PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: Retrospective population-based cohort study
AUTHORS	Watson, Samuel; Arulampalam, Wiji; Petrou, Stavros; Marlow, Neil; Morgan, Andrei; Draper, Elizabeth; Santhakumaran, Shalini; Modi, Neena

VERSION 1 - REVIEW

REVIEWER	Maria Altman Department of Medicine Solna, Clinical Epidemiology Unit, Karolinska Institutet
REVIEW RETURNED	12-Mar-2014

GENERAL COMMENTS	This is a large population-based observational study aiming to determine the effects of designation and volume of neonatal care on neonatal mortality and morbidity in very preterm infants. The question is clinically relevant and adds to the centralization debate on how to allocate and steer births of very and extremely preterm infants. The study is well performed and well communicated. However, I am not sure whether this is interesting enough for the readers of a general medicine journal like BMJOpen. **Major comments** I have to be honest and state that I am not familiar with the "Instrumental Variables methodology" used in the study, and I therefore appreciate the explanatory appendix on this method. However interesting as a method, I find it a bit strong to address it as an equivalent to an RCT in this case. The most important benefit of the RCT, is of course the randomization process and the balance of both known and unknown confounders between the two comparison groups. This cannot be done in an observational study. Although I agree with the authors that geographical distance to delivery unit is one of the most important confounders on the association between neonatal unit and infant mortality, there may also be other confounders, for example social standard, maternal smoking, BMI, pregnancy characteristics, air pollution and, of course, some completely unknown confounders that will not be randomized or controlled for with this method. I also have difficulties seeing that Instrumental variables would take care of other systematic errors, such as information or selection bias. None of the other sources on Instrumental Variables analyses that I have read talks about this

	method as an equivalent to RCT but again, this may be my own incompetence speaking. Maybe I am being simple, but to me, an added logistic regression model adjusting for geographical distance to delivery unit, would be easier to interpret than the Instrumental Variable model. However, I don't want to be one to slow down the process of statistical and epidemiological development, so I suggest the Instrumental analyses be left as a supplement, and compared to the logistic regression. Frankly, I think the Instrumental Variables analyses steals the reader's attention from an otherwise nicely performed observational study, with good validity. **Minor comments** <u>Study population, p7, line 56.</u> Infants who only received transitional care were excluded. Did you define transitional care according to a length of stay limit? What about infants who were transferred between units? Sometimes an infant spends a few weeks in a tertiary care clinic because of extreme prematurity or serious complications, then is transferred to a lower level care at another clinic. Sometimes the transfer goes in the opposite direction. Where did you allocate infants who spent more than a few days in each clinic and how many were they? There is a section in Discussion on the topic of transfers but it is not quite what I mean when I talk about study population and exposure assignment. <u>Study population</u> It is not clear to me how mortality was handled in the analyses of morbidity. Infants who die at an early age, say within 1-3 weeks from birth, will never be at risk of developing BPD or treatment for ROP, which are more long-term (relatively) outcomes. Were these infants included in analyses of morbidity? If so, a form of immortal bias would be introduced, and this could explain the differences in OR of BPD in Table B1 and B2. I would prefer to have the numbers of included infants in the different groups stated in the tables of sensitivity analyses. <u>Methods, p11, line 55</u> Unclear sentence, missing words? <u>Results</u> I think the results section overall could be presented more clearly, perhaps with separate headings and sections for Tertiary care and large-volume care or for extremely and very preterms separately. I get a little lost in the text. <u>Results, p12, line 20-24</u>. What was the comparison group here?

REVIEWER	Ciaran Phibbs VA Palo Alto Health Care System and Stanford University School of Medicine, USA

REVIEW RETURNED	14-Mar-2014

GENERAL COMMENTS	This paper uses British data to look at the issue of perinatal regionalization and the selection bias among the very preterm infants who do delivery in hospitals with big, tertiary-level NICUs. This is an important policy issue, as while the analyses that don't control for selection bias show better outcomes, they are understating the advantages of regionalization. This manuscript uses a different IV method to show what Lorch et al have already shown; that there is significant selection bias. All page numbers refer to the pages in the PDF provided to the reviewer. So that the authors can match the page numbers, the Introduction started on page 6 of the review document. As the authors have mostly addressed my previous comments, I only have a few minor comments. Minor comments: 1: Page 8, lines 8-10. The text indicates treatment for NEC and ROP, but elsewhere in the manuscript it appears that this refers to surgical treatment. Assuming that I am correct, the word "surgical" should be added before "treatment." 2. Page 8, line 48. I am pretty sure that the reference number should be 21, not 20. 3. Page 15, top. The discussion of the negative effects of neonatal transport should be added to this paragraph. Two excellent references for this are: Bowman E, Doyle LW, Murton LJ, Roy RN, Kitchen WH. Increased mortality of preterm infants transferred between tertiary perinatal centres. Bmj. Oct 29 1988;297(6656):1098-1100. Lee SK, Zupancic JA, Pendray M, et al. Transport risk index of physiologic stability: a practical system for assessing infant transport care. J Pediatr. Aug 2001;139(2):220-226. 4: Page 16, top. This discussion only addresses the problems of successful maternal transport. This discussion should be expanded to note that there are regions that have been able to achieve very high levels of the high-risk deliveries occurring in the designated centers. This includes published data from Portugal and Finland of over 90% of the VLBW, or GA<32 weeks being delivered in the designated regional centers. There is unpublished data from Western Australia of 95%. This discussion should note that this is for a much broader group than the <26 weeks that is targeted by the British guidelines. My recommendation of "Minor revision" should really be considered a "conditional acceptance" as there are only some minor editorial issues that need to be addressed. There is no need for an additional review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Maria Altman
Institution and Country Department of Medicine Solna, Clinical Epidemiology Unit, Karolinska Institutet

Major comments

I have to be honest and state that I am not familiar with the "Instrumental Variables methodology" used in the study, and I therefore appreciate the explanatory appendix on this method. However interesting as a method, I find it a bit strong to address it as an equivalent to an RCT in this case. The most important benefit of the RCT, is of course the randomization process and the balance of both known and unknown confounders between the two comparison groups. This cannot be done in an observational study. Although I agree with the authors that geographical distance to delivery unit is one of the most important confounders on the association between neonatal unit and infant mortality, there may also be other confounders, for example social standard, maternal smoking, BMI, pregnancy characteristics, air pollution and, of course, some completely unknown confounders that will not be randomized or controlled for with this method. I also have difficulties seeing that Instrumental variables would take care of other systematic errors, such as information or selection bias. None of the other sources on Instrumental Variables analyses that I have read talks about this method as an equivalent to RCT but again, this may be my own incompetence speaking.

Maybe I am being simple, but to me, an added logistic regression model adjusting for geographical distance to delivery unit, would be easier to interpret than the Instrumental Variable model. However, I don't want to be one to slow down the process of statistical and epidemiological development, so I suggest the Instrumental analyses be left as a supplement, and compared to the logistic regression. Frankly, I think the Instrumental Variables analyses steals the reader's attention from an otherwise nicely performed observational study, with good validity.

- The main point raised by the referee here is the usefulness of the instrumental variable (IV) methodology implemented in the paper. The use of this methodology is crucial to the argument forwarded in the paper where the principle aim is to determine the causal effect of volume and designation of the neonatal unit at the hospital of birth on infant clinical outcomes in a managed clinical network (MCN) setting. The IV methodology allows us to correct for unobserved confounding caused by transfers prior to birth leading to more severely ill infants being born in hospitals with higher designation or higher volume units. Inclusion of any variable (such as the geographical distance of the unit) that is related to the characteristic of the unit in the standard adjusted logit will not deal with the problem of unobserved confounding and will invalidate any inferences drawn from these models.
- We believe this paper makes an important methodological contribution to the literature, as suggested by the second referee.

Minor comments

Study population, p7, line 56. Infants who only received transitional care were excluded. Did you define transitional care according to a length of stay limit? What about infants who were transferred between units? Sometimes an infant spends a few weeks in a tertiary care clinic because of extreme prematurity or serious complications, then is transferred to a lower level care at another clinic. Sometimes the transfer goes in the opposite direction. Where did you allocate infants who spent more than a few days in each clinic and how many were they? There is a section in Discussion on the topic of transfers but it is not quite what I mean when I talk about study population and exposure assignment.

- All infants were allocated to the unit of the hospital in which they were born, subsequent transfers are not factored in to the model and are implicit in the interpretation of the observed effects as discussed in the Discussion section (see pages 15-16). Transitional care (TC) is defined according to English Department of Health's Healthcare Resource Group (HRG) 4 specification for neonatal care, - code "XA04Z". This has now been clarified in the text (pages 7-8 in the revised version). Only five infants were excluded who were recorded as receiving exclusively TC, this has also been clarified in the text (see page 7).

Study : It is not clear to me how mortality was handled in the analyses of morbidity. Infants who die at an early age, say within 1-3 weeks from birth, will never be at risk of developing BPD or treatment for ROP, which are more long-term (relatively) outcomes. Were these infants included in analyses of morbidity? If so, a form of immortal bias would be introduced, and this could explain the differences in OR of BPD in Table B1 and B2. I would prefer to have the numbers of included infants in the different groups stated in the tables of sensitivity analyses.

- In the main analysis, each morbidity outcome is considered separately. As the reviewer rightly points out this may introduce bias since those infants who die do not experience the morbidity outcome but may have had they not died. For this reason, in table B2 infants who died were excluded from the morbidity analyses. This has now been clarified in the text (see page 11). The total number of infants included in each morbidity analysis is provided in the table (see table B2), in addition the total number of infants experiencing each outcome is provided in table 1.

Methods, p11, line 55: Unclear sentence, missing words?

- This has been corrected (see page 12).

Results: I think the results section overall could be presented more clearly, perhaps with separate headings and sections for Tertiary care and large-volume care or for extremely and very preterms separately. I get a little lost in the text.

- We would like to thank the reviewer for this observation. The results are currently presented in the order in which the methods have been detailed. Some minor amendments to the results section have been made to improve the clarity of the text (page 12).

Results, p12, line 20-24. What was the comparison group here?

- We have now clarified this on page 12.

Reviewer: 2
Reviewer Name Ciaran Phibbs
Institution and Country VA Palo Alto Health Care System and Stanford University School of Medicine, USA

Comments for the Authors:
This paper uses British data to look at the issue of perinatal regionalization and the selection bias among the very preterm infants who do delivery in hospitals with big, tertiary-level NICUs. This is an important policy issue, as while the analyses that don't control for selection bias show better outcomes, they are understating the advantages of regionalization. This manuscript uses a different IV method to show what Lorch et al have already shown; that there is significant selection bias.

All page numbers refer to the pages in the PDF provided to the reviewer. So that the authors can match the page numbers, the Introduction started on page 6 of the review document. As the authors have mostly addressed my previous comments, I only have a few minor comments.

Minor comments:
1: Page 8, lines 8-10. The text indicates treatment for NEC and ROP, but elsewhere in the manuscript it appears that this refers to surgical treatment. Assuming that I am correct, the word “surgical” should be added before “treatment.”

- In response to the reviewer’s request, this has now been corrected now (page 8, 2nd paragraph).

2. Page 8, line 48. I am pretty sure that the reference number should be 21, not 20.

- This has been corrected now.

3. Page 15, top. The discussion of the negative effects of neonatal transport should be added to this paragraph. Two excellent references for this are:
Bowman E, Doyle LW, Murton LJ, Roy RN, Kitchen WH. Increased mortality of preterm infants transferred between tertiary perinatal centres. Bmj. Oct 29 1988;297(6656):1098-1100.
Lee SK, Zupancic JA, Pendray M, et al. Transport risk index of physiologic stability: a practical system for assessing infant transport care. J Pediatr. Aug 2001;139(2):220-226.

- In response to the reviewer’s request, the discussion around this point has been expanded and the recommended references inserted (see page 16).

4: Page 16, top. This discussion only addresses the problems of successful maternal transport. This discussion should be expanded to note that there are regions that have been able to achieve very high levels of the high-risk deliveries occurring in the designated centers. This includes published data from Portugal and Finland of over 90% of the VLBW, or GA<32 weeks being delivered in the designated regional centers. There is unpublished data from Western Australia of 95%. This discussion should note that this is for a much broader group than the <26 weeks that is targeted by the British guidelines.

- In response to the reviewer’s request, the discussion around this point has been expanded and further references provided (see pages 16 and 25).

My recommendation of "Minor revision" should really be considered a "conditional acceptance" as there are only some minor editorial issues that need to be addressed. There is no need for an additional review.

We do hope that we have responded adequately to all the comments and suggestions made by reviewers.

VERSION 2 – REVIEW

REVIEWER	Maria Altman Department of Medicine Solna, Clinical Epidemiology Unit, Karolinska Institutet
REVIEW RETURNED	06-May-2014

GENERAL COMMENTS	The authors have adressed the comments and questions from the reviewers appropriately and I have no further comments.