BMJ - Decision on
Manuscript ID
BMJ.2017.040488

Body: 29-Sep-2017

Dear Prof. Weng

Manuscript ID BMJ.2017.040488 entitled "Incidence of type 1 diabetes mellitus in China: population based study, 2010 – 2013"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

dr. Wim Weber
European editor, The BMJ
wweber@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Wim Weber (Chair), Jamie Kirkham (Statistics advisor), Sophie Cook, Elizabeth Loder, José Merino, Rubin Minhas, George Rőggla, Tiago Villanueva, Daoxin Yin.

Decision: Put points

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

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?

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?

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.

The discussion section is at places somewhat difficult to follow.

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?

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).
Methods pg 3:

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

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

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.
- ‘The resident population was defined consistently with the denominator’ – this is unclear – do you mean “The denominator was comprised of the resident population”?
- 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.

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?

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.

I think you mean covariate, rather than covariant.

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 ageroup/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.

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.

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.

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

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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.

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.

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.

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.

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.

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.

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.

How was ethnicity classified?

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

Reasonably well presented results.

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

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.

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

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

Seem adequately cited and up-to-date.

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

Satisfactory.

Other comments.

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

Additional Questions:
Please enter your name: Dr Richard Feltbower

Job Title: Senior Lecturer

Institution: University of Leeds

Reimbursement for attending a symposium?: No

A fee for speaking?: 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.

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?

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

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.

Additional Questions:
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