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

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**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\textsubscript{2}-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\textsubscript{2}-receptor antagonist for quintiles of stress level was estimated using Cox proportional hazard regression.

**Results** In total, 2,703 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 postprandial 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\textsubscript{2}-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\textsubscript{2}-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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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 per-
duced 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 immi-
gration [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 com-
pared 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 H2-receptor antagonist. The
ATC-codes A02BC01 through A02BC05 identified PPIs.
The ATC-codes A02BA01 through A02BA08 identified
H2-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 diag-
noses 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 edu-
cational level at baseline and was grouped as primary
(basic school of <10 years), secondary (high school edu-
cation 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 dichot-
omous 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 H₂-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

χ²-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 an H₂-receptor antagonist 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 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, 326 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 H₂-receptor antagonist prescription during follow-up (Fig. 1).

Individuals redeeming a drug during follow-up were, on average, 8.6 years older, 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.
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 increased considerably. After full model adjustment and the second stress quintile was 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
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

### Table 1. Baseline characteristics for respondents who did and did not redeem a prescription for a proton-pump inhibitor or an H2-receptor antagonist during 33 months of follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Levels</th>
<th>PPI(^a) (n = 2703)</th>
<th>No PPI(^a) (n = 13,421)</th>
<th>Total (n = 16,124)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS-10 quintiles</td>
<td>0 – Lowest level of stress</td>
<td>383 (14.2)</td>
<td>2930 (21.8)</td>
<td>3313 (20.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>388 (14.4)</td>
<td>2483 (18.5)</td>
<td>2871 (17.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>517 (19.1)</td>
<td>2767 (20.6)</td>
<td>3284 (20.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>612 (22.6)</td>
<td>2814 (21.0)</td>
<td>3426 (21.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 – Highest level of stress</td>
<td>803 (29.7)</td>
<td>2427 (18.1)</td>
<td>3230 (20.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1244 (46.0)</td>
<td>6827 (50.9)</td>
<td>8071 (50.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1459 (54.0)</td>
<td>6694 (49.1)</td>
<td>8153 (49.9)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Years [mean (SD)]</td>
<td>56.1 (15.8)</td>
<td>47.5 (16.7)</td>
<td>49.0 (16.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Educational level</td>
<td>Primary</td>
<td>1010 (37.4)</td>
<td>3957 (29.5)</td>
<td>4967 (30.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>1129 (41.8)</td>
<td>6055 (45.1)</td>
<td>7184 (44.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>564 (20.9)</td>
<td>3409 (25.4)</td>
<td>3973 (24.6)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>No, never</td>
<td>1048 (38.8)</td>
<td>6755 (50.3)</td>
<td>7803 (48.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No, but used to</td>
<td>974 (36.0)</td>
<td>5700 (42.5)</td>
<td>6674 (41.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes, &lt; 15 a day</td>
<td>381 (14.1)</td>
<td>1699 (12.7)</td>
<td>2080 (12.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes, &gt; 14 a day</td>
<td>300 (11.1)</td>
<td>1347 (10.0)</td>
<td>1647 (10.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Alcohol consumption(^b)</td>
<td>Within recommendation</td>
<td>2463 (91.1)</td>
<td>12,283 (91.5)</td>
<td>14,746 (91.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Over recommendation</td>
<td>240 (8.9)</td>
<td>1138 (8.5)</td>
<td>1378 (8.5)</td>
<td>3.624</td>
</tr>
<tr>
<td>NSAID use</td>
<td>No</td>
<td>641 (23.7)</td>
<td>5649 (42.1)</td>
<td>6290 (39.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2062 (76.3)</td>
<td>7772 (57.9)</td>
<td>9834 (61.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>Underweight</td>
<td>50 (1.8)</td>
<td>268 (2.0)</td>
<td>318 (2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal weight</td>
<td>1055 (39.0)</td>
<td>6354 (47.3)</td>
<td>7409 (46.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>1598 (58.1)</td>
<td>6799 (50.7)</td>
<td>8397 (52.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sleep (h/day)</td>
<td>&lt; 7</td>
<td>594 (22.0)</td>
<td>2351 (17.5)</td>
<td>2945 (18.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>&gt; 7</td>
<td>919 (34.0)</td>
<td>3536 (26.2)</td>
<td>4455 (27.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Income(^c)</td>
<td>&lt; 189 399</td>
<td>636 (23.5)</td>
<td>2824 (21.0)</td>
<td>3460 (21.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>189 399–326 834</td>
<td>831 (30.7)</td>
<td>3016 (22.5)</td>
<td>3847 (23.8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>326 834–449 335</td>
<td>631 (23.3)</td>
<td>3613 (26.9)</td>
<td>4244 (26.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>&gt; 449 335</td>
<td>605 (22.4)</td>
<td>3968 (29.6)</td>
<td>4573 (28.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Previous ulcer</td>
<td>No previous ulcer</td>
<td>2495 (92.3)</td>
<td>13,263 (98.8)</td>
<td>15,758 (97.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous ulcer</td>
<td>208 (7.7)</td>
<td>158 (1.2)</td>
<td>366 (2.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Exercise(^d)</td>
<td>Over recommendation</td>
<td>472 (17.5)</td>
<td>3734 (27.9)</td>
<td>4206 (26.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>1843 (68.2)</td>
<td>8481 (63.2)</td>
<td>10,324 (64.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Divorced/ widowed</td>
<td>484 (17.2)</td>
<td>1481 (11.0)</td>
<td>1945 (12.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Unmarried and single</td>
<td>396 (14.7)</td>
<td>3459 (25.8)</td>
<td>3855 (23.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Anxiety or depressive symptoms</td>
<td>No</td>
<td>1926 (71.3)</td>
<td>11,209 (83.5)</td>
<td>13,135 (81.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>777 (28.7)</td>
<td>2212 (16.5)</td>
<td>2989 (18.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>1826 (67.6)</td>
<td>11,088 (82.6)</td>
<td>12,914 (80.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>877 (32.4)</td>
<td>2333 (17.4)</td>
<td>3210 (19.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Previous PPI</td>
<td>No previous PPI</td>
<td>1031 (38.1)</td>
<td>11,295 (84.2)</td>
<td>12,326 (76.4)</td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>Previous PPI</td>
<td>1672 (61.9)</td>
<td>2126 (15.8)</td>
<td>3798 (23.6)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

PPI, proton-pump inhibitor.

\(^a\)PPI refers to redeeming a prescription for either a proton-pump inhibitor or an H2-receptor antagonist.

\(^b\)Recommended maximum consumption per week is 168 g for women and 252 g for men.

\(^c\)Income is reported in Danish Kroner and grouped into quartiles.

\(^d\)Recommendation for adults is more than 30 min a day of moderate-intensity to high-intensity exercise.

\(^e\)Married also includes individuals living with a partner or in a registered partnership and divorced includes separated.

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**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.
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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 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 or 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 H2-receptor antagonists without a prescription. Therefore, it is possible that some respondents in the sample consumed H2-receptor antagonists or bismuth-containing compounds. These individuals will not be identified in this study as dyspepsia patients elsewhere [12,19].

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 or 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

<table>
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<th>P-value</th>
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Fig. 3. Estimated hazard ratios for the risk of redeeming a proton-pump inhibitor or an H2-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.
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 to the reliability of the findings in this study.

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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.

Acknowledgements

The North Denmark Health Profile 2010 was funded by the North Denmark Region.

The authors are grateful for the support received from the Public Health and Epidemiology Group at the Department of Health Science and Technology, Aalborg University, Denmark.

H.B. and U.D. developed the idea for this study. U.D. was the main author of the manuscript and carried out data management and statistical analysis with guidance and advice from H.B. and C.T.P. All authors contributed toward the interpretation of results and revised and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

References


