

Answers to the reviewers and revised manuscript with marked changes

Reviewer 1

We would like to thank the reviewer for his valuable and important comments

1. The use of "two insulin prescriptions" as a proxy for new-onset DM1 is potentially problematic. Please clarify whether additional criteria (e.g., ICD codes, clinical records) were used to exclude misclassification, especially in distinguishing type 1 from type 2 diabetes in adolescents.

We sincerely thank the reviewer for this important and insightful comment. We used two insulin prescriptions as a marker for new-onset DM1, following the methodology used in a previous study (reference 19), as we found this approach to be the most reliable within our dataset. In our healthcare system, newly diagnosed patients with DM1 are routinely and immediately started on insulin therapy. Using two prescriptions helps minimize misclassification due to erroneous or isolated prescriptions. We chose not to rely on ICD codes or clinical records, as these can occasionally be incomplete or inconsistently recorded by medical staff. While we acknowledge that adolescents with type 2 diabetes may also receive insulin, restricting our cohort to individuals under 18 years of age significantly reduces the likelihood of their inclusion. We have added this clarification to the Methods section and acknowledged the limitation in the Discussion.

2. The observed changes in DM1 incidence during COVID-19 may also reflect altered healthcare-seeking behavior, diagnostic delay, or reduced access to care. These factors should be acknowledged and discussed as possible alternative explanations.

We thank the reviewer for this thoughtful suggestion and fully agree. In response, we have added a discussion of these alternative explanations

along with relevant references. These factors may indeed have influenced DM1 incidence during the pandemic and are now appropriately acknowledged in the revised manuscript.

3. The method by which viral PCR data (population-level) were linked temporally or epidemiologically to DM1 diagnoses (individual-level) should be elaborated. This is crucial for interpreting the correlation results and IRR estimates.

We appreciate the reviewer's observation and recognize the importance of clarifying this methodological point. As outlined in the revised Methods section, the viral PCR data were analyzed at the population level and were not linked to individual DM1 cases. Specifically, we assessed weekly aggregated viral PCR data and compared these temporal trends with DM1 incidence rates using Spearman correlation tests and individual Poisson regression analyses, while controlling for seasonal effects. We have clarified this approach in the revised manuscript to ensure accurate interpretation of our correlation results.

4. While the use of Fourier terms is appropriate, the biological interpretation of changes in sine and cosine coefficients is unclear to a general medical audience. Please provide a clearer explanation or visualization of what these changes imply for clinical seasonality.

Thank you for highlighting this important point. We have revised the Results section to provide a clearer and more accessible explanation of the seasonality patterns, supported by references to Figure 1a and 1b, which visually demonstrate the changes in seasonal trends. We hope this added context enhances the clarity and clinical relevance of the seasonal analysis for a broader readership.

5. The conclusion that respiratory viruses "may play a role" in DM1 development is plausible but speculative. The language throughout should be revised to avoid overinterpretation of weak correlations, particularly given the ecological nature of the viral data.

We thank the reviewer for this valuable feedback. In response, we have revised the Conclusion to reflect a more cautious interpretation of our findings, emphasizing the exploratory and ecological nature of the observed correlations. Additionally, we have carefully reviewed and adjusted the language throughout the manuscript to avoid overstating the associations and to maintain a balanced and scientifically accurate tone.

Reviewer 2

We would like to thank the reviewer for his valuable and important comments

1. First, the author is advised to make minor changes in the title. A suggested title is given as follows: "The Impact of the COVID-19 Outbreak on the Seasonality and Incidence of Type 1 Diabetes Mellitus: A Nationwide Cohort Study".

We thank the reviewer for the helpful suggestion. The title was updated accordingly but without the word "The" since we have been informed by the journal editor that the title should not begin with the word "The"

2. Clarify how the COVID-19 period (only one year) allowed inference on seasonality, which typically requires multiple cycles.

We appreciate this important point. Although the COVID-19 period comprised only one year, we measured diabetes incidence as new cases per day, allowing us to perform seasonality analysis, albeit with less depth than multiple cycles would provide. We have acknowledged this limitation in the manuscript: "The relatively short COVID-19 period (one year) limits the depth of seasonality analysis."

3. Consider refining this sentence: "The increased incidence of new-onset DM1 and the disruption of its seasonal pattern..." To "An increase in new-onset DM1 and disruption of its typical seasonal pattern during the COVID-19 lockdown..."

Thank you for the suggestion. The sentence in the Abstract conclusion has been revised accordingly.

4. On the second page, change the term "Objective" to "Introduction or Background" and provide a solid background on DM1 etiology, seasonal patterns, and viral triggers.

We have changed the sub-title to "Introduction" and expanded the section to include a more detailed background on DM1 etiology, viral triggers, and seasonality, as recommended.

5. Include more discussion on COVID-19 as a direct potential trigger of autoimmunity in the pancreas, referencing proposed mechanisms (e.g., molecular mimicry, beta-cell tropism).

Thank you for highlighting this. We added information on proposed mechanisms to the discussion section.

6. "The COVID-19 (Coronavirus Disease) pandemic began in March 2020..."
Better phrased as: "The COVID-19 pandemic, which began in March 2020, led to..."

The sentence was revised accordingly

7. Add a clear description of the study design, population, and data sources.

We added detailed information about the study design, population, and the MDCLONE system database used for data extraction in the Methods section.

8. Address potential misclassification more clearly: using insulin prescription as a proxy may include misdiagnosed T2DM cases, even in younger children.

We sincerely thank the reviewer for this important and insightful comment. We used two insulin prescriptions as a marker for new-onset DM1, following the methodology used in a previous study (reference 19), as we found this approach to be the most reliable within our dataset. In our healthcare system, newly diagnosed patients with DM1 are routinely and immediately started on insulin therapy. Using two prescriptions helps minimize misclassification due to erroneous or isolated prescriptions. We chose not to rely on ICD codes or clinical records, as these can occasionally be incomplete or inconsistently recorded by medical staff. While we acknowledge that adolescents with type 2 diabetes may also receive insulin, restricting our cohort to individuals under 18 years of age significantly reduces the likelihood of their inclusion. We have added this clarification to the Methods section and acknowledged the limitation in the Discussion.

9. Presents detailed demographic and virological data and incorporates appropriate statistical models and visual interpretation of seasonality.

Due to the aggregate, population-level nature of viral PCR data, demographic data for the viral samples are, unfortunately, not available.

10. Include confidence intervals (CIs) and p-values for all incidence rate comparisons

We used Spearman correlation for comparing DM1 incidence and different respiratory virus rates. As this method does not provide confidence intervals, we included p-values and correlation coefficients accordingly in Table 2.

11. Expand slightly on potential biological mechanisms for COVID-19 or other respiratory viruses triggering DM1.

We expanded on the potential biological mechanisms by which COVID-19 and other respiratory viruses may trigger DM1 in both the Introduction and Discussion sections.

12. If possible, include a brief discussion on post-pandemic trends or mention whether follow-up studies are ongoing.

We included a recent letter describing a post-COVID-19 decline in DM incidence (reference 25) in the Discussion and mentioned the need for further follow-up studies

13. Correct the statements that follow as; "and therefore may have a role" consider improving for fluency: "and may therefore contribute to the development of DM1." and "Further research is needed to explore..." perhaps specify: "...to explore causal pathways and preventative strategies."

These sentences revised accordingly

14. Carefully format the citations and references as per the guidelines of "World Journal of Diabetes".

All citations and references have been carefully revised according to the guidelines of the World Journal of Diabetes.

15. The conclusion section is too brief and misses the opportunity to restate major findings and implications. Consider revising this section as follows; Conclusion "This study suggests that reduced seasonal variation in type 1 diabetes incidence during the COVID-19 lockdown, combined with an overall increase in new cases, may reflect the role of respiratory viruses, including SARS-Cov-2, as environmental triggers of DM1. These findings highlight the need for further studies to confirm causality and inform preventive approaches."

We thank the reviewer for the improvement of the conclusion and revised it accordingly

Revision reviewer 1

Comment: Dear authors, After a careful re-evaluation of this manuscript I'm satisfied with the content and the revisions made by the authors. Furthermore, the points that I have highlighted in the previous version have been addressed properly. Therefore, I would like to accept this manuscript in its present form and recommend its further processing for publication in this journal. Thank you for the opportunity to review your study.

Reply: Thanks for your comments.

Revision reviewer 2

Point to point answers to the second round of review:

We thank the reviewer for his helpful comments and for his efforts to improve the manuscript.

The changes are marked in blue in the revised manuscript

Minor Revision Suggestions:

1.The terms "pre-COVID-19 period" and "COVID-19 period" are somewhat redundant. It is recommended to standardize these as "pre-pandemic" and "pandemic period" and to clarify them in the Introduction.

These terms were replaced accordingly in the manuscript

2.The term "seasonality" of DM1 is central to the study but is not clearly defined in the Introduction. It is suggested to briefly explain the concept of seasonality and the analytical indicators used (e.g., Fourier terms) to help readers better understand the analytical logic.

Explanation regarding seasonality and analytical indicators was added to the introduction

3. Certain expressions should be revised for academic precision. For instance, instead of “suggest COVID-19 may be a DM1 trigger,” it would be more appropriate to say “suggest a potential triggering role of COVID-19 in new-onset DM1.”

The language in the manuscript were revised according to the comment to be more precise

Revision journal editor

Comment: The manuscript should be re-evaluated by the original reviewers

Reply: Thanks for your comments.