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Demographic and Lifestyle Risk Factors for Gastric Intestinal Metaplasia Among US Veterans Authors' Reply

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We thank Drs. Zhu and Xu¹ for their interest in our paper and excellent editorial comments. Our cross-sectional study found older age, male sex, non-White race/ethnicity, and current smoking status as independent risk factors for gastric intestinal metaplasia in a veteran U.S. population². We agree that family history of gastric cancer is an important risk factor for gastric cancer and its precursor lesions, including gastric intestinal metaplasia. While our questionnaires ascertained family history, including gastric cancer, the data was not reliably available for this cohort (mostly missing due to lack of knowledge and when available, was non-specific or likely misclassified), and we elected to not include it in our analysis. Although family history is a well-known risk factor for gastric cancer, hereditary gastric cancers remain less than 3% of all gastric cancers³, and no specific single nucleotide polymorphisms has been associated with familial gastric cancers⁴. Therefore, shared environmental factors (i.e., *Helicobacter pylori* infection, CagA strains)⁵ rather than genetic factors are largely attributed as the underlying mechanism in those with a family history of gastric cancer. While our study did not include family history of gastric cancer, we did include *H. pylori*, which was assessed by both histopathology with specialized staining and culture.

We defined onset, frequency, and severity of gastroesophageal reflux disease (GERD) symptoms using a slightly modified version of the Gastroesophageal Reflux Questionnaire^{6, 7}. This validated questionnaire ascertains for presence of GERD based on typical GERD symptoms (i.e., heartburn and acid regurgitation) and atypical GERD symptoms (i.e., noncardiac chest pain, dysphagia, globus, dyspepsia, hoarseness, bronchitis).

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Authorship Statement:

(i) Guarantor of the article: Mimi C. Tan, MD, MPH

(ii) Specific author contributions:

MCT: conception and design, literature review and analysis, writing of manuscript, critical revision of the article

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(iii) All authors have approved the final version of the manuscript.

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We prospectively recruited patients from 2 sources: 1) asymptomatic patients in primary care clinics, and 2) symptomatic patients with previously scheduled upper endoscopy who agreed to study participation. We systematically conducted study questionnaires, including assessment of GERD, on all patients and performed gastric biopsies to assess for gastric intestinal metaplasia regardless of indication for endoscopy or endoscopic findings. As gastric intestinal metaplasia is poorly associated with gastrointestinal symptoms⁸, systematic biopsies independent of symptoms minimizes selection bias and is a strength of our study. Although there was a difference in proportion between cases and controls with GERD, we did not find an association of GERD with gastric intestinal metaplasia after controlling for potential confounders (adjusted OR 0.99, 95% CI 0.76–1.28).

In conclusion, we agree that family history of gastric cancer is important when assessing for gastric intestinal metaplasia risk, but family history may be a surrogate for environmental factors, such as *H. pylori* infection and virulence. Additionally, we used a validated GERD questionnaire and systematically performed gastric biopsies on all patients regardless of GERD symptoms or indication for endoscopy. The findings from our study can be used to develop risk stratification models for U.S. population-based gastric cancer screening.

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