

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Cumulative exposure to ionizing radiation from diagnostic imaging tests: a 12-year follow-up population-based analysis in Spain.
<b>AUTHORS</b>	Lumbreras Lacarra, Blanca; Salinas, Josee María; Gonzalez-Alvarez, Isabel

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Claire Marant Micallef International Agency for Research on Cancer, France
<b>REVIEW RETURNED</b>	14-May-2019

<b>GENERAL COMMENTS</b>	<p>Summary</p> <p>The topic and the setting of the study are interesting in the current context of assessing the risks related to medical ionizing radiation. The study population and the follow-up duration are large. However, the analysis should be clarified and more detailed, i.e. more information should be provided both on the methods used and in the results to make the paper more attractive. Moreover, the objective and the results need to be put in a wider international context: it looks like a more comprehensive literature review should be performed in order to elaborate more both the introduction and the conclusion. I am surprised to see that there is no other study mentioned in any country for comparison in terms of the estimation of such cumulative dose at the population level: for instance, the study recently published in France about fractions of cancer attributable to IR from medical diagnostic procedures provided some cumulative exposure by sex and age group (doses to organs) (<a href="https://www.ncbi.nlm.nih.gov/pubmed/30537057">https://www.ncbi.nlm.nih.gov/pubmed/30537057</a>). A similar study was published in the UK in 2012 (<a href="https://www.ncbi.nlm.nih.gov/pubmed/22158322">https://www.ncbi.nlm.nih.gov/pubmed/22158322</a>).</p> <p>It is also not very clear from the discussion what the perspectives of this analysis are: how can these results can be used to improve risk prevention? Please elaborate on this.</p> <p>Finally, I am concerned with some methodological issues (see details in comments by section), such as age and duration of follow up, representativity of the studied population, lack of exams outside the hospital...? The way these points would influence the results and their interpretation should be discussed much further.</p> <p>Abstract</p> <ul style="list-style-type: none"><li>- The median cumulative dose is not mentioned, whereas it is the main outcome of the study... Please reformulate the results to make it clearer.</li><li>- The % of the population with a cumulative dose &gt;50 mSv (5%) is not "significant"</li></ul>
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	<p><b>Introduction</b></p> <ul style="list-style-type: none"> <li>- The way it is presented now does not show the public health importance of the study. The introduction should start explaining why we should measure radiation doses associated with medical procedures, in terms of public health. And only after going into more details about new recommendations etc.</li> <li>- Do not use abbreviations (CT) without explaining them first.</li> </ul> <p><b>Methods</b></p> <ul style="list-style-type: none"> <li>- The method section does not provide enough details. Information is missing about: <ul style="list-style-type: none"> <li>o Are the tests included in the study only those performed at the hospital, or does the analysis also include the tests performed outside this setting? We get the information about this only in the discussion.</li> <li>o How was the effective dose estimated. Stating “we estimated the associated radiation effective dose using previous published evidence” is not enough!. That would be useful to see what is the effective dose which was used for each exam included, and a detailed list of those (maybe in supplementary material). Was the effective dose per exam the same for men and women? by age? Etc...</li> <li>o How was the cumulative dose estimated from the effective dose per exam? It is not explained at all, although this is the main outcome of the study.</li> <li>o The statistical analysis also needs to be described in more details: “the average dose...” page 7 line 42 : which dose are you referring to ? the cumulative dose? The effective dose? “Differences” line 46 : which differences are your referring to? “Categorical variables”: which ones? You need to detail which were the analyses planned. The tables presented in the manuscript do not match with this “statistical analysis” section. It looks like you did more than what is described in the method section, you should add all the analyses done in the method section (count of exams for example).</li> <li>o Line 56 page 7: don't you mean p-value of 0.05? otherwise, how do you justify this 0.005?</li> <li>o It is not clear why the clinical context of some patients was studied, and how. This is not stated in the objectives of the study. This is also not clear when the diagnosis of neoplasm was considered: at the start of the study or all over the study period? The analysis of this point is not detailed in the method section</li> <li>o It looks like you did not take into account the link between age and the follow-up duration in your analysis. The follow up duration being 12 years, it is much more likely for older people to die within the follow up period than for younger people, leading to lower amount of exams and then lower doses (which does not mean they had lower lifetime cumulative dose, as they got exams before the study started). The analysis should adjust for this in some way, and it should be at least discussed. Similarly, how do you account for the probability of leaving the catchment area? The more the people are likely to leave, the less likely they are to get some exam. I guess this differs depending on age and sex. Results should be discussed in line with this.</li> </ul> </li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>- Please add “table” in the title of each table.</li> <li>- In the first paragraph of the results, you mentioned “imaging test frequency”, but this is not defined anywhere. Do you refer to having</li> </ul>
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at least 1 exam during the study period? This should be detailed (in the method section). Similarly, table 1 refers to “exposure status”, which is not defined.

- As your study population corresponds to the catchment area of one specific hospital, it is important to compare the socio-demographic characteristics of your study population to the general population (age, sex, socioeconomic indicator distribution...). Is your population comparable to the general population? Otherwise, it is difficult to interpret your results.

- Line 34 p.8: “men were more likely...”: was it tested statistically? If so, it should be detailed how and the p-value should be provided. If not, it should just be stated “men were more exposed to CT than women”.

- Line 49-52: the 2 parts of the sentence are redundant.

- Line 54: what do you mean by “cumulative imaging tests”? is it the total number of tests during the study period? What do you mean then by IQR? Was this test mentioned in the method section?

- It is not clear why there is a focus on ages 0-15. This should be explained before the results section.

- Line 52: “all modalities”: is “modalities” referring to one type of exam? It was not used before.

#### Tables

- In all your tables, you should add the results for men and women combined, and more importantly provide the results by age AND by sex: you state there is a significant difference between men and women (line 16 p. 8), but then you provide only the results by age for both sexes combined...

- Don't use abbreviations without explaining them (No of people for ex in table 1 for ex)

- Table 1:

o Definitions of people “exposed” is missing

- Table 2:

o The content of the columns should be indicated: number of (exposed?) people (%)? Number of exams (%)? The title should also be more informative, according to this.

- Table 3

o Please shorten the title

o Does it include only exposed population?

- Table 4: is the term “incidence” of the title really appropriate (see previous comment).

- Table 5:

o Does it include only exposed population?

o The content of the columns should be indicated: number of (exposed?) people (%)? Or the title should be adapted: “number of people (%)...”

#### Discussion

- Comparison to similar studies is definitely missing.

- The threshold of 100 mSv should be mentioned much earlier (in the method section, when describing analysis of cumulative dose, which is missing). Please add a reference for the 100 mSv considered as significant risk.

- The text on the risk in relation to the dose (lines 37-78, p.11) should be explained earlier (introduction?) as this is the justification for doing this type of analysis

- What do you conclude from the analysis of recurrent exams (lines 51 p.11 to line 13 p.12)? the corresponding message is not clear to me.

	<ul style="list-style-type: none"> <li>- Lines 53 p.12 – line 20 p.13: I would recommend adding international examples showing the same.</li> <li>- Lines 22-36 p.13: assessing the amount of effective dose is not directly linked to reducing the cancer risk, but rather to raise awareness of clinicians and patients about the corresponding risks and then reduce the risk. Please reformulate.</li> <li>- Would you try to estimate how much of the dose you missed by not taking into account exams performed outside the hospital. This is a big limitation which may have big impact on the results. That would be very informative to provide quantification for this. The same for line 3 p.14: it is important to quantify how much your study could be generalised.</li> <li>- Line 53 p.13: which limitations are you referring to? They should be detailed!</li> <li>- You state “a significant proportion of patients received doses higher than 50 mSv”, but <ul style="list-style-type: none"> <li>o 1: it is only 5% of the population, including high risk patients</li> <li>o 2: the threshold for “at risk patients” discussed earlier is 100 mSv. How do you justify this?</li> </ul> </li> <li>- The duration of the follow up period and the link with age should be developed.</li> <li>- Usually, organ doses are more appropriate to study risks associated with medical IR (for instance, the BEIRVII model is based on organ doses, not effective doses). Why did you use effective doses and not organ doses? This point should definitely be discussed, and you should explain how the use of effective dose should be interpreted, compared to organ doses.</li> </ul> <p>Other</p> <ul style="list-style-type: none"> <li>- Has the text been reviewed by a native English speaker? English wording could definitely be improved to facilitate the flow.</li> <li>- Please harmonise the terms used to describe diagnostic procedures: “imaging tests” or “imagen tests”? both are mixed in the texts and are used sometimes with “tests” and sometimes with “procedures</li> <li>- What do you mean by “cumulative incidence radiation exposure”. It is used several times (but not all the time) and the term “incidence” is very confusing. It looks like you are estimating cumulative dose to radiation exposure over a 12 years follow-up period.</li> </ul>
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<b>REVIEWER</b>	Hai-Qiang Wang Institute of Integrative Medicine, Shaanxi University of Chinese Medicine, Xi'an 712046, Shaanxi Province, P. R. China
<b>REVIEW RETURNED</b>	22-May-2019

<b>GENERAL COMMENTS</b>	<p>The reviewer thanks the editor for the opportunity to review the study (bmjopen-2019-030905).</p> <p>The retrospective population-based study reported cumulative radiation exposure derived from diagnostic imaging. In general, the topic is relevant to the mostly neglected issue pertaining to the health of the public, which is of importance. It is well written.</p> <p>Specific comments:</p> <ol style="list-style-type: none"> <li>1. Page 7, line 25, please specify the methods used for the calculation of effective dose for diagnostic imaging. Moreover, please provide detailed information for different diagnostic imaging modalities.</li> <li>2. For CT scans, different body parts correspond to various radiation doses. For instance, radiation dose is higher for</li> </ol>
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	<p>abdominal CT scans than extremity CT scans. Please specify the data and impact on the results.</p> <p>3. During the follow-up studying period, did the authors observed increased cancer/tumor rates amongst involved people? Please clarify since this is important.</p> <p>4. There is great difference between plain radiographs and CT scans in terms of radiation dose. How about the results if sub-group analysis is considered?</p>
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**VERSION 1 – AUTHOR RESPONSE**

**Reviewer: 1**

**Reviewer Name**

**Claire Marant Micallef**

**Institution and Country**

**International Agency for Research on Cancer, France**

**Please state any competing interests or state ‘None declared’:**

**None declared**

**Please leave your comments for the authors below**

**Summary**

**The topic and the setting of the study are interesting in the current context of assessing the risks related to medical ionizing radiation. The study population and the follow-up duration are large. However, the analysis should be clarified and more detailed, i.e. more information should be provided both on the methods used and in the results to make the paper more attractive. Moreover, the objective and the results need to be put in a wider international context: it looks like a more comprehensive literature review should be performed in order to elaborate more both the introduction and the conclusion. I am surprised to see that there is no other study mentioned in any country for comparison in terms of the estimation of such cumulative dose at the population level: for instance, the study recently published in France about fractions of cancer attributable to IR from medical diagnostic procedures provided some cumulative exposure by sex and age group (doses to organs)**

**(<https://www.ncbi.nlm.nih.gov/pubmed/30537057>). A similar study was published in the UK in 2012 (<https://www.ncbi.nlm.nih.gov/pubmed/22158322>).**

**It is also not very clear from the discussion what the perspectives of this analysis are: how can these results can be used to improve risk prevention? Please elaborate on this.**

**Finally, I am concerned with some methodological issues (see details in comments by section), such as age and duration of follow up, representativity of the studied population, lack of exams outside the hospital...? The way these points would influence the results and their interpretation should be discussed much further.**

Thank you for your comments.

We have discussed all these points along the manuscript.

### **Abstract**

- **The median cumulative dose is not mentioned, whereas it is the main outcome of the study... Please reformulate the results to make it clearer. The % of the population with a cumulative dose >50 mSv (5%) is not "significant"**

We have included results related with effective dose in the results section in the abstract. In addition, we have reformulated the discussion section.

### **Introduction**

- **The way it is presented now does not show the public health importance of the study. The introduction should start explaining why we should measure radiation doses associated with medical procedures, in terms of public health. And only after going into more details about new recommendations etc.**
- **Do not use abbreviations (CT) without explaining them first.**

We have included those changes in the introduction section. Now this section shows the public health importance of the radiation exposure and clarifies the health problem (pages 4-6).

We have also included first the explanation of each abbreviation.

### **Methods**

- **The method section does not provide enough details. Information is missing about:**
  - o **Are the tests included in the study only those performed at the hospital, or does the analysis also include the tests performed outside this setting? We get the information about this only in the discussion.**

As we stated in the methods section, the majority of the Spanish population uses the National Health Care System as the main medical service (the publicly funded insurance scheme covers 98.5% of the Spanish population). However, we have added a sentence to clarify it: 'hence, only a small percentage of patients are likely to have had imaging tests outside this setting'. (page 7, lines 221-222).

- o **How was the effective dose estimated. Stating "we estimated the associated radiation effective dose using previous published evidence" is not enough!. That would be useful to see what is the effective dose which was used for each exam**

**included, and a detailed list of those (maybe in supplementary material). Was the effective dose per exam the same for men and women? by age? Etc...**

The reviewer is right. We have clarified this point and we have added this explanation in the methods section (page 9, lines 313-323). In addition, we have included a detailed list in supplementary material (tables 1 and 2).

**o How was the cumulative dose estimated from the effective dose per exam? It is not explained at all, although this is the main outcome of the study.**

Cumulative effective dose estimates were obtained by adding effective dose estimates received in each test in the patient's history. Data were expressed as the median, maximum and 25, 75, 95 percentiles. Differences by sex and age group were assessed using the Mann–Whitney U test. We have included this explanation in the method section. (page 10, lines 411-414).

**o The statistical analysis also needs to be described in more details: “the average dose...” page 7 line 42 : which dose are you referring to ? the cumulative dose? The effective dose? “Differences” line 46 : which differences are your referring to? “Categorical variables”: which ones? You need to detail which were the analyses planned. The tables presented in the manuscript do not match with this “statistical analysis” section. It looks like you did more than what is described in the method section, you should add all the analyses done in the method section (count of exams for example).**

We described in more detail the statistical analysis, including all the analysis carried out (page 9, lines 402-422).

**o Line 56 page 7: don't you mean p-value of 0.05? otherwise, how do you justify this 0.005?**

Yes, it was a mistake.

**o It is not clear why the clinical context of some patients was studied, and how. This is not stated in the objectives of the study. This is also not clear when the diagnosis of neoplasm was considered: at the start of the study or all over the study period? The analysis of this point is not detailed in the method section.**

We have included more detail of this aspect in the introduction (page 6, lines 188-192), objectives (page 6, lines 197-198) and in the method section (page 9, lines 324-331). We

aimed to analyze the clinical context of the patients following the American College of Radiology white paper recommendation, where it stated that clinicians should develop a surveillance mechanism to identify patients with high cumulative radiation doses due to repeat imaging. According to previous literature, patients with a diagnosis of neoplasm are prone to have recurrent imaging tests.

**o It looks like you did not take into account the link between age and the follow-up duration in your analysis. The follow up duration being 12 years, it is much more likely for older people to die within the follow up period than for younger people, leading to lower amount of exams and then lower doses (which does not mean they had lower lifetime cumulative dose, as they got exams before the study started). The analysis should adjust for this in some way, and it should be at least discussed. Similarly, how do you account for the probability of leaving the catchment area? The more the people are likely to leave, the less likely they are to get some exam. I guess this differs depending on age and sex. Results should be discussed in line with this.**

Cohort members remained in the study until their exit date or they left the catchment area. We assigned each person to the unexposed group from the date of entry until the date of the first imaging test, and to the exposed group from the date of the first imaging test until the exit date. In addition, in those patients who did not account for the 12 years of follow-up, we assumed future practice estimating the proportion of imaging tests that would have been carried out during the remaining period if the patients had been in the cohort, except for the > 80 age group, where did not implemented this strategy given that the expectancy life in Spain is 82.83 years old.

We have included this explanation in the method section (pages 7-8, lines 227-239).

We have also outlined it as a limitation in the discussion section (page 18, lines 823-827).

## **Results**

**- Please add “table” in the tile of each table.**

Done.

**- In the first paragraph of the results, you mentioned “imaging test frequency”, but this is not defined anywhere. Do you refer to having at least 1 exam during the study period? This should be detailed (in the method section). Similarly, table 1 refers to “exposure status”, which is not defined.**

Yes, the reviewer is right. We have included a detailed description of these terms in the method (page 9, lines 403-405) and in the result section (page 11, lines 487-488).

**- As your study population corresponds to the catchment area of one specific hospital, it is important to compare the socio-demographic characteristics of your study population to the general population (age, sex, socioeconomic indicator distribution...). Is your population comparable to the general population? Otherwise, it is difficult to interpret your results.**



We have included a new column in table 1 showing the Spanish general population by sex and age. We can observe that both population are similar.

- **Line 34 p.8: “men were more likely....”:** was it tested statistically? If so, it should be detailed how and the p-value should be provided. If not, it should just be stated “men were more exposed to CT than women”.

Following your advice regarding the presentation the results in the tables, we have now provided them by age and by sex. Thus, we have tested statistically any difference by sex in each age group.

- **Line 49-52: the 2 parts of the sentence are redundant.**

We have eliminated this part of the sentence to make it clearer.

- **Line 54: what do you mean by “cumulative imaging tests”?** is it the total number of tests during the study period? What do you mean then by IQR? Was this test mentioned in the method section?

Cumulative diagnostic imaging test was estimated during the period of study by adding up the number of tests received by each patient. We have defined it in the method section (page 11, lines 405-408).

We have defined IQR as interquartile range.

- **It is not clear why there is a focus on ages 0-15. This should be explained before the results section.**

We referred to the population where the risk of cancer is increased. However, it was a mistake, since we wanted to refer to 0-20 age group. Accordingly, we have included several explanations along the introduction and the method section and we have also included it in the objectives. In addition, we have changed the data in the result section from 0 to 15 age group to 0 to 20 age group.

- **Line 52: “all modalities”:** is “modalities” referring to one type of exam? It was not used before.

No, it refers to all imaging tests. We have changed it.

## Tables

- **In all your tables, you should add the results for men and women combined, and more importantly provide the results by age AND by sex: you state there is a significant difference between men and women (line 16 p. 8), but then you provide only the results by age for both sexes combined...**

We have reedited the tables. Now, we provided the results by age and by sex.

- **Don't use abbreviations without explaining them (No of people for ex in table 1 for ex)**

Done.

- **Table 1:**
  - o **Definitions of people "exposed" is missing**

We have changed it by 'people having at least 1 imaging test in the study'.

- **Table 2:**
  - o **The content of the columns should be indicated: number of (exposed?) people (%)? Number of exams (%)? The title should also be more informative, according to this.**

We have the description in the columns and in the title.

- **Table 3**
  - o **Please shorten the title**

We have shorten it.

- o **Does it include only exposed population?**

Yes, we have changed the title to clarify it.

- **Table 4: is the term "incidence" of the title really appropriate (see previous comment).**

The reviewer is right. We have eliminated it.

- **Table 5:**
  - o **Does it include only exposed population?**

Yes, we included only exposed population. We have changed the title to clarify it.

- o **The content of the columns should be indicated: number of (exposed?) people (%)? Or the title should be adapted: "number of people (%)."...**

Done.

## **Discussion**

- **Comparison to similar studies is definitely missing.**

We have compared our results with similar studies along the discussion section.

- **The threshold of 100 mSV should be mentioned much earlier (in the method section, when describing analysis of cumulative dose, which is missing). Please add a reference for the 100 mSv considered as significant risk.**

We have described this threshold according to the stochastic theory effect and added a reference. According with the following comment, we have moved this explanation to the introduction section (page 4, lines 118-128).

- **The text on the risk in relation to the dose (lines 37-78, p.11) should be explained earlier (introduction?) as this is the justification for doing this type of analysis**

The reviewer is right and we have included this explanation in the introduction section, so the explanation of the threshold of 100 mSv is clearer now (page 4, lines 118-128).

- **What do you conclude from the analysis of recurrent exams (lines 51 p.11 to line 13 p.12)? the corresponding message is not clear to me.**

I have added a sentence in the end of the paragraph explaining that: 'Additional measures should be applied to control these recurrent rates, particularly to subgroups who are more prone to recurrent controls such as patients with chronic diseases like cancer.' (pages 16, lines 698-700).

- **Lines 53 p.12 – line 20 p.13: I would recommend adding international examples showing the same.**

We have added international references (pages 17-18, lines 776-812).

- **Lines 22-36 p.13: assessing the amount of effective dose is not directly linked to reducing the cancer risk, but rather to raise awareness of clinicians and patients about the corresponding risks and then reduce the risk. Please reformulate.**

The reviewer is right and accordingly we have reformulated the sentence (page 18, lines 815-819).

- **Would you try to estimate how much of the dose you missed by not taking into account exams performed outside the hospital. This is a big limitation which may have big impact on the results. That would be very informative to provide quantification for this. The same for line 3 p.14: it is important to quantify how much your study could be generalised.**

As we stated in the method section, the majority of the Spanish population uses the NHS as the main medical service (the publicly funded insurance scheme covers 98.5% of the

Spanish population) and hence, only a small percentage of patients are likely to have had imaging tests outside this setting.

Moreover, as we have showed in the result section, the population included in the study is similar to general Spanish population.

We have mentioned these explanations in the discussion section (page 18, lines 823-826).

**- Line 53 p.13: which limitations are you referring to? They should be detailed!**

We have detailed these limitations, which are related with the fact that this estimation based on available literature does not take into account the examination date, the scanner model or the patient's characteristics (page 19, lines 765-766).

**- You state “a significant proportion of patients received doses higher than 50 mSv”, but**

**o 1: it is only 5% of the population, including high risk patients**

**o 2: the threshold for “at risk patients” discussed earlier is 100 mSv. How do you justify this?**

The reviewer is right. We have changed the conclusions of the study focusing on the number of people having doses between 50 and 100 mSv and greater than 100 mSv.

**- The duration of the follow up period and the link with age should be developed.**

As we stated previously, we have described it in the method section and we have included it as a limitation.

**- Usually, organ doses are more appropriate to study risks associated with medical IR (for instance, the BEIRVII model is based on organ doses, not effective doses). Why did you use effective doses and not organ doses? This point should definitely be discussed, and you should explain how the use of effective dose should be interpreted, compared to organ doses.**

We used effective dose to quantify the radiation exposure associated with each imaging test instead of organ doses. Absorbed organ doses are important for some procedures that either involve high doses or include sensitive tissues in the primary radiation beam. However, our aim was not to assess cancer risks associated with medical ionizing radiation but to compare across the different imaging tests evaluated in the population included. We have included this explanation as a limitation (page 19, lines 903-908).

**Other**

**- Has the text been reviewed by a native English speaker? English wording could definitely be improved to facilitate the flow.**

Yes, a native English speaker has reviewed the whole manuscript.

- **Please harmonise the terms used to describe diagnostic procedures: “imaging tests” or “imagen tests”? both are mixed in the texts and are used sometimes with “tests” and sometimes with “procedures**

Done. We have used the term imaging test along the document.

- **What do you mean by “cumulative incidence radiation exposure”. It is used several times (but not all the time) and the term “incidence” is very confusing. It looks like you are estimating cumulative dose to radiation exposure over a 12 years follow-up period.**

The reviewer is right. We have changed it by cumulative effective dose.

**Reviewer: 2**

**Reviewer Name**  
**Hai-Qiang Wang**

**Institution and Country**  
**Institute of Integrative Medicine, Shaanxi University of Chinese Medicine, Xi'an**  
**712046, Shaanxi Province, P. R. China**

**Please state any competing interests or state ‘None declared’:**  
**None declared.**

**Please leave your comments for the authors below**

**The reviewer thanks the editor for the opportunity to review the study (bmjopen-2019-030905).**

**The retrospective population-based study reported cumulative radiation exposure derived from diagnostic imaging. In general, the topic is relevant to the mostly neglected issue pertaining to the health of the public, which is of importance. It is well written.**

**Specific comments:**

**1. Page 7, line 25, please specify the methods used for the calculation of effective dose for diagnostic imaging. Moreover, please provide detailed information for different diagnostic imaging modalities.**

We have included a detailed description in pages 8-9, lines 313-3238).

**2. For CT scans, different body parts correspond to various radiation doses. For instance, radiation dose is higher for abdominal CT scans than extremity CT scans. Please specify the data and impact on the results.**

The reviewer is right. We have clarified this point and we have added this explanation in the methods section (page 9, lines 255-311). In addition, we have included a detailed list in supplementary material (tables 1 and 2).

**3. During the follow-up studying period, did the authors observed increased cancer/tumor rates amongst involved people? Please clarify since this is important.**

No, the cancer rates did not change amongst involved people along the period of study. We have added in the discussion this explanation (page 15, lines 622-623).

**4. There is great difference between plain radiographs and CT scans in terms of radiation dose. How about the results if sub-group analysis is considered?**

We have carried out a sub-group analysis on the cumulative effective dose (mSv) per person exposed during the period of study, considering plain radiograph and CT differently. According to another reviewer we have presented these results by age and by sex. These new tables are now in supplementary material.

Moreover, we have calculated the percentage of people with doses lower than 50 mSv, between 50 mSv and 100 mSv and higher than 100 mSv, considering plain radiograph and CT separately. These results are in the result section and they are discussed in the discussion section.