PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the Potential Return on Investment of the Proposed UK NHS Diabetes Prevention Programme in Different Population Subgroups: An Economic Evaluation
AUTHORS	Thomas, Chloe; Sadler, Susannah; Breeze, Penny; Squires, Hazel; Gillett, Michael; Brennan, Alan

VERSION 1 - REVIEW

REVIEWER	Andrew Palmer Menzies Institute for Medical Research, University of Tasmania, Australia.
REVIEW RETURNED	21-Nov-2016

GENERAL COMMENTS	I have seen some earlier papers about this model (submitted to other journals) and really like it - thoroughly documented and transparent and certainly a worthy model, but the current analysis is just too early relative to the availability of evidence supporting the proposed intervention. The problem with the current analysis is that it is not based on any concrete clinical data from the intervention, as this intervention does not yet exist and no evidence of its effectiveness or safety has been generated. The authors use data from systematic review(s) and make a huge and unjustified assumption that this will equally apply. They assume a 1 year hypothetical intervention will have 20 year beneficial effects. There are no assumptions about negative effects. Costs of the "intervention" are not documented at all. This analysis might be justified in a few years time when some evidence about its impact exists.

REVIEWER	Neal R. Barshes, MD, MPH Baylor College of Medicine United States of America
REVIEW RETURNED	03-Apr-2017

GENERAL COMMENTS	Page 9, lines 30 to 47: what outcomes or diabetes related complications were modeled? Page 9, line 45: the author should specify the currency used in this analysis (English pounds). Additionally, the authors should specify whether the costs were in 2014 or 2015 pounds (not “2014/2015”). Page 10, line 20: first, the word "fulfill" is misspelled. Also, it is not clear whether the authors intend to have guidelines number nine through number 12 implemented or whether the authors mean at least nine of the total guidelines implemented.

	Page 10, line 38 to page 11: The structure of this model and the sensitivity analyses are outstanding. It seems as though the authors have thought through all the details required to make the model a realistic representation of the actual implementation of a prevention efforts. Page 12, line 26: can the authors make any general comments about the parameter used for various groups of variables? For example were gamma distribution is used for (most) cost variables? Page 12, line 48: it is not clear to me what the difference between cost savings within the first year of implementation and recouping intervention costs would be. In other words, how could the program save money if intervention costs had not yet been recouped? Please clarify. Page 13, lines 41 to 57: since the variable BMI had a big impact on cost, it would be worthwhile performing additional sensitivity analyses that focus on this variable. In particular, I would be interested to know whether the return on investment in the high BMI groups was mitigated by advanced age. Similarly, I would favor replacing figure 3 with a graph that shows The interaction between BMI and age on total costs. Page 17, discussion section: The discussion section is an appropriate links. The discussion of the results is very good. The only other point not discussed that would deserve clarification is why there was lower return on investment in the younger patients (those less than 40 years of age).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Andrew Palmer
Institution and Country: Menzies Institute for Medical Research, University of Tasmania, Australia.
Please state any competing interests: None declared

Please leave your comments for the authors below

I have seen some earlier papers about this model (submitted to other journals) and really like it - thoroughly documented and transparent and certainly a worthy model, but the current analysis is just too early relative to the availability of evidence supporting the proposed intervention.

The problem with the current analysis is that it is not based on any concrete clinical data from the intervention, as this intervention does not yet exist and no evidence of its effectiveness or safety has been generated. The authors use data from systematic review(s) and make a huge and unjustified assumption that this will equally apply. They assume a 1 year hypothetical intervention will have 20 year beneficial effects. There are no assumptions about negative effects. Costs of the "intervention" are not documented at all. This analysis might be justified in a few years time when some evidence about its impact exists.

We thank reviewer 1 for his positive comments about our model and his insightful review which has been helpful to revise the manuscript.

We disagree with his stance that it is not worthwhile analysing a proposed intervention before evidence comes available about the effectiveness of the intervention. On the contrary, our position is that it is essential with such a large-scale and expensive national programme that a cost-effectiveness analysis is carried out, based on the best available current evidence from trials of similar interventions, in order to enable the NHS to: firstly, decide whether it is worth carrying out a Diabetes Prevention Programme at all; secondly, to determine what the expected return on investment might be over the next few years to enable effective budgeting; and thirdly, as stated in the discussion, to determine which subgroups might benefit the most given that the number of proposed available interventions (100,000 per year when fully rolled out) is much lower than the number of high risk individuals who could benefit (5 million according to a recent study from the National Cardiovascular Intelligence Network). Not only is this our position, it is also the position of the key government agencies involved in the decision making and investment around the NHS DPP i.e. NHS England and Public Health England, both of which have commissioned us to use our model to answer these and related questions. We have added the following sentence to the beginning of the discussion to reiterate the importance of the analysis:

'It is essential with large-scale and expensive national programmes such as the NHS DPP that a cost-effectiveness analysis using the best currently available data is carried out prior to implementation: firstly, to determine whether the intervention should be carried out at all; secondly, to enable effective budgeting; and thirdly, where interventions are limited, to estimate who is likely to benefit most and therefore should be prioritised.'

We agree with reviewer 1 that the analysis is not based on clinical data from the Diabetes Prevention Programme itself (because post implementation data does not yet exist). This is a fact of life in any prospective analysis of potential return on investment if the intervention has not yet been implemented at scale. The analysis is based upon data about similar intensive lifestyle interventions incorporating diet, physical activity and weight loss components, albeit under trial conditions. Whilst such effectiveness data may be more optimistic than is possible in a real world situation (despite the aim of the systematic review to incorporate only pragmatic trials of diabetes prevention interventions), using data from clinical trials in economic evaluation is a standard process in health technology assessment and public health evaluations by NICE (the National Institute of Health and Care Research) for new interventions which haven't yet been rolled out in NHS practice. Furthermore, to account for the possibility of less positive results in practice than were observed in the trials, we have carried out a range of sensitivity analyses where we have assumed either a 25% lower effectiveness, a much lower duration of intervention effect, or a higher cost (see Table S4 and the first paragraph of page 16 in the results of the revised manuscript).

Of course, we do agree with reviewer 1 that it will also be essential to update the analysis as evidence about its impact becomes available. Indeed the National Institute for Health Research (NIHR) is commissioning a formal evaluation of the NHS DPP which will include cost-effectiveness analysis, and we have added this fact to the end of the discussion section to provide context for further research. Nevertheless, there is wide interest at the present time from clinicians, commissioners and researchers for an estimate of the potential cost-effectiveness given the best currently available effectiveness estimates. Following the comments of reviewer 1, we have therefore made some changes to the wording of the article in order to make it clearer that this analysis provides an estimate of potential return on investment (see the first sentence of the abstract, this is already in the title of the paper) and that the effectiveness data is not derived from evaluation of the NHS DPP itself by addition of the following sentence to the beginning of the final paragraph of the discussion:

'Whilst this study is not based on actual clinical data from the NHS DPP, because such data does not yet exist as the national programme implementation is just beginning, it does use the most recently published estimates of intervention effectiveness from a PHE evidence review designed specifically to

inform the development of the NHS DPP.'

We have also added an extra limitation to the article summary section to state that the effectiveness is based on trial data and not data from the intervention itself as follows:

'The NHS DPP has recently begun national implementation and direct data collection on its effectiveness in practice in England has not yet been obtained, therefore the analysis assumes that effectiveness will be similar to that obtained in pragmatic trials of intensive lifestyle interventions aimed at preventing type 2 diabetes whilst also undertaking sensitivity analysis around this assumption.'

We also agree with Reviewer 1 that direct evidence on the safety of the NHS DPP intervention as implemented nationally has not yet been collected. However, current evidence around intensive lifestyle interventions does not indicate that there are any significant negative effects. The studies included in the systematic review that provides effectiveness estimates for our analysis do not examine adverse events. One study that does include adverse events (not included in the PHE systematic review) is the analysis of the US DPP . This indicated that gastrointestinal symptoms were slightly lower in individuals undertaking lifestyle intervention than in those taking placebo, whilst musculoskeletal symptoms were slightly higher, but there was no statistically significant difference reported (see Table 3 in reference). This was the basis of our assumption that the proposed NHS DPP would not have statistically significant adverse effects to be included into the modelling. To make this clearer, we have added a sentence referring to the US DPP paper, to the Methods section on page 10 stating that:

'Current evidence indicates that whilst there may potentially be a small number of adverse musculoskeletal events associated with intensive lifestyle intervention compared with control, these are not significant so were not incorporated into the analysis.'

Reviewer 1 states that the intervention costs were not documented and we have now revised the manuscript to address this. At the time of submitting the manuscript the details for deriving the intervention cost were not publicly available, and so we stated that the costs were derived from an impact assessment and given directly to us by PHE, referencing a personal communication from PHE. Since then, the NHS England impact assessment has now been published and is available online , so we have updated the manuscript to contain the reference to the analysis (which was performed by NHS England and not by us) instead. This cost represents the actual price that the NHS will pay a provider for an individual to enrol on the intervention. A short sentence describing this in the last paragraph of the 'intervention' section of the methods has also been added to the manuscript as follows:

'This is the cost price that the NHS is willing to pay per person starting the intervention and incorporates expected retention rates of participants'.

We would also like to reiterate that the perspective of the analysis is that of the NHS (national health service), as stated in the 'main outcome measures' section of the abstract and at the end of the 'model structure' section of the methods and therefore we do not incorporate any out of pocket costs to the individual that could be incurred through intervention attendance and adherence. We have added a sentence in the last paragraph of the 'intervention' section of the methods stating as follows:

'Due to the NHS perspective taken, potential out of pocket costs for intervention attendees were not included'

Finally, Reviewer 1 also states that we have assumed that benefits of the intervention last for 20

years. We are sorry for any confusion here. In fact we have assumed that the intervention effects (in terms of reduction in weight, blood pressure, cholesterol and HbA1c) only last for 5 years during which time the incremental gap between intervention and control linearly diminishes down to zero. In the sensitivity analysis, we test an assumption that the intervention effect lasts for only 3 years. These assumptions are set out in the methods section and, as referenced, have been used previously in analyses performed for NICE . The small delay in diabetes diagnosis and CVD that this creates is sufficient to have knock-on effects that endure beyond the 5 year period, because of the increased risk of death and further disease following diagnosis of diabetes or a first CVD event. To clarify this, we have expanded the description of intervention duration of effect in the methods as follows:

'A linear rate of weight regain (plus reduction in the intervention effects on HbA1c, SBP and cholesterol) was assumed over the first five years in line with the assumptions used to produce the NICE guidelines for diabetes prevention (PH38). This meant that individuals' metabolic trajectories returned to where they would have been without intervention, within five years of intervention implementation.'

Reviewer: 2
Reviewer Name: Neal R. Barshes, MD, MPH
Institution and Country: Baylor College of Medicine, United States of America
Please state any competing interests:None declared

Please leave your comments for the authors below

Page 9, lines 30 to 47: what outcomes or diabetes related complications were modeled?

We are not entirely sure what the reviewer would like us to add. The text in lines 30-47 already states all the complications that are modelled and contribute to the cost and QALY outcomes, all of which have links with diabetes and/or high BMI:

'Every year in the model, an individual may visit their GP or undergo a health check, and be diagnosed with and treated for hypertension, high cardiovascular risk, diabetes, microvascular complications of diabetes, cardiovascular disease (CVD), congestive heart failure, osteoarthritis, depression and breast or colon cancer, or may die.'

We have added an extra explanatory sentence about outcomes to make things clearer as follows:

'Total costs and QALYs are aggregated over all individuals in the model.'

Page 9, line 45: the author should specify the currency used in this analysis (English pounds). Additionally, the authors should specify whether the costs were in 2014 or 2015 pounds (not "2014/2015").

Following the suggestion of the author we have added that the currency is in English Pounds and that the costs are for 2014 (the tax year April 2014 to April 2015 is predominantly in 2014).

Page 10, line 20: first, the word "fulfill" is misspelled.

We are using British English spellings for the manuscript so fulfil appears to be correct.

Also, it is not clear whether the authors intend to have guidelines number nine through number 12 implemented or whether the authors mean at least nine of the total guidelines implemented.

To increase the clarity around guidelines (we mean at least nine), we have added the words ‘at least’ ahead of 9-12 guidelines.

Page 10, line 38 to page 11: The structure of this model and the sensitivity analyses are outstanding. It seems as though the authors have thought through all the details required to make the model a realistic representation of the actual implementation of a prevention efforts.

We thank reviewer 2 very much for these positive comments about our model and analysis.

Page 12, line 26: can the authors make any general comments about the parameter used for various groups of variables? For example were gamma distribution is used for (most) cost variables?

We have included tables of all parameters, including the distributions chosen, at the end of the supplementary appendix (Tables 42-60), and given the very large number of parameters in the model, we feel that it is more useful to refer readers to these tables than to make generalisations about the types of distribution used for certain variables. We have added the Table numbers to the text to make it easier for readers to find them.

Page 12, line 48: it is not clear to me what the difference between cost savings within the first year of implementation and recouping intervention costs would be. In other words, how could the program save money if intervention costs had not yet been recouped? Please clarify.

We realise that this can be confusing and it results from the differences in the way the intervention is funded compared to the way that healthcare is funded. We have included two sets of costs results in the model – NHS costs, which refer only to the healthcare costs, and Total costs which also include the intervention costs. Whilst the NHS cost is negative (i.e. cost-saving) from the first year, it is not sufficiently negative to recoup the intervention costs until year 12. To make this clearer in the first paragraph of the results section we have changed ‘start saving money for the NHS’ to ‘reduce healthcare costs’

Page 13, lines 41 to 57: since the variable BMI had a big impact on cost, it would be worthwhile performing additional sensitivity analyses that focus on this variable. In particular, I would be interested to know whether the return on investment in the high BMI groups was mitigated by advanced age. Similarly, I would favor replacing figure 3 with a graph that shows The interaction between BMI and age on total costs.

We agree with the reviewer that it would be interesting to see the interaction between subgroups. To this end we have run the model with some extra combinatorial subgroups to see the interactions between BMI and age, and BMI and HbA1c, which we thought might also be interesting.

We have moved the existing figure 3 into the supplementary appendix (now Figure S3) and have replaced it by a new figure (now Figure 4) showing the interactions of these characteristics on the return on investment. We have also added a short description of the new analysis to the methods section as follows:

‘A fifth sensitivity analysis was also carried out in which a series of combinatorial subgroups were modelled, defined by both BMI and age, or BMI and HbA1c, in order to observe the interaction between characteristics.’

And a paragraph describing the results in the sensitivity analysis section of the results:

‘Combinatorial analysis indicates that the high return on investment in the BMI 35+ subgroup is

mitigated in individuals who are also aged 75+ and reduced to only £1.54 per £1 spent, whereas in individuals aged 40-59 it is improved even further to £3.20 (Figure 4). An even higher return on investment of £3.52 could potentially be obtained if individuals who have both BMI 35+ and HbA1c 6.2-6.4% are selected for the NHS DPP intervention. This suggests that subgroups with high benefits can be combined to potentially increase the return on investment even further.'

Page 17, discussion section: The discussion section is an appropriate links. The discussion of the results is very good. The only other point not discussed that would deserve clarification is why there was lower return on investment in the younger patients (those less than 40 years of age).

We touched briefly on the reasons for lower benefit to younger patients (and therefore those of BME and socioeconomically deprived backgrounds) in the original manuscript, but have now expanded on these following the reviewer's comments by restructuring the sentence as follows:

'Low mean age results in lower health benefits and return on investment from the NHS DPP than high age due to the lower absolute risks of disease and mortality in such individuals and therefore lower ability to benefit.'

VERSION 2 – REVIEW

REVIEWER	Neal R Barshes,MD, MPH Baylor College of Medicine U.S.A.
REVIEW RETURNED	09-May-2017

GENERAL COMMENTS	Re Page 9, lines 30 to 47: outcomes or diabetes related complications that were modeled I was mainly asking for more detail here. For example, how are the costs of "micro vascular complications" modeled? This is really a large category. Did the authors include retinopathy laser treatment? Costs of treating painful foot neuropathy? Foot ulcers, foot infections, or amputations?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Neal R Barshes,MD, MPH
Institution and Country: Baylor College of Medicine, U.S.A.
Please state any competing interests: None declare

Please leave your comments for the authors below

Re Page 9, lines 30 to 47: outcomes or diabetes related complications that were modeled

I was mainly asking for more detail here. For example, how are the costs of "micro vascular complications" modeled? This is really a large category. Did the authors include retinopathy laser treatment? Costs of treating painful foot neuropathy? Foot ulcers, foot infections, or amputations?

We have included full details of how all costs were modelled in the supplementary appendix. This shows for example that the costs of microvascular complication include renal failure (with different procedures detailed), costs of treating foot ulcers, costs of amputation for first and subsequent years, and costs of blindness for first and subsequent years, with the latter two values coming from a cited

UKPDS costing study. This study calculated healthcare costs for patients with each complication and did not detail which procedures patients used. In p32 of the appendix we also describe our approach to modelling microvascular disease in that we model the occurrence of major events only (renal failure, amputation, foot ulcer, and retinopathy specifically) and not the earlier stages.

Due to the large number of different cost parameters in the model and the word limits for the article it isn't possible to detail all of these more closely in the manuscript text itself, and we don't feel that it would be useful to detail some costs and not others. However, to improve clarity, we have added a sentence on page 9 to direct the reader to the supplementary appendix if they are interested in reading about the model costs in more detail:

'Details of how all utilities and costs were modelled can be found in the supplementary appendix.'

We hope that this approach will satisfy Reviewer 2.

Reviewer: 1
Reviewer Name: Andrew J. Palmer
Institution and Country: Menzies Institute for Medical Research, The University of Tasmania, Australia
Please state any competing interests: None declared

Please leave your comments for the authors below

I believe the authors have substantially strengthened their paper by adequately address the reviewers' comments.

We thank reviewer 1 for his approval of the manuscript.

VERSION 3 – REVIEW

REVIEWER	Neal R. Barshes Baylor College of Medicine United States of America
REVIEW RETURNED	19-May-2017

GENERAL COMMENTS	Adequate revisions.