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Hospital admission in patients with type 2 diabetes mellitus in Thailand under the Universal Coverage Scheme: a time- and geographical-trend analysis, 2009–2016

--Manuscript Draft--

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Full Title:	Hospital admission in patients with type 2 diabetes mellitus in Thailand under the Universal Coverage Scheme: a time- and geographical-trend analysis, 2009–2016
Short Title:	Type 2 diabetes mellitus admission in Thailand under the Universal Coverage Scheme
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Keywords:	diabetes, type 2 diabetes mellitus, T2DM, DM, Thailand, admission rate, Universal Coverage Scheme, UCS, National Health Security Office, NHSO, non-communicable disease, disease burden
Abstract:	Background To estimate the time and geographical trends of nationwide admission rates of type 2 diabetes mellitus (T2DM) and its complications, including chronic kidney disease (CKD), myocardial infarction, cerebrovascular diseases, retinopathy, cataract, and diabetic foot amputation, descriptive analyses of 2009-2016 were performed using the data of the Universal Coverage Scheme (UCS) which covers nearly 70 percent of the Thai population. Methods and findings The database of T2DM patients aged 15-100 years who were admitted between 2009 and 2016 under the UCS and that of the UCS population were retrieved for the analyses. The admitted cases of T2DM were extracted from the database using disease codes of principal and secondary diagnoses defined by the International Classification of Diseases 9th and 10th Revisions. The T2DM admission rates in 2009-2016 were the number of admissions divided by the number of the UCS population. The standardized admission ratios (SARs)were further estimated in contrast to the expected number of admissions considering age and sex composition of the UCS population in each region. A linearly increased trend was found in T2DM admission rates from 2009 to 2016. Female admission rates were persistently higher than that of males. In 2016, an increase in the T2DM admission rates was observed among the older ages relative to that in 2009. Although the SARs of T2DM were generally higher in Bangkok and central regions in 2009, except that with CKD and foot amputation which had higher trends in northeastern regions, the geographical inequalities were fairly reduced by 2016. Conclusion Admission rates of T2DM and its major complications increased in Thailand from 2009 to 2016. Although the overall geographical inequalities in the SARs of T2DM were reduced in the country, further efforts are required to improve the health system and policies focusing on risk factors and regions to manage the increasing T2DM
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Opposed Reviewers:	
Response to Reviewers:	RESPONSE TO REVIEWERS We would like to thank the editor and reviewers for their helpful comments. Our responses to the comments from the editor and reviewers #1, #2 and #3 are given beneath each comment. The revised text is indented and edited in our response for ease of reference, with the section, page numbers and lines of the revised manuscript provided where necessary. Response to Reviewer #1 General comments: The selection of the patients is unclear and the presentation of the results is not clear either. This paper could have a great potential if presented in relation with incidence and prevalence. Major comments: Abstract Some results are only presented in the abstract. For example: “Among the five major diabetic complications, the average annual increase in admission rates in 2009–2016 for CKD, MI, stroke, cataracts, and amputation were 10.8%, 5.6%, 7.7%, 0.2%, and 6.1%, respectively.” Thank you very much for pointing this out. We missed reflecting the re-written parts of the main text to the abstract. We have substantially revised the abstract this time. (Abstract, page 3-4) Introduction Thailand has universal health coverage since 2002. Why your study report results only from 2009? Thank you very much for your observation. Although Thailand achieved UHC in 2002, we decided to use only data from 2009 onwards for our analyses since there were a number of missing values and errors in data before 2009. To make it clearer, we have added the following sentence in Materials and methods section as follows: “Although Thailand achieved UHC in 2002, we decided to use only data from 2009 onwards for our analyses since there were a number of missing values and errors in data before 2009 [13, 14].” (Materials and methods: Data, page 8, lines 17-19) Why only part of the population is covered (69.9%) by the universal health coverage as mentioned in the introduction? Thank you very much for your inquiry. Please see Introduction section (page 5 line 19 to page 6 line 3) where we explained that there are other major health protection schemes in Thailand, i.e. the Civil Service Medical Benefit Scheme and the Social Security Scheme, and the Universal Coverage Scheme (UCS) is the third scheme to cover the rest of the population, so that the country can achieve UHC. I strongly suggest to focus your paper in Thailand globally with prevalence, incidence and mortality if their data allow this kind of analysis and do not focus on the 13 regional offices. Otherwise, can you link the higher prevalence of diabetes observed in some regions to specific risk factors? We appreciate your thoughtful suggestion. Unfortunately, the available data did not allow us to analyse prevalence, incidence and mortality of the whole population in

Thailand, since our data were limited to people covered by the Universal Coverage Scheme (UCS) in Thailand. However, we have geographically covered Thailand globally as the 13 regions are all regions in the country (see Fig 1).

The last sentence of your introduction about preventive measures is not clear since you are exploring only hospital data and not ambulatory care data.

Thank you very much for your comment. As you pointed it out, we are unable to assess the current practice of preventive measures, as we did not have access to the ambulatory care data. However, we still believe we can discuss the importance of prevention to avoid unnecessary admissions and re-admissions.

Methods
The ICD-10 codes selected for CKD are very limited. Why not including E11.2 (Type 2 diabetes mellitus with kidney complications)?

Thank you very much for your concern. We regret it was not very clear, but E11.2 (Type 2 diabetes mellitus with kidney complications) was included in our analyses as we indicated “All admitted cases whose principle and secondary diagnoses were coded as T2DM (E11.1 to E11.9)…,” (Materials and methods: Definitions of T2DM and its complications, page 9, line 9-10) meaning that we included E11.1, E11.2, E11.3… E11.9.

Same question with ICD-10 codes N08.3 (Glomerular disorders in diabetes mellitus)?

Again, thank you very much for your suggestion. We have added N08.3 to definition of diabetic complication of chronic kidney disease, as shown below.

“All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1 to N18.6, N18.9, E11.2, E14.2, N08.3, N19 and N18.9.” (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11)

Why you did not include I22 (Subsequent myocardial infarction) in the MI category?

Thank you very much for your question. We have added I22 (Subsequent myocardial infarction) in the MI category, as shown below.

“All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), … MI (I21 and I22)” (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11)

Please correct your stroke codes to I60-I69.

Thank you very much for pointing it out. We have corrected the text as follows:

“All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), … cerebrovascular diseases (I60 to I69)” Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11)

Why you used ICD-9 codes for diabetic amputations?

We appreciate your sensible question. We used ICD-9 codes for diabetic amputations in our study because the National Health Security Office in Thailand makes payment based on ICD-9 codes with regards to amputation, and therefore the amputation records were kept based on the ICD-9 codes.

These ICD-9 codes do not seem appropriate. Please clarify their respective definitions. I recommend intervention codes.

Thank you very much for your comment and recommendation. We have carefully reviewed the ICD-9 codes and revised as shown below. Meanwhile, we remained procedure codes of ICD-9 for the above reasons.

	“All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), … or diabetic foot amputations (8410-8417) were included” Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-13) Moreover, did the authors excluded traumatic, cancer, congenital or sepsis related amputations? Thank you very much for your confirmation. It was rather difficult to exclude traumatic, cancer, congenital or sepsis related amputations with ICD-9 codes. It was the same condition for other types of complications. We indicated this condition as a limitation in our manuscript as follows: “… and absence of information indicating direct causality between diabetes and complicated conditions were the major limitations of this study.” (Discussion, page 23, lines 11-12) I would give further details about the definitions of T2DM and complications. As I understand the manuscript, all admission cases were collected for 2009-2016 in which either T2DM and/or a given complication occurs as a primary or secondary reason, for the whole population of the UCS (T2DM or not). Here is my question: Is the presence of T2DM is evaluated using the presence of T2D as a primary or secondary reason for admission OR all prevalent cases of diabetes were included initially before assessing admission? I would clarify this point (otherwise the reader might think the population are not prevalent cases of diabetes). We appreciate your advice. Our answer to your question is that the presence of T2DM is evaluated using the presence of T2D as a primary or secondary diagnosis (reason) for admission. Although we could not address the prevalent cases in this study, as we could only use the admission data due to the quality reasons, we added further definitions of the T2DM and its complications as shown below. Additionally, we have decided to change some definitions of T2DM and complications, and include retinopathy as the sixth diabetic complication in our study. “All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1 to N18.6, N18.9, E11.2, E14.2, N08.3, N19 and N18.9), MI (I21 and I22), cerebrovascular diseases (I60 to I69), retinopathy (H36.0), cataract (H25.0 to H25.2, H25.8, H25.9, H26.0 to H26.4, H26.8, H26.9, and H28.0), or diabetic foot amputations (8410-8417) were included, and any other cases were excluded from this study. Stage 3 or higher stages of CKD are usually considered as diabetic complications. However, stage 1 and 2 of CKD were also included in this study because the ICD-10 code, E11.2 includes all stages of kidney complications, and thus it was impossible to separate stage 1 and 2 of CKD cases. T2DM cases with acute and subsequent MI were included in this study. While only H36.0, diabetic retinopathy was considered as a diabetic complication, all types of cataract were included as diabetic complications in this study because diabetic cataract is often misdiagnosed as other type of cataract. Diagnosis of foot amputation was considered as a diabetic complication if it was performed from the toe to above the knee.” (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9 to page 10, line 2) Please specify how data are presented and what they represent for example, in Table 1 (rates, proportions, etc.). In other words, this section should be clarified with addition of specific definition that the authors have misclassified in the results section such as: “The number of admissions refers to how many times the UCS patients were admitted for T2DM with or without complications in each year, whereas the number of patients refers to how many patients were admitted in that year. A patient could be admitted multiple times in a year.” Thank you very much for your important comment. We have revised the title of Table 1 and added the note underneath Table 1 as follows. We also revised Result section as shown below. “Table 1. Number and demographic characteristics of the Universal Coverage Scheme patients admitted for type 2 diabetes mellitus in 2009-2016” (Results, page 12-14)

	“Note: The Universal Coverage Scheme (UCS) patients admitted for T2DM are the UCS beneficiaries who were admitted for type 2 diabetes mellitus (T2DM) between 2009 and 2016. The number of UCS patients was counted as one in a year. That is, a UCS patient who was admitted for T2DM for multiple times in a year was counted as one in that year. If the same patient was admitted for T2DM in another year, he/she was counted as one again in the separate year.” (Results, page 14) “Table 1 presents the number and demographic characteristics of the UCS patients admitted for T2DM in 2009-2016. The UCS population of 15 to 100 years of age represents approximately 54.0% of the total population of 2009-2016 in Thailand.” (Results, page 12, lines 2-4) Results Table 1 is not clear. It seems to be the whole population but the title mentioned with type 2 diabetes. The description of the whole population is not the objective of this paper. Please add units to this corrected Table Again, thank you very much for your comment. We have revised the title of Table 1 and added the note underneath Table 1 as follows. We also revised Result section as shown below. “Table 1. Number and demographic characteristics of the Universal Coverage Scheme patients admitted for type 2 diabetes mellitus in 2009-2016” (Results, page 12-14) “Note: The UCS patients admitted for T2DM are the UCS beneficiaries who were admitted for T2DM between 2009 and 2016. The number of UCS patients was counted as one in a year. That is, a UCS patient who was admitted for T2DM for multiple times in a year was counted as one in that year. If the same patient was admitted for T2DM in another year, he/she was counted as one again in the separate year.” (Results, page 14) “Table 1 presents the number and demographic characteristics of the UCS patients admitted for T2DM in 2009-2016. The UCS population of 15 to 100 years of age represents approximately 54.0% of the total population of 2009-2016 in Thailand.” (Results, page 12, lines 2-4) In Figures 2 and 3, please add 95% or 99% confidence intervals. Thank you very much for your suggestion. We added 95% confidence intervals to Fig 2 and 3 in Results section. In Fig 3, we added the 95% CIs to admission rate, but not to the number of patients and admissions because it makes the figure too busy to add the 95% CIs to all components. Are rates adjusted in Figure 3? Thank you for your important inquiry. The rates in Figure 3 were not adjusted. In the Figure 3, we would like to focus on describing temporal trends of crude, i.e. non-adjusted, numbers and rates. Aside from the Figure 3, we calculated admission rates adjusted by age and sex using the national UCS population of 2009 as the standard to discuss effects of age and sex difference between years in the discussion section. “While the number of patients, the number of admissions and admission rates of T2DM steadily increased from 2009 to 2016, the increased trend in the sex-and age-adjusted T2DM admission rates, which were estimated using the national UCS population of 2009 as the standard population, (12.1 in 2009 and 15.0 in 2016, results not shown) were rather gradual as compared with the numbers of crude admissions rates (12.1 in 2009 and 17.3 in 2016). This result suggests that the increase in the T2DM admission rates is partly due to the increased and aged population of the country.” (Discussion, page 20, lines 1-6) Please consider confidence intervals for the description of trends and correct this

sentence: “The increasing trend of T2DM admissions with MI and amputation are visually observable.” Please add the relative % of increase also.

Thank you very much for your suggestion. We added the 95% CIs to admission rate to Fig 3 in Results section and corrected the related sentences accordingly.

This sentence is repeated twice and should be placed in the Method Section: “The number of admissions refers to how many times the UCS patients were admitted for T2DM with or without complications in each year, whereas the number of patients refers to how many patients were admitted in that year. A patient could be admitted multiple times in a year. The admission rate is the number of admissions divided by the number of the UCS patients in the year, standardized by sex and 15 age categories in 2009.”

We are very sorry that it was not clear, but the description in Results section is a note of Figure 3, not part of the main text.

Discussion
Do all data from the different regions are collected similarly or there are differences in data collection (missing data)? Similarly, are there important differences in the number of people subscribed on the UCS, differences in resources, etc.? I think these elements could be important to explain the differences inter-regions, if still presented.

Thank you very much for your observation. The data from the different regions were collected similarly. The UCS beneficiaries are those who are not covered by other major health protection schemes, i.e. the Civil Servant Medical Benefit Scheme and the Social Security Scheme and the UCS beneficiaries account for nearly 70 percent of the population. We also did not find inter-regional difference in the number of UCS beneficiaries.

I suggest comparing with additional similar studies in order to discuss your results. I suggest to be careful with assumptions without references, since it might lead to overinterpretation of results.

Thank you so much for your suggestion. We compared with the following additional 9 studies and 2 reports to discuss our studies.

Studies
Komwong D, Sriratanaban J. Association between Structures and resources of primary care at the district level and health outcomes: a case study of diabetes mellitus care in Thaialn. Risk Manag Healthc Policy. 2018. 11, 199-208
Liabsuetrakul T, Sukmanee J, Thungthong J, Lumbiganon P. Trend of Cesarean Section Rates and Correlations with Advance Maternal and Nesecondary analysis of Thai Universal Coerage Scheme Data. AJP Rep. 2019; 9(4): 328-336.
Sex disparities in diabetes: bridging the gap. Lancet Diabetes Endocrinol: Editorial. 2017; 5(11):839
Aekplakorn W, Stolk RP, Neal B, Suriyawongpaisal P, Chongsuvivatwong V, Cheepudomwit S, et al. The Prevalaence and Management of Diabetes in Thai Adults. Diabetes Care. 2003; 26(10): 2758-2763. DOI: 10.2337/diacare.26.10.2758.
Lindelow M, Hawkins L, Osornprasop S. Government spending and central-local relations in Thailand’s health sector. Washington DC: The International Bank for Reconstruction and Developemnt/The World Bank; 2012.
Witthayapipopsakul W, Cetthakrikul N, Suphanchaimat R, Noree T, Sawaengdee K. Equity of health workforce distribution in Thailand: an implication of concentration index. Risk Manag Healthc Policy. 2019;12:13-22.
Ruamviboonsuk P, Krause J, Chotcomwongse P, Sayres R, Raman R, Widner K, et al. Deep learning versus human graders for classifying diabetic retinopathy severity in a nationwide screening program. npj Digit Med. 2019; 2(25).
Ong-ajyooth L, Vareesangthip K, Khonputsa P, Aekplakorn W. Prevalence of chronic kidney disease in Thai adults: a national health survey. BMC Nephrol. 2009; 10(35).
Chatterjee S, Riewpaiboon A, Piyauthakit P, Riewpaiboon W, Boupaijit K, Panpuwong N, et al. Cost of diabetes and its complications in Thailand: a complete picture ofeconomic burden. Health Soc Care Community. 2011; 19(3), 289–298.
Reports

Chittinan A, Eiam-ong S, Kantachuvesiri S, Chailimpamontri W. Clinical Practice Recommendation for the Evaluation and Management of Chronic Kidney Disease in Adults 2015. 1st ed. Bangkok: The Nephrology Society of Thailand; 2015. [cited 2020 Jan 10]. Available from: http://www.nephrothai.org/images/10-11-2016/Final_%E0%B8%84%E0%B8%A1%E0%B8%AD_CKD_2015.pdf
National Statistical Office, Kingdom of Thailand. The 2010 Population and Housing Census. Bangkok: National Statistical Office; 2012.

Do the authors have ideas about what could explain the disparities between males and females?

Thank you very much for your important observation. We added the explanations for the sex disparities as well as a caution to interpret them in Discussion section as follows.

“Biology might play a part in observed sex differences as women typically transition from prediabetes to diabetes with a worse cardiovascular risk profile and a higher BMI than men. However, psychosocial factors, such as health-seeking behavior and provision of health care, play more important part in the differences, which can be addressed through changes in policy and health-care delivery [22]. It should be noted that high admission rate does not necessarily mean high prevalence of the disease, as previous studies showed higher percentage of undiagnosed diabetes [2] and slightly higher fasting plasma glucose among males in Thailand [23]” (Discussion, page 19, lines 11-17)

The authors are writing about HbA1c in prevention of CKD. I think it might be relevant to give more details about this point (for example, what is used in Thailand nowadays and why HbA1c would be better for CKD particularly).

We appreciate your clarification. HbA1c is in fact recommended to be practiced regularly in prevention of CKD among people with diabetes in Thailand, although it has not been fully executed. Therefore, we have revised and added some information to the discussion section as follows.

“To prevent progression of CKD stage, the country should strengthen an effective measure, such as glycated hemoglobin control (HbA1c) ≦7.0% [21], as instructed in the Clinical Practice Recommendation for the Evaluation and Management of Chronic Kidney Disease in Adults 2015 [30].” (Discussion, page 21, lines 9-12)

Since diabetes is an ambulatory disease, can the authors give us a sense of the burden in the community in Thailand? If not, please refer to other countries.

Thank you very much for your suggestion. We have added information addressing a sense of burden in the community in Thailand as follows.

“Besides, community involvement in diabetic care should also be carefully monitored, as approximately 77.0% of cost is involved in non-medical activities [36], and community-based screening, study and health promotion would be increasingly important for diabetic care [4].” (Discussion, page 23, lines 15-18)

Minor comments
Introduction
First sentence, please add “in the world.”

Thank you very much for your suggestion. We assume the sentence starting with “globally” describes the situation “in the world”, but we changed “globally” to “in the world” to make the sentence clearer.

P.4, 2nd paragraph: review the units for fasting glucose levels (130/dL).

Thank you very much for correcting it. We have revised the unit from (130/dL) to (130mg/dL).

Methods

I would specify the nature of the study: Retrospective study.

Thank you very much for your suggestion. We have added the word, “retrospective data” in our manuscript as shown below.

“Descriptive analyses using the retrospective data were performed to summarize age, sex and regional structure of the UCS patients who were admitted for T2DM between 2009 and 2016 in Thailand and the trends in 2009 and 2016 were compared to depict the change in the trends over the eight years.” (Materials and methods: Data analysis, page 10, lines 5-7)

Why the approbation of the study was done in Japan?

Thank you very much for your enquiry. This is a study on Thailand, but the approbation was done in Japan because this is a Thai-Japan collaborative study based on the agreements made by the both national organizations.

Results
Please correct everywhere women to females and men to males since you have administrative data and not information about gender.

We appreciate your suggestion. We have corrected all the words “men and women” to “males and females” following your suggestion.

Figure 4 would be easier to understand without the grey lines if you still present regional data.

Thank you for pointing it out. We assume that “the grey lines” you mentioned are the ones shown on the right. These lines appear on some computers, but not all. In fact, we do not see the lines on our computers. We hope the editor has a technical means to solve this problem.

Response to Reviewer #2
General comments:
The authors extract for the universal coverage scheme data all hospitalizations with diabetes listed among the primary or secondary diagnoses (to study admissions caused by diabetes-related complications) in the period 2009-2016. The impressively large and detailed dataset covers over 1.4 million Thai age 15-100 and their 4.2 million admissions for type-2 diabetes (T2DM). They provide descriptive summaries, focusing on admission rates trends nationally and by region, for T2DM and major complications. The results show that standardizing for age and sex reduces the increasing trend in admission rates, suggesting that trends in population growth and aging are important determinants.

Specific comments:
Moreover, the authors speculate that the increase in elderly patients could be explained by greater longevity (i.e. reduced premature mortality) among DM patients. What does a life table for Thailand say about life expectancy conditional on surviving to age 50? 60? Is the growth rate in admissions comparable to the growth rate of survival at those ages? This could provide suggestive evidence confirming or refuting the authors’ hypothesis.

We have stated in our manuscript that “the increased trend in T2DM admission rates was rather gradual as compared with the number of patients and admissions.” This means that the increase in the T2DM admission rates was partly influenced by the increased and aged population of the country, while there were also other reasons behind. To avoid this unclarity, we have added values of “sex-and age-adjusted T2DM admission rates”, and changed the word, “largely” to “partly” in the sentence as shown below.

“While the number of patients, the number of admissions and admission rates of T2DM steadily increased from 2009 to 2016, the increased trend in the sex-and age-adjusted T2DM admission rates, which were estimated using the national UCS population of 2009 as the standard population, (12.1 in 2009 and 15.0 in 2016, results not shown)

were rather gradual as compared with the numbers of crude admissions rates (12.1 in 2009 and 17.3 in 2016). This result suggests that the increase in the T2DM admission rates is partly due to the increased and aged population of the country. Although further studies are required, it could imply that Thailand may face the greater burden of T2DM in the future if the trend of population growth and aging continues in the country." (Discussion, page 20, line 1-8)

Of particular note is the high and rising trend in admissions for chronic kidney disease. Unfortunately, the authors do not have any proxies for resource use, but could estimate, based on some estimate of average length of stay and average charges per diem, the associated total spending and out-of-pocket burden. Admittedly that might constitute a separate paper, but it would provide important additional evidence for prioritizing policy to address inequalities of health and access.

Thank you so much for your brilliant suggestion. We'll work on this issue in our next research.

The authors do not discuss gestational diabetes, but that could account for some of the young adult female hospitalizations with diabetes especially as a secondary code and, unless the authors were sure the ICD10/9 codes used excluded them, merit discussion as a sub-category.

Thank you very much for your sensible inquiry. However, we did not include gestational diabetes (ICD-10 code O24) in our study as described in the manuscript (please see below).

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1 to N18.6, N18.9, E11.2, E14.2, N08.3, N19 and N18.9), MI (I21 and I22), cerebrovascular diseases (I60 to I69), retinopathy (H36.0), cataract (H25.0 to H25.2, H25.8, H25.9, H26.0 to H26.4, H26.8, H26.9, and H28.0), or diabetic foot amputations (8410-8417) were included, and any other cases were excluded from this study." (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-14)

What are all the lines coming out of the graphs to the northwest in Figure 4? Fig 4. Comparisons of age- and sex- standardized admission ratios of type 2 diabetes mellitus and its complications in NHSO regions in 2009 and 2016

Thank you very much again. We assume that "the lines coming out of the graphs to the northwest" are the ones shown on the right. These lines appear on some computers, but not all. In fact, we do not see the lines on our computers. We hope the editor has a technical means to solve this problem.

Other explorations of the data that might be meaningful include correlation of the SAR with the % urban residents and/or per capita GDP and/or average years of schooling in each region; reporting and discussing the proportion of admissions in primary, secondary, and tertiary hospitals; at urban versus rural hospitals; at government vs private hospitals; at teaching hospitals vs non-teaching hospitals.

We appreciate your important suggestions. We revised the explanation of the geographical inequalities in Discussion section with the available data, as shown below.

"On the other hand, the persistently high SAR of T2DM with retinopathy in Bangkok is presumably due to high density of specialists as half of 1,500 ophthalmologists, including 200 retinal specialists, practice in Bangkok [33].

The persistently high SAR of T2DM with CKD in northeastern regions was consistent with a previous study and partly attributed to high prevalence of CKD in northeastern regions (10.8%) relative to other regions (north 8.9%, south 8.1% and Bangkok 6.2%) [34], but partly to an association with lower density of physicians and rurality of the region [13]. The density of physicians in northeastern regions is the lowest in the country [32], as low as seven times lower than Bangkok [9]. It is reasonable to assume that in a region where physicians are scarce, T2DM patients with CKD are unlikely to

receive timely, thorough and effective treatment, and consequently deteriorate in conditions. This assumption might explain the high readmission rates of T2DM with CDK, and the highest mortality rates due to diabetes in northeastern regions as found in another study [12]. Moreover, rurality of the northeastern regions, where 71.0% of the population reside in rural setting (north 65.6%, south 66.5% and Central 54.5%) [35], might have halted them from accessing adequate primary care. A previous study found a strong association between the high SAR of diabetes and rurality as the rural population tends to have lack of public transport alternatives and poor health literacy with less education which often limit accessibility to health care. The study also suggested that the percentage of patients who had received up to secondary education was lower in rural districts by approximately 10% [13].” (Discussions, page 22 line 10 to page 23, line 9)

To make the analyses comparable internationally and to allow even more precision in benchmarking the Thai national and regional trends in DM admissions, the authors could calculate the DM avoidable admissions rate as used in OECD metrics for the quality of primary care. This would simply involve standardizing to a comparable population, such as what the OECD does: rates per 100 000 population, age-sex standardized to the 2010 OECD population aged 15 and over (see references below). It would also provide an internationally comparable metric for benchmarking the Thai primary care system for DM management with other health systems, over the study period and as a baseline for tracking further improvements into the future. Of course, the authors may not be able to apply the full inclusion and exclusion criteria, so it would only be suggestive. For example, it does not seem that the authors can categorize the admissions according to whether or not the patient died during the admission. They may not be able to exclude those transferred from another hospital, although the date(s) of admission would be suggestive for creating that categorization from the raw admissions data. Again, estimating DM avoidable admissions rates could constitute a separate paper, but since it draws on exactly the kind if data the authors summarize in this paper, I would urge the authors to consider including this and thus able to attract a wider readership and evidence for policy top address the important trends they highlight.

We appreciate your sensible suggestion. We’ll work on these in our next research.

Response to Reviewer #3
General comments:
This is an interesting manuscript providing the big picture of type 2 diabetes in the Thailand population between 2009-2016. I appreciated the reading and the figures are well-chosen. The authors conclude to an increase in type 2 diabetes over time. There may be a need for improved health care system/policies/services/prevention for this population. Even though I appreciated the paper, I would have some questions for the authors.

Major comments
Aren't there any paper published with those databases to support what the authors claim in the data section of the Method?

Thank you very much for your inquiry. As you suggested, we have included the following reference papers to support our decision to use only the data of 2009 and onwards in Materials and methods: Data section.

Komwong D, Sriratanaban J. Association between Structures and resources of primary care at the district level and health outcomes: a case study of diabetes mellitus care in Thaialn. Risk Manag Healthc Policy. 2018; 11, 199-208
Liabsuetrakul T, Sukmanee J, Thungthong J, Lumbiganon P. Trend of Cesarean Section Rates and Correlations with Advance Maternal and Nesecondary analysis of Thai Universal Coerage Scheme Data. AJP Rep. 2019; 9(4): 328-336.

Definitions of T2DM: where was diabetic amputation (only) defined based on the ICD 9 coding (paralele database?)?

We appreciate your concern. Diabetic amputation defined based on ICD-9 codes was a parallel database, “the operation database,” as described below, but the operation

database also belongs to the National Health Security Office.

“Two are reports sent from hospitals to the Ministry of Public Health, namely the hospital admission database and the operation database...” (Materials and methods: Data, page 8, lines 3-5)

I think there is a typo for the stroke definition (I60 to I69 and not I6.0 to I6.9). Furthermore, if those are really the codes used, it does not only refer to stroke but rather largely to cerebrovascular diseases.

Thank you very much for pointing it out. We have corrected the text as follows:

“All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9) …cerebrovascular diseases (I60 to I69), …” (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11)

According to your suggestion, we also corrected the word “stroke” to “cerebrovascular diseases.”

Diabetic amputations codes selection (ICD9 8401-8415) would need a reference or more explanations for rational.
We appreciate your suggestion. We have carefully reviewed ICD-9 codes again and slightly changed the codes included this study and revised the text as follows.

“All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without … or diabetic foot amputations (8410-8417) were included … Diagnosis of foot amputation was considered as a diabetic complication if it was performed from the toe to above the knee.” (Materials and methods: Definitions of T2DM and its complications, page 9, line 9 to page 10, line 2)

Data analysis: the authors should explain how were the 2009-2016 trends compared (visually I think).

Thank you very much for your important suggestion. Please see Fig. 3 that explains the 2009-2016 trends visually.

The results would benefit from a more sophisticated trend analysis, using for example a binomial regression model to obtain the precise slope % and a contrast test to compare in sub-analyses. Even though different, this paper and its references may help: Leclerc J et al. Circulation: Cardiovascular Quality and Outcomes, 2017.

We very much appreciated your proposal with the useful reference for a more sophisticated trend analysis. We have conducted time series regressions with the following negative binomial regression model, and added the methods and results to our manuscript as shown below.

“To estimate temporal trend of admissions, we conducted time series regressions with the following negative binomial regression model.
$n_i \sim NegativeBinomial(\mu_i, \phi)$
$\mu_i = \exp(\beta_0 + \beta_1 x + \log〚N_i〛)$
where n_i is the number of admissions of ith time point, N_i is the number of UC population of ith time point, x is the indicator variable of time points, μ is the mean parameter and ϕ is dispersion parameter of Negative Binomial distribution, β_0 is the intercept, and β_1 is the slope parameter.” (Materials and methods: Data analyses, page 11, line 1 - 5)

“Table 2 presents the results of the time series regressions to estimate temporal trend of admissions showed that all types of T2DM admissions except that with cataract had a significant and positive temporal trend.

Table 2. Time series regressions parameters of temporal trend analysis for admissions
ParametersEstimateSEz valuep value
All DM admissions
β_0: intercept-4.4605290.006002-743.16p < 0.001

β_1: time point0.0505660.00118742.61 p < 0.001
DM with CKD admissions
β_0: intercept-6.1083890.009446-646.64p < 0.001
β_1: time point0.0956750.001861 51.41p < 0.001
DM with MI admissions
β_0: intercept-8.115380.02155-376.58p < 0.001
β_1: time point0.075410.0042417.78p < 0.001
DM with cerebrovascular diseases admissions
β_0: intercept-7.2516870.009935-729.93p < 0.001
β_1: time point0.0843580.00194143.47p < 0.001
DM with cataract admissions
β_0: intercept-7.604557 0.046891-162.175 p < 0.001
β_1: time point0.0152440.0092831.6420.101
DM with retinopathy admissions
β_0: intercept-8.9410960.028458-314.181p < 0.001
β_1: time point0.049766 0.0055998.888 p < 0.001
DM with amputation admissions
β_0: intercept-8.955374 0.023377-383.09p < 0.001
β_1: time point0.0509460.00458411.12p < 0.001
Note: SE: Standard error, CI: Confidence interval, DM: Diabetes mellitus, CKD: Chronic kidney disease, MI: Myocardial infarction
(Results, page 16, line 9 to page 17, line 2)

Was the age and sex distribution of the population in 2009 ever published? If so, a reference would be needed in the data analysis section.

Thank you so much for your inquiry. We are afraid the age and sex distribution of the UCS population in 2009 has not been published. The data of UCS population of 2009 we used was provided by the National Health Security Office (NHSO), Thailand.

as the standard for age- and sex-adjustment.

"the expected number of admissions in region": please provide more details (ex.: according to the literature, the country level of admission, etc.)

We appreciate your enquiry. "The expected number of admissions in region" is explained as follows in Materials and methods: Data analysis section.

“We estimated the standardized admission ratio (SAR) of each region using the following equation for each region.
〖SAR〗_i=o_i/e_i
e_i=∑_(j=1)^J▒〖p_j n_ij 〗
where SARi is standardized admission ratio in region i; oi is the observed number of admissions in region i; ei is the expected number of admissions in region i; j is the population stratum defined by age and sex; pj is standard admission rate in the 2009 UCS population for the population stratum j.” (Materials and methods: Data analysis, page 10, lines 9-15)

"Age was categorize into 15 groups of five-year intervals" is not fully accurate, and the last category is 85 to 100 years old. This should be adjusted.

Thank you so much for pointing it out. We have corrected the sentence as shown below and changed the value labels from “85+” to “85-100” in figures and tables.

“Age was categorized into 15 groups in intervals of five years, except the last category that includes 85 to 100 years of age” (Materials and methods: Data analysis, page 10, lines 16-17)

Minor comments:
Fig 3, "cases with ampulation" should be written "amputation"

Thank you for pointing it out. We corrected the word in the figure.

Fig 4, this would be beautiful without all the diagonals accross the pictures. Any way to

	remove it? Thank you very much again. We assume that “the diagonals across the pictures” are the ones shown on the right. These lines appear on some computers, but not all. In fact, we did not see the lines on our computers. We hope the editor has a technical means to solve this problem. Additional editor comments: Journal requirements: Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming. Thank you very much for your kind advice with useful URLs. We have carefully revised our manuscript in accordance with the PLOS ONE style. In ethics statement in the manuscript and in the online submission form, please provide additional information about the patient records used in your retrospective study. Specifically, please ensure that you have discussed whether all data were fully anonymized before you accessed them and/or whether the IRB or ethics committee waived the requirement for informed consent. If patients provided informed written consent to have data from their medical records used in research, please include this information. Moreover, in you Data statement, please ensure that it is clear how you obtained the data, and how other researchers can request access to the same database. Thank you very much for bringing out this issue. We obtained the data in the National Health Security Office which manages the database as the first author belongs to the organization. However, we added the sentence clarifying that all data were anonymous, as shown below. We also added the information of how others can access to the database in the “Data reporting” section, as follows. “All data were fully anonymized before we accessed them.” (Materials and methods: Data, page 8, lines 8-9) “All patient records were fully anonymized before we accessed. The relevant UCS data are available upon request to the National Health Security Office, Thailand, with the research outline and the details of the required data.” (Data reporting, page 25, lines 15-17) Our internal editors have looked over your manuscript and determined that it is within the scope of our Health Inequities and Disparities Research Call for Papers. If you would like your manuscript to be considered for this collection, please let us know in your cover letter and we will ensure that your paper is treated as if you were responding to this call. If you would prefer to remove your manuscript from collection consideration, please specify this in the cover letter. Thank you very much for inviting us to the special research call. As indicated in the cover letter, we would like our manuscript to be considered for this collection. We note that you have indicated that data from this study are available upon request. In your revised cover letter, please address the following prompts: a)If there are ethical or legal restrictions on sharing a de-identified data set, please explain them in detail (e.g., data contain potentially identifying or sensitive patient information) and who has imposed them (e.g., an ethics committee). Please also provide contact information for a data access committee, ethics committee, or other institutional body to which data requests may be sent. b)If there are no restrictions, please upload the minimal anonymized data set necessary to replicate your study findings as either Supporting Information files or to a stable, public repository and provide us with the relevant URLs, DOIs, or accession numbers. Please see http://www.bmj.com/content/340/bmj.c181.long for guidelines on how to de-identify and prepare clinical data for publication. For a list of acceptable repositories, please see http://journals.plos.org/plosone/s/data-availability#loc-recommended-repositories. Thank you very much for pointing this out. The National Health Security Office (NHSO) follows the Information Security Policy, Information Security Management System procedure (QP-407 10-001). An individual who wishes to use the UCS databases must

	sign the Non-Disclosure Agreement (NDA) with NHSO, and submit copies of documents, reports, articles or publications that use the dat. The use of the data is restricted within the research framework and the person should be responsible for his/her own actions in case of a lawsuit, etc. We have added the information to the revised cover letter. PLOS requires an ORCID iD for the corresponding author in Editorial Manager on papers submitted after December 6th, 2016. Please ensure that you have an ORCID iD and that it is validated in Editorial Manager. The corresponding author checked it and he ensured that the ORCID iD was validated in Editorial Manager. Your ethics statement must appear in the Methods section of your manuscript. Please also ensure that your ethics statement is included in your manuscript, as the ethics section of your online submission will not be published alongside your manuscript. Thank you very much for your kind reminder. We have added the ethics statement in the Methods section as shown below. “Ethics of the study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (NCGM) in Japan on 11 May 2018 (NCGM-G-002524-00).” (Materials and methods: Data analyses, page 11, lines 11-12) We note that Figure 4 in your submission contains map images which may be copyrighted. We require you to either (1) present written permission from the copyright holder to publish these figures specifically under the CC BY 4.0 license, or (2) remove the figures from your submission. We have created the map images with the geodatabase retrieved from the website, the Humanitarian Development Exchange (HDX). As far as our understanding, all the databases offered under the CC BY license are free to share and or adapt for any purpose, even commercially. It is also stated that no one can apply legal terms or technological measures that legally restrict others from doing anything the license permits (please see the website from https://data.humdata.org/about/license). If there are any problem about license of the map images, please let us know. Please upload a copy of Supporting Information Table 1 and 2, which you refer to in your text on page 14. Thank you very much for your concern. We finally decided not to include Supplementary table 1 and 2, but missed deleting the sentence which indicates the Supplementary tables in the manuscript. This time, we deleted the sentence.
Additional Information:	
Question	**Response**
Financial Disclosure Enter a financial disclosure statement that describes the sources of funding for the work included in this submission. Review the submission guidelines for detailed requirements. View published research articles from *PLOS ONE* for specific examples. This statement is required for submission and **will appear in the published article** if the submission is accepted. Please make sure it is accurate.	This study was partially funded by Institute for Global Health Policy Research (iGHP), Japan; the Japan International Cooperation Agency (JICA), Japan; and the National Health Security Office, Thailand. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Ethics Statement Enter an ethics statement for this submission. This statement is required if the study involved: • Human participants • Human specimens or tissue • Vertebrate animals or cephalopods • Vertebrate embryos or tissues • Field research Write "N/A" if the submission does not require an ethics statement. General guidance is provided below. Consult the submission guidelines for detailed instructions. **Make sure that all information entered here is included in the Methods section of the manuscript.**	The study was approved by the Institutional Review Board of the National Center for Global Health and Medicine in Japan on May 11, 2018 (NCGM-G-002524-00).

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Data Availability Authors are required to make all data underlying the findings described fully available, without restriction, and from the time of publication. PLOS allows rare exceptions to address legal and ethical concerns. See the PLOS Data Policy and FAQ for detailed information.	No - some restrictions will apply

A Data Availability Statement describing where the data can be found is required at submission. Your answers to this question constitute the Data Availability Statement and **will be published in the article**, if accepted. **Important:** Stating 'data available on request from the author' is not sufficient. If your data are only available upon request, select 'No' for the first question and explain your exceptional situation in the text box. Do the authors confirm that all data underlying the findings described in their manuscript are fully available without restriction?	
Describe where the data may be found in full sentences. If you are copying our sample text, replace any instances of XXX with the appropriate details. • If the data are **held or will be held in a public repository**, include URLs, accession numbers or DOIs. If this information will only be available after acceptance, indicate this by ticking the box below. For example: *All XXX files are available from the XXX database (accession number(s) XXX, XXX.*). • If the data are all contained **within the manuscript and/or Supporting Information files**, enter the following: *All relevant data are within the manuscript and its Supporting Information files.* • If neither of these applies but you are able to provide **details of access elsewhere**, with or without limitations, please do so. For example: *Data cannot be shared publicly because of [XXX]. Data are available from the XXX Institutional Data Access / Ethics Committee (contact via XXX) for researchers who meet the criteria for access to confidential data.* *The data underlying the results presented in the study are available from (include the name of the third party*	Data cannot be shared publicly because the owner of this data, the National Security Office, Thailand, prohibits us to share the data.

and contact information or URL). • This text is appropriate if the data are owned by a third party and authors do not have permission to share the data. * typeset	
Additional data availability information:	

Cover Letter (First time)

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September 17, 2019

Dear Editors:

We are writing to you to submit our manuscript, "Hospital admission in patients with type 2 diabetes mellitus in Thailand under the Universal Coverage Scheme: a time- and geographical-trend analysis, 2009–2016" for consideration for publication in *PLoS One*.

Thailand has achieved remarkable improvements in population health since the initiation of universal health coverage in 2002. However, it has not been assessed whether the system is reducing the burden of disease effectively in the country. One of the emerging disease burdens in Thailand is diabetes whose prevalence increased from 2.3% in 1991to 9.6% in 2016. Improper management of diabetes often results in complications including kidney failure, vision loss, and leg amputation. Diabetes increases premature death, reduces quality of life, and increases healthcare cost. The National Health Examination Survey reported that only 23.5% of people with type 2 diabetes mellitus (T2DM) that accounts for more than 94.0% of the total diabetic cases in the country, were treated with fasting plasma glucose levels below 130/dL, and moreover, 43.0% of cases were undiagnosed in 2014.

Our results show that the admission rates of T2DM and its five major complications increased and intra-country geographic inequalities were observed from 2009 to 2016 in Thailand. We warned the country to take this trend seriously and improve health system and policies to enhance primary and secondary prevention of T2DM at this point of population transition, while further studies to be conducted to investigate the reasons behind these trends. We strongly believe that this paper has extremely important implications as regards to accelerated global efforts to reduce burden of diseases, while pursuing universal health coverage.

This manuscript has not been published in part or in whole elsewhere. I attest to the fact that all authors listed on the title page have read and contributed to the manuscript substantially and agreed on its current submission to *PLoS One*. There are no conflicts of interest, corporate involvement or patent holdings for any of the authors.

Thank you for considering this manuscript for publication.

Yours sincerely,
Tanapat Laowahutanon

Full title: Hospital admission in patients with type 2 diabetes mellitus in Thailand under the Universal Coverage Scheme: a time- and geographical-trend analysis, 2009–2016

Short title: Type 2 diabetes mellitus in Thailand

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Abstract

Background

To estimate the time and geographical trends of nationwide admission rates of type 2 diabetes mellitus (T2DM) and its complications, including chronic kidney disease (CKD), myocardial infarction, cerebrovascular diseases, retinopathy, cataract, and diabetic foot amputation, descriptive analyses of 2009-2016 were performed using the data of the Universal Coverage Scheme (UCS) which covers nearly 70 percent of the Thai population.

Methods and findings

The database of T2DM patients aged 15-100 years who were admitted between 2009 and 2016 under the UCS and that of the UCS population were retrieved for the analyses. The admitted cases of T2DM were extracted from the database using disease codes of principal and secondary diagnoses defined by the International Classification of Diseases 9th and 10th Revisions. The T2DM admission rates in 2009-2016 were the number of admissions divided by the number of the UCS population. The standardized admission ratios (SARs)were further estimated in contrast to the expected number of admissions considering age and sex composition of the UCS population in each region.

A linearly increased trend was found in T2DM admission rates from 2009 to 2016. Female admission rates were persistently higher than that of males. In 2016, an increase in the T2DM admission rates was

observed among the older ages relative to that in 2009. Although the SARs of T2DM were generally higher in Bangkok and central regions in 2009, except that with CKD and foot amputation which had higher trends in northeastern regions, the geographical inequalities were fairly reduced by 2016.

Conclusion

Admission rates of T2DM and its major complications increased in Thailand from 2009 to 2016. Although the overall geographical inequalities in the SARs of T2DM were reduced in the country, further efforts are required to improve the health system and policies focusing on risk factors and regions to manage the increasing T2DM.

Introduction

In the world, approximately 451 million people aged 18 to 99 years lived with diabetes in 2017 [1], and this number is projected to further increase to 693 million by 2045 [1]. When diabetes is not properly managed, complications develop typically in kidney failure, vision loss, and foot amputation. Diabetes has increasingly become a global burden of disease that increases premature death, reduces quality of life and drives up healthcare cost [2]. The World Health Organization (WHO) emphasizes importance of prevention and early diagnosis of diabetes, particularly for type 2 diabetes mellitus (T2DM) which can be effectively reduced through population-based and individual prevention measures that target key risk factors [3].

In Thailand, prevalence of diabetes increased from 2.3% in 1991 [4] to 9.6% (6.5 million diabetes cases) in 2016 [5]. More than 94.0% of diabetic cases in the country are T2DM [2] and the six major diabetic complications that are annually screened in the country include chronic kidney disease (CKD), myocardial infarction (MI), cerebrovascular diseases, retinopathy, cataract and foot amputation [6]. The National Health Examination Survey in 2014 found that only 23.5% of people with T2DM were treated with fasting plasma glucose being less than 130 mg/dL, while 43.0% of them were undiagnosed [7].

Thailand has achieved remarkable improvements in population health since the achievement of universal health coverage (UHC) in 2002. Major health protection schemes in the country include the

Civil Service Medical Benefit Scheme, the Social Security Scheme and the Universal Coverage Scheme (UCS). The last one, taken care by the National Health Security Office (NHSO), covers more than 48 million people, approximately 69.9% of the Thai population as of 2019 [8]. NHSO has 13 Regional Offices (see Fig 1) sharing all resources and regulation [9]. The UCS is financed by general tax revenue. The UCS offers the patients with T2DM and its complications the comprehensive benefit package which includes prevention, curative and rehabilitation services. The beneficiaries are systematically required to visit the registered primary care facility as the first point of contact. In case of severe conditions, they are referred to secondary and tertiary care facilities [10]. The UCS applies mixed-method provider payments, with mainly close-ended capitation for outpatient care and based on diagnosis-related groups, with a global budget, for inpatient care [11].

Fig 1. National Health Security Organization regions

Despite the national efforts in the implementation of UCS, there is evidence of a rise in intra-national health inequalities in diabetic mortality rates in Thailand [12]. However, the level of health inequalities in morbidity measures such as hospital admission has not been well documented. To fill the knowledge gap, in this paper, we 1) described for the first time a time-trend analysis of nationwide admission rates of T2DM and its six major diabetic complications among the UCS beneficiaries in Thailand from 2009 to 2016, and 2) assessed regional inequality in trend of the admission ratios across the 13 NHSO

Regions. We aim to provide the basis for planning and carrying out action in terms of necessary health provision and preventive measures.

Materials and methods

Data

The data set stored at the NHSO compiled from three data sources were used for this study. Two are reports sent from hospitals to the Ministry of Public Health, namely the hospital admission database and the operation database, which include personal national identification number, sex, date of birth, the NHSO Region, province of hospitalization, hospital code of registration, hospital code of admission, date of admission, date of discharge, date of death, and principal and secondary diagnoses. The remaining is compiled from hospital reports sent to the NHSO for reimbursement. All data were fully anonymized before we accessed them.

All Thai citizens entitled to use the UCS are registered in a special table of the NHSO datasets. These are updated annually against birth and death registries taken care by the Ministry of Interior. Although the NHSO database contains admissions of patients covered by all medical benefit schemes, only those entitled to the UCS were used for this study. These data are regularly checked to prevent duplication based on personal national ID number, names and birthdates. After careful data cleaning, a total of 4,297,321 T2DM admitted cases of 2,689,642 UCS patients aged 15 to 100 years in Thailand between 2009 and 2016 were included in this study. Although Thailand achieved UHC in 2002, we decided to use only data from 2009 onwards for our analyses since there were a number of missing values and errors in data before 2009 [13, 14]. Ages of below 15 years were excluded because T2DM was rare in

children until recently [13] and above 100 years were considered to be primarily caused by typing errors. All subsequent analyses were done on data of the UCS population as denominators and those of the UCS admissions for T2DM as numerators.

Definitions of T2DM and its complications

A trained medical statistic officer at the hospitals entered diagnosis of T2DM and its complications, CKD, MI, cerebrovascular diseases, retinopathy and cataract based on the International Classification of Diseases 10th Revision (ICD-10) [14], and diabetic foot amputation based on the International Classification of Diseases 9th Revision (ICD-9) [15]. All UCS admitted cases whose principal or secondary diagnosis was coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1 to N18.6, N18.9, E11.2, E14.2, N08.3, N19 and N18.9), MI (I21 and I22), cerebrovascular diseases (I60 to I69), retinopathy (H36.0), cataract (H25.0 to H25.2, H25.8, H25.9, H26.0 to H26.4, H26.8, H26.9, and H28.0), or diabetic foot amputations (8410-8417) were included, and any other cases were excluded from this study. Stage 3 or higher stages of CKD are usually considered as diabetic complications. However, stage 1 and 2 of CKD were also included in this study because the ICD-10 code, E11.2 includes all stages of kidney complications, and thus it was impossible to exclude stage 1 and 2 of CKD cases. T2DM cases with acute, as well as subsequent MI were included in this study. While only H36.0, diabetic retinopathy was considered as a diabetic complication, all types of cataract were included in this study because diabetic cataract is often misdiagnosed as other types of cataract. Diagnosis of foot

amputation was considered as a diabetic complication if it was performed from the toe to above the knee.

Data analysis

Descriptive analyses using the retrospective data were performed to summarize age, sex and regional structure of the UCS patients who were admitted for T2DM between 2009 and 2016 in Thailand and the trends in 2009 and 2016 were compared to depict the change in the trends over the eight years.

We estimated the standardized admission ratio (SAR) of each region using the following equation for each region.

$$SAR_i = \frac{o_i}{e_i}$$

$$e_i = \sum_{j=1}^{J} p_j n_{ij}$$

where SAR_i is standardized admission ratio in region i; o_i is the observed number of admissions in region i; e_i is the expected number of admissions in region i; j is the population stratum defined by age and sex; p_j is standard admission rate in the 2009 UCS population for the population stratum j. Age was categorized into 15 groups in intervals of five years, except the last category that includes 85 to 100 years of age.

To estimate temporal trend of admissions, we conducted time series regressions with the following negative binomial regression model.

$$n_i \sim \text{NegativeBinomial}(\mu_i, \phi$$

$$\mu_i = \exp(\beta_0 + \beta_1 x + \log N_i)$$

where n_i is the number of admissions of ith time point, N_i is the number of UC population of ith time point, x is the indicator variable of time points, μ is the mean parameter and ϕ is dispersion parameter of Negative Binomial distribution, β_0 is the intercept, and β_1 is the slope parameter.

R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) [16] was used to analyze the data. To draw choropleth maps, we used R version 3.4.1 with package 'sf' [17] and package 'ggplot2' [18]. Ethics of the study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (NCGM) in Japan on 11 May 2018 (NCGM-G-002524-00).

Results

Table 1 presents the number and demographic characteristics of the UCS patients admitted for T2DM in 2009-2016. The UCS population of 15 to 100 years of age represents approximately 54.0% of the total population of 2009-2016 in Thailand. Over 60% of T2DM patients were female throughout the period, although the sex disparity narrowed in the eight years. The mean age (SD) of the UCS T2DM patients was 63.1 (12.2) years throughout the years and it annually rose by 0.2 years on average. The overall number of UCS patients with T2DM annually increased by 5.4%, and 14.4% among the 85 year-olds and older from 2009 to 2016. The number of T2DM patients proportionately increased in Region 9 (Nakhon Ratchasima), 10 (Ubon Ratchathani) and 11 (Songkhla), and decreased in Region 4 (Saraburi), 5 (Ratchaburi) and 13 (Bangkok) in the study period.

Table 1. Number and demographic characteristics of the Universal Coverage Scheme patients admitted for type 2 diabetes mellitus in 2009-2016

	2009	2010	2011	2012	2013	2014	2015	2016
	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
Sex								
Female	181,402 (66.1)	193,297 (65.8)	202,297 (64.9)	208,632 (64.2)	219,830 (63.6)	228,533 (63.1)	239,283 (62.9)	247,671 (62.4)
Male	92,938 (33.9)	100,420 (34.2)	109,310 (35.1)	116,190 (35.8)	125,870 (36.4)	133,426 (36.9)	141,304 (37.1)	149,239 (37.6)
Age								
15-19	364 (0.1)	355 (0.1)	393 (0.1)	373 (0.1)	393 (0.1)	449 (0.1)	489 (0.1)	478 (0.1)
20-24	547	608	628	703	755	776	801	876

	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)
25-29	1,113	1,104	1,133	1,209	1,253	1,335	1,486	1,551
	(0.4)	(0.4)	(0.4)	(0.4)	(0.4)	(0.4)	(0.4)	(0.4)
30-34	2,478	2,582	2,632	2,696	2,888	2,913	3,126	3,156
	(0.9)	(0.9)	(0.8)	(0.8)	(0.8)	(0.8)	(0.8)	(0.8)
35-39	5,603	5,938	5,976	6,100	6,233	6,541	6,739	6,822
	(2.0)	(2.0)	(1.9)	(1.9)	(1.8)	(1.8)	(1.8)	(1.7)
40-44	11,867	12,206	12,351	12,733	13,053	13,424	13,980	13,787
	(4.3)	(4.2)	(4.0)	(3.9)	(3.8)	(3.7)	(3.7)	(3.5)
45-49	20,490	21,236	21,809	22,798	23,893	24,565	25,236	25,353
	(7.5)	(7.2)	(7.0)	(7.0)	(6.9)	(6.8)	(6.6)	(6.4)
50-54	30,357	31,468	32,063	33,243	35,080	36,049	37,860	39,043
	(11.1)	(10.7)	(10.3)	(10.2)	(10.1)	(10.0)	(9.9)	(9.8)
55-59	39,833	42,140	43,507	44,951	46,174	47,384	49,119	50,468
	(14.5)	(14.3)	(14.0)	(13.8)	(13.4)	(13.1)	(12.9)	(12.7)
60-64	42,231	46,458	50,187	53,045	56,747	59,059	61,020	63,304
	(15.4)	(15.8)	(16.1)	(16.3)	(16.4)	(16.3)	(16.0)	(15.9)
65-69	41,038	43,357	45,925	47,328	51,427	55,209	60,056	64,124
	(15.0)	(14.8)	(14.7)	(14.6)	(14.9)	(15.3)	(15.8)	(16.2)
70-74	37,359	40,155	42,922	44,155	46,068	47,329	48,787	50,920
	(13.6)	(13.7)	(13.8)	(13.6)	(13.3)	(13.1)	(12.8)	(12.8)
75-79	24,996	27,241	30,523	32,103	34,926	37,129	39,243	40,946
	(9.1)	(9.3)	(9.8)	(9.9)	(10.1)	(10.3)	(10.3)	(10.3)
80-84	11,356	13,362	15,093	16,484	18,459	20,367	21,998	24,058
	(4.1)	(4.5)	(4.8)	(5.1)	(5.3)	(5.6)	(5.8)	(6.1)
85+	4,708	5,507	6,465	6,901	8,351	9,430	10,647	12,024
	(1.7)	(1.9)	(2.1)	(2.1)	(2.4)	(2.6)	(2.8)	(3.0)
Mean (SD)	62.4 (12.0)	62.6 (12.1)	63.0 (12.1)	63.1 (12.1)	63.3 (12.2)	63.5 (12.2)	63.7 (12.3)	63.9 (12.3)
NHSO Regions								
1. Chiang Mai	19,572	21,232	22,492	23,021	23,995	25,160	26,715	28,366
	(7.1)	(7.2)	(7.2)	(7.1)	(6.9)	(7.0)	(7.0)	(7.1)
2. Phitsanulok	14,631	15,857	16,760	18,195	19,024	19,455	20,411	20,937
	(5.3)	(5.4)	(5.4)	(5.6)	(5.5)	(5.4)	(5.4)	(5.3)
3. Nakhon Sawan	13,592	15,699	16,764	17,646	17,999	18,288	18,974	19,865
	(5.0)	(5.3)	(5.4)	(5.4)	(5.2)	(5.1)	(5.0)	(5.0)
4.Saraburi	23,401	25,965	26,257	25,344	26,249	27,420	28,995	30,772
	(8.5)	(8.8)	(8.4)	(7.8)	(7.6)	(7.6)	(7.6)	(7.8)

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5. Ratchaburi	27,208	28,203	30,047	29,901	31,538	32,479	33,122	34,033
	(9.9)	(9.6)	(9.6)	(9.2)	(9.1)	(9.0)	(8.7)	(8.6)
6. Rayong	22,439	24,207	26,634	27,231	28,588	29,743	30,891	33,143
	(8.2)	(8.2)	(8.5)	(8.4)	(8.3)	(8.2)	(8.1)	(8.4)
7. Khon Kaen	27,623	30,320	32,205	34,357	36,748	39,207	40,608	41,217
	(10.1)	(10.3)	(10.3)	(10.6)	(10.6)	(10.8)	(10.7)	(10.4)
8. Udon Thani	27,032	28,833	30,200	30,522	33,339	35,563	37,644	38,258
	(9.9)	(9.8)	(9.7)	(9.4)	(9.6)	(9.8)	(9.9)	(9.6)
9. Nakhon Ratchasima	26,587	27,945	30,292	33,091	36,295	38,139	41,198	44,157
	(9.7)	(9.5)	(9.7)	(10.2)	(10.5)	(10.5)	(10.8)	(11.1)
10. Ubon Ratchathani	20,241	20,368	22,361	23,425	25,384	26,835	29,299	30,886
	(7.4)	(6.9)	(7.2)	(7.2)	(7.3)	(7.4)	(7.7)	(7.8)
11. Surat Thani	14,498	15,659	16,723	18,423	19,504	21,075	21,777	22,817
	(5.3)	(5.3)	(5.4)	(5.7)	(5.6)	(5.8)	(5.7)	(5.7)
12. Songkhla	14,515	14,903	15,888	17,570	19,069	19,613	20,591	21,288
	(5.3)	(5.1)	(5.1)	(5.4)	(5.5)	(5.4)	(5.4)	(5.4)
13. Bangkok	23,001	24,526	24,984	26,096	27,968	28,982	30,362	31,171
	(8.4)	(8.4)	(8.0)	(8.0)	(8.1)	(8.0)	(8.0)	(7.9)
Total	274,340	293,717	311,607	324,822	345,700	361,959	380,587	396,910

Note: The Universal Coverage Scheme (UCS) patients admitted for T2DM are the UCS beneficiaries who were admitted for type 2 diabetes mellitus (T2DM) between 2009 and 2016. The number of UCS patients was counted as one in a year. That is, a UCS patient who was admitted for T2DM for multiple times in a year was counted as one in that year. If the same patient was admitted for T2DM in another year, he/she was counted as one again in the separate year.

Fig 2 shows the population pyramids of admitted cases with T2DM among the UCS beneficiaries in Thailand in 2009 and 2016. The female admission rates were persistently higher than that of males both in 2009 and 2016. The sex disparity in the admission rates widened between their 30s and 70s. In 2009, the admission rates of both sexes started increasing in their late 30s, females reached a peak at the ages of 70 to 74 and males at the ages of 75 to 79, and then both declined. In 2016, both sexes reached a

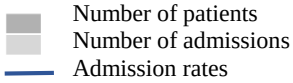
peak at the ages of 75-79. Although the trend was similar in the two years, the admission rates were persistently much higher and the overall increase occurred in older ages in 2016.

Fig 2. Population pyramids of admitted cases with type 2 diabetes mellitus (T2DM) among the Universal Coverage Scheme patients in Thailand in 2009 and 2016

Note: T2DM admission rates are per 1,000 population.

Fig 3 presents the number of patients, the number of admissions and the admission rates of T2DM and those with the six major complications: CKD, MI, cerebrovascular diseases, retinopathy, cataract and foot amputation from 2009 to 2016 in Thailand. Overall, there was a linearly increased trend in T2DM admission rates by 5.2% annually. Among the T2DM admissions, 24.0% was associated with CKD in 2009-2016, and the T2DM admission rates with CKD also had a positive linear trend by 10.0% per year. Admission rates of T2DM with CKD were 3.5/1000, cerebrovascular diseases 1.1/1000, cataract 0.5/1000, MI 0.4/1000, and retinopathy and foot amputation 0.2/1000 population, respectively. It is noted that the increasing trends of T2DM admission with CKD and cerebrovascular diseases were visually observable, while those with MI, retinopathy and foot amputation were rather subtle, and that with cataract was stable.

Fig 3. The number of patients, the number of admissions and admission rates of type 2 diabetes mellitus with and without the five major complications in Thailand from 2009 to 2016



Note: The number of admissions refers to how many times the Universal Coverage Scheme (UCS) patients were admitted for type-2 diabetes mellitus (T2DM) with or without complications in each year, whereas the number of patients refers to how many T2DM patients were admitted in the year. A patient could be admitted for multiple times in a year. The admission rate is the number of admissions divided by the number of the UCS population. The scale for all T2DM admission rates is different from others as it went up to 17.3/1000 in 2016.

Table 2 presents the results of the time series regressions to estimate temporal trend of admissions showed that all types of T2DM admissions except that with cataract had a significant and positive temporal trend.

Table 2. Time series regressions parameters of temporal trend analysis for admissions

Parameters	Estimate	SE	z value	p value
All DM admissions				
$\boldsymbol{\beta_0}$: intercept	-4.460529	0.006002	-743.16	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.050566	0.001187	42.61	p < 0.001
DM with CKD admissions				
$\boldsymbol{\beta_0}$: intercept	-6.108389	0.009446	-646.64	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.095675	0.001861	51.41	p < 0.001
DM with MI admissions				
$\boldsymbol{\beta_0}$: intercept	-8.11538	0.02155	-376.58	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.07541	0.00424	17.78	p < 0.001
DM with cerebrovascular diseases admissions				
$\boldsymbol{\beta_0}$: intercept	-7.251687	0.009935	-729.93	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.084358	0.001941	43.47	p < 0.001
DM with cataract admissions				
$\boldsymbol{\beta_0}$: intercept	-7.604557	0.046891	-162.175	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.015244	0.009283	1.642	0.101
DM with retinopathy admissions				
$\boldsymbol{\beta_0}$: intercept	-8.941096	0.028458	-314.181	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.049766	0.005599	8.888	p < 0.001

DM with amputation admissions				
$\boldsymbol{\beta_0}$: intercept	-8.955374	0.023377	-383.09	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.050946	0.004584	11.12	p < 0.001

Note: SE: Standard error, CI: Confidence interval, DM: Diabetes mellitus, CKD: Chronic kidney disease, MI: Myocardial infarction

Fig 4 presents SARs of T2DM and its complications in the NHSO 13 Regions in 2009 and 2016. The SARs of T2DM were high in central and northeastern regions: 1.20/1000 in Region 4 (Saraburi), 1.22/1000 in Region 5 (Ratchaburi), 1.31/1000 in Region 7 (Khon Kaen) and 1.22/1000 in Region 8 (Udon Thani) in 2009, but they all declined close to the national average by 2016 except Region 7 that further increased to 1.44/1000. In the same period, the SARs of T2DM increased from 0.88 to 1.05/1000 in Region 9 (Nakhon Ratchasima), and declined from 1.00 to 0.83/1000 in Region 13 (Bangkok). The SARs of T2DM with CKD were high in northeastern regions in 2009: 1.79/1000 in Region 7 (Khon Kaen), 1.58/1000 in Region 8 (Udon Thani) and 1.64/1000 in Region 10 (Ubon Ratchathani), but they all declined to 1.70/1000, 1.45/1000 and 1.60/1000 by 2016, respectively. On the other hand, the SAR of T2DM with CKD in Region 9 increased from 0.86 to 1.05/1000 in the same period. The SARs of T2DM with MI was high in Bangkok and central regions in 2009: 1.60/1000 in Region 4 and 1.69/1000 in Region 13 (Bangkok), but they both reclined to 1.43/1000 and 1.27/1000 by 2016, respectively. The SAR of T2DM with MI in Region 7 increased from 0.88 in 2009 to 1.01 in 2016. The SARs of T2DM with cerebrovascular diseases were also high in Bangkok and central regions in 2009: 1.46/1000 in Region 4 (Saraburi), 1.35/1000 in Region 5 (Ratchaburi), 1.34/1000 in Region 6 (Rayong) and 1.90/1000 in Region 13 (Bangkok), but they all declined to 1.25/1000, 1.17/1000, 1.30/1000 and

1.21/1000 by 2016, respectively. The SARs of T2DM with cerebrovascular diseases increased in Region 7 and 9 between 2009 and 2016, from 0.83 to 1.03/1000 and 0.65 to 1.11/1000, respectively. The SAR of T2DM with retinopathy in Region 13 was 4 times higher than the national average in 2009. Although it declined to 2.77/1000 by 2016, it was still much higher than other regions. In the same period, the SARs of T2DM with retinopathy increased in Region 8 and 11 (Surat Thani), from 0.43 to 1.11/1000 and 0.52 to 1.00/1000, respectively. The SARs of T2DM with cataract were high in Bangkok and central regions in 2009: 2.35/1000 in Region 4, 1.95/1000 in Region 5 and 1.64/1000 in Region 13, but they all declined to 1.40/1000, 1.33/1000 and 1.25/1000 by 2016, respectively. Whereas, the SARs of T2DM with cataract increased from 0.76 to 1.13/1000 in Region 11 in the same period. The SARs of T2DM with foot amputation was high in Bangkok and central and northeastern regions in 2009: 1.21/1000 in Regions 4, 1.35/1000 in Region 7, 1.24/1000 in Region 8 and 1.45/1000 in Region 13. By 2016, the SARs of T2DM with foot amputation in Regions 4 and 13 declined to 0.97/1000 and 1.16/1000, respectively, while those further increased in Region 7 and 8 to 1.61/1000 and 1.43/1000, respectively.

Fig 4. Comparison of age- and sex- standardized admission ratio of type 2 diabetes mellitus and its complications in the NHSO Regions in 2009 and 2016

Note: The standardized admission ratio (SAR) of type 2 diabetes mellitus (T2DM) and its complications were shown in white if it is the national average. The color changes into red if SAR is higher than the national average, and gray if it is lower than the national average. The scale for SARs of T2DM with retinopathy is different from others: it continues up to 5.0 because SAR of T2DM with retinopathy in Bangkok was substantially higher than other regions in 2009.

Discussion

A linearly increased trend of T2DM admission rates and that with the six major diabetic complications were found from 2009 to 2016 in Thailand. Female admission rates were persistently higher than that of males. In 2016, overall increase in the T2DM admission rates was observed among the older ages relative to that in 2009. Although geographical inequalities in the T2DM admission ratios were found, the reduced trend in the inequalities was also observed between 2009 and 2016.

The observed sex disparities in frequency of the T2DM admissions were consistent with the National Health Examination Surveys [2] and an assessment on quality of care among patients diagnosed with T2DM and hypertension, which presented that females in Bangkok were 1.13 times more likely to have HbA1C level of higher than 9.0% [21]. Biology might play a part in observed sex disparities as women typically transition from prediabetes to diabetes with a worse cardiovascular risk profile and a higher BMI than men. However, psychosocial factors, such as health-seeking behavior and provision of health care, play more important part in the differences, which can be addressed through changes in policy and health-care delivery [22]. It should be noted that high admission rate does not necessarily mean high prevalence of the disease, as previous studies showed higher percentage of undiagnosed diabetes [2] and slightly higher fasting plasma glucose among males in Thailand [23].

While the number of patients, the number of admissions and admission rates of T2DM steadily increased from 2009 to 2016, the increased trend in the sex-and age-adjusted T2DM admission rates, which were estimated using the national UCS population of 2009 as the standard population, (12.1 in 2009 and 15.0 in 2016, *results not shown*) were rather gradual as compared with the numbers of crude admissions rates (12.1 in 2009 and 17.3 in 2016). This result suggests that the increase in the T2DM admission rates is partly due to the increased and aged population of the country. Although further studies are required, it could imply that Thailand may face the greater burden of T2DM in the future if the trend of population growth and aging continues in the country.

The T2DM admission rates reached a peak at the ages of 70s and then declined in 2009 and 2016 presumably due to premature death of the T2DM patients. The shifted trend of the peak age toward elderly among females between 2009 and 2016 can be explained by the fact that the T2DM patients had aged and their longevity had been extended over the eight years [24]. This trend further implies the need of increased costs of providing diabetes-related care as older adults with diabetes is clearly more complicated with multiple coexisting medical conditions, particularly macrovascular complications such as acute myocardial infarction and cerebrovascular diseases and end-stage renal disease [25]. Age also affects the potential risks of overtreatment of hyperglycemia in the hospital, which often leads to longer hospitalization, higher medical costs and increased mortality [26][27].

Among the six diabetic complications, CKD showed the most significant increase between 2009 and 2016. Although Thailand has launched the "Thailand Healthy Lifestyle Strategy 2011-2020 Plan" [28] to reduce the prevalence, complications, disability, mortality and cost of non-communicable diseases including diabetes, national screening and prevention program has not yet been in place [4]. Additionally, renal replacement therapy including renal and peritoneal dialysis and kidney transplantation requires the UCS patients with a co-payment [29], which may have inhibited some of them from accessing to proper care. Thailand should take this trend seriously as this type of complication is associated with a substantial burden in terms of mortality, morbidity and healthcare cost as it often requires costly and long-term care including dialysis. To prevent progression of CKD stage, the country should strengthen an effective measure, such as glycated hemoglobin control (HbA1c) ≦7.0% [21], as instructed in the Clinical Practice Recommendation for the Evaluation and Management of Chronic Kidney Disease in Adults 2015 [30]. This study also found that the number of admitted cases with CKD were 1.7 times greater than the number of patients. This indicates that many of the patients with diabetic complication of CDK were readmitted, and implies that there might be unmet needs of inpatient care for the T2DM patients with CKD. Further study should be conducted to investigate the reasons behind the frequent readmissions and take measures to meet the needs of the patients.

While the SARs of T2DM were higher in Bangkok and central regions relative to other regions in 2009, except those with CKD and partly foot amputation, they declined in most of the regions by 2016. Additionally, there was an overall trend of SAR reduction in Bangkok and central regions, where human and financial resources were traditionally concentrated, and increase in northeastern regions, where the resources were traditionally scarce, over the eight years [9, 31]. This trend indicates Thailand's successful health reform by reducing geographical inequalities in inpatient care, which might be a result of equitably redistributed health professionals, health infrastructure development and rural retention policies over the past four decades [32].

On the other hand, the persistently high SAR of T2DM with retinopathy in Bangkok is presumably due to high density of specialists as half of 1,500 ophthalmologists, including 200 retinal specialists, practice in Bangkok [33].

The persistently high SAR of T2DM with CKD in northeastern regions was consistent with a previous study and partly attributed to high prevalence of CKD in northeastern regions (10.8%) relative to other regions (north 8.9%, south 8.1% and Bangkok 6.2%) [34], but partly to an association with lower density of physicians and rurality of the region [13]. The density of physicians in northeastern regions is the lowest in the country [32], as low as seven times lower than Bangkok [9]. It is reasonable to assume that in a region where physicians are scarce, T2DM patients with CKD are unlikely to receive

timely, thorough and effective treatment, and consequently deteriorate in conditions. This assumption might explain the high readmission rates of T2DM with CDK, and the highest mortality rates due to diabetes in northeastern regions as found in another study [12]. Moreover, rurality of the northeastern regions, where 71.0% of the population reside in rural setting (north 65.6%, south 66.5% and Central 54.5%) [35], might have halted them from accessing adequate primary care. A previous study found a strong association between the high SAR of diabetes and rurality as the rural population tends to have lack of public transport alternatives and poor health literacy with less education which often limit accessibility to health care. The study also suggested that the percentage of patients who had received up to secondary education was lower in rural districts by approximately 10% [13].

Inaccessibility to the outpatient data and absence of information indicating direct causality between diabetes and complicated conditions were the major limitations of this study. For the first limitation, it is important to monitor the long-term trends of diabetic morbidity starting at onset of disease, accessibility and quality of outpatient and inpatient care, and health outcome including mortality to assess the quality of T2DM healthcare in the country. Besides, community involvement in diabetic care should be also carefully monitored, as approximately 77.0% of cost is involved in non-medical activities [36], and community-based screening, study and health promotion would be increasingly important for diabetic care [4]. In this study, we looked at the trend of the inpatient care and tried to capture that of a series of healthcare, but future study should carefully assess the situations of accessibility and quality

of T2DM outpatient care, and coordination of outpatient and inpatient care for the most cost-effective T2DM healthcare policies in Thailand.

For the second limitation, we regarded the complications as if they were directly caused by T2DM, when we found T2DM as either principle or secondary diagnosis and one or more of the major complications in an individual record of the hospital admission database since it was the only available information.

Thailand has achieved great improvement in health care reform invested on equitable health finance and increased total budget for health expenditures in T2DM and its complications. It is time for the country to carefully identify the risk factors and regions in particular needs of care for T2DM and its complications, and plan on the effective and efficient health care which would not leave no one behind in the country.

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Contributors

TL acquired the data, conceived of and designed the study, and drafted the final manuscript. HT and HN analysed the data, interpret and discuss the results, and drafted the final manuscript. SN, AL and NS designed the statistical framework and supported data analysis. AL and NS confirmed the quality of data and the study design. VC, TL, KS and HM took responsibility for the integrity of the data and the accuracy of the data analysis and will oversee the study. All the authors made critical revisions to the manuscript for important intellectual content, gave final approval of the manuscript, and will support the interpretation and discussion of findings.

Data reporting

All patient records were fully anonymized before we accessed. The UCS data are available upon request to the National Health Security Office, Thailand, with the research outline and the details of the required data.

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Figure 1

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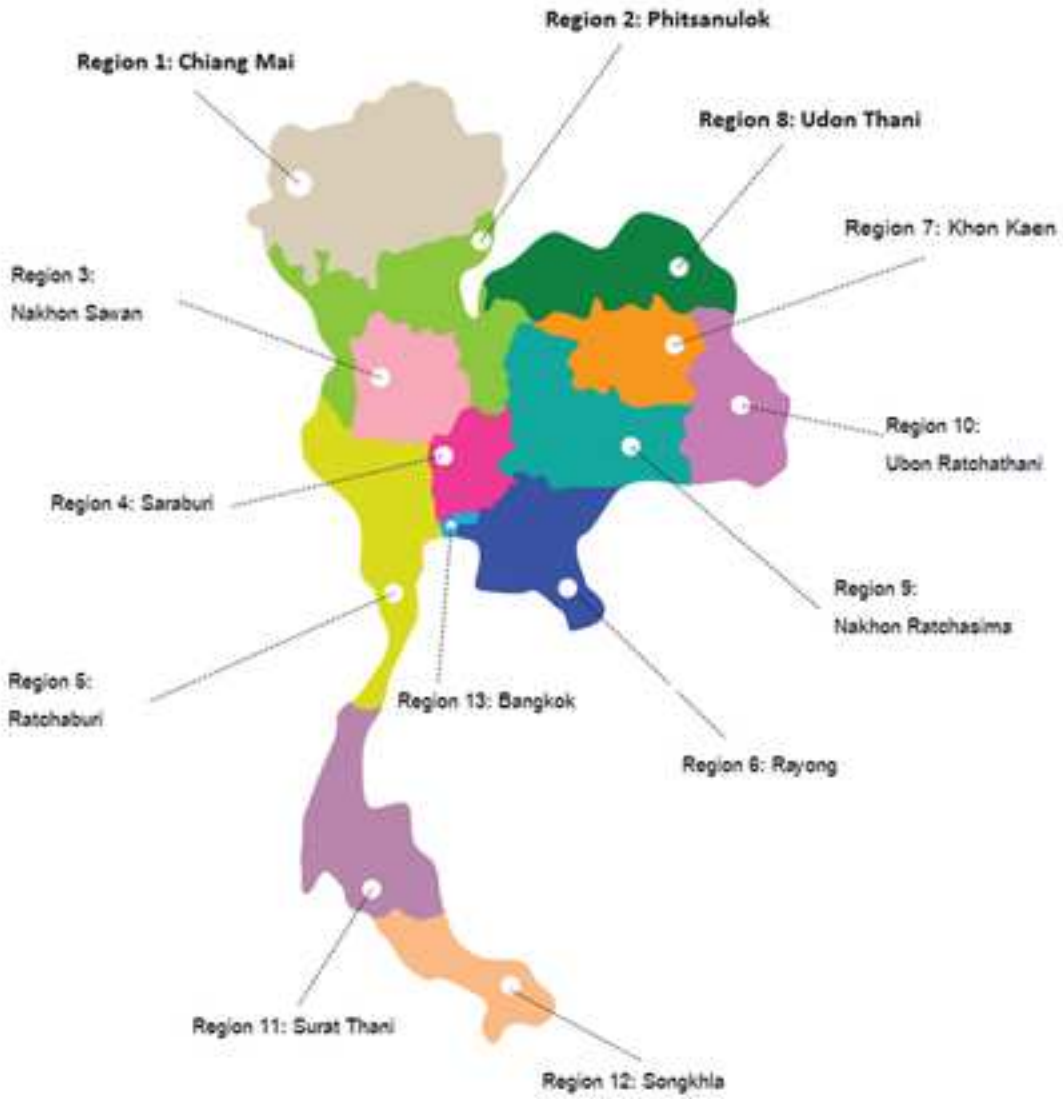

Figure 2

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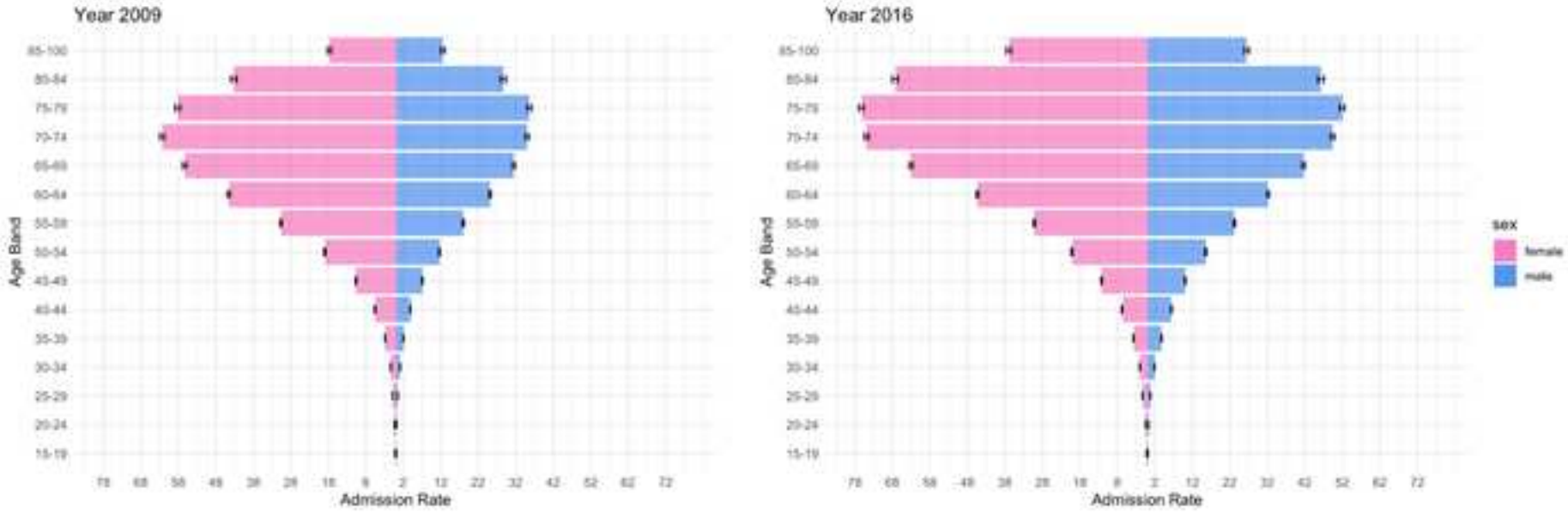

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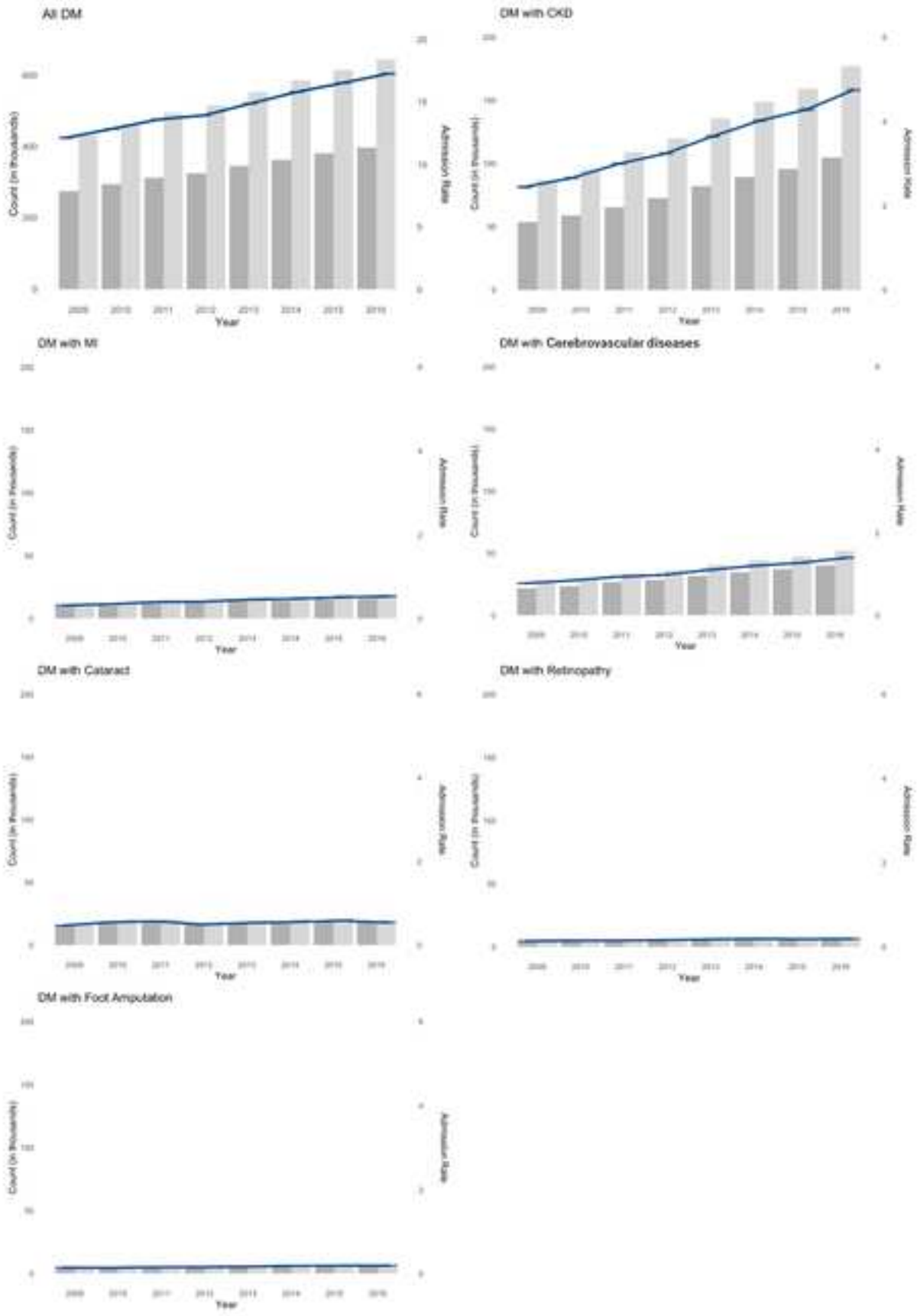

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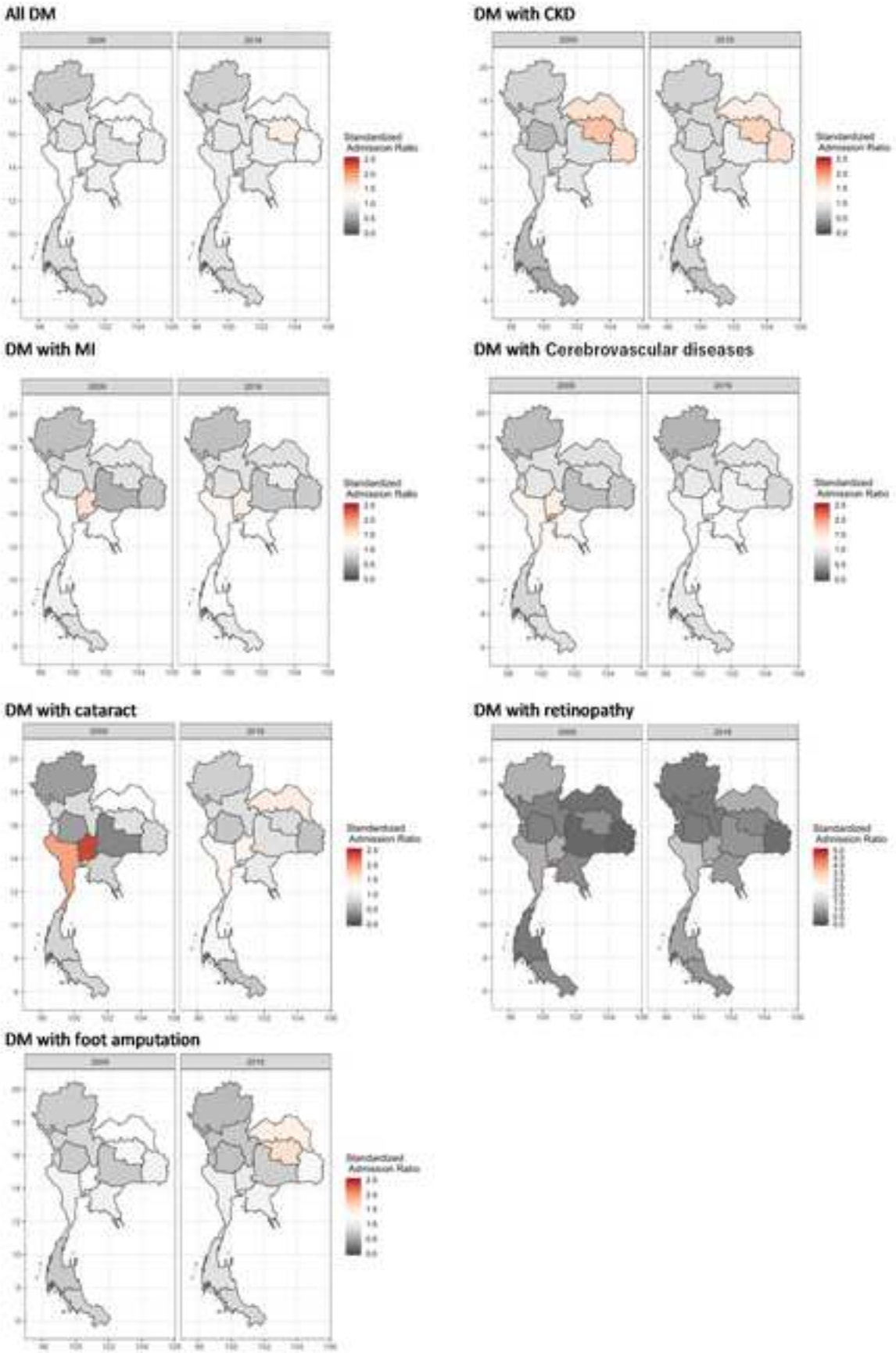

Full title: Hospital admission in patients with type 2 diabetes mellitus in Thailand under the Universal Coverage Scheme: a time- and geographical-trend analysis, 2009–2016

Short title: Type 2 diabetes mellitus in Thailand

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Abstract

Background

To estimate the time and geographical trends of nationwide admission rates of type 2 diabetes mellitus (T2DM) and its complications, including chronic kidney disease (CKD), myocardial infarction ~~(MI)~~, ~~stroke~~cerebrovascular diseases, retinopathy, cataract, and diabetic foot amputation, descriptive analyses of 2009-2016 were performed using the data of ~~among~~ the Universal Coverage Scheme (UCS) which covers nearly 70 percent of the Thai population~~beneficiaries across administrative regions of National Health Security Office (NHSO) in Thailand from 2009 to 2016.~~ .

Methods and findings

The database of T2DM patients aged 15-100 years who were admitted between 2009 and 2016 under the UCS ~~in Thailand~~ and that of the UCS population were retrieved for the analys~~e~~is. The admitted cases of T2DM were extracted from the database using disease code~~s~~~~ing~~ of principal and secondary diagnoses defined by~~of~~ the International Classification of Diseases 9th and 10th Revision~~s~~ ~~(ICD9 and ICD10)~~. The T2DM admission rates in 2009-2016 were the number of admissions divided by the number of the UCS population.~~were standardized by age and sex to the 2009 UCS population.~~ The standardized admission ratio~~s~~ (SAR~~s~~)~~ of each region~~ were further estimated in contrast to the expected number of admissions considering age and sex composition of the UCS ~~national~~ population in each region.

A linearly increased trend was found in T2DM admission rates from 2009 to 2016. Female admission rates were persistently higher than that of males. In 2016, an increase in the T2DM admission rates was observed among the older ages relative to that in 2009. Although the SARs of T2DM were generally higher in Bangkok and central regions in 2009, except that with CKD and foot amputation which had higher trends in northeastern regions, the geographical inequalities were fairly reduced by 2016.

~~A linearly increased trend of T2DM admission rates at national level from 2009 to 2016 with 3.1% increase per year was found. For the five major diabetic complications, the average annual increase in admission rates from 2009 to 2016 for CKD, myocardial infarction, stroke, cataract and amputation were 10.8%, 5.6%, 7.7%, 0.2%, and 6.1%, respectively. Female admission rates were 1.0 to 2.4 times higher than that of males persistently. In 2009 and 2016, the T2DM admission rates in both sexes started increasing at their late 30s, reached a peak at 60 to 64 and then declined. However, the overall increased rate was observed among the older ages in 2016. The SAR with major diabetic complications were particularly high in Region 3 (Nakhonsawan) (1.5/1,000) and Region 2 (Phitsanulok) (1.5/1,000) in 2009 and that in Region 3 (Nakhonsawan) further increased to 1.8/1,000 in 2016.~~

Conclusion

Admission rates of T2DM and its major complications ~~have been~~ increased~~ing~~ in Thailand from 2009 to 2016. Although ~~and~~ the overall ~~intra-country~~ geographical ~~difference~~inequalities in the SARs of T2DM were reduced in the country, ~~has been observed in Thailand.~~ further efforts are required to improve the health system and policies focusing on risk factors and regions to manage the increasing T2DM.~~Improving health system and policy to improve the both primary and secondary prevention of T2DM are required in the country.~~

Introduction

In the world~~Globally~~, approximately 451 million people aged 18 to 99 years lived with diabetes in 2017 [1], and this number is projected to further increase to 693 million by 2045 [1]. When diabetes is not properly managed, complications develop typically in kidney failure, vision loss, and ~~leg~~ foot amputation. Diabetes has increasingly become a global burden of disease that increases premature death, reduces quality of life and drives up healthcare cost [2]. The World Health Organization (WHO) emphasizes importance of prevention and early diagnosis of diabetes, particularly for type 2 diabetes mellitus (T2DM) which can be effectively reduced through population-based and individual prevention measures that target key risk factors [3].

In Thailand, prevalence of diabetes increased from 2.3% in 1991 [4] to 9.6% (6.5 million diabetes cases) in 2016 [5]. More than 94.0% of diabetic cases in the country are T2DM [2] and the ~~five~~six major diabetic complications that are annually screened in the country include chronic kidney disease (CKD), myocardial infarction (MI), ~~stroke~~cerebrovascular diseases, retinopathy, cataract and ~~amputation~~foot amputation [6]. The National Health Examination Survey in 2014 found that only 23.5% of people with T2DM were treated with fasting plasma glucose being less than 130 mg/dL~~l~~, while 43.0% of them were undiagnosed [7].

Thailand has achieved remarkable improvements in population health since the achievement of universal health coverage (UHC) in 2002. Major health protection schemes in the country include the Civil Service Medical Benefit Scheme, the Social Security Scheme and the Universal Coverage Scheme (UCS). The last one, taken care by the National Health Security Office (NHSO), covers more than 48 million people, approximately 69.9% of the Thai population as of 2019 [8]. NHSO has 13 Regional Offices (see Fig 1) sharing all resources and regulation [9]. The UCS is financed by general tax revenue. The UCS offers the patients with T2DM and its complications the comprehensive benefit package which includes prevention, curative and rehabilitation services. The beneficiaries are systematically required to visit the registered primary care facility as the first point of contact. In case of severe conditions, they are referred to secondary and tertiary care facilities [10]. The UCS applies mixed-method provider payments, with mainly close-ended capitation for outpatient care and based on diagnosis-related groups, with a global budget, for inpatient care [11].

Fig 1. National Health Security Organization regions

Despite the national efforts in the implementation of UCS, there is evidence of a rise in intra-national health ~~differences and~~ inequalities in diabetic mortality rates in Thailand [12]. However, the level of health inequalities in morbidity measures such as hospital admission has not been well documented. To fill the knowledge gap, in this paper, we 1) described for the first time a time-trend analysis of

nationwide admission rates of T2DM and its ~~five~~ six major diabetic complications among the UCS beneficiaries in Thailand from 2009 to 2016, and 2) assessed ~~difference~~regional inequality in trend of the admission rati~~o~~os across the 13 NHSO Regions. We aim to provide the basis for planning and carrying out action in terms of necessary health provision and preventive measures.

Materials and methods

Data

The data set stored at the NHSO compiled from three data sources were used for this study. Two are reports sent from hospitals to the Ministry of Public Health, namely the hospital admission database and the operation database, which include personal national identification number, sex, date of birth, the NHSO Region, province of hospitalization~~residence~~, hospital code of registration, hospital code of admission, date of admission, date of discharge, date of death, and principal and secondary diagnoses. The remaining is compiled from hospital reports sent to the NHSO for reimbursement. All data were fully anonymized before we accessed them.

All Thai citizens entitled to use the UCS are registered in a special table of the NHSO datasets. These are updated annually against birth and death registries taken care by the Ministry of Interior. Although the NHSO database contains admissions of patients covered by ~~of~~ all medical benefit schemes, only those entitled to the UCS were used for this study. These data are regularly checked to prevent duplication based on personal national ID number, names and birthdates. After careful data cleaning, a total of 4,297,321 T2DM admitted cases of 2,689,642 UCS patients aged 15 to 100 years in Thailand between 2009 and 2016 were included in this study. Although Thailand achieved UHC in 2002, we decided to use only data from 2009 onwards for our analyses since there were a number of~~many~~ missing values and errors in data before 2009 [13, 14]. Ages of below 15 years were excluded because T2DM

was rare in children until recently [13] and above 100 years were considered to be primarily caused by typing errors. All subsequent analyses were done on data of the UCS population ~~these~~ as denominators and those of the UCS admissions for T2DM as numerators.

Definitions of T2DM and its complications

A trained medical statistic officer at the hospitals entered ~~D~~diagnosis of T2DM and its complications, CKD, MI, ~~stroke~~cerebrovascular diseases, retinopathy and cataract ~~were entered at the hospital by a trained medical statistic officer~~ based on the International Classification of Diseases 10th Revision (ICD-10) [14], and diabetic ~~amputation~~foot amputation ~~was defined~~ based on the International Classification of Diseases 9th Revision (ICD-9) [15]. All UCS admitted cases ~~admitted cases~~ whose principal or~~and~~ secondary diagnose~~i~~s was~~ere~~ coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1~~2~~ to N18.6, ~~5 or~~ N18.9, E11.2, E14.2, N08.3, N19 and N18.9), MI (~~I21.0 to~~ I21~~.4 or I21.9~~ and I22), ~~stroke~~cerebrovascular diseases (I6~~.~~0 to I6~~.~~9), retinopathy (H36.0), cataract (H25.0 to H25.2, H25.8, H25.9, H26.0 to H26.4, H26.8, H26.9, and H28.0), or diabetic ~~amputation~~foot amputations (8410~~01~~-8415~~7~~) were included, and any other cases were excluded from this study. Stage 3 or higher stages of CKD are usually considered as diabetic complications. However, stage 1 and 2 of CKD were also included in this study because the ICD-10 code, E11.2 includes all stages of kidney complications, and thus it was impossible to exclude stage 1 and 2 of CKD cases. T2DM cases with acute, as well as subsequent MI were included in this study. While only H36.0, diabetic retinopathy was considered as

a diabetic complication, all types of cataract were included in this study because diabetic cataract is often misdiagnosed as other types of cataract. Diagnosis of foot amputation was considered as a diabetic complication if it was performed from the toe to above the knee.

Data analysis

Descriptive analyses~~statistics~~ using the retrospective data were ~~us~~performed to summarize age, sex and regional structure of the UCS patients who were admitted for T2DM between 2009 and 2016 in Thailand and the trends in 2009 and 2016 were compared to depict the change in the trends over the eight years.

~~Age- and sex-standardized T2DM admission rates were estimated using the national UCS population of 2009 as the standard population. Age was categorized into 15 groups in intervals of five years, except the last category that includes 85 to 100 years of age.~~ We estimated the standardized admission ratio (SAR) of each region using the following equation for each region.

$$SAR_i = \frac{o_i}{e_i}$$

$$e_i = \sum_{j=1}^{J} p_j n_{ij}$$

where SAR_i is standardized admission ratio in region i; o_i is the observed number of admissions in region i; e_i is the expected number of admissions in region i; j is the population stratum defined by age and sex; p_j is standard admission rate in the 2009 UCS population for the population stratum j. Age was

categorized into 15 groups in intervals of five years, except the last category that includes 85 to 100 years of age.

To estimate temporal trend of admissions, we conducted time series regressions with the following negative binomial regression model.

$$n_i \sim \text{NegativeBinomial}(\mu_i, \phi$$

$$\mu_i = \exp(\beta_0 + \beta_1 x + \log N_i)$$

where n_i is the number of admissions of ith time point, N_i is the number of UC population of ith time point, x is the indicator variable of time points, μ is the mean parameter and ϕ is dispersion parameter of Negative Binomial distribution, β_0 is the intercept, and β_1 is the slope parameter.

R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) [16] was used to analyze the data. To draw choropleth maps, we used R version 3.4.1 with package 'sf' [17] and package 'ggplot2' [18]. Ethics ~~The~~ of the study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (NCGM) in Japan on 11 May 2018 (NCGM-G-002524-00).

Results

Table 1 presents the number and demographic characteristics of the UCS patients~~opulation~~ admitted for T2DM in 2009-2016. The UCS population of 15 to 100 years of age represents approximately 54.0% of the total population of 2009-2016 in Thailand. Over 60% of T2DM patients were female throughout the period, although the sex disparity narrowed in the eight years. The mean age (SD) of the UCS T2DM patients~~opulation~~ wa~~i~~s ~~43~~63.1 (~~±~~12.2) years throughout the years and it annually rose by 0.~~6~~2 years on average. ~~The population of over 50 years annually increased by 3.1% on average among the UCS population.~~ The overall number of UCS patients with T2DM annually increased by 5.4%, and 14.4% among the 85 year-olds and older from 2009 to 2016.~~population in Region 4 (Saraburi), 6 (Rayong) and 13 (Bangkok) annually increased by 1.5%, 1.3% and 0.9%, respectively, while that of Region 1 (Chiangmai), 3(Nakhonsawan) and 7 (Khonkaen) annually decreased by 3.2%, 0.4% and 0.4%, respectively from 2009 to 2016.~~ The number of T2DM patients proportionately increased in Region 9 (Nakhon Ratchasima), 10 (Ubon Ratchathani) and 11 (Songkhla), and decreased in Region 4 (Saraburi), 5 (Ratchaburi) and 13 (Bangkok) in the study period.

Table 1. Number and d~~D~~emographic characteristics of the Universal Coverage Scheme patients admitted for ~~with~~ type 2 diabetes mellitus in 2009-2016

	2009	2010	2011	2012	2013	2014	2015	2016
	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
Sex								

Female	181,402 (66.1)	193,297 (65.8)	202,297 (64.9)	208,632 (64.2)	219,830 (63.6)	228,533 (63.1)	239,283 (62.9)	247,671 (62.4)
Male	92,938 (33.9)	100,420 (34.2)	109,310 (35.1)	116,190 (35.8)	125,870 (36.4)	133,426 (36.9)	141,304 (37.1)	149,239 (37.6)
Age~~Mean age~~	~~62.4 (±12.0)~~	~~62.6 (±12.1)~~	~~63.0 (±12.1)~~	~~63.1 (±12.1)~~	~~63.3 (±12.2)~~	~~63.5 (±12.2)~~	~~63.7 (±12.3)~~	~~63.9 (±12.3)~~
15-19	364 (0.1)	355 (0.1)	393 (0.1)	373 (0.1)	393 (0.1)	449 (0.1)	489 (0.1)	478 (0.1)
20-24	547 (0.2)	608 (0.2)	628 (0.2)	703 (0.2)	755 (0.2)	776 (0.2)	801 (0.2)	876 (0.2)
25-29	1,113 (0.4)	1,104 (0.4)	1,133 (0.4)	1,209 (0.4)	1,253 (0.4)	1,335 (0.4)	1,486 (0.4)	1,551 (0.4)
30-34	2,478 (0.9)	2,582 (0.9)	2,632 (0.8)	2,696 (0.8)	2,888 (0.8)	2,913 (0.8)	3,126 (0.8)	3,156 (0.8)
35-39	5,603 (2.0)	5,938 (2.0)	5,976 (1.9)	6,100 (1.9)	6,233 (1.8)	6,541 (1.8)	6,739 (1.8)	6,822 (1.7)
40-44	11,867 (4.3)	12,206 (4.2)	12,351 (4.0)	12,733 (3.9)	13,053 (3.8)	13,424 (3.7)	13,980 (3.7)	13,787 (3.5)
45-49	20,490 (7.5)	21,236 (7.2)	21,809 (7.0)	22,798 (7.0)	23,893 (6.9)	24,565 (6.8)	25,236 (6.6)	25,353 (6.4)
50-54	30,357 (11.1)	31,468 (10.7)	32,063 (10.3)	33,243 (10.2)	35,080 (10.1)	36,049 (10.0)	37,860 (9.9)	39,043 (9.8)
55-59	39,833 (14.5)	42,140 (14.3)	43,507 (14.0)	44,951 (13.8)	46,174 (13.4)	47,384 (13.1)	49,119 (12.9)	50,468 (12.7)
60-64	42,231 (15.4)	46,458 (15.8)	50,187 (16.1)	53,045 (16.3)	56,747 (16.4)	59,059 (16.3)	61,020 (16.0)	63,304 (15.9)
65-69	41,038 (15.0)	43,357 (14.8)	45,925 (14.7)	47,328 (14.6)	51,427 (14.9)	55,209 (15.3)	60,056 (15.8)	64,124 (16.2)
70-74	37,359 (13.6)	40,155 (13.7)	42,922 (13.8)	44,155 (13.6)	46,068 (13.3)	47,329 (13.1)	48,787 (12.8)	50,920 (12.8)
75-79	24,996 (9.1)	27,241 (9.3)	30,523 (9.8)	32,103 (9.9)	34,926 (10.1)	37,129 (10.3)	39,243 (10.3)	40,946 (10.3)
80-84	11,356 (4.1)	13,362 (4.5)	15,093 (4.8)	16,484 (5.1)	18,459 (5.3)	20,367 (5.6)	21,998 (5.8)	24,058 (6.1)
85+	4,708 (1.7)	5,507 (1.9)	6,465 (2.1)	6,901 (2.1)	8,351 (2.4)	9,430 (2.6)	10,647 (2.8)	12,024 (3.0)
Mean (SD)	62.4 (12.0)	62.6 (12.1)	63.0 (12.1)	63.1 (12.1)	63.3 (12.2)	63.5 (12.2)	63.7 (12.3)	63.9 (12.3)
	~~2009~~	~~2010~~	~~2011~~	~~2012~~	~~2013~~	~~2014~~	~~2015~~	~~2016~~

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NHSO Regions								
1. Chiang ~~m~~Mai	19,572 (7.1)	21,232 (7.2)	22,492 (7.2)	23,021 (7.1)	23,995 (6.9)	25,160 (7.0)	26,715 (7.0)	28,366 (7.1)
2. Phitsanulok	14,631 (5.3)	15,857 (5.4)	16,760 (5.4)	18,195 (5.6)	19,024 (5.5)	19,455 (5.4)	20,411 (5.4)	20,937 (5.3)
3. Nakhon ~~s~~Sawan	13,592 (5.0)	15,699 (5.3)	16,764 (5.4)	17,646 (5.4)	17,999 (5.2)	18,288 (5.1)	18,974 (5.0)	19,865 (5.0)
4.Saraburi	23,401 (8.5)	25,965 (8.8)	26,257 (8.4)	25,344 (7.8)	26,249 (7.6)	27,420 (7.6)	28,995 (7.6)	30,772 (7.8)
5. Ratchaburi	27,208 (9.9)	28,203 (9.6)	30,047 (9.6)	29,901 (9.2)	31,538 (9.1)	32,479 (9.0)	33,122 (8.7)	34,033 (8.6)
6. Rayong	22,439 (8.2)	24,207 (8.2)	26,634 (8.5)	27,231 (8.4)	28,588 (8.3)	29,743 (8.2)	30,891 (8.1)	33,143 (8.4)
7. Khon ~~k~~Kaen	27,623 (10.1)	30,320 (10.3)	32,205 (10.3)	34,357 (10.6)	36,748 (10.6)	39,207 (10.8)	40,608 (10.7)	41,217 (10.4)
8. Udon ~~t~~Thani	27,032 (9.9)	28,833 (9.8)	30,200 (9.7)	30,522 (9.4)	33,339 (9.6)	35,563 (9.8)	37,644 (9.9)	38,258 (9.6)
9. Nakhon ~~r~~Ratchasima	26,587 (9.7)	27,945 (9.5)	30,292 (9.7)	33,091 (10.2)	36,295 (10.5)	38,139 (10.5)	41,198 (10.8)	44,157 (11.1)
10. Ubon ~~r~~Ratchathani	20,241 (7.4)	20,368 (6.9)	22,361 (7.2)	23,425 (7.2)	25,384 (7.3)	26,835 (7.4)	29,299 (7.7)	30,886 (7.8)
11. Surat ~~t~~Thani	14,498 (5.3)	15,659 (5.3)	16,723 (5.4)	18,423 (5.7)	19,504 (5.6)	21,075 (5.8)	21,777 (5.7)	22,817 (5.7)
12. Songkhla	14,515 (5.3)	14,903 (5.1)	15,888 (5.1)	17,570 (5.4)	19,069 (5.5)	19,613 (5.4)	20,591 (5.4)	21,288 (5.4)
13. Bangkok	23,001 (8.4)	24,526 (8.4)	24,984 (8.0)	26,096 (8.0)	27,968 (8.1)	28,982 (8.0)	30,362 (8.0)	31,171 (7.9)
Total	274,340	293,717	311,607	324,822	345,700	361,959	380,587	396,910

Note: The Universal Coverage Scheme (UCS) patients admitted for T2DM are the UCS beneficiaries who were admitted for type 2 diabetes mellitus (T2DM) between 2009 and 2016. The number of UCS patients was counted as one in a year. That is, a UCS patient who was admitted for T2DM for multiple times in a year was counted as one in that year. If the same patient was admitted for T2DM in another year, he/she was counted as one again in the separate year.

Fig 2 shows the population pyramids of admitted cases with T2DM among the UCS beneficiaries in Thailand in 2009 and 2016. The female admission rates were persistently higher than that of males both in 2009 and 2016. The sex ~~inequal~~disparity~~ies~~ in the admission rates widened between their 30s and ~~early 8~~70s. In 2009, the admission rates of both sexes started increasing in their late 30s, females reached a peak at the ages of 70 to 74 and males at the ages of 75 to 79, and then both declined. In 2016, both sexes reached a peak at the ages of 75-79. Although the trend was similar in the two years, the admission rates were persistently much higher and the overall increase occurred in older ages in 2016.

Fig 2. Population pyramids of admitted cases with type 2 diabetes mellitus (T2DM) among the Universal Coverage Scheme patient~~beneficiarie~~s in Thailand in 2009 and 2016

Note: T2DM admission rates are per 1,000 population~~, standardized by age and sex using the 2009 national UCS population.~~

Fig 3 presents the number of patients, the number of admissions and the admission rates of T2DM and those with the ~~five~~six major complications: CKD, MI, ~~stroke~~cerebrovascular diseases, retinopathy, cataract and ~~amputation~~foot amputation from 2009 to 2016 in Thailand. ~~The number of admissions refers to how many times the UCS patients were admitted for type 2 diabetes mellitus with or without complications in each year, whereas the number of patients refers to how many patients were admitted in the year. A patient could be admitted for multiple times in a year.~~ Overall, there was a linearly increased trend in ~~the number of~~ T2DM admission rates~~s~~ ~~with~~by ~~about 5~~5.2~~9~~% annually~~increase per year~~. Among the T2DM admissions, 2~~0~~4.90% was associated with CKD in 2009-2016, and the T2DM

admission rates with CKD also ~~which also~~ has~~d~~ a positive linear trend by~~of~~ ~~5~~10.~~9~~0% ~~increase in the number of admissions p~~per year. ~~Of other four complications, a~~Admission rates of T2DM with CKD were 3.5/1000, ~~associated with stroke~~cerebrovascular diseases 1.1/1000, cataract 0.5/1000, MI 0.4/1000, and retinopathy ~~MI~~ and foot amputation 0.2/1000 population, respectively~~retinopathy/cataracts were comparable of around 0.4 per 1,000 population, while that with stroke and amputation were approximately 4 times less i.e. about 0.1 per 1,000 population~~. It is noted that the increasing trends of T2DM admission with CKD and ~~stroke~~cerebrovascular diseases ~~MI and amputation a~~were visually observable, while those ~~. The T2DM admission rates~~ with MI, ~~strokes and retinopathy/cataract~~retinopathy and foot amputation were rather subtle, and that with ~~s~~cataract wa~~w~~s~~ere both relatively~~ stable.

Fig 3. The number of patients, the number of admissions and admission rates of type 2 diabetes mellitus with and without the five major complications in Thailand from 2009 to 2016

Legend:

Number of patients
Number of admissions
Admission rates

Note: The number of admissions refers to how many times the Universal Coverage Scheme (UCS) patients were admitted for type-2 diabetes mellitus (T2DM) with or without complications in each year, whereas the number of patients refers to how many T2DM patients were admitted in the year. A patient could be admitted for multiple times in a year. The admission rate is the number of admissions divided by the number of the ~~Universal Coverage (~~UC~~) scheme~~S p~~opulation~~atients in the year standardized by sex and age of the~~ 2009 UCS ~~scheme~~ 2009 ~~population~~beneficiaries~~.~~ The scale for all T2DM admission rates is different from others as it went up to 17.3/1000 in 2016.

Table 2 presents the results of the time series regressions to estimate temporal trend of admissions showed that all types of T2DM admissions except that with cataract had a significant and positive temporal trend.

Table 2. Time series regressions parameters of temporal trend analysis for admissions

Parameters	Estimate	SE	z value	p value
All DM admissions				
β_0: intercept	-4.460529	0.006002	-743.16	p < 0.001
β_1: time point	0.050566	0.001187	42.61	p < 0.001
DM with CKD admissions				
β_0: intercept	-6.108389	0.009446	-646.64	p < 0.001
β_1: time point	0.095675	0.001861	51.41	p < 0.001
DM with MI admissions				
β_0: intercept	-8.11538	0.02155	-376.58	p < 0.001
β_1: time point	0.07541	0.00424	17.78	p < 0.001
DM with ~~stroke~~cerebrovascular diseases admissions				
β_0: intercept	-7.251687	0.009935	-729.93	p < 0.001
β_1: time point	0.084358	0.001941	43.47	p < 0.001
DM with cataract admissions				
β_0: intercept	-7.604557	0.046891	-162.175	p < 0.001
β_1: time point	0.015244	0.009283	1.642	0.101
DM with retinopathy admissions				
β_0: intercept	-8.941096	0.028458	-314.181	p < 0.001
β_1: time point	0.049766	0.005599	8.888	p < 0.001
DM with amputation admissions				
β_0: intercept	-8.955374	0.023377	-383.09	p < 0.001
β_1: time point	0.050946	0.004584	11.12	p < 0.001

Note: SE: Standard error, CI: Confidence interval, DM: Diabetes mellitus, CKD: Chronic kidney disease, MI: Myocardial infarction

Fig 4 presents ~~comparison in~~ SARs of T2DM and its complications in the NHSO 13 Regions in 2009 and 2016 ~~(see Supplementary table 1 for 2009 and Supplementary table 2 for 2016 for exact values)~~. The SARs of T2DM were high in central and northeastern regions: 1.20/1000 in Region 4 (Saraburi), 1.22/1000 in Region 5 (Ratchaburi), 1.31/1000 in Region 7 (Khon Kaen) and 1.22/1000 in Region 8 (Udon Thani) ~~were~~ in 2009, but they all declined close to the national average by 2016 except Region 7 that further increased to 1.44/1000. In the same period, ~~particularly high in Region 3 (Nakhonsawan)~~ the SARs of T2DM increased from 0.88 to 1.05/1000 in Region 9 (Nakhon Ratchasima), and declined from 1.00 to 0.83/1000 in Region 13 (Bangkok). ~~(1.5/1000) and Region 2 (Phitsanulok) (1.5/1000) in 2009 and the admission rates in Region 3 (Nakhonsawan) further increased from 2009 to 2016 (1.8/1000).~~ The SARs of T2DM with CKD were high in northeastern regions in 2009: 1.79/1000 in Region 7 (Khon Kaen), 1.58/1000 in Region 8 (Udon Thani) and 1.64/1000 in Region 10 (Ubon Ratchathani), but they all declined to 1.70/1000, 1.45/1000 and 1.60/1000 by 2016, respectively. On the other hand, the SAR of T2DM with CKD in Region 9 increased from 0.86 to 1.05/1000 in the same period. The SARs of T2DM with MI was high in Bangkok and central regions in 2009: 1.60/1000 in Region 4 and 1.69/1000 in Region 13 (Bangkok), but they both reclined to 1.43/1000 and 1.27/1000 by 2016, respectively. The SAR of T2DM with MI in Region 7 increased from 0.88 in 2009 to 1.01 in 2016. The SARs of T2DM with ~~stroke~~cerebrovascular diseases were also high in Bangkok and central regions in 2009: 1.46/1000 in Region 4 (Saraburi), 1.35/1000 in Region 5 (Ratchaburi), 1.34/1000 in Region 6 (Rayong) and 1.90/1000 in Region 13 (Bangkok), but they all declined to 1.25/1000,

1.17/1000, 1.30/1000 and 1.21/1000 by 2016, respectively. The SARs of T2DM with ~~stroke~~cerebrovascular diseases increased in Region 7 and 9 between 2009 and 2016, from 0.83 to 1.03/1000 and 0.65 to 1.11/1000, respectively. The SAR of T2DM with retinopathy in Region 13 was 4 times higher than the national average in 2009. Although it declined to 2.77/1000 by 2016, it was still much higher than other regions. In the same period, the SARs of T2DM with retinopathy increased in Region 8 and 11 (Surat Thani), from 0.43 to 1.11/1000 and 0.52 to 1.00/1000, respectively. The SARs of T2DM with cataract were high in Bangkok and central regions in 2009: 2.35/1000 in Region 4, 1.95/1000 in Region 5 and 1.64/1000 in Region 13, but they all declined to 1.40/1000, 1.33/1000 and 1.25/1000 by 2016, respectively. Whereas, the SARs of T2DM with cataract increased from 0.76 to 1.13/1000 in Region 11 in the same period. The SARs of T2DM with foot amputation was high in Bangkok and central and northeastern regions in 2009: 1.21/1000 in Regions 4, 1.35/1000 in Region 7, 1.24/1000 in Region 8 and 1.45/1000 in Region 13. By 2016, the SARs of T2DM with foot amputation in Regions 4 and 13 declined to 0.97/1000 and 1.16/1000, respectively, while those further increased in Region 7 and 8 to 1.61/1000 and 1.43/1000, respectively.

Fig 4. Comparison of age- and sex- standardized admission ratio of type 2 diabetes mellitus and its complications in the NHSO Regions in 2009 and 2016

Note: The standardized admission ratio (SAR) of type 2 diabetes mellitus (T2DM) and its complications were shown in white if it is the national average. The color changes into red if SAR is higher than the national average, and gray if it is lower than the national average. The scale for SARs of T2DM with retinopathy is different from others: it continues up to 5.0 because SAR of T2DM with retinopathy in Bangkok was substantially higher than other regions in 2009.

Discussion

A linearly increased trend of T2DM admission rates and that with the sixfive major diabetic complications were found from 2009 to 2016 in Thailand. Female admission rates were persistently higher than that of males. In 2016, overall increase in the T2DM admission rates was observed among the older ages relative to that in 2009. Although geographical inequalities The geographic difference in the T2DM admission ratesratios were also found, the reduced trend in the inequalities was also observed between 2009 and 2016.

The observed sex disparities in frequency of the T2DM admissions were consistent with the National Health Examination Surveys [2] and an assessment on quality of care among patients diagnosed with T2DM and hypertension, which presented that females in Bangkok were 1.13 times more likely to have HbA1C level of higher than 9.0% [21]. Biology might play a part in observed sex disparities as women typically transition from prediabetes to diabetes with a worse cardiovascular risk profile and a higher BMI than men. However, psychosocial factors, such as health-seeking behavior and provision of health care, play more important part in the differences, which can be addressed through changes in policy and health-care delivery [22]. It should be noted that high admission rate does not necessarily mean high prevalence of the disease, as previous studies showed higher percentage of undiagnosed diabetes [2] and slightly higher fasting plasma glucose among males in Thailand [23].

While the number of patients, the number of admissions and admission rates of T2DM steadily increased from 2009 to 2016, the increased trend in the sex-and age-adjusted T2DM admission rates, which were estimated using the national UCS population of 2009 as the standard population, ~~-~~(12.1 in 2009 and 15.0 in 2016, *results not shown*) w~~as~~ere rather gradual as compared with the numbers of crude admissions rates (12.1 in 2009 and 17.3 in 2016)~~and patients and the number of admissions~~. This result suggests that the increase in the T2DM admission rates ~~is largely due to~~ is partly due to the increased and aged population of the country~~the increased and aged population of the country.~~. Although further studies are required, it could imply that ~~This finding further suggests that~~ Thailand~~the country~~ may face the greater burden of T2DM in the future if the trend of population growth and aging ~~will~~ continues in the country~~.~~.

The T2DM admission rates reached a peak at the ages of 70s~~5 to 79~~ and then declined in 2009 and 2016 presumably due to premature death of the T2DM patients. The shifted trend of the peak age toward elderly among females between 2009 and 2016 can be explained by the fact that the T2DM patients had aged and their longevity had been extended over the eight years [24]. This trend further implies the need of increased costs of providing diabetes-related care as older adults with diabetes is clearly more complicated with multiple coexisting medical conditions, particularly macrovascular complications such as acute myocardial infarction and ~~stroke~~cerebrovascular diseases and end-stage renal disease [25].

Age also affects the potential risks of overtreatment of hyperglycemia in the hospital, which often leads to longer ~~hospitalizatio~~hospitalization, higher medical costs ~~n~~ and increased mortality [26][27].

Among the six~~five~~ diabetic complications, CKD showed the most ~~conspicuous~~ significant increase between~~from~~ 2009 ~~to~~and 2016. Although Thailand has launched the "Thailand Healthy Lifestyle Strategy 2011-2020 Plan~~,~~" [28] to reduce~~decrease~~ the prevalence, complications, disability, mortality and cost of non-communicable diseases including diabetes, national screening and prevention program has not yet been in place [4]. Additionally, renal replacement therapy including renal and peritoneal dialysis and kidney transplantation requires the UCS patients with a co-payment [29], which may have inhibited some of them from accessing to proper care. Thailand should take this trend seriously as this type of complication is associated with a substantial burden in terms of mortality, morbidity and healthcare cost as it often requires costly and long-term care including dialysis. To prevent progression of CKD stage, the country should strengthen~~consider~~ an effective measure, such as glycated hemoglobin control (HbA1c) ≦7.0% [21~~30~~], as instructed in the Clinical Practice Recommendation for the Evaluation and Management of Chronic Kidney Disease in Adults 2015 [30]. This study also found that the number of admitted cases with CKD were 1.7 times greater ~~more than twice as~~than the number of patients. This indicates that many of the patients with diabetic complication of CDK were readmitted, and implies that there might be unmet needs of inpatient care for the T2DM patients with

CKD. Further study should be conducted to investigate the reasons behind the frequent readmissions and take measures to meet the needs of the patients.

While the SARs of T2DM were higher in Bangkok and central regions relative to other regions in 2009, except those with CKD and partly foot amputation, they declined in most of the regions by 2016. Additionally, there was an overall trend of SAR reduction in Bangkok and central regions, where human and financial resources were traditionally concentrated, and increase in northeastern regions, where the resources were traditionally scarce, over the eight years [9, 31]. This trend indicates Thailand's successful health reform by reducing geographical inequalities in inpatient care, which might be a result of equitably redistributed health professionals, health infrastructure development and rural retention policies over the past four decades [32].

On the other hand, the persistently high SAR of T2DM with retinopathy in Bangkok is presumably due to high density of specialists as half of 1,500 ophthalmologists, including 200 retinal specialists, practice in Bangkok [33].

~~The T2DM admission rate was particularly high in Region 2 (Phitsanulok) and Region 3 (Nakhonsawan). Although high hospital admission rate could mean that the people with T2DM are receiving necessary healthcare, investigation should be carefully conducted to accurately understand~~

~~the situations in these regions. The~~ The persistently high SAR of T2DM with CKD in northeastern regions was consistent with a previous study and partly attributed to high prevalence of CKD in northeastern regions (10.8%) relative to other regions (north 8.9%, south 8.1% and Bangkok 6.2%) [34], but partly to an association with lower density of physicians and rurality of the region [13]. The density of physicians in northeastern regions is the lowest in the country [32], as low as seven times lower than Bangkok [9]. It is reasonable to assume that in a region where physicians are scarce, T2DM patients with CKD are unlikely to receive timely, thorough and effective treatment, and consequently deteriorate in conditions. This assumption might explain the high readmission rates of T2DM with CDK, and the highest mortality rates due to diabetes in northeastern regions as found in another study [12]. Moreover, rurality of the northeastern regions, where 71.0% of the population reside in rural setting (north 65.6%, south 66.5% and Central 54.5%) [35], might have halted them from accessing adequate primary care. A previous study found a strong association between the high SAR of diabetes and rurality as the rural population tends to have lack of public transport alternatives and poor health literacy with less education which often limit accessibility to health care. The study also suggested that the percentage of patients who had received up to secondary education was lower in rural districts by approximately 10% [13]. ~~most distinctive increase in T2DM diabetes admission rates were seen in the northeastern part of the country, namely Region 7 (Khon Kaen), Region 9 (Nakhon Ratchasima) and Region 10 (Ubon Ratchatani). This geographic trend was consistent with the previous study which found high mortality rates due to diabetes in these regions [12]. The increased admission rates could infer increased capacity~~

~~of health facility. However, it is not the case in these regions because of the high diabetes specific mortality rate. As the majority of the population in these regions presumably reside in rural areas, urban life style, a conventional risk factor of T2DM, cannot be applied to the population. Therefore, there is a need for substantial assessment for associated risk factors in Thai rural areas and quality of healthcare provided to the people in the regions.~~

Inaccessibility to the outpatient data and absence of information indicating direct causality between diabetes and complicated conditions were the major limitations of this study. For the first limitation, it is important to monitor the long-term trends of diabetic morbidity starting at onset of disease, accessibility and quality of outpatient and inpatient care, and health outcome including mortality to assess the quality of T2DM healthcare in the country. Besides, community involvement in diabetic care should be also carefully monitored, as approximately 77.0% of cost is involved in non-medical activities [36], and community-based screening, study and health promotion would be increasingly important for diabetic care [4]. In this study, we looked at the trend of the inpatient care and tried to capture that of a series of healthcare, but~~.~~ ~~F~~ future study should carefully assess the situations of accessibility and quality of T2DM outpatient~~ient~~ care, and coordination of outpatient and inpatient care for the most cost-effective T2DM healthcare policies in Thailand.

For the second limitation, we regarded the complications as if they were directly caused by T2DM, when we found T2DM as either principle or secondary diagnosis and one or more of the major complications in an individual record of the hospital admission database since it was the only available information.

~~Although~~ Thailand has achieved great improvement in health care reform invested on equitable health finance and increased total budget for health expenditures ~~, particularly~~ in T2DM and its complications. ~~,~~ ~~reduction of the T2DM burden has not been achieved.~~ It is time for the country to carefully identify the risk factors and regions in particular needs of care for T2DM and its complication~~s~~, and plan on the effective and efficient health care which would not leave no one behind in the country.

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Contributors

TL acquired the data, conceived of and designed the study, and drafted the final manuscript. HT and HN analysed the data, interpret and discuss the results, and drafted the final manuscript. SN, AL and NS designed the statistical framework and supported data analysis. AL and NS confirmed the quality of data and the study design. VC, TL, KS and HM took responsibility for the integrity of the data and the accuracy of the data analysis and will oversee the study. All the authors made critical revisions to the manuscript for important intellectual content, gave final approval of the manuscript, and will support the interpretation and discussion of findings.

Data reporting

All patient records were fully anonymized before we accessed. The ~~relevant~~ UCS data are available upon request to the National Health Security Office, Thailand, with the research outline and the details of the required data.

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Annalijn I Conklin
Academic Editor
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Re: Manuscript PONE-D-19-26129

Dear Dr Conklin,

I am writing to submit a revised version of the manuscript PONE-D-19-26129. We sincerely appreciate the helpful comments from you and the reviewers, and we have revised our manuscript according to their suggestions.

Please find below the responses to the comments from you and the reviewers.

Also, thank you for inviting us to responding to the Health Inequities and Disparities Research Call. We would appreciate if our paper is going to be part of your paper collection.

We hope that the revised manuscript will now be acceptable for publication in PLOS ONE and look forward to your decision. Thank you very much for your consideration of this manuscript.

Sincerely,

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RESPONSE TO REVIEWERS

We would like to thank the editor and reviewers for their helpful comments. Our responses to the comments from the editor and reviewers #1, #2 and #3 are given beneath each comment. The revised text is indented and edited in our response for ease of reference, with the section, page numbers and lines of the revised manuscript provided where necessary.

Response to Reviewer #1

General comments:

The selection of the patients is unclear and the presentation of the results is not clear either. This paper could have a great potential if presented in relation with incidence and prevalence.

Major comments:

Abstract

1) Some results are only presented in the abstract. For example: "Among the five major diabetic complications, the average annual increase in admission rates in 2009–2016 for CKD, MI, stroke, cataracts, and amputation were 10.8%, 5.6%, 7.7%, 0.2%, and 6.1%, respectively."

Thank you very much for pointing this out. We missed reflecting the re-written parts of the main text to the abstract. We have substantially revised the abstract this time. (Abstract, page 3-4)

Introduction

2) Thailand has universal health coverage since 2002. Why your study report results only from 2009?

Thank you very much for your observation. Although Thailand achieved UHC in 2002, we decided to use only data from 2009 onwards for our analyses since there were a number of missing values and errors in data before 2009. To make it clearer, we have added the following sentence in Materials and methods section as follows:

"Although Thailand achieved UHC in 2002, we decided to use only data from 2009 onwards for our analyses since there were a number of missing values and errors in data before 2009 [13, 14]." (Materials and methods: Data, page 8, lines 17-19)

3) Why only part of the population is covered (69.9%) by the universal health coverage as mentioned in the introduction?

Thank you very much for your inquiry. Please see Introduction section (page 5 line 19 to page 6 line 3) where we explained that there are other major health protection schemes in Thailand, i.e. the Civil

Service Medical Benefit Scheme and the Social Security Scheme, and the Universal Coverage Scheme (UCS) is the third scheme to cover the rest of the population, so that the country can achieve UHC.

4) *I strongly suggest to focus your paper in Thailand globally with prevalence, incidence and mortality if their data allow this kind of analysis and do not focus on the 13 regional offices. Otherwise, can you link the higher prevalence of diabetes observed in some regions to specific risk factors?*

We appreciate your thoughtful suggestion. Unfortunately, the available data did not allow us to analyse prevalence, incidence and mortality of the whole population in Thailand, since our data were limited to people covered by the Universal Coverage Scheme (UCS) in Thailand. However, we have geographically covered Thailand globally as the 13 regions are all regions in the country (see Fig 1).

5) *The last sentence of your introduction about preventive measures is not clear since you are exploring only hospital data and not ambulatory care data.*

Thank you very much for your comment. As you pointed it out, we are unable to assess the current practice of preventive measures, as we did not have access to the ambulatory care data. However, we still believe we can discuss the importance of prevention to avoid unnecessary admissions and re-admissions.

Methods

6) *The ICD-10 codes selected for CKD are very limited. Why not including E11.2 (Type 2 diabetes mellitus with kidney complications)?*

Thank you very much for your concern. We regret it was not very clear, but E11.2 (Type 2 diabetes mellitus with kidney complications) was included in our analyses as we indicated "All admitted cases whose principle and secondary diagnoses were coded as T2DM (E11.1 to E11.9)…," (Materials and methods: Definitions of T2DM and its complications, page 9, line 9-10) meaning that we included E11.1, **E11.2**, E11.3… E11.9.

7) *Same question with ICD-10 codes N08.3 (Glomerular disorders in diabetes mellitus)?*

Again, thank you very much for your suggestion. We have added N08.3 to definition of diabetic complication of chronic kidney disease, as shown below.

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1 to N18.6, N18.9, E11.2, E14.2, N08.3, N19 and N18.9." (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11)

8) Why you did not include I22 (Subsequent myocardial infarction) in the MI category?

Thank you very much for your question. We have added I22 (Subsequent myocardial infarction) in the MI category, as shown below.

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), … MI (I21 and I22)" (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11)

9) Please correct your stroke codes to I60-I69.

Thank you very much for pointing it out. We have corrected the text as follows:

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), … cerebrovascular diseases (I60 to I69)" Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11）

10) Why you used ICD-9 codes for diabetic amputations?

We appreciate your sensible question. We used ICD-9 codes for diabetic amputations in our study because the National Health Security Office in Thailand makes payment based on ICD-9 codes with regards to amputation, and therefore the amputation records were kept based on the ICD-9 codes.

11) These ICD-9 codes do not seem appropriate. Please clarify their respective definitions. I recommend intervention codes.

Thank you very much for your comment and recommendation. We have carefully reviewed the ICD-9 codes and revised as shown below. Meanwhile, we remained procedure codes of ICD-9 for the above reasons.

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), … or diabetic foot amputations (8410-8417) were included" Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-13）

12) Moreover, did the authors excluded traumatic, cancer, congenital or sepsis related amputations?

Thank you very much for your confirmation. It was rather difficult to exclude traumatic, cancer, congenital or sepsis related amputations with ICD-9 codes. It was the same condition for other types of complications. We indicated this condition as a limitation in our manuscript as follows:

"… and absence of information indicating direct causality between diabetes and complicated conditions were the major limitations of this study." (Discussion, page 23, lines 11-12)

13) I would give further details about the definitions of T2DM and complications. As I understand the manuscript, all admission cases were collected for 2009-2016 in which either T2DM and/or a given complication occurs as a primary or secondary reason, for the whole population of the UCS (T2DM or not). Here is my question: Is the presence of T2DM is evaluated using the presence of T2D as a primary or secondary reason for admission OR all prevalent cases of diabetes were included initially before assessing admission? I would clarify this point (otherwise the reader might think the population are not prevalent cases of diabetes).

We appreciate your advice. Our answer to your question is that the presence of T2DM is evaluated using the presence of T2D as a primary or secondary diagnosis (reason) for admission. Although we could not address the prevalent cases in this study, as we could only use the admission data due to the quality reasons, we added further definitions of the T2DM and its complications as shown below. Additionally, we have decided to change some definitions of T2DM and complications, and include retinopathy as the sixth diabetic complication in our study.

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1 to N18.6, N18.9, E11.2, E14.2, N08.3, N19 and N18.9), MI (I21 and I22), cerebrovascular diseases (I60 to I69), retinopathy (H36.0), cataract (H25.0 to H25.2, H25.8, H25.9, H26.0 to H26.4, H26.8, H26.9, and H28.0), or diabetic foot amputations (8410-8417) were included, and any other cases were excluded from this study. Stage 3 or higher stages of CKD are usually considered as diabetic complications. However, stage 1 and 2 of CKD were also included in this study because the ICD-10 code, E11.2 includes all stages of kidney complications, and thus it was impossible to separate stage 1 and 2 of CKD cases. T2DM cases with acute and subsequent MI were included in this study. While only H36.0, diabetic retinopathy was considered as a diabetic complication, all types of cataract were included as diabetic complications in this study because diabetic cataract is often misdiagnosed as other type of cataract. Diagnosis of foot amputation was considered as a diabetic complication if it was performed from the toe to above the knee." (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9 to page 10, line 2)

14) Please specify how data are presented and what they represent for example, in Table 1 (rates, proportions, etc.). In other words, this section should be clarified with addition of specific definition that the authors have misclassified in the results section such as: "The number of admissions refers to how many times the UCS patients were admitted for T2DM with or without complications in each year, whereas the number of patients refers to how many patients were admitted in that year. A patient could be admitted multiple times in a year."

Thank you very much for your important comment. We have revised the title of Table 1 and added the note underneath Table 1 as follows. We also revised Result section as shown below.

"Table 1. Number and demographic characteristics of the Universal Coverage Scheme patients admitted for type 2 diabetes mellitus in 2009-2016" (Results, page 12-14)

"Note: The Universal Coverage Scheme (UCS) patients admitted for T2DM are the UCS beneficiaries who were admitted for type 2 diabetes mellitus (T2DM) between 2009 and 2016. The number of UCS patients was counted as one in a year. That is, a UCS patient who was admitted for T2DM for multiple times in a year was counted as one in that year. If the same patient was admitted for T2DM in another year, he/she was counted as one again in the separate year." (Results, page 14)

"Table 1 presents the number and demographic characteristics of the UCS patients admitted for T2DM in 2009-2016. The UCS population of 15 to 100 years of age represents approximately 54.0% of the total population of 2009-2016 in Thailand." (Results, page 12, lines 2-4)

Results

15) Table 1 is not clear. It seems to be the whole population but the title mentioned with type 2 diabetes. The description of the whole population is not the objective of this paper. Please add units to this corrected Table

Again, thank you very much for your comment. We have revised the title of Table 1 and added the note underneath Table 1 as follows. We also revised Result section as shown below.

"Table 1. Number and demographic characteristics of the Universal Coverage Scheme patients admitted for type 2 diabetes mellitus in 2009-2016" (Results, page 12-14)

"Note: The UCS patients admitted for T2DM are the UCS beneficiaries who were admitted for T2DM between 2009 and 2016. The number of UCS patients was counted as one in a year. That is, a UCS patient who was admitted for T2DM for multiple times in a year was counted as one in that year. If the

same patient was admitted for T2DM in another year, he/she was counted as one again in the separate year." (Results, page 14)

"Table 1 presents the number and demographic characteristics of the UCS patients admitted for T2DM in 2009-2016. The UCS population of 15 to 100 years of age represents approximately 54.0% of the total population of 2009-2016 in Thailand." (Results, page 12, lines 2-4)

16) In Figures 2 and 3, please add 95% or 99% confidence intervals.

Thank you very much for your suggestion. We added 95% confidence intervals to Fig 2 and 3 in Results section. In Fig 3, we added the 95% CIs to admission rate, but not to the number of patients and admissions because it makes the figure too busy to add the 95% CIs to all components.

17) Are rates adjusted in Figure 3?

Thank you for your important inquiry. The rates in Figure 3 were not adjusted. In the Figure 3, we would like to focus on describing temporal trends of crude, i.e. non-adjusted, numbers and rates.

Aside from the Figure 3, we calculated admission rates adjusted by age and sex using the national UCS population of 2009 as the standard to discuss effects of age and sex difference between years in the discussion section.

"While the number of patients, the number of admissions and admission rates of T2DM steadily increased from 2009 to 2016, the increased trend in the sex-and age-adjusted T2DM admission rates, which were estimated using the national UCS population of 2009 as the standard population, (12.1 in 2009 and 15.0 in 2016, *results not shown*) were rather gradual as compared with the numbers of crude admissions rates (12.1 in 2009 and 17.3 in 2016). This result suggests that the increase in the T2DM admission rates is partly due to the increased and aged population of the country." (Discussion, page 20, lines 1-6)

18) Please consider confidence intervals for the description of trends and correct this sentence: "The increasing trend of T2DM admissions with MI and amputation are visually observable." Please add the relative % of increase also.

Thank you very much for your suggestion. We added the 95% CIs to admission rate to Fig 3 in Results section and corrected the related sentences accordingly.

19) This sentence is repeated twice and should be placed in the Method Section: "The number of

admissions refers to how many times the UCS patients were admitted for T2DM with or without complications in each year, whereas the number of patients refers to how many patients were admitted in that year. A patient could be admitted multiple times in a year. The admission rate is the number of admissions divided by the number of the UCS patients in the year, standardized by sex and 15 age categories in 2009."

We are very sorry that it was not clear, but the description in Results section is a note of Figure 3, not part of the main text.

Discussion

20) Do all data from the different regions are collected similarly or there are differences in data collection (missing data)? Similarly, are there important differences in the number of people subscribed on the UCS, differences in resources, etc.? I think these elements could be important to explain the differences inter-regions, if still presented.

Thank you very much for your observation. The data from the different regions were collected similarly. The UCS beneficiaries are those who are not covered by other major health protection schemes, i.e. the Civil Servant Medical Benefit Scheme and the Social Security Scheme and the UCS beneficiaries account for nearly 70 percent of the population. We also did not find inter-regional difference in the number of UCS beneficiaries.

21) I suggest comparing with additional similar studies in order to discuss your results. I suggest to be careful with assumptions without references, since it might lead to overinterpretation of results.

Thank you so much for your suggestion. We compared with the following additional 9 studies and 2 reports to discuss our studies.

<u>Studies</u>

13. Komwong D, Sriratanaban J. Association between Structures and resources of primary care at the district level and health outcomes: a case study of diabetes mellitus care in Thaialn. Risk Manag Healthc Policy. 2018. 11, 199-208
14. Liabsuetrakul T, Sukmanee J, Thungthong J, Lumbiganon P. Trend of Cesarean Section Rates and Correlations with Advance Maternal and Nesecondary analysis of Thai Universal Coerage Scheme Data. AJP Rep. 2019; 9(4): 328-336.
22. Sex disparities in diabetes: bridging the gap. Lancet Diabetes Endocrinol: Editorial. 2017; 5(11):839

23. Aekplakorn W, Stolk RP, Neal B, Suriyawongpaisal P, Chongsuvivatwong V, Cheepudomwit S, et al. The Prevalaence and Management of Diabetes in Thai Adults. Diabetes Care. 2003; 26(10): 2758-2763. DOI: 10.2337/diacare.26.10.2758.
31. Lindelow M, Hawkins L, Osornprasop S. Government spending and central-local relations in Thailand's health sector. Washington DC: The International Bank for Reconstruction and Developemnt/The World Bank; 2012.
32. Witthayapipopsakul W, Cetthakrikul N, Suphanchaimat R, Noree T, Sawaengdee K. Equity of health workforce distribution in Thailand: an implication of concentration index. Risk Manag Healthc Policy. 2019;12:13-22.
33. Ruamviboonsuk P, Krause J, Chotcomwongse P, Sayres R, Raman R, Widner K, et al. Deep learning versus human graders for classifying diabetic retinopathy severity in a nationwide screening program. npj Digit Med. 2019; 2(25).
34. Ong-ajyooth L, Vareesangthip K, Khonputsa P, Aekplakorn W. Prevalence of chronic kidney disease in Thai adults: a national health survey. BMC Nephrol. 2009; 10(35).
36. Chatterjee S, Riewpaiboon A, Piyauthakit P, Riewpaiboon W, Boupaijit K, Panpuwong N, et al. Cost of diabetes and its complications in Thailand: a complete picture ofeconomic burden. Health Soc Care Community. 2011; 19(3), 289–298.

Reports

30. Chittinan A, Eiam-ong S, Kantachuvesiri S, Chailimpamontri W. Clinical Practice Recommendation for the Evaluation and Management of Chronic Kidney Disease in Adults 2015. 1st ed. Bangkok: The Nephrology Society of Thailand; 2015. [cited 2020 Jan 10]. Available from: http://www.nephrothai.org/images/10-11-2016/Final_%E0%B8%84%E0%B8%A1%E0%B8%AD_CKD_2015.pdf
35. National Statistical Office, Kingdom of Thailand. The 2010 Population and Housing Census. Bangkok: National Statistical Office; 2012.

22) Do the authors have ideas about what could explain the disparities between males and females?

Thank you very much for your important observation. We added the explanations for the sex disparities as well as a caution to interpret them in Discussion section as follows.

"Biology might play a part in observed sex differences as women typically transition from prediabetes to diabetes with a worse cardiovascular risk profile and a higher BMI than men. However, psychosocial factors, such as health-seeking behavior and provision of health care, play more important part in the differences, which can be addressed through changes in policy and health-care delivery [22]. It should be noted that high admission rate does not necessarily mean high prevalence of the disease, as previous studies showed higher percentage of undiagnosed diabetes [2] and slightly higher fasting plasma glucose among males in Thailand [23]" (Discussion, page 19, lines 11-17)

23) The authors are writing about HbA1c in prevention of CKD. I think it might be relevant to give more details about this point (for example, what is used in Thailand nowadays and why HbA1c would be better for CKD particularly).

We appreciate your clarification. HbA1c is in fact recommended to be practiced regularly in prevention of CKD among people with diabetes in Thailand, although it has not been fully executed. Therefore, we have revised and added some information to the discussion section as follows.

"To prevent progression of CKD stage, the country should strengthen an effective measure, such as glycated hemoglobin control (HbA1c) ≦7.0% [21], as instructed in the Clinical Practice Recommendation for the Evaluation and Management of Chronic Kidney Disease in Adults 2015 [30]." (Discussion, page 21, lines 9-12)

24) Since diabetes is an ambulatory disease, can the authors give us a sense of the burden in the community in Thailand? If not, please refer to other countries.

Thank you very much for your suggestion. We have added information addressing a sense of burden in the community in Thailand as follows.

"Besides, community involvement in diabetic care should also be carefully monitored, as approximately 77.0% of cost is involved in non-medical activities [36], and community-based screening, study and health promotion would be increasingly important for diabetic care [4]." (Discussion, page 23, lines 15-18)

Minor comments

Introduction

25) First sentence, please add "in the world."

Thank you very much for your suggestion. We assume the sentence starting with "globally" describes the situation "in the world", but we changed "globally" to "in the world" to make the sentence clearer.

26) P.4, 2nd paragraph: review the units for fasting glucose levels (130/dL).

Thank you very much for correcting it. We have revised the unit from (130/dL) to (130mg/dL).

Methods

27) I would specify the nature of the study: Retrospective study.

Thank you very much for your suggestion. We have added the word, "retrospective data" in our manuscript as shown below.

"Descriptive analyses using the retrospective data were performed to summarize age, sex and regional structure of the UCS patients who were admitted for T2DM between 2009 and 2016 in Thailand and the trends in 2009 and 2016 were compared to depict the change in the trends over the eight years." (Materials and methods: Data analysis, page 10, lines 5-7)

28) Why the approbation of the study was done in Japan?

Thank you very much for your enquiry. This is a study on Thailand, but the approbation was done in Japan because this is a Thai-Japan collaborative study based on the agreements made by the both national organizations.

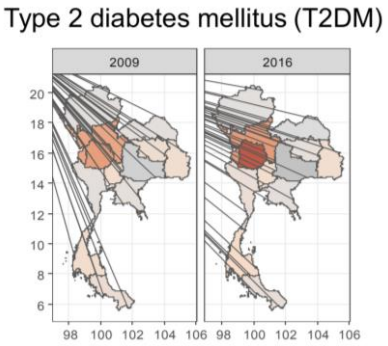
Results

29) Please correct everywhere women to females and men to males since you have administrative data and not information about gender.

We appreciate your suggestion. We have corrected all the words "men and women" to "males and females" following your suggestion.

30) Figure 4 would be easier to understand without the grey lines if you still present regional data.

Thank you for pointing it out. We assume that "the grey lines" you mentioned are the ones shown on the right. These lines appear on some computers, but not all. In fact, we do not see the lines on our computers. We hope the editor has a technical means to solve this problem.



Response to Reviewer #2

General comments:

The authors extract for the universal coverage scheme data all hospitalizations with diabetes listed among the primary or secondary diagnoses (to study admissions caused by diabetes-related complications) in the period 2009-2016. The impressively large and detailed dataset covers over 1.4 million Thai age 15-100 and their 4.2 million admissions for type-2 diabetes (T2DM). They provide descriptive summaries, focusing on admission rates trends nationally and by region, for T2DM and

major complications. The results show that standardizing for age and sex reduces the increasing trend in admission rates, suggesting that trends in population growth and aging are important determinants.

Specific comments:

1) Moreover, the authors speculate that the increase in elderly patients could be explained by greater longevity (i.e. reduced premature mortality) among DM patients. What does a life table for Thailand say about life expectancy conditional on surviving to age 50? 60? Is the growth rate in admissions comparable to the growth rate of survival at those ages? This could provide suggestive evidence confirming or refuting the authors' hypothesis.

We have stated in our manuscript that "the increased trend in T2DM admission rates was rather gradual as compared with the number of patients and admissions." This means that the increase in the T2DM admission rates was partly influenced by the increased and aged population of the country, while there were also other reasons behind. To avoid this unclarity, we have added values of "sex-and age-adjusted T2DM admission rates", and changed the word, "largely" to "partly" in the sentence as shown below.

"While the number of patients, the number of admissions and admission rates of T2DM steadily increased from 2009 to 2016, the increased trend in the sex-and age-adjusted T2DM admission rates, which were estimated using the national UCS population of 2009 as the standard population, (12.1 in 2009 and 15.0 in 2016, *results not shown*) were rather gradual as compared with the numbers of crude admissions rates (12.1 in 2009 and 17.3 in 2016). This result suggests that the increase in the T2DM admission rates is partly due to the increased and aged population of the country. Although further studies are required, it could imply that Thailand may face the greater burden of T2DM in the future if the trend of population growth and aging continues in the country." (Discussion, page 20, line 1-8)

2) Of particular note is the high and rising trend in admissions for chronic kidney disease. Unfortunately, the authors do not have any proxies for resource use, but could estimate, based on some estimate of average length of stay and average charges per diem, the associated total spending and out-of-pocket burden. Admittedly that might constitute a separate paper, but it would provide important additional evidence for prioritizing policy to address inequalities of health and access.

Thank you so much for your brilliant suggestion. We'll work on this issue in our next research.

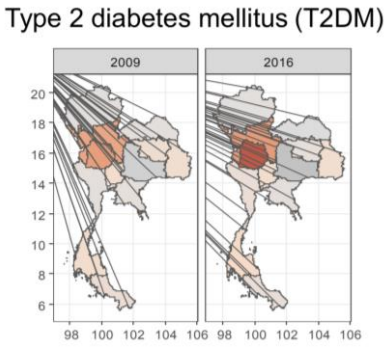
3) The authors do not discuss gestational diabetes, but that could account for some of the young adult female hospitalizations with diabetes especially as a secondary code and, unless the authors were sure the ICD10/9 codes used excluded them, merit discussion as a sub-category.

Thank you very much for your sensible inquiry. However, we did not include gestational diabetes (ICD-10 code O24) in our study as described in the manuscript (please see below).

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without CKD (N18.1 to N18.6, N18.9, E11.2, E14.2, N08.3, N19 and N18.9), MI (I21 and I22), cerebrovascular diseases (I60 to I69), retinopathy (H36.0), cataract (H25.0 to H25.2, H25.8, H25.9, H26.0 to H26.4, H26.8, H26.9, and H28.0), or diabetic foot amputations (8410-8417) were included, and any other cases were excluded from this study." (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-14)

4) What are all the lines coming out of the graphs to the northwest in Figure 4? Fig 4. Comparisons of age- and sex- standardized admission ratios of type 2 diabetes mellitus and its complications in NHSO regions in 2009 and 2016

Thank you very much again. We assume that "the lines coming out of the graphs to the northwest" are the ones shown on the right. These lines appear on some computers, but not all. In fact, we do not see the lines on our computers. We hope the editor has a technical means to solve this problem.



5) Other explorations of the data that might be meaningful include correlation of the SAR with the % urban residents and/or per capita GDP and/or average years of schooling in each region; reporting and discussing the proportion of admissions in primary, secondary, and tertiary hospitals; at urban versus rural hospitals; at government vs private hospitals; at teaching hospitals vs non-teaching hospitals.

We appreciate your important suggestions. We revised the explanation of the geographical inequalities in Discussion section with the available data, as shown below.

"On the other hand, the persistently high SAR of T2DM with retinopathy in Bangkok is presumably due to high density of specialists as half of 1,500 ophthalmologists, including 200 retinal specialists, practice in Bangkok [33].

The persistently high SAR of T2DM with CKD in northeastern regions was consistent with a previous study and partly attributed to high prevalence of CKD in northeastern regions (10.8%) relative to other regions (north 8.9%, south 8.1% and Bangkok 6.2%) [34], but partly to an association with lower density of physicians and rurality of the region [13]. The density of physicians in northeastern regions

is the lowest in the country [32], as low as seven times lower than Bangkok [9]. It is reasonable to assume that in a region where physicians are scarce, T2DM patients with CKD are unlikely to receive timely, thorough and effective treatment, and consequently deteriorate in conditions. This assumption might explain the high readmission rates of T2DM with CDK, and the highest mortality rates due to diabetes in northeastern regions as found in another study [12]. Moreover, rurality of the northeastern regions, where 71.0% of the population reside in rural setting (north 65.6%, south 66.5% and Central 54.5%) [35], might have halted them from accessing adequate primary care. A previous study found a strong association between the high SAR of diabetes and rurality as the rural population tends to have lack of public transport alternatives and poor health literacy with less education which often limit accessibility to health care. The study also suggested that the percentage of patients who had received up to secondary education was lower in rural districts by approximately 10% [13].” (Discussions, page 22 line 10 to page 23, line 9)

6) *To make the analyses comparable internationally and to allow even more precision in benchmarking the Thai national and regional trends in DM admissions, the authors could calculate the DM avoidable admissions rate as used in OECD metrics for the quality of primary care. This would simply involve standardizing to a comparable population, such as what the OECD does: rates per 100 000 population, age-sex standardized to the 2010 OECD population aged 15 and over (see references below). It would also provide an internationally comparable metric for benchmarking the Thai primary care system for DM management with other health systems, over the study period and as a baseline for tracking further improvements into the future. Of course, the authors may not be able to apply the full inclusion and exclusion criteria, so it would only be suggestive. For example, it does not seem that the authors can categorize the admissions according to whether or not the patient died during the admission. They may not be able to exclude those transferred from another hospital, although the date(s) of admission would be suggestive for creating that categorization from the raw admissions data. Again, estimating DM avoidable admissions rates could constitute a separate paper, but since it draws on exactly the kind if data the authors summarize in this paper, I would urge the authors to consider including this and thus able to attract a wider readership and evidence for policy top address the important trends they highlight.*

We appreciate your sensible suggestion. We’ll work on these in our next research.

Response to Reviewer #3

General comments:

This is an interesting manuscript providing the big picture of type 2 diabetes in the Thailand population between 2009-2016. I appreciated the reading and the figures are well-chosen. The authors conclude to an increase in type 2 diabetes over time. There may be a need for improved health care

system/policies/services/prevention for this population. Even though I appreciated the paper, I would have some questions for the authors.

Major comments

1) Aren't there any paper published with those databases to support what the authors claim in the data section of the Method?

Thank you very much for your inquiry. As you suggested, we have included the following reference papers to support our decision to use only the data of 2009 and onwards in Materials and methods: Data section.

1. Komwong D, Sriratanaban J. Association between Structures and resources of primary care at the district level and health outcomes: a case study of diabetes mellitus care in Thaialn. Risk Manag Healthc Policy. 2018; 11, 199-208

2. Liabsuetrakul T, Sukmanee J, Thungthong J, Lumbiganon P. Trend of Cesarean Section Rates and Correlations with Advance Maternal and Nesecondary analysis of Thai Universal Coerage Scheme Data. AJP Rep. 2019; 9(4): 328-336.

2) Definitions of T2DM: where was diabetic amputation (only) defined based on the ICD 9 coding (paralele database?)?

We appreciate your concern. Diabetic amputation defined based on ICD-9 codes was a parallel database, "the operation database," as described below, but the operation database also belongs to the National Health Security Office.

"Two are reports sent from hospitals to the Ministry of Public Health, namely the hospital admission database and the operation database..." (Materials and methods: Data, page 8, lines 3-5)

3) I think there is a typo for the stroke definition (I60 to I69 and not I6.0 to I6.9). Furthermore, if those are really the codes used, it does not only refer to stroke but rather largely to cerebrovascular diseases.

Thank you very much for pointing it out. We have corrected the text as follows:

"All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9) …cerebrovascular diseases (I60 to I69), …" (Materials and methods: Definitions of T2DM and its complications, page 9, lines 9-11)

According to your suggestion, we also corrected the word “stroke” to “cerebrovascular diseases.”

4) Diabetic amputations codes selection (ICD9 8401-8415) would need a reference or more explanations for rational.

We appreciate your suggestion. We have carefully reviewed ICD-9 codes again and slightly changed the codes included this study and revised the text as follows.

“All UCS admitted cases whose principal or secondary diagnosis were coded as T2DM (E11.1 to E11.9), with or without … or diabetic foot amputations (8410-8417) were included … Diagnosis of foot amputation was considered as a diabetic complication if it was performed from the toe to above the knee.” (Materials and methods: Definitions of T2DM and its complications, page 9, line 9 to page 10, line 2）

5) Data analysis: the authors should explain how were the 2009-2016 trends compared (visually I think).

Thank you very much for your important suggestion. Please see Fig. 3 that explains the 2009-2016 trends visually.

6) The results would benefit from a more sophisticated trend analysis, using for example a binomial regression model to obtain the precise slope % and a contrast test to compare in sub-analyses. Even though different, this paper and its references may help: Leclerc J et al. Circulation: Cardiovascular Quality and Outcomes, 2017.

We very much appreciated your proposal with the useful reference for a more sophisticated trend analysis. We have conducted time series regressions with the following negative binomial regression model, and added the methods and results to our manuscript as shown below.

“To estimate temporal trend of admissions, we conducted time series regressions with the following negative binomial regression model.

$$n_i \sim \text{NegativeBinomial}(\mu_i, \phi)$$

$$\mu_i = \exp(\beta_0 + \beta_1 x + \log N_i)$$

where n_i is the number of admissions of ith time point, N_i is the number of UC population of ith time point, x is the indicator variable of time points, μ is the mean parameter and ϕ is dispersion parameter of Negative Binomial distribution, β_0 is the intercept, and β_1 is the slope parameter.”

(Materials and methods: Data analyses, page 11, line 1 - 5）

"Table 2 presents the results of the time series regressions to estimate temporal trend of admissions showed that all types of T2DM admissions except that with cataract had a significant and positive temporal trend.

Table 2. Time series regressions parameters of temporal trend analysis for admissions

Parameters	Estimate	SE	z value	p value
All DM admissions				
$\boldsymbol{\beta_0}$: intercept	-4.460529	0.006002	-743.16	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.050566	0.001187	42.61	p < 0.001
DM with CKD admissions				
$\boldsymbol{\beta_0}$: intercept	-6.108389	0.009446	-646.64	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.095675	0.001861	51.41	p < 0.001
DM with MI admissions				
$\boldsymbol{\beta_0}$: intercept	-8.11538	0.02155	-376.58	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.07541	0.00424	17.78	p < 0.001
DM with cerebrovascular diseases admissions				
$\boldsymbol{\beta_0}$: intercept	-7.251687	0.009935	-729.93	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.084358	0.001941	43.47	p < 0.001
DM with cataract admissions				
$\boldsymbol{\beta_0}$: intercept	-7.604557	0.046891	-162.175	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.015244	0.009283	1.642	0.101
DM with retinopathy admissions				
$\boldsymbol{\beta_0}$: intercept	-8.941096	0.028458	-314.181	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.049766	0.005599	8.888	p < 0.001
DM with amputation admissions				
$\boldsymbol{\beta_0}$: intercept	-8.955374	0.023377	-383.09	p < 0.001
$\boldsymbol{\beta_1}$: time point	0.050946	0.004584	11.12	p < 0.001

Note: SE: Standard error, CI: Confidence interval, DM: Diabetes mellitus, CKD: Chronic kidney disease, MI: Myocardial infarction

(Results, page 16, line 9 to page 17, line 2)

7) Was the age and sex distribution of the population in 2009 ever published? If so, a reference would be needed in the data analysis section.

Thank you so much for your inquiry. We are afraid the age and sex distribution of the UCS population in 2009 has not been published. The data of UCS population of 2009 we used was provided by the National Health Security Office (NHSO), Thailand.

as the standard for age- and sex-adjustment.

8) "the expected number of admissions in region": please provide more details (ex.: according to the literature, the country level of admission, etc.)

We appreciate your enquiry. "The expected number of admissions in region" is explained as follows in Materials and methods: Data analysis section.

"We estimated the standardized admission ratio (SAR) of each region using the following equation for each region.

$$SAR_i = \frac{o_i}{e_i}$$

$$e_i = \sum_{j=1}^{J} p_j n_{ij}$$

where SARi is standardized admission ratio in region i; oi is the observed number of admissions in region i; ei is the expected number of admissions in region i; j is the population stratum defined by age and sex; pj is standard admission rate in the 2009 UCS population for the population stratum j." (Materials and methods: Data analysis, page 10, lines 9-15）

9) "Age was categorize into 15 groups of five-year intervals" is not fully accurate, and the last category is 85 to 100 years old. This should be adjusted.

Thank you so much for pointing it out. We have corrected the sentence as shown below and changed the value labels from "85+" to "85-100" in figures and tables.

"Age was categorized into 15 groups in intervals of five years, except the last category that includes 85 to 100 years of age" (Materials and methods: Data analysis, page 10, lines 16-17）

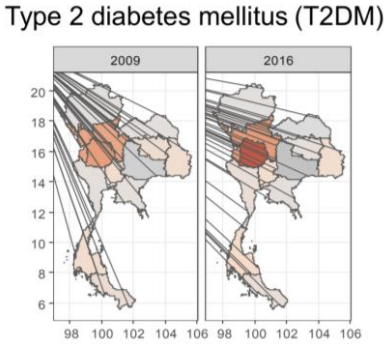
Minor comments:

10) Fig 3, "cases with ampulation" should be written "amputation"

Thank you for pointing it out. We corrected the word in the figure.

11) Fig 4, this would be beautiful without all the diagonals accross the pictures. Any way to remove it?

Thank you very much again. We assume that "the diagonals across the pictures" are the ones shown on the right. These lines appear on some computers, but not all. In fact, we did not see the lines on our computers. We hope the editor has a technical means to solve this problem.



Additional editor comments:

Journal requirements:

1) Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming.

Thank you very much for your kind advice with useful URLs. We have carefully revised our manuscript in accordance with the PLOS ONE style.

2) In ethics statement in the manuscript and in the online submission form, please provide additional information about the patient records used in your retrospective study. Specifically, please ensure that you have discussed whether all data were fully anonymized before you accessed them and/or whether the IRB or ethics committee waived the requirement for informed consent. If patients provided informed written consent to have data from their medical records used in research, please include this information. Moreover, in you Data statement, please ensure that it is clear how you obtained the data, and how other researchers can request access to the same database.

Thank you very much for bringing out this issue. We obtained the data in the National Health Security Office which manages the database as the first author belongs to the organization. However, we added the sentence clarifying that all data were anonymous, as shown below. We also added the information of how others can access to the database in the "Data reporting" section, as follows.

"All data were fully anonymized before we accessed them." (Materials and methods: Data, page 8, lines 8-9)

"All patient records were fully anonymized before we accessed. The relevant UCS data are available upon request to the National Health Security Office, Thailand, with the research outline and the details of the required data." (Data reporting, page 25, lines 15-17)

3) Our internal editors have looked over your manuscript and determined that it is within the scope of our Health Inequities and Disparities Research Call for Papers. If you would like your manuscript to be considered for this collection, please let us know in your cover letter and we will ensure that your paper is treated as if you were responding to this call. If you would prefer to remove your manuscript from collection consideration, please specify this in the cover letter.

Thank you very much for inviting us to the special research call. As indicated in the cover letter, we would like our manuscript to be considered for this collection.

4) We note that you have indicated that data from this study are available upon request. In your revised cover letter, please address the following prompts:

a) If there are ethical or legal restrictions on sharing a de-identified data set, please explain them in detail (e.g., data contain potentially identifying or sensitive patient information) and who has imposed them (e.g., an ethics committee). Please also provide contact information for a data access committee, ethics committee, or other institutional body to which data requests may be sent.

b) If there are no restrictions, please upload the minimal anonymized data set necessary to replicate your study findings as either Supporting Information files or to a stable, public repository and provide us with the relevant URLs, DOIs, or accession numbers. Please see http://www.bmj.com/content/340/bmj.c181.long for guidelines on how to de-identify and prepare clinical data for publication. For a list of acceptable repositories, please see http://journals.plos.org/plosone/s/data-availability#loc-recommended-repositories.

Thank you very much for pointing this out. The National Health Security Office (NHSO) follows the Information Security Policy, Information Security Management System procedure (QP-407 10-001). An individual who wishes to use the UCS databases must sign the Non-Disclosure Agreement (NDA) with NHSO, and submit copies of documents, reports, articles or publications that use the dat. The use of the data is restricted within the research framework and the person should be responsible for his/her own actions in case of a lawsuit, etc. We have added the information to the revised cover letter.

5) PLOS requires an ORCID iD for the corresponding author in Editorial Manager on papers submitted after December 6th, 2016. Please ensure that you have an ORCID iD and that it is validated in Editorial Manager.

The corresponding author checked it and he ensured that the ORCID iD was validated in Editorial Manager.

6) Your ethics statement must appear in the Methods section of your manuscript. Please also ensure that your ethics statement is included in your manuscript, as the ethics section of your online submission will not be published alongside your manuscript.

Thank you very much for your kind reminder. We have added the ethics statement in the Methods section as shown below.

"Ethics of the study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (NCGM) in Japan on 11 May 2018 (NCGM-G-002524-00)." (Materials and methods: Data analyses, page 11, lines 11-12)

7) We note that Figure 4 in your submission contains map images which may be copyrighted. We require you to either (1) present written permission from the copyright holder to publish these figures specifically under the CC BY 4.0 license, or (2) remove the figures from your submission.

We have created the map images with the geodatabase retrieved from the website, the Humanitarian Development Exchange (HDX). As far as our understanding, all the databases offered under the CC BY license are free to share and or adapt for any purpose, even commercially. It is also stated that no one can apply legal terms or technological measures that legally restrict others from doing anything the license permits (please see the website from https://data.humdata.org/about/license).

If there are any problem about license of the map images, please let us know.

8) Please upload a copy of Supporting Information Table 1 and 2, which you refer to in your text on page 14.

Thank you very much for your concern. We finally decided not to include Supplementary table 1 and 2, but missed deleting the sentence which indicates the Supplementary tables in the manuscript. This time, we deleted the sentence.