PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-Term Mortality After Community-Acquired Sepsis: A Longitudinal Population-Based Cohort Study
AUTHORS	Wang, Henry; Szychowski, Jeff; Griffin, Russell; Safford, Monika; Shapiro, Nathan; Howard, George

VERSION 1 - REVIEW

REVIEWER	Brad Winters Johns Hopkins University School of Medicine US of A
REVIEW RETURNED	05-Nov-2013

GENERAL COMMENTS	This is a well done study using a large cohort to examine the question of whether people who experience sepsis have an increased chance of death as compared to those who never had sepsis over a much longer time frame than that typically used in sepsis outcome studies. I have the following comments and requests for the authors in order to revise the manuscript prior to acceptance for publication. 1. In the abstract please spell out what HR means for the first use before using the abbreviation HR. 2. While you reference the "REGARDS" study, if you could elaborate in more detail what that study's intent was it would be helpful. Many readers will not have the time or inclination to go and look up that reference and it would be helpful to better understand what the "buckle" and "belt" means in terms of the cohort as well as other details since this may influence interpretation of the results. Was this based on a high geographical prevalence analysis for stroke? 3. I maybe misunderstanding this issue but it appears that the initial screen for sepsis was based on self-reporting by the participants of the REGARDS study and that these initial 1349 patient reports were then screened through their actual medical records to determine if they truly met the criteria for sepsis. this knocked the number of true septic patients down to 900 or so. My question is, how do we know if any of the other 28000 or so patients did have sepsis but just didn't report it and therefore weren't screened? Was there a method to know this? If not, you should mention this in the limitations section as a potential problem and how you think it might have affected the results if some septic patients were in the non-septic group. 4.You controlled for age but is the risk of death linear with age since it appears your control used a linear model? If the relationship is not linear then you should be using a non-linear model such as multiple categories for say decades of age. I realize this may affect your power. Did you check to see if the relationship is linear, if it is then you are good. 5.In your discussion, you comment on how we don't know how sepsis may complicate other conditions and thereby leading to this increased mortality. Perhaps a couple of short sentences on how

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	AKI in sepsis/severe sepsis may worsen CKI etc. 6. Please expand the limitations discussion especially the over 45 year old demographic since your incremental mortality is very high compared to the few other papers that have examined in a similar time frame. While the results are compelling, readers should realize that this group is not generalizable to all adults since 18-45 year old people have much less chronic disease burden and likely have a lower incremental mortality. 7. Finally, consider changing the title to "Long term mortality after community Acquired Sepsis" since that is really what your cohort is.

REVIEWER	Andrew Rhodes St George's Hospital London SW17 0QT UK
REVIEW RETURNED	06-Nov-2013

GENERAL COMMENTS	This study is an analysis of an available database from the US. The database is the REGARDS cohort (Reasons for Geographic And Racial Differences in Stroke). I would like the authors to provide a better description of this database. I cannot understand whether all participants have been enrolled into it due to them suffering a stroke or it is set up to longitudinally assess stroke development in an otherwise healthy cohort. Whichever, clearly this is important in understanding the cohort used for this study and an improved explanation would undoubtedly enhance the paper – even if it were in an expanded ESM. My main contention with the analysis is in the time-lag difference between the group who develop sepsis and those who are classified as not. This results as the group classified as having sepsis may be admitted to hospital some time (could be years) after being enrolled in the database whereas the control group is all enrolled at baseline. I could not find a description of how long this time lag was and this should be provided. My concern is that for a patient to be enrolled as sepsis they must already have fulfilled two criteria: (1) survived the period from recruitment to the dataset (making their survival as a group greater than the controls at this point and (2) by definition then being hospitalized which could define them as a weaker group. The authors have attempted to correct for this by adjusting for age, however this may not be sufficient. In addition the Cox analysis is also adjusted for other baseline factors collected within the database. These are obviously designed to explain the risk of stroke and may not be adequate to adjust for risk of death following sepsis. For instance immune-suppression, malignancy and chronic lung disease would all be predictors of death following sepsis but are not included in this dataset. The adjustment would also be greatly enhanced if it could include factors describing the origin of the patient prior to the hospital admission (home / skilled nursing facility etc.) and markers of function or quality of life. There should also be consideration given as to whether all the patients are in fact clustered within different health regions of the US, which could be adjusted for in a hierarchical multi-level model.

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	Minor comments 1. The abstract describes a 6-year follow up period with a median value of 6.1 years. Clearly it is more than a 6 year follow up. 2. It is not clear as to whether the inclusion criteria of SIRS variables all had to be present simultaneously or whether they could be fulfilled asynchronously over the 28-hour window. 3. The Table numbering (3 and 4) seems to be confused in the results section. 4. The results describe the risk of 'early' death, but I cannot find a description of what early is. 5. Table 5 (and Appendix 2) describe the hazard ratios. I presume these are the adjusted ratios but this is not clear. I would like to see in the ESM far greater detail as to what the model constructed contained and how well it performed.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Brad Winters

This is a well done study using a large cohort to examine the question of whether people who experience sepsis have an increased chance of death as compared to those who never had sepsis over a much longer time frame than that typically used in sepsis outcome studies. I have the following comments and requests for the authors in order to revise the manuscript prior to acceptance for publication.

1. In the abstract please spell out what HR means for the first use before using the abbreviation HR.

• We apologize for the oversight and have made the appropriate correction.

2. While you reference the "REGARDS" study, if you could elaborate in more detail what that study's intent was it would be helpful. Many readers will not have the time or inclination to go and look up that reference and it would be helpful to better understand what the "buckle" and "belt" means in terms of the cohort as well as other details since this may influence interpretation of the results. Was this based on a high geographical prevalence analysis for stroke?

• In the methods page 6 para 2, we expanded description of REGARDS and the terms "stroke belt" and "buckle."

3. I maybe misunderstanding this issue but it appears that the initial screen for sepsis was based on self-reporting by the participants of the REGARDS study and that these initial 1349 patient reports were then screened through their actual medical records to determine if they truly met the criteria for sepsis. This knocked the number of true septic patients down to 900 or so. My question is, how do we know if any of the other 28000 or so patients did have sepsis but just didn't report it and therefore weren't screened? Was there a method to know this? If not, you should mention this in the limitations section as a potential problem and how you think it might have affected the results if some septic patients were in the non-septic group.

• The identification of all events in REGARDS originates from participant description of a hospitalization. This is a typical approach in a population-based cohort study. For this study, the participant's description of a hospitalization for an infection (pneumonia, kidney infection, etc) triggered the process of medical record retrieval. Our team then systematically reviewed the medical record to determine if the case in fact fulfilled defined sepsis criteria.

• Using the current data we are unable to ascertain unreported hospitalizations for infection. We better

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articulated this limitation on page 15 para 2.

4.You controlled for age but is the risk of death linear with age since it appears your control used a linear model? If the relationship is not linear then you should be using a non-linear model such as multiple categories for say decades of age. I realize this may affect your power. Did you check to see if the relationship is linear, if it is then you are good.

• We thank Dr. Winters for his astute observations. We re-ran all models using age-decile instead of age.

5.In your discussion, you comment on how we don't know how sepsis may complicate other conditions and thereby leading to this increased mortality. Perhaps a couple of short sentences on how AKI in sepsis/severe sepsis may worsen CKI etc.

• We expanded discussion of this point on page 15 para 1.

6. Please expand the limitations discussion especially the over 45 year old demographic since your incremental mortality is very high compared to the few other papers that have examined in a similar time frame. While the results are compelling, readers should realize that this group is not generalizable to all adults since 18-45 year old people have much less chronic disease burden and likely have a lower incremental mortality.

• We expanded discussion of this point on page 15 para 2.

7. Finally, consider changing the title to "Long term mortality after community Acquired Sepsis" since that is really what your cohort is.

• We revised as suggested.

Reviewer Name: Andrew Rhodes

Thank you for asking me to review this fascinating manuscript on an interesting subject. It is well written and well presented.

This study is an analysis of an available database from the US. The database is the REGARDS cohort (Reasons for Geographic And Racial Differences in Stroke). I would like the authors to provide a better description of this database. I cannot understand whether all participants have been enrolled into it due to them suffering a stroke or it is set up to longitudinally assess stroke development in an otherwise healthy cohort. Whichever, clearly this is important in understanding the cohort used for this study and an improved explanation would undoubtedly enhance the paper – even if it were in an expanded ESM.

• We apologize for the confusion. REGARDS enrolls healthy individuals, following them into the future for stroke events. REGARDS is not a “stroke-only” cohort. We have appropriately expanded description of REGARDS on page 7 para 1.

My main contention with the analysis is in the time-lag difference between the group who develop sepsis and those who are classified as not. This results as the group classified as having sepsis may be admitted to hospital some time (could be years) after being enrolled in the database whereas the control group is all enrolled at baseline. I could not find a description of how long this time lag was and this should be provided. My concern is that for a patient to be enrolled as sepsis they must already

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have fulfilled two criteria: (1) survived the period from recruitment to the dataset (making their survival as a group greater than the controls at this point and (2) by definition then being hospitalized which could define them as a weaker group. The authors have attempted to correct for this by adjusting for age, however this may not be sufficient.

• Observation of non-sepsis participants started upon their recruitment to the REGARDS study in 2003-2005. Observation of sepsis participants started upon their hospitalization for their first sepsis event. We clarified the time lag from REGARDS enrollment to first sepsis in the Results page 12 para 1; “Median time to the first sepsis event was 1.9 years (IQR 3.5-5.0).”

• As astutely noted by Dr. Rhodes, for a range of reasons the sepsis individuals may be “weaker” or “stronger” than the non-sepsis individuals. We adjusted for a wide range of variables (Table 2) to account for the confounding influence of subject demographics, health behaviors and chronic medical conditions - not just age.

• As with all observational studies, residual confounding is always a concern. However, our risk adjustment strategy accounted for a comprehensive range of variables that were systematically identified for each participant at the beginning of the REGARDS study. We have adjusted for additional variables as noted below. The availability of comprehensive baseline information on each participant is a unique aspect of REGARDS and strength of our analysis. We articulate this point on page 16 para 2.

In addition the Cox analysis is also adjusted for other baseline factors collected within the database. These are obviously designed to explain the risk of stroke and may not be adequate to adjust for risk of death following sepsis. For instance immune-suppression, malignancy and chronic lung disease would all be predictors of death following sepsis but are not included in this dataset.

• We understand the reviewer’s concern. We did in fact adjust for history of cancer. We also did adjust for chronic lung disease. However, we were not able to ascertain immunosuppression.

• As alluded to, REGARDS was designed to study stroke, not sepsis. However, the study design was robust enough to allow us to characterize sepsis events and risk. It would be logistically and financially difficult to replicate a cohort of this scale. We note that there have been no population-based cohorts designed specifically to study sepsis. In fact, the sepsis literature contains very limited data indicating the “baseline” pre-hospitalization risk factors for sepsis. Our study has unique design features that address these gaps. We articulate this point on page 15 para 3.

The adjustment would also be greatly enhanced if it could include factors describing the origin of the patient prior to the hospital admission (home / skilled nursing facility etc.) and markers of function or quality of life. There should also be consideration given as to whether all the patients are in fact clustered within different health regions of the US, which could be adjusted for in a hierarchical multi-level model.

• We apologize – the origin of subject immediately prior to hospital admission is not available.

• For all participants, REGARDS determined health status using Short-Form-12 (SF-12) scores, which included a mental component score (MCS) and a physical component score (PCS). We added MCS and PCS quintiles to the multivariable analysis. Please see page 8 para 3, and Table 2.

• Dr. Rhodes alludes to the Dartmouth Atlas of Healthcare, which has exhaustively characterized community healthcare resources (http://www.dartmouthatlas.org/data/region/). Examples of healthcare geography described by the Dartmouth Atlas include hospital referral regions, hospital

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service areas, and primary care service areas. The relationship between healthcare regions and the risks of sepsis attack and mortality is an interesting but extremely complex question. Further clouding this hypothesis are questions about the socioeconomic characteristics of each community region. We made an a priori decision not to explore community healthcare resources in this analysis. We are exploring the associations between community healthcare resources, socioeconomic status and sepsis risk in a separate analysis.

• The geographic regions of interest in REGARDS are the stroke belt regions (stroke belt, stroke buckle, other). Dr. Rhodes' comment highlights that observations may be "clustered" (lack independence) within a geographic region. There are numerous strategies for handling clustered observations. In the original analysis we did directly adjust for region, incorporating stroke belt region as a covariate in the multivariable model. We added sensitivity analyses repeating the analysis using a robust variance estimator as well as by modeling stroke belt region as a shared frailty (analogous to a hierarchical model for cox regression); there were no major differences in the results. Please see page 10 para 3, and page 13 para 1.

Minor comments

1. The abstract describes a 6-year follow up period with a median value of 6.1 years. Clearly it is more than a 6 year follow up.

• We apologize for the oversight and have made appropriate corrections.

2. It is not clear as to whether the inclusion criteria of SIRS variables all had to be present simultaneously or whether they could be fulfilled asynchronously over the 28-hour window.

• We clarified that SIRS could be fulfilled asynchronously during the initial 28-hours. Please see page 7 para 3.

3. The Table numbering (3 and 4) seems to be confused in the results section.

• We apologize for the oversight and have made appropriate corrections.

4. The results describe the risk of 'early' death, but I cannot find a description of what early is.

• We revised page 13 para 2 to refer to "rates of death" rather than "early" death.

5. Table 5 (and Appendix 2) describe the hazard ratios. I presume these are the adjusted ratios but this is not clear. I would like to see in the ESM far greater detail as to what the model constructed contained and how well it performed.

• These are adjusted hazard ratios. We included the full multivariable model in new Appendix 1.

VERSION 2 – REVIEW

REVIEWER	Andrew Rhodes St George's Healthcare NHS Trust, London, UK
REVIEW RETURNED	14-Dec-2013

- The reviewer completed the checklist but made no further comments.

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