

### **#General consideration**

**These are comments on the margins of a Word document, provided in PDF format, with a truncated section. Responding to an anonymous author, who is clearly not an expert, is not straightforward.**

**COMMENT 1:** The headings of the paragraphs do not adhere to the established standards for a systematic review. 2.1. Literature search 2.2. Data extraction and processing 2.3. Risk of bias assessment 2.4. Meta-analysis/statistical analysis I leave here some examples (No Cochrane reviews which are more complicated): Battini V, Cirnigliaro G, Leuzzi R, et al. The potential effect of metformin on cognitive and other symptom dimensions in patients with schizophrenia and antipsychotic-induced weight gain: a systematic review, meta-analysis, and meta-regression. *Front Psychiatry*. 2023;14:1215807. Published 2023 Jul 12. doi:10.3389/fpsy.2023.1215807 Carnovale, C., Lucenteforte, E., Battini, V., Mazhar, F., Fornili, M., Invernizzi, E., Mosini, G., Gringeri, M., Capuano, A., Scavone, C., Nobile, M., Vantaggiato, C., Pisano, S., Bravaccio, C., Radice, S., Clementi, E., & Pozzi, M. (2021). Association between the glyco-metabolic adverse effects of antipsychotic drugs and their chemical and pharmacological profile: a network meta-analysis and regression. *Psychological medicine*, 1–13. Advance online publication. <https://doi.org/10.1017/S0033291721000180> Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7(1):64-77. doi:10.1016/S2215-0366(19)30416-X Skogler, J., Moberg, T., Tancredi, L., Styrnisdóttir, L., Hedayati, E., Alarcon-Ruiz, C. A., Khamis, A., Persad, E., Iskandarani, G., Hansson, S. R., & Bruschetini, M. (2023). Association between human chorionic gonadotropin

### **#Our reply**

**The different stages are clearly explained in our study and have been commented on by the reviewers. Our responses have been satisfactory. It should be noted that our study cannot claim exact measurement but should be seen as an estimation based on plausible assumptions.**

**COMMENT 2:** The first issue is that they did not register a protocol on Prospero: <https://www.crd.york.ac.uk/prospero/>

### **#Our reply**

**It is true, but this comment has no impact on the results.**

**COMMENT 3:** At least two databases are needed. Especially because we are considering the first wave of covid, when many studies were published without peer review. Otherwise, if you want to include only peer-reviewed articles, you must declare it and state why.

**#Our reply**

**There is no relation between the number of used databases and peer-review. The exploration of a second database might lead to capture additional data for countries with no or few estimates of HCQ exposure.**

**COMMENT 4:** I am concerned about the search period that was chosen. I can confirm from experience (we were asked for assistance from the hospital in Bergamo, Italy) that in March 2020, there was still nothing to be found in the literature; I had to retrieve data from studies in Chinese (and translated with Google Translator). At that time, monoclonal antibodies were being discussed, not hydroxychloroquine (HCQ). I also wonder why the end date is March 15, 2021; is it the publication date of the first RCT? In any case, they worked with observational studies, and if I understand correctly, they also included retrospective studies that, of course, can be published many years later. What should matter is the period of "recruitment" of the cohort, so to speak, not ...

**#Our reply**

**The comment is unclear, truncated and provides no reference. We cannot answer the author.**

**COMMENT 5:** Well... I'm not an expert of this kind of analysis, but it seems to me like a multiplicative model, namely a generalised linear model where you simply multiply your parameters. One of the parameters is fixed and is 1.11, which is the odds ratio from that previous meta-analysis mentioned above. In my opinion, it's a model that's too simplistic; in 2024 with a lot of data on COVID, we can't rely on such uncertain estimates anymore. No confounding parameters related to patients' disease have been taken into consideration. And apparently, from what I gather in the letters, the only parameter regarding therapy has a significant methodological flaw.

**#Our reply**

**There is no data suggesting an interaction in the treatment effect of hydroxychloroquine. The other comments are incomprehensible, with the author admitting their lack of expertise in the field.**