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Perceived stress and risk of colorectal cancer in men and women: a prospective cohort study

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Abstract. Nielsen NR, Kristensen TS, Strandberg-Larsen K, Zhang Z-F, Schnohr P & Grønbæk M (National Institute of Public Health, Copenhagen, Denmark; UCLA School of Public Health, Los Angeles, CA, USA; National Institute of Occupational Health, Copenhagen; and Bispebjerg University Hospital, Copenhagen; Denmark) *J Intern Med* 2008; 263: 192–202.

Objective. We aim to assess the relationship between stress and risk of primary colorectal cancer in men and women.

Design. A prospective cohort study

Setting. The Copenhagen City Heart Study, Denmark

Subjects. A total of 6488 women and 5426 men were included in the study. The participants were asked about intensity and frequency of stress at baseline in 1981–1983 and were followed until the end of 2000 in the Danish Cancer Registry. Less than 0.1% was lost to follow-up.

Main outcome measures. First time incidence of primary colorectal cancer.

Results. During follow-up 162 women and 166 men were diagnosed with colorectal cancer. Women with moderate and high stress intensity had a hazard ratio of 0.60 (95% CI: 0.37–0.98) and 0.52 (0.23–1.14) for colorectal cancer, respectively, compared to women with no stress. For colon cancer, a one-unit increase on a seven-point stress-score was associated with an 11% lower incidence of the disease (HR = 0.89, 95% CI: 0.81–0.99) amongst women. There was no consistent evidence of an association between stress and colorectal cancer in men.

Conclusion. Perceived stress was associated with lower risk of particularly colon cancer in women, whilst there was no clear relationship between stress and colorectal cancer in men.

Keywords: colorectal neoplasms, prospective studies, psychological stress.

Introduction

Colorectal cancer is the third most common cancer worldwide and there are sex differences in the incidence of the disease [1]. Psychological stress may directly affect the risk of colorectal cancer by suppressing immune function [2], which can lead to increased neoplastic growth. Stress may also indirectly affect the risk of colorectal cancer by altering physical activity levels and dietary habits, which are some of the major risk factors for colorectal cancer [3, 4]. Stress may increase the risk of colorectal cancer by these pathways. However, colorectal cell lines also express both functional oestrogen receptors, which mediate the proliferative activity of oestradiol, and enzymes capable to synthesize and metabolize oestrogens, which suggests that sex steroid hormones may also play a role in the aetiology of colorectal cancer

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[5–9]. This is supported by the fact that women with primary breast cancer, especially those receiving tamoxifen treatment, as well as men with primary testicular cancer, are at higher risk of developing colorectal cancer [10, 11]. Persistent activation of stress hormones seems to impair the gonadal synthesis of oestrogens and thereby reduce bioavailable oestradiol and testosterone [12]. Stress-induced impairment of oestrogen synthesis and metabolism may, therefore, protect against colorectal cancer. Whether stress increases the risk of colorectal cancer through a suppression of the immune function and changes in health-related behaviour or decreases the risk of colorectal cancer by impairment of the oestrogen synthesis and metabolism are yet to be established.

Only few studies have addressed a potential relationship between stress and colorectal cancer and the majority of these studies have focused on stressful life events or work-related stress and have been applied in case–control designs [13–16]. The physiological reaction to acute stress of stressful life events may be very different from the reaction to a more chronic state of stress in everyday life. Thus, the health consequences of these two measures are not directly comparable. Further, it is stressful to be diagnosed with cancer, which may render it difficult for cancer patients to recall their stress level prior to the diagnosis without recall bias, and thereby to validly assess the association between stress and risk of colorectal cancer in a case–control design. Only one previous prospective cohort study addressed the association between stress and colorectal cancer [17]. However, they used colorectal cancer mortality as their outcome measure, which does not allow for a distinction between causal and prognostic factors. We aim to address the association between perceived stress of everyday life and the incidence of primary colorectal cancer in a prospective design.

Materials and Methods

Study population

The Copenhagen City Heart Study is a longitudinal study initiated in 1976. An age-stratified sample of 19 698 men and women was randomly drawn from the Central Population Registry and invited to participate in the study. A physical examination was performed and the participants were asked to fill in a self-administered 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. This second examination with 12 698 participants included questions on stress and is therefore used as baseline for the present study. The response proportion was 70%. The vast majority of participants were Caucasians and all participants gave informed consent. A detailed description of the Copenhagen City Heart Study was previously published [18]. Individuals with colorectal cancer before the baseline ($n = 49$) or with lacking information on stress ($n = 42$) or other covariates ($n = 605$) were excluded. Women lacking information on reproductive and hormonal factors ($n = 88$) were also excluded, leaving 6488 women and 5426 men for the analyses.

Perceived stress

The study participants were asked two questions about their level of stress in terms of intensity and frequency with no time frame specified. In the questionnaire, stress was exemplified as the sensation of tension, nervousness, impatience, anxiety, or sleeplessness. To assess stress intensity, the participants were asked: ‘Do you feel stressed?’ The response categories were: (0) none, (1) light, (2) moderate, or (3) high. To measure stress frequency, the participants were asked: ‘How often do you feel stressed?’ The response categories were: (0) never/-hardly ever, (1) monthly, (2) weekly, or (3) daily. The scores of the two questions were added and combined into a continuous stress-score from 0 to 6. For example, if a woman reported moderate daily stress, this woman 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). This stress-score was 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.* [19]: Age (continuous), education (less than 8 years, 8–11 years, or 12 or more years), income (<$1000, $1000 to $2500, or more than $2500), cohabitation (living with partner and/or children, or living alone), physical activity during leisure time (none or very little activity, 2–4 h of light activity per week, more than 4 h of light activity or 2–4 h of high level activity, and competitional level or more than 4 h of hard level activity per week), alcohol consumption (<1, 1–14, >14 drinks per week), tobacco smoking (never-smoker, ex-smoker, smokers of 1–14 grams per day, 15–24 grams per day, and more than 24 grams per day), body mass index (<18.5, 18.5–30, >30 kg m^{-2}), and diabetes mellitus (yes/no). Analyses conducted in women were also adjusted for the current oral contraceptive use (yes/no), hormone therapy (yes/no), menopause (yes/no), and number of children (0, 1–2, 3 or more). All variables were measured at baseline in 1981–1983.

Follow-up

Participants were followed from date of the second examination till the date of the first diagnosis of primary colorectal cancer (162 in women and 166 in men), death from other causes (n = 4816), emigration (n = 55), or end of follow-up on December 31, 2000 (n = 6715). Thus, less than 0.1% of the participants were lost to follow-up due to emigration. Using the civil registry number, which is unique to every Danish citizen, diagnoses of primary colorectal cancer were identified through linkage to the Danish National Cancer Registry, which contains data on all cancer diagnoses in Denmark since 1942. The following ICD7-codes were used to identify primary invasive *colon cancer* cases: 153.0, 153.4, 153.5, 154.9, 253.0–253.4, 453.0–453.5, 453.8, 454.9, 853.0–853.5 and 854.9. The following ICD7-codes were used to identify primary invasive *rectal cancer* cases: 154.0, 454.0 and 854.0. The vital status of the study population was followed in the Central Death Registry.

Statistical methods

Data were analysed by means of proportional hazards regression models with age as the time scale using SAS/STAT software version 8.2 [20]. Stress intensity, stress frequency, and the stress score all met the assumption of proportional hazards. We estimated the age-adjusted and multi-adjusted hazard ratio of colorectal cancer associated with stress intensity, stress frequency, and the stress score. By including age as the time scale, the estimates were soundly adjusted for confounding by age. The analyses were also done separately for colon and rectal cancer. Trend analyses were used to address dose–response associations between stress and colorectal cancer. There appeared to be sex differences in the associations, and all analyses were therefore conducted separately for men and women. The associations between stress and the risk of colorectal cancer in women were also assessed in subgroups according to the menopausal status at the baseline. Finally, to address the possible effect of prolonged follow-up, we conducted the analyses between the stress score and colorectal cancer separately for the first and last nine years of follow-up.

Results

Baseline characteristics

The mean age at baseline was 57 years for women and 56 years for men ranging from 21 to 91 years. Ten per cent of the women and six per cent of the men reported high levels of stress (Table 1). Individuals with medium stress were slightly younger than individuals with both low and high stress levels. Mean body mass index and percentage with diabetes mellitus were similar at the different stress levels in both men and women. A higher proportion of men and women at the high stress level had low education, low income, high alcohol intake, were current smokers, and were physically inactive in their leisure time compared to men and women with low levels of stress. A lower proportion of highly stressed women were nulliparous, premenopausal, and used oral contraceptives compared to less stressed women, whilst a higher proportion received hormone therapy.

Table 1 Baseline characteristics of the 6488 women and 5426 men participating in the second examination of the Copenhagen City Heart Study in 1981–1983

	Study population	Stress score		
		Low	Medium	High
Women				
Persons, *n* (% of study sample)	6488	2745 (42)	3101 (48)	642 (10)
Mean age (SD)	57 (12)	58 (13)	55 (12)	58 (11)
<8 years of education (%)	2961 (45)	1286 (47)	1322 (43)	353 (55)
Income of < $1000/month (%)	2431 (37)	1080 (39)	996 (32)	355 (55)
None/little physical activity (%)	1124 (17)	417 (15)	494 (16)	213 (33)
>14 alcoholic drinks week^{-1} (%)	445 (7)	150 (5)	228 (7)	67 (10)
Mean body mass index, kg m^{-2} (SD)	25 (5)	25 (5)	25 (4)	25 (5)
Current smokers (%)	3468 (53)	1343 (49)	1727 (56)	398 (62)
Diabetes mellitus (%)	114 (2)	48 (2)	56 (2)	10 (2)
Nulliparous (%)	1608 (25)	726 (26)	739 (24)	143 (22)
Hormone replacement therapy (%)	995 (15)	315 (11)	539 (17)	141 (22)
Premenopausal, %	1716 (26)	655 (24)	949 (31)	112 (17)
Current oral contraceptive users (%)	249 (4)	99 (4)	143 (5)	7 (1)
Men				
Persons, *n* (% of study sample)	5426	2984 (55)	2984 (39)	329 (6)
Mean age (SD)	56 (13)	58 (13)	53 (12)	57 (11)
<8 years of education (%)	2122 (45)	1405 (47)	845 (40)	172 (52)
Income of <$1000/month (%)	1345 (25)	774 (26)	439 (21)	132 (40)
None/little physical activity (%)	854 (16)	425 (14)	323 (15)	106 (32)
>14 alcoholic drinks week^{-1} (%)	1791 (33)	911 (31)	760 (36)	120 (36)
Mean body mass index, kg m^{-2} (SD)	26 (4)	26 (4)	26 (4)	26 (4)
Current smokers (%)	3466 (64)	1870 (63)	1362 (64)	234 (71)
Diabetes mellitus (%)	187 (3)	99 (3)	77 (4)	11 (3)

Perceived stress and risk of colorectal cancer in women

During follow-up, 162 cases of primary colorectal cancer (125 colon and 37 rectal cancers) occurred in women. Women reporting moderate and high *stress intensity* had a hazard ratio of 0.60 (95% CI: 0.37–0.98) and 0.52 (0.23–1.14) for colorectal cancer, respectively, compared to women who reported no stress intensity (Table 2), and there appeared to be a linear dose–response association (*P*-value for trend: 0.02). For *stress frequency*, monthly and weekly stresses were not associated with the risk of colorectal cancer, but women reporting daily stress were at a lower risk of developing colorectal cancer (HR = 0.28, 95% CI: 0.11–0.67) compared to women who never experienced stress. For each unit increase in the combined seven-point *stress score*, women were 10 per cent less likely to develop colorectal cancer (HR = 0.90, 95% CI: 0.82–0.98). Dividing colorectal cancer into colon and rectal cancer made it clear that the association between high stress and lower risk of colorectal cancer was the strongest for colon cancer.

Stress intensity was associated with lower risk of *colon cancer* in an inverse dose–response manner (test for trend: $P = 0.03$). Daily stress was also associated with lower risk of colon cancer (HR = 0.23, 95% CI: 0.07–0.73), whilst monthly and weekly stresses were not associated with colon cancer. The

Table 2 *Women.* Incidence, hazard ratio (HR), and 95% confidence interval (CI) for first-time incidence of primary colorectal, colon, and rectal cancer associated with perceived stress amongst 6,488 women participating in the Copenhagen City Heart Study in 1981–1983

	Cancers, *n*	Incidence per 100 000 years	Age- and sex-adjusted HR (95% CI)	Multi-adjusted HR[a] (95% CI)
Colorectal cancer				
Stress intensity				
None (n = 2144)	62	185	1 (reference)	1 (reference)
Light (n = 2535)	71	173	1.08 (0.77–1.52)	1.06 (0.75–1.49)
Moderate (n = 1345)	22	103	0.62 (0.38–1.02)	0.60 (0.37–0.98)
High (n = 464)	7	101	0.55 (0.25–1.20)	0.52 (0.23–1.14)
P-value for trend			0.03	0.02
Stress frequency				
Never (n = 2772)	77	180	1 (reference)	1 (reference)
Monthly (n = 1947)	52	163	1.16 (0.81–1.65)	1.14 (0.80–1.63)
Weekly (n = 1122)	28	158	1.01 (0.66–1.56)	0.98 (0.63–1.51)
Daily (n = 647)	5	50	0.29 (0.12–0.71)	0.28 (0.11–0.67)
P-value for trend			0.05	0.04
Stress score (continuous)	162		0.91 (0.83–0.99)	0.90 (0.82–0.98)
Colon cancer				
Stress intensity				
None (n = 2144)	50	150	1 (reference)	1 (reference)
Light (n = 2535)	53	130	1.01 (0.69–1.49)	0.99 (0.67–1.47)
Moderate (n = 1345)	18	84	0.64 (0.38–1.10)	0.63 (0.37–1.09)
High (n = 464)	4	58	0.39 (0.14–1.09)	0.39 (0.14–1.08)
P-value for trend			0.03	0.03
Stress frequency				
Never (n = 2772)	59	137	1 (reference)	1 (reference)
Monthly (n = 1947)	41	128	1.22 (0.82–1.82)	1.21 (0.81–1.81)
Weekly (n = 1122)	22	124	1.06 (0.65–1.73)	1.04 (0.64–1.71)
Daily (n = 647)	3	30	0.23 (0.07–0.73)	0.23 (0.07–0.73)
P-value for trend			0.09	0.09
Stress score (continuous)	125		0.90 (0.81–1.00)	0.89 (0.81–0.99)
Rectal cancer				
Stress intensity				
None (n = 2144)	12	36	1 (reference)	1 (reference)
Light (n = 2535)	18	44	1.35 (0.65–2.81)	1.29 (0.62–2.71)
Moderate (n = 1345)	4	19	0.56 (0.18–1.74)	0.49 (0.16–1.52)
High (n = 464)	3	43	1.17 (0.33–4.14)	0.94 (0.26–3.41)
P-value for trend			0.68	0.43
Stress frequency				
Never (n = 2772)	18	42	1 (reference)	1 (reference)
Monthly (n = 1947)	11	34	0.97 (0.45–2.05)	0.95 (0.44–2.02)
Weekly (n = 1122)	6	34	0.87 (0.34–2.19)	0.77 (0.30–1.96)
Daily (n = 647)	2	20	0.47 (0.11–2.02)	0.38 (0.09–1.68)
P-value for trend			0.36	0.21
Stress score (continuous)	37		0.93 (0.78–1.12)	0.90 (0.75–1.09)

[a]Adjusted for age, education, income, physical activity in leisure time, alcohol consumption, body mass index, tobacco smoking, diabetes mellitus, cohabitation, number of children, hormone replacement therapy, menopause at baseline, and oral contraceptive use. Women with lacking information on any of these variables were excluded from the analyses.

association between perceived stress and the risk of *rectal cancer* in women was based on a few cases. Even though the stress frequency and the stress score seemed to be associated with lower risk of rectal cancer no clear picture emerged. In general, adjustment for potential confounders only slightly changed the risk estimates.

One hundred and forty-six colorectal cancer cases occurred in postmenopausal women, whilst only 33 cases occurred amongst premenopausal women. The inverse association between stress and the risk of colon cancer appeared to be the strongest in postmenopausal women, whilst a stronger association between stress and rectal cancer was suggested in premenopausal women (Table 3). Sixty-five cases of colorectal cancer occurred in women during the first nine years of follow-up and 97 cases occurred during the last 9 years of follow-up. The association between the stress score and colorectal cancer was stronger in the first 9 years (HR = 0.84, 95% CI: 0.72–0.97) than in the last nine years (HR = 0.94, 95% CI: 0.83–1.05) of follow-up (data not shown).

Perceived stress and risk of colorectal cancer in men

During follow-up, 166 cases of primary colorectal cancer (111 colon and 55 rectum cancers) occurred in men. High *stress intensity* was associated with a higher risk of colorectal cancer amongst men (HR = 1.96, 95% CI: 1.03–3.74) whilst moderate stress intensity appeared to be associated with lower risk of colorectal cancer (HR = 0.64, 95% CI: 0.37–1.10) compared to no stress (Table 4). There was no notable association between either *stress frequency* or the combined *stress score* and the risk of colorectal cancer in men. A similar picture emerged when studying colon cancer alone. High stress intensity was associated with a hazard ratio of 2.94 (95% CI: 1.09–7.93) for rectal cancer compared to no stress, whilst there was no association between neither stress frequency nor stress score and the risk of rectal cancer. The risk estimates for rectal cancer were rather unstable because of the low number of cases. Sixty-three cases of colorectal cancer in men occurred during the first nine years of the follow-up, whilst the other 103 cases occurred during the last 9 years of the follow-up. The associations between stress score and colorectal cancer were quite similar in the first nine years (HR = 0.97, 95% CI: 0.82–1.14) and the last 9 years (HR = 0.99, 95% CI: 0.88–1.12) of follow-up (data not shown).

Discussion

We found sex differences in the associations between perceived stress and the incidence of colorectal cancer amongst 11 914 men and women prospectively followed for 18 years. In women, higher stress intensity and daily stress were associated with a *lower* incidence of colon cancer in particular, whilst there was no clear association between these measures of stress and rectal cancer. In men, although high stress intensity appeared to be associated with a *higher* incidence of rectal cancer, this result was based on a few cases, and there was no clear evidence of a relation between

Table 3 Hazard ratio (HR), and 95% confidence interval (CI) for first-time incidence of primary colorectal, colon, and rectal cancer associated with perceived stress amongst 1716 premenopausal and 4772 postmenopausal women participating in the Copenhagen City Heart Study in 1981–1983

	Colorectal cancer		Colon cancer		Rectal cancer	
	Cancers, *n*	Multi-adjusted HR[a] (95% CI)	Cancers, *n*	Multi-adjusted HR[a] (95% CI)	Cancers, *n*	Multi-adjusted HR[a] (95% CI)
Premenopausal						
Stress score (continuous)	16	0.97 (0.70–1.35)	12	1.12 (0.78–1.62)	4	0.56 (0.21–1.46)
Postmenopausal						
Stress score (continuous)	146	0.89 (0.81–0.98)	113	0.88 (0.79–0.98)	33	0.92 (0.76–1.12)

[a]Adjusted for age, education, income, physical activity in leisure time, alcohol consumption, body mass index, tobacco smoking, diabetes mellitus, cohabitation, number of children, hormone replacement therapy, and oral contraceptive use.

Table 4 *Men.* Incidence, hazard ratio (HR), and 95% confidence interval (CI) for first-time incidence of primary colorectal, colon, and rectal cancer associated with perceived stress amongst 5426 men participating in the Copenhagen City Heart Study in 1981–1983

	Cancers, *n*	Incidence per 100 000 years	Age- and sex-adjusted HR (95% CI)	Multi-adjusted HR[a] (95% CI)
Colorectal cancer				
Stress intensity				
None (n = 2559)	91	258	1 (reference)	1 (reference)
Light (n = 1779)	48	181	0.94 (0.66–1.34)	0.93 (0.65–1.32)
Moderate (n = 892)	16	123	0.67 (0.39–1.14)	0.64 (0.37–1.10)
High (n = 196)	11	472	2.13 (1.14–3.99)	1.96 (1.03–3.74)
P-value for trend			0.84	0.96
Stress frequency				
Never (n = 2984)	106	256	1 (reference)	1 (reference)
Monthly (n = 1352)	31	150	0.82 (0.55–1.24)	0.81 (0.54–1.22)
Weekly (n = 747)	19	176	0.98 (0.60–1.61)	0.94 (0.57–1.55)
Daily (n = 343)	10	234	1.03 (0.54–1.96)	0.98 (0.51–1.89)
P-value for trend			0.85	0.69
Stress score (continuous)	166		1.00 (0.91–1.10)	0.99 (0.90–1.09)
Colon cancer				
Stress intensity				
None (n = 2559)	65	184	1 (reference)	1 (reference)
Light (n = 1779)	30	113	0.84 (0.54–1.30)	0.82 (0.53–1.27)
Moderate (n = 892)	10	77	0.60 (0.30–1.16)	0.57 (0.29–1.13)
High (n = 196)	6	258	1.65 (0.71–3.81)	1.51 (0.64–3.56)
P-value for trend			0.54	0.42
Stress frequency				
Never (n = 2984)	70	169	1 (reference)	1 (reference)
Monthly (n = 1352)	24	116	1.00 (0.62–1.59)	0.97 (0.60–1.55)
Weekly (n = 747)	12	111	0.97 (0.53–1.81)	0.94 (0.50–1.75)
Daily (n = 343)	5	117	0.79 (0.32–1.96)	0.76 (0.30–1.90)
P-value for trend			0.69	0.59
Stress score (continuous)	111		0.97 (0.86–1.09)	0.96 (0.85–1.08)
Rectal cancer				
Stress intensity				
None (n = 2559)	26	74	1 (reference)	1 (reference)
Light (n = 1779)	18	68	1.18 (0.64–2.16)	1.19 (0.65–2.19)
Moderate (n = 892)	6	46	0.84 (0.34–2.05)	0.80 (0.32–1.95)
High (n = 196)	5	215	3.27 (1.25–8.55)	2.94 (1.09–7.93)
P-value for trend			0.23	0.32
Stress frequency				
Never (n = 2984)	36	87	1 (reference)	1 (reference)
Monthly (n = 1352)	7	34	0.51 (0.23–1.16)	0.52 (0.23–1.18)
Weekly (n = 747)	7	65	0.99 (0.44–2.26)	0.92 (0.40–2.11)
Daily (n = 343)	5	117	1.45 (0.57–3.69)	1.34 (0.51–3.49)
P-value for trend			0.84	0.99
Stress score (continuous)	55		1.06 (0.91–1.24)	1.04 (0.89–1.22)

[a]Adjusted for age, education, income, physical activity in leisure time, alcohol consumption, body mass index, tobacco smoking, diabetes mellitus, and cohabitation.

stress and colorectal cancer. Whilst we addressed the *incidence* of colorectal cancer, sex differences in the effect of stress have previously been noted for colorectal cancer *mortality* in a cohort of Japanese men and women prospectively followed up for nine years [17]. Contrary to our results, perceived psychological stress, assessed by the question 'Do you feel stressed in your daily life?' with two response categories, was weakly associated with higher colon cancer mortality in women, but not in men, whilst stress was not associated with rectal cancer mortality in neither women nor men. There were no clear trends in these associations, and the analyses were based on mortality alone, which as already mentioned, does not allow for a distinction between causal and prognostic factors. Other studies have primarily focused on stressful life events or stressors at work, and have been conducted as case–control studies [13–16]. Different measures of stress have been applied in these studies, and the results are conflicting.

Strengths and weaknesses of the study

The prospective design of the Copenhagen City Heart Study ensured temporality between self-reported stress and incidence of colorectal cancer, and linkage of civil registry numbers to population-based registers with nationwide coverage enabled identification of virtually all cases of colorectal cancer and allowed for a nearly complete long-term follow-up.

Stress was defined as an individual state of high arousal and displeasure [21], and by using a measure of perceived stress, we accounted for the fact that each individual has a different capacity and ways to cope with stressful situations [22]. Stress was assessed by combining two questions on stress intensity and stress frequency asked at baseline. Using these two questions, instead of a more extensive scale, such as the Perceived Stress Scale [23], may have blurred an even stronger relationship between perceived stress and the risk of colorectal cancer. 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 [24]. This may provide some assurance that the single-item measurements used in the present study actually provided a reasonably valid measure of stress. Also, the same measure of stress was previously found to be predictive of several other diseases in the same cohort [25–27]. In the questionnaire, stress was exemplified as impatience, anxiety, and sleeplessness. Based on the two simple questions of stress applied in this study, we cannot fully exclude the possibility that we have also partly measured the effect of depressive symptoms or personality traits, which may be closely related to stress, as it was measured in this study. Stress was only assessed at baseline and the participants may have changed their stress level over time in a manner that is most likely independent of the subsequent development of colorectal cancer. The association between stress and the risk of colorectal cancer in women was strongest in the first 9 years compared to the last 9 years of follow-up. Thus, the long follow-up period may partly have blurred the associations especially in women. In another Danish cohort study [28], which included a question on perceived stress, a majority of the participants (62%) reported the same level of stress in 1994 as in 2000 (Nielsen 2006, unpublished data). Although this finding indicates that a measure of perceived stress may be relatively stable over time, a considerable minority changed stress levels over time. Thus, we cannot exclude the possibility that the relation between stress and the risk of colorectal cancer may have been partly blurred by nondifferential misclassification from changes in stress levels over time.

Information on some important risk factors for colorectal cancer, such as the family history of colorectal cancer and diet, were not obtained in the Copenhagen City Heart Study. However, to confound the results, these factors would also have to be related to stress. We cannot exclude that having experienced colorectal cancer in the near family may act as a stressor and thereby lead to higher levels of stress, which would result in a spurious positive association between stress and colorectal cancer. This is opposite to the inverse association between perceived stress and colon cancer observed amongst women, but it may explain some of the positive association between stress and rectal cancer in men. In order to determine potential confounding from

dietary factors, it is important to determine whether dietary habits are a cause or consequence of stress. Some evidence indicates that during chronic stress, individuals tend to eat smaller, but more frequently, amounts of energy-dense, fatty, low-protein foods [3]. Thus, diet is more likely to be an intermediate factor in the causal path from stress to colorectal cancer than a confounder.

Men and women with high levels of stress smoked more, drank more alcohol, and did less exercise. Also, they had lower income and education than those with lower levels of stress. We adjusted our analyses for baseline differences in these factors to avoid confounding, but one may still be concerned about residual confounding. The amount of residual confounding is, however, proportional to the confounding originally present [29], and adjustment for confounding only slightly changed the risk estimates, which makes residual confounding less of a concern.

The age range of the study participants was relatively broad and one may be concerned that the perceptions of stress in the general adult population may be different from that of the very old. To address this question, we reanalysed the data after excluding all persons above the age of 75 at baseline. This only led to minor changes in the risk estimates (data not shown).

More women in the high stress group (42%) than in the medium (31%) and low (37%) stress group died during follow-up. The pattern was similar in men and the proportions that died during follow-up were 58%, 41%, 51% for high, medium, and low stress respectively. Although this indicates no systematic difference, it may raise concern about how censoring has influenced the results. We assumed, in the statistical model, that censoring was independent of colorectal cancer risk within strata of stress. It is, however, possible that competing causes, such as death of cardiovascular disease, could be associated with the risk of colorectal cancer within strata of stress due to other common risk factors. Some of these common risk factors, such as alcohol consumption, have opposite effects on the two diseases, whilst other risk factors, such as low physical activity, increase the risk of both diseases. To some degree, we would expect the bias to level out and the average risk of colorectal cancer amongst women not censored to be similar to what it would have been if no such censoring had occurred. Also, both a higher proportion of men and a higher proportion of women in the high stress group died during follow-up, and we therefore find it unlikely to explain the sex differences observed in the present study. Thus, whilst our results may have been influenced by bias from nonindependent censoring, we find it unlikely to fully explain them.

Possible pathways from perceived stress to colorectal cancer

Stress may affect the risk of colorectal cancer directly through biological processes or indirectly by affecting health-related behaviour. Several possible pathways between perceived stress and the incidence of colorectal cancer may be identified. The importance of each of these pathways may be sex-specific and explain the observed sex differences in the present study.

First, the hypothalamic-pituitary-gonadal (HPG) axis regulates the synthesis of sex steroid hormones in a normally functioning reproductive system. Stress can affect the signals of this axis by activating the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. Several experimental studies have found that the activation of the HPA axis inhibits the function of the HPG axis and thereby decrease oestrogen and testosterone synthesis [12, 30–33]. In a recent epidemiologic study, significantly lower levels of bioavailable oestradiol were also found amongst female caregivers compared with noncaregivers [34]. *In vitro* treatment of a human colon cancer cell line with oestradiol was found to rapidly stimulate intermediates in a signal transduction pathway that is known to trigger cell proliferation [6]. Further, the intensity of the stimulatory effect of oestradiol in human colon cancer cells is similar to the oestradiol responsiveness of human mammary cancer cell lines, which are classical oestradiol sensitive cells [6]. A stress-induced distortion of oestrogen synthesis may thus explain the lower incidence of colon cancer amongst women with high levels of stress.

Secondly, long-term stress may lead to a persistent activation of the HPA-axis. Some of the mediators released by the HPA-axis, like corticosteroids and catecholamines, seem to be capable of suppressing the immune function and thereby reduce their ability to recognize and destroy neoplastic cell growth [2, 35]. A decrease in cytotoxic T-cell and natural-killer-cell activity and in general, cellular immune response has been found in laboratory animals exposed to stress [2]. Thus, by affecting the immune system and the DNA repair system, perceived stress may promote the initiation and progression of colorectal cancer. Men seem to respond to psychological stress with greater increases in cortisol than women [36], which may explain the higher incidence of colorectal cancer observed amongst men reporting high levels of stress.

Thirdly, there is growing evidence that chronic stress may lead to the development of obesity and insulin resistance, either by a behavioural pathway with altered dietary and activity patterns or through an abnormal diurnal cortisol rhythm, induced by the activation of the HPA-axis [37]. Obesity, insulin resistance, and the insulin growth factor are all potential metabolic mediators for tumour progression and may thereby increase the risk of colorectal cancer [37]. Experimental studies have also suggested that stress may alter bowel movement [3, 4, 38], and, thereby, indirectly affect the risk of colorectal cancer. Both pathways would result in a higher risk of colorectal cancer associated with stress and are, therefore, unlikely to explain the lower risk of colon cancer observed amongst stressed women in the present study.

Finally, stress may affect health-related behaviour and thereby alter the risk of colorectal cancer. Participants with high levels of perceived stress were more likely to also have a high alcohol intake, be current smokers, and be physically inactive at baseline, which may increase the risk of colorectal cancer. We adjusted our analyses for such differences in health-related behaviour in order to control for baseline confounding from these factors. However, we would also expect some of the effect of stress on the colorectal cancer risk to be mediated by changes in health-related behaviour, which may occur during follow-up. Also, some of the effect of stress on the risk of colorectal cancer may be mediated through mental processes such as depression or burnout. On the other hand, such behavioural and mental changes would again lead to an increased risk of colorectal cancer and thereby be in contrast to the lower risk of colon cancer observed amongst stressed women in the present study.

In conclusion, we found high stress to be associated with a lower risk of colon cancer in women, whilst there was no clear evidence of a relation between stress and the risk of colorectal cancer in men. The relation between perceived stress and the risk of colorectal cancer seemed to be a result of a complex system with different physiological, mental, and behavioural mechanisms working in opposite directions.

Conflicts of interests

None declared.

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Ethical approval

The Danish ethics committee for the City of Copenhagen and Frederiksberg approved the Copenhagen City Heart Study (no. 01-144/01). All participants gave written informed consent.

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