PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Spatial analysis of health effects of large industrial incinerators in England, 1998-2008: a study using matched case-control areas
AUTHORS	Reeve, Nicola; Fanshawe, Thomas; Keegan, Thomas; Stewart, Alex; Diggle, Peter

VERSION 1 - REVIEW

REVIEWER	John F. Bithell Honorary Research Fellow Childhood Cancer Research Group Richards Building Old Road Campus Headington Oxford OX3 7LG
REVIEW RETURNED	30-Aug-2012

GENERAL COMMENTS	Summary This paper is written in quite good, clear English and it discusses the science adequately and draws reasonable conclusions. Unfortunately it falls short in the quality of its explanation and the methodology used. The Methodology: design 1) The “novel design” (in fact a number of previous studies have used control areas) matches each study region with a control region, chosen to be demographically similar. I see a number of problems with this: a) Very little is said about how this matching is done. The basis is the “Local Authority”, which is taken to be synonymous with an administrative area. The criteria they use presumably overlap with the information available in the modelling process, but how are different components of the information combined? Or are they the same for both circle selection and modelling and determined solely by the IMD? And how is the centre of the control circle chosen within the LA district? Presumably it is not the centre of the LA district itself, which would typically be a centre of population – unlike a typical incinerator. But the demographic criteria used will vary from point to point within a district, so the actual circle selected may well not share the characteristics of the LA chosen. b) The actual correlation between the case and control circles appears to be weak. The Pearson correlation coefficient for the IMD is 0.336 and according to my calculations the chance is almost one in three that a random assignment of control to case circles would be more highly correlated. c) Choosing only five control areas makes the contrast between cases and controls weak compared with a contrast based on national rates: a difference between case and control areas may well be due to something unusual about the control areas rather than an interesting feature of the case areas. In any case the model takes

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	deprivation into account so it is hard to see what characteristic of the areas not presented by the available demographic data would be relevant. d) In any case, it is arguably better to model potential confounders than to match for them. 2) The models used are problematical. Each has objections and as a whole they leave the question: why could not a single model incorporate all the factors of interest? It is a well-established principle of experimentation (since the introduction of statistical analyses in the twentieth century) that it is better to have a model that looks simultaneously at different factors than a series of experiments varying one factor a time. This is even more so in observational studies, where other conditions cannot be held constant anyway. Specific points on the models include: a) Model 1 considers time trends, but the data are really too thin to do this effectively. Presumably any changes are attributed to population trends (on which there is much more information available in other studies) rather than to changes in the operation of the incinerator (a possibility not discussed) so the question of a trend becomes something of an irrelevance: aggregating over time as in models 2 and 3 is more sensible. b) Model 2 includes distance, which should surely be the factor of principal interest, though the inclusion of the controls in this analysis muddies the waters somewhat. But distance is included as a linear term and this is not a good way to detect the effect of most interest, which is proximity to the incinerator – or inverse of distance on some scale. The effect of any procedure that models distance linearly is to give most weight to large distances, which are the least interesting. It is true that an ideal model for distance does not exist within the class of log-linear models, but modelling proximity as the reciprocal of distance works quite effectively provided none of the centroids is very close to the centre of the circle: in the latter case the reciprocal of distance rank (or, perhaps its square root) has been shown to give reasonable results in the sense of being acceptably powerful against a range of alternatives. c) Model 3 is nearer the mark, though of course it is more difficult to fit. But why 1/distance2 rather than 1/distance? Neither this paper nor the one by Diggle et al. (ref. 6) really discuss this adequately. Certainly the inverse square laws of physics are irrelevant and a good case can be made for 1/distance as an alternative in a range of models for diffusion of effect. The point at least needs discussion. Specific points that are not clear 1) There are numerous references to “counts” and “case numbers” (e.g. in “Key Messages”) which leave the reader wondering if they have been interpreted without reference to the population denominators. Another example is on p.13, line 2: of course some circles will have higher counts than others and presumably the authors here mean incidence rates? 2) Details of the tumour groups studied are sketchy. Up to what age are the childhood tumours included? Presumably – and judging from Table 1 – childhood cancer includes childhood leukaemia, though this is not specified and of course it reduces the independence of the results. 3) Notation in the specification of the models is poor. It is good practice always to specify the range of variation of the subscripts. And isn’t v_j ≡ j in model 1? In model 2 this subscript seems to refer to the LSOA within a circle – otherwise how does distance come in? Yet the term ηv_j continues to appear – presumably still referring to

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	the control circles – leading to considerable confusion. 4) What does "to set a baseline for future work..." mean (p.7, line 54)? The issues appear to concern the difficulty of tumour latency, but nothing in the paper seems to address this difficulty constructively. 5) The phrase "consistent elevation" appears, but why should one expect consistency? The chemistry of different incinerator outputs will presumably differ and it is certainly not the case that a given carcinogen would affect all tumours equally. 6) On p.13, line 21, I do not understand the sentence beginning "Although the variation in IMD scores ... ". 7) The coefficients in Tables 2 – 4 are presumably values of exp(β) rather than β. Such factors also measure the change in risk per unit value of the respective covariates and it should be made clearer what this is – e.g. the risk per annum, risk per unit of deprivation, or the risk per unit of proximity in km^(-1). 8) It would also be desirable to give much more information about the modelling, especially an analysis of deviance for the model, including the residual deviance. 9) Figure 2 is problematical. On p. 12, line 51 we read that it depicts "mean counts" for circles of increasing diameters. Are the counts/100,000 people crude incidence rates and if so why haven't they been standardised? If we look at the last sub-figure, which has the largest numerators and therefore the most stable rates, we find that the three highest all-cause mortality plots relate to Doncaster, Derby (control circles) and Coventry (case circle) with published standardised mortality rates for the years in question respectively ranked fifth (721), tenth (665) and ninth (695 deaths per 100,000 p.a.) out of the ten circles studied. Even allowing that the population of a circle may not exactly match that of the local authority, such a disparity cannot possibly be accounted for in this way. The highest rate of the ten is for Manchester (863 deaths per 100,000 p.a.) and the line for this is just about the lowest in the plot at a numerical level that is imperceptible. The ratio of highest to lowest of the published standardised rates for the ten circles is around 1.3, whereas the ratio shown in the plot is huge. Unless I have completely misunderstood the nature of these plots, there must be something badly wrong with them. Summary The authors have used an approach which has incorporated a number of unusual features, but this is only a good thing if such features can be shown to improve on other methods available. They have not done this convincingly and they appear to be unaware of a large part of the literature discussing methods for the analysis of areal data.

REVIEWER	Oliver Robinson (on behalf of Mireille Toledano) Research Assistant Small Area Health Statistics Unit School of Public Health Imperial College London UK No competing interests
REVIEW RETURNED	25-Sep-2012

THE STUDY	-Why did you choose you only include large incinerators?

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	-If case circle contains more than one LA, how is control LA matched? -How were control circles selected? By eye? this should be stated -matching criteria as described is inadequate: What was the composite measure used for matching? was this created by authors or ONS?How did they choose which variables to include? Why was rural/urban not included? how was industry sector identified? These factors or composite measure should be included in table 1 -Would be helpful to include ICD codes. -would prefer more detail on parameters used in model 3
RESULTS & CONCLUSIONS	-Need to be clearer on selection of matched control circles, in order to properly judge results -figure 1 should have circle numbers on key -fig 2 should state which lines are case or control lines -table 1 should include more of the matching factors -IMD is relative measure so should be expressed in quantiles,not mean and SDs -pairs 2 and 4 do not appeare matched for population -fig 3 infant mortality over time appears different between case and control -difficult to understand fig 4-particularly rate of decay, what are the units? -what is the risk discussed in first paragraph of p.17? if it is not relative risk, it relationship to relative risk should be explained in prose. -Why are results different from positive results reported by Elliot et al?
REPORTING & ETHICS	-no reporting statement or check list is mentioned

REVIEWER	Andrea Ranzi Affiliation: Regional Centre for Environment and Health, Regional Agency for Environmental Prevention of Emilia-Romagna, Modena, Italy. Competing interests: none.
REVIEW RETURNED	02-Oct-2012

GENERAL COMMENTS	The present study aims to evaluate whether large-scale incinerators in England have an impact on the health of people living around them. The models presented by authors are interesting from a methodological point of view, addressing both temporal and spatial aspects. However, given the epidemiological scope of the work, the main comment on whole study is that the distance is considered as the only surrogate measure of exposure to these plants. The quantity of pollutants emitted from these plants is low, if compared to other sources such as traffic, heating or some industrial premises. Therefore the measures of exposure to be used are necessarily more sophisticated than in other contexts. Although work based on distance are still present in literature, in recent years several papers underline as dispersion models of pollutants emitted by incinerators can provide a better surrogate measure of exposure than distance. In presence of meteorological conditions such as those existing in the UK, the meteorological

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	variables and wind direction is certainly influential in modifying the shape of fallout, that probably will not a simple “Gaussian” relapse of pollutants, which would be approximated by distance and declining functions related to it, as those well modeled in this article. Moreover, the substantial absence of situation of no winds is an advantage in the use of Gaussian or quasi-Gaussian dispersion model, such as those used in many epidemiological studies. In detail: • Introduction: in the part related to existing literature works, the authors didn’t mention important papers, such as the series of works by Viel and colleagues on the incinerator of Besançon in France, who use dispersion models of dioxins for exposure assessment of the population (one of their work is dedicated to this specific topic, with a model validation of assessing exposure approach). Other recent works (Zambon et al. 2007, Cordier et al. 2010, Forastiere et al. 2011...) make also use of dispersion models of pollutants. • Control areas: the authors don’t discuss the choice of 10 km as a threshold of exposed people, providing only a couple of references in the Methods Section. • The way to define control areas is clearly understandable, but nothing is said about any other environmental pressure factors present in the control areas, which could be very influential, especially if similar, as emissions, to pollutants emitted by incinerators. In relation to this point, there are strange trends of some pathologies related to the distance in control areas (Figure 2), with irregular increases, with a suspect of local presence of other risk factors (environmental or not). Moreover some diseases are always higher in control areas. See for example Childhood cancer incidence or leukemia (figure. 2) • The issue on use of dispersion models is not addressed at all in the discussion section. The study provides a number of statistical models, very interesting from a methodological point of view. But, since the focus is on evaluation of health effects of incinerators, this type of study cannot fail to take into account models of fallout of pollutants for exposure assessment. A modification of the main objective of the article, and/or a substantial part of the discussion related to limitation in using distance as proxy of exposure is recommended. • Infant mortality and incidence of leukemia are most frequently related to exposure to incinerators than others. This is properly recall in discussion (page 19), with a possible explanation related to adjustments not made for "age-sex difference in structure or deprivation level." It should also be pointed out that these diseases have a latency compatible with observation period of the study (10 years), contrary to other types of cancer studied. This is

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	mentioned in the discussion, but this consideration should strengthen results on infant mortality, so a more detailed discussion is recommended. ○ The findings and comments on temporal analyses should be combined with information on the evolution of plants. The selection of plants that are “all active on or before 31st December 1998” is useful, but not exhaustive, as it is not indicated if and when these plants were renewed. Did new laws or regulations on emission limits appear during the study period? (this probably led to a renewal of the facilities). This information is of great importance, since it is well known that from the mid 90's to the late 2000 authorized emissions of the plants has declined significantly (for some pollutants up to 1-2 orders of magnitude) and diversified as pollutants emitted (eg. dioxins). • In the "Strengths and limitations of this study:" should be added a point about limitation in the use of distance as proxy of exposure • Pag.12: the first sentence after "Initial Analysis" is a repetition of a sentence at page 9 (third sentence).

VERSION 1 – AUTHOR RESPONSE

Reviewer: John F. Bithell
Honorary Research Fellow
Childhood Cancer Research Group
Richards Building
Old Road Campus

Summary
This paper is written in quite good, clear English and it discusses the science adequately and draws reasonable conclusions. Unfortunately it falls short in the quality of its explanation and the methodology used.
The Methodology: design
1) The “novel design” (in fact a number of previous studies have used control areas) matches each study region with a control region, chosen to be demographically similar. I see a number of problems with this:
a) Very little is said about how this matching is done. The basis is the “Local Authority”, which is taken to be synonymous with an administrative area. The criteria they use presumably overlap with the information available in the modelling process, but how are different components of the information combined? Or are they the same for both circle selection and modelling and determined solely by the IMD?

The measure used in the matching is described in detail at this referenced website:
Office for National Statistics. Methods for national statistics 2001 area classification for local authorities. 2001 Available: http://www.ons.gov.uk/ons/guide-method/geography/products/area-classifications/ns-area-classifications/index/methodology-and-variables/local-authorities/index.html.

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Office for National Statistics. Methods for national statistics 2001 corresponding local authorities. 2001 Available: http://www.ons.gov.uk/ons/guide-method/geography/products/area-classifications/ns-area-classifications/index/corresponding-authorities/local-authorities/index.html.
Briefly, the matching uses a combination of 42 variables obtained from the 2001 census that reflect the demographic structure, household composition, housing, socioeconomic character, employment and industry sector profile of each LA. A measure of similarity developed by the ONS (referenced above) identifies the most similar LA to each other LA. The five control regions were selected as the most similar LAs to the five case LAs (allowing for some constraints, described in the paper). We have reworded this in the paper to make it clearer, and added a second reference.

And how is the centre of the control circle chosen within the LA district? Presumably it is not the centre of the LA district itself, which would typically be a centre of population – unlike a typical incinerator. But the demographic criteria used will vary from point to point within a district, so the actual circle selected may well not share the characteristics of the LA chosen.
Each control circle was selected as the circle with radius 10km centred on the centroid of the control LA. We have explained this further in the text.

b) The actual correlation between the case and control circles appears to be weak. The Pearson correlation coefficient for the IMD is 0.336 and according to my calculations the chance is almost one in three that a random assignment of control to case circles would be more highly correlated.

The reviewer is right to point this out. However, IMD itself is not one of the variables used in the matching algorithm, although certain variables likely to be positively correlated with it are. For these reasons we chose to adjust for IMD in the analysis.

c) Choosing only five control areas makes the contrast between cases and controls weak compared with a contrast based on national rates: a difference between case and control areas may well be due to something unusual about the control areas rather than an interesting feature of the case areas. In any case the model takes deprivation into account so it is hard to see what characteristic of the areas not presented by the available demographic data would be relevant.

See comment to point b) above. We have added rows to table 1 showing some of the variables used in the measure for identifying similarity of LAs used by the ONS, and how they compare between case and control circles. It is variables such as these, which are likely to be associated with many of the disease outcomes that the matching is designed to balance between case/control pairs.

d) In any case, it is arguably better to model potential confounders than to match for them.

We agree in principal; many of the potential confounders were unavailable to us at LSOA level, hence our design to use the matched case-control region design.

2) The models used are problematical. Each has objections and as a whole they leave the question: why could not a single model incorporate all the factors of interest? It is a well-established principle of experimentation (since the introduction of statistical analyses in the twentieth century) that it is better to have a model that looks simultaneously at different factors than a series of experiments varying one factor a time. This is even more so in observational studies, where other conditions cannot be held constant anyway. Specific points on the models include:
a) Model 1 considers time trends, but the data are really too thin to do this effectively. Presumably any changes are attributed to population trends (on which there is much more information available in other studies) rather than to changes in the operation of the incinerator (a possibility not discussed) so the question of a trend becomes something of an irrelevance: aggregating over time as in models 2 and 3 is more sensible.

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In our opinion, it is difficult to argue that case numbers should be aggregated over time without at least presenting an initial investigation of spatial trends. For this reason we prefer to retain model 1 in the paper.

b) Model 2 includes distance, which should surely be the factor of principal interest, though the inclusion of the controls in this analysis muddies the waters somewhat. But distance is included as a linear term and this is not a good way to detect the effect of most interest, which is proximity to the incinerator – or inverse of distance on some scale. The effect of any procedure that models distance linearly is to give most weight to large distances, which are the least interesting. It is true that an ideal model for distance does not exist within the class of log-linear models, but modelling proximity as the reciprocal of distance works quite effectively provided none of the centroids is very close to the centre of the circle: in the latter case the reciprocal of distance rank (or, perhaps its square root) has been shown to give reasonable results in the sense of being acceptably powerful against a range of alternatives.

We have decided to remove Model 2 from the paper to avoid the possibility of confusing the results with those of Model 3. Thus Model 3 in the original paper is now renamed Model 2, and now the results of only one model including a distance term are included.

c) Model 3 is nearer the mark, though of course it is more difficult to fit. But why 1/distance2 rather than 1/distance? Neither this paper nor the one by Diggle et al. (ref. 6) really discuss this adequately. Certainly the inverse square laws of physics are irrelevant and a good case can be made for 1/distance as an alternative in a range of models for diffusion of effect. The point at least needs discussion.

We have investigated fitting a similar model to (the original) Model 3 with an exp(-distance) term used instead of exp(-distance^2). In all cases there was no improvement in deviance using the exp(-distance) model, so we retain the exp(-distance^2) model as this model is the more widely used elsewhere (e.g. Diggle et al. (1997)).

Specific points that are not clear

1) There are numerous references to “counts” and “case numbers” (e.g. in “Key Messages”) which leave the reader wondering if they have been interpreted without reference to the population denominators. Another example is on p.13, line 2: of course some circles will have higher counts than others and presumably the authors here mean incidence rates?

We have replaced Figure 2 with a version that presents the standardised mortality or incidence ratio, in order to make clear that allowance has been made for the population denominator. We have also rewritten the sentence on p13, line 2 to make this clearer.

2) Details of the tumour groups studied are sketchy. Up to what age are the childhood tumours included? Presumably – and judging from Table 1 – childhood cancer includes childhood leukaemia, though this is not specified and of course it reduces the independence of the results.

We defined ‘childhood tumours’ as those aged <15. To clarify the definitions, we have added ICD-10 codes for each of the tumour groups. Childhood cancer does include childhood leukaemia, and other relevant papers (e.g. Gouveia & Ruscitto (2010)) also report both outcomes separately.

3) Notation in the specification of the models is poor. It is good practice always to specify the range of variation of the subscripts. And isn’t v_j ≡ j in model 1? In model 2 this subscript seems to refer to

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the LSOA within a circle – otherwise how does distance come in? Yet the term ηv_j continues to appear – presumably still referring to the control circles – leading to considerable confusion.

In the specification of models looking at distance effects there should have been a triple subscript (to indicate pair, circle and LSOA). We have now corrected this.

4) What does “to set a baseline for future work...” mean (p.7, line 54)? The issues appear to concern the difficulty of tumour latency, but nothing in the paper seems to address this difficulty constructively.

The discussion now notes that “a repeat of our study at an appropriate interval may go some way to address” the issue of tumour latency.

5) The phrase “consistent elevation” appears, but why should one expect consistency? The chemistry of different incinerator outputs will presumably differ and it is certainly not the case that a given carcinogen would affect all tumours equally.

The source of fuel (municipal solid waste), and the resulting emissions, is likely to be fairly consistent over space and time given the common characteristics of English living across the country. Therefore, we believe that to argue for consistency in the incinerator outputs is reasonable, although we are unable to quantify the magnitude of any differences. For example, combustion conditions are probably more important than precursor content in waste for dioxin production (OSPAR Commission 2007 Update. Dioxins. http://www.ospar.org/documents/dbase/publications/p00308_revised%20bd%20on%20dioxins.pdf). We have rewritten parts of the discussion to reflect this.

We agree with the reviewer that the effect of a given carcinogen may vary according to cancer type, and it had not been our intention to claim that this was the case. Therefore we have removed the phrase ‘consistent evidence’ from the abstract and discussion.

6) On p.13, line 21, I do not understand the sentence beginning “Although the variation in IMD scores ... ”.

We have rewritten this sentence.

7) The coefficients in Tables 2 – 4 are presumably values of exp(β) rather than β. Such factors also measure the change in risk per unit value of the respective covariates and it should be made clearer what this is – e.g. the risk per annum, risk per unit of deprivation, or the risk per unit of proximity in km^(-1).

The coefficients are values of exp(β), which is now stated in the paper. The changes are relative to a unit increase in each variable. This is now explained in the legend to the tables.

8) It would also be desirable to give much more information about the modelling, especially an analysis of deviance for the model, including the residual deviance.

Deviance statistics are now given in a new table (Table 4). Additional information about the modelling and parameter estimation, sofaras space allows, is provided in the text. We have also included a detailed analysis of residuals as supplementary material.

9) Figure 2 is problematical. On p. 12, line 51 we read that it depicts “mean counts” for circles of increasing diameters. Are the counts/100,000 people crude incidence rates and if so why haven’t

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they been standardised? If we look at the last sub-figure, which has the largest numerators and therefore the most stable rates, we find that the three highest all-cause mortality plots relate to Doncaster, Derby (control circles) and Coventry (case circle) with published standardised mortality rates for the years in question respectively ranked fifth (721), tenth (665) and ninth (695 deaths per 100,000 p.a.) out of the ten circles studied. Even allowing that the population of a circle may not exactly match that of the local authority, such a disparity cannot possibly be accounted for in this way. The highest rate of the ten is for Manchester (863 deaths per 100,000 p.a.) and the line for this is just about the lowest in the plot at a numerical level that is imperceptible. The ratio of highest to lowest of the published standardised rates for the ten circles is around 1.3, whereas the ratio shown in the plot is huge. Unless I have completely misunderstood the nature of these plots, there must be something badly wrong with them.

We are grateful for the reviewer for alerting us to the error in this figure. Some of the expected values E_{ij} had been calculated incorrectly, leading to mistakes both in this figure and some of the results tables that appeared in the original version of the manuscript. This has now been corrected. We have also amended the figure to show standardised mortality or incidence ratio on the y-axis, in response to the reviewer's suggestion that this figure should present standardised rates. The method of standardisation used was described in the manuscript originally.

Summary

The authors have used an approach which has incorporated a number of unusual features, but this is only a good thing if such features can be shown to improve on other methods available. They have not done this convincingly and they appear to be unaware of a large part of the literature discussing methods for the analysis of areal data.

Reviewer: Oliver Robinson (on behalf of Mireille Toledano)
Research Assistant
Small Area Health Statistics Unit
School of Public Health
Imperial College London
UK

No competing interests

-Why did you choose you only include large incinerators?

This was a study design choice based on: (a) greater public health concerns focused specifically on the effects of larger incinerators, (b) our view that a study of this design would be unlikely to detect the smaller elevations in health risk in neighbourhoods that would be associated with smaller incinerators, and (c) our desire that the incinerators used in this study should be similar in size and duration of operation.

-If case circle contains more than one LA, how is control LA matched?

It was based on the LA in which the incinerator was located. We have amended our description of control region selection to clarify this.

-How were control circles selected? By eye? this should be stated

They were selected as a circle with radius 10km centred on the centroid of the control LA. We have explained this further in the text.

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-matching criteria as described is inadequate: What was the composite measure used for matching? was this created by authors or ONS?How did they choose which variables to include? Why was rural/urban not included? how was industry sector identified? These factors or composite measure should be included in table 1

See response to reviewer 1 point 1 above. This measure was created by the ONS. The rural/urban dichotomy was accounted for by several measures associated with urban location. Consequently, all of the case and control regions are in urban locations. We have added several of the factors used in the matching to Table 1 as suggested.

-Would be helpful to include ICD codes.

We have now included ICD codes.

-would prefer more detail on parameters used in model 3

We are unsure what extra information the reviewer requires. For more information on interpretation of the parameters, see Diggle et al (1997).

-Need to be clearer on selection of matched control circles, in order to properly judge results

We have added clearer description of the methods used to match case and control circles in the Methods section (see also response to reviewer 1 point 1 above).

-figure 1 should have circle numbers on key

We have added circle numbers to the key in Figure 1.

-fig 2 should state which lines are case or control lines

For clarity, the new version of Figure 2 shows only case lines.

-table 1 should include more of the matching factors

We have added several matching variables to Table 1.

-IMD is relative measure so should be expressed in quantiles,not mean and SDs

We have replaced mean and SD for IMD in Table 1 with percentiles.

-pairs 2 and 4 do not appeare matched for population

They were not matched for population. Population was accounted for using the expected values in the models, which allow for differing population sizes and age/sex structures (i.e. indirect standardisation).

-fig 3 infant mortality over time appears different between case and control

Please see the new version of Figure 3, which now shows SMRs rather than counts per 100,000 (and so adjusts for the demographic mix of the regions).

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-difficult to understand fig 4-particularly rate of decay, what are the units?

We have moved the results of this figure into Table 3 to improve clarity.

-what is the risk discussed in first paragraph of p.17? if it is not relative risk, it relationship to relative risk should be explained in prose.

We have rephrased this to read, “As the estimate of disease risk at a given distance…”

-Why are results different from positive results reported by Elliot et al?

There are many possible explanations; the simplest is that cases in Elliott et al (1996) are drawn from the period 1974-86, while those in our study are from the period 1998-2008.

-no reporting statement or check list is mentioned

We will check this during online re-submission of the manuscript.

Reviewer: Andrea Ranzi
Affiliation: Regional Centre for Environment and Health, Regional Agency for Environmental Prevention of Emilia-Romagna, Modena, Italy.
Competing interests: none.

The present study aims to evaluate whether large-scale incinerators in England have an impact on the health of people living around them.
The models presented by authors are interesting from a methodological point of view, addressing both temporal and spatial aspects. However, given the epidemiological scope of the work, the main comment on whole study is that the distance is considered as the only surrogate measure of exposure to these plants. The quantity of pollutants emitted from these plants is low, if compared to other sources such as traffic, heating or some industrial premises. Therefore the measures of exposure to be used are necessarily more sophisticated than in other contexts.
Although work based on distance are still present in literature, in recent years several papers underline as dispersion models of pollutants emitted by incinerators can provide a better surrogate measure of exposure than distance. In presence of meteorological conditions such as those existing in the UK, the meteorological variables and wind direction is certainly influential in modifying the shape of fallout, that probably will not a simple “Gaussian” relapse of pollutants, which would be approximated by distance and declining functions related to it, as those well modeled in this article. Moreover, the substantial absence of situation of no winds is an advantage in the use of Gaussian or quasi-Gaussian dispersion model, such as those used in many epidemiological studies.
In detail:

- Introduction: in the part related to existing literature works, the authors didn’t mention important papers, such as the series of works by Viel and colleagues on the incinerator of Besançon in France, who use dispersion models of dioxins for exposure assessment of the population (one of their work is dedicated to this specific topic, with a model validation of assessing exposure approach). Other recent works (Zambon et al. 2007, Cordier et al. 2010, Forastiere et al. 2011...) make also use of dispersion models of pollutants.

Although Viel and colleagues used dispersion models for Besançon dioxin exposure, this approach was only used after preliminary work showed a case to answer. Our study is more comparable to their early work, exploring possible distributions of disease rather than considering detailed exposure assessment.

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• Control areas: the authors don't discuss the choice of 10 km as a threshold of exposed people, providing only a couple of references in the Methods Section.

Based on the references provided, we think that 10km is a sufficient distance to capture any exposure-related effects. As we are using continuously-measured distance as the proxy measure of exposure, if any effect returned to background levels at a distance less than 10km, this should be detectable via the parameter estimates of our model (in particular, parameter γ).

• The way to define control areas is clearly understandable, but nothing is said about any other environmental pressure factors present in the control areas, which could be very influential, especially if similar, as emissions, to pollutants emitted by incinerators. In relation to this point, there are strange trends of some pathologies related to the distance in control areas (Figure 2), with irregular increases, with a suspect of local presence of other risk factors (environmental or not). Moreover some diseases are always higher in control areas. See for example Childhood cancer incidence or leukemia (figure. 2)

As described above, there was an error in Figure 2 originally submitted. The new version of Figure 2 does not give rise to concerns about local presence of other risk factors.

• The issue on use of dispersion models is not addressed at all in the discussion section. The study provides a number of statistical models, very interesting from a methodological point of view. But, since the focus is on evaluation of health effects of incinerators, this type of study cannot fail to take into account models of fallout of pollutants for exposure assessment. A modification of the main objective of the article, and/or a substantial part of the discussion related to limitation in using distance as proxy of exposure is recommended.

While we agree that accurate air dispersion modelling data validated against measurements made on the ground would have provided a much more powerful proxy of exposure, several factors prevented us from taking this approach. As this study was retrospective, many of the inputs required as inputs in such models were unavailable, and the regions included in the study were not adequately covered by monitoring networks. In addition, recent work in England (Gulliver et al. (2010)) does not suggest that dispersion model outputs are any more reliable proxy measures of exposure than a purely distance-based measure, especially when not directly validated. Despite these reservations, we think the reviewer raises an important point, and further analysis, possibly in relation to any suggested cohort study, may need to consider dispersion modelling of emissions, although wind roses in the UK show a full 360 degree coverage of wind. We have referred to these works and added additional comments in our discussion.

• Infant mortality and incidence of leukemia are most frequently related to exposure to incinerators than others. This is properly recall in discussion (page 19), with a possible explanation related to adjustments not made for "age-sex difference in structure or deprivation level." It should also be pointed out that these diseases have a latency compatible with observation period of the study (10 years), contrary to other types of cancer studied. This is mentioned in the discussion, but this consideration should strengthen results on infant mortality, so a more detailed discussion is recommended.

In the discussion we have added a comment to highlight the likely less than ten year lead time of infant mortality and childhood cancer.

o The findings and comments on temporal analyses should be combined with information on the evolution of plants. The selection of plants that are "all active on or before 31st December 1998" is useful, but not exhaustive, as it is not indicated if and when these plants were renewed. Did new laws

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or regulations on emission limits appear during the study period? (this probably led to a renewal of the facilities). This information is of great importance, since it is well known that from the mid 90's to the late 2000 authorized emissions of the plants has declined significantly (for some pollutants up to 1-2 orders of magnitude) and diversified as pollutants emitted (eg. dioxins).

We do not have specific information about emission changes that the incinerators included in this study may have undergone during the study period, but the time period of the study was based on the European Parliament and of the Council of 4 December 2000 on the incineration of waste, which came into force in December 2003 (2005 for existing incinerators). We have added this point and a reference to the methods section.

- In the "Strengths and limitations of this study:" should be added a point about limitation in the use of distance as proxy of exposure

We have added a comment, as suggested.

- Pag.12: the first sentence after "Initial Analysis" is a repetition of a sentence at page 9 (third sentence).

We have removed the repeated sentence.

VERSION 2 – REVIEW

REVIEWER	Oliver Robinson (on behalf of Mireille Toledano) Research Assistant Small Area Health Statistics Unit School of Public Health Imperial College London UK
REVIEW RETURNED	21-Dec-2012

GENERAL COMMENTS	I am happy that the author has addressed my comments. The paper is well written and its limitations clearly expressed.

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