PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence of diabetes-related complications in Chinese patients with type 1 diabetes: A population-based longitudinal cohort study in Taiwan
AUTHORS	Ou, Huang-tz; Lee, Tsung-Ying; Li, Chung-Yi; Wu, Jin Shang; Sun, Zih Jie

VERSION 1 - REVIEW

REVIEWER	Shona Livingstone University of Dundee
REVIEW RETURNED	01-Feb-2017

GENERAL COMMENTS	Appropriate statistical methods have been applied and have been adequately described to enable statistical review. Some minor edits to the text would improve readability. The last sentence of the conclusion could be re-expressed as "The incidence of diabetes-related complications after diagnosis differed by age and sex." The authors are correct to describe these as differences by age rather than differences between early and late-onset diabetes adjusted for current age, as in practice it would be difficult to disentangle the effect of age at onset from current age. The titles for tables 1 and 2 could, for example, be changed to simply "Overall Incidence density of diabetes-related complications among patients with incident type 1 diabetes diagnosed between 1999 and 2013" and "Incidence density of diabetes-related complications by age and sex among patients with incident type 1 diabetes diagnosed between 1999 and 2013". The median and percentiles for age at diagnosis should be shown for those aged <-12 y and >=13 at diabetes onset and overall. Minor typos where less than or equal symbol has been entered in place of the greater or equal to symbol when describing those diagnosed at age 13 years or older. These minor corrections can be made and agreed with the editor without re-review by a statistician.

REVIEWER	Maya Fayfman Emory University School of Medicine, USA
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	Abstract: Page 3; line 11-12: Please define late onset DM Introduction: Page 6; line 10-14: In reviewing variability in incidence of complications by country, it would be helpful to list the specific countries referenced.

	Methods: Page 7; line 43-46: Is there a reference that validates use of the LHDB as being representative of the Taiwan population. If this is not available, can you site what percentage of the population is under this system? Page 8, line 10: Do all patients with DM 1 receive the catastrophic Illness Card. Are there limitations to eligibility? Or are their any barriers/hurdles to enrollment" If yes, this may be a limitation as it potentially selects patients who are more ill or have more medical literacy to apply. There are several questions regarding the choices for the categorizations used to define complications. -Mild hypoglycemia: It seems that this is defined by hypoglycemia confirmed during an outpatient visit. This does not necessarily coincide since patients can have mild or severe hypoglycemia in the outpatient setting. Are actual BG values available? This would be a more precise way of classifying hypoglycemia severity (also consider hypoglycemia with symptoms if available). -hospital hypoglycemia is also problematic as it likely correlated with need for hospitalization. It is likely that patients hospitalized for DKA or other reasons are more likely to have hypoglycemia in the hospital. Is there a way to adjust hospital hypoglycemia for the frequency of hospitalizations? -Retinopathy is listed as a separate category from proliferative retinopathy and STDR. Are these subgroups of retinopathy or separate categories. Please clarify in the methods section Results Table 1: Number of cases refers to the number of patients who did not have a given complication at the time of diagnosis. This suggests that quite a few patients had some of these complications preceding dx of DM1. This does not seem to make sense for a number of these, particularly DKA and retinopathy, for which all patients are expected to not have prior to diagnosis with DM1. If this is not the correct interpretation of these values, please clarify "number of cases with event": Please specify whether this is number of cases with events preceding dx and during the 15 year f/u period? Supplementary figures: It seems that cumulative incidence stops before 15 years in multiple cases and is variable for different patient groups. In the figure for CVD for example, it seems that follow up for all males and males with dx ≥13 yo have follow up extending to 15 years, but other groups only go to 12 years. Is there a way to adjust these figures so that the categories can be distinguished? Supplementary figures are generally difficult to follow. Consider magnifying areas of interest where the different groups divers. You may also connect the symbols using lines so that the trends are easier to follow. Please include further details in the legend to note where differences are significant.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Shona Livingstone
Institution and Country: University of Dundee
Please state any competing interests: No competing interests
Please leave your comments for the authors below

1. Appropriate statistical methods have been applied and have been adequately described to enable statistical review.
Responses: We very appreciate your review for polishing this submission.

2. Some minor edits to the text would improve readability. The last sentence of the conclusion could be re-expressed as "The incidence of diabetes-related complications after diagnosis differed by age and sex." The authors are correct to describe these as differences by age rather than differences between early and late-onset diabetes adjusted for current age, as in practice it would be difficult to disentangle the effect of age at onset from current age.
Responses: We agree with your comments. In clinical practice, it is difficult to disentangle the effect of age at onset (or diagnosis) from current age. Therefore, to be conservative, we have revised the sentence according to your suggestion.
(In the conclusion of abstract)
“Conclusions: Ethnically Chinese patients with type 1 diabetes were greatly affected by DKA and retinopathy. The incidence of diabetes-related complications after diagnosis differed by age and sex.”

3. The titles for tables 1 and 2 could, for example, be changed to simply "Overall Incidence density of diabetes-related complications among patients with incident type 1 diabetes diagnosed between 1999 and 2013" and "Incidence density of diabetes-related complications by age and sex among patients with incident type 1 diabetes diagnosed between 1999 and 2013".
Responses: Thanks. We have revised the titles as you suggested.
The title of Table 1: “Overall incidence density of diabetes-related complications among patients with type 1 diabetes between 1999 and 2013”
The title of Table 2: “Incidence density of diabetes-related complications by age and sex among patients with type 1 diabetes between 1999 and 2013”

4. The median and percentiles for age at diagnosis should be shown for those aged <-12 y and >=13 at diabetes onset and overall.
Responses: Thanks. We have added the median and percentiles for age at diagnosis (i.e., aged 0-12, aged ≥ 13 years) in the description of cohort section.
(Page 9, Line 2-5)
“The 25th, 50th (median) and 75th percentiles of age in early-onset group were 5, 8, and 10, respectively, with the mean age of 7.69 (standard deviation: 3.22). And, for late-onset group, the 25th, 50th and 75th percentiles of age were 17, 24, and 33, respectively, with the mean age of 26.47 (standard deviation: 11.60).”

5. Minor typos where less than or equal symbol has been entered in place of the greater or equal to symbol when describing those diagnosed at age 13 years or older.
Responses: Sorry for confusing. We have carefully checked the text and corrected the mistakes in the symbol for age at 13 years or older (“late-onset: ≥13 years”).

6. These minor corrections can be made and agreed with the editor without re-review by a statistician.
Responses: Thanks for your review and comments. We have revised the manuscript carefully according to your suggestions.

Reviewer: 2
Reviewer Name: Maya Fayfman
Institution and Country: Emory University School of Medicine, USA
Please state any competing interests: I have no competing interests.

Please leave your comments for the authors below

1. Abstract: Page 3; line 11-12: Please define late onset DM
Responses: Thanks. We have described the definition for late-onset diabetes as “the age at diagnosis at 13 years or older (“late-onset: ≥13 years”)” in the Abstract.

2. Introduction: Page 6; line 10-14: In reviewing variability in incidence of complications by country, it would be helpful to list the specific countries referenced.
Responses: Thanks to your suggestion. We have added the specific countries we cited in the text. (Page 5, Line 17 TO Page 6, Line 5)
“However, there is very little longitudinal data (e.g., Pittsburgh Epidemiology of Childhood-Onset Diabetes Complications (EDC) Study,1 EURODIAB IDDM Complications Study2) on the incidence of complications for type 1 diabetes, and previous estimates widely varied with countries (e.g., European countries,12 Finland,13 Denmarks,14 and United States10) and entailed different follow-up periods (e.g., 7 years,12 12 years,13 18 years,14 and 30 years10).”

3. Methods: Page 7; Line 43-46: Is there a reference that validates use of the LHDB as being representative of the Taiwan population. If this is not available, can you site what percentage of the population is under this system?
Responses: Thanks. The Longitudinal Cohort of Diabetes Patients (LHDB) is a valid national dataset that consists of a 120,000 de-identified new-diagnosed diabetes cases randomly selected from each calendar year of the National Health Insurance (NHI) program claims data in Taiwan, who were tracked back to 1996 and followed up to 2013 to establish a longitudinal cohort of diabetes. The NHI program is a mandatory-enrollment, single-payment system that covers over 99% of Taiwan’s residents (ref # 20 in the text). So, the LHDB is a representative data of diabetes cases in Taiwan and has been used for many research (e.g., ref #21-26 in the text) to evaluate long-term outcomes of diabetes. We have provided citations to briefly describe the LHDB and references that utilized the data in the LHDB.
References:
20. Cheng T-M. Taiwan’s new national health insurance program: genesis and experience so far. Health Affairs 2003;22(3):61-76.
21.Ou H-T, Chang K-C, Li C-Y, Wu J-S. Risks of cardiovascular diseases associated with dipeptidyl peptidase-4 inhibitors and other antidiabetic drugs in patients with type 2 diabetes: a nation-wide longitudinal study. Cardiovascular diabetology 2016;15(1):41.
22.Ou HT, Chang KC, Liu YM, Wu JS. Recent trends in the use of antidiabetic medications from 2008 to 2013: A nation-wide population-based study from Taiwan. Journal of diabetes 2016.
23.Hou W-H, Chang K-C, Li C-Y, Ou H-T. Dipeptidyl peptidase-4 inhibitor use is not associated with elevated risk of severe joint pain in patients with type 2 diabetes: a population-based cohort study. Pain 2016;157(9):1954-1959.
24.Ou H-T, Yang C-Y, Wang J-D, Hwang J-S, Wu J-S. Life Expectancy and Lifetime Health Care Expenditures for Type 1 Diabetes: A Nationwide Longitudinal Cohort of Incident Cases Followed for 14 Years. Value in Health 2016;19(8):976-984.
25.Ou HT, Chang KC, Li CY, Wu JS. Comparative cardiovascular risks of dipeptidyl peptidase-4 inhibitors with other 2nd and 3rd line antidiabetic drugs in patients with type 2 diabetes. British Journal of Clinical Pharmacology 2017.
26.Ou H-T, Chen Y-T, Liu Y-M, Wu J-S. Comparative cost-effectiveness of metformin-based dual therapies associated with risk of cardiovascular diseases among Chinese patients with type 2 diabetes: Evidence from a population-based national cohort in Taiwan. Diabetes Research and Clinical Practice 2016;116:14-25.

4. Page 8, line 10: Do all patients with DM 1 receive the catastrophic Illness Card. Are there limitations to eligibility? Or are their any barriers/hurdles to enrollment” If yes, this may be a limitation

as it potentially selects patients who are more ill or have more medical literacy to apply.
Responses: Thank. It has been shown that the CIC data are accurate and reliable with a positive predictive value of 98.3% in identifying type 1 diabetes in Taiwan (Reference #19 in the text). Because the patients with CIC are eligible for exemption from insurance premiums and co-payment, the application for CIC for type 1 diabetes should be based on several clinical examination reports (i.e., C-peptide, autoimmune antibodies such as ICA, IAA, GAD65) and past episodes of diabetic ketoacidosis, if any, which are carefully reviewed by the Bureau of Taiwan's NHI. According to Taiwan's NHI which is aimed to provide a universal healthcare coverage (Reference # 20 in the text), the physicians generally have no conflict interest to file the CIC application for patients once they are eligible. And, patients usually have no barriers to apply for CIC. Therefore, the patients with CIC for type 1 diabetes are likely to be true cases of type 1 diabetes cases. And, with regarding to clinical practice in Taiwan, there is little likelihood that patients with type 1 diabetes have barriers (e.g., health literacy) to apply for CIC as long as they are eligible.
References:
19. Lin W-H, Wang M-C, Wang W-M, Yang D-C, Lam C-F, Roan J-N, Li C-Y. Incidence of and Mortality from Type I Diabetes in Taiwan From 1999 through 2010: A Nationwide Cohort Study. PloS one 2014;9(1):e86172.
20. Cheng T-M. Taiwan's new national health insurance program: genesis and experience so far. Health Affairs 2003;22(3):61-76.

5. There are several questions regarding the choices for the categorizations used to define complications.
(1) Mild hypoglycemia: It seems that this is defined by hypoglycemia confirmed during an outpatient visit. This does not necessarily coincide since patients can have mild or severe hypoglycemia in the outpatient setting. Are actual BG values available? This would be a more precise way of classifying hypoglycemia severity (also consider hypoglycemia with symptoms if available).
Responses: Thanks for your comments. In fact, it is difficult for us to define the severity of hypoglycemia (i.e., mild, severe) because, in the National Health Insurance claims data analyzed in our study, blood glucose (BG) values and patients' symptoms are not available. Therefore, to be more precise, we have revised the term of hypoglycemia as "outpatient" hypoglycemia and "hospitalized" hypoglycemia. They are more conservative to refer "defined" hypoglycemic events that required for "outpatient visit" or "hospitalization" (, rather than to use "mild" or "severe" hypoglycemia, which however, we did not have data to support the severity of hypoglycemia).
(Method)
(Page 9, Lines 7-11)
"The complications of interest included acute complications, namely DKA (confirmed by hospital admission or emergency room visit for DKA), hypoglycemia (confirmed by defined hypoglycemic events required for outpatient visits or hospitalization for medical assistance or interventions), and chronic complications, namely CVD, nephropathy, retinopathy, and neuropathy."

Also, we have addressed the limitations regarding the use of claims data to estimate the incidence of hypoglycemic events in this study.
(Page 21, Lines 4-12)
"Also, the claims data do not capture clinical/minor symptoms or signs of diabetes-related complications such as minor microalbuminuria. The glycemic biomarkers such as blood glucose were not available from the claims data so the identification of hyperglycemia or hypoglycemia was only based on the ICD-9 CM diagnosis codes. So, we might under-estimate the incidence of hypoglycemic events and may not be able to disentangle the severity of hypoglycemia. However, the claims records capture defined diabetes-related complications that are required for medical assistance or treatments, which lead to more conservative estimates and reveal important manifestations of diabetes-related

complications for clinical attention."

(2) Hospital hypoglycemia is also problematic as it likely correlated with need for hospitalization. It is likely that patients hospitalized for DKA or other reasons are more likely to have hypoglycemia in the hospital. Is there a way to adjust hospital hypoglycemia for the frequency of hospitalizations?
Responses: Thanks. According to our operational definition for hospitalized hypoglycemia (define hypoglycemic event based on five diagnosis code in inpatient file of claims data), the hospitalized hypoglycemia included two types of hypoglycemic events: (1) hospital admission for hypoglycemia, and (2) hypoglycemia occurred during hospitalization, but the patients had hospital admission for other reasons (e.g., DKA). In fact, it is difficult to differentiate these two types of hypoglycemic episodes based on the retrospective claims data we utilized. However, in clinical practice in Taiwan, the primary diagnosis code (i.e., the first code among the five diagnosis codes in hospitalization) is typically to be the main reason for hospital admission. Therefore, we have provided the results based on the primary diagnosis in hospitalization to define hospitalized hypoglycemia. This way may also ease the concern if the patients had hospital admission for other reasons (e.g., DKA). We have addressed the discussion aforementioned in the Limitation section and provided the results in the Supplementary Table 2, and Supplementary Figures 2 and 3.
(Limitation section)
(Page 21, Line 12 TO Page 22, Line 7)
Moreover, based on our operational definition for hospitalized hypoglycemia (i.e., any one of diagnosis codes with hypoglycemia from the five diagnosis codes in the inpatient files of the NHIRD), two types of hypoglycemic events could be included: (1) hospital admission for hypoglycemia, and (2) other reasons for hospital admission (e.g., DKA), and then hypoglycemia happened during hospitalization. It is difficult to differentiate these two types of hypoglycemic events based on the retrospective claims data that we utilized. However, in the clinical practice in Taiwan, the first code from the five diagnosis codes in hospitalization is typically to be the main/primary reason for hospital admission. With this regard, we re-run the analyses for hospitalized hypoglycemia which was identified from the first diagnosis code in hospitalization. The results were provided in the Supplementary Table 2, and Supplementary Figures 2 and 3. These re-analytical results may also ease the concern that patients who came to hospital primarily for reasons that may induce hypoglycemia during hospitalization.

(3) Retinopathy is listed as a separate category from proliferative retinopathy and STDR. Are these subgroups of retinopathy or separate categories. Please clarify in the methods section
Responses: Thanks to your question. Sorry for confusion. Retinopathy in this study is a broad and aggregated classification for diabetic retinopathy, while STDR and proliferative retinopathy are specific vision disorders under the retinopathy category (subgroups of retinopathy). We have addressed the detail definition on retinopathy in Supplementary Table 1 and provided the footnotes in Tables 1 and 2 to make clarification.
(Footnotes under Tables and 1 and 2)
"*** Retinopathy is a broad and aggregated category, while proliferative retinopathy and STDR are specific vision disorders under retinopathy (i.e., subgroups of retinopathy)."

6. Results
(1) Table 1: Number of cases refers to the number of patients who did not have a given complication at the time of diagnosis. This suggests that quite a few patients had some of these complications preceding dx of DM1. This does not seem to make sense for a number of these, particularly DKA and retinopathy, for which all patients are expected to not have prior to diagnosis with DM1. If this is not the correct interpretation of these values, please clarify
Responses: Thanks for your question. The symptoms such as DKA could occur before type 1 diabetes diagnosis is confirmed (as shown in the study from Finland [Reference: Hekkala et al. 2007]). Also, in our study, we did found a certain proportion of patients who had diabetes-related

symptoms such as DKA before type 1 diabetes was confirmed (via ICD-9 code and CIC status for type 1 diabetes with other supportive clinical documents such as C-peptide, autoimmune antibodies such as ICA, IAA, GAD65). The patients with prior diabetes-related complications such as DKA (before type 1 diabetes diagnosis was confirmed) were included in our study cohort in the beginning (Figure 1, n=4,007). However, for our purpose to estimate the incidence of diabetes-related complications (e.g., DKA) after type 1 diabetes diagnosis, those with prior diabetes-related complications were not included in the analysis. So, in Table 1, the "number of cases" refers to the number of patients who did not have a given complication before the time of type 1 diabetes diagnosis.

Reference:
Hekkala, Anne, Mikael Knip, and Riitta Veijola. Ketoacidosis at diagnosis of type 1 diabetes in children in Northern Finland. Diabetes care 2007:30(4);861-866.

(2) "Number of cases with event": Please specify whether this is number of cases with events preceding dx and during the 15 year f/u period?
Responses: Sorry for confusion. To clarify, the "number of cases with event" refers to the cases having event after type 1 diabetes has been diagnosed, while those who had event occurred preceding diagnosis have been excluded from this analysis. We also have provided a footnote to clarify this under tables 1 and 2
(Footnotes under Tables and 1 and 2)
"** No. of cases with event refers to the number of patients who had incident events after type 1 diabetes was confirmed."

7. Supplementary figures: It seems that cumulative incidence stops before 15 years in multiple cases and is variable for different patient groups. In the figure for CVD for example, it seems that follow up for all males and males with dx ≥13 yo have follow up extending to 15 years, but other groups only go to 12 years. Is there a way to adjust these figures so that the categories can be distinguished?
Responses: Thanks to your comments. We have modified the supplementary figures; for all complications and subgroups by age and gender, the patients were followed up to 15 years.

8. Supplementary figures are generally difficult to follow. Consider magnifying areas of interest where the different groups divers. You may also connect the symbols using lines so that the trends are easier to follow. Please include further details in the legend to note where differences are significant.
Responses: Thanks to your suggestions. First, we have revised the figures according to your suggestions (i.e., connect the symbols using lines). Second, we have performed the statistical test to assess differences in the cumulative incidences by age and sex. And, the significant differences in cumulative incidences between subgroups were addressed in the legends of Supplementary Figure 1. In the method, we have added the specific test we used.
(Method)
(Page 10, Line 6-8)
"The cumulative incidence of diabetes-related complications was estimated by using the life table method (using the SAS LIFETEST procedure) and significant difference in cumulative incidence between subgroups were examined according to K-sample tests.31"

Reference:
31. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of statistics 1988:1141-1154.

VERSION 2 – REVIEW

REVIEWER	Livingstone, Shona

	University of Dundee, UK
REVIEW RETURNED	30-Mar-2017

GENERAL COMMENTS	Suitable statistical methods have been used and adequately described. To design description in the abstract could be improved by adding the word "retrospective" to become "A population-based retrospective longitudinal cohort" . To emphasize the value of this study in terms of extended follow-up from diagnosis please add to the text the median (25th and 75th percentiles) for the overall follow-up time, defined as the time from diagnosis to the first of the end of study period, death or loss-to-follow-up for acute complications. A point for the clinical team: looking again at the ICD-9 CM codes for hypoglycaemia, I am not sure that codes 270.3, 775.0 and 775.6 should be included. The impact is likely to be negligible with such codes rarely being given as the main diagnosis, and any necessary edits should be easy to correct without further detailed review.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Shona Livingstone
Institution and Country: University of Dundee
Please state any competing interests: No competing interests
Please leave your comments for the authors below

1. Suitable statistical methods have been used and adequately described. To design description in the abstract could be improved by adding the word "retrospective" to become "A population-based retrospective longitudinal cohort".
Responses: Very appreciate your review for polishing this submission. We have added the word "retrospective" in the abstract to become "A population-based retrospective longitudinal cohort".
(In the Design of abstract)
“Design: A population-based retrospective longitudinal cohort study.”

2. To emphasize the value of this study in terms of extended follow-up from diagnosis please add to the text the median (25th and 75th percentiles) for the overall follow-up time, defined as the time from diagnosis to the first of the end of study period, death or loss-to-follow-up for acute complications.
Responses: We certainly agree with your suggestion. We have added the median (25th and 75th percentiles) for the overall follow-up times in the beginning of Result section.
(Page 10, Line 12-14)
“The median (25th and 75th percentiles) for the overall follow-up times (defined as the time from diabetes diagnosis to death, loss-to-follow-up, or the end of study period, whichever came first) are 6.74 years (3.43 and 10.02 years).”

3. A point for the clinical team: looking again at the ICD-9 CM codes for hypoglycaemia, I am not sure that codes 270.3, 775.0 and 775.6 should be included. The impact is likely to be negligible with such codes rarely being given as the main diagnosis, and any necessary edits should be easy to correct without further detailed review.
Responses: Thanks. We have confirmed that these codes have been used in the previous studies of hypoglycemia (Nutr Metab Cardiovasc Dis. 2014;24(1):10-7. and BMC Endocr Disord. 2008;8:4, the citations under Supplementary Table 1), while the number of cases with hypoglycemic episodes identified by using these codes are very few.

References:
Cammarota, S., et al. "Lower incidence of macrovascular complications in patients on insulin glargine versus those on basal human insulins: A population-based cohort study in Italy." Nutrition, Metabolism and Cardiovascular Diseases 24.1 (2014): 10-17.
Ginde, Adit A., et al. "Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits." BMC endocrine disorders 8.1 (2008): 4.

VERSION 3 – REVIEW

REVIEWER	Shona Livingstone University of Dundee
REVIEW RETURNED	14-Apr-2017

GENERAL COMMENTS	I am satisfied with your corrections.