Components of particulate matter air-pollution and brain tumors

Harbo Poulsen, Aslak; Arthur Hvidtfeldt, Ulla; Sørensen, Mette; Puett, Robin; Ketzel, Matthias; Brandt, Jørgen; Christensen, Jesper H.; Geels, Camilla; Raaschou-Nielsen, Ole

Published in:
Environment International

DOI:
10.1016/j.envint.2020.106046

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Harbo Poulsen, A., Arthur Hvidtfeldt, U., Sørensen, M., Puett, R., Ketzel, M., Brandt, J., Christensen, J. H., Geels, C., & Raaschou-Nielsen, O. (2020). Components of particulate matter air-pollution and brain tumors. *Environment International*, *144*, [106046]. https://doi.org/10.1016/j.envint.2020.106046

Environment International 144 (2020) 106046

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Components of particulate matter air-pollution and brain tumors

Aslak Harbo Poulsen[a,*], Ulla Arthur Hvidtfeldt[a], Mette Sørensen[a,b], Robin Puett[c,a], Matthias Ketzel[d,e], Jørgen Brandt[d], Jesper H. Christensen[d], Camilla Geels[d], Ole Raaschou-Nielsen[a,d]

[a] Danish Cancer Society Research Center, Copenhagen, Denmark
[b] Department of Natural Science and Environment, Roskilde University, Roskilde, Denmark
[c] Maryland Institute for Applied Environmental Health, University of Maryland School of Public Health, MD, USA
[d] Department of Environmental Science, Aarhus University, Roskilde, Denmark
[e] Global Centre for Clean Air Research (GCARE) Department of Civil and Environmental Engineering University of Surrey, Guildford, United Kingdom

ARTICLE INFO

Handling Editor: Mark Nieuwenhuijsen

Keywords:
Air-pollution
Particulate matter
Brain tumors
Epidemiology

ABSTRACT

Background: Air pollution is an established carcinogen. Evidence for an association with brain tumors is, however, inconclusive. We investigated if individual particulate matter constituents were associated with brain tumor risk.

Methods: From comprehensive national registers, we identified all (n = 12 928) brain tumor cases, diagnosed in Denmark in the period 1989–2014, and selected 22 961 controls, matched on age, sex and year of birth. We established address histories and estimated 10-year mean residential outdoor concentrations of particulate matter < 2.5 μm, primarily emitted black carbon (BC) and organic carbon (OC), and combined carbon (OC/BC), as well as secondary inorganic and organic PM air pollutants from a detailed dispersion model. We used conditional logistic regression to calculate odds ratios (OR) per inter quartile range (IQR) exposure. We adjusted for income, marital and employment status as well as area-level socio-demographic characteristics.

Results: Total tumors of the brain were associated with OC/BC (OR: 1.053, 95%CI: 1.005–1.103, per IQR). The data suggested strongest associations for malignant tumors with ORs per IQR for OC/BC, BC and OC of 1.063 (95% CI: 1.007–1.123), 1.036 (95% CI: 1.006–1.067) and 1.030 (95%CI: 0.979–1.085), respectively. The results did not indicate adverse effects of other PM components.

Conclusions: This large, population based study showed associations between primary emitted carbonaceous particles and risk for malignant brain tumors. As the first of its kind, this study needs replication.

1. Background

Brain tumors constitute a heterogeneous group of tumors. The incidence differs by tumor type, sex, race and age (Barnholtz-Sloan et al., 2018; McNeill, 2016). Hereditary symptoms have been estimated to account for around 5% of these tumors (Barnholtz-Sloan et al., 2018). The only established exogenous risk factor is ionizing radiation. Allergic and atopic conditions (Barnholtz-Sloan et al., 2018; Wang et al., 2016) as well as a range of medications (Amirian et al., 2019; Tong et al., 2012; Andersen et al., 2013; Andersen et al., 2015) have been investigated as potential risk factors, with strongest evidence for a protective association with allergic and atopic conditions. Some studies have indicated an association with pesticides or fertilizers (Carles et al., 2017; Samanic et al., 2008; Bassil et al., 2007; Schmidt et al., 2008) but the results remain inconclusive. At present, no occupational or environmental risk factors have been conclusively established (McNeill, 2016; Gomes et al., 2011).

Air pollution consists of a complex array of substances and has been classified as “carcinogenic to humans” by the International Agency for Research on Cancer (Loomis et al., 2013; Benbrahim-Tallaa et al., 2012) based primarily on mechanistic studies and epidemiological research demonstrating associations with lung cancer. Air pollution exposures have also been associated with stroke and impaired cognitive function (Bourdrel et al., 2017; Suades-Gonzalez et al., 2015; Schraufnagel et al., 2019; Schraufnagel et al., 2019) and neuroimaging has shown links with reduced brain white matter volume (de Prado et al., 2018). Ambient air pollution may be indirectly mutagenic/carcinogenic via oxidative stress or induced inflammation, but may also be directly mutagenic and may reach organs beyond the respiratory tract (Genc et al., 2012; Block and Calderon-Garciduenas, 2009). Studies suggest that

* Corresponding author at: Danish Cancer Society Research Centre, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark.
E-mail address: Aslak@Cancer.DK (A. Harbo Poulsen).

https://doi.org/10.1016/j.envint.2020.106046
Received 11 November 2019; Received in revised form 5 August 2020; Accepted 6 August 2020
Available online 25 August 2020

ultrafine particles (UFP < 0.1 μm) may enter the blood stream and cross the blood–brain barrier and particles may also reach the brain via the olfactory nerve (Genc et al., 2012; Oberdorster et al., 2004). One recent study has found UFP assessed at postal code level, to be associated with risk of malignant brain tumors (Weichenthal et al., 2020). Several other studies of air pollution and intracranial CNS tumors show inconsistent results (Weichenthal et al., 2020; Boeglin et al., 2006; Turner et al., 2017; McKean-Cowdin et al., 2009; Raaschou-Nielsen et al., 2011; Poulsen et al., 2016; Jorgensen et al., 2016; Andersen et al., 2018). The studies differed with regard to air pollutants investigated and case definition. The European ESCAPE project reported suggestive evidence of an association between malignant tumors and exposure to $PM_{2.5}$ absorbance, a quantity closely related to black carbon (BC) (Andersen et al., 2018). Particulate matter < 2.5 μm ($PM_{2.5}$) has been investigated in several studies but, only one has reported suggestions of a positive association with CNS tumors (Jorgensen et al., 2016). We have recently conducted the largest study to date on the issue and found indications that $PM_{2.5}$) was associated with risk for malignant non-glioma tumors of the brain and that BC, was associated with risk of glioma and non-glioma brain tumors

As our previous study pointed towards particulate matter pollution as a possible risk factor for tumors of the brain, we designed the present study to investigate if specific $PM_{2.5}$ constituents could better capture association with brain tumor risk. We used the same nationwide case-control setup as in our previous study and assessed the constituents from the same state-of-the-art exposure model.

2. Methods

The study was conducted in Denmark (population approx. 5.4 million), where all citizens can be followed across all health and administrative registers via a unique personal identification number introduced in 1968 (Schmidt et al., 2014; Thygesen et al., 2011).

2.1. Case ascertainment

We identified all Danes, aged 20 years or above, with a primary brain tumor in the period 1989 to 2014 from the Danish Cancer Register, that holds nearly complete records of all cancer diagnoses in Denmark since 1943 (Gjerstorff, 2011; Storm et al., 1997). We excluded cases that had other cancer diagnoses (except non-melanoma skin cancer) prior to their brain tumor. We included all brain tumors (ICD10: C70.0, C71.0–C71.9, C72.2, C72.5, D32.0, D33.0–D33.3, D42.0, D43.0–D43.3) and also classified tumors according to malignancy: non-malignant and malignant and the latter group was further divided as glioma (ICD-O3 morphology codes 9380/0–9480/9 within ICD10: C71.0–C71.9, D33.0–D33.3 D43.0–D43.2), and other and unspecified malignant tumors.

2.2. Sampling of controls

For each case, we sampled two random controls, matched on sex and month and year of birth (Kahn et al., 2019), and alive and without a cancer diagnosis at the time of diagnosis for their matched case (index-date) from the Danish Civil Registration System, which covers all residents in Denmark (Pedersen, 2011).

2.3. Exclusion criteria

We excluded cases and controls who at index-date had: 1) No recorded address in Denmark, 2) < 80% geocodable address history for the ten years preceding index date and 3) missing information on marital status, employment status, household disposable income or area of residence (parish). For some of these exclusion criteria, information was available only after initial matching and we excluded cases left without controls or vice versa, after all other exclusions.

2.4. Exposure assessment

Address histories since 1979 were obtained from the Danish Civil Registration System for all cases and controls (Pedersen, 2011). Addresses were geocoded and front door air pollutant concentrations at 2 m height were calculated using the Danish DEHM/UBM/AirGIS modelling system (Kahn et al., 2019; Brandt et al., 2001; Jensen et al., 2017). This multi-scale integrated air pollution model system incorporates detailed time-varying information based on three air pollution contributions. 1) The regional background, modelled with the DEHM model(Brandt et al., 2012) covering the northern hemisphere, with an increasing spatial resolution going from 150 km × 150 km far from Denmark to 5.6 km × 5.6 km over Denmark and based on international and national emission inventories (Cooperative programme for monitoring an evaluation of long-range transmission of air pollutants in Europe, and the national Danish emissions based on the SPREAD-model(Plejdrup et al., november 2018 2018.). Natural emissions are included via specific sub-models, included in DEHM(Plejdrup et al., november 2018 2018.). DEHM is driven by meteorology provided by the Weather Research and Forecasting (WRF) Model (https://www.mmm.ucar.edu/weather-research-and-forecasting-model) 2) the urban background modelled with the UBM model(Brandt et al., 2003) covering Denmark with a resolution of 1 km × 1 km, based on high resolution emission data for Denmark for all emission sectors (the national Danish emissions based on the SPREAD-model (Plejdrup et al., 2018), land-use data and building heights. The UBM model uses input data from the DEHM model for boundary conditions for regional air pollution to the local scale model. 3) the street-level local air pollution calculated with the OSPM model (Ketzel et al., 2012), based on street-level information on traffic type/intensity (from the Danish GIS traffic database (Jensen et al., 2019) combined with emission factors (from the European COPERT model) and taking into account meteorology (From DEHM model) as well as street and building configuration (originating from a GIS map containing all building footprints and heights). The model system is described in detail elsewhere (Kahn et al., 2019; Hvidtfeldt et al., 2019), the three models of the system all operate at 1-hour time resolution. Subsequently results are aggregated to yearly mean values of individual components as well as total $PM_{2.5}$, which is the sum of a number of different particle components that are either emitted directly (primary) or are formed in the atmosphere (secondary) due to both anthropogenic and natural emissions.

Overall, the spatial resolution of the secondary inorganic (SIA) and organic chemical (SOA) species is 5.6 km × 5.6 km (DEHM model). These species do not include local sources and are characterized by longer life times in the atmosphere and smoother spatial gradients and therefore it is not optimal to include these species in the local models, operating at scales smaller than 5.6 km. The local emitted species; BC and OC are included in UBM and modelled with a spatial resolution of 1 km × 1 km. $PM_{2.5}$ and the traffic dominated BC is modelled using OSPM at a spatial resolution of about 1 m for addresses located near busy streets with daily traffic above 500 vehicles/day. We include in this study the total $PM_{2.5}$ as well as a number of the components: black carbon (BC), primary organic carbon (OC, including the total mass of organic chemical compound not only carbon mass) and total primary emitted carbonaceous particles (OC/BC - the sum of the two former constituents), secondary organic aerosols (SOA) and secondary inorganic aerosols (SIA). For primary emitted $PM_{2.5}$ and BC, where traffic is a non-negligible source, the modeled values included street level variation, for other components regional exposure levels were interpolated to estimate exposure at each address. For each pollutant and each individual, we calculated a time-weighted average (TWA) concentration over residential addresses during the 10 years preceding the index date.

2.5. Covariates

Brain tumor risk varies by age and gender and some studies have suggested variation by ethnicity. For symptom-free tumors, the likelihood of being diagnosed may depend on the likelihood of receiving brain scans for other reasons. In addition, the likelihood of receiving a very specific tumor diagnosis rather than a more general diagnosis could conceivably vary. Such variation may occur both at the individual level and at the area level since quality and praxis of primary and secondary health care might be different in different areas of Denmark.

From Statistics Denmark, we obtained yearly individual-level information on disposable income, marital status, employment status and country of origin. We also obtained yearly information, calculated for all Danish parishes describing percentage of adult parish population: in lowest income quartile, unemployed, retired, doing manual labor, owning their own dwelling, living in social housing, being of Danish origin, previously convicted (theft, robbery, vandalism or violence), single parent families and having basic education as highest attained education level. In 1996, a total of 2160 parishes existed with a median number of 1032 inhabitants (range 33–35,979) and a mean area of 16.2 km^2 (range 0.1–126.2). As Denmark is a small, relatively homogeneous country with universal free health care it is not readily apparent what factors might relate to area level variations in health praxis and we therefore included a range of socio-demographic indicators, which alone or in combination could be related to such variation. Both the individual and area level covariates might also be related to where participants live and therefore also to exposure.

To minimize potential effects of prodromal symptoms, we assessed covariates one year before index date.

2.6. Statistical methods

We used conditional logistic regression to calculate odds ratios (OR) per inter quartile range (IQR). We tested for deviations from linearity for each air pollutant by likelihood ratio testing comparing models with and without the second-degree polynomial of the pollutant and found no significant deviations.

We analyzed data in three models: a crude model only taking into account the matching factors, a model additionally adjusting for individual-level covariates, and a final, main model, which also included parish-level covariates. Individual-level covariates included personal income in deciles (calculated annually based on the distribution among controls), marital status (currently living together, formerly married or never married) and employment status (retired, unemployed, blue-collar, low-level white-collar, high-level white-collar). Area level covariates were included linearly. Each pollutant was investigated separately and fully adjusted two-pollutant models including each of the other pollutants.

We used log-likelihood tests to evaluate interaction with sex, calendar time (before after years 2000) and living in greater Copenhagen area (Y/N) without finding consistent evidence of interaction across outcomes or exposures (Supplement table 1).

Statistical analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

In the years 1989 to 2014, 13 802 adults where diagnosed with a primary brain tumor in Denmark. For these cases we matched 27 604 controls. Cases (16 / 0.1%) and controls (2286 / 8.3%) not living in Denmark at the time of diagnosis were excluded. We also excluded cases (542 / 3.9%) and controls (1342 / 4.9%), who in the 10 years preceding index date had less than 80% geocodable Danish address history. Cases (33 / 0.2%) and controls (88 / 0.3%) lacking data on one or more covariates were also excluded. Cases (445 / 2.1%) and controls (1529 / 3.4%) left without matched cases or controls and were

Table 1
Descriptive characteristics of brain tumor cases and matched controls in Denmark, 1989–2014.

	Cases		Controls	
	n	%	n	%
TOTAL	12,928	100%	22,961	100%
Individual level factors:				
Female	5,891	53%	10,722	54%
Age at index date[a]				
median	62		63	
10 pctl	37		38	
90 pctl	80		81	
Region of origin				
Denmark	12,439	96%	21,924	95%
Non-Western	163	2%	378	2%
Western	326	3%	658	3%
Marital status				
Married	7,811	61%	13,472	59%
Previously married	3,132	25%	5,963	26%
Never married	1,985	14%	3,526	14%
Occupational status				
Unemployed	516	4%	873	4%
Blue collar	2,951	23%	5,000	22%
Low level white collar	2,079	16%	3,574	16%
High level white collar	989	8%	1,772	8%
Retired	6,393	49%	11,742	50%
Disposable income (DKK)				
median	122,592		119,929	
10 pctl	60,202		58,183	
90 pctl	251,651		250,410	
Parish level factors:				
% of population with only basic education				
median	28		28	
10 pctl	15		15	
90 pctl	42		43	
% of population in manual labour				
median	29		29	
10 pctl	18		18	
90 pctl	38		38	
% of population retired				
median	6		6	
10 pctl	3		3	
90 pctl	11		11	
% of population unemployed				
median	4		4	
10 pctl	1		1	
90 pctl	8		8	
% of population in 1st income quartile				
median	10		10	
10 pctl	5		5	
90 pctl	18		18	
Parish_dwell_ownalmen_pct				
median	13		13	
10 pctl	0		0	
90 pctl	43		43	
% of population owning own dwelling				
median	65		66	
10 pctl	30		29	
90 pctl	92		92	
% single-parent families				
median	5		5	
10 pctl	3		3	
90 pctl	7		7	
% of population of Danish origin				
median	94		95	
10 pctl	85		85	
90 pctl	98		98	
% of population previously convicted				
median	0		0	
10 pctl	0		0	
90 pctl	1	1	1	

a: index date = date of diagnosis of matched case.

Table 2
Descriptive data on 10-year time weighted average air pollutants among brain tumor cases and controls in Denmark, 1989–2014.

10 year time-weighted mean exposure		Percentiles									
		min	1st	5th	10th	25th	50th	75th	90th	95th	99th	max
PM2.5 (µg/m3)												
	Cases	9.93	11.83	12.87	13.44	14.7	16.99	20.26	22.64	23.68	26.30	41.46
	Controls	9.91	11.86	12.89	13.52	14.84	17.14	20.36	22.61	23.66	26.42	37.09
OC/BC (µg/m3)												
	Cases	0.95	1.20	1.36	1.46	1.66	2.03	2.84	3.55	3.82	4.95	14.70
	Controls	0.96	1.20	1.36	1.46	1.66	2.02	2.81	3.52	3.80	4.97	9.16
BC (µg/m3)												
	Cases	0.30	0.38	0.43	0.46	0.56	0.72	0.95	1.23	1.53	2.47	13.64
	Controls	0.29	0.37	0.43	0.47	0.55	0.72	0.94	1.21	1.50	2.43	8.00
OC (µg/m3)												
	Cases	0.64	0.79	0.90	0.97	1.09	1.28	1.78	2.43	2.63	2.80	2.93
	Controls	0.64	0.79	0.90	0.97	1.09	1.27	1.75	2.41	2.62	2.79	2.92
SIA (µg/m3)												
	Cases	3.51	4.37	4.76	5.07	5.82	7.45	9.82	11.56	12.27	13.53	14.93
	Controls	3.39	4.37	4.77	5.10	5.90	7.61	9.99	11.61	12.27	13.56	15.00
SOA (µg/m3)												
	Cases	0.20	0.24	0.26	0.27	0.28	0.31	0.34	0.36	0.37	0.38	0.39
	Controls	0.20	0.24	0.26	0.27	0.28	0.31	0.34	0.36	0.37	0.38	0.39

excluded. The final study population consisted of 12 928 cases and 22 961 controls. The majority (n = 7315) of tumors were glioma (by definition histologically verified). For the two other groups, malignant non-glioma (n = 2 301) and non-malignant tumors (n = 3123), 84% and 80% of tumors lacked histological verification.

Table 1 shows only minor differences between cases and controls regarding the socioeconomic factors. For all pollutants, the distribution of exposure was very similar for cases and controls (Table 2). For total OC/BC, BC and $PM_{2.5}$ the highest observed exposure levels were higher for cases.

$PM_{2.5}$ and SIA were strongly correlated (Table 3). The correlations between SIA and other pollutants never exceeded 0.21. SOA was most closely correlated with OC and OC/BC. OC/BC was strongly correlated with BC and OC, whereas these two were only moderately correlated.

For total tumors of the brain, the OR per IQR was 0.985 (95%CI: 0.906–1.071) for $PM_{2.5}$ and 1.053 (95%CI: 1.005–1.103) for OC/BC. The corresponding OR for BC and OC where 1.026 (95%CI: 1.001–1.052) and 1.034 (95%CI: 0.989–1.0381), respectively (Table 4). When included in the same model the OR per IQR for BC and OC were 1.022 (95%CI: 0.996–1.049) and 1.021 (95%CI: 0.975–1.070), respectively (Table 5).

Non-malignant tumors were inversely associated with SIA (OR: 0.687, 95%CI: 0.522–0.905 per IQR) (Table 4). The corresponding OR for $PM_{2.5}$ was 0.886 (95% CI: 0.753.1.043).

Malignant tumors were associated with OC/BC (OR: 1.063, 95%CI: 1.007–1.123, per IQR), BC (OR: 1.036, 95%CI: 1.006–1.067, per IQR), OC (OR: 1.030, 95%CI: 0.979–1.085 per IQR) and $PM_{2.5}$ (OR: 1.028, 95%CI: 0.932–1.134) (Table 4). In a two pollutant model, the ORs per IQR for BC and OC were 1.034 (95%CI: 1.003–1.066) and 1.013 (95% CI: 0.959–1.069) (Table 5).

Glioma was associated with OC/BC (OR: 1.067, 95%CI: 1.001–1.137, per IQR), BC (OR: 1.029 (95%CI: 0.994–1.066) and OC (OR: 1.050, 95%CI: 0.989–1.114) (Table 4). For $PM_{2.5}$, the OR was 0.944 (95%CI: 0.840–1.061). In a two-pollutant model with OC and BC the ORs where 1.037 (95% CI: 0.974–1.105) and 1.022 (95% CI: 0.985–1.060) respectively (Table 5). Glioma was inversely associated with SIA (OR: 0.805, 95% CI: 0.671–0.967) (Table 4). In a two-pollutant model including OC/BC and SIA, ORs were similar to those from single pollutant models (Table 5).

For malignant non-glioma tumors of the brain, we observed the strongest associations in the study for $PM_{2.5}$ (OR: 1.266, 95%CI: 1.053–1.523) and SIA (OR: 1.663, 95%CI: 1.216–2.274). For BC and OC/BC the OR per IQR were 1.052 (95%CI: 0.996–1.111) and 1.048 (95%CI: 0.940–1.168), respectively (Table 4). In the two-pollutant model including $PM_{2.5}$ and BC the OR per IQR for BC decreased to null whereas the OR for $PM_{2.5}$ was 1.122 (95%CI: 0.906–1.390) (Table 5). In a two pollutant model including $PM_{2.5}$ and SIA the ORs per IQR were 1.299 (95%CI: 0.967–1.746) and 1.510 (95%CI: 1.052–2.166), respectively.

Fully-adjusted models gave stronger associations between several pollutants and non-glioma malignant tumors but in general, adjustment had little effect on the risk estimates (Supplement table 2).

Graphical presentation of the functional form of the exposure–response associations is provided as supplement figure 1–5.

4. Discussion

In this nationwide study of brain tumors in Denmark, we found indications that carbonaceous particles was positively associated with malignant glioma and malignant non-glioma tumors of the brain, as well as the total group of malignant brain tumors. In two-pollutant models, OC ORs generally changed towards unity whereas the BC

Table 3
Spearman rank correlation coefficients for 10-year time weighted average air pollutant concentrations.

	SOA (µg/m^3)	SIA (µg/m^3)	OC (µg/m^3)	BC (µg/m^3)	OC/BC (µg/m^3)	PM25 (µg/m^3)
Air pollutants						
PM25 (µg/m^3)	0.10	0.93	0.31	0.50	0.41	1.00
OC/BC (µg/m^3)	0.72	0.14	0.95	0.93	1.00	0.41
BC (µg/m^3)	0.57	0.21	0.79	1.00	0.93	0.50
OC (µg/m^3)	0.77	0.07	1.00	0.79	0.95	0.31
SIA (µg/m^3)	−0.09	1.00	0.07	0.21	0.14	0.93
SOA (µg/m^3)	1.00	−0.09	0.77	0.57	0.72	0.10

Table 4
Fully adjusted[b], linear associations between time-weighted average air pollution (10 years before index date) and risk of brain tumors, Denmark 1989–2014.

			$PM_{2.5}$		OC/BC		BC		OC		SIA		SOA	
			IQR: 5.39		IQR: 1.16		IQR: 0.39		IQR: 0.67		IQR: 3.95		IQR: 0.05	
Tumor	Cases	Controls	OR[b]	95%CI	OR[b]	95%CI	OR[b]	95%CI	OR[b]	95%CI	OR[b]	95%CI	OR[b]	95%CI
Total brain tumors	12,928	22,960	0.985	(0.906–1.071)	1.053	(1.005–1.103)	1.026	(1.001–1.052)	1.034	(0.989–1.081)	0.888	(0.775–1.018)	1.007	(0.959–1.057)
Non-malignant	3,312	5,870	0.886	(0.753–1.043)	1.027	(0.938–1.125)	1.002	(0.955–1.051)	1.041	(0.953–1.138)	0.687	(0.522–0.905)	0.999	(0.907–1.100)
Malignant	9,616	17,090	1.028	(0.932–1.134)	1.063	(1.007–1.123)	1.036	(1.006–1.067)	1.030	(0.979–1.085)	0.968	(0.827–1.133)	1.009	(0.954–1.067)
Glioma	7,315	12,843	0.944	(0.840–1.061)	1.067	(1.001–1.137)	1.029	(0.994–1.066)	1.050	(0.989–1.114)	0.805	(0.671–0.967)	1.025	(0.961–1.094)
Non-glioma	2,301	4,247	1.266	(1.053–1.523)	1.048	(0.940–1.168)	1.052	(0.996–1.111)	0.969	(0.873–1.076)	1.663	(1.216–2.274)	0.955	(0.852–1.071)

a: interquartile range (IQR) calculated among all controls.
b: Matched on age, sex and month of birth and adjusted for marital status, occupational status, personal income, region of origin and area level information on % of parish population with income in lowest quartile, unemployed, manual labor, retired, basic education, living in social housing, owning their own dwelling, single parent families, previously convicted, of Danish origin.

estimates where less affected. This indicates that the observed associations with carbon particles might be mostly attributable to BC. However, one should be cautious with the interpretation of this result, as BC was modelled at address level whereas OC was modelled at regional level (5.6 km × 5.6 km). Also, ORs were consistently higher when considering OC/BC exposure rather than OC or BC alone. Therefore, while our data indicated BC to be the more important carbon particle our data do not allow firm conclusions.

The ESCAPE study found $PM_{2.5}$ absorbance, a proxy for BC/elemental carbon (Janssen et al., 2000), to be associated with elevated ORs for malignant intracranial CNS tumors, albeit with confidence intervals spanning the null, whereas there was no indication of an association with benign tumors. We have not found previous studies of organic carbon and brain tumor risk.

The SIAs were positively associated with risk of malignant non-glioma tumors of the brain and negatively associated with glioma and non-malignant tumors. We are not aware of plausible biological mechanisms that could explain these patterns. However, SIA levels in Denmark exhibit a declining gradient from south to north due to long-range transport from south. Therefore, exposure levels may differ between healthcare districts and several factors may suggest that the observed associations could relate to diagnostic practice rather than to the pollutants: 1) the range and distribution of SIA exposure among cases and controls was virtually identical. 2) The observed positive and negative associations more or less cancel each other out when analyzing all malignant tumors. 3) A large proportion of non-malignant tumors and non-glioma lack morphology information.

4.1. Strengths and limitations

A major strength of our study was the extensive and near complete Danish registers (Schmidt et al., 2014; Thygesen et al., 2011) that enabled inclusion of all registered cases diagnosed in Denmark over a 26-year period. The large number of cases allowed for investigation of CNS tumor subgroups. The Danish registers provided nearly complete address histories for the vast majority of participants. Combined with a state-of-the-art integrated air pollution system, the address data enabled estimation of TWA concentrations of outdoor pollution for almost all participants over the ten years prior to index date.

Our air pollution model has been evaluated against measured levels of SIA (Brandt et al., 2012), $PM_{2.5}$, BC and precursors of SOA with correlation coefficients ranging from 0.67 to 0.85 (Brandt et al., 2012; Hvidtfeldt et al., 2018; Zare et al., 2012). For SIA, $PM_{2.5}$ and BC the correlation coefficients were very similar. For SOA correlation coefficients ranged from 0.34 to 0.85 at measurement stations in Europa and the US (Zare et al., 2014), the wide range may reflect uncertainty relating to the primarily botanical sources and atmosphere chemistry. For OC it is a limitation that we could not account for address-specific variations in contributions from wood fire stoves and that no validation is presently available.

Non-differential exposure misclassification is inevitable and may have driven risk estimates towards the null and we cannot rule out that this may have masked associations with SOA. Also, if exposure misclassification differ by constituents, observed associations in two pollutant models may shift towards the better-modeled constituents (Zeger et al., 2000). This is a particular concern for OC were we contrary to other components could not model exposure on a scale reflecting the spatial variation of the major sources. We have previously found that a 10-year exposure time window before index date produced stronger association between air pollution and CNS tumors than longer or shorter windows, indicating that it better captures relevant aspects of exposure (Poulsen et al., 2016). However, the optimal time window, if one exists, remains elusive and exposure misclassification may therefore have driven results towards the null. We could not account for occupational exposures, but previous studies have found little or no effect of adjusting for occupation in the petrochemical industry

Table 5
Fully adjusted[a], linear associations between time-weighted average air pollution (10 years before index date) and risk of brain tumors from single- and two-pollutant models, Denmark 1989–2014.

	OR single pollutant	Model incl. PM2.5	Model incl. OC/BC	Model incl. SIA	Model incl. SOA	Model incl. BC	Model incl. OC
Brain							
PM2.5	0.985 (0.906–1.071)	–	0.898 (0.809–0.996)	1.033 (0.936–1.139)	0.983 (0.902–1.070)	0.844 (0.745–0.955)	0.970 (0.890–1.058)
OC/BC	1.053 (1.005–1.103)	1.092 (1.03–1.157)	–	1.050 (1.002–1.101)	1.079 (1.017–1.144)	1.037 (0.957–1.125)	1.068 (0.988–1.154)
SIA	0.888 (0.775–1.018)	0.864 (0.737–1.014)	0.897 (0.783–1.028)	–	0.889 (0.776–1.019)	0.891 (0.778–1.021)	0.896 (0.781–1.027)
SOA	1.007 (0.959–1.057)	1.009 (0.960–1.059)	0.96 (0.903–1.021)	1.004 (0.957–1.054)	–	0.996 (0.948–1.046)	0.949 (0.878–1.024)
BC	1.026 (1.001–1.052)	1.065 (1.026–1.106)	1.010 (0.967–1.054)	1.025 (1.000–1.051)	1.026 (1.001–1.053)	–	1.022 (0.996–1.049)
OC	1.034 (0.989–1.081)	1.037 (0.991–1.086)	0.983 (0.913–1.059)	1.030 (0.985–1.077)	1.074 (1.000–1.152)	1.021 (0.975–1.070)	–
Non-malignant							
PM2.5	0.886 (0.753–1.043)	–	0.788 (0.642–0.967)	0.988 (0.819–1.191)	0.884 (0.749–1.043)	0.749 (0.585–0.959)	0.866 (0.733–1.024)
OC/BC	1.027 (0.938–1.125)	1.115 (0.994–1.250)	–	1.016 (0.928–1.113)	1.044 (0.932–1.171)	1.079 (0.917–1.269)	0.983 (0.846–1.143)
SIA	0.687 (0.522–0.905)	0.695 (0.506–0.954)	0.690 (0.524–0.909)	–	0.686 (0.521–0.903)	0.687 (0.522–0.905)	0.694 (0.526–0.914)
SOA	0.999 (0.907–1.100)	1.011 (0.917–1.115)	0.971 (0.860–1.097)	0.988 (0.897–1.089)	–	0.998 (0.904–1.102)	0.914 (0.783–1.066)
BC	1.002 (0.955–1.051)	1.068 (0.993–1.149)	0.969 (0.890–1.056)	0.999 (0.953–1.049)	1.002 (0.954–1.053)	–	0.994 (0.945–1.046)
OC	1.041 (0.953–1.138)	1.059 (0.967–1.160)	1.055 (0.911–1.222)	1.028 (0.941–1.124)	1.111 (0.964–1.281)	1.045 (0.951–1.147)	–
Malignant							
PM2.5	1.028 (0.932–1.134)	–	0.945 (0.837–1.067)	1.055 (0.939–1.185)	1.026 (0.928–1.134)	0.881 (0.763–1.019)	1.016 (0.919–1.124)
OC/BC	1.063 (1.007–1.123)	1.083 (1.012–1.160)	–	1.063 (1.006–1.123)	1.093 (1.020–1.172)	1.022 (0.930–1.122)	1.105 (1.008–1.211)
SIA	0.968 (0.827–1.133)	0.925 (0.768–1.114)	0.979 (0.836–1.146)	–	0.970 (0.828–1.135)	0.972 (0.830–1.137)	0.975 (0.833–1.142)
SOA	1.009 (0.954–1.067)	1.007 (0.951–1.066)	0.955 (0.890–1.025)	1.009 (0.953–1.067)	–	0.994 (0.939–1.053)	0.961 (0.879–1.050)
BC	1.036 (1.006–1.067)	1.066 (1.020–1.114)	1.027 (0.976–1.079)	1.036 (1.006–1.067)	1.037 (1.006–1.069)	–	1.034 (1.003–1.066)
OC	1.030 (0.979–1.085)	1.029 (0.976–1.084)	0.956 (0.877–1.042)	1.030 (0.978–1.084)	1.060 (0.977–1.151)	1.013 (0.959–1.069)	–
Glioma							
PM2.5	0.944 (0.840–1.061)	–	0.829 (0.719–0.956)	1.026 (0.893–1.178)	0.934 (0.829–1.052)	0.776 (0.655–0.918)	0.919 (0.815–1.037)
OC/BC	1.067 (1.001–1.137)	1.133 (1.047–1.226)	–	1.062 (0.996–1.132)	1.083 (0.998–1.175)	1.066 (0.956–1.188)	1.068 (0.957–1.191)
SIA	0.805 (0.671–0.967)	0.788 (0.633–0.980)	0.813 (0.677–0.977)	–	0.808 (0.673–0.971)	0.808 (0.673–0.970)	0.813 (0.677–0.977)
SOA	1.025 (0.961–1.094)	1.033 (0.967–1.103)	0.976 (0.899–1.059)	1.021 (0.957–1.089)	–	1.014 (0.949–1.083)	0.963 (0.870–1.066)
BC	1.029 (0.994–1.066)	1.088 (1.032–1.146)	1.001 (0.943–1.062)	1.028 (0.993–1.065)	1.027 (0.991–1.065)	–	1.022 (0.985–1.060)
OC	1.050 (0.989–1.114)	1.060 (0.997–1.127)	0.999 (0.902–1.106)	1.044 (0.984–1.109)	1.079 (0.982–1.185)	1.037 (0.974–1.105)	–
Malignant non-glioma							
PM2.5	1.266 (1.053–1.523)	–	1.356 (1.070–1.719)	1.122 (0.906–1.390)	1.284 (1.066–1.547)	1.299 (0.967–1.746)	1.290 (1.069–1.556)
OC/BC	1.048 (0.940–1.168)	0.938 (0.816–1.077)	–	1.061 (0.951–1.183)	1.116 (0.976–1.275)	0.901 (0.747–1.087)	1.191 (1.007–1.409)
SIA	1.663 (1.216–2.274)	1.510 (1.052–2.166)	1.683 (1.229–2.305)	–	1.652 (1.208–2.261)	1.669 (1.220–2.284)	1.655 (1.208–2.267)
SOA	0.955 (0.852–1.071)	0.936 (0.833–1.051)	0.893 (0.775–1.028)	0.966 (0.861–1.084)	–	0.936 (0.833–1.052)	0.952 (0.792–1.146)
BC	1.052 (0.996–1.111)	0.990 (0.907–1.081)	1.098 (0.999–1.207)	1.053 (0.997–1.112)	1.058 (1.001–1.118)	–	1.060 (1.002–1.122)
OC	0.969 (0.873–1.076)	0.944 (0.849–1.050)	0.851 (0.723–1.002)	0.985 (0.887–1.095)	1.003 (0.848–1.187)	0.942 (0.845–1.049)	–

a: Odds ratios per interquartile range. For IQRs see Table 4. Analysis matched on age, sex and month of birth and adjusted for marital status, occupational status, personal income, region of origin and area level information on % of parish population with income in lowest quartile, unemployed, manual labor, retired, basic education, living in social housing, owning their own dwelling, single parent families, previously convicted, and of Danish origin.

(Raaschou-Nielsen et al., 2011; Andersen et al., 2018) and such chemical exposures are rare in Denmark. It was a major strength of our study that we had data on several individual PM components. We did not, however, have data on metals in the PM nor did we have information to analyze the ultrafine particle fraction. It was a major strength of our study that we, in a nationwide study, could adjust in detail for personal socioeconomic position and neighborhood sociodemographic factors. However, we cannot rule out that confounding from unknown risk factors or chance may have affected our findings, particularly since we performed a large number of analyses. A potential limitation for the benign tumors is that we had no information on scanning procedures prior to diagnosis. This may have affected our results for benign tumors if the quality or likelihood of scanning differed by air pollution level since some benign tumors, can be symptom free for many years and may only be detected by chance during routine scanning (Wiemels et al., 2010). It was also a limitation that the majority of non-glioma tumors did not have information about morphology and that we therefore could not subdivide tumor groups further. We did not account for pre-existing genetic conditions associated with risk for CNS tumors. If families with such genetic syndromes are more likely to live in urban or rural areas, it may have affected risk estimates. However, the potential size of this bias is limited by the low population prevalence of such conditions and the small proportion of CNS tumors related to such syndromes. We did not adjust for medical conditions such as allergy, which some studies have linked with CNS tumors. In a Danish context, these factors do, however, not appear to be relevant confounders.

This large study with detailed modelling of PM constituents showed associations between carbon particles in the air and risk for malignant tumors of the brain. As the first of its kind, this study needs replication.

CRediT authorship contribution statement

Aslak Harbo Poulsen: Formal analysis, Writing - original draft, Writing - review & editing. **Ulla Arthur Hvidtfeldt:** Resources, Writing - review & editing. **Mette Sørensen:** Conceptualization, Writing - review & editing. **Robin Puett:** Writing - review & editing. **Matthias Ketzel:** Resources, Writing - review & editing. **Jørgen Brandt:** Resources, Writing - review & editing, Funding acquisition. **Jesper H. Christensen:** Resources, Writing - review & editing. **Camilla Geels:** Resources, Writing - review & editing. **Ole Raaschou-Nielsen:** Conceptualization, Resources, Writing - review & editing.

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.

Acknowledgements

The exposure modeling was funded by NordForsk under the Nordic Programme on Health and Welfare (Project #75007: NordicWelfAir - Understanding the link between Air pollution and Distribution of related Health Impacts and Welfare in the Nordic countries). The funding source had no involvement in the study design, collection, analysis, interpretation, writing and decision to submit for publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106046.

References

Barnholtz-Sloan, J.S., Ostrom, Q.T., Cote, D., 2018. Epidemiology of brain tumors. Neurol. Clin. 36 (3), 395–419.
McNeill, K.A., 2016. Epidemiology of brain tumors. Neurol. Clin. 34 (4), 981–998.
Wang, G., Xu, S., Cao, C., et al., 2016. Evidence from a large-scale meta-analysis indicates eczema reduces the incidence of glioma. Oncotarget. 7 (38), 62598–62606.
Amirian, E.S., Ostrom, Q.T., Armstrong, G.N., et al., 2019. Aspirin, NSAIDs, and glioma risk: original data from the glioma international case-control study and a meta-analysis. Can. Epidemiol. Biomark. Prevent: A Publicat. Am. Assoc. Can. Res. Am. Soc. Prevent. Oncol. 28 (3), 555–562.
Tong, J.J., Tao, H., Hui, O.T., Jian, C., 2012. Diabetes mellitus and risk of brain tumors: a meta-analysis. Exp. Ther. Med. 4 (5), 877–882.
Andersen, L., Friis, S., Hallas, J., Ravn, P., Gaist, D., 2013. Hormone replacement therapy and risk of glioma: a nationwide nested case-control study. Can. Epidemiol. 37 (6), 876–880.
Andersen, L., Friis, S., Hallas, J., Ravn, P., Kristensen, B.W., Gaist, D., 2015. Hormonal contraceptive use and risk of glioma among younger women: a nationwide case-control study. Br. J. Clin. Pharmacol. 79 (4), 677–684.
Carles, C., Bouvier, G., Esquirol, Y., et al., 2017. Residential proximity to agricultural land and risk of brain tumor in the general population. Environ. Res. 159, 321–330.
Samanic, C.M., De Roos, A.J., Stewart, P.A., Rajaraman, P., Waters, M.A., Inskip, P.D., 2008. Occupational exposure to pesticides and risk of adult brain tumors. Am. J Epidemiol. 167 (8), 976–985.
Bassil, K.L., Vakil, C., Sanborn, M., Cole, D.C., Kaur, J.S., Kerr, K.J., 2007. Cancer health effects of pesticides: systematic review. Can. Fam. Physician. 53 (10), 1704–1711.
Schmidt, L.S., Nielsen, H., Schmiedel, S., Johansen, C., 2008. Social inequality and incidence of and survival from tumours of the central nervous system in a population-based study in Denmark, 1994–2003. Eur. J. Can. 44 (14), 2050–2057.
Gomes, J., Al, Z.A., Guzman, A., 2011. Occupational and environmental risk factors of adult primary brain cancers: a systematic review. Int. J. Occup. Environ. Med. 2 (2), 82–111.
Loomis, D., Grosse, Y., Lauby-Secretan, B., et al., 2013. The carcinogenicity of outdoor air pollution. Lancet Oncol. 14 (13), 1262–1263.
Benbrahim-Tallaa, L., Baan, R.A., Grosse, Y., et al., 2012. Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. Lancet Oncol. 13 (7), 663–664.
Bourdrel, T., Bind, M.A., Bejot, Y., Morel, O., Argacha, J.F., 2017. Cardiovascular effects of air pollution. Arch. Cardiovasc. Dis. 110 (11), 634–642.
Suades-Gonzalez, E., Gascon, M., Guxens, M., Sunyer, J., 2015. Air pollution and neuropsychological development: a review of the latest evidence. Endocrinology 156 (10), 3473–3482.
Schraufnagel, D.E., Balmes, J.R., Cowl, C.T., et al., 2019. Air pollution and non-communicable diseases: a review by the forum of international respiratory societies' environmental committee, Part 1: The damaging effects of air pollution. Chest 155 (2), 409–416.
Schraufnagel, D.E., Balmes, J.R., Cowl, C.T., et al., 2019. Air Pollution and non-communicable diseases: a review by the forum of international respiratory societies' environmental committee, Part 2: air pollution and organ systems. Chest 155 (2), 417–426.
de Prado, B.P., Mercader, E.M.H., Pujol, J., Sunyer, J., Mortamais, M., 2018. The effects of air pollution on the brain: a review of studies interfacing environmental epidemiology and neuroimaging. Curr. Environ. Health Rep. 5 (3), 351–364.
Genc, S., Zadeoglulari, Z., Fuss, S.H., Genc, K., 2012. The adverse effects of air pollution on the nervous system. J. Toxicol. 2012, 782462.
Block, M.L., Calderon-Garciduenas, L., 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 32 (9), 506–516.
Oberdorster, G., Sharp, Z., Atudorei, V., et al., 2004. Translocation of inhaled ultrafine particles to the brain. Inhal. Toxicol. 16 (6–7), 437–445.
Weichenthal, S., Olaniyan, T., Christidis, T., et al., 2020. Within-city spatial variations in ambient ultrafine particle concentrations and incident brain tumors in adults. Epidemiol. 31 (2), 177–183.
Boeglin, M.L., Wessels, D., Henshel, D., 2006. An investigation of the relationship between air emissions of volatile organic compounds and the incidence of cancer in Indiana counties. Environ. Res. 100 (2), 242–254.
Turner, M.C., Krewski, D., Diver, W.R., et al., 2017. Ambient air pollution and cancer mortality in the cancer prevention study II. Environ. Health Perspect. 125 (8), 087013.
McKean-Cowdin, R., Calle, E.E., Peters, J.M., et al., 2009. Ambient air pollution and brain cancer mortality. Cancer Causes Control. 20 (9), 1645–1651.
Raaschou-Nielsen, O., Andersen, Z.J., Hvidberg, M., et al., 2011. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ. Health. 10, 67.
Poulsen, A.H., Sorensen, M., Andersen, Z.J., Ketzel, M., Raaschou-Nielsen, O., 2016. Air pollution from traffic and risk for brain tumors: a nationwide study in Denmark. Cancer Causes Control. 27 (4), 473–480.
Jorgensen, J.T., Johansen, M.S., Ravnskjaer, L., et al., 2016. Long-term exposure to ambient air pollution and incidence of brain tumours: The Danish Nurse Cohort. Neurotoxicology. 55, 122–130.
Andersen, Z.J., Pedersen, M., Weinmayr, G., et al., 2018. Long-term exposure to ambient air pollution and incidence of brain tumor: the European Study of Cohorts for Air Pollution Effects (ESCAPE). Neuro Oncol. 20 (3), 420–432.
Schmidt, M., Pedersen, L., Sorensen, H.T., 2014. The Danish civil registration system as a tool in epidemiology. Eur. J. Epidemiol. 29 (8), 541–549.
Thygesen, L.C., Daasnes, C., Thaulow, I., Bronnum-Hansen, H., 2011. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand. J Public Health. 39 (7 Suppl), 12–16.

Gjerstorff, M.L., 2011. The Danish cancer registry. Scand. J Public Health. 39 (7 Suppl), 42–45.
Storm, H.H., Michelsen, E.V., Clemmensen, I.H., Pihl, J., 1997. The Danish Cancer Registry–history, content, quality and use. Dan. Med. Bull. 44 (5), 535–539.
Kahn, J., Kakosimos, K., Raaschou-Nielsen, O., et al., 2019. Development and performance evaluation of new AirGIS – a GIS based air pollution and human exposure modelling system. Atmos. Environ. 198, 102–121.
Pedersen, C.B., 2011. The Danish civil registration system. Scand. J Public Health. 39 (7 Suppl), 22–25.
Brandt JC, J.H.; Frohn, L.M.; Palmgren, F.; Berkowicz, R.; Zlatev, Z. Operational air pollution forecasts from European to local scale. Atmospheric Environment. 2001; 35(Suplement 1):8.
Jensen, S.S.K.M., Becker, T., Christensen, J., Brandt, J., Plejdrup, M., Winter, M., Nielsen, O.K., Hertel, O., Ellerman, T., 2017. High resolution multi-scale air quality modelling for all streets in Denmark. Transp. Res. Part D Transp. Environ. 52, 322–339.
Brandt, J., Silver, J.D., Frohn, L.M., et al., 2012. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. Atmos Environ. 53, 156–176.
Plejdrup, M.S., Nielsen, O.-K., Gyldenkærne, S., Bruun, H.G., 2018. Spatial high-resolution distribution of emissions to air -SPREAD 2.0. Aarhus University, DCE – Danish Centre for Environment and Energy: Aarhus University, Department of Environmental Science; november 2018 2018.
Brandt, J., Christensen, J.H., Frohn, L.M., Berkowicz, R., 2003. Air pollution forecasting from regional to urban street scale—implementation and validation for two cities in Denmark. Phys. Chem. Earth, Parts A/B/C. 28 (8), 335–344.
Ketzel, M., Jensen, S., Brandt, J., et al., 2012. Evaluation of the street pollution model OSPM for measurements at 12 streets stations using a newly developed and freely available evaluation tool. J. Civil Environ. Eng. 3 (1), s1–004.
Jensen, S.S., Plejdrup, M.S., Hilling, K., 2019. GIS-based National Road and Traffic Database 1960-2020. . Aarhus, Denmark: Aarhus University, DCE – Danish Centre for Environment and Energy November 2019 2019.
Hvidtfeldt, U.A., Geels, C., Sørensen, M., et al., 2019. Long-term residential exposure to PM2.5 constituents and mortality in a Danish cohort. Environ. Int. 133 (105268).
Janssen, N.A., de Hartog, J.J., Hoek, G., et al., 2000. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor, and outdoor concentrations. J. Air Waste Manage. Assoc. 50 (7), 1133–1143.
Hvidtfeldt, U., Ketzel, M., Sørensen, M., et al., 2018. Evaluation of the Danish AirGIS air pollution modeling system against measured concentrations of PM2.5, PM10, and black carbon. Environ. Epidemiol. 2 (2), e014.
Zare, A., Christensen, J.H., Irannejad, P., Brandt, J., 2012. Evaluation of two isoprene emission models for use in a long-range air pollution model. Atmos. Chem. Phys. 12 (16), 7399–7412.
Zare, A., Christensen, J.H., Gross, A., Irannejad, P., Glasius, M., Brandt, J., 2014. Quantifying the contributions of natural emissions to ozone and total fine PM concentrations in the Northern Hemisphere. Atmos. Chem. Phys. 14, 2735–2756.
Zeger, S.L., Thomas, D., Dominici, F., et al., 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ. Health Perspect. 108 (5), 419–426.
Wiemels, J., Wrensch, M., Claus, E.B., 2010. Epidemiology and etiology of meningioma. J Neurooncol. 99 (3), 307–314.