Author’s response to reviews

Title: Clinic and patient variation in intermediate clinical outcomes for type 2 diabetes: a multilevel analysis

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Response to editor and reviewers’ comments
Manuscript Title: Clinic and patient variation in intermediate clinical outcomes for type 2 diabetes: a multilevel analysis (FAMP-D-18-00289)

Jean-Francois Chenot (Editor)
Thank you for your time and practical comments! Please find our responses listed below.

1. Statistics. Please report on goodness fit of your regression models. Did you check for collinearity? (I would like to see the statistics (regression table).
Yes, we did check for collinearity between predictors used in the models. We have added the information on goodness of fit in the results (Table 3 and Supplementary table) and the findings on collinearity checks within the text. Kindly refer to:

Methods, Line 259:
“Improvement in goodness of fit is reflected in the reduction of ‘deviance’ statistics as variables were introduced consecutively into the models[26,27]”

Results, Table 3 and supplementary table:
Results on goodness of fit were added to Table 3 and Supplementary table.

Methods, Line 262:
“All variables were also checked for multicollinearity and no predictor pairs were found to be collinear (variance inflation factors range between 1.02 and 1.64).”
2. I have a problem that you included the diagnosis of Hypertension and SBP in one model. These variables are not independent, if there is no collinearity there is at least interaction. Did you check for that? I suggest calculating the model with either the SP or Hypertension. The same applies to hyperlipidemia and LDL-C.

We have checked for collinearity of the independent variables for each model. There was no evidence of collinearity among them. However, we agree that there can be potential interactions between the pairs mentioned (by visualising their correlation plots stratified by presence and absence of hypertension and hyperlipidaemia). Hence, we have removed hypertension and hyperlipidaemia in models which also contain systolic blood pressure and LDL-C as predictors. Changes to the model and their coefficients have been made to Tables 2 and 3 as well as the supplementary table.

3. Please give full spelling of each abbreviation you use under each table, to allow the reader to assess the table on a glance.

We have added full terms of the abbreviations under all three tables.

Mark Ashworth (Reviewer 1)
Thank you for asking me to review this interesting paper. The overall message is a strong one - that variation in achievement of intermediate DM outcome indicators is largely unrelated to clinic level effect and almost entirely due to individual patient level factors.

We thank Dr Mark Ashworth for his time and constructive comments. Please find our response to your comments as per listed below.

1. Line 110. Malaysia has a spectacularly high prevalence if DM at 17.5% of the population. This should be discussed. Are the individual factors that contribute to this high prevalence also the individual factors that contributed to poor achievement of the selected 3 outcome measures?
Yes, you have rightly pointed this out. Both high prevalence of DM and poor disease control in Malaysia is attributable to the high prevalence of risk factors such as being overweight or obesity, high calorie and sugar diets and low physical activity.

Discussion, Line 390:
“"It is also known that people with diabetes in Malaysia consume diets high in carbohydrates and fat while more than half are physically inactive [6,40]. These factors together with overweight or obesity contributed not only to the high prevalence of DM in the country but also poor disease control.""

2. Line 156: this study was conducted in public health clinics. Further description is required of the Malaysian healthcare system. Who attends public clinics, are they free at the point of use, are they insurance funded or tax funded? And what is the alternative - presumably private? And approximately what proportion of patients with DM attend each service?
We have added more description on the healthcare system and it now reads:
Methods, Line 159:
“Malaysia has a dual-sector healthcare system; consisting of a public and private sector. The private sector is mainly funded by out-of-pocket payments and private insurance [15]. Health services in the public sector are heavily subsidised by general taxation and patients pay a small fee of between US$0.30 and US$ 4.50 for outpatient consultation, depending on citizenship status [15]. Hence, the public health sector manages the bulk of chronic conditions in the country [16]. For diabetes, patients mainly sought treatment at public clinics (59.3%), followed by public hospitals (20.0%), private clinics (15.1%), private hospitals (3.6%) and a remaining small percentage purchased medications from pharmacies or sought traditional and alternative practitioners [2].

The EnPHC interventions focused on public clinics because diabetes was largely managed in this healthcare setting.”

3. Line 162: further description is needed of the staff providing DM care. It is unclear what qualifications the Medical Officer and FMS have; and whether they have postgraduate training in the provision of DM care?

A description is added for medical officer and FMS as follows.

Methods, Line 171:

“Patients with diabetes were mainly managed by medical officers, who were licensed medical doctors with basic medical training. Some of them practice under the guidance of a family medicine specialist (FMS), who has formal postgraduate training in primary care practice, depending on whether there is a full-time or visiting FMS at their respective clinics.”

4. Line 201: DM complications are addressed in a very broad group. Thus, microvascular complications include cataract, retinopathy, CKD, neuropathy, ED, foot ulcer, amputation. It’s very large. I was left wondering whether a sensitivity analysis would help? It might be possible that the observed lack of difference between clinics in this study was the result of such broad criteria. For example, an analysis of CKD alone (a commonly used intermediate outcome) might have been highly dependent on the clinic level, rather than patient level. Similarly, foot complications, a very treatable outcome, might have been highly dependent on clinic level variation but this got 'lost' in the analysis because it was lumped together with ED and cataracts (which are not likely to be greatly related to clinic level aspects of care).

We agree with Dr Mark Ashworth that development of micro- and macrovascular outcomes such as CKD and foot complications are dependent upon and vary with individual clinic’s practice. However, in this analysis we were interested in using the presence of micro- and macrovascular complications as a proxy for disease severity, which can affect the study outcomes, i.e. glycaemic and lipid control in patients. We do acknowledge that quantifying clinic level differences in the occurrence of DM complications would be an interesting topic and will consider studying it in our further research.

5. Line 230: "For the regression analyses, eight continuous variables were centered on their grand mean". This struck me as an unusual approach for constructing regression models. I did not entirely understand it. needs further explanation.

Thank you for pointing this out. In our analysis, we were also interested in interpreting the regression intercept (or constant), which gives the expected mean value of the outcome (whether HbA1c, systolic blood pressure or LDL-C values) in the study population when all independent variables, X are equal to 0. For categorical variables, X=0 has a meaningful value, that is it refers
to female sex, non-Malay ethnicity, absence of hypertension, hyperlipidaemia, complications or not being prescribed with a medication. However, for continuous variables such as age and BMI the value of 0 is not meaningful and a BMI of zero simply does not exist within the study population. Hence, we centered the value of, for example of BMI on the grand mean of the study population (create a new centered variable by subtracting mean BMI from each person’s BMI). This gives a meaningful zero for the centered variable, where it now refers to the mean BMI of the sample.

We have added the following description and a reference to the approach of centering to the Methods section.

Line 246:
“For the regression analyses, we intended to interpret the intercept (or constant) for each of the models. The intercept gives the expected mean outcome values for HbA1c, SBP and LDL-C for the study sample when all predictors, X are equal to zero. For categorical variables, X=0 refers to reference category for each variable. However, zero is not a meaningful value for continuous variables such as age and BMI. Therefore, we centred all eight continuous predictors in the models on their respective means, such that the value of 0 for these centred variables now refer to grand mean of the study sample [26].”

6. Line 247: only 2960 out of 5425 patients were included in the study because of incomplete data. We need to know whether this might have led to selection bias. What are the characteristics of excluded patients? Maybe the lack of clinic variation in the study was in part due to the fact that only those with a strong record of clinic attendance (complete records) were included and perhaps key differences between clinics were not detected because some clinics were, for example, not welcoming/accessible, and the experience of these patients has not been included. The study design in this respect cannot be altered. But the potential limitations and consequences of those limitations need further elaboration in the Discussion.

We agree that potential bias can arise from excluding cases with missing data. The patients which were excluded mainly had missing data on the outcome of interest, where 1150 cases (21%) did not have HbA1c values while 1762 cases (32.5%) did not have LDL-C. Both HbA1c and LDL-C values were required for all models used in this study. Also, we did not perform multiple imputation on the missing outcome variables because the data did not contain additional auxiliary variable which could be useful to impute HbA1c or LDL-C values. Hence, we chose to exclude these cases and performed complete case analysis.

We have added information on missing data rates in the Methods and a statement on its limitation in the Discussion.

Methods, Line 239:
“Missing data rates ranged from 0.06% to 33%. Missing values were highest for the outcomes of interest; 1150 (21%) and 1762 (33%) of patients did not have data for HbA1c and LDL-C values respectively. The data did not contain additional auxiliary variables which could be used to multiply impute these missing outcomes, hence we conducted complete case analysis for all models.”

Discussion, Line 440:
“About 45% of the patients had missing information on the outcome of interest and had to be omitted from the analysis. Therefore, we could not exclude the possibility of bias arising from missing data and its correlation with individual clinic’s practice. Also, there were 5 main categories of public health clinics Malaysia (categorised based on average daily patient attendances) but only 3 clinic types were involved in the implementation of the EnPHC interventions. The categories which were not represented in this study were the smallest and largest clinic types and this may partially explain the lack of variation found between clinics.”

7. Line 272: at several points in the paper, the authors refer to 'average'. This needs to be more precisely described as 'mean'.
We have changed the term to ‘mean’ as suggested at lines 295, 300, 350, 377 and in Figures 1(a), 1(b) and 1(c).

8. Line 326: the paper refers at several points to 'national targets' for the 3 intermediate outcome measurements included in this study. These targets need to be compared to international targets so that we can assess whether these are 'high' or 'low' targets compared to international norms
We have included a statement on comparison with international norms, it now reads:
Discussion, Line 349:
“Moreover, there is still a clear gap between average performances and national therapeutic targets for HbA1c and LDL-C control. These therapeutic targets of less than or equal 7% and 2.6 mmol/L for HbA1c and LDL-C are also consistent to those recommended by the International Diabetes Federation [35].”

Kristina Secnik Boye (Reviewer 2):
This is a well written manuscript that clearly outlines the objectives and methods used to conduct the study.
Thank you. We appreciate your time and comments on the manuscript. Please find our responses listed below.

1. Given that this study was based on baseline data from a larger study called EnPHC-Eva, it would be good to have a bit more information regarding this study included in the methods section and whether any of research from this larger study has already been published. If any research has been published, please include the key reference in the manuscript.
We have added more information regarding this study in the Methods section.
Methods, Line 150:
“The EnPHC-Eva was a quasi-experimental evaluation study which aimed to determine the effectiveness of a multifaceted intervention package called EnPHC on process of care and intermediate clinical outcomes of patients with T2D and hypertension in 40 public health clinics in Malaysia. At the time of writing, the EnPHC-Eva has just completed post-intervention data collection and analysis. A study protocol for the EnPHC-Eva study is currently under journal review.”
2. Can the authors suggest what other variables/information would have been helpful to have been collected or available to help further explain the factors that could influence the outcomes? Yes, we have added them to the statement in Discussion, Line 366: “This is potentially due to other patient determinants such as medication adherence, socioeconomic status, health beliefs and patient self-care practice that were not captured in this study.”

3. Given readers' potential limited knowledge of typical health care in Malaysia, it would be good if the authors mention how patients’ costs could or could not impact the study results. We acknowledge Dr Kristina Secnik Boye’s comment with whether cost of care could have impacted the study results. This study population are patients with diabetes who were treated in public clinics and health services provided within the public setting are subsidised. Hence, we believe that it is unlikely for health care costs to be a barrier to clinical care in this setting. We have added the following statements to provide clarity on the cost of care in public clinics.

Methods, Line 159: “Malaysia has a dual-sector healthcare system; consisting of a public and private sector. The private sector is mainly funded by out-of-pocket payments and private insurance[15]. Health services in the public sector are heavily subsidised by general taxation and patients pay a small fee of between US$0.30 and US$ 4.50 for outpatient consultation, depending on citizenship status[15].”

Discussion, Line 430: “Whilst financial barrier is a known determinant for access to healthcare, it is unlikely to have an impact on this study’s results because treatment at public clinics comes at almost no cost to patients.”