PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Analysis of the Bereavement Effect After the Death of a Spouse in the Amish
AUTHORS	Schaffer, Alejandro; Seifter, Ari; Singh, Sarabdeep; McArdle, Patrick; Ryan, Kathleen; Shuldiner, Alan; Mitchell,

VERSION 1 - REVIEW

REVIEWER	Geraldine Mineau Research Professor University of Utah USA I have no conflict of interest related to this manuscript.
REVIEW RETURNED	27-Aug-2013

THE STUDY	1. The authors state that the data are uncensored; however, the cohort 1901-1925 appears to exclude people that were alive in 2010. There would be some married couples and widow(er)s born in 1920-25 that would still be alive. The authors might exclude this cohort from the analysis. 2. There is no adjustment for the problem of people with few children also being people who die young--this may lead to more children being associated with better survival. Also this was treated as a time independent variable which means the values could not change over time; however, surely this cannot be true if the authors imposed no survival age restriction (i.e. the couples must survive until the wife lived past age 40 or 45)
RESULTS & CONCLUSIONS	The authors indicate that the Amish have a strong degree of social support and include community-managed health insurance. This needs to be discussed more. Would it have been in place across the whole time period? They control for education. Wouldn't this vary wildly over this period? Did women receive formal education in the beginning of the period?
GENERAL COMMENTS	This is a concise paper on a novel population and addresses the important topic of social support at the time of widowhood.

REVIEWER	Dr. Chris Sutton, CStat Principal Lecturer Lancashire Clinical Trials Unit (LCTU) School of Health University of Central Lancashire
REVIEW RETURNED	27-Aug-2013

THE STUDY	1) The outcome measure is not clearly or corectly defined. The

	outcome measure appears to be a survival outcome, with the time aspect 'age' and the event 'death'. This should be clearly stated in both the Abstract and main Methods section. 2) Most of the statistical methods are well described and in detail. However, details of how sex was taken into account in the modelling are absent. The authors suggest (by citing eg. Schaefer, Quesenberry and Wi (1995)) that they modelled males and females separately. It is vital that these details are included in a revised manuscript. 3) Large numbers of Amish couples have been excluded; reasons for excluding all couples with missing marriage dates AND for which either partner had missing birth OR death date are not all clear. In some cases, it would appear that individuals would have sufficient data to be included in the modelling, but it is unclear whether this would be a relatively small number. Moreover, this approach could cause bias and, without further details (see review of late sections), it is not possible to evaluate the potential magnitude of such bias. Sensitivity analysis to assumptions surrounding missing data (and the imposition of the stated exclusion criteria) would be advisable in most circumstances and should be considered. 4) The response to Section 13 c of the STROBE checklist indicates that Table 2 replaces a flow diagram; I do not agree that this is an adequate replacement for a flow diagram. It would be extremely beneficial to see the flow diagram illustrating the exclusion of members of the population under investigation (as could have been defined a priori in terms of 'cohort' membership) due to missing data (and other reasons).
RESULTS & CONCLUSIONS	1) Although most of the results are adequately presented, I have concerns about there is no test result or model fit statistic presented to support the assertion "... that there is an increase in risk of mortality for recently widowed hosbands and wives, and that the hazard decreases with time since bereavement..." P14, l46-51. Whilst the estimates suggest that this might be the case, sample sizes are relatively small, certainly compared with the overall sample size. Moreover, it is similarly unclear as to whether the interpretation of these findings (p.16, l13-18) are fully supported by the data.
REPORTING & ETHICS	The authors have completed a STROBE checklist. However, section 6 (Bias) does not reflect on potential bias due to excluding those with missing data, and section 12 (c) and (e) do not adequately address the exclusion of those with missing data and the lack of a sensitivity analysis to investigate the likely bias the missing data might induce. I have commented on Section 13 c in an earlier section.
GENERAL COMMENTS	Further minor queries and comments 1) p8 l4-6: Are the 136,213 Amish couples not included in the 539,822 Amish individuals? The current text implies that this is the case, but I feel it would be better if it gave the total number in the database and the number of couples. The 136,213 couples would normally be the population under investigation (probably restricted by date) and any subsequent exclusions illustrated in the flow diagram. 2) p14 l 25: "Number of surviving children >6 vs <=2..." This does not really make sense in isolation and merits further explanation. Are the authors implying that an active decision was made to merge the categories <=2 and 3-6 surviving children due to similar parameter (risk ratio) estimates? If so, this should be stated explicitly and the interpretation should reflect this; additionally, the caption of Figure 2 should state the acronym (NSC) and, if possible, the associated coding of this variable reflected in the figure.

	3) It is suggested that not needing to incorporate censoring methods whilst ignoring people with missing birth and death dates is a strenth of the study. However, a key reason for incorporating censoring into survival analysis is to enable proper handling of such people, albeit often based on untestable assumptions. The lack of information on how many Amish couples were excluded due to missing birth and/or death dates precudes further assessment of this statement (see also earlier comments regarding missing birth/death dates). 4) Could the findings potentially be explained as indicating that the it is close bond between spouses, providing emotional, psychological and social support which is important, rather than purely the social aspect. This is addressed to some degree on p17 (l48-53) but could be strengthened; moreoever, this could be seen as being supported by the finding on the effect of the number of children (with potentially closer bonds with smaller numbers of surviving children).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. The authors state that the data are uncensored; however, the cohort 1901-1925 appears to exclude people that were alive in 2010. There would be some married couples and widow(er)s born in 1920-25 that would still be alive. The authors might exclude this cohort from the analysis.

RESPONSE:

This is an excellent point. To address the reviewer's valid concern about the 1901-1925 cohort, we redid the combined analysis of Figure 3 using the three eldest cohorts only, omitting the 1901-1925 cohort. The results in Figure 3 do not change significantly (see Table R1 at the end of this document).

The flowchart (new Figure 1) that we added in response to comments from reviewer 2 does show the magnitude of the problem. There were 30044 couple excluded because of a missing death date, and more than 90% of these would have been in the 1901-1925 cohort had they been included.

To the paragraph that read:

"Hazard ratios and 95% CIs for the time since bereavement analysis are shown in Figure 3. These results were obtained using the CPH model and the design defined in Table 2c. The results show that there is an increase in risk of mortality for recently widowed husbands and wives, and the hazard decreases with time since bereavement but remains significantly greater than 1. Further, the hazard is higher (not significant) in wives vs husbands during the first 12 months following bereavement."

we added the following sentences in section Results, on page 16:

"To address the issue that many individuals in the 1901-1925 cohort may still have been alive at the last AGDB update and hence censored, we performed the analysis for time since bereavement omitting the cohort 1901-1925. The results show that the hazard ratios provided in Figure 4 have not changed significantly; for example, for 25-26 months post bereavement the hazard ratios change from 1.30 and 1.23 for all cohort to 1.25 and 1.17 for the three eldest cohorts."

2. There is no adjustment for the problem of people with few children also being people who die young--this may lead to more children being associated with better survival. Also this was treated as a time independent variable which means the values could not change over time; however, surely this cannot be true if the authors imposed no survival age restriction (i.e. the couples must survive until the wife lived past age 40 or 45)

RESPONSE:

To address the reviewer's concern, we performed the analysis of Figure 3 (was Figure 2 in the original submission) without the number of surviving children as a covariate. The results in Figure 3 do not change significantly (see Tables R2 and R3 at the end of this document).

In the middle of the paragraph on page 14 of our submission that read:

"Number of surviving children (> 6 vs ≤ 2) was included as a covariate in the models whose results are shown in Figure 2. In general, there was a very weak association between number of surviving children and mortality in widowed husbands and widowed wives. Contrary to our expectations and a prior study,8 in each case, a higher number of surviving children was associated with higher mortality in the widowed husband/wife. Further, the results in Figure 2 show that the effect of bereavement decreases if the widowed individual remarries."

we added the following sentence in section Results, now on page 15 second paragraph:

"When analyses were repeated without the number of surviving children as a covariate, the estimates of the hazard ratios were essentially unchanged (data not shown)."

3. The authors indicate that the Amish have a strong degree of social support and include community-managed health insurance. This needs to be discussed more. Would it have been in place across the whole time period?

RESPONSE:

We added the following text in the Introduction on pages 6-7:

"The Amish maintain a cultural identity distinct from mainstream American culture that is characterized by their traditional dress, a plain lifestyle, and non-adoption of modern technology (e.g., electricity, cars, telephones), German dialect, separate school system, and ultra-conservative Anabaptist religious practices. A central tenet of Amish culture throughout their history in the USA has been social cohesiveness with emphasis on family and community. Members of this tight-knit society have extraordinary social support from cradle to grave, including community-managed health insurance and support during times of need. Elderly parents are taken care of by their children and neighbors; they do not use assisted living or nursing homes to care for their elderly."

4. They control for education. Wouldn't this vary wildly over this period? Did women receive formal education in the beginning of the period?

RESPONSE:

We did not adjust for education in our analysis and stated so on page 10 of the revised version (see the response to reviewer 2, comment 1). Other studies of the bereavement effect could adjust for level of education, but we do not have data on education levels. Generally speaking, the level of education amongst the Amish may be more homogeneous than in other populations. Currently, all Amish boys and girls receive schooling up to the 8^{th} grade and schooling is not permitted beyond 8^{th} grade for cultural reasons. Because these requirements apply equally to boys and girls (at least now), and we do not have historical information about educational practices during the study period (and certainly not at the individual level), we did not adjust for education.

5. This is a concise paper on a novel population and addresses the important topic of social support at the time of widowhood.

RESPONSE:

We thank the reviewer for these remarks.

Reviewer 2:

1. The outcome measure is not clearly or correctly defined. The outcome measure appears to be a survival outcome, with the time aspect 'age' and the event 'death'. This should be clearly stated in both the Abstract and main Methods section.

RESPONSE:

We modified the outcome measure in the Abstract (page 2) to read:

"**Outcome measure** The survival time is 'age'; event is 'death'. Hazard ratios of widowed indivudals with respect to gender, age at widowhood, remarriage, number of surviving children, and time since bereavement."

We modified one paragraph in the Materials and Methods section on pages 9-10 to read:

"Similar to several past analyses,[2 8 13 16] we used the Cox Proportional Hazards (CPH) model where the response variable or survival time is 'age at widowhood or death' and the event is 'death'. The model is used to study the association of widowhood and mortality rates in the surviving spouse, while adjusting for covariates such as education, health habits, age in years, number of children, and remarriage. In some of our analyses, we adjusted for remarriage and number of children as covariates; we did not adjust for education or health habits. Widows and widowers were always analyzed separately."

2. Most of the statistical methods are well described and in detail. However, details of how sex was taken into account in the modeling are absent. The authors suggest (by citing eg. Schaefer, Quesenberry and Wi (1995)) that they modeled males and females separately. It is vital that these details are included in a revised manuscript.

RESPONSE:

We did indeed analyze males (widowers) and females (widows) separately in all analyses. We added the sentence:

"Widows and widowers were always analyzed separately."

at the end of the first paragraph of the "Statistical analyses" subsection of Materials and Methods, which is quoted in its entirety in the response to reviewer 2, comment 1.

3. Large numbers of Amish couples have been excluded; reasons for excluding all couples with missing marriage dates AND for which either partner had missing birth OR death date are not all clear. In some cases, it would appear that individuals would have sufficient data to be included in the modeling, but it is unclear whether this would be a relatively small number. Moreover, this approach could cause bias and, without further details (see review of late sections), it is not possible to evaluate the potential magnitude of such bias. Sensitivity analysis to assumptions surrounding missing data (and the imposition of the stated exclusion criteria) would be advisable in most circumstances and should be considered.

RESPONSE:

We added a flow diagram as Figure 1 to indicate the reasons for exclusion. The top reason for excluding couples was that the birthdate of the husband was more recent than 1925. Both reviewers are correct that many couples were excluded because of missing or incomplete dates. More than 90% of the 30044 couples excluded for missing death dates would have been in the 1901-1925 cohort had they been included. See our response to reviewer 1, comment 1.

4. The response to Section 13 c of the STROBE checklist indicates that Table 2 replaces a flow diagram; I do not agree that this is an adequate replacement for a flow diagram. It would be extremely beneficial to see the flow diagram illustrating the exclusion of members of the population under investigation (as could have been defined a priori in terms of 'cohort' membership) due to missing data (and other reasons).

RESPONSE: This is an excellent suggestion. A flow diagram has now been added as the new Figure 1 (see above). What were Figures 1, 2, 3 in our initial submission are now Figures 2, 3, 4 in our revised submission.

5. Although most of the results are adequately presented, I have concerns about there is no test result or model fit statistic presented to support the assertion "... that there is an increase in risk of mortality for recently widowed husbands and wives, and that the hazard decreases with time since bereavement..." P14, l46-51. Whilst the estimates suggest that this might be the case, sample sizes are relatively small, certainly compared with the overall sample size. Moreover, it is similarly unclear as to whether the interpretation of these findings (p.16, l13-18) are fully supported by the data.

RESPONSE:

We agree with the reviewer that checks of the model fit are important and we did such checks, although these checks have been omitted in many prior papers on the bereavement effect. We added supplementary tables with the model-checking results and we modified one paragraph in Results on page 16 to read:

“Graphical checks of the overall adequacy of the CPH models were performed.[18 19] Based on the Cox-Snell residuals plot, the final model gave a reasonable fit to the data (data not shown). The deviance residual plots revealed no obvious outliers in the data (data not shown). Further, the Wald test statistic was used to test the fit of the final model,[18] and according to this test statistic, the final model fits the data reasonably well (Supplementary Tables S1, S2, and S3).’’

The reviewer’s concern about overall sample size is addressed in the new Figure 1 (flow diagram).

6. The authors have completed a STROBE checklist. However, section 6 (Bias) does not reflect on potential bias due to excluding those with missing data, and section 12 (c) and (e) do not adequately address the exclusion of those with missing data and the lack of a sensitivity analysis to investigate the likely bias the missing data might induce. I have commented on Section 13 c in an earlier section.

RESPONSE:

This point is overlapping with reviewer 1, comment 1 and reviewer 2, comments 3 and 4. See the responses to those comments.

Further minor queries and comments

1) p8 l4-6: Are the 136,213 Amish couples not included in the 539,822 Amish individuals? The current text implies that this is the case, but I feel it would be better if it gave the total number in the database and the number of couples. The 136,213 couples would normally be the population under investigation (probably restricted by date) and any subsequent exclusions illustrated in the flow diagram.

RESPONSE:

Yes, the 136, 213 couples are included in the 539,822 individuals. The sentence with this information has been rewritten to multiple sentences on page 8, as follows:

"The "individual table" of AGDB contains information about 539,822 individuals. The "relationship table" includes information about 136,213 Amish couples. An individual who is married multiple times participates in multiple relationship table entries. There are 1,369 relationship entries among the 136,213 entries concerning children for whom one or both biological parents are unknown (Figure 1)."

2) p14 l 25: "Number of surviving children >6 vs <=2..." This does not really make sense in isolation and merits further explanation. Are the authors implying that an active decision was made to merge the categories <=2 and 3-6 surviving children due to similar parameter (risk ratio) estimates? If so, this should be stated explicitly and the interpretation should reflect this; additionally, the caption of Figure 2 should state the acronym (NSC) and, if possible, the associated coding of this variable reflected in the figure.

RESPONSE:

It is now stated explicitly in Materials and Methods (page 10) that: "The categories ≤ 2 children, 3-6 children, and > 6 children are separate. These boundaries were chosen to ensure categories that were roughly balanced in size." No merging of categories was done.

3) It is suggested that not needing to incorporate censoring methods whilst ignoring people with missing birth and death dates is a strength of the study. However, a key reason for incorporating censoring into survival analysis is to enable proper handling of such people, albeit often based on untestable assumptions. The lack of information on how many Amish couples were excluded due to missing birth and/or death dates precudes further assessment of this statement (see also earlier comments regarding missing birth/death dates).

RESPONSE:

The exclusion steps and numbers are now shown in a flow diagram (Figure 1) as the reviewer requested. The majority of exclusions are because individuals were not born in the period under study, which is not "censoring" in the sense in which that word is typically used in survival analysis. There were over 27000 exclusions due to missing death dates in the 1901-1925 cohort. In the Discussion, we changed the phrase:

"we did not need to incorporate censoring methods into our analysis because of the near completeness of birth and death dates of the Amish widows and widowers"

To:

"we did not incorporate censoring methods into our analysis because of the high availability of death dates of the Amish widows and widowers in the first three cohorts"

The Figure 1 legend added on page 25 is:

Figure 1. A flow diagram which represents all the steps performed for filtering 15,611 couples from total 136,213 couples available in AGDB. In the flow diagram, each couple is counted as excluded only once, even if multiple exclusion criteria apply. "Unknown spouse" refers to entries in the AGDB relationship table in which at least one parent is unknown; almost all of these entries are for adopted children for whom at least one of the biological parents is unknown. Because AGDB is used primarily in genetic studies (unlike this study), the distinction between biological and adoptive relationships is stored. "Birth year too late" means that the birth year of the husband is known and is > 1925. "Dates not recognized by R" are invalid dates such as the 31st of June, which got into AGDB due to errors in the original sources. "Implausible birth or death dates" refers to a few individuals who are shown as

married but have lifespans of less than 10 years likely due to typos in the birth year in the original sources.

4) Could the findings potentially be explained as indicating that the it is close bond between spouses, providing emotional, psychological and social support which is important, rather than purely the social aspect. This is addressed to some degree on p17 (l48-53) but could be strengthened; moreover, this could be seen as being supported by the finding on the effect of the number of children (with potentially closer bonds with smaller numbers of surviving children).

RESPONSE:

We modified the Discussion paragraph on pages 17-18 of our submission (now located on page 18-19) to read:

"Interestingly, increasing numbers of surviving children at the time of widowhood did not confer a survival advantage for Amish widows or widowers. This result was counter to our hypothesis that children can help provide social support for their parents. The hazard ratio was greater than 1.0 (but not significant) for all widowers and widows with number of surviving children > 6 as compared to ≤ 2. Spouses in the Amish society may also provide unique emotional, psychological, and social support to each other which cannot be provided by their surviving children. The lack of protective association was similarly observed when the number of surviving children was considered as a linear or as a categorical variable (data not shown). This contrasts with data from the Utah Population Database, in which increasing numbers of children were associated with a decreased hazard ratio.[8]"

Tables R1, R2, R3 are included in this document to address a concern of reviewer 1, but are not included in the revised manuscript.

Table R1: Hazard ratios are estimated after including and not including the cohort 1901-1925.

		Males		Females	
	TSB (months)	HR	95%CI	HR	95%CI
IC	0-6	1.41**	1.22,1.62	1.51**	1.32,1.73
NIC	0-6	1.37**	1.16,1.62	1.45**	1.24,1.71
IC	7-12	1.29**	1.11,1.49	1.38**	1.20,1.59
NIC	7-12	1.30**	1.09,1.54	1.31**	1.10,1.55
IC	13-24	1.32**	1.19,1.46	1.21**	1.09,1.35
NIC	13-24	1.30**	1.14,1.47	1.21**	1.07,1.38
IC	25-36	1.30**	1.16,1.44	1.23**	1.10,1.35
NIC	25-36	1.25**	1.10,1.43	1.17*	1.04,1.33
IC	37-48	1.21**	1.08,1.35	1.19**	1.07,1.33
NIC	37-48	1.16**	1.01,1.33	1.14*	1.01,1.31
IC	49-60	1.37**	1.23,1.53	1.34**	1.20,1.49
NIC	49-60	1.38**	1.21,1.57	1.33**	1.18,1.51
IC	> 60	1.21**	1.16,1.26	1.25**	1.20,1.30
NIC	> 60	1.18**	1.13,1.24	1.20**	1.14,1.26
	* P<0.05 and ** P<0.001; TSB: Time Since Bereavement; HR: Hazard Ratio; CI: Confidence Interval; IC: Including Cohort; NIC: Not Including Cohort				

Table R2: Hazard ratio of widowed husbands after accounting and not accounting for number of surviving children.

	Cohorts								
		Pre-1850		1850-1875		1876-1900		1901-1925	
	AW	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
ASC	< 45	1.50**	1.28,1.77	1.20*	1.03,1.39	1.71**	1.49,1.96	1.66**	1.37,2.02
NASC	< 45	1.51**	1.29,1.78	1.20*	1.03,1.40	1.71**	1.50,1.96	1.60**	1.32,1.93
ASC	45-54	1.30**	1.10,1.53	1.12	0.95,1.33	1.41**	1.21,1.65	1.38**	1.14,1.67
NASC	45-54	1.29**	1.09,1.52	1.13	0.95,1.33	1.41**	1.21,1.65	1.36**	1.13,1.64
ASC	55-64	1.34**	1.18,1.51	1.05	0.92,1.19	1.55**	1.37,1.75	1.40**	1.21,1.61
NASC	55-64	1.34**	1.18,1.51	1.05	0.92,1.19	1.55**	1.37,1.75	1.38**	1.20,1.59
ASC	65-74	1.30**	1.17,1.45	1.05	0.93,1.19	1.27**	1.15,1.41	1.36**	1.21,1.52
NASC	65-74	1.30**	1.17,1.45	1.05	0.94,1.19	1.27**	1.15,1.41	1.35**	1.21,1.51
ASC	> 75	1.16*	1.01,1.32	1.08	0.93,1.24	1.18*	1.06,1.31	1.26**	1.14,1.40
NASC	> 75	1.15*	1.01,1.31	1.07	0.93,1.24	1.18*	1.06,1.31	1.27**	1.15,1.40
ASC	Rem	0.76*	0.64,0.90	0.86	0.75,1.00	0.67**	0.60,0.76	0.72**	0.63,0.82

NASC	Rem	0.75* 0.63,0.89	0.86* 0.75,0.99	0.67** 0.60,0.76	0.73** 0.64,0.83
* P<0.05 and ** P<0.001; AW: Age at Widowhood; HR: Hazard Ratio; CI: Confidence Interval; ASC: Accounting for Surviving Children; NASC: Not Accounting for Surviving Children; Rem: Remarriage					

Table R3: Hazard ratio of widowed wives after accounting and not accounting for number of surviving children.

		Cohorts							
		Pre-1850		1850-1875		1876-1900		1901-1925	
	AW	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
ASC	< 45	1.43**	1.25,1.65	1.29**	1.10,1.53	1.33**	1.15,1.54	1.30*	1.07,1.58
NASC	< 45	1.42**	1.24,1.63	1.29**	1.09,1.52	1.31**	1.13,1.52	1.29*	1.06,1.57
ASC	45-54	1.12	0.98,1.28	1.20*	1.03,1.40	1.11	0.95,1.31	1.55**	1.33,1.81
NASC	45-54	1.12	0.97,1.27	1.20*	1.02,1.40	1.11	0.94,1.30	1.55**	1.33,1.80
ASC	55-64	1.15*	1.03,1.28	1.10	0.97,1.24	1.13*	1.00,1.26	1.17*	1.04,1.31
NASC	55-64	1.15*	1.03,1.28	1.10	0.97,1.24	1.13*	1.01,1.27	1.17*	1.04,1.31
ASC	65-74	1.17*	1.05,1.30	1.13	0.99,1.27	1.09	0.99,1.21	1.15*	1.04,1.27
NASC	65-74	1.17*	1.05,1.30	1.13	0.99,1.27	1.09	0.99,1.21	1.16*	1.05,1.28
ASC	> 75	1.08	0.94,1.25	1.12	0.96,1.30	1.05	0.94,1.17	1.25**	1.13,1.38
NASC	> 75	1.09	0.94,1.26	1.12	0.96,1.30	1.05	0.94,1.17	1.26**	1.14,1.39
ASC	Rem	0.65**	0.49,0.85	0.78*	0.65,0.95	0.74**	0.63,0.87	0.85	0.71,1.00
NASC	Rem	0.65**	0.50,0.86	0.78*	0.64,0.94	0.74**	0.63,0.87	0.84	0.71,1.00

* P<0.05 and ** P<0.001; AW: Age at Widowhood; HR: Hazard Ratio; CI: Confidence Interval; ASC: Accounting for Surviving Children; NASC: Not Accounting for Surviving Children; Rem: Remarriage

VERSION 2 – REVIEW

REVIEWER	Dr. Chris Sutton, CStat Principal Lecturer Lancashire Clinical Trials Unit (LCTU) School of Health University of Central Lancashire
REVIEW RETURNED	07-Oct-2013

GENERAL COMMENTS	Reviewer 1: 6. The authors state that the data are uncensored; however, the cohort 1901-1925 appears to exclude people that were alive in 2010. There would be some married couples and widow(er)s born in 1920-25 that would still be alive. The authors might exclude this cohort from the analysis. RESPONSE: This is an excellent point. To address the reviewer's valid concern

about the 1901-1925 cohort, we redid the combined analysis of Figure 3 using the three eldest cohorts only, omitting the 1901-1925 cohort. The results in Figure 3 do not change significantly (see Table R1 at the end of this document).

The flowchart (new Figure 1) that we added in response to comments from reviewer 2 does show the magnitude of the problem. There were 30044 couple excluded because of a missing death date, and more than 90% of these would have been in the 1901-1925 cohort had they been included.

To the paragraph that read:

"Hazard ratios and 95% CIs for the time since bereavement analysis are shown in Figure 3. These results were obtained using the CPH model and the design defined in Table 2c. The results show that there is an increase in risk of mortality for recently widowed husbands and wives, and the hazard decreases with time since bereavement but remains significantly greater than 1. Further, the hazard is higher (not significant) in wives vs husbands during the first 12 months following bereavement."

we added the following sentences in section Results, on page 16:

"To address the issue that many individuals in the 1901-1925 cohort may still have been alive at the last AGDB update and hence censored, we performed the analysis for time since bereavement omitting the cohort 1901-1925. The results show that the hazard ratios provided in Figure 4 have not changed significantly; for example, for 25-26 months post bereavement the hazard ratios change from 1.30 and 1.23 for all cohort to 1.25 and 1.17 for the three eldest cohorts."

This has not fully addressed the two reviewer's comments regarding the exclusion of those with missing birth or death dates. Whilst it may be reasonable to assume that the hazard 'process' causing birth or death dates to be truly missing is independent of the hazard of death, this is clearly not the case for those who are excluded because death has nto yet occurred. The impact of this on the results may well be limited, and a good indication of the potential effect is provided in Table R1 below; there appears to be, as would be expected, a small attenuation of the bereavement effect through the exclusion of couples for whom one, but not the other, of the couples has died. However, other statistics have a more obvious bias due to the selection of couples; for example, the statistics presented in the final column of Table 1 will be biased downwards as those surviving longest – both overall and after the death of their spouse – are excluded which will induce clear bias. The analyses should either include all eligible couples without imposing the restriction that both in the couple must have died prior to 2010 or, but less preferably, use an earlier cut-off for cohort membership (e.g. born prior to 1901, as suggested by reviewer 1).

7. There is no adjustment for the problem of people with few children also being people who die young--this may lead to more children being associated with better survival. Also this was treated as a time independent variable which means the values could not change over time; however, surely this cannot be true if the authors imposed no survival age restriction (i.e. the couples must survive until the wife lived past age 40 or 45)

	RESPONSE: To address the reviewer's concern, we performed the analysis of Figure 3 (was Figure 2 in the original submission) without the number of surviving children as a covariate. The results in Figure 3 do not change significantly (see Tables R2 and R3 at the end of this document). In the middle of the paragraph on page 14 of our submission that read: "Number of surviving children (> 6 vs ≤ 2) was included as a covariate in the models whose results are shown in Figure 2. In general, there was a very weak association between number of surviving children and mortality in widowed husbands and widowed wives. Contrary to our expectations and a prior study,8 in each case, a higher number of surviving children was associated with higher mortality in the widowed husband/wife. Further, the results in Figure 2 show that the effect of bereavement decreases if the widowed individual remarries." we added the following sentence in section Results, now on page 15 second paragraph: "When analyses were repeated without the number of surviving children as a covariate, the estimates of the hazard ratios were essentially unchanged (data not shown)." Whilst this is reassuring in terms of the effect of the number of surviving children on the bereavement effect, it does not appear to address the issue raised which relates to the measurement and interpretation of the number of surviving children on the risk of death in widowhood. Also, it appears from Table 2a that the covariate C is not the effect of the number of surviving children on the bereavement effect, but the effect of the number of surviving children on death (and so would apply equally both prior to bereavement and post bereavement); the effect of the number of surviving children on the bereavement effect would be the interaction between W and C. It is also unclear as to when C was assessed (as a time-independent covariate); was this assessed at the date of death of the first of the couple to die? If so, then the issue raised by the first reviewer persists; moreover, this covariate will be biased by the death, with those who die very young or very old typically having less children alive than those who die in middle age (after all potential children had been born but with lower risk of children having died). 8. The authors indicate that the Amish have a strong degree of social support and include community-managed health insurance. This needs to be discussed more. Would it have been in place across the whole time period? RESPONSE: We added the following text in the Introduction on pages 6-7: "The Amish maintain a cultural identity distinct from mainstream American culture that is characterized by their traditional dress, a plain lifestyle, and non-adoption of modern technology (e.g.,

	electricity, cars, telephones), German dialect, separate school system, and ultra-conservative Anabaptist religious practices. A central tenet of Amish culture throughout their history in the USA has been social cohesiveness with emphasis on family and community. Members of this tight-knit society have extraordinary social support from cradle to grave, including community-managed health insurance and support during times of need. Elderly parents are taken care of by their children and neighbors; they do not use assisted living or nursing homes to care for their elderly." This response to the reviewer's question implies that the community-managed health insurance was in place during the whole of the period i.e. from the date of the first bereavement (presumably in the mid-1700s) through to 2010. Is this really correct? 9. They control for education. Wouldn't this vary wildly over this period? Did women receive formal education in the beginning of the period? RESPONSE: We did not adjust for education in our analysis and stated so on page 10 of the revised version (see the response to reviewer 2, comment 1). Other studies of the bereavement effect could adjust for level of education, but we do not have data on education levels. Generally speaking, the level of education amongst the Amish may be more homogeneous than in other populations. Currently, all Amish boys and girls receive schooling up to the 8th grade and schooling is not permitted beyond 8th grade for cultural reasons. Because these requirements apply equally to boys and girls (at least now), and we do not have historical information about educational practices during the study period (and certainly not at the individual level), we did not adjust for education. OK. 10. This is a concise paper on a novel population and addresses the important topic of social support at the time of widowhood. RESPONSE: We thank the reviewer for these remarks. Reviewer 2: 7. The outcome measure is not clearly or correctly defined. The outcome measure appears to be a survival outcome, with the time aspect 'age' and the event 'death'. This should be clearly stated in both the Abstract and main Methods section. RESPONSE: We modified the outcome measure in the Abstract (page 2) to read: "**Outcome measure** The survival time is 'age'; event is 'death'. Hazard ratios of widowed indivudals with respect to gender, age at widowhood, remarriage, number of surviving children, and time

	since bereavement." We modified one paragraph in the Materials and Methods section on pages 9-10 to read: "Similar to several past analyses,[2 8 13 16] we used the Cox Proportional Hazards (CPH) model where the response variable or survival time is 'age at widowhood or death' and the event is 'death'. The model is used to study the association of widowhood and mortality rates in the surviving spouse, while adjusting for covariates such as education, health habits, age in years, number of children, and remarriage. In some of our analyses, we adjusted for remarriage and number of children as covariates; we did not adjust for education or health habits. Widows and widowers were always analyzed separately." The outcome measure definition provided is still confusing. The survival time is age (correctly stated in the Abstract but not in the Methods) and the event is death, as correctly stated. However, what is modeled, is still the hazard of death amongst the husbands and wives; the statement added on p.10 l17 is therefore confusing; it is the husbands and wives who were analysed separately, not the widowers and widows (e.g. Table 2a ID 3; this person was analysed but was never a widow/widower). 8. Most of the statistical methods are well described and in detail. However, details of how sex was taken into account in the modeling are absent. The authors suggest (by citing eg. Schaefer, Quesenberry and Wi (1995)) that they modeled males and females separately. It is vital that these details are included in a revised manuscript. RESPONSE: We did indeed analyze males (widowers) and females (widows) separately in all analyses. We added the sentence: "Widows and widowers were always analyzed separately." at the end of the first paragraph of the "Statistical analyses" subsection of Materials and Methods, which is quoted in its entirety in the response to reviewer 2, comment 1. OK. 9. Large numbers of Amish couples have been excluded; reasons for excluding all couples with missing marriage dates AND for which either partner had missing birth OR death date are not all clear. In some cases, it would appear that individuals would have sufficient data to be included in the modeling, but it is unclear whether this would be a relatively small number. Moreover, this approach could cause bias and, without further details (see review of late sections), it is not possible to evaluate the potential magnitude of such bias. Sensitivity analysis to assumptions surrounding missing data (and the imposition of the stated exclusion criteria) would be advisable in most circumstances and should be considered.

RESPONSE:

We added a flow diagram as Figure 1 to indicate the reasons for exclusion. The top reason for excluding couples was that the birthdate of the husband was more recent than 1925. Both reviewers are correct that many couples were excluded because of missing or incomplete dates. More than 90% of the 30044 couples excluded for missing death dates would have been in the 1901-1925 cohort had they been included. See our response to reviewer 1, comment 1.

See above. This is still an issue and will have induced bias into the estimation, to varying degrees depending on the analysis. This is likely to be most severe in Table 1, final column, but will also affect other estimates. The analyses should be performed by not excluding cohort members based on outcome (i.e. whether death has occurred by 2010).

10. The response to Section 13 c of the STROBE checklist indicates that Table 2 replaces a flow diagram; I do not agree that this is an adequate replacement for a flow diagram. It would be extremely beneficial to see the flow diagram illustrating the exclusion of members of the population under investigation (as could have been defined a priori in terms of 'cohort' membership) due to missing data (and other reasons).

RESPONSE: This is an excellent suggestion. A flow diagram has now been added as the new Figure 1 (see above). What were Figures 1, 2, 3 in our initial submission are now Figures 2, 3, 4 in our revised submission.

This is a welcome addition; however, it is still unclear how many couples were excluded due to a truly missing death date and how many were excluded due to being still alive in 2010. The former could have induced some bias, the latter will certainly have done so in some analyses.

11. Although most of the results are adequately presented, I have concerns about there is no test result or model fit statistic presented to support the assertion "... that there is an increase in risk of mortality for recently widowed husbands and wives, and that the hazard decreases with time since bereavement..." P14, l46-51. Whilst the estimates suggest that this might be the case, sample sizes are relatively small, certainly compared with the overall sample size. Moreover, it is similarly unclear as to whether the interpretation of these findings (p.16, l13-18) are fully supported by the data.

RESPONSE:

We agree with the reviewer that checks of the model fit are important and we did such checks, although these checks have been omitted in many prior papers on the bereavement effect. We added supplementary tables with the model-checking results and we modified one paragraph in Results on page 16 to read:

“Graphical checks of the overall adequacy of the CPH models were

	performed.[18 19] Based on the Cox-Snell residuals plot, the final model gave a reasonable fit to the data (data not shown). The deviance residual plots revealed no obvious outliers in the data (data not shown). Further, the Wald test statistic was used to test the fit of the final model,[18] and according to this test statistic, the final model fits the data reasonably well (Supplementary Tables S1, S2, and S3).'' The reviewer's concern about overall sample size is addressed in the new Figure 1 (flow diagram). Thank you for this addition. However, this does not address the original issue raised by reviewer 2, namely that an effect (increased risk, which decreases over time) is presented without the support of a test statistic (and p-value); it is therefore unclear as to whether this is a 'significant' finding or an observation which could easily be explained by chance. 12. The authors have completed a STROBE checklist. However, section 6 (Bias) does not reflect on potential bias due to excluding those with missing data, and section 12 (c) and (e) do not adequately address the exclusion of those with missing data and the lack of a sensitivity analysis to investigate the likely bias the missing data might induce. I have commented on Section 13 c in an earlier section. The authors have not adequately addressed these points. There is still potential bias due to missing data, the exclusion of participants who would need to be censored is a weakness rather than a strength and they have now performed a sensitivity analysis but not referred to this in the STROBE statement (section 12e), although I strongly advise the use of the censored individuals in the main analysis, rather than the current approach which is to perform a sensitivity analysis by excluding the most recent cohort (which would almost certainly include the only couples potentially still aliver in 2010). RESPONSE: This point is overlapping with reviewer 1, comment 1 and reviewer 2, comments 3 and 4. See the responses to those comments. Further minor queries and comments 5) p8 l4-6: Are the 136,213 Amish couples not included in the 539,822 Amish individuals? The current text implies that this is the case, but I feel it would be better if it gave the total number in the database and the number of couples. The 136,213 couples would normally be the population under investigation (probably restricted by date) and any subsequent exclusions illustrated in the flow diagram. RESPONSE: Yes, the 136, 213 couples are included in the 539,822 individuals. The sentence with this information has been rewritten to multiple sentences on page 8, as follows:

“The “individual table” of AGDB contains information about 539,822 individuals. The "relationship table” includes information about 136,213 Amish couples. An individual who is married multiple times participates in multiple relationship table entries. There are 1,369 relationship entries among the 136,213 entries concerning children for whom one or both biological parents are unknown (Figure 1).”

OK.

6) p14 l 25: "Number of surviving children >6 vs <=2..." This does not really make sense in isolation and merits further explanation. Are the authors implying that an active decision was made to merge the categories <=2 and 3-6 surviving children due to similar parameter (risk ratio) estimates? If so, this should be stated explicitly and the interpretation should reflect this; additionally, the caption of Figure 2 should state the acronym (NSC) and, if possible, the associated coding of this variable reflected in the figure.

RESPONSE:

It is now stated explicitly in Materials and Methods (page 10) that: “The categories ≤ 2 children, 3-6 children, and > 6 children are separate. These boundaries were chosen to ensure categories that were roughly balanced in size.” No merging of categories was done.

Sorry, this does not address the point raised. The statement "Number of surviving children >6 vs <=2..." does not make sense; either the authors included the factor ‘number of surviving children’ as two indicator variables (typically >6 vs ≤ 2 children and 3-6 vs ≤ 2 children) or they effectively merged the categories by including only one covariate, hence presumably comparing >6 vs ≤ 6 children. It is not possible only to include a covariate representing *only* >6 vs <=2 if there are individuals in the data set with values 3-6.

7) It is suggested that not needing to incorporate censoring methods whilst ignoring people with missing birth and death dates is a strength of the study. However, a key reason for incorporating censoring into survival analysis is to enable proper handling of such people, albeit often based on untestable assumptions. The lack of information on how many Amish couples were excluded due to missing birth and/or death dates precludes further assessment of this statement (see also earlier comments regarding missing birth/death dates).

RESPONSE:

The exclusion steps and numbers are now shown in a flow diagram (Figure 1) as the reviewer requested. The majority of exclusions are because individuals were not born in the period under study, which is not “censoring” in the sense in which that word is typically used in survival analysis. There were over 27000 exclusions due to missing death dates in the 1901-1925 cohort. In the Discussion, we changed the phrase:

“we did not need to incorporate censoring methods into our analysis because of the near completeness of birth and death dates of the Amish widows and widowers”

	To: "we did not incorporate censoring methods into our analysis because of the high availability of death dates of the Amish widows and widowers in the first three cohorts" The Figure 1 legend added on page 25 is: Figure 1. A flow diagram which represents all the steps performed for filtering 15,611 couples from total 136,213 couples available in AGDB. In the flow diagram, each couple is counted as excluded only once, even if multiple exclusion criteria apply. "Unknown spouse" refers to entries in the AGDB relationship table in which at least one parent is unknown; almost all of these entries are for adopted children for whom at least one of the biological parents is unknown. Because AGDB is used primarily in genetic studies (unlike this study), the distinction between biological and adoptive relationships is stored. "Birth year too late" means that the birth year of the husband is known and is > 1925. "Dates not recognized by R" are invalid dates such as the 31st of June, which got into AGDB due to errors in the original sources. "Implausible birth or death dates" refers to a few individuals who are shown as married but have lifespans of less than 10 years likely due to typos in the birth year in the original sources. The right-censoring refers to those in the latest cohort (1901-1925) who were still alive in 2010. It is unclear how many were excluded for this reason, although there exclusion (as described above) will clearly cause some bias, although this would appear not to be substantial for the main inferences (as suggested in the sensitivity analysis presented in Table R1, and mainly for the females, as would be anticipated). It is vital that this issue is recognized and addressed appropriately. 8) Could the findings potentially be explained as indicating that the it is close bond between spouses, providing emotional, psychological and social support which is important, rather than purely the social aspect. This is addressed to some degree on p17 (l48-53) but could be strengthened; moreover, this could be seen as being supported by the finding on the effect of the number of children (with potentially closer bonds with smaller numbers of surviving children). RESPONSE: We modified the Discussion paragraph on pages 17-18 of our submission (now located on page 18-19) to read: "Interestingly, increasing numbers of surviving children at the time of widowhood did not confer a survival advantage for Amish widows or widowers. This result was counter to our hypothesis that children can help provide social support for their parents. The hazard ratio was greater than 1.0 (but not significant) for all widowers and widows with number of surviving children > 6 as compared to ≤ 2. Spouses in the Amish society may also provide unique emotional, psychological, and social support to each other which cannot be provided by their surviving children. The lack of protective association was similarly observed when the number of surviving children was considered as a linear or as a categorical variable (data

	not shown). This contrasts with data from the Utah Population Database, in which increasing numbers of children were associated with a decreased hazard ratio.[8]"

VERSION 2 – AUTHOR RESPONSE

1. There is a potential for bias since death dates missing for some subjects who would otherwise be eligible for inclusion analysis.

   RESPONSE: This was a key concern raised by both reviewers on the initial review. In some situations, censoring methods can be used to minimize the impact of incomplete ascertainment of events, although censoring is of limited use in our study because the latest date at which individuals lost with missing death dates were known to be alive was relatively young – at the birthdate of their last child. In our first revision, we addressed the missing death date issue by re-analyzing the data after removing the most recent cohort that had the largest proportion of missing death dates. We also added additional information to the flowchart about numbers of exclusions due to missing data. The Reviewer asks that we address this issue further, stating that "the analyses should either include all eligible couples without imposing the restriction that both in the couple must have died prior to 2010 or, but less preferably, use an earlier cut-off for cohort membership (e.g. born prior to 1901, as suggested by reviewer 1)."

   Since we are unable to recover these missing birth and death dates, we changed our primary analysis entirely to include only the 10,892 couples in which both husband and wife were born before 1901 and for whom we have sufficient information about dates. All Figures and Tables were modified to exclude the 1901-1925 cohort which we had included in the analysis in previous versions of the manuscript. In the Discussion, we took out the claim that one the strengths of our study is the completeness of the data.

   In addition, we updated our STROBE checklist to account for the substantial analysis changes we made in response to this concern and others.

2. The number of children surviving at the death of the first spouse is a time-independent variable, but this is not sufficiently clear in the first revision. Treating the number of surviving children as time-independent may lead to two sources of bias. First, some individuals die young before their families are complete. Second, for people who die at later ages, more children may have died as the surviving spouse aged.

   RESPONSE: That the number of surviving children is treated as time-independent is now stated explicitly in Strengths and limitations of this study (page 5), Materials and Methods (page 10), reiterated in Results in the context of a sensitivity analysis (page 16), and addressed in the limitation paragraph of the Discussion section (page 21).

   We acknowledge that the widow(er)s of spouses who die relatively young (e.g,, before age 50) may have relatively few children if the couple had not fulfilled their reproductive potential. How this might impact the relation of number of children to survival of the widowed spouse is not clear. In our second revision, we have addressed this concern in two ways. First, we have repeated our analysis assessing the association of number of children with spouse survival after excluding all couples (n = 1303) where the first dying spouse died before age 50.

Second, we also address this issue in the limitation paragraph of the Discussion (page 21).

Regarding the second potential source of bias, we observe that our analysis was based on three categories for number of surviving children: <=2, 3-6, and > 6. Therefore, the potential bias the reviewer suggests could manifest only when the death of a child pushes the number of surviving children from one category to a lower category. We tabulated a category change happened in only 298/10892 (< 3%) of the couples. We redid the analysis of Figure 3 excluding those 298 couples and found essentially no change in the hazard ratios for the number of surviving children. We added a little text in Materials and Methods (page 10), in Results (page 16), and in the limitation paragraph of the Discussion (page 21) concerning the new analysis about the effect of children dying between the date of widowhood of the surviving spouse and the date of death of the surviving spouse. Since the new analysis shows a negligible change in hazard ratios, the new text is brief.

3. Concerns that “there is no test result or model fit statistic presented to support the assertion "... that there is an increase in risk of mortality for recently widowed husbands and wives, and that the hazard decreases with time since bereavement...".

RESPONSE: This concern was raised on the first review as well. Our assertion that there is an increase in risk of mortality for recently widowed husbands and wives is supported by the results shown in Figure 4, which indicate that for each time since bereavement interval, the hazards ratio for mortality in both widowed husbands and wives relative to their married counterparts is significantly greater than 1, with the lower limit of the 95% confidence intervals exceeding 1 in all cases. We addressed this issue by referring to p-values in the Results section whenever the Figures 2-4 are first introduced. We also make this clearer in the text in the antepenultimate and penultimate paragraphs of Results.

During our first revision, we addressed this issue by providing three supplementary tables with Wald statistics (model fit statistics). In our current revision, we addressed the significance of the hazard ratios shown in Figures 2-4 by providing the range of p-values (p-value<0.05 and p-value<0.001) associated with each hazard ratio. The legends of the Figures 2-4 have been updated to include the interpretation of * (p-value<0.05) and ** (p-value<0.001).

4. Only including the analysis of number of surviving children >6 vs. <=2 if there are individuals in the data set with values 3-6.

RESPONSE: This concern was raised during the first review. We apologize for not addressing this issue satisfactorily. We have addressed this issue in the current revision by updating the Page 15; 3rd paragraph 1st sentence and the legend of Figure 3. The implementation of Cox proportional hazards in R provides two hazard ratios >6 vs. <= 2 and 3-6 vs. <= 2. Previously, we reported only the first of the two; in this revision, we report both hazard ratios.

MINOR Comments:

5. Clarification of how long Amish community-managed health insurance has been in place.

RESPONSE: We rewrote the paragraph of Introduction concerning the tradition of societal support and mechanism of insurance in the Amish community. The reviewer’s understanding that the Amish have been self-insuring for centuries is substantively correct. The mechanism of the community insurance became increasingly formalized over time and it is now called Amish Aid and run as a formal program of self-insurance within the community.

6. Definition of the outcome measure was not clarified in Materials and Methods.

RESPONSE: We rewrote one paragraph of Materials and Methods (pages 9-10) to describe the outcome measure in the same manner in which we modified the outcome measure in the Abstract in the first revision. Reviewer 2 indicated that the outcome measure was “correctly stated” in the Abstract of the first revision.

VERSION 3 - REVIEW

REVIEWER	Dr Chris Sutton University of Central Lancashire UK
REVIEW RETURNED	24-Nov-2013

GENERAL COMMENTS	There are two issues which the authors have not addressed, of which, unfortunately, one appears to have been missed in their summary of my previous comments and the other misinterpreted. 1) My previous comment was that "... it appears from Table 2a that the covariate C is not the effect of the number of surviving children on the bereavement effect, but the effect of the number of surviving children on death (and so would apply equally both prior to bereavement and post bereavement); the effect of the number of surviving children on the bereavement effect would be the interaction between W and C." Therefore, either the covariate C is not correctly defined in Table 2a (and also in Table 2b) or, if it is defined correctly in Table 2a, the interpretation of the covariate effect (bottom of p.23 and top of p.24) is incorrect. If the latter is the case, the effect would be interpreted as suggesting an increased risk of death amongst those who have more children, assessed at the time of first death of one of the couple; this is effectively the average effect of the covariate C over the person's lifetime and could be 'dominated' by the risk of death for the first of the couple to die, the bereaved person, or apply equally to both. Without consideration of a possible interaction between bereavement and the variable C, it is not possible to validly draw the conclusion that "increasing numbers of surviving children at the time of death did not confer a survival advantage for Amish individuals"; likewise, the objective included under 'Article focus', namely "We evaluated the association of ... number of surviving children ... on the bereavement effect ..." is not what appears to be being investigated through the inclusion of covariate C in the Cox model. 2) As identified in both my previous reviews, the statement that " ... the hazard decreases with time since bereavement" is not fully supported by the statistical analysis, as there is no test of this decreasing trend; the results in Figure 4 do, as clearly stated in the manuscript and repeated in the authors' response, show that there is a significant increase in the risk of death following bereavement but not that this is not a consistent increase over the post-bereavement lifetime but declines (significantly) over the time since bereavement (and hence the increase in the hazard of death is greater amongst the recently widowed). This issue remains to be addressed.

VERSION 3 – AUTHOR RESPONSE

Black: Reviewer comments, verbatim

Green: Proposed third round response.

1) My previous comment was that "... it appears from Table 2a that the covariate C is not the effect of the number of surviving children on the bereavement effect, but the effect of the number of surviving children on death (and so would apply equally both prior to bereavement and post bereavement); the effect of the number of surviving children on the bereavement effect would be the interaction between W and C." Therefore, either the covariate C is not correctly defined in Table 2a (and also in Table 2b) or, if it is defined correctly in Table 2a, the interpretation of the covariate effect (bottom of p.23 and top of p.24) is incorrect. If the latter is the case, the effect would be interpreted as suggesting an increased risk of death amongst those who have more children, assessed at the time of first death of one of the couple; this is effectively the average effect of the covariate Cover the person's lifetime and could be 'dominated' by the risk of death for the first of the couple to die, the bereaved person, or apply equally to both. Without consideration of a possible interaction between bereavement and the variable C, it is not possible to validly draw the conclusion that "increasing numbers of surviving children at the time of death did not confer a survival advantage for Amish individuals"; likewise, the objective included under 'Article focus', namely "We evaluated the association of ... number of surviving children ... on the bereavement effect ..." is not what appears to be being investigated through the inclusion of covariate C in the Cox model.

We addressed this issue in our second revision (pages 8 and 9 of the long response), but we thank the reviewer for pointing out that further corrections needed to make unambiguous the interpretation of the covariate C. The reviewer's reference to "bottom of p. 23 and top of p. 24" in our second revision corresponds to the "tracked changes version". The same text is on the bottom of page 19 and top of page 20 in the untracked version, which explains why the change below is described for pages 19-20.

Following are the changes we made in the current manuscript:

Page 4; Article focus

- The focus of this article is to evaluate the relationship between bereavement and social support in the Amish population.

- We evaluated the association of surviving spouse gender, age at widowhood, remarriage, number of surviving children, and time since bereavement on the bereavement effect using Cox proportional hazard models.

has been replaced with

- The focus of this article is to evaluate the relationship between bereavement and the mortality of a surviving spouse in the Amish population.

- We evaluated the association of bereavement and mortality of a surviving spouse with respect to gender, age at widowhood, and time since bereavement while accounting for remarriage, and number of surviving children using Cox proportional hazard models.

Paragraph starting at the bottom of p. 19 and ending on p. 20

Interestingly, increasing numbers of surviving children at the time of widowhood did not confer a survival advantage for Amish individuals. This result was counter to our hypothesis that children can help provide social support for their parents. The hazard ratio was greater than 1.0 (but not significant) for all Amish individuals with number of surviving children > 6 as compared to ≤ 2. Spouses in the Amish society may also provide unique emotional, psychological, and social support to each other which cannot be provided by their surviving children. The lack of protective association was similarly observed when the number of surviving children was considered as a linear or as a categorical variable (data not shown). This contrasts with data from the Utah Population Database, in which increasing numbers of children were associated with a decreased hazard ratio.[8]

has been replaced with

Interestingly, more children at the time of the death of the first spouse was associated with increased the risk of death, though the hazard ratio for having > 6 surviving children as compared to ≤ 2 was not significantly greater than 1.0. This result does not support the hypothesis that more surviving children confer a survival advantage to parental longevity, as perhaps by providing social support for their parents. Spouses in the Amish society may also provide unique emotional, psychological, and social support to each other which cannot be provided by their surviving children. The lack of protective association was similarly observed when the number of surviving children was considered as a linear or as a categorical variable (data not shown). This contrasts with data from the Utah Population Database, in which increasing numbers of children were associated with a decreased hazard ratio.[8] We considered the number of surviving children as a separate term (Table 2a), but did not evaluate the interaction of number of surviving children with widowhood.

2) As identified in both my previous reviews, the statement that " ... the hazard decreases with time since bereavement" is not fully supported by the statistical analysis, as there is no test of this decreasing trend; the results in Figure 4 do, as clearly stated in the manuscript and repeated in the authors' response, show that there is a significant increase in the risk of death following bereavement but not that this is not a consistent increase over the post-bereavement lifetime but declines (significantly) over the time since bereavement (and hence the increase in the hazard of death is greater amongst the recently widowed). This issue remains to be addressed.

We apologize for misunderstanding the reviewer's concern about the interpretation of Figure 4, expressed in the second round of reviews. The reviewer is correct to question the claim of a trend (the hazard decreases with time since bereavement). A simple linear regression analysis (y-axis and x-axis representing hazard ratios and time since bereavement) does not support a declining trend in hazard ratios after the first 6 months post-widowhood; therefore, we withdraw the claim.

Following are the changes we made in the third revision compared to the second revision (again pages refer to the non-tracked version of the second revision):

Pages 16-17

Hazard ratios and 95% CIs for the time since bereavement analysis are shown in Figure 4. The significant p-values are indicated in Figure 4. These results were obtained using the CPH model and the design defined in Table 2c. The results show that there is an increase in risk of mortality for recently widowed husbands and wives, and the hazard decreases with time since bereavement but remains significantly greater than 1. Further, the hazard is higher (not significant) in wives vs. husbands during the first 12 months following bereavement.

has been replaced with

Hazard ratios and 95% CIs for the time since bereavement analysis are shown in Figure 4. The significant p-values are indicated in Figure 4. These results were obtained using the CPH model and the design defined in Table 2c. The results show that there is a high risk of mortality for recently widowed husbands and wives. Further, the hazard is higher (not significant) in wives vs. husbands during the first 12 months following bereavement.

Pages 18-19

In the present study, the association between bereavement and mortality is greater in the first 6 months for both men and women (Figure 4), consistent with previous findings.[2 3 5 20 21 23] The mortality risks in the first 6 months are lower in the Amish (Figure 4) compared to some studies,[2 5 20 21] but not all studies.[3 23] One common pattern observed in this and other studies is that the initially high bereavement effect first decreases but then increases with time since bereavement.[3 23] We speculate that the increased mortality during the first 6 months might reflect acute effects related to the loss of a spouse, while the gradual increases in mortality emerging in later life might reflect decreased survival from aging-related diseases that is unmasked in the absence of spousal support.

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In the present study, the association between bereavement and mortality is greater in the first 6 months for both men and women (Figure 4), consistent with previous findings.[2 3 5 20 21 23] The mortality risks in the first 6 months are lower in the Amish (Figure 4) compared to some,[2 5 20 21] but not all, studies.[3 23] One common pattern observed in this and other studies is that the bereavement effect is higher in the first 6 months and later life.[3 23] We did a regression analysis for trend in the data of Figure 4 and there is no significant declining trend after the first 6 months. We speculate that the higher mortality during the first 6 months might reflect acute effects related to the loss of a spouse, while the higher mortality in later life might reflect decreased survival from aging-related diseases that is unmasked in the absence of spousal support.