Long-term Exposure to Ambient Air Pollution and Incidence of Brain Tumor: the European

Study of Cohorts for Air Pollution Effects (ESCAPE)

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Background: Epidemiological evidence on the association between ambient air pollution and brain tumor risk is sparse and inconsistent.

Methods: In 12 cohorts from six European countries, individual estimates of annual mean air pollution levels at the baseline residence were estimated by standardized land-use regression models developed within the ESCAPE and TRANSPHORM projects: particulate matter (PM) ≤ 2.5, ≤ 10, and 2.5-10 μm in diameter ($PM_{2.5}$, PM_{10}, and PM_{coarse}), $PM_{2.5}$ absorbance, nitrogen oxides (NO_2 and NO_x) and elemental composition of PM. We estimated cohort-specific associations of air pollutant concentrations and traffic intensity with total, malignant and nonmalignant brain tumor, in separate Cox regression models, adjusting for risk factors, and pooled cohort-specific estimates using random-effects meta-analyses.

Results: Of 282,194 subjects from 12 cohorts, 466 developed malignant brain tumors during 12 years of follow-up. Six of the cohorts had also data on nonmalignant brain tumor, where among 106,786 subjects, 366 developed brain tumor: 176 nonmalignant and 190 malignant. We found a positive, statistically non-significant association between malignant brain tumor and $PM_{2.5}$ absorbance (Hazard Ratio and 95% Confidence Interval: 1.67; 0.89-3.14 per $10^{-5}/m^3$), and weak positive or null associations with the other pollutants. Hazard ratio for $PM_{2.5}$ absorbance (1.01; 0.38-2.71 per $10^{-5}/m^3$) and all other pollutants were lower for nonmalignant than for malignant brain tumors.

Conclusion: We found suggestive evidence of an association between long-term exposure to $PM_{2.5}$ absorbance indicating traffic-related air pollution and malignant brain tumors, and no association with overall or nonmalignant brain tumors.

Keywords: air pollution, traffic, brain tumor, brain cancer,

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Importance of the Study:

Increasing brain tumors incidence generated the interest in environmental exposures. Traffic-related air pollution was declared carcinogenic to humans and linked to lung cancer. Experimental studies illustrated that particles can reach the brain causing inflammation and oxidative stress, but the current epidemiological evidence on air pollution and brain tumor risk is sparse and inconclusive. Within the framework of European Study of Cohorts for Air Pollution Effects (ESCAPE), we examined the association between air pollution and brain tumor risk in 282,194 subjects from 12 cohorts in six countries, who developed 466 malignant brain tumors during 12 years. Air pollution levels at the residence were estimated by standardized land-use regression models for particulate matter (PM) ≤ 2.5, ≤ 10, 2.5-10 μm in diameter ($PM_{2.5}$, PM_{10}, PM_{coarse}), $PM_{2.5}$ absorbance, and nitrogen oxides (NO_2, NO_x). We found suggestive evidence of an association between the traffic-related metric $PM_{2.5}$ absorbance and malignant brain tumors, and no association with overall or nonmalignant brain tumors. The strength of the study was availability of data on non-malignant brain tumors.

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Introduction

The average incidence of primary adult brain tumors (nonmalignant or malignant) in Europe, in 2012, was 6.6 (7.8 in men and 5.6 in women) per 100,000 people and approximately half of these were malignant (brain cancers).[1] Incidence of brain tumors has been increasing in the industrialized countries, which is, in part, explained by improvements in diagnoses and high-resolution neuroimaging, and an aging population, but occupational and environmental exposures have been suspected to play a role.[2] Established brain tumor risk factors include age, ionizing radiation to the head, and inherited genetic risk,[3] while infectious agents, high income, white race, exogenous hormone exposure (for nonmalignant tumors in women), occupations in agriculture,[4] petrochemical industry and exposure to landfill pollution have been identified as potential risk factors.[3]Outdoor and traffic-related air pollution, such as gasoline and diesel engine exhaust, have been classified as carcinogenic to humans by the International Agency for Research on Cancer[5,6] and are established risk factors for lung cancer, cardiovascular and respiratory diseases.[7–9] Still, epidemiological evidence relating traffic-related air pollution to brain diseases is just emerging. Air pollution was recently linked to stroke,[10] and the biological mechanism relevant for stroke were also suspected of being relevant for neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases and dementia.[11] Experimental evidence in animals showed how particles,[11] and most recently, mineral magnetite,[12] can reach the brain, via inhalation or directly through the nose and olfactory nerve, and cause neuroinflammation, oxidative stress, and neurodegeneration.[11,13–17] Inflammation is suggested to be important in the pathogenesis of brain cancer.[18] Furthermore, gene expression pattern similar to that seen in human brain tumors, were found in rats after exposure to concentrated particles, in particular the coarse fraction.[19] However, epidemiological evidence is sparse, consisting of two ecological studies,[20,21] three cohort[22–24] and a case-control study.[25] A US study found association between airborne toxicant volatile

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organic compounds (VOCs) emissions at a country-level and the incidence of brain cancer,[20] while a recent nationwide study found no association of brain cancer incidence and mortality at county-level with any of 30 different hazardous air pollutants (HAPs) examined.[21] The earliest cohort study from 2009, based on the US Cancer Prevention Study cohort found no associations between brain cancer mortality (n=1,284) and residential exposure to particulate matter with diameter < 2.5 and 10 μg/m^3 ($PM_{2.5}$ and PM_{10}) or nitrogen dioxide (NO_2).[22] A study from 2011 detected a strong association between long-term exposure to nitrogen oxides (NO_x) and brain cancer incidence (n=95) (hazard ratio and 95% confidence interval (CI): 2.28; 1.24-4.17 per 100 μg/m^3) in the Danish Diet, Cancer and Health cohort,[23] which was however not reproduced in a nationwide Danish case-control study with 4,183 brain tumor cases.[25] Finally, the recent study in the Danish Nurse Cohort (n=121) found no association between brain tumor incidence (malignant or nonmalignant) and $PM_{2.5}$, PM_{10} or NO_2.[24] With air pollution established as carcinogenic to humans, suggestive experimental evidence on the biological plausibility, and sparse and inconclusive epidemiological evidence, the rationale of this study was to examine association between air pollution and brain tumor in a large study combining information from several European cohorts.

With Using the 12 European cohorts within the framework of European Study of Cohorts for Air Pollution Effects (ESCAPE; http://www.escapeproject.eu/)[26,27] in this study we aim to examine the association between long-term exposure to ambient air pollution and incidence of brain tumor in total and separately for malignant and nonmalignant tumors.

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Materials and Methods

Study Population

We invited 22 cohorts which have contributed to earlier analyses within the ESCAPE framework on the association of air pollution with lung cancer.[26] Of these we included 12 cohorts from six European countries (see Supplementary Figure S1) which had information on brain tumor incidence, at least 20 cases of brain tumor per cohort, and had the resources (statistical analyst available) for participation.

The 12 included cohorts were as follows (Table 1, see Supplementary Figure S1):

a. Five Swedish cohorts: European Prospective Investigation into Cancer and Nutrition (EPIC)-Umeå, Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/Twin gene), Stockholm 60 years old and IMPROVE study (60 y/IMPROVE), and Stockholm Diabetes Prevention Program (SDPP);

b. One Norwegian cohort: Oslo Health Study (HUBRO);

c. One Danish cohort: Diet, Cancer and Health (DCH) study, with only Copenhagen included;

d. Two Dutch cohorts: EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (EPIC-MORGEN) and (EPIC-PROSPECT);

e. One Austrian cohort: Vorarlberg Health Monitoring and Prevention Programme (VHM&PP);

f. Two Italian cohorts: EPIC-Varese and EPIC-Turin.

The majority of cohorts recruited participants from large cities and the surrounding suburban or rural communities, while few covered large regions of the country, such as EPIC-MORGEN in the Netherlands and the VHM&PP cohort in Austria. For DCH and VHM&PP, exposure to air pollution was assessed for the Copenhagen (DCH) and population in the

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valley (VHM&PP) part of the original cohort. Data from the four Swedish cohorts from Stockholm (SNAC-K, SALT/Twin gene, 60 y/IMPROVE and SDPP) as well as the two Dutch cohorts (EPIC-MORGEN and EPIC-PROSPECT) were pooled by the local analyst, and analysed as single cohorts, named Cardiovascular Effects of Air pollution and Noise in Stockholm (CEANS) and EPIC Netherlands (EPIC-NL), respectively. The use of cohort data in ESCAPE was approved by the local ethical and data protection authorities. Each cohort study followed the rules for ethics and data protection set up in the country in which they were based.

Brain Tumor Definition

Cohort members were followed for brain tumor incidence via linkage to national or regional cancer registries among cohort members who did not have cancer before cohort baseline (excluding non-melanoma skin cancers). Our main outcome was incident primary tumor of the brain, meninges and cranial nerves, defined according to International Classification of Diseases (ICD)-10 code (ICD10): C70.0, C71.0-C71.9, C72.2-C72.5, D32.0, D33.0-D33.2, D33.3, D42.0, D43.0-D43.2, D43.3. We aimed to consider the following five outcomes: the total of all tumors combined; subtypes by malignancy of the tumors: malignant (brain cancer) (C70.0, C71.0-C71.9, C72.2-C72.5) and nonmalignant (benign) tumors (D32.0, D33.0-D33.2, D33.3, D42.0, D43.0-D43.2, D43.3); and subtypes by the location of the tumor: tumors of the brain (ICD10: C71.0-C71.9, D33.0-D332, D43.0-D43.2) or tumors of meninges (C70.0, D32.0 and D42.0).

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Exposure Assessment

We estimated annual average concentrations of air pollution at baseline residence for each cohort participant by standardized area-specific land-use regression (LUR) models developed within the ESCAPE study, described in detail elsewhere.[28,29] In brief, the LUR models are based on measurements of NO_2 and NO_x in all 12 cohorts, and $PM_{2.5}$, PM_{10}, and $PM_{2.5}$ absorbance in ten study areas (due to budgetary reasons) during one year between October, 2008 and May, 2011.[30,31] The concentration of PM_{coarse} was calculated as the difference between PM_{10} and $PM_{2.5}$. Subsequently LUR models were developed for each pollutant in each study area to predict air pollution concentration at the baseline residence of the cohort participants. Data from the nearest routine monitoring stations were used to back-extrapolate the LUR estimates to the baseline year in fourteen of the fifteen study areas using the ratio-method. We also used traffic intensity (annual average number of motor vehicles per day) on the nearest road to the exact residential address at the cohort baseline for each participant, as indicator of exposure to traffic-related air pollution.

Furthermore, we used estimated annual concentrations of eight elements in $PM_{2.5}$ and PM_{10} (Cu, Fe, Zn, S, Ni, V, Si and K) with area-specific LUR models developed within framework of the European study of Transport-related Air Pollution and Health Impacts—Integrated Methodologies for Assessing Particulate Matter (TRANSPHORM; www.transphorm.eu/)[32,33] (see Supplementary data).

Statistical Analyses

We have used a two-step approach by first estimating the association between different air pollutants and brain tumor in each cohort, and then combining the estimates from each cohort, for each pollutant and each brain tumor subtypes, by meta-analyses. Pooling of the cohort data was not possible due to data transfer and privacy issues.

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Cohort Specific Statistical Analyses

We used Cox proportional hazards models for the cohort specific analyses, with age as the underlying timescale, and censoring at the time of any other cancer diagnosis (except non-melanoma skin cancer), death, emigration (to another country), or end of follow-up, whichever came first. We ran a model for total brain tumors, and separate models for tumors by malignancy (malignant and nonmalignant brain tumors), and by location (tumors in the brain and meninges). We analyzed all air pollutants and traffic intensity as linear variables in separate single-pollutant model. The potential confounders were available from questionnaires at baseline. We specified three confounder models *a priori*: Model 1, adjusted for age (time axis), sex, and calendar time (years of enrolment); Model 2, additionally adjusted for educational level (low, medium, or high) and occupation in petrochemical or chemical industry (yes, no); and Model 3, adjusted additionally for area-level socio-economic status (SES) variables using random effects of the spatial area units in each cohort to check for spatial clustering of residuals of the models. Various definitions of area-level SES were used including unemployment rate at the municipality (EPIC-Umeå, HUBRO, CEANS, and EPIC-Varese), mean income in the municipality (DCH, VHM&PP), percentage of people with low income in the neighborhood (EPIC-NL), or area deprivation index at the census block (EPIC-Turin). We a priori chose Model 3 as the main confounder model. All cohorts except VHM&PP had information on education and only CEANS, DCH, EPIC-Varese, and EPIC-Turin had information on occupation in petrochemical or chemical industry. Only participants with no missing information in any of the exposures and confounders in the Model 3 were included in all analyses. Individual cohorts adjusted with the maximum possible confounders in the Model 3. We performed a number of sensitivity analyses within each cohort: we restricted analyses to participants who were long-term residents (lived at

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least 10 years at the baseline address); we restricted analyses to long-term residents who did not move between the baseline and the end of follow-up; we added the indicator of rural areas to adjust for different degree of urbanization within the study area; we performed diagnostic tools to check the proportional hazards (PH) assumption for the categorical predictors in the Model 3, and stratified the Cox model for the predictors that did not meet the PH assumption. We examined the shape of the association between each pollutant and brain tumor by: a) inputting the exposure term as a natural cubic spline with two inner knots (i.e. three degrees of freedom), and by comparing the model fit of the linear and the spline models by a likelihood-ratio test. All cohort-specific analyses were performed in STATA versions 10-12 using a common script, except for models with random effects, for which we used R software, version 2.11–2.15.

Meta-analyses

We performed meta-analyses of cohort-specific effect estimates with the DerSimonian-Laird method with random effects.[34] As main analyses, we performed separate meta-analyses for each of seven pollutants for malignant brain tumors in 12 cohort, and for nonmalignant and total brain tumors in 6 cohorts. Additionally, as presented in Supplementary Material, we performed meta-analyses for elemental components of $PM_{2.5}$ and PM_{10} and malignant brain tumors, and a number of sensitivity analyses. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for fixed increments that were chosen to cover the range in concentrations within the different cohorts and to keep increments broadly comparable between pollutants. We evaluated the heterogeneity between cohort-specific results by applying the chi-square test from Cochran's Q statistic, which was quantified by the I^2 statistic.[35] We tested effect modification with a meta-analysis of the pooled estimates from the different strata and by computing the $\chi2$ test of heterogeneity. We considered cohort

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specific estimates to be significantly heterogeneous when $I^2 > 50\%$ or the p-value of the chi-square test was < 0.05. We investigated the robustness of the results for malignant brain tumors by examining the effect of all pollutants after excluding the VHM&PP from the meta-analyses, since this was the largest and most influential cohort which lacked the data on tumor in the meninges, and had the smallest number of confounders available in Model 3. We used STATA version 12.1 for all meta-analyses.

Results

Study Population

All 12 cohorts had data on malignant brain tumors (Table 1), where a total of 282,194 men and women and were diagnosed with 466 primary malignant brain tumors during a mean follow-up of 13.3 years or 4,186,476 person-years. Six of these cohorts (five from Sweden: EPIC-Umeå and CEANS (consisting of 4 cohorts) and the Austrian VHM&PP) did not have information on nonmalignant tumors. Of 106,786 men and women from six cohorts with data on both nonmalignant and malignant tumors (HUBRO, DCH, EPIC-NL (consisting of two cohorts), EPIC-Varese, and EPIC-Turin), 366 in total developed primary brain tumors in total during a mean follow-up of 12.6 years (1,319,523 person-years), of which 176 (48%) were nonmalignant and 190 (52%) malignant. Of these six cohorts, EPIC-Varese did not have information on tumor subtype by location (meninges or brain). Thus, analyses on the subtypes of brain tumors by location were based on 5 cohorts with complete data on total brain tumors (malignant and nonmalignant) and on brain tumor location (meninges or brain): HUBRO, DCH, EPIC-NL (consisting of 2 cohort), and EPIC-Turin. Among the 96,215 subjects from these 5 cohorts, 303 developed brain tumor in total during a mean follow-up of

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12.7 years or 1,205,547 person-years. Of these 303 brain tumors, 115 (38%) were in the meninges and 188 (62%) in the brain.

Mean age at the time of enrolment ranged from 41.3 years in VHM&PP to 56.8 years in DCH (Table 1). Proportion of women ranged from 43.9% in EPIC-Turin to 78.9% in EPIC-Varese, while the proportion of highly educated ranged from 7.1% in EPIC-Varese to 45.2% in HUBRO, whereas VHM&PP did not have data on education (see Supplementary Table S1).

Air Pollution Exposure

The air pollution levels at residence varied substantially within and between study areas, with increasing levels from Northern to Southern study areas (Table 2). EPIC-Umeå and EPIC-Varese did not have data on PM, and EPIC Varese on traffic intensity. The mean concentration of $PM_{2.5}$ ranged from 7.1 µg/m^3 in CEANS, Sweden to 30.2 µg/m^3 in EPIC-Turin, Italy. NO_2 ranged from 5.3 µg/m^3 in EPIC-Umeå, Sweden to 53.0 µg/m^3 in EPIC-Turin, Italy. Average traffic intensity on the nearest road was lowest in EPIC-Umeå (849 vehicles/day) and highest in EPIC-Turin (4,044 vehicles/day). Mean levels of $PM_{2.5}$ and PM_{10} elements also varied substantially between study areas (see Supplementary Table S2). The estimates in this study were given per fixed increments (10 µg/m^3 for PM_{10} and NO_2, 5 µg/m^3 for $PM_{2.5}$, etc.), which were selected a priori by a protocol for entire ESCAPE project, as they reflect a broadly comparable contrasts in exposure for the different pollutants, and are most commonly used in literature and in meta-analyses. These contrasts/increments should be considered in the context of the mean air pollution concentrations in different areas. For example, 10 µg/m^3 represents 58% of the average PM_{10} concentration in Copenhagen Denmark, and only 21% of average PM_{10} concentration in Turin, Italy.

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Associations between air pollutants and malignant brain tumor in 12 cohorts

We found positive, statistically non-significant association between malignant brain tumor and $PM_{2.5}$ absorbance (HR = 1.67; 95% CI: 0.89-3.14 per 10^{-5}/m, p-value=0.11) in the fully adjusted model (Model 3), with moderate heterogeneity in the individual cohort estimates (I^2 = 39.9%) (Table 3, Figure 1). Summary estimates for $PM_{2.5}$ absorbance were enhanced or remained unchanged in the sensitivity analyses (see Supplementary Table S3). We found borderline significant positive associations with traffic intensity on the nearest road (HR = 1.08; 95% CI: 0.99-1.16 per 5,000 vehicles/day, *p*-value=0.07), but it is notable that 3 cohorts had HR above 1 and 4 cohorts HR below 1 (Table 3, Figure 2). We found weak positive associations with PM_{10}, NO_2 and NO_x, and none with $PM_{2.5}$ or PM_{coarse}. There was moderate or no heterogeneity in the summary estimates, except for NO_2 and NO_x, which showed substantial, statistically significant heterogeneity between individual cohort estimates.

HRs for all pollutants were slightly attenuated after adjustment for individual level confounders (Table 3). There was no evidence of deviation from linearity in associations between air pollutants and total brain tumor (results not shown).

Associations between elemental components of PM and malignant brain tumor

In the secondary analyses of the elemental components of $PM_{2.5}$ and PM_{10}, no statistically significant associations were detected for any component and malignant brain tumor. We detected strongest association with the V component of $PM_{2.5}$ (HR = 1.40; 95% CI: 0.75-2.60 per 2 ng/m^3) and PM_{10} (HR = 1.31; 95% CI: 0.69-2.49 per 3 ng/m^3) and Ni component of $PM_{2.5}$ (HR = 1.27; 95% CI: 0.44-3.64 per 1 ng/m^3) and PM_{10} (HR = 1.28; 95% CI: 0.98-1.66 per 2 ng/m^3), though with statistically significant heterogeneity between individual cohort estimates for Ni component of $PM_{2.5}$ (I^2 = 76.3) (see Supplementary Table S4 and Figure

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S2).We also found positive association with copper component of $PM_{2.5}$ and PM_{10}, and iron and sulphur component of $PM_{2.5}$ (but not PM_{10}).

Associations between air pollutants and total and nonmalignant brain tumor in six cohorts

We found no association between any pollutant and nonmalignant brain tumor (Table 4), and even strong inverse association with PM_{coarse} and PM_{10} (Table 4, see Supplementary Figures S3 and S4). We found positive, but statistically non-significant associations between total brain tumor and $PM_{2.5}$ absorbance (HR = 1.58; 95% CI: 0.73-3.40 per 10^{-5}/m) and statistically significant association with traffic intensity on the nearest road (HR = 1.07; 95% CI: 1.00-1.14 per 5,000 vehicles/day) (Table 4, see Supplementary Figures S5 and S6). It is notable that for traffic intensity only a single cohort had HR above 1, and the rest below 1.

Associations between air pollutants and brain tumor by malignancy in six cohorts

In the analyses based on six cohorts with data on both malignant and nonmalignant brain tumors, HRs for all pollutants, except for traffic intensity on the nearest road, were higher for malignant (see Supplementary Table S5 and Supplementary Figures S7 and S8) than for nonmalignant (see Supplementary Figures S5 and S6) brain tumors, reaching statistical significance for malignant tumors and $PM_{2.5}$ absorbance (HR = 2.03; 95% CI: 1.05-3.91 per 10^{-5}/m).

Associations between air pollutants and brain tumor by location

In the analyses in five cohorts with data on all brain tumors and subtypes by location (brain or meninges) there was no clear pattern (See Supplementary Table S6). HRs for the most pollutants were generally higher for tumors in the brain (see Supplementary Figure S9 and S10) than in the meninges (see Supplementary Figure S11 and S12), except for $PM_{2.5}$, for

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which a very strong positive association was detected (HR = 2.53; 95% CI: 0.87-7.41; I^2 = 0.0, per 5 μg/m^3) and traffic intensity on the nearest road.

A schematic presentation of a number of analyses presented in the paper is given in Supplementary Material (see Figure S13).

Discussion

In this large, multicentre European study, we found suggestive evidence of an association between long-term exposure to the traffic related marker $PM_{2.5}$ absorbance and risk of malignant brain tumors, and no association with nonmalignant brain tumors.

Comparison with previous studies

Our results suggesting relevance of traffic related PM air pollution, in terms of $PM_{2.5}$ absorbance, for malignant brain tumor are novel. Lack of statistically significant associations between malignant brain tumor incidence and $PM_{2.5}$, PM_{10}, and NO_2 in our study agree with the findings by McKean-Cowden et al. from 2009, based on US Cancer Prevention Study, of no association between brain cancer mortality (1,284 cases) and residential exposure to $PM_{2.5}$, PM_{10} or NO_2 (all HRs below one).[22] McKean-Cowdin et al. had data only on brain cancer mortality, which, in contrast to incidence, captures more aggressive types of malignant brain cancers. Our results agree with a study by Jørgensen et al.[24] in 28,731 female nurses from a Danish Nurse Cohort (121 cases of total brain tumor) that found no association of $PM_{2.5}$ or PM_{10} with malignant brain tumor incidence (HRs for all pollutants below 1) consistent with McKean-Cowden et al.[22] We found strongest effects for $PM_{2.5}$ absorbance, which captures fraction of $PM_{2.5}$ originating from incomplete combustion from motorized traffic, highly correlated to elemental carbon.[36] $PM_{2.5}$ absorbance may be a better proxy for traffic related

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particles in the ultrafine size range (ultrafine particles (UFPs): diameter < 100 nm) than PM$_{2.5}$. In Augsburg, Germany, average UFP level was highly correlated with PM$_{2.5}$ absorbance (correlation coefficient (R)=0.81), but the correlations with NO$_2$ and NO$_x$ were even higher.[37] In Amsterdam, average UFP was highly correlated with PM absorbance (R=0.85) at 46 sites, and correlations with PM$_{2.5}$ and PM coarse were lower.[38] UFPs are of particular concern with respect to brain, because experimental studies in animals indicate that inhaled UFPs can reach the brain by crossing the blood-brain barrier or directly via nasal passage and olfactory neurons, and accumulate in the brain,[16,39,40] causing inflammation, oxidative stress and DNA damage.[13,41,42]

Our results of weak positive, statistically non-significant associations with NO$_2$ and NO$_x$ disagree with a study from 2011 by Raaschou-Nielsen et al. on malignant brain tumor incidence (95 cases) in 54,304 participants from the DCH cohort which detected strong association with NO$_x$ (HR = 2.28; 95% CI: 1.25-4.19 per 100 µg/m^3) and proximity to major street (< 50 m) (HR = 1.89; 95% CI: 1.07-3.36).[23] In current analysis inlcuding half of the DCH cohort participants living in Copenhagen, association for NO$_x$ in DCH cohort was also strong positive and statistically significant (HR = 1.22; 95% CI: 1.05-1.42 per 20 µg/m^3), as it was with traffic intensity (HR = 1.09; 95% CI: 1.02-1.17 per 5,000 mv/day) (Figure 2), showing consistency in the DCH cohort with two different estimation methods for NO$_x$ and two different proxies for traffic intensity However, two recent Danish studies[24,25] did not reproduce this strong association between NO$_x$ and brain tumor detected in DCH, in agreement with our findings. Poulsen et al. in Danish nationwide case-control study (2000-2009) with 4,183 brain tumor cases in total, found only a weak positive association with NO$_x$ (HR = 1.11; 95% CI: 0.84-1.46 per 100 µg/m^3)[25], in line with our findings, but detected a statistically significant positive association with non-glioma tumors (HR = 1.53; 95% CI: 1.02-2.29 per 100 µg/m^3). Similarly, Jørgensen et al.[24] has in 28,731 female nurses from a

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Danish Nurse Cohort (121 brain tumor cases) found no association with NO_x (HR = 1.02; 95% CI: 0.93-1.12 per 10.2 μg/m^3) agreeing with the current study. However, neither Poulsen et al. nor Jørgensen et al. had data on the traffic intensity on the nearest road. While we detected strongest associations with malignant tumors, both Poulsen et al.[25] and Jørgensen et al.[24] found slightly stronger effects for nonmalignant brain tumors. Overall, evidence from this study does not support association between $PM_{2.5}$, PM_{10}, NO_2 and NO_x with brain tumor development, but suggests that PM originating from traffic, in terms of $PM_{2.5}$ absorbance, may play a role for the development of malignant brain tumors. However, due to high heterogeneity in findings in the existing literature, it is premature to conclude on the causal relationship between air pollution and brain tumor. More studies with data with long-term exposure to $PM_{2.5}$ absorbance, and preferably UFPs, are needed to confirm our novel findings.

Particle composition findings

We present a novel suggestive finding of the relevance of V and Ni components of $PM_{2.5}$ and PM_{10} for malignant brain tumor development (see Supplemental Table S5 and Figure S2). Environmental exposure to V occurs in areas of persistent burning of fossil fuel. This metal is known to induct oxidative stress and oligodendrocyte damage, and has been linked with carcinogenic, immunotoxic and neurotoxic insults.[43] Ni is a transitional heavy metal originating primarily by the combustion of fossil fuels,[44] found to be carcinogenic to humans, causing cancers of the lung and of the nasal cavity.[45] Ni component of PM_{10} was the PM element that showed strongest association with lung cancer incidence (HR=1.59; 95% CI: 1.12-2.26 per 2 ng/m^3) in a related study in 14 European cohorts.[46] These novel results call for replication in other studies and should be taken with caution, especially for Ni component $PM_{2.5}$, where a large heterogeneity between individual cohorts is observed.

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Strengths and limitations

Our study benefited from a multicenter design and a large number of subjects recruited from general populations from around Europe, with large variation in air pollution levels, well defined information on the brain tumor risk factors and standardized definition of brain tumor from national and regional cancer registers. The major strength of our study is the standardized exposure assessment for a number of different air pollutants and PM elements, and standardized statistical analyses across all cohorts. The air pollution LUR models have been validated and were earlier linked to lung cancer.[26] We adjusted the analyses for the most important risk factors, but found little evidence of confounding in air pollution estimates. Finally, the strength of the study is that we had data on nonmalignant brain tumors.

Of 22 original ESCAPE cohorts, we included only the 12 cohorts, which had data on brain tumor, at least 20 cases of brain tumor in total, and resources in terms of statistical analyst to perform analyses. Of the cohorts not included in current analyses are the cohorts from Southern Europe, including those from Greece (EPIC-Athens), Italy (SIDRIA-Rome) and Spain (San Sebastian and Basque country), as well as those from United Kingdom (UK) (EPIC-Oxford), Switzerland (SAPALDIA), France (E3N), and Germany (SALIA and KORA), while all the Nordic and Dutch cohorts (except Finish FINRISK) are included. Thus, some of the original 22 ESCAPE cohorts with highest levels of air pollution from Southern Europe are missing from current analyses, while there is an overrepresentation of cohorts from Northern countries, with lower air pollution levels.

Weakness of our study is lack of data on brain tumor subtypes in all 12 cohorts. We have detected significant positive association between $PM_{2.5}$ absorbance and malignant brain

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tumor only in six cohorts which had information on all brain tumors (HR=2.12; 95% CI: 1.06-4.25 per 10^{-5}/m, see Supplementary Table S5), but not in a larger sample of total 12 cohorts with information on malignant tumors (HR=1.67; 95% CI: 0.89-3.14 per 10^{-5}/m). However, all sensitivity analyses of associations between $PM_{2.5}$ absorbance and malignant brain tumor based on six cohorts showed enhanced HRs, ranging between 1.67 to 2.37 (see Supplementary Table S3), suggesting that the associations may be real and rather robust. Furthermore, we lacked information on brain tumor histology and morphology, and could not study whether air pollution differentially affects more aggressive types of brain tumors, such as glioblastomas or anaplastic astrocytomas, opposed to more nonmalignant tumors such as meningiomas or low grade gliomas. We lacked information on detailed occupational exposures to chemicals that may be related to brain tumor risk, apart from a crude definition of occupation in petrochemical industry available in eight out of 12 cohorts. We also lacked data on other potential risk factors, such as genetic predisposition, residential radon exposure, occupation in agriculture, exposure to radiation to head and neck, but all of these are most likely not related to air pollution levels at residence. We used air pollution exposure estimated close to the time of the brain tumor diagnosis, and lack data on distant exposures during adulthood and early-life, which may be more relevant for the development of brain tumor. We have used LUR model in this study developed on air pollution measurements between 2008 and 2011, but applied them to baseline addresses typically 10 to 15 years earlier, which likely resulted in some exposure misclassification. Several studies have documented stable spatial contrast of NO_2 over study periods of 10-15 years.[47–49] As motorized traffic is a major source of NO_2, spatial contrasts likely have been stable for other traffic-related pollutants including PM2.5 absorbance. Another weakness of the study is that we used information on air pollution and confounders at the cohort baseline, and did not have information on changes over time. Furthermore, we lacked information on participant's

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activity patterns, time spent outdoors and away from home, commuting to work, etc. Exposure misclassification and lack of early-life exposures to air pollution may have biased our estimates towards zero, meaning that real associations would be even stronger than those observed here. Majority of the cohorts included in current analyses were recruited from urban areas, typically large cities and surrounding areas, except VHM&PP, which included primarily rural communities and several towns. However, there is still large variation in air pollution levels within the cohorts (Table 2), and especially between the cohorts with example of NO_2 levels ranging from 8.8 µg/m^3 in Umeå, Sweden to 96.1 in Turin, Italy.*Conclusion*

In a large meta-analyses based on 12 European cohorts, on long-term exposure to ambient air pollution and brain tumor incidence, we found a suggestive evidence of an association between traffic-related $PM_{2.5}$ absorbance and malignant brain tumors, and no association with overall or nonmalignant brain tumors.

Acknowledgements

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Table 1. Description of the 282,194 participants from 12 European cohorts included in the study.

| | Enrolment | Original N | Final N | % Total Cohort | Mean age, years | Person-years at risk | Mean follow-up time, years | N Total Brain Tumor | Tumor by Malignancy | | | Tumor by Location | |
									N Nonmalignant Brain Tumor	N Malignant Brain Tumor		N Tumor in Meninges	N Tumor in Brain
EPIC-Umeå, Sweden	1992-96	25,600	24,997	97%	45.9	335,293	14	-	-	63		21	34
HUBRO, Norway	2000-01	21,363	18,974	89%	48.2	161,377	9	39	19	20		12	21
CEANS, Sweden[a]	1992-2002	22,036	19,224	87%	56.5	199,113	11	-	-	37		21	16
DCH, Denmark	1993-97	38,064	37,250	98%	56.8	552,776	16	200	106	94		73	108
EPIC-NL, Netherlands[b]	1993-97	36,505	31,826	87%	50.3	375,875	12	64	23	41		18	43
VHM&PP, Austria	1985-2005	131,907	131,187	99%	41.3	2,332,547	19	-	-	176		-	182
EPIC-Varese, Italy	1993-97	11,893	10,571	89%	51.6	113,976	12	34	20	15		-	-
EPIC-Turin, Italy	1993-2008	8,774	8,165	93%	50.3	115,519	14	28	8	20		12	16

EPIC - European Prospective Investigation into Cancer and Nutrition; HUBRO - Oslo Health Study; CEANS - Cardiovascular Effects of Air Pollution and Noise in Stockholm; DCH - Danish Diet, Health and Cancer cohort; VHM&PP - Vorarlberg Health Monitoring and Prevention Programme; [a]Pooled data from the 4 cohorts from Stockholm, Sweden: SNACK-K, SALT/Twin gene, 60 y/IMPROVE, and SDPP; [b]Pooled data from 2 Dutch cohorts: EPIC MORGEN and EPIC PROSPECT.

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Table 2. Mean and standard deviation of the air pollution and traffic intensity levels at the 282,194 participants addresses in 12 European cohorts.

Cohort	$PM_{2.5}$, µg/m^3	$PM_{2.5}$ absorbance, 10^{-5}/m	PM_{10}, µg/m^3	PM_{Coarse}, µg/m^3	NO_2, µg/m^3	NO_x, µg/m^3	Traffic intensity on the nearest road (vehicles/day)
EPIC-Umeå, Sweden	-	-	-	-	5.3 (2.5)	8.8 (5.8)	849 (1,521)
HUBRO, Norway	8.9 (1.3)	1.2 (0.3)	13.5 (3.1)	4.0 (2.0)	20.9 (8.0)	38.2 (15.5)	2,509 (5,098)
CEANS, Sweden[a]	7.1 (1.3)	0.6 (0.2)	14.7 (4.1)	7.1 (3.1)	10.8 (4.6)	19.1 (10.2)	1,557 (4,494)
DCH, Denmark	11.3 (0.8)	1.2 (0.2)	17.2 (1.9)	5.7 (1.0)	16.5 (7.0)	27.2 (18.5)	3,109 (7,412)
EPIC-NL, Netherlands[b]	16.9 (0.6)	1.4 (0.2)	25.4 (1.5)	8.5 (0.9)	25.2 (6.2)	37.9 (12.3)	1,290 (3,797)
VHM&PP, Austria	13.6 (1.2)	1.7 (0.2)	20.7 (2.4)	6.7 (0.9)	20.0 (5.5)	40.1 (9.6)	1,718 (3,647)
EPIC-Varese, Italy	-	-	-	-	43.4 (17.3)	85.9 (41.9)	-
EPIC-Turin, Italy	30.2 (1.6)	3.1 (0.4)	46.6 (4.1)	16.6 (2.7)	53.0 (10.3)	96.1 (20.3)	4,044 (9,596)

EPIC - European Prospective Investigation into Cancer and Nutrition; HUBRO - Oslo Health Study; CEANS - Cardiovascular Effects of Air Pollution and Noise in Stockholm; DCH - Danish Diet, Health and Cancer cohort; VHM&PP - Vorarlberg Health Monitoring and Prevention Programme; [a]Pooled data from the 4 cohorts from Stockholm, Sweden: SNACK-K, SALT/Twin gene, 60 y/IMPROVE, and SDPP; [b]Pooled data from 2 Dutch cohorts: EPIC MORGEN and EPIC PROSPECT.

Table 3. Association between exposure to air pollution and malignant brain tumor incidence in 12[a] European cohorts.

	Fixed increase	N cohorts	N	Model 1[c] HR (95% CI)	Model 2[d] HR (95% CI)	Model 3[e] HR (95% CI)	P value Model 3	I^2 (%) (p value)
$PM_{2.5}$	5 µg/m^3	10[b]	246,626	1.04 (0.66-1.63)	1.01 (0.64-1.60)	0.98 (0.62-1.56)	0.94	0.0 (0.44)
$PM_{2.5}$ absorbance	10^{-5}/m	10[b]	246,626	1.76 (0.90-3.43)	1.72 (0.91-3.25)	1.67 (0.89-3.14)	0.11	39.9 (0.14)
PM_{10}	10 µg/m^3	10[b]	246,626	1.17 (0.73-1.87)	1.15 (0.74-1.78)	1.15 (0.72-1.83)	0.55	13.8 (0.33)
PM_{coarse}	5 µg/m^3	10[b]	246,626	1.03 (0.72-1.47)	1.02 (0.71-1.46)	1.00 (0.69-1.45)	0.99	0.0 (0.82)
NO_2	10 µg/m^3	12[a]	282,194	1.04 (0.82-1.33)	1.05 (0.83-1.32)	1.04 (0.82-1.31)	0.75	55.2 (0.03)
NO_x	20 µg/m^3	12[a]	282,194	1.06 (0.85-1.31)	1.06 (0.86-1.30)	1.05 (0.86-1.28)	0.63	47.8 (0.06)
Traffic intensity	5,000mv/day	10[b]	282,194	1.08 (1.00-1.16)	1.07 (0.99-1.16)	1.08 (0.99-1.16)	0.07	0.0 (0.75)

[a]EPIC-Umeå, CEANS (pooled data from the 4 cohorts from Stockholm, Sweden: SNACK-K, SALT/Twin gene, 60 y/IMPROVE, and SDPP), HUBRO, DCH, EPIC-NL (pooled data from 2 cohorts: EPIC-MORGEN and EPIC-PROSPECT), VHM&PP, EPIC-Varese, and EPIC-Turin; [b]CEANS (pooled data from the 4 cohorts from Stockholm, Sweden: SNACK-K, SALT/Twin gene, 60 y/IMPROVE, and SDPP), HUBRO, DCH, EPIC-NL (pooled data from 2 cohorts: EPIC-MORGEN and EPIC-PROSPECT), VHM&PP, and EPIC-Turin.
[c]Adjusted for age, sex and year of enrolment; [d]Model 1plus educational, and occupation in petrochemical industry; [e]Model 2 plus area-level socioeconomic status.

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Table 4. Association[a] between long-term exposure to air pollution and beingn and total brain tumor incidence in six[a] European cohorts.

	Fixed increase	N cohorts	N	Bening brain tumor HR (95% CI)	P value	I^2 (%) (p value)	Total brain tumor HR (95% CI)	P value	I^2 (%) (p value)
$PM_{2.5}$	5 µg/m³	5[b]	96,215	1.12 (0.46-2.73)	0.81	0.0 (0.39)	1.13 (0.61-2.09)	0.69	0.0 (0.51)
$PM_{2.5}$ absorbance	10^{-5}/m	5[b]	96,215	1.01 (0.38-2.71)	0.98	49.8 (0.11)	1.58 (0.73-3.40)	0.25	63.6 (0.04)
PM_{10}	10 µg/m³	5[b]	96,215	0.54 (0.14-2.13)	0.38	60.3 (0.05)	0.97 (0.36-2.57)	0.95	68.3 (0.02)
PM_{coarse}	5 µg/m³	5[b]	96,215	0.51 (0.24-1.10)	0.08	0.0 (0.68)	0.87 (0.55-1.38)	0.56	0.0 (0.68)
NO_2	10 µg/m³	6[c]	106,786	0.95 (0.72-1.267	0.73	50.9 (0.09)	1.04 (0.83-1.31)	0.74	67.0 (0.02)
NO_x	20 µg/m³	6[c]	106,786	0.97 (0.75-1.25)	0.80	49.3 (0.10)	1.01 (0.84-1.22)	0.91	59.6 (0.04)
Traffic intensity	5,000 v/day	5[b]	96,215	1.07 (0.97-1.18)	0.17	0.0 (0.82)	1.07 (1.00-1.14)	0.04	0.0 (0.46)

P value – for Model 3; [a]Model 3, adjusted for age, sex, year of enrolment, education, occupation in petrochemical industry, and area-level socioeconomic status; [b]HUBRO, DCH, EPIC-NL (which includes 2 cohorts: EPIC-MORGEN and EPIC-PROSPECT), and EPIC-Turin; [c]HUBRO, DCH, EPIC-NL (pooled data from 2 Dutch cohorts: EPIC-MORGEN and EPIC-PROSPECT), EPIC-Varese, and EPIC-Turin;

Figure 1. Adjusted associations between malignant brain tumor and $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10}, and PM_{coarse} (main Model 3) in ten European cohorts (CEANS (pooled data from the 4 cohorts from Stockholm, Sweden: SNACK-K, SALT/Twin gene, 60 y/IMPROVE, and SDPP), HUBRO, DCH, EPIC-NL (pooled data from 2 cohorts: EPIC-MORGEN and EPIC-PROSPECT), VHM&PP, and EPIC-Turin) results from cohort-specific analyses and random-effects analyses.

Figure 2. Adjusted associations between malignant brain tumor and NO_2, NO_x, and traffic intensity on the nearest road (main Model 3) in 12 European cohorts ([a]EPIC-Umeå, CEANS (pooled data from the 4 cohorts from Stockholm, Sweden: SNACK-K, SALT/Twin gene, 60 y/IMPROVE, and SDPP), HUBRO, DCH, EPIC-NL (pooled data from 2 cohorts: EPIC-MORGEN and EPIC-PROSPECT), VHM&PP, EPIC-Varese, and EPIC-Turin) results from cohort-specific analyses and random-effects analyses.
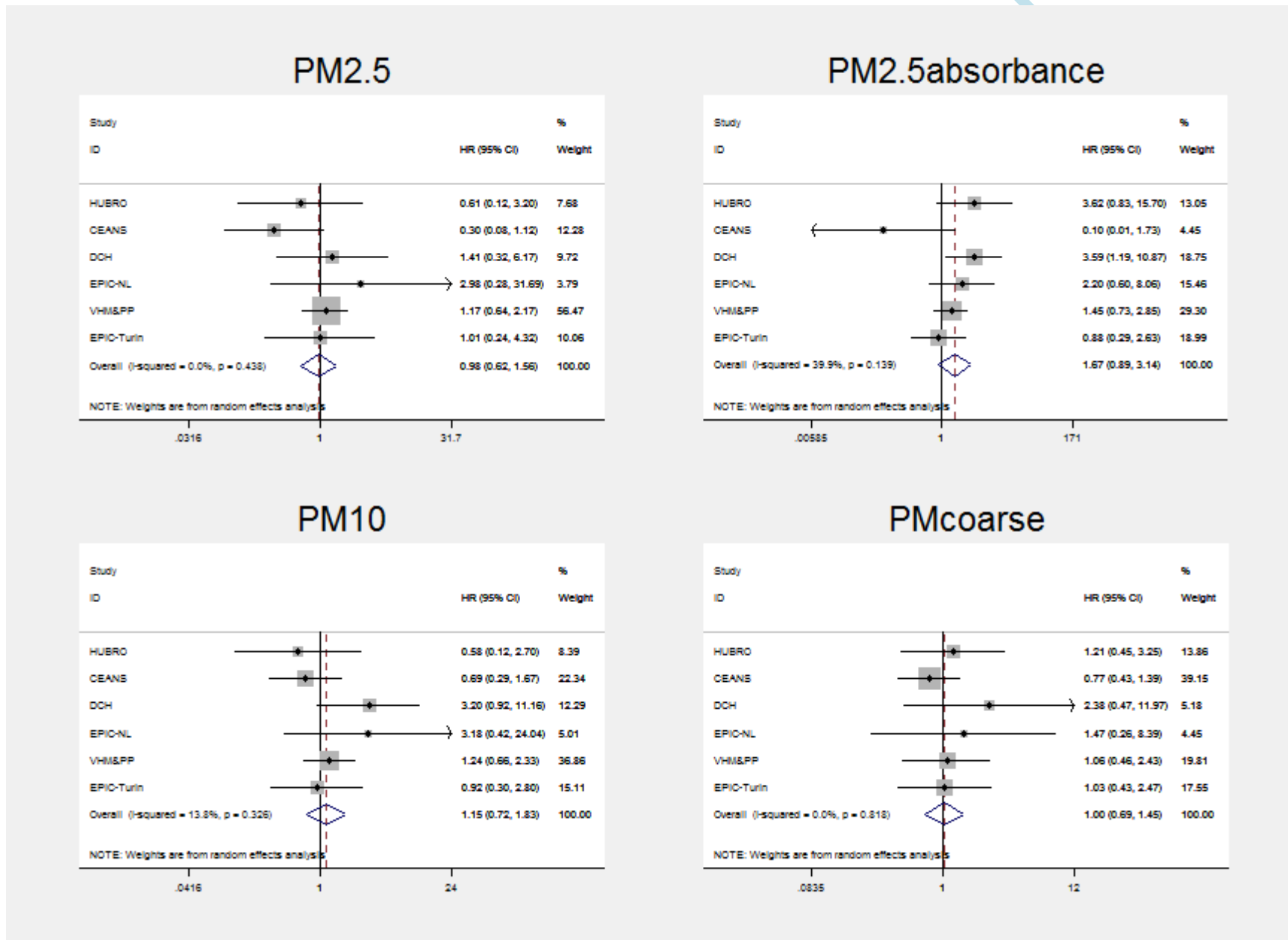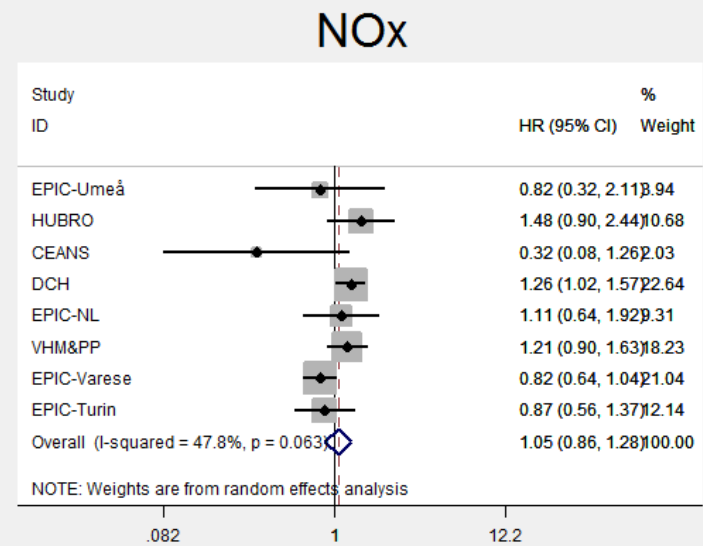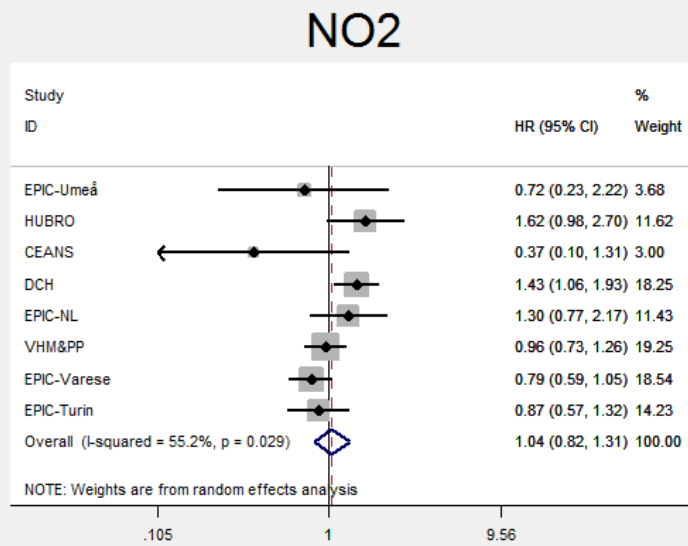
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Figure 1

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Figure 2

NO2

Study ID	HR (95% CI)	% Weight
EPIC-Umeå	0.72 (0.23, 2.22)	3.68
HUBRO	1.62 (0.98, 2.70)	11.62
CEANS	0.37 (0.10, 1.31)	3.00
DCH	1.43 (1.06, 1.93)	18.25
EPIC-NL	1.30 (0.77, 2.17)	11.43
VHM&PP	0.96 (0.73, 1.26)	19.25
EPIC-Varese	0.79 (0.59, 1.05)	18.54
EPIC-Turin	0.87 (0.57, 1.32)	14.23
Overall (I-squared = 55.2%, p = 0.029)	1.04 (0.82, 1.31)	100.00

NOTE: Weights are from random effects analysis

.105   1   9.56

NOx

Study ID	HR (95% CI)	% Weight
EPIC-Umeå	0.82 (0.32, 2.11)	3.94
HUBRO	1.48 (0.90, 2.44)	10.68
CEANS	0.32 (0.08, 1.26)	2.03
DCH	1.26 (1.02, 1.57)	22.64
EPIC-NL	1.11 (0.64, 1.92)	9.31
VHM&PP	1.21 (0.90, 1.63)	18.23
EPIC-Varese	0.82 (0.64, 1.04)	21.04
EPIC-Turin	0.87 (0.56, 1.37)	12.14
Overall (I-squared = 47.8%, p = 0.063)	1.05 (0.86, 1.28)	100.00

NOTE: Weights are from random effects analysis

.082   1   12.2

Trafnear and Brain cancer

Study ID	HR (95% CI)	% Weight
EPIC-Umeå	1.10 (0.52, 2.30)	1.11
HUBRO	0.93 (0.56, 1.57)	2.24
CEANS	0.48 (0.12, 1.90)	0.33
DCH	1.10 (1.00, 1.21)	69.33
EPIC-NL	0.96 (0.61, 1.50)	3.01
VHM&PP	1.09 (0.91, 1.31)	19.07
EPIC-Turin	0.87 (0.61, 1.24)	4.90
Overall (I-squared = 0.0%, p = 0.746)	1.08 (0.99, 1.16)	100.00

NOTE: Weights are from random effects analysis

.124   1   8.07