Letter to the Editor

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

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To the Editor,

Federica Braga and coworkers [1] stated recently that hyperuricemia shows to be an independent predictor of coronary heart disease (CHD) risk (RR CHD = 1.206 [1.066–1.364]; RR CHD death = 1.209 [1.003–1.457]), mainly for the results found in women. That message seems to be of great importance: if it is true, the treatment of hyperuricemia should be included in the landscape of the therapeutic strategies to reduce the coronary risk. To ascertain the methodologic validity and robustness of that work, we considered it as a critical appraisal of some methodological aspects.

In our approach, (a) we evaluated the overall quality of that systematic review through the AMSTAR checklist [2]; (b) we recovered the nine studies selected by Braga and colleagues [1] in order to repeat the meta-analysis and quantified the heterogeneity through I^2 statistic [3]; (c) we launched new subgroup and sensitivity and metaregression analyses in order to better explore the heterogeneity, considering the following as potential effect modifiers: gender, number of CHD covariates used in the adjustment models (i.e. age, BMI, total cholesterol or LDL-cholesterol or presence of dyslipidemia, blood pressure values or presence of hypertension, smoke, glucose values or presence of diabetes) and lack of nutritional information; (d) we estimated the prevalence of metabolic syndrome in single-trial samples using an Italian epidemiological research as reference sample [4]; (e) we investigated the quality of included trials and their risk of bias through the ACROBAT Cochrane checklist [5]; and (f) we used a generalized least-squares regression model to inspect some dose-response effect [6] both at trial level and with a dose-response meta-analysis; the goodness of fit was explored with a χ^2-test [7]. We restricted all our described analyses to the end point 'CHD incidence'; their methodological details are available in the online Supplementary material.

What were our results?

1. The quality of the meta-analysis assessed with the AMSTAR checklist [2] appears to be medium/low: only 4/11 items were fully satisfied, 3/11 not satisfied and 4/11 uncertain.
2. The metaregression (Figure 1) demonstrates that the number of confounders could be an important cause of heterogeneity, with the risk ratio of CHD associated to hyperuricemia decreasing by 13% for each covariate added to the model (p = 0.056). The subgroup analysis using the number of covariates as effect modifier coherently indicates that the role of hyperuricemia tends to disappear in the best adjusted models (test of interaction, p = 0.056). Notably, the trials that were not adjusted for nutritional status [8–10] represent 48.14% of the information power of the whole pool, and the presence of 74,138 cases of metabolic syndrome not accounted for by the regression adjustments can be estimated in their samples. The sensitivity analysis performed excluding these trials [8–10] shows a lowering effect and a loss of statistical significance (RR = 1.09 [0.94–1.26]), and stratifying that analysis by sex, the effect of hyperuricemia on CHD risk coherently does not appear to be significant both in men (RR = 1.07 [0.89–1.29]) and in women (RR = 1.22 [0.83–1.80]) (test of interaction, p = 0.58).
3. The dose-response relationship between uricemia and CHD risk at trial level showed a positive and significant trend only for Liese's [11] and Holme's [9] trials but was inconsistent for all the others. Figure 2 illustrates a dose-response analysis at trial level; Figures 3 and 4 two dose-response meta-analysis: a weak but significant trend between uricemia and CHD

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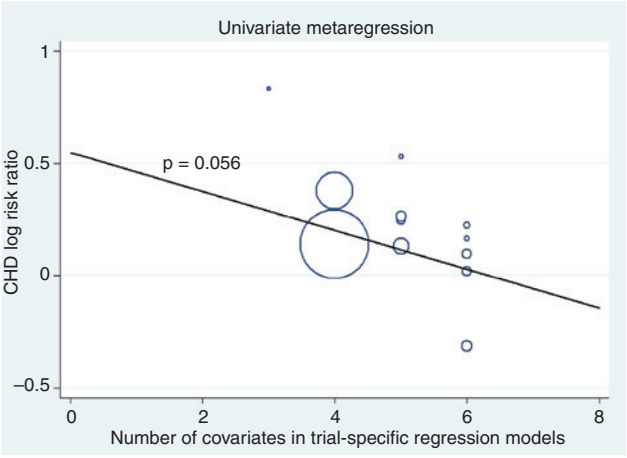

Figure 1: The statistical association between CHD and uricemia appears to be inversely proportional to the number of covariates used in the adjustments made at trial level.
Our metaregression analysis refers to the efficacy results produced by the most adjusted models (see text). We considered the number of clinically important covariates (i.e. age, BMI, total cholesterol or LDL-cholesterol or presence of dyslipidemia, blood pressure values or presence of hypertension, smoke, glucose values or presence of diabetes) selected by each multivariate regression model exploring the relation between hyperuricemia and log risk of CHD. That number ranged from x = 3 to x = 6 between trials considered by the meta-analysis of Braga et al. [1]. The graph shows that adding one more covariate to a multivariate regression model produces in the new model a −0.144 lowering of the log-risk ratio of CHD (t = −2.16, p = 0.056). In exponential form, this means that if RR1 corresponds to a risk ratio product by a regression model with (n1 = x) covariates and RR2 corresponds to a risk ratio product by a model with (n2 = x + 1) covariates, the ratio of these RRs corresponds to RR1/RR2 = 0.865 (p = 0.056). The metaregression analysis shows in other words that the risk ratio of CHD linked to hyperuricemic condition appears be 13.5% lower for every covariate added to the regression model. This discovery seriously questions the importance of hyperuricemia as an independent CHD factor.

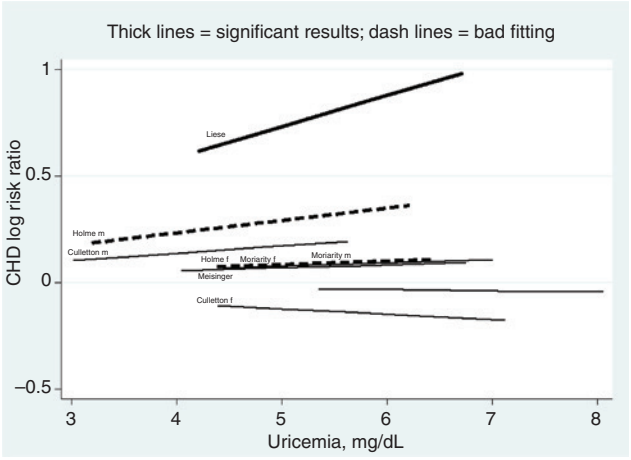

Figure 2: Dose-response analysis at trial level.
Generalized least-squares regression graphical results for dose-response analysis [9] at trial level (see also Supplementary Table G1). The analysis was possible only for trials with sufficient information (i.e. quantiles of uricemia, number of cases and non-cases for each stratum, efficacy measure with relative standard errors/confidence intervals) [5, 11 and Supplementary material: Refs. 18, 19]. The dash lines represent the models in which the fit was not good (that is Holme's trials [5], see text); the thick lines represent the models in which the results were significant.

risk was demonstrated for the whole pool (ratio of risk ratios = 1.02, p < 0.0001), but the model fitted very poorly (GOF test, p < 0.0001); thus, the results of this model are unreliable (Figure 3). Excluding Holme's [9] trials, the model nevertheless loses its statistical significance (ratio of risk ratios = 1.00, p = 0.455) and the fit shows to be at the same time very good (GOF test, p = 0.153) (Figure 4).

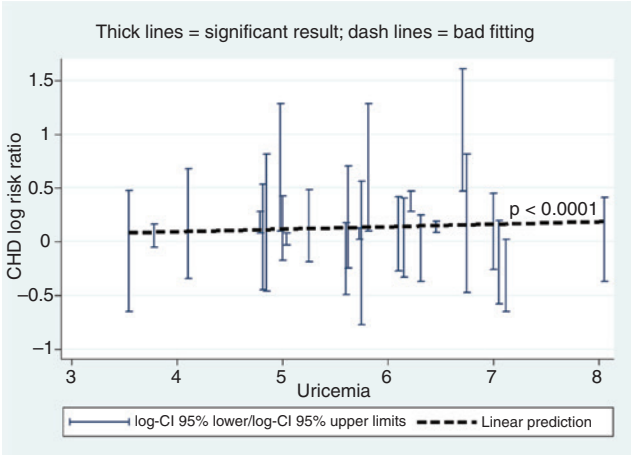

Figure 3: Dose-response meta-analysis.
Dose-response meta-analysis fixed effect based. The graph illustrates a weak but significant linear relationship between the log risk ratio of CHD and the uricemia (non-exponentialized coefficient = 0.023, z = 7.269, p < 0.001). In exponential format, the ratio of risk ratios is 1.02, z = 7.269, p < 0.001. That is, for every unit of augment of uricemia, the risk ratio of CHD augments of 2% with statistical significance. Nevertheless, the goodness of fit is very weak (GOF test χ^2-test 80.84 with 25 degrees of freedom, p < 0.00001; in other terms, that model does not work). We repeated the analysis through a random effect model obtaining identical results (not shown).

What results do other meta-analysis show?

Three other meta-analyses explored the relation between uricemia and fatal or non-fatal CHD end points in the last decade [12–14].

– Kim et al. [12] concluded that 'hyperuricemia slightly increases the risk of CHD events in the general

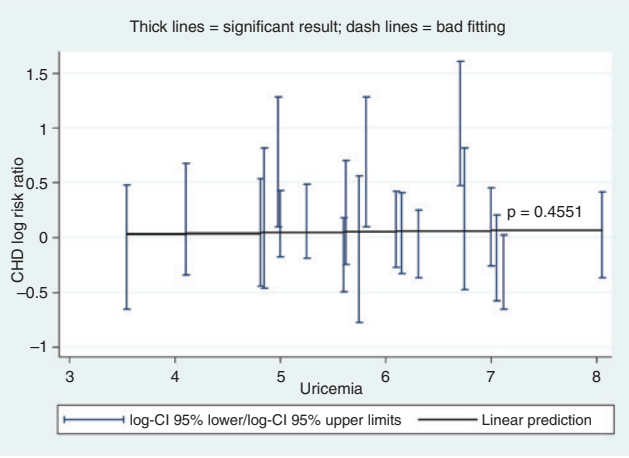

Figure 4: Dose-response meta-analysis after exclusion of Holme's trial.
Dose-response meta-analysis fixed effect based (see Figure 3). Excluding Holme's [5] trials (in which the analysis was not adjusted for nutritional status), the statistical significance of the model is lost (non-exponentialized coefficient = 0.0084239, z = 0.75, p = 0.455). In exponential format, the ratio of risk ratios (see Figure 3) is 1.00, z = 0.75, p = 0.455. In other words, no trend is demonstrated for the relationship between uricemia and CHD risk. The test of goodness of fit (GOF test) reveals that the model works very well (GOF test χ^2-test 25.22 with 22 degrees of freedom, p = 0.1534).

population (RR = 1.09 [1.03–1.18]); nevertheless, the declared presence of publication bias does not allow us to draw confident conclusions.

- Zhao et al. [13] concludes that hyperuricemia 'is an independent predictor for future cardiovascular mortality (men RR = 1.30 [1.07–1.59]; women RR = 1.35 [1.06–1.72]) but increases the risk of all-cause mortality only in men' (men RR = 1.23 [1.08–1.42]; women RR = 1.05 [0.79–1.39]). Contrary to what he says, his own test for interaction shows, however, that the difference between the sexes is just casual (p = 0.851). No dose-response investigation was done in that work to support some causal relationships between uricemia and CV events, in which that analysis is one of the most important among Hill's criteria [6].
- Li and colleagues [14] concluded that hyperuricemia increases the risk of CHD events (RR = 1.13 [1.05–1.21]). Notably, these authors were nevertheless unable to demonstrate any dose-response relationship between the exposition and the CHD end point, so their conclusions are epidemiologically unacceptable. Furthermore, that meta-analysis suffered from a clamorous error in the data entry: all acute myocardial infarction patients recruited by AMORIS trial [9] were in fact erroneously included in the CHD-mortality pool.

What can be argued from our results?

In our opinion, the contribution of Braga and colleagues [1] does not help to resolve the clinical dilemma.

A potentially serious problem of the meta-analysis of Braga et al. [1] is the lack of any (explicit) assessment of the validity of the trials included. Even well-conducted observational studies can in fact be subject to important and insidious biases: about this, the quality of the trials of Braga et al. [1] appears very far from excellent: 89% have missed adjustments for cointerventions, which is for an important prognostic factor for CVD, and 100% were burdened by moderate/serious bias due to confounding. Also taking into account this qualitative approach, it seems very difficult to have full confidence in its [1] conclusions.

Another major problem for Braga's meta-analysis [1] seems to be the presence of residual confounding. The metaregression and the subgroup analyses we have performed show, in fact, that the number of predictors considered in single trials could represent an important cause of heterogeneity, and the role of hyperuricemia completely disappears when the model is well adjusted (i.e. with a sufficient number of covariates). These findings can seriously question the importance of hyperuricemia as an independent coronary risk-factor.

An important contribution to biased quantifications of the true relationship between hyperuricemia and CHD is linked to results of the Holme's [9] AMORIS's trial (n = 417,734), which contributes to 91.2% of the whole sample size of meta-analysis and to 36.97% of her 'information power', and that along with two other smallest studies [8, 10], AMORIS [9] did not adjust for nutritional status. The (estimated) 74,138 patients affected by metabolic syndrome in the studies of Baba et al. [8], Bos et al. [10] and AMORIS can thus represent the 16.1% of the whole sample of the meta-analysis. Clearly, the incomplete adjustment for confounders made in these trials could have contributed to biased results.

In conclusion, our critical appraisal of the study of Braga et al. [1] does not confirm the sustained positive and independent association between hyperuricemia and coronary risk. Results of that meta-analysis appear to be seriously distorted by bias due to confounding, and the included trials were unable to demonstrate a dose-response relationship between the exposure and the end point. At that time, the medical meta-analytical literature lacked convincing answers to this problem, which is burdened by important methodological pitfalls.

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