Long-Term Exposure to Ambient Air Pollution and Myocardial Infarction-A systematic review and meta-analysis

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Research

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Abstract

Background and Objective: An increasing amount of epidemiological original studies suggested that long-term exposure to particulate matter (PM 2.5 and PM 10) could be associated with the risk of myocardial infarction(MI), but the results were inconsistent. We aimed to synthesized available cohort studies to identify the association between ambient air pollution (PM 2.5 and PM 10) and MI risk by a meta-analysis.

Methods: PubMed and Embase were searched through September 2019 to identify studies that met predetermined inclusion criterion. Reference lists from retrieved articles were also reviewed. A random-effects model was used to calculate the pooled relative risk (RR) and 95% confidence intervals (CI).

Results: Twenty-two cohort studies involving 6,567,314 participants and 865,98 patients with MI were included in this systematic review. The pooled results showed that higher levels of ambient air pollution (PM 2.5 and PM 10) exposure were significantly associated with the risk of MI. The pooled relative ratio (RR) for each 10-μg/m 3 increment in PM 2.5 and PM 10 were 1.20 (95% CI : 1.11–1.29), and1.03 (95% CI :1.00-1.07) respectively. Exclusion of any single study did not materially alter the combined risk estimate.

Conclusions: Integrated evidence from cohort studies supports the hypothesis that long-term exposure to PM 2.5 and PM 10 as a risk factor for MI.

Introduction

The incidence and prevalence of cardiovascular diseases have increased in the last decades and became one of the main causes of death among adults [1–3]. Myocardial infarction (MI) is an acute and severe cardiovascular disease that generally can endanger the life of patients and has become a serious public health problem [4]. The causes of MI are complex and are related to lifestyle, diet structure, genetic factors and environmental factors, including air pollution [5–7]. Studies have shown that reducing modifiable risk factors may contribute to the prevention and control of MI [8–10], which is of considerable public health importance.

Air pollution especially particulate matter (PM) has been increasingly investigated as an environmental risk factor for MI morbidity and mortality recently. However, these studies had modest sample sizes and reported inconclusive results [11–13]. These inconsistent and controversial results indicate the need to quantitatively synthesize and interpret the available evidence to provide more explicit information for policy decisions and clinical use. Meta-analysis is a statistical tool that can be used to integrate results of multiple independent studies considered to be ‘combinable’ for a more precise estimation [14, 15]. Although previous meta-analyses have examined associations between air pollution exposure and MI, their studies most included cross-sectional literatures [13], and many new researches have been recently published. Therefore, more meta-analyses with cohort studies are urgently needed.

Taken into consideration of the inconsistent conclusions and the limitation of existing epidemiological studies and the flaw of previous meta-analyses, we therefore performed a systematic review and meta-analysis of cohort epidemiological studies to examine the potential associations between air pollution exposure and the risk of MI. Given the heavy economic and health burden of curing MI, the results of our study may provide additional practical and valuable clues for the prevention of MI.

Materials And Methods

Ethical approval is not required for this systematic review.

Literature search strategy

We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16] and the checklist of items in the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [17]. A systematic literature search of PubMed and Embase was conducted through September 2019 by using

the following search terms with no restrictions: ‘air pollution’ or ‘particulate matter’ or ‘air pollutants’ or ‘PM_{10}’or ‘$PM_{2.5}$’ in combination with ‘myocardial infarction’ or ‘heart attack’ or ‘acute coronary syndrome’. The language was restricted to English. Additionally, reference lists of the retrieved original articles and relevant review articles were also scrutinized to identify further pertinent studies.

Study selection

Studies meeting the following criteria were included in the meta-analysis: (1) the study design was cohort; (2) the exposure of interest was ambient air pollution; the endpoint of interest was incidence of MI; and (3) the relative risk (RR) and the corresponding 95% confidence interval (CI) of MI relating to ambient air pollution were reported or could be calculated from the data provided. Animal studies, clinical trials, reviews, letters and commentaries were excluded. Only studies with detailed information on both ambient air pollution and the incidence of MI was included.

Data extraction and quality assessment

Two investigators (WF and SC) extracted the following information from the studies: first author, publication year, country, study period, age, number of cases, size of cohort and time windows of exposure. Discrepancies were resolved by discussion with a third investigator (SC).

The Newcastle-Ottawa Scale was used to evaluate the qualities of cohort studies [18], which is a nine-point scale allocating points based on the selection of participants, comparability of groups, and exposure/outcome. This scale awards a maximum of nine points to each study: four for selection of participants and measurement of exposure, two for comparability of cohorts or cases and controls on the basis of the design or analysis, and three for assessment of outcomes and adequacy of follow-up. Studies scoring 0–3 points, 4–6 points, and 7–9 points were categorized as low, moderate, and high quality of studies, respectively. When studies had several adjustment models, we extracted those that reflected the maximum extent of adjustment for potentially confounding variables. Each study was rated independently by two authors (WF and JM). Discrepancies were resolved by discussion with a third investigator (SC).

Statistical analyses

We used RR to measure the association between ambient air pollution and the risk of MI and the random effects model was used to calculate an overall pooled RR for the main analysis.

Q statistic with a significance level at $P < 0.10$ and I^2 statistic were used to test the heterogeneity. The I^2 statistic measures the percentage of total variation across studies due to heterogeneity rather than chance. It was calculated according to the formula by Higgins [19]. We used I^2 to quantify the heterogeneity, with 25%, 50%, and 75% indicating low, moderate and high degrees of heterogeneity, respectively.

In our meta-analysis, the following formula was used to calculate the standardized risk estimates for each study:

$$RR_{(\text{standardized})} = \mathrm{RR}^{\frac{\text{Increment}(10)/\text{Increment}(\text{original})}{(\text{original})}}$$

Subgroup analyses were conducted to determine the possible influence of some factors such as state and publication years. We conducted a sensitivity analysis to explore potential sources of heterogeneity and to investigate the influence of various exclusion criteria on the pooled risk estimate. The Begg's rank correlation and the Egger's linear regression tests were used to assess the potential publication bias [20, 21]. Using Duval and Tweedie's nonparametric trim-and-fill method to adjust potential publication bias [22]. All analyses were performed using STATA statistical software (version 12.0; College Station, TX, USA) and all tests were two-sided with a significance level of 0.05.

Results

Literature search

Figure1 shows the process of study identification and inclusion. Initially 2977 and 3109 citations were retrieved from PubMed database and Embase, respectively. After excluding 236 duplicates, 5850 potentially relevant studies from electronic database were identified. Of these, we excluded 5698 papers because they were experimental, biomechanics, reviews or irrelevant studies. After full-text review of the remaining 152 articles, 28 articles were excluded because of insufficient data to calculate the risk estimates, and 102 were excluded because they were not a risk factor. Finally, 22 studies [23–44] were included.

Characteristics of the included studies

The main characteristics of the 22 studies on MI and long-term PM exposure in our meta-analysis were summarized in Table I. These studies were published between 2004 and 2019. Among them, eight studies were from Europe, two studies were from Asia and twelve studies were from America. The size of the cohorts ranged from 1120 to 4,404,046 with a total of 6,567,314 subjects. The exposure measure was $PM_{2.5}$ in seventeen studies and PM_{10} in eleven studies; six publications investigated the association of MI with exposure to

both $PM_{2.5}$ and PM_{10}.The end point was MI incidence (thirteen studies), MI mortality (ten studies), only one study MI hospital, and two studies included MI incidence and mortality. Fifteen studies were published after 2010, and seven study before 2010. The quality assessment scores ranged from 6 to 9, with an average score of 7 points, representing satisfactory quality of the studies.

Results of meta-analysis

We employed Meta-analysis to assess the association of $PM_{2.5}$ and PM_{10} with MI.

Association between PM2.5 and the risk of MI

The results from random-effects meta-analysis of ambient air pollution ($PM_{2.5}$ and PM_{10}) and the risk of MI were shown in Fig. 2. Seventeen studies reported the effect of $PM_{2.5}$ exposure on the risk of MI and the pooled estimates suggested a positive relationship. Results from standardized data showed that a 10 mg/m^3 increase in $PM_{2.5}$ exposure was positively associated with the risk of MI (RR = 1.20, 95%CI: 1.11 to 1.29), and there was a moderate heterogeneity (P = 0.002; I^2 = 57.2%). Subgroup analyses by state, and publication year (before 2010 versus after 2010) showed no statistically significant difference in results (Table 2). Every single pooled result of subgroup showed the positive and statistically significant relationship between exposure to $PM_{2.5}$ and the risk of MI.

Association between PM_{10} and the risk of MI

Eleven studies investigated the association of PM_{10} exposure with the risk of MI (Fig. 3). The pooled estimates of these studies indicated that a 10 mg/m^3 increase in PM_{10} was associated with a higher risk of MI (RR = 1.03, 95%CI: 1.00 to 1.07), and the heterogeneity is (P = 0.061, I^2 = 43.3%). We conducted subgroup analyses by state, and publication year (before 2010 versus after 2010). In general, these subgroup analyses showed no statistically significant difference in results.

Sensitivity

Sensitivity analyses was conducted to find potential sources of heterogeneity in the association between air pollution ($PM_{2.5}$ and PM_{10}) and MI risk, to examine the influence of various exclusions on the combined RR, and assess the robustness of all results. The pooled RR did not materially change, for $PM_{2.5}$ and PM_{10}, the both overall combined RR did not materially change, with a range from1.18 (95% CI: 1.10–1.26) to 1.22 (95%CI: 1.13–1.31), and 1.03 (95% CI: 1.0-1.07) to 1.05 (95%CI: 1.02–1.08), respectively.

Publication bias

Visual inspection of the funnel plot showed significant asymmetry ($PM_{2.5}$ Fig. 4 and Fig. 5 PM_{10} Fig. 6 and Fig. 7). For $PM_{2.5}$ and PM_{10}, the Egger test indicated of publication bias, but the Begg test did not ($PM_{2.5}$ Egger, Z = 4.248 p = 0.000, Begg, t = 1.04 p = 0.315; PM10 Egger, Z = 3.11 p = 0.002, Begg, t = 1.83 p = 0.104). We used the trim-and-fill method to evaluate the impact of any potential publication bias, the results showed that one and five potentially missing studies would be needed to obtain funnel plot symmetry for the association of MI and air pollution ($PM_{2.5}$, PM_{10}), respectively. After using the trim-and-fill method, both the corrected RR for PM $_{2.5}$ was 1.18 (95% CI: 1.08 to 1.29; random-effects model, p = 0.012), for PM_{10} was 1.04 (95% CI: 1.02 to 1.07; random-effects model, p = 0.002), which suggested the both pooled RRs were not substantially changed by the correction for potential publication bias.

Discussion

Myocardial infarction has a high medical burden for families and society, and remains a worldwide public health challenge [45]. Ascertaining the risk factors of MI could provide significant information for the prevention of MI. Our meta-analysis has quantitatively examined the association between long-term exposure to ambient air pollution ($PM_{2.5}$ and PM_{10}) and MI. The pooled analysis included 22 cohort studies with more than 6.5 million people showed an inverse association between exposures to air pollutants ($PM_{2.5}$ and PM_{10}) and the risk of MI, which was consistent with previous reviews and meta-analysis [13]. However, previous meta-analysis only included studies published before 2014, while more recent studies were not included which might report lower estimates or negative results. Additionally, our meta-analysis included all cohorts studies, which data reliable, the effect of exposure can be fully and directly analyzed, and conclusions are relatively stable.

The mechanisms by air pollution exposure could contribute to the development of MI might include inflammation, induction of autophagy and down-regulation of membrane repair protein MG53. Researchers found that inflammation plays an important role in the formation of coronary atherosclerosis and aggravation of plaque instability, and air pollutants can also promote MI via promoting inflammation [46]. The second potential mechanism is induction of autophagy. Several observational studies have shown that autophagy is a normal process for

cells to achieve their own metabolism and organelle renewal. Autophagy can maintain the body's metabolism to reduce damage and protect the organism. However, excessive autophagy can lead to apoptosis of cardiomyocytes and aggravate the damage of ischemic-related sites [47]. Studies have found that autophagic levels for exposure to air pollutants are significantly higher than the control group, while, the corresponding protein expression levels, MI size decreases, and myocardial cell damage decrease in Farnesoid X recertor(FXR)knock out SD rats. Therefore, it is speculated that the exposure of air pollutants promotes the development of MI through FXR-induced autophagy [48]. The third possible mechanism is down-regulation of membrane repair protein MG53.Exposure to air pollutants can affect membrane repair through down-regulating the expression of MG53 protein, and aggravates the severity of ischemia and hypoxia in MI [49].

We also found that long-term exposure to $PM_{2.5}$ has a more pronounced effect than PM_{10} on MI risk in each 10 μg/m^3 increase, which is in line with previous related researches [13]. Compared with PM_{10}, $PM_{2.5}$ can remain suspended for a longer time in the air and be inhaled into the respiratory tract and directly into the pulmonary alveoli. In addition, $PM_{2.5}$ has a larger superficial area and hence absorbs more chemical constituents than PM_{10}. Therefore, $PM_{2.5}$ is probably more harmful on human health than PM_{10} [50, 51].

Considering the different diets, lifestyles of people, and the prevalence of MI in different regions, we also conducted subgroup analysis by region, and statistically significant differences across subgroups were found but not for PM_{10}. In Asia, a 10 mg/m^3 increase in $PM_{2.5}$ exposure was positively associated with the risk of MI (RR = 1.38), which was inconsistent with previous studies. The possible reasons for the differences including inconsistency in study designs and potentially selective reporting of the results for pollutants. However, it is suggested that Asia region should pay attention to the relationship between air pollution and MI, and more works about air pollution and epidemiology remain to be done. We conducted a subgroup analysis by publication years but found the pooled result of studies before 2010 was not significantly different from that after 2010.

There are several strengths in this meta-analysis. Firstly, all the studies in our analysis were cohort studies, which is considered as stronger measure for demonstrating causation and identification of risk factors than other observational study designs [52]. Secondly,

in this comprehensive literature review, we pooled data of 22 cohort studies from several geographical regions in 1 meta-analysis, thus increasing the statistical power and allowing an investigation of regional patterns. Thirdly, sensitivity analysis and consistent results from various subgroup analyses indicated that our findings were reliable and robust, although heterogeneity existed among the included studies. Furthermore, all these studies were published in the past decade, indicating that data on both the exposure and the outcome are recent and relevant.

Some limitations in the present meta-analysis should be of concern. First of all, the heterogeneity of the included studies was significant and existed through the whole analyses. But we explored the potential heterogeneity resources by subgroup analyses and sensitivity analysis. Secondly, the number of included studies is not enough, especially for the mortality and hospital of MI and subgroup-analysis. Third, other air pollutants may have interaction with $PM_{2.5}$ and PM_{10}. A compounding effect of all these air pollutants should be examined and quantified on increasing the risk of MI.

Conclusion

In conclusion, our meta-analysis identified long-term exposure to $PM_{2.5}$ and PM_{10} as a significant risk factors of MI. Given the heavy economic burden of MI, the results of our study provide additional valuable clues for the prevention of MI. For future studies, more high-quality longitudinal and interventional studies are needed to explore the underlying mechanisms of the relationships between ambient air pollution and MI, especially in Asia and other middle and low-income countries. Besides, it is recommended that relevant departments must adopt a comprehensive particulate matter control policy to promote health and reduce the burden of MI.

Declarations

Ethical Approval and Consent to participate

Ethical approval is not required for this systematic review.

Consent for publication

Not applicable.

Availability of supporting data

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. Additionally, this study is a meta-analysis, no new data is generated.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wenning Fu, Jing Mao, Zuxun Lu and Shiyi Cao had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Wenning Fu and Li Zou independently extracted the related data information.

Check the related data information again: Wenning Fu, Li Zou, Hongbin Xu, Xiantao Zeng, Shijiao Yan, Zeyu Zhang.

Data analysis and writing articles: Wenning Fu and Jing Mao.

Analysis, or interpretation of data: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

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Abbreviations

MI: Myocardial Infarction; RR: relative ratio; PM: particulate matter; PRISMA: Systematic Reviews and Meta-Analysis; MOOSE: Meta-Analysis of Observational Studies in Epidemiology; CI: confidence interval.

References

1. Brunekreef, B. and S.T. Holgate, *Air pollution and health.* Lancet, 2002. **360**(9341): p. 1233-42.
2. Li, J., et al., *ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data.* Lancet, 2015. **385**(9966): p. 441-51.
3. Pope, C.A., 3rd, et al., *Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution.* JAMA, 2002. **287**(9): p. 1132-41.
4. Cendon, S., et al., *Air pollution effects on myocardial infarction.* Rev Saude Publica, 2006. **40**(3): p. 414-9.
5. Anand, S.S., et al., *Risk factors for myocardial infarction in women and men: insights from the INTERHEART study.* Eur Heart J, 2008. **29**(7): p. 932-40.
6. Dahabreh, I.J. and J.K. Paulus, *Association of episodic physical and sexual activity with triggering of acute cardiac events: systematic review and meta-analysis.* JAMA, 2011. **305**(12): p. 1225-33.
7. Finegold, J.A., P. Asaria, and D.P. Francis, *Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations.* Int J Cardiol, 2013. **168**(2): p. 934-45.
8. Smyth, A., et al., *Physical Activity and Anger or Emotional Upset as Triggers of Acute Myocardial Infarction: The INTERHEART Study.* Circulation, 2016. **134**(15): p. 1059-1067.

9. Teo, K.K., et al., *Potentially modifiable risk factors associated with myocardial infarction in China: the INTERHEART China study.* Heart, 2009. **95**(22): p. 1857-64.
10. Colombo, A., et al., *Triggers of acute myocardial infarction: a neglected piece of the puzzle.* J Cardiovasc Med (Hagerstown), 2014. **15**(1): p. 1-7.
11. Bhaskaran, K., et al., *Effects of ambient temperature on the incidence of myocardial infarction.* Heart, 2009. **95**(21): p. 1760-9.
12. Madrigano, J., et al., *Long-term exposure to PM2.5 and incidence of acute myocardial infarction.* Environ Health Perspect, 2013. **121**(2): p. 192-6.
13. Mustafic, H., et al., *Main air pollutants and myocardial infarction: a systematic review and meta-analysis.* JAMA, 2012. **307**(7): p. 713-21.
14. DerSimonian, R. and N. Laird, *Meta-analysis in clinical trials.* Control Clin Trials, 1986. **7**(3): p. 177-88.
15. Zeng, X., et al., *The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review.* J Evid Based Med, 2015. **8**(1): p. 2-10.
16. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* BMJ, 2009. **339**.
17. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* JAMA, 2000. **283**(15): p. 2008-12.
18. Wells, G., B. Shea, and J. O'Connell, *The Newcastle-Ottawa Scale (NOS) for Assessing The Quality of Nonrandomised Studies in Meta-analyses.* Ottawa Health Research Institute Web site, 2014. **7**.
19. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* BMJ, 2003. **327**(7414): p. 557-60.
20. Begg, C.B. and M. Mazumdar, *Operating characteristics of a rank correlation test for publication bias.* Biometrics, 1994. **50**(4): p. 1088-101.
21. Egger, M., et al., *Bias in meta-analysis detected by a simple, graphical test.* BMJ, 1997. **315**(7109): p. 629-34.
22. Duval, S. and R. Tweedie, *Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis.* Biometrics, 2000. **56**(2): p. 455-63.
23. Hartiala, J., et al., *Ambient Air Pollution Is Associated With the Severity of Coronary Atherosclerosis and Incident Myocardial Infarction in Patients Undergoing Elective Cardiac Evaluation.* J Am Heart Assoc, 2016. **5**(8).
24. Atkinson, R.W., et al., *Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases.* Epidemiology, 2013. **24**(1): p. 44-53.
25. McGuinn, L.A., et al., *Association between satellite-based estimates of long-term PM2.5 exposure and coronary artery disease.* Environ Res, 2016. **145**: p. 9-17.
26. Kim, H., et al., *Cardiovascular Effects of Long-Term Exposure to Air Pollution: A Population-Based Study With 900 845 Person-Years of Follow-up.* J Am Heart Assoc, 2017. **6**(11).
27. To, T., et al., *Chronic disease prevalence in women and air pollution--A 30-year longitudinal cohort study.* Environ Int, 2015. **80**: p. 26-32.
28. Koton, S., et al., *Cumulative exposure to particulate matter air pollution and long-term post-myocardial infarction outcomes.* Prev Med, 2013. **57**(4): p. 339-44.
29. McGuinn, L.A., et al., *Fine particulate matter and cardiovascular disease: Comparison of assessment methods for long-term exposure.* Environ Res, 2017. **159**: p. 16-23.
30. Lipsett, M.J., et al., *Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort.* Am J Respir Crit Care Med, 2011. **184**(7): p. 828-35.
31. Miller, K.A., et al., *Long-term exposure to air pollution and incidence of cardiovascular events in women.* N Engl J Med, 2007. **356**(5): p. 447-58.
32. Downward, G.S., et al., *Long-Term Exposure to Ultrafine Particles and Incidence of Cardiovascular and Cerebrovascular Disease in a Prospective Study of a Dutch Cohort.* Environ Health Perspect, 2018. **126**(12): p. 127007.
33. Zanobetti, A. and J. Schwartz, *Particulate air pollution, progression, and survival after myocardial infarction.* Environ Health Perspect, 2007. **115**(5): p. 769-75.
34. Puett, R.C., et al., *Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study.* Environ Health Perspect, 2009. **117**(11): p. 1697-701.
35. Puett, R.C., et al., *Chronic particulate exposure, mortality, and coronary heart disease in the nurses' health study.* Am J Epidemiol, 2008. **168**(10): p. 1161-8.

36. Héritier, H., et al., *A systematic analysis of mutual effects of transportation noise and air pollution exposure on myocardial infarction mortality: a nationwide cohort study in Switzerland.* European Heart Journal.
37. Chen, H., et al., *Ambient Fine Particulate Matter and Mortality among Survivors of Myocardial Infarction: Population-Based Cohort Study.* Environ Health Perspect, 2016. **124**(9): p. 1421-8.
38. Pope, C.A., 3rd, et al., *Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease.* Circulation, 2004. **109**(1): p. 71-7.
39. Puett, R.C., et al., *Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study.* Environ Health Perspect, 2011. **119**(8): p. 1130-5.
40. Beelen, R., et al., *The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study.* Occup Environ Med, 2009. **66**(4): p. 243-50.
41. Tonne, C., et al., *Long-term traffic air and noise pollution in relation to mortality and hospital readmission among myocardial infarction survivors.* Int J Hyg Environ Health, 2016. **219**(1): p. 72-8.
42. von Klot, S., et al., *Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities.* Circulation, 2005. **112**(20): p. 3073-9.
43. Beelen, R., et al., *Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts.* Epidemiology, 2014. **25**(3): p. 368-78.
44. Huss, A., et al., *Aircraft noise, air pollution, and mortality from myocardial infarction.* Epidemiology, 2010. **21**(6): p. 829-36.
45. Nielsen, S.H., et al., *Understanding cardiac extracellular matrix remodeling to develop biomarkers of myocardial infarction outcomes.* Matrix Biol, 2019. **75-76**: p. 43-57.
46. Frangogiannis, N.G., *Cell biological mechanisms in regulation of the post-infarction inflammatory response.* Curr Opin Physiol, 2018. **1**: p. 7-13.
47. Hill, S.M., L. Wrobel, and D.C. Rubinsztein, *Post-translational modifications of Beclin 1 provide multiple strategies for autophagy regulation.* Cell Death Differ, 2019. **26**(4): p. 617-629.
48. Tong, F. and H. Zhang, *Pulmonary Exposure to Particulate Matter (PM2.5) Affects the Sensitivity to Myocardial Ischemia/Reperfusion Injury Through Farnesoid-X-Receptor-Induced Autophagy.* Cell Physiol Biochem, 2018. **46**(4): p. 1493-1507.
49. Li, C., *Effect of fine particulate matter on myocardial infarction and MG53 expression in infracted heart of rats.* 2015.
50. Guo, Y., et al., *The relationship between particulate air pollution and emergency hospital visits for hypertension in Beijing, China.* Sci Total Environ, 2010. **408**(20): p. 4446-50.
51. Parker, J.D., et al., *Air pollution and birth weight among term infants in California.* Pediatrics, 2005. **115**(1): p. 121-8.
52. Thiese, M.S., *Observational and interventional study design types; an overview.* Biochem Med (Zagreb), 2014. **24**(2): p. 199-210.

Tables

Table 1 Main characteristics of the included studies involving ambient air pollution and the risk of myocardial infarction

Author	Year	Country(state)	Exposure	Study period	Age	Sample size	Gender, Female (%)	Time windows of exposure	Endpoints	No. of Cases
Jaana Hartiala	2016	American (North America)	$PM_{2.5}$	1998-2010	≥64	6575	32	2001-2007	Incidence	288
Laura A	2016	American (North America)	$PM_{2.5}$	2001-2011	20-93	9334	39	2002-2009	Incidence	704
Hyeanji Kim	2017	Korea (Asia)	$PM_{2.5}$	2006-2013	≥18	136 094	50.9	2007-2013	Incidence	1881
Teresa To	2015	Canada (North America)	$PM_{2.5}$	1980-2007	40-59	29549	100	1980-2006	Incidence	1233
Silvia Koton	2013	Israel(Asia)	$PM_{2.5}$	1995-2011	≤65	1120	18.8	2005-2011	Incidence	432
Laura A	2017	American (North America)	$PM_{2.5}$	2001-2010	60.8 ± 12.1	5679	39	2003–2009	Incidence	704
Michael J	2011	American (North America)	$PM_{2.5}$ PM_{10}	1996-2005	≥20	124614	NA	1999-2000	Incidence	722
Kristin A	2007	American (North America)	$PM_{2.5}$	1994-2000	50-79	65,893	100	1998-2000	Incidence	584
Richard W	2012	London(Europe)	PM_{10}	2003-2007	40-89	836557	NA	12 months	Incidence	13965
George S	2018	Netherlands(Europe)	$PM_{2.5}$ PM_{10}	1993-2010	20-65	23100	77	2005-2010	Incidence	797
Antonella Zanobetti	2007	American (North America)	PM_{10}	1985–1999	≥65	196131	49.6	1 year	Incidence	22552
Robin C	2009	South Carolina (North America)	$PM_{2.5}$ PM_{10}	1992-2002	62.4 ± 7.6	66250	100	48 months	Incidence Mortality	854
Robin C	2008	South Carolina (North America)	PM_{10}	1992-2002	30–55	121,700	100	4years	Incidence Mortality	2696
Harris He´ritier	2018	Switzerland(Europe)	$PM_{2.5}$	2000-2008	>30	4 404 046	52	2003-2008	Mortality	19 261
Hong Chen	2016	Canada (North America)	$PM_{2.5}$	1999-2011	>35	8873	35	2001-2011	Mortality	4016

C. Arden Pope	2004	Canada	$PM_{2.5}$	1982-1988	≥30	319 000 to 500 000	NA	1984 1986 1988	Mortality	NA
Rob Beelen	2014	Netherlands(Europe)	$PM_{2.5}$ PM_{10}	1992–1996	46.0 ±10.2	22136	NA	NA	Mortality	117
R Beelen	2009	Netherlands(Europe)	$PM_{2.5}$	1987–2000	55-69	120 852	30.9	1996-2000	Mortality	4243
Cathryn Tonnea	2015	London(Europe)	$PM_{2.5}$ PM_{10}	2003-2007	≥25	18,138	32	NA	Mortality	390
Robin C	2011	South Carolina(North America)	$PM_{2.5}$ PM_{10}	1986-2003	40–75	17545	NA	24 36 46 months	Mortality	646
Stephanie von Klot	2005	Finland(Europe)	PM_{10}	1992-2001	≥35	22 006	NA	1995-1999	Hospital	2321
Anke Huss	2010	Switzerland(Europe)	PM_{10}	1990-2005	>30	12122	NA	2000-2005	Mortality	8,192

Table 2 Results of subgroup analyses about ambient air pollution and the risk of myocardial infarction

group	**$PM_{2.5}$**					**PM_{10}**				
	Number of studies	***RR***	**95%*CI***	***P* for heterogeneity**	**I-square (%)**	**Number of studies**	***RR***	**95%*CI***	***P* for heterogeneity**	**I-square (%)**
North ica	10	1.13	1.06-1.19	0.105	37.9	5	1.07	1.01-1.11	0.473	0
pe	5	1.09	0.98-1.23	0.105	47.7	6	1.03	0.99-1.06	0.015	64.7
	2	1.38	1.21-1.57	0.466	—	—	—	—	—	—
cation										
e	4	1.12	0.87-1.44	0.016	71.1	4	1.06	0.99-1.13	0.187	37.5
2010	13	1.14	1.07-1.21	0.024	48.8	7	1.03	0.99-1.07	0.048	52.8

Figures

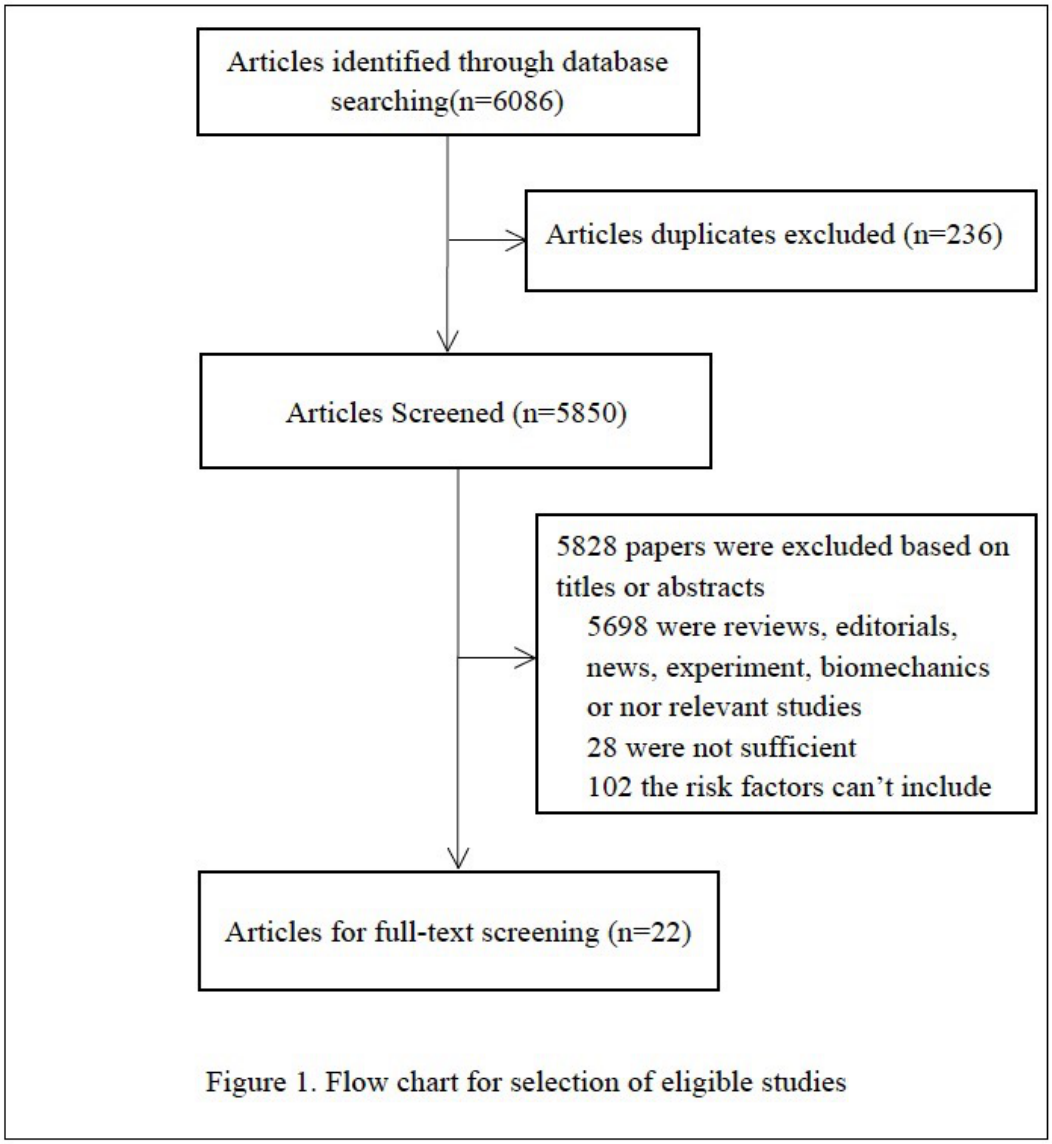

Figure 1

Flow diagram of identification of relevant observational studies of ambient air pollution in relation to the risk of MI.

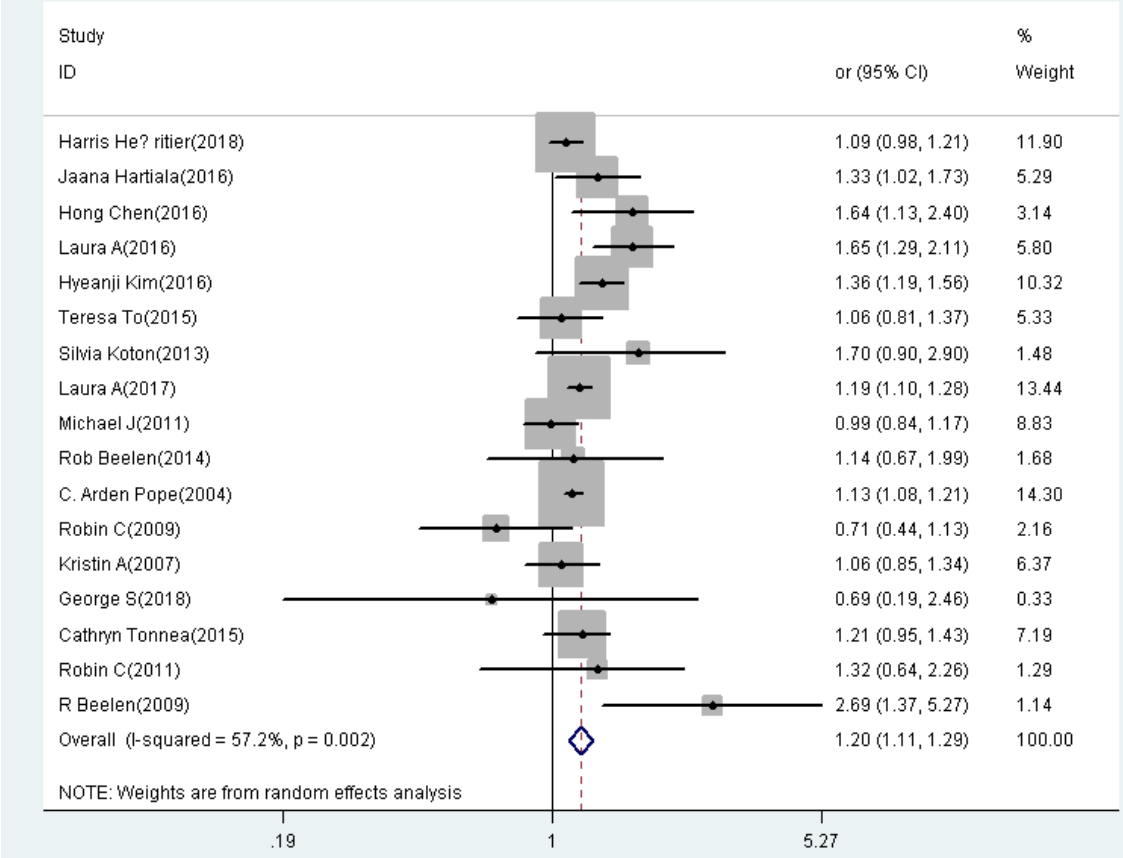

Figure 2

Association between exposure to PM2.5 and the risk of MI in a meta-analysis of cohort studies.

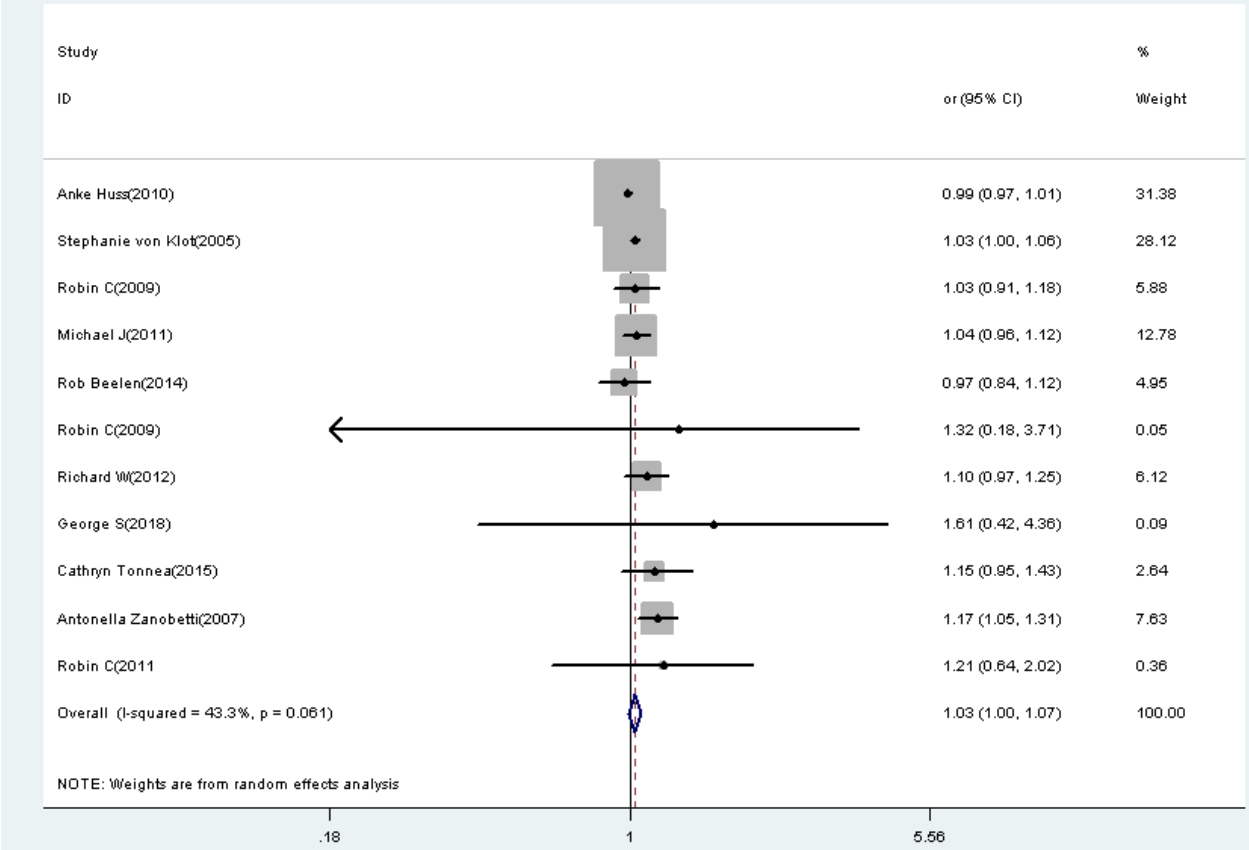

Figure 3

Association between exposure to PM10 and the risk of MI in a meta-analysis of cohort studies.

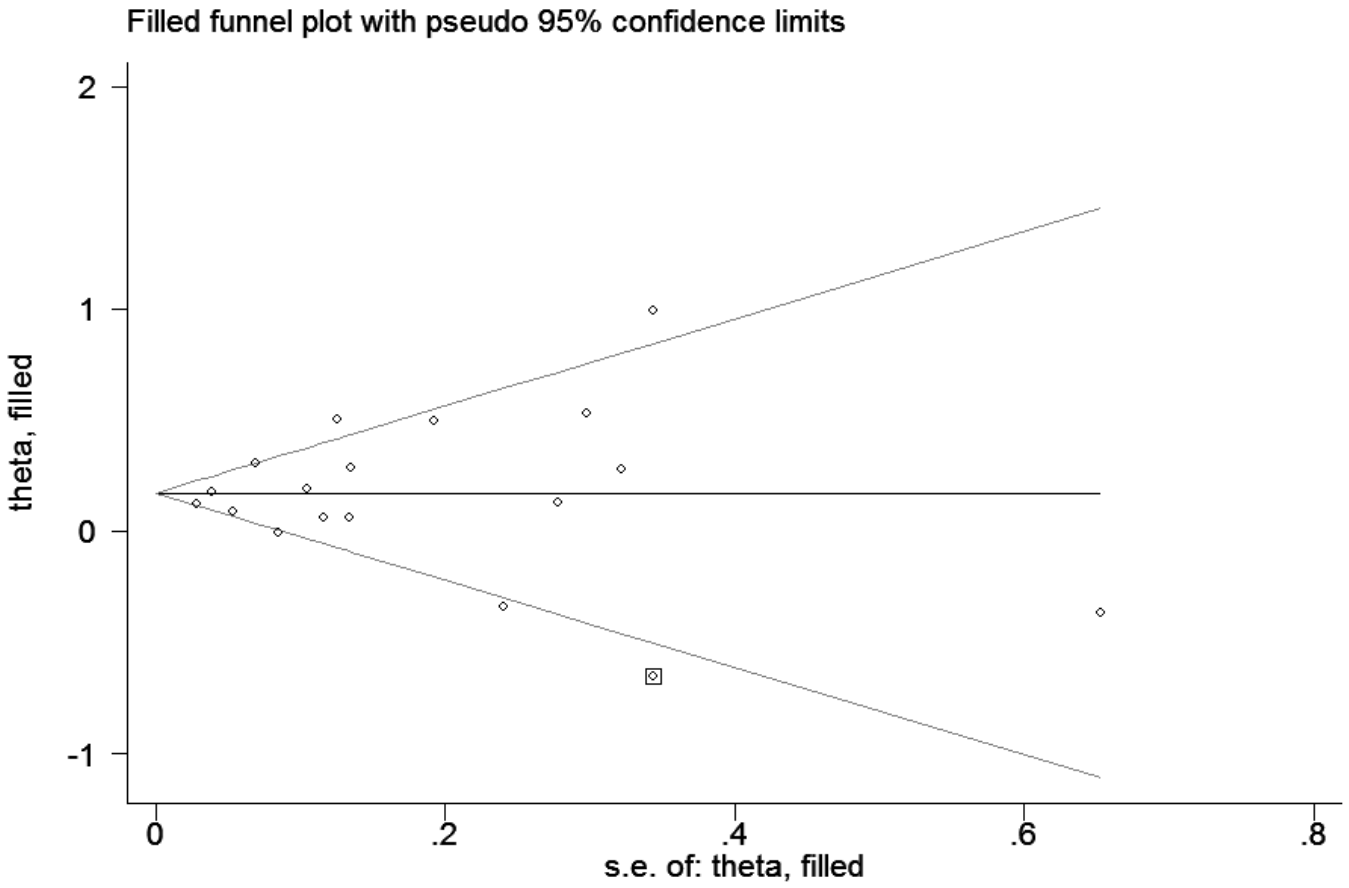

Figure 4

Funnel plot with 95% confidence limits of PM2.5 and the risk of MI.

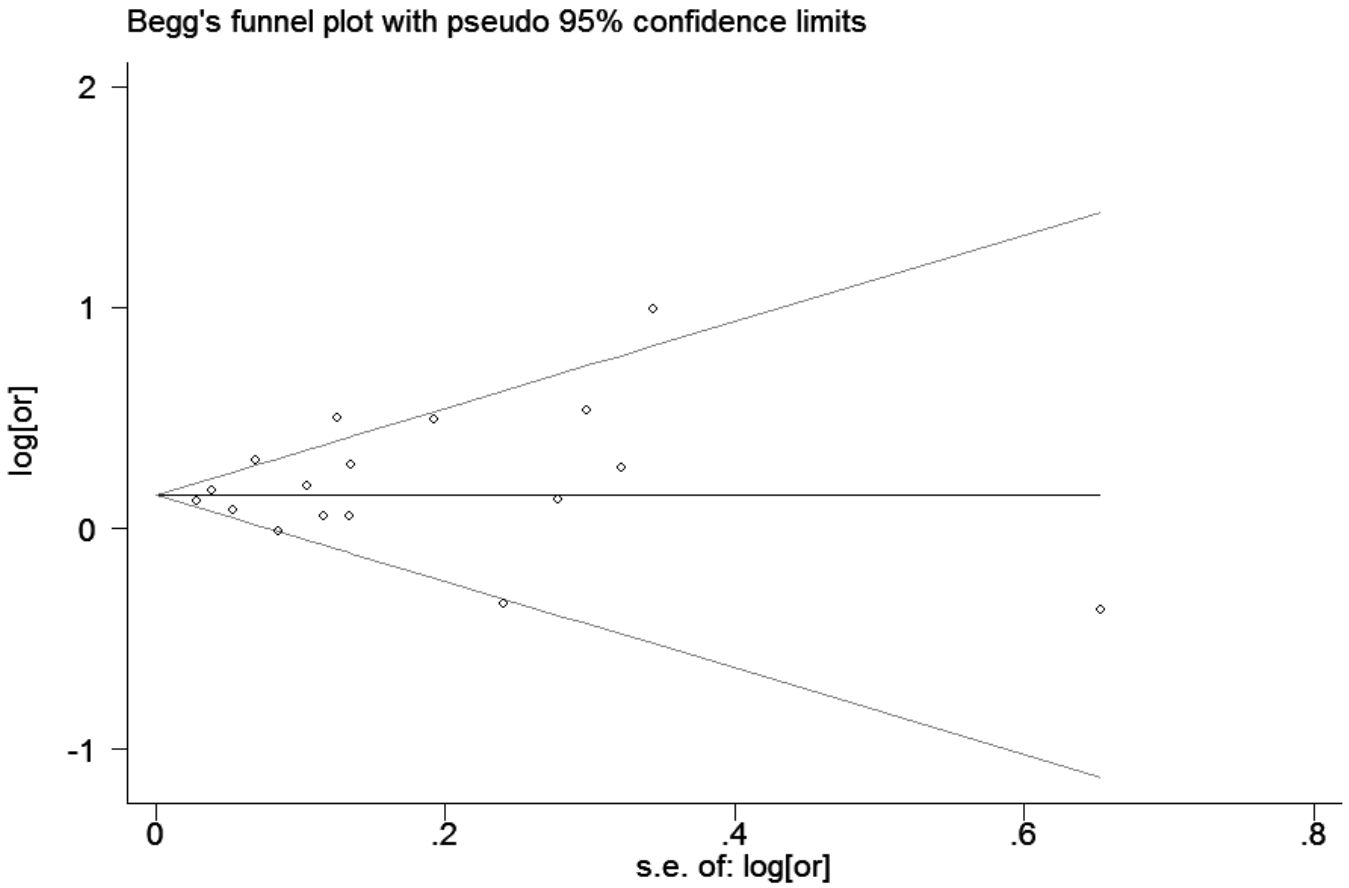

Figure 5

Filled funnel plot of RR from studies that investigated the association between PM2.5 and the risk of MI.

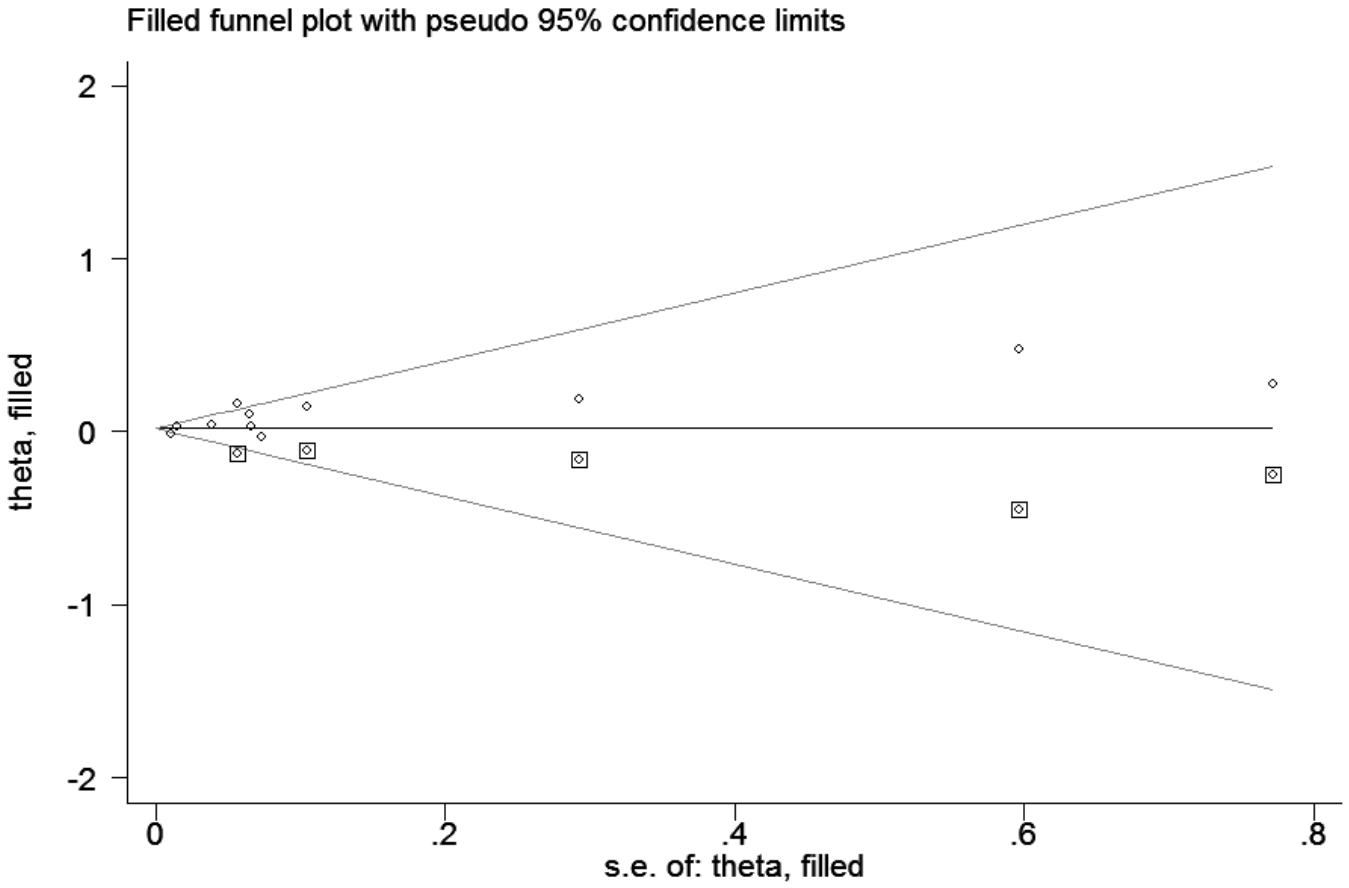

Figure 6

Funnel plot with 95% confidence limits of PM10 and the risk of MI.

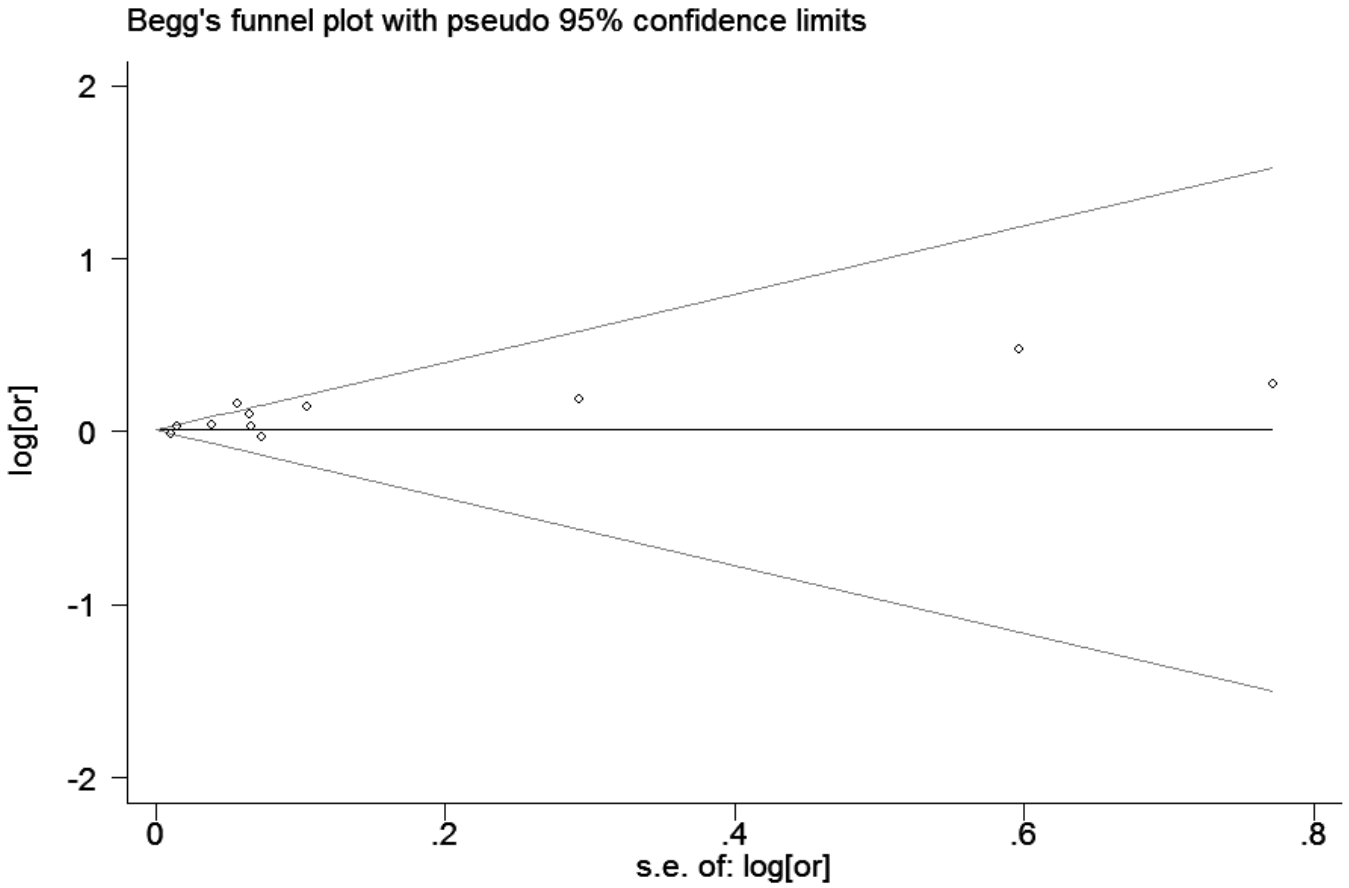

Figure 7

Filled funnel plot of RR from studies that investigated the association between PM10 and the risk of MI.