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Air pollution exposure and depression: A comprehensive updated systematic review and meta-analysis☆

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ABSTRACT

We provide a comprehensive and updated systematic review and meta-analysis of the association between air pollution exposure and depression, searching PubMed, Embase, and Web of Sciences for relevant articles published up to May 2021, and eventually including 39 studies. Meta-analyses were performed separately according to pollutant type [particulate matter with diameter ≤10 μm (PM_{10}) and ≤2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO)] and exposure duration [short- (<30 days) and long-term (≥30 days)]. Test for homogeneity based on Cochran's Q and I^2 statistics were calculated and the restricted maximum likelihood (REML) random effect model was applied. We assessed overall quality of pooled estimates, influence of single studies on the meta-analytic estimates, sources of between-study heterogeneity, and publication bias. We observed an increased risk of depression associated with long-term exposure to $PM_{2.5}$ (relative risk: 1.074, 95% confidence interval: 1.021–1.129) and NO_2 (1.037, 1.011–1.064), and with short-term exposure to PM_{10} (1.009, 1.006–1.012), $PM_{2.5}$ (1.009, 1.007–1.011), NO_2 (1.022, 1.012–1.033), SO_2 (1.024, 1.010–1.037), O_3 (1.011, 0.997–1.026), and CO (1.062, 1.020–1.105). The publication bias affecting half of the investigated associations and the high heterogeneity characterizing most of the meta-analytic estimates partly prevent to draw very firm conclusions. On the other hand, the coherence of all the estimates after excluding single studies in the sensitivity analysis supports the soundness of our results. This especially applies to the association between $PM_{2.5}$ and depression, strengthened by the absence of heterogeneity and of relevant publication bias in both long- and short-term exposure studies. Should further investigations be designed, they should involve large sample sizes, well-defined diagnostic criteria for depression, and thorough control of potential confounding factors. Finally, studies dedicated to the comprehension of the mechanisms underlying the association between air pollution and depression remain necessary.

1. Introduction

Depression is a psychiatric disorder whose lifetime prevalence is estimated to be around 11%, with higher frequencies in females than males (Lim et al., 2018) and increasing trends reported in the general population (Moreno-Agostino et al., 2021). The severity of depression symptoms causes diminished quality of life, functional impairment, and substantial economic burden (Hammer-Helmich et al., 2018; Vos et al., 2015), which have led to consider depression as one of the leading causes of disability worldwide (James et al., 2018). Consequently, the identification and management of risk factors for depression is relevant for public health strategies.

Ambient air pollution consists of both particulate ($PM_{2.5}$, particles with an aerodynamic diameter ≤2.5 μm; PM_{10}, particles with an aerodynamic diameter ≤10 μm) and gaseous pollutants (NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; CO, carbon monoxide) (Wu et al., 2016). It ranks among the top five risks for attributable deaths globally (Abbafati et al., 2020; Cohen et al., 2017) and may cause a variety of

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health effects, such as cardiovascular and respiratory diseases, along with other chronic disorders like type 2 diabetes, obesity, systemic inflammation, Alzheimer's disease and dementia (World Health Organization, 2016).

Recent research has focused on the relationship between air pollution exposure and depression (Altuğ et al., 2020; Gu et al., 2020; Helbich et al., 2020; Petkus et al., 2020), also investigating the potentially underlying biological triggers. Mechanistic studies have shown that air pollution causes neuroinflammation, oxidative stress, and cerebrovascular damage (Babadjouni et al., 2017), which in turn have been associated with the onset of depression as a result of neurotransmitter and hormonal dysregulation (Li et al., 2017). Of note, imbalance of serotonin and noradrenalin in the central nervous system represents a well-accepted etiological mechanism of depression (Blier, 2016). Recent meta-analyses examining the relationship between air pollution and depression (Braithwaite et al., 2019; Fan et al., 2020; Liu et al., 2021; Zeng et al., 2019) were based on a limited number of studies and selected pollutants. In particular, the most updated one (Liu et al., 2021), evaluated only particulate matter and examined 20 studies.

The present meta-analysis updated the literature review, adding 19 more studies and investigating both ambient particulate ($PM_{2.5}$ and PM_{10}) and gaseous pollutants (i.e., NO_2, SO_2, O_3, and CO).

2. Methods

2.1. Search strategy

In conducting the systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Tables 1 and 2) (Moher et al., 2009). We did not publish a systematic review protocol beforehand but formulated the following specific research question: "Does exposure to ambient air pollution influence the risk of depression?" according to the "Participants", "Exposure", "Comparator", and "Outcomes" (PECO) framework.

We identified relevant publications in PubMed®, Embase®, and Web of Science™ (WoS), up to May 20, 2021. Our search strategy combined air pollution terms with depression terms as follows:

- PubMed: ("air pollution" [MeSH] OR "air pollutant*" [MeSH] OR "nitrogen dioxide" [MeSH] OR "sulfur dioxide" [MeSH] OR "carbon monoxide" [MeSH] OR "ozone" [MeSH] OR "particulate matter" [MeSH] OR particle OR "nitrogen oxides" [MeSH] OR "PM2.5" OR "PM10" OR "NO2" OR "NOx" OR "O3" OR "SO2" OR "black carbon") AND (depress* OR depression [MeSH] OR depressive OR depress OR depressed OR "unipolar disorder*" OR "mood disorder*" [MeSH] OR "mental health" [MeSH] OR "affective disorder*" OR "bipolar disorder*" [MeSH]). We limited our search to publications in English or Italian, studies conducted on humans, and with an available abstract.
- Embase: ("air pollution" OR "air pollutant*" OR "nitrogen dioxide" OR "sulfur dioxide" OR "carbon monoxide" OR "ozone" OR "particulate matter" OR particle OR "nitrogen oxides" OR "PM2.5" OR "PM10" OR "NO2" OR "NOx" OR "O3" OR "SO2" OR "black carbon") AND ("depress*" OR "depression" OR "depressive" OR "depress" OR "depressed" OR "unipolar disorder*" OR "mood disorder*" OR "mental health" OR "affective disorder*" OR "bipolar disorder*"). Search terms had to be present in the title or abstract of publications written in English or Italian, and with an available abstract.
- WoS: we ran the following search string applied to the "Topic" field tag: ((("air pollution" [MeSH] OR "air pollutant*" [MeSH] OR "nitrogen dioxide" [MeSH] OR "sulfur dioxide" [MeSH] OR "carbon monoxide" [MeSH] OR "ozone" [MeSH] OR "particulate matter" [MeSH] OR particle OR "nitrogen oxides" [MeSH] OR "PM2.5" OR "PM10" OR "NO2" OR "NOx" OR "O3" OR "SO2" OR "black carbon") AND (depress* OR depression [MeSH] OR depressive OR depress OR depressed OR "unipolar disorder*" OR "mood disorder*" [MeSH] OR "mental health" [MeSH] OR "affective disorder*" OR "bipolar disorder*" [MeSH]))). The search was limited to articles written in English and to the following "WoS categories": environmental sciences, neurosciences, public environmental occupational health, meteorology atmospheric sciences, psychiatry, biology, clinical neurology, environmental studies, psychology, psychology multidisciplinary, medicine research experimental, multidisciplinary sciences, psychology clinical, psychology developmental.

Reference lists of eligible reviews and included studies were also screened.

2.2. Selection criteria

We included all studies meeting the following criteria: (1) original research articles; (2) studies focusing on short- (<30 days) and/or long-term (≥30 days) exposures to air pollution; (3) studies comparing individuals exposed to different levels of air pollution. Exclusion criteria were: (1) source of pollution different from outdoor atmosphere (e.g., indoor air pollution); (2) study outcomes different than depression or depression group not clearly defined (e.g., reported outcome: "mental disorders"); (3) study outcomes referred to a specific nosological subgroup (e.g., post-partum depression) or to a particular population (e.g., pregnant women); (4) study subjects younger than 18 years old; (5) conference articles and reviews. After removing duplicates, titles, abstracts, and full texts were screened for eligibility (study selection process is shown in Fig. 1) by two of the co-authors (EB and MC). When in disagreement, a third author (ACP) was involved.

2.3. Data extraction

For each included study, two authors (EB and MC) independently retrieved information on first author's name, publication year, location, study period, design, sample size, outcome definition, list of air pollutants evaluated and their method of assessment, mean or median level of air pollutants, exposure duration, adjustment variables, and effects estimates with corresponding 95% confidence intervals (CI). The data extraction processes performed individually were eventually integrated to return an overall comprehensive set of results.

2.4. Standardization of data

Most studies presented results as either risk ratios, hazard ratios, or odds-ratios. We chose to report all these measures of association synthetically referring to them as "relative risk" (RR). We transformed the percent variation of morbidity into RR by dividing the percentage by 100 and adding 1 (Szyszkowicz et al., 2009; Wang et al., 2018). In studies reporting beta slopes (i.e., natural log relative risks), we exponentiated the regression coefficient to obtain the RR. Confidence intervals of the RRs were calculated after computing the confidence interval of the beta slopes through the standard error [$\beta \pm (1.96*SE)$], and then transforming the obtained estimates into RRs as explained above.

To make RRs from different studies comparable, we standardized the RR units across studies to a 10 μg/m^3 increase in air pollutant concentrations, except for carbon monoxide, for which RRs were expressed per increase in 1 mg/m^3. If the exposure variables were expressed as categories, we first computed the delta in exposure for which the RR was reported in the original publication, and then standardized per 10 μg/m^3. When studies reported their results in ppb or ppm, we first converted those measures as follows: (a) nitrogen dioxide (NO_2): 1 ppb = 1.88 μg/m^3; (b) sulfur dioxide (SO_2): 1 ppb = 2.62 μg/m^3; (c) ozone (O_3): 1 ppb = 2.00 μg/m^3; and (d) carbon oxide (CO): 1 ppm (i.e., 1000 ppb) = 1.145 mg/m^3. Afterwards, we standardized RRs for each study as follows (Yang et al., 2014):

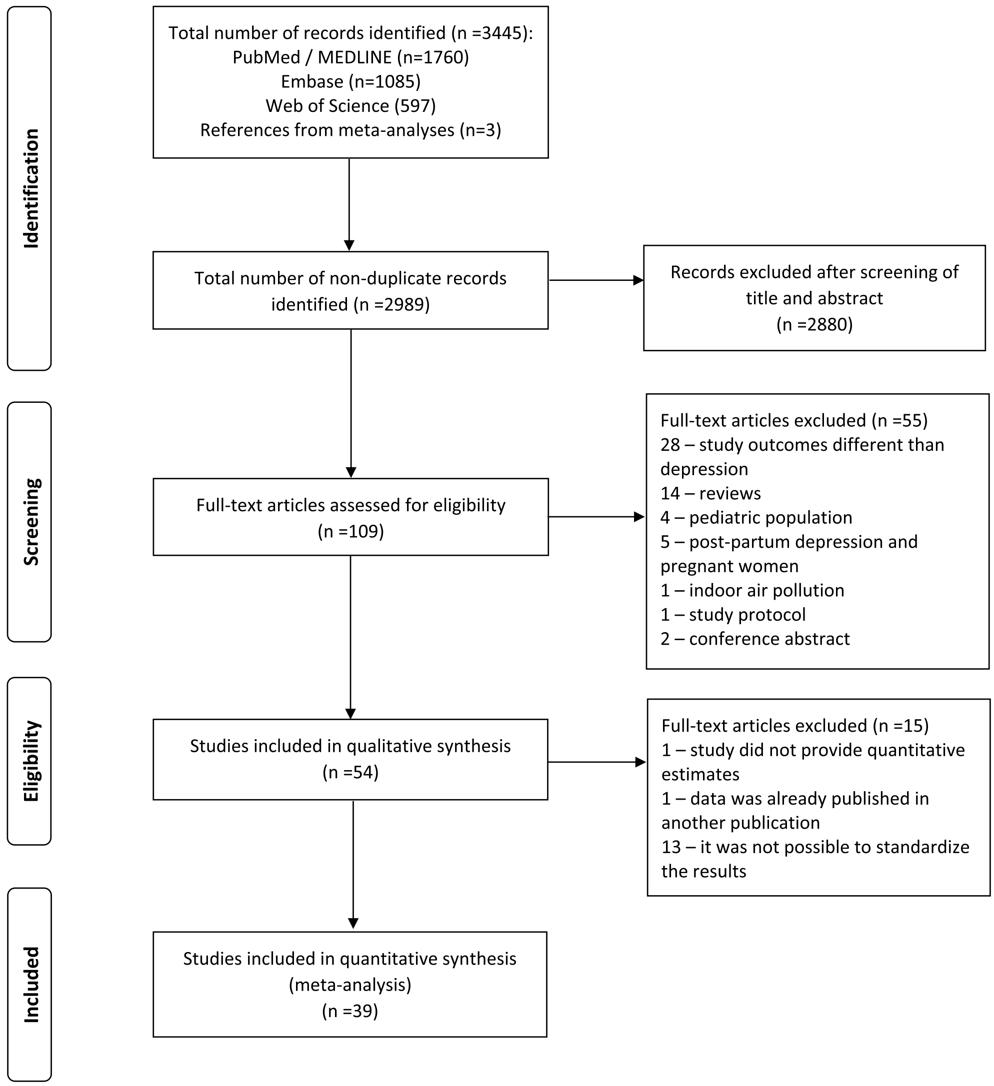

Fig. 1. Flowchart of study selection procedure.

$$Standardized\ RR = exp\left[\frac{\text{natural log}(original\ RR)}{original\ increment} * standardized\ increment\right].$$

Depression diagnosis was made using different methods (e.g., doctor's diagnosis, antidepressants' use, clinical assessment, questionnaire or scale, or self-reported). When the outcome assessment tools were not mutually exclusive, we chose the most objective method, according to the following classification: (1) clinical assessment [International Classification of Diseases (ICD) or International Classification of Primary Care (ICPC)]; (2) antidepressants' use or doctor's diagnosis; (3) scale; (4) self-reported.

In short-term exposure studies, different lag patterns were used to define time windows of exposure. Some studies reported multiple estimates for single-day lags (e.g., lag 0, 1, 2 days), while others reported cumulative lags (e.g., lag 0–7 days). To make the combination of estimates from various studies possible, we selected lags based on the following criteria: (a) when only one lag estimate was reported, this was used; or (b) when multiple lags were reported, in order of precedence we chose the lag that authors focused on or declared as a priority, the lag that was statistically significant, or the lag with the largest effect estimates (Yang et al., 2018).

When studies reported unadjusted and adjusted results, we considered the adjusted estimates. When studies reported results obtained from several adjusted models or sensitivity analyses, we chose the results from the model including the largest number of adjusting covariates. We also decided to report the estimates derived from single-pollutant models, as multipollutant models were rarely applied. When authors provided stratified estimates, we considered the overall estimates, if reported; otherwise, we used the estimates stratified by sex.

2.5. Meta-analysis methods

Meta-analyses were performed separately according to pollutant type and exposure duration. For each analysis, test for homogeneity based on Cochran's Q (Cochran, 1954) and I^2 (Higgins et al., 2003) statistics were calculated. I^2 was first calculated assuming a fixed effects model, according to the following formula:

$$I^2 = \frac{Q - (K - 1)}{Q}$$

with K being the number of included studies. Since all I^2 values were around or above 50%, we eventually used the restricted maximum likelihood (REML) random effect model. The REML model assumes that the true effects from individual studies are different from each other and that these differences follow a normal distribution with a common variance. When applying the REML model, we also re-calculated I^2 according to the following formula

$$I^2 = \frac{\widehat{tau^2}}{\widehat{tau^2} + s^2}$$

with $\widehat{tau^2}$ being an estimator of the between-study variance and s^2 representing the within-study variance. Cochran's Q, I^2, and Tau^2 were all listed alongside meta-analytic estimates.

We evaluated the presence of publication bias using funnel-plots in combination with Egger's test. When publication bias was present (i.e. Egger's p-value < 0.05), we also applied the trim-and-fill method (using the R_0 estimator) to produce an overall estimate of the effect adjusted for publication bias itself (Shi et al., 2019).

Source of heterogeneity was evaluated with univariate meta-regression models, when at least 10 studies were included and heterogeneity was large or extreme (Higgins and Green, 2011) (i.e. I^2 from REML model $\geq$50%). We considered the following variables as possible sources of heterogeneity: study location (Europe, Asia, and North America), study design (cross-sectional, cohort, case-control/case-crossover, time-series), method of depression definition (clinical assessment, antidepressants' use or doctor's diagnosis, questionnaire or scale, self-reported), method of exposure assessment [Land-Use Regression (LUR) model, spatiotemporal or chemical transport model, monitoring sites], age (mean/median age of participants $\geq$65 years, and $<$65 years), gender proportion (male proportion $\geq$50%, and $<$50%) and mean or median air pollutant level (air pollutant $>$ WHO guideline level and $\leq$WHO guideline level). For long-term exposure, we also considered the adjustment of important confounders such as smoking, education, employment status, presence of comorbidities, and socio-economic status as a possible source of heterogeneity. For short-term exposure, we also considered lag patterns used to define time windows of exposure [single lag, short cumulative lags ($\leq$lag 0–8), long cumulative lags ($>$lag 0–8 up to lag 0–30)] and sources of health data (emergency room visits and other sources). Sensitivity analyses were performed by examining the influence of excluding each study on the consistency of the results.

All statistical analyses were performed using Stata 17 (StataCorp. 2021; College Station, TX, USA).

2.6. Quality of the overall pooled estimates assessment

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group guideline (Morgan et al., 2019) to evaluate the overall quality of pooled estimates. This tool is composed of five items: 1) risk of bias (ROB) (e.g., bias from exposure assessment, outcome assessment and confounding, selection bias, attrition/exclusion bias, selective reporting bias, conflict of interest); 2) inconsistency across studies (high heterogeneity and disparate results across studies); 3) indirect evidence (the evidence cannot directly answer the research question); 4) imprecision (e.g., small sample size, wide CI); and 5) publication bias (using funnel plots and Egger's test).

We first evaluated the ROB of each study using the National Institutes of Environmental Health Sciences - National Toxicology Program - Office of Health Assessment and Translation (OHAT) ROB tool for cohort and cross-sectional studies (U.S. Department of Health and Human Services, 2015). ROB of time-series and case-control/case-crossover studies was assessed according to the OHAT tool as well as the University of California at San Francisco (UCSF) Navigation Guide (Lam et al., 2016; Woodruff and Sutton, 2014). The included studies were thus assessed according to eight items: exposure assessment, outcome assessment, confounding bias, selection bias, attrition/exclusion bias, selective reporting bias, conflict of interest, and other sources of bias (Supplementary Table 3).

Once we evaluated the single-items of ROB for each study, we assigned the study-level ROB according to the most severe item-level judgement (Morgan et al., 2019). Afterwards, we verified whether ROB was an effect modifier of the meta-analytic estimate. According to the obtained results, we evaluated the overall ROB for each pooled estimate.

The obtained overall ROB judgments were integrated into the GRADE judgements. As a final step, we rated the overall quality of evidence as "high", "moderate", "low", and "very low", starting at the same "high quality" score regardless of study design.

3. Results

3.1. Literature retrieval and study characteristics

Out of 3,445 identified publications, 2,989 were non-duplicates and 109 were eligible for inclusion after the screening of title and abstract. Of these, 54 papers met our inclusion criteria and 39 were eventually included in the meta-analysis. Fifteen articles were excluded because did not provide quantitative estimates, reported data already published, or it was not possible to standardize the RRs (Fig. 1).

The main characteristics of included studies are shown in Table 1. Five were cohort studies (K.N. Kim et al., 2016; Kioumourtzoglou et al., 2017; Pun et al., 2017; Wang et al., 2014; Zhang et al., 2019), 16 cross-sectional (Altuğ et al., 2020; Bakolis et al., 2020; Kim et al., 2020; Kim and Kim, 2017; Klompmaker et al., 2019; Lin et al., 2017; Lo et al., 2021; Pelgrims et al., 2021; Shi et al., 2020; Shin et al., 2018; Vert et al., 2017; Yang et al., 2021; Zhao et al., 2020; Zhou and Liu, 2020; Zijlema et al., 2016; Zock et al., 2018), 11 time-series (Chan et al., 2018; Chen et al., 2018; Gu et al., 2020; Li et al., 2020; Nguyen et al., 2021; Qiu et al., 2019; Szyszkowicz, 2007; Szyszkowicz et al., 2009; Thilakaratne et al., 2020; Wei et al., 2020; Zhou et al., 2021), six case-crossover (Cho et al., 2014; Lu et al., 2020; Szyszkowicz, 2011; Szyszkowicz et al., 2016; Tsai et al., 2020; Wang et al., 2018), and one nested case-control (Kim et al., 2021). Twenty-one studies were conducted in Asia, nine in North America, eight in Europe, and one in multiple countries.

With regard to duration of exposure, 21 studies evaluated short-term effects of air pollution exposure, 16 studies long-term effects and two studies both short and long-term effects. The outcome was defined using the ICD code in 19 studies, the ICPC code in one study, whereas 11 studies used self-administered questionnaires or scales, and five antidepressants' prescriptions or doctor's diagnosis. In two studies the presence of depression was self-reported, and in one study definition of outcome assessment was not specified. Exposure to air pollutants was derived from monitoring sites in 26 studies, while it was estimated through Land Use Regression (LUR) models in six studies and chemical transport or spatiotemporal models in six other studies. One study did not specify the method of exposure assessment.

3.2. Long-term air pollution exposure and depression

The relationship between long-term exposure to air pollution and depression was evaluated for PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, and CO. Overall, we included in the analyses 17 studies for PM_{10}, 16 for $PM_{2.5}$, 14 for NO_2, three for SO_2, four for O_3, and three for CO. All studies considered air pollution as average exposure in one or more years preceding diagnosis.

Pooled estimates with corresponding 95%CI, I^2 statistics, Cochran's Q, and Tau^2 values are shown in Table 2 and Figs. 2A-7A. Under the REML model, all pollutants except for CO and $PM_{2.5}$ showed substantial heterogeneity (I^2>60%, Cochran's Q < 0.001). No statistically significant associations were observed for PM_{10}, and O_3 (PM_{10}: RR = 1.092, 95%CI: 0.988–1.206, Fig. 2A; O_3: RR = 0.965, 95%CI: 0.896–1.039, Fig. 6A). A 10 $\mu g/m^3$ increase in long-term $PM_{2.5}$ and NO_2 was associated with increased risk of depression (RR = 1.074, 95%CI: 1.021–1.129, Fig. 3A; RR = 1.037, 95%CI: 1.011–1.064, Fig. 4A, respectively). An augmented risk was observed also for 1 mg/m^3 increase in CO (RR = 1.143, 95%CI: 1.034–1.263, Fig. 7A), even if based on a considerable lower number of studies. With regard to SO_2, we observed a RR of 0.917 (95%CI: 0.847–0.992, Fig. 5A) derived from very

Table 1
Principal characteristics of studies included in the meta-analysis.

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/median, µg/m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
Kim et al., 2021 (Korea)	Nested case-control	25,589 depressed subjects and 102,356 controls from the NHIS-HEALS study	ICD-10 (F31-33)	PM_{10}, NO_2, SO_2, O_3, CO	Short: PM_{10}: 53.3	Local ambient monitoring stations	Short- and long-term	Obesity, smoking, alcohol, meteorological variables, Charlson Comorbidity Index score	Short term: PM_{10} (10 µg/m^3): OR: 1.01 (1.00, 1.02)
					NO_2: 46.0				NO_2 (188 µg/m^3): OR: 1.05 (0.88, 1.25)
					SO_2: 14.7				SO_2 (26.2 µg/m^3): OR: 0.88 (0.82, 0.94)
					O_3: 46.3				O_3 (20 µg/m^3): OR: 0.98 (0.96, 0.99)
					CO: 660.4				CO (1.146 mg/m^3): OR: 1.06 (0.98–1.14)
					Long: PM_{10}: 53.4				Long-term: PM_{10} (10 µg/m^3): OR: 1.02 (1.00, 1.04)
					NO_2: 46.1				NO_2 (188 µg/m^3): OR: 1.02 (0.82, 1.27)
					SO_2: 14.6				SO_2 (26.2 µg/m^3): OR: 0.66 (0.58, 0.74)
					O_3: 45.4				O_3 (20 µg/m^3): OR: 0.92 (0.88, 0.95)
					CO: 665.4				CO (1.146 mg/m^3): OR: 1.14 (1.00–1.30)
Lo et al., 2021 (Taiwan)	Cross-sectional	568 patients with sleep related breathing disorder recruited from a sleep center (2015–2017)	BDI	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO	PM_{10}: 33.0	Local ambient monitoring stations	Short-term	Sex, BMI, education	PM_{10} (10.1 µg/m^3): OR: 1.022 (0.996, 1.048)
					$PM_{2.5}$: 16.2				$PM_{2.5}$ (6.1 µg/m^3): OR: 1.021 (0.977, 1.066)
					NO_2: 34.8				NO_2 (7.9 µg/m^3): OR: 1.040 (0.992, 1.090)
					SO_2: 7.3				SO_2 (2.1 µg/m^3): OR: 1.133 (0.841, 1.528)
					O_3: 57.4				O_3 (12.4 µg/m^3): OR: 0.995 (0.957, 1.033)
					CO: 572.5				CO: (0.344 mg/m^3): OR: 2.981

(continued on next page)

Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, μg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
									(1.032, 8.611)
Nguyen et al., 2021 (USA)	Time-series	1,997,992 subjects who visited hospital emergency department (2005–2013)	ICD-9-CM (311)	$PM_{2.5}$, O_3	$PM_{2.5}$: 12	Local ambient monitoring sites	Short-term	Temperature, day of the week, national holidays, and seasonal/long-term trends	$PM_{2.5}$ (10 μg/m^3): % RR: 0.58 (−0.40, 1.57)
					O_3: 60				O_3 (20 μg/ m^3): %RR: 1.87 (0.62; 3.15)
Pelgrims et al., 2021 (Belgium)	Cross-sectional	1,325 subjects living in Brussels-Capital Region (2008–2013)	SCL-90-R	PM_{10}, $PM_{2.5}$, NO_2, O_3	PM_{10}: 26.1	Local ambient monitoring sites	Long-term	Age, sex, family composition, income, education and year	PM_{10} (10 μg/m^3): OR: 1.75 (1.51, 2.42)
					$PM_{2.5}$: 19.2				$PM_{2.5}$ (10 μg/m^3): OR: 1.12 (0.95, 1.32)
					NO_2: 34.6				NO_2 (10 μg/ m^3): OR: 1.02 (0.99, 1.05)
					O_3:36.3				O_3: (10 μg/ m^3): OR: 0.88 (0.55, 0.95)
Yang et al., 2021 (China)	Cross-sectional	52,568 subjects recruited from China Family Panel Studies	CES-D	$PM_{2.5}$	$PM_{2.5}$: 57.59	Chemical transport model	Long-term	Age, sex, marital status, education, smoking, drinking, physical activity, income, urbanicity	$PM_{2.5}$ (1 μg/ m^3): β: −0.003 (−0.004, −0.001)
Zhou et al., 2021 (China)	Time-series	92,387 subjects identified through hospital outpatients' visits (2010–2013)	ICD-10 (F32–F33)	PM_{10}, NO_2, SO_2	PM_{10}: 142.6	Local ambient monitoring sites	Short-term	Temperature, humidity, day of the week, time	PM_{10} (10 μg/m^3): % RR: 0.16 (0.00, 0.33)
					NO_2: 48.5				NO_2 (10 μg/ m^3): %RR: 1.36 (0.44, 2.28)
					SO_2: 44.7				SO_2 (10 μg/ m^3): %RR: 0.69 (0.02, 1.37)
Altuğ et al., 2020 (Germany)	Cohort-based cross-sectional	821 older women living in urban Ruhr area and two rural towns and participating at SALIA study (2007–2010)	Self-reported and CESD-R	PM_{10}, $PM_{2.5}$, NO_2, $PM_{2.5\ abs}$, PM_{coarse}, NO_x	PM_{10}: 26.4	LUR model	Long-term	Age, BMI, smoking, education, residence, living alone, physical activity, diabetes, cardiovascular disease, chronic respiratory problems, CERAD cognitive test z-score	PM_{10} (2.2 μg/m^3): OR: 1.25 (0.94, 1.67)
					$PM_{2.5}$: 17.4				$PM_{2.5}$ (1.8 μg/m^3): OR: 1.62 (1.06, 2.46)
					NO_2: 25.9				NO_2 (9.5 μg/m^3): OR: 1.54 (1.08, 2.19)
Bakolis et al., 2020 (United Kingdom)	Cross-sectional	1,052 adults from the SELCoH study and residing in UK (2008–2010)	CIS-R	PM_{10}, $PM_{2.5}$, NO_2, NO_x, O_3	PM_{10}: 18.5	Chemical transport model	Long-term	Age, sex, socio-economic status, smoking, ethnicity, drinking, physical activity and 24-h noise metric	PM_{10} (4.6 μg/m^3): OR: 1.08 (0.92, 1.26)
					$PM_{2.5}$: 13.7				$PM_{2.5}$ (2.6 μg/m^3): OR: 1.06 (0.95, 1.19)
					NO_2: 35.8				NO_2 (19.6 μg/m^3): OR: 1.17 (0.93, 1.45)
					O_3:31.7				O_3: (14.9 μg/m^3): OR: 0.81 (0.66, 1.01)

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Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/median, µg/m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
Gu et al., 2020 (China)	Time-series	111,620 hospitalized subjects identified from data of two major health insurance systems (2013–2017)	ICD-10 (F32–F33)	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO	PM_{10}: 91.3 $PM_{2.5}$: 54.4 NO_2: 34.6 SO_2: 26.5 O_3: 64.2 CO: 1271.0	Local ambient monitoring sites	Short-term	Calendar time, admission day of week, temperature, relative humidity, holidays	Total: PM_{10} (10 µg/m^3): %RR: 0.41 (0.05, 0.78) $PM_{2.5}$ (10 µg/m^3): %RR: 0.52 (0.03, 1.01) NO_2 (10 µg/m^3): %RR: 1.78 (0.73, 2.83) Men: SO_2 (10 µg/m^3): %RR: 1.85 (−0.39, 4.14) O_3 (10 µg/m^3): %RR: 0.45 (−0.60, 1.50) CO (1 mg/m^3): %RR: 9.54 (2.69, 16.85) Women: SO_2 (10 µg/m^3): %RR: 2.45 (0.55, 4.39) O_3 (10 µg/m^3): %RR: 0.33 (−0.65, 1.32) CO (1 mg/m^3): %RR: 3.98 (0.23, 7.88)
Kim et al., 2020 (Korea)	Cross-sectional	2,729 subjects from the EPINEF study (2014–2017)	SGDS-K	PM_{10}, $PM_{2.5}$, NO_2	PM_{10}: 44.33 $PM_{2.5}$: 25.59 NO_2: 24.14	Chemical transport model	Long-term	Age, sex, SBP, BMI, smoking, alcohol, education, income, physical activity, daily life condition, disease morbidities	PM_{10} (1 unit): β: 0.0098 (p-value = 0.0004) $PM_{2.5}$ (1 unit): β: −0.0512 (p-value = 0.0204) NO_2 (1 unit): β: 0.0040 (p-value = 0.0003)
Li et al., 2020 (Huizhou –China)	Time-series	293,148 subjects identified through hospital informational systems (2013–2018)	ICD-10 (F30–F31)	PM_{10}, $PM_{2.5}$, NO_2, SO_2	PM_{10}: 52.6 $PM_{2.5}$: 30.4 NO_2: 24.7 SO_2: 11.5	Local monitoring sites	Short-term	Temperature, relative humidity, day of the week, public holidays, time of the year	PM_{10} (10 µg/m^3): %RR: 0.41 (−0.34, 1.15) $PM_{2.5}$ (10 µg/m^3): %RR: 0.70 (−0.36, 1.77) NO_2 (10 µg/m^3): %RR: 4.94 (2.70, 7.23)

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Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, µg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
									SO_2 (10 µg/ m^3): %RR: 2.80 (−0.14, 5.83)
Li et al., 2020 (Shenzhen – China)	Time-series	649,052 identified through hospital informational systems (2016–2018)	ICD-10 (F30–F31)	PM_{10}, $PM_{2.5}$, NO_2, SO_2	PM_{10}: 43.3 $PM_{2.5}$: 26.6 NO_2: 30.1 SO_2: 7.8	Local monitoring sites	Short-term	Temperature, relative humidity, day of the week, public holidays, time of the year	PM_{10} (10 µg/m^3): %RR: 1.11 (0.44, 1.80) $PM_{2.5}$ (10 µg/m^3): %RR: 1.41 (0.41, 2.41) NO_2 (10 µg/ m^3): %RR: 8.02 (6.23, 9.84) SO_2 (10 µg/ m^3): %RR: 9.50 (1.43, 18.22)
Li et al., 2020 (Zhaoqing – China)	Time-series	191,020 identified through hospital informational systems (2016–2018)	ICD-10 (F30–F31)	PM_{10}, $PM_{2.5}$, NO_2, SO_2	PM_{10}: 57.5 $PM_{2.5}$: 38.0 NO_2: 33.4 SO_2: 14.4	Local monitoring sites	Short-term	Temperature, relative humidity, day of the week, public holidays, time of the year	PM_{10} (10 µg/m^3): %RR: 0.99 (0.23, 1.76) $PM_{2.5}$ (10 µg/m^3): %RR: 1.12 (0.11, 2.14) NO_2 (10 µg/ m^3): %RR: 1.69 (−0.27, 3.69) SO_2 (10 µg/ m^3): %RR: 2.06 (−1.52, 5.76)
Lu et al., 2020 (China)	Case-crossover	111,842 subjects identified through hospital outpatients visits for mental disorders (2013–2015)	Not specified	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3	Not specified	Local monitoring sites	Short-term	Temperature, relative humidity, wind speed	PM_{10} (10 µg/m^3): %RR: 0.553 (0.110, 0.999) $PM_{2.5}$ (10 µg/m^3): %RR: 1.039 (0.344, 1.739) NO_2 (10 µg/ m^3): %RR: 3.690 (2.239, 5.160) SO_2 (10 µg/ m^3): %RR: 1.026 (−0.248, 2.316) O_3 (10 µg/ m^3): %RR: 0.822 (0.182, 1.467)
Shi et al., 2020 (China)	Cross-sectional	2,043 subjects from the Sub-Clinical Outcomes of Polluted Air (2018–2019)	PHQ-9	$PM_{2.5}$	$PM_{2.5}$: 74.3	Local monitoring sites	Short-term	Age, sex, education, income, social support level, marital status, residential status, smoking, drinking, chronic diseases,	$PM_{2.5}$ (39.2 µg/m^3): OR: 1.92 (1.19, 3.12)

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Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, µg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
								temperature, relative humidity, season	
Thilakaratne et al., 2020 (USA)	Time-series	82,017 subjects who visited hospital emergency department for depression (2005–2013)	ICD-9-CM (296.2–3, 298.00, 300.4, 309.1, 311)	NO_2, CO	NO_2: 23.58 CO: 446.6	Local monitoring sites	Short-term	Daily mean apparent temperature, holidays, day-of-the-week, season	NO_2 (20.3 µg/m^3): % RR: −1.25 (−2.96, 0.49) CO: (0.321 mg/m^3): % RR: −1.93 (−3.74, −0.08)
Tsai et al., 2020 (Taiwan)	Case-crossover	80,813 subjects identified through insurance claims from the National Health Insurance's Research Database (2009–2013)	ICD-9 (296, 298, 311)	O_3	O_3: 49.38	Local monitoring sites	Short-term	Temperature, humidity	Warm days: O_3 (25.66 µg/m^3): OR: 1.12 (1.10, 1.15) Cool days: O_3 (25.66 µg/m^3): OR: 1.30 (1.27, 1.34)
Wei et al., 2020 (China)	Time-series	16,225 depressed subjects identified from regional health information system (2013–2018)	ICD-10 (F32–F33)	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO	PM_{10}: 69.0 $PM_{2.5}$: 43.6 NO_2: 39.8 SO_2: 15.9 O_3: 73.1 CO: 1156.5	Local monitoring sites	Short-term	Temperature, humidity, long-term trend, seasonality, day of week and holiday	PM_{10} (41.74 µg/m^3): %RR: 3.08 (1.05, 5.16) $PM_{2.5}$ (28.54 µg/m^3): %RR: 2.59 (0.72, 4.49) NO_2 (23.25 µg/m^3): % RR: 4.94 (2.03, 7.92) SO_2 (8.65 µg/m^3): % RR: 3.22 (1.16, 5.32) O_3 (48.42 µg/m^3): % RR: −2.70 (−5.17, −0.17) CO: (0.410 mg/m^3): % RR: 4.38 (1.83, 6.99)
Zhao et al., 2020 (Germany)	Cross-sectional	1,126,014 subjects from a large German statutory health insurance company (2005–2014)	ICD-10-GM (F32–F33)	PM_{10}, O_3	PM_{10}: 20.0	Local monitoring sites	Long-term	year of birth, sex, year of observation, individual access to healthcare	PM_{10} (10 µg/m^3): RR: 1.180 (1.160, 1.200) O_3 evaluated with number of days that exceeds limits
Zhou and Liu, 2020 (China)	Cross-sectional	3,406 subjects from the China Health and Retirement Longitudinal Study	Self-reported through a 3-point score	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO	PM_{10}: 67.7 $PM_{2.5}$: 38.4 NO_2: 28.6	Local monitoring sites	Short-term	Location, month	PM_{10} (1 µg/m^3): β: 0.005 (0.002) $PM_{2.5}$ (1 µg/m^3): β: 0.009 (0.003) NO_2 (1 µg/m^3): β:

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Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, μg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
									−0.003 (0.005)
					SO_2: 13.6				SO_2 (1 μg/ m^3): β: 0.013 (0.006)
					O_3: 165.5				O_3 (1 μg/ m^3): β: 0.000 (0.001)
					CO:1248.1				CO (1 mg/ m^3): β: −0.048 (0.173)
Klompmaker et al., 2019 (Netherlands)	Cross-sectional	354,827 subjects from the PHM survey (2012).	Prescriptions of antidepressants	PM_{10}, $PM_{2.5}$, NO_2, $PM_{2.5\ abs}$, PM_{coarse}	PM_{10}: 24.4	LUR model	Long-term	Age, sex, marital status, region of origin, paid occupation, household income, education, neighborhood SES, smoking, alcohol, degree of urbanization	PM_{10} (1.24 μg/m^3): OR: 0.99 (0.97, 1.01)
					$PM_{2.5}$: 16.7				$PM_{2.5}$ (0.83 μg/m^3): OR: 1.01 (0.99, 1.03)
					NO_2: 23.4				NO_2 (7.85 μg/m^3): OR: 1.03 (1.00, 1.05)
Qui et al., 2019 (China)	Time-series	1,193 subjects identified through hospital records (2015–2016).	ICD-10 (F32–F33)	PM_{10}, $PM_{2.5}$, PM_{coarse}	PM_{10}: 94.7	Local ambient monitoring sites	Short-term	Season, mean temperature, relative humidity, day of the week, public holidays	PM_{10} (10 μg/m^3): % RR: 1.46 (0.11, 2.84)
					$PM_{2.5}$: 57.3				$PM_{2.5}$ (10 μg/m^3): % RR: 2.59 (0.36, 4.87)
Zhang et al., 2019 (Korea)	Cohort	123,045 subjects from the Kangbuk Samsung Health Study (2011–2015)	CES-D or doctor's diagnosis or antidepressant prescription	PM_{10}, $PM_{2.5}$	PM_{10}: 50.6	LUR model	Long-term	Age, sex, study center, year of visit, education, smoking, body mass index, alcohol, physical activity	PM_{10} (10 μg m^3): HR: 1.21 (1.01, 1.45)
					$PM_{2.5}$: 24.3				$PM_{2.5}$ (10 μg m^3): HR: 0.96 (0.64, 1.43)
Chan et al., 2018 (China)	Time-series	44,600 subjects from daily hospital admissions	ICD-9 (311)	NO_2	NO_2: 56.75	Local ambient monitoring sites	Short-term	Temperature, day of study, day of year, day of week, relative humidity	NO_2 (64 μg/ m^3): RR: 1.18 (0.55, 2.53)
Chen et al., 2018 (China)	Time-series	39,143 subjects from daily hospital admissions (2013–2015)	ICD-10 (F32-33)	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO	PM_{10}: 76	Local ambient monitoring sites	Short-term	Calendar time, temperature, day of the week, public holidays	PM_{10} (10 μg/m^3): % RR: 0.54 (−1.25, 2.33)
					$PM_{2.5}$: 56				$PM_{2.5}$ (10 μg/m^3): % RR: −0.05 (−2.18, 2.08)
					NO_2: 46				NO_2 (10 μg/ m^3): %RR: −1.36 (−5.44, 2.73)
					SO_2: 19				SO_2 (10 μg/ m^3): %RR: 3.33 (−4.33, 11.00)
					O_3: 100				O_3 (10 μg/ m^3): %RR: −0.02 (−2.37, 2.33)
					CO: 820				

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Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, μg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
									CO (0.010 mg/m^3): % RR: 0.12 (−0.14, 0.37)
Shin et al., 2018 (Korea)	Cross-sectional	124,205 subjects from the Korean Community Health Survey (2013)	Doctor's diagnosis and self-reported	PM_{10}, NO_2, SO_2, CO	PM_{10}: 48.6 NO_2: 45.1 SO_2: 14.7 CO: 606.9	Nationwide ambient monitoring sites	Long-term	Age, sex, smoking, drinking, physical activity, education, marital status, employment, income, sleep duration, residence, medical history	Males: PM_{10} (29.5 $\mu g/m^3$): OR: 0.978 (0.758, 1.263) NO_2 (23.96 $\mu g/m^3$): OR: 1.280 (1.010, 1.623) SO_2 (31.2 $\mu g/m^3$): OR: 0.944 (0.738, 1.208) CO (0.566 mg/m^3): OR: 1.204 (0.946, 1.533) Females: PM_{10} (29.5 $\mu g/m^3$): OR: 1.022 (0.886, 1.179) NO_2 (23.96 $\mu g/m^3$): OR: 1.223 (1.066, 1.403) SO_2: (31.2 $\mu g/m^3$): OR: 0.804 (0.701, 0.922) CO (0.566 mg/m^3): OR: 1.100 (0.964, 1.256)
Wang et al., 2018 (China)	Case-crossover	19,646 cases identified through hospital admissions (2014–2015)	ICD-10 (F32, F33, F34.1, F41.2)	PM_{10}, $PM_{2.5}$	PM_{10}: 106.8 $PM_{2.5}$: 63.5	Local ambient monitoring sites	Short-term	Temperature, humidity	PM_{10} (76.9 $\mu g/m^3$): % RR: 3.55 (1.69, 5.45) $PM_{2.5}$ (47.5 $\mu g/m^3$): % RR: 3.65 (2.09, 5.24)
Zock et al., 2018 (Netherlands)	Cross-sectional	4,450 subjects identified through the list of GP patients (2013)	ICPC (P03–P76)	PM_{10}, $PM_{2.5}$, NO_2	PM_{10}: 25.7 $PM_{2.5}$: 17.0 NO_2: 27.5	LUR model	Long-term	Sex, age, income, socio-economic status	PM_{10} (10 $\mu g/m^3$): OR: 2.33 (0.73, 7.44) $PM_{2.5}$ (10 $\mu g/m^3$): OR: 6.42 (1.39, 29.7) NO_2 (10 $\mu g/m^3$): OR: 1.15 (0.95, 1.39)
Kim and Kim, 2017 (Korea)	Cross-sectional	23,139 subjects from the Community Health Survey (2013)	Self-reported	PM_{10}	PM_{10}: 44.6	Local ambient monitoring sites	Long-term	Age, sex, education, labor market participation, presence of	PM_{10} (10 $\mu g/m^3$): OR: 1.01 (0.98–1.05)

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Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, µg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
								comorbidities, sleep duration, smoking, drinking	
Kioumourtzoglou et al., 2017 (USA)	Cohort	41,844 women from the NHS cohort (1996–2008)	Doctor's diagnosis or antidepressant prescription	$PM_{2.5}$, O_3	$PM_{2.5}$: 12.6 O_3: 63.5	Nationwide spatiotemporal model	Long-term	Socioeconomic status, race, physical activity, BMI, smoking, pack-years, dietary habits, vitamin intake, participation in social groups, Mental Health Inventory score	$PM_{2.5}$ (10 µg/m^3): HR: 1.08 (0.97, 1.20) O_3 (20 µg/ m^3): HR: 1.06 (1.00, 1.12)
Lin et al., 2017 (China, Ghana, India, Mexico, Russia, South Africa)	Cross-sectional	41,785 subjects from the SAGE cohort (2007–2010)	WMH-CIDI	$PM_{2.5}$	$PM_{2.5}$: 23.75	Chemical transport model	Long-term	Age, gender, BMI, education, income, alcohol, physical activity, cooking-related air pollution	$PM_{2.5}$ (10 µg/m^3): OR: 1.10 (1.02–1.19)
Pun et al., 2017 (USA)	Cohort	4,008 subjects from the NSHAP study (2005–2006; 2010–2011)	CESD-11	$PM_{2.5}$	$PM_{2.5}$: 9.95	Spatiotemporal generalized additive mixed model	Short-term and long-term	Age, sex, race/ ethnicity, year, season, day of week, region, residence, education, income, percentage of population below poverty in the census tract of residence	$PM_{2.5}$ (5 µg m^3): Short-term: OR: 1.08 (1.00–1.16) Long-term: OR: 1.14 (0.97–1.34)
Vert et al., 2017 (Spain)	Cross-sectional	958 subjects from the ALFA cohort (2013–2014)	Self-reported or antidepressant medication use	PM_{10}, $PM_{2.5}$, NO_2, $PM_{10\ coarse}$, $PM_{2.5\ abs}$, NO_x	PM_{10}: 37.7 $PM_{2.5}$: 16.8 NO_2: 57.3	LUR model	Long-term	Gender, age, education, living alone, BMI, physical activity, smoking, sleep difficulties, perceived social support, caregiver status	PM_{10} (10 µg/m^3): OR: 1.95 (1.00, 3.80) $PM_{2.5}$ (5 µg/ m^3): OR: 1.23 (0.70, 2.16) NO_2 (10 µg/ m^3): OR: 1.12 (0.89, 1.40)
Kim et al., 2016 (Korea)	Cohort	27,270 subjects from the NHID cohort (2002–2010)	ICD-10 (F32)	$PM_{2.5}$	$PM_{2.5}$: 26.7	Local ambient monitoring sites	Long-term	Sex, age, household income, smoking, alcohol, regular exercise	$PM_{2.5}$ (10 µg/m^3): HR: 1.59 (1.02, 2.49)
Szyszkowicz et al., 2016 (Canada)	Case-crossover	118,602 subjects who visited hospital emergency department for depression (2004–2011)	ICD-10 (F32)	$PM_{2.5}$, NO_2, SO_2, O_3	$PM_{2.5}$: 9.8 NO_2: 34.8 SO_2: 11.3 O_3: 57 (max>100)	Local ambient monitoring sites	Short-term	Daily temperature, humidity	Males: $PM_{2.5}$ (7.12 µg/m^3): OR: 1.023 (1.001, 1.045) NO_2 (16.92 µg/m^3): OR: 1.015 (0.987, 1.043) SO_2 (6.55 µg/m^3): OR: 1.018 (0.997, 1.039) O_3 (29.00 µg/m^3): OR: 1.034 (1.012, 1.056) Females: $PM_{2.5}$ (7.12 µg/m^3): OR: 1.014

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Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, μg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
									(0.996, 1.032) NO_2 (16.92 μg/m^3): OR: 1.026 (1.002, 1.049) SO_2 (6.55 μg/m^3): OR: 1.022 (1.005, 1.039) O_3 (29.00 μg/m^3): OR: 1.030 (1.012, 1.048)
Zijlema et al., 2016 (LifeLines – Netherlands)	Cohort-based cross-sectional	32,145 subjects from the LifeLines cohort	MINI (DSM-IV)	PM_{10}, $PM_{2.5}$, NO_2, $PM_{2.5\ abs}$	PM_{10}:23.95 $PM_{2.5}$: 15.4 NO_2: NA	LUR model	Long-term	Sex, age, education, income, myocardial infarction, asthma, COPD, urbanity, road traffic noise	PM_{10} (10 μg/m^3): OR: 0.70 (0.15, 3.31) $PM_{2.5}$ (5 μg/m^3): OR: 1.20 (0.41, 3.54) NO_2 (10 μg/m^3): OR: 1.09 (0.77, 1.56)
Zijlema et al., 2016 (KORA – Germany)	Cohort-based cross-sectional	5,314 subjects from the KORA cohort	PHQ-9	PM_{10}, $PM_{2.5}$, NO_2, $PM_{2.5\ abs}$	PM_{10}: NA $PM_{2.5}$: NA NO_2: 18.8	LUR model	Long-term	Sex, age, education, income, myocardial infarction, asthma, COPD, urbanity, road traffic noise	PM_{10} (10 μg/m^3): OR: 0.93 (0.36, 2.37) $PM_{2.5}$ (5 μg/m^3): OR: 1.54 (0.44, 5.38) NO_2 (10 μg/m^3): OR: 1.16 (0.67, 2.03)
Zijlema et al., 2016 (HUNT – Norway)	Cohort-based cross-sectional	32,102 subjects from the HUNT cohort	HADS-D	PM_{10}, NO_2,	PM_{10}: 11 NO_2: NA	LUR model	Long-term	Sex, age, education, income, myocardial infarction, asthma, COPD, urbanity, road traffic noise	PM_{10} (10 μg/m^3): OR: 0.39 (0.21, 0.70) NO_2 (10 μg/m^3): OR: 0.77 (0.65, 0.93)
Zijlema et al., 2016 (FINRISK – Finland)	Cohort-based cross-sectional	1,367 subjects from the FINRISK cohort	CES-D	PM_{10}, $PM_{2.5}$, NO_2, $PM_{2.5\ abs}$	PM_{10}: NA $PM_{2.5}$: NA NO_2: NA	LUR model	Long-term	Sex, age, education, income, myocardial infarction, asthma, COPD, urbanity, road traffic noise	PM_{10} (10 μg/m^3): OR: 1.05 (0.50, 2.21) $PM_{2.5}$ (5 μg/m^3): OR: 1.32 (0.62, 2.80) NO_2 (10 μg/m^3): OR: 0.93 (0.57, 1.52)
Cho et al., 2014 (Korea)	Case-crossover	4,985 subjects who visited hospital emergency department for depression (2005–2009)	ICD-10 (F32)	PM_{10}, NO_2, SO_2, O_3, CO	PM_{10}: 54.15 NO_2: 64.94 SO_2: 14.23	Local ambient monitoring sites	Short-term	National holidays, sunlight hours, temperature, relative humidity, air pressure	PM_{10} (36.7 μg/m^3): OR: 1.155 (1.058, 1.262) NO_2 (22.64 μg/m^3): OR: 1.098 (1.011, 1.127)

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Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, µg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
									SO_2 (6.10 µg/m^3): OR: 1.126 (1.020, 1.243)
					O_3: 34.44 (max<100)				O_3 (20.08 µg/m^3): OR: 1.004 (0.896, 1.125)
					CO: 652.7				CO (0.275 mg/m^3): OR: 1.077 (1.026, 1.130)
Wang et al., 2014 (USA)	Cohort	765 subjects from the MOBILIZE-Boston study (2005–2008)	CESD-R	$PM_{2.5}$, NO_2, O_3, CO, NO	$PM_{2.5}$: 8.6	Local ambient monitoring sites	Short-term	Age, sex, race/ ethnicity, time period, season, day of week, income, education, neighborhood socioeconomic status, BMI, physical activity, alcohol, smoking, diabetes mellitus, hypertension, hyperlipidemia, use of antidepressant medication	$PM_{2.5}$ (3.40 µg/m^3): OR: 0.67 (0.46, 0.98)
					NO_2: 31.40				NO_2 (7.65 µg/m^3): OR: 1.32 (0.99, 1.76)
					O_3: 49.0				O_3 (26.9 µg/ m^3): OR: 0.71 (0.46, 1.09)
					CO: 355.0				CO (0.137 mg/m^3): OR: 1.14 (0.90, 1.44)
Szyszkowicz (2011) (Canada)	Case-crossover	680 subjects who visited hospital emergency department for depression (1999–2002)	ICD-9 (296)	SO_2	NA	Not specified	Short-term	Not specified	SO_2 (10.2 µg/m^3): OR: 1.12 (0.99–1.25)
Szyszkowicz et al., 2009 (Canada)	Time-series	27,047 subjects who visited hospital emergency department for depression (1992–2003)	ICD-9 (296)	PM_{10}, $PM_{2.5}$, NO_2, O_3, SO_2, CO	PM_{10}: 19.4	Local ambient monitoring sites	Short-term	Temperature, relative humidity	PM_{10} (19.4 µg/m^3): % RR: 6.4 (3.6, 9.4)
					$PM_{2.5}$: 8.3				$PM_{2.5}$ (8.3 µg/m^3): % RR: 2.3 (−0.2, 4.7)
					NO_2: 37.8				NO_2 (37.8 µg/m^3): % RR: 10.0 (6.6, 13.6)
					SO_2: 12.1				SO_2 (12.1 µg/m^3): % RR: 2.6 (−0.1, 5.3)
					O_3: 37.8				O_3 (37.8 µg/ m^3): %RR: −4.0 (−7.3, −0.6)
					CO: 916				CO (0.916 mg/m^3): % RR: 6.9 (3.8, 10.1)
Szyszkowicz (2007) (Canada)	Time-series	15,556 subjects who visited hospital emergency department for depression (1992–2002)	ICD-9 (311)	PM_{10}, $PM_{2.5}$, NO_2, O_3, SO_2, CO	PM_{10}: 22.6	Local ambient monitoring sites	Short-term	Temperature, relative humidity	PM_{10} (15.0 µg/m^3): % RR: 2.7 (0.4, 5.0)
					$PM_{2.5}$: 8.5				$PM_{2.5}$ (6.2 µg/m^3): % RR: 7.2 (2.0, 12.8)
					NO_2: 41.2				NO_2 (24.1 µg/m^3): %

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Table 1 (*continued*)

Author, publication year (country)	Study Design	Study participants	Outcome definition	Studied pollutants	Exposure concentration (mean/ median, µg/ m^3)	Exposure assessment	Exposure duration	Adjustment variables	Main results
									RR: 3.9 (1.3, 6.6)
					SO_2: 6.8				SO_2 (6.0 µg/ m^3): %RR: 3.0 (0.2, 5.8)
					O_3: 37.2				O_3 (28.0 µg/ m^3): %RR: 6.9 (0.6, 13.6)
					CO: 801.5				CO (0.458 mg/m^3): %RR: 2.4 (0.4, 4.4)

Acronyms: ALFA: ALzheimer and FAmilies; BDI: Beck Depression Inventory; BMI: body mass index; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CES-D: Center for Epidemiologic Studies Depression Scale; CESD-11: Center for Epidemiological Studies Depression Scale (11-item version); CESD-R: 20-item Revised Center for Epidemiological Studies Depression Scale; CIS-R: Revised Clinical Interview Schedule; CO: carbon monoxide; COPD: chronic obstructive disease; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; EPINEF: Environmental Pollution-Induced Neurological Effects; FINRISK: National Cardiovascular Risk Factor Survey; HADS-D: depression subscale of the Hospital Anxiety Depression Scale; GP: General Practitioner; HR: hazard-ratio; HUNT: Trøndelag Health Study; ICD-9: International Classification for Diseases, 9th Revision; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10: International Classification of Diseases, 10th Revision; ICD-10-GM: German Modification of the International Classification of Diseases, 10th Revision; ICPC: International Classification of Primary Care; KORA: The Cooperative Health Research in the Region of Augsburg; LUR: land use regression; MINI: Mini-International Neuropsychiatric Interview; NHID: National Health Insurance Database; NHIS-HEALS: Korean National Health Insurance Service-Health Screening Cohort; NHS: Nurses' Health Study; NO: nitrogen monoxide; NO_2: nitrogen dioxide; NO_x: nitrogen oxides; NSHAP: the National Social Life, Health and Aging project; O_3: ozone; OR: odds-ratio; PHM: Public Health Monitor; PHQ-9: Patient Health Questionnaire; PM_{coarse}: particulate matter with an aerodynamic diameter between 2.5 µm and 10 µm; $PM_{2.5\ abs}$: reflectance on $PM_{2.5}$ filters, i.e. a marker of black carbon; $PM_{2.5}$: particulate matter with an aerodynamic diameter less than or equal to 2.5 µm; PM_{10}: particulate matter with an aerodynamic diameter less than or equal to 10 µm; RR: relative risk; SAGE: the World Health Organization Study on global AGEing and adult health; SALIA: Study on the influence of air pollution on lung function, inflammation and aging; SBP: systolic blood pressure; SCL-90-R: Symptom Checklist - 90-Revised Scale; SELCoH: The South East London Community Health study; SES: socioeconomic status; SGDS-K: Geriatric Depression Scale-Short Form; SO_2: sulfur dioxide; 95% CI: 95% confidence interval; WMH-CIDI: World Mental Health Composite International Diagnostic Interview.

Table 2
Meta-analytic estimates (RR) with corresponding 95% confidence intervals (95% CI), I^2 statistics, Cochran's Q, and Tau^2 for the association between evaluated air pollutants and depression, estimated under the restricted-maximum likelihood (REML) model.

Pollutant	Long-term exposure					Short-term exposure				
	Nr studies	RR (95% CI)	I^2	Cochran's Q	Tau^2	Nr studies	RR (95% CI)	I^2	Cochran's Q	Tau^2
PM_{10}	17	1.092 (0.988–1.206)	*96.9%*	<0.001	0.024	16	1.009 (1.006–1.012)	*79.1%*	<0.001	0.000
$PM_{2.5}$	16	1.074 (1.021–1.129)	*19.8%*	0.016	0.002	19	1.009 (1.007–1.011)	*0.02%*	0.002	0.000
NO_2	14	1.037 (1.011–1.064)	*62.7%*	<0.001	0.001	19	1.022 (1.012–1.033)	*87.8%*	<0.001	0.000
SO_2	3	0.917 (0.847; 0.992)	*84.3%*	0.002	0.004	18	1.024 (1.010–1.037)	*76.3%*	<0.001	0.001
O_3	4	0.965 (0.896–1.039)	*89.1%*	<0.001	0.004	17	1.011 (0.997–1.026)	*97.2%*	<0.001	0.001
CO	3	1.143 (1.034–1.263)	*0.00%*	0.698	0.000	12	1.062 (1.020–1.105)	*69.9%*	0.001	0.002

few studies.

Univariate meta-regression models were applied to evaluate the sources of heterogeneity in PM_{10} and NO_2 estimates (Supplementary Table 4). Study design, method of outcome assessment, and adjustment for level of education and socio-economic status represented sources of heterogeneity for studies investigating NO_2 exposure. Higher estimates were found in cross-sectional investigations vs. other study designs, in studies based on self-reported diagnosis vs. those using ICD-codes, and when adjustment for education or socio-economic status was applied. Adjustment for smoking status or presence of comorbidities produced lower estimates for PM_{10} exposure.

Funnel plots (Supplementary Figures 1-6), in combination with Egger's tests, showed that publication bias was present only for $PM_{2.5}$ ($p = 0.002$). Two studies were imputed with the trim-and-fill method but estimates were unaltered (Supplementary Table 6).

When single studies were excluded, no substantial changes were evident for any of the pollutants considered, with the only possible exception of $PM_{2.5}$: the exclusion of the investigation by Yang et al. (2021) brought to a detectable increase in the meta-analytic estimate (Supplementary Table 7).

ROB judgements for each included study are shown in Supplementary Table 9. For PM_{10}, 10 studies had probably high ROB and two studies had high ROB. For $PM_{2.5}$ and O_3, one study had probably low ROB and all the other studies had probably high ROB. For NO_2, SO_2 and CO, all the included studies had probably high ROB. For O_3, stratified analyses by ROB judgements showed that the only study with a probably low ROB had a statistically significantly higher estimate as compared to studies with probably high ROB (data not shown). Meta-analytic estimates for the other pollutants remained unchanged after stratifying by ROB judgements.

With regard to GRADE scores, we observed a moderate quality of evidence for PM_{10}, $PM_{2.5}$, NO_2, SO_2, and CO, and a low quality of evidence for O_3 (Supplementary Table 10).

3.3. Short-term air pollution exposure and depression

The relationship between short-term air pollution exposure and depression was evaluated for all available pollutants. Overall, we

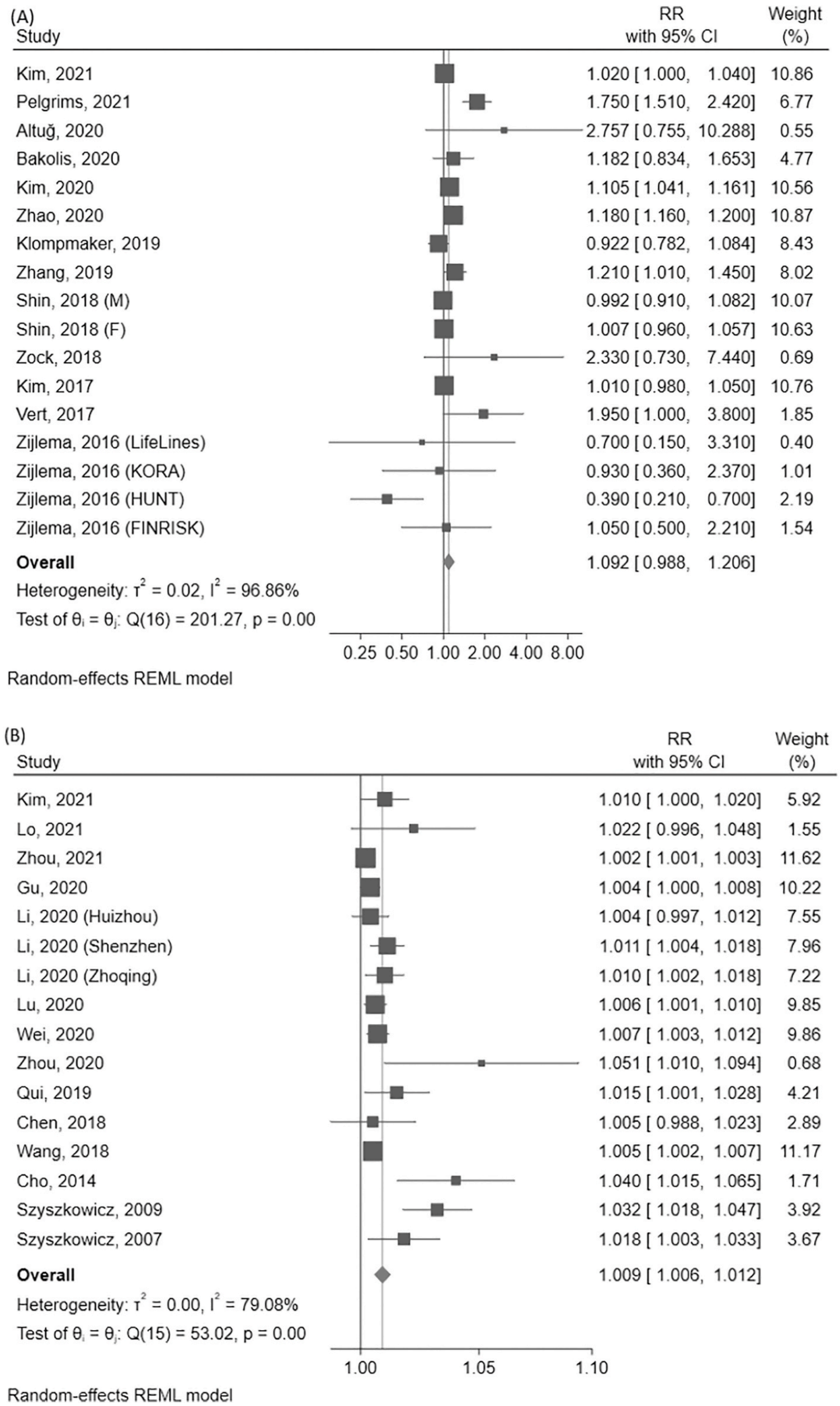

Fig. 2. Meta-analysis results for the association between long-term (A) and short-term (B) PM_{10} exposure and depression.

included in the analysis 16 studies for PM_{10}, 19 for $PM_{2.5}$, 19 for NO_2, 18 for SO_2, 17 for O_3, and 12 for CO.

Meta-analytic estimates with corresponding 95%CI, I^2 statistics, Cochran's Q, and Tau^2 values are shown in Table 2 and Figs. 2B-7B. Under the REML model, all pollutants except for $PM_{2.5}$ showed large heterogeneity (I^2>65%, Cochran's Q < 0.001). We found a positive effect for all pollutants investigated, even if the estimate for O_3 was borderline significant (RR = 1.011, 95%CI: 0.997–1.026, Fig. 6B). In particular, a 10 μg/m^3 increase in both PM_{10} and $PM_{2.5}$ was associated with a ≈1% increase in risk of depression (RR = 1.009, 95%CI: 1.006–1.012, Fig. 2B; and RR = 1.009, 95%CI: 1.007–1.011, Fig. 3B, respectively). Measures of association were higher for NO_2 (RR: 1.022, 95%CI: 1.012–1.033, Fig. 4B) and SO_2 (RR = 1.024, 95%CI: 1.010–1.037, Fig. 5B). The highest estimate was observed for CO, with an augmented risk of +6% per 1 mg/m^3 increase in the pollutant concentration (RR = 1.062, 95%CI: 1.020–1.105, Fig. 7B).

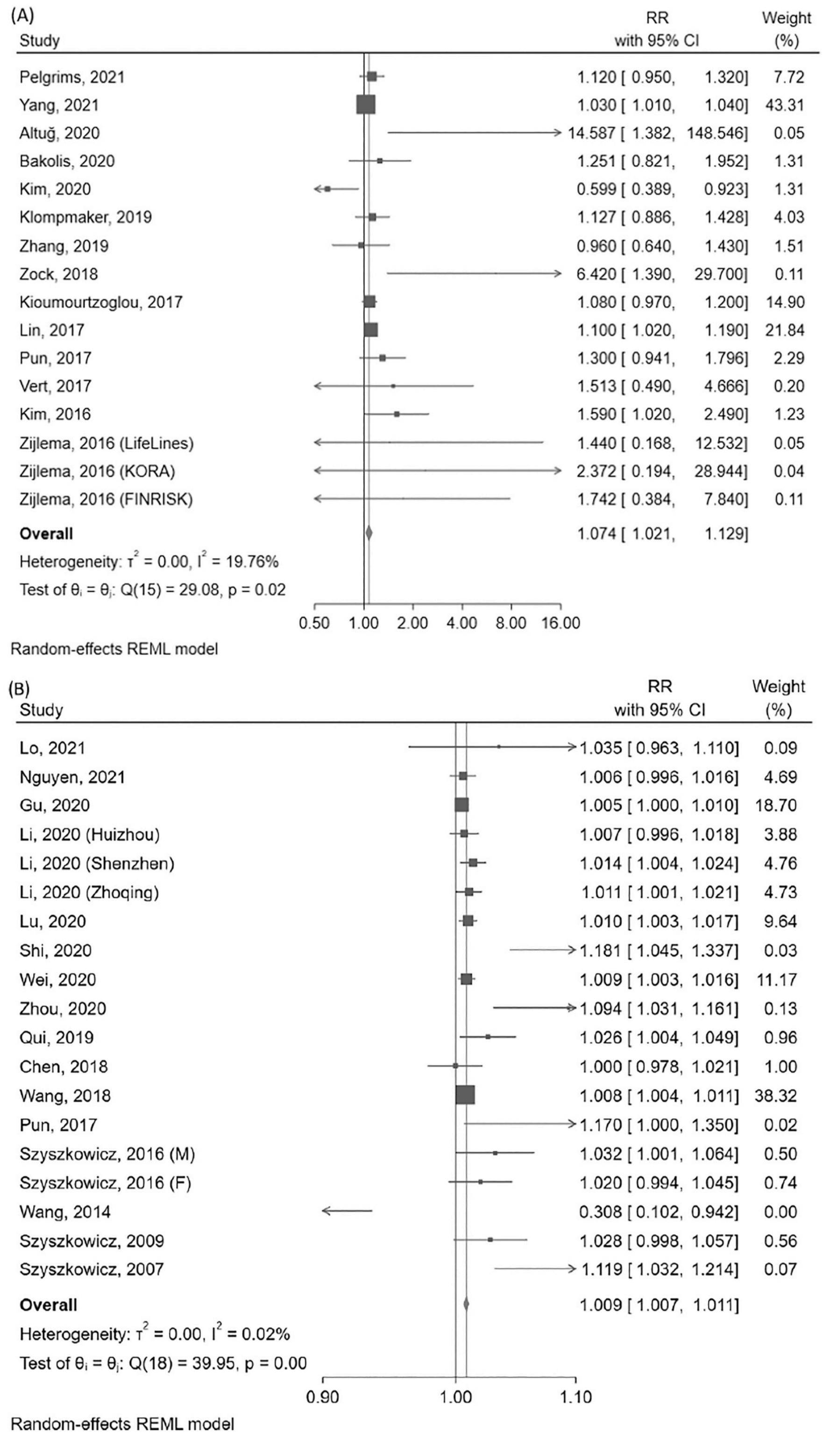

Fig. 3. Meta-analysis results for the association between long-term (A) and short-term (B) $PM_{2.5}$ exposure and depression.

Several potential sources of heterogeneity were identified (Supplementary Table 5). For PM_{10}, studies conducted in North America seemed to return higher RRs if compared to studies conducted in Asian countries; cross-sectional investigations produced higher RRs than time-series studies; studies using diagnostic scales tended to estimate higher RRs than investigations classifying outcomes based on diagnostic codes; higher effect estimates were also returned by studies conducted in areas were PM_{10} levels were lower than WHO standards and when emergency room (ER) visits were used as source for health data. The use of different lag patterns appeared as a potential source of heterogeneity for both NO_2 and SO_2. Finally, studies investigating the effect of SO_2 and O_3 exposure on older populations ($\geq$65) tended to return higher measures of association.

Funnel plots (Supplementary Figures 7-12) in combination with Egger's tests showed that publication bias was present for PM_{10}, $PM_{2.5}$, SO_2, and CO (Supplementary Table 6). Adjustment for publication bias

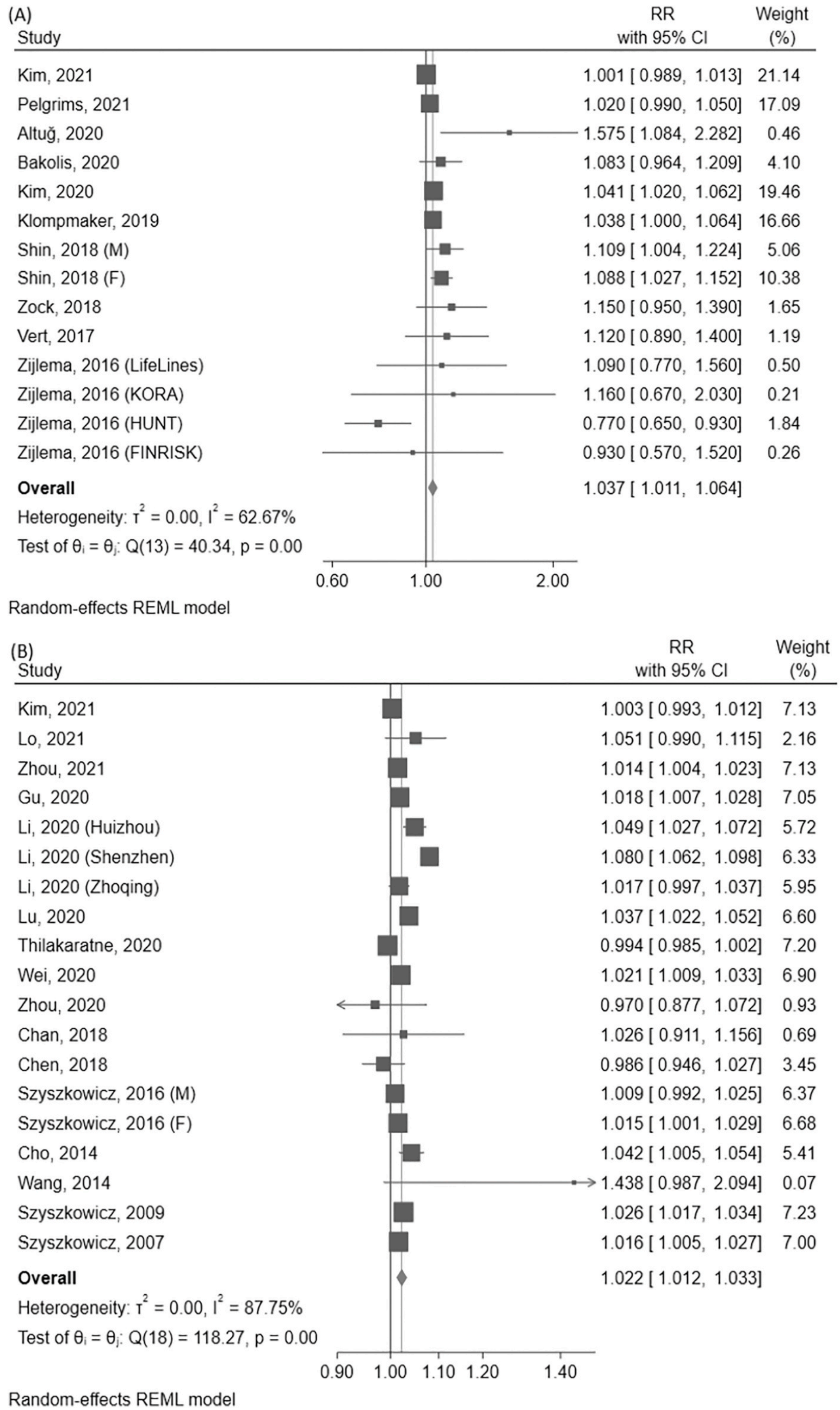

Fig. 4. Meta-analysis results for the association between long-term (A) and short-term (B) NO_2 exposure and depression.

produced substantially unaltered estimates.

The exclusion of each single study did not change the overall estimates for any of the pollutants considered (Supplementary Table 8).

ROB judgements for each included study are shown in Supplementary Table 9. For PM_{10}, and SO_2, one study had probably high ROB and 13 studies had high ROB. For $PM_{2.5}$, three studies had probably high ROB and 13 studies had high ROB. For NO_2, 14 studies had high ROB and the remaining two studies had probably high ROB. For O_3, 12 studies had high ROB and all the other studies had probably high ROB. For CO, two studies had probably high ROB and the remaining studies had high ROB. For $PM_{2.5}$, stratified analyses by ROB judgements showed that the three studies with a probably high ROB had statistically significant higher estimates as compared to the other 13 studies that have received high ROB judgements (data not shown). For SO_2, stratified analyses showed that the only study with a probably high risk of bias returned a significantly lower estimate as compared to other studies

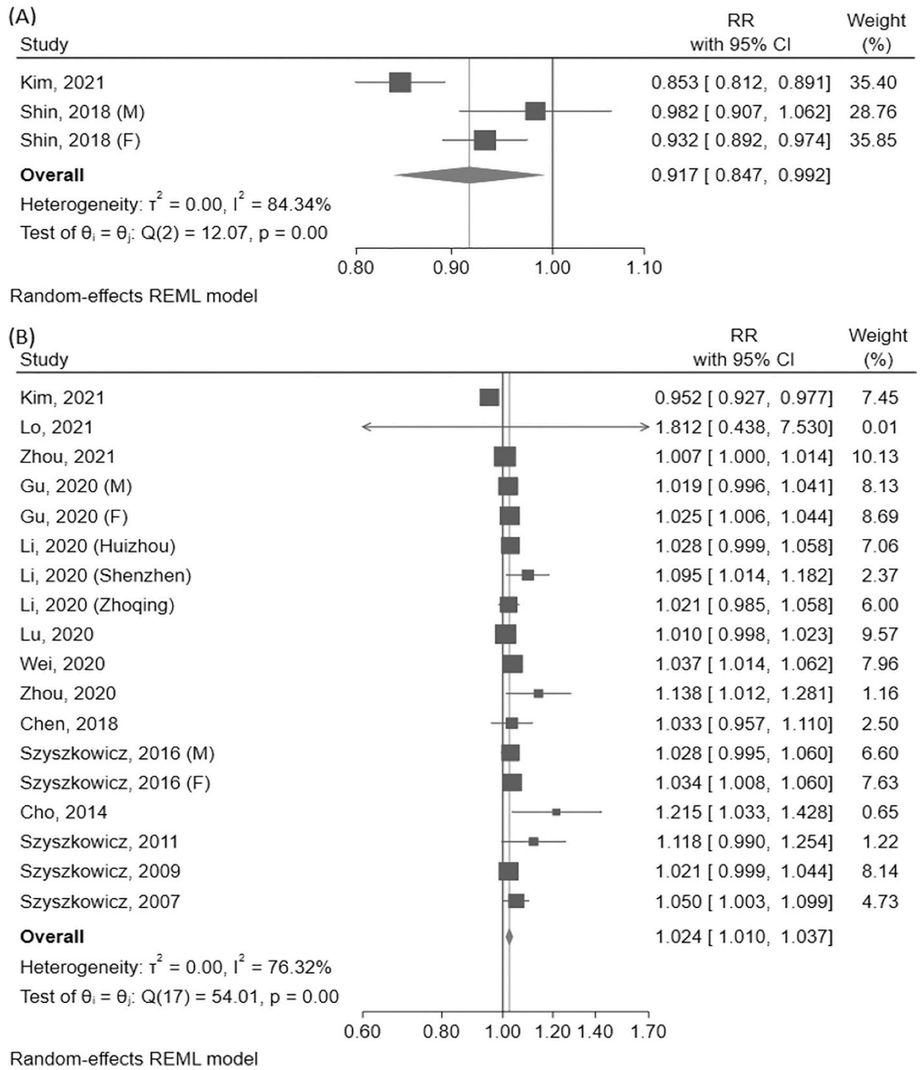

Fig. 5. Meta-analysis results for the association between long-term (A) and short-term (B) SO_2 exposure and depression.

with high ROB. Pooled estimates for the other pollutants did not change after stratification by ROB judgements.

With regard to GRADE, we obtained a very low quality of evidence for SO_2, a low quality for PM_{10}, $PM_{2.5}$, and CO, and a moderate quality for NO_2 and O_3 (Supplementary Table 10).

4. Discussion

In the present meta-analysis, we examined 39 studies from different countries to evaluate the association between long- and short-term air pollution exposure and depression.

With regard to long-term exposure, we found significant associations between depression and exposure to $PM_{2.5}$, NO_2, SO_2, and CO.

In particular, a 7% increased risk of depression was estimated per each 10 μg/m^3 increase in $PM_{2.5}$, with very low heterogeneity across studies. This finding is consistent with previous meta-analyses, reporting RRs ranging from 1.10 to 1.18 (Supplementary Table 11). This association appeared not to be strongly influenced by single studies, with the possible exception of the investigation by Yang et al. (2021) whose exclusion brought to a slight increase in the meta-analytic estimate. In addition, adjustment for publication bias returned a substantially unaltered meta-analytic estimate. All the above thus suggests the presence of an effect.

Exposure to NO_2 was associated with a 4% increased risk of depression per each 10 μg/m^3 increase in the pollutant concentration. This association was not affected by publication bias nor was influenced by single studies. Heterogeneity was above 60%, with study design, method of outcome assessment, and adjustment for education or socioeconomic status emerging as potential sources. Only two previous meta-analyses (Fan et al., 2020; Zeng et al., 2019), including a very limited number of studies, investigated long-term exposure to this pollutant, and found similar yet more uncertain and non-significant results.

Results regarding exposure to SO_2 or CO, although reaching statistical significance, were based on a very small number of studies, which prevents any firm conclusion.

Method of outcome assessment appeared as a source of heterogeneity for NO_2, with higher estimates when depression was self-reported in comparison to diagnosis based on ICD codes: this was somewhat expected, as referred symptoms might overestimate the risk (Thombs et al., 2018) and classification systems based on codes tend to be more accurate (and thus conservative), even because diagnoses were mostly made in hospitals and during outpatient visits. This seems consistent with a recent Swedish study, aimed to explore whether the prevalence of depression varied when using different diagnostic criteria, that estimated a much lower prevalence when using ICD-10 vs. other depression definitions (Sjöberg et al., 2017).

Study design also appeared as a source of heterogeneity for NO_2;

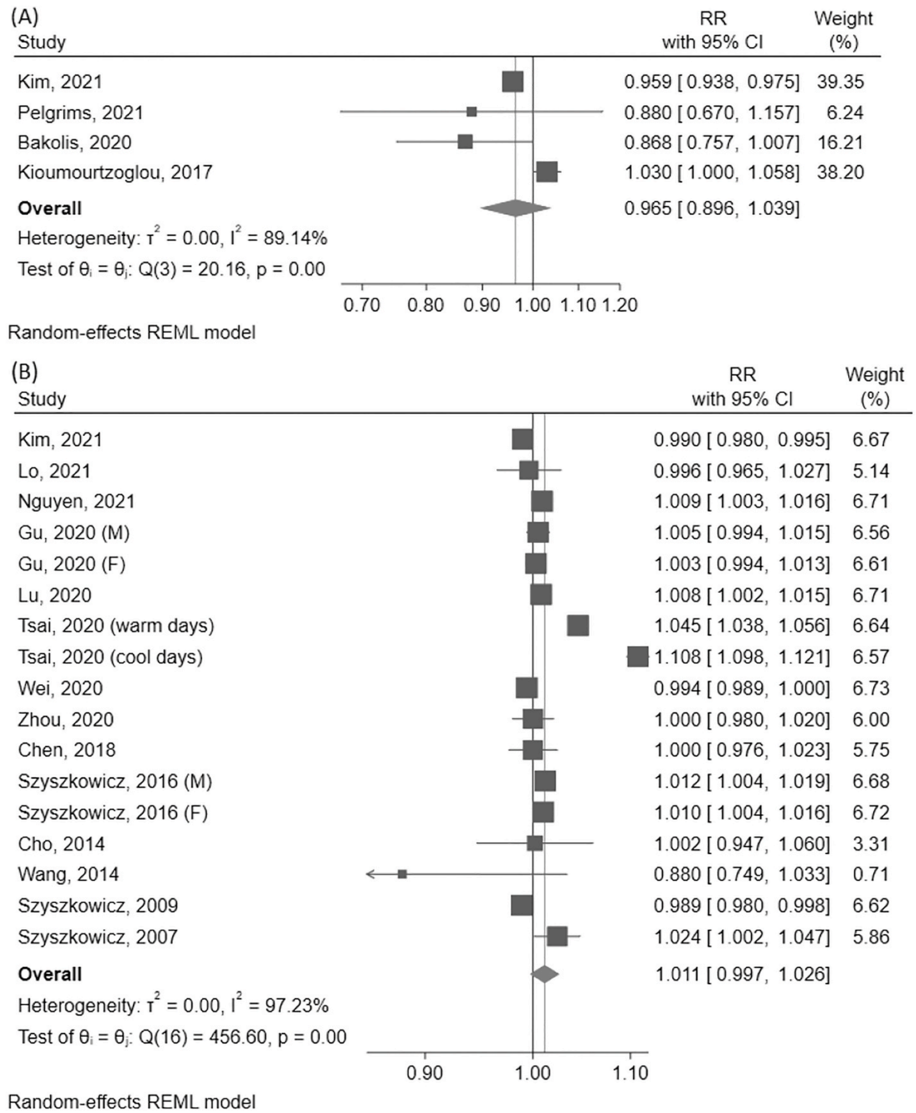

Fig. 6. Meta-analysis results for the association between long-term (A) and short-term (B) O_3 exposure and depression.

however, the reference category in the meta-regression analysis (i.e. "other study designs") was indeed represented by one single nested case-control study (Kim et al., 2021), which mitigates the relevance of this finding.

Finally, adjustment for smoking or comorbidities returned significantly lower estimates in studies on PM_{10}, while adjustment for education and socioeconomic status returned higher estimates in investigations on NO_2. Although we find it hard to explain the opposite direction of the effects observed between the two pollutants, this finding might reflect the multifaceted impact of uncontrolled residual confounding.

When looking at short-term effects of air pollution exposure, all investigated pollutants showed a positive association with depression, that seemed not to be influenced by any particular study.

Both PM_{10} and $PM_{2.5}$ were associated with a $\approx$1% increased depression risk. Although publication bias was present, the trim-and-fill method did not change the meta-analytic estimate for $PM_{2.5}$, while it returned a halved estimate for PM_{10}.

A similar magnitude of the association was observed for O_3: even if it formally failed to reach statistical significance by including the null value in the confidence interval, this estimate seemed not to be hampered by publication bias. Heterogeneity was, however, substantial.

Two other gaseous pollutants (i.e. NO_2 and SO_2) showed a 2% increase in depression per each 10 μg/m^3 increase in their concentration. Heterogeneity was large for both pollutants. With regard to NO_2, the meta-analytic estimate seemed a bit more robust, considering the absence of publication bias and the overall moderate quality of the evidences. For SO_2, the Egger's test confirmed the presence of publication bias and the trim-and-fill method imputed four additional studies; although slightly reduced, the meta-analytic estimate remained unaltered.

Lastly, carbon monoxide exposure was associated with a 6% increase in depression, with an estimate that, although characterized by large heterogeneity and publication bias, remained unaltered when two missing studies were imputed.

The increased risk we observed for short-term exposure to PM_{10} and $PM_{2.5}$ is consistent with findings from previous meta-analyses (Supplementary Table 11), which detected a 2–3% excess for 10 μg/m^3 increase in pollutant concentration. The only exception is the analysis by Fan et al., which however found a comparable result when applying a random-effect model. The picture emerging from the available evidence seems thus to be coherent. Nonetheless, the presence of heterogeneity (at least for PM_{10}) and of publication bias, as well as the overall low quality of the evidences (indicated by the GRADE evaluation) partly reduce the confidence in our summary estimate. Only two meta-analyses considered short-term effects of NO_2, SO_2, and O_3 exposure and one

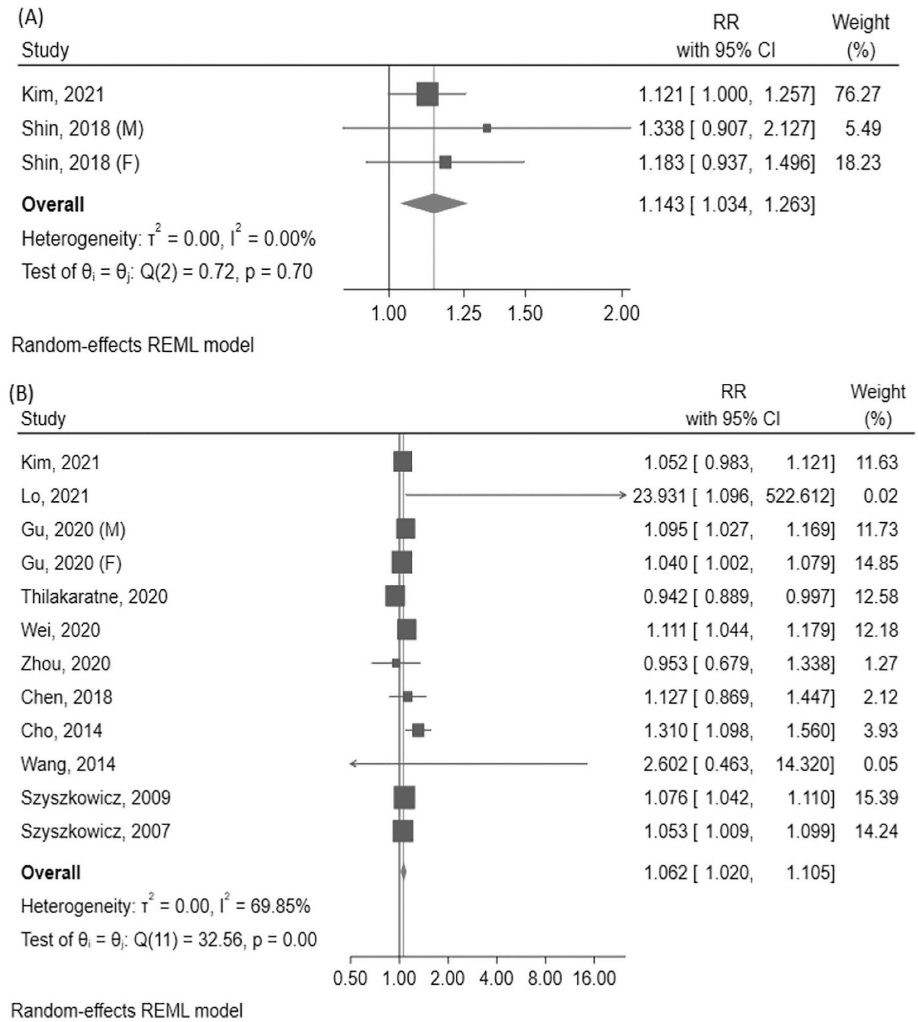

Fig. 7. Meta-analysis results for the association between long-term (A) and short-term (B) CO exposure and depression.

investigated the effect of carbon monoxide: with a much higher number of included investigations (19, 18, 17, and 12, respectively), we found coherent results confirmed by the sensitivity analysis and supported by the absence of relevant publication bias.

Meta-regression analysis showed several potential sources of heterogeneity. North-American studies returned ≈2% higher RRs than Asian ones when studying PM_{10} exposure; consistently, investigations conducted in areas characterized by concentration levels lower than the 20 μg/m^3 WHO reference value (annual average) estimated higher effects. Asian countries are well-known to present air pollution levels that are, on average, higher than the ones that can be found in Western countries (Brauer et al., 2016). Our finding might reflect the flattening of the concentration-response function linking air pollution and health, which has been postulated at high exposure values (Sun et al., 2019). Also method of outcome assessment appeared as a source of heterogeneity for PM_{10}, with studies using scales producing higher estimates than those identifying depressed subjects based on ICD codes: this result resembles what observed in long-term association studies, as diagnostic scales are mostly based on referred symptoms. Indeed, this difference on method of outcome assessment might also at least partly explain the role of study design as a source of heterogeneity, as all cross-sectional studies (that returned higher association estimates for PM_{10}) used diagnostic scales, while time-series studies used ICD codes. Interestingly, studies on PM_{10} that used ER visits to retrieve data (rather than other sources) returned a higher meta-analytic estimate. ER visits usually follow an abrupt onset of symptoms and might thus better capture the short-term temporal association between exposure and health effects (Beiser et al., 2019), rather than medical settings, such as primary care, which might be programmed even based on chronic rather than acute symptomatology (Vourilehto et al., 2007). When looking at different lag patterns, apparently inconsistent findings emerged which might be partly explained by the different time windows of exposure considered. Finally, studies on older populations (≥65 years) found SO_2 and O_3 exposure to be associated with a greater risk of depression if compared with investigations on younger subjects. This might be due to the potential confounding effect of comorbidities (Loop et al., 2013) and the higher susceptibility of the elderly population to the health effects of air pollution (Simoni et al., 2015).

Air pollutants are thought to play a role in the pathogenesis and worsening of depression mainly through neuroinflammation and related oxidative stress, hormonal dysregulation, and direct neurotoxicity (Calderón-Garcidueñas et al., 2015). Over-inflammation might cause neurotransmitter dysfunction, by activation of the indoleamine 2, 3-dioxygenase accelerated degradation of tryptophan that is essential for the synthesis of serotonin (Altamura et al., 2014), and consequently serotonin depletion in the central nervous system (CNS). Imbalance of serotonin and noradrenalin in the CNS represents a well-accepted etiological mechanism of depression (Blier, 2016). Abnormal inflammation might also cause hormonal dysregulation (Doolin et al., 2017; Y.K. Kim et al., 2016) and a change in the expression of those genes whose protein products are involved in the generation and regulation of circadian rhythms (i.e. clock genes) (Satyanarayanan et al., 2020). Systemic oxidative stress and inflammation can also interplay with innate or cell-mediated immunity that has been related to depression onset (Camkurt et al., 2016; Haapakoski et al., 2016). Of note, short- and long-term exposure to PMs has been found to be associated with increased plasma levels of cytokines belonging to innate immunity, similarly to what happens for depression (e.g., IL-6, IL-1β, and TNFα) (Pope et al., 2016; Tsai et al., 2019; Zhu et al., 2021). Some authors have proposed also a direct neurotoxicity of traffic-related air pollution in the CNS (Costa et al., 2017). Experimental studies have also observed increased levels of proinflammatory cytokines in the brain tissue of mice exposed to particulate matter (Campbell et al., 2005), as well as altered antioxidants activity in the brain tissue of rats following a repetitive inhalation exposure to NO_2 (Li et al., 2012). Similar results were reported in a study on rats and Guinea pigs exposed to SO_2, that showed increased oxidative stress, together with augmented release of pro-inflammatory factors (such as interleukins and TNF-alpha) and induced neurotoxicity (Yao et al., 2015). Analogously, rats exposed to O_3 showed increases in the levels of the inflammatory mediators TNF-a, IL-6, NF-kB p50 and GFAP in the cerebral cortex (González-Guevara et al., 2014). In addition, generation of reactive oxygen species has been proposed as one of the inflammatory mechanisms of CO toxicity (Rose et al., 2017), and might thus partly support also the associations we observed with this pollutant. Finally, the difference in the magnitude of the effects that we observed, on average, between long- and short-term exposure may be attributable to more persistent cumulative effects from long-term exposures. Similar findings, with smaller effect estimates for short-term exposures, have been previously documented when assessing the association between air pollution and mortality (Beverland et al., 2012).

This study provides the most comprehensive evaluation of the association between outdoor air pollution and depression. Indeed, we included all studies (N = 39) published up to May 2021 across different geographical areas (Asia, Europe, and North America): we were thus able to add 19 investigations to the most recently published meta-analysis, and to evaluate not only particulate matter but also gaseous pollutants. We assessed the quality of each study by using validated tools as well as the quality of the summary estimates, by following guidelines specifically developed for non-randomized studies of exposures (Morgan et al., 2019).

The relevance of our results can be better understood if we consider that our meta-analytic estimate for, e.g., long-term $PM_{2.5}$ corresponds to 0.64 (95%CI 0.19; 1.08) to 1.3 (95%CI: 0.38; 2.16) million attributable cases of depression in Europe. These are calculated by multiplying a population attributable fraction of 2.68% (95%CI: 0.79; 4.51), derived from our meta-analytic estimate, to the number of prevalent European depressed subjects (further details of the methods for calculation of attributable cases can be found as Supplementary Material).

Our meta-analysis also has some limitations. The between-study heterogeneity was high for most of the associations considered. Although we used *ad hoc* tools to ascertain the source of heterogeneity and properly pool study-specific estimates, differences across studies might be too relevant to render meta-analysis the most appropriate approach. This is partly supported by the several elements that were identified as potential sources of heterogeneity, especially among studies investigating short-term exposures.

Finally, the GRADE evaluation of pooled estimates classified them as of very low (N = 1), low (N = 4) and moderate (N = 7) quality, and it is important to acknowledge that the classification system necessarily reflects the authors' subjective assessment and might thus be prone to criticism.

5. Conclusions

In summary, the present meta-analysis suggests that an increase in long-term exposure to $PM_{2.5}$ and NO_2, and in short-term PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3 (although less robustly), and CO exposure is associated with an augmented risk of depression. The publication bias affecting almost half of the investigated associations and the high heterogeneity characterizing most of the meta-analytic estimates partly prevent to draw very firm conclusions. On the other hand, the coherence of all the estimates after excluding single studies in the sensitivity analysis supports the soundness of our results. This especially applies to the association between $PM_{2.5}$ and depression, strengthened by the absence of heterogeneity and of relevant publication bias in both long- and short-term exposure studies. Should further investigations be designed, they should involve large sample sizes, well-defined diagnostic criteria for depression, and thorough control of potential confounding factors. Finally, studies dedicated to the comprehension of the mechanisms underlying the association between air pollution and depression remain necessary.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.118245.

Author statement

Elisa Borroni: Methodology, Software, Formal analysis, Data curation, Writing – original draft, Visualization. **Angela Cecilia Pesatori**: Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Massimiliano Buoli**: Writing – review & editing, Funding acquisition. **Valentina Bollati**: Writing – review & editing, Funding acquisition. **Michele Carugno**: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project Administraton, Funding acquisition.

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