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DISCUSSION FORUM
Epidemiology, prevention, and health care policies

COVID-19 vaccinations in adults and evaluation of cardiovascular events: critical methodological issues

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This commentary refers to 'Cardiovascular events following coronavirus disease 2019 vaccination in adults: a nationwide Swedish study', by Y. Xu *et al.*, https://doi.org/10.1093/eurheartj/ehae639 and the discussion piece 'Clarification on methodology used in the study investigating COVID-19 vaccination and cardiovascular events', by Y. Xu *et al.*, https://doi.org/10.1093/eurheartj/ehaf063.

Xu *et al.*[1] in their manuscript, published in the Journal, entitled 'Cardiovascular events following coronavirus disease 2019 vaccination in adults: a nationwide Swedish study' report the results of a study carried out to evaluate the risk of myocarditis after anti-COVID-19 vaccination/pericarditis, arrhythmias, heart failure, myocardial infarction, and cerebrovascular events compared to non-vaccinated COVID-19 subjects. Based on the results, they conclude that the risk of myopericarditis, extrasystole, and transient ischaemic attacks was transiently increased after COVID-19 vaccination, but that full vaccination substantially reduced the risk of several associated more severe cardiovascular outcomes to COVID-19, underlining the protective benefits of full vaccination. This could be a very interesting and beautiful result. However, to reach a definitive conclusion of this type, i.e. that the risk of cardiovascular outcomes is reduced in fully vaccinated patients compared to non-vaccinated patients, several methodological questions should be addressed.

First, in the Methods, we read that 'After Week 6, individuals were classified as exposed for that dose but outside the risk windows of interest, until they received the next dose'. This sentence leaves open a very wide and imprecise time window, so that it is difficult to rely on data on the adverse effects of vaccines in the long term, i.e. after 6 weeks (a month and a half).

Afterwards, it is stated that 'For each outcome, individuals with any prior registered record from 1 January 2015 to 26 December 2020 of that particular diagnosis were excluded'. This type of exclusion makes it impossible to evaluate the protective or adverse effects of vaccines on people already suffering from very common clinical conditions, who are a good part of the elderly in Western societies.

Another critical point is that 'Health-seeking behaviours and prior comorbidities were considered surrogates for baseline health status and access to care'. The fact that 'health-seeking behaviours' are combined with 'prior comorbidities' does not clarify whether they are healthier or sicker than others. Actually, some subjects, who turn to doctors more often, could have healthier behaviours, given that to make many visits can be understood as a behaviour. In this case, the analysis could ultimately be affected by the well-known 'healthy vaccine bias'.[2–4]

It is stated that the analysis was done by adjusting for covariates including the presence of coagulation disorders prior to vaccination. However, the authors do not report whether the possible interaction between these conditions and vaccination was tested in the model. In fact, among other things, coagulation disorders can alter the body's response to vaccination. This latter causes the production of the spike protein, which, in turn, can interact with vascular endothelia.[5]

Furthermore, two of the authors received grants from the manufacturer of the same vaccine analysed in the study.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

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