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Anxiety Is Linked to New-Onset Dyspepsia in the Swedish Population: A 10-Year Follow-up Study

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BACKGROUND & AIMS: Functional dyspepsia (FD) is associated with anxiety but it is not clear if one causes the other. We investigated whether anxiety and depression precede the onset of FD (based on the modified Rome III criteria) and gastroesophageal reflux symptoms (GERS) in a population-based follow-up study. **METHODS:** Participants from the Kalixanda study (n = 3000), randomly selected from the national population register of Sweden, were given the validated Abdominal Symptom Questionnaire 1998–2001; 1000 of these participants then were selected randomly to undergo esophagogastroduodenoscopy and were given the Abdominal Symptom Questionnaire along with the Hospital Anxiety and Depression Scale questionnaire. All eligible subjects who underwent endoscopy (n = 887) were invited to participate in a follow-up study in June–August 2010 and were given the same questionnaires. Data were analyzed by logistic regression. **RESULTS:** Of the 703 subjects who completed the follow-up questionnaires (79.3%); 110 were found to have FD at baseline (15.6%) and 93 at the follow-up examination (13.3%); 48 of these were new cases of FD. GERS without organic disease was reported by 273 individuals (38.8%) at baseline and by 280 at follow-up examination (39.8%); 93 cases were new. Major anxiety was associated with FD at the follow-up evaluation (odds ratio [OR], 6.30; 99% confidence interval [CI], 1.64–24.16). Anxiety was associated with postprandial distress syndrome at baseline (OR, 4.83; 99% CI, 1.24–18.76) and at the follow-up examination (OR, 8.12; 99% CI, 2.13–30.85), but not with epigastric pain syndrome. Anxiety at baseline was associated with new-onset FD at the follow-up examination (OR, 7.61; 99% CI, 1.21–47.73), but not with GERS. **CONCLUSIONS:** In a study of the Swedish population, anxiety at baseline, but not depression, increased the risk for development of FD by 7.6-fold in the next 10 years. Anxiety did not affect risk for GERS.

Keywords: Psychological Factors; Functional Disorder; Population Study.

Functional dyspepsia (FD) and gastroesophageal reflux symptoms (GERS) are common and costly disorders in the adult population.[1–4] The prevalence of FD in different studies depends on the definition used,[5–7] but the prevalence of FD in the Western world defined according to the Rome III definition is between 11% and 20%,[4,8] whereas the prevalence of gastroesophageal reflux symptoms (GERS) once a week or more often is approximately 20%.[9,10]

Psychological distress has been reported to be linked with dyspepsia,[11–14] as has depression.[15] In a multicenter study of uninvestigated dyspepsia, dyspeptic symptoms were reported to cause emotional distress.[16] We earlier described the association of FD with anxiety,[4] but longitudinal follow-up studies in the general population applying the Rome III definition largely are unavailable.[17] There was one 5-year follow-up study on FD patients applying the Rome II definition that showed the association of anxiety with FD,[18] and another Australian 12-year follow-up study of functional gastrointestinal disorders that showed the association of anxiety with functional gastrointestinal disorders overall, but not dyspepsia.[19]

A Norwegian population-based, cross-sectional, case-control study found a strong association of anxiety and depression with GERS,[20] whereas Eslick and Talley[21] in Australia did not find anxiety or depression to be risk factors for GERS. Longitudinal follow-up studies to determine if there is an association of psychological factors with GERS are not available.

Any link between gastrointestinal (GI) symptoms and mental distress could be confounded by other environmental risk factors such as smoking or alcohol use.[22–25] Smoking is linked to postinfectious FD[26] and to GERS,[21] but whether this environmental factor drives a new onset of symptoms is unknown. An association of nonsteroidal anti-inflammatory drugs (NSAIDs) with FD is controversial; a meta-analysis of uninvestigated dyspepsia identified an association for some NSAIDs and for a high dose of any NSAID,[27] whereas an Italian population-based endoscopic study failed to find any association of NSAIDs with FD.[8] There are also inconsistent reports of whether obesity and GI symptoms are linked.[28–30] There was no relation between body mass index and GERS in a Swedish population-based study,[28] whereas other studies have found that being overweight and obese are independent risk factors of GERS.[29]

Abbreviations used in this paper: **ASQ, Abdominal Symptom Questionnaire; BMI, body mass index; CI, confidence interval; EGD, esophagogastroduodenoscopy; EPS, Epigastric Pain Syndrome; FD, functional dyspepsia; GERS, gastroesophageal reflux symptoms; GI, gastrointestinal; HADS, Hospital Anxiety and Depression Scale; *H pylori*, *Helicobacter pylori*; IBS, irritable bowel syndrome; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PDS, Postprandial Distress Syndrome; PPI, proton pump inhibitor.**

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The aim of this study was to define whether there may be a causal relation between anxiety and depression with functional dyspepsia and FD/or GERS. We also aimed to study the overlap of FD and GERS, and predictors for new onset of symptoms. We hypothesized that anxiety and/or depression drive FD and/or GERS and predict the new onset of FD.

Materials and Methods

The baseline data for the 10-year follow-up study were gathered from a representative random sample (N = 3000) of the general population in 2 Swedish communities between 1998 and 2001. At baseline, the participants were selected randomly from the national population register, which covers all inhabitants of Sweden and the participants were surveyed by a validated and widely used Abdominal Symptom Questionnaire (ASQ).[31,32] One thousand of them were selected randomly for esophagogastroduodenoscopy and for survey by a more comprehensive ASQ assessing troublesome gastrointestinal symptoms and by the Hospital Anxiety and Depression Scale (HADS)[33] to define depression and anxiety. Organic reasons for dyspepsia were excluded by esophagogastroduodenoscopy (EGD) and medical history—the baseline Kalixanda study.[34] All eligible individuals from this endoscoped cohort (n = 887) were invited to participate in a follow-up study in June–August 2010 with the same postal questionnaires 10 years after the primary investigation (Figure 1). During these years the subjects could consult and be treated as ordinary patients.[9,34,35]

Aside from the individual symptoms from the questionnaires, the participants were asked about their level of education, GI medication and weight, as well as their use of tobacco (smoking or moist snuff) and alcohol.

The baseline study was approved by the Umeå University Ethics Committee and the follow-up study was approved by the Ethical Approval Committee of the Karolinska Institutet and conducted in accordance with the revised 1998 Declaration of Helsinki.

Baseline Endoscopy

The upper EGDs were performed by 3 experienced endoscopists in the 2 clinics (Kalix and Haparanda) that provide the only medical coverage for the area. Internal validity was assessed by means of consensus sessions before the initiation of the basic study. The endoscopists had been participating in regular quality-assessment programs over several years. The endoscopists were unaware of the symptoms of the subjects before endoscopy. Only topical anesthesia was used.[34]

Definitions of Dyspepsia, Gastroesophageal Reflux Symptoms, and Irritable Bowel Syndrome

FD was defined based on the Rome III definition: weekly bothersome postprandial fullness or early satiation; or epigastric pain and/or epigastric burning without findings of esophagitis, peptic ulcer, celiac disease, or cancer; and no evidence of other structural disease at endoscopy that was likely to explain the symptoms. FD, according to the Rome III definition, was divided into the following categories: Postprandial Distress Syndrome (PDS), consisting of bothersome postprandial fullness and/or early satiation; and Epigastric Pain Syndrome (EPS), consisting of pain or burning localized to the epigastric area and not generalized or localized to other abdominal or chest regions, and not relieved by defecation. Overlap between PDS and EPS was allowed in line with the Rome III definition. The presence of heartburn/GERS or irritable bowel syndrome (IBS) did not exclude the diagnosis of FD.[7]

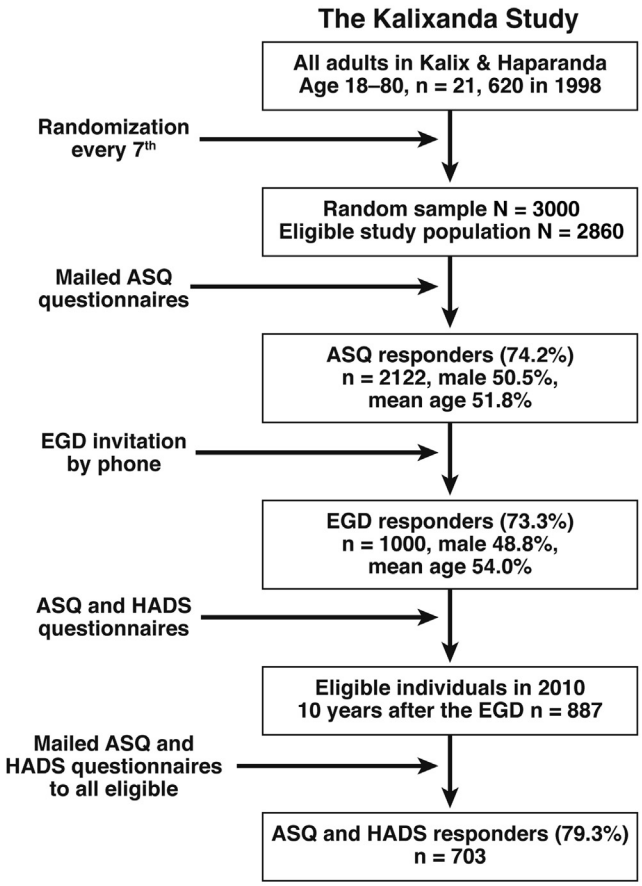

Figure 1. Flow-chart of the Kalixanda population-based study from 1998 to 2010. HADS, Hospital Anxiety and Depression Scale.

The ASQ was designed before the Rome era but the questionnaire has been updated to meet both the Rome II and III criteria and it measures all of the Rome III criteria aside from the symptom onset (3 vs 6 months).[31,32]

GERS were defined as troublesome heartburn and/or acid regurgitation over the past 3 months. The presence of FD or IBS did not exclude the diagnosis of GERS.[36,37]

IBS was defined as troublesome abdominal pain or discomfort located at any site plus concomitant bowel habit disturbances (constipation, diarrhea, or alternating constipation and diarrhea). This simple definition has been used previously and has been shown to produce results reasonably concordant with the Rome I criteria for IBS.[38–40]

Definition of Anxiety and Depression

A HADS score from 8 to less than 11 was used to define suspected anxiety and depression, and a score of 11 or higher was used as the cut-off level for both clinically relevant (major) anxiety and depression.[33]