Disregarding Study Design of the Primary Studies Produces Misleading Meta-analyses

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Meta-analyses use statistical methods to combine the findings from several studies that address similar research questions. The basic premise of the meta-analysis is that the combined results from a group of studies produce a more precise estimate of an effect than the individual studies when testing a hypothesis. In the era of evidence-based medicine, meta-analyses play a vital role as the findings from meta-analyses are considered to produce higher level of evidence. As such, results of some of the meta-analyses have led to major changes in clinical practice over the past decades.

The level of certainty of the pooled estimates, however, depends largely on the quality of studies that is being aggregated (1). In particular, meta-analyses have the potential to produce seriously misleading results when it is not done correctly. As the Cochrane methods group argues that "*for the meta-analyses to be reliable, appropriate attention should be given to formulating the review question; specifying eligibility criteria; identifying and selecting studies; collecting appropriate data; considering risk of bias; planning intervention comparisons; and deciding what data would be meaningful to analyse"* [2]. As such, a wrongly done meta-analyses can provide very misleading results, particularly, when the specific study designs, within-study biases, variation across studies, and reporting biases were not carefully considered (2).

In this commentary we aimed to demonstrate how meta-analyses can produce misleading findings when the design structure of the primary studies

is ignored, while extracting data for synthesis. This is an area that is not well discussed in the literature, yet it is vitally important, if we were to avoid producing misleading conclusions. We will demonstrate this with an example of a recently published meta-analysis.

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The meta-analysis in question was carried out by Pardamean et al (3) who attempted to quantify the increase in mortality after contracting COVID-19 among patients with schizophrenia. They claimed to compare the mortality experience of Schizophrenia cases with that of the general population. In their review, the authors presented what they called the solid evidence to support the idea that risk of death after COVID in patients with schizophrenia is 2.2 times higher than in the general population.

However, their conclusion is based on wrong data extraction ignoring the study design and as such their meta-analysis ended up falsely finding significant association between mortality and schizophrenia while the primary studies were showing no such associations. In other words, while the primary studies indicated non-significant or lack of association between mortality and schizophrenia, the authors attributed significant association to those non-significant studies.

This happened as the data extraction ignored the study design structure and the hypothesis that authors were testing was different to the aim and objectives of the individual studies that they synthesized. We are presenting this as an example so that the systematic review and evidence-based community becomes aware of such issues in critically evaluating meta-analytical findings for their clinical practice applications.

Pardamean et al. (3) have included 10 primary studies that were predominantly, retrospective cohort and case-control studies. The brevity of this communication will not permit us to discuss each of these 10 papers included in their review to demonstrate how most of the papers included were not possibly even eligible to explore the hypothesis that authors were testing. However, the wrong relative risk attributed to individual studies possibly the most serious. That led to incorrect pooled estimates and led the authors to wrongly conclude that there are significantly more deaths among patients with schizophrenia, compared to the general population.

To demonstrate this point, we have taken one individual study they included as an example to highlight the issue. Tyson et.al (4) is one of the papers they included in their meta-analysis. Tyson and colleagues were attempting to find the predictors for mortality among hospitalized COVID patients in general. They carried out a case-control study with 75 COVID

patients who died in-hospital and an age-gender matched group of 75 COVID patients who survived after hospitalisation. In the whole paper, only one place Schizophrenia is mentioned that was in their first baseline characteristics table, in fact, as the last item in the long list of baseline characteristics. History of schizophrenia was not statistically different in their study. Only 1 patient in the survival group and 5 patients in those who died had any history of schizophrenia. They also provided a bivariate p-value to compare all the baseline characteristics and reported a p-value of 0.096 for differences in the history of schizophrenia between those who died and survived after COVID.

As Tyson et.al (4) were looking for predictors for COVID mortality and schizophrenia was not considered in the multivariate models as they were not different at crude level. Unfortunately, in the meta-analyses of Pardamean et al. (3), a relative risk (RR) of 1.71 (along with a significant 95% confidence interval of 1.15 – 2.55) were attributed to Tyson et.al (4). How did they get such an estimate? In my view, this happened as the way data were extracted to form the 2 X 2 table to create the forest plot. Tyson et.al (4) reported 5 patients among the cases (died) and 1 in the control group (survived) to have Schizophrenia. Rather than using the correct fraction of 5/75 (cases) compared to 1/75 (control), they instead computed the risk of death among Schizophrenia as 5/6 and compared to 70/144 as non-schizophrenia controls. As though the study took 6 patients with schizophrenia as cases and compared to 144 controls, completely ignoring the age-matched case-control study of 75 cases of those who died out of COVID in-hospital compared to 75 controls who did not die after COVID! While Tyson et.al (4) found other major predictors to be significantly associated with COVID mortality at univariate and multivariate levels and schizophrenia was not a predictor at crude or multivariate levels, the meta-analysis by Pardamean et al. (3) attributed Tysen et.al a significant association between schizophrenia and mortality after COVID.

Ignoring the study design also created a serious selection bias. The meta-analysis of Pardamean et al. (3) was based on mortality experience of about 2 million COVID patients, but Schizophrenia subjects consisted of less than 1.5% of their study population, i.e., over 98.5% of the study population had no Schizophrenia. Moreover, 8 out of 10 studies had less

than 5% of people with any history of Schizophrenia, indicating a serious selection issue. This is important as they predominantly pooled retrospective cohort and case-control studies where 2,773 Schizophrenia cases were compared to 193,159 control patients. This happens as the more balanced case-control and retrospective cohort structures were ignored.

Ignoring the design structure while extracting data can happen when there is paucity of primary studies that review authors wish to evaluate. When there is lack of primary studies that focuses on the hypothesis that a researcher is interesting in exploring there is not much a systematic review can do when there are insufficient data to synthesize. Systematic reviews and meta-analyses are simply meant to summarize the best evidence related to the hypothesis that is being tested. Lack of primary studies does not permit one to resort to include inappropriate studies with inappropriately extracted data to synthesize the evidence. Evidence synthesized in such manner would not be of any use as they will not be the best evidence to answer the query at hand. Authors who are pooling observation studies should also pay attention to pooling estimates that are appropriately adjusted for potential confounders.

Given the importance of maintaining the design structure in extracting data for meta-analyses from primary studies, this commentary is meant to warn the evidence-based research community on an issue that is probably wide-spread, yet not well discussed in the literature.

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