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Long-term exposure to ambient air pollution and incidence of brain tumours: The Danish Nurse Cohort

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ABSTRACT

Background: Air pollution has been considered a potent environmental risk factor for neuropathology through neuroinflammation and oxidative stress, which might also cause brain tumour formation. However, epidemiological evidence on the association between air pollution and brain tumours in humans is sparse, with no data on exposure to particles. In this study we aim to examine associations between long-term exposure to ambient air pollution and risk for development of brain tumours.

Methods: We used the Danish Nurse Cohort with 28,731 female nurses (age ≥ 44 years) recruited in 1993 or 1999 when self-reported information on lifestyle was collected. We obtained data on the incidence of brain tumours until 2013 from the Danish Cancer Register, and estimated annual mean concentrations of particulate matter with diameter < 2.5 μm ($PM_{2.5}$), particulate matter with diameter < 10 μm (PM_{10}), nitrogen oxides (NO_x) and nitrogen dioxide (NO_2) at the residence since 1990 using an atmospheric integrated chemistry-transport models system, and examined the association between the 3-year running mean of pollutants and brain tumour incidence using time-varying Cox regression, separately for total brain tumours, and for tumour subtypes by location (brain or meninges), and by malignancy (malignant or benign), and estimated hazard ratios and 95% confidence intervals per increase in interquartile range of exposure.

Results: Of 25,143 tumour-free nurses at recruitment, 121 developed brain cancer during 15.7 years of follow-up. We found a weak positive association between total brain tumours and $PM_{2.5}$ (1.06; 0.80–1.40 per 3.37 μg/m^3), NO_2 (1.09; 0.91–1.29) per 7.5 μg/m^3, and NO_x (1.02; 0.93–1.12 per 10.22 μg/m^3), and none with PM_{10} (0.93; 0.70–1.23 per 3.31 μg/m^3). Associations with $PM_{2.5}$ and NO_2 were stronger for tumours located in meninges than in brain, and for benign than for malignant tumours. Finally, association of total brain tumours with $PM_{2.5}$ was modified by BMI, and was statistically significantly enhanced in obese women (2.03; 1.35–3.05).

Conclusion: We found weak evidence for association between risk of brain tumours and long-term exposure to air pollution in women older than 44 years. However, we present novel results that obese women may be susceptible, as well as a positive tendency towards elevated risk for meninges and benign tumours, which require further investigation.

Abbreviations: IQR, Interquartile range; HR, Hazard ratio; CI, confidence intervals; $PM_{2.5}$, Particulate matter with aerodynamic diameter 2.5 μm/m^3; PM_{10}, Particulate matter with aerodynamic diameter 10 μm/m^3; NO_x, Nitrogen oxides; NO_2, Nitrogen dioxide; BMI, Body mass index (kg/m^2).

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1. Introduction

Tumours of the brain and central nervous system are rare, comprising 4% of all new cancers in Denmark in 2014. However, incidence of brain tumours has increased by over 50% during the last 25 years in Denmark, and little is known about risk factors and mechanisms (Sundhedsdatastyrelsen, 2015). Established brain cancer risk factors are radiation to the head and inherited genetic risk, whereas HIV infection, cigarette smoking and environmental pollution (chemicals) have been identified as potential risk factors (Bondy et al., 2008). A Danish study found a higher risk for developing tumours of the central nervous system with occupation in agriculture and high income among men (Schmidt et al., 2008), while a US study found association between volatile organic compounds and the incidence of brain cancer (Boeglin et al., 2006). Particulate matter (PM) air pollution is an established risk factor for lung cancer, respiratory and cardiovascular morbidity and mortality (Franklin et al., 2015; Newby et al., 2015; Raaschou-Nielsen et al., 2013), while its effects on the brain are still debated. Air pollution has been considered a potent environmental risk factor for neurological diseases and neuropathology although the potential mechanisms of action including neuroinflammation and neurodegeneration are unclear (Calderón-Garcidueñas et al., 2016). Experimental studies have suggested that ultrafine particles (particulate matter with diameter $< 0.1\ \mu g/m^3$, UFP) can reach the brain by crossing the blood-brain barrier or directly via the olfactory nerves, causing inflammatory and oxidative stress responses (Block and Calderón-Garcidueñas, 2009; Kreyling et al., 2009; Oberdörster, 2002), which may be relevant for the development of neurodegenerative disease such as Parkinson's and Alzheimer's disease (Costa et al., 2015). Systemic inflammation and neuronal signalling may also be relevant for brain pathology related to air pollution (Calderón-Garcidueñas et al., 2016). Inflammation is important in the pathogenesis of brain cancer (Sowers et al., 2009). Moreover, gene expression pattern similar to that seen in human brain tumours were found in rats after exposure to concentrated particles in particular the coarse fraction (Ljubimova et al., 2013). Diesel exhaust was recently classified as carcinogenic by the International Agency for Research on Cancer (Benbrahim-Tallaa et al., 2012; Loomis et al., 2013), suggesting that air pollution may be risk factor for brain cancer, but epidemiological evidence is very sparse. An ecological study in US failed to find association of brain cancer incidence and mortality at county-level with any of 30 different hazardous air pollutants examined (Valberg and Long, 2010). Similarly, McKean-Cowdin et al. failed to detect association between brain cancer mortality (n = 1284) and residential exposure to particulate matter < 2.5 and $10\ \mu g/m^3$ ($PM_{2.5}$ and PM_{10}), or nitrogen dioxide (NO_2) in a large US Cancer Prevention Study cohort (McKean-Cowdin et al., 2009). Finally, two Danish studies on brain tumour incidence and air pollution report conflicting results. Raaschou-Nielsen et al. detected a strong positive association between long-term exposure to nitrogen oxide (NO_x) and brain cancer incidence (n = 95) (hazard ratio and 95% confidence interval (CI): 2.28; 1.24–4.17 per $100\ \mu g/m^3$) in Danish Diet, Cancer and Health cohort (Raaschou-Nielsen et al., 2011), which was however not reproduced in a nationwide case-control study (n = 4183) showing only a weak albeit positive association (odds ratio and 95% CI: 1.11; 0.84–1.46 per $100\ \mu g/m^3$) (Poulsen et al., 2016), calling for more research.

In this study we aim to examine the association between long-term exposure to ambient air pollution ($PM_{2.5}$, PM_{10}, NO_2, and NO_x) and incidence of brain tumours in Danish Nurse Health Study.

2. Materials and methods

2.1. The Danish Nurse Cohort study

The Danish Nurse Cohort was initiated in 1993 when 23,170 female members of the Danish Nurse Organization older than 44 years were invited to participate (Hundrup et al., 2012), and 19,989 (86%) responded. The cohort was reinvestigated in 1999, when 10,534 nurses who turned 44 years in the meantime were included, and in 2009, without further inclusion. The cohort was inspired by the American Nurses' Health Study (NHS) to initially investigate the health effects of hormone replacement therapy in a European population. Cohort participation involved answering comprehensive questionnaire on socio-economic and working conditions, parents' occupation, weight and height including weight at birth, lifestyle (diet, smoking alcohol consumption and leisure time physical activity), self-reported health, family history of cardiovascular and cancer diseases, parity, age at first birth, age of menarche and menopause, use of oral contraceptives and hormone replacement therapy, removal of uterus and ovaries. In this study we included earliest available baseline information from 1993 (19,898) or 1999 (8833) for 28,731 female nurses, who were linked to the Central Population Register (CPR) (Pedersen, 2011), in order to obtain information on residential address since 1971 until 2013, and vital status at 31st December 2012 (active or date of death or emigration).

2.2. Brain tumour definition

The Danish Cancer Register contains information on all incident malignant neoplasms since 1943 (Gjerstorff, 2011). We linked the records of 28,731 nurses using the unique personal identification number to the Danish Cancer Register to extract all cancer diagnoses until 2013. First, we extracted data for nurses with diagnoses for any cancer type before baseline (1st April 1993 or 1st April 1999). Secondly, among nurses without cancer diagnoses before baseline, we extracted information on brain tumours, defined as primary tumours of the brain, meninges and cranial nerves (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), both benign and malignant, from recruitment (1993 or 1999) until 2013. The main outcome was the total of all tumours combined, however we also considered subtypes by the location of the tumour: tumours of the brain (ICD10: C71.0-C71.9, D33.0-D332, D43.0-D43.2) or tumours of meninges (C70.0, D32.0 and D42.0), as well as by malignancy of the tumour: malignant (C70.0, C71.0-C71.9, C72.2-C72.5) and non-malignant tumours (D32.0, D33.0-D33.2, D33.3, D42.0, D43.0-D43.2, D43.3).

2.3. Exposure assessment

We used the newly updated, high-resolution Danish air pollution dispersion modelling system (AirGIS, http://envs.au.dk/en/knowledge/air/models/airgis/) to estimate exposure to outdoor air pollution (more detail in the ESM) (Jensen et al., 2001). The necessary input data for carrying out the exposure modelling has been established for the first time in Denmark for particulate matter ($PM_{2.5}$ and PM_{10}) starting in 1990, whereas for the gaseous nitrogen oxide pollutants (NO_2 and NO_x) input data have been established since 1971. AirGIS made use of a series of air pollution models in the integrated air pollution model system THOR (Brandt, 2001). For the long-range transport components the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012; Frohn et al., 2002) is applied with a nested grid setup covering the Northern Hemisphere with higher resolution over selected areas (150 km × 150 km for the Northern Hemisphere, 50 km × 50 km for