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The Relationship between Ambient Fine Particulate Matter (PM2.5) Pollution and Depression: An Analysis of Data from 185 Countries

Ravi Philip Rajkumar[1,*]

[1] Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605 006, India
* Correspondence: jd0422@jipmer.ac.in; Tel.: +91 413 229 6280

Abstract: Several studies have identified a relationship between air pollution and depression, particularly in relation to fine particulate matter (PM2.5) exposure. However, the strength of this association appears to be moderated by variables such as age, gender, genetic vulnerability, physical activity and climatic conditions, and has not been assessed at a cross-national level to date. The current study examines the association between the prevalence of depression in each country, based on the most recent Global Burden of Disease Study data, and the average national level of PM2.5 based on the World Health Organization's database. The observed associations were adjusted for age, gender, level of physical activity, income, education, population density, climate, and type of depression. It was observed that there was a modest but significant positive correlation between PM2.5 level and the prevalence of depression even after adjusting for the above confounders. This association was slightly stronger in men than in women, and applied chiefly to major depressive episodes. These findings are of significant public health importance in terms of preventive strategies aimed at reducing the population-level burden of depression.

Keywords: air pollution; PM2.5; depression; inflammation; ecological analysis; climate; gender

1. Introduction

Depression is the commonest mental disorder worldwide. Based on data from the Global Burden of Disease Study (2019) it is estimated that over 279 million people suffer from depression, and depression is the 13th leading cause of disease burden and disability at a global level [1]. The pathophysiology of depression is complex, and involves an interaction between genetic risk, mediated by multiple genes of small effect, and a wide range of environmental factors [2, 3]. Much of the research on gene-environment interactions in depression has been focused on the harmful effects of psychological or social stress [4, 5]. However, there is a rapidly expanding evidence base suggesting various aspects of an individual's living environment, such as access to green areas and exposure to various forms of pollution, are also significantly associated with depression [6]. Among these environmental factors, air pollution has been associated with depression most frequently and consistently. Air pollution, particularly exposure to fine particulate matter ($PM_{2.5}$) and nitrogen oxides (NO_x), has been associated with depression in youth [7], adults in the general population [8, 9], women in the post-partum period [10, 11] and the elderly [12]. Exposure to these forms of air pollution has also been associated with worse outcomes in patients with depression, such as suicide [13] and increased use of mental health services [14].

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There are several pathophysiological processes that may account for the increased rates of depression observed after exposure to various air pollutants. Exposure to $PM_{2.5}$ has been associated with increased expression of genes involved in the immune-inflammatory response [15], which is known to be associated with disease onset, severity and treatment outcomes in depression [16, 17]. In animal models, $PM_{2.5}$ exposure led to activation of microglia, leading to central nervous system inflammation and neuronal toxicity, which was associated with depressive-like behaviors [18]. These effects were associated with elevated release of tumor necrosis factor-alpha (TNF-α), which is also elevated in patients suffering from depression [19]. Specific air pollutants may also interact with innate genetic vulnerability factors to increase susceptibility to depression. These gene x environment interactions appear to lead to increased systemic inflammation and oxidative stress, thereby altering the functioning of specific brain circuits involved in memory, problem solving, and the ability to cope with stress [20]. Thus, air pollution may act synergistically with chronic psychological or social stress in the genesis of depression [21]. Over and above these brain-specific mechanisms, particulate matter exposure is associated with an increased risk of several chronic medical conditions, including cardiovascular, cerebrovascular and respiratory illnesses. These chronic illnesses are themselves associated with an increased risk of depression [22].

However, two recent meta-analyses of the existing literature have reached divergent conclusions. In the first analysis, published in 2020, depression was associated with short-term exposure to nitrogen dioxide (NO_2), but not with other forms of air pollution [23]. In the second analysis, published in 2022, depression was significantly associated with short-term and long-term exposure to $PM_{2.5}$ as well as with exposure to nitrogen dioxide, sulphur dioxide, ozone and carbon monoxide [24]. Similarly, some studies of the relationship between air pollution and depression in specific countries have yielded negative results [25]. A part of this variation may be due to the specific type of pollutant(s) ($PM_{2.5}$, PM_{10}, nitrogen oxides, sulphur dioxide or ozone) included in the analysis, but much of the variability in these results can be ascribed to host-related factors. These factors include age, gender, vitamin D status, level of physical activity, income, education, population density, and physical health, as well as innate genetic variations [10-12, 15, 20, 26-28]. Furthermore, climatic conditions can influence the impact of air pollution [29]. It is therefore possible that a more accurate picture of the relationship between air pollution and depression could be obtained if at least some of these interacting or confounding factors were taken into account, and if individual pollutants were examined individually.

The research presented in this paper represents an initial step in this process. In this study, data on the levels of a specific pollutant (fine particulate matter with a diameter less than 2.5 microns, $PM_{2.5}$) are examined in relation to the estimated prevalence of depression across 185 countries and territories, while attempting to account for the confounding effect of the variables enumerated above. Based on the results of earlier researchers, the following hypotheses were formulated:

H1: Fine particulate matter pollution ($PM_{2.5}$) is positively correlated with the prevalence of depression across multiple countries and territories

H2: The correlation between $PM_{2.5}$ and depression will remain significant after adjusting for the effects of age, gender, physical activity, income and geographical location.

2. Materials and Methods

The current study is a cross-sectional, ecological association study based on the most recently available data for 185 countries and regions. For the purpose of this study, atmospheric levels of fine particulate matter of diameter less than 2.5 microns (henceforth designated $PM_{2.5}$) was selected as the exposure of interest, and the estimated prevalence of

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depression for each country was taken as the dependent variable. $PM_{2.5}$ was selected as the exposure for the following reasons:

- Across research studies, $PM_{2.5}$ has been one of the pollutants most consistently associated with the risk of depression [7, 9, 11, 12, 25]
- There are biologically plausible mechanisms, identified through translational and clinical research, linking $PM_{2.5}$ exposure with depression [15, 18, 20]
- Reliable and recent cross-national data on levels of $PM_{2.5}$ are available from a reliable source [30]

2.1 Data sources

Information on the estimated levels of $PM_{2.5}$ for each country were obtained from the World Health Organization's Global Health Observatory (GHO). The GHO provides estimates of this parameter for a total of 185 countries and regions, and these values were last updated for the year 2018 [30]

To examine the estimated prevalence of depression, data was retrieved through specific queries from the Global Burden of Disease 2019 Study (GBD 2019) database [31]. This database provides the most recent, nation-wise estimates of the incidence, prevalence and disease burden associated with specific illnesses, based on the most recent epidemiological research [1]. The GBD 2019 provides estimates of depression under three categories: depressive disorder, major depression and dysthymia. "Depressive disorder" includes all cases of depression and represents the sum of the latter two categories. "Major depression" refers to more severe but episodic forms of depression, generally lasting for weeks to months and characterized by intervals of reduced or absent symptoms. "Dysthymia" refers to chronic, mild or "low-grade" depression lasting for more than two years [32]. Given the exploratory nature of the current study, data on all three of these categories was retrieved (i) for the general population as a whole, and (ii) for men and women separately. The confounding effects of age were adjusted for by obtaining age-standardized estimates of the prevalence of depression from the database. These estimates are adjusted for the age distribution of a "standard" population, and thereby control for variations in age distribution across countries.

Apart from age and gender, which were adjusted for in the manner described above, several other factors may influence the association between $PM_{2.5}$ exposure and depression. These confounding variables, the rationale for their inclusion, and the data source for each of these variables are summarized in **Table 1** below.

Table 1. Confounding factors analyzed in the current study.

Variable	Rationale for inclusion	Data source
Gross national income (GNI) per capita	Income levels may mediate the link between air pollution and mental health [26]	World Bank database [33]
Average years of education per adult	Within income groups, education may influence the link between air pollution and depression [26]	Our World in Data [34]

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Prevalence of insufficient physical activity in adults (%)	Physical activity may moderate the impact of air pollution on depression [27]	WHO Global Health Observatory [35]
Population density	Population density may influence the links between air pollution and mental health [26]	World Population Review [36]
Distance from the equator (absolute value of the latitude)	Climatic conditions can influence the impact of air pollution, and may also influence vitamin D levels [29, 37]	Google Earth [38]

2.2 Data analysis

All study variables were tested for normality prior to analysis using the Shapiro-Wilk test. The estimated prevalence of depression conformed to an approximately Gaussian distribution; however, all other study variables deviated significantly from this distribution ($p < .01$, Shapiro-Wilk test) and were subjected to a natural logarithmic transformation (ln) prior to data analysis.

In the first phase of the data analysis, unadjusted bivariate correlations (Pearson's r) were computed for the associations between the concentration of $PM_{2.5}$ and the prevalence of depressive disorders (depression as a whole, major depression and dysthymia) in the general population overall, as well as in men and in women specifically. To rule out the possibility of a Type I error involving H_1, Bonferroni's correction was applied to the correlation matrix, and both corrected and uncorrected p-values were mentioned in the relevant section of the Results. The magnitude of observed correlations was classified as poor ($0.1 < r < 0.3$), fair ($0.3 \leq r < 0.6$), moderate ($0.6 \leq r < 0.8$) or strong ($r \geq 0.8$) based on standard guideline values for biomedical research [39].

In the second stage of the analysis, the above analyses were repeated with adjustments for the confounding variables listed in **Table 1**, using Pearson's partial correlation coefficient (partial r). These adjustments were made for each variable individually, as well as for all of them taken together.

In the third and final analysis, a stepwise multivariate linear regression analysis was used to confirm the consistency and strength of the association between $PM_{2.5}$ concentration and the prevalence of depression while taking relevant confounding factors into account. Confounding variables were selected for inclusion in the analysis only if they were associated with the prevalence of depression at $p < .05$ (uncorrected) in bivariate analyses. Variance inflation factors (VIF) were computed for each variable included in this model. If the VIF exceeded 4 for any particular variable, indicating significant multicollinearity, the analysis was repeated with the relevant variable excluded.

Finally, the possibility of a threshold effect was also examined. According to World Health Organization guidelines, a 24-hour mean exposure level of 15 $\mu g/m^3$ is considered "safe" for fine particulate matter ($PM_{2.5}$) [40]. To examine this possibility, countries were classified as "safe" or "unsafe" based on an estimated $PM_{2.5}$ of ≤ 15 $\mu g/m^3$ and > 15 $\mu g/m^3$ respectively, and the mean prevalence of depression was compared across these two groups using the independent samples t-test. As a confirmatory analysis, correlations between $PM_{2.5}$ and the prevalence of depression were computed separately for each group.

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All statistical tests were two-tailed, and a significance level of $p < .05$ was used for all bivariate analyses.

3. Results

Data was available for a total of 185 countries and regions. The median estimated prevalence of depression was 3.97% for all countries, with an interquartile range (IQR) of 1.33. The maximum estimated prevalence was 6.95% (Uganda), while the minimum was 1.75% (Brunei). The prevalence of depression was higher in women (4.81%) than in men (3.13%). When considering the subtypes of depression, similar results were obtained (major depression: 2.73% overall, 2.09% in men, 3.34% in women; dysthymia: 1.25% overall, 1.08% in men, 1.41% in women).

The median estimated concentration of $PM_{2.5}$ for all the countries included in this study was 22.01 (24.63) $\mu g/m^3$, with a maximum of 93.18 $\mu g/m^3$ (Niger) and a minimum of 5.73 $\mu g/m^3$ (Sweden).

3.1. Bivariate correlations between $PM_{2.5}$ and the prevalence of depression

The results of unadjusted bivariate correlations between $PM_{2.5}$ and the prevalence of depression are presented in **Table 2**.

Table 2: Bivariate correlations between $PM_{2.5}$ and the estimated prevalence of depression, unadjusted for confounders

Disorder	Total population	Men	Women
Depression, total	**.36 (<.001; .008)**	**.36 (<.001; .008)**	**.35 (<.001; .009)**
Major depression	**.35 (<.001; .009)**	**.38 (<.001; .007)**	**.32 (<.001; .01)**
Dysthymia	.13 (.075; NS)	.08 (.283; NS)	.18 (.015; .135)

Note: All values are presented as Pearson's *r* (unadjusted *p* value; Bonferroni-corrected *p*-value). NS, corrected *p*-value ≈ 1. Correlations that remained significant after Bonferroni's correction are highlighted in boldface.

It can be seen from these results that the prevalence of depression, and more specifically of major depression, were positively correlated with levels of atmospheric $PM_{2.5}$. Though the magnitude of these correlations was only fair ($r = .32$ to $.38$), they remained significant even after Bonferroni's correction for multiple comparisons. In contrast, the prevalence of dysthymia was not significantly correlated with $PM_{2.5}$ levels. These results represent a partial confirmation of $\mathbf{H_1}$.

3.2 Correlations between possible confounding variables and the prevalence of depression

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The correlation matrix for the association between the variables listed in **Table 1** and the estimated prevalence of depression, both overall and by gender, is presented in **Table 3.**

Table 3: Bivariate correlations between confounding variables and the estimated prevalence of depression

Variable	Gross national income per capita ($)	Education (years)	Population density (population/km²)	Insufficient physical activity (prevalence %)	Distance from the equator (degrees)
Depression, prevalence (all)	**-.32 (<.001)**	**-.37 (<.001)**	-.12 (.096)	**-.19 (.021)**	**-.17 (.023)**
Major depression, prevalence (all)	**-.22 (.003)**	**-.30 (<.001)**	-.12 (.121)	-.09 (.290)	-.13 (.085)
Dysthymia, prevalence (all)	**-.48 (<.001)**	**-.37 (<.001)**	-.03 (.644)	**-.46 (<.001)**	**-.21 (.004)**
Depression, prevalence (male)	**-.33 (<.001)**	**-.38 (<.001)**	-.13 (.071)	**-.23 (.005)**	**-.24 (<.001)**
Major depression, prevalence (male)	**-.28 (<.001)**	**-.35 (<.001)**	-.14 (.063)	**-.16 (.049)**	**-.24 (.001)**
Dysthymia, prevalence (male)	**-.34 (<.001)**	**-.24 (.001)**	-.02 (.838)	**-.38 (<.001)**	-.08 (.295)
Depression, prevalence (female)	**-.27 (<.001)**	**-.34 (<.001)**	-.10 (.179)	-.13 (.124)	-.11 (.141)
Major depression, prevalence (female)	-.15 (.051)	**-.25 (.001)**	-.10 (.198)	-.02 (.852)	-.05 (.547)
Dysthymia, prevalence (female)	**-.51 (<.001)**	**-.41 (<.001)**	-.03 (.713)	**-.46 (<.001)**	**-.27 (<.001)**

Note: All values are given as Pearson's *r* (significance level). Correlations significant at $p < .05$ are indicated in boldface.

From this table, it can be observed that gross national income and average years of education were negatively correlated with the prevalence of all forms of depression. These associations were observed both for the entire population and for men and women considered separately. All correlation coefficients were in the poor to fair range (r = -.51 to -.22). Population density was not significantly correlated with the prevalence of any type of depression, regardless of gender. The prevalence of insufficient physical activity and the distance from the equator were also negatively correlated with the prevalence of depression, though these results were inconsistent across genders and were observed more for dysthymia than for major depression.

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When considering these variables in relation to the level of $PM_{2.5}$, it was observed that $PM_{2.5}$ was negatively correlated with gross national income (r = -.52, p < .001), education (r = -.59, p < .001) and distance from the equator (r = -.23, p = .001), but not with population density or the prevalence of insufficient physical activity.

3.3 Bivariate correlations between $PM_{2.5}$ and the prevalence of depression, adjusted for confounders

Based on the findings presented in Section 3.2, the analyses in Section 3.1 were repeated while taking into account the following confounders: gross national income per capita, average years of education per adult, prevalence of insufficient physical activity in adults, and distance from the equator. The results of these partial correlation analyses are presented in **Table 4**.

Table 4: Bivariate partial correlations between $PM_{2.5}$ and the estimated prevalence of depression, adjusted for confounders

Variable(s) adjusted for (columns)	Gross national income per capita ($)	Education (years)	Insufficient physical activity (prevalence %)	Distance from the equator (degrees)	All confounders
Depression, prevalence (all)	**.26 (<.001)**	**.20 (.007)**	**.33 (<.001)**	**.33 (<.001)**	**.21 (.010)**
Major depression, prevalence (all)	**.30 (<.001)**	**.23 (.003)**	**.32 (<.001)**	**.32 (<.001)**	**.24 (.003)**
Dysthymia, prevalence (all)	**-.15 (.047)**	-.08 (.280)	.09 (.277)	.10 (.197)	-.13 (.135)
Depression, prevalence (male)	**.27 (<.001)**	**.22 (.004)**	**.35 (<.001)**	**.33 (<.001)**	**.24 (.004)**
Major depression, prevalence (male)	**.30 (<.001)**	**.24 (.001)**	**.35 (<.001)**	**.34 (<.001)**	**.26 (.002)**
Dysthymia, prevalence (male)	-10 (.178)	-.05 (.494)	.06 (.455)	.07 (.346)	-.06 (.452)
Depression, prevalence (female)	**.28 (<.001)**	**.21 (.006)**	**.33 (<.001)**	**.33 (<.001)**	**.22 (.008)**
Major depression, prevalence (female)	**.31 (<.001)**	**.22 (.003)**	**.30 (<.001)**	**.31 (<.001)**	**.24 (.004)**
Dysthymia, prevalence (female)	-.12 (.120)	-.05 (.475)	.13 (.110)	.13 (.072)	-.10 (.220)

Note: All correlations are between the concentration of $PM_{2.5}$ and the prevalence of depression, adjusted for the variables listed in the rows. All values are in the form: Pearson's partial r (significance level). Correlations significant at p < .05 are indicated in boldface.

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From these analyses, it can be observed that after adjusting for several confounding factors, a modest (r = .21 to .34) but positive correlation remained between levels of $PM_{2.5}$ and the prevalence of depression, particularly major depression, regardless of gender. In contrast, the prevalence of dysthymia was not significantly associated with $PM_{2.5}$ concentrations following these adjustments.

3.4 Multivariate linear regression analyses of the relationship between $PM_{2.5}$ and depression

Based on the above results, separate linear regression analyses, using a stepwise method, were carried out to confirm the association between $PM_{2.5}$ and depression. Dysthymia was excluded from the analysis on the basis of the negative findings presented in **Table 4**. The results of these analyses are presented in **Table 5.**

Table 5: Linear regression analyses of the associations between $PM_{2.5}$ and the estimated prevalence of depression

Dependent variable	Variables retained in regression model	Regression coefficient (β)	Significance level	Variance inflation factor (VIF)	Percentage of variance explained
Depression, prevalence	PM2.5 Insufficient physical activity	.32 -.16	<.001 .036	1.02 1.02	12.9%
Major depression, prevalence	PM2.5	.35	<.001	1.00	12.0%
Depression, prevalence in men	PM2.5 Insufficient physical activity	.34 -.20	<.001 .010	1.02 1.02	15.7%
Major depression, prevalence in men	PM2.5	.35	<.001	1.00	11.9%
Depression, prevalence in women	PM2.5 Average years of education	.25 -.19	.005 .029	1.53 1.53	14.2%
Major depression, prevalence in women	PM2.5	.32	<.001	1.00	9.6%

Abbreviations: $PM_{2.5}$, atmospheric concentration of fine particulate matter of diameter ≤2.5 microns (μg/m^3)

It can be seen that the concentration of $PM_{2.5}$ was retained as a significant predictor of the prevalence of depression across genders. The only additional variables retained were physical activity (in men) and education (in women). For major depression, $PM_{2.5}$ was the only variable retained in the regression models for both genders. This single variable appeared to explain 9.6%-12% of the variation in the prevalence of major depression (R^2

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= .100 to .125; adjusted R^2 = .096 to .120). Variance inflation factors were below 4 in all cases, indicating that multicollinearity was not significant for any of the analyses. Taken together, the results in **Tables 4 and 5** can be seen as confirming **H_2**, except for dysthymia.

3.5 Assessment of a possible threshold effect

To assess for a possible threshold effect, countries were classified according to whether their $PM_{2.5}$ concentration was above or below the threshold specified by the World Health Organization [40] and the mean prevalence of depression was compared between groups. The results of these analyses are presented in **Table 6**.

Variable	Prevalence in countries with $PM_{2.5} \leq 15$ μg/m3	Prevalence in countries with $PM_{2.5} > 15$ μg/m3	Test statistic (*t*)	Significance level
Depression	**3.75 (.75)**	**4.08 (.96)**	**-2.54**	**.012**
Major depression	**2.83 (.91)**	**2.52 (.72)**	**-2.30**	**.015**
Dysthymia	1.23 (.20)	1.25 (.20)	-.55	.586
Depression (men)	**2.97 (.56)**	**3.27 (.85)**	**-2.80**	**.006**
Major depression (men)	**1.89 (.51)**	**2.19 (.82)**	**-3.06**	**.003**
Dysthymia (men)	1.09 (.16)	1.08 (.14)	.26	.794
Depression (women)	**4.49 (.98)**	**4.87 (1.14)**	**-2.18**	**.031**
Major depression (women)	**3.11 (1.02)**	**3.45 (1.08)**	**-1.98**	**.046**
Dysthymia (women)	1.38 (.27)	1.42 (.27)	-1.04	.300

Note: All prevalence values are given as mean (standard deviation). *t*, independent samples *t*-test statistic. Significant differences are indicated in boldface.

These analyses are consistent with the overall results observed for $PM_{2.5}$ concentration, with significant differences being observed both for depression overall and for major depression, but not dysthymia, regardless of gender. These findings provide some support for the notion that there is a threshold of exposure to $PM_{2.5}$ above which the risk of depression increases slightly.

To confirm this possibility, bivariate correlations between $PM_{2.5}$ levels and depression were computed separately for countries above and below the WHO guideline value. These results are presented in **Table 7**.

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Table 7: Bivariate correlations between $PM_{2.5}$ and the estimated prevalence of depression, grouped according to World Health Organization guideline values

Variable	Correlation in countries with $PM_{2.5} \leq 15$ μg/m³	Correlation in countries with $PM_{2.5} > 15$ μg/m³
Depression	**.50 (.001)**	-.22 (.099)
Major depression	**.47 (<.001)**	-.16 (.226)
Dysthymia	.26 (.003)	-.22 (.105)
Depression (men)	**.49 (<.001)**	-.22 (.098)
Major depression (men)	**.47 (<.001)**	-.19 (.152)
Dysthymia (men)	.25 (.005)	-.16 (.219)
Depression (women)	**.50 (<.001)**	-.22 (.106)
Major depression (women)	**.46 (<.001)**	-.15 (.276)
Dysthymia (women)	**.31 (<.001)**	-.23 (.087)

Note: All correlation statistics are in the form: Pearson's *r* (*p*-value). Correlations that are significant at $p < .05$ after applying Bonferroni's correction are highlighted in bold.

These results provide a clearer confirmation of the possibility of a threshold effect. In countries with a $PM_{2.5}$ above the guideline value for safety, the positive correlations observed in **Table 2** remained significant, but with a greater effect size ($r = .46$ to .50). On the other hand, in those countries where $PM_{2.5}$ was below the guideline value, non-significant negative correlations between $PM_{2.5}$ and depression were observed. The associations between $PM_{2.5}$ and depression, particularly major depression, remained significant even after correction for multiple comparisons.

4. Discussion

The results of the current study are consistent with existing epidemiological findings of a significant link between atmospheric levels of $PM_{2.5}$ and the depression. In this study, the use of age-standardized prevalence estimates and the inclusion of separate analyses for men and women were used to correct for the possible influence of age and gender. The association between $PM_{2.5}$ and depression remained significant in both genders, and also retained its significance after adjustment for the population-level confounding variables identified by earlier researchers. In other words, this study was able to partially confirm both H_1 and H_2.

These results suggest that atmospheric $PM_{2.5}$ pollution contributes significantly to variations in the prevalence of depression across countries. The magnitude of this effect is modest (univariate $R^2 = .123$-.130; partial adjusted $R^2 = .044$-.058; R^2 in regression models = .096-.120), but it remains significant even after adjustment for age, gender and other confounding demographic variables. While $PM_{2.5}$ cannot be considered the sole or even the most important causal factor in the pathogenesis of depression, it is likely to interact with a number of other variables, including genetic vulnerability and social stress, to influence the onset and persistence of this disorder [41]. There is evidence that the association between $PM_{2.5}$ exposure and depression is partly mediated through reductions in the

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volume of key brain regions involved in mood and cognition, which may reflect the inflammation-induced neurotoxicity caused by exposure to this pollutant [42]. Exposure to $PM_{2.5}$ can also cause oxidative stress and mitochondrial functioning, both of which are likely to occur in brain regions that have a high energy demand, such as the prefrontal cortex, hippocampus and amygdala. These brain regions play a key role in the pathogenesis of depression [43]. Particulate matter exposure also appears to cause autonomic nervous system dysfunction, including reduced heart rate variability (HRV), which is a frequently replicated biomarker of depression [44, 45]. Finally, evidence from animal models has shown that prenatal exposure to particulate matter can increase susceptibility to depressive-like behaviors in adult life; the relevant mechanism in this case appears to be impaired differentiation of cortical neurons [46]. Thus, the effect of $PM_{2.5}$ on depression appears to be mediated through multiple mechanisms; the relative contribution of each of these processes to the pathogenesis of depression in humans remains to be elucidated. This multiplicity of mechanisms also accounts for the finding that prolonged exposure to $PM_{2.5}$ is more strongly associated with depression than short-term exposure [47].

A novel finding in the current study is the apparent specificity of the association between $PM_{2.5}$ exposure and major depression; such an association could not be identified for dysthymia. Major depression is a more severe but intermittent form of depression, characterized by individual episodes lasting several weeks or months and a high lifetime recurrence rate. There is significant evidence that major depression is associated with alterations in stimulus-induced activity in the brain regions affected by $PM_{2.5}$ exposure; these alterations are associated with heightened responses to negative stimuli and difficulty in processing and reappraising such inputs [48]. Therefore, $PM_{2.5}$-induced alterations in brain activity could make an individual more vulnerable to the effects of negative life events, leading to depressive episodes. Major depression is also associated with elevated levels of cytokines, such as TNF-α, whose expression can be induced by exposure to $PM_{2.5}$ [19, 49]. Thus, an association between $PM_{2.5}$ and major depression is biologically plausible. On the other hand, little is known about the neuroanatomical correlates of dysthymia [50], and this condition appears to be associated with an inflammatory profile distinct from that of major depression [51]. Personality factors and psychosocial stressors appear to play a greater role in the genesis of this disorder [52, 53]. The variations in the association between $PM_{2.5}$ levels and depression observed by earlier researchers may be partly explained by this differential effect on specific types of depression.

A significant limitation of existing research on air pollution and depression is that much of it is based on data from industrialized, high-income countries, with few studies from low- and middle-countries [9]. In the current dataset, there was a significant negative correlation between national income and $PM_{2.5}$ levels (r = -.52, p < .001). This is consistent with existing data which suggests that the effects of air pollution may be more severe in lower-income countries, particularly where measures to reduce pollution are often absent or ineffective [54, 55]. In contrast, in countries with low levels of outdoor air pollution and effective legislation to minimize this phenomenon, the associations between $PM_{2.5}$ and depression may be weak or absent [25, 56]. This hypothesis is supported by the study findings suggesting a threshold above which the link between $PM_{2.5}$ and depression becomes significant, as seen in **Tables 6 and 7**. These results suggest that efforts to lower $PM_{2.5}$ to at least 15 $\mu g/m^3$ are of particular importance in low- and middle-income countries.

There are certain limitations of the current study findings. First, they are based on country-level estimates, and cannot be directly extrapolated to individuals. Second, there is a certain degree of uncertainty regarding the reliability of the estimates for the prevalence of depression, particularly in lower-income countries [57]. Third, certain other confounding factors may also influence the link between $PM_{2.5}$, but these could not be adjusted for in the current study due to a lack of cross-national data. These include both additional risk factors, such as cigarette smoking, urbanization and vitamin D deficiency [25, 27, 54],

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and potential protective factors, such as access to green spaces or sunlight exposure [54, 58]. Fourth, the association between $PM_{2.5}$ and depression may not be specific: instead, prolonged $PM_{2.5}$ exposure may be a non-specific risk factor for a number of mental illnesses, including anxiety disorders, bipolar disorder and psychosis [47]. Fifth, due to the cross-sectional nature of the data analysis, firm conclusions regarding causality cannot be drawn. Sixth, this study examined $PM_{2.5}$ levels because data was available on this variable; it was not possible to examine the Finally, it was not possible to analyze the effects of relevant genetic variants on vulnerability to depression following $PM_{2.5}$ exposure, as relevant data on allele frequencies is available only for a small number of countries.

5. Conclusions

Despite certain limitations, the results presented in this paper are of importance, not just for healthcare professionals, but for all those involved in mitigating the health and environmental impacts of outdoor air pollution. The finding that fine particulate matter pollution could account for around 10% of the variance in the prevalence of depression, and that this figure may be doubled in countries with higher levels of $PM_{2.5}$, is both a cause for global concern and a call to action. Given the personal, social and economic burden associated with depression, particularly in low- and middle-income countries where patients with this disorder are often undiagnosed and treated, prompt measures to prevent or at least mitigate the effects of $PM_{2.5}$ are required. Such measures would require changes in policy, a commitment to change by individuals, industries and other non-state actors, as well as an enhancement of possible protective mechanisms and processes.

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