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.

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*H*elicobacter 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