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Review article

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

Tianyu Zhao[a], Iana Markevych[a,b], Marcel Romanos[c], Dennis Nowak[a], Joachim Heinrich[a,b,*]

[a] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany
[b] Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany
[c] Centre of Mental Health, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

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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

* Correspondence to: Institute and Clinic for Occupational, Social and Environmental Medicine University Hospital, LMU Ziemssenstraße 1, 80336 Munich, Germany.
E-mail address: Joachim.Heinrich@med.uni-muenchen.de (J. Heinrich).

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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