PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Societal costs of permanent childhood hearing loss at teen age: a cross-sectional cohort follow-up study of universal newborn hearing screening
AUTHORS	Kennedy, Colin; Chorozoglou, Maria; Mahon, Merle; Pimperton, Hannah; Worsfold, Sarah

VERSION 1 - REVIEW

REVIEWER	Beltempo, Marc McGill Healthcare Center, Neonatalogy Competing Interests: No competing interest.
REVIEW RETURNED	29-Aug-2017

GENERAL COMMENTS	The authors conducted as cost-consequence study evaluating the societal costs of bilateral permanent childhood hearing loss in the preceding year for children ages 13 to 19 years in a previously described cohort. Long-term economic evaluations of the burden of neonatal onset disease are important to provide data for cost-effectiveness studies that integrate short and long-term costs of universal hearing screening programs. However, I recommend the authors address the following questions: MAJOR 1. The authors conclude that early interventions that can improve long-term language may also reduce long-term costs. This is not supported by the data in teenagers as in the adjusted analysis the language and reading z-score were not associated with long-term cost reductions. The authors may want to comment on why there was an association of the receptive language z-score at 7-9 years but not in teenagers. In the current analysis, it is possible that the unadjusted association of higher language scores with lower costs is simply driven by the confounding effect of associated medical conditions since the adjusted analysis did not find any association. 2. The discussion mentions economic comparisons to the costs at 5-7.9 years old. The authors should provide some comment on the effect of time (comparing the annual cost at 7-9 y.o vs teenagers when considering inflation). Because, when considering inflation, the overall annual costs of PCHL seems to be decreasing with age. This is important as it justifies the need for long-term economic evaluations of neonatal onset disease to develop better economic models to predict long-term costs. 3. The cost of the cochlear implant was annuitized in the table, please mention this in methods. And mention if it was discounted.

	Also, is the cost in the table the annuitized cost of the 60 years ? Then this means the cost of implant is 20,333 x 60 ? 4. As a general comment for tables 2,3 and 4: I would suggest using the same headers and titles for the first column to facilitate reading and interpretation. a. For example: table 2 hospital inpatient has only one subdivision (other hospital inpatient admissions) but table 3 has 3 subdivisions (pediatric ward, cochlear implants and other). Further when going to table 4, several of the cost domains included like outpatient care, total hospital care, etc are not defined and since headers are not the same as in Tables 2-3, reader cannot be sure to what they refer to. I would suggest using uniform line titles to facilitate understanding (and by doing so, you would not need to define all these terms in the manuscript). 5. Page 4 lines 35-37: “powered to detect moderate effect size” is unclear. Please clarify the sample size justification of the original cohort (this is clear in the previous paper). 6. Was cost of medication included in the evaluation? 7. This is a cost consequence study evaluating the economic burden of PCHL. I would recommend using the specific term « cost consequence study » in the design description. 8. Where the CHEERS guideline for reporting economic evaluations followed? If so, please mention. MINOR (in order of the manuscript) Abstract - The objective in the abstract and manuscript should be more specific (in mentions societal costs during teenage years but the paper only looks at 1 year prior the survey). For example “Estimate the economic cost of PCHL for society in the preceding year for children age X to X years and to compare the costs of infants exposed to UNHS to those who were not.” Introduction - Page 3 lines 21-24 “UNHS adds to financial costs in the first year of life (9)”. Could the authors clarify this statement: does UNHS increase the cost for the individual that is being screened or do UNHS programs increase costs of neonatal care (from a population perspective). - In the introduction (page 3 lines 50-55), the authors hypothesize that early detection of PCHL reduces costs of education in the long term and that long-term cost-effectiveness evaluation of UNHS is needed. I am concerned that readers will confound this study with a cost-effectiveness study. I would recommend adding a comment saying, “Rigorous data on long-term economic consequences of PCHL are required to conduct cost-effectiveness evaluation of UNHS programs that take into account the long-term consequences of hearing impairment.” Methods - Considering this is long-term follow-up economic analysis of a study that has extensively been described in previous paper, I would recommend simplifying the description of the original trial (page 4 lines 37-57) - Table 3 refers to equipment loaned, do the costs refer to annual cost of the loan of the equipment? - The evaluation was done in patients aged 13-20 years old (NB it is written 13-20 on page 4 line 19 but is written 13-19 on page 14 lines

	29, please correct): why is the range so wide? And this should be addressed in the limitations but that even though the age range is wide the costs seem relatively constant during this age period (if this statement is supported by the data). - From my understanding this data was collected at the same moment as the data for the 2016 paper on literacy outcomes (HOT project, n=114 based on Pimperton et al., ADC 2016) but the number of infants in this paper differs slightly (n=110) why is this? - How many bootstrapping replications were used ? Results - Several overall costs seem similar to 2006, but “lost productivity” by the family has decreased significantly (£ 120 in 2003 (2006 paper) and to £ 33 in 2013 (current paper) for all children with PCHL). This is surprising since most other resource use seems relatively similar (when considering inflation), is there an explanation? Are children more self-sufficient to attend appointments? Or is it because most resources are within schools and parents do not need to attend? Discussion - In discussion page 11 lines 28-35 “Since superior….management strategies made possible by UNHS could have the potential to reduce costs further in the future.” is a strong statement not supported by the presented data (UNHS was not associated with lower costs). Tables - Table 2 o What does the line « cochlear implant » refer to since the title of the table is « resource use in preceding 12 months »? Is it the mean number of new implant per child? - Table 3 o In column 2, for lines that have varying unit costs, some have mean (or median but this is not specified) + range and others only have range, please specify. o Why is cochlear implant under “hospital inpatient admission” is this the cost for the implant hospitalization (excluding the equipment cost)? And does this mean some adolescents had revisions of their implants ? o The unilateral cochlear implant is £ 20,333 but the line says “annuitized over 60 years”, is this correct ? same for bilateral implants (also would suggest specified “unilateral cochlear implant” in column one instead of putting that information in column 2). o General practitioner contact minute = £ 53, this seems a bit high for each minute o Also, when comparing table 3 costs to the 2006 paper costs, some cost lines have nearly doubled from 2003 to 2013 (example: pediatrician hour in 2003 was £ 88 compared to £ 223 in 2013, or orthodontist). Some form of short comment/explanation on theses significant increases for similar services over 10 years. For exmaple, inflation in UK for the 2003-1013 period has been exceptionally high compared to North America (approx 40% vs 25%) would be helpful for readers less familiar with the economic context in the UK. - Table 4 in its could benefit from a review of all the cost categories (I count more than 13). Following similar line titles as in table 2 and 3 would likely help to simplify the table (see comments above).

REVIEWER	Wroblewska-Seniuk, Katarzyna Poznan Univeristy of Medical Sciences, Department of Neonatal Infectious Diseases Competing Interests: I declare that I have no competing financial, professional or personal interests that might have influenced the review of this manuscript.
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	This is a very interesting study on the costs of permanent childhood hearing loss. It should be of great interest to the pediatricians, audiologists and public health specialists. It shows clearly that the societal costs of PCHL increase with its severity and the presence of additional medical conditions. There is also the inverse relationship between costs and language skills. One of the conclusions is that universal neonatal hearing screening is associated with benefits to language abilities and therefore might reduce costs of PCHL in the future. The manuscrpit is well written, the statistical analysis is appropriate and very complex. The discussion and conclusions are very interesting. The paper needs some minor revisions as given below: 1. I do not quite understand the numbers given in Table 2 in Education section. n given in the top row does not correspond to the numbers specified in different categories, e.g. Total PCHL n=73 and education, no of children attending in the same column n=79 (119.4%). HCG n=37, education n=33 (100%). Does that mean that some children did not attend any school and others attended more than one school? 2. I found some inconsistency between Results and Discussion as far as costs of PCHL in the presence of AMC are concerned. It seems that the presence of AMC in addition to PCHL increased costs fivefold (p 9. lines 31-36) and not threefold as you say in discussion (p.10 lines 46-48). 3. The limitation of the study is not very high number of participants and loss of participants at follow-up. However I think that the long period of follow-up, which is of great value, makes it inevitable and it is probably not possible to collect larger group of patients in such a study.

REVIEWER	Ridout, Deborah Institute of Child Health, Paediatric Epidemiology Biostatistics Competing Interests: None
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	This is an interesting study which describes and investigates societal costs of permanent childhood hearing loss. Exposure to the Universal Newborn Hearing Screening is the main factor of interest (I think, but the main conclusion makes no reference to this), along with the severity of hearing loss. In general I find the manuscript very difficult to read (e.g. medical condition additional (AMC) in the abstract) and I feel important methodology is not explained in sufficient detail, I have some specific comments: 1. The description of the study design is unclear and a schematic would be helpful, making it clear this data is from a trial. Furthermore no details are provided on how the controls were selected. 2. The study was powered to detect a 'moderate' effect size of UNHS on reading comprehension. I am not sure of the relevance of

	this, given reading comprehension is not the main outcome described in this manuscript, in addition why is a generic effect size mentioned when reading comprehension is a standard assessment. Why was an unbalanced study design chosen, what was the power of the study? 3. Was the complex structure of the data (paired hospital, multiple periods of 'intervention', different district and different cohorts) taken in to account in the statistical analysis. It is good to see the authors considered the Normality assumptions of their data and I presume they are referring to the cost model as violating the Normality assumption. 'Discounting was not necessary' needs to be explained further to a more general audience. 4. In the abstract a CI is presented as (10,106 to -£2,918) – I presume this is 95%CI, the numbers should be presented in reverse order and both should be proceeded with a £ sign. All costs should include units and there should be consistency when referring to CIs. 5. In the section: Effect of additional medical conditions (AMC): Of those with AMC 0.56 of participants. What does 0.56 mean? And similar throughout the paragraph 6. Tables 2 and 3 could be combined, units are not given for table 4

REVIEWER	Jiang, Zedong Children's Hospital, Fudan University, Paediatrics Competing Interests: I declare that I have no competing interest that might relate to the article.
REVIEW RETURNED	24-Sep-2017

GENERAL COMMENTS	This is a generally well designed follow-on study. The conclusions drawn are expectable, with moderate novelty. The results add valuable information for the societal costs of PCHL at teenage years. Abstract: the authors aimed to investigate the effects of bilateral Permanent Childhood Hearing Loss (PCHL) >40 dB and of exposure to Universal Newborn Hearing Screening (UNHS) on societal costs during the teenage years. However, in conclusion, they did not mention the effect of UNHS. In the introduction, the authors reviewed literature and emphasized that UNHS adds to financial costs in the first year of life, but earlier identification of children born with PCHL and early intervention can reduce cost subsequent to infancy. Nevertheless, this study only found a very small benefit of costs of UNHS at teenage period. Birth with UNHS was not associated with significantly lower overall costs. It appears that whether UNHS is cost-effective remains debatable, considering the significant costs of UNHS and the extremely low rate of PCHL in the newborns which can be found some time after the neonatal period. Please provide a brief description of what early interventions can be implemented for newborns with hearing loss detected by UNHS.

	As the authors pointed out in Discussion, one of the greatest limitation of the study were modest numbers of participants at the outset and further reduction in its power to look at subgroups (e.g. severities of PCHL) by slow but steady loss of participants over the 17 years of follow-up. There were only 32 (44%), 18 (25%) and 23 (32%) participants with moderate, severe and profound PCHL, respectively. This relatively small sample size made their results less solid and conclusions less convincing. What is already known on this topic' is too lengthy, and should be more concise. There are too many details in the tables. The table should be reduce and condensed.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

The authors conducted as cost-consequence study evaluating the societal costs of bilateral permanent childhood hearing loss in the preceding year for children ages 13 to 19 years in a previously described cohort. Long-term economic evaluations of the burden of neonatal onset disease are important to provide data for cost-effectiveness studies that integrate short and long-term costs of universal hearing screening programs. However, I recommend the authors address the following questions:

MAJOR

1. *The authors conclude that early interventions that can improve long-term language may also reduce long-term costs. This is not supported by the data in teenagers as in the adjusted analysis the language and reading z-score were not associated with long-term cost reductions. The authors may want to comment on why there was an association of the receptive language z-score at 7-9 years but not in teenagers. In the current analysis, it is possible that the unadjusted association of higher language scores with lower costs is simply driven by the confounding effect of associated medical conditions since the adjusted analysis did not find any association.*

Response: Agree that this was not well justified in the manuscript. We have also now presented two multiple regression models alongside the unadjusted univariate analysis in Table 5. In the first multivariate model , in addition to examining the variable of interest listed in the left hand column, we have included only the two other main cost drivers, namely the presence of an additional medical condition (AMC) and use of cochlear implant(s) (CI). This analysis, taken together with the large effect of receptive language ability on costs in univariate analysis, provides some evidence for the lower costs associated with superior language that we also reported in this study cohort when they were aged 5-10 years. This effect is large enough to be economically important but the confidence intervals around it are wide (and statistical significance therefore marginal) because of the limited sample size. In the second multivariate model, we have added severity of PCHL to the first model. We have explained in highlighted text added to the results and discussion why the first model may be most appropriate for examination of the effects of UNHS, language, and reading and the second model for the examination of the effects of early confirmation.

2. *The discussion mentions economic comparisons to the costs at 5-7.9 years old. The authors should provide some comment on the effect of time (comparing the annual cost at 7-9 y.o vs*

teenagers when considering inflation). Because, when considering inflation, the overall annual costs of PCHL seems to be decreasing with age. This is important as it justifies the need for long-term economic evaluations of neonatal onset disease to develop better economic models to predict long-term costs.

Response: Agree. We now include (Discussion, page 11, final para.) consideration of inflation in our comparison between costs in the current study and costs at the previous evaluation time point.

3. *The cost of the cochlear implant was annuitized in the table, please mention this in methods. And mention if it was discounted. Also, is the cost in the table the annuitized cost of the 60 years ? Then this means the cost of implant is 20,333 x 60 ?*

Response: The unit cost we used for the cochlear implant procedure is from the NHS Reference Costs, as referenced. This is the actual cost of the equipment and procedure and we have deleted the confusing reference to annuitisation of cost in Table 3.

4. *As a general comment for tables 2,3 and 4: I would suggest using the same headers and titles for the first column to facilitate reading and interpretation. For example: table 2 hospital inpatient has only one subdivision (other hospital inpatient admissions) but table 3 has 3 subdivisions (pediatric ward, cochlear implants and other). Further when going to table 4, several of the cost domains included like outpatient care, total hospital care, etc are not defined and since headers are not the same as in Tables 2-3, reader cannot be sure to what they refer to. I would suggest using uniform line titles to facilitate understanding (and by doing so, you would not need to define all these terms in the manuscript).*

Response: Agree. Tables 2, 3 and 4 have been modified to provide the same headers and titles for the first column in the same order.

5. *Page 4 lines 35-37: "powered to detect moderate effect size" is unclear. Please clarify the sample size justification of the original cohort (this is clear in the previous paper).*

Response: Agree. The precise power calculation is now given at that point in the text in place of the unclear text quoted by the reviewer.

6. *Was cost of medication included in the evaluation?*

Response: No, the cost of medication is not included in our analysis.

7. *This is a cost consequence study evaluating the economic burden of PCHL. I would recommend using the specific term « cost consequence study » in the design description.*

Response: The term cost consequence study is, we believe, used to refer to head to head comparisons of a medical intervention as a means for leaders and decision-makers to estimate whether the value of results obtained from the medical intervention is worth the investment. Although our study explores the medical intervention of universal newborn hearing screening, it also examines the relationship between cost, as the dependent variable, and other variables of interest i.e. the presence (or not) of bilateral hearing loss, of additional medical conditions, the detection of hearing loss before age 9 months, and language ability. It is therefore broader than a cost consequence study. Furthermore this is a cohort follow-up study rather than a trial to which the STROBE guidelines (rather than the CONSORT guidelines) apply.

8. *Where the CHEERS guideline for reporting economic evaluations followed? If so, please mention.*

Response: The CHEERS guidelines are the economic equivalent of the CONSORT guidelines which are not appropriate for a cohort follow-up study. We submitted the completed STROBE guidelines with the manuscript.

MINOR (in order of the manuscript)

Abstract

- The objective in the abstract and manuscript should be more specific (in mentions societal costs during teenage years but the paper only looks at 1 year prior the survey). For example “Estimate the economic cost of PCHL for society in the preceding year for children age X to X years and to compare the costs of infants exposed to UNHS to those who were not.”

Response: Agree. We have reworded the objective as:

‘To investigate the effects in adolescence of bilateral Permanent Childhood Hearing Loss (PCHL) ≥40 dB and of exposure to Universal Newborn Hearing Screening (UNHS) on societal costs accrued over the preceding 12 months.’

Introduction

- Page 3 lines 21-24 “UNHS adds to financial costs in the first year of life (9)”. Could the authors clarify this statement: does UNHS increase the cost for the individual that is being screened or do UNHS programs increase costs of neonatal care (from a population perspective).

Response: We have clarified this at the point in the manuscript cited by rephrasing as:

‘UNHS adds to financial costs in the first year of life, both because of the cost of administering a UNHS programme, estimated in 1998 as £13,881 per annum for a district with 1,000 births,(9) and because of the additional costs of management of identified cases during the months that would otherwise precede identification of the PCHI.’

- In the introduction (page 3 lines 50-55), the authors hypothesize that early detection of PCHL reduces costs of education in the long term and that long-term cost-effectiveness evaluation of UNHS is needed. I am concerned that readers will confound this study with a cost-effectiveness study. I would recommend adding a comment saying, “Rigorous data on long-term economic consequences of PCHL are required to conduct cost-effectiveness evaluation of UNHS programs that take into account the long-term consequences of hearing impairment.”

Response: We have added the sentence suggested by the reviewer at the point in the manuscript suggested.

Methods

- Considering this is long-term follow-up economic analysis of a study that has extensively been described in previous paper, I would recommend simplifying the description of the original trial (page 4 lines 37-57)

Response: The design of the study is, we believe, central to understanding this paper. Very few readers will pursue the references given and readers’ understanding of its design will be considerably enhanced by this concise description of it. For example, the fact that it was a five year birth cohort evaluated in a three year follow-up study explains the 7 year age range. The fact that part of the sample was drawn from a study of quasi-experimental design (The Wessex Trial) and the remainder were drawn from an observational cohort study is also important and explains the fact that overall this is a cohort follow-up study.

- Table 3 refers to equipment loaned, do the costs refer to annual cost of the loan of the equipment?

Response: Yes, our cost estimates refer to the annual costs incurred.. This is specified in the NHS reference costs that are referenced at that point. '(annual cost)' but the reviewer's point is well taken since, as noted in the previous comment, few readers will pursue the references. We have clarified the fact that these are annual costs in the relevant section of Table 3.

- The evaluation was done in patients aged 13-20 years old (NB it is written 13-20 on page 4 line 19 but is written 13-19 on page 14 lines 29, please correct):

Response: The mean age of the full sample (PCHL+ HCG) is 16.8, and the range of age was from 13.67 to 20.42. The mean age of the PCHL group was 17.0, from 13.67 to 20.42 and the mean age of the HCG was 16.3, with an age range of 14.17 to 19. Both the age ranges given in the manuscript were, in fact correct, in that the age range given at the earlier point in the manuscript refers to all participants while that given at the later time point refers to participants with normal hearing. We nevertheless appreciate that this was confusing and have rephrased the latter sentence to read:

'Compared with participants of similar age with normal hearing, the presence of bilateral moderate or severe PCHL at age 13 to 20 years was associated with 2.7 fold higher costs in the preceding 12 month period,…..'

why is the range so wide? And this should be addressed in the limitations but that even though the age range is wide the costs seem relatively constant during this age period (if this statement is supported by the data).

Response: The explanation of the wide age range is apparent from the description of the study sample (see response to minor comment on Methods above). We have now spelt this out in the discussion section (page 12, penultimate paragraph) as follows:

'The seven year range of age at time of assessment is consequent upon the study design i.e. an evaluation of a five-year birth cohort conducted over a three year study period. This is both a limitation, in that it makes the estimate for any one year of age less precise, and a strength, in that it makes the findings more generalizable to teenagers in general.'

- From my understanding this data was collected at the same moment as the data for the 2016 paper on literacy outcomes (HOT project, n=114 based on Pimperton et al., ADC 2016) but the number of infants in this paper differs slightly (n=110) why is this?

Response: We have added as the opening sentence of the Results:

'Four of 114 participants in the HOT study did not return the completed economic questionnaire and resource use is therefore reported in 110 participants in this economic study.'

- How many bootstrapping replications were used ?

Response: We have added to the relevant sentence in the Methods: '(1,000 replications)'

Results

- Several overall costs seem similar to 2006, but "lost productivity" by the family has decreased significantly (£ 120 in 2003 (2006 paper) and to £ 33 in 2013 (current paper) for all children with

PCHL). This is surprising since most other resource use seems relatively similar (when considering inflation), is there an explanation? Are children more self-sufficient to attend appointments? Or is it because most resources are within schools and parents do not need to attend?

Response: This is an expected finding principally attributable to the fact that children become more independent with age so that parents are less often obliged to accompany their children to appointments. We have not added this to the manuscript as the principal focus of the paper is to describe costs rather than to make detailed comparisons between costs at the two evaluation time points.

Discussion

- In discussion page 11 lines 28-35 “Since superior….management strategies made possible by UNHS could have the potential to reduce costs further in the future.” is a strong statement not supported by the presented data (UNHS was not associated with lower costs).

Agree that this statement was not well justified in the submitted manuscript. To address this comment, we have rephrased the relevant sentence as follows:

‘The receptive language skills, which we found to be superior in children with PCHL born in periods with UNHS [reference to Schroeder et al. 2006] in our study population,[reference to Kennedy et al. 2006] should receive greater benefit in current and future birth cohorts than those observed in our study cohort because of the much clearer care pathways that now lead from UNHS to early intervention for PCHL. We therefore predict that the significantly lower costs associated with superior language skills that we observed in this study population in childhood and also, at a marginal level of significance, in adolescence would be more strongly associated with UNHS in a current or future birth cohort. In other words, management strategies made possible by UNHS could have the potential to lead to significantly reduced future costs as a result of superior language skills.’

Tables

- Table 2

o What does the line « cochlear implant » refer to since the title of the table is « resource use in preceding 12 months »? Is it the mean number of new implant per child?

Response: The numbers within Table 2 are estimates of group mean resource use and the Table title now states this. In this instance, the number in the table is the number of cochlear implantations divided by the number of children in the group.

- Table 3

o In column 2, for lines that have varying unit costs, some have mean (or median but this is not specified) + range and others only have range, please specify.

Response: The unit cost in Table 3, refers to the mean cost of the procedure as reported by NHS Reference Costs. The Table title now states this. We have provided a range of costs when the costs vary under the specific cost item/category. This is now explained in a footnote.

o Why is cochlear implant under “hospital inpatient admission” is this the cost for the implant hospitalization (excluding the equipment cost)? And does this mean some adolescents had revisions of their implants ?

Response: The procedure takes place in hospitals and, in the UK, is part of the secondary care category. We have added a footnote which states: ‘UK NHS Reference Costs include both the equipment and the services provided, i.e. unit cost for the procedure as a whole.’

o The unilateral cochlear implant is £ 20,333 but the line says “annuitized over 60 years”, is this correct ? same for bilateral implants (also would suggest specified “unilateral cochlear implant” in column one instead of putting that information in column 2).

Response: Cochlear implants, already included in the ‘Hospital inpatient admissions’ category, have been removed from the ‘Equipment loaned’ category of Table 3.

o General practitioner contact minute = £ 53, this seems a bit high for each minute

Response: This is not per minute of consultation but was intended to indicate the cost of the mean number of contact minutes of consultation. We have rephrased this as “per consultation”.

o Also, when comparing table 3 costs to the 2006 paper costs, some cost lines have nearly doubled from 2003 to 2013 (example: pediatrician hour in 2003 was £ 88 compared to £ 223 in 2013, or orthodontist). Some form of short comment/explanation on theses significant increases for similar services over 10 years. For exmaple, inflation in UK for the 2003-1013 period has been exceptionally high compared to North America (approx 40% vs 25%) would be helpful for readers less familiar with the economic context in the UK.

Response: The same source of data, i.e. NHS Reference Costs and PSSRU data, was used for both studies but we have not performed head-to-head comparison of unit costs used in the previous publication compared to the present manuscript which is not the focus of the report. Two possible explanations for the cost differences observed are:

1. There is a significant price difference between the unit cost of the Community Paediatrician is significantly lower than that of the Consultant Paediatrician. In our costing, we used Consultant Paediatrician NHS Reference Cost.
2. The NHS Reference Costs in the UK are calculated using information from all different providers on the costs they incurred in the different activities they performed. These are then averaged across all the providers. Therefore, the cost of performing a procedure may vary systematically according to characteristics of the patients or the institutions involved. In the published reference costs, heterogeneity in ‘organisational level data’ leads to variability in the average costs.

We have added reference in Table 3 to the source of NHS Reference Costs.

- Table 4 in its could benefit from a review of all the cost categories (I count more than 13). Following similar line titles as in table 2 and 3 would likely help to simplify the table (see comments above).

Response: Agree. We have modified our tables adopting the same titles and order as Tables 2 and 3. In the previously submitted manuscript we had attempted to adopt the Table format of the previous publication relating to this sample when evaluated earlier in their lives in order to retain comparability.

Reviewer: 2

Comments to the Author

This is an interesting study on the costs of permanent childhood hearing loss. It should be of interest to the pediatricians, audiologists and public health specialists. It shows clearly that the societal costs of PCHL increase with its severity and the presence of additional medical conditions. There is also the inverse relationship between costs and language skills. One of the conclusions is that universal

neonatal hearing screening is associated with benefits to language abilities and therefore might reduce costs of PCHL in the future.

The manuscrpit is well written, the statistical analysis is appropriate and very complex. The discussion and conclusions are very interesting. The paper needs some minor revisions as given below:

1. *I do not quite understand the numbers given in Table 2 in Education section. n given in the top row does not correspond to the numbers specified in different categories, e.g. Total PCHL n=73 and education, no of children attending in the same column n=79 (119.4%). HCG n=37, education n=33 (100%). Does that mean that some children did not attend any school and others attended more than one school?*

Response: We have added a footnote to the table which states:

'The categories presented for education, are not mutually exclusive. For example the special school categories stated in this column could be residential or not. There are also cases of children that did not attend school.'

2. *I found some inconsistency between Results and Discussion as far as costs of PCHL in the presence of AMC are concerned. It seems that the presence of AMC in addition to PCHL increased costs fivefold (p 9. lines 31-36) and not threefold as you say in discussion (p.10 lines 46-48).*

Response: Agree. The baselines against which the increases were being compared were not clear. We have simplified the summary statement (page 13, Discussion, para 1, line 4) to:

'Compared with participants of similar age with normal hearing, the presence of bilateral PCHL ≥40 dB at age 13 to 20 years was associated with 2.7 fold higher costs in the preceding 12 month period and the presence of pre-specified medical conditions in addition to PCHL increased costs almost two fold.'

3. *The limitation of the study is not very high number of participants and loss of participants at follow-up. However I think that the long period of follow-up, which is of great value, makes it inevitable and it is probably not possible to collect larger group of patients in such a study.*

Response: Agree. We appreciate the reviewer's understanding of the enormous challenges that a 17 year follow-up study presents.

Reviewer: 3

Comments to the Author

This is an interesting study which describes and investigates societal costs of permanent childhood hearing loss. Exposure to the Universal Newborn Hearing Screening is the main factor of interest (I think, but the main conclusion makes no reference to this), along with the severity of hearing loss. In general I find the manuscript very difficult to read (e.g. medical condition additional (AMC) in the abstract) and I feel important methodology is not explained in sufficient detail, I have some specific comments:

Response: Agree with the awkwardness of phrasing of the example given which we have rephrased Abstract Results) to read:

'The presence of not only PCHL but also an additional medical condition (AMC)….'

We have also attempted to increase readability at other points in the manuscript but only those specifically mentioned in reviewers' comments are highlighted.

1. The description of the study design is unclear and a schematic would be helpful, making it clear this data is from a trial. Furthermore no details are provided on how the controls were selected.

Response: In the abstract, we have now stated that this is an observational cohort study. The description provided in the methods tells the reader that the Wessex subgroup were graduates of a trial of the performance of UNHS as a screening test and were exposed or not exposed to a programme of UNHS by a quasi-experimental design. We have added to the Methods section (page 6, para 2, line 6):

'A flow diagram of participants through to completion of the HOT study was published as Figure 1 in our report of the effect of UNHS on reading comprehension, the primary outcome.(reference 29)'

2. The study was powered to detect a 'moderate' effect size of UNHS on reading comprehension. I am not sure of the relevance of this, given reading comprehension is not the main outcome described in this manuscript,

Response: The relevance is that the study was, as is usual, powered to detect a difference in the primary outcome measure which was reading comprehension. This has been added to the description of the statistical analysis (page 8, final paragraph).

Why was an unbalanced study design chosen, what was the power of the study?

Response: The study design was balanced in that it was designed:

a) to detect differences between two groups of participants with PCHI of equal size, one exposed and the other not exposed to a universal newborn hearing screening programme

b) to have a hearing comparison group (HCG) of participants with normal hearing that was the same size as each of the above-mentioned groups of participants with PCHI and that also provided a study-specific hearing comparison group (HCG) of typically developing children that was closely similar to the groups of participants with PCHI with respect to place and date of birth. This maximised the efficiency of the study to examine outcomes between either of the two groups of participants with PCHI and the HCG. It also enabled outcome scores to be expressed as z scores where z is the number of standard deviations of scores in the HCG by which the reading scores of the participants with PCHI differed from the mean score in the HCG group. This point is made in our earlier reports referenced in the manuscript (e.g. Kennedy et al. 2006 reference 13).

……in addition why is a generic effect size mentioned when reading comprehension is a standard assessment.

Response: The expression of outcome scores of participants with PCHL as z scores has methodological advantages over their expression as standard scores. First the z scores are derived from the HCG that was closely comparable to participants with PCHI with respect to date and place of birth. This contrasts with standard scores, derived from scores established in a reference population at another time and place in individuals born in a different time and place.

Second, it enables scores on two different measures to be both expressed in a common metric and combined into a composite measure. The receptive language score used in this manuscript is an example of this.

Third, it enables effect sizes to be compared between different outcomes. Thus the beta coefficients for receptive language and for reading comprehension in Table 5 are both expressed relative to a change of 1 SD of the range of outcome scores observed in the HCG on that measure. The relative

strengths of the relationships between these two variables and the dependent variable (costs in the preceding 12 months) is thus immediately apparent. The reviewer might be reassured to know that the analyses were also run with standard scores instead of z scores for language and the findings were unchanged. We reported this in Pimperton et al. 2017 (manuscript reference 27).

3. Was the complex structure of the data (paired hospital, multiple periods of 'intervention', different district and different cohorts) taken in to account in the statistical analysis.

Response: The study was powered to examine the effect of birth in periods of UNHS and designed to minimise any confounding between exposure to UNHS and the dependent variables. In particular, the Wessex subgroup were exposed to UNHS according to a quasi-experimental design and 95% of participants in each pair of districts were managed by the same audiology services irrespective of whether they were born in periods with or without UNHS. They did not receive experimental interventions other than exposure to UNHS and it is a reasonable assumption that on average differences in management between of the groups exposed and not exposed to programmes of UNHS arose as a result of that exposure.

The study was not designed or powered to compare subgroups but the Wessex subgroup was compared with the remainder of the participants (i.e. the Greater London subgroup) and 'Associations between early confirmation of hearing impairment or exposure to universal new-born screening and later language abilities were similar in the Wessex and Greater London sub-groups' (Kennedy et al. 2006, manuscript reference 13).

It is good to see the authors considered the Normality assumptions of their data and I presume they are referring to the cost model as violating the Normality assumption. 'Discounting was not necessary' needs to be explained further to a more general audience.

Response: We have rephrased as follows:

'As the time-frame for the cost analysis was one year, discounting applied to economic evaluations in excess of a one-year time frame, was not necessary.'

4. In the abstract a CI is presented as (10,106 to -£2,918) – I presume this is 95%CI, the numbers should be presented in reverse order and both should be proceeded with a £ sign. All costs should include units and there should be consistency when referring to CIs.

Response: We have made the suggested changes.

5. In the section: Effect of additional medical conditions (AMC): Of those with AMC 0.56 of participants. What does 0.56 mean? And similar throughout the paragraph

Response: We have now presented these proportions as percentages.

6. Tables 2 and 3 could be combined, units are not given for table 4

Response: Separate reporting of resource use and unit costs is the usual practice. Other reviewers have commented that the Tables need simplification and we would like to retain the separation of Tables 2 and 3. Furthermore this was the format in which we presented our previous evaluation of the same study cohort undertaken nine years early and this will facilitate comparison of the methodology.

Reviewer: 4

Comments to the Author

This is a generally well designed follow-on study. The conclusions drawn are expectable, with moderate novelty. The results add valuable information for the societal costs of PCHL at teenage years.

Abstract: the authors aimed to investigate the effects of bilateral Permanent Childhood Hearing Loss (PCHL) >40 dB and of exposure to Universal Newborn Hearing Screening (UNHS) on societal costs during the teenage years. However, in conclusion, they did not mention the effect of UNHS.

Response: Agree. We have added to the conclusion of the abstract:

'There was no statistically significant reduction in costs associated with birth in periods with UNHS.'

In the introduction, the authors reviewed literature and emphasized that UNHS adds to financial costs in the first year of life, but earlier identification of children born with PCHL and early intervention can reduce cost subsequent to infancy. Nevertheless, this study only found a very small benefit of costs of UNHS at teenage period. Birth with UNHS was not associated with significantly lower overall costs. It appears that whether UNHS is cost-effective remains debatable, considering the significant costs of UNHS and the extremely low rate of PCHL in the newborns which can be found some time after the neonatal period.

Response: The introduction states, correctly, that 'early identification of children born with PCHL can facilitate earlier access to linguistic input and better language and literacy skills and may thus reduce cost subsequent to infancy.' The reviewer states, also correctly, that birth in periods with UNHS was not associated with significantly lower overall costs in the present study. We agree with the reviewer that whether UNHS is cost-effective remains debatable but since it improves language and reading skills and the best estimates of costs in the preceding 12 months in periods of UNHS relative to periods without UNHS are negative at both 5-10 years and 13-20 years, the evidence in favour of cost-effectiveness is accumulating.

At a conservative estimate, the incidence of bilateral PCHL >40 dB in the newborn is 112 per 100,000. The cost of UNHS was estimated as £13,000 per 1,000 population (Stevens et al. 1998, reference 9) who concluded that 'the most cost effective overall approach is to use UNS with alternative systems …. for the identification of cases of late onset hearing losses.' It is by far the commonest condition for which universal newborn screening is recommended, is the commonest sensory impairment and its incidence exceeds that of childhood epilepsy or, indeed, childhood cancer. The effectiveness of UNHS in decreasing the age at confirmation of PCHL and the association between early confirmation and superior language and reading skills are evident from systematic reviews of previous research in the field, including our ownand have been judged sufficient to warrant the introduction of UNHS as standard of care by, among others, the US Preventative Services Task Force and the UK National Screening Committee. We have amended the introduction to include the statement (page 4 bottom 3 lines and over):

'From 2003 onwards, UNHS has been implemented in in the UK, USA and numerous other countries in the light of high grade evidence of the benefits of UNHS (14, 19) and there has been significant progress in the provision of paediatric audiological services (21, 22). In 2009 an estimated 5073 cases of PCHL were detected by UNHS(20) and accounted for over 43% of the confirmed cases of all 29 medical conditions for which universal newborn screening is mandated in the USA (ibid).'

Please provide a brief description of what early interventions can be implemented for newborns with hearing loss detected by UNHS.

Response: Please note that the manuscript was a cohort study of UNHS and was not a trial of early intervention. Early intervention for newborns with hearing loss detected by UNHS consists of early management of the hearing loss. Numerous standards of care have been published in Europe, North America, Australasia and elsewhere. A brief summary of the situation a decade ago written from a

North American perspective (taken from a systematic review by the US Preventative Services Task Force - manuscript reference 19) is as follows:

'With legislation for UNHS being enacted in 39 US states in recent years, screening practices and procedures have become routine in the postpartum hospital setting. ….. The JCIH [Joint Committee on Infant Hearing] recommends that early intervention services should be designed to meet the individualized needs of the infant and family, including acquisition of communication competence, social skills, emotional well-being, and positive self-esteem.4 Early intervention includes evaluation for amplification or sensory devices, surgical and medical evaluation, and communication assessment and therapy. Cochlear implants are often considered in infants with severe-to-profound hearing loss after inadequate response to hearing aids.25–28 Research in neurologic and auditory cortical development suggests that early verses late implantation may be linked to more normal cortical auditory pathway development.29–31' We do not think this detail of possible interventions in infancy is relevant to include in the manuscript evaluating costs in teenage of participants with PCHI some of whom will have received interventions in infancy.'

In our report of the effect of UNHS on language skills (Kennedy et al. 2006) referenced in the manuscript, we described the management of our study cohort, half of whom were born in periods with UNHS, as follows:

'Remedial therapy for hearing impairment was provided to all participants, since it is a public service available to all deaf preschool children in the United Kingdom. All the children with hearing impairment in this study had received advice in their homes from a teacher of the deaf and hard of hearing (87 percent within three months after confirmation of impairment), and all had been offered audiology services, including high-quality commercial hearing aids fitted according to published national quality standards. Hearing aids were always in place during the assessments reported here. Five participants born during periods with universal newborn screening had cochlear implants, as did 11 children born during periods without the screening. Confirmation of hearing loss occurred at a median of 10 months of age (interquartile range, 3 to 25), enrollment in a management program at 13 months of age (inter-quartile range, 8 to 32), and fitting with a hearing aid at 15 months of age (interquartile range, 10 to 40). The median ages were similar in the Wessex and Greater London subgroups.'

As the authors pointed out in Discussion, one of the greatest limitation of the study were modest numbers of participants at the outset and further reduction in its power to look at subgroups (e.g. severities of PCHL) by slow but steady loss of participants over the 17 years of follow-up. There were only 32 (44%), 18 (25%) and 23 (32%) participants with moderate, severe and profound PCHL, respectively. This relatively small sample size made their results less solid and conclusions less convincing.

Response: Agree. We also agree with Reviewer 2 who states 'I think that the long period of follow-up, which is of great value, makes it inevitable and it is probably not possible to collect larger group of patients in such a study.' In fact the difficulty of completing such a study is probably the reason that these data are so far unique in providing long term follow-up data on costs following birth in periods with and without UNHS.

What is already known on this topic' is too lengthy, and should be more concise.

Response: We have shortened 'What is already known' reducing it from four to three bullet points.

There are too many details in the tables. The table should be reduce and condensed.

Response: We have simplified the Tables as requested while retaining comparability with our evaluation when children were younger (manuscript reference 25). More specifically we have

1) Used the same headings and order of headings in Tables 2, 3 and 4 and

2) included in the manuscript only that part of Table 4 that indicates costs by UNHS status.
3) The remaining part of the Table, which presents costs by early confirmation status is no longer included in the manuscript and is now added to the additional materials submitted (appendix 2).

VERSION 2 – REVIEW

REVIEWER	Wroblewska-Seniuk, Katarzyna Department of Newborn's Infectious Diseases Poznan University of Medical Sciences Poznan, Poland Competing interests: I have read and understood BMJ policy on declaration of interests and declare that we have no competing interests
REVIEW RETURNED	14-Dec-2017

GENERAL COMMENTS	1. The authors have addressed all previous comments properly, introduced adequate changes in the manuscript and answered the questions. 2. It is an interesting study, investigating societal costs of permanent childhood hearing loss. It shows that the societal costs of PCHL increase with severity and the presence of additional medical conditions. 3. Statistical analysis is very complex but clearly explained and understandable.

REVIEWER	Jiang, Ze Dong 1. Children's Hospital, Fudan University, Shanghai, China 2. Department of Paediatrics, Unversity of Oxford, UK Competing interests: No
REVIEW RETURNED	23-Dec-2017

GENERAL COMMENTS	The authors have answered my queries, and revised as appropriate.

REVIEWER	Beltempo, Marc Montreal Children's Hospital-McGill University Health Centre, Montreal, QC, Canada McGill University, Montreal, QC, Canada Competing interests: None
REVIEW RETURNED	28-Dec-2017

GENERAL COMMENTS	The authors conducted an economic evaluation of the cost of permanent bilateral childhood hearing loss at 13-20 years of age and compared the costs to a control group. Patients from a previously described cohort study were interviewed. They report detailed data on long-term costs for the care of children with permanent bilateral childhood hearing. Authors have adequately responded to the comments of the previous reviewers. 1. In the discussion, the authors adequately state that birth during universal hearing screening and early confirmation of bilateral

	hearing loss is not associated with lower costs in adolescence. Universal hearing screening has been associated with early intervention and also with improvement in receptive language scores. However, this has not been shown to translate into lower overall costs during adolescence if objectively comparing birth during universal hearing screening vs none. Authors should mention that full economic evaluation integrating all costs from birth to adolescence and the costs of screening are required to better assess the cost effectiveness of universal hearing screening. 2. In the discussion, authors mention that the regression model "may represent overadjustment if the effect severity of PCHL on costs is mediated by the well-recognized inverse relationship between severity of PCHL and receptive language." Although this is possible, the previous 2006 economic evaluation by the same group found a significant association (P=0.009) between receptive language ability and costs despite adjusting for severity of PCHL. The absence of significant difference in the current evaluation may be due to the lower contribution of receptive language to total excess annual cost in adolescence compared to children 5-10 years old. This should be mentioned. Also, the total overall costs (from 0 to 20 years) may still be affected by receptive language score and further economic evaluation are required to assess this. 3. The paragraph on "effect of birth periods with UNHS" is confusing and hard to follow (page 12 lines 2-21). Authors refer to results that are not in table 5 (effect of AMC on costs within children born during UHS). I would suggest reviewing the paragraph and focusing on the results presented in table 5 (ie birth during UNHS is not associated with lower costs at 13-20 years of age). 4. I would remove the phrasing "was associated with non-significantly lower" (page 12 line 25) and replace by "was not associated with a significant difference in cost." 5. Page 2 line 31 Abstract: results would read better, "Mean cost per participant…" 6. Page 2 line 45: does the 842 to 2,389 refer to range or 95% CI interval ?

VERSION 2 – AUTHOR RESPONSE

Response to comments of Reviewer 3 on revised manuscript bmjpo-2017-000228.R1.

Reviewer: 3 Comments to the Author

The authors conducted an economic evaluation of the cost of permanent bilateral childhood hearing loss at 13-20 years of age and compared the costs to a control group. Patients from a previously described cohort study were interviewed. They report detailed data on long-term costs for the care of children with permanent bilateral childhood hearing. Authors have adequately responded to the comments of the previous reviewers.

1. *In the discussion, the authors adequately state that birth during universal hearing screening and early confirmation of bilateral hearing loss is not associated with lower costs in adolescence. Universal hearing screening has been associated with early intervention and also with improvement in receptive language scores. However, this has not been shown to translate into lower overall costs during adolescence if objectively comparing birth during universal hearing screening vs none. Authors should mention that full economic evaluation*

integrating all costs from birth to adolescence and the costs of screening are required to better assess the cost effectiveness of universal hearing screening.

Response: We have added to the relevant place in the manuscript (discussion, top of page 14): **'A full economic evaluation integrating all costs from birth to adolescence and the costs of screening would be required to better assess the cost effectiveness of universal hearing screening.'**

2. *In the discussion, authors mention that the regression model "may represent over-adjustment if the effect severity of PCHL on costs is mediated by the well-recognized inverse relationship between severity of PCHL and receptive language." Although this is possible, the previous 2006 economic evaluation by the same group found a significant association (P=0.009) between receptive language ability and costs despite adjusting for severity of PCHL. The absence of significant difference in the current evaluation may be due to the lower contribution of receptive language to total excess annual cost in adolescence compared to children 5-10 years old. This should be mentioned. Also, the total overall costs (from 0 to 20 years) may still be affected by receptive language score and further economic evaluation are required to assess this.*

Response: We have added to the relevant place in the manuscript, bottom of page 13 and overleaf): **'The absence of significant difference in the current evaluation may be due to this lower contribution of receptive language to total excess annual cost in adolescence compared to children 5-10 years old but the total overall costs (from 0 to 20 years) may still be affected by receptive language score and further economic evaluation are required to assess this.'**

3. *The paragraph on "effect of birth periods with UNHS" is confusing and hard to follow (page 12 lines 2-21). Authors refer to results that are not in table 5 (effect of AMC on costs within children born during UHS). I would suggest reviewing the paragraph and focusing on the results presented in table 5 (ie birth during UNHS is not associated with lower costs at 13-20 years of age).*

Response: We have deleted from this paragraph the final sentence relating to the effect of AMC on costs within children born during UHS.

4. *I would remove the phrasing "was associated with non-significantly lower" (page 12 line 25) and replace by "was not associated with a significant difference in cost."*

Response: We have replaced the relevant text with the reviewer's suggested revision.

5. *Page 2 line 31 Abstract: results would read better, "Mean cost per participant…"*

Response: We have replaced with **'Mean total costs per participant……..'.**

6. *Page 2 line 45: does the 842 to 2,389 refer to range or 95% CI interval ?*

Response: We have inserted **'95%CI'** prior to the figures.