Editorial office
International Journal of Environmental Research and Public Health

July 15, 2019

Dear Editors and Reviewers,

On behalf of all my coauthors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for your positive and constructive comments and suggestions on our manuscript entitled “Seasonal and monthly patterns, weekly variations and the holiday effect of type 2 diabetes mellitus outpatient visits in China” to International Journal of Environmental Research and Public Health. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied the comments carefully and have made corrections which we hope will meet with your approval. We have made revision marked in red in the paper. Attached please find the revised version, which we would like to submit for your kind consideration. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Reviewer 1

Question 1:
This is an interesting paper that explores a relevant issue: patterns of use of health care services by the diabetic population. For this purpose authors explore and analyze the data using appropriate methods to assess the seasonal, monthly, holiday and weekly fluctuations. The main problem with this paper is when authors try to address the second part of the objectives: "infer possible influencing factors" which is based on an assumption (that they do not test) that: "that the outpatient service utilization ... follows the same seasonal pattern with the changes of glycaemia". Based on the date they incorporate in their models it is not possible to answer this specific objective.

Answer:
Completed. Please see page 2, line 76-8. We deleted “infer possible influencing factors by assuming that the outpatient service utilization of T2DM patients follows the same seasonal pattern with the changes of glycaemia” and replaced the statement with "compare the seasonal patterns of outpatient visits by T2DM patients with the seasonal changes of glycaemia found in previous studies". In page 6, line 194-6. We deleted “infer possible
influencing factors” and replaced the statement with “compare the seasonal patterns of outpatient visits by T2DM patients with the seasonal changes of glycaemia found in previous studies”. In addition, revisions to other related sentences were also made and are clearly highlighted in the revised manuscript.

We described yearly seasonal patterns of T2DM outpatient visits, but also monthly, holiday and weekly outpatient visit effects in this study, and the point we want to make is that seasonal patterns of diabetics medical treatment exists and the pattern of medical treatment among the population is irregular and unbalanced. The current data are supportive for this purpose, but the results need careful interpretation. We went over the wording in the manuscript and tried to avoid any inappropriate extensions. The relevant modifications and corrections can be found in the introduction and discussion section, which also address Reviewer 2’s comments, including page 6 lines 192—8; 208-11; 213-6; 221-4 and page 7 line 245-7; 250-1; 271-5.

Question 2:
In fact, what authors try in the manuscript is to provide hypothesis on how several variables could explain their findings. However, although authors do not test the validity of these hypotheses is in this paper, they assume that their ideas are the explanation for the fluctuations identified in the visits of patients with diabetes, leading them even to make concrete recommendations about how to organize healthcare, clinical practice and what messages patients with diabetes have to receive about their disease.

Answer:
Completed. Please see page 6, line 213-6. We deleted “This phenomenon may be caused by that patients insured by URBMI were almost farmers who were busy in spring for agriculture, and they did not access hospital outpatient clinics neglecting their treatment” and replaced the statement with “Higher summer seasonal index of URBMI patients indicated that the blood glucose management of URBMI patients might be more irregular with suggestive, but not definitive evidence, that URBMI patients suffer from a higher risk of exacerbation in hot seasons or weather”. In page 6, line 221-4. We added “Interestingly, in the busy March and April agricultural seasons in Shandong province, the seasonal index of URBMI patients, who were mainly farmers, was significantly lower than that of UEBMI patients. Whether there is an association between the two remains to be evaluated by further studies”. In page 7, line 245-7; 250-1, we modified the sentence to “There was the reluctance of T2DM patients to seek medical treatment during China’s traditional Spring and Lantern Festivals leading to the winter period low point in T2DM medical care[36,37]. This is consistent with our data analysis results, which suggests that the low seasonal index during the holiday period may be partly due to the above reasons”.

Our paper provides data supportive of previous research findings, and our suggestions for improvement are based on our results and previous research findings, which is made clear in the revised manuscript. Please see page 7, line 270-5, “Our findings indicate that the frequency of seeking outpatient medical services by T2DM patients
exhibits obvious seasonality in holidays, seasons, months and weeks and the underlying mechanisms need further investigation. Consistent with previous research, low presentations at clinics during holidays, certain seasons and months mean patients going without proper treatment. As suggested in previous studies, this unhealthy medical treatment mode should attract the attention of policy makers and clinicians.”

Based on the above feedback, extensive modifications and corrections have been made to the manuscript so that the expression and presentation are consistent with the research results.

Reviewer 2

Question 1:
Firstly, in analysis of seasonal effect, it needs to eliminate the effect of holiday effect.

Answer:
Completed. Please see page 3, line 112-9. We added a statement about methods to eliminate holiday factors, expressed as “In addition, as the number of weekends and statutory holidays may not be consistent within two months, if the influence of these factors collectively referred to as “holidays” is not excluded, the seasonal change trend of outpatient service cannot be truly reflected. Therefore, in the time series analysis of monthly and seasonal data, the influence of holiday factors must be removed from the original series, which is called “seasonal adjustment”. The non-parametric, Scaling factor, method of the holiday effect adjustment was adopted [33,34] and the seasonal index calculated after eliminating the holiday factor, which more accurately reflects the basic medical treatment trend of diabetic patients”. The results are shown in the revised table 2. Please also see page 4, line 140. In addition, the data results have been fully revised in the text.

We provide below a detailed discussion of our statistical tests (which is not included in the paper).

By referring to relevant literature, we found a appropriate and practical method to adjust the effects of different holiday types. Before the presentation, we think it is necessary to briefly explain the calculating method of the seasonal index in time series analysis according to this manuscript. Traditional time series theory decomparts the observed value $Y$ of a variable into trend change ($T$), seasonal change ($S$), cyclic change ($C$) and irregular variation ($I$), it is expressed by the formula as $Y_t = f(T_t, S_t, C_t, I_t)$. There are usually three different assumptions about the relationship between the changing factors in time series: additive relation, multiplicative relation and mixed relation. The calculation of seasonal index in this manuscript is based on the common multiplication relation. As the number of weekends and statutory holidays may not be consistent within two months, if the influence of these factors collectively referred to as “holidays” is not excluded, the seasonal change trend of outpatient service cannot be truly reflected. Therefore, as you suggested, in the time series analysis of
monthly and seasonal data, the influence of holiday factors must be removed from the original series. In the current classification of seasonal adjustment methods, it can be roughly divided into two methods: seasonal adjustment based on moving average and seasonal adjustment based on model. The seasonal adjustment method based on moving average is adopted in this manuscript. To our knowledge, X-12-ARIMA is the most commonly used seasonal adjustment method, which is based on the festival holidays in western countries, without taking into account the holiday factors in China. For example, the Spring Festival cannot be introduced as a regression factor in X-12-ARIMA. Moreover, the X-12-ARIMA model generally requires more than three years of data but the data we used in the manuscript don't meet the requirements. In fact, seasonal adjustment in China has its particularity. The official Chinese calendar is the solar calendar, while some important Chinese festivals are determined by the lunar calendar. According to the solar calendar, there are no fixed dates for Chinese lunar holidays, which are often called “mobile holidays”. As the most important mobile holiday in China, the Spring Festival has a great impact on the fluctuation of outpatient visits. Therefore, the seasonal adjustment of “mobile holiday effect” is a difficult and key point. Based on the above situation, we reviewed a lot of literature and adopted the non-parametric method (Scaling factor method) of mobile holiday adjustment in the manuscript according to the actual situation. The specific operation process is as follows (the other two types of holidays effect, major holidays in fixed months and regular legal holidays, are processed similarly):

1. Definition of several variables.
   \( D_t \) — Represents the number of days remaining each month after deducting the Spring Festival holiday during the study period.
   \( \bar{D}_j \) (j=1,2) — Represents the average number of days in January and February after deducting the Spring Festival holiday during the study period.
   \( P_t \) — Prior Monthly Adjustment Factors.
   \( \tilde{y} \) — Represents the sequence after eliminating holiday factor effect.

2. The sequence calculation after eliminating the holiday factor effect.
   \[
   P_t = \begin{cases} 
   D_t / \bar{D}_1, & t = 1 \\
   D_t / \bar{D}_2, & t = 2 \\
   1, & t = 3,4,...12 
   \end{cases}
   \]
   \[
   \tilde{y}_t = y_t / P_t, \quad t = 1,2,...n
   \]

3. The calculation of seasonal index.
   On the basis of the adjusted sequence, the seasonal index is calculated by trend elimination method.
Finally, we need to pointed out that although scaling factor method is used to eliminate the holidays effect, the holiday effect still can not be completely eliminated due to major national holidays and regular holidays effect were simply considered to be equivalent in the model. In fact, the data show that different holidays produce different outpatient effects. For example, the 7-day Spring Festival holiday has a greater impact on outpatient visits than the 7-day National Day holiday. The effect of national legal holidays is greater than that of regular holidays. Different weights need to be assigned to eliminate the effects of different holidays, which involves more complex model construction and accurate calculation. Technically, there is no way to completely eliminate the effects of holidays because of two reasons. Firstly, the model cannot measure the length of effective period and the weight of effect, which need subjective judgment. Secondly, even the best mathematical model will produce errors. Nankai university and the National Bureau of statistics jointly developed software “NBS–SA”, a professional seasonally adjusted software aiming at eliminating Chinese holidays effects including Spring Festival effect, National day holiday effect and so on. “NBS–SA” deal with the Spring Festival effect in three different ways of the uniform distribution, sections of uniform distribution, sections of non-uniform distribution. However, due to the limited availability of “NBS – SA” and length of time series, we cannot do further processing at present.

Reference

Question 2:
Secondly, to provide inferentially statistical support for the descriptive statistics, such as confidence interval or P value.

Answer:
Completed. Please see page 4, line 138-9, and the revised table 2.

In response to the Reviewer, we provide below a detailed discussion of the descriptive statistics.

The traditional estimation of seasonal index only stops at descriptive statistics, that is, we can only get the point estimate of seasonal index. Even the most commonly used X-12-ARIMA seasonal adjustment method has problems and limitations that can only give descriptive statistics. By referring to relevant literature, we found that some scholars have conducted professional and innovative research on this issue. Three main statistical inference
methods for seasonal indexes of different data types were proposed, which includes regression model of seasonal dummy variable with no obvious long-term trend, regression model of seasonal dummy variable with long-term trend and sampling estimation of seasonal index. According to the research data type, we established the regression model of seasonal dummy variable without intercept term to estimated the parameters of seasonal dummy variable, and indirectly obtained the interval estimation of seasonal index and hypothesis test. To be specific, we used two step method to establish the long-term trend components modeling and seasonal components modeling, respectively. A new time series data (SI) containing only seasonal component (S) and irregular change (I) composition was obtained after eliminating the long-term trend (T) and the cycle trend (C) components from the original time series data and then we set four seasonal dummy variable to establish the regression model without intercept term. As to whether the difference of seasonal indexes between two seasons is statistically significant, we judged by calculating the 95% confidence interval of the difference using the formula as follows.

\[
(Q_1 - Q_2) \pm t_{\alpha/2,v} \sqrt{\frac{(S_1)^2}{n_1} + \frac{(S_2)^2}{n_2}}
\]

However, in spite of our best efforts to answer your questions as perfectly as possible, we must admit that the regression model of seasonal dummy variable also has its limitations. It only solves some problems in traditional seasonal index estimation, but not all of them. When the number of dummy variables increases, the data requirements will be further improved. For example, when the analysis of seasonal index changes from quarterly data to monthly data, the analysis will be complicated and the data requirements will be higher. Due to the complexity of data analysis and regression model establishment, we cannot give the confidence interval of monthly data, nor make multiple comparisons of monthly seasonal indexes. We look forward to a more in-depth, targeted and professional analysis of this issue in the future research.

Reference

Reviewer 3

Question1: General: Please be consistent in referring to the study patients as “patients with type 2 diabetes mellitus” throughout the manuscript.

Answer1: Completed. Please see page 2 and page 3, line 92-8. In Materials and Methods, we added a statement about study subjects expressed as “Based on the main diagnosis and International Classification of Diseases
(ICD-10: E11- E14), 904,488 T2DM patients were identified from the medical insurance management database, including non-insulin-dependent diabetes mellitus, diabetic complications and diabetic comorbidities, which constituted a 3-year dynamic cohort. Information on all outpatient visits made by T2DM patients, regardless of the reason, during the 3-year period (2015–2017) was extracted, resulting in 8,417,914 consultations”. The study subjects have been identified as “T2DM patients” throughout the manuscript.

**Question2:** Line 2-5, Title: “of type 2 diabetes mellitus outpatient visits”;
Line 21, Abstract: “of outpatient service utilization in type 2 diabetes mellitus patients”;
Line 34, Abstract: “utilization of outpatient services for patients with type 2 diabetes”

Comment: A clarification is needed to sort out the differences pointed out here. Is the study examining a) outpatient visits where diabetes-related care was provided or b) diabetes-related outpatient visits by patients with type 2 diabetes mellitus or c) “all” outpatient visits by patients with type 2 diabetes mellitus. Please clarify and be consistent throughout the manuscript.

**Answer2:** Completed. Please see Answer1 (Information on all outpatient visits made by T2DM patients, regardless of the reason, during the 3-year period (2015–2017) was extracted). The other relevant issues have also been revised in the text.

**Question3:** Line 24, Abstract: Please mention that seasonal indices (Si) were calculated for seasons, months, and weeks.

**Answer3:** Completed. Please see page1, line 26-7. We deleted “The seasonal index (S_i) was calculated by the moving average method” and replaced the statement with “The seasonal index (S_i) was calculated in terms of seasons, months and weeks by the moving average method”.

**Question4:** Line 25, Abstract: “a total of 904,488 patients received outpatient services during the study period”.

Comment: How were study patients identified? From an insurance database or from data on outpatient visits itself? Was it a fixed and/or closed cohort (i.e. did you study fixed set of patients who had follow-up data for 3-year duration)? Was it a dynamic cohort?

**Answer4:** Completed. Please see page 3, line 93-8. “Based on the main diagnosis and International Classification of Diseases (ICD-10: E11- E14), 904,488 T2DM patients were identified from the medical insurance management database, including non-insulin-dependent diabetes mellitus, diabetic complications and diabetic comorbidities, which constituted a 3-year dynamic cohort. Information on all outpatient visits made by T2DM patients, regardless of the reason, during the 3-year period (2015–2017) was extracted, resulting in 8,417,914 consultations”. (See also Answer 1).
**Question 5:** Line 26-28, Abstract: One suggestion would be to provide the seasonal indices for the four seasons in parentheses after each season and combine two redundant sentences.

**Answer 5:** Completed. Please see page 1, line 28-30. We deleted “The outpatient visits by type 2 diabetes patients were seasonal, with seasonal indexes of 102.67% spring, 99.04% summer, 108.36% autumn and 89.92% winter. Autumn was the peak, and winter the low, season for outpatient services by type 2 diabetes mellitus patients” and replaced the statement with “The seasonal indices of outpatient visits by type 2 diabetes patients were higher in autumn (108.36%) and spring (102.67%), while lower in winter (89.92%) and summer (99.04%), exhibiting an obvious seasonality”.

**Question 6:** Line 30-33, Abstract: It appears that large deviations in seasonal indices (from 100%) in seasonal, monthly, and weekly patterns occurred only during holiday periods. Is it fair to attribute all variations to just “holiday affect”? Or is the “holiday affect” an additional source of variation?

**Answer 6:** Completed. Holiday effect was eliminated in the time series analysis of monthly and seasonal data. Please see Reviewer2, Question 1 and the Answer.

**Question 7:** Line 35, Abstract: “variations in blood glucose fluctuations”. Since, the blood glucose measures were not collected and analyzed as part of this study, one suggestion would be to say “previously published patterns of blood glucose fluctuations” to prevent any confusions.

**Answer 7:** Completed. Please see page 1, line 37. We added “found in previous studies” in the sentence.

**Question 8:** Line 37, Keywords: How come there is no mention of outpatient visits?

**Answer 8:** Completed. Please see page 1, line 40. We added “outpatient visits” in Keywords.

**Question 9:** Line 49 and Line 53, Introduction: References are needed.

**Answer 9:** Completed. Please see page 2, line 52 and line 56. We added the references.

**Question 10:** Line 53-55, Introduction: “T2DM seasonality followed a sinusoidal pattern” Can you please clarify what “T2DM seasonality” means. Is it glucose levels, clinical events, visits, hospitalizations?

**Answer 10:** Completed. Please see page 2, line 57. It means the seasonality of T2DM incidence.

**Question 11:** Line 67, Introduction: It appears Ref 29 doesn’t pertain to diabetes and was not retrievable.

**Answer 11:** Completed. Please see page 2, line 70. We replaced reference 30 with “Honeyford K, Cecil E, Lo M, et al. The weekend effect: does hospital mortality differ by day of the week? A systematic review and meta-analysis[J]. BMC HEALTH SERVICES RESEARCH, 2018,18(870)”. 
Answer12: Completed. Please see page 2, line 78. We added “found in previous studies” in the sentence.

Question13: Line 79-85, Materials and Methods: A few additional lines on how the study cohort was identified and study setting should be added. Also refer to item 4. Was data on comorbidity, use of insulin/oral anti-glycemic medications, length of diabetes, and reason for visit available? Since, the readership is global, additional lines explaining the types of insurance would have provided better context. Were patients hospitalized included in the study? Was study limited to visits made to outpatient clinics attached to hospitals only?
Answer13: Completed. Please see Answer1 and page 2, line 87-9. We added “The type of medical insurance consists of Urban Resident Basic Medical Insurance (URBMI) and Urban Employee Basic Medical Insurance (UEBMI), forming the basic medical insurance systems after New cooperative medical insurance merging into URBMI from 2015 in Shandong province”. The study included all the outpatients visiting hospitals and pharmacies that can handle basic medicare billing.

Question14: Line 85, Materials and Methods: “T2DM outpatients presenting for T2DM treatment during the study period”. Refer to item 2.
Answer14: Completed. Please see Answer1 and page 2, line 90-1.

Question15: Line 87-102, Materials and Methods: Think “methods” and “statistical analysis” can be combined. Please arrange this section in the order in which the analyses were performed and presented in the manuscript.
Answer15: Completed. Please see page 3, line 100-21.

Question16: Line 94-96 and Line 100-102, Materials and Methods: It is not clear how many times statistical tests were performed and was it using raw data on visits or smoothed data. Please resolve the differences.
Answer16: Completed. Please see page 3, line 100-19. Chi-square test was used to analyze the effects of gender, age, and medical insurance types on differences in proportion between seasons basing on the raw data; the seasonal indexes of each season, month and week of the general and different medical insurance types subgroups were calculated by the moving average trend elimination method basing on smoothed data.

Question17: Line 109, Results: Parentheses is missing for S.D. of age. Assuming 10.7 represents S.D.
Answer17: Completed. Please see page 3, line 128.

Question18: Line 114-115, Results, Table 1: Use commas as the numbers are large and difficult to follow without commas. Suggest to replace p-value for insurance as < 0.0001 rather than leave it as 0.000.
Answer18: Completed. Please see page 4, line 133, Table 1.
**Question 19:** Line 121-137, Results: There is mentioning of significant differences of seasonal indices. Were these differences statistically tested?

**Answer 19:** Completed. Inferentially statistical support for the descriptive statistics, such as confidence interval or P value was provided. Please see Reviewer 2, Question 2 and the Answer.

**Question 20:** Line 139-155, Results: Peak SI was indicated to be in week 9 and week 41. But Figure 1 appears to show higher SI in weeks 48-52. Please clarify.

**Answer 20:** Completed. Please see page 5, line 164-6. In week 9 and week 41, there were two small peaks after the holidays. In week 52, the seasonal index reached the highest peak.

**Question 21:** Line 157, Results: It is not clear where and how the comparison of actual and expected visits were presented in Figure 2. Please expand.

**Answer 21:** Completed. Please see page 5, line 180-2. We added the statement with “The proportion of daily outpatient visits should be 1/7 (14.29%) if outpatient visits are evenly distributed over the seven days of the week, but this was not the case”.

**Question 22:** Line 166-266, Discussion and Conclusion: The seasonal and weekly patterns appear to be related to holidays and holidays-related migration; insurance types; insurance reimbursement policies; appointments scheduling. The seasonal indices for January/February vs December alone appear to be significantly different. Were differences for other months statistically significantly different? So, most of the differences appear to be attributable to holidays/scheduling/availability/insurance policies. Due to this linking the study findings to glucose levels and other factors, which were not collected and studied in the study appears to an overreach. Lastly, one would think we would find similar results for any chronic disease (ex. Hypertension, mental health illnesses). Would like to know what the authors have to say about this.

**Answer 22:** Completed. 1. For holidays effect and statistical support, please see Reviewer 2, Question 1, Question 2 and the Answer. 2. We described yearly seasonal patterns of T2DM outpatient visits, but also monthly, holiday and weekly outpatient visit effects in this study, and the point we want to make is that seasonal patterns of diabetics medical treatment exists and the pattern of medical treatment among the population is irregular and unbalanced. The current data are supportive for this purpose, but the results need careful interpretation. We went over the wording in the manuscript and tried to avoid any inappropriate extensions. The relevant modifications and corrections can be found in the introduction and discussion section, which also address Reviewer 2’s comments, including page 6 lines 192—8; 208-11; 213-6; 221-4 and page 7 line 245-7; 250-1; 271-5. Our paper provides data supportive of previous research findings, and our suggestions for improvement are based on our results and previous research findings, which is made clear in the revised manuscript. Please see page 7, line 270-
5. “Our findings indicate that the frequency of seeking outpatient medical services by T2DM patients exhibits obvious seasonality in holidays, seasons, months and weeks and the underlying mechanisms need further investigation. Consistent with previous research, low presentations at clinics during holidays, certain seasons and months mean patients going without proper treatment. As suggested in previous studies, this unhealthy medical treatment mode should attract the attention of policy makers and clinicians.” Based on the above feedback, extensive modifications and corrections have been made to the manuscript so that the expression and presentation are consistent with the research results. It is possible and reasonable that the seasonal patterns of chronic diseases have some commonality for the same characteristics of being susceptible to a pathogenic factor, lifestyle, extreme weather and temperature etc, which doesn’t mean that seasonal patterns among chronic diseases will be exactly the same. Just as a previous study basing on outpatient data has found that the peak of mental illness occurs in summer, August; distinguishing from our study findings.

We have improved the manuscript according to the Reviewers’ comments, making significant changes in the manuscript.

Sincerely yours,

Jian Wang, Professor
Dong Fureng Institute of Economic and Social Development
Wuhan University