Point to point answers to reviewers

Reviewer #1:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Rejection
Specific Comments to Authors: General comments

The authors addressed the interesting question of the relationship between emissions of toxic airborne molecules and type 1 diabetes incidence in European countries. This is a quite interesting topic, and the authors have made great efforts to collect the epidemiologic data of type 1 diabetes over the recent 30 years in 19 European countries.

We thank the reviewer for the interest in our work.

However, based on their results, we can not conclude a positive correlation between several types of toxic airborne molecules and type 1 diabetes. To the contrary, the authors' data indicated that with the gradual reduction in the toxic airborne molecules, the incidence of type 1 diabetes showed a significant increasing trend in all European countries. The northern European countries (such as Finland, Sweden) have the highest incidence of type 1 diabetes, but most of their toxic airborne molecules levels are lower than the western European countries.

We thank the reviewer for this comment, which allowed us to better explain this aspect in the manuscript. The statistical association, described in our results, between the type 1 diabetes incidence and the global burden of pollutants (i.e., tonnes of emissions per year) does not express a temporal trend. This analysis correlates the type 1 incidence recorded in a specific period with the global burden of pollutants emitted in the same explored period. As showed in the new supplementary table 3, countries with the highest emissions (i.e., II and III tertiles, as also Finland and Sweden) have the highest incidence of type 1 diabetes. This finding is confirmed by logistic regression models and analysis of variance (see Figure 4, Tables 1 and 2). To better clarify this point, a new table (supplementary Table 3) and the following paragraph (discussion section) have been now added in the manuscript:

"An additional aspect emerging from this study was the apparent contradiction between the increased incidence of type 1 diabetes over time, and the progressive nationwide decrement of pollutants. It should be underlined that, in the whole group of explored countries, the statistical association between the type 1 diabetes incidence and the global burden of pollutants (i.e., tonnes of emissions per year) does not express a temporal trend. The analysis correlates the type 1 incidence recorded in a specific period, with the burden of pollutants emitted in the same explored period. From this point of view, the countries with the highest emissions of PM10, VOCs and NO (i.e., nationwide emissions in the II and III tertiles) have the highest incidence of type 1 diabetes in corresponding time periods. This finding is confirmed by logistic regression models exploring the odds of elevated type 1 diabetes incidence in countries divided according to tertiles of emissions, and by an analysis of variance exploring differences between the average incidence of type 1 diabetes in countries with low, medium and high production of pollutants".

More importantly, the other known risk factors of type 1 diabetes, such as genetic risk factors and family history, have not been adjusted in the correlation analysis between toxic airborne molecules and type 1 diabetes.

The study design employed in the present work (ecological study) can only indicate the existence of ecological associations at a population level, and does not allow to evaluate individual variables. Individual factors influencing type 1 incidence can be only explored by specific approaches as cohort studies or case-control studies. These aspects should be better explored in further studies, with an appropriate and specific

study design. This methodological limitation of the ecologic approach has been commented in the discussion section:

"…the present study used an ecological approach. This methodology can only indicate the existence of ecological associations, which not necessarily point to pathogenic associations between explored pollutants and type 1 diabetes onset at an individual level. Further studies are needed to examine in details pathophysiological and epidemiological links between individual exposure to PM10, NO and VOCs and the onset of type 1 diabetes. Future analyses, in particular, should comprehensively consider in utero exposures, epigenetic mechanisms, and individual variables exploring other known risk factors of type 1 diabetes as genetic factors, viral infection history, family history, individual diet and lifestyle."

Specific comments 1. The classifications based on tertiles of each pollutant emissions will hide a lot of important information. Therefore, the authors should clearly provide the level of each pollutant in the 19 European countries, separately, and do correlation analysis with the incidence of type 1 diabetes in these 19 countries directly.

The available studies which met the inclusion criteria (n=18) and were selected to identify the national incidence of type 1 diabetes, only allowed to examine a limited number of periods for each country (mean 3.7, range 1-7 periods of observation, see Supplementary Table 1). Thus, the scant number of points of observation for each country does not allow separate correlation analysis. Furthermore, the analysis of type 1 diabetes incidence in each single country and in a limited time series could generate statistical errors, also depending on possible autocorrelation. Grouping countries according to tertiles of emissions in homogeneous time periods allowed us to avoid this possible bias. However, we agree with the reviewer that the lack of a time-trend analysis within each of the explored countries can be considered a limitation of the study, and the following sentence has been added in the discussion section:

"Finally, the present study was not designed to explore time variations in type 1 diabetes incidence according to temporal trends of emission in each country. Studies conducted at a national level could correlate local epidemiologic and environmental data on a wide time window, possibly in different age classes [8]."

2. Other known risk factors of type 1 diabetes, such as family history of diabetes, viral infection history, diet and lifestyle, should be fully adjusted in the statistic model on the relationship between toxic airborne molecules and type 1 diabetes.

As previously discussed, the present study employed an ecological, population-based approach and cannot consider individual confounders. However, we agree with the reviewer on the relevance on the cited individual risk factors. The following text has been added in the discussion section:

"the present study used an ecological approach. This methodology can only indicate the existence of ecological associations, which not necessarily point to pathogenic associations between explored pollutants and type 1 diabetes onset at an individual level. Further studies are needed to examine in details pathophysiological and epidemiological links between individual exposure to PM10, NO and VOCs and the onset of type 1 diabetes. Future analyses, in particular, should comprehensively consider in utero exposures, epigenetic mechanisms, and individual variables exploring other known risk factors of type 1 diabetes as genetic factors, viral infection history, family history, individual diet and lifestyle."

3. A comparison of the incidence of type 1 diabetes between people with similar genetic background but living in different European countries might help the control the potential confounders and answer the question of the relationship between emissions of toxic airborne molecules and type 1 diabetes incidence.

We agree with the reviewer. The following sentence has been added in the discussion section:

"Although genetic factors seem to play a limited role in the epidemiological variations of type 1 diabetes incidence [21-23], nation-based cohort or case-control studies should also allow comparisons between subgroups with similar genetic background but living in different countries."

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors:

please add abbreviation list in the manuscript

An abbreviation list has been now added in the title page of the manuscript.