The global burden of gastro-oesophageal reflux disease: more than just heartburn and regurgitation

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in a phase 3 trial. A follow-up study should preferably be done in a global setting and should include a larger proportion of non-HBV-infected patients with an age-range similar to that in other clinical trials involving patients with HCC.

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The global burden of gastro-oesophageal reflux disease: more than just heartburn and regurgitation

Gastro-oesophageal reflux disease is a common condition caused by the reflux of stomach contents into the oesophagus, leading to uncomfortable symptoms and complications. The prevalence of this disorder is increasing and this increase has been linked to population ageing and the obesity epidemic worldwide. As these trends continue, especially in countries such as India and China, we need to consider their impact on the global burden of gastro-oesophageal reflux disease.

In The Lancet Gastroenterology & Hepatology, the GBD 2017 Gastro-oesophageal Reflux Disease Collaborators used data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 and applied statistical tools that incorporate predictive covariates and adjustments for differences in study design to assess the global burden of gastro-oesophageal reflux disease. The global age-standardised prevalence of gastro-oesophageal reflux disease was stable over time, at 8791 (95% UI 7772–9834) cases per 100 000 population in 1990 and 8819 (7781–9863) cases per 100 000 population in 2017, and the disease was responsible for an estimated 0·7% (95% UI 0·4–1·1) of all years lived with disability globally in 2017. Furthermore, although the age-standardised prevalence appeared to be stable between 1990 and 2017, all-age prevalence increased by 18·1% between 1990 and 2017, while years lived with disability increased by 67·1% between 1990 and 2017, reflecting the increased prevalence in older age groups and population ageing over time.

As with any such analysis, the results depend on the quality of data and assumptions made by the authors about the disease. In this study the prevalence of gastro-oesophageal reflux disease was defined by the presence or absence of typical reflux symptoms, specifically heartburn and acid regurgitation. However, there is an important difference between symptoms (which are based on a subjective description), and disease (diagnosis of which is based on objective evidence of reflux). Patients with typical symptoms and reflux oesophagitis or Barrett’s oesophagus on endoscopy have gastro-oesophageal reflux disease; however, about half of patients with pathological acid exposure in the oesophagus do not have mucosal disease (ie, non-erosive reflux disease). Ambulatory reflux monitoring also identifies individuals with symptoms related to reflux events that have normal levels of acid
exposure (reflux hypersensitivity). All three groups are classified as forms of gastro-oesophageal reflux disease; however, the same symptoms are reported by individuals with functional heartburn in whom there is no pathological reflux and no association of reflux events with symptoms. Additionally, typical reflux symptoms can be reported by patients with other conditions including eosinophilic oesophagitis, motility disorders (eg, achalasia), and other functional disorders (eg, rumination). The prospective Diamond study showed that, for gastroenterologists, the sensitivity of symptom-based diagnosis of gastro-oesophageal reflux disease compared to objective pH studies was only 67%, and specificity was 70%, with no improvement if a validated questionnaire was applied. Furthermore, symptom response to proton pump inhibitor therapy was neither sensitive nor specific to the diagnosis.

Conversely, not all patients with pathological acid exposure complain of typical symptoms. Up to a third of individuals with Barrett’s oesophagus are asymptomatic, probably because metaplastic columnar mucosa has reduced sensitivity to acid. In other patients, gastro-oesophageal reflux disease presents with non-cardiac chest pain or laryngo-pharyngeal complaints (eg, chronic cough or hoarseness). Atypical symptoms are less often triggered by reflux events (approximately 25% compared to approximately 50%). Nonetheless, excluding these presentations will systematically underestimate the burden of gastro-oesophageal reflux disease.

These findings make it clear that clinical history and response to therapy are insufficient to identify this condition. An international working group published the Lyon Classification, an approach to diagnosis of gastro-oesophageal reflux disease that uses objective information from endoscopy and physiological investigation. Conclusive evidence for the diagnosis includes severe mucosal disease on endoscopy or oesophageal acid exposure time longer than 6% on ambulatory reflux studies (even where endoscopy is normal). When endoscopy and pH-impedance monitoring are inconclusive (ie, acid exposure time 4–6%), then supportive evidence including the presence of a positive reflux-symptom association or ineffective oesophageal motility on manometry add confidence to confirm or refute the diagnosis.

The present study confirms that the prevalence of reflux symptoms increases with age, however, age-standardised prevalence was stable over the past 25 years. This implies that the increase in obesity during this time has had no effect on the risk of gastro-oesophageal reflux disease, which seems unlikely in the face of consistent evidence to the contrary. The authors themselves question whether this result is driven more by measurement error than underlying epidemiology. One technical reason for this discrepancy is that bodyweight increases with age, making it difficult to detect independent effects of these variables in the model. Another confounding factor is that, at any given level of reflux severity, older patients are less likely to report symptoms, a pattern observed in many disorders.

Determining the burden of diseases in an ageing population is important in planning health-care services. This study provides up to date information about the prevalence of typical reflux symptoms and the level of disability that is associated with gastro-oesophageal reflux disease; however, the results are conservative because the analysis did not include the full spectrum of symptoms and disease caused by this condition. Nevertheless, it will be of interest to compare results for gastro-oesophageal reflux disease against those for other common conditions that affect both young and old populations, in developed and developing regions worldwide.

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Oesophageal cancer represents the sixth most common cause of cancer mortality worldwide. Underlying this cancer type are two distinct diseases characterised by different histologies: oesophageal adenocarcinoma and oesophageal squamous cell carcinoma.

Oesophageal adenocarcinoma predominately arises from Barrett’s oesophagus, with histological progression from metaplasia through to invasive carcinoma, and is typically localised to the distal oesophagus. The main risk factors are gastro-oesophageal reflux and obesity; high intake of red meat and low intake of fruits and vegetables are also associated with development of oesophageal adenocarcinoma. Oesophageal squamous cell carcinoma develops from squamous epithelial cells and is typically localised to the upper two-thirds of the oesophagus. Tobacco consumption and alcohol intake are the most notable risk factors, although their relative risk varies by region.

The GBD 2017 Oesophageal Cancer Collaborators used data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 dataset to provide a global overview of the distribution of oesophageal cancer and the morbidity, mortality, and key risk factors associated with the disease. They describe national trends in incidence between 1990 and 2017 as well as the impact of risk factors on a regional level. Between 1990 and 2017, age-standardised incidence rates declined overall by 22·0% (95% uncertainty interval 18·6–25·2). This decline in age-standardised incidence was observed in all regions except for high-income North America (where oesophageal adenocarcinoma is predominant) and western sub-Saharan Africa. At the country level, there was an association between a higher proportion of squamous cell carcinoma (out of all oesophageal cancer cases) and lower socioeconomic development. The global variation to a large extent recapitulates that seen from an analysis of data from the Global Cancer Observatory (GLOBOCAN) and Cancer Incidence in Five Continents, Volume X (CI5X).

A major limitation of this analysis of GBD 2017 data, acknowledged by the authors, is the inability to clearly demarcate between oesophageal adenocarcinoma and oesophageal squamous cell carcinoma. Summary data on oesophageal cancer as a whole should not mask the differing global distribution, risk factors, and temporal changes occurring between the two diseases. Their distinct biology is reflected in their management approaches.

Although endoscopic management is appropriate for early-stage oesophageal squamous cell carcinoma and oesophageal adenocarcinoma, treatment patterns frequently diverge for later stages. For more locally advanced oesophageal cancer, survival outcomes with surgery alone are poor and a multimodal approach is recommended for patients who are deemed fit to undergo surgery. Oesophageal squamous cell carcinoma is more sensitive than oesophageal adenocarcinoma to radiotherapy, therefore definitive chemoradiotherapy is an option for patients with oesophageal squamous cell carcinoma, with equivalent survival outcomes but higher rates of local relapse necessitating salvage oesophagectomy. Alternatively, both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma can be treated by either perioperative chemotherapy or neoadjuvant chemoradiotherapy followed by surgery, with treatment preferences varying globally depending on the region. Given the reduced sensitivity of oesophageal adenocarcinoma to radiotherapy, patients with oesophageal adenocarcinoma should proceed to surgery even after showing good response to neoadjuvant chemoradiotherapy.