Correspondence to 'Associations of regular glucosamine use with all-cause and cause-specific mortality: a large prospective cohort study' by Li *et al*

With great interest, we have read the recent article from Li *et al*, which addressed the link between regular glucosamine use and all-cause and cause-specific mortality in a large prospective cohort from the UK biobank.¹ These authors are dedicated to providing valuable insights and comprehensive analysis for HRs associated with glucosamine use, 0.85 (95% CI 0.82 to 0.89) of all-cause mortality, 0.82 (95% CI 0.74 to 0.90) of cardiovascular disease mortality, 0.94 (95% CI 0.88 to 0.99) of cancer mortality, 0.73 (95% CI 0.66 to 0.81) of respiratory mortality and 0.74 (95% CI 0.62 to 0.90) of digestive mortality. However, some methodological issues of these findings must be considered.

First, the definition of regular glucosamine use should be described more detailed. It is important to present factors such as dosage, frequency and treatment adherence, which may make confounded dose-response effects. Optimal dosage, which builds a basis for exhibiting the effectiveness of drugs at various levels of dosage, can also provide a better approach to assess the protective effect of glucosamine. For example, Simon *et al* used high/low dose, date, number of pills, defined daily dose, cumulative dose and duration to evaluate the association of aspirin with hepatocellular carcinoma and liver-related mortality.² Second, we observed that some residual confounders would have to be strongly related to HRs of mortality, like stress, air pollution and nutrition status. To the best of our knowledge, negative controls can be a method of detecting uncontrolled confounding. They are irrelevant factors designed for finding spurious causal inference and generally expected to give a result of no association after an analysis. When it turns out different, the main association may be biased by the same procedures which brought about the failure of negative-control experiment.³⁻⁵ Therefore, we recommend negative-control outcome (ie, glucosamine and accidental trauma) and negative-control exposure (ie, dental care participation and mortality) as two kinds of negative control design to improve causal inference of this study. Third, the habits of glucosamine use are likely to have inference with HRs of mortality. Glucosamine users often take glucosamine as a nutritional supplement. They regard it as one of the methods to keep a healthy lifestyle, thus be more physically active as well as attentive to keep their bodies in a robust condition. Therefore, the protective effect of glucosamine in mortality might be overestimated.

Besides, glucosamine is also used for treatments in patients with the history of osteoarthritis who may have relatively poor prognoses.¹ Therefore, the protective effect of glucosamine in mortality might be underestimated. These choices cause doubts of confounding by indication that tends to happen when the clinical indication for selecting a particular medicine is also linked to the outcome of interest.⁶

As mentioned above, the bias of (1) confounded dose-response effect, (2) residual confounders and (3) confounding

by indication should be taken into consideration to make this study more convincing based on the adequate database.

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