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Letter to the Editor

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Letter to the Editor: 'Association between composite dietary antioxidant index and *Helicobacter pylori* infection: a population-based and Mendelian randomisation study'

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Dear Editor,

We commend Zou et al. (2025) for their innovative integration of National Health and Nutrition Examination Survey (NHANES) data and Mendelian randomisation to explore the association between the composite dietary antioxidant index (CDAI) and *Helicobacter pylori* infection[1]. Their finding that a higher CDAI is associated with decreased odds of *H. pylori* infection is highly intriguing. We wish to offer a systematic perspective on several unresolved aspects highlighted by the study.

First, while the authors appropriately acknowledge the inherent limitation of the cross-sectional design – namely, the temporal ambiguity preventing definitive conclusions on whether a lower CDAI precedes infection or results from infection-induced dietary changes (e.g. reduced intake of antioxidant-rich foods due to dyspepsia) – it is worth noting that extensive existing evidence supports the relationship between dietary antioxidants and *H. pylori* status. Beyond the CDAI, specific compounds such as carotenoids and polyphenols have been implicated, as summarised in several comprehensive reviews[2,3].

Second, the observed protective association between dietary Cu intake and reduced *H. pylori* infection risk (cross-sectional OR: 0·75, $P = 0·049$) contrasts with the null Mendelian randomisation finding for genetically predicted circulating Cu levels (OR: 1·02, $P = 0·703$). This apparent discrepancy likely stems from key methodological distinctions: (1) The Mendelian randomisation analysis was substantially limited by the very small number of Cu-associated SNP (only two), compromising statistical power and genetic coverage and (2) Mendelian randomisation assessed systemic circulating Cu, whereas dietary Cu may exert localised protective effects within the gastric microenvironment independently of systemic concentrations. Consequently, the null MR result does not invalidate the observational association but underscores the need for larger-scale Genome-Wide Association Studies (GWAS) and investigations into tissue-specific mechanisms of Cu action.

Third, we wish to emphasise that the CDAI, by standardising and integrating multiple antioxidant components, aims to reflect their synergistic antioxidant capacity rather than a simple additive effect. Its established associations with inflammatory markers and disease risk often surpass those of individual components[4]. Therefore, while the component-wise analysis presented in Table 4 offers intuitive appeal, it inadvertently diverges from the CDAI's conceptual foundation. Regressing individual antioxidants (e.g. vitamin A, Zn) separately against *H. pylori* status disregards potential biological synergies (e.g. vitamin C regenerating vitamin E) and assumes independence among components. This approach also inflates the risk of false discoveries without appropriate multiplicity correction. Instead, we suggest that methodologies preserving the composite nature of the index while quantifying individual contributions, such as weighted quantile sum regression, could be more conceptually aligned and statistically robust.

In conclusion, despite areas for potential refinement, the study by Zou et al. provides valuable insights into the relationship between CDAI and *H. pylori* infection. We encourage future research to systematically investigate the role of antioxidant-rich foods in modulating *H. pylori* risk, ultimately informing public health strategies for prevention and management.

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