MASTER'S THESIS

Are mental health problems in children and adolescents associated with outdoor air pollution?
A systematic review

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Are mental health problems in children and adolescents associated with outdoor air pollution?
A systematic review

Bestaat er een associatie tussen problemen met de mentale gezondheid bij kinderen en adolescenten en buitenluchtvervuiling? Een systematische review

Thesis committee

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Words of gratitude

I would like to thank the thesis committee and my family, not in the least for their patience.

Abstract — Mental health issues can gravely impair people's functioning in everyday life. In the general population and in adults, these issues have been linked to air pollution. Currently, little is known about the association between exposure to air pollution and mental health in children and adolescents. This study addresses the possible association between airborne, outdoor particulate matter with an aerodynamic diameter ≤ 2.5 µm ($PM_{2.5}$) and mental health problems in children and adolescents (ages 0 up to and including 18 years) – a crucial period for psychological development.

A systematic review was performed using the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) methodology. Several search terms related to air pollution and mental health were used. As per the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) approach, the quality of the body of evidence was assessed by evaluating risk of bias, inconsistency, indirectness, imprecision, and publication bias, as well as magnitude of effect, dose-response relationships, and residual confounding. Results were summarized in a table of summary, and in a PRISMA flowchart.

The systematic review yielded more than 2200 papers, 10 of which were included for further analysis. Our results indicate a possible association of $PM_{2.5}$ with mental health problems in children and adolescents – specifically: anxiety, depression, mood disorders, schizophrenia, and suicidality. However, the current quality of evidence was assessed to be very low. Further research into the association is warranted. Future research should especially try to address the role of possible confounders and multiple exposures to $PM_{2.5}$ and other air pollutants. Governments should (continue to) heed the precautionary principle, and implement (additional) measures that address air pollution.

Samenvatting – Mentale gezondheidsproblemen kunnen het dagelijks functioneren van mensen ernstig beperken. In de algemene bevolking en bij volwassenen werden deze problemen gelinkt aan luchtvervuiling. Momenteel is weinig gekend over de link tussen de blootstelling aan luchtvervuiling en mentale gezondheid bij kinderen en jongeren. Deze studie beschouwt de mogelijke associatie tussen vaste stofdeeltjes met een aerodynamische diameter ≤ 2.5 µm ($PM_{2.5}$) in de buitenlucht en mentale gezondheidsproblemen bij kinderen en jongeren (0- tot en met 18-jarigen) – een cruciale periode voor de psychologische ontwikkeling.

Er werd een systematische review uitgevoerd volgens de PRISMA ("Preferred Reporting Items for Systematic Reviews and Meta-Analyses") methodologie. Meerdere zoektermen gerelateerd aan luchtvervuiling en mentale gezondheid werden gebruikt. Conform de GRADE ("Grading of Recommendations Assessment, Development and Evaluation") benadering werd de bewijskracht van het bronmateriaal ingeschat door een evaluatie van het risico op bias, de inconsistentie, de indirectheid, de onnauwkeurigheid, en de publicatiebias, evenals de effectgrootte, de dosis-responsrelatie, en resterende, niet-gemeten factoren die de relatie onrechtstreeks kunnen beïnvloeden. De resultaten werden samengevat in een samenvattende tabel en in een PRISMA flowchart.

De systematische review leverde meer dan 2200 artikelen op, waarvan er 10 werden opgenomen voor verdere analyse. Volgens onze resultaten zijn er enige indicaties voor een associatie van $PM_{2.5}$ met mentale gezondheidsproblemen bij kinderen en jongeren – meer bepaald: angststoornis, depressie, stemmingsstoornissen, schizofrenie en zelfdoding(spogingen). De huidige kwaliteit van het bewijsmateriaal werd evenwel ingeschat als zeer laag. Bijkomend onderzoek naar de associatie strekt tot aanbeveling. Toekomstig onderzoek moet vooral trachten de mogelijke rol van andere niet-gemeten, maar gelinkte, factoren te beschouwen, evenals de mogelijke rol van meervoudige blootstelling aan $PM_{2.5}$ en andere polluenten in de lucht. Overheden zouden het voorzorgsprincipe moeten (blijven) hanteren, en (bijkomende) maatregelen tegen luchtvervuiling nemen.

Introduction

According to an estimate by the United Nations' *Department of Economic and Social Affairs, Population Division*, 55.3% of the world's population lived in cities in 2018. In the more developed regions – Europe, Northern America, Australia/New Zealand and Japan – only about a fifth of the population still lived in rural areas in that year (UN DESA, 2018a). Worldwide, more people have lived in cities than in the countryside since at least 2010 (UN DESA, 2018b). On a global level, positive growth rates of urban population are expected for the following decades, though these growth rates are expected to decrease over time (UN DESA, 2018c).

Some epidemiological studies, though not all, link exposure to "urban" environment to a higher risk of mental health problems – e.g. to mood and anxiety disorders, such as depression (e.g. Generaal et al., 2019; Kim, 2008; Peen et al., 2010; Pun, Manjourides, and Suh, 2019). Differences between "urban" and "rural" rates of psychotic disorders are often ascribed to more social fragmentation, and more social stress in cities compared to rural areas (Buoli et al., 2018). The pathogenesis might also be mediated by other factors, such as lower access to green space, higher exposure to noise, differences in individual behavior, e.g. lower physical activity, and higher levels of exposure to air pollution (Generaal et al., 2019; Pun, Manjourides, and Suh, 2019). In the general population and in adults, mental health issues have been linked to air pollution (e.g. Buoli et al., 2018; Generaal et al., 2019; Pun, Manjourides, and Suh, 2019; Ha and Shao, 2021). For example, exposure to toxic airborne substances have been associated with mental disorders, such as depression (e.g. Wang et al., 2019). The link manifests itself both regarding the *onset* of mental health issues (e.g. increase in risk), and their *exacerbation* (Buoli et al., 2018).

Mental health issues can gravely impair people's functioning in everyday life (e.g. Roberts et al., 2019; World Health Organisation [WHO], 2018b). Additionally, mental health problems represent a significant part of the Years Lived with Disability (YLD) quantified by the Global Burden of Disease study. Globally, depressive disorders, anxiety disorders and schizophrenia were amongst the top 20 leading causes for YLD in 2016. Together, these issues accounted for approximately 11% of the total, worldwide YLD both in 2016 (WHO, 2018a).

The built environment is associated with relatively higher air concentrations of toxic substances (e.g. Pun, Manjourides, and Suh, 2019; Roberts et al., 2019), amongst which traffic-related particles, such as fine particulate matter with an aerodynamic diameter $d \leq 2.5\ \mu m$ ($PM_{2.5}$; Anenberg et al., 2012).

Exposure to components of airborne particulate matter mainly happens through inhalation, and possibly also via ingestion, e.g., after clearance of particles from the lungs (Thompson, 2018). Particulate matter can migrate to brain tissues (e.g., Lovisolo et al., 2018; Wang et al., 2019). Presumably, this happens directly through the olfactory nerve, and indirectly through the blood-brain barrier after absorption via the alveoli – notably for small particles, such as $PM_{2.5}$ (e.g. Gładka, Rymaszewska, and Zatoński, 2018; Lovisolo et al., 2018; Roberts et al., 2019; Thompson, 2018). Hence, $PM_{2.5}$ is of interest for research into the association between air pollution and mental health issues – even though $PM_{2.5}$ is only one component of the complex mixture of inhaled outdoor air pollutants.

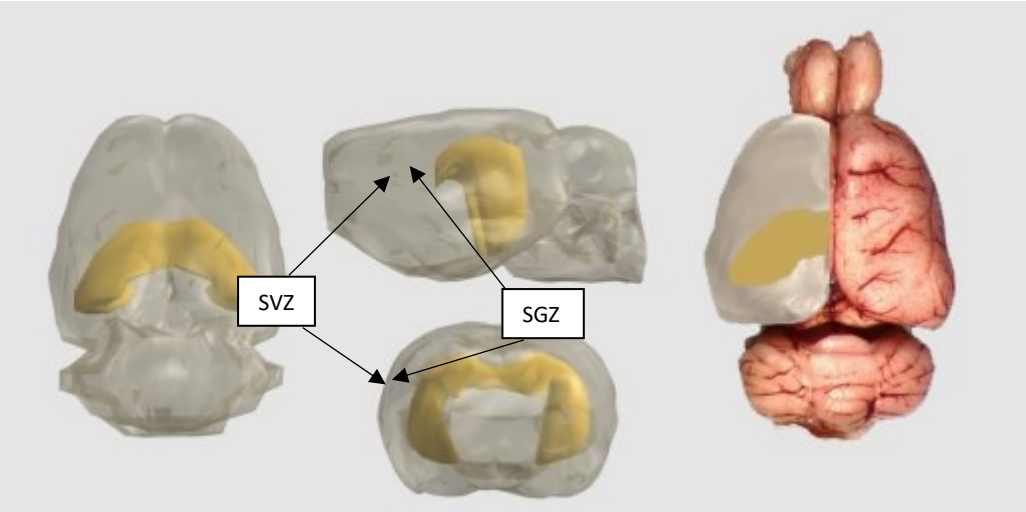
Several different biopsychosocial pathways, some of which are mentioned above, have been hypothesized for the possible link between air pollution and mental health issues, notably the toxic interaction of particles with biological tissues, particularly the central nervous system (e.g. Buoli et al., 2018; Pun, Manjourides, and Suh, 2019; Wang et al., 2019). For instance, it has been proposed that the ablation of neurogenesis in certain brain regions can explain some of the symptoms of mental health issues (Coburn, Cole, Dao, & Costa, 2018). However, it should be noted that the nature of this

association is not well established (e.g. Kays, Hurley, and Taber, 2012; Toda, Parylak, Linker, & Gage, 2019).

Neurogenesis consists of the "birth" of new neurons and their functional integration into existing neural circuitry (e.g. Coburn et al., 2018). The new neurons are formed from adult neuronal stem or progenitor cells (Borsini, Sawyer, Zunszain, & Pariante, 2018; Toda et al., 2019). It seems to be restricted to two specific brain regions in adult rodents (see Figure 1; Coburn et al., 2018):

1. The subgranular zone (SGZ) of the dentate gyrus in the hippocampal complex; and
2. The subventricular zone (SVZ).

(a)



(b)

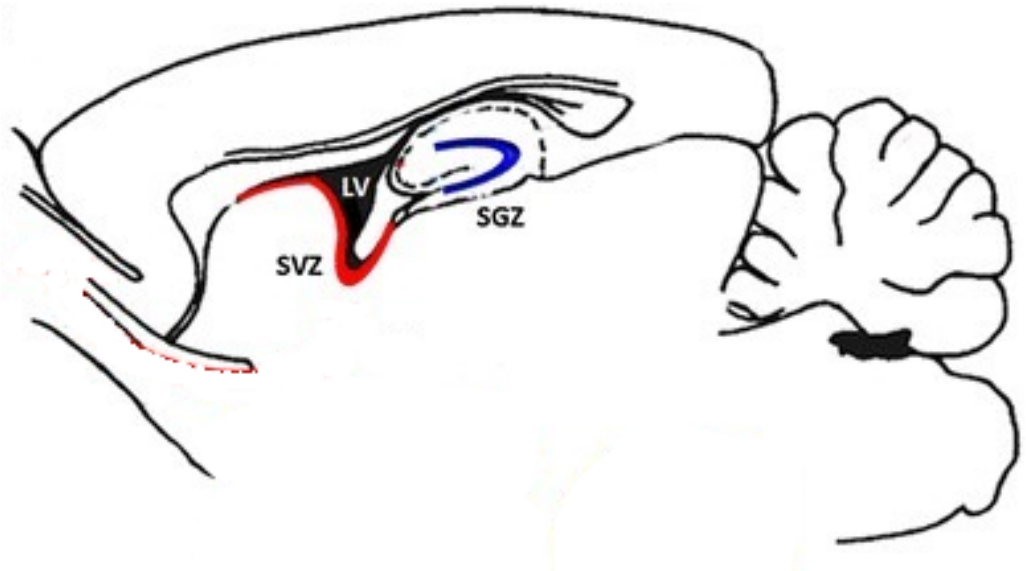


Figure 1. (a) 3D reconstructions indicating the location of the hippocampus (yellow) in an adult rat brain, as well as the approximate location of the SVZ and the SGZ. Adapted from Figure 1 in Fiala and Spacek (2020) (edited). (b) Hippocampal region of an adult rat brain (sagittal plane). Adapted from Figure 1, a in Rojczyk-Gołębiewska, Pałasz & Wiaderkiewicz (2014) (edited). SVZ: subventricular zone, LV: lateral ventricle, SGZ: Subgranular zone of the dentate gyrus.

Notably, $PM_{2.5}$ and similar airborne pollutants induce systemic and neuroinflammation (Block & Calderón-Garcidueñas, 2009; Buoli et al., 2018; Calderón-Garcidueñas et al., 2015; Coburn et al., 2018; Fonken et al., 2011; Roberts et al., 2019; Thompson, 2018). Particulate matter induces oxidative stress, which ultimately leads to inflammation, even in the absence of adsorbed pollutants (Bové, 2017). Oxidative stress also leads to other adverse effects.

Oxidative stress and neuroinflammation have been associated with ablation of hippocampal neurogenesis, presumably through microglial activation (Borsini et al., 2018; Coburn et al., 2018). Microglia are the brain's resident phagocytes, which are activated upon detection of exogenous substances or pathogens (Kettenmann, Hanisch, Noda, & Verkhratsky, 2011). Notably, the toxicity of diesel exhaust particles depends on the activity of microglia (Block et al., 2004; Coburn et al., 2018), and diesel exhaust induced microglial activation has indeed been reported in rats and cell-cultures (respectively: Levesque et al., 2011, 2013). Accordingly, microglia of mice with an impairment of the DISC1 (*Disrupted in schizophrenia 1*) gene have been found to phagocytize ambient black carbon particles (*unpublished results*; H. Bové, personal communication, July 2019).

The process of neurogenesis is well established in human children (Snyder, 2019). Although some controversy remains, adult neurogenesis in the human SGZ has been generally accepted, and neurogenesis in the adult SVZ is accepted by some researchers as well (Kays et al., 2012; Snyder, 2019). Importantly, there is a causal link between adult neurogenesis and the functioning of the hippocampus. The "birth" of new neurons allows for behavioral and endocrine adaptation in response to emotional challenges (Snyder, 2019), through the ensuing structural and functional plasticity of synapses in the hippocampal circuit (Toda et al., 2019), resulting in the ability to cope with stressors (Borsini et al., 2018). This is consistent with the finding that decreased neurogenesis results in impaired synaptic plasticity, which has been linked to depressive and anxiety disorders (e.g. Toda et al., 2019). Furthermore, the process of adult neurogenesis in rodents and non-human primates seems to be highly sensitive to environmental factors. Possibly, this holds for humans as well (Toda et al., 2019). Neurogenesis is also required for the beneficial therapeutic effects of antidepressants through $5HTA_{1A}$ receptors (Toda et al., 2019; see also Coburn et al., 2018).

Neurogenesis may thus well be involved in mental health disorders that impact the hippocampus, notably depression, anxiety, schizophrenia, and addiction (Snyder, 2019; Toda et al., 2019), even if evidence points to a complex interplay between the physiological state of the individual and the physical and psychosocial environment (compare Toda et al., 2019), and even if other mechanisms have been proposed.

Importantly, childhood is a crucial period for psychological development (e.g. Roberts et al., 2019; WHO, 2013). Additionally, "up to 50% of mental disorders in adults begin before the age of 14 years" (WHO, 2013, p. 16).

Children are particularly susceptible to exposure to air pollution for several reasons, among which:

i) Due to their higher metabolic rates, they breathe more rapidly than adults. Relative to their body weight, they inhale a bigger volume of air than adults in the same amount of time. This implies that, generally speaking and for any given time interval, children inhale more pollutants than adults, certainly in relation to their body weight, and possibly even in absolute terms.
ii) Their brains, lungs and other organs are still developing, making them more susceptible to possible pollutant-induced disruption(s).

iii) In relation to the previous point, their defense mechanisms are less well developed than in adults. This potentially leads to greater adverse effects, even if exposed to exactly the same concentration/volume of air pollutants.

iv) According to the developmental origin of health and disease (DOHaD) hypothesis small physiological changes in early life can influence disease risk in later life (e.g. O'Donnell and Meaney, 2017).

Unfortunately, little is currently known about the association between exposure to air pollution and mental health issues in children and adolescents.

Several recent systematic reviews have addressed the association between air pollution and mental disorders in the general population (Buoli et al., 2018; Gładka, Rymaszewska, and Zatoński, 2018; Xu, Ha, and Basnet, 2016; and Gu et al., 2019 [retracted]). These reviews do not exclude children and adolescents. There are, however, no recent systematic reviews on the aforementioned association with regards to children or adolescents specifically.

The current study addresses whether there is an association of the air pollutant $PM_{2.5}$ with mental health problems in children and adolescents (0 to 18 year olds [including]). The results could lead to valuable insights to inform air pollution policies and protective measures. As such, this study embraces the notion of *evidence-informed policy*, which corresponds with the objectives of the global Air Quality Guidelines (WHO, 2021, pp. 2-3).

Methods

A systematic review of the scientific literature was conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (Liberati et al., 2009; Moher et al., 2009; Page et al., 2021). *First*, the search query and inclusion/exclusion criteria for the records found were specified. *Second*, the following databases were queried: *Academic Search Elite, GreenFILE, E-Journals, PsycINFO, PsycARTICLES, Psychology and Behavioral Sciences Collection* (all through *EBSCOhost*), as well as *PubMed/MEDLINE*. The search of the EBSCOhost databases was performed on September, 22nd, 2020. PubMed/MEDLINE was searched two days later. *Third*, the eligibility of each record was assessed based on the previously determined inclusion/exclusion criteria. *Fourth*, after the database searches, the references contained in the (currently) included studies were screened to identify further studies of interest ("snowballing"). This fourth step was repeated for each "original" and each additional record found, until no further "new" records of interest were identified. *Fifth*, once the record list was final, an additional search with the internet search engine DuckDuckGo was performed with some relevant keywords. This search engine was chosen to avoid personalized search results. The goal was to discover possibly important grey literature, such as reports from conferences. *Sixth*, the included records were analyzed and summarized. *Finally*, the quality of the body of evidence was assessed according to the GRADE approach (*Grading of Recommendations Assessment, Development and Evaluation*; e.g. Morgan et al., 2016). That is, by evaluating risk of bias, inconsistency, indirectness, imprecision, and publication bias, as well as magnitude of effect, dose-response relationships, and residual confounding.

The search query and the inclusion/exclusion criteria were informed by the PECOS framework. PECO stands for Population, Exposure, Comparator, Outcome (e.g. Morgan et al., 2018). The S stands for Study Design. Before reviewing the literature, each of these aspects was defined as follows.

Population. [P]: humans worldwide, in the age range [0, 18] years.

Exposure. [E]: outdoor ambient exposure, either prenatal or postnatal, to one or more of the following: $PM_{2.5}$, diesel exhaust particles, carbon black particles, ultrafine and fine particulate matter. The terms other than $PM_{2.5}$ were included to avoid not identifying possibly relevant studies. For instance, some authors might use "fine particulate matter" instead of "$PM_{2.5}$", even if they consider the definitions of both these terms to be the same.

Comparator. [C]: differential exposure to $PM_{2.5}$. No specific operationalization of possible comparisons were explicitly included or excluded beforehand.

Outcome. [O]: the diagnosis of onset, additional occurrences or exacerbation of the included mental health issues, whether acute (exacerbation) or chronic. Issues diagnosed by professional medical or psychological practitioners were taken into account, as well as validated (self-)assessment tests.

Several different mental health outcomes were of interest, such as schizophrenia, bipolar disorder, depression, suicide or anxiety, whereas other, less related, disorders were not, e.g., autism, Alzheimer's disease, or personality disorder (for all of the included/excluded outcomes, see the *pseudocode* in the Appendix).

The outcomes of interest mainly fall under blocks F20-F29 (Schizophrenia, schizotypal and delusional disorders) and F30-F39 (Mood [affective] disorders) of the International Statistical Classification of Diseases and Related Health Problems – 10th Revision (ICD-10; Version: 2016; WHO, 2015). Before performing the review, a list was established containing the ICD and Medical Subject Headings (MeSH, PubMed) designations and codes of both the included and excluded conditions.

Study Design, Methodology. [S]: Finally, two study designs were excluded a priori, namely (a) *in vitro* studies and (b) studies with non-human subjects. Studies with human subjects were included.

Briefly, then, the search query combined a series of terms related to P, E, and O with boolean operators (see the query's *pseudocode* in the Appendix for details), and the inclusion/exclusion criteria covered both C and S. In addition, the following inclusion/exclusion criteria were defined (see also Appendix).

Inclusion criteria. All published and peer-reviewed scientific studies that were available electronically or physically through university or scientific libraries were included. Studies in English, Dutch, German, or French were considered, although search terms were not translated from English into these other languages. Finally, an inclusion criterion regarding Study Design was used. Specifically, studies with human subjects were included.

Exclusion criteria. Studies not using diseases on the list established for this study were excluded, as were *in vitro* studies. Furthermore, several types of publication were excluded. Specifically: citations, reviews, letters, editorials and patents. Finally, duplicate studies were excluded as well.

All results were summarized in a table of summary (see Table 1 in *Results*).

GRADE

The assessment of the quality of the body of evidence was done using the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) approach.

The GRADE method yields an indication of the quality of the evidence, as judged by a systematic reviewer. Conceptually, the quality of evidence "reflects the extent to which we are confident that an estimate of the effect is correct" (Schünemann et al., 2013, paragraph 8 of *Section 5. Quality of Evidence*).

In GRADE, several factors that potentially influence the quality of the evidence are considered and judged either separately per outcome, or for the body of evidence on the whole. Concretely, the quality of the body of evidence was assessed by evaluating risk of bias, inconsistency, indirectness, imprecision, and publication bias, as well as magnitude of effect, dose-response relationships, and residual confounding.

Each of these factors can either lead to a downgrade, to an upgrade, or to no change in the grading of the quality of evidence. The reviewer makes a subjective, yet reasoned judgment which pertains to the current research question.

Results

Of the 2234 records found via PubMed and EBSCOhost, six were eventually included in the review (see PRISMA Flowchart, Figure 2). The repeated application of the "snowballing" approach yielded an additional four records not yet identified through the database searches. The search with the internet search engine yielded no further records of interest. Thus, a total of 10 studies was reviewed (see Figure 2). The table of summary (Table 1) presents a general overview of the results. For each outcome of interest, Table 2 lists the *total* number of studies addressing it, as well as the number of studies reporting *increased risk*, *decreased risk*, and *no significant association*.

Overall, six of the included studies reported an association between $PM_{2.5}$ and at least one mental health issue (in children and/or adolescents) addressed in that study. Four studies found no association. The detailed results per outcome of interest are summarized below.

The study populations were either psychiatric patients (4 studies), the general population, amongst which children and adolescents (3), twin children (2), or 7th-12th grade students (1). All studies reported results for both men and women, though not necessarily separately. Most studies were done in China and in high income countries, such as the USA, Canada or Europe. Collectively, the studies analyzed data from the last decade of the 20th century, up to the year 2015.

Each study addressed exposure to $PM_{2.5}$, sometimes amongst other pollutants. All papers used $PM_{2.5}$ concentrations as the comparator, either expressed as an increase in concentration (9 papers) or in terms of "high" and "low" levels (1 paper; Newbury et al., 2019). All studies estimated postnatal exposure using geographical models, and Jorcano et al. (2019) additionally estimated prenatal exposure. Some studies focused on acute, short-term effects (e.g., a lag of 0-5 days in Wang et al., 2018). Other studies addressed long-term effects, using yearly averages as a proxy for long-term exposure. To illustrate, Fan et al. (2019) studied the association of long-term exposure and outcomes in 2014-2015 by using three-year (2011-2013) average concentrations of $PM_{2.5}$ as an estimate for long-term exposure (Table 1). Outcomes and their operationalization differed substantially between studies. Take, for instance, suicidality. Fan et al. (2019) administered a survey to assess the number of suicide attempts of 7th-12th graders during the last 12 months. In contrast, Fernández-Niño et al. (2018) used daily suicide rates of the general population.

Several different study designs were used by the respective studies, e.g., cross-sectional; time-stratified, case-crossover; or longitudinal (Brokamp et al., 2019; Fan et al., 2019; Fernández-Niño et al., 2018; Jorcano et al., 2019; Newbury et al., 2019; Oudin et al., 2016; Roberts et al., 2019; Szyszkowicz et al., 2020; Wang et al., 2018; Yue et al., 2020). Other methodological choices could also vary substantially, even if a similar outcome was addressed. For example, Jorcano et al. (2019) studied, amongst others, general anxiety symptoms of 7 to 11 year olds in the general population. The symptoms were assessed with questionnaire scores. Szyszkowicz et al. (2020), on the other hand,

studied 8 to 18 year old psychiatric patients, using emergency department visits for anxiety disorders as outcome measure.

The results per mental health issue can be summarized as follows (for details, see Table 1 and Table 2).

Four papers reported no significant association with **anxiety** (Brokamp et al., 2019; Jorcano et al., 2019; Roberts et al., 2019; Yue et al., 2020). The only paper containing any significant results for anxiety (Szyszkowicz et al., 2020), reported a higher risk for visits to the emergency department by males aged 13 to 18 (lag: 1 day; RR = 1.08, 95% CI = (1.004, 1.16), p = 0.04), yet a lower risk for females aged 8 to 12 (lag: 5 days; RR = 0.82, 95% CI = (0.70, 0.95), p = 0.01; see also Table 1).

Brokamp et al. (2019) conducted the only study that addressed **bipolar disorder**. Analyzing emergency department encounters, this study found no association of bipolar disorder with exposure to $PM_{2.5}$ (median age: 14.4 years, lag: 0-3 days).

Roberts et al. (2019) found an increased risk between exposure to $PM_{2.5}$ at age 12 and psychiatric diagnosis for **depression** at age 18, whereas the other three studies addressing this mental health issue did not (Brokamp et al., 2019 – emergency department encounters, median age: 14.4 years, lag: 0-3 days; Jorcano et al., 2019 – symptoms, 7 to 11 year olds, annual average concentrations; Wang et al., 2018 – hospital admissions, 0 to 17 year olds, lag: 0-5 days). Roberts et al. (2019) did not find an association for continuous phenotypic outcomes for depression at age 12. Additionally, in contrast to the association with *diagnosis*, depressive *symptoms* at age 18 were not associated with exposure to $PM_{2.5}$ at age 12 (Roberts et al., 2019).

Brokamp et al. (2019) reported an increased risk in emergency department visits by children and adolescents (median age: 14.4 years) for **schizophrenia** within zero to three days after exposure to $PM_{2.5}$. Similarly, Szyszkowicz et al. (2020) found an association of exposure to $PM_{2.5}$ and emergency department visits for **schizophrenic and psychotic disorders** in 13 to 18 year old males for lags of 1 and 3 days (1-day lag: RR = 1.083615, 95% CI = (1.003827, 1.169745), p = 0.0396); 3-day lag: RR = 1.097544, 95% CI = (1.019689, 1.181344), p = 0.01316).

Suicidality was associated with a significant increase in risk according to two papers. Brokamp et al. (2019) reported on emergency department visits shortly after $PM_{2.5}$ exposure (median age: 14.4 years, lag: 0-3 days). Fan et al. (2019) analyzed suicide attempts as reported by the subjects (mean age: 15.4 years, exposure in the previous three years as a proxy for long term exposure). The remaining third paper did not find an association for suicide by children younger than 15 years (Fernández-Niño et al., 2018; short term exposure).

The only study looking into **psychotic experiences** (Newbury et al., 2019) found no association of that outcome with one year's mean exposure to $PM_{2.5}$ in 12 to 18 year olds. As stated above, Szyszkowicz et al. (2020) found an increased risk of visiting an emergency department for **schizophrenic and psychotic disorders** in 13 to 18 year old males for a lag of 1 and 3 days.

Oudin et al. (2016) estimated the annual mean concentrations of several air pollutants in the year of a subject's inclusion in their study as a proxy for long-term exposure. They found a significant increase in risk between long term PM_{10} exposure and prescriptions for medication for **psychiatric diagnoses** in 0 to 17 year olds (including). The authors state that results for $PM_{2.5}$ were "very similar". No other included studies addressed this specific outcome.

Finally, two included studies addressed **(other) mood disorders**. Both studies pertained to records of emergency department visits. Brokamp et al. (2019) reported an increased risk for children and

adolescents (median age: 14.4 years) and zero to three day lags. Szyszkowicz et al. (2020) reported a decreased risk for male children and similar lags (ages 8-12 years, lag: 0-5 days).

GRADE

The overall quality of the evidence (per outcome) was assessed to be "very low" via the GRADE approach. This result was obtained as follows.

Starting level. Only observational studies were included. Hence, to start, each of the outcomes was set to a "low" quality of evidence.

Risk of Bias. Risk of bias was assessed by scrutinizing the methodological choices and the possible consequences on the results, as they pertain to my research question. Some risk of bias was indeed present in the body of evidence, most notably regarding the possible confounding due to other pollutants, such as NO_2. However, I judged the overall bias in the body of evidence (per outcome) to be low or unclear. Thus, in my opinion, the possible bias did not weaken the results seriously enough to warrant a downgrade – though important concerns for further research remain (see below).

Inconsistency. Inconsistency can only be assessed across studies (Schünemann et al., 2013). The inconsistency assessment was done for all outcomes having more than one study result, i.e., for all outcomes except (a) bipolar disorder and (b) psychiatric diagnosis (Table 3). Only the inconsistency between the results for depression was deemed to be sufficiently unexplainable to warrant a downgrade.

More specifically, Roberts et al. (2019) reported a significant association of exposure to air pollution at age 12 with a *psychiatric diagnosis* of depression at age 18 (OR = 1.63, 95% CI = (1.08, 2.46), p = 0.021). Yet, the same authors also reported no association between exposure at age 12 and *continuous phenotypic outcomes* for depression at age 18 (beta = 0.16, 95% CI = (0.00, 0.33), p = 0.056). There are several reasons that may explain this apparent inconsistency. *First*, a psychiatric diagnosis arguably also entails psychiatric treatment (with antidepressants or otherwise), which presumably suppresses the symptoms. *Second*, the results might be due to a difference in outcome measure: the diagnoses were made by trained researchers based on private interviews, whereas the symptoms were self-reported by participants. There were no other methodological differences, except for the (justly) different modeling for each outcome. *Finally*, the researchers may have split the population in (at least) two groups, only looking at the symptoms for subjects without a psychiatric diagnosis. However, it is unclear to me which possible reasons (discussed above or otherwise) can explain the difference, as this is not explicitly addressed further by the authors. Hence the downgrade for depression.

The inconsistencies between results for other outcomes could plausibly be explained by differences in population (P), exposure (E), outcome measures (O), or methodology (S).

Indirectness of Evidence. I downgraded the quality of evidence for all outcomes, except for bipolar disorder and mood disorder. For anxiety, depression and suicidality, I downgraded the quality due to the use of questionnaires as measuring instruments, some of which were responded to by the subjects or their parents (rather than using a diagnosis by medical practitioners). The results of all the studies regarding psychiatric diagnosis, psychosis and schizophrenia (inseparably) contained one or more outcomes that are not of interest for this study. Since the exact number of such outcomes is unknown, the impact on the results is not known either. In consequence, I downgraded the quality of the evidence.

Imprecision. The imprecision, as indicated by the reported 95% confidence intervals (CI), was quite high for all studies, except for the study by Oudin et al. (2016), with a 95% CI = (1.003, 1.076). For

instance, Brokamp et al. (2019) reported an odds ratio OR = 1.25 for suicidality in psychiatric patients (mean age: 14.4 years), with an associated 95% CI = (1.03, 2.02). Similarly large confidence intervals were reported by other studies (Table 1). Except for Oudin et al. (2016), the differences between lower and upper bounds were quite large, even for the smallest confidence intervals reported. As an example, consider the confidence interval reported by Szyszkowicz et al. (2020) for schizophrenic and psychotic disorders in 13-18 year old males after a 1 day lag: 95% CI = (1.00, 1.17) (RR = 1.08). Consequently, the quality of evidence was downgraded for all outcomes, except for psychiatric diagnosis, which was the outcome (singularly) addressed by Oudin et al. (2016).

Publication Bias. Publication bias can only reasonably be assessed for a number of studies N > 5, and ideally even N ≥ 10 (Schünemann et al., 2013). Due to the low number of records per outcome of interest, publication bias was not assessed, except for anxiety (N = 5). For anxiety, no publication bias was suspected, since four studies reported "no association" and one study reported both a positive and a negative association (Szyszkowicz et al., 2020; Table 1), whereas the bias is expected to lean towards only reporting positive associations. In conclusion, the body of evidence was not downgraded due to publication bias for any of the outcomes.

"Upgrading" Factors. The GRADE Handbook (Schünemann et al., 2013) mentions factors that might warrant an upgrade of the quality of evidence, as well. These are addressed now.

Magnitude of effect. In principle, a sufficiently large magnitude of effect might warrant an upgrade. Here, conforming to the guidelines in the GRADE Handbook (Schünemann et al., 2013), I operationalized "sufficiently large" as a relative risk (RR) smaller than 0.5 (RR < 0.5) or RR > 2, or similar. As per the Handbook, these guidelines immediately apply to both RR, and hazard ratios (HR). For odds ratios (OR) a conversion to RR is warranted (Schünemann et al., 2013). I assessed the magnitude of effect for all the results that were reported as "statistically significant" by the respective authors (for an overview, see table of summary, Table 1).

Oudin et al. (2016) reported a hazard ratio HR = 1.038, with an upper bound for the 95% CI of 1.076. This HR is notably smaller than 2. Similarly, Szyszkowicz et al. (2020) reported relative risks that clearly fall within the range [0.5, 2].

Wang et al. (2018) reported percentage change values (Table 1). The highest value reported is the upper bound of the confidence interval: 22%. This result is of too low magnitude to warrant an upgrade.

The (adjusted) odds ratios ([A]OR) of the remaining significant results were converted to RR. Since all of the studies concerned used logistic regression models, this was done with the following conversion formula (Zhang and Yu, 1998): $RR = OR / [(1 - P) + (P \times OR)]$, where P is a real number between 0 and 1. It stands for the prevalence of the outcome in the non-exposed population. I set $P = 0$. As such, this is an invalid value, but it represents the relatively low prevalence of mental diseases (e.g., 0.4% for depressive disorders in 0 to 14 year olds world-wide; Institute for Health Metrics and Evaluation, 2021). Furthermore, for $P = 0$ the formula yields maximum RR. The reasoning was to explore whether I could detect any kind of relevant magnitude, when maximizing the resulting RR. Since RR = OR when $P = 0$, no actual conversion was necessary.

All of the "significant" (A)OR in Table 1 are well within the range [0.5, 2], with only two exceptions.

The upper bound of the confidence interval for suicidality after one day, reported by Brokamp et al. (2019) was 2.02. I judged this to be too little above 2 to warrant an upgrade, especially when also considering the other results for suicidality and given that this is the upper bound.

Similarly, Roberts et al. (2019) reported 2.46 as upper bound for diagnosis of depression at age 18. Although this is clearly higher than a RR of 2, I decided against upgrading for magnitude of effect, given the other results for depression, including the other results reported by the authors themselves – for instance, the lower bound of the CI was 1.08 (Table 1). Of note, even an upgrade would not have resulted in another GRADE result for depressive disorder. It would have remained "very low" (compare Table 3).

In conclusion, none of the included studies had a large enough magnitude of effect to warrant an upgrade of the quality of evidence.

Dose-response gradient. For none of the outcomes does the body of evidence represent a sufficiently clear dose-response relationship to warrant an upgrade.

Plausible residual confounding. I considered several possible confounders such as age, sex, socioeconomic status, weather conditions, exposure to other air pollutants, and family history of the outcome. Some studies explicitly address other pollutants as confounding factors (notably Newbury et al., 2019). However, overall the body of evidence per outcome does not suggest that upgrading is warranted.

GRADE: Overall assessment. Although some of the mentioned decisions might appear too strict when assessed separately, it should be noted that on the whole there are arguably sufficient reasons for downgrading the quality of evidence for each of the outcomes from "low" to "very low". Also, the quality of evidence was not upgraded for any of the studies included. With this regard, note that even with one or two upgrades the overall quality of evidence would remain "very low" for each outcome.

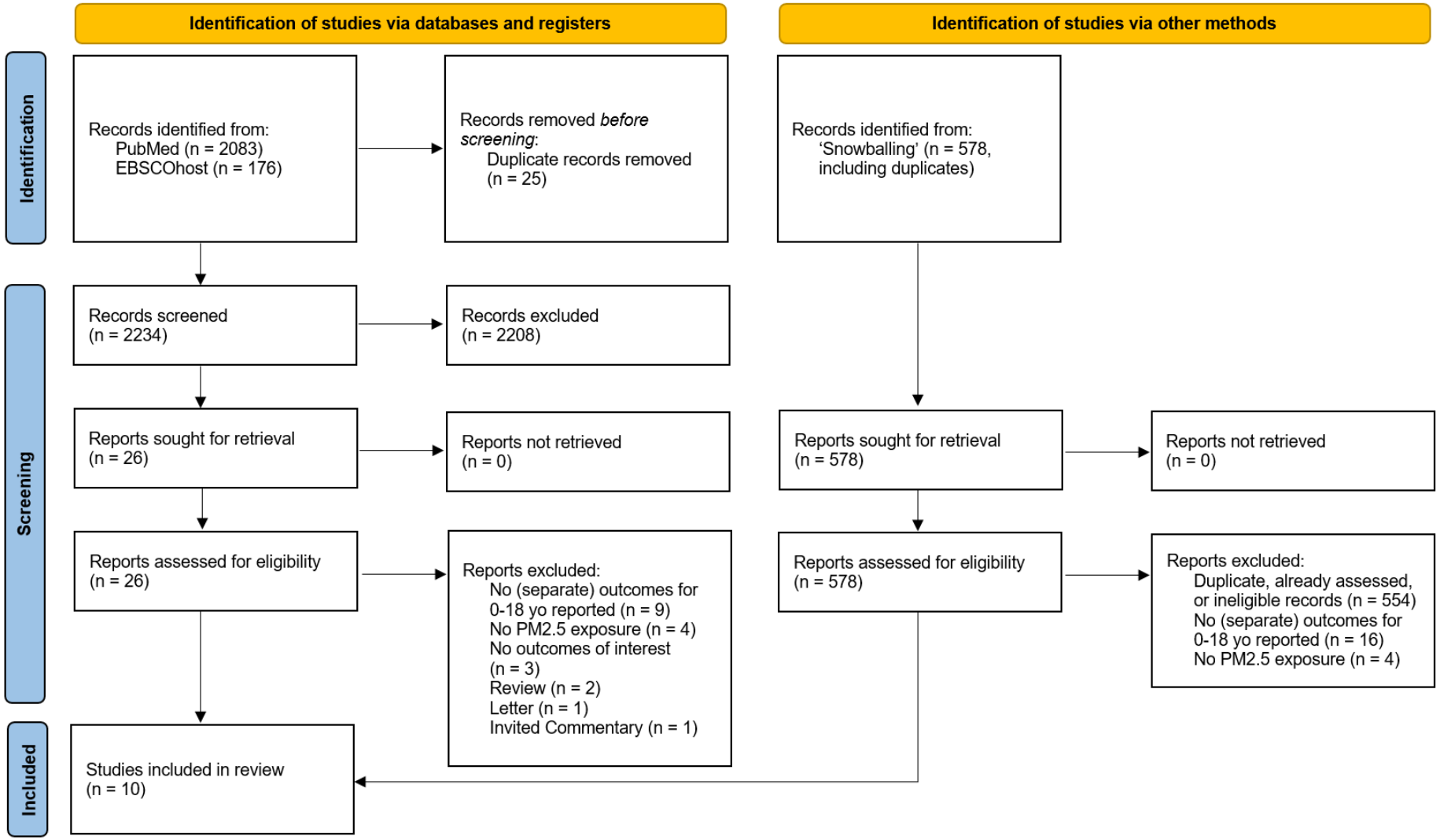


Figure 2. PRISMA Flowchart. Adapted from: Page et al. (2021). n: number of records, reports, or studies. $PM_{2.5}$: particulate matter with an aerodynamic diameter aerodynamic diameter $d \leq 2.5$ µm; yo: year old(s). See text for more details.

Record	Population	Age (y)	Region	Years	Exposure (µg/m³)	Outcomes	Comparison characteristics	Results
Brokamp et al. (2019)	psychiatric patients	Median 14.4, IQR (11.7, 16.1)	Hamilton County / Cincinnati, Ohio (USA)	2011-2015	Short term (days) Median: 10.5, IQR: (8.1, 14.5) Estimates based on satellite data calibrated with ground-based data	ED encounters for anxiety, bipolar, depressive, and other mood disorders, schizophrenia and suicidality Estimates based on conditional logistic regression models (one per outcome) adjusted for temperature, humidity, and holidays	10-µg/m³ increase in $PM_{2.5}$ exposure	• schizophrenia on the same day: OR=1.25 (1.00-1.57) • other mood disorders 2d later: OR=1.15 (1.02-1.30) • suicidality 1d later: OR=1.44 (1.03-2.02) • Not significant for any other outcome of interest
Fan et al. (2019)	7th–12th grade students	Mean 15.4, SD 1.9	Guangdong province (China)	2011-2015	3 year average ambient concentration: 28.5, SD: 4.2 Estimates based on satellite data and land use regression models	suicide attempts Estimates based on multivariable multi-level logistic regression models; adjusting for age, sex, ethnicity, household socioeconomic status, classmate relations, living arrangements (with parents/alone/others), lifetime smoking, lifetime drinking, depressive symptoms	10-µg/m³ increase in $PM_{2.5}$ concentration	AOR=1.25 (1.03-1.56), $p < 0.05$
Fernández-Niño et al. (2018)	general population	<15	Bogota, Bucaramanga, Cali and Medellin (Colombia)	2011-2015	Short term (days) Mean: 27.06, SD: 10.54 Estimates based on averaging information from different monitoring stations	suicide rates Main confounders: meteorological variables (temperature, relative humidity, precipitation) and holidays	5-µg/m³ increase in $PM_{2.5}$ concentration	• Men: IRR=0.97 (0.76-1.23), p=0.79 • Women: IRR=0.79 (0.53-1.16), p=0.23
Jorcano et al. (2019)	general population	7-11	Europe (The Netherlands, Germany, Portugal, France, Italy, Spain)	1995-2008	Average annual concentration at the home address of each participant Prenatal, mean: ranged from 13.9 to 23.0,	depressive and anxiety symptoms Estimates based on generalized additive models (to assess linearity of $PM_{2.5}$ with outcomes); logistic regression models	5-pg/m³ increase in $PM_{2.5}$ concentration, and 10^{-5} m^{-1} for $PM_{2.5\ abs}$	$PM_{2.5}$ • Prenatal exposure: OR=0.83 (0.64-1.09), p-heter=0.896 • Postnatal: OR=0.69 (0.47-1.01), p-heter=0.904

					depending on the studied region Postnatal, mean: ranged from 11.8 to 28.4, depending on the studied region Estimates based on land use regression models			$PM_{2.5\ abs}$ • Prenatal: OR=0.92 (0.76-1.1), p-heter=0.569 • Postnatal: OR=0.79 (0.58-1.06), p-heter=0.711
Newbury et al. (2019)	twin children	12-18	England and Wales (UK)	2005-2013	Annual exposure in 2012, mean of three addresses: home and two other addresses where the participants spent their time Mean: ranged from 10.0 in rural to 12.9 in urban settings Estimates based on the local-scale Community Multiscale Air Quality Modeling System	psychotic experiences Estimates based on ordinal logistic regression; family socioeconomic status, family psychiatric history, maternal psychosis, childhood psychotic symptoms, adolescent smoking, cannabis dependence, alcohol dependence, neighborhood socioeconomic status, neighborhood crime, and neighborhood social conditions	high level vs. low level of exposure; cutoff: top quartile of exposure (= 12.4 µg/m³)	null when $PM_{2.5}$ is simultaneously modeled with NO_x
Oudin et al. (2016)	general population	0-17	Counties Stockholm, Västra Götaland, Skåne and Västerbotten (Sweden)	2007-2010	! PM_{10}, not $PM_{2.5}$, which was assessed to be "very similar" Annual mean for base year 2010: ranged from 5.7 to 15.8, depending on the studies region Estimates based on a Land Use Regression model, in combination	dispensed medicine for psychiatric diagnoses Statistical analysis: Cox regression; main model adjusted for: age at the start of follow-up (continuous variable), sex, maternal and paternal education level (four categories), maternal body mass index in early pregnancy (continuous variable) and maternal smoking during early pregnancy (three categories) and for	10-µg/m³ increase in $PM_{2.5}$ concentration	! HR for PM_{10}, since only this HR is presented; HRs for PM_{10} and $PM_{2.5}$ were assessed to be "very similar"; HR PM_{10}=1.038 (1.003-1.076)

					with a model for the regional background levels for the entire Swedish population	group-level education level (continuous variable); additional analysis also adjusted for: maternal and paternal income		
Roberts et al. (2019)	twin children	12-18	London, England (UK)	2006-2013	Exposure at the twins' residential addresses in 2007, at age 12 Annualized average concentration: 14.09, SD: 0.69 Estimates based on the KCLurban model (kernel modeling)	concurrent or continuous symptoms, or diagnosis of depression and anxiety Association with continuous symptom outcomes: linear regression; association with diagnostic outcomes: binary logistic regression; confounders: sex, ethnicity, neighborhood SES, family SES, family psychiatric history, exposure to severe victimization, and smoking	1 SD change in concentration (SD = 0.69 $\mu g/m^3$ $PM_{2.5}$)	<u>Depression</u> • Age 12: beta=0 (-0.15-0.14), p=0.951 • Age 18: beta=0.16 (0–0.33), p=0.056 • Age 18: OR=1.63 (1.08-2.46), p=0.021 <u>Anxiety</u> • Age 12: beta=-0.04 (-0.19-0.11), p=0.582 • Age 18: beta=-0.01(-0.19–0.18), p=0.917 • Age 18: OR=1.05 (0.45–2.44), p=0.916
Szyszkowicz et al. (2020)	psychiatric patients	8-18	Toronto, Ontario (Canada)	2004-2015	Short term (days) Mean: 7.7; Median: 6.0 Estimates based on daily concentration levels, calculated as an average among different monitoring stations	daily counts of ED visits for schizophrenic and psychotic disorders, anxiety disorders, as well as mood disorders Estimates based on conditional Poisson models; daily average temperature, year:month:day of week	IQR (= 6.03 $\mu g/m^3$) increase in concentration	• Mood disorders, Male, Age 8-12, only for lag 0 days: RR=0.736197 (0.556831-0.973342), p=0.031582 • Schizophrenic and psychotic disorders, Male, Age 13-18, lag 1d: RR=1.083615 (1.003827-1.169745), p=0.0396; lag 3d: RR=1.097544 (1.019689-1.181344), p=0.01316 • Anxiety disorders, Male, Age 13-18, only for lag 1 day: RR=1.077932 (1.004531-1.156697), p= 0.037011; Female, Age 8-12, only for lag 5 days: RR=0.819734, (0.704565-0.953729), p=0.010073 • Null for all other combinations of interest for this study

Wang et al. (2018)	psychiatric patients	0-17	26 Chinese cities	2014-2015	Short term (days) Mean: 63.5, SD: 50.6 Estimates based on daily mean concentrations, averaged across all monitoring stations per studied city	depression related hospital admission Cases were their own controls $PM_{2.5}$ concentration on the day of hospital admission vs. reference period of 3 to 4 days Confounders: temperature and relative humidity; public holidays	IQR (= 79 – 31.5 = 47.5 µg/m³) increase in $PM_{2.5}$ concentration	• Lag 0-5 days: %change=11.59 (1.8-22.32) • Results for separate lag (0 to 5) not shown in this table
Yue et al. (2020)	psychiatric patients	0-17	26 Chinese cities, including 4 municipalities, 21 provincial capitals, and Dalian City	2014-2015	Short term (days) Mean: 63.5, SD: 50.6 Estimates based on daily mean concentrations averaged across monitoring stations for each city	anxiety related hospital admission Cases were their own controls $PM_{2.5}$ concentration on the day of hospital admission vs. reference period of 3 to 4 days Confounders: daily 24-h average temperature and relative humidity; public holidays	10-µg/m³ increase in $PM_{2.5}$ concentration	• Lag 0-5 days: %change=1.54 (-1.68-4.85) • Results for separate lag (0 to 5) not shown in this table

Table 1. Table of Summary. For all the records, the table only contains information on the outcome(s) and age group of interest. All records found studied outdoor pollution, $PM_{2.5}$, and both genders. The significance level was $p < 0.05$ for all studies.
(a-b): 95% confidence interval; a: lower bound, b: upper bound; AOR: adjusted odds ratio (OR); beta: standardized beta coefficient from linear regression; d: day(s); ED: emergency department; HR: hazard ratio; IQR: interquartile range; IRR: incidence rate ratio; lag: time interval between exposure and outcome; NO_x: nitrogen oxides; OR: odds ratio; $PM_{2.5}$ (PM_{10}): particulate matter with an aerodynamic diameter aerodynamic diameter d ≤ 2.5 µm (10 µm); SD: standard deviation; SES: socioeconomic status; Years: refers to the whole period of follow-up.

	Number of studies reporting			
Mental health problem	**increased risk**	**decreased risk**	**no significance**	**Total studies**
anxiety, anxiety symptoms, anxiety disorder	1*	1*	4	5*
bipolar disorder	0	0	1	1
depressive disorder, depressive symptoms, depression, major depressive disorder	1†	0	4†	4†
mood disorder, other mood disorder	1	1	0	2
schizophrenia, schizophrenic and psychotic disorder	2	0	0	2
suicidality	2	0	1	3
psychotic experiences, schizophrenic and psychotic disorder	1	0	1	2
medication for psychiatric diagnoses	1	0	0	1

Table 2. Total number of studies addressing each mental health problem (outcome of interest), and number of studies reporting increased risk, decreased risk and no significant association with exposure to ambient, airborne $PM_{2.5}$. For more details on age groups, etc., see Table 1. For the abbreviations used in the notes below, see legend for Table 1.

** Only Szyszkowicz et al. (2020) report significant results for anxiety, but whether the risk is higher or lower depends. For males aged 13-18, lag 1 day: RR = 1.077932, 95% CI = (1.004531, 1.156697), p = 0.037011. For females, aged 8-12, lag 5 days: RR = 0.819734, 95% CI = (0.704565, 0.953729), p = 0.010073.*

†Roberts et al. (2019) found an increased risk between exposure to $PM_{2.5}$ at age 12 and psychiatric diagnosis for depression at age 18 (OR=1.63, 95% CI = (1.08, 2.46), p=0.021). The same researchers did not find an association for continuous phenotypic outcomes for depression neither at age 12 (beta=0, 95 % CI = (-0.15, 0.14), p=0.951), nor at age 18 years (beta=0.16, 95% CI = (0, 0.33), p=0.056).

			Level change due to							
Outcome	**N studies**	**Overall assessment**	**Risk of bias**	**Inconsis-tency**	**Indirect-ness**	**Imprecision**	**Publication bias**	**Magnitude of effect**	**Dose-response**	**Effect of plausible residual confounding**
Anxiety	5	very low	0	0	-1	-1	0	0	0	0
Bipolar disorder	1	very low	0	Not applicable	0	-1	Not applicable	0	0	0
Depressive disorder	4	very low	0	-1	-1	-1	Not applicable	0	0	0
Mood disorder	2	very low	0	0	0	-1	Not applicable	0	0	0
Medication for psychiatric diagnosis	1	very low	0	Not applicable	-1	0	Not applicable	0	0	0
Psychosis	2	very low	0	0	-1	-1	Not applicable	0	0	0
Schizophrenia	2	very low	0	0	-1	-1	Not applicable	0	0	0
Suicidality	3	very low	0	0	-1	-1	Not applicable	0	0	0

Table 3. Overview of the GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation; Schünemann et al., 2013).
-1: downgrade one level; 0: no downgrade, no upgrade; N studies: number of studies. See text for further details.

Discussion and Conclusion

This systematic review addressed the possible association between pre- and postnatal exposure to airborne, outdoor $PM_{2.5}$ and mental health in 0-18 year olds. The mental health issues considered were: anxiety, bipolar disorder, depression, schizophrenia, suicide and (other) mood disorders (see the Pseudocode in the Appendix for details). Ten papers were included in the review, of which six reported an association with at least one of the mental health outcomes considered in this study. The remaining four papers found no association (Table 1, Table 2). The GRADE assessment yielded "very low" for each of the different outcomes of interest.

One paper reported significant results for emergency department visits for **anxiety** (Szyszkowicz et al., 2020). However, the risk was different for males aged 13 to 18 at a 1 day lag (RR = 1.08, 95% CI = (1.004, 1.16), p = 0.04) and females aged 8 to 12 at a 5 day lag (RR = 0.82, 95% CI = (0.70, 0.95), p = 0.01). The four other papers addressing anxiety did not find an association (Brokamp et al., 2019 – emergency department encounters, median age 14.4 years, lag: 0-3 days; Jorcano et al., 2019 – symptoms, 7 to 11 year olds, annual average concentrations; Roberts et al., 2019 – symptoms at ages 12 and 18 and diagnosis at age 18, exposure at age 12; Yue et al., 2020 – hospital admissions, 0-17 year olds, lag: 0-5 days).

The only study which addressed **bipolar disorder** found no association of emergency department encounters with exposure to $PM_{2.5}$ (median age: 14.4 years, lag: 0-3 days; Brokamp et al., 2019).

One study (Roberts et al., 2019) reported an association between exposure to $PM_{2.5}$ at age 12 and a psychiatric diagnosis of **depression** at age 18. The other three studies addressing this mental health issue did not find an association (Brokamp et al., 2019 – emergency department encounters, median age 14.4 years, lag: 0-3 days; Jorcano et al., 2019 – symptoms, 7 to 11 year olds, annual average concentrations; Wang et al., 2018 – hospital admissions, 0 to 17 year olds, lag: 0-5 days). Similarly, Roberts et al. (2019) found no association for continuous phenotypic outcomes for depression – neither at age 12, nor at age 18.

Exposure to $PM_{2.5}$ was reported to be associated with emergency department visits by children and adolescents for **schizophrenia** (lag: 0-3 days, median age: 14.4 years; Brokamp et al., 2019). Consistent results were reported by Szyszkowicz et al. (2020), who studied emergency department visits as well. The authors reported an increased risk for visits pertaining to schizophrenic and psychotic disorders (13 to 18 year old males, lag: 1 day and 3 days).

Two of the three papers concerning **suicidality** reported a significant increase in risk, respectively for short term and long term exposure (Brokamp et al., 2019 – emergency department encounters, median age: 14.4 years, lag: 0-3 days; Fan et al. 2019 – self-reported suicide attempts, mean age: 15.4 years, long term exposure). The remaining third paper did not find an association between long term $PM_{2.5}$ exposure and suicide by children younger than 15 years (Fernández-Niño et al., 2018).

One included study addressed **psychotic experiences** (Newbury et al., 2019). The authors report no association between this outcome and one year's mean exposure to $PM_{2.5}$ in 12 to 18 year olds. As mentioned, Szyszkowicz et al. (2020) report an increased risk for emergency department visits for schizophrenic and psychotic disorders in 13 to 18 year old males at a lag of 1 and 3 days.

Oudin et al. (2016) found a significant increase in risk between PM_{10} and prescriptions for medication for **psychiatric diagnoses** in 0 to 17 year olds. The authors state that results for $PM_{2.5}$ were "very similar" (see also Table 1). No other included studies addressed this specific outcome.

Finally, two included studies addressed **(other) mood disorders**. Both studies analyzed records of emergency department visits at small lags of respectively 0-3 (Brokamp et al., 2019) and 0-5 day lags (Szyszkowicz et al., 2020). Brokamp et al. (2019) reported an increased risk for children and adolescents (median age: 14.4 years). Szyszkowicz et al. (2020) reported a decreased risk for male children (ages 8-12 years).

In summary, the total number of studies in which an outcome of interest was addressed ranges from only one to five per outcome (Table 2).

A more detailed discussion is warranted for suicidality, depression, and schizophrenia.

The estimated odds ratios for **suicidality** are quite high compared to the other mental health issues considered in this study for which Odds Ratios are available. This can be seen in Table 1: Brokamp et al. (2019) reported an OR = 1.44, 95% CI = (1.03, 2.02), and Fan et al. (2019) an AOR = 1.25, 95% CI = (1.03, 1.56), for similar age groups (14-15 year olds) and the same increase in $PM_{2.5}$ concentration (10 µm/m³). Given the extreme (possible) outcome of suicide, this should get high priority in future research, even if Fernández-Niño et al. (2018) found no association with suicide in children younger than 15.

The results for **depression** are inconsistent (Table 2), yet Roberts et al. (2019) report an OR = 1.63, 95% CI = (1.08, 2.46) for diagnosis of depression at age 18 with exposure at age 12. This is quite a high OR, given the associated small increase in the annual average $PM_{2.5}$ concentration (0.69 µg/m³), and considering that the authors controlled for sex, ethnicity, neighborhood socioeconomic status (SES), family SES, family psychiatric history, exposure to severe victimization, and smoking. The inconsistency and the magnitude of effect warrant further research into depression and possible comorbidities. Additionally, in the Global Health Estimates for 2016, depressive disorder was the third leading cause of Years Lived with Disability (YLD) worldwide and for all ages (WHO, 2018a).

Finally, **schizophrenia** in adolescents should be high on the research agenda. Both Brokamp et al. (2019) and Szyszkowicz et al. (2020) found an association between $PM_{2.5}$ exposure and emergency department visits for schizophrenia. This happened within days after exposure and at quite small increases of $PM_{2.5}$ concentration: respectively 10 µg/m³ and 6.03 µg/m³. Furthermore, in the Global Health Estimates for 2016, schizophrenia was the sixteenth leading cause of YLD globally and considering all ages (WHO, 2018a).

Differences of more than 10 µg/m³ above annual mean concentrations are not uncommon. For instance, mean annual concentrations in the Brussels Capital Region (Belgium) for the pre-COVID-19-pandemic year 2019 were around 10 to 15 µg/m³, depending on the location of the measuring station. However, maximum daily concentrations peaked to up to 47, 71 or 75 µg/m³ at different measuring stations in the region (Institut Bruxellois de Statistique et d'Analyse, 2022). "Acute" peaks in outdoor $PM_{2.5}$ concentration might thus cause an acute exacerbation of schizophrenia and suicidality, especially in vulnerable individuals living in areas with high (peak) $PM_{2.5}$ concentrations. In addition, within-country variation in annual mean $PM_{2.5}$ concentrations can exceed differences of 10 µg/m³ or more (European Environment Agency, 2022), some of which might be due to the extent of the country.

The association between air pollution (specifically $PM_{2.5}$) and mental health problems in children and adolescents is quite a recent subject of study. In the five year period 2016-2020, scientists published (only) ten papers addressing this association. The oldest included paper was from 2016, and all of the other studies were from 2018, 2019 or 2020 (table of summary; Table 1).

Exposures and outcomes varied amongst studies (e.g. schizophrenia versus anxiety), making direct comparison difficult. Even when the same issue was addressed, differences in methodologies/study designs, populations, or comparators made comparison uncalled for. To illustrate, consider Jorcano et al. (2019) versus Szyszkowicz et al. (2020). Both of these studies addressed "anxiety" in some form or another. However, Jorcano et al. (2019) studied 7 to 11 year olds in the general population, and general symptoms of anxiety through questionnaire scores, whereas Szyszkowicz et al. (2020) studied 8 to 18 year old psychiatric patients, and used emergency department visits for anxiety disorders as outcome measure.

The body of evidence for each outcome was assessed using GRADE, yielding an overall assessment of "very low" (Table 3). The starting level was set to "low" for each outcome, due to the fact that only observational studies were included. Additionally, only a (very) low number of studies matched this research's inclusion criteria (e.g., only human studies): 1 to 5 studies per outcome of interest.

GRADE is a useful tool to systematically assess a medical body of evidence. However, another tool or a variant of GRADE would be more suitable for assessing bodies of evidence that are observational in nature, as is the case for air pollution research with human subjects. The large majority of this kind of research is "inherently" observational, due to ethical and practical considerations. Given the potential health implications, researchers cannot simply expose their subjects to air pollutants in different concentrations. This implies that, for this kind of research, it is not viable to use a randomized control trial design – the "gold standard" in medical science. Yet, such a design would almost certainly score a lot better in a GRADE assessment, since it starts at the highest possible GRADE level. In contrast, observational studies start at the level "low" (Schünemann et al., 2013). Under the assumption that no upgrade is warranted, only one downgrade suffices to arrive at a "very low" rating. Thus, it comes as no surprise that the eventual end result is "very low" as well.

Another factor which can influence the GRADE assessment is the *type* of outcome. For instance, if sufficiently evident, dose-response gradients warrant an upgrade in level (Schünemann et al., 2013). However, dose-response relationships are harder to establish when considering binary outcomes, such as psychiatric diagnoses, than when considering continuous outcome measures, such as biomarker-related ones. A similar argument holds for the difficulty to upgrade for magnitude of effect in air pollution studies, which "typically" exhibit effect sizes that are "too small" to warrant an upgrade according to the GRADE recommendations. Again, this is probably a consequence of the GRADE approach's original focus on medical research.

Depending on the research field, a "low" or "very low" quality of evidence is not unusual in systematic reviews. As one example from another discipline, consider the results reported by Pandis, Fleming, Worthington and Salanti (2015). The authors included and analyzed 91 systematic reviews or meta-analyses on oral health published from 2008 to 2013. 26 studies (29%) reported "very low" quality of evidence. 43 studies (47%) assessed the quality to be "low". Finally, 20 studies (22%) reported "moderate" GRADE ratings, and only 2 studies (2%) judged the quality of evidence to be "high".

For the purpose of this study, the included studies did not always sufficiently control for other outdoor (and indoor) air pollutants and confounders, such as psychiatric family history or socio-economic status. It is important to note that this was not necessarily the authors' fault, but was possibly due to a lack of suitable data.

Additionally, the research question of an included study could be slightly or substantially different from this study's research question. In consequence, the authors might make sound methodological choices for their purposes, yet these same choices could negatively impact the usefulness of their results for this study. For example, this study focused on $PM_{2.5}$ specifically, whereas the authors of a report might

be interested in air pollution in general. Consequently, separately modeling different air pollutants was not necessary to answer the original study's research question, if even possible. However, to answer the research question of the present study, correcting , e.g., for NO_2 in $PM_{2.5}$ models would have been essential (see, e.g., Newbury et al., 2019). Analogously, a study's choice of age categories was not always suitable for this study. For instance, a non-negligible amount of studies were excluded due to age ranges unfit for this study's purpose (e.g. "15-29 year olds" or "< 23 years of age"). Such characteristics resulted in only a low number of included studies in this systematic review.

To facilitate further systematic reviews, it would be commendable if studies systematically used international classification systems, such as ICD-10 codes or DSM-V diagnoses, and explicitly report them (for a good example, see the supplemental materials of Szyszkowicz et al., 2020). Unfortunately, data on mental health issues are not always available in medical records. Even so, it would suffice if the authors would, e.g., mention the code blocks from ICD-10 as keywords or in the text.

A future systematic review could also address mental well-being in children and adolescents more broadly, rather than addressing the binary outcome of the presence or the absence of symptoms or disease.

Finally, governments should heed the precautionary principle. In essence, this principle entails that uncertainty about scientific knowledge must not be (mis)used as a reason not to act. This is especially the case when the possible consequences of inaction are big. This holds even more so when we consider that the results pertain to children and adolescents – people in full development, which can be seriously disrupted during certain crucial developmental periods. More specifically, the developmental origin of health and disease (DOHaD) hypothesis states that (even) small physiological changes in the early stages of life can accumulate over a lifetime and lead to adverse health effects more or less later in life (compare, e.g., O'Donnell and Meaney, 2017).

Considerations on the current body of evidence also point to being prudent and implementing precautionary measures. There are some indications that airborne $PM_{2.5}$ might negatively influence processes in the developing brain, and this study found an association of exposure to $PM_{2.5}$ pollutants with at least some mental health issues in children and adolescents (Table1, Table 2). Furthermore, even small effect sizes can have a non-negligeable impact on and an importance for public health, since the whole population is exposed to ($PM_{2.5}$) air pollution.

Thus, governments should stimulate and finance further research with all the mentioned goals in mind. Furthermore, measures to cut $PM_{2.5}$ emissions might be warranted. This holds even if other air pollutants are the root cause for the reported effect, since if $PM_{2.5}$ and, e.g., NO_2 are indeed strongly correlated, there is a very high chance that these pollutants are emitted from the same source(s). One example of such a measure would be to reduce the traffic, e.g., through financial or economic incentives. Another, complementary one, would be to stimulate public transport even more.

In September 2021, the WHO published new Air Quality Guidelines which englobe both indoor and outdoor environments. The guidelines consist of evidence-informed recommendations to WHO Member States (WHO, 2021). The threshold averaging over a year is 5 $\mu g/m^3$, and the threshold for the 24-hour average is 15 $\mu g/m^3$. This "daily" threshold must not be exceeded on more than three to four days each year.

The Air Quality Guidelines were not specifically developed for mental health issues, but rather as recommendations for health in general. Additionally, the guidelines are not legally binding (WHO, 2021). Even so, they highlight the importance of taking emission reduction measures. After all, their

objective is to inform legislation and policy, and to help reduce levels of air pollution to ultimately reduce the global health burden (WHO, 2021).

Accordingly, the European Commission have announced their intention to align their current air quality standards to the cited WHO guidelines. As of January 1st, 2020, the EU's most strict threshold for $PM_{2.5}$ is 20 µg/m³ averaging over a year, with no permitted exceedances per year defined (European Commission – DG Environment, 2022). In contrast to the WHO guidelines, the EU's thresholds are legally binding in EU Member States. This new legislation is a first step in addressing the possible consequences of $PM_{2.5}$ air pollution. Effectively reducing emissions would be a necessary second one.

To conclude, given the current state of the body of evidence, further research into the association is warranted, since some results suggest an association between $PM_{2.5}$ and (the exacerbation of) certain mental health issues, such as schizophrenia, in children and adolescents. Future research should especially try to address multiple exposure to $PM_{2.5}$ and other air pollutants – specifically nitrogen oxides, such as NO_2 (compare, e.g., Newbury et al., 2019), as well as possible confounders, such as family history of mental disease or socioeconomic status. Authors should preferably report results for different, small age categories and mental health issues, and always use ICD-10 codes and/or DSM-V diagnoses, if available. Future systematic reviews could also try to mental well-being more broadly, rather than addressing the binary outcome of presence or absence of symptoms or disease. Finally, governments should (continue to) heed the precautionary principle and implement (additional) measures addressing air pollution in general, and $PM_{2.5}$ emissions specifically.

Appendix

Search Query – Pseudocode

Note: ICD and MeSH codes were added to the database queries as appropriate. They are not shown in the pseudocode below for clarity's sake.

```
PERIOD: FROM <startDateDatabase> TO <now>

SEARCH ONE_OR_MORE_OF: air pollution, air pollutants, particulate matter, airborne particulate matter, air quality, outdoor air pollution, PM2.5, carbon black, black carbon, soot, fine particulate matter, ultrafine particulate matter, fine particles, ultrafine particles, UFP, diesel exhaust

AND

ONE_OR_MORE_OF: baby, toddler, child*, adolesc*, human <or, if possible> AGE_RANGE <years>: [0, 18]

AND

ONE_OR_MORE_OF: mental health, well-being, schizophrenia, schizoaffective disorder, bipolar disorder, bipolar affective disorder, bipolar II, depression, suicide, anxiety, mood disorder, affective disorder, major depressive disorder, depressive disorder, depressive episode, depressive symptom, bipolar symptom

AND

<if possible> [IN_TITLE OR IN_KEYWORD_LIST] NONE_OF: autism, Parkinson's, Alzheimer's, Huntington's, obsessive-compulsive disorder, Attention Deficit Hyperactive Disorder, ADHD, eating disorder, personality disorder, postnatal depression, post-traumatic stress disorder, PTSD, amyotrophic lateral sclerosis, ALS, addiction
```

Inclusion criteria

- All published and peer-reviewed scientific literature that were available electronically or physically through university or scientific libraries.
- Language: studies in English, Dutch, German, or French were considered, although search terms were not translated from English into these other languages.
- Study design: observational studies, with human subjects

Exclusion criteria

- Studies not using diseases on the list established for this study, which was based on ICD-codes and MeSH.
- In vitro studies
- Types of publication: citations, reviews, letters, editorials and patents
- Duplicates

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