Author’s response to reviews

Title: A stratification method based on clustering for the minimization of data masking effect in signal detection

Authors:

Jianxiang Wei (jxwei@njupt.edu.cn)
Yue Ding (b14070501@njupt.edu.cn)
Ming Li (526540057@qq.com)
Jun Sun (574278909@qq.com)

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Author’s response to reviews:

Dear Editor and Reviewer: Thank you for your letter and for the reviewer’s comments concerning our manuscript entitled ”A stratification method based on clustering for the minimization of data masking effect in signal detection” (MIDM-D-18-00274R2). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied comments carefully and have made correction which we hope to meet with approval. All corrections can be found in the revised manuscript (Manuscript-revised version3), in which all changes are marked in red. The main corrections in the paper and the responds to the reviewer’s comments are as follows:1. Abstract: Please report the actual values for precision, recall, and F1-score in the abstract. The relative differences obfuscate the absolute differences (e.g. from 38% to 44% recall?), which are more useful to readers. Response: Thank you for your suggestions. The revision can be found in the Results of Abstract section in page 2 of the revised manuscript.[Abstract section] Recall increased by 34.95% from 29.93% to 40.39%, Precision reduced by 10.52% from 54.56% to 48.82%, while F-measure increased by 14.39% from 38.65% to 44.21%.2. Abstract: Quantify the second result in terms of how well the results were confirmed for ADRIB (and correct the typo in ADRIIB). Response: Thank you for your comments. We have added the description of ADRIB in the method section and quantified the results related to ADRIB in the results section respectively. The typo in ADRIIB has been corrected. The revision can be found in the Abstract section in page 2 of the revised manuscript.[Abstract section-methods]In addition, some DECs from the Adverse Drug Reactions Information Bulletin (ADRIB) issued by CFDA were collected for further reliability evaluation.[Abstract section-results] According to ADRIB after 2011, 5 DECs related to Potassium Magnesium Aspartate, 61 DECs related to Levofloxacin Hydrochloride and 26 DECs related to Cefazolin were highlighted. 3. [Optional] Background: There was a paper recently published as a research letter in (I think) JAMA Internal Medicine that showed that when the FDA issued safety issues for the drugs they approved, around 1/3 of them relied on evidence from trials, and 1/3 (from memory) relied on information from adverse event reporting systems. It would be worth digging up that reference for use in the background because there are unsubstantiated claims in the
first sentenceResponse: Thank you for your suggestions. This reference has been cited in our paper. The revision can be found in the background section in page 3 of the revised manuscript.

Background section: Tau N et al. demonstrated that the most frequent information sources that served as the basis of the initial safety signal in the United States were Food and Drug Administration’s adverse event reporting system (87 [38%]) and randomized clinical trials (81 [36%]) or observational studies among the 228 drug safety communications.[1],[1]


Background: A major issue with spontaneous reporting is that it can be "gamed" by malicious actors to increase the volume of reports to the point where a signal would be found, and that is why ADRs are not used as evidence but can be used to generate hypotheses. This nuance did not appear in the manuscript as far as I saw.

Response: Thank you for your comments. The revision can be found in the background section in page 3 of the revised manuscript.

[Background section] As the quality of reports varies greatly, all reports of SRS are mainly used for hypothesis generation of suspicious signals rather than evidence. 5. [Optional] Background: I am not a fan of the "laundry list" approach to literature reviews that simply summarise each paper in order. I much prefer to see a real synthesis of the knowledge to show how often the research agrees, what might account for differences, and a clear elucidation of the gaps.

Response: Thank you for your comments. We have reorganized and revised the content of the literature review. The revision can be found in the background section in page 3 and page 4 of the revised manuscript.

6. Background: Typo "As we known" and then problems with grammar through the rest of the paragraph: "Nevertheless, the OE ratios of some specific *DECs rarely reported but actually exist* would decline *on account of* the over-reporting of other related drugs or ADRs, which may mask some true signals. Therefore, *we can draw that the general cause* of data masking is frequency difference. In order to address this issue, it is reasonable to stratify the data into some sub clusters, in which the data follows the similar order of magnitude." Given that this is the critical statement and implicitly includes the aim of the study, it needs to be as precise as possible and grammatically correct.

Response: Thank you for your good advice. We have revised the contents and made grammar corrections. The revision can be found in the background section in page 4 of the revised manuscript.

[Background section] These adjusted methods for signal detection are mainly based on measures of disproportionality, in which suspected DECs signals are highlighted by disproportionate observed-to-expected (OE) ratios. The OE ratios are strongly affected by over-reported drugs or ADRs, and some specific DECs corresponding to true signals which are rarely reported may be masked with lower OE ratios. Therefore, frequency difference of ADEs is an important factor of data masking, which has not been considered in the above methods. It is reasonable to stratify the data into some clusters, among which the data is of similar order of magnitude. The aim of this study is to explore a novel stratification method to reduce the impact of frequency differences on true signals masking.

7. Stratification strategy: Define unusual terms on first use - remember that the audience for MIDM is likely to be quite broad, so even things like "decline rate" should be defined briefly.

Response: Thank you for your suggestions. A definition of decline rate has been added below Table 1. The revision can be found in the Tables section in page 14 of the revised manuscript.

[Tables section] *Decline rate: the percentage of decrease in frequency of masking signals compared to the overall average. 8. Stratification strategy: Be consistent with the representation of numbers: e.g. 1102.06 should be 1,102.06 I think? It might also help to include the "units" for these numbers because the writing is not especially clear and the units will