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Psychological Stress Increases Risk for Peptic Ulcer, Regardless of *Helicobacter pylori* Infection or Use of Nonsteroidal Anti-inflammatory Drugs

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BACKGROUND & AIMS: **There is controversy over whether psychological stress contributes to development of peptic ulcers. We collected data on features of life stress and ulcer risk factors from a defined population in Denmark and compared these with findings of confirmed ulcers during the next 11–12 years.**

METHODS: **We collected blood samples and psychological, social, behavioral, and medical data in 1982–1983 from a population-based sample of 3379 Danish adults without a history of ulcer participating in the World Health Organization's MONICA study. A 0- to 10-point stress index scale was used to measure stress on the basis of concrete life stressors and perceived distress. Surviving eligible participants were reinterviewed in 1987–1988 (n = 2809) and 1993–1994 (n = 2410). Ulcer was diagnosed only for patients with a distinct breach in the mucosa. All diagnoses were confirmed by review of radiologic and endoscopic reports. Additional cases of ulcer were detected in a search of all 3379 subjects in the Danish National Patient Register.**

RESULTS: **Seventy-six subjects were diagnosed with ulcer. On the basis of the stress index scale, ulcer incidence was significantly higher among subjects in the highest tertile of stress scores (3.5%) than the lowest tertile (1.6%) (adjusted odds ratio, 2.2; 95% confidence interval [CI], 1.2–3.9; $P < .01$). The per-point odds ratio for the stress index (1.19; 95% CI, 1.09–1.31; $P < .001$) was unaffected after adjusting for the presence of immunoglobulin G antibodies against *Helicobacter pylori* in stored sera, alcohol consumption, or sleep duration but lower after adjusting for socioeconomic status (1.17; 95% CI, 1.07–1.29; $P < .001$) and still lower after further adjustments for smoking, use of nonsteroidal anti-inflammatory drugs, and lack of exercise (1.11; 95% CI, 1.01–1.23; $P = .04$). The risk for ulcer related to stress was similar among subjects who were *H pylori* seropositive, those who were *H pylori* seronegative, and those exposed to neither *H pylori* nor nonsteroidal anti-inflammatory drugs. On multivariable analysis, stress, socioeconomic status, smoking, *H pylori* infection, and use of nonsteroidal anti-inflammatory drugs were independent predictors of ulcer.**

CONCLUSIONS: **In a prospective study of a population-based Danish cohort, psychological stress increased the incidence of peptic ulcer, in part by influencing health risk behaviors. Stress had similar effects on ulcers associated with *H pylori* infection and those unrelated to either *H pylori* or use of nonsteroidal anti-inflammatory drugs.**

Keywords: Psychosocial Factors; Epidemiology; Gastric; Duodenal.

Abbreviations used in this paper: **CI, confidence interval; ELISA, enzyme-linked immunosorbent assay.**

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Helicobacter pylori and nonsteroidal anti-inflammatory drugs have long displaced stress as accepted causes of peptic ulcer, and authoritative sources now commonly discount or ignore a role for psychosocial factors.[1,2]

Only a minority of *H pylori* or nonsteroidal anti-inflammatory drug–exposed individuals develop ulcers, however, and in 16%–31% of ulcers neither can be implicated, so co-factors and alternative pathways must be common.[3–5] The concept that psychological factors contribute to ulcer etiology has not disappeared,[6–8] but no prospective studies have linked stress with incident medically confirmed ulcer in population-based data sets taking all major risk factors into consideration. Changes in ulcer epidemiology and medical practice since 1990, notably a drop in the prevalence of uncomplicated ulcer and the widespread empirical treatment of dyspepsia with *H pylori* eradication and/or using potent prescription and over-the-counter antisecretory agents without diagnostic confirmation, have made valid research increasingly difficult to perform. Thus, doubt remains whether the frequently reported association between stress and ulcer might be due to confounding, diagnostic bias, or the stressful effect of ulcer symptoms.

The present study sought to resolve this doubt by examining life stress at baseline among a defined Danish population cohort in relation to medically confirmed ulcers during the next 11–12 years; earlier analyses on a subject subset had suggested associations with psychological factors.[9,10] The availability of baseline data on a broad range of potential ulcer risk factors, collected in a period early enough to be free of potential confounding stemming from the recent innovations in medical practice just described, allowed exploration of the relative importance and interactions of psychological, social, behavioral, and bacteriologic factors.

It was hypothesized that life stress would be a predictor of documented incident ulcer, that the association between stress and ulcer would be attributable in part to health risk behaviors and in part to confounding by low socioeconomic status, and that psychological stress and *H pylori* would be additive, independent ulcer risk factors.

Methods

Subjects and Outcomes

In 1982 as part of the World Health Organization's MONICA study on the risk and development of cardiovascular diseases,[11] the Research Centre for Prevention and Health identified an age- and sex-stratified random sample of adults living in Western Copenhagen County who were born in 1922, 1932, 1942, or 1952. A total of 4807 persons were invited, and all 3785 interviewed subjects were considered for inclusion in the present analyses. Subjects were then excluded if they were not Danish, reported at baseline having had a peptic ulcer, or had missing baseline *H pylori* antibody measures, for a final sample of 3379 (Figure 1).

Surviving Danish participants (110 had died in the interim) were reinvited in 1987–1988, and 2987 attended the interview, including 2809 subjects eligible for this study. All were asked whether since 1982 they had undergone gastroscopy or barium swallow, and whether an ulcer had been diagnosed. In 1993–1994, 4130 surviving subjects from the original cohort were reinvited, 2656 were reexamined and asked whether an ulcer had been diagnosed since 1982, and 2410 were eligible for the present project. Attempts were made to review reports of all 209 endoscopy and radiology examinations reported in 1987 and were successful in 170 cases including all cases of self-reported ulcer; diagnostic reports were also reviewed for all new ulcers self-reported in 1993. Additional ulcer cases were detected via a search performed on all 3379 subjects in the Danish National Patient Register, which since 1977 has listed discharge diagnoses for all patients admitted to non-psychiatric hospitals.[12] Ulcer was diagnosed only in the presence of a distinct breach in the mucosa; gastroduodenal erosions without appreciable depth were not classified as ulcers.

Independent Variables

Baseline socioeconomic status was calculated from education, occupation, and number of employees and classified according to the highest-rated family member. Unemployment was determined from respondents' descriptions of their current main activity. Other real-life stressors examined were working more than 40 hours a week and an ad hoc measure asking whether the subject had economic, work, family, housing, or personal problems.

Past and present cigarette, cigar, and pipe smoking were recorded as grams of tobacco consumed per day, alcohol consumption as drinks per week, leisure time physical activity as none, walking, or intense, and sleep duration as hours per day. Frequency of current and past use of 19 types of medication was ascertained; consumption of aspirin, arthritis medications, and minor tranquilizers (which did not include antidepressants) was examined for the present analyses.

Subjects answered 22 items from the Mental Vulnerability Scale (formerly called the Psychic Vulnerability Scale), a questionnaire constructed by the Danish Military Psychological Services in the 1960s with the purpose of detecting young men unsuitable for military service.[13] The 12-item version used in the present

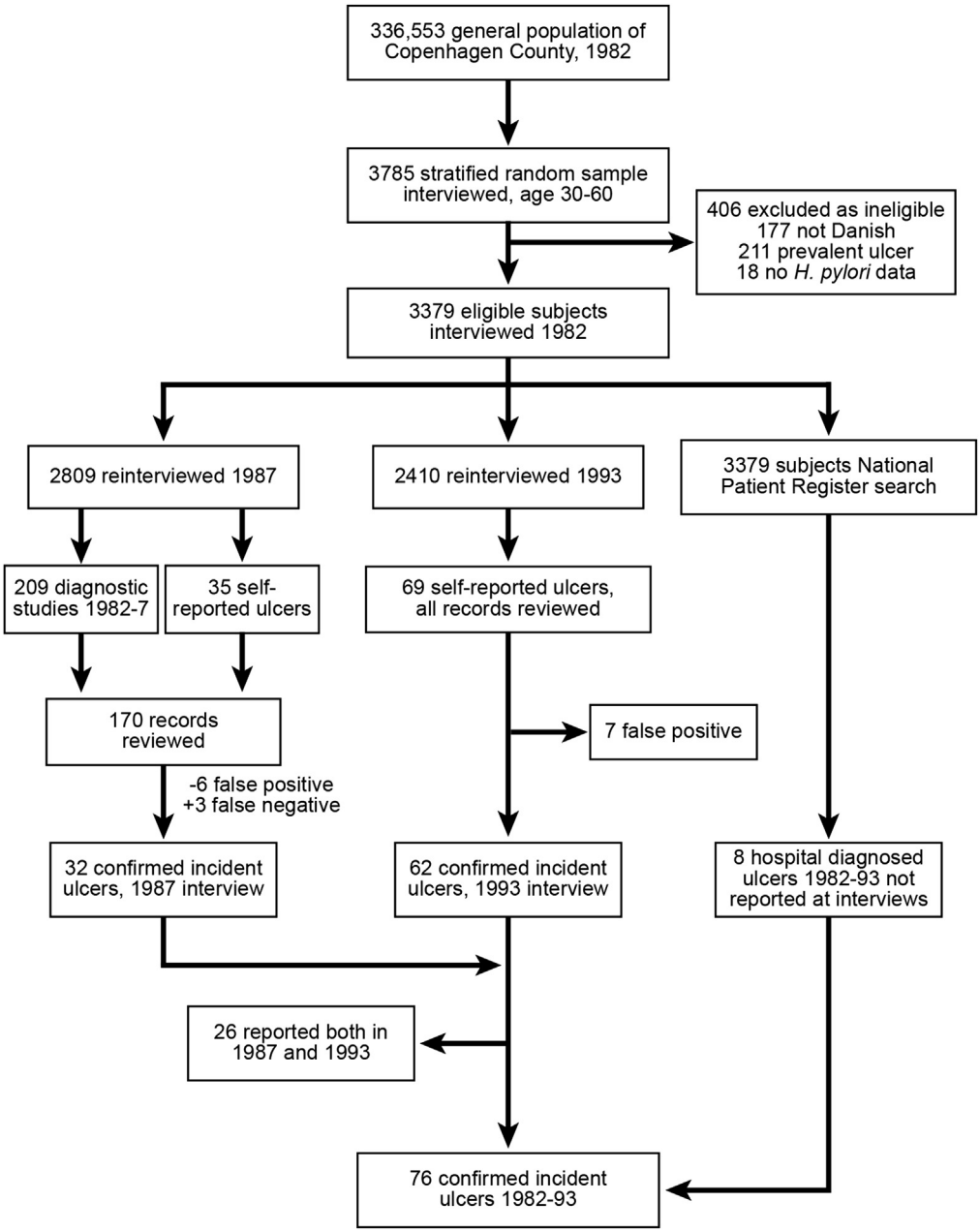


Figure 1. Flow chart of enrollment, procedures, and outcomes.

analyses (Appendix) has been validated in the general Danish population, where it is predictive of both incident coronary disease and mortality and is associated ($r = 0.41$–0.67) with somatization, neuroticism, depression, and anxiety.[14–16]

A stress index with a theoretical range from 0 to 10 was designed a priori to combine baseline Mental Vulnerability (score of 1 = 1 point, 2 = 2 points, 3–4 = 3 points, ≥5 = 4 points); tranquilizer use (any, past or present = 2 points); economic, work, family, housing, or personal problems (1 problem area = 1 point, 2–5 problem areas = 2 points); unemployment (1 point)[17]; and working >40 hours/week (1 point).

Blood samples were drawn at baseline, and the sera were frozen. They were thawed in 1993, and immunoglobulin G *H pylori* antibodies were measured with a validated in-house indirect enzyme-linked immunosorbent assay (ELISA) (sensitivity 99%, specificity 54%, positive predictive value 76%, negative predictive value 96%) that classified antibody levels as negative (≤100 ELISA units), borderline (100–400 ELISA units), or positive (>400 ELISA units).[18]

Socioeconomic status and age were treated as continuous variables; leisure time exercise (sedentary versus other), nonsteroidal anti-inflammatory drug exposure (current ≥ once a week versus less or no use), tranquilizer use (ever during past 5 years versus never), *H pylori* status (borderline or positive versus negative), and sleep duration (<7 hours versus adequate) were dichotomized; and smoking categories were collapsed into never, ex, and current. Alcohol use was categorized as none, moderate (1–14 drinks/week for women, 1–21 for men), and heavy (>14 drinks/week for women, >21 for men) because of a possible U-shaped association with ulcer.[9,19] The stress

index was usually treated as a continuous variable, but critical analyses were repeated, for heuristic reasons, with stress levels trichotomized into high (index score = 3–10), medium (1–2), and low stress (0).

The MONICA I study was approved by the Regional Research ethics committee of Copenhagen County. Present analyses fall under National Institutes of Health exemption 4 (study of existing data).

Statistical Methods

All statistical analyses were performed with logistic regression models by using the statistical package SAS, version 9.3 (SAS Institute Inc, Cary, NC). All *P* values were two-sided and interpreted with significance level of 5%. Model fit was evaluated with the Hosmer and Lemeshow goodness-of-fit test.

It was considered desirable to limit the number of degrees of freedom in any individual model following the rule of 10 outcome events per parameter. This condition was generally fulfilled, but occasionally we chose to construct larger models. Although some caution is necessary when interpreting results from these models, all the models converged, and the estimated odds ratios were in line with results from smaller models. In subgroup analyses with fewer events, we also conducted the nonparametric Kruskal–Wallis test to compare participants with and without an ulcer. The results from these Kruskal–Wallis tests were in line with results from the logistic regression models.

The stress index was initially examined as a predictor of incident ulcer to be adjusted for age and sex as indicated. This model was adjusted for socioeconomic class as a confounder and then for nonsteroidal anti-inflammatory drugs, smoking, heavy drinking, inadequate sleep, and lack of exercise, individually and collectively, as potential behavioral mediators. Possible effect modifiers were explored by examining the association of stress with ulcer in subgroupings according to *H pylori* and nonsteroidal anti-inflammatory drug status and according to sex and by examining interaction terms; the expected interaction between *H pylori* and smoking,[20] potentially relevant to the causal mechanisms of stress, was similarly investigated.

One item of the Mental Vulnerability scale, "Do you often have pain in different parts of your body, eg, your stomach, neck, back or chest?", could be affected by undiagnosed baseline ulcer, and another, "Do you often take medicine, such as headache tablets, sleeping pills, tranquilizers, or the like?", creates double-counting issues. The impact of possible confounding on our results was investigated by creating versions of the Mental Vulnerability scale modified to omit each of these items in turn and then using them to construct modified stress indices. In sensitivity analyses, the modified stress indices were examined against incident ulcer.

The population attributable fraction was calculated for each risk factor by using age-adjusted and socioeconomic status–adjusted odds ratios and the prevalence of exposure.

Results

Baseline data were collected on 3379 eligible subjects (Table 1). Forty-three percent were borderline or seropositive for *H pylori* immunoglobulin G antibodies, 16% were taking nonsteroidal anti-inflammatory drugs at least once a week, 56% were current smokers, and 39% were in the lower socioeconomic categories IV or V.

Medically confirmed ulcers with onset between 1982 and 1993–1994 were detected in 76 subjects (Figure 1). Thirty had gastric ulcers, 39 had duodenal ulcers, and 1 had both; in 6 cases the location was unknown. Diagnosis was made by endoscopy in 53 cases, by contrast radiology in 17 cases, and at surgery in 6.

The composite stress index, low socioeconomic status, *H pylori*, smoking, and nonsteroidal anti-inflammatory drugs were each significantly associated with subsequent ulcer; lack of leisure time physical exercise was marginally significant (Table 2). Adjustment for socioeconomic status decreased but did not eliminate most associations (Table 2). The incidence of documented ulcer was 1.6% among subjects with stress index scores in the bottom tertile, 1.5% among subjects in the middle tertile, and 3.5% among subjects with scores in the upper tertile, with an adjusted odds ratio for high- versus low-tertile stress of 2.2 (95% confidence interval [CI], 1.2–3.9; $P = .004$). Sex was not associated with ulcer. Among the 2774 subjects interviewed in 1987 who answered the item about interim upper gastrointestinal diagnostic testing, 3.8% of subjects in the low stress tertile, 5.4% of those in the middle tertile, and 10.2% of those in the upper tertile reported having been tested.

Crude rates of ulcer incidence increased fairly smoothly as scores on the 10-point stress index rose from 0 to 9 (data not shown). The odds ratio for incident ulcer per point of the stress index (1.19; 95% CI, 1.09–1.31) was unchanged by addition of *H pylori*, inadequate sleep, or alcohol consumption to the model (Table 3). It fell to 1.17 (95% CI, 1.07–1.29) with adjustment for socioeconomic status, suggesting some confounding. The odds ratio changed little with addition individually of smoking, lack of exercise, or nonsteroidal anti-inflammatory drug use, but when adjusted for all 3 health risk behaviors as well as socioeconomic status, the odds ratio per point of the stress index fell to 1.11 (95% CI, 1.01–1.23; $P = .04$). The socioeconomic status–adjusted per-point odds ratio of 1.17 indicates excess risk of 17% per point on the stress index, and the fully adjusted odds ratio of 1.11 indicates an 11% excess risk. Examining the relations among these odds ratios, it would appear that approximately one-third of the excess risk associated with stress is due to mediation by behavioral changes ((17%–11%)/17% = 6%/17% = 35%).

When baseline stress, socioeconomic status, smoking, *H pylori*, and nonsteroidal anti-inflammatory drug

Table 1. Baseline Characteristics of Study Population in 1982

Categorical variables	Number (%)
Age (*y*)	
30	892 (26.4)
40	892 (26.4)
50	841 (24.9)
60	754 (22.3)
Sex	
Female	1694 (50.1)
Male	1685 (49.9)
Household socioeconomic status	
Classes I-II (professional, managerial, technical)	926 (27.4)
Class III (skilled workers, manual or nonmanual)	1125 (33.3)
Class IV (partly skilled workers)	924 (27.4)
Class V (unskilled workers)	404 (12.0)
H pylori immunoglobulin G antibody status	
Negative (0–100 ELISA units)	1929 (57.1)
Borderline (101–400 ELISA units)	642 (19.0)
Positive (>400 ELISA units)	808 (23.9)
Nonsteroidal anti-inflammatory drugs[a] (N = 3375)	
None in past 5 years	515 (15.3)
Moderate or past use	2325 (68.9)
Current, ≥ once/week	535 (15.9)
Tobacco smoking (cigarettes, pipe, cigars)	
Never smoked	854 (25.3)
Ex-smoker	626 (18.5)
Current, <15 g/day	863 (25.5)
Current, 15–24.999 g/day	839 (24.8)
Current, ≥25 g/day	197 (5.8)
Alcohol consumption (N = 3378)	
None	439 (13.0)
Moderate (1–14 drinks/wk for women, 1–21 for men)	2488 (73.7)
Heavy (≥15 drinks/wk for women, ≥22 for men)	451 (13.4)
Leisure time exercise (N = 3378)	
None	912 (27.0)
Walking regularly	1772 (52.5)
Intense exercise or competitive sport	694 (20.5)
Hours of sleep per day (N = 3299)	
>8	117 (3.5)
8	844 (25.6)
7	1628 (49.3)
<7	710 (21.5)
Use of minor tranquilizers (N = 3377)	
None in past 5 years	2751 (81.5)
Previous	252 (8.1)
Current	354 (10.5)
Current work status	
Working	2733 (80.9)
Retired	292 (8.6)
Not in work force (students, housewives)	185 (5.5)
Unemployed	169 (5.0)
Hours of work per wk (N = 3357)	
<37	712 (21.2)
37–40	1511 (45.0)
>40	488 (14.5)
Not currently working	646 (19.2)
Economic, work, family, housing, or personal problems (N = 3374)	
No problems	2189 (64.9)
Problems in 1 area	557 (16.5)
Problems in 2 areas	362 (10.7)
Problems in ≥3 areas	266 (7.9)
Stress index[b] (N = 3338)	
Low stress (index score = 0)	927 (27.8)
Medium stress (index score = 1–2)	1240 (37.1)
High stress (index score = 3–10)	1171 (35.1)

Table 1. continued

Continuous variables	25th percentile	Mean	Median	75th percentile
Mental Vulnerability, 12-item (N = 3365)	0	1.3	1	2
Stress index[b] (N = 3338)	0	2.1	2	3

NOTE. N = 3379 except where otherwise specified.
[a]Current use ≥ once/week of antirheumatic drugs or analgesics.
[b]A 10-point scale combining Mental Vulnerability score (1 = 1 point, 2 = 2 points, 3–4 = 3 points, 5+ = 4 points); past or present tranquilizer use (2 points); economic, work, family, housing, or personal problems (1 problem area = 1 point, 2–5 problem areas = 2 points); unemployment (1 point); and working >40 hours/week (1 point).

use were entered into a single age-adjusted multivariable model, all 5 risk factors remained significant predictors (Table 4), indicating that stress is predictive of ulcer even when the other major risk factors are taken into consideration. The socioeconomic status–adjusted population attributable fraction was 29.6% for high tertile stress, as compared with 50.7% for *H pylori* and 17.1% for nonsteroidal anti-inflammatory drugs.

Stress increased the risk for both gastric and duodenal ulcers, with an adjusted odds ratio of 1.19 per point in gastric ulcers (95% CI, 1.03–1.37; $P = .02$) and 1.11 in duodenal ulcers (95% CI, 0.98–1.27; $P = .10$).

There was no significant effect modification by other ulcer risk factors on the association, meaning that the increase in ulcer risk in relation to stress was statistically similar regardless of *H pylori* or nonsteroidal anti-inflammatory drug status. Specifically, the per-point odds ratio for the stress index was 1.19 for *H pylori*–borderline or –seropositive subjects, 1.13 for *H pylori*–seronegative subjects, 1.07 for nonsteroidal anti-inflammatory drug users, and 1.14 for subjects exposed to neither *H pylori* nor nonsteroidal anti-inflammatory drugs (Table 5; P for interaction $> .2$). Stress also had a statistically similar impact at all levels of socioeconomic status (data not shown) and in both sexes.

The interaction between smoking and *H pylori* was not significant ($P = .08$), and introduction of an interaction term did not change the associations of stress with ulcer.

When the stress index was modified to exclude the pain item or the medication item in the Mental Vulnerability scale, the results were substantially unchanged.

Discussion

Findings

In these prospective analyses of a Danish population sample with no history of peptic ulcer, a composite stress index was associated with medically confirmed subsequent ulcers (whose definition excluded mere erosions). High tertile stress more than doubled the odds of developing an ulcer, with attributable risk of nearly 30%.

Table 2. Risk for Incident Peptic Ulcer by 1993–1994 According to Baseline Characteristics in 1982, Multiple Logistic Regression

	Age-adjusted			Age- and SES-adjusted		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age, per 10 y	1.07	0.87–1.32	.51	1.03	0.84–1.27	.76
Female sex	1.05	0.67–1.65	.83	1.01	0.64–1.60	.96
Stress index,[a] per point	1.19	1.09–1.31	<.001	1.17	1.07–1.29	<.001
Stress index tertile (versus low)			.002			.004
Medium (1–2)	0.95	0.47–1.89		0.96	0.48–1.93	
High (≥3)	2.24	1.23–4.05		2.16	1.19–3.92	
Socioeconomic status[b]	1.46	1.16–1.83	.001			
Smoking (versus never-smoker)			.002			.004
Ex-smoker	1.66	0.65–4.25		1.64	0.64–4.19	
Current smoker	3.32	1.58–6.98		3.10	1.47–6.53	
Alcohol use (versus none)			.77			.88
Moderate	0.82	0.43–1.54		0.80	0.33–1.93	
Heavy	0.74	0.31–1.77		0.91	0.48–1.74	
NSAIDs[c]	2.34	1.42–3.86	<.001	2.30	1.39–3.79	.001
Sleeping <7 h/day	1.25	0.74–2.11	.41	1.18	0.69–2.00	.55
Sedentary in leisure time	1.60	1.00–2.57	.05	1.48	0.92–2.39	.10
H pylori[d]	3.62	2.16–6.05	<.001	3.44	2.05–5.76	<.001

NOTE. N = 3379, number of ulcers = 76.
SES, socioeconomic status.
[a]A 10-point scale combining Mental Vulnerability score (1 = 1 point, 2 = 2 points, 3–4 = 3 points, 5+ = 4 points); past or present tranquilizer use (2 points); economic, work, family, housing, or personal problems (1 problem area = 1 point, 2–5 problem areas = 2 points); unemployment (1 point); and working >40 hours/week (1 point).
[b]Per step on 4-point scale: I-II, III, IV, V.
[c]Nonsteroidal anti-inflammatory drugs; current use ≥ once/week of antirheumatic drugs or analgesics.
[d]Serum immunoglobulin G antibodies borderline or positive (>100 ELISA units).

Stress remained a significant predictor in a multivariable model including *H pylori*, nonsteroidal anti-inflammatory drugs, socioeconomic status, and smoking; odds ratios associated with established ulcer risk factors were similar to those in previous reports.[21]

Table 3. Possible Confounders and Mediators of Association Between Stress and Peptic Ulcer: Associations of Baseline Stress Index (per Point) With Incident Ulcer in Logistic Regression Models Including Known Ulcer Risk Factors

Variables in addition to stress and age	Odds ratio per stress index point	95% CI	P value, OR of stress vs unity
None	1.19	1.09–1.31	<.001
Socioeconomic status	1.17	1.07–1.29	<.001
H pylori[a]	1.19	1.08–1.31	<.001
Alcohol (none, moderate, heavy)	1.19	1.09–1.31	<.001
Sleeping <7 h/day	1.19	1.08–1.31	<.001
Smoking (never-, ex-, current)	1.16	1.05–1.30	.002
NSAIDs[b]	1.15	1.04–1.27	.005
Sedentary in leisure time	1.18	1.07–1.29	<.001
SES + smoking + NSAIDs + sedentary	1.11	1.01–1.23	.04

NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; SES, socioeconomic status.
[a]Serum immunoglobulin G antibodies borderline or positive (>100 ELISA units).
[b]Current use ≥ once/week of antirheumatic drugs or analgesics.

Context

A vast literature links peptic ulcer to stress, but its weaknesses are such that the National Institute of Diabetes and Digestive and Kidney Diseases Web site for the general public summarizes it as "Peptic ulcers are not caused by stress."[22] Some of the stronger evidence is

Table 4. Multivariable Logistic Regression Model Including All Major Baseline Risk Factors in 1982 Versus Incident Peptic Ulcer by 1993–1994

	Odds ratio	95% CI	*P* value
Stress index, per point[a]	1.12	1.01–1.23	.03
Socioeconomic status[b]	1.29	1.02–1.62	.03
Smoking (reference: never smoked)			.008
Ex-smoker	1.57	0.61–4.04	
Current smoker	2.91	1.38–6.16	
H pylori[c]	3.39	2.02–5.69	<.001
Nonsteroidal anti-inflammatory drugs[d]	1.77	1.03–3.03	.04

NOTE. Odds ratios for each risk factor are adjusted for age and for all other risk factors. N = 3337, number of ulcers = 76.
[a]On 0- to 10-point scale.
[b]Per step on 4-point scale: socioeconomic class I-II, III, IV, V.
[c]Serum immunoglobulin G antibodies borderline or positive (>100 ELISA units).
[d]Current use ≥ once/week of antirheumatic drugs or analgesics.

Table 5. Possible Moderators of Association Between Stress and Peptic Ulcer: Age- and Socioeconomic Status–adjusted Associations of Baseline Stress Index (per Point) With Subsequent Incident Ulcer in Selected Subgroups

	Number of ulcers/subjects	Odds ratio per index point	95% CI	*P* value
H pylori status				
Seronegative	21/1912	1.13	0.95–1.35	.17
Borderline or positive[a]	55/1426	1.19	1.06–1.33	.003
NSAIDs[b]				
Less than once per week	53/2754	1.16	1.04–1.31	.01
At least once per week	23/507	1.07	0.90–1.28	.46
Both *H pylori* and NSAIDs	16/240	1.11	0.89–1.38	.35
Neither *H pylori* nor NSAIDs	14/1621	1.14	0.91–1.44	.26
Sex				
Female	39/1673	1.12	0.98–1.27	.09
Male	37/1665	1.26	1.09–1.44	.001

NOTE. All group differences are nonsignificant (*P* for interaction with stress index > .2).
NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Serum immunoglobulin G antibodies borderline or positive (>100 ELISA units).
[b]Current use ≥ once/week of antirheumatic drugs and/or analgesics.

indirect: surges in ulcer diagnoses after societal stressors such as wartime bombing or earthquake[23–25] and worsening of prognosis by psychological factors.[26–28] Cross-sectional studies are unconvincing, because their results may be inflated by recall bias and by the distressing effects of disease.[29]

Several longitudinal studies of defined epidemiologic cohorts have reported baseline stress to increase the risk of developing ulcer during a period of 5–15 years.[17,19,30–32] Ulcer diagnoses in these studies have been based on self-report either exclusively[17,19,31] or in part,[30,32] however, and differential self-reporting causing bias could arise from psychological characteristics. Furthermore, none have taken into account both *H pylori* and socioeconomic status. The present study has none of these weaknesses, and because its sample is population-based (although in an area slightly less rural than Denmark as a whole[33]), its results can be reliably generalized to other Western countries and, although with somewhat less confidence, also to populations with different rates of *H pylori* infection.

Limitations

The data analyzed here were gathered 2 decades ago. This apparent limitation is potentially an advantage, however, considering the subsequent evolution of ulcer epidemiology and medical culture. At baseline, *H pylori* had not been discovered, excluding prior eradication therapy as a potential confounder.[34] During the follow-up period, histamine-2 blockers (and later, proton pump inhibitors) were available only by prescription, *H pylori* was rarely tested for and was only treated if verified during gastroscopy, and dyspepsia was routinely evaluated by using endoscopic or radiologic studies, so that incident ulcers were likely to be accurately diagnosed. At present, dyspepsia is commonly treated or self-treated empirically, with definitive testing reserved for refractory or "red flag" symptoms.[35–38] Many ulcers thus probably remain undiagnosed, whereas psychological influences on dyspeptic symptoms, on health care seeking behavior, and on the decision to perform definitive testing constitute unavoidable sources of confounding (as they do to some extent, as demonstrated by the excess of upper gastrointestinal testing in high-stress subjects, in the earlier period covered by the present study).[39,40] Furthermore, performance of similar analyses on later cohorts could face serious power considerations, because the incidence of uncomplicated ulcers has fallen sharply.[1,38] Bleeding and perforated ulcers, which may be particularly linked to stress,[23–25,41] have decreased to a lesser extent, however, and continue to cause substantial morbidity and mortality in the United States as well as elsewhere.[35,42–45] The statistical power of the present analyses sufficed to document a robust independent association between stress and ulcer but did not allow formal mediation analyses or full examination of effect modification and somewhat limited the reliability of larger multivariable models.

The stress index used in these analyses had the merit of taking into account objective life stressors such as unemployment as well as the subjective distress measured in the well-validated Mental Vulnerability scale. However, this index was developed ad hoc for the present study by using a priori weightings of its component items, with the aim of maximally exploiting relevant information available in a preexisting data base, and it has not undergone independent validation.

While often used for screening larger populations, serum immunoglobulin G antibodies are an imperfect measure of *H pylori* infection because antibodies can reflect either ongoing or past infection. In this study population, seropositivity likely reflected current *H pylori* infection, because the population was unexposed to eradication therapy; spontaneous clearance of infection is unusual in nonelderly adults.[46] The proportion of subjects considered *H pylori* infected was slightly overestimated because of the inclusion of borderline as well as seropositive serologies.

Both gastric and duodenal ulcers were associated with stress; in the literature, risk factors including stress are quite similar for both types.[24,25,31]

No data were available regarding subjects' baseline use of antisecretory agents or of low-dose aspirin. Such use was likely to be minimal in 1982; fewer than 0.5% of MONICA I subjects without known ulcers were taking antisecretory agents even 11 years later,[9] and aspirin use

for primary cardiovascular prevention was uncommon before publication of the Physicians' Health Study in 1989.

Finally, the observed 0.20% per-year rate of new ulcers during follow-up underestimates the true incidence rate, both because ulcers diagnosed as outpatients among subjects lost to follow-up were not included and because asymptomatic ulcers were unlikely to have been detected.

Mechanisms

Stress may promote peptic ulcer through increased acid load, effects of hypothalamic-pituitary-adrenal axis activation on healing, altered blood flow, or cytokine-mediated impairment of mucosal defenses.[47–50] Behavioral mediators such as smoking account for approximately one-third of the ulcerogenic effect of psychological stress in the present analyses as in previous studies.[19] Two previously reported behavioral mediators, heavy alcohol consumption and poor sleep, were not confirmed in the present analyses.[19] Synergy between stress and *H pylori*[3] and effect modification by socioeconomic status[51] were also not observed. An impact of stress was at least as evident in *H pylori*–positive as in "idiopathic" ulcer, as 2 previous studies have suggested[52,53] but contrary to 1 recent report.[25] Because various chronic diseases may be related to infection, either directly or via immune mechanisms, the ability of stress to affect the course of *H pylori* infection could extend to other conditions as well.[54–56]

Conclusions

Life stress at baseline increased the risk of subsequent confirmed peptic ulcer in a population-based cohort without a history of ulcer at baseline. The increased risk was not fully explained by confounding by socioeconomic status or by associations with nonsteroidal anti-inflammatory drugs and smoking, although the impact of stress on these health risk behaviors accounted for a portion of the increased risk. Stress affected *H pylori*–related ulcers at least as much as those related to neither *H pylori* nor nonsteroidal anti-inflammatory drugs. These results support a multicausal model of peptic ulcer etiology with intertwined biological and psychosocial components. Clinicians treating ulcer patients should investigate potential psychological stress among other risk factors.

References

1. Malfertheiner P, Chan FKL, McColl KEL. Peptic ulcer disease. Lancet 2009;374:1449–1461.
2. Anand BS. Peptic ulcer disease: etiology. Available from: http://emedicine.medscape.com/article/181753-overview- aw2aab6b2b4aa. Accessed September 18, 2012.
3. Graham DY. Helicobacter pylori infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. Gastroenterology 1997;113:1983–1991.
4. Jyotheeswaran S, Shah AN, Jin HO, et al. Prevalence of Helicobacter pylori in peptic ulcer patients in greater Rochester, NY: is empirical triple therapy justified? Am J Gastroenterol 1998;93:574–578.
5. Gisbert JP, Calvet X. Review article: Helicobacter pylori-negative duodenal ulcer disease. Aliment Pharmacol Ther 2009;30:791–815.
6. Levenstein S. Stress and peptic ulcer: life beyond Helicobacter. Br Med J 1998;316:538–541.
7. Levenstein S. The very model of a modern etiology: a biopsychosocial view of peptic ulcer. Psychosom Med 2000;62:176–185.
8. Soll AH. Peptic ulcer disease: genetic, environmental, and psychological risk factors and pathogenesis. In: Basow DS, ed. UpToDate. Waltham, MA: UpToDate, 2012.
9. Rosenstock S, Jorgensen T, Bonnevie O, et al. Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults. Gut 2003;52:186–193.
10. Rosenstock SJ, Jørgensen T, Bonnevie O, et al. Does Helicobacter pylori infection explain all socio-economic differences in peptic ulcer incidence? genetic and psychosocial markers for incident peptic ulcer disease in a large cohort of Danish adults. Scand J Gastroenterol 2004;39:823–829.
11. Tunstall-Pedoe H, ed. MONICA: monograph and multimedia sourcebook—world's largest study of heart disease, stroke, risk factors, and population trends 1979-2002. Geneva: World Health Organization, 2003.
12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(Suppl 7):30–33.
13. Sabroe K, Kousgaard E, Knox-Seith B, et al. P-faktoren i FOUSHIP-klassificerings-systemet [in Danish, with English summaries]. Copenhagen: MPT, 1968–1970.
14. Eplov LF, Jørgensen T, Birket-Smith M, et al. Mental vulnerability as a predictor of early mortality. Epidemiology 2005;16:226–232.
15. Eplov LF, Jorgensen T, Birket-Smith M, et al. Mental vulnerability: a risk factor for ischemic heart disease. J Psychosom Res 2006;60:169–176.
16. Eplov LF, Petersen J, Jørgensen T, et al. The mental vulnerability questionnaire: a psychometric evaluation. Scand J Psychol 2010;51:548–554.
17. Levenstein S, Kaplan GA, Smith M. Sociodemographic characteristics, life stressors, and peptic ulcer: a prospective study. J Clin Gastroenterol 1995;21:185–192.
18. Andersen LP, Espersen F, Souckova A, et al. Isolation and preliminary evaluation of a low molecular (LMW) antigen preparation for improved detection of Helicobacter pylori IgG antibodies. Clin Diagnostic Lab Immunol 1995;2:156–159.
19. Levenstein S, Kaplan GA, Smith MW. Psychological predictors of peptic ulcer incidence in the Alameda County Study. J Clin Gastroenterol 1997;24:140–146.
20. Martin DF, Montgomery E, Dobek AD, et al. *Campylobacter pylori*, NSAIDs, and smoking: risk factors for peptic ulcer disease. Am J Gastroenterol 1989;84:1268–1272.
21. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer: nonsteroidal antiinflammatory drugs, Helicobacter pylori, and smoking. J Clin Gastroenterol 1997;24:2–17.
22. National Institute of Diabetes and Digestive and Kidney Diseases. 2012. Available from: http://digestive.niddk.nih.gov/ddiseases/pubs/hpylori/. Accessed August 26, 2012.
23. Spicer CC, Stewart DN, Winser DMR. Perforated peptic ulcer during the period of heavy air raids. Lancet 1944;i:14.

24. Aoyama N, Kinoshita Y, Fujimoto S, et al. Peptic ulcers after the Hanshin-Awaji earthquake: increased incidence of bleeding gastric ulcers. Am J Gastroenterol 1998;93:311–316.
25. Kanno T, Iijima K, Abe Y, et al. Peptic ulcers after the Great East Japan earthquake and tsunami: possible existence of psychosocial stress ulcers in humans. J Gastroenterol 2013;48:483–490.
26. Holtmann G, Armstrong D, Pöppel E, et al. Influence of stress on the healing and relapse of duodenal ulcers. Scand J Gastroenterol 1992;27:917–923.
27. Levenstein S, Prantera C, Varvo V, et al. Long-term symptom patterns in duodenal ulcer: psychosocial factors. J Psychosom Res 1996;41:465–472.
28. Levenstein S, Prantera C, Scribano ML, et al. Psychologic predictors of duodenal ulcer healing. J Clin Gastroenterol 1996; 22:84–89.
29. Wilhelmsen I, Berstad A. Reduced relapse rate in duodenal ulcer disease leads to normalization of psychological distress: twelve-year follow-up. Scand J Gastroenterol 2004;39:717–721.
30. Anda RF, Williamson DF, Escobedo LG, et al. Self-perceived stress and the risk of peptic ulcer disease: a longitudinal study of US adults. Arch Intern Med 1992;152:829–833.
31. Medalie JH, Stange KC, Zyzanski SJ, et al. The importance of biopsychosocial factors in the development of duodenal ulcer in a cohort of middle-aged men. Am J Epidemiol 1992;136:1280–1287.
32. Raiha I, Kemppainen H, Kaprio J, et al. Lifestyle, stress, and genes in peptic ulcer disease: a nationwide twin cohort study. Arch Intern Med 1998;158:698–704.
33. Rosenstock SJ, Jorgensen T. Prevalence and incidence of peptic ulcer disease in a Danish County: a prospective cohort study. Gut 1995;36:819–824.
34. Marshall BJ, Warren R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; i:1311–1315.
35. Lewis JD, Bilker WB, Brensinger C, et al. Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. Am J Gastroenterol 2002;97:2540–2549.
36. Delaney B, Ford AC, Forman D, et al. Initial management strategies for dyspepsia. Cochrane Database Syst Rev 2005; 19:CD001961.
37. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther 2009;29:938–946.
38. Raghuram A, Holub JL, Lieberman DA. Lower prevalence of peptic ulcer disease in the era of over the counter proton pump inhibitors. Gastroenterology 2011;140:S726–S727.
39. Cheng C. Seeking medical consultation: perceptual and behavioral characteristics distinguishing consulters and non-consulters with functional dyspepsia. Psychosom Med 2000; 62:844–852.
40. Van Oudenhove L, Vandenberghe J, Geeraerts B, et al. Determinants of symptoms in functional dyspepsia: gastric sensorimotor function, psychosocial factors or somatisation? Gut 2008;57:1666–1673.
41. Lam SK, Hui WM, Shiu LP, et al. Society stress and peptic ulcer perforation. J Gastroenterol Hepatol 1995;10:570–576.
42. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002;122:1500–1511.
43. Feinstein LB, Holman RC, Yorita Christensen KL, et al. Trends in hospitalizations for peptic ulcer disease. United States, 1998–2005. Emerg Infect Dis 2010:6 [serial on the Internet].
44. Laine L, Yang H, Chang SC, et al. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. Am J Gastroenterol 2012;107: 1190–1195.
45. Rosenstock S, Møller MH, Larsson H, et al. Improving quality of care in peptic ulcer bleeding: nationwide cohort study of 13,498 consecutive patients in the Danish clinical register of emergency surgery. Am J Gastroenterol 2013;108:1449–1457.
46. Xia HH, Talley NJ. Natural acquisition and spontaneous elimination of Helicobacter pylori infection: clinical implications. Am J Gastroenterol 1997;92:1780–1787.
47. Peters MN, Richardson CT. Stressful life events, acid hypersecretion, and ulcer disease. Gastroenterology 1983;84:114–119.
48. Takeuchi K, Furukawa O, Okabe S. Induction of duodenal ulcers in rats under water-immersion stress conditions: influence of stress on gastric acid and duodenal alkaline secretion. Gastroenterology 1986;91:554–563.
49. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, et al. Slowing of wound healing by psychological stress. Lancet 1995;346: 1194–1196.
50. Arakawa T, Watanabe T, Fukuda T, et al. Ulcer recurrence: cytokines and inflammatory response-dependent process. Dig Dis Sci 1998;43(Suppl):61S–66S.
51. Lazzarino AI, Hamer M, Stamatakis E, et al. The combined association of psychological distress and socioeconomic status with all-cause mortality: a national cohort study. JAMA Intern Med 2013;173:22–27.
52. Levenstein S, Prantera C, Varvo V, et al. Patterns of biologic and psychologic risk factors for duodenal ulcer. J Clin Gastroenterol 1995;21:110–117.
53. Matsushima Y, Aoyama N, Fukuda H, et al. Gastric ulcer formation after the Hanshin-Awaji earthquake: a case study of Helicobacter pylori infection and stress-induced gastric ulcers. Helicobacter 1999;4:94–99.
54. Sriram S, Stratton CW, Yao S, et al. Chlamydia pneumoniae infection of the central nervous system in multiple sclerosis. Ann Neurol 1999;46:6–14.
55. Jaeckel E, Manns M, Von Herrath M. Viruses and diabetes. Ann N Y Acad Sci 2002;958:7–25.
56. Hitchon CA, El-Gabalawy HS. Infection and rheumatoid arthritis: still an open question. Curr Opin Rheumatol 2011;23:352–357.

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Appendix. The 12-item Mental Vulnerability Scale

Instructions: We would like to ask you some questions regarding your personal well-being. Please do not think too much about the answers; just answer as you find most suitable.

1. Do your hands easily shake?
2. Do you often suffer from loss of appetite?
3. Do you often suffer from sleeplessness?
4. Do you often feel very tired?
5. Do you often take medicine, such as headache tablets, sleeping pills, tranquilizers, or the like?
6. Do you often have pain in different parts of your body, eg, your stomach, neck, back, or chest?
7. Do you often suffer from fits of dizziness?
8. Does your heart often beat very fast for no particular reason?
9. Is it difficult for you to make friends?
10. Do small things get on your nerves?
11. Do you constantly have thoughts that trouble and worry you?
12. Do you usually feel misunderstood by other people?