

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Do emissions from landfill fires affect pregnancy outcomes? A retrospective study after arson at a solid waste facility in Sicily.
AUTHORS	MAZZUCCO, WALTER; Tavormina, Elisa; Macaluso, M; Marotta, Claudia; Cusimano, Rosanna; Alba, Davide; Costantino, Claudio; Grammauta, Rosario; Cernigliaro, Achille; Scondotto, Salvatore; Vitale, Francesco

VERSION 1 – REVIEW

REVIEWER	Xi Gong University of New Mexico, United States.
REVIEW RETURNED	30-Nov-2018

GENERAL COMMENTS	<p>The manuscript conducted an epidemiological study using the vital statistics data to evaluate the association between the landfill fire emission and different adverse birth outcomes. The major finding was maternal exposure to the landfill fire emissions during conception or early pregnancy were associated with higher risk of very low birth weight in offspring. Overall, the basic idea is clear. The manuscript addresses a problem and offers a solution. However, there are several issues which need to be reconsidered by the authors:</p> <p>Major issues:</p> <ol style="list-style-type: none">1) Line 103-120: This section has duplicate information, and need to be combined and simplified. The authors can talk about the CedAP registry data first, then discuss the criteria (area, time) that they used to select data for the analysis.2) Line 116: The study group also includes live births and stillbirths, so it's better to use "all live births and stillbirths" instead of "births".3) Line 121-135: There are a total of 4 different comparisons, please reorganize the sentences to improve the readability, e.g. using transitional phrases between comparisons or listing the comparisons with numbers.4) Line 136-143: It is better to start a new paragraph for this section and add transitional phrases. e.g. "For each comparison, we evaluated the following...."5) Line 159-160: There is no need to report this OR as it is not statistically significant.6) Line 161: The authors should be more careful in the use of the terms risk and odds. These have different meanings (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640017/). Since the authors calculate odds ratios, they should interpret the results using the term odds instead of risks throughout the manuscript.
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	<p>7) Line 239-245: These are duplicated with the methods section, consider removing this part.</p> <p>8) Line 259-261: These study results are too general which is not directly related to the current study. Please replace them with more specific examples like the ones in Line 262-267.</p> <p>9) Line 293: This study can only identify associations but not cause-effect relationships, so please present the result as “associated with” not “causally related to”.</p> <p>10) Figure 1: The caption for the figure is incorrect. Besides the 4 group of exposure periods, there is no description of the extra arrows (e.g. stillbirths, VLBW), which could confuse the readers. Please add some descriptions of how these arrows (periods) are defined and what they represent in the manuscript text.</p> <p>11) Page 24, the top map: Include map elements in the map, such as north arrow, scale bar. The legend also needs to include all the features in the map, e.g. the red circle, the administrative boundaries.</p> <p>12) The numbering of tables and the references to the tables do not match in the text, please double check.</p> <p>13) This study performed multiple statistical tests on different birth outcomes in different comparison groups. There might be multiple comparison issue that could lead to false positives in the results. Although the authors later mentioned that these results are probably due to chance, It would be informative to see how many of the significant associations would survive a multiple comparison correction.</p> <p>14) This study simplify maternal exposure assessment as whether the pregnancy period overlapped with the time of the fire. This method does not consider how the pollutant dispersed over time and the spatial locations of the pregnant mothers, which could cause exposure misclassification in the results. The authors may consider using other exposure assessment methods to improve the accuracy. E.g. “direct surrogate models” which uses data from the closest monitors as a surrogate for exposure, or “proximity models” which take distances to the emission source into account. More details about the comparison of these methods can be found at https://www.ncbi.nlm.nih.gov/pubmed/27152989.</p> <p>15) Line 146-147: “ORs were adjusted by maternal age and newborn sex for comparisons based on all births, and by maternal age for comparisons based on singleton live births”. However, based on the literature, more potential covariates need to be adjusted when considering the birth outcomes in this study. e.g. the covariates for LBW include child's sex, gestational weeks, maternal age, education, race/ethnicity, marital status, prenatal care, tobacco use during pregnancy, etc. Ideally, all these covariates need to be adjusted when calculating the adjusted odds ratios. If the study cannot adjust all the covariates because of the limited number of births, this study needs to at least keep the number of adjusted covariates consistent (e.g. use maternal age and newborn sex consistently) in different statistical tests. Also, please add some texts on why these covariates were selected instead of others.</p> <p>Minor issues:</p> <p>1) Line 58: Change it to “near the landfill plants”.</p> <p>2) Line 91: Use the lowercase letters for “Public Health”.</p> <p>3) Line 100 & 115: The Supplementary File can be listed as figures instead (e.g. Figure 2, Figure 3).</p> <p>4) Line 111: Use “0.4” not “0,4”.</p>
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	5) Line 146-148: Use “for maternal age” instead of “by maternal age”; remove “by” in “by using STATA”. 6) Line 263-264: Merge them into one paragraph.
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REVIEWER	Lisbeth E. Knudsen University of Copenhagen, Denmark
REVIEW RETURNED	10-Dec-2018

GENERAL COMMENTS	The manuscript clearly describes reproductive effects from environmental exposures to landfill with birth weight significantly affected from exposures. Table 1 is difficult to understand and may be taken out? More characterisation of the exposures would be of interest but probably not possible.
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REVIEWER	Emily Harville Tulane University, US
REVIEW RETURNED	03-Feb-2019

GENERAL COMMENTS	<p>The study aims to examine the relationship between living near a landfill fire and birth outcomes. The authors have a limited exposure measure (residence in the area during a time frame) and no individual-level exposure measures. Nonetheless, the authors are fairly circumspect in their interpretations and such analyses are useful to have on file, so to speak, as background to more detailed analyses and for high-level indicators of possible results of such exposures.</p> <p>I have to admit I was not aware of arson at a solid waste facility as being a frequent occurrence, though, given that it happens, it makes sense to see if it leads to health effects. I presume it is not arson per se, but exposures resulting from the fire?</p> <p>Exposure is measured ecologically and extremely approximately (area and time of residence). This limitation is somewhat mitigated by the fairly short-term nature of the exposure (two weeks, more or less). What consequences did the fire have for the area beyond environmental exposures? Were roads or schools shut down or traffic increased, for instance? Such information would help in assessing environment as a likely source.</p> <p>The authors exclude urban areas to avoid confounding by other types of pollution. This rationale is reasonable as far as it goes, but likely excludes the most exposed women. What do the results look like if these areas are included (or studied as a separate group)? Also, it looks like the extra-urban area was a fairly small proportion of the surveillance area.</p> <p>Why the limited set of control variables (maternal age and newborn sex)? Did they consider other possible confounders? Preterm births have less opportunity to be exposed than full-term gestations; did the authors do anything to address this besides limiting to <36 weeks?</p> <p>LBW is generally considered to be a combination of the effects of FGR, indicated by SGA, and preterm birth, but neither part individually seemed to have an effect. Do the authors have an explanation for this? Since an effect was found on very LBW, was there an effect on VPTB?</p> <p>One of the more common issues with this sort of paper is selective reporting of results. The authors’ discussion is fairly balanced on possible true and chance associations, but I wonder whether they looked at other outcomes that they did not report?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Xi Gong

Institution and Country: University of New Mexico, United States.

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

The manuscript conducted an epidemiological study using the vital statistics data to evaluate the association between the landfill fire emission and different adverse birth outcomes. The major finding was maternal exposure to the landfill fire emissions during conception or early pregnancy associated with higher risk of very low birth weight in offspring. Overall, the basic idea is clear. The manuscript addresses a problem and offers a solution. However, there are several issues which need to be reconsidered by the authors:

Major issues:

1) Line 103-120: This section has duplicate information, and need to be combined and simplified. The authors can talk about the CedAP registry data first, then discuss the criteria (area, time) that they used to select data for the analysis.

R: We have simplified the text according to the reviewer's suggestion, as follows (Page 4, lines 192-207): "We obtained limited data from the regional Certificate of Birth Attendance (CedAP) registry, which collects information on all births to women of childbearing age (10-55 years old) who deliver in Sicily, including parental socio-demographic characteristics, obstetric history, prenatal care, and characteristics of pregnancy and birth. The CedAP registry does not include data on births to resident mothers who delivered outside the region or wanted to preserve anonymity (0.4%). Date of conception was estimated using the date of birth and gestational age at birth reported in the registry. The study included all live births and stillbirths to mothers residing within the surveillance zone, whose estimated conception date occurred from 36 weeks prior to the peak of the fire (from 2:00PM on July 29, 2012 to 2:00PM on July 30, 2012), until 4 weeks after the fire. To remove confounding by exposure to pollutants deriving from anthropic activities and vehicular traffic within metropolitan areas, we restricted the main focus of the analysis to residents of the extra-urban section of the surveillance area (Supplementary file). Thus, the study group included all live births and stillbirths in the extra-urban surveillance area from pregnancies that were potentially exposed to the fire around the time of conception as well as pregnancies that were exposed at later stages (through the 36th week). The reference group comprised all live births and stillbirths to mothers residing in the remaining extra-urban, low-density and unindustrialized areas of Sicily, during the same time interval."

2) Line 116: The study group also includes live births and stillbirths, so it's better to use "all live births and stillbirths" instead of "births".

R: We have changed the sentence according to the reviewer's suggestion, as follows (Page 5, line 212): "Thus, the study group included all live births and stillbirths in the extra-urban surveillance area from pregnancies that were potentially exposed to the fire around the time of conception as well as pregnancies that were exposed at later stages (through the 36th week)." We have also rephrased the first sentences of the Results section as follows (Page 5, lines 367-371): "Mothers residing in the exposed extra-urban area (the study group) gave birth to a total of 551 infants (548 live born + 3 stillborn) conceived during the interval of interest (11/20/2011-08/26/2012). There were 22,341 births (22,264 live births + 65 stillbirths) from pregnancies conceived during the same period by mothers

residing in the remaining Sicilian low population-density, low industrialization areas (the comparison group).”

3) Line 121-135: There are a total of 4 different comparisons, please reorganize the sentences to improve the readability, e.g. using transitional phrases between comparisons or listing the comparisons with numbers.

R: We thank the reviewer for this useful suggestion. In order to improve the readability we have rephrased the text related to the study group. Furthermore, we have better explained that we have performed two supplementary analyses. Consequently, the text was modified as follows (Page 5, lines 215-293): “The reference group comprised all live births and stillbirths to mothers residing in the remaining extra-urban, low-density and unindustrialized areas of Sicily, during the same time interval. To distinguish pregnancy periods of susceptibility to acute exposure to the fire emissions, we stratified the study group and the reference population according to the following four sub-periods of exposure (Figure 1):

- i) peri-conception (conception occurring on July 29, 2012 or up to 4 weeks later);
- ii) first trimester (conception date 12-0 weeks before July 29, 2012);
- iii) second trimester (24-13 weeks before July 29, 2012);
- iv) third trimester (36-25 weeks before July 29, 2012).

For each stage of the pregnancy at the time of exposure, we compared birth outcomes of the study group with those of the reference group. We also carried out internal comparisons within the study group, contrasting outcomes across the four sub-periods of exposure.

We conducted two supplementary analyses: first, we compared birth outcomes to mothers in the metropolitan area of Palermo (the main metropolitan area served by the Bellolampo MSW-L, 656,829 inhabitants) with those to mothers residing in the two other Sicilian metropolitan areas of Catania (293,104 inhabitants) and Messina (242,914 inhabitants) in the same study period. Second, to assess any systematic difference between the study group and the reference group independently from the fire, we repeated the comparison using data on births that occurred during the year preceding the arson (specifically, births conceived within -36 and +4 weeks from July 29, 2011). ”

4) Line 136-143: It is better to start a new paragraph for this section and add transitional phrases. e.g. “For each comparison, we evaluated the following....”

R: We thank the reviewer again for the useful suggestion. We have provided to modify the text as follows (Page 6, line 294): “For each comparison, we evaluated the following proportions, defined according to European guidelines for perinatal statistics adopted by the PERISTAT system[16,17]: a) among all births (i.e., live births and stillbirths combined): proportion of stillbirths, proportions of male and female births, and proportions of singleton and multiple births; b) among live births: preterm birth (gestational age <37 weeks), very preterm birth (gestational age <32 weeks) low birth weight (<2,500 grams), very low birth weight (<1,500 grams) and small for gestational age (SGA) (birth weight under the tenth percentile of the national distribution of birth weights of the same gestational age or birth of gestational age ≥37 weeks weighing <2,500 grams).”

5) Line 159-160: There is no need to report this OR as it is not statistically significant.

R: We have removed this OR from the text according to the reviewer’s suggestion. Consequently, we have rephrased the text as follows (Page 7, line 371): “We observed a two-fold increase in risk of very preterm (OR adjusted for maternal age and infant gender= 2.29; 95%CI= 1.12 - 4.68) and a two-fold increase in risk of very low birth weight (OR adjusted for maternal age and infant gender= 2.20; 95%CI= 1.02 - 4.72) among singleton live births (Table 1).”

6) Line 161: The authors should be more careful in the use of the terms risk and odds. These have different meanings (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640017/>). Since the authors calculate odds ratios, they should interpreted the results using the term odds instead of risks throughout the manuscript.

R: We understand the reviewer's concern about the difference between risk and odds, but we note that the odds ratio closely approximates the risk ratio when the absolute risk for the any exposed category is below 10%. Because (except for the gender ratio) most outcomes of interest have risks <10%, we believe that our interpretation is appropriate. We have added a comment to this effect in the methods section (Page 6, line 307): "Throughout this paper we treated the OR as an estimate of the risk ratio. This is appropriate as the absolute risks for most of the outcomes considered are well below 10%, and under these conditions the OR closely approximates the RR."

7) Line 239-245: These are duplicated with the methods section, consider removing this part.

R: Following the suggestion of the reviewer, we have removed this part.

8) Line 259-261: These study results are too general which is not directly related to the current study. Please replace them with more specific examples like the ones in Line 262-267.

R: We appreciate the suggestion. Anyway, we believe that the evidence about the association between exposure to particulates (a product of combustion, although mostly produced by combustion engines) and adverse pregnancy outcomes is relevant to the hypothesis that emission from burning landfills may have similar effects. Therefore, we think that the references proposed can be considered "specific" and useful for the discussion.

9) Line 293: This study can only identify associations but not cause-effect relationships, so please present the result as "associated with" not "causally related to".

R: We have changed the sentence according to the reviewer suggestion as follows (Page 15, line 871): "Thus, the excess of stillbirths to mothers exposed during the third trimester could be associated with the arson."

10) Figure 1: The caption for the figure is incorrect. Besides the 4 group of exposure periods, there is no description of the extra arrows (e.g. stillbirths, VLBW), which could confuse the readers. Please add some descriptions of how these arrows (periods) are defined and what they represent in the manuscript text.

R: Once again, we thank the reviewer for the useful suggestion. We have added a more detailed caption to the figure, highlighting the meaning of the "arrows". Furthermore, we have edited the figure description as follows (Page 24): "Bellolampo solid waste landfill arson: pregnancy stage at exposure among resident mothers and key statistically significant findings documented for the extra-urban area (the arrows represent the health outcomes associated to the exposure to the pollutants emitted by the arson)."

11) Page 24, the top map: Include map elements in the map, such as north arrow, scale bar. The legend also needs to include all the features in the map, e.g. the red circle, the administrative boundaries.

R: In order to better focus the comprehension of the reader, we have decided to unify the two maps in one, complete with all the features required (north arrow, scale bar, legends). Consequently, we have implemented the text as follows:

- Method section (Page 4, line 187): "In response to the arson, the Sicilian Regional Health Authority defined an administrative area around the landfill, whose resident population was considered as potentially exposed to the MSW-L emissions and placed under surveillance (Supplementary file)."

- Supplementary file. Under surveillance area exposed to emissions deriving from the Bellolampo municipal solid waste landfill (Borgetto, Capaci, Carini, Giardinello, Montelepre, Torretta):

Metropolitan area (Palermo) and extra-urban area (in red).

12) The numbering of tables and the references to the tables do not match in the text, please double check.

R: We thank the reviewer for the very important revision. We have double checked the numbering of the tables and corrected the text according to the reviewer's suggestion. At the same time, we have modified the tables' description in order to improve the comprehension by the readers.

13) This study performed multiple statistical tests on different birth outcomes in different comparison groups. There might be multiple comparison issue that could lead to false positives in the results. Although the authors later mentioned that these results are probably due to chance, It would be informative to see how many of the significant associations would survive a multiple comparison correction.

R: We appreciate the reviewer's concern about multiple comparisons, which might lead to false positive results. As the reviewer acknowledges, we show restraint in interpreting the findings and caution the reader in that regard. In addition, our presentation and discussion of the results is largely focused on the precision of the estimates, as represented by the width of the 95% confidence interval. The CI has a direct relation with hypothesis testing, as a CI that excludes the null value indicates that the p-value for the null hypothesis is <0.05 . The CI, however, conveys a lot more information than a simple test of significance, and this is what we leverage in interpreting the results. If we wanted to translate the multiple comparison adjustment (e.g., via the Bonferroni correction) into a change in the CIs, we would have to add to the conventional 95% CIs a new set of CIs based on the nominal confidence level obtained after the correction. This is typically not done in epidemiologic analyses, and we would recommend not to pursue this complication. Our text points the reader to the width of the 95% CI, which in many instances is close to the null and suggests that the data is compatible with a near-null association: this is sufficient warning to take the association with a grain of salt.

14) This study simplify maternal exposure assessment as whether the pregnancy period overlapped with the time of the fire. This method does not consider how the pollutant dispersed over time and the spatial locations of the pregnant mothers, which could cause exposure misclassification in the results. The authors may consider using other exposure assessment methods to improve the accuracy. E.g. "direct surrogate models" which uses data from the closest monitors as a surrogate for exposure, or "proximity models" which take distances to the emission source into account. More details about the comparison of these methods can be found at <https://www.ncbi.nlm.nih.gov/pubmed/27152989>.

R: We agree that models based on the residence address of the mother at the time of the exposure would enhance our ability to estimate the impact of the landfill fire on pregnancy outcomes. Unfortunately, we are limited by the information provided to us, which identifies the births to mothers residing in the at-risk area designated by the authorities without providing detailed addresses. Thus, the rather simple analysis presented is the best approach we can apply to the data at hand.

15) Line 146-147: "ORs were adjusted by maternal age and newborn sex for comparisons based on all births, and by maternal age for comparisons based on singleton live births". However, based on the literature, more potential covariates need to be adjusted when considering the birth outcomes in this study. e.g. the covariates for LBW include child's sex, gestational weeks, maternal age, education, race/ethnicity, marital status, prenatal care, tobacco use during pregnancy, etc. Ideally, all these covariates need to be adjusted when calculating the adjusted odds ratios. If the study cannot adjust all the covariates because of the limited number of births, this study needs to at least keep the number of adjusted covariates consistent (e.g. use maternal age and newborn sex consistently) in different statistical tests. Also, please add some texts on why these covariates were selected instead of others.

R: We thank the reviewer for the very useful comments. Odds Ratios were already adjusted by maternal age and infant gender. We have provided to correct the methods section as follows (Page 6, line 304): "To make statistical inference about the comparisons between the different study groups and the references, we used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) of the ORs, with and without adjusting for maternal age and infant gender, the only two potential confounders made available to us." We have also corrected the legend in the Tables.

Lastly, we have implemented the text of the methods section as follows (Page 6, line 302): “Because of CedAP data flow at the time in study was relatively new, we were only able to use the limited information described in this manuscript. ”

Minor issues:

1) Line 58: Change it to “near the landfill plants”.

R: We have provided to modify the text according to the suggestion.

2) Line 91: Use the lowercase letters for “Public Health”.

R: We have provided to modify the text according to the suggestion.

3) Line 100 & 115: The Supplementary File can be listed as figures instead (e.g. Figure 2, Figure 3).

R: We appreciate the suggestion of the reviewer but the guidelines for authors state a maximum limit of 5 tables/figures. Therefore, in order to preserve the information reported in the 4 Tables and in the Figure already included in the main text, we preferred not to relist the Supplementary File as a Figure file.

4) Line 111: Use “0.4” not “0,4”.

R: We have provided to modify the text according to the suggestion.

5) Line 146-148: Use “for maternal age” instead of “by maternal age”; remove “by” in “by using STATA”.

R: We have provided to modify the text according to the reviewer suggestion

6) Line 263-264: Merge them into one paragraph.

R: We appreciate the suggestion of the reviewer but we believe that the evidence about the health effect of the combustion of waste needs to be highlighted separately from the evidence deriving from other types of fires or exposure to other combustion products. Thus, we would like to keep these separate.

Reviewer: 2

Reviewer Name: Lisbeth E. Knudsen

Institution and Country: University of Copenhagen, Denmark

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

Please leave your comments for the authors below

The manuscript clearly describes reproductive effects from environmental exposures to landfill with birth weight significantly affected from exposures.

Table 1 is difficult to understand and may be taken out?

R: Authors thank the reviewer for the suggestion. We have moved this table along the text and renumbered as Table 3 to improve the comprehension by the readers.

More characterisation of the exposures would be of interest but probably not possible.

R: We appreciate the request to better characterise the exposure but we can assure the reviewer (and the readers) that we are reporting on all the outcomes for which we were able to obtain from the institutional data flows. Moreover, we have implemented the text of the methods section as follows (Page 6, line 302): “Because of CedAP data flow at the time in study was relatively new, we were only able to use the limited information described in this manuscript.”

Reviewer: 3

Reviewer Name: Emily Harville

Institution and Country: Tulane University, US

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The study aims to examine the relationship between living near a landfill fire and birth outcomes. The authors have a limited exposure measure (residence in the area during a time frame) and no individual-level exposure measures. Nonetheless, the authors are fairly circumspect in their interpretations and such analyses are useful to have on file, so to speak, as background to more detailed analyses and for high-level indicators of possible results of such exposures.

R: We are grateful for the positive assessment of our work and share the sentiment that these results are important to share with the scientific community even if the quality of the information is not high. We have strived to turn the limited data available into usable information that adds to the growing body of evidence linking exposure to fires to adverse reproductive health outcomes.

I have to admit I was not aware of arson at a solid waste facility as being a frequent occurrence, though, given that it happens, it makes sense to see if it leads to health effects.

- I presume it is not arson per se, but exposures resulting from the fire?

R: Yes. The event was attributed to arson by the judicial and political authorities and we report it as such, but of course the concern is about exposure to the multiple pollutants released to the atmosphere during the fire. We have tried to clarify this in the text, starting from the title that was modified in "Do emissions from landfill fires affect pregnancy outcomes? A retrospective study after arson at a solid waste facility in Sicily."

- Exposure is measured ecologically and extremely approximately (area and time of residence). This limitation is somewhat mitigated by the fairly short-term nature of the exposure (two weeks, more or less). What consequences did the fire have for the area beyond environmental exposures? Were roads or schools shut down or traffic increased, for instance? Such information would help in assessing environment as a likely source.

R: The waste management facility on fire is in a relatively remote area. Although the smoke produced by the fire formed a cloud whose movement was followed by the environmental protection agency and led to the administrative designation of the at-risk area, it was not reported to disrupt the flow of people and traffic in the area. The Regional Health Authority implemented public health control measures, banning the consumption and sale of milk and milk products, meat and eggs produced in the extended protection area after July 29, 2012, as well as mushrooms harvesting, grazing and use of local forage. Thorough washing of fruit and vegetables was also strongly recommended to the general population. We decided not to report these control measures in the manuscript because we don't think this information would change the interpretation of the study findings.

- The authors exclude urban areas to avoid confounding by other types of pollution. This rationale is reasonable as far as it goes, but likely excludes the most exposed women. What do the results look like if these areas are included (or studied as a separate group)? Also, it looks like the extra-urban area was a fairly small proportion of the surveillance area.

R: We agree with this comment and in fact an analysis of the impact on urban areas was included in the manuscript, although it was not highlighted properly. We have modified the methods section and renumbered the Tables in the results section to improve this aspect. In particular, Table 3 reports the comparison between the metropolitan area of Palermo and other metropolitan areas in Sicily: this analysis suggests that the outcomes of interest were not in excess in the Palermo metropolitan area during the exposure period. On the contrary, the analysis presented in Table 1 compares the extra-urban area of Palermo with other extra-urban areas of Sicily, and documents the excess of infants born with very low birth weight.

- Why the limited set of control variables (maternal age and newborn sex)? Did they consider other possible confounders?

R: We thank the reviewer for the very useful comment. Odds Ratios were already adjusted by maternal age and infant gender. We have provided to correct the methods section as follows (Page 6, lines 304-307): "To make statistical inference about the comparisons between the different study groups and the references, we used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) of the ORs, with and without adjusting for maternal age and infant gender, the only two potential confounders made available to us." We have also corrected the legend in the Tables.

We appreciate as well the request to better characterise the exposure but we can assure the reviewer (and the readers) that we are reporting on all the outcomes for which we were able to obtain from the institutional data flows. In fact (see page 6, line 302), "Because of CedAP data flow at the time in study was relatively new, we were only able to use the limited information described in this manuscript."

-Preterm births have less opportunity to be exposed than full-term gestations; did the authors do anything to address this besides limiting to <36 weeks?

R: This comment may be appropriate for a chronic exposure that could cover the entire pregnancy. We describe an event that led to a short-term exposure, which could have affected a pregnancy at different stages of gestation, depending on the date of conception. We evaluated the potential for impact in the analyses summarized in Table 2.

- LBW is generally considered to be a combination of the effects of FGR, indicated by SGA, and preterm birth, but neither part individually seemed to have an effect. Do the authors have an explanation for this? Since an effect was found on very LBW, was there an effect on VPTB?

R: In agreement to the suggestion coming from the reviewer, we have implemented the analysis on very preterm live births (see Tables 1 and 2). Consequently, we have implemented the main text as follows:

Results section (Page 7, line 371): "We observed a two-fold increase in risk of very preterm birth (OR adjusted for maternal age and infant gender= 2.29; 95%CI= 1.12 - 4.68) and a two-fold increase in risk of very low birth weight (OR adjusted for maternal age and infant gender= 2.20; 95%CI= 1.02 - 4.72) among singleton live births (Table 1)." (Page 8, lines 566-569): "Among singleton live births we observed a three-fold increase in risk of very preterm between the extra-urban area and the remaining Sicilian low inhabitants density and unindustrialized areas for births whose pregnancies were in the third trimester (OR adjusted for maternal age and infant gender= 3.41; 95%CI= 1.04 - 11.16) when the fire began (Table 2)."

Discussion section (Page 14, lines 821-832): "In the study group, the analysis documented a three-fold excess risk of very preterm birth (<32weeks, OR adjusted for maternal age and infant gender= 3.41; 95%CI= 1.04 - 11.16) and a two-fold excess risk of very low birth weight (<1500g) among singleton live births. The effect on very low birth weight appeared to be concentrated among births whose conception date was between 12 weeks prior to the beginning of the fire to 4 weeks after, suggesting that the largest impact of the exposure may have been on pregnancies that were conceived during the fire (OR adjusted for maternal age and infant gender= 4.64; 95%CI= 1.04 - 20.6) or were exposed to the fire during the first trimester (OR adjusted for maternal age and infant gender = 3.66; 95%CI= 1.11 - 12.1). On the other hand, the effect on the risk of very pre-term birth did not appear to be confined to any particular subgroup at risk. These findings are compatible with a toxic effect on placentation or early embryo development leading to restricted intrauterine growth and premature delivery.[18,19]"

- One of the more common issues with this sort of paper is selective reporting of results. The authors' discussion is fairly balanced on possible true and chance associations, but I wonder whether they looked at other outcomes that they did not report?

R: We understand the concern about selective reporting but we can reassure the reviewer (and the readers) that we are reporting on all the outcomes for which we were able to obtain tabulated data.

VERSION 2 – REVIEW

REVIEWER	Emily W Harville Tulane University
REVIEW RETURNED	22-May-2019

GENERAL COMMENTS	The authors have addressed the reviewers' concerns.
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VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 3

Reviewer Name: Emily W Harville

Institution and Country: Tulane University

- Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors have addressed the reviewers' concerns.

R: We do not see comments to the authors that need action.