PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Non-cancer morbidity among Estonian Chernobyl cleanup workers: a register-based cohort study
AUTHORS	Rahu, Kaja; Bromet, Evelyn; Hakulinen, Timo; Auvinen, Anssi; Uusküla, Anneli; Rahu, Mati

VERSION 1 - REVIEW

REVIEWER	Lydia Zablotska University of California, San Francisco, USA
REVIEW RETURNED	28-Feb-2014

GENERAL COMMENTS	Rahu et al. present an interesting analysis using non-cancer outcomes among Estonian Chernobyl cleanup workers. Comparison of non-cancer diagnoses from the health insurance database with those of the general Estonian population during 2004-2012 indicated some increased risks of thyroid diseases. These findings should be treated very cautiously in the absence of accurate radiation doses and a possibility to verify the accuracy of diagnoses in the health insurance database. While interesting in itself, the manuscript would benefit from a much more cautious interpretation of study findings and a more careful discussion of the numerous study limitations. Abstract - The use of the term “unexposed controls” is misleading. Readers will be confused whether this is a cohort or a case-control study. Suggest changing to “compared to the general population.” - The Conclusions section should list the numerous limitations of this analysis, which were noted in the Discussion section. All interpretations should be much more carefully balanced against the numerous limitations. Article Summary - Looking at the Abstract, the Results section and study tables, psychological disorders do not appear to be the focus of this analysis. Therefore, it comes as a surprise that they are highlighted as one of the two main focuses of this paper. - Key messages do not note any of the study design and analysis limitations and should be significantly tempered down. Introduction - Page 4, para#1: o Reference 1 is incomplete (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2011). Please provide a year of the report and specify scientific annex. o Please specify what is meant by “contaminated area”? Do you mean the 30-km exclusion zone? o Please clarify that individual missions to the 30-km exclusion zone could not have exceeded 2 weeks and that the 3-months average duration is based on repeated missions by the same workers to the zone. - Page 4, para#2:

	o In ref#4, general population was exposed to radiation from byproducts of uranium mining. A more relevant group of environmentally exposed subjects would be from the Techa River cohort (Krestinina et al., 2012). o While radiation risks of CVD in the 15-country study were negative (ref#5), a very large study of UK radiation workers found significantly increased excess risks of cerebrovascular diseases (Muirhead et al., 2009). o A recent meta-analysis of low-dose studies (Little et al., 2012) analyzed precisely the group with exposures <0.5 Gy and found significantly increased risks of all circulatory diseases. - Page 4, para#3: o The recent 2010 UNSCEAR report on Chernobyl studies (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2011) raised serious concerns about Russian morbidity studies based on various registers, thus some caution is necessary while citing references #10 and #11. - Page 5: o The Introduction section does not provide background on "radiation-related" diseases which would be examined in this study. A careful review of the pertinent literature to clarify which non-cancer outcomes were considered a priori would be very useful. Methods: - Page 5, para#1: o Please clarify what is meant by "the area"? Do you mean the 30-km exclusion zone? o Please clarify why the age range of cleanup workers was limited to 35-69 years. o Please explain the exclusion of 4831-3680=1151 Chernobyl cleanup workers. Did all of them die prior to start of follow-up in 2004 or were some lost to follow-up? Also, it is not clear how "alive" status was established in 2004. o Please explain if the 87 Chernobyl workers who were identified among the general population were included in the exposed cohort of 4831. If not, then it would appear that not all eligible Chernobyl cleanup workers were included in the exposed cohort, i.e. selection bias. - Page 7, para#1: o This paragraph describes a fairly typical standardized morbidity analysis (SMR), performed in occupational studies. Essentially, the morbidity experience of exposed is compared to the general population to identify possible differences. o I am not convinced of the advantages of doing the SMR analysis by comparing a small cohort of exposed with 2:1 frequency-matched general population subjects. In fact, the morbidity rates in this small group of the general population would have higher variability compared to the overall Estonian population morbidity rates. Thus, there is no advantage of doing this from the statistical point of view. Conventional SMR analyses use population morbidity rates for 5-year age and calendar time groups and calculate expected based on the person-time distribution of the exposed. I would like to know if the results of these analyses are different from the analyses based on a select group presented in the paper. - Page 7, para #2: o Please clarify which variables were evaluated as confounders and which as effect modifiers, as well as what methods were used to determine significance of these variables in the multiple regression models.

	o The last 4 sentences of para#2 belong in the Discussion section. Instead, the section should include information on availability of alcohol consumption and smoking for the study population. If such data are not available, it should be clearly stated. o Very limited data on radiation doses is presented. I would have liked to see a more broad discussion of study doses from military passports. Results - Page 8, para#2: Please clarify here and in other places in the manuscript that the first visit to the Chernobyl zone was used to construct the variable "year of arrival." - Page 9: External analysis would be more properly called "SMR analysis comparing observed and expected diseases" in the cohort. - Page 10, para#2: o The authors state that "including education and ethnicity in the model did not alter" the results. However, the footnote to Table 3 states that all analyses already were adjusted for education. Please clarify. o Please provide a p-value from the trend test for various categories of whole-body reported doses from military passports in relation to thyroid diseases. Also, please specify that these analyses are not shown in Table 3. Discussion - Page 10, para#3: The findings with regards to thyroid diseases are overstated. The authors should caution readers that these findings are: 1) above those expected in the general population and could be due to pointed screening for thyroid diseases among Chernobyl cleanup workers; and 2) that the doses from the military passports have little relevance to thyroid diseases because they are not thyroid doses. - Page 10, last para: Discuss possible direction of bias due to diagnostic errors. A more detailed discussion of the effects of rescinding preliminary diagnoses from the health insurance database on the study findings is necessary. - Page 12, para#1: Use (Little et al., 2012). - Page 13, para#1: Study limitations should also note a possible random error due to multiple comparisons. Tables: - Table 1: o I thought that using a select group of the general population to compare to Chernobyl cleanup workers was not advantageous (see above). o "Time of first arrival in the Chernobyl 30-km exclusion zone" o "Total duration of stay in the Chernobyl 30-km exclusion zone (days)" - Table 2: o Indicate significant findings by an asterisk or some other sign. - Table 3: - Show a separate column with observed cases and cumulative person-years. - Specify the size of the analysis cohort in the table title. STROBE statement Items # 6 (methods of follow-up), 7 (confounders and effect modifiers), 9, 12 (sensitivity analyses), 14 (smoking and alcohol consumption in the cohort), 15 (cases in Table 3), 18 and 21 would benefit from careful expansion. References

	Krestinina, L. Y., Epifanova, S., Silkin, S., et al., 2012. Chronic low-dose exposure in the Techa River Cohort: risk of mortality from circulatory diseases. Radiat. Environ. Biophys. Little, M. P., Azizova, T. V., Bazyka, D., et al., 2012. Systematic Review and Meta-analysis of Circulatory Disease from Exposure to Low-Level Ionizing Radiation and Estimates of Potential Population Mortality Risks. Environ. Health Perspect. 120, 1503-11. Muirhead, C. R., O'Hagan, J. A., Haylock, R. G., et al., 2009. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br. J. Cancer. 100, 206-12. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), Sources and Effects of Ionizing Radiation. UNSCEAR 2008 Report to the General Assembly with Scientific Annexes. Volume II. Annex D: Health Effects Due to Radiation from the Chernobyl Accident. United Nations, New York, 2011.

REVIEWER	Alina V Brenner NCI, NIH, USA
REVIEW RETURNED	03-Mar-2014

GENERAL COMMENTS	General comments The current study is concerned with non-cancer morbidity in the Estonian Chernobyl clean-up workers cohort with special focus on radiation-related diseases and mental health disorders. The cohort includes 3,680 exposed male cleanup workers and 7,631 non-exposed comparison individuals from the general population matched to exposed workers on age. The follow-up was from 2004-2012 through the Estonian Population Registry and Health Fund Insurance Fund database. The authors conclude that no excess morbidity consistent with radiation effects was observed except perhaps for benign thyroid diseases. There was however excess risk for intentional self-harm and certain alcohol-related diagnoses. In general, the manuscript is well written and addresses relevant scientific questions. However, I suggest that several areas of it would benefit from clarification and additional information. Specific comments 1. Please clarify reasons for which 1,151 exposed individuals from the original cohort were excluded from the current study: How many of them died and how many of them emigrated from Estonia prior to Jan 1, 2004? 2. Clarify if EHIF allows for multiple diagnoses per 1 health care contact (either ambulatory or hospital) and, if so, how multiple diagnoses per contact were handled in the analysis (any assumptions about primary diagnosis vs. secondary, etc.). 3. The analysis section needs more detail and clarification. Were analyses based on grouped survival data, how was the person-year table for Poisson regression constructed (classification on what parameters)? It also is unclear to me if ‘external’ vs. ‘internal’ analyses were really different or ‘internal’ analyses simply were limited to the exposed cohort. 4. It is evident from Table 1 and acknowledged by the authors in the

	Results that there are some differences between exposed and non-exposed individuals in terms of ethnicity and education. Therefore, I am surprised that the 'external' analyses comparing rates in exposed and unexposed groups were not controlled for these differences. Why? I think these should be adjusted for. 5. Explain what the absolute numbers in Table 2 refer to. For example, 43,170 for 'exposed' cohort most likely refers to reported diagnoses and not individual cases as overall number of exposed workers is 3,680. If this is the case, the title of Table 2 needs to be fixed. Personally, I would be more interested to know how many of the exposed/unexposed individuals had at least one diagnosis/reporting of, for example, thyroid disease. The presented numbers of 167 and 211 may mean something else. 6. Several associations presented in Table 2 including cataract are significantly below one. This needs to be acknowledged in the Results and invites comment in the Discussion as cataract is a radiation-related outcome. Is there any reason for why diagnoses among workers might be under-reported (specialty eye clinic not reporting to EHIF, etc.)? 7. With respect to thyroid disease, even though there seems to be no overall indication of radiation-effect, it might be worth breaking the analysis for 1986 (if data permit) by April-June (when I-131 was present in the environment) and July-December (external exposure only). Comparison of types of thyroid diagnoses (using even 3 digit ICD-10 codes) in exposed and unexposed individuals may also be informative. 8. Finally, I suggest adding to the study limitations that a relatively small size of exposed population would limit statistical power to detect small excess morbidity due to radiation exposure.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Lydia Zablotska

Rahu et al. present an interesting analysis using non-cancer outcomes among Estonian Chernobyl cleanup workers. Comparison of non-cancer diagnoses from the health insurance database with those of the general Estonian population during 2004-2012 indicated some increased risks of thyroid diseases. These findings should be treated very cautiously in the absence of accurate radiation doses and a possibility to verify the accuracy of diagnoses in the health insurance database. While interesting in itself, the manuscript would benefit from a much more cautious interpretation of study findings and a more careful discussion of the numerous study limitations.

Response: We thank the reviewer for her helpful and detailed comments and suggestions. In the following we address these comments.

Abstract

1. The use of the term "unexposed controls" is misleading. Readers will be confused whether this is a cohort or a case-control study. Suggest changing to "compared to the general population."

Response: Thank you for the clarification: „... compared to the population sample..."

2. The Conclusions section should list the numerous limitations of this analysis, which were noted in the Discussion section. All interpretations should be much more carefully balanced against the numerous limitations.

Response: We have listed the limitations in the Article Summary section as recommended by the instructions for authors (http://bmjopen.bmj.com/site/about/guidelines.xhtml). We have tried to balance the content of the manuscript.

Article Summary

3. Looking at the Abstract, the Results section and study tables, psychological disorders do not appear to be the focus of this analysis. Therefore, it comes as a surprise that they are highlighted as one of the two main focuses of this paper.

Response: We have reworded the text to make it hopefully less controversal.

4. Key messages do not note any of the study design and analysis limitations and should be significantly tempered down.

Response: Modified study limitations are addressed after Key messages. The messages have been revised to take into account this suggestion.

Introduction

- Page 4, para#1:

5. Reference 1 is incomplete (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2011). Please provide a year of the report and specify scientific annex.

Response: Thank you for this point and for the complete reference.

6. Please specify what is meant by “contaminated area”? Do you mean the 30-km exclusion zone?

Response: The words „contaminated area“, „the area“, „the Chernobyl area“ are used interchangeably as synonyms to refer to the territory where cleanups, construction of buildings, radiation measurement, guard duty, etc., have been taken place. Thus, these words denote the 30-km zone AND areas outside where the men of the cohort worked. We have explained this issue in the Methods section.

7. Please clarify that individual missions to the 30-km exclusion zone could not have exceeded 2 weeks and that the 3-months average duration is based on repeated missions by the same workers to the zone.

Response: The 3-months average duration takes into account the whole time of work/ being in the Chernobyl area. We do not have information on whether or not an each daily individual mission was undertaken inside or outside the 30-km zone. This 2-weeks-on, 2-weeks-off schedule was applied in the vicinity of the Chernobyl plant only, but not in the 30-km zone as a whole.

- Page 4, para#2:

8. In ref#4, general population was exposed to radiation from byproducts of uranium mining. A more relevant group of environmentally exposed subjects would be from the Techa River cohort (Krestinina et al., 2012).

Response: As Krestinina et al. 2013 considered their results to be taken as preliminary, we decided not to include this publication. Instead, we have included a meta-analysis by Little et al. (2012) – see comment 10.

9. While radiation risks of CVD in the 15-country study were negative (ref#5), a very large study of UK radiation workers found significantly increased excess risks of cerebrovascular diseases (Muirhead et al., 2009).

Response: In a paper by Muirhead et al (2009) the ERR/Sv for cerebrovascular diseases was 0.161 (95% CI -0.42–0.91) that did not encourage us to include this publication. Instead, we have included a meta-analysis by Little et al. (2012) – see next comment.

10. A recent meta-analysis of low-dose studies (Little et al., 2012) analyzed precisely the group with exposures <0.5 Gy and found significantly increased risks of all circulatory diseases.

Response: We have expanded the text by including this paper.

- Page 4, para#3:

11. The recent 2010 UNSCEAR report on Chernobyl studies (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2011) raised serious concerns about Russian morbidity studies based on various registers, thus some caution is necessary while citing references #10 and #11.

Response: We are aware of this cautionary note. At the same time, the reference #11 (Ivanov et al, 2006) has been considered of enough quality to be included in the meta-analysis of the article by Little et al, 2012 mentioned in your previous comment.

- Page 5:

12. The Introduction section does not provide background on “radiation-related” diseases which would be examined in this study. A careful review of the pertinent literature to clarify which non-cancer outcomes were considered a priori would be very useful.
Response: We have made some additions to the text to address this suggestion. In fact, relatively little literature exists on the long-term effects of protracted low-level radiation on the population health.
Methods:
- Page 5, para#1:
13. Please clarify what is meant by “the area”? Do you mean the 30-km exclusion zone?
Response: We have addressed this point above (response 6).
14. Please clarify why the age range of cleanup workers was limited to 35-69 years.
Response: By Jan. 1, 2004 there were 9 cleanup workers under the age of 35, and 13 aged 70 or over. In order to obtain more homogeneous age group we excluded these 22 subjects from the analysis. We have added this comment in the text.
15. Please explain the exclusion of 4831-3680=1151 Chernobyl cleanup workers. Did all of them die prior to start of follow-up in 2004 or were some lost to followup? Also, it is not clear how “alive” status was established in 2004.
Response: Those 1151 workers are divided into five groups: lost for follow-up (21), died (602), emigrated (506), age under 35 (9) and over 69 years (13) on Jan. 1, 2004. For the whole follow-up period from Jan. 1, 2004 to Dec. 31, 2012, in the exposed cohort and comparison cohort the vital status (alive/ dead/ emigrated) with a related date was obtained via record linkage from the Estonian Population Registry (https://www.siseministeerium.ee/35796/?lang=). We have modified the text to make these points clearer.
16. Please explain if the 87 Chernobyl workers who were identified among the general population were included in the exposed cohort of 4831. If not, then it would appear that not all eligible Chernobyl cleanup workers were included in the exposed cohort, i.e. selection bias.
Response: As there was not any reason to exclude them, they stayed included.
- Page 7, para#1:
17. This paragraph describes a fairly typical standardized morbidity analysis (SMR), performed in occupational studies. Essentially, the morbidity experience of exposed is compared to the general population to identify possible differences. I am not convinced of the advantages of doing the SMR analysis by comparing a small cohort of exposed with 2:1 frequency-matched general population subjects. In fact, the morbidity rates in this small group of the general population would have higher variability compared to the overall Estonian population morbidity rates. Thus, there is no advantage of doing this from the statistical point of view.
Conventional SMR analyses use population morbidity rates for 5-year age and calendar time groups and calculate expected based on the person-time distribution of the exposed. I would like to know if the results of these analyses are different from the analyses based on a select group presented in the paper.
Response: First, in fact, the database of the Estonian Health Insurance Fund is the only source with individual identifiable data on cases of morbidity. (Mentioning the Estonian Cancer Registry and Tuberculosis Registry would be out of the context.) At the same time, there does not exist overall Estonian population morbidity tabulations based on this database because it is out of scope of health insurance system. Second, national morbidity rates are available, but the mechanism of data collection is different. Thus, we were not able to perform SMR calculations because observed cases came from the insurance system, and expected cases could have been derived from population morbidity rates produced by another non-comparable statistical system of health care providers. Instead, the Poisson regression modeling was applied and morbidity rate ratios presented.
The ratio 2:1 was chosen for rate ratio analysis to get more stable morbidity rates for the unexposed cohort, and to increase the study power.
- Page 7, para #2:
18. Please clarify which variables were evaluated as confounders and which as effect modifiers, as well as what methods were used to determine significance of these variables in the multiple

regression models.
Response: In the paper, the exposed cohort was compared to the unexposed cohort, randomly frequency-matched in 1:2 ratio by age-group, and both cohorts restricted to the follow-up from 2004 to 2012. Adjustments were applied to age at diagnosis, year of arrival, duration of stay, ethnicity and education that were regarded as potential confounders. The study was not designed to explore effect modifications. Age at first exposure as usual potential time-related effect modifier was not taken into account because all clean-up workers were adults when arriving to the Chernobyl area.
We have computed the 95% confidence interval for the rate ratio and related p-value with Stata 12 procedure “poisson”.
19. The last 4 sentences of para#2 belong in the Discussion section. Instead, the section should include information on availability of alcohol consumption and smoking for the study population. If such data are not available, it should be clearly stated.
We have made some rearrangements in the text and explained the situation with alcohol and smoking information.
20. Very limited data on radiation doses is presented. I would have liked to see a more broad discussion of study doses from military passports.
Response: We have made this more specific in the text.
Results
21. Page 8, para#2: Please clarify here and in other places in the manuscript that the first visit to the Chernobyl zone was used to construct the variable “year of arrival.”
Response: We have clarified in the text the meaning of the „Chernobyl area“. Thus, the „year of arrival“ means the year of arrival in the Chernobyl area, that was the most likely cleanup workers’ camp site outside the 30-km zone. (See explanations above points 6 and 7.)
22. Page 9: External analysis would be more properly called “SMR analysis comparing observed and expected diseases” in the cohort.
Response: As explained above (point 17), no conventional SMR analysis was done. The first para of the subsection „ Morbidity measures and statistical analysis“ describes that the exposure effect is measured by the rate ratio.
- Page 10, para#2:
23. The authors state that “including education and ethnicity in the model did not alter” the results. However, the footnote to Table 3 states that all analyses already were adjusted for education. Please clarify.
Response: The sentence has been modified and now it reads: „Including education and ethnicity in the model did not alter markedly the crude point estimates of RR for year of arrival or duration of stay (rate ratios not presented).”
24. Please provide a p-value from the trend test for various categories of whole-body reported doses from military passports in relation to thyroid diseases. Also, please specify that these analyses are not shown in Table 3.
Response: p-value for trend is 0.7 (dose categories <5; 5–9.9; ≥10). We did not include the p-value to the text because no trend is clearly seen from the RRs.
Discussion
25. Page 10, para#3: The findings with regards to thyroid diseases are overstated. The authors should caution readers that these findings are: 1) above those expected in the general population and could be due to pointed screening for thyroid diseases among Chernobyl cleanup workers; and 2) that the doses from the military passports have little relevance to thyroid diseases because they are not thyroid doses.
Response: We have expanded a discussion of this cautionary note. We are not aware of permanent pointed screening for thyroid diseases in Estonia.
26. Page 10, last para: Discuss possible direction of bias due to diagnostic errors. A more detailed discussion of the effects of rescinding preliminary diagnoses from the health insurance database on the study findings is necessary.
Response: We have addressed this issue in the manuscript. For estimating morbidity, the limits of

using administrative data, including those collected for maximizing medical reimbursement, are universal without any specific features in Estonia. As an example, we have added three references to demonstrate that other researchers have used the EHIF for research purposes too.
27. Page 12, para#1: Use (Little et al., 2012).
Response: We have included this source.
28. Page 13, para#1: Study limitations should also note a possible random error due to multiple comparisons.
Response: We have touched the issue of multiple comparisons under the Limitations subsection.
Tables:
- Table 1:
29. I thought that using a select group of the general population to compare to Chernobyl cleanup workers was not advantageous (see above).
Response: As we have explained in our reply above (see point 17) that there was no other choice to conduct this kind of study: the Estonian Health Insurance Fund is the only source that contains individual identifiable cases of morbidity (not speaking of population-based registration of cancers and tuberculosis), but it does not provide national morbidity statistics needed for calculation of expected cases.
30. “Time of first arrival in the Chernobyl 30-km exclusion zone”
Response: We have explained it already (see above points 6, 7, 21).
31. “Total duration of stay in the Chernobyl 30-km exclusion zone (days)”
Response: We have explained it already (see above points 6, 7, 21).
32. Table 2: Indicate significant findings by an asterisk or some other sign.
Response: Statistically significant rate ratios ($p<0.05$) are now marked with a symbol (Tables 2 and 3).
- Table 3:
33. Show a separate column with observed cases and cumulative person-years.
Response: We have tried to keep this table as easy to read as possible, and not to include data already present in the manuscript. Although an exlusion of 174 subjects (4.7% of the exposed cohort) from the analysis in Table 3 has somewhat altered the numerical values related to the exposed cohort, the number of observed cases by disease category can be found in Table 2 and of cumulative person-years in Table 1.
34. Specify the size of the analysis cohort in the table title.
Response: We have included this size in Table 3 title.
35. STROBE statement. Items # 6 (methods of follow-up), 7 (confounders and effect modifiers), 9, 12 (sensitivity analyses), 14 (smoking and alcohol consumption in the cohort), 15 (cases in Table 3), 18 and 21 would benefit from careful expansion.
Response: Considered.
References
Krestinina, L. Y., Epifanova, S., Silkin, S., et al., 2012. Chronic low-dose exposure in the Techa River Cohort: risk of mortality from circulatory diseases. Radiat. Environ. Biophys.
Little, M. P., Azizova, T. V., Bazyka, D., et al., 2012. Systematic Review and Meta-analysis of Circulatory Disease from Exposure to Low-Level Ionizing Radiation and Estimates of Potential Population Mortality Risks. Environ. Health Perspect. 120, 1503-11.
Muirhead, C. R., O'Hagan, J. A., Haylock, R. G., et al., 2009. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br. J. Cancer. 100, 206-12.
United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), Sources and Effects of Ionizing Radiation. UNSCEAR 2008 Report to the General Assembly with Scientific Annexes. Volume II. Annex D: Health Effects Due to Radiation from the Chernobyl Accident. United Nations, New York, 2011.

Reviewer: Alina V Brenner

General comments

The current study is concerned with non-cancer morbidity in the Estonian Chernobyl clean-up workers cohort with special focus on radiation-related diseases and mental health disorders. The cohort includes 3,680 exposed male cleanup workers and 7,631 non-exposed comparison individuals from the general population matched to exposed workers on age. The follow-up was from 2004-2012 through the Estonian Population Registry and Health Fund Insurance Fund database. The authors conclude that no excess morbidity consistent with radiation effects was observed except perhaps for benign thyroid diseases. There was however excess risk for intentional self-harm and certain alcohol-related diagnoses. In general, the manuscript is well written and addresses relevant scientific questions. However, I suggest that several areas of it would benefit from clarification and additional information.

Response: We thank the reviewer for her helpful and detailed comments and suggestions. In the following we address these comments.

Specific comments

1. Please clarify reasons for which 1,151 exposed individuals from the original cohort were excluded from the current study: How many of them died and how many of them emigrated from Estonia prior to Jan 1, 2004?

Response: Lost for follow-up (21), died (602), emigrated (506), age under 35 (9) and over 69 years (13) on Jan. 1, 2004. We have included these numbers in the text.

2. Clarify if EHIF allows for multiple diagnoses per 1 health care contact (either ambulatory or hospital) and, if so, how multiple diagnoses per contact were handled in the analysis (any assumptions about primary diagnosis vs. secondary, etc.).

Response: When the contact with a health care provider resulted in multiple diagnoses, each diagnosis was taken into analysis if it was the first occurrence of the 3-digit ICD code (or, in a special case, 4-digit code for some alcohol-induced diseases). In the EHIF database, no distinction is made between „primary“ or „secondary diagnosis“. We have modified the text in the Methods section to address this issue.

3. The analysis section needs more detail and clarification. Were analyses based on grouped survival data, how was the person-year table for Poisson regression constructed (classification on what parameters)? It also is unclear to me if ‘external’ vs. ‘internal’ analyses were really different or ‘internal’ analyses simply were limited to the exposed cohort.

Response: For the construction of the person-year table, data for each person have been split by an attained age group, cohort (exposed/ unexposed), duration of stay, year of arrival, ethnicity, education, dose category and person-years. After that, these data were summed in a frequency table by aforementioned characteristics. We have reported in the Morbidity measures and statistical analysis subsection, that in external analysis the exposed cohort was compared with an unexposed cohort (population sample), and that internal analysis was carried out within the exposed cohort.

4. It is evident from Table 1 and acknowledged by the authors in the Results that there are some differences between exposed and non-exposed individuals in terms of ethnicity and education. Therefore, I am surprised that the ‘external’ analyses comparing rates in exposed and unexposed groups were not controlled for these differences. Why? I think these should be adjusted for.

Response: Information on ethnicity and education was available for almost the whole exposed cohort, but education was unknown for 16.4% of the unexposed cohort. We have used in modeling available information (no imputation was applied for missing data), and made adjustments for ethnicity and education too. The results were in line with point estimates of age-adjusted rate ratios in Table 2 and therefore not presented in paper for reasons of brevity. Following this comment, we have addressed this issue in the manuscript.

5. Explain what the absolute numbers in Table 2 refer to. For example, 43,170 for ‘exposed’ cohort most likely refers to reported diagnoses and not individual cases as overall number of exposed workers is 3,680. If this is the case, the title of Table 2 needs to be fixed. Personally, I would be more

interested to know how many of the exposed/unexposed individuals had at least one diagnosis/reporting of, for example, thyroid disease. The presented numbers of 167 and 211 may mean something else.
Response: In Table 2 footnote, we have now commented the principle of counting morbidity cases. In the Methods section, we have explained that the first occurrence of the 3-digit ICD code was accounted in analyses (with the exception of some alcohol-induced diseases). Regarding the second issue, the 167 thyroid diagnoses (within the range of ICD rubrics E00–E07) among the Chernobyl workers were determined from 126 Chernobyl workers. In other words, 41 of these workers had more than one thyroid diagnosis based on their 3-digit ICD codes.
6. Several associations presented in Table 2 including cataract are significantly below one. This needs to be acknowledged in the Results and invites comment in the Discussion as cataract is a radiation-related outcome. Is there any reason for why diagnoses among workers might be under-reported (specialty eye clinic not reporting to EHIF, etc.)?
We have improved the wording to emphasize the deficit of cataract – an occasional finding – in the exposed cohort. Presumably, radiation doses received were too low to induce cataract. Differential under-reporting of cataract by expose status does not seem likely.
7. With respect to thyroid disease, even though there seems to be no overall indication of radiation-effect, it might be worth breaking the analysis for 1986 (if data permit) by April-June (when I-131 was present in the environment) and July-December (external exposure only). Comparison of types of thyroid diagnoses (using even 3 digit ICD-10 codes) in exposed and unexposed individuals may also be informative.
In some of our previous biodosimetry (Inskip et al, 1997; Littlefield et al, 1998) and cancer incidence/mortality (Rahu et al, 2006, 2013) analyses data for 1986 were broken down either by three (April-May, June-July, August-December), or two (April-May, June-December) groups. In a current study, age-adjusted rate ratios for April-May and June-December (reference 1987 and later) were 0.98 (95% CI 0.68–1.42) and 0.89 (95% CI 0.60–1.33), respectively. We have not included these ratios in the text, but inserted a brief statement of this into the text. Also, we have split the range of E00–E07 into subcategories, but no additional clue was derived.
8. Finally, I suggest adding to the study limitations that a relatively small size of exposed population would limit statistical power to detect small excess morbidity due to radiation exposure.
Response: Done.

VERSION 2 – REVIEW

REVIEWER	Lydia B. Zablotska University of California, San Francisco, USA
REVIEW RETURNED	15-Apr-2014

GENERAL COMMENTS	The authors have done an excellent job addressing the comments of both reviewers. The manuscript is significantly strengthened by clarifications added to the text. Some small points for author's consideration include: - In the Article Summary, "the documented radiation doses were not entirely reliable" is not very accurate. Since the authors do not present any evidence from reliability studies of Chernobyl doses, it is not possible to make such a statement. UNSCEAR and other reports cast significant doubts about reported Chernobyl doses. Also, there is a difference between "documented doses" and "doses from documents." In this case, doses came from contemporary documents, but not all workers had these documents. I would suggest changing to "the accuracy and precision of Chernobyl-associated doses from contemporary documents is questionable."

	- There remains a concern about the 87 Chernobyl cleanup workers identified among the 'unexposed' from the population sample. The authors need to explain whether these study subjects were among exposed and if not how this might affect the study findings. If these workers were not included in the exposed cohort, it raises concerns that this cohort is incomplete. Furthermore, this raises some concerns about possible selection bias whereby some workers were systematically not selected into the exposed cohort. - The Methods section still does not explain how the confounders were selected and evaluated for inclusion in the final models.

REVIEWER	Alina V Brenner National Cancer Institute, USA
REVIEW RETURNED	14-Apr-2014

GENERAL COMMENTS	Non-cancer morbidity among Estonian Chernobyl clean-up workers: a register-based cohort study The current manuscript is the revised version of a previously submitted analysis. The authors were reasonably responsive in addressing reviewers' suggestions and comments. The revised version clarifies methodological aspects of the study and data presented in the Tables, the main areas where in my opinion the manuscript had shortcomings. My only concern is a sentence added on p.13 (lines 8-10). While a whole body dose is indeed not equivalent to radiation dose received by the thyroid, in the case of external, homogeneous gamma irradiation, it is not that difficult to transition from a whole body dose to organ-specific doses. The main limitation though is the reliability of the recorded dose and lack of information on I-131 thyroid dose from internal exposure for those who were in the zone through June, 1986.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Lydia Zablotska
The authors have done an excellent job addressing the comments of both reviewers. The manuscript is significantly strengthened by clarifications added to the text.
Some small points for author's consideration include:
1. In the Article Summary, "the documented radiation doses were not entirely reliable" is not very accurate. Since the authors do not present any evidence from reliability studies of Chernobyl doses, it is not possible to make such a statement. UNSCEAR and other reports cast significant doubts about reported Chernobyl doses. Also, there is a difference between "documented doses" and "doses from documents." In this case, doses came from contemporary documents, but not all workers had these documents. I would suggest changing to "the accuracy and precision of Chernobyl-associated doses from contemporary documents is questionable."
Response: Thank you for this direction. We have reworded the sentence as follows: "questionable accuracy and precision of officially documented doses" We have retained the term "documented dose" the explanation of which is given in the Methods section. This term has been in use for long time already (e.g., UNSCEAR 2000 Report (Annex J) (2000); IARC, Reconstruction of Doses for Chernobyl Liquidators (20 March 2003); UNSCEAR 2008 Report (Annex D) (2011); EC, Radiation

Protection No. 170 (2011)) without causing any confusion. We hope that adding the word “officially” brings better clarity.
2. There remains a concern about the 87 Chernobyl cleanup workers identified among the 'unexposed' from the population sample. The authors need to explain whether these study subjects were among exposed and if not how this might affect the study findings. If these workers were not included in the exposed cohort, it raises concerns that this cohort is incomplete. Furthermore, this raises some concerns about possible selection bias whereby some workers were systematically not selected into the exposed cohort.
Response: We cannot imagine why a potential reader should think that exclusion of 87 cleanup workers from the unexposed comparison cohort results in exclusion them from the exposed cohort too. As we failed to find any hint of that in the manuscript, we believe that the slightly reworded sentence – “In the unexposed cohort, after excluding 87 men who had worked in the Chernobyl area (cleanup workers), there remained 7631 men” – clarifies the situation.
3. The Methods section still does not explain how the confounders were selected and evaluated for inclusion in the final models.
Response: We have reworded two paragraphs in the Methods section concerning variables used in the models. No stepwise selection was used.
Reviewer: Alina V Brenner
The current manuscript is the revised version of a previously submitted analysis. The authors were reasonably responsive in addressing reviewers’ suggestions and comments. The revised version clarifies methodological aspects of the study and data presented in the Tables, the main areas where in my opinion the manuscript had shortcomings.

My only concern is a sentence added on p. 13 (lines 8-10). While a whole body dose is indeed not equivalent to radiation dose received by the thyroid, in the case of external, homogeneous gamma irradiation, it is not that difficult to transition from a whole body dose to organ-specific doses. The main limitation though is the reliability of the recorded dose and lack of information on I-131 thyroid dose from internal exposure for those who were in the zone through June, 1986.
Response: We have deleted this sentence in response to your comment. The issue of uncertainties of recorded doses is addressed in the manuscript.