Letter to the Editor

Federica Braga*, Simona Ferraro, Sara Pasqualetti and Mauro Panteghini

Reply to: Hyperuricemia does not seem to be an independent risk factor for coronary heart disease

hiips://doi.org/10.1515/cclm-2017-0954
Received October 17, 2017; accepted October 18, 2017; previously published online November 15, 2017

Keywords: coronary heart disease; meta-analysis; uric acid.

To the Editor,

We read the letter by Battaggia et al. [1] commenting our systematic review and meta-analysis on the association between hyperuricemia (HU) and coronary heart disease (CHD) incidence and mortality [2], and we thank the authors for giving us the opportunity to better explain and emphasize some important points of our work.

In our study, we updated the literature search and reviewed available observational prospective cohort studies about the relationship between HU and future CHD incidence and mortality in the CHD-free population that fulfilled well-defined selection criteria, including the explicit definition of the urate threshold above which the risk, if present, became clinically important. Regarding the CHD incidence, which is the outcome preferentially considered by Battaggia et al., our meta-analysis showed a slight but significant ($p = 0.003$) increase of CHD risk [risk ratio (RR) = 1.206 (1.066–1.364)] in hyperuricemic subjects, becoming more evident in hyperuricemic women [RR = 1.446 (1.323–1.581)]. Based on these results, Battaggia et al. conclude that the main message of our study was that the treatment of HU should be included in the therapeutic strategies to reduce the CHD risk. We would like to clarify, however, that we never wrote this recommendation anywhere in the text. On the contrary, we believe that, for many reasons, the message of our paper is just opposite to what these authors have deduced.

First, it should be noted that the primary studies included in our meta-analysis are all observational, meaning that they are designed to investigate risk factors (defined as distinct volume categories) and not interventions or the need for promoting therapeutic strategies [3]. Second, we clearly stated that further specifically designed trials are needed to confirm the meta-analysis outcome because of the low number of retrieved trials fulfilling inclusion criteria and the significant heterogeneity found among them (I^2 statistic, ~65%). Finally, in our opinion, our results have the merit to revaluate down the stronger statistical significance obtained in some previous meta-analyses on the association between HU and future cardiovascular disease mortality, raising therefore further perplexity about a possible treatment focused on HU. If one wishes to find a practical indication from our results, they might just suggest promoting more surveillance in subjects with HU, mainly if women, through, e.g. diet modification without necessarily resorting to drugs.

Battaggia et al. evaluated our meta-analysis by using the AMSTAR checklist [4], obtaining a medium/low methodological quality. In particular, they considered 4/11 items fully satisfied, 3/11 not satisfied and 4/11 uncertain. As the AMSTAR questionnaire asks reviewers to answer "Yes", "No", "Can't answer" or "Not applicable", we are a little surprised about the final judgment because they declare uncertainty in answering to more than one-third of questions. It has been already reported that some items of AMSTAR are difficult to interpret and theoretically hinder an accurate assessment [5]. Furthermore, the reliability of AMSTAR checklist as a tool to assess quality of systematic reviews of observational studies is prone to several criticisms, and assessors should be aware of this as well as to consider that speculations on the need for primary prevention programs according to observational data may be useless [6]. Even if not explicitly mentioning AMSTAR checklist, we reported the poor applicability of some AMSTAR items to our meta-analysis. For instance, AMSTAR item 7 (critical appraisal of included studies) is difficult to apply in order to obtain the true methodological quality of primary studies included in our meta-analysis [5]. As a matter of fact, there is no gold standard

***Corresponding author: Federica Braga,** Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Via G.B. Grassi 74, Milano, Italy, Phone: +39 02 39042766, E-mail: federica.braga@unimi.it
Simona Ferraro, Sara Pasqualetti and Mauro Panteghini: Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

for the critical appraisal of non-randomized studies, and thus it is difficult to provide any characteristics that should be covered to assess the methodological quality of these studies, particularly if resorting to an observational design [6]. This is relevant if we consider that Battaggia et al. declare our meta-analysis "very far from excellent" because of the lack of any (explicit) assessment of the validity of the included studies. Appropriately combining findings of retrieved studies (AMSTAR item 9) is also very challenging in doing meta-analysis from observational studies. Theoretically, randomized controlled trials (RCTs) provide unbiased estimate of the effect, whereas observational studies may not reflect the true effect for the presence of confounding factors and bias [7]. To overcome this, we followed running recommendations and accordingly we pooled bias-adjusted results for each study instead [8].

Battaggia et al. demonstrate through a metaregression that the association between HU and CHD tends to decrease by increasing the number of confounders considered. Being aware about this problem, in our meta-analysis we selected the first RR value resulting statistically significant after adjustment for as many confounders as possible. Unfortunately, we found a very high heterogeneity among confounder adjustments in different individual studies and this was clearly expressed in the paper as the main limitation [2]. Battaggia et al. claim that three of nine primary studies considered in our meta-analysis were not adjusted for nutritional status, and therefore, they hypothesize that metabolic syndrome was not accounted for a high number of enrolled subjects. However, specific mention about the presence/absence of metabolic syndrome is lacking in the quoted papers and in none of them the information about metabolic syndrome is reported in tables showing baseline characteristics of subjects or even in the text describing populations. On the other hand, it is important to highlight that some of the factors concurring to the definition of metabolic syndrome have been adjusted in these three papers (see Table 1 of our paper). Similarly, there were other factors not always considered as confounders in primary studies. To this regard, we reported the example of renal function that has been evaluated as confounder only in one study. It is noteworthy that there are no main indications on how to deal with different adjustments in various observational studies. Regression models are generally used to account for confounding factors and bias, but they often fail in fully correcting for all biases [9]. Furthermore, understanding and assessing the quality of regression models is much more difficult in observational studies than in RCTs [10].

In conclusion, the position of Battaggia et al. about the topic of HU as CHD risk factor is not far from ours. Many of the issues raised by these authors, including the lack of reliable clinical evidence able to support the use of urate-lowering drugs for preventing CHD events, were already addressed in our paper.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Battaggia A, Scalisi A, Puccetti L. Hyperuricemia does not seem to be an independent risk factor for coronary heart disease. Clin Chem Lab Med 2018;56:e59–62.
2. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clin Chem Lab Med 2016;54:7–15.
3. Pieper D, Mathes T, Eikermann M. Can AMSTAR also be applied to systematic reviews of non-randomized studies? BMC Res Notes 2014;7:609.
4. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10.
5. Faggion CM Jr. Critical appraisal of AMSTAR: challenges, limitations, and potential solutions from the perspective of an assessor. BMC Med Res Methodol 2015;15:63.
6. Kelly SE, Moher D, Clifford TJ. Quality of conduct and reporting in rapid reviews: an exploration of compliance with PRISMA and AMSTAR guidelines. Syst Rev 2016;5:79.
7. Egger M, Schneider M, Davey SG. Spurious precision? Meta-analysis of observational studies. Br Med J 1998;316:140–4.
8. Thompson S, Ekelund U, Jebb S, Lindroos AK, Mander A, Sharp S, et al. A proposed method of bias adjustment for meta-analyses of published observational studies. Int J Epidemiol 2011;40:765–77.
9. Reeves BC, Higgins JP, Ramsay C, Shea B, Tugwell P, Wells GA. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. Res Synth Meth 2013;4:1–11.
10. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:iii–x, 1–173.