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Review

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Ambient air pollution and depression: a systematic review with meta-analysis up to 2019

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ABSTRACT

Although epidemiological studies have evaluated the associations of ambient air pollution with depression, the results remained mixed. To clarify the nature of the association, we performed a comprehensive systematic review and meta-analysis with the Inverse Variance Heterogeneity (IVhet) model to estimate the effect of ambient air pollution on depression. Three English and four Chinese databases were searched for epidemiologic studies investigating associations of ambient particulate (diameter ≤ 2.5 μm ($PM_{2.5}$), ≤ 10 μm (PM_{10})) and gaseous (nitric oxide (NO), nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2) and ozone (O_3)) air pollutants with depression. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated to evaluate the strength of the associations. We identified 22 eligible studies from 10 countries of the world. Under the IVhet model, per 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ (OR: 1.12, 95% CI: 0.97-1.29, I^2: 51.6), PM_{10} (OR: 1.04, 95% CI: 0.88-1.25, I^2: 85.7), and NO_2 (OR: 1.05, 95% CI: 0.83-1.34, I^2: 83.6), as well as short-term exposure to $PM_{2.5}$ (OR: 1.01, 95% CI: 0.99-1.04, I^2: 51.6), PM_{10} (OR: 1.01, 95% CI: 0.98-1.04, I^2: 86.7), SO_2 (OR: 1.03, 95% CI: 0.99-1.07, I^2: 71.2), and O_3 (OR: 1.01, 95% CI: 0.99-1.03, I^2: 82.2) was not significantly associated with depression. However, we observed significant association between short-term NO_2 exposure (per 10 μg/m^3 increase) and depression (OR: 1.02, 95% CI: 1.00-1.04, I^2: 65.4). However, the heterogeneity was high for all of the pooled estimates, which reduced credibility of the cumulative evidence. Additionally, publication bias was detected for six of eight meta-estimates. In conclusion, short-term exposure to NO_2, but not other air pollutants, was significantly associated with depression. Given the limitations, a larger meta-analysis incorporation future well-designed longitudinal studies, and investigations into potential biologic mechanisms, will be necessary for a

more definitive result.

Keywords: Particulate matter; Gaseous pollutants; Depressive disorder; Random effects model; Inverse Variance Heterogeneity (IVhet) model

1. Introduction

Ambient or outdoor air pollution (referred to as air pollution hereafter) has become a major global environmental issue. According to the recent Global Burden of Diseases report (GBD), air pollution was responsible for 4.90 million deaths and 1.47 billion disability-adjusted life-years (DALYs) in 2017, with most of the burden related to cardiovascular disease, respiratory disease, and lower respiratory infections (GBD 2017 Risk Factor Collaborators, 2018). More recently, the hazardous effects of air pollution on mental health, such as depression, have attracted interest and have global public health implications (Buoli et al., 2018; Gu et al., 2019; Pun et al., 2017; Kim et al. 2016; Lam et al., 2016).

Depression is characterized by persistent poor mood, diminished interest in activities, exhaustion, and low energy, and it is one of the most prevalent mental disorders (American Psychiatric Association, 2013). Depression has been associated with decreased work productivity, lower quality of life, and an increased risk of all-cause mortality (Walker et al., 2015; Ferenchick et al., 2019; Spitzer et al., 1995). The GBD (2018) report estimated more than 43 million years lived with disability (YLDs) attributable to depression in 2017 (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Depression prevalence is increasing, and access to effective treatments remains limited (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; Ramanuj et al., 2019). Therefore, identification of risk factors for depression and consequent development of prevention strategies is of public health significance.

Mechanistic studies indicate that air pollutants inhalation can trigger neuro-inflammation and oxidative stress as well as induce dopaminergic neurotoxicity

(Risom et al., 2005; Ng et al., 2008; Hurley and Tizabi, 2013; Dantzer et al., 2008). Additionally, previous studies demonstrated that exposure to higher levels of air pollution could affect people's residential satisfaction and self-perceived health, which have been associated with mental health (von Lindern et al., 2016; Liu et al., 2018; Nguyen et al., 2017). Therefore, it has been plausibly hypothesized that air pollution may contribute to depression pathogenesis. During the past decade, multiple studies investigated the relationship between long-term or short-term air pollution exposure and depression (Szyszkowicz et al., 2009; Lim et al., 2012; Wang et al., 2014; Cho et al., 2014; Zijlema et al., 2016; Szyszkowicz et al., 2016; Kim et al., 2016; Vert et al., 2017; Pun et al., 2017; Lin and Guo et al., 2017; Lin and Zhou et al., 2017; Kioumourtzoglou et al., 2017; Kim and Kim, 2017; Wang et al., 2018; Zock et al., 2018; Roberts et al., 2019; Zhao et al., 2019). However, the results were inconsistent and contradictory; some studies detected positive air pollution-depression associations (Lim et al., 2012; Cho et al., 2014; Kim et al., 2016; Vert et al., 2017; Roberts et al., 2019) and the others found no association (Wang et al., 2014; Lin and Guo et al., 2017; Kioumourtzoglou et al., 2017; Kim and Kim, 2017; Zhao et al., 2019). A recent meta-analysis reported a higher odds ratio for depression in association with increasing ambient fine particulate matter ($PM_{2.5}$) but not with inhalable particulate matter (PM_{10}) exposure. However, the meta-analysis did not assess gaseous pollutants, and several key or recent papers were not included (Gu et al., 2019). Thus, the weight of evidence was difficult to interpret, limiting the data available to provide specific suggestions to policy makers. In addition, due to high heterogeneity, Gu et al. (2019) applied random effects model to pool the effect estimates. However, the model was criticized for overestimating effects and underestimating the statistical error (Doi et al. 2015).

To help address the pending data gap, we systematically identified and reviewed epidemiological studies of short- and long-term exposure to ambient particulate and gaseous air pollutants, including all epidemiologic study design, up to 2019. Furthermore, we used the Inverse Variance Heterogeneity (IVhet) model to pool the data, which outperforms the random effects model in reducing the estimator mean squared error and maintaining the correct coverage probability of the confidence interval (CI) (Doi et al., 2015). Our aim was to provide a more comprehensive and accurate assessment of the state of the literature to inform policy makers, investigators, and healthcare professionals on likely magnitude of effects and to recommend next steps for more definitively addressing the association between air pollutants and depression.

2. Methods

2.1. Search strategy

We conducted the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines as shown in Table S1 (Moher et al., 2009). We did not publish a systematic review protocol beforehand. A specific research question was formulated according to the "Participants", "Exposure", "Comparator", and "Outcomes" (PECO) framework. The focused question of the present systematic review and meta-analysis was: "Is exposure to ambient air pollution associated with the risk of depression?". Studies on the relationships of ambient air pollution and depression (published before 21 August 2019) indexed in three English databases (PubMed, Web of Science and Scopus) and four Chinese databases (China National Knowledge Infrastructure, China Biological Medicine Database, Chongqing VIP Chinese Science and Technology Periodical

Database, and Wanfang Data), were identified. Our search strategies were based on combinations of air pollution terms ("air pollution", "particulate matter", "air pollutants", particle, "sulfur dioxide", "nitrogen oxide", "nitrogen dioxide", ozone, and "carbon monoxide") and depression terms (depress*, depression, depressive, depress, depressed, "unipolar disorder", and "bipolar disorder"). Detailed search strategy is shown in Table S2. The search was limited to the English and Chinese languages. We also searched the references lists of eligible articles and grey literature databases (British National Bibliography for Report Literature, Social Care Online, System for Information on Grey Literature in Europe, and National Technical Information Service) to find additional potentially pertinent studies.

2.2. Selection criteria

The following *a priori* eligibility criteria were based on the PECO framework: (P) the study was conducted among humans; (E) the study focused on short-term (< 30 days) or long-term (≥ 30 days) exposures to ambient air pollution; (C) the study provided quantitative effect estimates with 95% CIs (or standard errors) by comparing humans exposed to lower air pollution levels with the greater exposed humans; (O) depression was assessed and defined using questionnaire (e.g. Center for Epidemiological Studies Depression Scale, Diagnostic and Statistical Manual of Mental Disorders, Hospital Anxiety Depression Scale, and Korean version of the Geriatric Depression Scale, etc.), clinical assessment (International Classification of Diseases (ICD), International Classification of Primary Care (ICPC), and doctor-diagnosed), or antidepressant medication. If more than one publication was identified for the same study population, the one with more thorough reporting or adjustments was included.

After removing duplicates, two (SF and WF) of the co-authors independently

screened titles, abstracts, and full text for eligibility (Fig. 1). If a disagreement arose, the article was referred to a third co-author (BY) for adjudication.

2.3. Data extraction

Two (SF and YS) of the co-authors independently extracted the following information from each included study: authors' names, publication year, study period, setting, and design, the size, exposure assessment strategy and lag pattern, outcome (depression) definition, and effect estimates including odds ratio (OR), risk ratio (RR), and hazard ratio (HR) with their corresponding 95% CIs. For studies reporting sub-stratified risk estimates rather than overall risk estimates, each stratified risk estimate was considered as an independent data set (Szyszkowicz et al., 2016). Any conflict was resolved by discussion with a third co-author (BY).

2.4. Methodological Quality assessment

We used the popular Newcastle Ottawa scale (NOS) (Wells et al., 2010) and the Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument (JBI, 2016) to assess the quality of cohort and cross-sectional studies, respectively. Each study was assessed an NOS score from 0 to 9 and a JBI score from 0 to 20. An NOS score greater than 7 or a JBI score greater than 16 was considered as "high quality"; otherwise, the study was considered as "low quality".

To the best of our knowledge, no validated scale is available to assess the quality of time-series, panel, and case-crossover study designs. We therefore assessed their quality using a scale suggested by Mustafić et al. (2012), which was adapted from the validated NOS scale and the Cochrane risk of bias tool (Higgins et al., 2011). Mustafić's adapted scale included three items, and "0-3" points were assigned for the

following elements: validation of depression (0: absence of valid criteria; 1: presence of valid criteria), the quality of air pollutant measurements (0: measurements were not performed at least daily or > 25% data were missing; 1: measurements were performed at least daily and missing data < 25%), and the extent of confounder adjustments (0: no adjustment was made for long-term trends, season, and air temperature; 1: only long-term trends, season, and air temperature were adjusted; 2: adjustment was made either for humidity or day of week in addition to the corresponding adjustments with a score of 1; 3: adjustment was made for holidays in addition to the corresponding adjustments with a score of 2) (Mustafić et al., 2012). If the maximum score was achieved for all the three items (i.e., 5 points in total), the study was categorized as "high quality"; otherwise, the study was categorized as "low quality".

2.5. Risk of bias assessment

We further assessed the risk of bias (ROB) for each study, which is a new concept in environmental health study and related to but different from the methodological quality assessment. ROB was defined as characteristics of a study that can introduce systematic errors in effect estimate (the magnitude or direction) (Woodruff and Sutton, 2014). A study conducted with high methodological standards may still have high ROB, which will ultimately influence the magnitude or direction of an association. To evaluate ROB for cohort and cross-sectional studies, we applied the National Institutes of Environmental Health Sciences National Toxicology Program Office of Health Assessment and Translation (OHAT) ROB (OHAT, 2015). In the absence of a validated ROB tool for time-series and case-crossover studies, we evaluated the ROB of such studies according to the OHAT tool as well as using the University of

California at San Francisco (UCSF) Navigation Guide (Lam et al., 2016; Woodruff and Sutton, 2014).

We used the OHAT tool and UCSF Navigation Guide to assess the selected studies for key (exposure assessment, outcome assessment, and confounding bias) and other methodologic criteria (selection bias, attrition/exclusion bias, selective reporting bias, conflict of interest, and other sources of bias). We tailored adapted criteria for the ROB assessment of each study to our specific systematic review, which is provided in Table S3. For example, in the "confounding bias" of the key criteria, we extracted all adjustments from the individual studies and developed a directed acyclic graph (DAG) to select the most parsimonious confounders for adjusting and potential mediators. Then, we ranked the risk of confounding bias according to the selected covariates and mediators. The potential confounders selected using DAG included meteorological factors (e.g. temperature, relatively humidity, barometric pressure, sunlight hours, and wind speed), age, sex, ethnicity, household income, smoking, physical activity, day of week, season, urbanity, population density, region, occupation, domestic fuel type and ventilation, social-economic status, and the spent outside and time spent in front of a screen. The potential mediators included triglycerides levels, health status, social satisfaction, sleep difficulties, and SBP (Fig. S1). The selected studies were classified as "low", "probably low", "probably high", or "high" risk levels for each of these domains. Following OHAT tool guidelines, we excluded studies from the systematic review that were classified as "high" or "probably high" risk on the key criteria and most of the other criteria.

2.6. Standardization of data

We summarized measures of association between air pollutant and depression as ORs.

To facilitate a comparison of effect sizes from the different studies, we standardized the effect estimate units across studies to a 10 μg/m^3 change in air pollutant concentrations prior to pooling. Other reported quantities were first converted into μg/m^3 as: (a) 1 ppm = 1000 ppb; (b) nitrogen dioxide (NO_2): 1 ppb = 46/22.4 μg/m^3; (c) sulfur dioxide (SO_2): 1 ppb = 64/22.4 μg/m^3; and (d) ozone (O_3): 1 ppb = 48/22.4 μg/m^3. We calculated the standardized OR for each study as (Kim et al., 2018):

$$OR_{Standardized} = e^{\left(\frac{\ln(OR_{Origin})}{Increment_{Origin}} \times Increment_{Standardized}\right)}$$

For short-term exposure studies, authors used different lag patterns to evaluate immediate and delayed effects of ambient air pollutants exposure on odds for depression. Some studies provided multiple estimates for single-day lags (e.g., lag 0, 1, 2 days), while others provided cumulative lags (e.g., lag 0-7 days). To facilitate pooling across studies, we selected lags based on the following criteria: (a) if only one lag estimate was provided, the estimate was used; or (b) if multiple lags were provided, in order of precedence we chose the lag that the investigators focused on or stated as a priority, the lag that was statistically significant, or the lag with the largest effect estimates (Atkinson et al., 2012; Yang et al., 2018).

Most studies did not perform or report results from multi-pollutant models. Therefore, we only extracted and pooled effect estimates generated from single-pollutant models. When studies provided results from several nested adjusted models or sensitivity analyses, we only chose results from the "main model" designated by the investigators.

2.7. Meta-analysis methods

We retrieved effect estimates (OR, RR, or HR) and 95% CI for associations between

each air pollutant and depression in the included studies. Most studies reported ORs, thus we used it as measure of association across all studies. Since depression was rare (the prevalence was approximately 4.4%, WHO, 2017), we considered OR as equivalent to RR and HR (Eze et al., 2015). Between-study heterogeneity was tested by calculating I^2 (I^2=0-25% represents no heterogeneity; I^2=25-50% represents moderate heterogeneity; I^2=50-75% represents large heterogeneity; I^2=75-100% represents extreme heterogeneity). If I^2 < 50%, the Mantel-Haenszel fixed effects model was used; otherwise, the IVhet model (Doi, et al., 2015; Doi, et al., 2017) was used. We also reported the pooled effects from the random effects model. However, the IVhet model outperforms the random effects model, which favours larger studies, retains a correct coverage probability, and exhibits a lower observed variance, regardless of heterogeneity (Doi et al., 2015). We performed sensitivity analysis to test the stability of the overall estimate by examining the influence of excluding each study. Additionally, univariate meta-regression was performed to explore the source of heterogeneity for meta-analysis with ≥ 10 studies included (Higgins and Green, 2011). Potential moderators including study location (Europe, Asia, North America, and Mixed areas), study design (cross-sectional and cohort), age (mean/median age of participants ≥ 45 years, and < 45 years), background $PM_{2.5}$ level (mean/median of background $PM_{2.5}$ levels ≥ 15 μg/m^3, and < 15 μg/m^3), $PM_{2.5}$ levels measurement method (monitoring station and models), depression definition (questionnaire, ICD code, ICPC code, and use antidepressants), gender proportion (male proportion ≥ 50%, and < 50%), sample size (studies with ≥ median number of participants, and < median number), and type of effect estimate (OR and HR). Publication bias was examined using Doi plot and the Luis Furuya-Kanamori (LFK) index. LFK index < |1| indicates "no asymmetry", LFK index between |1| and |2| indicates "minor asymmetry", and

LFK index > |2| indicates "major asymmetry" (MetaXL User Guide, www.epigear.com).

We graded the overall quality of the pooled evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group guideline (Morgan et al., 2019). The ROB (e.g., bias from exposure assessment, outcome assessment and confounding, selection bias, attrition/exclusion bias, selective reporting bias, conflict of interest), inconsistencies (high heterogeneity and disparate results across studies), indirect evidence (the evidence cannot directly answer the research question), imprecision (e.g., small sample size, wide CI), and publication bias (assessed using LFK index) are considered. All studies were started at the same "high quality" rating regardless of study design. Credibility of evidence was finally classified as "high", "moderate", "low", and "very low".

All statistical analyses were performed using the STATA package version 11.0 software program (StataCorp, College Station, TX, USA) and MetaXL v.5.3 software (EpiGear International Pty Ltd, Sunrise Beach, Queensland, Australia, www.epigear.com), and a two-tailed *P*-value less than 0.05 was defined as statistically significant.

3. Results

3.1. Literature retrieval and study characteristics

After removing duplicates, we were left with 10,896 papers for screening on titles and abstracts levels (Fig.1). We retrieved the full text of 51 relevant papers. Finally, we retained 19 papers describing the results of 22 studies (or data sets), that met our inclusion criteria, in the meta-analysis.

Table 1 summarizes the baseline characteristics of the 22 studies in our retained papers. Seven of the 22 studies were performed in Asia, five in North America, nine in Europe, and one in multiple countries. Most studies adopted a cohort design (n = 10), followed by cross-sectional (n = 7), case-crossover (n = 3), time-series (n = 1), and panel (n = 1) designs. Thirteen studies investigated the long-term effects of air pollution on depression, and the sample sizes for these studies ranged from n = 284 to n = 354,827. Seven studies investigated the short-term effects and their sample sizes ranged from n = 537 to n = 69,132. Two studies explored both long-term and short-term effects. Of the 22 studies, 20 were conducted among healthy populations (Szyszkowicz et al., 2009; Lim et al., 2012; Wang et al., 2014; Zijlema et al., 2016; Szyszkowicz et al., 2016; Kim et al., 2016; Vert et al., 2017; Pun et al., 2017; Lin and Guo et al., 2017; Lin and Zhou et al., 2017; Kioumourtzoglou et al., 2017; Kim and Kim, 2017; Wang et al., 2018; Roberts et al., 2019; Zhao et al., 2019; Zhang et al., 2019; Klompmaker et al., 2019), while the remaining two studies were based on specific populations with cardiovascular diseases, diabetes mellitus, or asthma (Cho et al., 2014; Zock et al., 2018).

For exposure assessment, nine studies used data from fixed air monitoring stations to assess air pollution exposure (Szyszkowicz et al., 2009; Lim et al., 2012; Wang et al., 2014; Cho et al., 2014; Szyszkowicz et al., 2016; Kim et al., 2016; Lin and Zhou et al., 2017; Kim and Kim, 2017; Wang et al., 2018), twelve studies used air pollution data predicted by models, such as land use regression (LUR), and spatiotemporal models (Zijlema et al., 2016; Vert et al., 2017; Pun et al., 2017; Lin and Guo et al., 2017; Kioumourtzoglou et al., 2017; Zock et al., 2018; Roberts et al., 2019; Zhang et al., 2019; Klompmaker et al., 2019), and the remaining one study used monitoring stations data for short-term exposure and LUR model for long-term exposure (Zhao et

al., 2019). For outcome assessment, five and one studies used the ICD code and the ICPC code, respectively. Thirteen studies used depression scales or interviews, and the remaining three studies used doctor-diagnosed depression and/or antidepressant medication use.

3.2. Study quality and risk of bias

According to the NOS and JBI scales (Table S4), seven cohort studies (Wang et al., 2014; Zijlema et al., 2016; Kim et al., 2016; Pun et al., 2017; Kioumourtzoglou et al., 2017; Roberts et al., 2019; Zhang et al., 2019), seven cross-sectional studies (Vert et al., 2017; Lin and Guo et al., 2017; Lin and Zhou et al., 2017; Kim and Kim, 2017; Zock et al., 2018; Zhao et al., 2019; Klompmaker et al., 2019), and one case-crossover study (Wang et al., 2018) were regarded as "high quality", whereas none of the time-series, panel, or the remaining two case-crossover studies were "high quality" according to Mustafić's criteria.

With respect to the study ROB assessment, none of the 19 articles presented a high risk of bias. The detailed account of each study's ROB assessment is provided in Table S4.

3.3. Long-term air pollution exposure and depression

Pooled effect estimates examining the associations between long-term air pollution exposure and depression are illustrated in Table 2 and Table S5. Twelve studies investigated $PM_{2.5}$ and depression. Under the IVhet model, exposure to $PM_{2.5}$ was not significantly associated with depression (OR = 1.12, 95% CI = 0.97 - 1.29; I^2 = 51.6%) (Fig.2). However, the association was significant under the random effects model (Table S5). Doi plot with LKF index indicates major asymmetry (Fig.S2). When any

single study or some specific studies were excluded (Zock et al., 2018; Robert et al., 2019), the pooled estimates were not materially changed (Fig.S3-S4). For example, when Zock et al. (2018) and Robert et al. (2019) were excluded at the same time, the pooled OR for long-term $PM_{2.5}$ exposure was 1.11 (0.99, 1.24) (Fig.S4). Meta-regression results showed that study location (P = 0.299), study design (P = 0.983), age (P = 0.777), background $PM_{2.5}$ level (P = 0.938), $PM_{2.5}$ exposure measurement methods (P = 0.128), depression definition (P = 0.686), gender ratio (P = 0.420), sample size (P = 0.234), and type of effect estimate (P = 0.740) were not the source of the between-study heterogeneity.

The associations between long-term PM_{10} and NO_2 exposure with depression were estimated by eight and seven studies, respectively (Table 2). None of the associations was significant either under the IVhet model (PM_{10}: OR = 1.04, 95% CI = 0.88 - 1.25, Fig.S5; NO_2: OR = 1.05, 95% CI = 0.83 - 1.34, Fig.2) or the random effects model (PM_{10}: OR = 1.06, 95% CI = 0.94 - 1.20; NO_2: OR = 1.12, 95% CI = 0.99 - 1.28; Table S5). The between-study heterogeneities were extreme for both PM_{10} (I^2 = 85.7%) and NO_2 (I^2 = 83.6%). The Doi plot showed major asymmetry for PM_{10} and NO_2 (Fig.S6-S7). In sensitivity analyses, when any single study or some specific studies were excluded (Zock et al., 2018; Robert et al., 2019), the pooled estimates were not materially changed, indicating the robustness of the pooled estimates (Fig.S8-S10). For example, when Zock et al. (2018) and Robert et al. (2019) were excluded at the same time, the pooled OR for long-term NO_2 exposure was 1.05 (0.73, 1.51) (Fig.S10). Due to the limited number of studies, we did not perform meta-regression analyses for them. Additionally, our confidence in the cumulative evidence was “very low” or “low” for the pooled associations of long-term $PM_{2.5}$, PM_{10}, and NO_2 with depression based on the GRADE system (Table S6).

The associations of $PM_{2.5absorbance}$ and NOx with depression were investigated by one study each, and both reported positive associations (Vert et al., 2017). Two studies looked at O_3 and depression, but the results were mixed (Kioumourtzoglou et al., 2017; Zhao et al., 2019). Due to limited data, we did not perform meta-analyses for $PM_{2.5absorbance}$, NO_x, or O_3 exposure.

3.4. Short-term air pollution exposure and depression

Pooled effect estimates describing the associations between short-term air pollution exposure and depression are summarized in Table 2 and Table S5. Six, five, seven, six, and seven studies focused on short-term exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3, respectively (Fig.3 and Fig.S11-S13). The pooled results under the IVhet model showed that only NO_2 was significantly associated with higher odds for depression (OR = 1.02, 95% = 1.00 - 1.04), and no significant association was found for the remaining four air pollutants ($PM_{2.5}$: OR = 1.01, 95% CI = 0.99 - 1.04; PM_{10}: OR = 1.01, 95% CI = 0.98 - 1.04; SO_2: OR = 1.03, 95% CI = 0.99 - 1.07; O_3: OR = 1.01, 95% CI = 0.99 - 1.03). However, under the conventional random effects model, the odds for depression were significantly associated with all the four pollutants (Table S5).

The heterogeneity was large to extreme for all the five pooled associations (I^2 ranged from 51.6% to 86.7%). The Doi plot showed major asymmetry in PM_{10}, NO_2, and O_3, and symmetrical in $PM_{2.5}$ and SO_2 (Fig.S14-S18). Sensitivity analyses excluding single studies did not materially change the pooled results (Fig.S19-S23). The credibility of the cumulative evidence was “low” or “very low” for short-term exposure to NO_2, PM_{10}, and O_3, and was “moderate” for $PM_{2.5}$ and SO_2 according to GRADE criteria (Table S6).

One study investigated the association between short-term NO exposure and

depression, and detected non-significant association (Wang et al., 2014). Two studies focused on short-term CO exposure and depression, but reported inconsistent results (Wang et al., 2014; Cho et al., 2014). Due to the limited number of studies, we did not generate pooled effect estimates for short-term NO or CO exposure and depression.

4. Discussion

4.1. Principal findings

In this systematic review and meta-analysis, we synthesized 22 studies from 10 countries to comprehensively evaluate the associations of long-term and short-term ambient air pollutants exposure with depression. We only observed significant association between short-term exposure to NO_2 and depression under the advanced IVhet meta-analyses, although more significant associations were detected under the conventional random effects model. Due to high between-study heterogeneity, the confidence in the pooled estimates were ranked as low or moderate, so a future meta-analysis incorporating additional study populations will be necessary to draw more definitive conclusions. A handful of studies explored the impact of other air pollutants, like NO, CO, and O_3, and the results were mixed.

4.2. Comparison with other studies

We systematically searched seven databases in two languages and were aware of one recently published meta-analysis on air pollution and depression (Gu et al., 2019, Table S7). In that meta-analysis, the authors investigated short-term effects of PM_{10} and $PM_{2.5}$ as well as long-term effects of $PM_{2.5}$. They included seven studies (n = 255,181) on $PM_{2.5}$ and PM_{10} exposure and depression, and reported that both long-term (OR = 1.25, 95% CI = 1.07 - 1.45) and short-term $PM_{2.5}$ (OR = 1.18, 95%

CI = 1.04 - 1.34) exposure were associated with higher odds for depression. No significant association was observed for short-term PM_{10} exposure. By comparison, we not only focused on PM_{10} and $PM_{2.5}$, but also NO_2, SO_2, O_3, CO, and NO. Thus, our pooled estimates were based on triple the number of studies and a substantially larger study population, which provided a more precise estimate of the association between ambient air pollution and depression. In addition, while the prior meta-analysis only adopted the random effects model, our current analysis applied both the random effects model and the IVhet model. Under the conventional random effects model, our pooled effects for both long- and short-term $PM_{2.5}$ exposure with depression were consistent with those from Gu et al.'s meta-analysis. However, the significant relationships disappear under the IVhet model. As is aforementioned in the methods section, the IVhet model outperforms the random effects model (Doi et al., 2015), thus our current pooled estimates would be more robust. Moreover, apart from study quality assessment, we also did ROB assessment for each study, performed meta-regression analyses to explore the sources of heterogeneity, and graded the credibility of the cumulative evidence. Collectively, our systematic review and meta-analysis builds on the prior meta-analysis by covering more air pollutants, including more studies and participants, and performing more thorough assessment for the included studies. As such, the evidence from our study might be more comprehensive and precise.

We excluded five studies concerning air pollution and depression that did not provide sufficient quantitative data for pooling in the current meta-analysis (Wang and Yang, 2018; Wang et al., 2019; Qiu et al., 2019; Sheffield et al., 2018; Shin et al., 2018). Specifically, two cross-sectional studies in China observed that greater levels of $PM_{2.5}$, SO_2, and total suspended particulate emission intensities were consistently associated

with a higher prevalence of depression (Wang and Yang, 2018; Wang et al., 2019). A time-series study of 10,947 participants showed that short-term $PM_{2.5}$ exposure contributed to 12.07% of total hospital admissions for depression (Qiu et al., 2019). A cohort study of 557 pregnant U.S. women observed greater mid-pregnancy $PM_{2.5}$ exposures to be associated with a greater frequency of depressive symptoms (Sheffield et al., 2018). Finally, Shin et al. also reported higher odds for depression in association with greater quartiles of ambient CO, NO_2, and PM_{10} levels in more than 120,000 Koreans (Shin et al., 2018). The results from these studies collectively supported a positive association between air pollution and depression, which were consistent with our meta-analytical estimates under the conventional random effects model, but were contrary with the estimates from the IVhet model.

Our results also indicate that the exposure period may modify associations between air pollution exposure and depression. More specifically, we found a significant association for depression with short-term exposure to NO_2, yet non-significant association with long-term exposure for NO_2. Still, most included short-term exposure studies did not adjust for long-term air pollution exposure, and we were thus unable to disentangle mutually confounded short- and long-term NO_2 effects. Participants' characteristics like age, sex, and income were also hypothesized to modify the association between air pollution and health outcomes. However, most included studies did not report stratified results, and thus we were unable to conduct subgroup analyses to assess the potential modification by these variables.

4.3. Pathophysiological mechanisms

The pathophysiological mechanisms underlying the association between ambient air pollution exposure and depression remain unclear, but several pathways have been

proposed (Block and Calderón-Garcidueñas, 2009; MohanKumar et al., 2008). It has been well-documented that inhalation of air pollutants can cause oxidative stress and systemic inflammation (Risom et al., 2005; Araujo, 2010; Møller and Loft, 2010). Mechanistic evidence indicates that ambient air pollutants might affect psychological status by causing oxidative stress and neuro-inflammation (Ng et al., 2008; Hurley and Tizabi, 2013). Oxidative stress can damage dopaminergic neurons; depletion of central nervous system dopamine is likely involved in the neuropathology of depression (Hasler, 2010; Block et al., 2004). Additionally, ambient air pollutions exposure may cause cerebrovascular damage and neurodegeneration by increasing expression of inflammatory mediators (e.g., hippocampal pro-inflammatory cytokines), upregulating expression of innate immunity, promoting autoantibodies to cell junction and neural proteins production, and activating neuro-inflammation responses (Fonken et al., 2011; Sama et al., 2007; Calderón-Garcidueñas et al., 2003). Moreover, many neuroimaging studies also found that air pollutants can hurt brain tissues (e.g., white matter, cortical gray matter, and basal ganglia) and thus cause cognitive disorders in humans (de Prado Bert et al., 2018; Wilker et al., 2015). Additionally, previous researches demonstrated that air pollution exposure impaired people's residential satisfaction and self-perceived health, which have been associated with mental health (von Lindern et al., 2016; Liu et al., 2018; Nguyen et al., 2017). Furthermore, exposure to ambient air pollutions has been linked to cardiovascular diseases, asthma, and chronic obstructive pulmonary diseases, and cancers (Franklin et al., 2015; Guarnieri and Balmes, 2014; Zhang et al., 2016; Hamra et al., 2014), which are also important predictors of depression (Ng et al., 2008; Maurer et al., 2008; Scott et al., 2007; Ossola et al., 2018; Sotelo et al., 2014). The positive associations between NO_2 exposure and depression in our meta-analysis are consistent with these

hypothesized mechanisms.

4.4. Strengths and limitations

The current study has several strengths. First, we provide the most comprehensive evidence on the relationship between depression and ambient air pollution exposure to date. The total number of participants was large, we not only estimated airborne PM, but also airborne gaseous pollutants. Second, we assessed the quality and ROB for each included study according to validated or widely accepted scales and determined confidence of our pooled estimates according to the GRADE system. Thus, our pooled results may be valuable for researchers in this area to identify research gaps and to improve future study designs. Third, we conducted multiple sensitivity analyses by excluding any single study or some specific studies (e.g., two studies that included children and teenagers < 18 years of age as participants (Zock et al., 2018; Robert et al., 2019)), and found that the effects estimates were consistent with those from the overall analyses. This indicates that these pooled results were reliable.

However, our study also has some limitations. First, there was high between-study heterogeneity for all of the pooled air pollutants-depression associations, although we adopted the robust IVhet model to generate pooled estimates. With a limited number of studies, we were unable to perform sub-group and meta-regression analyses to identify the sources of the heterogeneity except for the association between long-term $PM_{2.5}$ exposure and depression. However, we found that none of the detected potential moderators contributed to the heterogeneity for the association of long-term $PM_{2.5}$ exposure and depression. This indicates that other unmeasured or unreported variables would be more responsible for the heterogeneity. Second, according to the GRADE system, the credibility of the cumulative evidence was “low” or “very low” for all

meta-analyses except that for short-term exposure to $PM_{2.5}$ and SO_2 (moderate). The main causes for degrading the quality of the cumulative evidence included high heterogeneity and inconsistent results across studies as well as publication bias. The strength of recommendation in healthy and environmental policy-making guidelines was therefore greatly compromised. Third, while the included cohort and cross-sectional studies were ranked as "high" quality, those with a time-series, panel, or case-crossover design has low quality. The main reason for the low quality was that such short-term studies did not control for long-term air pollution exposure, which preclude us to disentangle between short-term triggering effects of air pollution and long-term effects. In addition, about half of the included studies assessed exposure using data from fixed air monitoring stations, which might have caused exposure misclassification. Further, many studies defined depression using questionnaires, but not clinically diagnosed, thus outcome misclassification is also possible. Fourth, the number of studies (or data sets) for some air pollutants (e.g., NO and CO) was small ($n \leq 2$) (Wang et al., 2014; Cho et al., 2014), which precluded meta-analysis. Fifth, the included studies were not representative of global populations, as nearly all included were from China, Korea, North America, and Europe, and so our results may not be generalizable to other areas. Sixth, most studies only reported estimates from single-pollutant model, thus we were unable to explore potential synergistic or additive effects of correlated exposures in multi-pollutant mixtures (Billionnet et al., 2012). Seventh, most studies used a linear model to fit the air pollutant-depression associations, but associations may be non-linear. Eighth, nearly all of our included studies controlled for potential confounders, yet confounding factors varied among the studies, and some important confounding factors such as noise and greenspace were not considered. Thus, we cannot rule out the possibility for residual and unmeasured

confounding in our pooled estimates. Ninth, we did not convert HR and RR to OR, but pooled them directly, this might have biased the pooled results. Finally, the approach used to select lag for short-term exposure studies might have biased to a greater pooled effect estimate.

5. Conclusions and Future perspectives

In summary, the present systematic review and meta-analysis indicates an association for short-term exposure to NO_2 and depression, but not for the other air pollutants. However, due to high between-study heterogeneity and small sample sizes for some pollutants, it is difficult to draw a robust conclusion on the plausibility of an air pollution-depression association. In the future, research focus should be extended to other geographic areas, especially those with high ambient air pollution levels like Africa and India. Advanced methods should be applied to assess individual air pollution exposure, and more strict definition and diagnosis for depression should be adopted. More sophisticated statistical analyses including multi-pollutant models, non-linear association investigation, and effect modification assessment, should be employed. Some important confounding variables, including meteorologic factors, noise, and green space, should be collected and adjusted. To facilitate future quantitative synthesis, authors should improve results importing, providing numerical estimates and describing bias concerns. Finally, mechanistic studies remain needed to clearly elucidate the biological pathways underlying associations between air pollution and depression.

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Conflicts of interest

The authors declare no competing interests.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). American Psychiatric Association Publishing, Washington, DC.

Araujo, J.A., 2010. Particulate air pollution, systemic oxidative stress, inflammation, and atherosclerosis. Air Qual. Atmos. Health 4, 79-93.

Atkinson, R.W., Cohen, A., Mehta, S., Anderson, H.R., 2012. Systematic review and meta-analysis of epidemiological time-series studies on outdoor air pollution and health in Asia. Air Qual. Atmos. Health 5 (4), 383-391.

Billionnet, C.; Sherrill, D.; Annesi-Maesano, I. Estimating the health effects of exposure to multi-pollutant mixture. Ann. Epidemiol. 2012;22:126-141.

Block, M.L., Calderón-Garcidueñas, L., 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends. Neurosci. 32, 506-516.

Block, M.L., Wu, X., Pei, Z., Li, G., Wang, T., Qin, L., et al., 2004. Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. FASEB J. 18, 1618-1620.

Buoli, M., Grassi, S., Caldiroli, A., Carnevali, G.S., Mucci, F., Iodice, S., et al., 2018. Is there a link between air pollution and mental disorders? Environ. Int. 118:154-168.

Calderón-Garcidueñas, L., Maronpot, R.R., Torres-Jardon, R., Henríquez-Roldán, C., Schoonhoven, R., Acuña-Ayala, H., et al., 2003. DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration. Toxicol. Pathol. 31, 524-538.

Cho, J., Choi, Y.J., Suh, M., Sohn, J., Kim, H., Cho, S.K., et al., 2014. Air pollution as a risk factor for depressive episode in patients with cardiovascular disease,

diabetes mellitus, or asthma. J. Affect. Disord. 157, 45-51.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46-56.

de Prado Bert, P., Mercader, E.M.H., Pujol, J., Sunyer, J., Mortamais, M., 2018. The effects of air pollution on the brain: a review of studies interfacing environmental epidemiology and neuroimaging. Curr. Environ. Health Rep. 5, 351-364.

Doi, S.A., Barendregt, J.J., Khan, S., Thalib, L., Williams, G.M., 2015. Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model. Contemp. Clin. Trials 45, 130-138.

Doi, S.A.R., Furuya-Kanamori, L., Thalib, L., Barendregt, J.J., 2017. Meta-analysis in evidence-based healthcare: a paradigm shift away from random effects is overdue. Int. J. Evid. Based Healthc. 15, 152-160.

Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Künzli, N., et al., 2015. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ. Health Perspect. 123, 381-389.

Ferenchick, E.K., Ramanuj, P., Pincus, H.A., 2019. Depression in primary care: part 1-screening and diagnosis. BMJ 365, l794. doi: 10.1136/bmj.l794.

Fonken, L.K., Xu, X., Weil, Z.M., Chen, G., Sun, Q., Rajagopalan, S., et al., 2011. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Mol. Psychiatry 16, 987-995, 973.

Franklin, B.A., Brook, R., Arden Pope, C. 3rd., 2015. Air pollution and cardiovascular disease. Curr. Probl. Cardiol. 40, 207-238.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1789-1858.

GBD 2017 Risk Factor Collaborators, 2018. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1923-1994.

Gu, X., Liu, Q., Deng, F., Wang, X., Lin, H., Guo, X., et al., 2019. Association between particulate matter air pollution and risk of depression and suicide: systematic review and meta-analysis. Br. J. Psychiatry 1-12. doi:10.1192/bjp.2018.295.

Guarnieri, M., Balmes, J.R., 2014. Outdoor air pollution and asthma. Lancet 383, 1581-1592.

Hamra, G.B., Guha, N., Cohen, A., Laden, F., Raaschou-Nielsen, O., Samet, J.M., et al., 2014. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ. Health Perspect. 122, 906-911.

Hasler, G., 2010. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry 9, 155-161.

Higgins, J.P.T., Green, S., 2011. Selection of Study Characteristics for Subgroup Analyses and Meta-regression. Cochran Handbook for Systematic Reviews of Interventions, Version 5.1.0. http://www.handbook.cochran.org. (Accessed 1 January 2017).

Higgins, J.P., Altman, D.G., Gøtzsche, P.C., et al., 2011. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928. doi:10.1136/bmj.d5928.

Hurley, L.L., Tizabi, Y., 2013. Neuroinflammation, neurodegeneration, and depression. Neurotox. Res. 23, 131-144.

Kim, H.B., Shim, J.Y., Park, B., Lee, Y.J., 2018. Long-term exposure to air pollutants and cancer mortality: a meta-analysis of cohort studies. Int.J.Environ.Res.Public Health 15, 2608.

Kim, J., Kim, H., 2017. Demographic and Environmental Factors Associated with Mental Health: A Cross-Sectional Study. Int. J. Environ. Res. Public Health 14, pii: E431.

Kim, K.N., Lim, Y.H., Bae, H.J., Kim, M., Jung, K., Hong, Y.C., 2016. Long-Term Fine Particulate Matter Exposure and Major Depressive Disorder in a Community-Based Urban Cohort. Environ. Health Perspect. 124, 1547-1553.

Kioumourtzoglou, M.A., Power, M.C., Hart, J.E., Okereke, O.I., Coull, B.A., Laden, F., et al., 2017. The Association Between Air Pollution and Onset of Depression Among Middle-Aged and Older Women. Am. J. Epidemiol. 185, 801-809.

Klompmaker, J.O., Hoek, G., Bloemsma, L.D., Wijga, A.H., van den Brink, C., Brunekreef, B., et al., 2019. Associations of combined exposures to surrounding green, air pollution and traffic noise on mental health. Environ. Int. 129:525-537.

Lam, J., Sutton, P., Kalkbrenner, A., Windham, G., Halladay, A., Koustas, E., et al., 2016. A Systematic Review and Meta-Analysis of Multiple Airborne Pollutants and Autism Spectrum Disorder. PLoS One 11, e0161851.

Lim, Y.H., Kim, H., Kim, J.H., Bae, S., Park, H.Y., Hong, Y.C., 2012. Air pollution

and symptoms of depression in elderly adults. Environ. Health Perspect. 120, 1023-1028.

Lin, H., Guo, Y., Kowal, P., Airhihenbuwa, C.O., Di, Q., Zheng, Y., et al., 2017. Exposure to air pollution and tobacco smoking and their combined effects on depression in six low- and middle-income countries. Br. J. Psychiatry 211, 157-162.

Lin, Y., Zhou, L., Xu, J., Luo, Z., Kan, H., Zhang, J., et al., 2017. The impacts of air pollution on maternal stress during pregnancy. Sci. Rep. 7, 40956.

Liu, S., Ouyang, Z., Chong, A.M., Wang, H., 2018. Neighborhood environment, residential satisfaction, and depressive symptoms among older adults in residential care homes. Int.J.Aging Hum.Dev. 87(3):268-288.

Maurer, J., Rebbapragada, V., Borson, S., Goldstein, R., Kunik, M.E., Yohannes, A.M., et al., 2008. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest. 134, 43S-56S.

MohanKumar, S.M., Campbell, A., Block, M., Veronesi, B., 2008. Particulate matter, oxidative stress and neurotoxicity. Neurotoxicology 29, 479-488.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., **PRISMA** Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151, 264-269, W64.

Møller, P., Loft, S., 2010. Oxidative damage to DNA and lipids as biomarkers of exposure to air pollution. Environ. Health Perspect. 118, 1126-1136.

Morgan, R.L., Thayer, K.A., Santesso, N., Holloway, A.C., Blain, R., Eftim, S.E., et al., 2019. A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE. Environ. Int. 122, 168-184.

Mustafic, H., Jabre, P., Caussin, C., Murad, M.H., Escolano, S., Tafflet, M., et al., 2012. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. JAMA 307, 713-721.

Ng, F., Berk, M., Dean, O., Bush, A.I., 2008. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int. J. Neuropsychopharmacol. 11, 851-76.

Nguyen, H.A., Anderson, C.A.M., Miracle, C.M., Rifkin, D.E., 2017. The Association between Depression, Perceived Health Status, and Quality of Life among Individuals with Chronic Kidney Disease: An Analysis of the National Health and Nutrition Examination Survey 2011-2012. Nephron. 136(2):127-135.

OHAT, 2015. Translation (OHAT) Division of the National Toxicology Program National Institute of Environmental Health Sciences.

Ossola, P., Gerra, M.L., De Panfilis, C., Tonna, M., Marchesi, C., 2018. Anxiety, depression, and cardiac outcomes after a first diagnosis of acute coronary syndrome. Health Psychol. 37, 1115-1122.

Pun, V.C., Manjourides, J., Suh, H., 2017. Association of Ambient Air Pollution with Depressive and Anxiety Symptoms in Older Adults: Results from the NSHAP Study. Environ. Health Perspect. 125, 342-348.

Qiu, H., Zhu, X., Wang, L., Pan, J., Pu, X., Zeng, X., et al., 2019. Attributable risk of hospital admissions for overall and specific mental disorders due to particulate matter pollution: A time-series study in Chengdu, China. Environ. Res. 170, 230-237.

Ramanuj, P., Ferenchick, E.K., Pincus, H.A., 2019. Depression in primary care: part 2-management. BMJ 365, l835. doi: 10.1136/bmj.l835.

Risom, L., Møller, P., Loft, S., 2005. Oxidative stress-induced DNA damage by

particulate air pollution. Mutat. Res. 592, 119-137.

Roberts, S., Arseneault, L., Barratt, B., Beevers, S., Danese, A., Odgers, C.L., et al., 2019. Exploration of NO_2 and $PM_{2.5}$ air pollution and mental health problems using high-resolution data in London-based children from a UK longitudinal cohort study. Psychiatry Res. 272, 8-17.

Sama, P., Long, T.C., Hester, S., Tajuba, J., Parker, J., Chen, L.C., et al., 2007. The cellular and genomic response of an immortalized microglia cell line (BV2) to concentrated ambient particulate matter. Inhal. Toxicol. 19, 1079-1087.

Scott, K.M., Von Korff, M., Ormel, J., Zhang, M.Y., Bruffaerts, R., Alonso, J., et al., 2007. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen. Hosp. Psychiatry 29, 123-133.

Sheffield, P.E., Speranza, R., Chiu, Y.M., Hsu, H.L., Curtin, P.C., Renzetti, S., et al., 2018. Association between particulate air pollution exposure during pregnancy and postpartum maternal psychological functioning. PLoS One 13, e0195267.

Shin, J., Park, J.Y., Choi, J., 2018. Long-term exposure to ambient air pollutants and mental health status: A nationwide population-based cross-sectional study. PLoS One 13, e0195607.

Sotelo, J.L., Musselman, D., Nemeroff, C., 2014. The biology of depression in cancer and the relationship between depression and cancer progression. Int. Rev. Psychiatry 26, 16-30.

Spitzer, R.L., Kroenke, K., Linzer, M., Hahn, S.R., Williams, J.B., deGruy, F.V. 3rd., et al., 1995. Health-related quality of life in primary care patients with mental disorders. Results from the PRIME-MD 1000 Study. JAMA 274, 1511-1517.

Szyszkowicz, M., Rowe, B.H., Colman, I., 2009. Air pollution and daily emergency department visits for depression. Int. J. Occup. Med. Environ. Health 22,

355-362.

Szyszkowicz, M., Kousha, T., Kingsbury, M., Colman, I., 2016. Air Pollution and Emergency Department Visits for Depression: A Multicity Case-Crossover Study. Environ. Health Insights 10, 155-161.

The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews: Checklist for Analytical Cross Sectional Studies. 2016. Accessed at: http://joannabriggs.org/research/critical-appraisaltools.html; accessed date: January 21, 2018.

Vert, C., Sánchez-Benavides, G., Martínez, D., Gotsens, X., Gramunt, N., Cirach, M., et al., 2017. Effect of long-term exposure to air pollution on anxiety and depression in adults: A cross-sectional study. Int. J. Hyg. Environ. Health 220, 1074-1080.

Von Lindern, E., Hartig, T., Lercher, P., 2016. Traffic-related exposures, constrained restoration, and health in the residential context. Health Place. 39:92-100.

Walker, E.R., McGee, R.E., Druss, B.G., 2015. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA psychiatry 72, 334-341.

Wang, F., Liu, H., Li, H., Liu, J., Guo, X., Yuan, J., et al., 2018. Ambient concentrations of particulate matter and hospitalization for depression in 26 Chinese cities: A case-crossover study. Environ. Int. 114, 115-122.

Wang, Q., Yang, Z., 2018. Does chronic disease influence susceptibility to the effects of air pollution on depressive symptoms in China? Int. J. Ment. Health Syst. 12, 33.

Wang, R., Liu, Y., Xue, D., Yao, Y., Liu, P., Helbich, M., 2019. Cross-sectional associations between long-term exposure to particulate matter and depression in

China: The mediating effects of sunlight, physical activity, and neighborly reciprocity. J. Affect. Disord. 249, 8-14.

Wang, Y., Eliot, M.N., Koutrakis, P., Gryparis, A., Schwartz, J.D., Coull, B.A., et al., 2014. Ambient air pollution and depressive symptoms in older adults: results from the MOBILIZE Boston study. Environ. Health Perspect. 122, 553-558.

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., et al., 2010. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_ epidemiology/oxford.asp. 50(4): p. 1088-1101.

Wilker, E.H., Preis, S.R., Beiser, A.S., Wolf, P.A., Au, R., Kloog, I., et al., 2015. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke 46, 1161-1166.

Woodruff, T.J., Sutton, P., 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ. Health Perspect. 122, 1007-1014.

World Health Organization, April 7, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. Available at: https://www.who.int/mental_health/management/ depression/prevalence_ global_heath_estima tes/en/. (Accessed 22 March 2018).

Yang, B.Y., Qian, Z., Howard, S.W., Vaughn, M.G., Fan, S.J., Liu, K.K., et al., 2018. Global association between ambient air pollution and blood pressure: A systematic review and meta-analysis. Environ. Pollut. 235, 576-588.

Zhang, S., Li, G., Tian, L., Guo, Q., Pan, X., 2016. Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: A systematic

review and meta-analysis. Environ. Res. 148, 15-23.

Zhang, Z., Zhao, D., Hong, Y.S., Chang, Y., Ryu, S., Kang, D., et al, 2019. Long-Term Particulate Matter Exposure and Onset of Depression in Middle-Aged Men and Women. Environ. Health Perspect. 127, 77001.

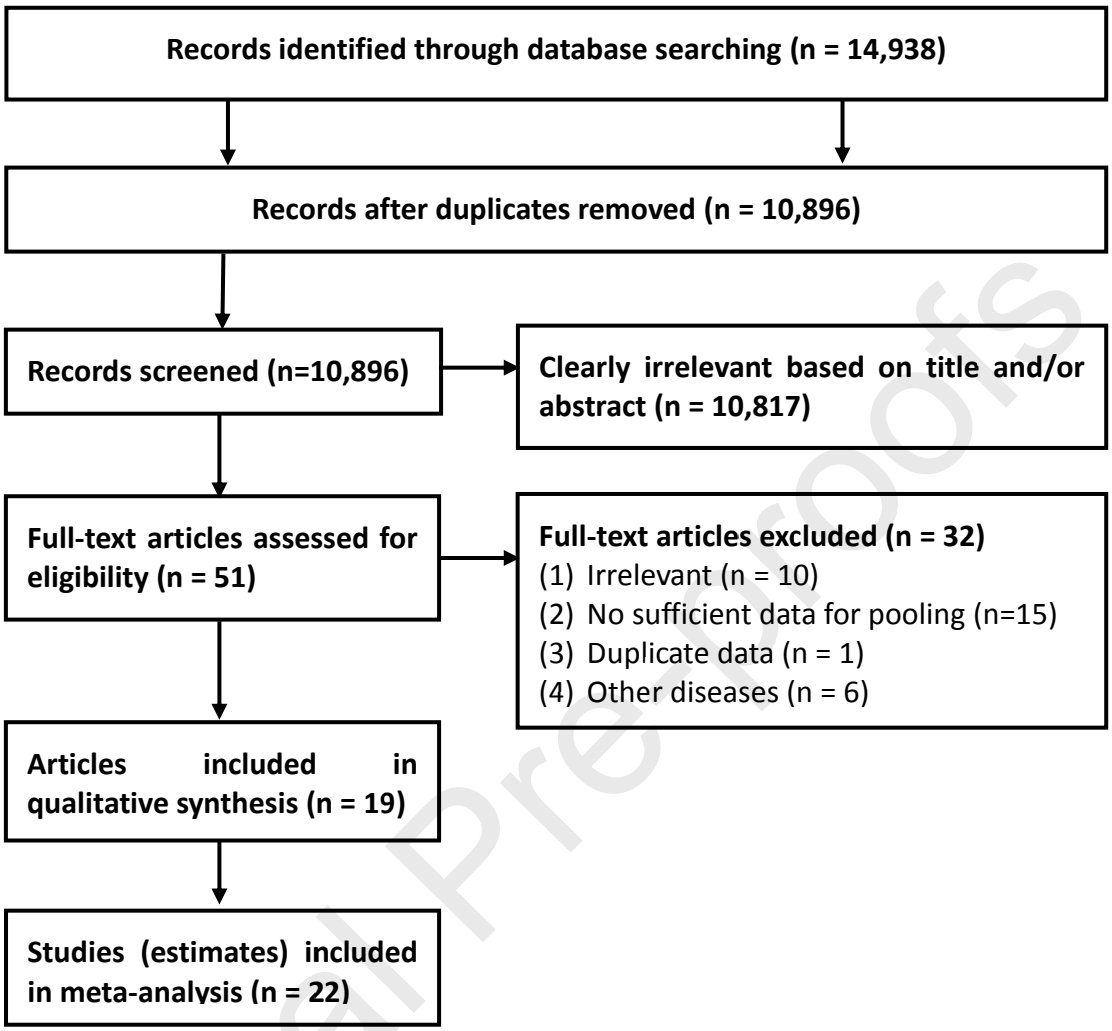
Zhao, T., Markevych, I., Standl, M., Schulte-Körne, G., Schikowski, T., Berdel, D., et al., 2019. Ambient ozone exposure and depressive symptoms in adolescents: Results of the GINIplus and LISA birth cohorts. Environ. Res. 170, 73-81.

Zijlema, W.L., Wolf, K., Emeny, R., Ladwig, K.H., Peters, A., Kongsgård, H., et al., 2016. The association of air pollution and depressed mood in 70,928 individuals from four European cohorts. Int. J. Hyg. Environ. Health 219, 212-219.

Zock, J.P., Verheij, R., Helbich, M., Volker, B., Spreeuwenberg, P., Strak, M., et al., 2018. The impact of social capital, land use, air pollution and noise on individual morbidity in Dutch neighbourhoods. Environ. Int. 121, 453-460.

Tables

Figure Legends



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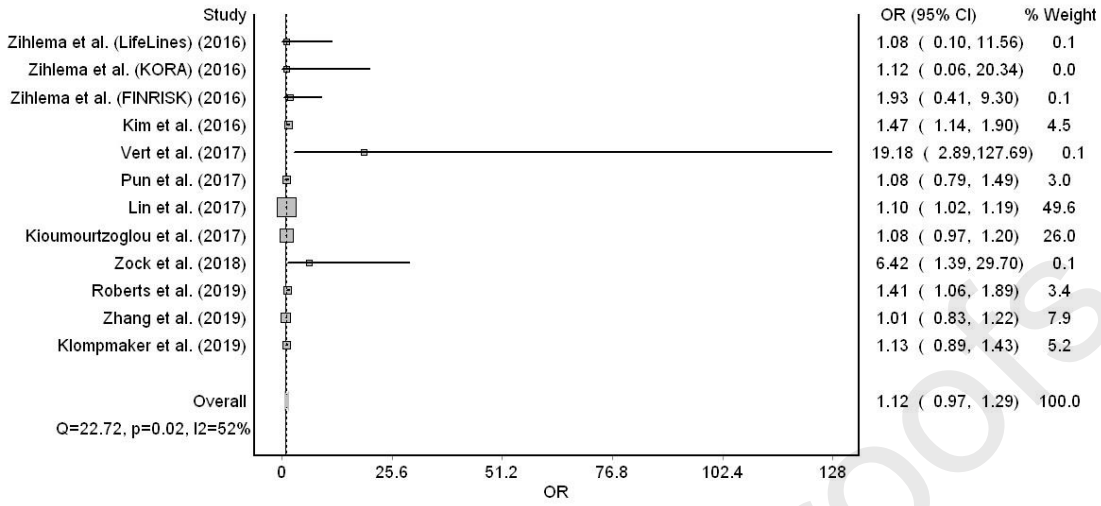

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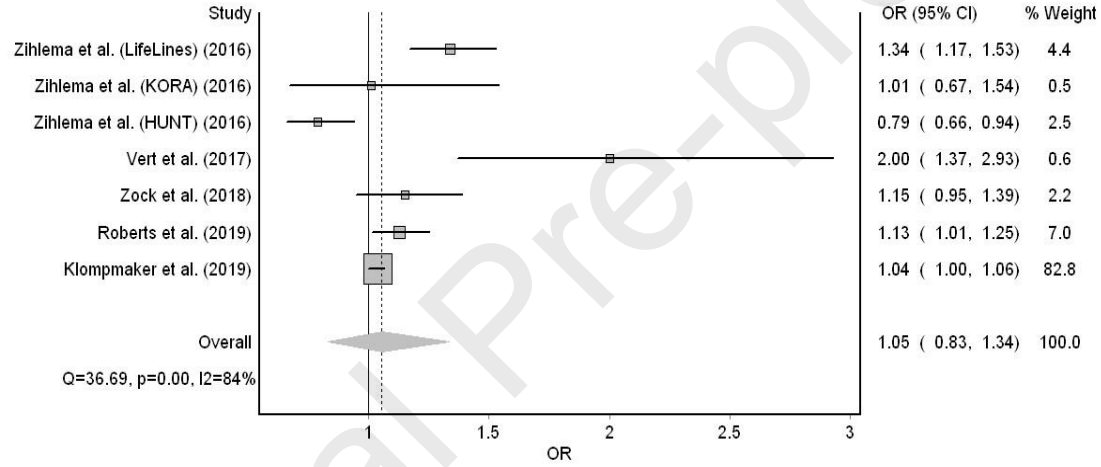

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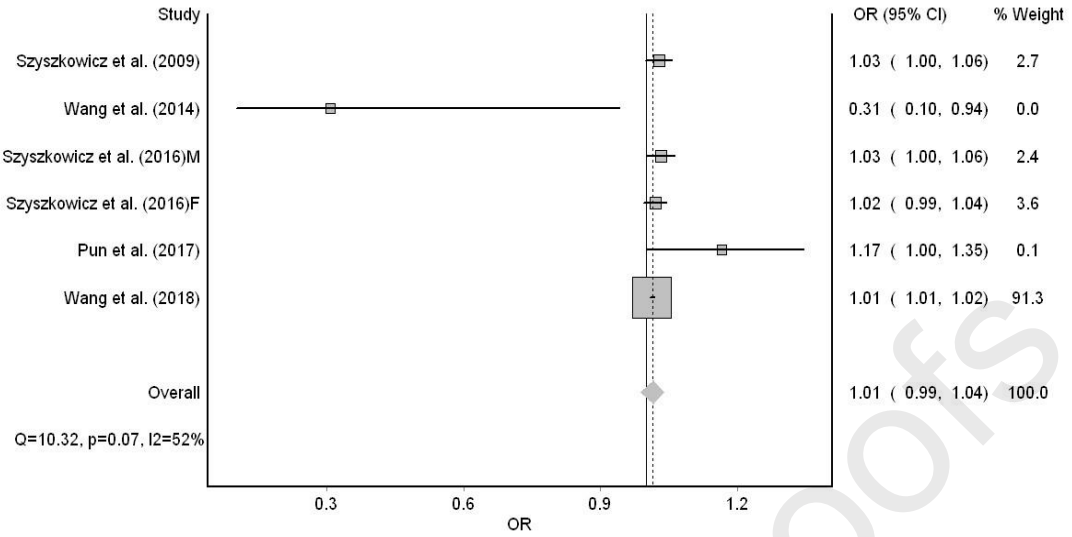

B

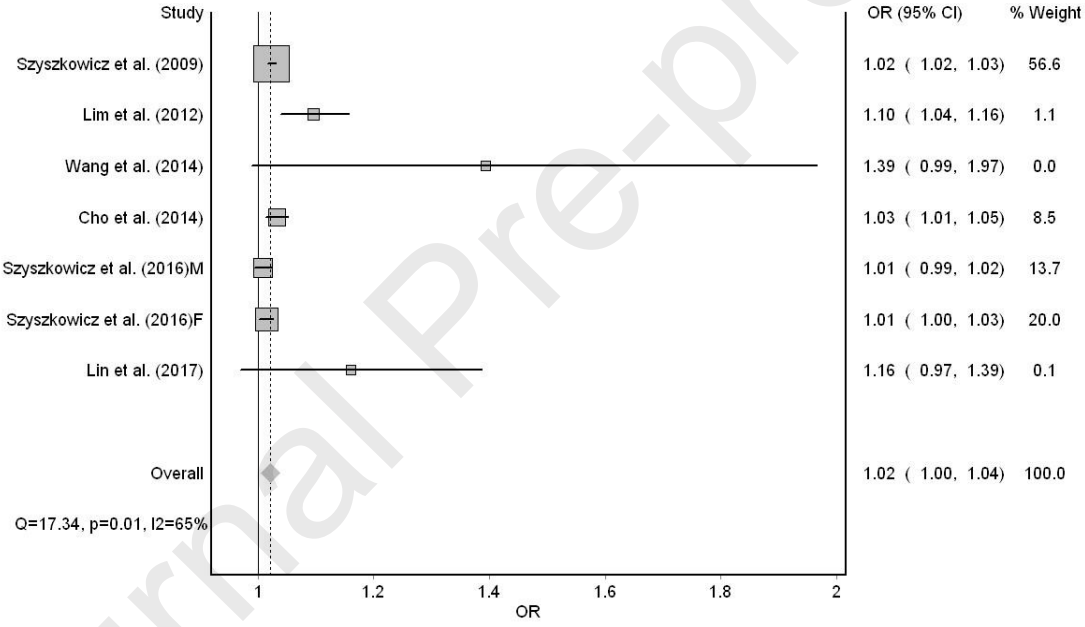

Table 1. Characteristics of the studies included in the meta-analysis.

Authors (publication year)	Study Location	Study Design	Study Participants	Studied Pollutants	Exposure duration	Exposure assessme
Szyszkowicz et al. (2009)	Canada (North America)	Time-series	Emergency visits for depression from six cities in Canada (n = 27, 047)	$PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, O_3	Short-term	National Surveillar (Monitori
Lim et al. (2012)	Korea (Asia)	Panel	Participants who visited a community center for the elderly located in Seoul, Korea (2008 -2010), with an average age of 71 years (n = 537)	PM_{10}, SO_2, NO_2, O_3	Short-term	Monitorir
Wang et al. (2014)	United States (North America)	Cohort	Participants from the MOBILIZE Boston Study (2005-2008) aged greater than 65 years (n = 732).	$PM_{2.5}$, NO_2, O_3, CO, NO	Short-term	Harvard S Public He Stationary monitorir
Cho et al. (2014)	Korea (Asia)	Case-crossover	Patients (cardiovascular disease, diabetes mellitus, or asthma patients) visited the emergency department for depression, with a mean age of 44 years (n = 4985)	PM_{10}, SO_2, NO_2, O_3, CO	Short-term	Monitorir
Szyszkowicz et al. (2016)	Canada (North America)	Case-crossover	People who visited hospital emergency departments for depression (n = 118, 602)	$PM_{2.5}$, SO_2, NO_2, O_3	Short-term	Environm (Monitori
Zijlema et al. -LifeLines (2016)	Netherlands (Europe)	Cohort	Participants of LifeLines cohort (2007-2013) with a mean age of 43.8 years at baseline (n = 32, 145)	PM_{10}, $PM_{2.5}$, NO_2,	Long-term	LUR moc
Zijlema et al. -KORA (2016)	Germany (Europe)	Cohort	Participants of KORA cohort (2004-2005 and 2006-2008) with a mean age of 55.3 years at baseline (n = 5314)	PM_{10}, $PM_{2.5}$, NO_2,	Long-term	LUR moc
Zijlema et al. -HUNT (2016)	Norway (Europe)	Cohort	Participants of HUNT cohort (2006-2008) with a mean age of 54.7 years at baseline (n = 32, 102)	PM_{10}, $PM_{2.5}$, NO_2,	Long-term	LUR moc
Zijlema et al. -FINRISK (2016)	Finland (Europe)	Cohort	Participants of FINRISK cohort (2007) with a mean age of 51.9 years at baseline (n = 1367)	PM_{10}, $PM_{2.5}$, NO_2	Long-term	LUR moc
Kim et al. (2016)	Korea (Asia)	Cohort	Participants of NHID cohort (2002-2010) aged 15-79 years at baseline (n= 27,270)	$PM_{2.5}$	Long-term	Monitorir

Vert et al. (2017)	Spain (Europe)	Cross-sectional	Participants from the ALFA cohort (2013-2014) with a mean age of 56.5 years (n=958)	PM_{10}, $PM_{2.5}$, NO_2, PM coarse, NOx	Long-term	LUR mod
Lin and Guo et al. (2017)	China, Ghana, India, Mexico, Russia, South Africa	Cross-sectional	Participants from SAGE cohort (2007-2010) aged 18 years or older (n = 41, 785)	$PM_{2.5}$	Long-term	GEOS-Cl transport
Kioumourtzoglou et al. (2017)	United States (North America)	Cohort	Women from the NHS cohort (1996-2008) with a mean age of 66.6 years (n = 41, 844)	$PM_{2.5}$, O_3	Long-term	Nationwi spatiotem
Kim et al. (2017)	Korea (Asia)	Cross-sectional	Residents living in 25 communities in Seoul aged 19 years or older (n = 23, 139)	PM_{10}	Long-term	National Environm Research (Monitori
Pun et al. (2017)	United States (North America)	Cohort	Participants from the NSHAP cohort (2005-2006 and 2010-2011) with a mean age of 69.3 at baseline (n = 4008)	$PM_{2.5}$	Both	Generaliz mixed mo
Lin and Zhou et al. (2017)	China (Asia)	Cross-sectional	Pregnant women who regularly visited prenatal-care Clinics in Shanghai (2010) with a mean age of 28 years (n=1,931)	PM_{10}, SO_2, NO_2	Short-term	Shanghai Environm Monitorin
Wang et al. (2018)	China (Asia)	Case-crossover	Hospital admissions related to depression from 26 cities of China (n = 19, 646)	PM_{10}, $PM_{2.5}$	Short-term	National Monitorin
Zock et al. (2018)	Netherlands (Europe)	Cross-sectional	4450 residents from 135 neighbourhoods in 43 Dutch municipalities, aged 40.5 years	$PM_{2.5}$, PM_{10}, NO_2	Long-term	ESCAPE
Roberts et al. (2019)	England (Europe)	Cohort	284 children living in London drawn from the Environmental Risk Longitudinal Twin study	$PM_{2.5}$, NO_2	Long-term	KCLurba
Zhao et al. (2019)	Germany (Europe)	Cross-sectional	Participants from two German birth cohorts (GINIplus and LISA cohorts), with an average age of 15.20 years (n = 2827)	O_3	Both	Monitorin short-tern LUR mod long-term
Zhang et al. (2019)	Korea (Asia)	Cohort	Adults underwent a comprehensive annual or biennial health examination at clinics (n = 123,045)	$PM_{2.5}$, PM_{10}	Long-term	LUR mo subjects' codes
Klompmaker et al. (2019)	Netherlands (Europe)	Cross-sectional	Adults from a national health survey (n = 354,827)		Long-term	LUR mo home add

Abbreviations: ALFA: Alzheimer and Families; CESD-11: 11-item form of the Center for Epidemiological Studies-Depression; CESD-R: Revised Center for Epidemiological Studies Depression Scale; CO: carbon monoxide; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; FINRISK: the Finnish National Cardiovascular Risk Factor Survey; GEOS: Geodetic Satellite; HADS-D: depression subscale of the Hospital Anxiety Depression Scale; HR: hazard ratio; HUNT: Helseundersøkelsen i Nord-Trøndelag; ICD-9: International Classification for Diseases, 9th revision; ICD-10: International Classification of Diseases, 10th revision; ICPC, International Classification of Primary Care; KORA: Cooperative Health Research in the Region Augsburg; LUR: land use regression; NO_2 : nitrogen dioxide; NHID: National Health Insurance database; NHS: Nurses' Health Study; NSHAP: National Social Life, Health and Aging Project; NO: nitrogen monoxide; NO_x: oxynitride; O_3: ozone; OR: odd ratio; PHQ-9: depression module of the patient health questionnaire; PM_{10}: particle with aerodynamic diameter ≤ 10 μm; $PM_{2.5}$: particle with aerodynamic diameter ≤ 2.5 μm; PM: particulate matter; RR: relative risk; SAGE: Study on global AGEing and adults health; SCL-90-R: Symptom Checklist-90-Revised Scale; SGDS-K: The Korean version of the Geriatric Depression Scale-Short Form; SO_2: sulfur dioxide; WHO: World Health Organization; WMH-CIDI:

World Mental Health Survey version of the Composite International Diagnostic Interview.

Table 2. Meta-analysis results for associations between long-term and short-term air pollution exposure and depression under the IVhet model.

	No. of studies	Sample size	OR (95% CI)	Cochran's Q	I^2	$P_{heterogeneity}$	LFK index
Long-term							
$PM_{2.5}$	12	637,297	1.12 (0.97, 1.29)	22.72	51.6	0.019	4.52 (Major asymmetry)
PM_{10}	8	575,980	1.04 (0.88, 1.25)	48.99	85.7	< 0.001	2.12 (Major asymmetry)
NO_2	7	430,080	1.05 (0.83, 1.34)	36.69	83.6	< 0.001	2.67 (Major asymmetry)
Short-term							
$PM_{2.5}$	6	170,027	1.01 (0.99, 1.04)	10.32	51.6	0.067	-0.58 (No asymmetry)
PM_{10}	5	54,146	1.01 (0.98, 1.04)	29.97	86.7	< 0.001	6.57 (Major asymmetry)
NO_2	7	153,826	1.02 (1.00, 1.04)	17.34	65.4	0.008	6.00 (Major asymmetry)
SO_2	6	153,094	1.03 (0.99,	17.37	71.2	0.004	-0.13 (No asymmetry)

			1.07)				
O_3	7	154,722	1.01 (0.99, 1.03)	33.71	82.2	< 0.001	-2.34 (Major asymmetry)

Abbreviations: CI: confidence interval; IVhet: Inverse Variance Heterogeneity; LKF: Luis Furuya-Kanamori; NO_2: nitrogen dioxide; O_3: ozone; OR: odd ratio; PM_{10}: particle with aerodynamic diameter ≤ 10 µm; $PM_{2.5}$: particle with aerodynamic diameter ≤ 2.5 µm; SO_2: sulfur dioxide.

Highlights

1. A systematic review identified 22 studies from 10 countries of the world.
2. Short-term exposure to NO_2 was associated with an increased odds of depression.
3. Long-term $PM_{2.5}$, PM_{10}, and NO_2 exposure was not associated with depression.
4. Short-term $PM_{2.5}$, PM_{10}, SO_2, and O_3 exposure was not associated with depression.

	No. of studies	I^2	IVhet model, OR (95% CI)
Long-term			
PM_{10}	8	85.7	1.04 (0.88, 1.25)
NO_2	7	83.6	1.05 (0.83, 1.34)
Short-term			
$PM_{2.5}$	6	51.6	1.01 (0.99, 1.04)
PM_{10}	5	86.7	1.01 (0.98, 1.04)
NO_2	7	65.4	1.02 (1.00, 1.04)
SO_2	6	71.2	1.03 (0.99, 1.07)
O_3	7	82.2	1.01 (0.99, 1.03)