Authors' response to R Pellicano and S Fagoonee

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We recently conducted a population-based cohort study and reported in the *International Journal of Epidemiology* that adults with peptic ulcer disease (PUD; ICD-9-CM codes 530–534) were 1.77 times more likely to develop herpes zoster (shingles) than the general population.[1] We thank Drs Pellicano and Fagoonee for their critical comments.[2] They stated that there is no clear evidence linking PUD to depressed immunity and that PUD patients are not more prone to infections than the general population. They also implied that the statistical association between PUD and shingles could be causal, indirect or an artefact. The probability of a causal relationship is assessed by several criteria including biological plausibility. It is well known that *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug (NSAIDs) usage are two major risk factors for peptic ulcer. Accumulated evidence has linked *H. pylori* infection to extragastric manifestations, such as ascorbate and iron deficiency which may impair the host immunity and lead to infectious diseases.[3,4] Interestingly, intravenous ascorbate has been demonstrated to have beneficial effects on the treatment of shingles.[5] NSAIDs can impair the intracellular processing of the phagocytized antigens, antigens presenting functions of dendritic cells, and the proliferation and activation of T cells, all of which are critical for host immunity against viral infections.[6,7] Furthermore, NSAID usage has been found to be strongly associated with severe soft tissue infections.[8,9] The aforementioned biologically plausible mechanisms add to the weight of the causal relationship between PUD and shingles. In addition, epidemiological studies have also identified that gastroesophageal reflux and reflux oesophagitis (ICD-9-CM 530) are significantly associated with increased risks for infections.[10,11]

We also wish to emphasize our diagnostic accuracy. In our study, PUD was not only identified by clinical symptoms and ICD-9-CM codes but also by claims of gastrointestinal endoscopy and specific prescriptions for PUD. More importantly, the reimbursement policy of Taiwan's national health insurance strictly requires that all patients should be documented for *H. pylori* infection or endoscopy-confirmed ulcers before receiving specific medicines.[1] Therefore, the identified associations between PUD and shingles in our study are valid because of the diagnostic accuracy. Furthermore, in comparison with the control cohorts, the adjusted hazard ratios for shingles among the risk factors for PUD were in the order: two risk factors (non-selective NSAID usage and *H. pylori* infection) > non-selective NSAIDs usage only > *H. pylori* infection only > others.[1] This gradient relationship also suggests that the association between PUD and shingles is causal.

In summary, all cumulative evidence highly suggests that the statistical association between PUD and shingles in our study is biologically plausible and likely causal.

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Estrogenic endocrine disruptors and autoimmune disease

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Harpsøe *et al*. provide a fascinating study showing, in a large cohort of women from Denmark, that adiposity may precede diagnosis of a range of autoimmune diseases.[1] Given rising rates of auto immune disease globally,[2] identification of a reversible mechanism could facilitate prevention and substantially reduce morbidity. Harpsøe *et al*. suggest a common aetiology linking adiposity to autoimmunity via effects on immune subsets, leptin or perhaps other mechanisms.[1] We wonder whether a mechanism operating via estrogen might provide a more generic underlying explanation for the role of adiposity in autoimmune disease, encompassing all these elements while also providing a guide to potential intervention targets. Specifically, adiposity raises estrogen levels,[3] which in turn promotes both immune response[4] and autoimmunity[5] as well as raising leptin.[6] Consistent with this potential mechanism the anti-estrogen, tamoxifen, suppresses immune function and is associated with less autoimmune disease.[7] As such, interventions to prevent autoimmune disease might focus on the role of maintaining a healthy weight and on the identification and removal from the environment of estrogenic endocrine disruptors, such as dioxins, phthalates and polychlorinated biphenyls.[8] Moreover, such an approach is unlikely to generate adverse unintended consequences for other diseases or for the major causes of death, as large-scale trials have shown the harms of raising estrogens, among women in the Women's Health Initiative trial[9] and among men in the Coronary Drug Project.[10]

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