PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Type 2 diabetes: a cohort study of treatment, ethnic and social group influences on glycated haemoglobin.
AUTHORS	Robson, John ; James, Gareth; Mathur, Rohini; Baker, Peter; Hull, Sally; Badrick, Ellena

VERSION 1 - REVIEW

REVIEWER	Denise Bonds National Heart Lung and Blood Institute National Institute of Health, USA (this review represents my opinion and not necessarily those of NHLBI, NIH or the US government) I have no competing interests
REVIEW RETURNED	20-Jun-2012

GENERAL COMMENTS	The authors have conducted a secondary analysis of the medical records of a large number of clinics in London. The study has several strengths including the large sample size, and the diversity of the patient population. Given these strengths, the study has the opportunity to provide insight into the treatment of diabetes in patients from a variety of ethnic/racial backgrounds. To fully realize this opportunity, thought, the authors should consider obtaining additional data and conducting additional analysis of the population. Further thought should also be given to the wording of various sentences in the paper. These are outlined below: Major: 1. The current measure of diabetes treatment is somewhat crude. For example, combined oral could be metformin and a sulfonylurea or could be a combination of 4 different oral agents. Similarly, the number of medication may have stayed the same with an increase in the dose (especially in the case of insulin). Within a 2 year time period, individuals within the combine oral could have significant changes in the number or dose of their medication. Similarly, those in the insulin could have significant changes in their dose. Given the access the authors have to the prescriptions, they should consider refinement of their measure to include a more sophisticated measure of intensification of therapy. This measure could also account for appropriateness of intensification. For example, if the patient is on metformin

and has an A1C meeting the definition of control, this is an appropriate "no change". If the A1C is still elevated and an additional medication is added, this is an appropriate intensification of care. This would be very important in light of their findings that one group of patients has consistently poorer control of their diabetes and would help elucidate whether this continued poor control is due to clinical inertia or a physiological difficulty in controlling the patient's diabetes. If data permits, time to intensification could also be examined by race/ethnic group.

2. The authors state they are unable to determine the length of time the patients in their study have had diabetes. However, the data used in this study was obtained from an EMR. Can the investigators retrieve information prior to 2007 from the EMR to determine length of diabetes diagnosis? Even relatively crude measures (diabetes >1 year, >5 years, >10 years) would help in the interpretation of the results of this study.

3. Further clarification is needed in the paragraph on line 30-40 on page of the results section. The authors provide an interpretation of their model coefficients for the reader. This is a helpful device for assisting clinically oriented reader understand the statistical models used. However, the authors should, 1) consider moving this explanatory paragraph to the discussion section of the paper, and 2) provide some additional explanation. The authors currently state that "…a patient on Metformin is 25 (1/0.04) times as likely to achieve HbA1c control that a patient on Insulin". This implies that metformin is a more effective drug than insulin when the reality is that there are a variety of other reasons that may account for this finding. For example, patients on metformin alone may be earlier in their disease process making it easier to obtain good control of their diabetes; insulin is generally saved for treating those patients with the most severe form of diabetes and the cases that are the most difficult to control.

4. The authors' use of a closed cohort as a strength is specious one. Per the first paragraph in the results section and their limitation paragraph in the discussion section, nearly one third of the patients in the practice with uncontrolled diabetes at baseline were not included in the final analysis. This should be removed.

Minor Clarifications needed:

1. Incident versus prevalent diabetes: Currently the authors state that the "sample was drawn from all people diagnosed with type 2 diabetes… in 2007" which implies incident diabetes. I believe that was the authors meant was that the sample was drawn from all individuals who carried a diagnosis of diabetes at the start of the observation period –

	prevalent diabetes.
	2. Clarify if the Towsend score is a standard part of the EMR or if it was calculated for this paper. Providing a frame of reference for the reader for each level of deprivation would assist reader unfamiliar with the Townsend score unfamiliar with interpreting the results (for example, individuals in the highest level of deprivation typically make less than XX a year, live in public housing and do not own a car).
	3. Please clarify if the insulin category includes individuals on insulin and oral agents.

REVIEWER	Neil Raymond Associate Professor of Epidemiology Warwick Medical School University of Warwick, UK No competing interests to declare.
REVIEW RETURNED	18-Jul-2012

THE STUDY	Research question No clear research question here, but study objectives (in Abstract). Sentence at the end of the Introduction leads into the study, but research question needs to be stated more clearly, making aim of the paper explicit. Cohort study design should be suitable for the planned analyses. Participants: Participants are defined in a confusing way - it's not clear whether these are meant to be all incident cases in 2007 "sample was drawn from all people diagnosed with type 2 diabetes in the 101 practices, aged 37 to 71 years in 2007,....etc." In the Results 1st paragraph: "over the three years of the study, a total of 28041 people in the study age range were diagnosed with type 2 diabetes and 17670 (63%) had an HbA1c recording in 2007" – this seems to suggest that this is an incident cases cohort? but all incident cases after 2007 excluded because no 2007 HbA1c recorded? i.e. 2007 incident cohort - needs clarification. Also, the authors suggest that this "closed" cohort offers advantages in bias reduction as patients are neither added nor removed (lines 55-57 p10 & 3-4, p11), which seems in conflict with an incident cohort. Study participants selected from this GP practice database should be representative sample, if clearly defined. Methods section needs clarification e.g. cohort recruitment. Choosing only those with HbA1c > 7.5 % inherently runs the risk of follow-up results being subject to the effects of regression to the mean; simply selecting a full range of patients with HbA1c recorded would allow a fair comparison of changes in HbA1c over time. It's not really clear how useful broad categorisation of diabetes treatments to reduce HbA1c may be. There are extensive guidelines for the treatment of diabetes and its complications, often requiring complex polypharmacy, plus health professional input from a number of healthcare professionals; reducing this to a simple 4 stage set of categories with transitions may be over simplistic. Main outcome measure was clear.

	Limitations
	Duration of diabetes was not available for analysis in this cohort and the authors acknowledge this as a problem, but if this was an incident cohort, with 2 years follow-up, then all patients have similar short disease duration.
	Description of statistical methods was far too brief. Complex multilevel models were used and there was very limited attempt to describe how these were to be constructed, e.g. use of random and fixed effects, etc. Interestingly, this complex modelling is referenced in one of the authors previous papers; the current reads like a paper designed to demonstrate the proposed 4 level multilevel modelling method.
	It's not entirely clear whether this 4 level modelling is the best approach here; e.g. one level was PCT, but only one PCT was included in the study and one level was year, when in fact measures were made on the same patients in different years and these changes were the main focus of analyses.
RESULTS & CONCLUSIONS	Results presented do answer the question posed.
	Very difficult to interpret results, which jump from a very basic descriptive Table 1 to complex results of 4 level modelling Tables 2a & b, with insufficient detail. Some more detailed presentation of unadjusted changes over time would help the reader, before moving to the more complex adjusted estimates. Clarification of presentation would help. In Table 1 it would be useful to see the proportions of participants achieving good control at baseline; thesis reported for years 1 & 2. The HbA1c changes in CfB are quite small (-0.4 to -0.8) over 1-2 years, but some of the OR in Table 2b, regarding treatment group are huge; further clarification of these would be useful.
	It's difficult to really get a handle on interpretation since there are a number of issues which need clarification. If these are incident newly diagnosed T2DM patients, then it's not clear how suitable this cohort might be for this purpose. Using primary care based diabetes care records is a sensible and efficient use of data. Designing studies to take advantage of data routinely collected to inform clinical care is a good strategy, requiring no further data collection. It is important that datasets used in this kind of cohort study are appropriate for purpose and one disadvantage may be failure to record potentially important variables.
	HbA1c is often considered to be influenced by duration of diabetes, with a gradual increase in HbA1c with increasing duration, although HbA1c measurements in individuals may be subject to substantial fluctuation.
	It's not quite clear whether newly diagnosed patients may have their first ever HbA1c recorded and used to classify them as uncontrolled diabetes (HbA1c >7.5%) - it is often useful to leave a period before recruiting to management studies. This may further compound the regression to the mean issue mentioned previously.
	The lack of recorded duration of diabetes in this cohort does raise questions as to its usefulness for analysis of diabetes related outcomes with time; duration is a known risk factor for multiple diabetes related outcomes - this is not an issue if the cohort are all incident 2007 new cases.
	Overall, whilst some clear differences are identified and reported it's not so clear how useful these are either in terms of the epidemiology of type 2 diabetes, or for disease management; much of the complexity of disease management may be lost in the broad treatment categories used.
	Much of the discussion is useful and set appropriately within a wider diabetes treatment context.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Denise Bonds
National Heart Lung and Blood Institute
National Institute of Health, USA

(this review represents my opinion and not necessarily those of NHLBI, NIH or the US government)

I have no competing interests

The authors have conducted a secondary analysis of the medical records of a large number of clinics in London. The study has several strengths including the large sample size, and the diversity of the patient population. Given these strengths, the study has the opportunity to provide insight into the treatment of diabetes in patients from a variety of ethnic/racial backgrounds. To fully realize this opportunity, thought, the authors should consider obtaining additional data and conducting additional analysis of the population. Further thought should also be given to the wording of various sentences in the paper. These are outlined below:

Major:

1. The current measure of diabetes treatment is somewhat crude. For example, combined oral could be metformin and a sulfonylurea or could be a combination of 4 different oral agents. Similarly, the number of medication may have stayed the same with an increase in the dose (especially in the case of insulin). Within a 2 year time period, individuals within the combine oral could have significant changes in the number or dose of their medication. Similarly, those in the insulin could have significant changes in their dose. Given the access the authors have to the prescriptions, they should consider refinement of their measure to include a more sophisticated measure of intensification of therapy. This measure could also account for appropriateness of intensification. For example, if the patient is on metformin and has an A1C meeting the definition of control, this is an appropriate "no change". If the A1C is still elevated and an additional medication is added, this is an appropriate intensification of care. This would be very important in light of their findings that one group of patients has consistently poorer control of their diabetes and would help elucidate whether this continued poor control is due to clinical inertia or a physiological difficulty in controlling the patient's diabetes. If data permits, time to intensification could also be examined by race/ethnic group.

RESPONSE
Unfortunately we are unable to analyse data on treatment intensification, although we agree this would be useful. Our dataset provides information on dose strength but not number of doses per day. For example, a 500mg Metformin prescription record has no information on dose per day so the patient may receive one 500mg tablet, or two (1000mg) or three (1500mg) per day. We cannot identify the number of tablets prescribed. The absence of this information makes the "appropriateness of intensification" and "time to intensification" unsuitable. We cannot tell if a patient with uncontrolled HbA1c on Metformin treatment is on maximum dose or not. If the patient is on maximum dose, their treatment should be intensified to include sulphonylurea, if not, their Metformin dose could be increased or their treatment could be intensified to also include Sulphonylurea.

We have provided more information patients in the 'Combined Oral' group and broken this down further by ethnic group (Table 3) as requested by the reviewer.
We agree our choice of treatment groups are broad and would ideally be more detailed (a point we make in discussion under weaknesses). However, they are satisfactory for the aim of this paper and

accord with the major divisions of progression of treatment intensity – metformin only, combined oral and insulin with any other medication. Further division of these categories would result in small numbers unsuitable for modelling.

2. The authors state they are unable to determine the length of time the patients in their study have had diabetes. However, the data used in this study was obtained from an EMR. Can the investigators retrieve information prior to 2007 from the EMR to determine length of diabetes diagnosis? Even relatively crude measures (diabetes >1 year, >5 years, >10 years) would help in the interpretation of the results of this study.

RESPONSE
We thank the reviewer for this suggestion which provides some additional useful information.
We have developed a diabetes duration measurement to categorise 0-2 years and 2+ years to explain some of the time-with-diabetes effect, re-run the models to adjusted for it and updated the tables. There was very little change to the model coefficients and the models interpretation and paper conclusions remain the same.

We are able to identify the year of diagnosis for patients diagnosed with diabetes from 2004 onwards, but not if they were diagnosed before 2004. Therefore we can reliably say a patient has diabetes for >2 years at baseline (2007) if they have a diabetes codes in 2004 or before, and 0-2 years at baseline if their first diabetes code was in 2005-2007. Further categorisation of diabetes duration i.e. >5, >10 years would be useful but unreliable as we would miss some patients out which may bias results.

3. Further clarification is needed in the paragraph on line 30-40 on page of the results section. The authors provide an interpretation of their model coefficients for the reader. This is a helpful device for assisting clinically oriented reader understand the statistical models used. However, the authors should, 1) consider moving this explanatory paragraph to the discussion section of the paper, and 2) provide some additional explanation. The authors currently state that "…a patient on Metformin is 25 (1/0.04) times as likely to achieve HbA1c control that a patient on Insulin". This implies that metformin is a more effective drug than insulin when the reality is that there are a variety of other reasons that may account for this finding. For example, patients on metformin alone may be earlier in their disease process making it easier to obtain good control of their diabetes; insulin is generally saved for treating those patients with the most severe form of diabetes and the cases that are the most difficult to control.

RESPONSE
We agree; this study is unable to compare the effectiveness of different diabetes treatments and will make this clear in the text. We have moved the interpretation to the discussion and included an explanation of this as requested.

4. The authors' use of a closed cohort as a strength is specious one. Per the first paragraph in the results section and their limitation paragraph in the discussion section, nearly one third of the patients in the practice with uncontrolled diabetes at baseline were not included in the final analysis. This should be removed.

RESPONSE

We have removed this statement

Minor Clarifications needed:

1. Incident versus prevalent diabetes: Currently the authors state that the "sample was drawn from all people diagnosed with type 2 diabetes… in 2007" which implies incident diabetes. I believe that was the authors meant was that the sample was drawn from all individuals who carried a diagnosis of diabetes at the start of the observation period – prevalent diabetes.

RESPONSE
Correct; we looked at prevalent diabetes cases and have reworded this sentence.

2. Clarify if the Towsend score is a standard part of the EMR or if it was calculated for this paper. Providing a frame of reference for the reader for each level of deprivation would assist reader unfamiliar with the Townsend score unfamiliar with interpreting the results (for example, individuals in the highest level of deprivation typically make less than XX a year, live in public housing and do not own a car).

RESPONSE

Townsend score is a standard aspect of the electronic medical record in the EMIS computer system We have clarified this in the text and expanded the explanation of the score.

3. Please clarify if the insulin category includes individuals on insulin and oral agents.

RESPONSE
Yes it does. We have clarified this in the text

Reviewer: Neil Raymond
Associate Professor of Epidemiology
Warwick Medical School
University of Warwick, UK

No competing interests to declare.

Research question
No clear research question here, but study objectives (in Abstract). Sentence at the end of the Introduction leads into the study, but research question needs to be stated more clearly, making aim of the paper explicit.

RESPONSE
We have reworded the aim to make it more explicit.

Participants:
Participants are defined in a confusing way - it's not clear whether these are meant to be all incident cases in 2007 "sample was drawn from all people diagnosed with type 2 diabetes in the 101 practices, aged 37 to 71 years in 2007,....etc."

RESPONSE
Correct; We looked at prevalent diabetes cases. We have reworded this sentence.

In the Results 1st paragraph: "over the three years of the study, a total of 28041 people in the study age range were diagnosed with type 2 diabetes and 17670 (63%) had an HbA1c recording in 2007" – this seems to suggest that this is an incident cases cohort? but all incident cases after 2007 excluded because no 2007 HbA1c recorded? i.e. 2007 incident cohort - needs clarification.

RESPONSE
Patients diagnosed with diabetes after 2007 were not included in this cohort. We have reworded this sentence accordingly.

Also, the authors suggest that this "closed" cohort offers advantages in bias reduction as patients are neither added nor removed (lines 55-57 p10 & 3-4, p11), which seems in conflict with an incident cohort.

RESPONSE
We have removed the sentence describing the closed cohort as a strength

Study participants selected from this GP practice database should be representative sample, if clearly defined.

RESPONSE
Yes this is an almost complete and thus highly representative sample of individuals with type 2 diabetes in a large contiguous urban area.

Methods section needs clarification e.g. cohort recruitment. Choosing only those with HbA1c > 7.5 % inherently runs the risk of follow-up results being subject to the effects of regression to the mean; simply selecting a full range of patients with HbA1c recorded would allow a fair comparison of changes in HbA1c over time.

RESPONSE
We did not include all patients with diabetes as the specific aim of this paper was to consider the impact of treatment in those individuals who did not attain standard targets for control of HbA1c. This is the group for whom general practitioners have the most concern and are likely to uptitrate treatment to reduce HbA1c still further, whereas there is no such management plan for those already attaining this goal and current treatment is simply maintained. By examining the group of patients with uncontrolled HbA1c we can explore whether HbA1c reduction and ability to achieve HbA1c control varies by ethnic & social group. This group also impacts on pay for performance schemes.

RESPONSE
We agree that in selecting a sample at higher than average HbA1c level for the study, that there will be regression to the mean. However, there was no substantive difference within our sample between baseline HbA1c levels of different ethnic groups and no reason to suppose that there is differential regression to the mean within our sample that would account for the failure of more complex treatments to reduce HbA1c in different ethnic groups.

It's not really clear how useful broad categorisation of diabetes treatments to reduce HbA1c may be. There are extensive guidelines for the treatment of diabetes and its complications, often requiring complex polypharmacy, plus health professional input from a number of healthcare professionals;

reducing this to a simple 4 stage set of categories with transitions may be over simplistic.

RESPONSE
We agree that categorisation into 4 treatment groups is a simplification. However, it does broadly represent the sequence of treatment progression and complexity. Further division of the analysis runs the risk of fragmentation into a much larger number of subdivisions without any clear reason why they have been created as many individuals are in several drug classes. This would run the risk of arbitrary divisions, small numbers and complexity in interpreting results across multiple subgroups. We have included an additional table to break down the 'Combined Oral' treatment further.

Main outcome measure was clear.

Limitations

Duration of diabetes was not available for analysis in this cohort and the authors acknowledge this as a problem, but if this was an incident cohort, with 2 years follow-up, then all patients have similar short disease duration.

RESPONSE
We have rerun the models to include a duration of diabetes variable with categories 0-2 years and >2 years. See comment to previous reviewer.

Description of statistical methods was far too brief. Complex multilevel models were used and there was very limited attempt to describe how these were to be constructed, e.g. use of random and fixed effects, etc. Interestingly, this complex modelling is referenced in one of the authors previous papers; the current reads like a paper designed to demonstrate the proposed 4 level multilevel modelling method.

RESPONSE
We have clarified these points. We agree that we were not intending to demonstrate 4 level modelling per se and have replaced this reference with a more general multi-level model reference. Greater explanation of the multilevel model would be useful and we have explained which variables are random effects.

It's not entirely clear whether this 4 level modelling is the best approach here; e.g. one level was PCT, but only one PCT was included in the study and one level was year, when in fact measures were made on the same patients in different years and these changes were the main focus of analyses.

RESPONSE
There were in fact 2 PCTs (Tower Hamlets and Newham). As the data is structured at four levels (year, patient, practice, PCT) a multilevel model with 4 levels for analysis to account for the variation in the outcomes explained by the structure seems appropriate. Hypothesis testing indicated that PCT had a significant effect on the outcomes (P7, L20) so we wanted to account for PCT in order to reduce bias in our estimates of interest. If PCT was not significant we would have no need to adjust for it so we would have simplified the model to a 3 level multilevel model.

Results presented do answer the question posed.

Very difficult to interpret results, which jump from a very basic descriptive Table 1 to complex results of 4 level modelling Tables 2a & b, with insufficient detail. Some more detailed presentation of unadjusted changes over time would help the reader, before moving to the more complex adjusted estimates. Clarification of presentation would help. In Table 1 it would be useful to see the proportions of participants achieving good control at baseline; thesis reported for years 1 & 2. The HbA1c changes in CfB are quite small (-0.4 to -0.8) over 1-2 years, but some of the OR in Table 2b, regarding treatment group are huge; further clarification of these would be useful.

It's difficult to really get a handle on interpretation since there are a number of issues which need clarification. If these are incident newly diagnosed T2DM patients, then it's not clear how suitable this cohort might be for this purpose. Using primary care based diabetes care records is a sensible and efficient use of data. Designing studies to take advantage of data routinely collected to inform clinical care is a good strategy, requiring no further data collection. It is important that datasets used in this kind of cohort study are appropriate for purpose and one disadvantage may be failure to record potentially important variables.

RESPONSE
We agree and have provided some extra presentation of changes over time to include a table of CFB HbA1c and HbA1c control for each categorical variable (Table 1B). Please note Figure 1 is provided to support the reader's understanding of these complicated models. In terms, of clarification of the treatment effect, we already explained the interpretation of the coefficients in the results (now conclusions). Insulin coefficient is 1.11, so Metformin will have 1.11 greater reduction then Insulin. We hope Table 1B makes this clearer.

HbA1c is often considered to be influenced by duration of diabetes, with a gradual increase in HbA1c with increasing duration, although HbA1c measurements in individuals may be subject to substantial fluctuation.

It's not quite clear whether newly diagnosed patients may have their first ever HbA1c recorded and used to classify them as uncontrolled diabetes (HbA1c >7.5%) - it is often useful to leave a period before recruiting to management studies. This may further compound the regression to the mean issue mentioned previously.

RESPONSE
Now that we have adjusted for diabetes duration (0-2 and 3+ years) this is unlikely to be an issue. We have commented previously on regression to the mean.

The lack of recorded duration of diabetes in this cohort does raise questions as to its usefulness for analysis of diabetes related outcomes with time; duration is a known risk factor for multiple diabetes related outcomes - this is not an issue if the cohort are all incident 2007 new cases.

RESPONSE
We have captured an important element of early and later duration by including age, treatment and diabetes duration (0-2 years and 3+ years) in the models.

Overall, whilst some clear differences are identified and reported it's not so clear how useful these are either in terms of the epidemiology of type 2 diabetes, or for disease management; much of the complexity of disease management may be lost in the broad treatment categories used.
Much of the discussion is useful and set appropriately within a wider diabetes treatment context.

RESPONSE

The results suggest that south Asians have less benefit from diabetes treatment than the white population, whether they have just been diagnosed with the disease (0-2 years) or had it for a longer period (3+ years). This means south Asian patients may require more intense monitoring and treatment then other ethnic groups. These ethnic differences remained after adjustment for social deprivation so the reduced benefit from treatment that south Asians receive is not fully explained their current social circumstance. Practices serving communities with large south Asian populations may be disadvantaged in achieving target levels set in the UK Quality and Outcomes Framework which impacts on pay for performance.

VERSION 2 – REVIEW

REVIEWER	Denise Bonds, Medical Officer NHLBI, NIH USA I have no competing interests The views expressed here represent my own and not the National Heart Lung and Blood Institute, National Institutes of Health, or the US government.
REVIEW RETURNED	29-Aug-2012

GENERAL COMMENTS	The authors have addressed my concerns

REVIEWER	Mr Neil Raymond Associate Professor of Epidemiology Warwick Medical School University of Warwick, UK I confirm that I have no competing interests to declare.
REVIEW RETURNED	06-Sep-2012

THE STUDY	Issues raised in previous comments have been addressed adequately.