PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Burden of non-accidental mortality attributable to ambient temperatures: a time-series study in a high plateau area of southwest China
AUTHORS	Deng, Changyu; Ding, Zan; LI, Liujiu; Wang, Yanfang; Guo, Pi; Yang, Shaoyi; Liu, Ju; Wang, Yue; Zhang, Qingying

VERSION 1 – REVIEW

REVIEWER	Hyewon Lee Institute of Health and Environment, Seoul National University
REVIEW RETURNED	01-Aug-2018

GENERAL COMMENTS	This manuscript presents the mortality burden by temperature in Yuxi, China. Overall, I don't feel that this is worth being published in that the paper is not unique except the study area, a high plateau city. The authors even did not mention what this unique characteristic resulted in and what the difference between the paper and previous studies conducted in 'not high plateau' cities is. A strength is the assessment of potential effect modifications by demographic factors. To be published, the authors must emphasize the study's originality, the improved points compared to previous studies, and how your unique area affected the association between mortality and temperature. Also, careful editing by a native English speaker is desirable for better understanding. Title: the title could be reduced more concisely Abstract: Overall, the abstract lacks the necessity of the study and public health implications line 10: specific causes and -> specific causes of death and conclusions: Most of the burden of death: 4.75 % is most? Strengths and limitations page 3, line 3: this study will~ -> to our knowledge, this study evaluated ~~ for the first time. Methods page 6, line 3: Why did you use a median value as a reference? the first paper about the association used a 75th percentile value (Gasparrini 2015, Lancet). I suggest conducting an analysis using a 75th percentile value as a reference. page 6, line 6~8: " These model specifications were consistent with previous studies."

	Is it reasonable to specify the model based on those previous studies although the study area in this study and other cities have different climate? page 6, line 42: mention the temperature value of 2.5th and 97.5 percentiles. line 45: Monte-Carlo~ You need to include references for the method that you did not conduct for the first time. page 7, line 3: from 2009-2016-> from ~ to or between line 15: insert Celsius line 23: presented in figure 2. Discussions page 9, line 14~page 10, line 6: you compared the results with those from previous studies only using 'heat', 'cold', 'extreme cold', 'extreme heat'. However, I think that these studies used different temperature values to define heat and cold. Is it reasonable to compare without consideration of real temperature values? For examples, for more cold cities, the temperature defining 'cold' would be more lower, whereas for tropical or subtropical cities, the temperature defining 'heat' would be more higher. Moreover, you mentioned that Yuxi has a unique climate. I expected you would explain how this unique climate affected the association compared to previous cities. Biological mechanisms: the manuscript lacks possible explanations why cold showed a more significant effect than heat. Given the increasing temperature with climate change, most people worry about heat and high temperature. But your results show that future climate with hotter temperature will not result in significant mortality burden. Can readers conclude like this? What is your conclusion after this study? what is the implication of this study? Limitations: Study limitations should be mentioned in Discussion section.

REVIEWER	Hualiang Lin Sun Sat-sen University, China
REVIEW RETURNED	05-Sep-2018

GENERAL COMMENTS	1. The author used median value of temperature as the reference to examine the effects of high and low temperatures, which might not be appropriate, I would suggest to used minimal mortality temperature. 2. The above might be the underlying reason for the non-significant effect of heat. 3. Also, the analysis did not control for the potential confounding effects from various air pollution. 4. The mortality data used in this study should have a quality assessment, any underreporting? 5. For the attributable fraction, the authors are suggested to refer to a few important studies: Mortality burden of ambient fine particulate air pollution in six Chinese cities: Results from the Pearl River Delta study. Environ Int. 2016, 96: 91-97.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Hyewon Lee
Institution and Country: Institute of Health and Environment, Seoul National University
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below
This manuscript presents the mortality burden by temperature in Yuxi, China. Overall, I don't feel that this is worth being published in that the paper is not unique except the study area, a high plateau city. The authors even did not mention what this unique characteristic resulted in and what the difference between the paper and previous studies conducted in 'not high plateau' cities is. A strength is the assessment of potential effect modifications by demographic factors.
To be published, the authors must emphasize the study's originality, the improved points compared to previous studies, and how your unique area affected the association between mortality and temperature. Also, careful editing by a native English speaker is desirable for better understanding.

Question No. 1:

Title: the title could be reduced more concisely

Response: We have reduced the title to be "Burden of non-accidental mortality attributable to ambient temperatures in a high plateau area of southwest China". Please see **page 1, line 1-2.**

Question No. 2:
Overall, the abstract lacks the necessity of the study and public health implications
Response: Thanks a lot for raising this issue. We have added the necessity and public health implications in the Abstract. (**Page 2, line 3-4, 26-27**)

Question No. 3:

line 10: specific causes and -> specific causes of death and
Response: Done. Please see **Page 2, line 3-4.**

Question No. 4:

conclusions: Most of the burden of death: 4.75 % is most?

Response: Sorry for confusion. In our description, 4.75% was an attributable fraction caused by overall temperatures for non-accidental deaths, "most" means that cold temperatures were responsible for most of the attributable fractions accounting for 85.9% (4.08% verbs 4.75%). Please see **Page 7, line 22-26.**

Question No. 5:
page 3, line 3: this study will~ -> to our knowledge, this study evaluated ~~ for the first time.

Response: Done. Please see **page 3, line 1-3**

Question No. 6:
Methods
page 6, line 3: Why did you use a median value as a reference? the first paper about the association used a 75th percentile value (Gasparrini 2015, Lancet). I suggest conducting an analysis using a 75th percentile value as a reference.
Response: Thanks a lot for raising this issue. The 75th percentile value might be used to model the exposure-response curve with a quadratic B-spline with 3 internal knots placed at the 10th, 75th, and 90th percentiles of location specified temperature distributions, or conducted a sensitive analysis with the different cutoff at the 10th, 25th, 50th, 75th, and 90th percentiles of the temperature distribution. According to the first paper (Gasparrini 2015, Lancet), the minimum mortality temperature (MMT) was used as the referent temperature to evaluate the temperature–mortality relationship. The original description was “The minimum mortality temperature, which corresponds to a minimum mortality percentile between the first and the 99th percentiles, was derived from the best linear unbiased prediction of the overall cumulative exposure-response association in each location. We referred to this value as the optimum temperature and deemed it the reference for calculating the attributable risk by re-centering the quadratic B-spline that models the exposure-response”. In our study, the reasons why we used a median temperature instead of MMT as a reference were as follow:

1) In the previous multicountry or multicenter studies, MMT was reasonably used to assess the temperature–mortality associations, because their studies included multiple locations. However, we only conducted one city in our study, and it seem to makes no sense to capture the relationships using different MMT calculated by different categories for the identical residents in one region.

2) In addition, the risks of cold decreased monotonously with increased temperature, and those due to heat (both mild and extreme) were very low and changed slightly, approximately equal to 1, which indicating that the MMT were approximately equal to the median temperature (presented in Fig. 2). However, in some sub-groups (i.e. heart disease, aged 65–74 and ethnic minorities), the MMT were almost equal to the maximum temperature, leading to the effect caused by heat achieved 0. Since the attributable fraction was obtained from the sum of the contributions from all days in the series, and the unstable results might be owing to a relatively smaller sample size for these groups. So we attempted to expand the range of the temperature by setting the median temperature as the referent value to capture the underlying effect of heat.

3) Moreover, we performed a sensitive analysis by using the MMT as the referent temperature, showing that all the results were stable substantially when compared with the results estimated by median temperature, and the MMT was different among the sub-groups, leading the results incomparable. (Please see Table A). Thus, consistent with the previous single-city studies (Guo et al., 2017; Ding et al., 2015; Schwartz et al., 2015; Guo et al., 2012), we selected the median temperature as the common referent value, which could compare the effect due to ambient temperature between the total non-accidental group and all specified subgroups.

Table A. Attributable fraction (%) of total non-accidental mortality and by specific causes and individual characteristics due to mean daily temperature and cold and heat over lag 0-28 days in Yuxi, China.

	Total death	MMT	Total(%)	Cold(%)	Heat(%)
Total non-accident	89,467	16.7	4.66 (2.26,6.85)	3.93 (0.6,7.01)	0.73 (-2.69,3.88)
Cause-specific					
Cardiovascular	41,794	19.7	6.57 (-1.01,12.97)	6.42 (1.82,9.37)	0.15 (-1.4,1.62)
Heart	17,793	24.7	8.76 (-33.2,36.26)	8.76 (0.35,9.26)	0 (0,0)
Stroke	22,589	17.7	6.48 (1.76,10.02)	5.92 (-0.45,11.17)	0.57 (-4.22,4.94)
Respiratory	16,565	14.7	5.89 (-3.58,13.34)	3.67 (-4.89,10.02)	2.23 (-8.88,11.19)
Age, years					
≤64	21,678	17.7	1.94 (-2.77,5.73)	1.68 (-4.87,7.06)	0.26 (-4.83,4.96)
65-74	20,072	24.7	6.84 (-30.05,32.26)	6.84 (-2.53,6.33)	0 (0,0)
≥75	47,717	16.7	6.72 (3.6,9.47)	5.19 (0.65,9.2)	1.54 (-2.87,5.51)
Gender					
Male	48,939	17.7	4.08 (0.77,6.75)	3.52 (-0.97,7.46)	0.56 (-2.85,3.73)
Female	40,528	16.7	5.44 (2.04,8.43)	4.5 (-0.18,8.73)	0.95 (-3.72,5.23)
Occupation					
Farmer	68,278	16.7	5.52 (2.95,7.9)	4.75 (1.1,8.1)	0.77 (-2.93,4.18)
Nonfarmer	21,189	15.7	1.87 (-5.49,7.85)	1.22 (-5.8,7.16)	0.66 (-8.75,8.56)

Ethnic					
Han nationality	63,275	14.7	6.49 (1.48,10.89)	3.24 (-1.29,6.3)	3.25 (-2.54,8.5)
Ethnic minorities	26,192	24.7	19.55 (-7.14,38.61)	19.55 (-1.87,6.2)	0 (0,0)
Married status					
Married	54,971	15.7	4.6 (0.53,8.18)	2.8 (-1.59,6.48)	1.8 (-3.55,6.54)
Unmarried	34,496	20.7	6.89 (-4.51,16.26)	6.86 (1.89,8.74)	0.03 -0.77,0.81)

Question No. 7: page 6, line 6~8: " These model specifications were consistent with previous studies." Is it reasonable to specify the model based on those previous studies although the study area in this study and other cities have different climate?

Response: Thanks a lot for raising this issue. We agreed with the reviewer for the setting of model specifications. However, these model specifications consistent with previous studies were mainly considered comparability and further highlighted the effect of this region. According to the previous study by Gasparrini, which included 384 locations across 13 countries, their models were set by the same parameters among the different locations so that the results could be comparable between different region with various climates. In addition, we have conducted a sensitive analysis, the models were robust when changed the model parameters one by one (Please see the Supplemental Table 2).

Question No. 8:

page 6, line 42: mention the temperature value of 2.5th and 97.5 percentiles.

Response: Done. We have mention the temperature value of 2.5th (5.4°C) and 97.5th percentiles (23.1°C) in **Page 6, line 21-22.**

Question No. 9:

line 45: Monte-Carlo~

You need to include references for the method that you did not conduct for the first time.

Response: We have added the reference of “Greenland et al., 2004” and “Gasparrini et al., 2014” **(Page 6, line 26)**

Question No. 10:

page 7, line 3: from 2009-2016-> from ~ to or between

Response: Done. **Page 7, line 1**

Question No. 11:
line 15: insert Celsius
Response: Done. **Page7, line 8**

Question No. 12:
line 23: presented in figure 2.
Response: Sorry for missing, we have revised the sentence in **Page 7, line 13**

Question No. 13:
Discussions
page 9, line 14~page 10, line 6: you compared the results with those from previous studies only using 'heat', 'cold', 'extreme cold', 'extreme heat'. However, I think that these studies used different temperature values to define heat and cold. Is it reasonable to compare without consideration of real temperature values?
For examples, for more cold cities, the temperature defining 'cold' would be more lower, whereas for tropical or subtropical cities, the temperature defining 'heat' would be more higher.
Response: We agreed with the reviewer that different regions have different definition for “cold” or “heat”. Thus the perception of heat or cold with same temperature was different, and the specified temperature percentile would reflect “cold” or “heat” for residents in the specified region. Besides, since the attributable fraction was obtained from the sum of the contributions from all days in the series, the results were incomparable if using the absolute temperature values which might lead to unequal series lengths between regions. The definition in our study for “cold” or “heat” was consistent with the previous studies so that the result could be comparable with them. What’s more, based on previous studies, such as Gasparrini et al. (including 384 locations of 13 countries) and Yang et al. (including 16 larger cities in China), both of the study defined the “heat”, “cold”, “extreme cold”, and “extreme heat” with the same scale (specified temperature percentile) instead of using a real temperature value to define the temperature among all the regions.

Question No. 14:

Moreover, you mentioned that Yuxi has a unique climate. I expected you would explain how this unique climate affected the association compared to previous cities.

Response: Thanks a lot for raising this issue. The underlying reasons might be concluded as follow:

1) Our study area has a distinct subtropical plateau monsoon climate, with four spring-like seasons year round, giving the city a stable daily mean temperature but large temperature difference between day and night, morning or evening and daytime, indoor and outdoor. Although the city has a stable daily

mean temperature of 16.1 ± 4.9°C full year, the daily diurnal temperature range was averaging 10.4 °C (ranging from 1.1°C to 21.7°C).

2) Unlike the previous studies, the temperature–mortality associations were nonlinear and followed slide-shaped curves (presented in Fig. 2). The relative risks of cold decreased monotonously with increased of temperature, and those due to heat (both mild and extreme) were very low and changed slightly, approximately equal to 1.

3) What's more, the increased cold-related cardiovascular deaths mainly involved changes in vascular tone, autonomic nervous system response, arrhythmia, and oxidative stress, and the population structure (the composition of occupation and nationality) or climate adaptation might be also a reason for these differences.

Question No. 15:

Biological mechanisms:

the manuscript lacks possible explanations why cold showed a more significant effect than heat. Given the increasing temperature with climate change, most people worry about heat and high temperature. But your results show that future climate with hotter temperature will not result in significant mortality burden. Can readers conclude like this? What is your conclusion after this study? what is the implication of this study?

Response: Thanks a lot for raising this issue. We agree with the reviewer that the temperature would be elevated under the impact of climate change, and most people would worry about heat and high temperature. Our study was conducted in high plateau area with a unique, subtropical, plateau monsoon climate. Interestingly, even in the context of global warming scenario, "cold" is still a main risk factor on disease burden for populations in Yuxi compared to "heat" over a study period of 8 years, and the maximum daily mean temperature was only 25.6°C. We have added the implication into the conclusion section (Please see **Page 12, line 4-13).** The potential explanations were involved: 1) The differences between minimum and referent temperature was 20.3°C (-3.3°C vs 17.0°C), while those between referent and maximum temperature was 8.6°C (17.0°C vs 25.6°C), which may contribute to the different effects between exposure to cold and heat days (We have added in discussion sections, Please see **Page 9, line 22-24**). 2) The population structure (the composition of occupation and nationality) or climate adaptation also might be a reason for different effect. 3) Previous study conducted in London from 1986 to 1996 found that attributable fraction of mortality for each 1°C decrease below a threshold of 15°C was 5.42% (4.13, 6.69), with no burden due to heat, which was consistent with our result (Please see **Page 9, line 27-31**).

Generally, our present study was performed to quantify the impact of a specified temperature range on mortality during the study period between 2009 and 2016. The maximum daily mean temperature in this high plateau region was only 25.6°C, which might be the underlying reason for the non-significant estimated effect of heat, while the maximum temperature of another 16 cities in China conducted by Yang et al., were almost over than 30 °C (Table B). Thus, we can only conclude that

result within the temperature distribution (ranging from -3.3°C to 25.6°C) in the study period, and no effect was due to heat.

Table B Comparation of temperature in 17 cities of China

Area	Period	Min	Median	Max	Mean
Yuxi	2009-2016	-3.3	17.0	25.6	16.1
Harbin	2008-2013	-28.0	8.0	30.6	5.1
Changchun	2008-2011	-27.6	8.7	30.4	6.2
Shenyang	2010-2013	-24.0	9.2	28.4	7.6
Beijing	2007-2013	-12.5	14.9	34.5	13.2
Tianjin	2007-2013	-14.1	14.4	32.4	12.9
Yinchuan	2008-2013	-17.7	12.1	30.6	10.3
Jinan	2011-2013	-9.4	16.3	33.0	14.4
Zhengzhou	2011-2013	-4.4	17.4	34.2	15.6
Shanghai	2007-2012	-3.4	18.3	35.7	17.4
Nanjing	2007-2013	-4.5	17.8	34.6	16.5
Hefei	2011-2013	-2.9	18.4	34.4	16.6
Chengdu	2008-2013	-0.5	17.4	29.3	16.3
Wuhan	2009-2012	-2.9	18.1	35.3	16.8
Chongqing	2011-2013	3.0	19.1	36.7	19.0
Changsha	2007-2013	-3.0	19.1	35.8	18.4
Guangzhou	2011-2013	5.1	23.0	30.8	21.6

Question No. 16:

Limitations: Study limitations should be mentioned in Discussion section.

Response: Thanks a lot for reminding us of this issue. Accordingly, we have added the limitations as follows (Please see in discussion section **Page 11, line 28-34., Page 12, line 1-2**):

1) First, the data were from a single city, so generalizing the findings to other geographic areas or climates should be cautioned.

2) Second, the data of temperature were from monitoring sites rather than exposure measuring of individual.

3) Third, although the concentration of daily mean PM_{10}, NO_2 and SO_2 in Yuxi are much lower than those in other 17 Chinese cities [56], we did not control for the potential confounding effects by air pollution due to the unavailability of the complete pollution data in the study area.

Reviewer: 2
Reviewer Name: Hualiang Lin
Institution and Country: Sun Sat-sen University, China
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
Question No. 1: The author used median value of temperature as the reference to examine the effects of high and low temperatures, which might not be appropriate, I would suggest to used minimal mortality temperature.

Response: Thanks a lot for reminding us of this issue. We agreed with the reviewer that it is reasonable to use the MMT as the reference in previous studies. As for our study, the reasons why we used a median temperature instead of MMT as a reference were as follow:

1) In the previous multicountry or multicenter studies, MMT was reasonably used to assess the temperature–mortality associations, because their studies included multiple locations. However, we only conducted one city in our study, and it seem to makes no sense to capture the relationships using different MMT calculated by different categories for the identical residents in one region.

2) In addition, the risks of cold decreased monotonously with increased temperature, and those due to heat (both mild and extreme) were very low and changed slightly, approximately equal to 1, which indicating that the MMT were approximately equal to the median temperature (presented in Fig. 2). However, in some sub-groups (i.e. heart disease, aged 65–74 and ethnic minorities), the MMT were almost equal to the maximum temperature, leading to the effect caused by heat achieved 0. Since the attributable fraction was obtained from the sum of the contributions from all days in the series, and the unstable results might be owing to a relatively smaller sample size for these groups. So we attempted to expand the range of the temperature by setting the median temperature as the referent value to capture the underlying effect of heat.

3) Moreover, we performed a sensitive analysis by using the MMT as the referent temperature, showing that all the results were stable substantially when compared with the results estimated by median temperature, and the MMT was different among the sub-groups, leading the results incomparable. (Please see Table A). Thus, consistent with the previous single-city studies (Guo et al., 2017; Ding et al., 2015; Schwartz et al., 2015; Guo et al., 2012), we selected the median temperature as the common referent value, which could compare the effect due to ambient temperature between the total non-accidental group and all specified subgroups.

Table A. Attributable fraction (%) of total non-accidental mortality and by specific causes and individual characteristics due to mean daily temperature and cold and heat over lag 0-28 days in Yuxi, China.

	Total death	MMT	Total(%)	Cold(%)	Heat(%)
Total non-accident	89,467	16.7	4.66 (2.26,6.85)	3.93 (0.6,7.01)	0.73 (-2.69,3.88)
Cause-specific					
Cardiovascular	41,794	19.7	6.57 (-1.01,12.97)	6.42 (1.82,9.37)	0.15 (-1.4,1.62)
Heart	17,793	24.7	8.76 (-33.2,36.26)	8.76 (0.35,9.26)	0 (0,0)
Stroke	22,589	17.7	6.48 (1.76,10.02)	5.92 (-0.45,11.17)	0.57 (-4.22,4.94)
Respiratory	16,565	14.7	5.89 (-3.58,13.34)	3.67 (-4.89,10.02)	2.23 (-8.88,11.19)
Age, years					
≤64	21,678	17.7	1.94 (-2.77,5.73)	1.68 (-4.87,7.06)	0.26 (-4.83,4.96)
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Nonfarmer	21,189	15.7	1.87 (-5.49,7.85)	1.22 (-5.8,7.16)	0.66 (-8.75,8.56)
Ethnic					
Han nationality	63,275	14.7	6.49 (1.48,10.89)	3.24 (-1.29,6.3)	3.25 (-2.54,8.5)
Ethnic minorities	26,192	24.7	19.55 (-7.14,38.61)	19.55 (-1.87,6.2)	0 (0,0)
Married status					
Married	54,971	15.7	4.6 (0.53,8.18)	2.8 (-1.59,6.48)	1.8 (-3.55,6.54)
Unmarried	34,496	20.7	6.89 (-4.51,16.26)	6.86 (1.89,8.74)	0.03 (-0.77,0.81)

Question No. 2: The above might be the underlying reason for the non-significant effect of heat.

Response: Thanks a lot for reminding us of this issue. According to the exposure-response association curve presented in Fig. 2, the temperature–mortality associations were nonlinear and followed slide-shaped curves. The relative risks of cold decreased monotonously with increased of temperature, and those due to heat (both mild and extreme) were very low, changed slightly, and approximately equal to 1, which showing that the risks due to heat were unconspicuous. Since the attributable fraction was obtained from the sum of the contributions from all days in the series, we attempted to expand the range of the temperature (setting the median value as the referent value) to capture the underlying effect of heat. Even so, the attributable fractions of heat (both mild and extreme) were still low and non-significant.

Question No.3: Also, the analysis did not control for the potential confounding effects from various air pollution.

Response: Thanks a lot for raising this issue. The analysis did not control for the potential confounding effects from various air pollution due to the unavailable data of pollution in this study area, which is one of the limitations of our study. The air quality of Yuxi is quite good among the Chinese cities. For example, compared to an article “Associations between short-term exposure to nitrogen dioxide and mortality in 17 Chinese cities: The China Air Pollution and Health Effects Study (CAPES)” (Chen et al., 2012), the daily mean of PM_{10}, NO_2 and SO_2 in Yuxi is much lower than those in other 17 Chinese cities (Table B).

Table B. Comparison of the air pollution in the cities of China

City	PM_{10} ($\mu g/m^3$)	NO_2 ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Yuxi	**51.8**	**20.2**	**23.2**
Anshan	111	26	59
Beijing	178	58	41
Fuzhou	72	45	16
Guangzhou	74	66	50
Hangzhou	121	56	51
Hong Kong	52	59	18
Lanzhou	156	46	66

Nanjing	101	51	48
Shanghai	102	67	45
Shenyang	114	37	55
Suzhou	90	45	45
Taiyuan	132	23	77
Tangshan	98	41	84
Tianjin	101	47	67
Urumqi	144	65	100
Wuhan	130	53	52
Xi'an	132	38	48

Question No.4: The mortality data used in this study should have a quality assessment, any underreporting?

Response: Thanks for raising this issue. Daily mortality data during January 1, 2009 to May 31, 2016 were obtained from the Yuxi Center for Disease Control and Prevention (CDC), which maintains detailed quality assurance and control measures. In China, the CDC is the government agency responsible for health data collection and a death must be reported to the local CDC. The hospital or community/village doctors filled in a standard Death Certificate and the information was then reported to a higher administrative level of CDC through a network reporting system. The standard information collected individual-level information, such as cause of death, date of death, age, gender, married status, and occupation. We have added the quality assessment of data in **Page 5, line 4**.

Question No.5: For the attributable fraction, the authors are suggested to refer to a few important studies: Mortality burden of ambient fine particulate air pollution in six Chinese cities: Results from the Pearl River Delta study. Environ Int. 2016, 96: 91-97.

Response: We agreed that the addition of appropriate references will certainly enhance the quality of the study. Thus, we have added the citation to support the theory of attributable fraction **(Page 3, line 22).**

VERSION 2 – REVIEW

REVIEWER	Hyewon Lee Institute of Health and Environment, Seoul National University, South Korea
REVIEW RETURNED	16-Dec-2018

GENERAL COMMENTS	Authors provided good and complete responses. I suggest that authors include some contents of the response letter in Limitation section in the revised manuscript. #1. Please include the contents of Question 6 (comparison with MMT) in Limitation section, and a sensitivity analysis result #2. Please include the contents of Question 14 in Discussion section in the revised manuscript.

REVIEWER	Hualiang LIn Sun Yat-sen University, China
REVIEW RETURNED	26-Nov-2018

GENERAL COMMENTS	The authors have well addressed the comments and suggestions.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

I suggest that authors include some contents of the response letter in Limitation section in the revised manuscript.

#1. Please include the contents of Question 6 (comparison with MMT) in Limitation section, and a sensitivity analysis result

Response: Thanks for your suggestion. We have added the contents of Question 6 in Limitation section (page 12, line 9-17 in revised manuscript) and a sensitivity analysis result in the supplemental materials (Please see Table S5 in supplemental materials).

#2. Please include the contents of Question 14 in Discussion section in the revised manuscript.

Response: Done, we have included the contents of Question 14 in Discussion section. Please see page 9, line 8-19.