Dear Editor:

We would like to thank you for providing us with the opportunity to revise our manuscript. We have given the comments thoughtful consideration and modified the manuscript according to the suggestions. Below you will find point by point responses according to the commentaries. Changes in the text are highlighted in grey.

Manuscript No.: 47187

Title: Correlating the global increase in type 1 diabetes incidence across age groups with national economic prosperity: A systematic review

We hope that you will find this revised manuscript suitable for publication.

Sincerely yours,

Natalia Gómez Lopera
Biologist, PhD(c)
Grupo Mapeo Genetico
Departamento de Pediatria
Facultad de Medicina
Universidad de Antioquia
Medellin-Colombia
Cra 51 D # 62-29, AA 1226
natalia.gomezl@udea.edu.co

Editor Comments:

-Please provide and upload the approved grant application form(s).

We included the approved grant application form. You can find it in the file *47187-Approved Grant Application Form.*

-Please write the article highlight section according to the guidelines.

We included the article highlight section. You can find it between line 435 and 487

-We found that the content of the figures cannot be edited by our staff. Authors have to provide the figures as separate electronic files.

We provided the figures as separate electronic files. You can find it in the *file 47187-Image File.zip*

Reviewer 1:

1) My major concern is that the authors have greatly extrapolated their results. Emphasis is placed on the "traditional" suggestion that type 1 diabetes is an "autoimmune" disorder. Do the authors have information to support the view (from multiple other disorders) that exposure to an environmental agent or factor in an individual with a genetic predisposition may lead to a chronic disease? Specifically do the authors have sufficient data to look for a Birth Cohort Effect?

Dear Reviewer, we are thankful for your comments. Type 1 Diabetes is thought to be immune-associated destruction of the pancreatic β cells. T1D is a complex disease resulting from the interplay of genetic, epigenetic, and environmental factors [1]. The heterogeneous nature of the disease has made it very difficult to elucidate the factors and mechanisms responsible for disease onset. Eisenbarth in 1986 [2] proposed that T1D is a chronic autoimmune disorder that develops in stages: In individuals with a genetic predisposition who have been exposed to an environmental trigger factor, occurs a breakdown in immunological tolerance that leads to a β-cell loss, then appears dysglycaemia that conducts to clinical diabetes, and the end a rapid progression to a complete β-cell loss. Although useful, this model does not address the complexity of type 1 diabetes pathogenesis, knew today [3]. We do not have information to support the view that exposure to a specific environmental agent or factor in an individual with a genetic predisposition may lead to disease. In this manuscript, we tried to explore the possible influence of socioeconomic status on type 1 diabetes, as Patterson et al[4] demonstrated in a study conducted throughout Europe.

On the other hand, we have sufficient data to look for a Birth Cohort Effect. In fact, Paula-Diaz Valencia analyzed the age-period cohort of the global incidence trends of T1D on her PhD thesis [5]. This work has not published yet. Through the systematic review, she generated a large database containing global information about the incidence of T1D; then using methodological approach based on Mixed Poisson Regression Models and introducing a random effect by country, she estimated the Age-Period-Cohort (APC) rates of the global incidence of T1D, considering all three variables: age, calendar and birth cohort. She found an association between incidence trends and birth cohort effects. Describing briefly her results, she found that the birth cohort effects showed a steady increase after 1975; been a risk relative of 1 in the 1980s and risk relative of 2.5 in the 2000s.

2) The authors could more systematically describe how factors potentially related to national economic prosperity might function as an environmental agent or factor, such as **obesity**, rates of immunization (? inadequate blocking antibodies), nutritional factors, and population density.

- We included this information in the discussion section. You can find it between line 370 and 385 page 14 and here addressed:

"Other environmental factors potentially related to national economic prosperity must be mentioned. One of these is the nutritional component that has undergone major changes in many developed countries. Early nutrition seems to modulate the development of T1D, for example, the absence or short duration of breastfeeding and early introduction of cow's milk formulae are thought to be risk factors for this disease[6]. *Also, rapid weight gain in infancy, associated with improper feeding, increases the risk of developing T1D* [7]. *Other possible factors that experiment in wealthier countries are a higher degree of urbanization, which are associated with an increased incidence of T1D, supporting the hygiene hypothesis* [8]. *In addition, there are differences in caesarean deliveries between low- and high-income countries, where wealthier countries have high levels of caesarean use without medical indication*[9]. *Delivered by caesarean section are at slightly increased risk of T1D, and it has been postulated that differences in the gut microbiota of these children compared with those born by normal vaginally delivery* [10]. *Also, the wealth of countries is associated with environmental pollution. An association between air pollution and T1D incidence has been described. Researchers proposed that chemical and air pollutant exposures have multiple effects that may directly affect the risk of T1D*[11]*"*

3) Page 14, line 372: "epidemiological studies of T1D …to determine genetic and environmental factors". It is unlikely that epidemiological or demographic studies will prove cause and effect, but certainly epidemiological and demographic studies can provide evidence to develop a hypothesis to then be further tested.

Thank you for highlighting this point. We modified the text according to your recommendation. You can find in page 15, lines 390-392, and here address:

More epidemiological studies of T1D are needed to develop new hypotheses about the genetic and environmental factors that trigger the disease, which should be further tested.

3) In Limitations, page 15, consider describing the geographical distribution of the 26 countries that were used to generate the major results.

Thank you very much for the recommendation, we greatly appreciate the comment. We included this information in page 15, lines 406-408, and here address.

These 26 countries are mainly from Europe (n=23), and Asia (n=3). Regrettably, we do not have information to conduct comparison in the two periods for countries in Africa, Oceania, and America.

References

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