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# Perceived stress as a risk factor for dyspepsia: a register-based cohort study

Ulrik Deding<sup>a</sup>, Christian Torp-Pedersen<sup>a,b</sup> and Henrik Bøggild<sup>a</sup>

**Objective** Dyspepsia is a common condition and has a huge impact on quality of life and working capacity, but its causes are not well understood. An association between stress and dyspepsia has been debated for decades, but the issue has not been resolved. We examined the 3-year risk of redeeming a proton-pump inhibitor or an H<sub>2</sub>-receptor antagonist as a proxy of dyspepsia according to the level of perceived stress.

**Participants and methods** Perceived stress was measured in a general health survey of 16 124 Danes aged older than 16 years of age in 2010 using Cohen's Perceived Stress Scale. Data were linked individually to national registries, including the Danish National Prescription Registry. The risk of redeeming a proton-pump inhibitor or an H<sub>2</sub>-receptor antagonist for quintiles of stress level was estimated using Cox proportional hazard regression.

**Results** In total, 2703 redeemed one of these drugs during the 33 months of follow-up. The cumulative incidence proportion of dyspepsia increased gradually, from 11.6 to 24.9%, with quintiles of stress. After full model adjustment, the four highest stress quintiles had a statistically significantly increased risk of redeeming a drug compared with the lowest stress quintile. The hazard ratios were 1.16 [95% confidence interval (CI): 1.00–1.34] for the second quintile, 1.21 (95% CI: 1.06–1.39) for the third quintile, 1.20 (95% CI: 1.05–1.38) for the fourth quintile, and 1.30 (95% CI: 1.12–1.50) for the fifth quintile.

**Conclusion** Higher levels of self-reported perceived everyday life stress increased the risk of redeeming a drug for dyspepsia significantly during 33 months of follow-up. *Eur J Gastroenterol Hepatol* 29:560–567

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## Background

Dyspepsia is prevalent and affects 27–40% of the general population [1–3], with symptoms of bothersome post-prandial fullness, early satiation, epigastric pain, and epigastric burning [4,5]. Dyspepsia affects the quality of life [6,7] and increases the cost of healthcare [5]. The initial pharmaceutical treatment recommended for these patients is treatment with a proton-pump inhibitor (PPI) or an H<sub>2</sub>-receptor antagonist for up to four weeks. A *Helicobacter pylori* test is used to determine whether treatment should further include a course of two antibiotics (triple therapy) [5,8]. In scientific research, NSAIDs [3,9], exercise [1],

peptic ulcer [3], age [3,9–13], sex [1,9–11,14,15], smoking [9,16], marital status [10], depression [9,11,13,17,18], sleep [1], BMI, and hypertension [9] have all been associated with dyspepsia. Psychological stress has been investigated as a risk factor for dyspepsia, with contradictory results. Different measures of stress have been associated with dyspepsia, most often in nonwestern populations. The measures of stress in research are frequently based not on everyday life stress but on life events [10–12,15,16,19] or induced stress [20–22]. It has been suggested that psychological stress affects the symptom severity rather than the development of dyspepsia [2,23], but this suggestion has been disputed for perceived stress [13]. Stress management programs have also been investigated as a way to reduce the symptoms of dyspepsia and have led to encouraging results [2].

These results suggest an association between stress and dyspepsia, although the measures of stress are most commonly based on life events or induced stress. The effect of everyday life stress on the development of dyspepsia over time has not been examined in detail.

Therefore, the aim of this study was to examine whether a high self-reported perceived stress level at baseline, as measured by Cohen's Perceived Stress Scale (PSS-10), is associated with an increased risk of treatment with proton-pump inhibitors or H<sub>2</sub>-receptor antagonists in subsequent years.

## Participants and methods

We linked data from the North Denmark Health Profile 2010 survey [24] with existing Danish registers in a cohort study. The primary aim of the survey was to describe

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**Keywords:** Cohen's Perceived Stress Scale, dyspepsia, functional dyspepsia, H<sub>2</sub>-receptor antagonist, nonulcer dyspepsia, perceived stress, Perceived Stress Scale-10, proton-pump inhibitor, psychological stress

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citizens' health states. There were 570 000 inhabitants in the Region of North Denmark and there were 35 700 citizens older than 16 years of age across 11 municipalities covering the entire northern Jutland who received the questionnaire. The selection of participants was stratified on the basis of municipality. Data collection was performed from 5 February to 22 March 2010. Nonresponders received two reminders by mail [24]. Included in the North Denmark Health Profile 2010 was Cohen's PSS-10 [25].

Data from the survey were linked to several Danish registers. The Danish Civil Registration System included information on unique personal identification numbers [Civil Personal Registration (CPR)]. A CPR number is assigned to all individuals in Denmark at birth or immigration [26]. These CPR numbers made it possible to link data from all other included registers. The Danish National Prescription Registry had information on all prescriptions redeemed in Denmark and included the date and specific anatomical therapeutic chemicals (ATC)-codes of the drugs that were redeemed [27]. The Danish National Patient Register provided ICD-10 diagnoses for all hospital contacts [28]. Using data gathered from the Central Taxpayers' Register and the Salary Information Register, the Income Statistics Register recorded individual income [29]. The Population's Education Register [30] had information on each citizen's educational history.

### Exposure

The PSS-10 [25] score was generated from the respondents' answers to the North Denmark Health Profile 2010. The PSS-10 consisted of 10 items on predictability, controllability, and life overload, as perceived by the individual during the last month [31,32]. Each question had five possible answers scaled from never to very often. Each answer was coded from 0 to 4. The cumulative score for all ten items was the total PSS-10 score and ranged from 0 to 40. Respondents were then divided into quintiles on the basis of their PSS-10 score. In accordance with the description of the PSS-10, we compared quintiles of stress level [33]. Higher PSS-10 scores indicated a greater feeling of psychological stress [32].

### Outcome

Dyspepsia was defined as the first redeemed prescription after baseline for a PPI or an H<sub>2</sub>-receptor antagonist. The ATC-codes A02BC01 through A02BC05 identified PPIs. The ATC-codes A02BA01 through A02BA08 identified H<sub>2</sub>-receptor antagonists. Individuals who were diagnosed in the hospital with a peptic ulcer during follow-up were censored. If an individual had redeemed a prescription and was diagnosed with peptic ulcer within the 60 days after redeeming the prescription, they were not categorized as a dyspepsia patient and were censored. Peptic ulcer diagnoses were identified using ICD-10 codes [28] K25 through K279 in the National Patient Register.

### Covariates

Age was derived from the Danish Civil Registration System [26] and was included in the model as a continuous variable.

Sex was derived from The Danish Civil Registration System [26].

Educational level indicates the highest completed educational level at baseline and was grouped as primary (basic school of <10 years), secondary (high school education of +3 years or vocational education of +4 years), or higher (short/medium length higher education of +2 to 4 years or long length higher education of +≥5 years). Educational data were identified through the Population's Education Register [30].

NSAID usage was included in the model as a dichotomous variable. Respondents with NSAID usage during the 3 months preceding baseline measurements were identified through the prescription database and were grouped with respondents who reported using non-prescription painkillers in the North Denmark Health Profile 2010.

Smoking data were generated from respondents' answers on the North Denmark Health Profile 2010. The respondents answered whether they smoked or used to smoke on a daily basis. If confirmed, they were asked how many cigarettes, cigars, pipe bowls, and/or cheroots they smoked per day on average [24]. The smoking variable was included as a categorical variable and was grouped as never smoked, former smoker, smoking 1–14 cigarettes/day and/or cheroots, cigars, or pipe bowls daily, and smoking more than 14 cigarettes/day.

Alcohol consumption was included as a dichotomous variable at baseline on the basis of the recommendations for moderate alcohol intake from the Danish Health Authorities [34]. Respondents were identified as within recommendations (≤168 g/week for women and ≤252 g/week for men) or over recommendations (>168 g/week for women and >252 g/week for men). Respondents reported units of alcohol per week in the North Denmark Health Profile 2010. One unit was calculated as equivalent to 12 g of alcohol.

BMI was grouped as underweight (BMI <18.5), normal weight (BMI = 18.5–25.0), or overweight (BMI >25.0). BMI calculations were based on self-reported height and weight in the North Denmark Health profile 2010.

Sleep was grouped as less than 7, 7, and more than 7 h/day. Respondents reported in the North Denmark Health Profile 2010 on how many hours of sleep they had in a typical weekday.

Income was examined as quartiles. Income was a measure of the total household income in the year 2009 and was used to estimate the economic status for the respondents at baseline. Household income was identified through the income statistics register [29] and was an equalized income estimate on the basis of the number of adults and children in the household [35].

Marital status was included as a categorical variable on the basis of two items in the North Denmark Health Profile 2010, which asked for marital status and whether they were living with a partner. Marital status was grouped as 1 – married, in a registered partnership, or living with a partner, 2 – separated, divorced, or widowed, or 3 – unmarried and single.

Anxiety or depressive symptoms were based on an item from the North Denmark Health Profile 2010. Respondents were grouped as not having symptoms if they reported not being anxious or depressed and as having

symptoms if they reported being moderately or extremely anxious or depressed.

Hypertension was included as a dichotomous variable grouped as hypertension/side effects from former hypertension and no current hypertension/no side effects from former hypertension. Data were based on items in the North Denmark Health Profile 2010.

Exercise was included as a dichotomous variable. The respondents in the North Denmark Health Profile 2010 were asked which description most accurately described their physical activity level in the last year. The possible answers were 1 – exercising hard and participating in competitive sports regularly and several times a week; 2 – participating in sports or doing heavy gardening or the like for at least 4 h a week; 3 – walking, riding bicycles, or doing other light exercise for at least 4 h a week; or 4 – reading, watching television, or doing another type of sedentary occupation. Respondents who answered participating in sports or more were grouped as exercising and the rest as not exercising because the Danish Health Authorities recommend that adults have more than 30 min a day of moderate-intensity to high-intensity exercise [36].

Previous ulcer was based on ICD-10 codes [28] K25–K27.9 for diagnoses of any type of peptic ulcer before baseline and as far back as January 1989.

Previous PPI use was included as a dichotomous variable on the basis of whether respondents had redeemed a prescription for a PPI or an H<sub>2</sub>-receptor antagonist before baseline. Prescriptions were identified by the same procedure as the outcome variable. PPI use was identified as far back as permitted by the register, which was from 1 January 1995.

### Statistics

$\chi^2$ -tests were used to compare the baseline characteristics for categorical variables and a *t*-test for continuous age variable. Cumulative incidence proportion curves of the first redeemed prescription after baseline were created, in which individuals who died or were diagnosed in hospital with peptic ulcer during follow-up were censored. Descriptive statistics were calculated, describing the distribution of first redeemed prescriptions during follow-up. Cox proportional hazards regression was used to estimate the association between stress quintiles at baseline and redeeming a prescription of a PPI or a H<sub>2</sub> antagonist during 33 months of follow-up. When calculating the estimates, the stratified sampling design was taken into account using the R-package *Svycoxph* [37]. Schönfeld residuals were examined to verify the proportional hazard assumption. Age, sex, NSAID use, smoking, alcohol consumption, BMI, sleep, income, marital status, depression, hypertension, exercise, previous ulcer, and previous PPI use were included in the analysis as covariates and the analysis was divided into four models. Age was included as a continuous variable after checking the linearity assumption. Tests for interactions between PSS-10 quintiles and covariates for previous PPI use and sex on the risk of nonulcer dyspepsia showed no statistically significant interactions. As psychological disorders may be associated with level of stress, a sensitivity analysis was carried out, testing a possible interaction between PSS-10 quintiles and anxiety and depressive symptoms. To examine the severity

of dyspepsia, total cumulated defined daily doses (DDD) of PPIs and H<sub>2</sub>-receptor antagonists were calculated and tested for any differences between PSS-10 quintiles by carrying out an analysis of covariance, still taking the stratified sampling design into account and including full model covariates. Because of the large exclusion of respondents because of missing data on smoking, alcohol consumption, BMI, sleep, exercise, marital status, depression/anxiety, and hypertension, imputation was performed as a sensitivity analysis. Sensitivity analyses were also carried out either with only PPI use as the outcome or with a sample that censored individuals receiving triple therapy. Further, an analysis including all individuals redeeming prescriptions, without censoring those diagnosed with peptic ulcer during follow-up, was carried out. Data management was performed using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Statistical analysis was carried out using R statistical software package, version 3.2.2 (R Development Core Team, Vienna, Austria).

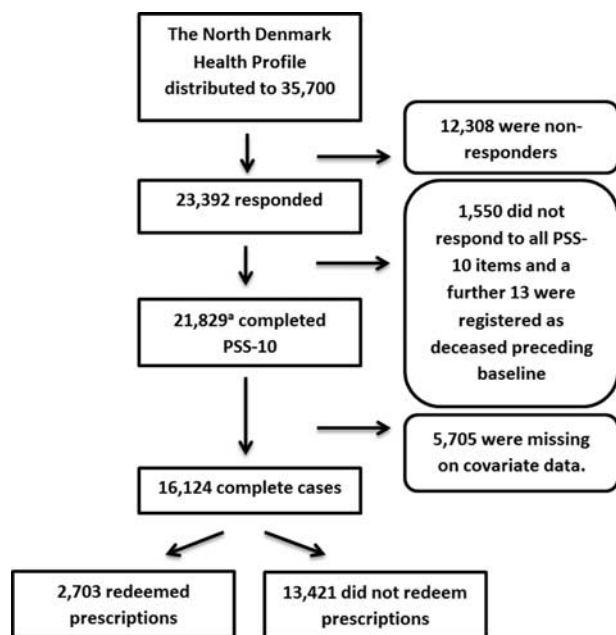
### Ethics

The Danish Data Protection Agency approved this study (Ref. GEH-2014-014). All data used were linked and stored in computers held by Statistics Denmark. Anonymity was maintained as data were made available with deidentified personal information. Only aggregated statistical analyses and results were published in accordance with the Act on Processing of Personal Data [38,39]. Retrospective anonymized register-based studies do not require written informed consent and ethical approval [38,39].

### Results

In total, 23 392 (65.52%) individuals responded to the questionnaire, 21 842 of whom answered all 10 PSS-10 items. Thirteen respondents were excluded because they were registered as deceased before the start of follow-up and 5705 were excluded because they had not completed all questions on the covariates for full model adjustment. The numbers of respondents missing data on covariates were 444 for educational level, 346 for smoking, 2993 for alcohol consumption, 484 for BMI, 523 for sleep, 538 for exercise, 526 for marital status, 199 for anxiety or depressive symptoms, and 1085 for hypertension. This resulted in a sample of 16 124 individuals for statistical analysis, with 2703 individuals who redeemed a PPI or an H<sub>2</sub>-receptor antagonist prescription during follow-up (Fig. 1).

Individuals redeeming a drug during follow-up were, on average, 8.6 years older, were more often female, had a lower educational level, smoked more, used NSAIDs more often, were more often overweight, slept less, had a lower income, had been diagnosed with peptic ulcer before baseline more frequently, exercised less, reported anxiety or depressive symptoms more often, were more often married or separated, had a higher frequency of hypertension, and had redeemed prescriptions for the same group of drugs preceding baseline more frequently compared with the individuals who did not redeem a drug



**Fig. 1.** Flow chart from the 35 700 individuals who received the North Denmark Health Profile 2010, leading to final sample of 16 124 individuals. The North Denmark Health Profile 2010 was distributed to 35 700 individuals. Individuals who were registered as deceased, did not respond to all, did not respond to all perceived stress scale (PSS-10) items, or did not respond to all included covariates were excluded. The final sample size for statistical analysis was 16 124. a, sample used for imputed data analysis.

during follow-up. There were no significant differences in alcohol consumption between the groups (Table 1).

The cumulative incidence proportion was higher with an increasing level of self-perceived stress. The risk of redeeming a drug over 33 months was ~11.6, 13.5, 15.7, 17.9, and 24.9% from the lowest to the highest stress quintile. The cumulative incidence proportions increased throughout follow-up for all PSS-10 groups (Fig. 2). The mean interval between baseline and redemption of first prescription during follow-up was 341 days, with a lower quartile of 67 days and an upper quartile of 578 days. The distribution of redeemed prescriptions during follow-up has been included in Appendix A (Supplemental digital content 1, <http://links.lww.com/EJGH/A171>).

The results of Cox proportional hazard regression analyses are shown in Fig. 3. At the univariate level (model 1), the four highest stress quintiles all had a statistically significantly higher risk of redeeming medications than did the lowest stress quintile, with hazard ratios (HRs) of 1.18, 1.40, 1.61, and 2.37, respectively. After adjusting for age and sex (model 2), all HRs increased slightly. On further adjusting for previous PPI use and previous ulcers (model 3), the HRs decreased considerably. After full model adjustment for all covariates (model 4), the HRs decreased even further, but the risk of redeeming medicine for dyspepsia remained significantly higher in the four highest stress quintiles compared with the lowest quintile. The estimate for the second quintile had an HR of 1.16 [95% confidence interval (CI): 1.00–1.34], the third quintile had an HR of 1.21 (95% CI: 1.06–1.39), the fourth quintile had an HR of 1.20 (95% CI: 1.05–1.38), and the fifth quintile had an HR of 1.30 (95% CI: 1.12–1.50).

### Other analyses

When using only PPIs as a measure for dyspepsia, the total number of individuals redeeming prescriptions was 2688. The HR for the highest stress quintile was 1.31 (95% CI: 1.14–1.51) after full model adjustment. When censoring individuals who received triple therapy for *Helicobacter* treatment (a PPI or an H<sub>2</sub>-receptor antagonist combined with two antibiotics), the total number of individuals redeeming prescriptions was 2675. The HR for the highest stress quintile was 1.31 (95% CI: 1.14–1.51) after full model adjustment. Tests for interaction between PSS-quintiles and anxiety and depressive symptoms were not statistically significant and the inclusion of the interaction term in the full model analysis did not alter the conclusion as HRs ranged from 1.17 to 1.34. Including all individuals who had redeemed prescriptions for PPI or H<sub>2</sub>-receptor antagonists during follow-up, irrespective of peptic ulcer diagnosis, did not alter the conclusion as HRs ranged from 1.18 to 1.31. The severity of dyspepsia was examined by calculating the total DDD redeemed during follow-up for each individual, with no statistical differences between PSS-10 quintiles. Among those 2703 individuals redeeming at least one prescription during follow-up, the mean cumulated number of PPIs and H<sub>2</sub>-receptor antagonists was 356.5 DDD. By imputing missing values for the covariates of smoking, alcohol consumption, BMI, sleep, exercise, marital status, anxiety or depressive symptoms, and hypertension, the sample remained at 21 829 individuals, with 3917 redeeming prescriptions. The HR for the highest stress quintile was 1.34 (95% CI: 1.19–1.51) after full model adjustment and the second stress quintile was no longer statistically significantly different from the lowest stress quintile (HR: 1.11; 95% CI: 0.98–1.26).

### Discussion

The main result of the study was that after full model adjustment (model 4, Fig. 3), the four highest stress quintiles had a statistically significantly increased risk of dyspepsia treatment during 33 months of follow-up. In particular, adjusting for previous PPI use and previous peptic ulcer affected the HRs, and it is recommended that these factors be included in future research.

In a cross-sectional study, 15 dyspepsia patients had significantly higher median stress scores than did controls on the basis of a stress profile test [18]. The 2547 individuals who fulfilled the ROME III criteria for functional dyspepsia or irritable bowel syndrome felt both more stressed and more susceptible to stress than did controls [1]. Stress, as measured by the BEPSI-K 5 item questionnaire, was calculated as an independent risk of functional dyspepsia (odds ratio: 1.713) for the 9.4% of the patients with the highest stress level compared with the rest in a sample of 23 698 respondents [9]. These findings support the results from our study that stress increased the risk of dyspepsia; however, all of these previous studies used a cross-sectional design, whereas the individuals in our sample felt stressed before dyspepsia treatment. Only one of those studies could contribute with an estimate of association. The discrepancy between our increased risk of 1.3 for the highest quintile of stress and that of 1.713 may

**Table 1.** Baseline characteristics for respondents who did and did not redeem a prescription for a proton-pump inhibitor or an H<sub>2</sub>-receptor antagonist during 33 months of follow-up

Variables	Levels	n (%)			P-value
		PPI <sup>a</sup> (n = 2703)	No PPI <sup>a</sup> (n = 13 421)	Total (n = 16 124)	
PSS-10 quintiles	0 – Lowest level of stress	383 (14.2)	2930 (21.8)	3313 (20.5)	< 0.0001
	1	388 (14.4)	2483 (18.5)	2871 (17.8)	
	2	517 (19.1)	2767 (20.6)	3284 (20.4)	
	3	612 (22.6)	2814 (21.0)	3426 (21.2)	
	4 – Highest level of stress	803 (29.7)	2427 (18.1)	3230 (20.0)	
Sex	Male	1244 (46.0)	6827 (50.9)	8071 (50.1)	< 0.0001
	Female	1459 (54.0)	6594 (49.1)	8053 (49.9)	
Age	Years [mean (SD)]	56.1 (15.8)	47.5 (16.7)	49.0 (16.9)	< 0.0001
Educational level	Primary	1010 (37.4)	3957 (29.5)	4967 (30.8)	< 0.0001
	Secondary	1129 (41.8)	6055 (45.1)	7184 (44.6)	
	Higher	564 (20.9)	3409 (25.4)	3973 (24.6)	
Smoking	No, never	1048 (38.8)	6755 (50.3)	7803 (48.4)	< 0.0001
	No, but used to	974 (36.0)	3620 (27.0)	4594 (28.5)	
	Yes, < 15 a day	381 (14.1)	1699 (12.7)	2080 (12.9)	
	Yes, > 14 a day	300 (11.1)	1347 (10.0)	1647 (10.2)	
Alcohol consumption <sup>b</sup>	Within recommendation	2463 (91.1)	12 283 (91.5)	14 746 (91.5)	3.624
	Over recommendation	240 (8.9)	1138 (8.5)	1378 (8.5)	
NSAID use	No	641 (23.7)	5649 (42.1)	6290 (39.0)	< 0.0001
	Yes	2062 (76.3)	7772 (57.9)	9834 (61.0)	
BMI	Underweight	50 (1.8)	268 (2.0)	318 (2.0)	< 0.0001
	Normal weight	1055 (39.0)	6354 (47.3)	7409 (46.0)	
	Overweight	1598 (59.1)	6799 (50.7)	8397 (52.1)	
Sleep (h/day)	< 7	594 (22.0)	2351 (17.5)	2945 (18.3)	< 0.0001
	7	919 (34.0)	5382 (40.1)	6301 (39.1)	
	> 7	1190 (44.0)	5688 (42.4)	6878 (42.7)	
Income <sup>c</sup>	< 189 399	636 (23.5)	2824 (21.0)	3460 (21.5)	< 0.0001
	189 399–326 834	831 (30.7)	3016 (22.5)	3847 (23.9)	
	326 834–449 335	631 (23.3)	3613 (26.9)	4244 (26.3)	
	> 449 335	605 (22.4)	3968 (29.6)	4573 (28.4)	
Previous ulcer	No previous ulcer	2495 (92.3)	13 263 (98.8)	15 758 (97.7)	< 0.0001
	Previous ulcer	208 (7.7)	158 (1.2)	366 (2.3)	
Exercise <sup>d</sup>	Over recommendation	472 (17.5)	3734 (27.8)	4206 (26.1)	< 0.0001
	Under recommendation	2231 (82.5)	9687 (72.2)	11 918 (73.9)	
Marital status	Married <sup>e</sup>	1843 (68.2)	8481 (63.2)	10 324 (64.0)	< 0.0001
	Divorced <sup>e</sup> or widowed	464 (17.2)	1481 (11.0)	1945 (12.1)	
	Unmarried and single	396 (14.7)	3459 (25.8)	3855 (23.9)	
Anxiety or depressive symptoms	No	1926 (71.3)	11 209 (83.5)	13 135 (81.5)	< 0.0001
	Yes	777 (28.7)	2212 (16.5)	2989 (18.5)	
Hypertension	No	1826 (67.6)	11 088 (82.6)	12 914 (80.1)	< 0.0001
	Yes	877 (32.4)	2333 (17.4)	3210 (19.9)	
Previous PPI treatment	No previous PPI	1031 (38.1)	11 295 (84.2)	12 326 (76.4)	< 0.0001
	Previous PPI	1672 (61.9)	2126 (15.8)	3798 (23.6)	

PPI, proton-pump inhibitor.

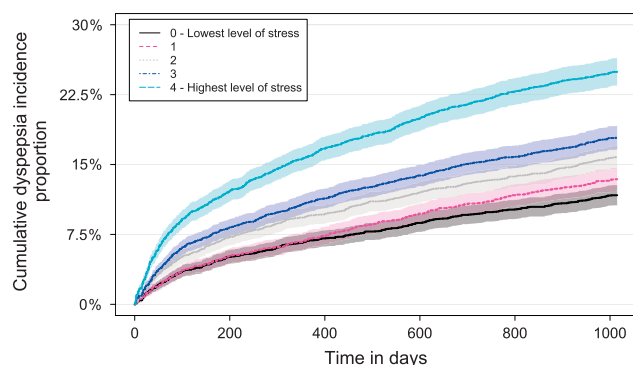
<sup>a</sup>PPI refers to redeeming a prescription for either a proton-pump inhibitor or an H<sub>2</sub>-receptor antagonist.

<sup>b</sup>Recommended maximum consumption per week is 168 g for women and 252 g for men.

<sup>c</sup>Income is reported in Danish Kroner and grouped into quartiles.

<sup>d</sup>Recommendation for adults is more than 30 min a day of moderate-intensity to high-intensity exercise.

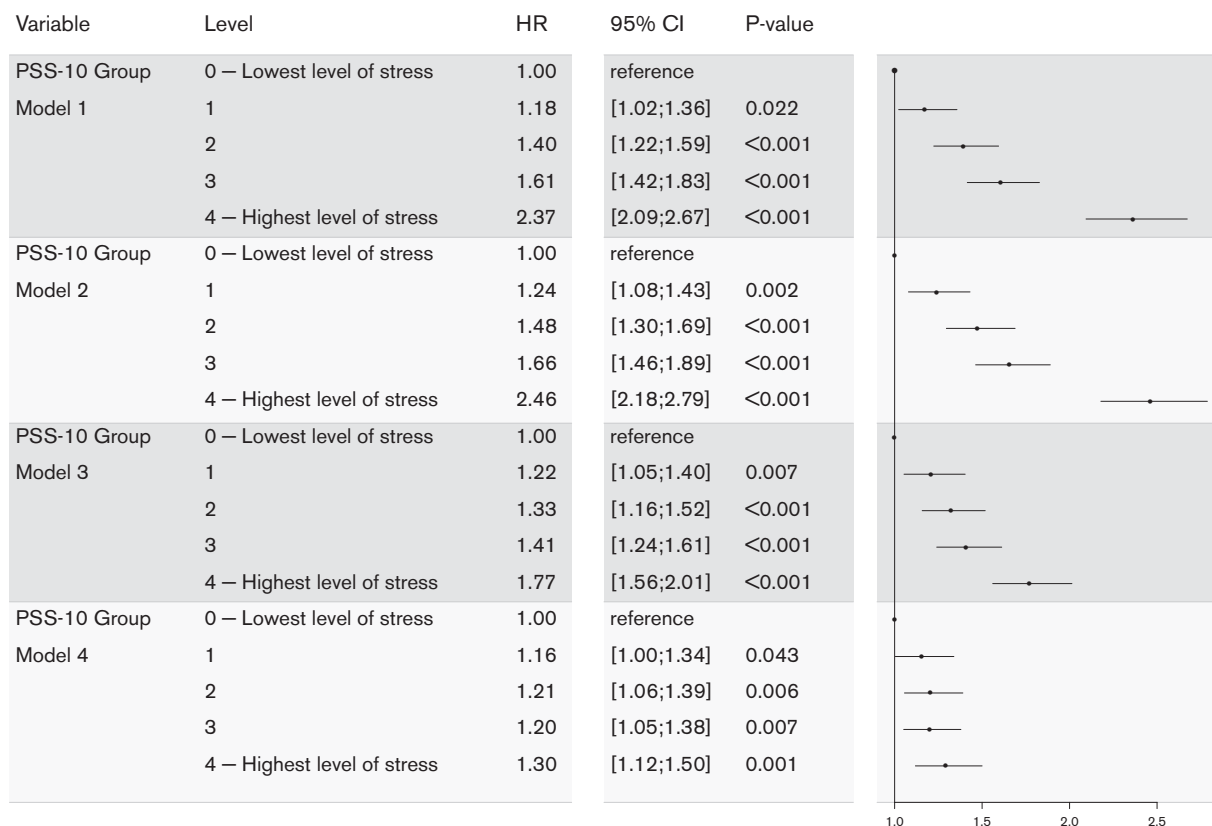
<sup>e</sup>Married also includes individuals living with a partner or in a registered partnership and divorced includes separated.



**Fig. 2.** Cumulative incidence proportion of redeeming medicine for dyspepsia for a sample of 16 124 individuals, participating in the North Denmark Health profile 2010, illustrated for each quintile of self-perceived stress scale (PSS-10), with 95% confidence intervals.

be because of our different choice of questionnaires used for stress measurement.

The perceived stress level in this study was measured using Cohen's PSS. This measurement tool has been validated and is often used as an instrument to estimate everyday life stress [31]. Because the outcome measure for dyspepsia is based on collected prescriptions, it cannot be confirmed that they actually had dyspepsia, but it is likely that they had symptoms because a physician prescribed the drug. Because dyspepsia patients are not hospitalized with dyspepsia, using prescriptions for drugs used in treatment is considered more valid in this sample than using a hospital diagnosis for functional dyspepsia to identify patients. Only two individuals were diagnosed with dyspepsia in the hospital during follow-up. As a proxy for severity of dyspepsia, we examined individual cumulated



**Fig. 3.** Estimated hazard ratios for the risk of redeeming a proton-pump inhibitor or an H<sub>2</sub>-receptor antagonist, for each quintile of stress level measured by Cohen's perceived stress scale (PSS-10), compared with PSS-10 group zero (first quintile), unadjusted, and adjusted models (*N*=16 124). Model 1: univariate model. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, previous proton-pump inhibitor use, and previous peptic ulcer. Model 4: adjusted for age, sex, previous PP use, previous peptic ulcer, educational level, income, marital status, exercise, smoking, alcohol consumption, NSAID use, BMI, sleep, depression or anxiety, and hypertension.

daily doses redeemed among those redeeming prescriptions. This showed no difference in severity between PSS-10 quintiles, indicating no difference in the severity of dyspepsia symptom severity on the basis of stress level. Furthermore, a recent study did not find differences in distress in patients who were referred for the gastric emptying test and did or did not fulfill the ROME III criteria [40], which supports our method of investigating this group of individuals collectively.

The implications of this study should be an increased focus on dyspepsia symptoms in individuals with stress and an increased focus on stress signals in dyspepsia patients as a possible factor in the development of their symptoms. Even modest increases in stress levels may be associated with an increased risk of redeeming prescriptions for PPIs. The results support future directions in risk stratification and strengthen the notion of an association between perceived stress and dyspepsia.

Drugs used for treating dyspepsia are also prescribed for patients with gastroesophageal reflux disease. As these two diseases are often treated without a confirmed diagnosis and share some symptoms, they can be difficult to distinguish. Some of the patients identified in our study could have suffered from gastroesophageal reflux disease instead of from both. Therefore, there is a possibility that some of the effects from stress on gastrointestinal symptoms will result in gastroesophageal reflux disease rather than dyspepsia. This is also a possibility for individuals

with an undiagnosed peptic ulcer. Individuals with peptic ulcer disease whose symptoms are eliminated with treatment will not be diagnosed in hospital and could therefore be included as dyspepsia patients in this study. Dyspepsia patients are liable to self-medication [14], and Danish patients can buy smaller quantities of H<sub>2</sub>-receptor antagonists without a prescription. Therefore, it is possible that some respondents in the sample consumed H<sub>2</sub>-receptor antagonists or bismuth-containing compounds. These individuals will not be identified in this study as dyspepsia patients. Therefore, the total incidence of dyspepsia, in this study, is most likely an underestimation of the incidence in the Danish population. To affect the conclusion, there would have had to be an uneven distribution of individuals using nonprescription H<sub>2</sub>-receptor antagonist among the PSS-10 quintiles, which seems unlikely. Testing the hypothesis with only PPIs as the outcome measure did not alter the conclusion. It has been suggested that stressed individuals visit their general practitioner more often than others [17,41], but this finding has been disputed for dyspepsia patients elsewhere [12,19].

By using Danish national registries, information bias is probably limited because registries limit the self-reported data to the North Denmark Health Profile 2010 questionnaire. The stratified administration of the North Denmark Health Profile 2010 by municipality helped maintain the large sample and increased the generalizability of the results. The comprehensive adjustment in

the four models suggests that confounding was not responsible for our results. The response rate of the North Denmark Health Profile 2010 was 65.5% [24]. There was a possibility that the nonresponders did not respond because of a high stress level or that the nonresponders had different stress levels than the responders. This issue would not lead to selection bias unless the nonresponders also differed from responders in terms of dyspepsia risk. This eventuality was considered unlikely. The Danish National Prescription Registry, the Danish registers on personal income, and the Danish Civil Registration System are of high quality [26,27,29]. The Danish National Patient register may be affected by changes over time in the organization and provision of health services [28], but no relevant changes were made from baseline until the end of follow-up in this study, and the register is internationally recognized as one of the most comprehensive of its kind [28]. The registries eliminate the risk of selection bias because there is no loss to follow-up, which also adds power to the analysis as the large sample size is maintained.

### Conclusion

Higher levels of self-perceived everyday life stress increased the risk of redeeming a drug for dyspepsia significantly during 33 months of follow-up. The group with the second lowest stress level had an increased risk of dyspepsia of 1.16. The group with the third and second highest stress levels had an increased risk of dyspepsia of 1.2 and the group with the highest stress level had an increased risk of dyspepsia of 1.3. The proportions of dyspepsia patients in the stress level groups ranged from 11.6 to 24.9%. Therefore, even modest increases in risk resulted in large numbers of extra patients, and practitioners should be aware of stress signals in patients with dyspepsia symptoms.

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### Conflicts of interest

There are no conflicts of interest.

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