

Multiple sclerosis in Iran: An epidemiological update with focus on air pollution debate

Masoud Amiri

Corresponding author

Masoud Amiri

Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

*Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center,
Rotterdam, The Netherlands*

Generation R Study Group, Erasmus Medical Center, Rotterdam, The Netherlands

Handling editor:

Michal Heger

Department of Pharmaceutics, Utrecht University, the Netherlands

Department of Pharmaceutics, Jiaying University Medical College, Zhejiang, China

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Journal of Clinical and Translational Research

Dear Dr. Amiri,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below and attached to this email.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jan 05, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission

record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The manuscript seems pretty interesting to publish in this journal but there is some comment to follow:

1. some parts of abstract should be rewrite. for example method, putting year in the first sentence is out of question. In systematic review, authors try to show their given time range.
2. The authors only reviewed a handful of articles, so they can not mention definite results for example alteration of disease pattern and the exact effect of air pollution and industrialization on MS in Iran.
3. The conclusion and the conclusion part of abstract should be rewrite. In the conclusion part of abstract, authors only focused on the effect of air pollution, while other factors can play a role and they also make some roughly definite conversations in review work.
4. The Authors can also add a risk factor as socioeconomic factors including income, lifestyle and so on.
5. Both air pollution and exposure with heavy metals can be classified as environmental risk factors, while they are bolded in the text meaning they are differ from environmental factors.
6. Please be aware from the meaning of pollution in line 15 p9. Are you sure that you use the exact word for the head title of the paragraph?
7. On of the main group of soil pollutants in the soil are heavy metals, but they are separated and discussed in a different paragraph.
8. Conclusion part should be rewrite. It is pretty simple and irrelevant with the main points of manuscript. The authors do not focused on ethnicity in the manuscript, while it is mentioned in the conclusion.
9. I think that authors should add a discussion part in the text and some paragraph should be moved to the discussion.
10. I suggest that the author could some review and original article listed below again and make their study stronger.

Multiple sclerosis-A disease on a dramatically rising trend in Iran: Review of possible reasons
The evaluation of multiple sclerosis dispersal in Iran and its association with urbanization, life style and industry

Epidemiology of multiple sclerosis in Torbat-e Heydarieh (Northeast of Iran) during 1982-2016

Do socioeconomic factors affect the prevalence of multiple sclerosis in Iran?

Potential Impact of Air Pollution on Multiple Sclerosis in Tehran, Iran

Air pollution by particulate matter PM10 may trigger multiple sclerosis relapses

Multiple sclerosis and air pollution exposure: Mechanisms toward brain autoimmunity

Exposure to particulate matter air pollution and risk of multiple sclerosis in two large cohorts of US nurses

Overall, avoid definite expression of your result in a review manuscript.

Reviewer #3: This is a review paper aiming to update information about MS in Iran and its potential association to air pollution. It is well-written. However, there is no clear evidence-based method to follow/reach the aim of the study. The manuscript looks like a chapter in a book rather than a peer-reviewed paper in a scientific journal. I would therefore suggest to re-arrange the study into a "systematic review (with or without meta analysis)". After then, authors may re-submit the manuscript for further review in this journal.

Reviewer #4: Thanks to authors

Please read detailed comments as shown in the table in attachment.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response

Dear Editor

We thank each of the reviewers and the Editor for their time and effort in providing important feedback on our manuscript. We believe we have addressed all the comments and the paper is improved as a result. We have provided our responses below for each comment and copied any additional text with a reference to the page number. These additions are highlighted in red in the revised file. Please see the answers to the comments in the following sentences.

Reviewer #1:

1. *Some parts of abstract should be rewrite. for example method, putting year in the first sentence is out of question. In systematic review, authors try to show their given time range.*

Thank you for your comment. It has been moved from the first sentence to the last sentence of method section. In addition, this article is not a systematic review, but an epidemiological update.

2. *The authors only reviewed a handful of articles, so they can not mention definite results for example alteration of disease pattern and the exact effect of air pollution and industrialization on MS in Iran.*

Thank you for your comment. This article is not a systematic review. It is just an epidemiological update focusing on air pollution. In addition, there are many factors affecting disease pattern, air pollution and industrialization that considering their exact effects needs a comprehensive study with reliable data for many variables. Moreover, there is not mentioned about definite results and exact effects of air pollution in the article.

3. *The conclusion and the conclusion part of abstract should be rewrite. In the conclusion part of abstract, authors only focused on the effect of air pollution, while other factors can play a role and they also make some roughly definite conversations in review work.*

Thank you for your suggestion. It is right. This sentence has been added to conclusion section in abstract: **There are many risk factors of MS in Iran including age, gender, vitamin D deficiency, smoking, and air pollution.**

4. *The Authors can also add a risk factor as socioeconomic factors including income, lifestyle and so on.*

Thank you for this suggestion. “Lifestyle” has already existed in “Environmental factors” section. There were no reliable data for income and socioeconomic status available.

5. *Both air pollution and exposure with heavy metals can be classified as environmental risk factors, while they are bolded in the text meaning they are differ from environmental factors.*

Thank you for your comment. Now, Heavy metals and air pollution are subtitles of environmental risk. They highlighted by **red color**.

6. *Please be aware from the meaning of pollution in line 15 p9. Are you sure that you use the exact word for the head title of the paragraph?*

Thank you for your comment. I have checked the original reference again. It is the same word.

7. *On of the main group of soil pollutants in the soil are heavy metals, but they are separated and discussed in a different paragraph.*

Thank you for your comment. Now, they are as a subgroup of “Environmental factors” now. The subtitle has been highlighted with **red color**.

8. *Conclusion part should be rewrite. It is pretty simple and irrelevant with the main points of manuscript. The authors do not focused on ethnicity in the manuscript, while it is mentioned in the conclusion.*

Thank you for your comment. The ethnicity has been removed now.

9. *I think that authors should add a discussion part in the text and some paragraph should be moved to the discussion.*

Thank you for your suggestion. It has been done. There is section named “Discussion” now. It is highlighted in **red color**. Please see pages 10 to 12.

10. *I suggest that the author could some review and original article listed below again and make their study stronger.*

Thank you for your Suggestion. All articles have been used in the article now.

Multiple sclerosis-A disease on a dramatically rising trend in Iran: Review of possible reasons

Different factors like the increased rate of smoking, lifestyle changes, modernization, and contact with toxic solvents might be considered as reasons for this sudden rise in the prevalence of MS in Iran; however, they are not definite causes ³⁷.

The evaluation of multiple sclerosis dispersal in Iran and its association with urbanization, life style and industry

Smoking might be considered as a potential factor to increase the risk of MS, urbanization can also be an augmentative factor; however, it is a combination of several complex factor ³⁸.

Epidemiology of multiple sclerosis in Torbat-e Heydarieh (Northeast of Iran) during 1982-2016

The prevalence rate of MS in Torbat-e Heydarieh has also been increased from 1982 to 2016 ³¹.

Do socioeconomic factors affect the prevalence of multiple sclerosis in Iran?

Socioeconomic status (SES) in Iran is different from other countries; it seems that Iranian provinces with a higher SES level have higher prevalence rates of MS ³⁹.

Potential Impact of Air Pollution on Multiple Sclerosis in Tehran, Iran

In a study in Tehran, a significant difference was observed in exposure to PM₁₀, SO₂, NO₂, and NO_x in MS cases compared with controls, which confirms that the long-term exposure to air pollutants can be act as an environmental risk factor in MS ⁹⁵.

Air pollution by particulate matter PM₁₀ may trigger multiple sclerosis relapses

There is evidence to confirm the potential effect of PM₁₀ on the risk of relapse in MS patients, might be through oxidative stress mechanisms ⁹⁶.

Multiple sclerosis and air pollution exposure: Mechanisms toward brain autoimmunity

The exposure to air pollutants may initiate destructive mechanisms inducing reduction of immunological self-tolerance, inflammatory-oxidative cascades and neurodegeneration leading to brain autoimmunity, might be considered as a potential hypothesis ⁹⁷.

Exposure to particulate matter air pollution and risk of multiple sclerosis in two large cohorts of US nurses

Although in a study in USA, the exposure to PM air pollution was not related to MS risk ⁹², recent studies have shown that fine PM (PM 2.5) and three pollutants (SO₂, CO, and lead) were statistically associated with higher pediatric MS ⁹³.

Overall, avoid definite expression of your result in a review manuscript.

Thank you for your suggestion. It has been done now.

Reviewer #3:

This is a review paper aiming to update information about MS in Iran and its potential association to air pollution. It is well-written.

- 1- *There is no clear evidence-based method to follow/reach the aim of the study. The manuscript looks like a chapter in a book rather than a peer-reviewed paper in a scientific journal.*

Thank you for your comment. Main used evidence sources were Medline, ISI, Google scholar, and Scopus. Now, it has been changed. After an introduction, explanation of MS in Iran, risk factors, "Discussion" section has also been added.

- 2- *I would therefore suggest to re-arrange the study into a "systematic review (with or without meta analysis)". After then, authors may re-submit the manuscript for further review in this journal.*

Thank you for your suggestion. This is a very good idea to have a systematic review. However, it is just an epidemiological update of MS in Iran focusing on air pollution.

Reviewer #4:

- 1- *Page 2 line 15: The main issue in this research is air pollution and MS patients as whole. Why are you emphasizing on women?*

Thank you for your comment. You are right. It has been removed now.

- 2- *Page 2 line 54: The age range of MS is wider than you noted. Please correct the age range according to more precise studies in under age 17 (Natural History of Multiple Sclerosis with Childhood Onset, DOI: 10.1056/NEJMoa067597) and after age 50 (Multiple sclerosis after age 50, DOI: 0.1212/WNL.33.12.1537) and after age 50 (Multiple sclerosis after age 50, DOI: 0.1212/WNL.33.12.1537)*

Thank you for your suggestions. They are used in the article now.

The appearance and symptoms of this disease are suddenly occurring and may cause decease of the patient over several weeks to months, with usual age range of 17 to 50 years ¹; but with the late onset of MS (after age 50) ⁵ with age ranges from 27 to 80 years, 31-95 years ⁶. In addition, MS patients with childhood-onset of MS may take longer to reach states of irreversible disability; however, they do so at a younger age compared to patients with adult-onset multiple sclerosis ⁷.

- 3- Page 3 line 19: *It's better to point out rejection of Kurtzke hypothesis by past studies (Epidemiologic study of multiple sclerosis in Mazandaran, Iran, 2007. J Mazandaran Univ Med Sci. 2008; 18 (66) :82-86 URL: <http://jmums.mazums.ac.ir/article-1-513-en.html>) or newer ones (Does the multiple sclerosis (MS) map need to change again? An update of MS prevalence in Mazandaran province of Iran in 2018. <https://doi.org/10.1186/s12883-020-1618-6> AND Age and sex-adjusted incidence and yearly prevalence of multiple sclerosis (MS) in Mazandaran province, Iran: An 11-years study. <https://doi.org/10.1371/journal.pone.0235562>)*

Thank you for your suggestions. They have been added now:

Considering the recent trends, the hypothesis of Kurtzke has been rejected ²⁷⁻²⁹.

- 4- Page 3 line 21: *Because of the title and main goal of the study you have to consider all MS patients. Do not focus on women, that's not your main goal.*

Thank you for your comment. It has been corrected now.

- 5- Page 3 line 31: *It's better to use updated information from Atlas of MS 2020 available at:
<https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms>*

Thank you for your suggestion. It has been added now for Iran and other countries. The number of Iranian MS patients was 75000 with prevalence rate of 90/100 000 in 2020 ¹⁹.

Prevalence of 20 (1995) ¹⁶ and 39 (2005) ¹⁷ in Jordan, 14.77 (2000) ¹⁸, 85 (2013) ¹⁶ and 105 (2020) ¹⁹ in Kuwait, 25 (1998) ¹⁶, 40 (2008) ²⁰, 31-55 (2013) ¹⁶ and 41 (2020) ¹⁹ in Saudi Arabia, 65 (2010) ¹⁶ and 98 (2020) ¹⁹ in Qatar, 42 in Cyprus (2010) ¹⁶, 51 (2011) ¹⁶ and 70 (2020) ¹⁹ in Turkey, 55 (2007) ¹⁶ and 7 (2020) ¹⁹ in United Arab Emirates, 5.9 (1982-1984) ²¹ and 15 (2020) ¹⁹ in Libya, 4 (1990-2000) ²² and 16 (2020) ¹⁹ in Oman, 59 (2020) ¹⁹ in Egypt, 12 (2020) ¹⁹ in Iraq, 40 (2020) ¹⁹ in Syria, and 12/100 000 (1985) ²³ in Tunisia. In addition, study of demographic characteristics of MS in two ethnic groups, Persian and Arabic, showed that incidence and prevalence were higher in Persians ^{24,25}. This higher rates of Persian than other ethnicities were also observed in Parsis (people originated from Persian) in India ²⁶.

- 6- Page 3 line 35: *It's better to point out by most recent studies (Does the multiple sclerosis (MS) map need to change again? An update of MS prevalence in Mazandaran province of Iran in 2018. <https://doi.org/10.1186/s12883-020-1618-6> AND Age and sex-adjusted incidence and yearly prevalence of multiple sclerosis (MS) in Mazandaran province, Iran: An 11-years study. <https://doi.org/10.1371/journal.pone.0235562>)*

Thank you for your suggestion. They have been added now:

The prevalence of MS in Mazandaran province, in north of Iran, has been increased from 20-60/100 000 in 2013 to 72.5/100 000 in 2018 ^{27,28}.

- 7- Page 3 line 47: *Because of the title and main goal of the study you have to consider all MS patients. Do not focus on women, that's not your main goal.*

Thank you for your comment. Now, it has been corrected.

- 8- Page 3 line 60: *It's better to use most recent studies (Does the multiple sclerosis (MS) map need to change again? An update of MS prevalence in Mazandaran province of Iran in 2018. <https://doi.org/10.1186/s12883-020-1618-6> AND Age and sex-adjusted incidence and yearly prevalence of multiple sclerosis (MS) in Mazandaran province, Iran: An 11-years study. <https://doi.org/10.1371/journal.pone.0235562>)*

Thank you for your comment. They have been added now:

The prevalence of MS in Mazandaran province, in north of Iran, has been increased from 20-60/100 000 in 2013 to 72.5/100 000 in 2018 ^{27,28}.

- 9- Page 4 line 58-59: *State the concentration of advanced medical services in the city of Isfahan and its scientific authority in the center of the country, which leads to patients referring to it from elsewhere, as a possible reason for the higher number of patients.*

Thank you for your comment. It has been done.

Concentration of advanced medical services in the city of Isfahan and its scientific authority in the center of Iran, can lead to patients referring to Isfahan from elsewhere, as a possible reason for the higher number of patients.

- 10- Page 5 line 4: *State the concentration of advanced medical services in these cities and their scientific authority in the center of the country, which leads to patients referring to them from elsewhere, as a possible reason for the higher number of patients.*

Thank you for your comment. It has been updated.

Moreover, existence of advanced medical services in Isfahan with high scientific authority in the center part of Iran, can result in more referring of patients to Isfahan, as a potential reason for the bigger number of patients.

- 11- Page 5 line 12-14: *please use updated definitions from Atlas of MS 2020 available at: <https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms>*

Thank you for your comment. It has been updated.

However, the MS prevalence rate in Armenia were 3.75, 3.66 and 10/100 000 in 1981, 2007, and 2020, respectively ^{19,52,53}.

- 12- Page 5 line 35: *Please change " Zayanderud" to " Zayandeh Rud"*

Thank you for your comment. It has been changed and highlighted with red color.

- 13- Page 6 line 30: *Please use updated information from Atlas of MS 2020 available at: <https://www.atlasofms.org/chart/iran-islamic-republic-of/epidemiology/female-to-male-ratio-of-people-with-ms>*

Thank you for your comment. It has been updated.

In 2020, 26 and 74 percent of Iranian MS patients were men and women, respectively ¹⁹.

14- Page 7 line 26: *In Iranian context you can refer to another study:*
MICB GENE EXPRESSION ON PERIPHERAL BLOOD
MONONUCLEAR CELLS AND SUSCEPTIBILITY TO MULTIPLE SCLEROSIS IN
NORTH OF IRAN
<https://www.sid.ir/en/journal/ViewPaper.aspx?ID=251310>

Thank you for your comment. It has been updated now.

In a study in north of Iran, it has been suggested that low or no gene expression of major histocompatibility complex class I chain- related gene B (MICB) has a beneficial effect to prevent of autoimmune response in the MS patients ⁶⁶.

15- Page 10 line 17: *It's better to replace "health outcomes" with " health consequences" or " health problems".*

Thank you for your comment. It has been changed and highlighted with red color.

16- Page 13 line 24: *please use updated demographic data from Atlas of MS 2020 available at:*
<https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms>

Thank you for your comment. It has been updated.

In 2020, the prevalence rate of MS was 90/100 000 in Iran ¹⁹.

2nd Editorial decision
13-Jan-2022

Ref.: Ms. No. JCTRes-D-20-00111R1
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Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #4: Thanks to Authors
They did all needed corrections.