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LETTER TO THE EDITOR Open Access

Letter to the Editor: Is Omeprazole a contributing risk factor for osteoarthritis (OA)?

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Dear Editor,

Recently, Cao et al. provided evidence that omeprazole is a contributing risk factor for osteoarthritis (OA) development via Mendelian randomization (MR) analysis [1], which could lead to more cautious clinical practices in prescribing omeprazole, especially for patients with pre-existing or high risks of osteoarthritis. However, upon thorough review, we have identified potential methodological flaws that warrant reconsideration of their conclusions, as indicated in the following aspects:

(1) Pleiotropy bias: the authors used the intercept of MR-Egger (the term used to control pleiotropy) to evaluate the pleiotropy (in original Table 4). However, since the MR-Egger test is non-significant, the "mild" pleiotropy effect (identified by a model rejecting causal effect) may not have much substantive meaning. To investigate the pleiotropy, we reanalyzed their data by excluding IVs affecting exposure and outcome (with nominal significance). As shown in Table S1, this study didn't allow for this situation as 3 SNPs in ukb-a-106 and 1 in ukb-b-14,486 directly influenced the outcome datasets, rather than by the pathway of exposure exclusively. As shown in Fig. 1, we compared the causal effect fitting with and without removing these potential pleiotropic SNPs (Table S1) and figured out lower slopes of IVW fitting and insignificantly causal relationships by removing these confounding SNPs.

(2) Sample overlapping bias: The authors use a "two-sample" analysis on a "one-sample" design. Both the exposure and outcome of GWAS are generated from the UKB population, which violates the third essential principle mentioned in this paper, namely, "the exclusive effect of IVs on outcomes through the designated exposure, without alternative pathways." On the contrary, the exposure and outcome should originate from non-overlapping data [2]. We explored more accessible datasets (Table S2) to validate our MR results. For exposures, we included three more UKB traits related to using omeprazole. For outcomes, we selected 3 traits from another European-based osteoarthritis cohort (i.e., arcOGEN study). Among 12 analyses in Fig. 2, the IVW estimates are universally non-significant. The weak evidence couldn't support that omeprazole was a contributing risk factor for OA.

(3) Interpretation bias: The authors attributed the contributing risk factor that omeprazole accelerated OA progression to hypomagnesemia, Vitamin B12 malabsorption, intestinal flora disturbance, and other clinical implications, suggesting that the main effect of omeprazole was dependent on the

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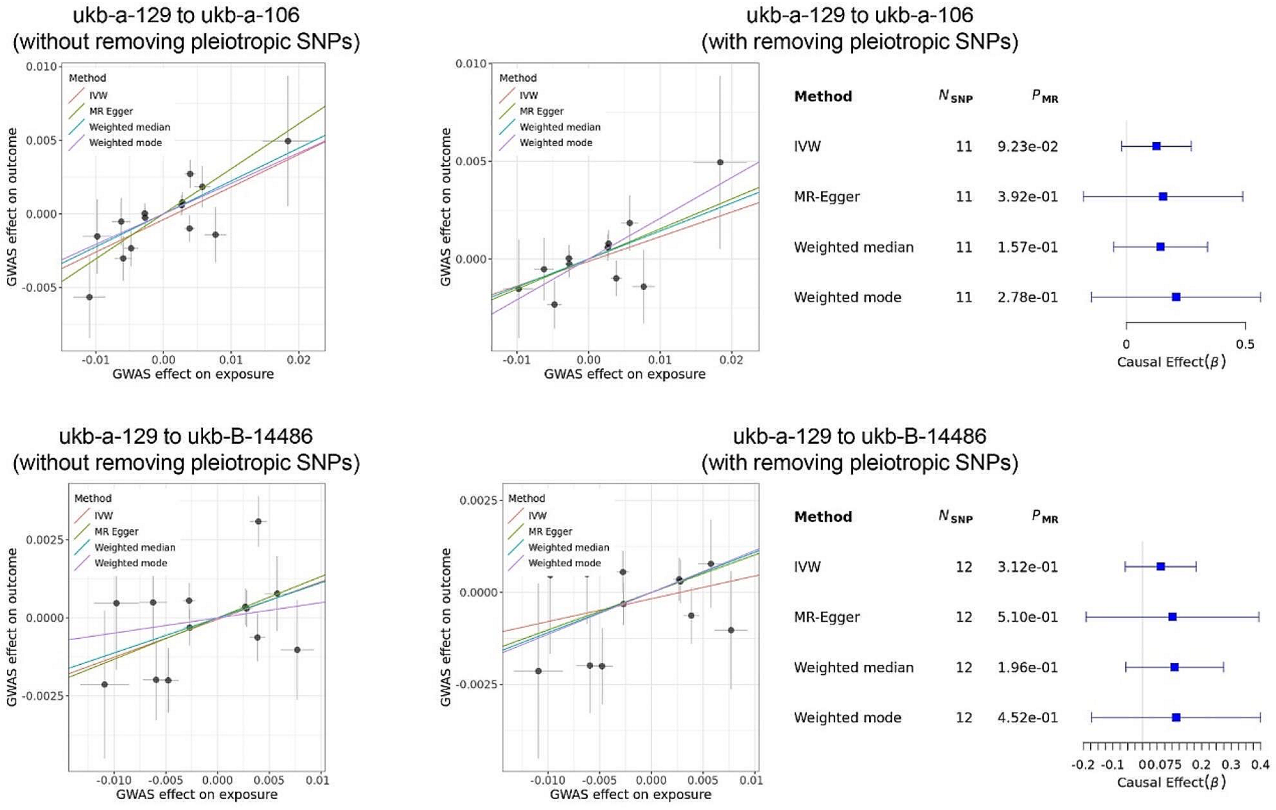

Fig. 1 Re analysis of causal effect after removing potential pleiotropic SNPs

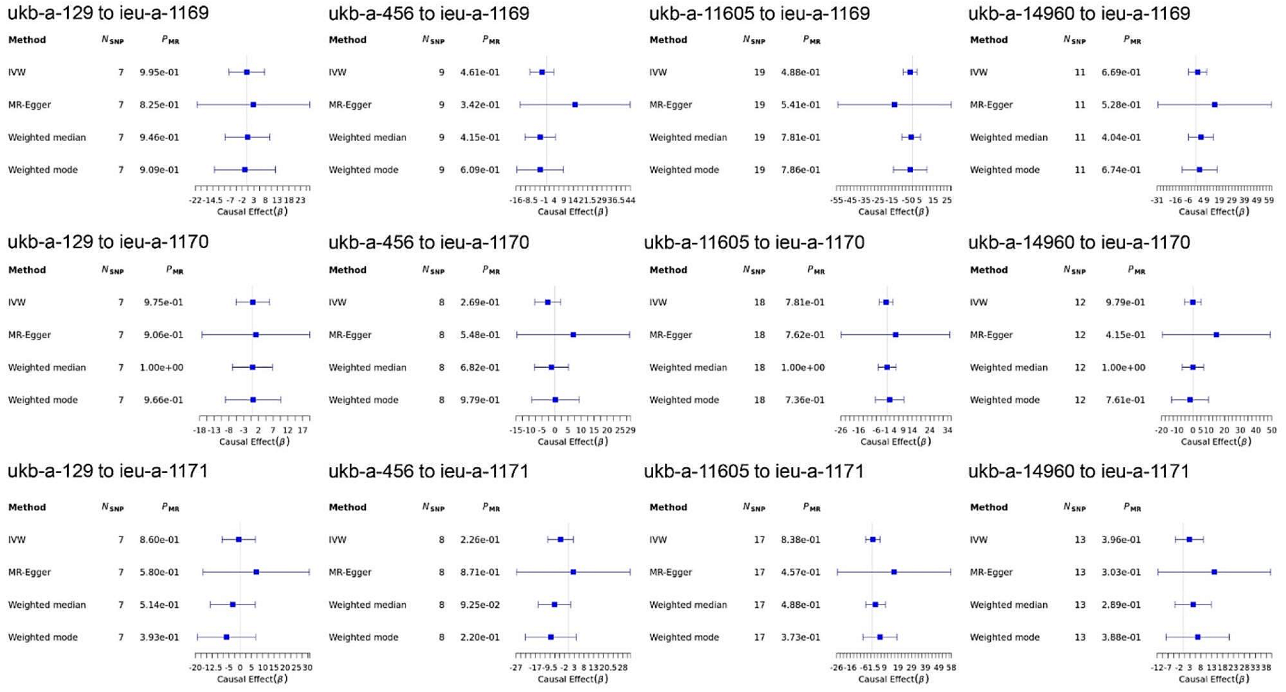

Fig. 2 Exploring possible causality with alternative datasets

functional alterations of the gastrointestinal system [1]. Nevertheless, systematic administration of omeprazole could not only act on gastrointestinal cells but also bone-related cells involved in the progression of OA. The proton pump plays a crucial role in osteoclasts in producing H^+ for bone resorption, whereas the over-activated bone remodeling mediated by osteoclasts has been proven vital in the initial stage of OA. Also, the alteration of osteoclasts is different in distinct OA stages. Excessively activated osteoclasts can induce bone loss in early-stage OA, while exhausted osteoclasts in late-stage OA can induce sclerosis. In the current work, the authors only used "osteoarthritis" for the MR analysis, which is not consistent with the pathological process of OA.

In light of these methodological concerns and our reanalysis, we sincerely expect the authors and the journal to reconsider the conclusions drawn about the causal link between omeprazole and OA. More importantly, this letter is not intended to provide a critique of an interesting and pioneering study from an MR analysis standpoint. We appreciate all the authors' efforts and the opportunity to provide this feedback. We hope this letter presents some material to fuel the ongoing scientific discourse and contributes to a more accurate and comprehensive understanding of the relationship between omeprazole and OA. To the best of our knowledge, OA is a complex condition with several factors contributing to its development and progression, such as older age, gender, obesity, joint injuries, occupational hazards, genetics, bone deformities, and other diseases [3–5]. We strongly recommend that future studies adopt more rigorous methodologies to identify causal relationships and avoid potential misleading inferences.

Supplementary Information

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Supplementary Material 1

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