Author’s response to reviews

Title: Mortality following acute pancreatitis: social deprivation, hospital size and time of admission: record linkage study

Authors:

Stephen E Roberts (stephen.e.roberts@swansea.ac.uk) 
Kymberley Thorne (k.thorne@swansea.ac.uk) 
Adrian Evans (Phillip.A.Evans@wales.nhs.uk) 
Ashley Akbari (a.akbari@swansea.ac.uk) 
David G Samuel (daisams@doctors.org.uk) 
John G Williams (j.g.williams@swansea.ac.uk)

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Author’s response to reviews:

The Editor, 
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Dear Editor

Thank you for your e-mail. We are grateful for the reviewer comments provided, we have responded to each in detail and think they have improved the manuscript.

Please find uploaded the revised manuscript with all revisions denoted in blue font.

Yours sincerely

Dr Stephen E Roberts, reader in epidemiology and public health
Dr Kymberley Thorne, research officer
Professor P Adrian Evans, consultant and professor of emergency medicine
Mr Ashley Akbari, data analyst
Dr David G Samuel, specialist registrar in gastroenterology
Professor John G Williams, consultant gastroenterologist and professor of health services research

Reviewer’s report
Title:
Mortality following acute pancreatitis: social deprivation, hospital size and
time of admission: record linkage study

Reviewer's report:

I have been asked to comment primarily on the statistical methods. I think the analysis is mostly OK, though I have some quibbles. Also, the justification for the study and the reporting and interpretation of the results need some more work.

We have responded in detail to the statistical review comments as follows:

MAJOR COMPULSORY REVISIONS

1). The study’s main objectives are given as, “to establish whether mortality is influenced by the following five factors; social deprivation, size of hospital, week day of admission, recruitment of newly qualified junior doctors each August and EWTDs for junior doctors' working hours.” What I think is missing from the introduction is an argument why any of these factors should or might correlate with mortality following admission for acute pancreatitis. Gaps in the literature are not sufficient reason.

As suggested, we have now provided further justification for this study as follows: “There is large variation in mortality following emergency admissions, including acute pancreatitis, across hospitals in the UK. Although some of this variation is explained by patient case mix, there is major concern that it may be linked to factors such as changes in junior doctor’s working hours, recruitment of newly qualified doctors in August each year, the week day of admission and the hospital size.” (page 4, para 2).

We have also now provided additional explanation as to why the study factors may be linked to mortality following acute pancreatitis (page 4, para 2 and para 3).

We should add that this study is funded by the Wellcome Trust and is an important investigation.

2). Methods: there were rather a lot of hypothesis and sensitivity tests performed. Some justification of the usual alpha of 5% is therefore needed in the methods, and some discussion of the possibility of false positive results is needed in the discussion. It strikes me that this is a big potential reason for various findings, such as the subgroup alcohol-related disease and the large-hospital group. On the subject of p values, I find it odd that there aren’t any. “P<0.05” isn’t enough information given the multiple testing.

As indicated, we have now used a bonferroni correction to adjust for multiple testing and to further assess false positive results (page 11, para 1). When using this bonferroni correction, none of the study factors were significant. We had previously stated that the study factors had limited impact on mortality following acute pancreatitis (Abstract, discussion) and have now further emphasised that
they had no significant impact after adjusting for multiple comparisons (in the Abstract Discussion and also in the main Discussion, page 24, para 1).

We have provided 95% confidence intervals extensively throughout the Tables, Figures and text as they are conventionally preferred to p-values as a superior measure of the precision of study findings.

However, we have now also included p-values for the significant findings in Tables 2 and 3. If the Editor would prefer additional p-values we would be happy to oblige.

3). Why were models run with and without adjustment for comorbidities?

We provided logistic regression findings with and without adjustment for co-morbidities, which is a standard practice, as no single methodology is perfect. As the reviewer would appreciate when using routine administrative inpatient data to measure co-morbidities, there is some under-recording from the co-morbidity diagnoses. Although we additionally record linked the inpatient data to national primary care data to improve on this, as we have commented (page 19, para 2, lines 9-11) it would still not be complete. Importantly there was little difference between the study findings whether adjusting for co-morbidities or not.

We do not have a strong preference for presenting the findings with/without co-morbidity adjustment (or with both - at present) especially as they make little difference to the study findings.

4). Why was direct standardisation used? Some of the strata will be pretty small.

We have now further clarified that direct standardisation was used to standardise mortality and admission rates across the month of year (see Methods section, page 10, para 2 and also the footnotes to Figure 1. This is a very well established and respected methodology for this purpose. We have employed it extensively in many studies published in journals such as the BMJ, Lancet and Gut – and have not received any queries from reviewers about its suitability. To prevent low numbers of cases, we combined age groups where there were low counts.

5. Was hierarchical logistic regression modelling considered to deal with the clustering of patients within hospitals? In theory, this ought to be done, esp with hospital-level covariates such as size and potentially important variations in staffing / junior changeover / weekend effects involved. I recommend you do this. What may happen is that some of the stat signif findings will become non-signif due to the correct standard errors being used – or nothing at all – but it needs to be checked.

As suggested we have now used hierarchical logistic regression to separate the hospital level covariate (size of hospital) from the patient level covariates (all other study factors; page 11 para 1). As we report on page 16, para 1, this made little difference to the study findings.
Non-hierarchical logistic regression is a conventional method of analysis used in large studies of hospital mortality - including many that the statistical reviewer has co-authored.

MINOR ESSENTIAL REVISIONS

6). Introduction: “The mortality rate following acute pancreatitis typically varies between about 4% and 10% [2-9], but increases to about 15% to 30% in cases of severe necrotising [2].” Over what time periods?

We have now further clarified that this time period refers to recent years (page 4, para 1).

7. Discussion: some reference is needed for the accuracy of primary diagnosis coding in Wales. I used PEDW in the late 1990s, and it was pretty ropy.

We have already provided a reference [32] to a study that validated primary diagnoses in PEDW inpatient data (page 19, para 1, last sentence) as well as references to some of the many studies based on PEDW that have been published in international Medline journals.[20-25].

This study also validated the (more widely used) English equivalent national inpatient data source (HES) and found higher validation rates in PEDW than in HES. Having used both HES and PEDW extensively over the last 15 years, the considered opinion is that PEDW is at least as accurate if not more accurate than HES in this respect. This is largely because of the smaller number of hospitals that provide data for PEDW than for HES – and as we found in our validation study - with less scope for poor data quality from some hospitals (as in HES). Both HES and PEDW have improved greatly since the 1990s.

Our study was from 2004 to 2012 rather than from the late 1990s.

8). “We found evidence of increased mortality for alcoholic acute pancreatitis during the months from August to October, but no significant increase for acute pancreatitis overall or for gallstone acute pancreatitis. It is possible that an increase in mortality during popular holiday months such as August and September may be linked to a lack of senior consultant cover and low senior to junior doctor ratios, as well as the recruitment of newly qualified junior doctors in August.”

I don’t see why you’d see a junior changeover effect for alcoholic acute pancreatitis and not the other types. If not simply due to multiple testing, why might this be the case? The junior changeover effect was hypothesised to last one, two and then three months. While the odds ratios were similar for each version of this variable, why would one have expected the effect to last so long for acute pancreatitis? Might something like summer drinking be a possible alternative explanation?
We assessed the 'August effect' cumulatively over one, two and three months as it relates to the recruitment of newly qualified doctors in August each year in the UK, rather than 'changeover' months for junior doctors which occur during other months. Experience is cumulative.

It is also possible that alcohol aetiology pancreatitis may receive lower priority care - as widely reported for other alcoholic conditions such as alcoholic liver cirrhosis - during these months, as we now comment (page 22, para 2, last sentence).

We had already commented that the increased mortality may be linked to higher alcohol consumption during the holiday month of August (page 22, para 2, penultimate sentence) and have now further emphasised this.

9). Figures 1 and 2: are those lines error bars? They don’t help us compare the pairs of proportions, which is presumably part of the purpose of this plot.

As stated in the caption to Figure 1, "vertical bars represent 95% confidence intervals". For additional clarity, we have now repeated this statement in the caption to Figure 2.

95% confidence intervals are the recommended means of illustrating precision graphically (for example, BMJ guidelines) and are used extensively by the statistical reviewer.

10). I think Fig 3 is missing a caption.

There is no Figure 3 in this manuscript.

We have included Professor John Williams, consultant gastroenterologist, as a co-author because of his specialist and study design advice (as a main investigator of this Wellcome Trust study, previously acknowledged but now increased) and also because of his writing contribution of the manuscript.