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Attributed Medical Cost of Annual Multiple Sclerosis Relapses in Iran Related to Exposure of Ambient Air Particulate Matter

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ABSTRACT

Multiple Sclerosis (MS) imposes a substantial burden on the healthcare system and society. In addition, air pollution has a high economic burden in terms of health impacts. There is growing evidence that associates the MS onset and relapse with environmental factors, including ambient air particulate matters (PM). The objective of this study was to estimate the additional direct medical costs of MS relapses related to PM exposure within a one-year timeframe in Iran. The cost of relapse management was estimated from the healthcare system perspective. Using the relevant relapse probabilities associated with PM reduction, the incremental total cost was estimated and reported as a saving cost from PM reduction. The calculated direct medical cost for managing mild relapses was 9.90 (US dollars) USD per episode, and the average costs for moderate and severe relapses were 115.17 and 515.48 USD per episode, respectively. In Iran, relapse management in relapsing-remitting MS (RRMS) patients was estimated to cost 5,365,896 USD per year. A reduction of PM per 10 μg/m³ could result in an average cost savings of 13.84 USD per RRMS patient in a given year and an average annual cost savings of 1,041,279 USD for all patients with RRMS, equal to a reduction of 19.40% of MS relapse management costs. These findings will assist policymakers in developing well-informed decisions to improve public health outcomes, including the quality of life of MS patients, besides decreasing healthcare costs.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS) that involves activation of the immune system, leading to progressive impairment and disability in affected patients (Lublin et al., 2020; Oh et al., 2018; Tremlett et al., 2010). MS is the predominant cause of enduring impairment in young adults among CNS disorders (Stenager, 2019). In Iran, the estimated prevalence of MS is 100 cases per 100,000 individuals (Mirmosayyeb et al., 2022). Due to its high prevalence and early onset during economically active years, MS imposes a

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substantial financial burden (Fattahi et al., 2021). The weight of this burden is intensified by the prolonged survival time and the significant influence of MS on the quality of life of patients and their families (Orlewska, 2006; Torabipour et al., 2014). Approximately 53% of individuals with MS discontinue employment, while 37% experience a decline in their quality of life (Casado et al., 2006). Cost-of-illness studies have attributed a considerable financial burden of MS to patients, healthcare systems, and society. Furthermore, an increase in the severity of the disease is associated with a higher level of disability, as determined by the increased Expanded Disability Status Scale (EDSS). The higher severity results in a significant rise in total disease costs (Orlewska, 2006; Torabipour et al., 2014). MS encompasses different subtypes, with relapsing-remitting MS (RRMS) being the most common type, representing 85% of all cases. Relapse is defined as an episode of acute neurological impairment that has a major impact on the patients' quality of life and results in high healthcare costs (Repovic & Lublin, 2011). The main objective of MS treatment is to reduce the frequency and intensity of relapses. Relapses may result in long-term, irreversible disability, and their management focuses on addressing functional impairment along with neurological deficits (Repovic & Lublin, 2011).

There is growing evidence that associates the MS onset and relapse with environmental factors, including ambient air particulate matters (PM). Several epidemiological studies have demonstrated a link between exposure to PM and an increased risk of MS, coupled with higher rates of active inflammatory MS lesions (Angelici et al., 2016; Bergamaschi et al., 2018; Jeanjean et al., 2018; Mehrpour et al., 2013; Oikonen et al., 2003; Roux et al., 2017). Furthermore, air pollution has been observed to be correlated with higher scores of EDSS, reduced rates of MS remission, increased severity of MS, and impaired recovery following the initial MS event (Ashtari et al., 2018). PM has the ability to penetrate the respiratory system and enter the bloodstream, potentially stimulating inflammatory reactions that exacerbate MS symptoms (Lotfi et al., 2022; Tang et al., 2021).

Although several studies have evaluated the correlation between PM exposure and the progress of MS, the economic implications of PM-induced relapses in MS patients, especially in Iran, are inadequately assessed. The rising occurrence of MS in Iran, as evidenced by conducted studies (Azami et al., 2019; Fattahi et al., 2021; Mirmosayyeb et al., 2022), along with significant levels of air pollution (Taghizadeh et al., 2023), necessitates an investigation into the financial impact of yearly MS relapses caused by PM exposure. The objective of this study was to fill this gap by measuring the financial burden of MS relapses caused by ambient air PM exposure in MS patients in Iran.

MATERIALS AND METHODS

This study estimated the additional direct medical costs of MS relapses related to PM exposure within a one-year time horizon. Relapse was defined as an episode of acute neurological impairment. The considered population consisted of Iranian RRMS patients who had been diagnosed with the disease for one year or more, and the healthcare system was the study perspective. The cost of medical management for relapses was calculated precisely, and the specific cost share attributable to PM exposure was determined. The total financial impact for a given year was calculated using the prevalence approach and the estimated cost per relapse episode, as MS is a chronic disease.

The following model (Figure 1) was utilized to estimate the costs related to MS relapse under two different scenarios: one with no change in PM levels and the other with the reduction of PM.

In both scenarios, patients could either experience a relapse or remain stable without relapse. Based on clinicians' opinions, three levels of relapse severity (mild, moderate, and severe) were considered, reflecting the varying management strategies and associated medical costs.

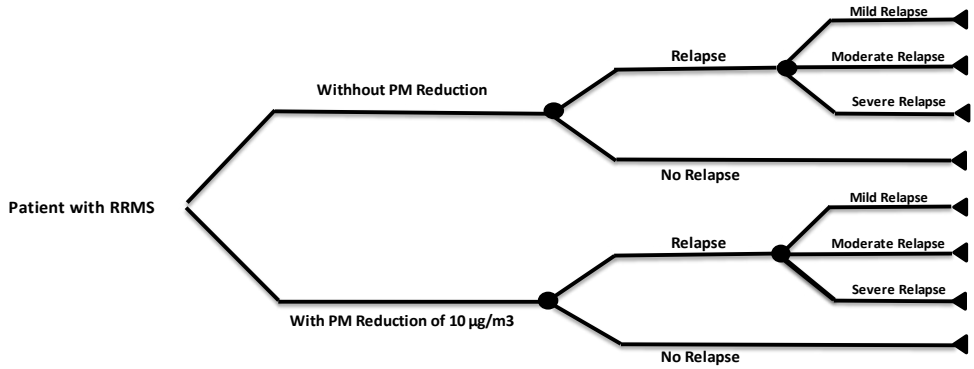

Fig. 1. Model Overview for Different Cost Scenarios
PM: particulate matter; RRMS: relapsing-remitting Multiple Sclerosis.

Table 1. Yearly Probabilities of the Model

Probability (Yearly)	Mean	Lower Limit	Upper Limit	Source
Mild Relapse	0.2	0.16	0.24	(Orme et al., 2007), Expert opinion
Moderate Relapse	0.6	0.48	0.72	(Orme et al., 2007), Expert opinion
Severe Relapse	0.2	0.16	0.24	(Huygens & Versteegh, 2021; Nicholas et al., 2021; Orme et al., 2007), Expert opinion
Annual Relapse rate	0.33	0.26	0.39	(Kalincik, 2015), (Confavreux & Compston, 2006), Expert opinion
Relapse Rate Attributed to 10 µg/m^3 PM	0.41	0.31	0.53	(Lotfi et al., 2022)

PM, particulate matter

The yearly probabilities derived from the literature review and expert opinions in Table 1 were applied in each model branch to calculate the costs for each type of patient relapse. The incremental total cost was then calculated and reported as either a saving or an increase in cost per 10 µg/m³ PM reduction.

In this study, we employed a top-down approach for the data-gathering process. To provide a detailed picture of the direct medical costs associated with relapse management, an itemized list of all services was employed to estimate the cost of managing each episode of relapse. A resource use profile for each severity of relapse was developed by identifying the healthcare services relevant to relapse and quantifying the frequency of use for each service in the management of one episode of relapse. The relapse characteristics, associated resource use, duration, and management details were based on similar literature, relevant international and national practical guidelines, and expert opinion. According to the heterogeneity of the relapse intensity, the associated costs were calculated for mild, moderate (inpatient and outpatient settings), and severe relapses separately. Direct medical costs included the initial medical assessments and follow-up visits, investigational and monitoring tests, medication, and hospital admission costs. Consequently, a professional MS neurologist reviewed all cost components.

The unit costs for drug acquisition were obtained from the Iranian Food and Drug Association's (IFDA) official website in June 2024. Iran's official tariff list and national tariff book were used for administration and monitoring costs, with a ratio of 20–80% and 35–65% for the private and public sectors in the inpatient and outpatient settings, respectively. The US Dollar (USD) exchange rate of 1 USD equaling 430,000 Iranian Rials (IRRs) was used for all cost calculations. Because the prices and tariffs were calculated for a single current year, an adjustment was not required. The final relapse management cost was calculated for each episode per patient as well as the total cost over one year for the entire patient population.

All information on the prevalence of MS in Iran, the RRMS population, the annual relapse

rate, and the distribution of each severity of relapse in the patient population was extracted from the literature review in addition to the confirmation of a professional MS neurologist (Azami et al., 2019; Hawton & Green, 2016; Huygens & Versteegh, 2021; Kalincik, 2015; Nicholas et al., 2021; Orme et al., 2007; Vollmer, 2007). The reported results of the previous meta-analysis were also used to find the risk ratio (RR) of MS relapses linked to PM exposure (Lotfi et al., 2022). In our estimations, we assumed that there is no threshold below which PM is harmless and that no variations exist in the exposure level and susceptibility to PM effects among the patient population of this study. Table 1 shows the applied probabilities in the model.

To evaluate the impact of individual and combined uncertain variables on cost saving as an outcome, deterministic and probabilistic sensitivity analyses (D/PSA) were performed. The one-way DSA was performed using a 95% confidence interval (CI), an assumption's range extracted from the literature, or 20% in cases where statistical measures of variance were not available. The factors incorporated in DSA encompassed the medical costs of management of mild, moderate, and severe relapse episodes; probabilities of relapse with mild, moderate, and severe intensity; the annual probability of relapse in RRMS patients; and the probability of relapse attributed to 10 $\mu g/m^3$ PM. A tornado diagram was created to illustrate the impact of different variables.

In order to quantify the level of confidence in the calculated cost saving, a probabilistic sensitivity analysis (PSA) was performed, and the effect of the combined variable uncertainties was evaluated. The medical costs and probabilities were assumed to have gamma and beta distributions, respectively. The process was iterated one thousand times using a tornado diagram Monte-Carlo simulation. Repeating calculations in Monte-Carlo analysis aims to determine the percentage of cases in which reduced PM in one unit results in cost savings.

RESULTS AND DISCUSSION

According to objective clinical evidence, an episode of relapse was defined as neurological symptoms persisting for a minimum of 24 hours and not being associated with fever or infection. The cost components involved the expenses of initial medical assessments and follow-up visits, investigational and monitoring tests (blood tests, infection screening, and imaging tests), medications (symptom-related treatment and corticosteroids), hospital admission, and rehabilitation services (physiotherapy). We calculated direct medical costs for relapse episodes according to the relevant defined management settings for each severity. A mild relapse was identified by minimal disability, necessitating only symptom-related management or a short course of corticosteroid. A moderate relapse required medical intervention, such as short-term intravenous (IV) methylprednisolone in an outpatient or hospital setting. Severe relapses were associated with more severe disability, necessitating hospitalization, IV administration of methylprednisolone, and rehabilitation services. Plasmapheresis was also contemplated as a treatment option for individuals who had substantial remaining impairments that did not improve with IV methylprednisolone (Vollmer, 2007; Yamout et al., 2024). Furthermore, the cost estimates for each management level encompassed the daily expenses of drugs prescribed for symptom management during a relapse episode, including pantoprazole, gabapentin, and oxybutynin. Table 2 displays management services categorized by relapse severity.

The calculated direct medical cost for managing mild relapses was 9.90 USD per episode, and the costs for moderate and severe relapses were 115.17 and 515.48 USD per episode, respectively (Table 3). The severity of an MS relapse influenced the duration and frequency of each cost component in its management. Mild relapses typically involve short-term and infrequent interventions, whereas severe relapses demand extended and more intensive care, leading to significantly higher overall costs. For a mild relapse episode, the majority of the expenses were attributed to drug costs, comprising approximately 38% of the total cost. Monitoring and other

Table 2. Cost (Direct Medical) Components of Relapse Management According to Severity

Relapse Severity	Medical and Follow-up Assessments		Medication Costs and Administration		Laboratory Assessment and Rehabilitation Services	
Mild	Physician visit		Symptom-related medications		CBC, UA	
Medium	Physician visit, Hospital admission	Follow-up Office Visit	IV Corticosteroid	Symptom-related medications	CBC, UA, MRI	
Severe	Physician visit, Hospital admission	Follow-up Office Visit	IV Corticosteroid, Plasmapheresis	Symptom-related medications	CBC, (K^+, Na^+, FBS), UA, MRI	Physiotherapy

CBC, complete blood count; FBS, fasting blood sugar; IV, intravenous; MRI, magnetic resonance imaging; UA, urine analysis.

Table 3. Direct Medical Costs for Managing a Relapse (per episode, USD) and Summary of Cost Category Involvement

Per Episode	Mild	Moderate-Outpatient	Moderate-Hospitalized	Severe	Severe-Refractory
Total Cost (USD)	9.90	47.39	182.94	285.87	1433.89
% Of Total					
Drug Costs	38.10	33.26	8.62	8.84	48.59
Monitoring Costs	38.76	55.83	15.02	9.61	1.92
Other Medical Costs	23.14	10.91	2.70	2.88	14.23
Hospitalization Costs	-	-	73.66	78.66	31.39
Rehabilitation Costs	-	-	-	-	3.87

USD, US Dollar.

medical costs also contribute significantly, reflecting the need for consistent patient evaluation and supportive care. In moderate cases, relapses were managed on an outpatient basis andthe monitoring costs constitute more than half of the total expenses. This suggests that extensive diagnostic and follow-up procedures are crucial to managing moderate relapses effectively. According to expert opinion and practical experience data, half of patients with moderate relapse severity require hospitalization. Hospitalization significantly escalated the overall cost, accounting for approximately 73.66% of the total cost for these patients. This indicates the substantial financial impact of inpatient care on the healthcare system. Severe relapses require corticosteroid therapy and result in high costs, mainly due to extended hospitalization. While the cost of medications and monitoring was significant, it was overshadowed by the extensive inpatient care required, which was estimated to account for 78.66% of overall costs. Based on the local expert opinion, approximately 20% of patients do not recover with corticosteroid pulse therapy. The total cost further escalated due to the addition of hospital stays, rehabilitation services, and plasmapheresis costs. Table 3 provides a summary of costs by major cost categories used in this analysis.

The applied probabilities from Table 1 and the costs for each scenario in the model were used to calculate total and incremental costs, as shown in Table 4. A reduction of PM per 10 μg/m³ could result in an average cost savings of 13.84 USD per RRMS patient in a given year.

The estimated annual cost of managing relapses in Iran, taking into account the country's population and RRMS prevalence, is 5,365,896 USD. The reduction in PM of 10 μg/m³ could lead to an average annual cost savings of 1,041,279 USD for all patients with RRMS, equal to a reduction of 19.40% of MS relapse management costs (Table 5).

The DSA results, depicted in Figure 2, showed that the overall cost saving model is generally robust. The analysis showed that cost saving was robust across most scenarios, with slight variation in cost saving. However, a significant sensitivity is noted in the probabilities of relapse attributed to PM.

Table 4. Total and Incremental Annual Relapse Costs (Per Patient, USD) in the Base Case and Particulate Matter Reduction Scenarios

Scenarios	Probabilities	Cost (USD)	Mean Cost (USD)	Delta Cost (USD)
RRMS in condition without PM reduction, Mild relapse	0.082	9.90	0.81	(13.84)
RRMS in condition without PM reduction, Moderate relapse	0.246	115.17	28.29	
RRMS in condition without PM reduction, Severe relapse	0.082	515.48	42.21	
RRMS in condition without PM reduction, No relapse	0.591	0	0	
Total	**1.0**		**71.32**	
RRMS in condition with PM reduction of 10 μg/m^3, Mild relapse	0.066	9.90	0.65	
RRMS in condition with PM reduction of 10 μg/m^3, Moderate relapse	0.198	115.17	22.80	
RRMS in condition with PM reduction of 10 μg/m^3, Severe relapse	0.066	515.48	34.02	
RRMS in condition with PM reduction of 10 μg/m^3, No relapse	0.67	0	0	
Total	**1.0**		**57.48**	

PM, particulate matter; RRMS, relapsing-remitting Multiple Sclerosis; USD, US Dollar.

Table 5. Annual Budget Impact of Particulate Matter Reduction of 10 μg/m³

Iran Population (2024)	**86,000,000**
MS Population	88,514
RRMS Patients	75,237
Incremental Cost Attributed to PM per 10 μg/m^3 (USD)	13.84
Annual Budget Impact (USD)	1,041,279

MS, Multiple Sclerosis; PM, particulate matter; RRMS, relapsing-remitting Multiple Sclerosis; USD, US Dollar.

The PSA results, depicted in Figure 3, indicated that when the model inputs are adjusted based on a beta distribution for probabilities and a gamma distribution for costs, cost savings are achieved in 54% of the cases.

The current study's findings highlight the significant economic consequences of PM exposure for MS patients. The annual number of relapse episodes was estimated to be between 22,571 and 37,619, with a substantial financial impact on the healthcare system. The likelihood of MS relapses will increase with PM exposure, resulting in a 19.40% increase in the overall annual cost of medical management. This puts more financial strain on the healthcare system, in addition to increasing the health burden on patients. The total additional annual cost of MS relapses caused by PM exposure in Iran was estimated to be 1,041,279 USD. Given the significant annual additional cost associated with PM-induced relapses, environmental health policies aimed at reducing air pollution levels are imperative. Although it should be noted that the estimated costs in this study were specific to Iran, which, compared to developed and high-income countries, has lower overall healthcare expenditures. This variation is due to higher prices for healthcare services in high-income countries (Anderson et al., 2003; Mosadeghrad et al., 2022; Papanicolas et al., 2018). Therefore, the adjustment should be considered before extrapolation of these findings to other countries in policy decisions (Lorenzoni & Dougherty, 2022).

Our results indicated that relapse severity is a significant factor in determining the costs associated with relapse management. However, both relapses and disease progression are associated with considerable expenses (Torabipour et al., 2014). The results of this study have broader implications than just direct medical costs. In addition to the immediate costs, each relapse episode leaves residual disabilities, requiring continuous treatment and significantly reducing patients' productivity and quality of life. Although a complete recovery can occur, typically early in the disease process, the residual deficit may persist and contribute to the stepwise progression of disability across the course of MS (Goodin et al., 2016; Repovic & Lublin, 2011). The progression of disability over time is the most important issue in MS. There

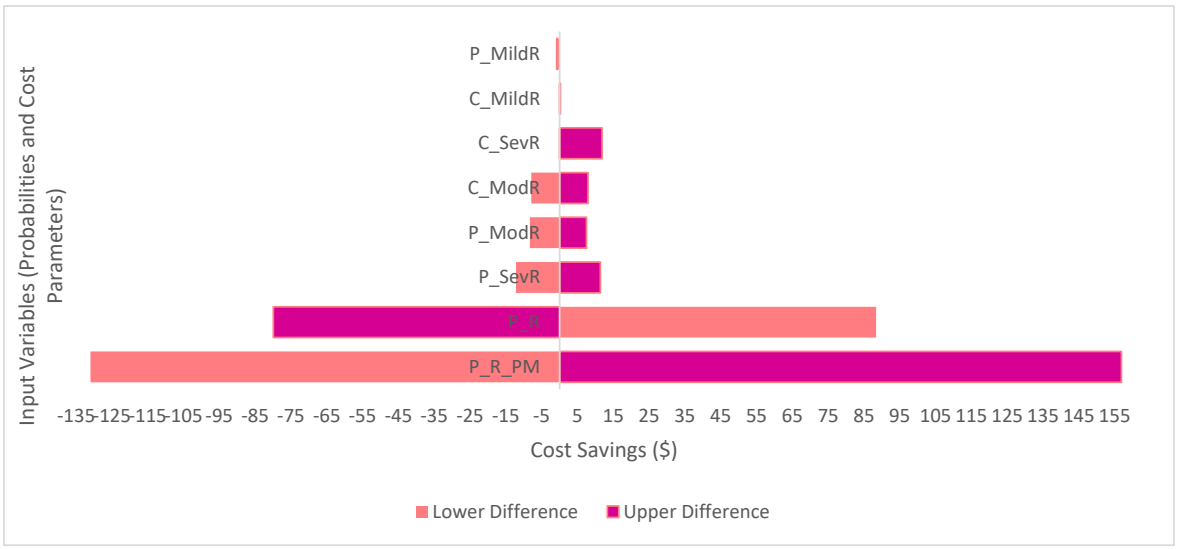

Fig. 2. Tornado Diagram for deterministic sensitivity analyses (DSA) results

The DSA results demonstrated that the model is generally robust; as shown by the diagram, the cost saving results remained consistent in most scenarios by changing the key input variables. It also showed that the model's output was significantly affected by the probabilities of relapse attributable to a PM. This implies that variations in the probability of a relapse can have a significant impact on the total cost-effectiveness. DSA: deterministic sensitivity analyses; PM: particulate matter.

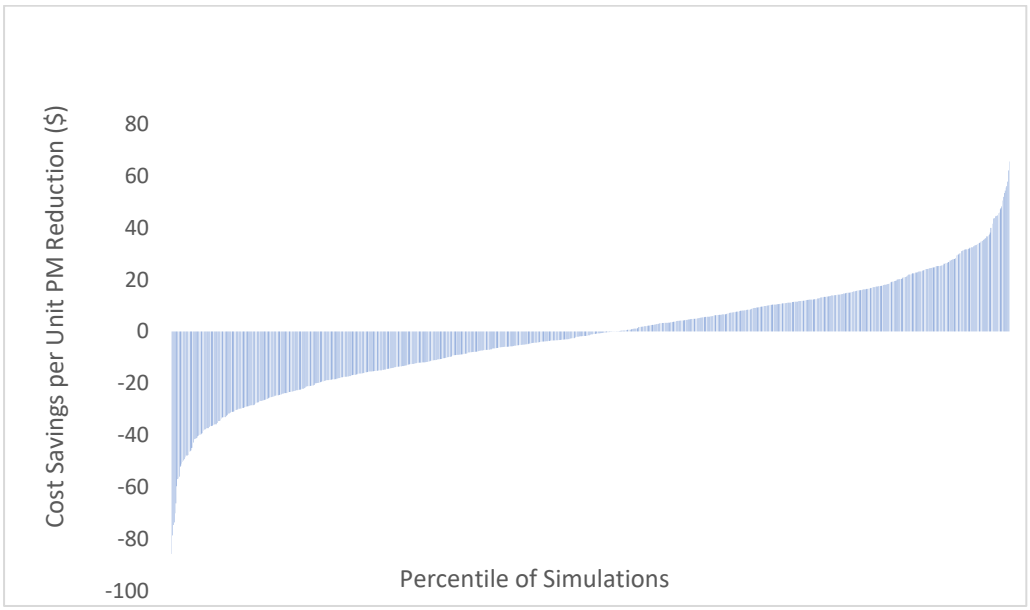

Fig. 3. Probabilistic sensitivity analyses (PSA) outcomes

The PSA examined the uncertainty in model inputs by adjusting probabilities and costs based on statistical distributions, using the beta distribution for probabilities and the gamma distribution for costs. The results indicated that cost savings were achieved in 54% of the cases. This indicated that although there is a certain level of uncertainty, the model still shows a positive outcome in over half of the simulated situations. PSA: probabilistic sensitivity analyses.

is a direct relationship between the number of relapses and the rate at which MS progresses. The degree of neurological impairment caused by MS is determined by the intensity of signs and symptoms, the frequency of relapses, the rate of deterioration, and the remaining disability (Kister et al., 2013). Therefore, minimizing the risk of relapses has been the mainstay of current MS management (Repovic & Lublin, 2011). Identifying potential factors that could increase the frequency of MS relapses is essential due to the great financial consequences. The higher

exposure to PM could result in more frequent and severe relapses, accelerating the overall progress of MS. Accordingly, it is critical to prioritize reducing PM emissions as a matter of public health.

This study's theoretical addition is its economic assessment of the direct costs associated with PM-induced MS relapses, expanding upon previous studies regarding air pollution and chronic diseases. There has been a growing body of research on the association between environmental pollutants, specifically PM, and health outcomes. These studies have investigated the impact of PM on respiratory and cardiovascular disorders, and there is also a rising emphasis on its impacts on neurological conditions such as MS (Alhussaini et al., 2023; Angelici et al., 2016; Ashtari et al., 2018; Bergamaschi et al., 2018; Heydarpour et al., 2014; Jeanjean et al., 2018; Mehrpour et al., 2013; Oikonen et al., 2003; Roux et al., 2017). While our study was the first to estimate the cost attributed to PM-induced relapses in MS patients, there are several further studies on various chronic diseases (Cohen et al., 2017). Brandt et al. highlighted the economic losses associated with pediatric asthma caused by traffic air pollution. In 2012, the annual asthma burden caused by air pollution was estimated to be 18 million USD (Brandt et al., 2012). Moreover, a study by El-Fadel and Massoud (2000) evaluated the economic benefits of decreasing PM in Lebanon. This study forecasted the magnitude and economic value of health advantages resulting from reduced levels of PM, with a specific emphasis on both physical and monetary health effects (El-Fadel & Massoud, 2000). Similarly, Karimzadegan et al. (2008) quantified the preventable deaths associated with ambient air pollution in Tehran and assessed the economic consequences of these health effects (Karimzadegan et al., 2008). Safari et al. conducted an analysis on the health impacts and economic value of reducing PM2.5 air pollution in Qom. It estimated the number of deaths caused by stroke, chronic obstructive pulmonary disease (COPD), lung cancer, and ischemic heart disease, and also estimated related costs. The total associated cost was reported as 855.91 and 451.40 million USD based on two different proposed scenarios (Safari et al., 2022). These studies further emphasize the potential cost-effectiveness of air pollution mitigation solutions.

Decreasing PM levels reduces the long-term financial burden on healthcare systems. There is extensive evidence that reducing PM has positive effects on other health issues, such as ischemic heart disease, stroke, (COPD), lung cancer, asthma, and lower respiratory infections. Research suggests that a significant reduction in the number of deaths in the country can be accomplished by ensuring high-quality air (Karimzadegan et al., 2008; Naddafi et al., 2019). By reviewing the cost estimation programs for air pollution reduction, it's evident that these solutions come with substantial prices. On the other hand, taking into account the healthcare expenditures associated with the mortality and morbidity burden of all these different diseases associated with air pollution, these solutions may be considered economically feasible. The cost value we reported for MS relapses attributed to PM can be included and utilized in regional PM reduction programs, along with the financial measured effect for other diseases. Therefore, reducing PM emissions could have a major beneficial impact on health, making the implementation of such measures not only efficient but also cost-benefit. Also, in the context of policy-making, it is important to determine the correlation between PM reduction and the decrease in the frequency of relapses in order to quantify the extent to which PM reduction can avert relapse management costs. Thus, conducting a cost-benefit analysis is recommended to evaluate these points in the future studies (Prüss-Ustün & Corvalán, 2007).

Cost-of-illness studies have demonstrated a substantial economic impact of MS on healthcare systems and society (O'Connell et al., 2014; Orlewska, 2006) and confirmed an association between the costs of the illness and the severity of disease in patients (Nicholas et al., 2021). Torabipour et al. reported that 62% of MS costs may be attributed to patients with EDSS levels of 6-7 and greater than 7 (Torabipour et al., 2014). Moreover, the estimated average direct medical cost of managing a relapse episode per person was 12,870, 1,847, and 243 USD, for

severe, moderate, and mild relapses respectively, in the United States in 2002 (O'Brien et al., 2003). Our study also estimated comparable outcomes for managing relapse costs, as we calculated a noticeable higher direct medical cost for managing a severe episode of relapse per patient (515.48 USD) compared to the mild (9.90 USD) and moderate relapses (115.17 USD).

Although this study reports valuable results, it is important to acknowledge its limitations when interpreting the results. We calculated the direct medical costs associated with relapse management. However, we recommend considering all direct and indirect costs, covering productivity loss, informal care, and intangible costs associated with relapses and increased disease severity in future research. Furthermore, the total cost was computed for a single year, and given the chronic nature of the disease, it can be extrapolated over multiple years. In addition, we assumed that there were no variations in the exposure level or susceptibility to PM effects among the patient population of this study, which does not accurately reflect the real-world condition. Air pollution is a mixed combination of gases and particles with different PM chemical compositions and concentrations based on source, seasonal, and geographical varieties. Albeit, a significant percentage of the population is subjected to the related health risks, and provinces in Iran with greater MS incidence and prevalence have been reported to have a higher level of air pollution (Heydarpour et al., 2014; Mehrpour et al., 2013).

The data from Lotfi et al. study was used in our estimations as the PM effect on MS relapses (Lotfi et al., 2022). The subgroup analysis in this meta-analysis reported an RR without statistical significance (CI: 0.952-1.621). Nevertheless, the result was considered clinically important, as the RR of 1.242 suggests a 24.2% higher risk of MS relapse associated with PM exposure, which has significant implications for real-world practice for MS patients. Therefore, unless the CI indicated some uncertainty, the point estimates highlighted potential meaningful effects. Furthermore, a similar observed trend in a meta-analysis indicates the clinical relevance of this finding (Tang et al., 2021). Rather than relying exclusively on statistical significance thresholds, the magnitude of the effect and the context of individual patients were noted in this study (Amrhein et al., 2019; Kent et al., 2010; McShane et al., 2019). Moreover, statistically significant risks have been reported for various diseases, and taking all risks into account, it is more likely that a reduction in air pollution will result in cost- savings in healthcare expenditures. In the same way, given the high prevalence of MS, the probability of cost- savings due to reducing air pollution will increase. In order to address the limitation of uncertainty in the risk ratio, providing more conclusive evidence will be required in future epidemiological analyses. Although in general, accurate measurement of attributable disease burden to environmental factors, such as ambient air PM, is challenging due to limited established, precise evidence given complex interactions, a variety of exposure levels, and other confounding factors (Prüss-Ustün et al., 2008).

CONCLUSION

MS imposes a significant socioeconomic burden with a major burden on patients, healthcare systems, and society (Orlewska, 2006; Torabipour et al., 2014). Multiple lines of evidence suggest an association between ambient air PM and MS which contribute to a significant disease burden and economic loss both globally and in Iran (Cohen et al., 2017; Naddafi et al., 2019). Any policy that would decrease air pollution should be evaluated by weighing the financial advantages of the program regarding its costs (Karimzadegan et al., 2008). The purpose of this study was to quantify the additional cost of relapse management attributed to PM exposure in MS patients in Iran. This study provided an overview of the healthcare expenditure on MS relapses and the specific cost elements of medical management according to the severity of the relapse. Furthermore, the potential financial benefit from decreasing PM was calculated. The results showed that MS relapses have a significant financial burden, as well as the extra

expenditure associated with PM exposure. These findings will assist policymakers in developing well-informed decisions to improve public health outcomes, including the quality of life of MS patients, besides decreasing healthcare costs. The findings suggest that environmental policy measures designed to decrease PM exposure may result in significant healthcare expense reductions, particularly in countries with high air pollution levels such as Iran.

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CONFLICT OF INTEREST

The authors declare that there is not any conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/ or falsification, double publication and/or submission, and redundancy has been completely observed by the authors.

LIFE SCIENCE REPORTING

No life science threat was practiced in this research.

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