

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Pleural mesothelioma risk in the construction industry: a case-control study in Italy. 2000-2018
AUTHORS	Stella, Simona; Consonni, Dario; Migliore, Enrica; Stura, Antonella; Cavone, Domenica; Vimercati, Luigi; Miligi, Lucia; Piro, Sara; Landi, Maria Teresa; Caporaso, Neil E.; Curti, Stefania; mattioli, stefano; Brandi, Giovanni; Gioscia, Carmela; Eccher, Silvia; Murano, Stefano; Casotto, Veronica; Comiati, Vera; Negro, Corrado; D'Agostin, Flavia; Genova, Carlo; Benfatto, Lucia; Romanelli, Antonio; Grappasonni, Iolanda; Madeo, Gabriella; Cozzi, Ilaria; Romeo, Elisa; Tommaso, Staniscia; Carrozza, Francesco; Labianca, Michele; Tallarigo, Federico; Cascone, Giuseppe; Melis, Massimo; Marinaccio, Alessandro; Binazzi, Alessandra; Mensi, Carolina; ReNaM, Working Group

VERSION 1 – REVIEW

REVIEWER	Markowitz, Steven Queen's College, Commoner Center
REVIEW RETURNED	04-May-2023

GENERAL COMMENTS	<p>This is an excellent study from the gold standard of national mesothelioma registries, ReNaM, in Italy.</p> <p>Its distinctive strengths include national coverage, very high quality data, completeness of case identification, high number of cases, and recency of cases (through 2018.) These features make this a worthy study to publish even if there are numerous prior case control studies in multiple countries on the same topic.</p> <p>There are a couple of issues that the authors might address:</p> <ol style="list-style-type: none">1. The Discussion says little about the specific findings regarding particular occupations included in the study. For example:<ol style="list-style-type: none">a. Bricklayers account for 40% of the MM in blue collar trades in this study, far more than any other occupation. This is unusual compared to other national studies. See LaCourt 2014, Rolland 2010, Agudo 2000, DeBono 2021. How did their use of asbestos in Italy differ, or lead to this result?b. Roofers do not appear frequently in other similar studies as having much OR elevation for MM but have among the highest OR's in this study. Again, the authors should remark on their use of asbestos-containing materials and how it might differ from some other countries.c. Where do sheet metal workers appear in Table 2? Under "structural metal preparers"?
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	<p>d. Nearly 20% of blue collar cases were among “construction workers NEC.” And they had quite a high OR (3.49). This OR meets or exceeds plumbers and carpenters. This has happened before (See Rolland 2000), but would benefit from discussion, if possible. The NEC category is a catchall for a variety of trades. But the trades with the most direct contact with asbestos (and therefore the highest MM risk) are the familiar titles: insulator, plumber, carpenter, electrician, etc. How is it that these NEC cases have so much contact with asbestos. (I realize the NEC means that little may be known about what they do.)</p> <p>2. At first blush, a doubling of risk of MM among blue collar construction workers seems like a relatively modest increase in risk of an otherwise rare disease for a group of trades who commonly had asbestos exposure. This has been seen in other studies, though there is considerable variation in MM risk among trades in the different studies. One relevant aspect is the choice of reference group. In this study, that group is represented by people who were not employed in construction. Rake (2009) in a similar case control study selected a reference group of people who had never worked in industrial jobs or had worked less than 5 years in such jobs. This makes some sense, because the interest is not in how much higher is the MM risk of construction workers compared to a group that includes industrial workers (who may have had asbestos exposure) but rather how much higher is MM risk in construction workers compared to workers (or the general population) who generally did not have, or who had only a modest level, of occupational exposure to asbestos. The authors may wish to explore this approach as an additional analysis. Actually, it might be quite interesting to compare the two approaches to reference groups.</p>
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REVIEWER	Farina, Elena S.C. Servizio Sovrazonale di Epidemiologia
REVIEW RETURNED	12-May-2023

GENERAL COMMENTS	<p>Thank you for giving me the opportunity to review this interesting paper, which deepens the relationship between pleural mesothelioma and occupational exposure in a particularly affected sector, such as construction.</p> <p>Here are some suggestions that I think could improve the manuscript, plus some typos to correct within the text.</p> <p>WHAT’S NEW SECTION Here I would suggest to review like this: - What is already known about this subject? I would delete the sentence “However, relative risks of mesothelioma in this sector has never been investigated at a country-wide level” and add that construction is among the industries with the largest asbestos use in the past. - What are the new findings? I would add at the beginning that this is the first country-level study in Italy on this issue. - How might this impact on policy or clinical practice in the foreseeable future? I would add also the idea that the results are relevant to encourage the adoption of adequate preventive measures to reduce exposure.</p>
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	<p>METHODS</p> <p>Controls</p> <ul style="list-style-type: none"> - page 6 / line 59 : "...261 out of 725 municipalities..." in figure 1 for EAGLE controls it is reported 216 municipalities. Can you correct the wrong one? - page 7 / line 18-21 : Regarding the set of control taken from CARA I suggest to complete the description specifying the range of age, the period of availability (2014-2016) and the type of interview. This is in analogy with the descriptions of the other two sets of controls. <p>Coding of industries and occupations</p> <ul style="list-style-type: none"> - I suggest to report here the code of the industry of interest (instead of page 8, line 2) and I would write here also the list of occupations of interest with the code. <p>Statistical analysis</p> <ul style="list-style-type: none"> - It is mentioned in the introduction that a "control-initiated case-control study" design was used. I suggest to spend few lines in this section to specify what it consists of, since it is a rather unusual method, and above all specify the analyses in which it was used (if I understand correctly in sensitivity analyses where time and space restrictions are made on the basis of controls availability). - A question: would have been possible to deepen the analyses considering a multi-level exposure? So why did you decide to consider only a dichotomous exposure (ever/never expose to construction industry)? <p>RESULTS</p> <ul style="list-style-type: none"> - page 8 / line 54: "...were 603 (490 from MISEM, 103 from CARA)." The 603 should be corrected to 593. - page 9 / line 9: the 59.9% should be corrected to 59.0%, as in Table 1. - I suggest to review the decimals of the percentages of table 1 to make sum 1. - The biggest change I would suggest for the results section is to delete Table 2 and supplementary table 1, 2, 3 by adding to figure 2 some new lines regarding overall analysis (Ever employed in construction vs never employed), white collar and blue collars for the 4 models. Indeed, at the moment the figure exactly repeats the information already contained in the tables, which becomes in my opinion redundant. - In any case I suggest to verify the consistency of IC values between tables and figure, as I found some typos (e.g. IC for electrical wiremen, analysis A1 to make an example). Even if I know that the substance of the results doesn't change!
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Steven Markowitz, Queen's College

Comments to the Author:

This is an excellent study from the gold standard of national mesothelioma registries, ReNaM, in Italy. Its distinctive strengths include national coverage, very high quality data, completeness of case identification, high number of cases, and recency of cases (through 2018.) These features make this

a worthy study to publish even if there are numerous prior case control studies in multiple countries on the same topic.

Answer: we thank the reviewer for his appreciation

There are a couple of issues that the authors might address:

1. The Discussion says little about the specific findings regarding particular occupations included in the study. For example:

Answer: we didn't discuss particular occupations for two reasons: 1) It would be cumbersome to discuss each in detail, rendering the paper less readable; 2) Most importantly, we think the overall picture indicates a diffuse higher risk of pleural mesothelioma in several occupations, rather than in specific ones, especially with the new approach (see below). We added a general comment on this in Discussion. See also specific comments below.

a. Bricklayers account for 40% of the MM in blue collar trades in this study, far more than any other occupation. This is unusual compared to other national studies. See LaCourt 2014, Rolland 2010, Agudo 2000, DeBono 2021. How did their use of asbestos in Italy differ, or lead to this result?

Answer: We added possible explanations in Discussion.

b. Roofers do not appear frequently in other similar studies as having much OR elevation for MM but have among the highest OR's in this study. Again, the authors should remark on their use of asbestos-containing materials and how it might differ from some other countries.

Answer: The result is based on a relatively small number of cases/controls. See also response above.

c. Where do sheet metal workers appear in Table 2? Under "structural metal preparers"?

Answer: no, the ISCO-68 code for sheet metal workers is 873. We added ISCO some codes to the Tables/Figure, even when controls are few, so that to have a more complete picture of results. Note that we removed results for white collars: we realized that make little sense "ever white collar" if one had also been a blue collar.

d. Nearly 20% of blue collar cases were among "construction workers NEC." And they had quite a high OR (3.49). This OR meets or exceeds plumbers and carpenters. This has happened before (See Rolland 2000), but would benefit from discussion, if possible. The NEC category is a catchall for a variety of trades. But the trades with the most direct contact with asbestos (and therefore the highest MM risk) are the familiar titles: insulator, plumber, carpenter, electrician, etc. How is it that these NEC cases have so much contact with asbestos. (I realize the NEC means that little may be known about what they do.)

Answer: In the new analyses (see next response), OR for construction workers NEC are lower than for plumbers/carpenters. See also response above.

2. At first blush, a doubling of risk of MM among blue collar construction workers seems like a relatively modest increase in risk of an otherwise rare disease for a group of trades who commonly had asbestos exposure. This has been seen in other studies, though there is considerable variation in MM risk among trades in the different studies. One relevant aspect is the choice of reference group. In this study, that group is represented by people who were not employed in construction. Rake (2009) in a similar case control study selected a reference group of people who had never worked in industrial jobs or had worked less than 5 years in such jobs. This makes some sense, because the interest is not in how much higher is the MM risk of construction workers compared to a group that includes industrial workers (who may have had asbestos exposure) but rather how much higher is MM risk in construction workers compared to workers (or the general population) who generally did not have, or who had only a modest level, of occupational exposure to asbestos. The authors may wish to explore this approach as an additional analysis. Actually, it might be quite interesting to

compare the two approaches to reference groups.

Answer: We thank the reviewer for this comment. As a matter of fact, we had a similar idea in mind, but since it is usually difficult to find a sufficiently sized reference group (eg, Rolland 2020), we preferred to follow a more classical approach (ever employed in a job vs never employed in that job). However, we fully agree and took the opportunity of your comment and followed the approach you suggested (to reduce negative confounding), with the additional restriction of exclusion of >5 years also for the “exposed” (ever construction) category (we think this is appropriate to reduce potential positive confounding). Moreover, we reported results of this approach as “primary” (more valid) and results of the old one as “secondary” (less valid). We hope you agree with this choice.

Reviewer: 2

Dr. Elena Farina, S.C. Servizio Sovrazonale di Epidemiologia

Comments to the Author:

Thank you for giving me the opportunity to review this interesting paper, which deepens the relationship between pleural mesothelioma and occupational exposure in a particularly affected sector, such as construction.

Answer: we thank the reviewer for her appreciation

Here are some suggestions that I think could improve the manuscript, plus some typos to correct within the text.

WHAT'S NEW SECTION

Here I would suggest to review like this:

- What is already known about this subject?

I would delete the sentence “However, relative risks of mesothelioma in this sector has never been investigated at a country-wide level” and add that construction is among the industries with the largest asbestos use in the past.

- What are the new findings?

I would add at the beginning that this is the first country-level study in Italy on this issue.

- How might this impact on policy or clinical practice in the foreseeable future?

I would add also the idea that the results are relevant to encourage the adoption of adequate preventive measures to reduce exposure.

Answer: This parts had been written when we submitted the paper to OEM, which refused it; then the paper was transferred to BMJ Open, which asks to add a section entitled “Strengths and limitations of this study’ (immediately after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The novelty, aims, results or expected impact of the study should not be summarised here.” Therefore, we completely updated this section.

METHODS

Controls

- page 6 / line 59 : “...261 out of 725 municipalities...” in figure 1 for EAGLE controls it is reported 216 municipalities. Can you correct the wrong one?

Answer: Thanks for spotting the mistake, corrected.

- page 7 / line 18-21 : Regarding the set of control taken from CARA I suggest to complete the description specifying the range of age, the period of availability (2014-2016) and the type of interview. This is in analogy with the descriptions of the other two sets of controls.

Answer: We agree, done.

Coding of industries and occupations

- I suggest to report here the code of the industry of interest (instead of page 8, line 2) and I would write here also the list of occupations of interest with the code.

Answer: Useful suggestion; done

Statistical analysis

- It is mentioned in the introduction that a “control-initiated case-control study” design was used. I suggest to spend few lines in this section to specify what it consists of, since it is a rather unusual method, and above all specify the analyses in which it was used (if I understand correctly in sensitivity analyses where time and space restrictions are made on the basis of controls availability).

Answer: Useful suggestion, we added a few lines to explain what this type of study is. It was used for all analyses. Analyses A2 to A4 were performed to check validity of A1. We also added other few lines in Introduction.

Also note that we took the opportunity of a comment by Reviewer 1 and followed two different approaches, one excluding and the other including subjects employed >5 years from both the “exposed” (ever construction) and reference categories. We reported results of this approach as “primary” (more valid) and results of the old one as “secondary” (less valid). For both approaches we performed analyses A1-A4.

- A question: would have been possible to deepen the analyses considering a multi-level exposure? So why did you decide to consider only a dichotomous exposure (ever/never expose to construction industry)?

Answer: We used a dichotomous exposure because the main objective of the paper is the risk of having been ever employed in a given occupation; this would be important for compensation of affected workers. However, we agree a multi-level scale could be informative: we applied (primary approach, analysis A1) it to a few occupations (with 20+ controls). See Supplementary Table 1.

RESULTS

- page 8 / line 54: “...were 603 (490 from MISEM, 103 from CARA).” The 603 should be corrected to 593.

Answer: Thanks for spotting the mistake, corrected.

- page 9 / line 9: the 59.9% should be corrected to 59.0%, as in Table 1.

Answer: Thanks for spotting the mistake, corrected.

- I suggest to review the decimals of the percentages of table 1 to make sum 1.

Answer: we rounded to a different integer for some decimals; in other cases we did not because we should not arbitrarily round incorrectly to the non-nearest integer. We would prefer to add a note to Table 1 (we added “Percentages may not add to 100 due to rounding”).

- The biggest change I would suggest for the results section is to delete Table 2 and supplementary table 1, 2, 3 by adding to figure 2 some new lines regarding overall analysis (Ever employed in construction vs never employed), white collar and blue collars for the 4 models. Indeed, at the moment the figure exactly repeats the information already contained in the tables, which becomes in my opinion redundant.

Answer: We agree results are redundant. We deleted Suppl. Tables 1-3. We would only keep Table 2 and Supplementary Table 2 because they show the main results. We added OR for construction and blue collars to the results. We also added a few other ISCO-68 codes (see answer to Reviewer 1 above). Note that we removed white collars: we realized that make little sense “ever white collar” if one had also been a blue collar.

- In any case I suggest to verify the consistency of IC values between tables and figure, as I found some typos (e.g. IC for electrical wiremen, analysis A1 to make an example). Even if I know that the substance of the results doesn't change!

Answer: We checked the CIs: in some situations the second decimal differs only due to the Stata

command used to produce the Figure.

Reviewer: 1

Competing interests of Reviewer: I provide medico-legal reports in cases of asbestos-related disease. This work does not influence my objectivity in reviewing this study.

Reviewer: 2

Competing interests of Reviewer: None

VERSION 2 – REVIEW

REVIEWER	Markowitz, Steven Queen's College, Commoner Center
REVIEW RETURNED	03-Jul-2023

GENERAL COMMENTS	<p>The manuscript is excellent and requires just a few clarifications. Please see attached file (manuscript text) for some comments and grammar suggestions. In addition:</p> <p>Discussion, paragraph 2:</p> <p>The points made in this paragraph need to be re-phrased, especially since the study results are quite similar to study results in other countries, as authors acknowledge in the next paragraph. It looks like the only substantial difference between this and other similar studies is the prominence of the OR's associated with bricklayers and perhaps roofers. Over-emphasis is placed on differences in fiber type in this paragraph. As authors note, a number of factors may be at play: differential quantity of type of asbestos products used, work practices, organization of the construction industry, differences in work tasks by occupation, and maybe other IN ADDITION TO relative quantities of different fiber types used in the Italian construction industry.</p> <p>Discussion, paragraph 3: The current text says that preventive measures failed because they were too difficult to employ. But, in the 1950's-1980's, when the included PM cases worked, were preventive measures even seriously attempted? In the U.S. at least, the problem was that workers were not informed of risks, employers made no or limited efforts to minimize exposure, and manufacturers provided no or few warnings. Preventive measures were not seriously employed. Was it that different in Italy?</p>
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REVIEWER	Farina, Elena S.C. Servizio Sovrazonale di Epidemiologia
REVIEW RETURNED	20-Jun-2023

GENERAL COMMENTS	Thanks to the authors for the revisions, I think the article has improved!
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Elena Farina, S.C. Servizio Sovrazonale di Epidemiologia

Comments to the Author:

Thanks to the authors for the revisions, I think the article has improved!

Answer: thank you for your contribution in making the manuscript better.

Reviewer: 1

Dr. Steven Markowitz, Queen's College

Comments to the Author:

The manuscript is excellent and requires just a few clarifications.

Please see attached file (manuscript text) for some comments and grammar suggestions.

In addition:

Answer: thank you for your appreciation and also for grammar suggestions.

Discussion, paragraph 2:

The points made in this paragraph need to be re-phrased, especially since the study results are quite similar to study results in other countries, as authors acknowledge in the next paragraph. It looks like the only substantial difference between this and other similar studies is the prominence of the OR's associated with bricklayers and perhaps roofers. Over-emphasis is placed on differences in fiber type in this paragraph. As authors note, a number of factors may be at play: differential quantity of type of asbestos products used, work practices, organization of the construction industry, differences in work tasks by occupation, and maybe other IN ADDITION TO relative quantities of different fiber types used in the Italian construction industry.

Answer: We agree. We amended the text.

Discussion, paragraph 3:

The current text says that preventive measures failed because they were too difficult to employ. But, in the 1950's-1980's, when the included PM cases worked, were preventive measures even seriously attempted? In the U.S. at least, the problem was that workers were not informed of risks, employers made no or limited efforts to minimize exposure, and manufacturers provided no or few warnings. Preventive measures were not seriously employed. Was it that different in Italy?

Answer: You are right, and the situation was the same in Italy. We revised the text accordingly.

VERSION 3 – REVIEW

REVIEWER	Markowitz, Steven Queen's College, Commoner Center
REVIEW RETURNED	07-Jul-2023
GENERAL COMMENTS	Agree with changes. Nice paper!