PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The trends and the risk of type 1 diabetes over the past 40 years: an analysis by birth cohorts and by parental migration background in Sweden
AUTHORS	Hussen, Hozan; Persson, Martina; Moradi, Tahereh

VERSION 1 - REVIEW

REVIEWER	Gisela Dahlquist, MD, PhD, Senior professor Dept. of Clinical sciences, Paediatrics Umeå University Sweden I have no conpeting interests
REVIEW RETURNED	10-Jul-2013

GENERAL COMMENTS	General comments: This study takes advantage of a newly established Swedish official register focusing on migration and health that may yield potentially interesting data on environmental risk exposures when comparing time trend data from migrating populations from different countries. The present study, however suffers methodological problems as specified below: Major concerns: 1. The use of ICD codes for incidence of diabetes is well known to be unreliable especially in age groups over 15 years when T2DM is often mixed with T2DM. Since different ethnic groups are in focus this is a problem since it is clear that T2DM is dependent on ethnicity especially in children and young adults. The subgroup analysis for patients with diagnosis 1997-2009 should be clearly presented (appendix) and the problem with mixed diagnosis further discussed. The method for assessing correct incidence by using time when the diagnosis first appeared in inpatient and/or outpatient registers should be stated and discussed . 2. The incidence data from the used official registers should be compared and commented on in relation to previously published Swedish data for similar age groups/ years based on prospectively collected standardized and ascertained research registers (see Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002. Ostman J, Lönnberg G, Arnqvist HJ, Blohmé G, Bolinder J, Ekbom Schnell A, Eriksson JW, Gudbjörnsdottir S, Sundkvist G, Nyström Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007: an analysis of time trends. Dahlquist GG, Nyström L, Patterson CC; Swedish Childhood Diabetes Study Group; Diabetes Incidence in Sweden Study Group) 3. In time trend analysis it is most important to assure that data do

	not vary in accuracy over time. In this study different sources for onset time of diabetes are used (inpatient register since 1987 and the more recently started outpatient register for certain types of care).The level of ascertainment for the different sources over different time periods should be mentioned (if available) including the method for ascertainment (to justify the expression “all outpatient visits to…”).The ascertainment could certainly differ by ethnicity and time spent in Sweden. 3. The main focus of this manuscript is to compare time trends for incidence of T1DM in different migration groups and native groups in Sweden but no formal testing for differences in trends are presented. 4. It must be mentioned that the statistical strengths in incident data from different immigrant groups are extremely variable despite ”statistical significance by 95%C.I” (e.g. a total of n=692 from Finland and n=66 from eastern Africa) which must be taken into account for the interpretation of data. Thus when comparing percentage decrease or increase in diabetes incidence among offspring of migrants relative to that of offspring of in Sweden born parents (n= 16358) e.g. the unexpected finding for immigrants from eastern Africa should be discussed with great caution.

REVIEWER	Anders Green, Professor and Consultant (Clinical Epidemiology), Univeristy of Southern Denmark and Odense University Hospital. No competing interests to be declared.
REVIEW RETURNED	17-Jul-2013

REPORTING & ETHICS	There is no section with a description of the ethical aspects of the stud0079
GENERAL COMMENTS	This paper reports that that the risk of type 1 diabetes is decreased in children and young adults with one or both parents born abroad Sweden is less than for offspring of Swedes. The effect is most pronounced for offspring with both parents born outside Sweden. The study makes use of the internationally unique opportunities for registry-based epidemiological research covering the Swedish population for an extensive period of calendar year. Thus more than 7 million subjects aged 0-30 years have been monitored since 1969 using the unique personal identification coding system established in Sweden (and the other Nordic countries). Some 30,000 cases of diabetes are represented in the analysis. This reviewer is concerned about the use of the phrase ’type 1 diabetes’ in the present context, with implications concerning completeness of ascertainment of patients with diabetes. According to p.8 ’we had no specific ICD codes before 1997 to distinguish between type 1 and type 2 diabetes”. However, the ICD code systems before the 10th revision actually contain code 249.X for type 1 diabetes. Why not have these codes been used? In addition, the same patient may on different occasions be registered with codes for type 1 diabetes, type 2 diabetes and diabetes of unclassifiable type – even for diabetes diagnosed in childhood. However, neither ICD10-codes for type 2 diabetes nor ICD10-codes for unclassifiable diabetes have been employed according to the description in the section Follow-up (p.7). In summary, the search criteria for diabetes have not been exhaustive for reasons that differ between the early part (lack of codes for type 1 diabetes) and the late part (lack of codes for type 2 diabetes and unclassified diabetes) of the cohort, respectively. These shortcomings may have different implications for population segments by ethnic grouping: The authors may be right that for individuals of (Northern) European

	ancestry, diabetes diagnosed before age 30 year may for practical purposes be equivalent with type 1 diabetes. However, this may not be true for individuals of ancestry other than (Northern) European. The authors should consider to use the more neutral term 'early onset diabetes' throughout the paper. Furthermre, they should provide a qualified account and discussion of these aspects in the light of potential implications for the findings. In the discussion it would be good to have some more specific suggestions on how the unique study settings in Sweden may be used for further explanatory studies, for example within the framework of a nested case-control design. For example, can differences in early environmental exposures of potential importance (like nutrional habits and attending daycare institutions in childhood) explain the trends observed? Minor comment: P.6, Study cohort: The description of the study cohort mention that "The study population comprised .... between 0 to 30 years of age, born and living in Sweden any time between January 1st, 1969 and December 31st, 2009". Does this mean that an individual born January 1st 1969 are censored for follow-up on January 1st 1999 (when achieving the age of 30 years)? If so, this should be made clear in the description of the follow-up of the cohort members (Follow-up, p.7).

VERSION 1 – AUTHOR RESPONSE

Reviewer: Gisela Dahlquist, MD, PhD, Senior professor Dept. of Clinical sciences, Paediatrics
Umeå University
Sweden
I have no conpeting interests

General comments:
This study takes advantage of a newly established Swedish official register focusing on migration and health that may yield potentially interesting data on environmental risk exposures when comparing time trend data from migrating populations from different countries. The present study, however suffers methodological problems as specified below:

Thank you for the pertinent comments, which helped to improve the quality of the manuscript. I have addressed them as indicated below.

Major concerns:

1. The use of ICD codes for incidence of diabetes is well known to be unreliable especially in age groups over 15 years when T2DM is often mixed with T2DM. Since different ethnic groups are in focus this is a problem since it is clear that T2DM is dependent on ethnicity especially in children and young adults.

Thanks for pointing this out. Now we have discussed this for the age group over 15 years (end of page 13 to page 14, 1st paragraph).

1. Continued: The subgroup analysis for patients with diagnosis 1997-2009 should be clearly presented (appendix) and the problem with mixed diagnosis further discussed. The method for assessing correct incidence by using time when the diagnosis first appeared in inpatient and/or outpatient registers should be stated and discussed.

The subgroup analyses, for patients with diagnosis 1997-2009 are now clearly presented (Method; page 7, 3rd paragraph. Results; page 9, 2nd paragraph, line 5-7 and page 10, 2nd paragraph. Discussion; end of page 13 to page 14, 1st paragraph and supplementary Tables 1S and 2Sa)

In addition, since, the result of sensitivity analysis starting from 1997 includes only children with the age group 0 to 13 years of age. , we performed the analysis for the entire cohort but confined them to ages 0-13 for comparability reason (page 10, 2nd paragraph and supplementary Table 2Sb).

2. The incidence data from the used official registers should be compared and commented on in relation to previously published Swedish data for similar age groups/ years based on prospectively collected standardized and ascertained research registers (see Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002.
Ostman J, Lönnberg G, Arnqvist HJ, Blohmé G, Bolinder J, Ekbom Schnell A, Eriksson JW, Gudbjörnsdottir S, Sundkvist G, Nyström
Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007: an analysis of time trends.
Dahlquist GG, Nyström L, Patterson CC; Swedish Childhood Diabetes Study Group; Diabetes Incidence in Sweden Study Group)

We have revised the text and added references in the manuscript to make this clear (page 11, 2nd paragraph, line 6-14).

3. In time trend analysis it is most important to assure that data do not vary in accuracy over time. In this study different sources for onset time of diabetes are used (inpatient register since 1987 and the more recently started outpatient register for certain types of care).The level of ascertainment for the different sources over different time periods should be mentioned (if available) including the method for ascertainment (to justify the expression “all outpatient visits to…”).The ascertainment could certainly differ by ethnicity and time spent in Sweden.

We have added a paragraph regarding the quality of these registers in Methods (page 5, 1st paragraph, line 1-4) and a paragraph in the discussion about how and if this limitation could have affected our results (end of page 10 to page 11, 1st paragraph).

3. The main focus of this manuscript is to compare time trends for incidence of T1DM in different migration groups and native groups in Sweden but no formal testing for differences in trends are presented.

We have performed a formal statistical testing. The results are now presented in the manuscript (Methods; page 8, 2nd paragraph. Results; page 8, last paragraph).

4. It must be mentioned that the statistical strengths in incident data from different immigrant groups are extremely variable despite ”statistical significance by 95%C.I” (e.g. a total of n=692 from Finland and n=66 from eastern Africa) which must be taken into account for the interpretation of data. Thus when comparing percentage decrease or increase in diabetes incidence among offspring of migrants relative to that of offspring of in Sweden born parents (n= 16358) e.g. the unexpected finding for immigrants from eastern Africa should be discussed with great caution.

We agree with the reviewer that the number of cases among offspring to immigrants including those from eastern Africa is small compared to that of offspring of Swedish born parents and they may not represent the risk of the countries of origin (selective migration). (We have changed the text accordingly, page 12, 2nd paragraph, line 5-7).

However, we believe that we have enough statistical power in all offspring groups that we have presented. We also would like to mention that our results are not unexpected and it has been observed in other Swedish register study (Hjern A, Söderström U, Åman J. East Africans in Sweden have a high risk for type 1 diabetes. Diabetes Care. 2012 Mar;35(3):597-8. doi: 10.2337/dc11-1536. Epub 2012 Feb 1.) and in the first generation of eastern African (Hussen HI, Yang D, Cnattingius S, Moradi T. Type I diabetes among children and young adults: the role of country of birth, socioeconomic position and sex. Pediatr Diabetes. 2013 Mar;14(2):138-48. doi: 10.1111/j.1399-5448.2012.00904.x. Epub 2012 Aug 28.)

Reviewer: Anders Green, Professor and Consultant (Clinical Epidemiology), University of Southern Denmark and Odense University Hospital.
No competing interests to be declared.

Thank you for the pertinent comments, which helped to improve the quality of the manuscript. We have addressed them as indicated below.

There is no section with a description of the ethical aspects of the study

Please see Page 5, 2nd paragraph, line 4 and 5.

This paper reports that that the risk of type 1 diabetes is decreased in children and young adults with one or both parents born abroad Sweden is less than for offspring of Swedes. The effect is most pronounced for offspring with both parents born outside Sweden. The study makes use of the internationally unique opportunities for registry-based epidemiological research covering the Swedish population for an extensive period of calendar year. Thus more than 7 million subjects aged 0-30 years have been monitored since 1969 using the unique personal identification coding system established in Sweden (and the other Nordic countries). Some 30,000 cases of diabetes are represented in the analysis.

This reviewer is concerned about the use of the phrase 'type 1 diabetes' in the present context, with implications concerning completeness of ascertainment of patients with diabetes. According to p.8 'we had no specific ICD codes before 1997 to distinguish between type 1 and type 2 diabetes". However, the ICD code systems before the 10th revision actually contain code 249.X for type 1 diabetes. Why not have these codes been used? In addition, the same patient may on different occasions be registered with codes for type 1 diabetes, type 2 diabetes and diabetes of unclassifiable type – even for diabetes diagnosed in childhood. However, neither ICD10-codes for type 2 diabetes nor ICD10-codes for unclassifiable diabetes have been employed according to the description in the section Follow-up (p.7). In summary, the search criteria for diabetes have not been exhaustive for reasons that differ between the early part (lack of codes for type 1 diabetes) and the late part (lack of codes for type 2 diabetes and unclassified diabetes) of the cohort, respectively. These shortcomings may have different implications for population segments by ethnic grouping: The authors may be right that for individuals of (Northern) European ancestry, diabetes diagnosed before age 30 year may for practical purposes be equivalent with type 1 diabetes. However, this may not be true for individuals of ancestry other than (Northern) European. The authors should consider to use the more neutral term 'early onset diabetes' throughout the paper. Furthermore, they should provide a qualified account and discussion of these aspects in the light of potential implications for the findings.

We do not have such code (249.X) for the diagnosis of type 1 diabetes in Swedish register.

We have used The Swedish National Patient Register, in which diagnosis are coded according to the Swedish International Classification of Disease (ICD) system (ICD-8: 250, 1969-1986; ICD-9: 250, 1987-1996; ICD-10: E10, 1997 and onwards).

Regarding the problem with mixed diagnosis between type 1 and type 2 diabetes, Please see response to reviewer 1, 1st comment.

In the discussion it would be good to have some more specific suggestions on how the unique study settings in Sweden may be used for further explanatory studies, for example within the framework of a nested case-control design. For example, can differences in early environmental exposures of potential importance (like nutrional habits and attending daycare institutions in childhood) explain the trends observed?

We thank the reviewer and have revised the text and added sentences to make this clear according to your comment.
Please see page 14, 3rd paragraph.

Minor comment:

P.6, Study cohort: The description of the study cohort mention that ”The study population comprised .... between 0 to 30 years of age, born and living in Sweden any time between January 1st, 1969 and December 31st, 2009”. Does this mean that an individual born January 1st 1969 are censored for follow-up on January 1st 1999 (when achieving the age of 30 years)? If so, this should be made clear in the description of the follow-up of the cohort members (Follow-up, p.7).

Yes, every individual in the cohort followed for maximum 30 years of age. We have now added a sentence in the text to make it understandable (page 6, 1st paragraph, line 5 and 6).

VERSION 2 – REVIEW

REVIEWER	Gisela Dahlquist Umeå university Dept of clinical sciences,paediatrics Umeå Sweden No competing Interests
REVIEW RETURNED	03-Oct-2013

- The reviewer completed the checklist but made no further comments.