



MACQUARIE
University
SYDNEY · AUSTRALIA

Macquarie University PURE Research Management System

This is the accepted author manuscript version of an article published as:

Andreasson, A., Talley, N. J., Walker, M. M., Jones, M. P., Platts, L. G., Wallner, B., Kjellström, L., Hellström, P. M., Forsberg, A. & Agréus, L. (2021). An Increasing Incidence of Upper Gastrointestinal Disorders Over 23 Years: A Prospective Population-Based Study in Sweden. *Official journal of the American College of Gastroenterology* | *ACG*, 116(1), 210-213.

Access to the published version: <http://doi.org/10.14309/ajg.0000000000000972>

Copyright 2020. This manuscript version is made available under the CC-BY-NC 4.0 license <https://creativecommons.org/licenses/by-nc/4.0/>. Version archived for private and non-commercial use with the permission of the author/s. For further rights please contact the author/s or copyright owner.

An increasing incidence of upper gastrointestinal disorders over 23 years: A prospective population-based study in Sweden

Short title: Natural history of upper gastrointestinal symptoms

Associate Professor Anna Andreasson^{* 1,2,3}, Professor Nicholas J. Talley⁴, Professor Marjorie M. Walker⁴, Professor Michael P. Jones², Dr Loretta G. Platts¹, Dr Bengt Wallner⁵, Dr Lars Kjellström⁶, Professor Per M. Hellström⁷, Dr Anna Forsberg³, Professor Lars Agréus⁸

¹Stress Research Institute, Department of Psychology, Stockholm University, Stockholm, Sweden,

²Department of Psychology, Macquarie University, North Ryde, Australia, ³Department of Medicine Solna, Karolinska Institutet, Sweden, ⁴Faculty of Health and Medicine, University of Newcastle,

Newcastle, Australia and NHMRC Centre of Research Excellence in Digestive Health, ⁵Umeå

University, Umeå, Sweden, ⁶Gastromottagningen City, Stockholm, Sweden, ⁷Uppsala University,

Uppsala, Sweden, ⁸Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

***Corresponding author**

Anna Andreasson

Stress Research Institute

Department of Psychology

Stockholm University

SE-106 91 Stockholm, Sweden

Phone: +46 (0)8 5537 8951

Fax: +46 (0)8 5537 8900

E-mail: anna.andreasson@su.se

Word count: 1000

Financial support: The data collection was supported by Stockholm County Council, the Medical Faculty of Uppsala University, Karolinska Institutet, Uppsala County Council, Astra Pharmaceutical and Olympus. The study sponsors were not involved in interpretation of data, study design, collection, analysis or interpretation of data, nor in the writing of or the decision to publish the report.

Abbreviations: FD=Functional dyspepsia, PDS=Postprandial distress syndrome, EPS=Epigastric pain syndrome, GERD=Gastroesophageal reflux disease, GERS=Gastroesophageal reflux disease symptoms, GI=gastrointestinal, PPI=Proton pump inhibitors, OR=Odds ratio, CI=Confidence interval

Guarantor of article: Anna Andreasson

Author contributions:

Study concept and design: AA, NJT, LA

Acquisition of data: LA, BW, LK, PMH, AF

Analysis and interpretation of data: AA, MPJ, LGP, NJT, MMW, LA

Drafting of the manuscript: AA, MMW, NJT, LA, MPJ

Critical revision of the manuscript for important intellectual content: AA, NJT, MMW, LGP, MPJ, LA, BW, LK, PMH, AF, LA

Statistical analysis: AA, MPJ, LGP

Obtained funding: LA

Administrative, technical, or material support; study supervision: LA

All authors have approved the final draft submitted.

Disclosures: none

Writing assistance: none

Abstract

We hypothesized that the prevalence of FD and GERD in the community may be increasing.

Randomly selected adults were surveyed on four occasions: 1988 (n=1151, 21–79 years, response rate (rr)=90%), 1989 (n=1097, 22–80 years, rr=87%), 1995 (n=1139, 20–85 years, rr=76%), 2011 (n=1175, 20–93 years, rr=63%). In FD, the odds of post-prandial distress syndrome (PDS) tripled over 23 years' follow-up (OR:3.55; 95%CI:2.60–4.84, mixed effect regression analysis), while a small decrease in epigastric pain syndrome (EPS) was observed (OR:0.65, 95%CI:0.42–1.00). The odds of reporting GERD doubled (OR:2.02; 95%CI:1.50–2.73). The underlying mechanisms remain to be determined.

Keywords: functional dyspepsia; gastroesophageal reflux disease; incidence; epidemiology

INTRODUCTION

Highly prevalent chronic upper gastrointestinal (GI) disorders that impact on quality of life include functional dyspepsia (FD) and gastroesophageal reflux disease (GERD).¹⁻³ The aim of the present study was to investigate time trends in the prevalence of upper GI symptoms in a 23-year prospective study drawn from the community adult population.

MATERIALS AND METHODS

All adult inhabitants in Östhammar community, Sweden, born on the 3rd, 12th or 24th day of each month were sent a validated questionnaire for abdominal symptoms (ASQ)⁴ in 1988, 1989, 1997 and 2011 (Table 1).⁵ In the 2011 survey, non-responders 80 years and younger were called and asked seven key questions from the ASQ⁴. The ASQ asked whether, during the past three months, the participant had been troubled by any of a list of abdominal symptoms,⁴ and, in 2011, whether they were using proton pump inhibitors (PPI). FD was defined as the presence of postprandial fullness (PDS: early satiety or postprandial fullness) or epigastric pain syndrome (EPS: any pain modality isolated to the epigastric region).⁶ GERD was defined as the presence of either acid regurgitation or heartburn.

Trends in the prevalence over time were calculated in Stata 16.1 using mixed effects logistic regressions with study period (0=1988 to 1=2011) as the fixed effect explanatory variable and participant identity slope as random effect, adjusting for age and sex. Odds ratios should be interpreted as the relative increase in odds over the study period. Differences in prevalences between birth cohorts (participants born before 1930, 1931–1950, 1951–1970 and 1971 and later) and associations between prevalences and age were investigated using logistic regression with the GI symptom as the dependent variable and birth cohort as the explanatory variable adjusted for age clustered on participant identity. Statistical power for this study was high (>0.9 power for

unconditional logistic regression $n=1000$ at each time point, baseline prevalence=15%, effect size=2.0 over the follow-up window, two-tailed $\alpha=0.01$).

RESULTS

The odds of FD doubled over the 23-year study period (OR=2.04; 95%CI: 1.57–2.64, Table 2) corresponding to a crude increase of 8.8%. This rise was driven by an increase in the odds of PDS during follow-up (OR=3.55; 95%CI: 2.60–4.84), while a decrease in EPS was observed (OR=0.65, 95%CI: 0.42-1.00). The odds of GERD doubled over the same period (OR=2.02, 95%CI 1.50–2.73), which corresponds to an increase in crude prevalence of 6.6%. The increased odds of GERD were mainly driven by the increased odds of acid regurgitation; a small but significant increase was also seen in heartburn (Table 2).

We performed two sensitivity analyses. The increase in reflux over the 23-year follow-up remained when including the GERD ratings from the non-response study to the analysis of effect of time on prevalence of GERD (OR=1.85, 95%CI: 1.42–2.42, $p<0.001$, 4821 observations, 2058 individuals).

While participants in the non-response study ($n=308$) reported a lower prevalence of GERD (22.4%) compared to responders (24.2%), this difference was not statistically significant (OR=0.89, 95%CI 0.65–1.20, $p=0.44$, logistic regression adjusted for age and sex). In 2011, 12% of the population (134 out of 1108, 12.1%, 95% CI: 10.2%-14.0%) were PPI users; 28.5% of FD, 37.5% of GERD and 46.3% of the 108 participants with both FD and GERD reported PPI use. Including PPI use in 2011 in the analyses of GERD raised the OR (Table 2), suggesting that the increase in individuals suffering from upper gastrointestinal symptoms may be larger than shown in the main analyses.

In Figure 1, prevalences of FD and its subtypes and GERD and its symptoms are displayed by birth cohort, enabling cohort differences and age trends within cohorts to be observed. In terms of FD, some differences by birth cohorts are observable. The two younger cohorts (born 1951–70 and 1971–90) had a significantly higher prevalence of FD compared to the oldest cohort (born 1909–30, Supplementary table 1). These differences appeared to be driven by inter-cohort variation in the

prevalence of PDS; differences in the prevalence of EPS were small and inconsistent. In each cohort, PDS increased with age while EPS became less common as participants aged (data not shown).

Turning to GERD, small differences existed by birth cohort for acid regurgitation, with the two younger cohorts reporting a statistically significant higher prevalence than the oldest cohort (Supplementary table 1). While very low levels of heartburn were reported in 1995 for the youngest 1971–90 cohort, only 51 individuals from this cohort participated in that survey. In each cohort, acid regurgitation became more common as participants aged while the association between age and heartburn was weak and non-significant (data not shown).

DISCUSSION

This unique study prospectively investigated the epidemiology of upper GI symptoms over 23 years in a large population-representative cohort. The prevalence of PDS and GERD substantially increased while a slight decrease in EPS was seen. The inclusion of the non-response study meant that data on GERD was available for 80% of the survey sample, and there was no significant difference in GERD between responders and non-responders in the last survey, suggesting little selection bias. We relied on symptoms to identify GERD and FD, but endoscopic population-based research suggests misclassification bias is small.^{2,5}

A weakness with the present study was the lack of information on possible confounders, most notably smoking, body mass index and mental health. FD prevalence is significantly higher in smokers.⁷ However, smoking rates are falling in Sweden⁸ and, if smoking was the explanation, we would expect to see a fall not increase in PDS. Increasing rates of obesity⁹ may be an explanation for the increase in GERD we observed, however, weight loss rather than weight gain is associated with FD.¹⁰ Anxiety is increasing in the community¹¹ and linked to FD, but the stable prevalence of EPS contradicts this explanation.

In conclusion, this is the first study, to our knowledge, to demonstrate that FD, specifically PDS, and GERD is increasing in the general population. While confounding by other factors seems unlikely to explain the associations, the underlying mechanisms remain to be determined.

REFERENCES

1. Agreus L, Svardsudd K, Talley NJ, et al. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population-based study. *Am J Gastroenterol* 2001;96:2905-14.
2. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005;40:275-85.
3. Aziz I, Palsson OS, Tornblom H, et al. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study. *Lancet Gastroenterol Hepatol* 2018;3:252-262.
4. Agreus L, Svardsudd K, Nyren O, et al. Reproducibility and validity of a postal questionnaire. The abdominal symptom study. *Scand J Prim Health Care* 1993;11:252-62.
5. Agreus L, Hellstrom PM, Talley NJ, et al. Towards a healthy stomach? *Helicobacter pylori* prevalence has dramatically decreased over 23 years in adults in a Swedish community. *United European Gastroenterol J* 2016;4:686-696.
6. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology* 2016;150:1257-61.
7. Ford AC, Marwaha A, Sood R, et al. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut* 2015;64:1049-57.
8. Ramstrom L, Borland R, Wikmans T. Patterns of Smoking and Snus Use in Sweden: Implications for Public Health. *Int J Environ Res Public Health* 2016;13.
9. Overweight and obesity. Volume 2020: Public Health Agency of Sweden, 2018.
10. Tack J, Jones MP, Karamanolis G, et al. Symptom pattern and pathophysiological correlates of weight loss in tertiary-referred functional dyspepsia. *Neurogastroenterol Motil* 2010;22:29-35, e4-5.
11. Waller Lidstrom M, Wennberg P, Lundqvist R, et al. Time trends of comparative self-rated health in adults aged 25-34 in the Northern Sweden MONICA study, 1990-2014. *PLoS One* 2017;12:e0187896.

Figure 1. Prevalence of GI-symptoms per survey divided by birth cohorts.

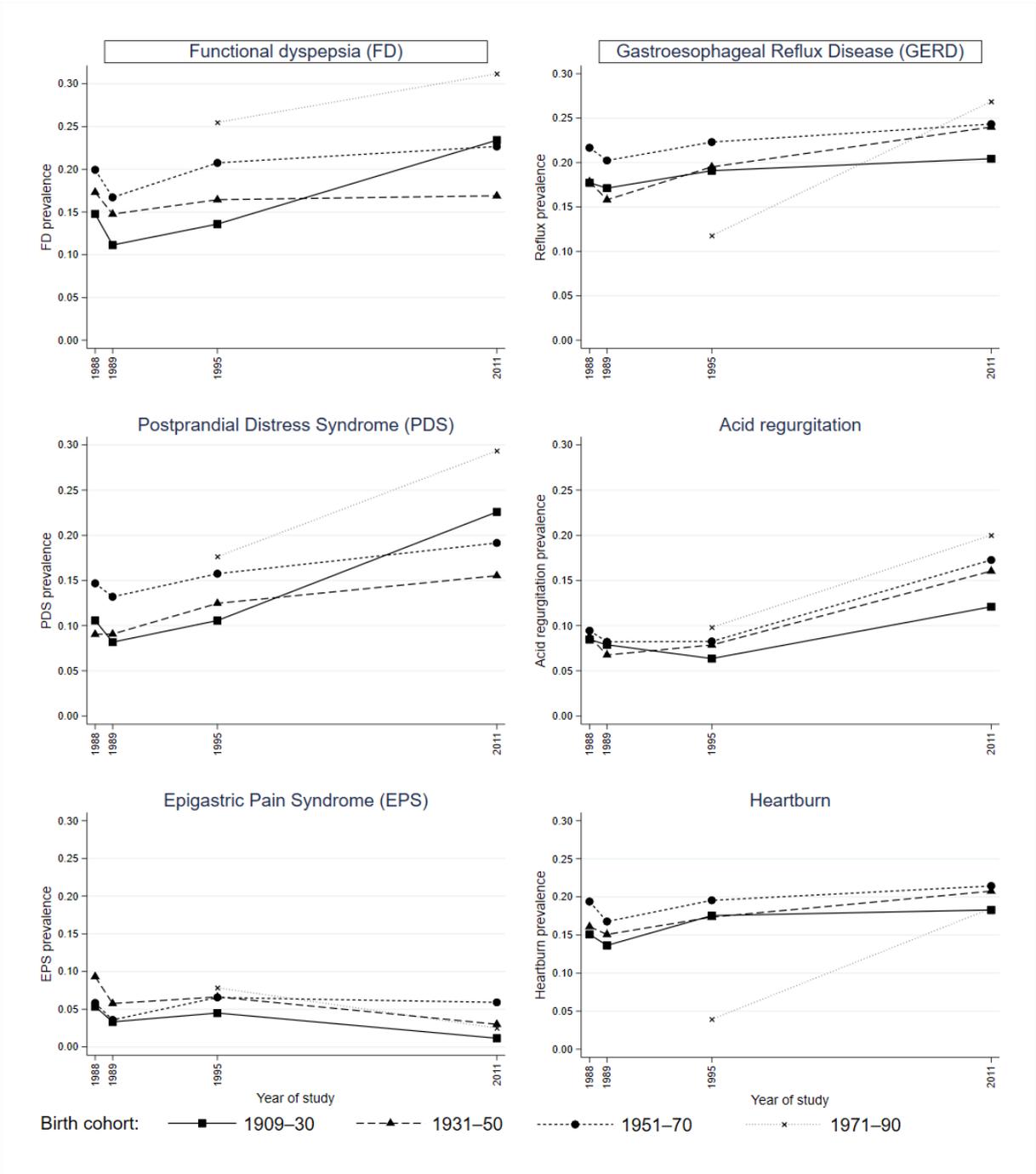


Table 1. Participant characteristics in the four surveys. Symptoms are given as % (95% confidence intervals).

	1988	1989	1995	2011	2011 non- response study
Time follow-up (years)	0	1	7	23	23
N responders	1151	1097	1102	1159	308
Response rate (%)	90	87	76	63	48
Women (%)	49.5	50.2	52.2	51.7	44.5
Mean age (range)	47.9 (21-79)	48.9 (22-80)	50.2 (21-85)	56.5 (19-93)	46.8 (20-80)
Functional dyspepsia	17.2 (15.0-19.4)	14.1 (12.1-16.2)	17.8 (15.5-20.0)	22.1 (19.7-24.5)	-
Postprandial distress syndrome (PDS)	11.3 (9.4-13.1)	10.0 (8.3-11.8)	13.4 (11.4-15.4)	19.9 (17.6-22.2)	-
Epigastric pain syndrome (EPS)	6.9 (5.4-8.4)	4.3 (3.1-5.5)	6.2 (4.8-7.6)	3.9 (2.8-5.0)	-
Gastroesophageal reflux disease (GERD) symptoms	18.9 (16.6-21.1)	17.6 (15.3-19.9)	20.1 (17.6-22.4)	24.2 (21.9-26.8)	22.4 (17.7-27.1)
Acid regurgitation	8.8 (7.3-10.6)	7.6 (6.1-9.3)	7.7 (6.2-9.4)	16.9 (14.8-19.2)	12.3 (8.64-16.0)
Heartburn	16.7 (14.6-19.9)	15.1 (13.0-17.3)	17.5 (15.3-19.9)	20.4 (18.1-22.9)	19.2 (14.7-23.6)

Table 2. Odds ratios for change in upper gastrointestinal symptoms during the 23-year follow-up adjusted for age and sex.

	OR	95% CI	P-value	N observations	N individuals
Functional dyspepsia	2.04	1.57-2.64	<.001	4526	1885
Postprandial distress syndrome (PDS)	3.55	2.60-4.84	<.001	4514	1883
Epigastric pain syndrome (EPS)	0.65	0.42-1.00	0.049	4420	1866
GERD	2.02	1.50-2.73	<.001	4511	1882
Acid regurgitation	4.06	2.89-5.70	<.001	4505	1881
Heartburn	1.71	1.25-2.34	0.001	4510	1881
GERD and/or use of PPI	2.59	1.94-3.47	<.001	4549	1890

Abbreviations: GERD=gastroesophageal reflux disease symptoms, OR=odds ratio, CI=confidence interval