PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The cost of hospital treatment of Type 1 diabetes (T1DM) and Type 2 diabetes (T2DM) compared to the non-diabetes population: a detailed economic evaluation
AUTHORS	Stedman, Mike; Lunt, Mark; Davies, Mark; Livingston, Mark; Duff, Christopher; Fryer, Anthony; Anderson, Simon; Gadsby, Roger; Gibson, Martin; Rayman, Gerry; Heald, Adrian

VERSION 1 – REVIEW

REVIEWER	Henk Bilo Department of Internal Medicine, University Medical Center Groningen, the Netherlands
REVIEW RETURNED	28-Aug-2019

GENERAL COMMENTS	The authors of this manuscript have used available data to assess the financial impact of being known with the diagnosis T1DM or T2DM on costs of hospital treatment. The data used are derived from reliable countrywide databases, thus allowing a high degree of reliability. The main conclusions are that in subjects known with diabetes there are higher hospital treatment costs compared to subjects not known with diabetes. This manuscript adds to this known information by adding detailing. Although a large part of the conclusions is supported by the results, there are still some points which need to be addressed: - why have data been corrected for age in T2DM only? why are only GP practices included with more than 200 T2DM of 20 T1DM patients? When analyzing data on hospital costs, the arguments for this restriction are not there in my opinion. Suggesting that lower amount of patients known with diabetes could possibly be caused by not identifying subjects with diabetes because of low detection rates (or efforts) would by unwise, since first of all, no total practice size is described (which would allow for more insight), and second (and also addressed by the authors), many factors are known to influence especially T2DM prevalence, also throughout the UK. - overcorrecting (page 7) prevalence data partly because of the presumption of under- (or for that sake over-) reporting looks to me like a unnecessary step. hospital data are the available data, theoretical adjustment of GP practice associated prevalence data will not further enhance the outcomes in the presented manuscript. I am very much curious whether I am wrong in my presumptions with regards to this and look forward to be convinced. - on page 9, lines 279-281 the authors describe hypertension, CAD, and age as "predictors" of T2DM prevalence. Although of course I acknowledge the very well known associations, it would

	look to me that this is an assocation more than a predictor, but I am looking forward to the arguments for this choice. - in the discussion, the authors suggest some possible directions for changing management and treatment of subjects with diabetes in order to diminish the large difference in hospital related costs, and in their conclusion they allocate more than half of the words to supposed impact of these possibly beneficial interventions (and spend the whole discussion section of their abstract on this). Although I appreciate the need for intervention strategies and the enthusiasm of the authors for possible interventions, it should be nevertheless concluded, that this was in no way part of the presented research. I would suggest to concentrate on the facts found when reporting their findings both in the abstract and the conclusion.

REVIEWER	Marcelo Goulart Correia Instituto Nacional de Cardiologia - Brazil
REVIEW RETURNED	09-Sep-2019

GENERAL COMMENTS	1 - It is important to briefly introduce the reasons why your research is being developed. Looking at your abstract, I missed an introductory section briefly detailing your research. 2 - It is common that cost variables are not symmetrical. I found no explanation or diagnostic tests showing that your data does not violate assumptions for use linear regression.

REVIEWER	Sandro Gentile Campania University “Luigi Vanvitelli”, Naples, Italy
REVIEW RETURNED	11-Oct-2019

GENERAL COMMENTS	The paper deals with a very important topic, analyzing the costs in detail with a correct methodology. The results are very interesting and well described. The conclusions are useful and propose a model to reduce costs.

REVIEWER	Artitaya Lophatananon University of Manchester , Division of Population Health, Health Services Research and Primary Care
REVIEW RETURNED	07-Nov-2019

GENERAL COMMENTS	I have been asked to review statistical section. My comments are as follows; 1. row 183- ge profile? i am not sure what ge stand for? 2- row 190-194- can authors put the formula to compute the cost as this will make it clearer to the readers. 3. In the statistical section-Authors should list the dependent variable (outcome), statistical package use. 4. in the methodology section, there are two periods mention including 2016-1017 and 2017-2018, however later on all the results only relate to 2017-2018, please explain why only one period was included in your analysis. 5. table 1 , please define source of reference cost. 6. figures use black colour as background making it very hard to see and read the figures. Overall comment, this is a very interesting paper which can produce an impact on how the NHS can modify diabetes management. I feel the paper can be improved and reach the

	wider audiences for example, there are two parts in the article, one is about the summation of the cost and comparison between various sources, two is about the prediction by using the various variables to adjust for the true effect on cost. The authors can make it clearer so the readers can follow the flow of the article better. The statistical use is appropriate but visual presentation of results can be improved.

REVIEWER	Brian Potter Centre Hospitalier de L\'Universite de Montreal, Cardiology
REVIEW RETURNED	17-Nov-2019

GENERAL COMMENTS	This study sought to determine the average health care expenditure (hospital-based) associated with diabetes (type 1 and 2) compared to the non-diabetic population using administrative databases. My comments will be mostly limited to a discussion of the methodology. General comments: 1) Line 183; there is suspected typo: “ge profile” shoulde be “age profile”. 2) There are also a few other passages that are grammatically awkward due to the lack of a definite article or conjunction. A close review is recommended prior to publication. 3) The graphics need to be reviewed for quality of presentation. The colour choices make them exceedingly difficult to read. 4) Other than a cursory statement of the “weaknesses” of the paper after the summary, the authors neglect any formal discussions of the limitations of the analysis. This is inappropriate. Specific comments: 1) The method for calculation the total overall hospital cost is unclear to me. “The total overall hospital costs for each practice in each of the three classes (T1DM, T2DM, and non-diabetes) were calculated by adding the provided total elective & non-elective tariff charges to the Outpatient and Accident & Emergency attendances each multiplied by the national overall average cost / attendance taken from the 2017-18 national reference costs.” Why was this method employed? What is the precedent for it? What is the rationale? Based on this passage I understand that the total hospital cost for each patient group would be calculated as follows: (Total Inpatient Cost * National Avg Cost)/Attendance + (Total Outpatient cost * Naitonal Avg cost)/Attendance= National Avg Cost*Total Costs/Attendance Such that the total cost estimate will be inflated by a factor of the national average cost (?) I am sure that there is something in the methodology that remains unclear to me. The authors must clarify and support their methodological choices.

	2) The authors calculated a rate of T2D identification for each jurisdiction. This is, on the surface, interesting because T2DM may go undiagnosed for some time though it is manifest and exerting an influence on patient outcomes. However, it is never detailed how the authors might use this to adjust their results. Moreover, the implication is that patients with undiagnosed (uncoded) T2DM are contributing to the costs of the presumed non-diabetic population. This does not appear to be adjusted for or discussed at any point. 3) The authors state that “the T2DM % on patients over 75 was adjusted to the level of the non-diabetes population” without detailing how this was done. This is essentially the only adjustement that was done on clinical grounds and requires further elaboration in order to make a judgement as to whether it was done correctly. 4) Patients with T2DM typically have many comorbid conditions, none of which (other than age) are taken into account in the analysis. The authors therefore have not provided an estimate of the independent cost of diabetes in the UK system. While they do not directly claim to have done this, the use of terms such as “net cost” of diabetes and the way in which the cost of diabetes is discussed is somewhat disingenuous. The authors would do well to (a) redo the analysis, adjusting for important co-morbid conditions or (b) revisit the language of the document to make it plain that this is the cost associated with diabetes. Alternatively, an analysis limited to diabetes admissions could be of interest.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Henk Bilo

Institution and Country: Department of Internal Medicine, University Medical Center Groningen, the Netherlands Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below The authors of this manuscript have used available data to assess the financial impact of being known with the diagnosis T1DM or T2DM on costs of hospital treatment.

The data used are derived from reliable countrywide databases, thus allowing a high degree of reliability. The main conclusions are that in subjects known with diabetes there are higher hospital treatment costs compared to subjects not known with diabetes. This manuscript adds to this known information by adding detailing.

Thank you for your helpful review.

Although a large part of the conclusions is supported by the results, there are still some points which need to be addressed:

- why have data been corrected for age in T2DM only?

MS Response: Hospital activity has a strong older age bias. As T2DM occurs at an older age, T2DM patients may be over-represented in hospital just because of their age profile. Most T1DM incidence occurs at <30 so we show in Fig 2A that there is not a great difference between the age profile of T1DM and the non-DM population. We feel that T1DM hospital costs do not need to be adjusted for age.

why are only GP practices included with more than 200 T2DM of 20 T1DM patients? When analyzing data on hospital costs, the arguments for this restriction are not there in my opinion. Suggesting that lower amount of patients known with diabetes could possibly be caused by not identifying subjects with diabetes because of low detection rates (or efforts) would by unwise, since first of all, no total practice size is described (which would allow for more insight), and second (and also addressed by the authors), many factors are known to influence especially T2DM prevalence, also throughout the UK.

Response: Practice size was included as a variable within the analysis. However, this was not significant in most cases. In our experience in this type of analysis including smallest practices which tend to fall at both extremes of any indicator value decreases the R2 and reliability of the results.

Identification is important for T2DM as there may be no clear clinical start point - so both patients must present and clinical staff re diabetes/pre-diabetes must then appropriately classify. Hospital activity is evaluated / total population ie the sum of both attending and non-attending hospital patients are used as the denominator for this, and so a calculated estimate of the local levels of T2DM identification is an important factor within the statistical model.

- overcorrecting (page 7) prevalence data partly because of the presumption of under- (or for that sake over-) reporting looks to me like an unnecessary step. hospital data are the available data, theoretical adjustment of GP practice associated prevalence data will not further enhance the outcomes in the presented manuscript. I am very much curious whether I am wrong in my presumptions with regards to this and look forward to be convinced.

Response: See above the under/over-reporting of diabetes changes the base population and so average rate of hospital activity use/head of population is dependent on local levels of identification. This is confirmed by the fact that % case identification does appear in the regression analysis as a significant independent variable.

- on page 9, lines 279-281 the authors describe hypertension, CAD, and age as "predictors" of T2DM prevalence. Although of course I acknowledge the very well known associations, it would look to me that this is an association more than a predictor, but I am looking forward to the arguments for this choice.

Response: We agree and have changed “predictor” to “association” in the document.

You allude to what actually may predict the risk of T2DM developing in any individual. While insulin resistance, hypertension and macrovascular disease may all act as predictors of T2DM risk, we are not able with the data set and analysis done here to address this matter.

- in the discussion, the authors suggest some possible directions for changing management and treatment of subjects with diabetes in order to diminish the large difference in hospital related costs, and in their conclusion they allocate more than half of the words to supposed impact of these possibly beneficial interventions (and spend the whole discussion section of their abstract on this). Although I appreciate the need for intervention strategies and the enthusiasm of the authors for possible interventions, it should be nevertheless concluded, that this was in no way part of the presented research. I would suggest to concentrate on the facts found when reporting their findings both in the abstract and the conclusion.

Response

We feel that the findings need to be put in the context of our previous work. We have toned down the inferences in the abstract and the discussion and shorted some sections.

Reviewer: 2

Reviewer Name: Marcelo Goulart Correia

Institution and Country: Instituto Nacional de Cardiologia - Brazil Please state any competing interests or state 'None declared': None declared

Thank you for your review.

Please leave your comments for the authors below

1 - It is important to briefly introduce the reasons why your research is being developed. Looking at your abstract, I missed an introductory section briefly detailing your research.

Response: Our objective/aim was to quantify more exactly the additional overall impact of diabetes on different hospital services - we have now made that clearer in both abstract and discussion sections.

2 - It is common that cost variables are not symmetrical. I found no explanation or diagnostic tests showing that your data does not violate assumptions for use linear regression.

Response: The variation under consideration is the average consolidated cost across different cohorts (T1DM/T2DM/ non-DM patients & practices). These fall relatively symmetrically. Overall hospital costs / various practice populations were normal distributed with skew and kurtosis factors for non-DM = 0.06 & 1.7; T2DM = 0.8 & 2.2 and T1DM= 1.6 & 2.7, mostly within the +/- 2 acceptable range

Reviewer: 3

Reviewer Name: Sandro Gentile

Institution and Country: Campania University "Luigi Vanvitelli", Naples, Italy Please state any competing interests or state 'None declared': None declared'

Please leave your comments for the authors below The paper deals with a very important topic, analyzing the costs in detail with a correct methodology. The results are very interesting and well described. The conclusions are useful and propose a model to reduce costs.

Response: Thank you for this positive review

Reviewer: 4

Reviewer Name: Artitaya Lophatananon

Institution and Country:

Division of Population Health, Health Services Research and Primary Care School of Health Sciences Faculty of Biology, Medicine and Health The University of Manchester

UK

Please state any competing interests or state 'None declared': I am working at the same institute as three co-authors, however, I did not know or have been working with any person listed in the article.

Thank you for your helpful comments

Please leave your comments for the authors below I have been asked to review the statistical section. My comments are as follows; 1. row 183- ge profile? I am not sure what ge stand for?

Response: Thank you "ge" should read "age" this has been changed

2- row 190-194- can authors put the formula to compute the cost as this will make it clearer to the readers.

Response: We have included a more formula based description. This has been added to the Methods Section.

3. In the statistical section-Authors should list the dependent variable (outcome), statistical package use.

Response: We have made clear the outcome is average hospital costs/total local population. We have also added the stats package we used.

4. in the methodology section, there are two periods mention including 2016-1017 and 2017-2018, however, later on, all the results only relate to 2017-2018, please explain why only one period was included in your analysis.

Response: We used the 2 years of data to identify those patients in hospital with a diagnosis of diabetes, we then used activity in the latest year associated with those patients to calculate total annual activities. We have now made that clearer in the analysis.

5. table 1, please define the source of reference cost.

Response: The reference costs are the annual published NHS Improvement of total annual activity figures and we should have referenced this source and this has now been done

6. figures use black colour as the background making it very hard to see and read the figures.

Response: This is an artefact of BMJOpen Pdf creation. We have changed/updated our figures in the resubmission

Overall comment, this is a very interesting paper which can produce an impact on how the NHS can modify diabetes management. I feel the paper can be improved and reach the wider audiences, for example, there are two parts in the article, one is about the summation of the cost and comparison between various sources, two is about the prediction by using the various variables to adjust for the true effect on cost. The authors can make it clearer so the readers can follow the flow of the article better. The statistical use is the appropriate but visual presentation of results can be improved.

Response: Thank you for your comments we have tried to take into account your feedback

Reviewer: 5

Reviewer Name: Brian Potter

Institution and Country:

Centre hospitalier de l'Université de Montréal, Montreal, Canada Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below This study sought to determine the average health care expenditure (hospital-based) associated with diabetes (type 1 and 2) compared to the non-

diabetic population using administrative databases. My comments will be mostly limited to a discussion of the methodology.

Thank you for your detailed review

General comments:

1) Line 183; there is suspected typo: “ge profile” should be “age profile”.

Response: should read age - it has been changed

2) There are also a few other passages that are grammatically awkward due to the lack of a definite article or conjunction. A close review is recommended prior to publication.

Response: Thanks for this we have had another detailed read through and clarified structure and added a number of articles/conjunction

3) The graphics need to be reviewed for quality of presentation. The colour choices make them exceedingly difficult to read.

Response: This is an artefact of the PDF engine we will try to make sure clearer charts are loaded

4) Other than a cursory statement of the “weaknesses” of the paper after the summary, the authors neglect any formal discussions of the limitations of the analysis. This is inappropriate.

Response: We have added a paragraph on the weakness of this approach. However, there seems to be no other approach that has come close to delivering this in terms of national-level data. Specifically, we have said in the Analysis Section:

As diabetes can have many wide-ranging health impacts establishing the overall additional all-cause hospital costs of diabetes on top of expected normal healthcare needs is difficult. Using a practice population-based approach allows us to allow at the population level to allow for confounding factors such as age and disease identification. However, it remains a statistical analysis relying on large amounts of data entered during clinical treatments so will contain normal administrative errors. Nevertheless, it is hoped that both the scale of this data capturing over 160 million episodes and as these errors can be either over or under-reported that the outcomes should correspond to the actual values.

Specific comments:

1) The method for calculating the total overall hospital cost is unclear to me.

“The total overall hospital costs for each practice in each of the three classes (T1DM, T2DM, and non-diabetes) were calculated by adding the provided total elective & non-elective tariff charges to the Outpatient and Accident & Emergency attendances each multiplied by the national overall average cost/attendance taken from the 2017-18 national reference costs.”

Why was this method employed? What is the precedent for it? What is the rationale? Based on this passage I understand that the total hospital cost for each patient group would be calculated as follows:

(Total Inpatient Cost * National Avg Cost)/Attendance + (Total Outpatient cost * National Avg cost)/Attendance=

National Avg Cost*Total Costs/Attendance

Such that the total cost estimate will be inflated by a factor of the national average cost (?) I am sure that there is something in the methodology that remains unclear to me. The authors must clarify and support their methodological choices.

Response: We have not double-count costs as suggested. We added together activities where costs total were provided (elective and emergency admissions) and where only activity was given (outpatients and A&E) we multiplied those by the average costs/activity. In order to ensure that our methodology is explained clearly, we have now adjusted the related paragraph to be more formulaic "For each of the T1DM, T2DM and Non-diabetes population: Total Hospital Costs = Total Recorded Elective Tariff Charges + Total Recorded Non-Elective Tariff Charges+ Total Outpatient Recorded Attendances x Average annual Outpatient tariff cost/attendance + Total Accident & Emergency recorded attendances x average cost/attendance (both taken from the 2017-18 national reference costs)".

2) The authors calculated a rate of T2D identification for each jurisdiction. This is, on the surface, interesting because T2DM may go undiagnosed for some time though it is manifest and exerting an influence on patient outcomes. However, it is never detailed how the authors might use this to adjust their results. Moreover, the implication is that patients with undiagnosed (uncoded) T2DM are contributing to the costs of the presumed non-diabetic population. This does not appear to be adjusted for or discussed at any point.

Response: This is one of the key points of this approach. We have:

a) **In the hospital data captured activity for all those patients whose hospital record as having diagnosis diabetes at any visit during the previous 2 years**
b) **In the practice data captured local total local populations having records of diabetes diagnosis**
c) **In the latter, there will be an identification gap as practices will over or under diagnose compared to average. This gap will make those practices costs/head relatively higher or lower and so we make it clear that some of these costs may be due to over/under diagnosis**
d) **Also by calculating and bringing this identification gap into the age impact calculation, we remove this potential confounder from age impact**

As this was not clear to this critical reviewer we have added this to our Discussion.

3) The authors state that "the T2DM % on patients over 75 was adjusted to the level of the non-diabetes population" without detailing how this was done. This is essentially the only adjustment that was done on clinical grounds and requires further elaboration in order to make a judgement as to whether it was done correctly.

Response: We have now made it clear that we have in the multiple regression allowed for other possible local confounding factors, so we hope that the age effect >75 is clearer. We then used the calculated regression coefficient for population age>75 applied to the difference between %>75 in non-DM and T2DM value to carry out this adjustment. Specifically, we have said:

To remove the effect of the age difference between T2DM and non-diabetes population on the cost impact of diabetes, the regression coefficient was applied to the difference between % on patients over 75 in T2DM and the non-diabetes population, to give a "net" T2DM disease impact on each of the activities and cost levels including:

- **Overall Costs**

- **Emergency Admissions, Bed days & Tariff**
- **Elective Admissions, Day case, Bed days & Tariff**
- **A&E Attendances**
- **Outpatient Attendances**

4) Patients with T2DM typically have many comorbid conditions, none of which (other than age) are taken into account in the analysis. The authors, therefore, have not provided an estimate of the independent cost of diabetes in the UK system. While they do not directly claim to have done this, the use of terms such as “net cost” of diabetes and the way in which the cost of diabetes is discussed is somewhat disingenuous. The authors would do well to (a) redo the analysis, adjusting for important co-morbid conditions or (b) revisit the language of the document to make it plain that this is the cost associated with diabetes. Alternatively, an analysis limited to diabetes admissions could be of interest.

Response: We have tried to make it clear that we are looking at the all causes additional costs of diabetes on top of the normal non-diabetes patient hospital costs. Some of which are directly related (renal, CV etc), others being more tangential (infection, frailty, etc) but we cannot separate these. By looking at the overall hospital costs and then uprating the Non-DM costs/population for the age of T2DM we are capturing the underlying overall all-cause difference in costs between T1DM / T2DM and Non-D populations (allowing for age). As we do not have more details of specific activities within hospital classes in our data we cannot split these further. We have adjusted the language of the paper accordingly.

VERSION 2 – REVIEW

REVIEWER	Henk Bilo Department of Internal Medicine, University Medical Center Groningen, the Netherlands
REVIEW RETURNED	17-Feb-2020

GENERAL COMMENTS	The authors have improved the manuscript, and the results are very much worth publishing. Still, I want to point out again, that they did a very thorough job of answering the primary research question, but that in my opinion theey did NOT study opportunities to reduce future additional costs. The conclusion to be drawn is, that people with diabetes do cost considerably more within healthcare. After formulating that conclusion, the authors can of course give their thoughts how to break trends in costs; such thoughts are important, but cannot be considered to be the conclusion based on the study results. Except for this (in my opinion rather important) detail, this manuscript deserves publication since it contains important information

VERSION 2 – AUTHOR RESPONSE

We have amended the end of the discussion accordingly. We now state:

While not a conclusion that we can draw directly from our analysis, it is possible that improved management of T1DM and T2DM in primary care in terms particularly of measures to prevent the longer-term development of complications, may reduce the level of hospital activity and hospital costs.

The role of the secondary care specialist team in supporting primary care and ensuring that most people with diabetes are being well managed, not just focussing on the smaller in number hardest to treat group will be a key factor in improving primary care management outcomes will be critical in this endeavour.

We have also changed the Conclusion of the Abstract to say:

This analysis shows that additional costs of provision of hospital services due to their diabetes comorbidities is £3 billion above those for non-diabetes and that within this T1DM have three time as much cost impact as T2DM. We suggest that supporting

VERSION 3 – REVIEW

REVIEWER	Henk Bilo Department of Internal Medicine, University Medical Center Groningen, the Netherlands
REVIEW RETURNED	11-Mar-2020

GENERAL COMMENTS	I appreciate the changes the authors made. While the texts in the conclusion of the abstract and in the conclusion are now reflecting the difference between the facts found and the possible suggestions for improvement, it would be advisable to also change the last bullet point of the key message: • There are still opportunities to reduce potential future additional costs further through increased investment in local services and medication for diabetes treatment. To all intents and purposes, this study deserves publication.