Dear Dr. Weber,

On behalf of the study group of T1D China, I am writing this letter to reply.

First of all, thank you very much for your interest in our study and the opportunity for revision. We appreciate the informative comments and constructive suggestions from the editors and the reviewers. We have gone over all the comments and suggestions thoroughly within our study group. We have replied to the comments and queries below, and revised our manuscript and supplemental materials accordingly. We sincerely hope that our reply and the revision could let you and the reviewers better understand our study, and help you to reach the final decision.

Besides, I would like to express my greatest gratitude to the participating investigators from the 505 hospitals, and the patients who volunteered self-report. I am very honoured to have their collaboration. Without their dedication, this study could not be completed.

As a clinical doctor, I love this study. The results reveal, for the first time the large number of patients newly onset each year in China, and their situation, which would be of importance to health policy making, and probably change the management of type 1 diabetes (T1D). Also, the results provide new insights into the epidemiology of T1D, and may intrigue further study into the etiology of T1D.

I look forward to your response.

Yours sincerely,

Jianping Weng, MD& PhD on behalf of the T1D China study group

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The following content is the reply to the comments and queries from the editors and reviewers.

Detailed comments from the meeting:

We thought your study addresses an interesting and potentially important research question. We had the following queries:

Might you explain what your study adds to this recent paper:

Incidence and temporal trends of type 1 diabetes in China: a systematic review and meta-analysis

http://www.thelancet.com/pdfs/journals/landia/PIIS2213-8587(16)30368-0.pdf

Answer: Thank you for your comments. This article is an abstract of meta-analysis and systematic review about the change T1D incidence in Chinese Mainland between 1994 to 2015 published in a special issue for 2016 Annual Scientific Meeting of Chinese Diabetes Society. We looked up this study from PROSPERO (ID CRD42016039284, accessed on October 14, 2017), found that it was still undergoing formal manual checking exclusive criteria. We are not able to achieve the full text nor the list of included literature of this study. Our study is an original investigation. As far as we know, it is the only nationwide, population-based study reporting T1D incidence in China since the report, which is a part of the WHO Diamond Project [1] published in 1998. It provides, we believe, the most up-to-date and accurate estimate of T1D incidence in China.

Reference:

1. Yang Z, Wang K, Li T, et al., Childhood diabetes in China. Enormous variation by place and ethnic group. Diabetes Care, 1998; 21: 525-9.

We felt that the adjustment variables in the Poisson regression needed explaining (e.g. latitude and sunlight exposure) - while you talk a little about latitude in the results, this wasn't that obvious why these were chosen. Were there any important adjustment variables missing?

Answer: Thank you for your comments. As for your concern for the choice of covariates, when we established the Poisson model, we reviewed literature on possible influencing factors on incidence of T1D. It is reported that apart from genetic background, latitude, ultra-violet exposure, air pollution level, 25-(OH)-vitamin D level, early exposure to dietary cow's milk proteins, virus infection and etc. are possible influencing factors.[1-5] Therefore, based on accessibility of data, as shown in supplemental materials section 6, we analysed the correlation of T1D incidence rate and latitude, longitude, birth rate, urban population proportion and sunlight exposure (representing ultra-violet exposure), and finally included latitude and sunlight exposure as covariates to the Poisson model. We did not collect blood sample, nutrition information, or detailed early history of the patients. Air pollution data was not available during our study period. We believe that we have included as many as achievable covariates. We would revise our manuscript (results, paragraph 5, p.10) and supplemental materials (section 6, part 1, p.28) to give more details.

Reference:

1. Staples J A, Ponsonby A L, Lim L L, et al., Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect, 2003; 111: 518-23.

2. Atkinson M A, Eisenbarth G S, and Michels A W, Type 1 diabetes. Lancet, 2014; 383: 69-82.

3. Craig M E, Nair S, Stein H, et al., Viruses and type 1 diabetes: a new look at an old story. Pediatr Diabetes, 2013; 14: 149-58.

4. Beyerlein A, Krasmann M, Thiering E, et al., Ambient air pollution and early manifestation of type 1 diabetes. Epidemiology, 2015; 26: e31-2.

5. Akerblom H K, Vaarala O, Hyoty H, et al., Environmental factors in the etiology of type 1 diabetes. Am J Med Genet, 2002; 115: 18-29.

Ditto a reviewers comment about claims this is a nationwide study, when only 13 regions (we do not know how many regions there are in total in China) were considered representing about 10% of the population. Can this data be extrapolated as a nationwide study?

Answer: Thank you for your comments. We selected these 13 investigated areas based on the following considerations:

1) China spans from 73°33′E to 135°05′E in longitude, and 3°51′to 53°33′N in latitude, covering approximately 9.6 million km^2, bearing more than 1.3 billion population in 2010. She is divided into 7 Administrative Regions (as shown in Figure 1, Northeast,

North, Northwest, Southwest, Central, East and South) according to geographic location, climate, culture, ethnicity and population. We chose our investigated areas based on the representativeness of these 7 Administrative Regions. We selected at least one investigated area from each of these Administrative Regions. Besides, huge imbalance in population density exists in China: more than 90% of the population reside in the southeast part. And we ensured that there was at least one investigated area every 5° of latitude (Figure 1, Table S1 in Supplemental Materials). Therefore, we selected 1 to 2 additional investigated area(s) in some of the administrative regions.

2) The investigated areas also consist of areas of different economic development levels as represented by gross domestic production (GDP) in 2010[1]. The investigated areas covered the less developed, moderately developed and well-developed areas in China.

This basis of selection ensured the socio-demographic and geographic representativeness of the investigated areas. Furthermore, to estimate the nationwide T1D incidence rate, we develop a model to adjust possible influencing factors. We believe that by investigating the selected areas could be defined as a nationwide study.

More details were added into the manuscript (methods paragraph 2, p.3) and the supplemental materials (section 2, part 1, p.15)

Reference:

1. National Bureau of Statistics of the People's Republic of China. [accessed 2017 October 16]; Available from: http://www.stats.gov.cn/.

Perhaps the etiology of some of the findings needs investigating / discussing a bit. For example IR are lower in females overall but higher in the <15 group with non-overlapping CI's.

Answer: Thank you for your comments. Our data showed that the incidence of T1D was higher among girls in age group 0 - 14 years, consistent with previous reports. But in overall, the incidence rates in female were lower. We did not discuss this in particular previously. As shown in our results (manuscript, results, paragraph 2, p.9), the incidence in female ≥15 years was even lower. Likewise, we also observed in our data that the incidence rates were higher in the north than in the south in age group 0 - 14 years, while similar change was not seen in the overall incidence rates. These phenomena may suggest different trigger between childhood onset and adult onset T1D. Further investigation should be done to clarify the underlying mechanism. We would revise our manuscript to discuss briefly. (discussion, paragraph 6, p.14)

The discussion section is at places somewhat difficult to follow.

Answer: Thank you for pointing out.

According to the characteristics of our results and potential influencing factors on T1D incidence, originally, we organised our discussion in the following aspects: (1) age, (2) gender, (3) latitude, (4) strength and weakness. We are glad to see that reviewer 1 (Dr. Lee Nedkoff) and reviewer 3 (Dr. Torild Skrivarhaug) have given nice comments

and suggestions on our discussion. Reviewer 2 (Dr. Richard Feltbower) pointed out that we had spelling and grammatical mistakes in our manuscript. We believe that the complexity of the study, the abundant details in the supplemental materials, and the language may cause difficulty in following our discussion. Based on the comments and suggestions from the editors and reviewers, we would revise our discussion to make it more readable for general readers from broader academic society.

Might you discuss briefly why China has a relatively low incidence of Type 1 Diabetes (In contrast to Finland e.g.) and why there was the increase in the incidence of T1DM in China in recent years?

Answer: Thank you for your comment. Our study once again confirmed that the T1D incidence remains low in China, even after 3.9-fold increase compared with what was reported by the WHO DIAMOND project [1] two decades ago. The factors most probably attribute low incidence in China are genetic, environmental, and behavioral factors. Taking the comparison between China and Finland as example, the T1D incidence in China under 15 years is merely 1/30 of that in Finland. Finland is a country of high latitude (~60.1°N), which may contribute to higher incidence of T1D. But if we compare the incidence rate in Finland[2] to that in Harbin in Northern China (45.8°N) investigated in our study, the incidence rate is still much lower (64.9 vs 3.59 per 100,000 person years). This may indicate that genetic factor plays a more important role in the incidence of T1D, compared to other factors. Our study population has a homogenous gene background of Han population. But in the 0-14 years age group, we could observe an up to 3-fold difference in T1D incidence rate

comparing the north and the south areas, suggesting the influence of environment factors.

As for the increase of T1D incidence in China, we did not measure the trend in our study. Rather, as we mentioned in our manuscript, we compared our results roughly with the results from part of the WHO DIAMOND project[1] which was performed in different design. We may propose that the increase may be due to different investigation methodology, environment and behavioral change over these years. Further investigation on how these factors influence the T1D incidence and on the interaction of these factors should be done to provide more insight on the etiology of T1D.

We would revise our manuscript accordingly to give a brief discussion (discussion, paragraph 2, p.12).

References:

1. Yang Z, Wang K, Li T, et al., Childhood diabetes in China. Enormous variation by place and ethnic group. Diabetes Care, 1998; 21: 525-9.

2. Harjutsalo, V., et al., Incidence of type 1 diabetes in Finland. Jama, 2013. 310(4): p. 427-8.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

This study has estimated the incidence of type 1 diabetes in 13 regions in China, using these data to estimate national incidence in China. This is a generally well written paper and provides important epidemiological information about this condition. Many of my queries below are clarifications, many relating to the fact that the Methods were sometimes unclear because so much information was put into the Supplementary materials (and particularly statistical analyses). Within the word limit, it would be helpful to better describe some aspects in the main text (as indicated below).

Methods:

This is a study of incidence of T1D, defined as newly diagnosed cases in the specified period. It is not clear from each of the data source descriptions and case ascertainment methods how you decided whether a case was 'newly' diagnosed. For example, description of hospital records databases provides no description of how you decided whether a case was diagnosed between 2010 and 2013 when selecting the cases for investigator review. Were previous hospitalisation records checked and if so, going how far back? This is important to know as being admitted to hospital for the first time during the study period does not preclude them from having being diagnosed many years before.

Similarly for the pharmacies and medical insurance databases – how was the decision made that these were newly diagnosed cases. Did you rely on the providers checking their historical records for whether patients had insulin prescriptions prior to the study period to determine 'newly diagnosed' status? (This information could go in the Supp section).

Answer: Thank you for the nice comments and constructive suggestions. We would rearrange our manuscript and supplemental materials accordingly. Details can be found in the answers below.

When we designed the study, we went over all large epidemiology study on T1D and developed the definition of ‘newly diagnosed T1D’ case. And we gave clear instructions regarding this to our participating investigators, who are endocrinology and/or pediatric specialists. We relied on them to search the medical record database in their hospitals using the pre-specified searching strategy. With the medical record database, they were able to navigate all the hospitalization episodes for a particular patient in the same hospital, as well as the details of each admission (all including present history and past medical history). The regulation required that the database should keep hospitalization records for at least 15 years. Our investigators would then report any potentially eligible cases based on this information and their judgement to the Data Coordinating Service Provider (DCSP). (supplemental materials, section 3, 1.1, p.19)

For cases reported from pharmacies, we relied on our participating investigators to report eligible cases whenever they encountered any during our study period (supplemental materials, section 3, 1.2, p.20). They would determine the eligibility of a case based on interviewing the patient and out-patient medical records.

For cases reported from the medical insurance database, we were able to achieve the information of the hospitals where the patient obtained their prescription of insulin. We asked the participating investigators via DCSP to check the outpatient medical record from corresponding hospitals to determine the date of T1D diagnosis, as we have suggested in our supplemental materials (section 3, 1.3, p.20).

Surely, our investigators might make mistakes, though it is not very probable. And when they had doubt about the diagnosis, we had the Expert Committee on T1D Diagnosis to decide whether a case should be included. We would add more details to our supplemental materials as noted above.

Methods pg 3:

– 'physician diagnosed T1D' – cases ascertained from the diabetes communities are included based on self-report of diabetes, not physician diagnosis.

Answer: Thank you for your comments. The patient self-report from diabetes communities was a data source for recapture. The total number of cases ascertained in this source is 443. During data collection via questionnaire, hospital name where the patient was first diagnosed was collected. Then the details of the collected cases would be sent to the corresponding hospitals to be validated by the DCSP. Once it was found that the case could not be matched with medical record database, the participating investigator modified the record according to the medical record if it fitted the inclusion criteria, or excluded the case if it was not eligible. The feedback would

be sent to the DCSP, the latter anonymised submitted the eligible cases. Therefore, the diagnosis criteria was the same as the cases from the other data sources. We did not attach questionnaires from self- report in the submitted materials in our previous submission. We would provide a copy as part of the supplemental materials this time. (supplemental materials, section 3, appendix, p.22-23) Also, we have revised the manuscript (methods, paragraph 5, p.5) and the supplemental materials. (section 3, 1.4, p.20)

- '…resident population in the investigated areas in the index years' – what are the index years – study years?

Answer: Yes, the index year means the study year. To avoid confusion, we would change our manuscript and supplemental materials. Thank you for your suggestion.

Methods pg 4:

- On-site inspection (para 1): this terminology and context is unclear in the main methods section. The description in the Supp materials describes this as a quality assurance activity. I suspect it would be better to use this terminology in the main Methods section, as you have done in the Supp materials (pg 22). I'm unclear why the 18 month time period after the end of the study period was required, and wonder if it needs to be mentioned in the main methods.

Answer: Thank you for your comments.

For the terminology of "on-site inspection", actually the "on-site inspection" mentioned in the manuscript contains two procedures: 1) data validation to see if the cases reported was eligible and if it contained any deficit; and 2) data inspection to confirm

the fidelity of the cases reported as mention in the Supplemental materials. We agreed with your opinion that the terminology would cause confusion, so we would revise our manuscript.

For the 18-month time period, previous studies on diabetes differential diagnosis found that the diagnostic time window from first time patient seeing a doctor to final diagnosis clarification was about 18 months.[1] In our medical record searching strategy, to avoid missing cases, we included the ICD codes coded for unclassified diabetes. Therefore, some cases of type 2 diabetes, MODY or other types of diabetes could be included. The 18 months period allowed us to have reasonable time window to clarify the diagnosis. We would add the details to our manuscript. (methods, paragraph 10, p.6-7)

Reference：

1. Zhong VW, Pfaff ER, Beavers DP, Thomas J, et al. Use of administrative and electronic health record data for development of automated algorithms for childhood diabetes case ascertainment and type classification: the SEARCH for Diabetes in Youth Study. Pediatr Diabetes.2014,15:573-584

- 'The resident population was defined consistently with the denominator' – this is unclear – do you mean "The denominator was comprised of the resident population"?

Answer: By this sentence we meant "we only included the newly diagnosed cases from the the resident population." We would delete it in our manuscript to avoid confusion. Thank you for pointing out.

- Case ascertainment: - (+ Supp materials pg 18) ascertainment from medical record databases. You used Type 1 diabetes ICD codes to select patients from participating hospital databases and investigators then reviewed medical records and lab results for these patients. Firstly, this method would miss some T1D patients, as misclassification in hospital coding of diabetes type is possible and a known issue (ie, patients could be coded as type 2 diabetes – E11.x – but are actually type 1 – you would not have picked up these patients with your method). Do you have an estimate of the degree of misclassification and therefore proportion of patients missed? This should be mentioned in the Limitations.

Answer：Thank you for your comments. Using ICD codes for searching strategy could cause some missing cases. In order to avoid missing cases, we asked the participating investigators to search for all the cases of children under 15 years who had diagnosis of diabetes regardless of classification. Then the investigator should examine the medical records of these cases to clarify the diagnosis, and report any potentially eligible cases.

For persons over 15 years, we included “diabetes-unclassified” in our searching strategy. It was technically infeasible to collect data with ICD code E.11x, due to large diabetic population. The prevalence of diabetes in China is approximately 10% in adults, among which more than 90% of them were type 2 diabetes. [1] But according to a report, [2] the prevalence of latent autoimmune diabetes in adults with low-titer GAD who are most often misdiagnosed as type 2 diabetes at onset, is no more than 5% of all the prevailing diabetes. Certainly, we cannot completely avoid missing cases due to excluding E11.x, but the actual missed case number would be extremely low.

We would revise our manuscript (discussion, paragraph 11, p.16) to state the issue. Also, we would revise our supplemental materials (section 3, 1.1, p.19) adding these details.

Reference:

1. Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, et al. Prevalence of diabetes among men and women in China. N Engl J Med. 2010;362(12):1090-101.

2. Liu L, Li X, Xiang Y, Huang G, Lin J, Yang L, et al. Latent Autoimmune Diabetes in Adults with Low-Titer GAD Antibodies: Similar Disease Progression With Type 2 Diabetes. A Nationwide, Multicenter Prospective Study (LADA China Study 3). 2015;38(1):16-21.

Methods pg 5 – initials of name as a mandatory identification marker – this sounds unusual to only use initials as this would greatly reduce the correct identification of patients to allow capture/recapture method to be implemented. Did you have surname and first/middle name, or only initials for first name?

Answer: Thank you for your comments. Regarding the initials of the name of the patient, the name of a Chinese generally consists of 2 to 4 Chinese characters, and each character has a pinyin initial letter. Take our first author for example. Jianping Weng contains 3 characters, and can be abbreviated into WJP. We believe that together with the other mandatory markers and optional markers available, we could have enough information for deduplication. And in case we were not sure about the matching, we sent the doubtful cases back to DCSP for clarification.

Methods, pg 7, I was unclear why you included the covariates that you did in the Poisson model (and where sunlight exposure came from), and how they were tested for, until I read Section 6 in the Supp methods. I can see your sentence on using Spearman correlation

testing but its not clear who it relates to the Poisson models, so it should be mentioned before the description of calculating IRs, and should be more detailed (similar to the intro paragraph of Section 6 – this gives a good description).

I think it also needs to be clearer in this section that you calculated incidence rates for the 13 areas (and how this was done), and that you then separately extrapolated these data to calculate a national IR for T1D in China – the models for each of these are just not clear at the moment. It is well described in Section 6 but not enough detail in the manuscript.

Answer: Thank you for your comments. We reviewed literature on possible influencing factors on incidence of T1D. It is reported that apart from genetic background, latitude, ultra-violet exposure, air pollution level, 25-(OH)-vitamin D level, early exposure to dietary cow's milk proteins, virus infection and *etc*. are possible influencing factors. [1-5] We did not collect blood sample, nutrition information, or detailed early history of the patients. Air pollution data was not available during our study period. Therefore, based on accessibility of data, we analysed the relationship of T1D incidence and sunlight duration, birth rate, proportion of urban population, latitude and longitude. We would revise our manuscript and rearrange the supplemental material to clarify how and why we chose the covariates for our Poisson model, to provide more details on calculation of the incidence rates of the 13 areas. (results paragraph 5, p.10; supplemental materials, section 6, p.28)

References:

1. Staples J A, Ponsonby A L, Lim L L, et al., Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect, 2003; 111: 518-23.

2. Atkinson M A, Eisenbarth G S, and Michels A W, Type 1 diabetes. Lancet, 2014; 383: 69-82.

3. Craig M E, Nair S, Stein H, et al., Viruses and type 1 diabetes: a new look at an old story. Pediatr Diabetes, 2013; 14: 149-58.

4. Beyerlein A, Krasmann M, Thiering E, et al., Ambient air pollution and early manifestation of type 1 diabetes. Epidemiology, 2015; 26: e31-2.

5. Akerblom H K, Vaarala O, Hyoty H, et al., Environmental factors in the etiology of type 1 diabetes. Am J Med Genet, 2002; 115: 18-29.

I think you mean covariate, rather than covariant.

Answer: Thank you for your suggestion. We do mean covariate. We would revise the manuscript.

Results pg 8:

- You state that the overall estimated IR was adjusted for age, gender, population size and annual change in population from 2010-2013. What do you mean by adjusting for population size? Presumably log person-years was included in the Poisson model, thereby representing the population size in each 5-yr age group/gender stratification and is therefore not an adjustment covariate. Similarly, how (and why) did you adjust for annual change in pop per year? This is not described in the Methods.

Answer: Thank you for the comments.

The overall estimated incidence rate meant the incidence rate in 13 investigated areas as a whole, not the estimation for the whole nation. Thus, we did not used the Poisson model for this “overall rates”. We calculated the overall rates as main

methods noted, incidence rate was the number of newly physician diagnosed T1D cases between 2010 to 2013 divided by the number of the resident population at risk in the 13 investigated areas during the study period. But as you have suggested, we did not adjust for population size for the overall rate. Rather, we derived the number of resident population in the 13 investigated areas by gender and age stratifications, with annual change of population adjusted according to government reports. We would revise the manuscript (results, paragraph 2, p.9) to make it clear.

As for the national rates estimated by Poisson model, we adjusted population size in a different way from including it as a covariate. It is not a classic Poisson model. In the final calculation step (the last equation shown in Supplemental Material, Section 6, p.28), we have adjusted our national estimated rates using the population size data from the 31 provinces in 2010 as weight, to better reflect the population distribution in the whole nation. We had considered the effect of annual change of population on incidence of T1D during the study year, as reflected by birth rate. But correlation analysis showed that it was not significantly correlated with the incidence rate, so we did not include it in the model. We would revise the manuscript to clarify this. (results, paragraph 5, p.10)

Discussion is well written. Given your emphasis on the higher proportion of newly diagnosed cases in adults in your study (although lower IRs than younger groups), it would be worth elaborating on possible reasons for this in the context of diabetes onset, diagnosis and other possible confounders, in China. Particularly given that other studies (eg, ref 2) seem to indicate that there may be a shifting to diagnosis at younger ages. Additionally, how confident are you of the accurate ascertainment of the older (especially very old T1D) cases?

Was extra checking done in these cases? Surely there is an increasing likelihood that some of these cases are not newly diagnosed.

Answer: Thank you for your nice comments and constructive suggestions.

Our study is the first nationwide study to report T1D incidence in all age groups. Our results provide novel data on the constituent ratio of newly onset T1D cases regarding age, revealing that the majority of the newly diagnosed cases was adult onset. This may be due to the large proportion of adult in the population, though lower incidence rates. Similar findings were seen in a population based study held in a county in Sweden, [1] reporting that 69.0% (109/158) newly diagnosed cases of T1D was over 20 years of age. But the incidence rates were still higher in younger age groups. We did not measure the trends in the incidence rates, and thus we are not able to determine if there is a shifting to diagnosis at younger ages as Patterson et al suggested in the EURODIAB study. [2]

As for the accuracy of case ascertainment, in our study, as in most large-scale epidemiology studies, the diagnosis of T1D was clinical diagnosis. We relied on the participating investigators, who are endocrinology and/or pediatric specialists, as well as our Expert Committee for T1D diagnosis, to make the judgement. Also, we tried to further confirm the T1D diagnosis in adult-onset patients via presence of diabetic autoimmune antibodies (DAAs). As shown in Table 3, in patients aged ≥15 years who received DAAs tested by radiobinding assay confirmed by the Islet Autoantibody Standardization Program at the First Affiliated Hospital of Nanjing University or the

Second Xiangya Hospital of Central South University, more than 55% had at least 1 DAA positive within 6 month of diabetes onset. Moreover, if there was doubt in the classification of diabetes of a particular case, especially for very old adult-onset cases, apart from DAA(s) tests, we had an 18-month follow up period for each of the included cases to make the diagnosis as firm as possible. Through these means, though certain mistakes were inevitable, we are pretty confident of our diagnosis for these adult-onset patients.

Reference:

1. Thunander M, Petersson C, Jonzon K, Fornander J, Ossiansson B, Torn C, et al. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. Diabetes research and clinical practice. 2008;82(2):247-55.

2. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet (London, England). 2009;373(9680):2027-33.

Conclusion:

You state that you found a rapid increase in T1D incidence in <15 yr olds over the past 2 decades. You should reword this as your study did not measure trends and you are in fact comparing your data to previously published studies.

Answer: Thank you for your suggestions. Indeed, we did not measure the trends in incidence of T1D. This increasing rate was calculated based on comparison of this study and the results from a part of the WHO DIAMOND project. We would revise our manuscript to make it clearer. (discussion, paragraph 3, p.13)

Additional Questions:

Please enter your name: Lee Nedkoff

Job Title: Research Fellow

Institution: The University of Western Australia

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:

Originality

This study from China purports to be a nationwide population-based registry study of T1D incidence, although on closer scrutiny covers 10% of the total population and 6% of the Chinese 0-14 year old population. These data are then used to estimate national incidence of T1D across all age groups. The work is therefore novel and important, comprises relatively large case numbers but relies on a highly restrictive sample size.

Answer: Thank you for your concern on sample size and study population selection.

China is a country with low incidence of T1D and with a large population. We recognised that it needed a large, well sampled study population to estimate T1D incidence rate properly.

According to our calculation, coverage no less of 60 million population could provide enough power to estimate the incidence rate over 1.0 per 100,000 person-years. Our study population covered over 133 million person-years at risk, which offers a population size large enough.

We selected these 13 investigated areas based on the following considerations: 1) China is divided into 7 Administrative Regions (as shown in Figure 1) according to geographic location, climate, culture, ethnicity and population. We chose our investigated areas based on the representativeness of these Administrative Regions. We selected at least one investigated area from each of these Administrative Regions. Besides, huge imbalance in population density exists in China: more than 90% of the population reside in the southeast part. And we ensured that there was at least one investigated area every 5° of latitude (Figure 1, Table S1 in Supplemental Materials). Therefore, we selected 1 to 2 additional investigated area(s) in some of the administrative regions. 2) The investigated areas also consist of areas of different economic development levels as represented by gross domestic production (GDP) in 2010. The investigated areas covered the less developed, moderately developed and well-developed areas in China. This basis of selection ensured the socio-demographic and geographic representativeness of the investigated areas.

Therefore, we believe that the study population selected were national representative.

Importance of work to general readers

If the data related to a larger proportion of the population of China and the authors gave greater justification for the choice of hospitals used in the study in terms of generalisability, then this would be an appropriate study to be reported in the journal. Unfortunately, neither of these criteria are satisfied.

Answer: Thank you for your comments. As we have addressed in the previous question, our selected population was national representative, and adequate to give a proper estimate of T1D incidence of China. As for hospitals participated in the study, we did not choose particular hospitals. Instead, we included all the hospitals in the investigated areas that were capable to provide diabetes care, as we mentioned in the main methods. Therefore, we believe that we have fulfilled the requirements in terms of generalisability.

Scientific reliability

Research Question - clearly defined and appropriately answered?

The research question is somewhat misleading as it states that nationwide T1D incidence rates will be 'investigated', when in actual fact, this is a sub-national study of 13 areas of China comprising 10% of the total population and the authors extrapolate national incidence rates based on this sample.

Answer: Thank you for your comment. As has mentioned previously, the study population came from 13 areas. These areas are selected from 7 Administrative Regions across China based on geographic location, climate, culture, ethnicity, population density, and economic development levels. And according to our calculation, this provided enough power to estimate the incidence rate over 1.0 per 100,000 person-years.

Furthermore, to estimate the nationwide T1D incidence rate, we develop a model to adjust possible influencing factors.

Therefore, we believe that the study population is national representative, and able to provide proper estimate of T1D incidence in China.

Overall design of study - adequate ?

A reasonable study design, clearly involving many hours of dedicated research time across multiple centres. The authors should be congratulated on compiling these data on T1D. However, there are serious questions about the generalisability of the results. How were these 13 areas selected? Are they representative of the socio-demographic characteristics of China? The paper gives little insight into this crucial issue.

Answer: Thank you for your comments. As we have stated previously, we selected these 13 investigated areas based on the following considerations:

1) China spans from 73°33′E to 135°05′E in longitude, and 3°51′to 53°33′N in latitude, covering approximately 9.6 million km^2, bearing more than 1.3 billion population in 2010. She is divided into 7 Administrative Regions (as shown in Figure 1, Northeast, North, Northwest, Southwest, Central, East and South) according to geographic location, climate, culture, ethnicity and population. We chose our investigated areas based on the representativeness of these Administrative Regions. We selected at least one investigated area from each of these Administrative Regions. Besides, huge imbalance in population density exists in China: more than 90% of the population reside in the southeast part. And we ensured that there was at least one investigated area every 5° of latitude (Figure 1, Table S1 in Supplemental Materials). Therefore, we selected 1 to 2 additional investigated area(s) in some of the administrative regions.

2) The investigated areas also consist of areas of different economic development levels as represented by gross domestic production (GDP) in 2010. The investigated areas covered the less developed, moderately developed and well-developed areas in China.

This basis of selection ensured the socio-demographic and geographic representativeness of the investigated areas.

Furthermore, to estimate the nationwide T1D incidence rate, we develop a model to adjust possible influencing factors. We believe that by investigating the selected areas could be defined as a nationwide study.

Moreover, the SEARCH study[1] investigated the population from selected areas as follows to estimate the diabetes in youth of the USA: (1) in geographically defined populations in Ohio, Washington, South Carolina, and Colorado; (2) among health plan enrollees in Hawaii and California; and (3) 3 American Indian reservation-based populations in Arizona and New Mexico, and some participants in Pima Indian study in Arizona.

Reference:

1. Dabelea D, Bell RA, D'Agostino RB, Jr., Imperatore G, Johansen JM, Linder B, et al. Incidence of diabetes in youth in the United States. Jama. 2007;297(24):2716-24.

Participants studied - adequately described and their conditions defined?

Diagnosis of T1D was adequately classified. Clear justification for focusing on cases diagnosed from 2010-2013 was missing.

Answer: Thank you for your comments. We focused on cases diagnosed during 2010 to 2013 because in 2010 the National Bureau of Statistics of China carried out a national population census. The results from the census provides us with accurate estimate of the denominator, data for birth rates, economic development status, urban population proportion. And from 2011 on, we estimated the change in the denominator by the governmental released data in each region as we noted in the supplemental materials. We stopped collecting data by the end of 2013, because we had to ensure that the diagnostic time window was long enough (no less than 18 months) for cases potentially eligible when we started on-site data validation and inspection in June 2015. We have included these considerations in our supplemental materials (section 2, part 1, p.15). We would revise our manuscript accordingly. (methods, paragraph 4, p.4)

Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ?

Statistical analysis appeared satisfactory with a reasonable level of detail describing the estimation of national incidence rates of T1D. The choice of covariates included in the prediction modelling seemed to lack any substantial justification.

Answer: Thank you for your nice comments regarding to our statistical methods.

As for your concern for the choice of covariates, before we established the Poisson model, we reviewed literature on possible influencing factors on incidence of T1D. It is reported that apart from genetic background, latitude, ultra-violet exposure, air pollution level, 25-(OH)-vitamin D level, early exposure to dietary cow's milk proteins, viruses infection and etc. are possible influencing factors.[1-5] Therefore, based on accessibility of data, we included latitude, longitude birth rate, urban population proportion and sunlight exposure (representing ultra-violet exposure) into correlation analysis shown in Supplemental Material, Section 6, part 1, and decided which covariates were included in the Poisson model. We did not collect blood sample, nutrition information, or detailed early history of the patients. Air pollution data was not available during our study period. But we have included as many influencing factors as possible. We would revise our manuscript (results, paragraph 5, p.10) and supplemental materials (section 6, part 1, p.28) to give more details.

Reference:

1. Staples J A, Ponsonby A L, Lim L L, et al., Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect, 2003; 111: 518-23.

2. Atkinson M A, Eisenbarth G S, and Michels A W, Type 1 diabetes. Lancet, 2014; 383: 69-82.

3. Craig M E, Nair S, Stein H, et al., Viruses and type 1 diabetes: a new look at an old story. Pediatr Diabetes, 2013; 14: 149-58.

4. Beyerlein A, Krasmann M, Thiering E, et al., Ambient air pollution and early manifestation of type 1 diabetes. Epidemiology, 2015; 26: e31-2.

5. Akerblom H K, Vaarala O, Hyoty H, et al., Environmental factors in the etiology of type 1 diabetes. Am J Med Genet, 2002; 115: 18-29.

There was also some concern in confirming all eligible cases of T1D were ascertained. This was based on mandatory marker including 'initials of name, gender, date of birth,…'. Why was no national identifying number not used? This would have made the de-duplication process much simpler and arguably more reliable. The matching process carried out by data managers also needs more detail and insight into the methods that were used to identify duplicate records.

Answer: Thank you for your comments. We did not use national identifying number due to personal privacy protection. The matching process including matching the mandatory markers in all the cases, within the investigated region, as well as across the investigated regions. If all the mandatory markers were identical in any two or more cases, we regarded that these records were duplicates. The optional markers, when available, would also be compared to assist the matching process. After this, if there was any doubt, the data managers contacted the DCSP to ask the investigators from participating hospitals to confirm if they were duplicates. The description of the matching process would be added to our supplemental materials (section 3, part 4, p.22).

How was ethnicity classified?

Answer: Thank you for your comment. Over 90% of the Chinese population is of the Han race. The data of ethnicity from the primary data sources (medical record databases, out-patient pharmacy registry and medical insurance database) was from authorized personal identity certificate. Only the data from a very small number (less than 50) of patients who only presented in the diabetes communities source (one of our recapture sources) was self-report.

Results - answer the research question? Credible? Well presented?

Reasonably well presented results.

Answer: Thank you for your nice comments.

What was the purpose of the questionnaire mentioned in the Patient Involvement section? I couldn't see a copy included in the paper.

Answer: Thank you for your comment. We used a questionnaire, mentioned in the Patient involvement section, to collected self-report information from patients from diabetes communities. We did not attach it in the submitted materials in our previous submission. We would provide a copy as part of the supplemental materials (section 3, appendix, p.22-23) this time.

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear?

Conclusions were inadequately presented due to the reasons given above in terms of questions over generalisability. Strengths and weaknesses section did not address the main study limitations.

Answer: Thank you for your comment. As we have provided elaborate explanation for the rationale for the national representativeness of our study population in previous questions, we believe that our conclusion is reasonable.

A 6.5% annual increase in incidence appears highly questionable and unsustainable.

Answer: Thank you for your comment. We calculated this increasing rate based on comparison between this study and the results from part of the WHO DIAMOND project, assuming that T1D incidence rates in China grew annually at the same speed. Provided the differences of study design in these two study and the assumption mentioned, this is a very rough estimation and should be interpreted with caution. We have addressed this in our manuscript. (discussion, paragraph 3, p.13)

References - up to date and relevant? Any glaring omissions?

Seem adequately cited and up-to-date.

Answer: Thank you.

Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?

Satisfactory.

Answer: Thank you.

Other comments.

The paper contains multiple spelling and grammatical errors. I suggest the authors have the paper proof-read to improve this aspect.

Answer: Thank you for your comment. We have gone over our manuscript repeatedly manually and using the spelling and grammar checking tool in the Word software, but could not figure out the problems. This may be due to difference criteria of the tool in Word of British English and American English, and the fact that we are not native speakers. Would you and the editors be kind to give more detail regarding spelling and grammar to help us to improve?

Additional Questions:

Please enter your name: Dr Richard Feltbower

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Institution: University of Leeds

Reimbursement for attending a symposium?: No

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Reviewer: 3

Recommendation:

Comments:

Review BMJ

Manuscript ID BMJ.2017.040488.

Incidence of type 1 diabetes mellitus in China: population based study, 2010 – 2013.

Thank you for asking me to review this very interesting manuscript.

I apologise for the delay in my report.

This study aimed to estimate type 1 diabetes incidence in all age-groups in China during 2010-2013. It is the first population-based registry study of T1D incidence in China in the past two decades. This registry study includes data from multiple independent sources, during the period 2010 – 2012, covering over 133 billion person-years at risk. The authors have estimated the study to cover approximately 10% of the whole Chinese population.

They find the estimated total incidence of T1D in China to be 1.01 per 100,000 PYR. Stratified into age-groups the incidence is 1.93, 1.28 and 0.69 per 100,000 PYS for age-groups 0-14 years, 15-29 years and > 30 years, with a peak in incidence at age 10-14 years.

Only the incidence in childhood-onset T1D (<15 years) was positively correlated with latitude.

The study period started on Jan 1, 2010, and ended on Dec 31, 2013. This includes at least 18 months of follow-up time of all patients before the project started the on-site inspection in June 2015. The patients were divided into cases with “Definitive T1D” and “Uncertain cases”. The uncertain cases were followed over time and were, based on the registration investigator grouped into “Confirmed T1D”, “Denied the diagnosis of T1D”, “Registration investigator doubted the diagnosis”. The last group was re-examined by the Expert Committee on the Diagnosis of T1D.

The registration of cases included standardized information about the onset of T1D as; clinical symptoms and DKA at onset, family history, C-peptid and diabetes autoantibodies (at any time), and anti-hyperglycemia treatment after diagnosis.

Novel

This is a very large and impressive study which reports important and novel data on type 1 diabetes in China, in all age-groups. Few international studies include data on incidence of T1D after the age of 15 years, mainly because this is data difficult to collect.

Confidence-building

The manuscript is well written and includes a clear flow-chart for this impressive and very resource intensive study. With the knowledge of how difficult it is to collect this data I find it confidence-building the way the authors in detail describe the data collection in the Methods.

Conclusion:

This is a well written, comprehensive study. The study is well presented in Methods and with a clear flow chart. I find the Discussion well written with a balanced discussion of the results and a balanced presentation of strengths and limitations.

I have only a few criticisms:

1) The incidence of DKA within 6 months of diagnosis was high with a range from 51.5% to 30.8% in the age-groups 0-14 years, 15-29 years and > 30 years. It is not made clear what the percentage of DKA at onset of diabetes was. “Within 6 months is unclear, and should be divided in “at onset” and “after onset, within 6 months”. This number represents to different situations, the first one “DKA at onset of T1D”; lack of awareness in the population and health professionals. “DKA after onset” might reflect an insufficient teaching of the patient about diabetes or lack of insulin. This results should have been discussed.

Answer: Thank you for your comments. We could not decide the exact time of the incidence of DKA within 6 months of diagnosis. It could be at onset, after onset, or within 6 months of diagnosis. We were not able to distinguish among them. Certainly, as you indicated, it represented different situations. We would revise our manuscript to briefly discuss this. (discussion, paragraph 9, p.16)

2) Also DKA of 51.5 % in children is very high. The study does not report any numbers on mortality caused by DKA at onset. With the high number of DKA reported in all age-groups, one would expect this to occur as well. Are any dead cases included in the study?

Answer: Thank you for your comment. We did collect data of dead cases due to diabetes/hyperglycaemia/DKA. In all the included cases, we documented 2 dead cases due to DKA. One is a 24-year-old young male, the other is a 4-year-old girl. We would add the data to our results. (Table 2)

3) The definition of DKA should be included in Methods, as well as the definition of T1D.

Answer: Thank you for this suggestion. When we designed the study, based on available guidelines[1-2] and data availability in China, patients with following history and lab results were diagnosed as DKA.

A. Hyperglycaemia (glucose >11.1mmol/L) or known diabetes mellitus;

B. Ketonemia: elevated blood ketobody level as judged by participating investigators or significant ketonuria (more than 2+ on standard urine sticks);

C. Acidemia: Bicarbonate($HCO3^-$) <15.0mmol/L and/or venous pH<7.3.

We would add this DKA diagnosis criteria to our manuscript. (methods paragraph 9, p.6)

As for the diagnosis criteria of T1D, it is a physician judged, clinical diagnosis. It was established based on American Diabetes Association descriptions of T1D and World Health Organization reports for the classification of diabetes, as we stated in our manuscript. Details are provided in the supplemental materials. Although these details

would be important to decide if we determined the diagnosis properly, and we would very much like to include them into our main methods in the manuscript as you suggested. But it goes too long, and we have to leave it to the supplemental. Please understand.

Reference:

1. Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis (DKA) in adults - revised - second edition 2013 [updated September 2013; accesed 2016 October 26, available from: https://www.diabetes.org.uk/professionals/position-statements-reports/specialist-care-for-children-and-adults-and-complications/the-management-of-diabetic-ketoacidosis-in-adults].

2. Wolfsdorf JI, Allgrove J, Craig ME, et cl. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes. 2014 Sep;15 Suppl 20:154-79.

4) In many incidence studies of T1D the age <1 year is excluded, mainly because insulin dependent diabetes in this age-group can be MODY-diabetes.

Answer: Thank you for your comment. Neonatal diabetes apparent T1D with onset before 6 months of age. In this study, Cases with diabetes onset before 6 months of age were excluded. MODY is diabetes with onset age under 25 years, and insulin free for at least 5 years after diabetes diagnosis. Cases with C-Peptide>0.5nmol/L or independent of insulin after 6 month of diabetes onset were excluded. We would add this details to our supplemental materials. (section 3, part 2, p.21)

Additional Questions:

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