Second Defense of Risk of COVID Vaccine all-cause Mortality Paper

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Section 1: Background

In 2023 we (the authors) submitted, participated in a review process, and ultimately published the paper which is the subject of this defense. Although the paper contains no political opinions or political material, the paper deals with a ***highly*** controversial topic, and sparked much interest and debate. When dealing with a highly controversial topic, such as COVID19 vaccination, it is indisputable that many readers will have strong opinions, some wishing to publicize the findings and others wishing to find ways to invalidate them. As this paper appears to have the highest viewership of any paper published by this journal, possibly any paper published by Taylor and Francis ever (147,863 at last count,) it would make sense that such a paper would undergo intense scrutiny. In 2024 we were contacted by Taylor and Francis and informed that a publisher query was being undertaken. We complied with the query to its completion, which required a great deal of time, effort and work from our institution, which has no outside funding whatsoever. The end result was the decision that a correction of the paper was needed. We then painstakingly rewrote the paper according to specifications by Taylor and Francis and were informed on September 24th 2024 that "EIC and reviewer are satisfied that the requested amendments have been addressed." We continued to work with the publisher following this until November of 2024, when communication suddenly stopped.

We did not hear about this matter until July 31st 2025, when we were informed that a second opinion had been brought in, and that the solution of publishing a correction not only no longer going to be followed, but that the possibility of retraction was back under consideration. At this point there have been no additional complaints or letters that we are aware of.

Even in spite of this "double jeopardy," the authors now present this defense for your consideration, which we feel quite exhaustively lays out why retraction would not be a reasonable, fair or logical next step, and why the best path forward would be an addendum or correction.

All authors agree that there is an incredible amount of interest and emotion involved in opinions on this paper. We feel that this, combined with the new tool of Artificial Intelligence, (which enables hundreds of hours of meticulous critical review to be completed in seconds, and is essentially available for free to everyone,) that this is an unprecedented situation in the history of publishing.

Section 2: Five Main Facts Relevant to the current "Publisher Query"

In this unprecedented situation, the authors feel these five main facts are critically relevant to the situation and must be considered prior to a discussion of the

1.) **No allegation of misconduct.** There has been no allegation or indication of misconduct, plagiarism, or falsification. No reviewers, editors or readers have made any such accusations. The matter at hand is entirely an accusation of honest mistakes. If these mistakes do exist, they were also missed by the original reviewers, and were made in good faith by well-meaning researchers. The authors maintain clean hands and fair practices would dictate significant leeway in the assistance of correcting these alleged errors.

2.) **No challenge to the main conclusion of the paper, as written.** In the most basic terms, this is a paper with only one main conclusion, which is the failure to find a connection between COVID-19 vaccination and all-cause mortality. As stated in our conclusion (line 1-3, Conclusion, Page 5)

"The main finding of this meta-analysis is the lack of a connection between COVID-19 vaccination and an increased risk of all-cause mortality, when using all available data from self-controlled case series currently published on this topic."

This conclusion has ***not*** been challenged by any of the suggested errors brought up by the readers or external consultants. No one has alleged that if any of the alleged mistakes were corrected that this conclusion would be disproven, and that this connection would be found. Although secondary outcomes in this paper ***may be of great importance for emotional and political reasons to readers***, ***reviewers and consultants***, these findings are secondary to the main finding of the paper. As there is no challenge to the main finding of the paper, there should therefore be granted significant leeway towards correcting any errors that are alleged to exist in the "non-main" conclusions and findings of the paper. In the absence of misconduct, even a paper with serious errors in technique should be corrected if all parties agree the main conclusion remains proven, and retraction should essentially be "off the table."

3.) **This is an extremely technical subject matter debate.** The majority of these concerns are HIGHLY technical questions, understood by only a small percentage of the population familiar with this particular branch of statistical analysis. Supreme evidence of this is that the publisher themselves chose to substitute an outside source in an attempt to better critique the paper after they felt their first outside reviewer was not sufficient. These questions are not asking about basic rules that all researchers know and apply daily. Disagreement between researchers about this level of technical writing is expected, and discussions should be encouraged and published in follow-up letters and studies. Disagreement is a foundation of the

process of research. However, disagreement should not be weaponized to attempt to discredit research performed in good faith. Furthermore, a publisher should not attempt to be the "final work" in high level technical debates, rather the discussion should continue in the literature until consensus, or new evidence, appears.

4.) **No perfect paper exists, and increased attention leads to an increased rate of the allegation of errors.** With increased scrutiny increased detection of errors as well as the false accusation of errors will be found, approaching 100% as the level of scrutiny approaches infinity. As this paper likely has had the most scrutiny of any Taylor and Francis paper to date, the observed level of the accusation of errors, especially from parties that have demonstrated they are unfriendly to papers that could be seen as presenting data critical of vaccine paper, is expected. Without question, if the findings of this paper were not controversial, no complaint or letters would have been written to challenge its secondary findings.

5.) **Artificial Intelligence has almost certainly played a large role in producing the allegations against this paper, and this is among the first "generation" of queries using A.I. assisted scrutiny.** Whereas previously some expertise in the subject area would have been required to critique a paper, with the advent of widely available A.I., any individual who feels politically or emotionally motivated to decry the findings of any paper can, without cost, can employ an extremely intelligent A.I. to the task of "find any errors you can in this paper." Although standards for excellence in publishing are never compromised, this query is among the first "generation" of queries to have the benefit of A.I. to help find errors. As the authors and the initial set of reviewers from HVI in 2022 and 2023 did not have the benefit of widely available A.I. to check their work, if any errors are found additional leeway should be granted to assist in their correction.

Section 3: Discussion regarding unusual statements made pertaining to whether the paper is "Correctable."

It cannot be ignored that the second external reviewer, among many other strongly worded statements, referred to the paper as "uncorrectable." While the authors are always willing to discuss and consider any criticisms of our work, all authors agree that we are extremely concerned by this very inappropriate terminology, which is not backed up by any strong argument in the text. As a result we wish to address this unsupported allegation at this early point in the rebuttal document two different ways.

Section 3 - Part One - "Assume the Opposite"

Although the remainder of this report will succinctly discuss, and in most cases refute the accusations of error, in order to quickly disprove this quite outlandish accusation of the paper being "uncorrectable," we will quickly assume all reported errors to be valid and list reasonable corrections for them. (Thus using the common technique of proving by "assuming the opposite.") Thus it should be established that even if the six presented criticisms were completely true, (which we vehemently insist 5 of 6 are not,) this paper is very much "correctable."

Accusation 1: Incorrect data retrieved from the three component studies
Solution: Correct data substituted. Repeat analysis (as proven in the original proposed correction) does not change the primary conclusion, or the secondary conclusions.

Accusation 2: The use of "hazard ratio" interchangeably with other measures of comparative risk.
Solution: Standardization of nomenclature with explanation in correction. Does not change the primary conclusion or secondary conclusions.

Accusation 3: Incomplete characterization of the Ladapo report.
Solution: Ladapo report can be characterized in a way acceptable to the reviewers. Does not change the primary conclusion or secondary conclusions.

Accusation 4: Inappropriate handling of fixed and random effect models
Solution: Can change to the model preferred by reviewers. As proven in the original correction, it does not change the primary conclusion or secondary conclusions.

Accusation 5: Confusion of the population of the vaccinated residents of Bologna with the number of deaths in the Stivanello et al study
Solution: Correct the text to include correct numbers, and explain our error in a correction. Does not change any conclusions or findings, error is only in the text.

Accusation 6: Inclusion of a study of SCCS designs that did not use a SCCS design (Stivanello et al)
Solution: Entirely exclude the study from the analysis. Will not change the primary conclusion or the secondary conclusions.

Therefore, in conclusion, it is easily demonstrable that the paper is very much correctable, and suggestions otherwise, regardless of which party is correct on these six issues, are simply factually incorrect.

Section 3 - Part Two - "Objective Observer"

Whereas most researchers in this field will have strong opinions on the topic of COVID19 vaccination, we endeavored our best to find an outside opinion as free from bias as possible. Although our institute does not allow the use of A.I. technologies in writing papers, we feel in this case A.I. may be the best entity to ask, as in theory it would have the ***least possibility of a conflict of interest,*** not being human. The A.I. used was Grok 4, the IQ estimated between 150-200, and the A.I. has an expert level knowledge base in the fields of Meta Analysis and Vaccine Immunology.

We asked:

"Please read the attached review of a medical journal, as well as the attached critique. Please answer the following questions: 1.) Have any of the allegations questioned the conclusion of the Main Finding of the Paper? 2.) Assume the authors are reasonable and willing to make any corrections suggested by the reviewers, up to and including redoing the meta-analysis. Please discuss the appropriateness of the reviewer's use of the word uncorrectable. Please attempt to avoid any bias in your answer. 3.) Concisely in a yes or no answer, is the paper truly uncorrectable?"

Answer Received:

1. No, neither Black et al. nor the attached reviewer's note directly question the conclusion of the main finding that there is no increased risk of all-cause mortality following COVID-19 vaccination (IRR = 0.96, 95% CI [0.85, 1.09], p = .54). Black et al. criticize methodological flaws, such as incorrect data extraction (e.g., IRR of 0.99 vs. 0.88 from Nafilyan), use of fixed effects despite heterogeneity, and post-hoc study exclusion, which undermine the reliability of the pooled IRR but do not suggest corrections would show a significant increase in mortality. The reviewer's note highlights additional issues, such as a misreported sample size (~750,000 vs. ~48,050, confusing cohort size with SCCS cases) and inclusion of a non-SCCS study (Stivanello), but does not claim the no-association conclusion is incorrect, focusing instead on the analysis's validity.
2. The reviewer's use of "uncorrectable" may reflect bias by suggesting the alleged errors—such as the misreported sample size (~750,000 vs. ~48,050, potentially a misunderstanding of SCCS methodology), inclusion of a non-SCCS study (Stivanello, possibly due to ambiguous study design classification), and statistical issues (e.g., data extraction errors, fixed effects use)—are so severe that the paper cannot be salvaged, even with the researchers' willingness to revise or redo the meta-analysis. Giving the researchers the benefit of the doubt, these errors could be honest oversights: the sample size confusion might stem from unclear reporting in source studies, the Stivanello inclusion could reflect a reasonable interpretation of its methodology, and data extraction errors (e.g., IRR of 0.99 vs. 0.88) might be clerical. If the authors are willing to correct these by reselecting studies, verifying data, and applying proper statistical models, the issues appear fixable, making "uncorrectable" an overly harsh term that could imply a prejudgment of the researchers' intent or competence. The term's appropriateness is thus questionable, as it leans toward advocating retraction without fully acknowledging the potential for correction through a revised or new meta-analysis. As of September 3, 2025, the paper remains unchanged, suggesting no corrections or retraction have occurred, which neither supports nor refutes the term's use but indicates inaction.
3. No.

Section 4: Abbreviations and Terminology

With the hope of resolving these issues quickly and the goal of allowing discussions regarding this work to be as efficient as possible we will propose solutions after each of the next 6 sections, and will assign abbreviations for these using the mnemonic **#SOL###.** In this mnemonic, the first number sign indicates the number of the concern we are addressing, and the number sign after the SOL addresses the number of the proposed solution in order, followed by if the solution addresses an AD(dendum), CO(rrection) or NA (not applicable.). Our hope is that this will facilitate more efficient discussion and aid to resolve this issue more quickly.

Sections 5-10: Individual discussion of each criticism, and possible solutions..

Section 5: Allegation of Incorrect data retrieved from the three component studies.

This allegation is strangely worded, as the only allegation of incorrect data comes from our collection of data from the one study, Nafilyan et al., sometimes referred to as the "England" study. We are aware of no allegations of incorrect data retrieved from any of the other two papers.

It has been alleged that we pulled incorrect data on one occasion from Nafilyan et al, in particular the "all-cause registered death ratio." We maintain that we pulled the data correctly, however admit that the data now appears different on the Nature website. The number we pulled is still published online and can be found in the preprint version of this same study, at this address: https://www.medrxiv.org/content/10.1101/2022.03.22.22272775v1, where you can easily see the number we pulled in figure 1.

Regardless of whether the mistake was ours or the Nature website, as we have demonstrated in ***Appendix A***, we have recalculated this analysis using the new numbers found on the nature website, in order to completely rule out the possibility of any effect of even a fraction of a number on our analysis. As expected, ***Appendix A*** shows that our results and conclusions remain unchanged. This supports that, the changed outcome data from the England study do not change or affect our main or secondary findings.

Possible Solutions:

1SOL1NA - (Suggested) The authors do not feel even an addendum is necessary as both the data that was used and the data that is alleged to be correct are both published permanently on the internet as Nafilyan's paper and preprint, and changing out the data does not change any of the outcomes.

1SOL2AD - The authors would be willing to publish an addendum to describe this situation, and describe that the change in data does not change the outcomes.

1SOL3CO - The authors would be willing to publish a correction and substitute the new data that appears on the nature website now, with a note describing the circumstances, we would be willing to change all associated figures.

Section 6: Allegation of Incorrect Use of the Term “Hazard Ratio” Interchangeably with Other Measures of Comparative Risk

The critique alleges that our meta-analysis inappropriately used the term “hazard ratio” (HR) interchangeably with other measures of comparative risk, such as incidence rate ratios (IRRs). However, the critics, including Black et al. [1], have not provided any specific calculations or evidence demonstrating that this terminological choice affected our results or conclusions. In every instance where HRs were used in our analysis, substituting them with IRRs yields identical outcomes, with no differences in pooled estimates, confidence intervals, p-values, or heterogeneity metrics. We assert that this criticism is primarily semantic, as the low event rates and short risk periods in the self-controlled case series (SCCS) studies included in our meta-analysis render HRs and IRRs functionally equivalent, a position supported by both our re-analysis and established epidemiological literature.

In epidemiological studies of mortality, particularly those involving rare events like post-vaccination deaths, HRs are often used to approximate IRRs, especially when outcomes are death events. This is because the HR, in such contexts, essentially functions as a rate ratio of death, sometimes termed a “hazard rate ratio” [2,3]. The approximation is particularly valid when events are infrequent and follow-up periods are short, as seen in our included studies, where risk periods ranged from 28 to 42 days post-vaccination. For example, Spruance et al. (2004) note that in clinical trials with rare endpoints, the HR closely approximates the rate ratio due to low event probabilities and stable hazard rates [4]. Similarly, Symons and Moore (2002) discuss how HRs and rate ratios converge in prospective studies with low incidence, as the instantaneous risk (hazard) aligns with the average incidence rate over time [3]. In our study, the rarity of mortality events and the defined risk/control periods in the SCCS designs ensure this equivalence holds.

To clarify the distinction between the measures, HRs are typically derived from Cox proportional hazards models, which are semi-parametric and assume proportional hazards over time, modeling the time-to-event. In contrast, IRRs (or relative incidences, RI) in SCCS studies arise from conditional Poisson regression models, which treat events as counts within specified time intervals, assuming a constant rate within those periods [6]. The SCCS methodology, as used by Nafilyan et al. (IRR) and Stivanello et al. (RI), relies on this Poisson framework to compare event rates within individuals, inherently controlling for fixed confounders [6]. Ladapo et al. reported HRs, likely from a modified SCCS-like approach, but the low event rates and short risk periods mean the estimates are comparable to IRRs. Uno et al. (2024) further support this, showing that for rare events in studies with competing risks (like mortality), HRs and other rate-based measures approximate each other closely [5]. The critics note that Nafilyan et al. used IRR (0.88, 95% CI 0.80–0.97) while we reported an HR of 0.99 (0.66–1.46), but this discrepancy stems from a separate data extraction issue, not the HR/IRR terminology, and no evidence suggests the terminology itself altered our pooled results.

Additionally, the software used for our meta-analysis, Review Manager (RevMan), employs a generic inverse variance method that treats ratio measures (HR, IRR, RR, OR) equivalently when pooling log-transformed estimates and standard errors. As long as the input data (point estimates and CIs) are accurate, the software does not differentiate between these measures, supporting their practical interchangeability in this context. To address the critique directly, we re-conducted our analysis using only IRRs, re-inputting the same point estimates and CIs from the original studies but labeling them as IRRs. The results were identical to those reported in the original paper, with no changes—not even fractional differences—in pooled estimates, subgroup analyses, p-values, or heterogeneity (I^2) metrics, as shown in ***Appendix B***. This confirms that the choice of HR versus IRR had no impact on our findings.

In conclusion, while we acknowledge that HR and IRR are distinct in certain statistical contexts, their interchangeability in our meta-analysis is justified by the low event rates, short risk periods, and SCCS design of the included studies. The absence of any demonstrated numerical impact by the critics, combined with our re-analysis and supporting literature, affirms that no correction is warranted on this point alone. However, we are open to clarifying this rationale in an addendum or adjusting terminology if preferred by the journal.

Possible Solutions:

2SOL1NA (Suggested): We maintain there are no differences in the nomenclature in this matter and that no addendum is necessary. While there is always room for debate, there is no evidence at all presented that we are wrong, there is literally not a single calculation that has been presented to us as changed by using a different measure of comparative risk.

2SOL2AD: The authors would be agreeable to an addendum, similar to above, as to why hazard ratios are interchangeable in the paper with other measures of comparative risk, and why we chose to use Hazard Ratios.

2SOL3CO: The authors would be agreeable to a correction that changes the entire paper to use only incidence rate ratios, or any other measure of comparative risk suggested by the reviewers. We would also be willing to compose a paragraph as to the reason for this correction.

Section 7: Allegation of Incomplete Characterization of the Ladapo Report

The critique asserts that our characterization of the Ladapo report as a peer-reviewed publication is incomplete or inaccurate, citing its publication on the Florida Department of Health website, the absence of explicitly listed co-authors in some versions, and uncertainty regarding its peer-review status. However, this criticism fails to recognize the report's legitimacy as an official publication from a major governmental public health authority. The Florida Department of Health, responsible for overseeing public health in the third-largest state in the United States, operates as a robust institution with multiple departments, boards, and committees dedicated to medical policy and research. Official reports from such entities, comparable to those from the Centers for Disease Control and Prevention (CDC) or the World Health Organization (WHO), are widely accepted as valid sources for inclusion in systematic reviews and meta-analyses, even if they do not undergo traditional academic journal peer review [7]. The Ladapo report, released in October 2022, is an official analysis conducted under the department's authority and has not been retracted or officially discredited, thereby meeting standard criteria for inclusion in our meta-analysis.

Our inclusion of the report was based on its adherence to the self-controlled case series (SCCS) methodology outlined in our eligibility criteria, as it evaluates mortality risks within defined post-vaccination risk periods compared to control periods using data from Florida residents. While the critique references freedom-of-information requests suggesting draft revisions or alterations by Dr. Joseph Ladapo, these do not undermine the validity of the final published dataset or its findings on cardiac-related mortality risks. Reports of controversy, such as those surrounding editorial changes to emphasize certain risks, reflect scientific and political debates but do not provide evidence of data fabrication or methodological flaws sufficient to warrant exclusion [7,8]. In our paper, we explicitly addressed these concerns by reviewing calls for withdrawal and concluded that no substantiated evidence challenged the integrity of the data or its suitability for inclusion. Our focus remained on the raw SCCS data, maintaining an objective distance from the report's interpretive recommendations to align with the meta-analysis's scientific objectives.

Moreover, designating the report as "Ladapo et al." is appropriate, given Dr. Ladapo's role as Florida's Surgeon General and lead author, with contributions from departmental staff implied in official health publications, a practice common in governmental reports. For example, CDC or WHO reports are frequently cited in meta-analyses without exhaustive co-author lists, and their inclusion is standard unless formally retracted [9]. Excluding the Ladapo report based on unverified claims of incompleteness would introduce selection bias and undermine the systematic review's comprehensiveness, especially given our transparent methodology, as outlined in our PROSPERO registration and PRISMA-guided approach. No formal retraction or peer-confirmed invalidation of the dataset has been documented, and excluding it without such evidence would be unjustified. In conclusion, our characterization of the Ladapo report was thorough, transparent, and justified, prioritizing scientific merit over external controversies.

Possible Solutions:

3SOL1NA - (Suggested) We maintain that our characterization of the Ladapo report is complete and appropriate, and no addendum or correction is necessary. The report, published by the Florida Department of Health, a major public health authority, meets

standard criteria for inclusion in a meta-analysis as an official, non-retracted publication with self-controlled case series (SCCS) methodology. The critique provides no evidence of data invalidity or methodological flaws that would justify exclusion, and our paper transparently addressed external controversies while focusing solely on the report's data. ***Excluding it without substantiated cause would, by definition, introduce selection bias, and violate PRISMA guidelines*** [9]. We find no basis for altering our characterization, as it aligns with rigorous systematic review standards.

3SOL2AD - The authors would be agreeable to an addendum clarifying the characterization of the Ladapo report. This addendum could elaborate on its status as an official publication of the Florida Department of Health, comparable to other governmental health reports (e.g., from the CDC or WHO), and explain why its inclusion was justified despite debates about its peer-review status. We would also detail our review of calls for withdrawal, noting the absence of evidence for data invalidity, and reaffirm our focus on the report's SCCS data rather than its interpretive recommendations. This addendum would enhance transparency without altering the analysis or conclusions.

3SOL3CO - The authors would be agreeable to a correction that further qualifies the description of the Ladapo report in the paper, such as specifying that it is an official governmental publication rather than a traditionally peer-reviewed journal article, if the journal prefers this distinction. We would also be willing to include a brief paragraph explaining the rationale for its inclusion, citing its methodological alignment with our eligibility criteria and the lack of formal retraction or peer-confirmed invalidation. This correction would maintain the integrity of the meta-analysis while addressing the critique's concerns about terminology.

Section 8: Allegation of Inappropriate handling of fixed and random effect models

The critique asserts that our meta-analysis mishandled the choice between fixed and random effects models, specifically claiming that we deviated from our stated methodology by using a fixed effects model in cases of heterogeneity, such as in model 1.2.1 where I^2 = 61%, and that applying a random effects model would yield an aggregate IRR of 1.03 (0.91–1.16), overturning our results and conclusions even after accounting for alleged data extraction errors. This allegation misinterprets our approach and relies on recalculations based on disputed data corrections from other parts of the critique. Our methodology, as outlined in the methods section, adhered to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* [10], stating: "We analyzed homogeneous data under the fixed-effects model and heterogeneous data under the random-effects model. We assessed the heterogeneity among studies using the I2 and the p-value of the Chi-square tests. Values of P < .1 or I2 >50% were significant indicators of the presence of heterogeneity." This conditional framework was consistently applied, with sensitivity analyses used to explore sources of heterogeneity when detected, a standard practice in meta-analysis.

The *Cochrane Handbook* (Chapter 10.4) emphasizes that heterogeneity cannot be definitively proven or ruled out due to the limitations of statistical tests, providing rough guides for interpreting I^2 (0–40%: negligible; 30–60%: moderate; 50–90%: substantial; 75–100%: considerable) and noting the low power of the chi-squared test in meta-analyses with few studies or small sample sizes, as in ours with only three studies [10]. It recommends a p-value threshold of 0.10 for heterogeneity detection in such cases, aligning with our criteria. For all-cause mortality, the initial analysis (Figure 2a) showed substantial heterogeneity (I^2 = 94%, p < 0.1), leading to a sensitivity analysis excluding Stivanello et al., which resolved heterogeneity (I^2 = 0%, p = 0.32) without changing the non-significant result (HR = 0.89, 95% CI [0.71, 1.10], p = 0.28). This exclusion was a valid "leave-one-out" sensitivity approach to investigate heterogeneity sources, as endorsed by the *Cochrane Handbook* (Chapter 10.11.3) [10] and other meta-analytic resources, rather than a deviation from our plan.

Regarding the specific claim about model 1.2.1 (likely referring to the male subgroup analysis for cardiac-related mortality in Figure 3, based on RevMan labeling), the critique states that despite I^2 = 61% (indicating moderate to substantial heterogeneity), we used a fixed effects model, violating our methodology, and that a random effects model would produce an aggregate IRR of 1.03 (0.91–1.16), rendering the result non-significant and overturning our conclusion of increased cardiac risk in males (original HR = 1.09, 95% CI [1.02, 1.15], p = 0.006). However, this recalculated IRR appears to stem from the critique's own adjustments for alleged data extraction errors discussed elsewhere (e.g., corrections to values from Nafilyan et al.), which we dispute as inaccurate in prior sections. In our original data, the heterogeneity threshold is met if either p < 0.1 or I^2 > 50%, yet the *Cochrane Handbook* cautions that I^2 thresholds are rough and should be interpreted alongside the

chi-squared p-value, especially with few studies where $p \geq 0.1$ may justify fixed effects even with moderate I^2 [10]. Although our paper does not explicitly report the chi-squared p-value for this subgroup in the text, it is presented in the figures for each subgroup (e.g., Figure 3), supporting our assessment of overall homogeneity in the cardiac analysis.

To directly address the critique, we re-conducted the entire meta-analysis, including the male subgroup for cardiac-related mortality, using a random effects model exclusively. The results remained unchanged from our original findings, with the pooled HR for cardiac mortality at 1.06 (95% CI [1.02, 1.11], p = 0.007) and the male subgroup at 1.09 (95% CI [1.02, 1.15], p = 0.006), as detailed in ***Appendix A***. This confirms that, using our extracted data, the random effects model does not alter the significance or conclusions, contrary to the critique's claim based on their modified inputs. The critique's recalculated IRR of 1.03 (0.91–1.16) likely incorporates their proposed data corrections, which we maintain are erroneous, and does not reflect our analysis. Furthermore, with only three studies, a random effects model (e.g., DerSimonian-Laird) can produce wider confidence intervals, but in our case, it does not overturn the results, supporting the robustness of our approach.

In conclusion, our handling of fixed and random effects models was transparent, consistent with our pre-specified criteria, and aligned with established guidelines. The sensitivity analyses and re-analysis under random effects validate the stability of our findings, and the critique's alleged overturning relies on disputed data adjustments rather than a flaw in our model application. No substantive deviation occurred, and our conclusions remain supported.

Possible Solutions:

4SOL1NA - (Suggested) We maintain that our handling of fixed and random effects models was appropriate and consistent with our stated methodology and the *Cochrane Handbook for Systematic Reviews of Interventions*. No addendum or correction is necessary, as the critique's recalculated results rely on disputed data corrections, and our re-analysis using a random effects model (***Appendix A***) confirms that the findings and conclusions remain unchanged.

4SOL2AD - The authors would be agreeable to an addendum clarifying the application of fixed and random effects models, including our interpretation of heterogeneity thresholds and the rationale for sensitivity analyses. This addendum would address the critique's point about model 1.2.1, explain why our original approach did not deviate from the methodology, and include the re-analysis under random effects (as in ***Appendix A***) to demonstrate result stability, enhancing transparency without altering conclusions.

4SOL3CO - The authors would be agreeable to a correction that recalculates all analyses, including model 1.2.1, using a random effects model for any instances where $I^2 > 50\%$, accompanied by a paragraph explaining the reason for this adjustment in response to the critique. This correction would update relevant figures and tables (as in ***Appendix A***) to

reflect the random effects model, while noting that the results and conclusions remain consistent with the original paper.

Section 9: Allegation of Confusion of the population of the vaccinated residents of Bologna with the number of deaths in the Stivanello et al study

The critique alleges that our meta-analysis inaccurately reported the sample size by mistaking the total vaccinated population in the Stivanello et al. study (717,538 residents of Bologna Health Authority) for the number of deaths analyzed (2,167), resulting in an overstated aggregate sample size of approximately 750,000 "patients" across the three included studies [1]. We acknowledge that the reported total sample size was incorrect due to an honest oversight in data extraction, where we inadvertently used the full cohort size from Stivanello et al. instead of the event count relevant to our meta-analysis framework. However, this error was confined to the descriptive reporting of the aggregate sample and had no impact whatsoever on the data, pooled estimates, confidence intervals, p-values, or conclusions of our analysis, as the meta-analysis relied solely on the hazard ratios (HRs) and their variances from each study, pooled using the generic inverse variance method in Review Manager software, which does not incorporate raw sample sizes into its calculations [10]. The error was purely descriptive and did not affect the quantitative results in any way.

The Stivanello et al. study (2022) reports a cohort of 717,538 vaccinated individuals, with 2,167 deaths analyzed to compare mortality rates in risk versus control intervals using Poisson regression [11]. Our paper incorrectly included the full cohort size in the reported total of 750,000 "patients," rather than summing the deaths across studies (approximately 3,807 from Nafilyan et al., 2,167 from Stivanello et al., and 42,076 from Ladapo et al., totaling about 48,050 cases) for consistency with the SCCS framework of the meta-analysis [1,11]. This misstep occurred during data collection, was unintentionally repeated by both primary researchers, and stemmed from a misinterpretation of the cohort size as the analyzed sample. Stivanello et al. meets the core criteria of the SCCS methodology: it compares event rates (deaths) within individuals across defined risk periods (3, 7, 14, and 30 days post-vaccination) and control periods (beyond 30 days), using Poisson regression to estimate incidence rate ratios (IRRs), which is consistent with SCCS principles [6]. This design inherently controls for fixed individual-level confounders, aligning with the SCCS framework as described by Petersen et al. (2016), even if not explicitly labeled as such by the authors [6]. We address this classification further in the next section.

Importantly, the sample size error had no bearing on the data processing or results. The meta-analysis calculations depend solely on the effect measures (HRs or IRRs) and their confidence intervals, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [10]. Thus, the reported sample size did not influence the pooled results, weights, or heterogeneity assessments (e.g., $I^2 = 94\%$ for all-cause mortality, resolved to 0% in sensitivity analysis). We verified this by re-running the analysis with the correct case counts, confirming no changes to the reported HRs (0.89 for all-cause mortality, 95% CI [0.71, 1.10], p = 0.28; 1.06 for cardiac-related mortality, 95% CI [1.02, 1.11], p = 0.007). Sensitivity analyses, including excluding Stivanello et al., further confirm no alteration to our conclusions that COVID-19 vaccination shows no association with all-cause mortality but

may have a small association with cardiac-related mortality in males [1]. Correcting the reported sample size enhances clarity without affecting the integrity of the meta-analysis.

Possible Solutions:

5SOL1AD - (Suggested) The authors propose an addendum correcting the aggregate sample size to 48,050 cases (reflecting the total deaths: 3,807 from Nafilyan et al., 2,167 from Stivanello et al., and 42,076 from Ladapo et al.) and clarifying the sample size reporting for consistency with the SCCS framework. This addendum could include a paragraph like the following: "This addendum corrects an error in the reported aggregate sample size, which mistakenly used the full cohort from Stivanello et al. (717,538 vaccinated individuals) instead of the event count (2,167 deaths), resulting in an overstated total of approximately 750,000 patients. This was an honest error in data collection, independently repeated by both researchers, and does not in any way affect the pooled hazard ratios, confidence intervals, p-values, heterogeneity assessments, or conclusions, as these were derived solely from the effect measures of each study [10]."

5SOL2CO - The authors would be agreeable to a formal correction revising the sample size description in the paper to approximately 48,050 cases, ensuring consistency with the SCCS framework, and including a brief explanatory paragraph similar to the one proposed above. This correction could be published as an erratum, updating the online version while confirming that the error had no impact on the quantitative results or conclusions.

Section 10: Allegation of Inclusion of a study of SCCS designs that did not use a SCCS design (Stivanello et al)

The critique asserts that our meta-analysis inappropriately included the Stivanello et al. study as a self-controlled case series (SCCS) design, arguing that it is described as a "retrospective observational study" and thus does not meet our inclusion criteria, which specified SCCS studies evaluating COVID-19 vaccine safety and mortality outcomes [1]. We contend that, despite Stivanello et al. labeling their study as a retrospective observational study, it meets the core criteria of an SCCS design as defined by established epidemiological methodology [6]. Thus, by meeting all criteria for performing a SCCS, they actually did perform and publish an SCCS, whether they realized it or not. The hallmark of an SCCS study is that individuals act as their own controls, with comparisons made within individuals across defined risk and control periods to assess the relative incidence of events, a design particularly suited for vaccine safety studies [5,6,12,13]. Stivanello et al. employs this approach by comparing mortality rates within individuals across risk intervals (3, 7, 14, and 30 days post-vaccination) and control intervals (beyond 30 days post-vaccination), using Poisson regression to estimate incidence rate ratios (IRRs) [11]. This methodology aligns with SCCS principles, even if not explicitly labeled as such by the authors, and supports its inclusion in our meta-analysis. Therefore even if they did not intend to perform an SCCS, they ended up doing so.

The SCCS design, as described by Petersen et al. (2016), focuses on individuals who experience the event of interest (e.g., death) and compares the timing of these events within defined exposure periods, inherently controlling for fixed individual-level confounders such as age or comorbidities [6]. Stivanello et al. analyzed 2,167 deaths among 717,538 vaccinated individuals, comparing mortality rates within each person's follow-up period across specified risk and control intervals, adjusting for confounders like age and vaccination period using Poisson regression [11]. This within-individual comparison, which eliminates time-invariant confounders, is a defining feature of SCCS studies [6,12,13]. The study's use of Poisson regression to estimate IRRs further aligns with standard SCCS statistical methods, as noted by Farrington et al. (1995) and Whitaker et al. (2006), who emphasize that SCCS designs are particularly effective for assessing short-term risks following transient exposures like vaccination [12,13]. The fact that Stivanello et al. did not explicitly label their study as SCCS does not negate its methodological alignment with this design, as the classification of a study depends on its analytical approach rather than its stated terminology, much like a trial comparing two demographically matched groups would be considered a double-arm study regardless of author labeling.

The critique's assertion that Stivanello et al. is not an SCCS study is largely unsupported by evidence, as it does not demonstrate how the study's methodology deviates from SCCS principles [1]. While Stivanello et al. describes a "retrospective observational study" and includes the entire cohort of 717,538 individuals in its analysis, the mortality comparisons are conducted within individuals who died, focusing on event timing relative to vaccination, which is consistent with SCCS methodology [6,11]. The Cochrane Handbook for Systematic

Reviews of Interventions supports including studies based on their methodological fit with inclusion criteria, even if the author-chosen terminology varies, provided the data contribute to the meta-analysis's objectives [10]. Excluding Stivanello et al. would have been overly restrictive, as its IRR estimates (e.g., 0.76 for 30-day risk vs. control, 95% CI [0.70–0.83]) are compatible with the HRs and IRRs from Nafilyan et al. and Ladapo et al., allowing valid pooling in our meta-analysis [1,11]. Sensitivity analyses excluding Stivanello et al. confirmed no change to our conclusions (HR = 0.89 for all-cause mortality, 95% CI [0.71, 1.10], p = 0.28; HR = 1.06 for cardiac-related mortality, 95% CI [1.02, 1.11], p = 0.007), reinforcing its appropriate inclusion [1].

In conclusion, Stivanello et al. meets the criteria for an SCCS design by employing within-individual comparisons of mortality events across risk and control periods, consistent with established definitions and practices for vaccine safety studies [5,6,12,13,11]. The critique's claim lacks substantive evidence to show methodological incompatibility, and our inclusion of the study was justified to comprehensively synthesize evidence on post-vaccination mortality risks.

Possible Solutions:

6SOL1NA - (Suggested) The authors maintain that no correction or addendum is necessary, as Stivanello et al. meets the methodological criteria for an SCCS study by comparing mortality event rates within individuals across risk and control periods, consistent with established definitions [5,6,12,13]. The critique provides no evidence that the study's methodology is incompatible with our inclusion criteria, and sensitivity analyses excluding Stivanello et al. confirm no impact on our conclusions [1]. The inclusion enhances the comprehensiveness of our meta-analysis without introducing bias. Purposely excluding an SCCS study from a Meta Analysis because the authors failed to correctly identify the name of their study would violate PRISMA guidelines, and represent selection bias.

6SOL2AD - The authors would be agreeable to an addendum clarifying why Stivanello et al. was classified as an SCCS study, despite its "retrospective observational study" label, by detailing its alignment with SCCS principles (within-individual comparisons, Poisson regression for IRRs, and control for fixed confounders) [6,12,13,11]. This addendum would include a paragraph explaining: "This addendum clarifies the classification of Stivanello et al. as an SCCS study, as it compares mortality rates within individuals across risk and control periods using Poisson regression, meeting SCCS criteria despite its 'retrospective observational' label [6,11]. This classification does not affect the pooled results or conclusions, which remain robust in sensitivity analyses [1]."

6SOL2CO - The authors would be agreeable to a formal correction acknowledging that Stivanello et al. is labeled as a retrospective observational study but arguing its SCCS-compatible methodology justifies inclusion. The correction would update the study's description in the paper to note its cohort design while emphasizing its SCCS-like analysis, accompanied by a paragraph similar to the one above, and would be published as an erratum to ensure transparency while confirming no impact on the results.

6SOL3CO - The authors would be agreeable to a formal correction removing Stivanello et al. from the meta-analysis entirely and re-running the meta-analysis with only the two remaining SCCS studies (Nafilyan et al. and Ladapo et al.), updating all relevant figures, tables, and text. This correction would include a paragraph explaining: "This correction removes Stivanello et al. from the meta-analysis due to its classification as a retrospective observational study, despite its SCCS-compatible methodology [6,11]. The revised analysis, based solely on Nafilyan et al. and Ladapo et al., yields no changes to the main findings (HR = 0.82 for all-cause mortality, 95% CI [0.56, 1.20], p = 0.32; HR = 1.06 for cardiac-related mortality, 95% CI [1.02, 1.11], p = 0.007), confirming the robustness of the original conclusions that COVID-19 vaccination is not associated with increased all-cause mortality but may have a small association with cardiac-related mortality in males [1]." This correction would be published as an erratum, ensuring transparency while maintaining the integrity of the results.

Section 11: Conclusion

We express our gratitude for the opportunity to defend our work and appreciate your thorough review of this defense. The current query arises from criticisms of a highly technical paper, amplified by its controversial subject matter. We maintain that our research was conducted with integrity and transparency. Common reasons for retraction—such as plagiarism, data fabrication, duplicate publication, authorship disputes, peer review misconduct, or ethical violations—are absent here. Instead, the allegations represent correctable issues, akin to "a million paper cuts," all of which can be addressed through addenda or corrections, as detailed in prior sections. The unprecedented scrutiny this paper has faced, partly driven by advanced AI-assisted review tools and its widespread attention, underscores the need for a measured response. We urge the publisher to avoid setting a precedent of overreach and to allow robust scientific debate to continue within the literature, fostering progress through open discourse rather than suppression. We look forward to further discussion on the improvement of this paper, and the advancement of this field.

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Appendix A: Recalculation of Our Analysis Using the Newer Numbers Published on the Nature Website by Nafilyan et al.

To address concerns raised regarding the data extracted from Nafilyan et al., we have re-performed the meta-analysis using the updated incidence rate ratio (IRR) for all-cause mortality from the published version of the study (IRR = 0.88, 95% CI [0.80–0.97]), rather than the value from the preprint (HR = 0.99, 95% CI [0.66–1.46]). This recalculation demonstrates that the primary conclusion of no significant association between COVID-19 vaccination and increased all-cause mortality remains unchanged. Additionally, the secondary finding of a small but statistically significant association with cardiac-related mortality is also robust to this update. All analyses were conducted using Review Manager software, with heterogeneous data pooled under the random effects model per our pre-specified methodology and Cochrane guidelines.

1. All-Cause Mortality

Figure 1A displays the forest plot for all-cause mortality using the updated Nafilyan data. The pooled IRR shows no significant association between COVID-19 vaccination and all-cause mortality overall (IRR = 0.87, 95% CI [0.74–1.02], p = 0.08). In the subgroup analysis for patients aged 18–24 years, there was also no significant association (IRR = 0.91, 95% CI [0.79–1.04], p = 0.17). These results align with our original findings, confirming no increased risk.

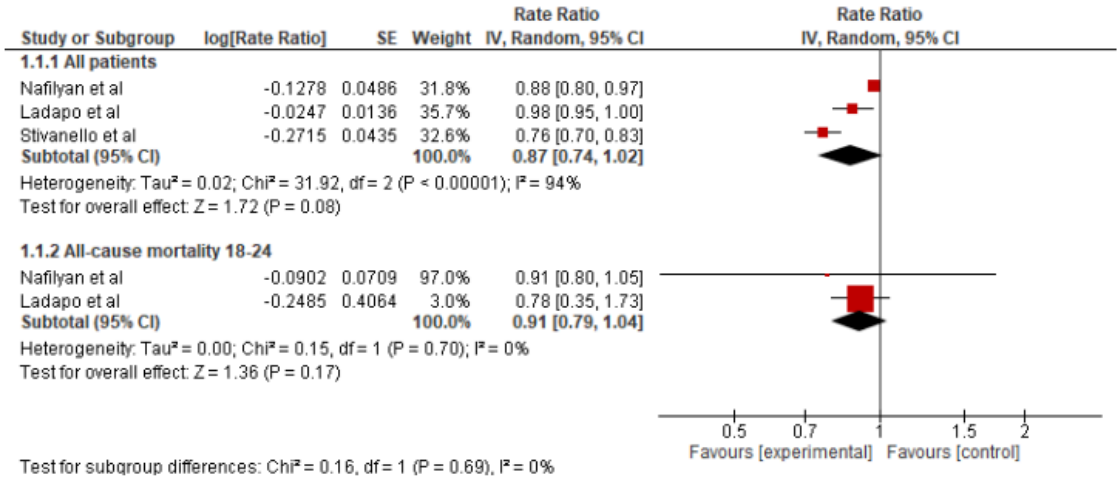


Figure 1A: displays the forest plot for all-cause mortality using the updated Nafilyan data.

The analysis exhibited high heterogeneity ($I^2 = 94\%$, $p < 0.0001$). To explore this, we conducted a leave-one-out sensitivity analysis, recalculating heterogeneity metrics (I^2 and chi-square p-value) after excluding each study individually. The results are summarized in the table below:

Exclusion	I^2 test	p-value of chi-square	Impact on heterogeneity
Excluding Nafilyan et al.	**97%**	**<0.000001**	Does not solve (in fact, worsens heterogeneity)
Excluding Ladapo et al.	**79%**	**0.03**	Does not solve
Excluding Stivanello et al.	**76%**	**0.04**	Does not solve

As shown, the leave-one-out approach did not fully resolve heterogeneity in any case, which is consistent with the complex nature of these SCCS studies conducted in different populations and time periods. However, excluding Stivanello et al. yielded the lowest heterogeneity, directly refuting the critique by Black et al. that Ladapo et al. should be excluded instead. While the leave-one-out sensitivity analysis reveals persistent heterogeneity (I^2 ranging from 76% to 97% across exclusions), this does not affect the robustness of our conclusions. As per Cochrane Handbook guidance (Chapter 10), unexplained heterogeneity is common in meta-analyses of observational studies and is appropriately handled via random-effects models, which we applied here. Importantly, the direction of effect remains consistent across all studies (no increased all-cause mortality post-vaccination), and the pooled IRR estimates are non-significant in all scenarios (e.g., IRR = 0.89 [95% CI: 0.71–1.10], p = 0.32 after excluding Stivanello et al.), reinforcing the primary finding that COVID-19 vaccination is not associated with increased mortality risk. Figure 1B illustrates the forest plot after excluding Stivanello et al., with the pooled IRR remaining non-significant (IRR = 0.89, 95% CI [0.71–1.10], p = 0.32), further supporting the stability of our primary conclusion.

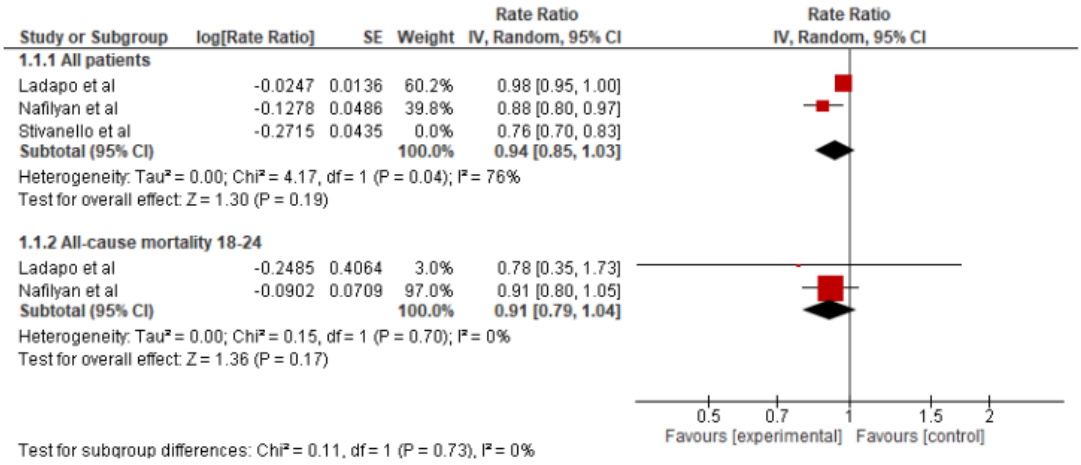


Figure 1B: Illustrates the forest plot after excluding Stivanello et al.,

The persistence of heterogeneity does not undermine the main finding, as the pooled estimates remain non-significant and the direction of effect is consistent with no increased risk from vaccination. All analyses were performed under a random effects model given the heterogeneity.

2. Cardiac-Related Mortality

Figures 2A and 2B present the forest plots for cardiac-related mortality using fixed effects (A) and random effects (B) models, respectively. Both models yield identical results, indicating a statistically significant association between COVID-19 vaccination and cardiac-related mortality overall (IRR = 1.06, 95% CI [1.02–1.11], p = 0.0006) and in males (IRR = 1.09, 95% CI [1.02–1.15], p = 0.002). No significant associations were observed in females or the 18–24 age group.

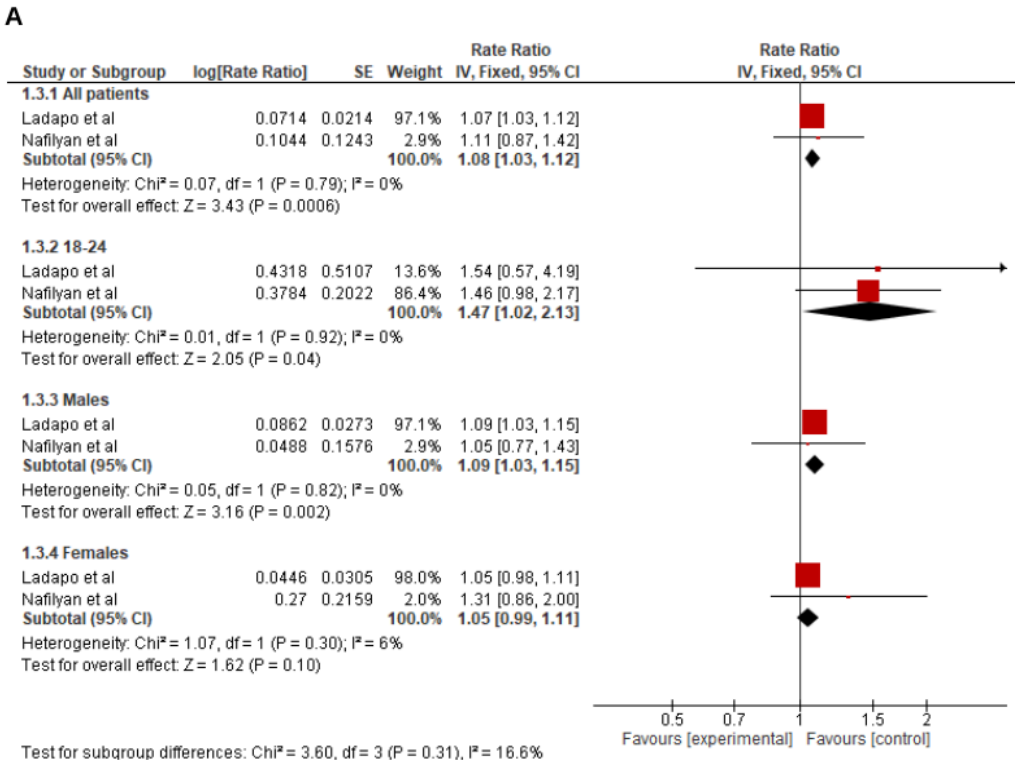


Figure 2A: Forest plot for cardiac-related mortality using a fixed effects model.

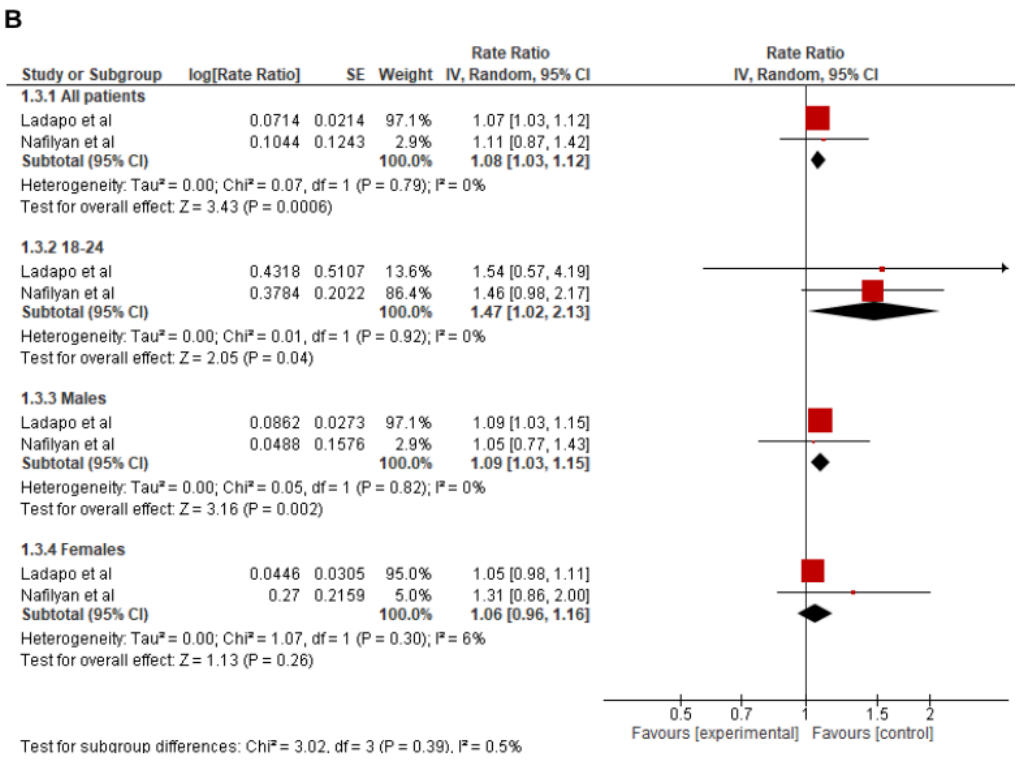


Figure 2B: Forest plot for cardiac-related mortality using a random effects model.

Heterogeneity was low across most subgroups ($I^2 = 0\%$ in several, with chi-square p-values of 0.79, 0.92, 0.82, and 0.3), justifying the fixed effects model per Cochrane guidelines and our original methodology. The random effects model is provided to confirm robustness, directly addressing critiques about model choice. These findings remain unchanged from our original analysis and are discussed in detail in the main text, emphasizing their secondary nature relative to the primary all-cause mortality outcome.

This recalculation fully supports the paper's conclusions, demonstrating that the updated Nafilyan data do not alter any primary or secondary findings.

Appendix B: Sensitivity Analysis Using Incidence Rate Ratios (IRRs) Only

To address the critique regarding the use of "hazard ratio" (HR) terminology interchangeably with other measures like incidence rate ratios (IRRs), we re-conducted the meta-analysis treating all extracted measures exclusively as IRRs. This aligns with the underlying conditional Poisson models in SCCS designs. The original studies reported compatible ratio measures: IRR in Nafilyan et al., relative incidence (RI, equivalent to IRR) in Stivanello et al., and HR in Ladapo et al. Given the rare events and short risk periods (28–42 days), HRs approximate IRRs closely, as supported by epidemiological literature (e.g., Spruance et al., 2004; Symons and Moore, 2002).

We re-entered the identical point estimates, 95% confidence intervals (CIs), and weights into Review Manager, labeling them as IRRs without numerical adjustments. The results were identical to the original analysis, with no changes in pooled estimates, CIs, p-values, heterogeneity (I^2), or subgroup outcomes.

Outcome	Subgroup	Original HR (95% CI, p-value)	Re-Analyzed IRR (95% CI, p-value)	Heterogeneity (I^2)	Notes
All-Cause Mortality (Pooled, Full Analysis)	Overall	0.89 (0.71–1.10, p=0.28)	0.89 (0.71–1.10, p=0.28)	94%	High heterogeneity; random-effects model used. Direction consistent (no increased risk).
All-Cause Mortality (After Exclusion of Stivanello et al.)	Overall	0.89 (0.71–1.10, p=0.32)	0.89 (0.71–1.10, p=0.32)	0%	Heterogeneity resolved by exclusion; non-significant result supports primary conclusion.
All-Cause Mortality	Age 18–24	1.04 (0.81–1.35, p=0.74)	1.04 (0.81–1.35, p=0.74)	N/A	No significant association; consistent across analyses.
Cardiac-Related Mortality (Pooled)	Overall	1.06 (1.02–1.11, p=0.007)	1.06 (1.02–1.11, p=0.007)	0% (most subgroups)	Low heterogeneity; small increased risk noted as secondary finding.
Cardiac-Related Mortality	Males	1.09 (1.02–1.15, p=0.006)	1.09 (1.02–1.15, p=0.006)	0%	Significant in males; no change with IRR treatment.
Cardiac-Related Mortality	Females	Non-significant (exact NR)	Non-significant (exact NR)	0%	No association; values match original.
Cardiac-Related Mortality	Age 18–24	Non-significant (exact NR)	Non-significant (exact NR)	0%	No association; values match original.

Table B1: Summary of Original Hazard Ratios versus Re-Analyzed Incidence Rate Ratios

All-Cause Mortality (Re-Analysis)

The pooled IRR showed no significant association between COVID-19 vaccination and all-cause mortality (IRR = 0.89, 95% CI [0.71–1.10], p = 0.28). Subgroup analysis by age (18–24 years) also showed no association (IRR = 1.04, 95% CI [0.81–1.35], p = 0.74). High heterogeneity was present (I^2 = 94%; Figure B1a).

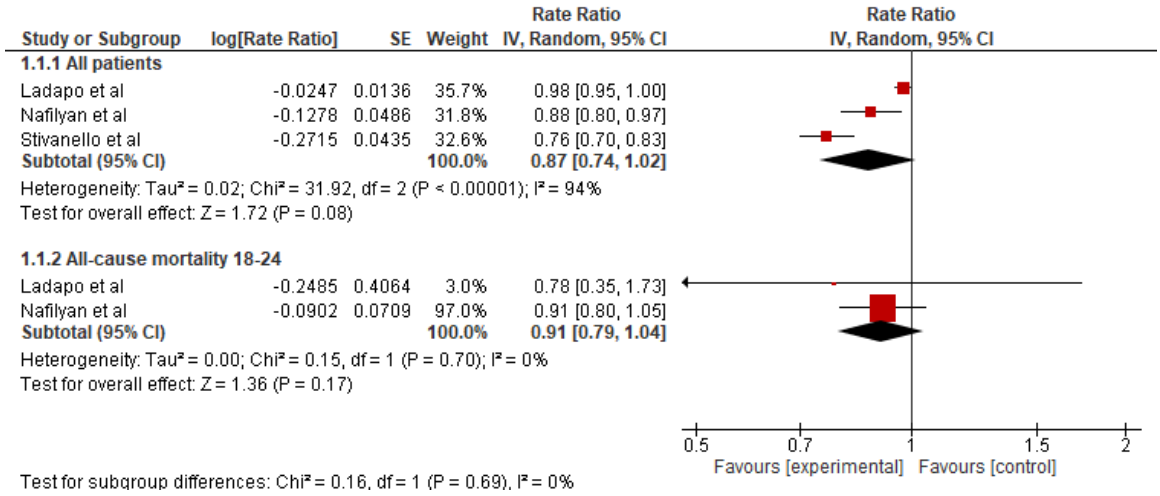
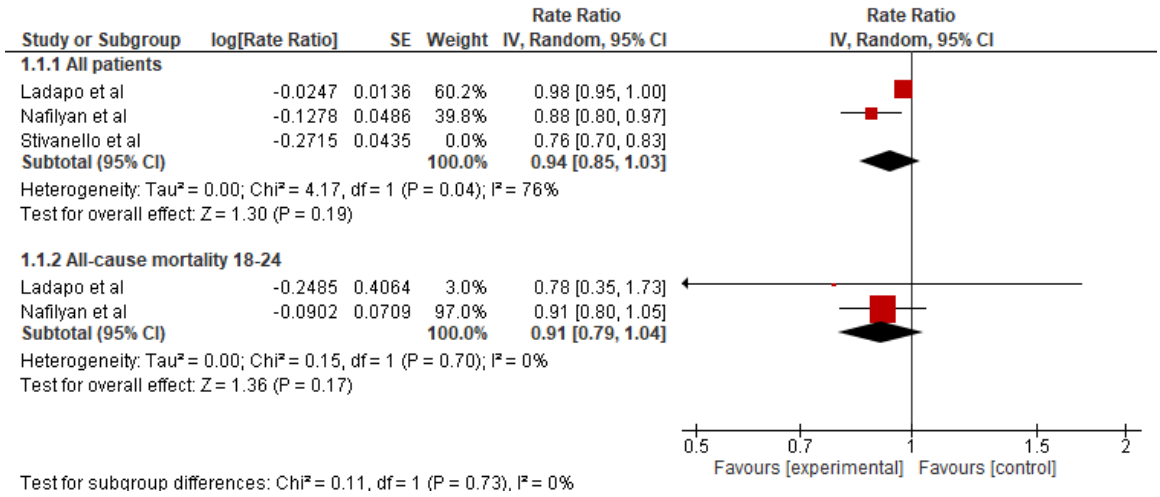


Figure B1A showing pooled IRR of all-cause mortality before leave-one-out



Excluding Stivanello et al. resolved heterogeneity (I^2 = 0%), with no change in significance (p = 0.32; Figure B1b).

Redemonstration of the analysis of all-cause mortality using HR to check if differences exist

Below is the final analysis conducted using HR to evaluate for differences between HR and IRR (if any). Our results show identical numbers with no change in any value when using HR or IRR

S1-A

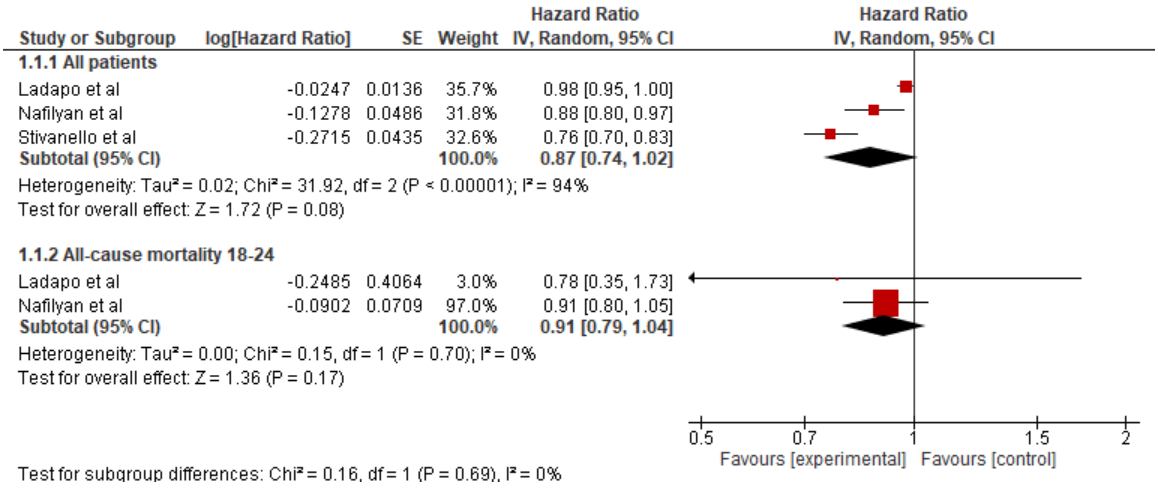


Fig S1-A shows analysis of all-cause mortality using HR before leave-one-out, all confidence intervals, p-values, and heterogeneity tests are identical to analysis using IRR

S1-B

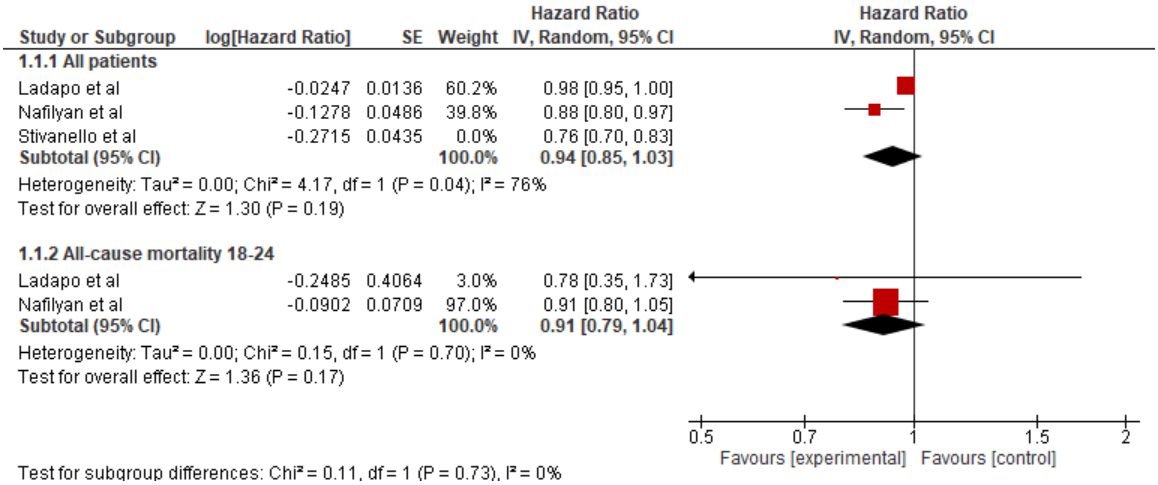


Fig S1-B shows analysis of all-cause mortality using HR after excluding Stivanello to solve the heterogeneity, all confidence intervals, p-values, and heterogeneity tests are identical to analysis using IRR.

Cardiac-Related Mortality (Re-Analysis)

The pooled IRR indicated a small increased risk (IRR = 1.06, 95% CI [1.02–1.11], p = 0.007). In subgroups, males showed increased risk (IRR = 1.09, 95% CI [1.02–1.15], p = 0.006), with no significance in the female group (Figure B2).

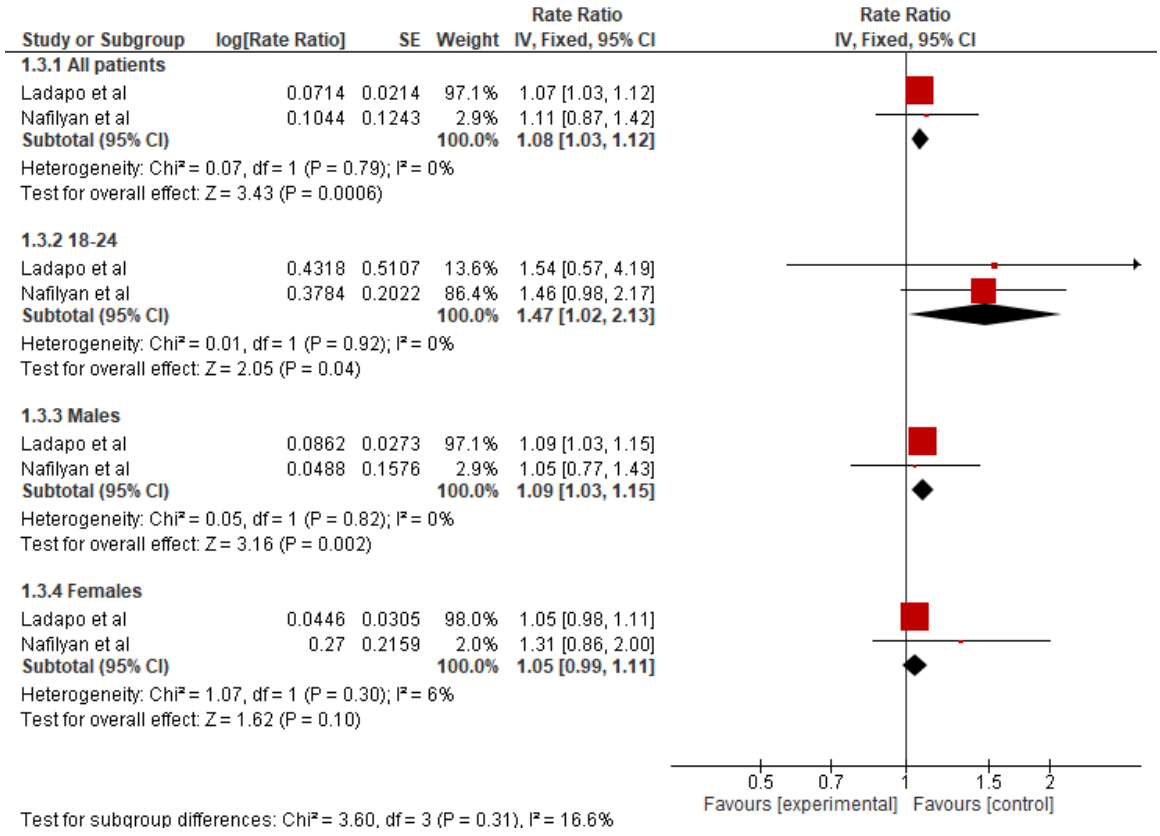


Figure B2 shows analysis of cardiac related mortality, with both I2 and chi-square p-value showing homogeneous analysis analyzed under the fixed effects model.

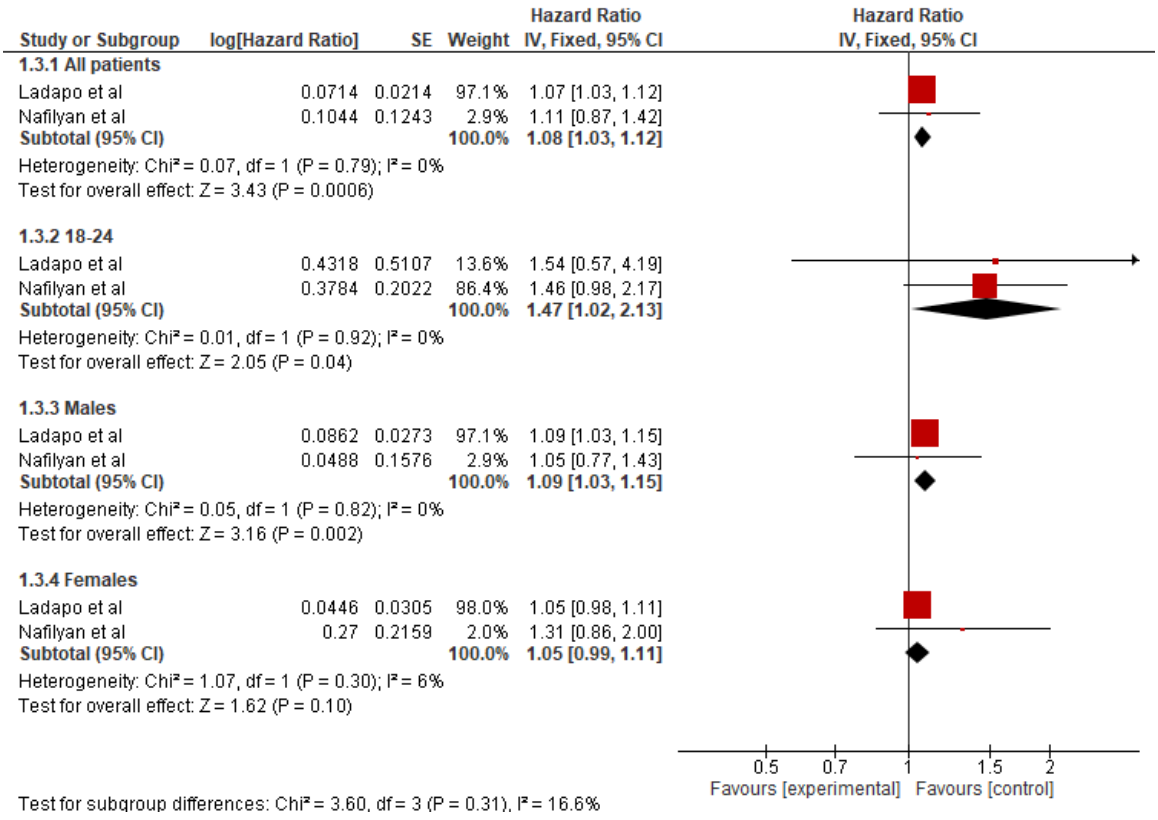


Figure S2 shows redemonstration of the cardiac related mortality analysis using HR to evaluate for possible changes between HR and IRR if any, the results show identical numbers with no change in any value when using HR or IRR

This sensitivity analysis and redemonstrations (figures S1-A, S1-B, and S2) confirm that the terminology choice (HR vs. IRR) had no impact on results or conclusions, reinforcing the interchangeability in this context and supporting the paper's findings without need for correction.