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LETTER TO THE EDITOR

# Reply to Little et al.: dose–responses from multi-model inference for the non-cancer disease mortality of atomic bomb survivors

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We appreciate the comment by Little et al. (2013) related to the study of Schöllnberger et al. (2012) and thank our colleagues for the time they took to deal with our analysis.

Little et al. (2013) state "… there are biological data suggesting [that] many inflammatory endpoints potentially relevant to circulatory disease may be differentially regulated below and above about 0.5 Gy, emphasizing the importance of assessing risks associated with exposures <0.5 Gy." We agree with the statement and take it as a support of our approach to analyze the available data with a variety of models that take several possible dose dependences into account.

Little et al. (2013) express a concern "… that the method of Schöllnberger et al. 2012 (multi-model inference, MMI) may not adequately assess the uncertainties in model parameters" without elucidating reasons of their concern. However, seemingly to backup their concern, they cite Wang et al. (2012), a paper describing the development of a novel approach to "adjustment uncertainty" (i.e., the uncertainty about which variables should be included in the model to properly adjust for confounding), called Bayesian adjustment for confounding. We will argue below that the pre-conditions on which Wang et al. (2012) built their interesting, though not uncontested (Gutman and Rubin 2012), methodology do not apply to our analysis.

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When the effect of exposure on outcome is estimated, a proper adjustment for confounding variables[1] is a general concern in epidemiology. A series of papers by Wang et al. (2012), Crainiceanu et al. (2008) and Dominici et al. (2004) addressed this problem for the correlation of air pollution and mortality. A big challenge in air pollution epidemiology is to control for possible confounding by changes in weather parameters such as temperature or humidity, which determine both the concentration of particulate matter in air and have a direct impact on mortality rates, especially among older persons and those with pre-existing health conditions. Hence, such covariables are clearly correlated with exposure *and* outcome and can be considered as true confounders.

In our study of the association between circulatory diseases and ionizing radiation, we have adjusted the risk for the main covariables of city $c$, sex $s$, age at exposure $e$ and attained age $a$, for which the correlation with the radiation dose is generally small: see bottom row of the correlation matrix (Table 1), which was calculated from the raw data of LSS Report 13 with follow-up since January 1, 1968 (Preston et al. 2003), the data set that has been analyzed by Schöllnberger et al. (2012). Additional adjustment for other covariables such as smoking, alcohol intake, education, type of household occupation, obesity and diabetes mellitus "had almost no impact on the associations with radiation" (see Table 3 and Discussion in Shimizu et al. (2010)). We have not calculated the correlation with exposure for the latter covariables but we expect again small correlations similar to those for $c$, $s$, $e$ and $a$.

[1] A confounder or confounding variable correlates with both the outcome and the risk factor investigated. For example, given a dose of radiation and an outcome, in the form of an excess risk at a given dose level, then a variable is a confounder if it is correlated with both the outcome and the dose.

**Table 1** Correlation matrix calculated from the raw data of LSS Report 13 (Preston et al. (2003); data file R13MORT.DAT from http://www.rerf.or.jp) with follow-up since January 1, 1968

| | City | Gender | Age at exposure | Age attained | Weighted dose |
|---|---|---|---|---|---|
| City | 1 | | | | |
| Gender | −0.0125 | 1 | | | |
| Age at exposure | −0.0640 | 0.00647 | 1 | | |
| Age attained | −0.0619 | 0.0155 | 0.856 | 1 | |
| Weighted dose | −0.0216 | 0.0152 | −0.132 | −0.133 | 1 |

The correlation coefficients have been calculated for the main covariables included in the data set—city, gender, age at exposure, age attained and weighted dose—any potential confounders for outcome and dose can be identified in the bottom row of the correlation matrix

The fact that the above covariables lack strong correlations with both exposure (dose) and outcome (circulatory disease) indicates that they are not confounders. Hence, concerns of not properly adjusting for confounders can be easily dismissed since such confounders were absent in our MMI analysis.

It can be noted that when we are interested in the excess risk at a given level of absorbed gamma dose to the colon, the covariable absorbed neutron dose to the colon could indeed be a potential confounder because it is highly correlated with gamma dose and may be highly correlated with outcome. However, since only weighted doses in the form "absorbed gamma dose + 10× absorbed neutron dose" are considered this confounding effect is not explicitly included in our models. This is also the case in nearly all analyses of the LSS cohort (see, however, Walsh (2012) for a separate consideration of gamma dose and neutron dose).

In their comment, Little et al. (2013) continue: "There are no biological data to persuasively suggest the existence of a threshold (below which there is no modulation of effect) for inflammation or other markers relevant to circulatory disease." We agree with this assertion. However, there is no persuasive evidence for a linear dose–response with no threshold either.

A recent study by Takahashi et al. (2012) examined the association between ionizing radiation and stroke incidence among atomic bomb survivors in the adult health study (AHS), a sub-group of atomic bomb survivors under special medical surveillance. The authors considered nonlinear relationships between radiation dose and stroke incidence, including a threshold analysis. Takahashi et al. (2012) report that for men, the incidence of hemorrhagic stroke (a sub-group of cerebrovascular disease (CVD)) increased consistently with increasing exposure levels without evidence for a threshold. In women, however, the risk of hemorrhagic stroke increased with increasing radiation exposure but not until doses reached a threshold of 1.3 Gy. This result is especially interesting given our own finding of some support for a threshold in the dose–response for CVD at 0.62 Gy below which there is only a weak increase of the disease (Schöllnberger et al. 2012). Furthermore, a protective effect for atherosclerotic lesions has been observed at the lowest dose rate (1 mGy/min) used in experiments with $ApoE^{-/-}$ mice (Mitchel et al. 2011). Protective effects were observed at the lowest dose tested, 25 mGy, and were highly nonlinear with dose. These results found confirmation in the latest study by Mitchel et al. (2013, *in press*), but also demonstrated the importance of p53 functional status and disease state at the time of exposure on that outcome. The recent review of Rödel et al. (2012) showed that low-dose ionizing radiation modulates inflammatory immune reactions mostly with discontinuous or biphasic dose dependencies. Given these findings, it certainly is justified to test threshold and various other models. The correspondence of Schöllnberger and Kaiser (2012) and the reply of Little et al. (2012) address similar issues. Interestingly, polynomial fits of the data for CVD also point to a threshold in the low-dose range (at around 0.6 Gy) and exhibit a shallow U shape but have not been used for MMI due to larger values of the AIC (unpublished results).

A main point of criticism stated by Little et al. (2013) relates to the fact that we had not used the most recent LSS data (i.e., those of Shimizu et al. (2010)) but older data (Preston et al. 2003). We would like to emphasize that our analysis of the latest LSS data by Shimizu et al. (2010) on non-cancer effects including a comparative analysis of the two time periods is ongoing and the main conclusions presented here are expected to remain valid after this analysis is completed.

We restricted our analysis to deaths in proximal survivors from 1968 onwards to exclude the potential healthy survivor effect on the risk estimates. Here, we followed the approach of Preston et al. (2003) which was based on the finding that proximal survivors included in the LSS were initially healthier than the general population for reasons related to their selection by having survived the bombings. The difference almost vanished in the late 1960s (Preston et al. 2003).

Furthermore (with the potential exception of leukemia), there is no evidence for an impact of doses below 1 Gy on the mortality in the LSS before 1966 (Ozasa et al. 2012). For circulatory diseases, the statistical power is not sufficient to cause the form of the dose–response to be significantly different from that observed in the later mortality data (Fig. 6B in Ozasa et al. 2012). Nevertheless, the expressed differences of the best estimates of the mortality risk from circulatory diseases in the two time periods justify an analysis of the subset of the data that is most likely

less affected by a potential healthy survivor effect than the full data set.

Little et al. (2013) point out that "It is the broad range of scientific evidence, epidemiological and experimental, that will eventually provide an answer as to whether low-level radiation increases the risk of circulatory disease (…)." We would like to respectfully extend this statement as follows: it is the broad range of *all* scientific evidence, epidemiological and experimental, that will eventually provide an answer as to whether low-level radiation *influences* the risk of circulatory disease.

We agree with Little et al. (2013) that the comparison of different radiation-exposed populations is essential for drawing general conclusions on circulatory disease risks at low doses and low-dose rates. Considering the ongoing discussions on biological response mechanisms, such analyses have to consider a variety of possible dose–responses. This is a fascinating new research field, which is expected to give a new basis for regulating the safe use of ionizing radiation in our society.

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