1 (ref)	1.03	0.94, 1.13	1.31	1.11, 1.55
$\geq$6.2	1 (ref)	1.13	0.99, 1.29	1.42	1.11, 1.83
Baseline disease					
No	1 (ref)	1.08	0.99, 1.18	1.29	1.10, 1.52
Yes	1 (ref)	0.96	0.81, 1.14	1.40	1.06, 1.86

* Multiple adjusted for age, marital status, educational level, tobacco smoking, alcohol intake, physical activity in leisure time, body mass index, systolic blood pressure, serum cholesterol, and baseline morbidity: ischemic heart disease, stroke, cancer, and diabetes mellitus.

† All covariates were measured at baseline (1981–1983).

‡ HR, hazard ratio; CI, confidence interval; ref, referent.

when external or internal forces, the stressors, challenge this allostasis. The sympathetic nervous system and the hypothalamic-pituitary-adrenal axis are the main mediators of the stress response. Most allostatic mediators have a biphasic role, with protective effects in the short term and damaging effects under chronic stress. Long-term stress may therefore play a role both in the development and the progression of diseases and thereby explain the increased mortality risk we observed in the present study. Compared with women, men seem to respond to stress with greater reactivity of the hypothalamic-pituitary-adrenal axis (24), which may partly explain the observed sex differences.

Some of the mediators released by the hypothalamic-pituitary-adrenal axis seem to be capable of suppressing the immune function (3, 25), which may explain the higher respiratory disease mortality observed among stressed men. Other possible explanations may be that stressed men are more reluctant to quit smoking during follow-up or that they are more susceptible to progression of smoking-related diseases. Stress can also 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 (3)—which may explain the observed higher risk of ischemic heart disease mortality among stressed men younger than age 55 years.

Stress was associated with a markedly higher risk of death due to external causes, particularly suicide, among men. This higher mortality risk may be mediated through either risk behavior or mental processes such as depression or burnout. To prevent stress-related deaths due to external causes, the underlying causal mechanisms need to be further explored. It is also unclear why stress was associated with a higher risk of death from symptoms/abnormal findings that were insufficiently defined. A hypothetical explanation may be that young, presumably healthy men who suddenly die from stress are more likely to be classified in this diagnostic category.

We found stress to be associated with lower cancer mortality among especially younger women. Breast cancer is the major cause of cancer death among younger women, and we previously found stress to be associated with a lower incidence of breast cancer among stressed women in the same cohort (5). A prolonged physiologic stress response may impair the normal synthesis of estrogens (26, 27) and thereby explain the lower incidence and mortality of hormone-dependent cancers among women.

In conclusion, perceived stress, measured by a single item, seems to increase the risk of total and cause-specific mortality among men but not among women. If these results can be confirmed in other studies with more comprehensive measures of stress, future preventive strategies may be targeted toward stress as an important risk factor for premature death in young and middle-aged, presumably healthy men.

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