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The association between air pollutants and hippocampal volume from magnetic resonance imaging: A systematic review and meta-analysis

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ABSTRACT

Growing epidemiological evidence suggests that air pollution may increase the risk of cognitive decline and neurodegenerative disease. A hallmark of neurodegeneration and an important diagnostic biomarker is volume reduction of a key brain structure, the hippocampus. We aimed to investigate the possibility that outdoor air nitrogen dioxide (NO_2) and particulate matter with diameter ≤2.5 μm ($PM_{2.5}$) and ≤10 μm (PM_{10}) adversely affect hippocampal volume, through a meta-analysis. We considered studies that assessed the relation between outdoor air pollution and hippocampal volume by structural magnetic resonance imaging in adults and children, searching in Pubmed and Scopus databases from inception through July 13, 2021. For inclusion, studies had to report the correlation coefficient along with its standard error or 95% confidence interval (CI) between air pollutant exposure and hippocampal volume, to use standard space for neuroimages, and to consider at least age, sex and intracranial volume as covariates or effect modifiers. We meta-analyzed the data with a random-effects model, considering separately adult and child populations. We retrieved four eligible studies in adults and two in children. In adults, the pooled summary β regression coefficients of the association of $PM_{2.5}$, PM_{10} and NO_2 with hippocampal volume showed respectively a stronger association (summary β −7.59, 95% CI −14.08 to −1.11), a weaker association (summary β −2.02, 95% CI −4.50 to 0.47), and no association (summary β −0.44, 95% CI −1.27 to 0.40). The two studies available for children, both carried out in preadolescents, did not show an association between $PM_{2.5}$ and hippocampal volume. The inverse association between $PM_{2.5}$ and hippocampal volume in adults appeared to be stronger at higher mean $PM_{2.5}$ levels. Our results suggest that outdoor $PM_{2.5}$ and less strongly PM_{10} could adversely affect hippocampal volume in adults, a phenomenon that may explain why air pollution has been related to memory loss, cognitive decline, and dementia.

1. Introduction

The hippocampus is a key structure of human brain with reference to memory, cognition, emotion and other behavioral domains (Kharabian Masouleh et al., 2020). Therefore, changes in the structure of the hippocampus and particularly its volume reduction, beyond what is

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expected with aging (Nobis et al., 2019), may impair cognitive functions such as memory. Then, hippocampal volume is considered a pathological hallmark of neurodegeneration (Dugger and Dickson, 2017; Ewers et al., 2012; Jack et al., 2010). Other structural parameters involving the hippocampus, such as the volumes of its subfields or the properties of its surface, are worth consideration and are currently being increasingly investigated (Ono et al., 2021; Xu et al., 2008), though not in relation with air pollutants so far.

Several studies indicated a detrimental role of atmospheric environmental factors on human health (Filippini et al., 2020, 2021b; Gabet et al., 2021; Southerland et al., 2021; Vinceti et al., 2016; Wang et al., 2021), including neurodegenerative diseases (Bai et al., 2018; Filippini et al., 2021a; Tsai et al., 2019; Yu et al., 2021). In particular, air pollutants may result in cognitive decline and dementia etiology (Livingston et al., 2020; Ran et al., 2021; Yang et al., 2015), thus it is no surprise that some epidemiological studies have evaluated if these chemicals may induce adverse effects on the hippocampus. These studies considered different world populations of cognitively unimpaired participants and participants with mild cognitive impairment (MCI), showing either null (Power et al., 2018) or adverse (Hedges et al., 2019) effects of air pollution. Toxicological studies in animals have also confirmed the potential adverse effects of air contaminants on the hippocampus (Ehsanifar et al., 2021; Fonken et al., 2011). Therefore, given the relevance of the topic and the lack of pooled analyses on it, we carried out a systematic review and meta-analysis.

The assessment of hippocampal reduction in epidemiologic studies on humans has been generally carried out by evaluating its volume through magnetic resonance imaging (MRI) with structural techniques (de Prado Bert et al., 2018; Delgado-Saborit et al., 2021; Power et al., 2016). In particular, T1-weighted images were generally considered being appropriate for volumetric assessment, in contrast to functional images or Fluid Attenuated Inversion Recovery (FLAIR) images, mainly employed to investigate white matter (Johnson et al., 2012; Svenningsson et al., 2012). The main outcome of the latter methodologies are images whose primary purpose is to show areas in the brain that are activated under various control conditions or lesion locations. Furthermore, their parameters are not standardized enough to be adequately compared, due to their variations in scanning parameters and individual variability. T1-weighted images are not subject to these limitations and are well-suited to volumetric assessments.

2. Methods

We performed a literature search in order to retrieve studies relating air pollution exposure with hippocampal volume in children and adults, including particulate matter (PM) and nitrogen dioxide (NO_2). We considered adult (age$\geq$18) and child (age$<$18) populations and searched within keywords and MeSH terms in Scopus and PubMed databases from inception to July 13, 2021. As search terms, we used "air pollution" or "particulate matter" or "$PM_{2.5}$" or "PM_{10}" or "nitrogen dioxide" or "NO_2" and "neuroimaging" or "brain volume" or "hippocampus" or "MRI" or "magnetic resonance imaging". On the base of title and abstract, we firstly excluded the papers not performing neuroimaging evaluations through MRI or not including exposure assessment.

We then assessed the full-text of the papers (Fig. 1), to identify those eligible for the meta-analysis. We selected the studies reporting at least one linear regression coefficient with its standard error or 95% confidence interval (CI) for one or more air pollutants, as related to neuroimaging parameters including hippocampal volume assessment. When the coefficient was not reported but a regression analysis was mentioned in the paper, we asked the authors to provide the estimates, for the right and the left hippocampi combined or for each of them separately. As an inclusion criterion, we also required that intracranial volume from neuroimaging analysis, sex and age as critical covariates be considered in the regression analysis.

We performed a meta-analysis when the association between a certain air pollutant and hippocampal volume was considered by at least two studies. The included studies carried out brain volume computation with automatic FMRIB Software Library (FSL) (Smith et al., 2004) and FreeSurfer (Fischl et al., 2002) procedures, which register brain images into the same standard coordinate space, thus allowing comparisons across different studies. Given the non-linearity of the registration methods for hippocampal volume assessment, the results from unstandardized methods could not be included.

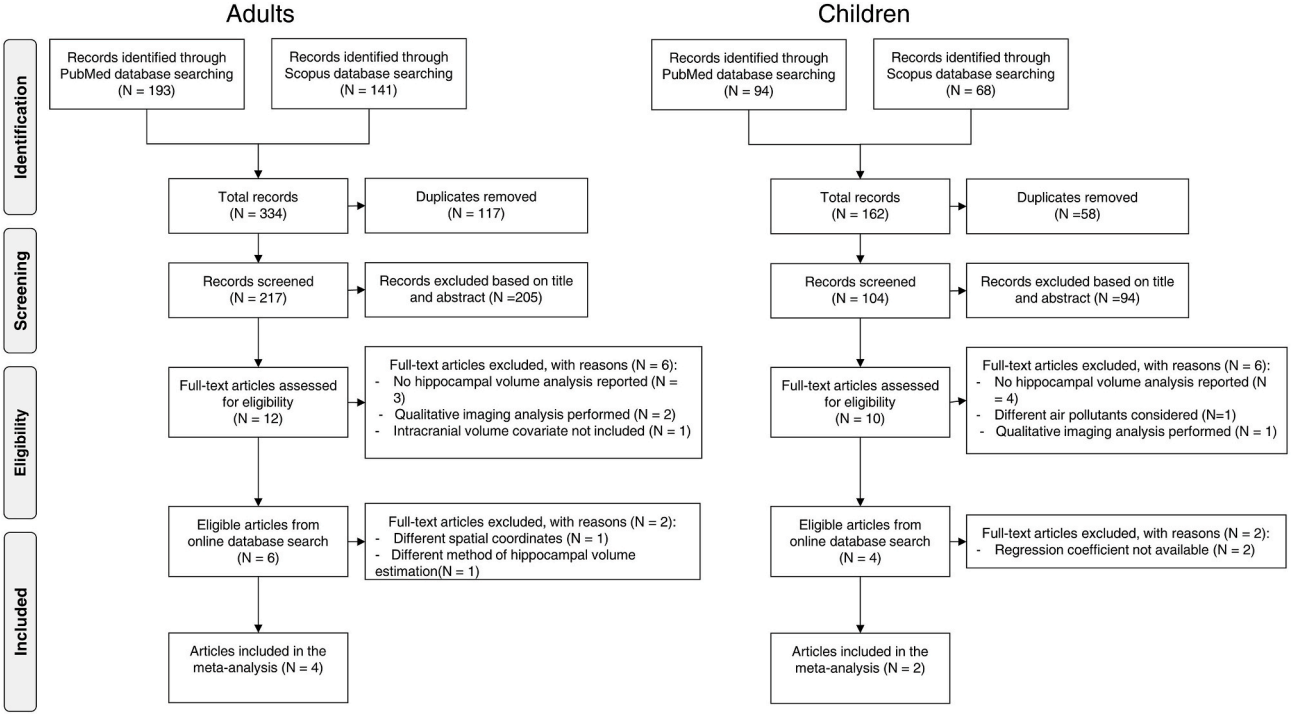

Fig. 1. Flow chart of study identification and selection, separated for adults and children.

We meta-analyzed the regression beta coefficients using a random-effects model with restricted maximum likelihood (REML) method of weight estimation. To compute this overall estimate we used the 'meta' routine of Stata 17.0 software (StataCorp, College Station, TX, 2021). We also tested the effect of higher amounts of pollutant concentrations through meta-regression, by comparing beta coefficients with mean concentration of air pollutant and by using the 'meta regress' command. We finally checked publication bias by computing Egger's test of estimation of small-study effects, using the 'meta bias' command.

We considered as outcome the volumetric change in one hippocampus, as 1 mm^3 change for 1-unit increase of an air pollutant (i.e. 1 $\mu g/m^3$ for PM and 1 ppm for NO_2). Thus, we needed to introduce some changes to the raw estimates to make different analyses comparable. First, beta coefficients of one paper were divided by a factor of 10, as they estimated linear changes in hippocampal volume per a 10-$\mu g/m^3$ increase in PM, and a 10-ppb increase in NO_2 instead of 1-unit increase (Cho et al., 2020). Second, we divided beta coefficients by 5 in two studies (Cserbik et al., 2020; Lubczynska et al., 2021), as they estimated linear changes in hippocampal volume per 5-$\mu g/m^3$ increase in $PM_{2.5}$. Third, for a study using the sum of left and right hippocampal volumes and as unit of measurement cm^3 (Power et al., 2018), we divided beta coefficients by a factor of 2, in order to give an estimate of the single hippocampal volume change, then beta coefficients were multiplied by a thousand, to change the unit of measure.

Finally, we considered in the overall meta-analyses, when available, β coefficients stratified for pollutant exposure level, sex, and brain laterality, to provide a greater detail of individual outcomes. We decided a minimum number of three studies performing the same stratified analysis to conduct a stratified meta-analysis.

3. Results

We eventually found twelve studies satisfying inclusion criteria for adults (Casanova et al., 2016; Chen et al., 2015; Cho et al., 2020; Crous-Bou et al., 2020; Erickson et al., 2020; Gale et al., 2020; Hedges et al., 2019; Lee et al., 2020; Power et al., 2018; Wilker et al., 2015, 2016; Younan et al., 2020), but only four of them were suitable for a meta-analysis of the association of air pollutants, namely $PM_{2.5}$, PM_{10} and NO_2, with hippocampal volume.

Six of these twelve studies conducted linear regressions between particulate matter ($PM_{2.5}$ and/or PM_{10}) and hippocampal volume. One of these studies was excluded because it used an alternative methodology for hippocampal volume estimate, considering ventricular horn volume, thus making their results not comparable with the others due to the unknown relationship between hippocampal and ventricular horn volumes (Wilker et al., 2016). One study used the HAMMER software for hippocampus computation, thus resulting in different volume outcomes, and therefore could not be included in this meta-analysis (Chen et al., 2015). Three of the remaining four studies also investigated the association between NO_2 and hippocampal volume, which was considered in our meta-analysis (Cho et al., 2020; Crous-Bou et al., 2020; Hedges et al., 2019).

We retrieved 10 studies (Alemany et al., 2018; Beckwith et al., 2020; Calderon-Garciduenas et al., 2011; Cserbik et al., 2020; Guxens et al., 2018; Lubczynska et al., 2021; Mortamais et al., 2017, 2019; Peterson et al., 2015; Pujol et al., 2016) in children, four of which included an evaluation of the correlation between air pollutants and hippocampal volume. However, two of them (Calderon-Garciduenas et al., 2011; Mortamais et al., 2017) did not perform a regression and numerical outcomes on the hippocampus were not available. Therefore, only two studies were eligible for a meta-analysis. They were carried out on preadolescents (age 9–12) and they investigated the association between prenatal $PM_{2.5}$ exposure and hippocampal volume.

The main characteristics of the six studies considered in the meta-analyses are described in detail in Table 1, including information about cohort, statistical analysis and neuroimaging techniques. Almost all adult samples included participants without cognitive impairment, with the exception of one study which also considered participants with mild cognitive impairment and included cognitive status as a covariate (Cho et al., 2020).

Some covariates possibly influencing brain characteristics (age, sex, education level, smoking status) were taken into account by all studies. In adult studies, other covariates possibly influencing cognitive status (history of cardiovascular disease, hypertension, diabetes mellitus or general vascular risk) were included, with one exception (Power et al., 2018). Body mass index was considered only in studies on adults, and two studies in adults did not consider alcohol intake (Crous-Bou et al., 2020; Power et al., 2018), while one study also considered the APOE 4 positivity (Crous-Bou et al., 2020). In these studies, exposure assessment was performed using different statistical models (Table 1), based on the participants' residential addresses. $PM_{2.5}$ and PM_{10} exposures were estimated using the same model.

One study was carried out in four different populations in the United States, Minnesota (MN), North Carolina (NC), Maryland (MD) and Mississippi (MS), which had different mean air pollutant levels (Power et al., 2018). This study found no association between $PM_{2.5}$ and PM_{10} and hippocampal volume, however they showed that $PM_{2.5}$ was correlated with lesions in the hippocampal region. A second study carried out in Barcelona, Spain, found no specific association of $PM_{2.5}$, PM_{10} and NO_2 exposure with hippocampal volume (Crous-Bou et al., 2020). They also found a β coefficient, related to $PM_{2.5}$ and PM_{10} exposure, higher for right hippocampus. The third study was carried out in the Republic of Korea and conducted a separate analysis for male and female participants (Cho et al., 2020). The authors found evidence of an association between PM_{10} levels and hippocampal volume. A study using UK Biobank data found an inverse association between left but not right hippocampal volume and $PM_{2.5}$, while no association with PM_{10} nor NO_2 (Hedges et al., 2019). Differently from the previous study (Crous-Bou et al., 2020), they detected a higher β coefficient, concerning $PM_{2.5}$ and PM_{10} exposure, higher for the left hippocampus.

Concerning the two studies on children, the first considered exposure to $PM_{2.5}$, PM_{10} and NO_2 during pregnancy and childhood, for children population (age 9–12) (Lubczynska et al., 2021), finding an inverse association between prenatal $PM_{2.5}$ exposure and left hippocampal volume, similarly to the previous study on adults (Hedges et al., 2019), and differently from another one (Crous-Bou et al., 2020). The other study on a young population conducted a separate analysis for male and female children (age 9–10) and for right and left hemispheres, considering exposure to $PM_{2.5}$ (Cserbik et al., 2020). In this study, no association between $PM_{2.5}$ concentration and hippocampal volume was detected.

Concerning the main findings of the studies that could not be included in the meta-analyses for lack of suitable data (Supplemental eTable 1), two studies on adults (Chen et al., 2015; Wilker et al., 2016) found no association between $PM_{2.5}$ and hippocampal volume. Another study (Casanova et al., 2016) provided little evidence of $PM_{2.5}$ increased exposure in association with hippocampal atrophy. Studies carried out in children did not reveal any association between $PM_{2.5}$ and hippocampal volume (Calderon-Garciduenas et al., 2011), or did not report any results about hippocampus (Mortamais et al., 2019).

Results of the meta-analysis for the β regression coefficient based on the aforementioned studies are reported in Figs. 2–6. The forest plot of the meta-analysis evaluating the association between $PM_{2.5}$ exposure and hippocampal volume in adults is shown in Fig. 2. For $PM_{2.5}$, the summary β regression coefficient was −7.59 (95% CI −14.08 to −1.11) for a 1 $\mu g/m^3$ increase in $PM_{2.5}$.

The forest plot of the regression coefficient of PM_{10} concentration on hippocampal volume, shown in Fig. 3, consistently showed a negative association though smaller than for $PM_{2.5}$, yielding a summary estimate of −2.02 (95% CI −4.50 to 0.47). NO_2 exposure showed a weak inverse association with hippocampal volume, as shown in Fig. 4, with a summary β of −0.44 (95% CI = −1.27 to 0.40).

In a meta-regression model, we assessed the relation between

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

Study reference	Study population				Study Characteristics				Neuroimaging evaluation
	Cohort name and Sample size (N)	Age and sex	Description	Location	Study design	Mean exposure	Exposure assessment	Considered covariates	Brain volumes
Power et al. (2018)	ARIC (Atherosclerosis Risk in Communities) N = 1745	67–90 Both	Cognitive unimpaired participants	United States	Longitudinal retrospective study	$PM_{2.5}$ 13.3 μg/m^3 PM_{10} 19.1 μg/m^3	Spatio-temporal model using PM monitoring and geographic and meteorological data	- Age, Sex, Education - Body mass index - Smoking status - Socioeconomic status - Intracranial volume	- GM, of total brain and separately of the four lobes - Hippocampus - Deep-grey structures - Total volume of multiple GM regions known to atrophy preferentially in Alzheimer's disease
Crous-Bou et al. (2020)	ALFA (Alzheimer Disease and Families) N = 228	45–74 Both	Cognitive unimpaired participants	Barcelona, Spain	Prospective cohort study	$PM_{2.5}$ 17 μg/m^3 PM_{10} 37.6 μg/m^3 NO_2 7.5 ppb	Land use regression model	- Age, Sex, Education - Body mass index - Smoking status - Physical activity - APOE 4 positivity - Family history of AD - Hypertension, Diabetes mellitus - Intracranial volume	- Cortical thickness in lobe - Hippocampus - Ventricles - Cortical Thickness of specific brain areas, affected by Alzheimer's disease
Hedges et al. (2019)	UK Biobank N = 18,278	40–69 Both	Cognitive unimpaired participants	United Kingdom	Prospective cohort study	$PM_{2.5}$ 9.90 μg/m^3 PM_{10} 16.0 μg/m^3 NO_2 25.61 ppb	Land use regression model	- Age, Sex, Education - Body mass index - Smoking status, Alcohol intake - Socioeconomic status - Distance to major roads - Intracranial volume	- Hippocampus
Cho et al. (2020)	EPINEF (Environmental Pollution-Induced Neurological Effects) N = 957	>50 Both	Cognitive unimpaired participants and participants with mild cognitive impairment	Republic of Korea	Longitudinal retrospective study	$PM_{2.5}$ 26.0 μg/m^3 PM_{10} 50.7 μg/m^3 NO_2 29 ppb	Universal Kriging model, based on air quality monitoring sites	- Age, Sex, Education - Body mass index - Smoking status, Alcohol intake - Socioeconomic status - Cardiovascular disease, Stroke - Transient ischemic attack - Hypertension, Diabetes mellitus - Intracranial volume	- Thalamus - Caudate - Putamen - Pallidum - Hippocampus - Amygdala - Nucleus accumbens
Lubczynska et al. (2021)	Generation R Study N = 3133	9–12 Both	Cognitive unimpaired participants	The Netherlands	Prospective cohort study	$PM_{2.5}$ 16.7 μg/m^3 PM_{10} 26.3 μg/m^3 NO_2 332.4 ppb	Land use regression model	- Age, Sex, Education - Maternal smoking - Maternal alcohol consumption - Socioeconomic status - Intracranial volume	- Total Grey Matter, Total White Matter - Total Brain Volume - Hippocampus - Other subcortical structures

(*continued on next page*)

Table 1 (*continued*)

Study reference	Study population				Study Characteristics				Neuroimaging evaluation
	Cohort name and Sample size (N)	Age and sex	Description	Location	Study design	Mean exposure	Exposure assessment	Considered covariates	Brain volumes
Cserbik et al. (2020)	ABCD (Adolescent Brain Cognitive Development) study N = 10,341	9–10 Both	Cognitive unimpaired participants	United States	Prospective cohort study	$PM_{2.5}$ 7.6 μg/m^3	Spatiotemporal model integrated with land use regression, chemical transport and aerosol optical depth models	- Age, Sex, Parental education - Maternal smoking - Maternal alcohol consumption - Socioeconomic status - Intracranial volume	- Corpus callosum, Cerebellum - Total Grey Matter, Total White Matter - Total Brain Volume, Ventricles - Hippocampus - Other subcortical structures - Corpus callosum, Cerebellum - Cortical thickness in various areas

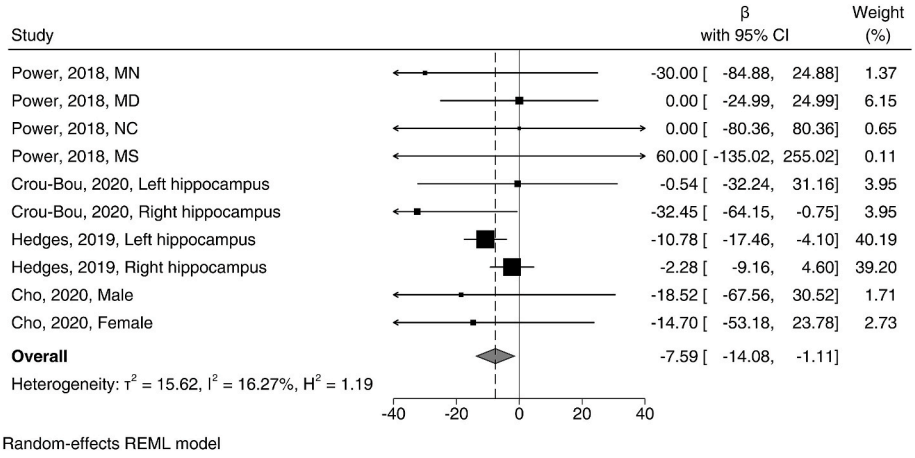

Fig. 2. Forest plot of the meta-analysis on association between $PM_{2.5}$ concentrations [μg/m^3] and hippocampal volume [mm^3] in adults. Arrows indicate that interval bound exceeds axis limits. We indicated first authors, year of publication and population group in study label. MN, MD, NC and MS are respectively Minnesota, Maryland, Mississippi and North Carolina, considered separately in one study (Power et al., 2018). Two studies conducted the analysis separately for left and right hippocampi (Crous-Bou et al., 2020; Hedges et al., 2019). The dashed line indicates the comprehensive β coefficient.

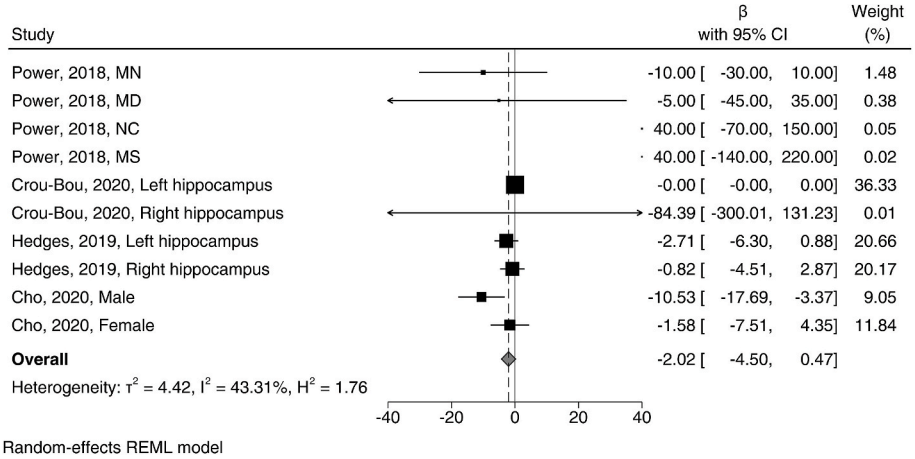

Fig. 3. Forest plot of the meta-analysis on association between PM_{10} concentration [μg/m^3] and hippocampal volume [mm^3] in adults. Arrows indicate that interval bound exceeds axis limits. We indicated first authors, year of publication and population group in study label. MN, MD, NC and MS are respectively Minnesota, Maryland, Mississippi and North Carolina, considered separately in one study (Power et al., 2018). Two studies conducted the analysis separately for left and right hippocampi (Crous-Bou et al., 2020; Hedges et al., 2019). The dashed line indicates the comprehensive β coefficient.

average background $PM_{2.5}$ concentrations and the regression coefficient of each individual study (Fig. 5). The coefficient (β_{meta}) was negatively though imprecisely correlated with air pollution, since the β_{meta} was −0.5 (95% CI −2.2 to 1.2).

For PM_{10}, the meta-regression yielded little evidence of any trend across the investigated range of air pollution (β_{meta} −0.063, 95% CI −0.274 to 0.148; Supplemental eFig. 1). Finally, the β_{meta} for NO_2 showed a slight and statistically imprecise inverse association between

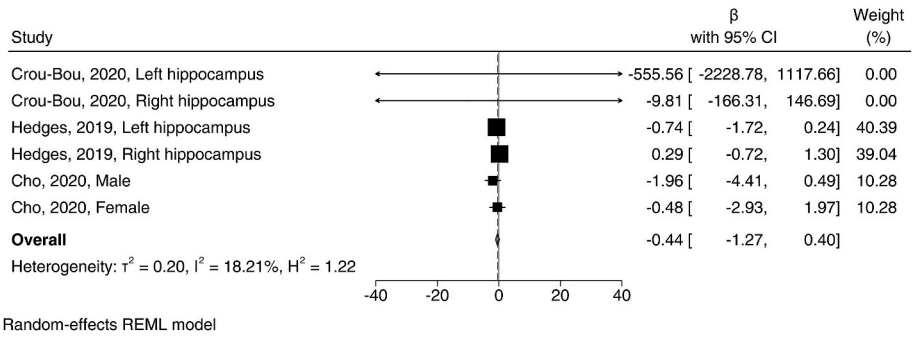

Fig. 4. Forest plot of the meta-analysis on association between NO_2 concentration [μg/m^3] and hippocampal volume [mm^3] in adults. Arrows indicate that interval bound exceeds axis limits. We indicated first authors, year of publication and population group in study label. MN, MD, NC and MS are respectively Minnesota, Maryland, Mississippi and North Carolina, considered separately in one study (Power et al., 2018). Two studies conducted the analysis separately for left and right hippocampi (Crous-Bou et al., 2020; Hedges et al., 2019). The dashed line indicates the comprehensive β coefficient.

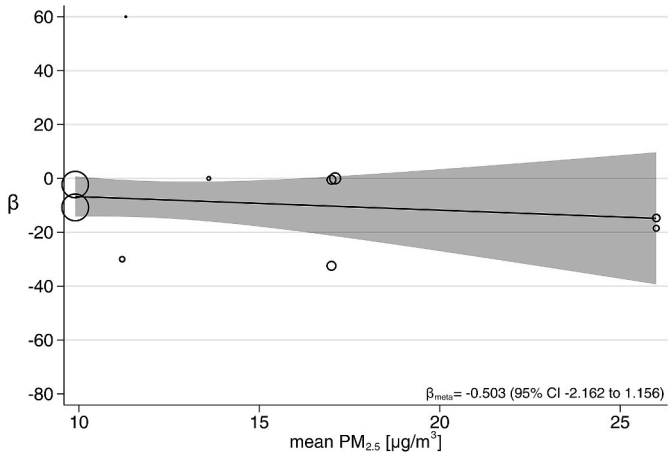

Fig. 5. Meta-regression concerning the effect of higher $PM_{2.5}$ concentrations [μg/m^3] and beta coefficients of studies evaluating the association between $PM_{2.5}$ concentration and hippocampal volume [mm^3] in adults. The black solid line fits data from different studies and the shadowed area indicates 95% confidence intervals.

air pollution and hippocampal volume −0.29 (95% CI −0.90 to 0.32; Supplemental eFig. 2).

Results of the meta-analysis of the two studies on children are shown in Fig. 6. These two studies were very heterogeneous, and only estimates for $PM_{2.5}$ were available in both studies. No overall association between hippocampal volume and particulate matter emerged (β_{meta} 0.60, 95% CI −2.99 to 4.20). Mean $PM_{2.5}$ concentration was rather different in these studies as mean $PM_{2.5}$ concentration was 7.6 μg/m^3 in that by for the United States study (Cserbik et al., 2020), in which no association was present, and 16.8 μg/m^3 in the Dutch study (Lubczynska et al., 2021) were an inverse association between hippocampal volume and $PM_{2.5}$ was detected. No publication bias was found with Egger's tests in the various meta-analyses (Supplemental eFig. 3).

4. Discussion

In the meta-analysis on the relation between air pollution and hippocampal volume, based on four individual studies on adults, we found that outdoor air pollution when estimated as $PM_{2.5}$ concentrations was strongly and inversely associated with hippocampal volume, while the association was weaker though still evident for PM_{10}. On the contrary, both NO_2 exposure in adults and the only exposure investigated in children, outdoor $PM_{2.5}$, showed little association with hippocampal volume based on the pooling of three and two studies, respectively. Outcomes of the full-text evaluated studies which could not be included in the meta-analyses were consistent with these results.

The relations we found are of public health and clinical relevance, given the detrimental effects of air pollutants on human health (Dominski et al., 2021; Filippini et al., 2019) and the key role of hippocampus in cognitive function (Ewers et al., 2012; Jack et al., 2010). The hippocampus, as included in the limbic system, plays a crucial role in emotional processing, and is involved in episodic and semantic memory and in spatial processing. Hippocampal reduction is a signature of cognitive decline, it occurs in normal aging while becoming particularly evident in neurodegenerative disease (Ewers et al., 2012; Jack et al., 2010; Svenningsson et al., 2012). Hippocampal decrease has been observed in patients suffering from depressive disorders (Jaworska et al., 2016), schizophrenia (Tregellas, 2014) and epilepsy (Scott et al., 2002).

The rate of hippocampal volume decrease has been estimated to be approximately 1.7% per year in normal aging, 2.55% per year for patients with mild cognitive impairment and 3.5% per year for patients with Alzheimer's disease (Jack et al., 2000). In our research we found 7.6 mm^3 decrease per each increase in 1 μg/m^3 $PM_{2.5}$ concentration, which means about 0.2% decrease for a standard hippocampus of about 4000 mm^3 in standard space (Bycroft et al., 2018). Being the difference in $PM_{2.5}$ concentration between rural and city environments in the order of 10 μg/m^3 (Putaud et al., 2010), it implies a 2% difference in hippocampal volume, which is comparable to the change observed in one year of normal aging. Such a change would occur at amounts of air pollution

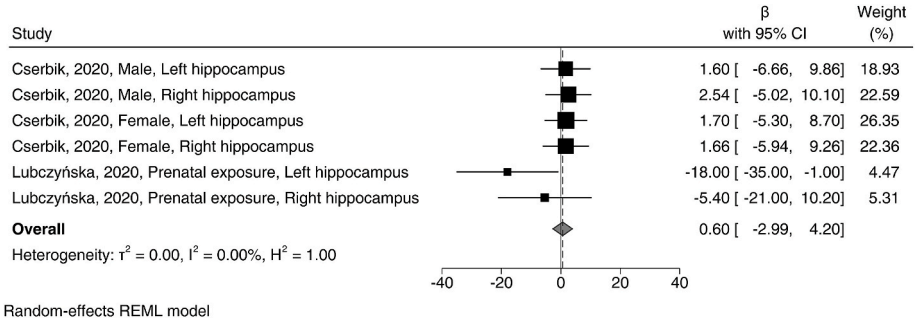

Fig. 6. Forest plot of the meta-analysis on association between $PM_{2.5}$ concentration [μg/m^3] and hippocampal volume [mm^3] in children. We indicated first authors, year of publication and population group in study label. The dashed line indicates the comprehensive β coefficient.

not 'extreme' and largely prevalent in many countries all over the world, and such exposure ubiquity adds to the concerns generated by the findings of this study.

The association between PM and hippocampal volume finds additional support from its biological plausibility. In fact, previous epidemiological studies showed an association of $PM_{2.5}$ with cognitive decline and dementia through an assessment of neuropsychological outcomes (Livingston et al., 2020; Ran et al., 2021; Yang et al., 2015). Moreover, hippocampal morphology changes following $PM_{2.5}$ exposure have been observed in mice studies, through dissection followed by histological examinations (Ehsanifar et al., 2021; Fonken et al., 2011) and through neuroimaging evaluations (Nephew et al., 2020). Additionally, this study shows that $PM_{2.5}$ has a stronger effect on hippocampal volume than PM_{10}. This could be explained by the smaller size of $PM_{2.5}$ that could ease its penetration and transportation into the body (Kim et al., 2020).

We also conducted a separate analysis for left and right hippocampal volumes, in which the only three available studies yielded inconsistent results, suggesting either no differential effect of PM on the two hippocampi or an influence of the study population and of the exposure levels. The low number of available studies, however, represents a relevant limitation when assesisng the possible subtle differences.

Interestingly, the only study reporting sex-specific estimates found a stronger inverse association between air pollution, as assessed through PM_{10} levels, and hippocampal volume in males, compared with females (Cho et al., 2020). Such sex-related difference await confirmation from other studies and was not detectable in children (Cserbik et al., 2020). In mice, evidence have been provided indicating that male hippocampal volume may be particularly susceptible to particulate matter exposure (Cole et al., 2016).

The meta-regression model yielded results consistent with the meta-analyses and provided additional findings, as it showed a stronger association between $PM_{2.5}$ and hippocampal volume at higher mean $PM_{2.5}$ concentrations. These findings were not unexpected and may suggest the presence of a threshold above which the association between air pollution and hippocampal damage is more meaningful. The possibility that such an association becomes meaningful only at high concentrations of particulate matter deserves to be carefully investigated, also considering the more deleterious potential of air pollution expected to occur on brain structures, including hippocampus, at an early age (de Prado Bert et al., 2018). Therefore, it may be interesting to assess in future studies if there are thresholds of exposure to air pollutants below which there is little increase of the risk of dementia, and to take into account in such assessment the different clinical subtypes and the age of disease onset (Chiari et al., 2021).

The main limitation of this meta-analysis is that it includes a relatively low number of papers, with inherent implications on the statistical precision of the summary estimates, and on a larger potential for heterogeneity. However, the consistency of the apparent effects we detected across the studies in adults, and the increased stability of the effect estimates over the individual studies, support the reliability of the overall finding, i.e. an association between higher air particles exposure and decreased volume of a key brain structure for cognitive function, the hippocampus.

Some misclassification in air pollutants exposure assessment may have occurred in the considered studies and therefore may have been source of heterogeneity of the effect estimates. In fact, methods for exposure assessment have generally evaluated the mean or median pollutant levels at the participants' residence, without considering variations of exposure due commuting for work, study or other activities. Additional sources of heterogeneity across studies and of statistical imprecision of summary estimates could have been differences in the confounding factors considered in the analyses. However, all studies implemented adjusted models in multivariable analysis that took into account most relevant confounders, such as age, sex, educational attainment, and smoking, and in many cases also cardiovascular risk factors possibly affecting cognition. Nonetheless, the occurrence of residual confounding cannot be entirely ruled out, due to some misclassification in the assessment of these factors and unmeasured confounding, as inherent in the observational study design.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111976.

Credit author statement

EB, MV and TF designed the original study. LDE, MC-B and MG provided unpublished data. EB performed the analysis and with MV and TF interpreted the data, with the contribution of LDE, MC-B and MG. EB drafted the original manuscript with MV and TF. LDE, MC-B and MG provided revision. All authors read and approved the final manuscript.

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