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Review article

Ambient ozone exposure and mental health: A systematic review of epidemiological studies

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ABSTRACT

Background: An increasing number of studies have suggested adverse effects of air pollution on mental health. Given the potentially negative impacts of ozone exposure on the immune and nervous system driven from animal experiments, ozone might also affect mental health. However, no systematic synthesis of the relevant literature has been conducted yet. This paper reviews the studies that assessed the link between ozone exposure and mental health thus far.

Methods: We followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). PubMed, Web of Science, and EMBASE were systematically searched for epidemiological studies on ambient ozone exposure and mental or behavioral disorders according to the International Classification of Disease. The period was from January 1st, 1960 to December 14st, 2017. We evaluated the risk of bias by the Office of Health Assessment and Translation (OHAT) Approach and Navigation Guide for each included study.

Results: The keyword search yielded 567 results. 31 papers met the selection criteria and were included in the review. We found only inconclusive evidence that ozone affects autism spectrum disorders, impairment of cognitive functions and dementia, depression, and suicide. The large heterogeneity of study designs, outcome definitions and study quality in general prevented us from conducting meta-analyses.

Conclusions: Current evidence for an association between ambient ozone exposure and mental health outcomes is inconclusive and further high quality studies are needed to assess any potential links given the strong biologic plausibility.

1. Introduction

More than a decade ago, it was proposed that the central nervous system (CNS) may be subject to detrimental effects from exposure to particulate matter as found in air pollution (Oberdorster and Utell, 2002). At present, increasing evidence from experimental, clinical and epidemiological studies suggests that certain neurological diseases, such as Alzheimer's (Block and Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2002) and Parkinson's disease (Kremens et al., 2014; Ritz et al., 2016), may be associated with ambient air pollution.

Mechanistically, air pollution may affect the CNS through a variety of molecular and cellular pathways that either directly damage brain tissue or lead to a predisposition to neurological diseases (Genc et al., 2012). Possible adverse effects are related to the physical and chemical characteristics of the pollutants themselves (Kremens et al., 2014). Although the exact mechanisms of air-pollutant induced brain pathology are not fully understood, recent evidence points toward neuroinflammation, oxidative stress, and disturbance of neurotransmitter systems (Block and Calderon-Garciduenas, 2009; Oberdorster and Utell, 2002) as possible pathways.

Ozone is one of the most important air pollutants in terms of its chemical characteristics as a powerful oxidant (Lauer, 2010). Animal studies that investigated the neurotoxic effects of ozone inhalation in various experimental settings indicate that ozone exposure may increase lipid peroxidation (Pereyra-Munoz et al., 2006), reduce the dopaminergic neurons (Pereyra-Munoz et al., 2006), increase vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), tumor necrosis factor α (TNF α) (Araneda et al., 2008), and c-Fos expression in different brain regions (Gackiere et al., 2011). These findings suggest that ozone may significantly interfere with central nervous physiology, and thus, one may reasonably hypothesize that ozone may have relevant impact on human behavior, cognitive processes and emotion. In this line of thought, ozone may be a potential environmental risk factor for impaired mental health mediated by the above mentioned suggestive

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pathomechanisms.

In the absence of any synthesis of the relevant literature on this topic, here we aim to systematically review the epidemiological studies on ambient ozone exposure and mental or behavioral disorders to describe consistent associations as they exist or identify gaps in our current knowledge.

2. Methods

For the systematic review, we followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (Moher et al., 2015). A complete PRISMA checklist can be found in the Supplementary A.

The work was conducted by one reviewer (TZ) and in case of indetermination a second reviewer (JH) checked.

The overall Population-Exposure-Comparator-Outcome (PECO) statement is as follow, Participants: Humans; Exposures: ambient ozone; Comparisons: comparison group is varied with studies. We are investigating whether exposure to higher concentrations of ambient ozone is associated with mental and behavioral disorders; Outcomes: any mental and behavioral disorder. Study design: observational epidemiological studies

2.1. Search strategy

A systematic literature search was conducted in three different electronic databases: PubMed, Web of Science and EMBASE, for publication dates between January 1, 1960 and December 14, 2017. In accordance with the terminology in “Mental and behavioural disorders (F00–F99)”, International Classification of Disease-10 (ICD-10) (WHO, 2016), combinations of both Mesh headings and free terms connected with ozone and different mental or behavioral disorders were used for the search. In addition, we also manually searched the reference lists of included studies and other related review articles. A more detailed account of the different search strategies is provided in the Supplementary B.

2.2. Studies selection

The search results were filtered and only epidemiological studies that were written in English and investigated the relationship between ambient ozone exposure and mental or behavioral disorders were included. Reviews, letters to the editor, clinical research studies, animal experiments and studies concerned with indoor or occupational exposure to ozone were not considered.

2.3. Data extraction

For each study, information on paper (author and publication time), study location, study design, participants, exposure assessment, outcomes, covariates, and results was extracted. Furthermore, a detailed account of each study's PECO statement is provided in the Supplementary C.

2.4. Assessment of studies

2.4.1. Quality assessment

The Newcastle-Ottawa scale (Wells et al., 2013) was adopted in this review to evaluate the quality of cohort and case-control studies. It contains eight items grouped into three dimensions. Items can be scored with 0 or 1 star except for one item that can be scored with 0–2 stars resulting in a maximum score of 9 stars. The total score is meant to be an indication of the overall quality of a study: 0–5 stars indicate low quality while 6–9 stars are typically taken to indicate high quality.

In addition, we used the criterion from Mustafić (Mustafic et al., 2012) to rate the quality of time-series and case-crossover studies. This criterion consists of three dimensions: exposure (scores between 0 and 1), outcome (0–1) and confounders (0–3). Studies that achieved a total combined score of 5 are regarded as being of high quality while studies that scored 0 in any of the three dimensions are judged to be of low quality. Studies reaching any intermediate score are classified as medium quality.

We did not perform any quality evaluation on cross sectional studies and ecological studies.

2.4.2. Risk of bias assessment

Assessment of risk of bias is related to but distinguished from assessment of methodological quality (OHAT, 2015). Thereby risk of bias assessment was also conducted. Given no established tool for time series and case-crossover study (Achilleos et al., 2017), we evaluated the risk of bias on the Office of Health Assessment and Translation (OHAT) tool by the National Institutes of Environmental Health Sciences National Toxicology Program (OHAT, 2015) and Navigation Guide by the University of California (Lam et al., 2016; Woodruff and Sutton, 2014) for each included study.

We assessed our studies for key criteria (Exposure assessment, Outcome assessment, Confounding bias) and Other Criteria (Selection bias, Attrition/exclusion bias, Selective reporting bias, Conflict of interest, Other source of bias). Each of above domain is evaluated as “low”, “probably low”, “probably high”, or “high” risk according to specific criteria. The criteria of risk of bias assessment is provided in the Supplementary D.

According to OHAT Approach (OHAT, 2015) studies for which the key criteria and most of the other criteria are characterized as “high” or “probably high” risk are recommended to remove.

3. Results

3.1. Search results

The flowchart in Fig. 1 illustrates the selection process for inclusion of studies in the present review. The database search yielded 567 unique hits, 43 of which passed a first selection based on the title and abstract only. These 43 articles underwent a full text evaluation which brought the total number down to 31 published articles that met our inclusion criteria.

The study characteristics of the 31 selected publications are summarized in Table 1 ordered by outcomes, date of publication and results. Seven studies investigated autism or autism spectrum disorder (ASD), two looked into impairment of cognitive functions, five addressed dementia, six researched depression, and five examined suicide. The remaining studies assessed disorders of sex preference, mental disorders, neurobehavioral disorders, panic attacks, psychiatric emergencies and sexual dysfunction (one paper per outcome).

Among the 31 articles, there were seven cohort, six case-control, four case-crossover, six time-series, six cross-sectional and two ecological studies. Additionally, between these 31 studies, 16 focused on long-term exposure and the other 15 on short-term exposure. These details can be checked in the Table 1, column “exposure assessment” as well.

3.2. Assessment of studies

All selected cohort studies received at least 7 stars on the Newcastle–Ottawa scale, and five of the six case-control studies received more than 5 stars. They can thus all be regarded as high quality studies. Two of the selected case-crossover studies and three time-series studies reached at least 3 points according to the Mustafić’s criterion (Mustafic et al., 2012) and are therefore considered to be of medium to high quality. A more detailed account of each study's quality assessment is provided in the Supplementary C

Based on the risk of bias assessment, none of these 31 articles was

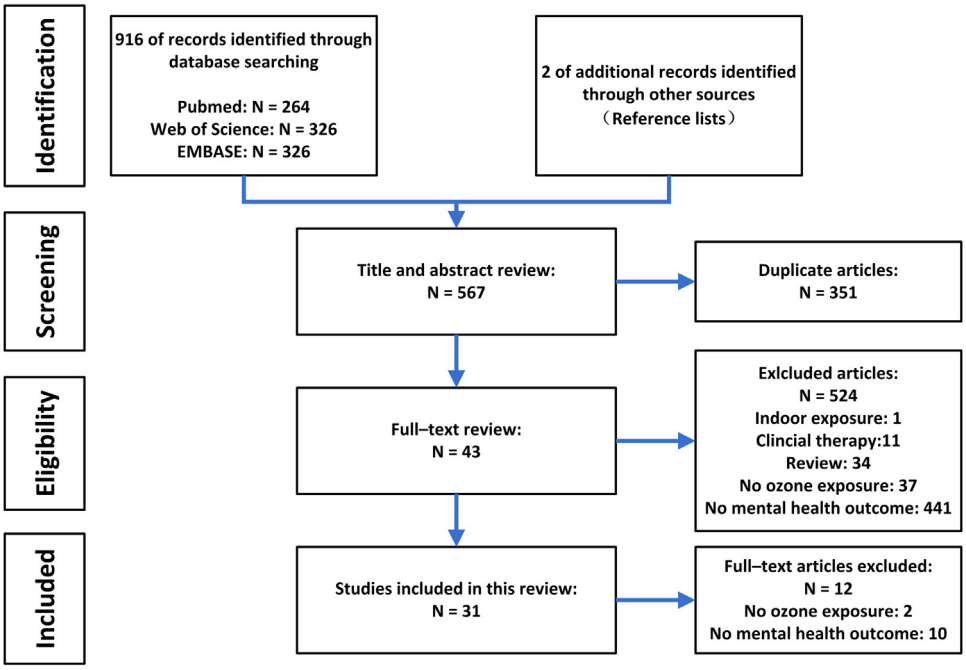

Fig. 1. Flow chart illustrating the literature search and subsequent study selection process.

excluded for being assessed as high risk of bias. However, two studies (Biermann et al., 2009; Oudin et al., 2018) might be regarded as "nearly excluded" as they got one "High" and one "Probably high" risk of bias evaluation within the three key criteria. The heat map illustrating this rating process is provided in Table 2. The detailed account of each study's risk of bias assessment is listed in the Supplementary C.

3.3. Autism and Autism spectrum disorder

Seven articles evaluated the association between ozone and autism spectrum disorder (ASD) or autism (Becerra et al., 2013; Goodrich et al., 2017; Jung et al., 2013; Kerin et al., 2017; Kim et al., 2017; Volk et al., 2014, 2013) but only two studies reported an increase in incidence risk. In particular, Becerra et al. (Becerra et al., 2013) investigated the associations of air pollution during pregnancy on the development of ASD among children aged 3–5 years. Prenatal exposure to an ozone concentration increase of 11.54 parts per billion (ppb) was associated with a 12% higher probability of developing ASD. Another study by Jung et al. (Jung et al., 2013) with children below 3 years of age found that each 10 ppb increase in ambient ozone concentration in the preceding 1 year to 4years may increase the risk of developing ASD by 59%.

Five studies (Goodrich et al., 2017; Kerin et al., 2017; Kim et al., 2017; Volk et al., 2014, 2013) were conducted within the same population as part of the Childhood Autism Risks from Genetics and Environment programme in California. They reported no direct association between ozone and ASD or autism per se, but saw some association modifications by folic acid intake and by genotype. Goodrich et al. (2017) illustrated joint associations of prenatal air pollution exposure and maternal folic acid (FA) supplementation. Children of mothers who were exposed to higher concentrations of ozone (33.41 $\mu g/m^3$) during the first trimester of pregnancy and who reported low FA intake were at a 19% higher risk of developing ASD compared to children of mothers who were exposed to lower levels of the same air pollutant and who reported high first month FA intake. Kim, (2017) reported a gene-environment interaction between ozone and autism in subjects with different copy number variations. The study indicated that a 1-standard-deviation (SD) increase in duplication burden (1,356,513 base pairs) combined with a 1-SD increase in ozone exposure (6.2 ppb) was associated with elevated odds of autism (odds ratio (OR) = 3.4, $P < 0.005$). The latter were much greater than the increased odds of either genomic duplication (OR = 1.85, 95% confidence interval (CI) = 1.25–2.73) or elevated ozone exposure (OR = 1.20, 95% CI = 0.93–1.54) alone. However, Volk et al. (2013) found no statistically significant correlation between autism form and ozone exposure, or *MET* genotype. Subjects with both *MET* rs1858830 CC genotype and high air pollution exposure were at an increased risk of autism compared to subjects who had both the CG/GG genotype and a lower air pollution exposure. Another study (Volk et al., 2014) also reported no statistically significant correlation between continuous regional ozone exposure and ASD. The ecological study conducted by Kerin et al. (2017) reported no statistically significant correlation between ozone and autism severity or functioning.

Although two high quality articles (Becerra et al., 2013; Jung et al., 2013) point toward a positive association between ozone exposure and ASD or autism, this correlation was not confirmed by the other studies included in this review and the association should thus be regarded as unclear.

3.4. Impairment of cognitive functions and dementia

Two cross-sectional studies (Chen et al., 2009; Gatto et al., 2014) from the USA found a correlation between ozone exposure and impairment of cognitive functions. Chen et al. (2009) indicated that each 10 ppb increase in the annual averaged ozone concentration was associated with a cognitive impairment leading to lower test scores in the symbol-digit substitution and serial-digital learning tests by 0.16 and 0.56, respectively. Gatto et al. (2014) reported that exposure to ozone concentrations above 49 ppb was associated with a lower executive function ($\beta = -0.66$).

Five of the selected articles (Calderon-Garciduenas et al., 2015; Chen et al., 2017; Cleary et al., 2018; Linares et al., 2017; Wu et al., 2015) investigated the correlation between ozone exposure and dementia. The case-control study by Wu et al. (2015) observed increased odds of Alzheimer's disease (highest vs lowest tertiles in ozone exposure: OR = 2.00) and of vascular dementia (OR = 2.09). A high quality cohort study by Cleary et al. (2018) investigated ozone exposure, *APOE* genotype and cognitive function. They found a

Table 1
Description of the 31 selected studies on ozone exposure and mental and behavioral disorders. (Ordered by outcomes, paper publication time and results).

Paper	Study location	Study design	Participants	Exposure assessment	Outcomes	Covariates	Results	Quality assessment
Autism spectrum disorder (ASD) or Autism								
1. Becerra et al., 2013	Los Angeles, California, USA	Case-control study	7594 cases and 75635 controls (aged 3-14 years)	Ozone data from nearest monitoring stations; hourly measurements (1000 – 1800 hours) were averaged for each day, daily average exposure for the entire pregnancy and specific pregnancy periods; short-term exposure	Children with ASD were identified by Department of Developmental Services between 36 and 71 months of age	Maternal age, education, race, maternal place of birth, type of birth, parity, insurance type, gestational weeks at birth	Per 11.54 parts per billion (ppb) increase in ozone, a 12 -15 % relative increase in odds, odds ratio (OR) = 1.12, 95% confidence interval (CI): 1.06 - 1.19.	8/9[§]
2. Jung et al., 2013	Taiwan	Cohort study (Longitudinal health insurance database 2000)	49073 children aged less than 3 years in 2000, followed up from 2000 through 2010	Ozone data from three nearest monitoring stations within 25 km combined with inverse distance weighting method (100 m resolution); yearly mean concentration (monthly average of daily maximum value, post-code level address); short-term exposure	342 cases of ASD diagnosed by doctors from January 1st, 2000 to December 31st, 2010	Age, anxiety, sex, intellectual disabilities, preterm, municipal-level socioeconomic status	Per 10 ppb increase in ozone, a 59% risk was increased, adjusted hazard ratio (HR) = 1.59, 95% CI: 1.42 - 1.78.	8/9[§]
3. Kim et al., 2017	California, USA	Case-control study (Childhood Autism Risks from Genetics and Environment study, CHARGE study)	158 cases and 147 controls (aged 24 – 60 months at the time of recruitment)	Ozone data from up to four monitoring stations within 50 km of each residence (if one or more stations were located within 5 km, only data from these were used) combined with inverse distance-squared weighting; average range of ozone measurements from 1000 to 1800 hour (reflecting the high 8-hr daytime exposure); long-term exposure	Children with ASD were identified by Department of Developmental Services (children were born between 1999 and 2008)	Maximum education level of parent, child's sex, child's ethnicity	Per 1356513 base pair increase in duplication burden combined with a 6.2 ppb increase in ozone exposure was associated with an elevated autism risk, OR = 3.4, $P < 0.005$; genomic duplication alone: OR = 1.85, 95% CI: 1.25 – 2.73; ozone alone: OR = 1.20, 95% CI: 0.93 – 1.54.	6/9[§]
4. Volk et al., 2013	California, USA	Case-control study (Childhood Autism Risks from Genetics and Environment study, CHARGE study)	279 cases and 245 controls (aged 24 – 60 months at the time of recruitment)	Ozone data from up to four monitoring stations within 50 km of each residence (if one or more stations were located within 5 km, only data from these were used) combined with inverse distance-squared weighting; average range of ozone measurements from 1000 to 1800 hour (reflecting the high 8-hr daytime exposure); long-term exposure	Children with ASD were identified by Department of Developmental Services	Sex, child ethnicity, maximum education of parents, maternal age, prenatal smoking	No statistically significant association. Suggested increase in odds for autism with ozone exposure in different periods (e.g. first year, OR = 1.15, 95% CI: 0.72 – 1.86, all pregnancy OR = 1.09, 95 % CI: 0.76 – 1.55, per increase of 16.1 ppb ozone).	6/9[§]
5. Volk et al., 2014	California, USA	Case-control study (Childhood Autism Risks from Genetics and Environment study, CHARGE study)	252 cases and 156 controls (aged 24 – 60 months at the time of recruitment)	Ozone data from up to four monitoring stations within 50 km of each residence (if one or more stations were located within 5 km, only data from these were used) combined with inverse distance-squared weighting; average range of ozone measurements from 1000 to 1800 hour (reflecting the high 8-hr daytime exposure); long-term exposure	Children with ASD were identified by Department of Developmental Services	Sex, child ethnicity, maximum education of parents, maternal age, prenatal smoking, home ownership	No statistically significant correlation between *MET* rs1858830 CC genotype and ozone (ozone concentration ≥ 41.8 ppb, with CC *Met* genotype, OR = 0.95, 95% CI: 0.42 – 2.2).	6/9[§]
6. Goodrich et al., 2017	California, USA	Case-control study (Childhood Autism Risks from Genetics and Environment study, CHARGE study)	346 cases and 260 controls (aged 24 – 60 months at the time of recruitment)		Children with ASD were identified by Department of Developmental Services	Self-reported financial hardship between 3 months before pregnancy to time of interview, child's year of birth, vitamin A and zinc intake during the first month of pregnancy		6/9[§]

(*continued on next page*)

Table 1 (*continued*)

Paper	Study location	Study design	Participants	Exposure assessment	Outcomes	Covariates	Results	Quality assessment
				Ozone data from up to four monitoring stations within 50 km of each residence (if one or more stations were located within 5 km, only data from these were used) combined with inverse distance-squared weighting; average range of ozone measurements from 1000 to 1800 hour (reflecting the high 8-hr daytime exposure); long-term exposure			No statistically significant association. FA intake is dichotomized at 800 μg, median ozone = 33.41 μg/m^3, OR (high ozone and low FA) = 1.08, 95% CI: 0.56 - 2.08; OR (low ozone and low FA) = 1.19, 95% CI: 0.61 - 2.30.	
7. Kerin et al., 2017	California, USA	Ecological study (Childhood Autism Risks from Genetics and Environment study, CHARGE study)	325 children with ASD (aged 24 – 60 months at the time of recruitment)	Ozone data from up to four monitoring stations within 50 km of each residence (if one or more stations were located within 5 km, only data from these were used) combined with inverse distance-squared weighting; average range of ozone measurements from 1000 to 1800 hour (reflecting the high 8-hr daytime exposure); long-term exposure	Severity score calibrated by the Mullen Scales of Early Learning (MSEL), the Vineland Adaptive Behavior Scales (VABS), the Autism Diagnostic Observation Schedule (ADOS)	Sex, max education in the home, referral center, race, mother's age, prenatal smoking, season of conception, home ownership	No statistically significant association between ozone and autism severity or functioning (P > 0.05, per 11.1 ppb increase of ozone, Prenatal: VABS composite score – 0.91 %, 95 % CI: - 8.74 % – 6.98 %; MSEL composite development quotient – 0.06, 95 % CI: - 2.78 - 2.66; Year 1: VABS composite score 0.91 %, 95 % CI: - 11.74 % – 13.4 %; MSEL composite development quotient 1.43, 95 % CI: - 2.58 – 5.71).	
Impairment of cognitive functions								
8. Chen et al., 2009	USA	Cross- sectional study (the Third National Health and Nutrition Examination Survey, NHANES III)	1764 adult subjects (age 37.5 ± 10.9) from the Third National Health and Nutrition Examination Survey in 1988 - 1991	Ozone data from Environmental Protection Agency and combined with inverse distance weighting; annual ozone at geocoding residential information; long-term exposure	Scores of simple reaction time test (SRTT), symbol – digit substitution test (SDST), serial – digital learning test (SDLT)	Age, sex, race, demographics, socioeconomic status, lifestyle, household and neighborhood characteristics, cardiovascular risk factors	A per 10 ppb increase in annual ozone prior to testing was associated with increased SDST and SDLT scores (regression coefficient β, 0.16, 95% CI: 0.01 – 0.23 and 0.56, 95% CI: 0.07 – 1.05, respectively).	
9. Gatto et al., 2014	Los Angeles, USA	Cross- sectional study	1496 healthy, cognitively intact adult participants (age 60.5 ± 8.1) enrolled during 2000-2006	Ozone from monitoring station (one for station located within 5 km, otherwise 3 closest ones for located within 100 km) and combined with inverse distance weighting; annual average ozone (8h maximum concentration for daily ozone, geocoded residence address); long-term exposure	Cognitive tests (executive function, verbal learning, logical memory, visual processing, visual episodic memory, semantic memory) conducted by psychometrist	Age, gender, race, education, income, study, mood	Exposure above 49 ppb ozone was associated with lower executive function (beta coefficient β = -0.66, 95% CI: - 1.35, 0.03; P = 0.059).	

(*continued on next page*)

Table 1 (*continued*)

Paper	Study location	Study design	Participants	Exposure assessment	Outcomes	Covariates	Results	Quality assessment
Dementia								
10. Calderon-Garciduenas et al., 2015	Mexico and Polotitlán,Mexico	Cross- sectional study	57 right – handed children (age 12.45 ± 3.4) and their 48 right – handed parents (age 37.5 ± 6.77) from Mexico City; 9 control children (age 9.77 ± 0.83) and their 7 control parents (age 34.57 ± 6.02) from Polotitlán	Ozone in Mexico City (high ozone) and Polotitlán (control, low ozone); long-term exposure	NNA/Cr, Cho/Cr and mI/Cr ratios [N–acetylaspartate (NAA), choline, creatine (Cr) and myoinositol (mI)]	Age, gender, body mass index, apolipoprotein E (*APOE*) genotype	The right hippocampus NAA/Cr ratio was significantly different between control (P = 0.007). *APOE* ε4 carriers are at higher risk.	
11. Wu et al., 2015	Taiwan	Case-Control study	249 Alzheimer's disease (AD) patients, 125 vascular dementia (VaD) patients and 497 controls from 2007 to 2010 (aged ≥ 60)	Ozone data from Environmental Protection Administration combined with Bayesian maximum entropy method; annual average exposure (residential place); long-term exposure	AD or VaD was diagnosed based on criteria	Age, sex, *APOE* ε4 status, PM_{10} level, education years, alcohol consumption	Increased risk observed for dementia with ozone exposure, for AD (highest vs. lowest tertile: aOR = 2.00, 95% CI: 1.14 – 3.50) and for VaD (highest vs. lowest tertile: aOR = 2.09, 95% CI: 1.01 – 4.33). Ozone exposure: lowest tertile, < 20.22 ppb, highest tertile > 21.56 ppb.	5/9[§]
12. Linares et al., 2017	Madrid, Spain	Time-series study	1175 dementia-related emergency from January1st 2001 to December 31st 2009	Ozone data from the Madrid Municipal Air Quality Monitoring Grid; daily mean concentration; short-term exposure	1175 dementia – related emergencies (ICD – 10 codes 290.0 – 290.2, 290.4 – 290.9, 294.1 - 294)	Day of week	An increase of 10 μg/m^3 in ozone, RR = 1.09, 95% CI: 1.04 – 1.15, (lag 5). And a higher RR can be observed when daily ozone concertation surpass a threshold of 45 μg/m^3.	2/5[§§]
13. Cleary et al., 2018	USA	Cohort study (National Alzheimer's Disease Center program)	5419 participants aged 60 or more, with a baseline Mini – Mental Status Examination score > 0 and a diagnosis of cognitive impairment in at least on follow – up visit	Ozone data from Environmental Protection Agency combined with space – time Hierarchical Bayesian Model (12 km ×12 km resolution covering the east and 36 km ×36 km resolution across USA) and inverse distance weighting; yearly ozone (average the 8-h maximum over year, ZIP code residence address); long-term exposure	3624 participants with normal cognition, 1492 participants with cognitive impairment, diagnosed based on examination	Age, sex, education, race, apolipoprotein E (*APOE*) genotype, smoking status, vitamin B12 deficiency, population density,	Baseline cognitive performance was significantly reduced by highest (> 40 ppb) versus lowest level (< 36.7 ppb) of ozone for assessing both the Mini - Mental State Examination (MMSE) (β - coefficient = 0; β - coefficient = 0.83, 95% CI: 0.5 - 1.2) and Cognitive Dementia Rating - Sum of Boxes (CDR - SB) (β - coefficient = 0; β - coefficient = -0.60, 95% CI: - 0.8 - -0.3). *APOE* ε 4 alleles exhibited a faster rate of cognitive decline.	8/9[§]
14. Chen et al., 2017	Ontario, Canada	Cohort study (Ontario Population Health and Environment Cohort)	2066639 individuals (were 55 – 85 years old on 1st April 2001), resided in Ontario for > 5 years, Canadian-born, free of physician-diagnosed dementia. Follow-up extended till 31st March 2013	Ozone data from optimal interpolation technique; annual exposure (postal code residence address); long-term exposure	257816 incident cases of dementia in 2001 - 2013	Age, sex, pre-existing comorbidities (diabetes, hypertension, coronary heart disease, stroke, congestive heart failure, arrhythmia, traumatic brain injury), income quintile, urban residency, north/south indicator, unemployment rate education, immigrants,	No statistically significant association was found for ozone and dementia. Hazard ratios was 0.98, 95% CI: 0.96 – 1.00 (per 6.3 ppb increase for ozone).	7/9[§]

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Table 1 (*continued*)

Paper	Study location	Study design	Participants	Exposure assessment	Outcomes	Covariates	Results	Quality assessment
Depression disorder								
15. Szysykowicz et al., 2007	Edmonton, Canada	Time-series study	15556 emergency department visit for depression between 1992 and 2002 (70.9 & aged between 20 and 50 years)	Ozone data from fixed monitoring stations; averaged hourly data over 24-h periods; short-term exposure	Emergency department visits for depression	Temperature, relative humidity, sex, season	An increase 14.0 ppb in ozone, an increment in daily depression-related emergency department visits could be noted: 6.9% (95% CI: 0.6 - 13.6) for ground level ozone (1-day lagged) for female patients in warm season could be noted.	2/5[§§]
16. Lim et al., 2012	Seoul, South Korea	Cohort study	537 participants (averaged age 71 ± 5) performed from 2008 to 2010	Ozone data from the nearest monitoring site to residential address; moving average of daily maximum values between 09:00 and 18:00 hours; short-term exposure	Depression diagnosed by the Korean version of the Geriatric Depression Scale-Short Form	Age, sex, number of school, body mass index, alcohol consumption, regular exercise, creatinine-adjusted urine cotinine level, systolic blood pressure, triglyceride, daily mean temperature, follow-up time, day of week	Per 37 ppb increase in ozone (3 - day moving average) was associated with depressive symptomatology (43.7%, 95% CI: 11.5 - 85.2). Per 37 ppb increase for ozone (28 - day moving average) emotional symptoms (emotional symptoms: 132.5%, 95% CI: 32.0 – 309.3).	7/9[§]
17. Szyszkowicz et al., 2016	Canada	Case-crossover study	118602 emergency department visits for depression from April 2004 to December 2011	Ozone data from National Air Pollution Surveillance stations within 35 km of each patient's postal code; averaged hourly data over 24-h periods; short-term exposure	Emergency department visits for depression	Sex, day of week,	Per increase 14.5 ppb in ozone was associated with increased risk of an emergency department visit for depression: for females, between 1 and 7 days after exposure, ORs ranging between 1.02 and 1.03; for males, was between 1 and 5, and 8 days, ORs ranging between 1.02 and 1.03.	2/5[§§]
18. Kioumourtzoglou et al., 2017	USA	Cohort study (Nurses' Health Study)	41844 women (averaged age 66.6 ± 7.6) followed from 1996 to 2006	Ozone data from up to 5 monitors and at least 1 monitor within 50 km to participant's house, using the squares of the distances as weights; monthly averaged ozone concentrations (residence address, May – September); long-term exposure	Defined as first report of either a physician diagnosis or use of antidepressant medication	Calendar year and month at questionnaire return, census region, living in a metropolitan statistical area, race, physical activity, body mass index, pack-years of smoking, smoking status, dietary habits, participation in social groups, baseline abbreviated Mental Health Inventory score, educational level, parental education, marital status, husband's education, tract-level median income, house value, population density	Per 10 ppb increase in ozone, hazard ratio (HR) = 1.06, 95% CI: 1.00 – 1.12; associations were stronger when only antidepressant use to define cases (for ozone, HR = 1.08, 95% CI: 1.02 – 1.14).	8/9[§]
19. Szyszkowicz et al., 2009	Canada	Time-series study	27047 emergency department visit for depression; Starting date: April; Study period: 13709 days	Ozone data from National Air Pollution Surveillance system; averaged hourly data over 24-h periods; short-term exposure	Emergency department visits for depression	Season (period)	No positively association between emergency department visits for depression disorder and ozone, RR% (worm period) = -1.1, 95% CI: - 5.9 - 3.9, in relation to an increase of 18.9 ppb ozone.	2/5[§§]
20. Wang et al., 2014	Boston, USA	Cohort study (MOBILIZE Boston Study)	732 Boston-area adults ≥ 65 years of age (78.1 ± 5.5) recruited between 2005 and 2008	Ozone data from a single monitoring site within 20 km radius to participant's home; moving average of daily mean value form hourly data; short-term exposure	Depressive symptoms by 20-item Revised Centre for Epidemiological Studies Depression Scale (CESD-R)	Age, sex, race/ethnic, visit, ambient and dew point temperatures, barometric pressure, day of week, season, long -term temporal trends		7/9[§]

(*continued on next page*)

Table 1 (*continued*)

Paper	Study location	Study design	Participants	Exposure assessment	Outcomes	Covariates	Results	Quality assessment
							No evidence of a positive association between depressive symptom short-term changes in pollution levels. OR of CESD-R = 0.71, 95% CI: 0.46 - 1.09 (13.45 ppb for an interquartile range).	
Suicide								
21. Biermann et al., 2009	Bavaria, Germany	Cross-sectional study	1008 suicides and 917 suicide attempts from 2004 to 2007	Ozone data from the Institute of Chemical Analysis of the City of Nuremberg; daily average value for ozone; short-term exposure	1008 suicides as well as 917 suicide attempts leading to police procedures from register of suicides	Not reported	The ozone levels differed statistically significant (T = -0.25; p = 0.014) between days where one or no suicide were observed (mean ozone: 79.8 μg/m^3; SD: 36.3) and days with two more suicides (mean ozone: 86.4 μg/m^3; SD: 39.4). No association between ozone levels and suicide attempts.	
22. Yang et al., 2011	Taiwan	Ecological study	4857 deaths by suicide from January 1st 1991 to 31st December 2008	Ozone from Environmental Protection Administration; monthly average; long-term exposure	4857 deaths by suicide, average counts 22.5 ± 9.6 cases, range = 6 -59 cases from Department of Health	Age, gender, means of suicide (violent, non - violent)	Ozone was particularly associated with suicide (for violent, r = 0.231, p = 0.002; for male, r = 0.213, p = 0.004; for female, r = 0.202, p = 0.006; for age 20 -65, r= 0.194, p value was not reported; for age > 65, r = 0.312, p <0.001) and total, r = 0.244, p=0.001); for 119.1 month/cycle (intrinsic mode function), r = 0.338, p <0.001.	
23. Kim et al., 2015	Korea	Time-series study	The suicide rate per 10 million persons in the 16 administrative regions from January 1st 2006 to December 31st 2011	Ozone data from the Korea Ministry of Environment, ; daily concentration (averaged value for each region); short-term exposure	The variation of weekly suicide rate from the Korea National Statistical Office	Celebrity suicides, meteorological variables (sunlight hours and temperature), economic data, the regional weekly suicide rate, the average national monthly suicide number for the past 5 years	Extending back to 4 weeks, over the range of 2 standard deviations (0.016 ppm) around the annual mean ozone concentration, the adjusted suicide rate increased by an estimated 7.8 % of the annual mean rate(29.1 per 100000 persons per year).	3/5[§§]
24. Casas et al., 2017	Belgium	Case-crossover study	Suicide deaths registered between January 1st 2002 and December 31st 2011	Ozone data from monitoring stations and satellite images, in kriging interpolation model (4 × 4 km grid); 8-h average ozone concentrations; short-term exposure	20533 suicide deaths, aged from 5 to more than 85 years old from the National Population Register	Season, age, sex, the method to commit suicide (non – violent, violent); day of week, duration of sunshine	Per 10 μg/m^3 increase in ozone was associated with suicide mortality in all seasons except winter (P < 0.05 for lags 0 – 2 and 0 – 6, OR ranging from 1.02 to 1.07); 1 -2 % increase in the odds of suicide mortality for all the suicide lags among the adult population; an 8% increase odds of suicide (95% CI: 1 – 16%) among adolescents (in lag 0 -1 ozone); and individuals committed suicide using violent methods. No association between sex and ozone.	3/5[§§]
25. Szyszkowicz et al., 2010	Vancouver, Canada	Case-crossover study				Daily temperature and relative humidity, sex, season		2/5[§§]

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Table 1 (*continued*)

Paper	Study location	Study design	Participants	Exposure assessment	Outcomes	Covariates	Results	Quality assessment
			Emergency department visits with suicide attempt / ideation from July 8,1999 to February 28, 2003	Ozone data from fixed monitoring stations; daily shared exposure (daily mean value form hourly data and an average among monitors); short-term exposure	1605 emergency department visits with suicide attempt / ideation in hospital		No statistically significant association between ozone and suicide attempts ($P > 0.05$, the effect size is not given), the highest positive value was obtained for ozone lagged by 1 day (per 0.9 ppb increase in ozone).	
Disorders of sex preference								
26. Rotton, 1993	Dayton, Ohio, USA	Cross-sectional study	584 reports of rape, 674 complaints about obscene phone calls, 288 calls about indecent exposure and 547 more complaints within 731 days (January 1st, 1975 to December 31st, 1976)	Ozone data from Environmental Protection Agency; average ozone (24-hour readings on 712 days); long-term exposure	Sex crimes reported by police department	Series for 731-day long term trend, season, day of week, holidays	Ozone was associated with complains about obscene phone call (regression coefficients = 0.003, $P < 0.01$)	
Mental disorders (hospital admissions)								
27. Chen et al., 2018	Shanghai, China	Time-series study	Cases of hospital admissions for mental disorder (10^{th} version of the international classification of diseases, F01- F99) identified during January 1st, 2013 to December 31st, 2015	Ozone data from the Shanghai Environmental Monitoring Center; maximum 8-h average ozone; short-term exposure	39143 cases of daily hospital admissions for mental disorder (maniac episode, depressive disorder and others)	Long-term and season trends, temperature, humidity, day of work, holiday	No statistically significant associations. Per 10 $\mu g/m^3$ increase in ozone (lag 01 day) was associated with increment of 0.34%, 95% CI: - 1.08 – 1.75.	4/5[§§]
Neurobehavioral disorder								
28. Lin et al., 2014	Taiwan	Cross-sectional study (Taiwan Birth Cohort Pilot Study, TBCS-q)	533 mother – infant pairs from 11 towns in Taiwan, babies born between October 2003 and January 2004	Ozone data from the Taiwan Air Quality Monitoring Network; daytime (7 a.m. to 7 p.m.) average level (monitoring stations of town); short-time exposure	The 6- and 18-month scales (the Bayley Scales of Infant Development, consists of: gross motor, fine motor, language / communication, social / self – care abilities)	Maternal education level, maternal nationality, gestational age, infant sex, breastfeeding, environmental tobacco smoke exposure, nursery type	No statistically significant association between ozone exposure and subclinical neurodevelopment in early childhood ($P > 0.05$, six months of age, total for 18 months of age, 1^{st} trimester: $\beta = -0.026$, SE = 0.093; 2^{nd} and 3^{rd} trimester: $\beta = -0.140$, SE = 0.137; birth – 12 month: $\beta = -0.102$, SE = 0.101).	
Panic attacks								
29. Cho et al., 2015	Seoul, South Korea	Time-series study	Individuals who visited the emergency department with panic attack (F 41.0) from 2005 - 2009	Ozone data from the Ministry of Environment;; daily average (an average of hourly measurements from 27 monitoring stations); short-term exposure	2320 emergency department visits for panic attacks (F41.0)	Date of the visit, day of week, national holiday, daily mean temperature and relative humidity	Per increment for 10.04 ppb ozone, the adjusted RR of emergency department visits for panic attacks was 1.051 (95% CI: 1.014 – 1.090) for the same – day exposure to ozone; and 1.059 (1.021 – 1.099) in lag 0 – 1, 1.068 (1.029 – 1.107) in lag 0 – 2 and 1.074 (1.035 – 1.114) in lag 0 – 3.	3/5[§§]

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Table 1 (*continued*)

Paper	Study location	Study design	Participants	Exposure assessment	Outcomes	Covariates	Results	Quality assessment
Psychiatric emergency								
30. Oudin et al., 2018	Gothenburg, Sweden	Case-cross over study	Psychiatric emergency visits (PEV) data from July 1st 2012 to November 24st 2016	Ozone data form a measuring station; average ozone; long-term exposure	Number of PEV was 27 ± 6	Daily mean temperature and public holiday	No clear association between outcome and ozone. Per 10 μg/m^3 increase in ozone, change PEV 0.1%, 95% CI: - 0.6 – 0.9; in the three-pollutant models ($PM_{2.5}$, NO_2, O_3) the increase was 3.3%, 95% CI: -0.2 – 6.9.	2/5[§§]
Sexual dysfunction								
31. Tallon et al., 2017	USA	Cohort study (National Social Life, Health, and Aging Project)	412 household-resident older adults aged 57 – 85, conducted from July 2005 to March 2006 and August 2010 to May 2011	Ozone data from the nearest monitor stations (within 60 km of the participants' home); 1 -7 year average exposure based on warm season (April – September); long-term exposure	Erectile dysfunction (ED) status obtained through self- reported questionnaire: 132 men with ED, 280 men without ED	Age, geographic region, ethnic group, education, current smoking status, obesity, diabetes, depression, season, median household income	No association between ozone exposure and odds in incident ED. ORs for 1 and 7 years moving average equaled 1.16 (95% CI: 0.87 – 1.55; IQR = 8.21 ppb) and 1.16 (95% CI: 0.92 – 1.46; IQR = 6.81 ppb).	7/9[§]

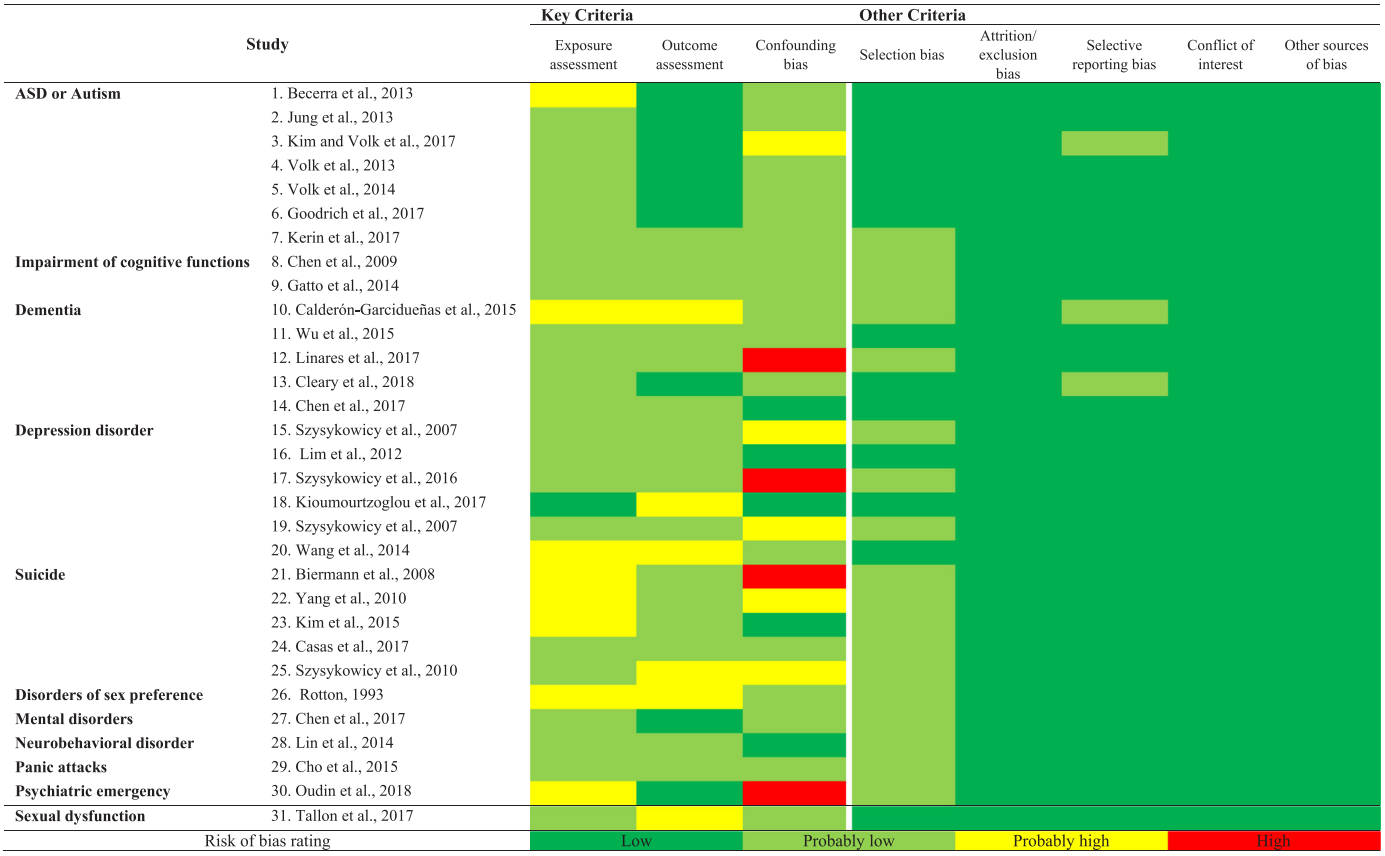
Note:

§ The Newcastle-Ottawa scale (Wells G, 2013) was adopted in this review to evaluate the quality of cohort studies and case-control studies. The Newcastle-Ottawa scale contains eight items grouped into three dimensions. Items can be scored with 0 or 1 star except for one item that can be scored with 0 to 2 stars resulting in a maximum score of 9 stars. The total score is meant to be an indication of the overall quality of a study: 0 to 5 stars indicate low quality while 6 to 9 stars are typically taken to indicate high quality.

§§ The criterion from Mustafić's study (Mustafic et al., 2012) was used to evaluate the quality of time-series and case-crossover studies. The evaluation is based on three dimensions that can reach a combined top score of 5. The dimensions are exposure (score of 0 to 1), outcome (0 to 1) and confounders (0 to 3). The studies reaching a total score of 5 were regarded as being of high quality while studies that scored 0 in any one dimension were judged as being of low quality. All remaining studies were regarded as being of medium quality.

The cross-sectional and ecological studies were not given any quality evaluation

Table 2
Heat map of risk of bias rating for 31studies.



Note:
Risk of bias assessment was conducted on the Office of Health Assessment and Translation (OHAT) Approach by the National Institutes of Environmental Health Sciences National Toxicology Program (OHAT, 2015) and Navigation Guide by the University of California (Lam et al., 2016; Woodruff and Sutton, 2014) for each included study. We assessed our studies for key criteria (Exposure assessment, Outcome assessment, Confounding bias) and Other Criteria (Selection bias, Attrition/ exclusion bias, Selective reporting bias, Conflict of interest, Other source of bias). Each of above domain is evaluated as “low”, “probably low”, “probably high”, or “high” risk according to specific criteria. The criteria and a detailed account of each study’s risk of bias assessment is provided in the Supplementary D. According to OHAT Approach (OHAT, 2015) studies for which the key criteria and most of the other criteria are characterized as “high” or “probably high” risk are recommended to remove.

significantly reduced baseline cognitive performance for that part of the cohort that was exposed to the highest ozone concentration of more than 40 ppb compared to the lowest concentration of less than 36.7 ppb using both the Mini-Mental State Examination and Cognitive Dementia Rating-Sum of Boxes for the assessment. In addition, they pointed out that *APOE ε4* alleles exhibited a faster rate of cognitive decline.

A cross sectional study by Calderon-Garciduenas et al. (2015) investigated the same gene-environment interaction. Using brain MRI scans they found that chronic overexposure to ozone may lead to neurodegenerative processes that already start in childhood, with *APOE ε4* carriers being at a particularly high risk. However, the study could not distinguish between effects from ozone and fine particulate matter. Linares et al. (2017) observed that ozone might exacerbate the risk of developing dementia symptoms by a factor of 1.09 in an ecological study analyzing dementia-related emergencies in Madrid.

However, a high quality cohort study in Ontario by Chen et al. (2017)) reported no statistically significant association for ozone and dementia.

In summary, we found one high quality cohort study (Cleary et al., 2018), one low quality case-control study (Wu et al., 2015), one low quality time-series study (Linares et al., 2017) and three cross-sectional studies (Calderon-Garciduenas et al., 2015; Chen et al., 2009; Gatto et al., 2014) that reported an association between ozone exposure and cognition impairment. This suggests that ozone exposure might be a possible cause of cognition impairment or even dementia. However, the verdict on a possible association between ozone exposure and dementia is not unanimous due to the heterogeneity in study design and quality.

3.5. Depression disorder

Two cohort (Kioumourtzoglou et al., 2017; Lim et al., 2012) studies demonstrated that an increase in ozone was associated with an increase in depression disorder diagnoses. The high quality study by Lim et al. (2012) showed that for elderly adults in Seoul the depressive symptomatology was positively associated with the increase in ozone. Another high quality study by Kioumourtzoglou et al. (2017) showed a hazard ratio increase by a factor of 1.06 per 10 ppb in ozone increase among middle-aged and older women.

Szysykowicz et al. conducted three studies in Canada (Szyszkowicz, 2007; Szyszkowicz et al., 2016, 2009). One low quality time-series study (Szysykowicz et al., 2007) showed a positive association between ozone and emergency department visits for depression disorder by female patients. One low quality case-crossover study (Szyszkowicz et al., 2016) examining emergency department visits for depression disorder demonstrated a positive association with odds ratios ranging from 1.02 to 1.03 per interquartile range for a daily mean ozone concentration of 14.5 ppb. Nevertheless, another time-series study (Szyszkowicz et al., 2009) examining the same association between ozone and emergency

department visits for depression disorder did not find any significant correlation.

The high quality cohort study by Wang et al. (2014) found no evidence of an association between depressive symptom and short-term changes in pollution levels among older adults.

Based on the heterogeneous study designs and quality, no clear association between ozone and depression can be postulated.

3.6. Suicide

Of the two medium to low quality case-crossover studies (Casas et al., 2017; Szyszkowicz et al., 2010), one medium quality time-series study (Kim et al., 2015), one cross-sectional studies (Biermann et al., 2009) and one ecological study (Yang et al., 2011) on ozone in relation to suicide outcomes, only one (Szyszkowicz et al., 2010) failed to report positive associations. However, the outcome “Emergency department visits with suicide attempt/ideation” (Szyszkowicz et al., 2010) is different and unique from other studies, and this study observed no association.

The time-series study by Kim et al. (2015) found that a 0.016 ppm increase in the average ozone concentrations during the previous 4 weeks (equivalent to 2 standard deviations) led to an increase in the weekly suicide rate in Korea by 7.8% which corresponds to 29.1 additional suicides per 100,000 persons per year. One case-crossover study by Casas et al. (2017) observed that ambient ozone concentrations were associated with suicide mortality in Belgium during all seasons except winter, producing a 1–2% increase in the odds of suicide mortality among the adult population and an 8% increase in the odds among adolescents.

An ecological study conducted by Biermann et al. (2009) found a statistically significant difference in ozone levels between days where one or no suicide occurred (mean ozone level: 79.8 $\mu g/m^3$; SD: 36.3) and days with two or more suicides (mean ozone level: 86.4 $\mu g/m^3$; SD: 39.4). Yang et al. (2011) reported that ozone was correlated with suicide rate ($P < 0.001$; total, $r = 0.244$).

Even though the majority of studies points towards positive association between elevated ozone levels and increased suicide rates, the low quality in relevant studies precludes us from drawing a definitive conclusion.

3.7. Other mental and behavioral disorder

One publication was identified for each of these five outcomes: disorders of sex performance, mental disorders with hospital admission, neurobehavioral disorders, panic attacks, psychiatric emergencies and sexual dysfunctions. Already in 1993, the cross-sectional study by James et al. (Rotton, 1993) reported that higher ozone levels were associated with complaints about obscene phone calls ($\beta = 0.003$, $P < 0.01$).

A time-series study from Shanghai (Chen et al., 2018) reported no association between ozone and cases of hospital admission for mental disorders (maniac episodes, depressive disorders and others). Similarly, a case-crossover study from Sweden by Oudin et al. (2018) found no association between ozone and psychiatric emergencies.

A cross-sectional study from Taiwan (Lin et al., 2014) found no association between ozone exposure and subclinical neurodevelopment in early childhood.

The time-series study by Cho et al. (2015) demonstrated that for each 10.04 ppb increase in the ambient ozone concentration the adjusted relative risks of emergency department visits for panic attacks were between 1.051 and 1.074 for different lags in ozone exposure.

The cohort study by Lindsay et al. (Tallon et al., 2017) found no association between ozone exposure and the odds of incident erectile dysfunction.

Due to the insufficient number of studies for each outcome, no final conclusions can be draw at this point.

4. Discussion

To the best of our knowledge, the present study provides the first systematic literature review on possible associations between ozone and mental or behavioral outcomes such as ASD, impairment of cognitive functions and dementia, depression and suicide. We conducted a broad literature search and selected a total of 31 studies that met our selection criteria for inclusion in this review. All 31 studies exhibited very heterogeneous study designs, sample sizes, outcomes, exposure assessment methods and qualities making meta-analyses impossible.

ASD is a complex developmental disorder characterized by impairments in social interaction, abnormalities in verbal and nonverbal communication and deficits in behavioral flexibility (Bhat et al., 2014). Our analyses did not provide evidence for a conclusive association between ambient ozone exposure and ASD or autism although our literature search delivered some high quality studies (Becerra et al., 2013; Goodrich et al., 2017; Jung et al., 2013; Kim et al., 2017; Volk et al., 2014, 2013). The gene-environmental interaction between ozone exposure and ASD was addressed in studies (Kim et al., 2017; Volk et al., 2014) that found that ozone exposure was only associated with autism risk when accompanied by a high number of genetic copy number aberrations (Kim et al., 2017). Although further research on the complex interactions of heterogeneous genetic predisposition with environmental modifiers is warranted, these findings also suggest that some subpopulations affected by psychiatric morbidity may be more susceptible to ozone exposure than others (Dales and Cakmak, 2016). Furthermore, it may indicate that associations of ozone exposure may not necessarily map to specific disorders per se, but rather impact underlying pathophysiological mechanisms related to them. Hence, genotypic variation should be considered in more detail in future studies.

The dementia, even caused by Alzheimer's disease or Parkinson's disease is categorized as a type of mental health disorder (F00, F02) in ICD-10 (WHO, 2016). A positive association between air pollution and Alzheimer's disease (Block and Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2002) or Parkinson's disease (Kremens et al., 2014; Ritz et al., 2016) has already been reported. However, we focus here on the association between ozone and dementia, as this association is less-reported and Alzheimer's disease or Parkinson's disease is more typically categorized as a type of “Diseases of the nervous system” in ICD-10 (WHO, 2016). As a precursor of dementia, impairment of cognitive functions, also cataloged in “Mental and behavioural disorder” ICD-10 (WHO, 2016), may deteriorate into dementia which can in turn result in a three-fold increase in the number of dementia patients by 2050 compared to an already high number of 47 million cases in 2015 (WHO, 2015). While no explicit association was found in this review, ozone as a possible cause for cognition impairment and dementia should be studied in a more systematic manner.

Although suicide (for example X60-X84) is not included in the official ICD-10 F00.0–F99.9 codes (WHO, 2016), it is regarded as a severe consequence of mental disorders such as depression (Draper, 2014; Miret et al., 2013). Therefore, we decided to include studies on ozone and suicide in this review. However, given the heterogeneous study designs and low quality no conclusive results can be derived.

The complex and heterogeneous etiology of mental health problems is still under-investigated and mechanistic models of basically all disorders are either lacking or hypothetical at best. Ozone exposure, a so far scarcely considered environmental risk factor, may be another piece in this puzzle. Based on results from existing animal studies, there are at least five possible mechanisms to explain associations between ozone exposure and mental health. Firstly, ozone is a strong irritant that can result in headache, dizziness, nausea and feelings of ill health (Kleno and Wolkoff, 2004), thereby affecting mental states (Petersen, 2010; Russell, 2017; Walker, 2017). Secondly, inhalation of ozone can provoke inflammatory effects resulting in the production of pro-inflammatory cytokines that are capable of crossing the blood-brain barrier and thereby affect brain function (Dantzer and Kelley, 2007;

Dunn and Swiergiel, 1998), ozone is furthermore known to increase VEGF, IL-6 and TNF α (Araneda et al., 2008) expression in some brain regions. Thirdly, ozone may reduce dopaminergic neurons in CNS (Pereyra-Munoz et al., 2006). Fourthly, ozone can activate the hypothalamo-pituitary-adrenal axis function. Dysregulated hypothalamo-pituitary-adrenal axes with abnormal secretion of hormones take part in the pathological process of mental disorder (Gonzalez-Pina and Paz, 1997). Finally, ozone or its reaction products can affect the metabolism of neurotransmitters like serotonin thereby influencing the function of the nervous system (Odermatt and Gumy, 2008; Thomson et al., 2013).

Although several studies linked ozone exposure to adverse mental outcomes in our review, the evidence presented to date is limited.

According to our quality and risk of bias assessment, controlling for confounding factors is necessary for an accurate estimation of the associations of ozone on mental health. Most of the selected studies already involved several confounders but more covariates should be considered in the future, in particular, meteorological factors. Increasing evidence indicates the importance of gene-environment interactions in associations with ozone (Kim et al., 2017; Volk et al., 2014). Therefore, confounders and effect modifiers, including correlated genotypes, may allow for the derivation of more accurate associations.

Assessment of ozone exposure is another concern. In all selected studies, exposure estimates were simply assigned from monitor stations alone or interpolated with geographic information system techniques such as the inverse-squared weighting method. These techniques are better for estimating long-term exposure but might underestimate spatial contrasts (Brauer et al., 2007) and cannot be used to accurately gauge the exposure of an individual for whom personal monitoring (Choi et al., 2006) or biomonitoring (Autrup et al., 1999) may be more suitable. Furthermore, the definitions of outcomes often represent significant challenges. Future studies should preferentially be based on diagnosis standard criteria for defining the outcome.

Although we attempted to include all published studies on ozone and mental health outcomes, there is a possibility that some published articles were accidentally neglected. Since the studies on each mental and behavioral disorder are few (less than ten), the publication bias and selective reporting are inevitable (Sterne et al., 2011). Additionally, studies with negative results are typically less likely to be published (Siddiqi, 2011; Song et al., 2010) and studies not written in English were excluded from this review. Publication bias is thus likely but cannot be quantified due to the small overall number of studies.

Nevertheless, OHAT approach (OHAT, 2015) extend existing systematic review methods to integrate data from human studies, animal studies and mechanistic studies. A comprehensive review that involve well-designed and result-reasonable animal studies and mechanistic studies would better reveal the association between ozone and mental health.

5. Conclusion

Overall, this review could showcase the large heterogeneity encountered in published studies on ozone exposure and mental health outcomes. Although results from animal models support the notion of adverse effects of ozone on mental health, the little epidemiological evidence we found to date is often inconclusive and does not permit a final verdict. Further high quality studies with more accurate exposure measurements and holistic covariates are warranted.

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Declarations of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2018.04.015.

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