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ORIGINAL PAPER

Parental occupational exposure and risk of childhood central nervous system tumors: a pooled analysis of case–control studies from Germany, France, and the UK

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Abstract
Purpose To assess the risk of childhood central nervous system (CNS) tumors associated with parental occupational exposure to polycyclic aromatic hydrocarbons (PAH), diesel motor exhaust (DME), asbestos, crystalline silica, and metals, which are established carcinogens in adults.
Methods We pooled data from three population-based case–control studies from Germany, France, and the UK. Cases were children aged up to 15 years and diagnosed with CNS tumor, and controls were frequency-matched by age and sex. Socio-demographic data and parental occupation around conception/pregnancy and at diagnosis were collected using standardized interviews, face-to-face or by telephone. A general population job-exposure matrix was used to assign a level of exposure to each job. Logistic regression models were fitted to compute odds ratios and 95 % confidence intervals.
Results Our study included 1,361 cases of CNS tumors and 5,500 controls. Paternal exposure to PAH, asbestos, and metals around conception was associated with an increased moderate risk of CNS tumors, although statistically non-significant. The association with exposure to asbestos around conception and diagnosis was stronger when fathers were exposed to high levels. Paternal exposure to DME and silica, and maternal exposure to PAH, DME, asbestos, silica, and metals, were not associated with an increased risk of CNS tumors.
Conclusion Our large pooled study showed weak evidence of a modest association between paternal occupational exposure to PAH and CNS tumor risk. Our findings need further exploration in the future studies.

Keywords Central nervous system tumor · Child · Occupational exposure · Case–control study · Job-exposure matrix

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Introduction

Central nervous system (CNS) tumors are the most common childhood solid tumor and account for about 20 % of all pediatric tumors, while leukemias are the most common childhood cancer overall (about 30 % of all childhood cancer) [1, 2]. Astrocytomas, CNS embryonal tumors [including primitive neuroectodermal tumors (PNET)/medulloblastoma], and ependymomas are the most common histological subtypes, representing 52, 21, and 9 % of all CNS tumors, respectively [1, 3]. Overall, CNS tumors are more common among boys than girls, with a boys-to-girls ratio of 1.1 for astrocytomas, 1.6 for embryonal tumors, and 1.3 for ependymomas [1]. In 2008, the brain and CNS tumors incidence rate among children aged 0–14 years was 1.2 per 100,000 person-years worldwide [4]. There was a trend of increasing incidence of childhood CNS tumors between 1978 and 1997, with an estimated average annual increase of 1.7 % in Europe, although incidence varied widely according to histological subtypes [1] and region [5]. This trend should, however, be interpreted with caution and may merely reflect improvements in diagnosis and better cancer registration. Alternatively, the increase over the past decades could also suggest an evolution of risk factors [6].

The causes of CNS tumors remain largely unknown. A few genetic conditions (such as Li–Fraumeni syndrome and neurofibromatosis) and exposure to high-dose ionizing radiation are confirmed risk factors but explain only a small percentage (<10 %) of all cases [2, 7]. The brain is not entirely developed at birth, which implies continuation of cell growth and cell differentiation processes after birth. During this development in the postnatal period, brain cells are still vulnerable to any insult from carcinogens [3]. Parental occupational exposure may play a role around time of conception, during pregnancy, and even after the child's birth [8]. Paternal exposure can lead to a genetic alteration in the father's sperm before conception, which could lead to increased cancer susceptibility in the child [9]. Maternal exposure to toxic agents can cross the placenta barrier and enter the fetal bloodstream [3]. Harmful substances can also cross the blood–brain barrier of the child, which remains incompletely developed up to the first 6 months of life, and can be permeable to toxic compounds [3]. After the child's birth, exposure of the parents can be transferred to their child by bringing home substances for instance on their clothes [3, 10].

The agents investigated in the present study are all classified as carcinogenic to humans by the International Agency for Research on Cancer: polycyclic aromatic hydrocarbons (PAH), diesel motor exhaust (DME), asbestos, crystalline silica, chromium, and nickel [11]. For CNS tumors, the association with parental PAH exposure shows inconsistent results, with some positive associations being reported [12–15], while other studies did not find a significant association [10, 16]. There has also been a previous report from Peters et al. [14], who found an increased risk of childhood brain tumors associated with both maternal and paternal exposure to DME before the child's birth. Previous studies that have investigated parental exposure to asbestos, silica, chromium, and nickel were few, small, and lacked statistical power to study possibly only moderate risks, and no study reported a significant association with CNS tumors so far [10, 16]. With a view of providing further insight, we pooled data from three existing case–control studies to achieve a large study population with increased statistical power. The objective of our study was to assess the risk of CNS tumors associated with parental occupational exposures to PAH, DME, asbestos, crystalline silica, chromium, and nickel, using an independently developed general population job-exposure matrix (JEM) for those agents.

Methods

Study population

We pooled data obtained from children with CNS tumors who were recruited for three population-based case–control studies of childhood cancer conducted in Germany (1988–1994), France (2003–2004), and the UK (UK) (1991–1996) [17–19]. Case and control ascertainment are described in Table 1. In the present study, controls were frequency-matched and all controls from the original studies were used.

Data collection

Information about the socio-demographic characteristics and the parental occupation was assessed by interviews (telephone or face-to-face) of both parents when possible, and only one parent if the other was not reachable. In the French study, only the biological mothers were interviewed and used as proxy respondent for the father. Interviews were done by trained personnel using a standardized questionnaire. For the studies in Germany and UK, parents filled in a self-administered questionnaire prior to the interview.

Exposure assessment

Information about occupation of the parents during pregnancy and at diagnosis were available in the three countries, while occupation around conception (job(s) held

Table 1 Description of the three studies included in the pooled analysis

Study	Diagnostic years	Case ascertainment	Control ascertainment	Study entry criteria	Matching control criteria
Germany	1988–1994	All cancers diagnosed <15 years in Lower Saxony (July 1988–June 1993) and West Germany (October 1992–September 1994) and reported to the German Childhood Cancer Registry. Those who were eligible for both studies were only used once in present study	In Lower Saxony: two controls were recruited, one from the same community as the case and one from a population-weighted sampling scheme In former West Germany: one control randomly selected from population registers	Living for at least half a year in the community. Participation rate: 81 % among cases and 69 % among controls	In Lower Saxony: matched for sex and date of birth within one year In former West Germany: matched for sex, date of birth within one year and community For this pooling project, a pool of all control irrespective of the diagnosis of the individual matched case was created
France	2003–2004	All malignant cancer diagnosed <15 years recruited through the French National Registry of Childhood Solid Tumors	List of 60,000 phone numbers from the French national telephone company Enriched with random selection of phone numbers to reach people not on the list	Residing in mainland France at the time of diagnosis. Not being adopted Exclusion of mothers who could not speak French or had a serious psychiatric disorder. No child on palliative care before inclusion. Participation rate: 80 % among cases and 71 % among controls	Frequency-matched for sex and age
UK	1991–1996	All cancers diagnosed <15 years in England, Scotland and Wales in 10 study regions. Selected from regional pediatric oncology units using cross-check to regional and national cancer registries	Two controls randomly selected from population registers	Born in the UK. Not living outside Great Britain in the 3 months before diagnosis. No prior malignancy. Participation rate: 87 % among cases and 64 % among controls	Matched for sex, age, and area of residence

12 months before the birth of the child) was collected in the German and UK studies, but not in the French study. As occupations around conception and during pregnancy were virtually always the same in Germany and in the UK (Spearman correlation coefficients were 0.94 and above for the exposure to the agents we studied), we used exposure during pregnancy as a proxy for exposure around conception in France. To estimate parental exposure to PAH, DME, asbestos, crystalline silica, chromium, and nickel, we used DOM–JEM. The DOM–JEM is a general population JEM that attributes a level of exposure based on intensity and prevalence of exposure (0 = no/1 = low/2 = high) to each job held by the parents [20]. Three experts individually assigned levels of exposure to each job code, conflicting scores were settled by consensus; the initial agreement was 84 % for PAH, 91 % for DME, 77 % for asbestos, 95 % for crystalline silica, 89 % for chromium, and 91 % for nickel. Assignment of the exposure to asbestos took into account the ban of asbestos in each country, i.e., 1993 in Germany, 1997 in France, and 1999 in the UK, i.e., after the ban, no parent was assigned exposure [21]. To apply the DOM–JEM, all jobs had to be coded to the International Standard Classification of Occupations from 1968 (ISCO-68) [22]. The French study used ISCO-68 in its original version, whereas the German and the UK studies used national occupational classification ("Klassifizierung der Berufe, Ausgabe 1988" [23] and "Standard Occupational Classification 1990" [24], respectively). First, we recoded the job titles for the German and UK studies to ISCO-88, based on official conversion tables between the national classifications and ISCO-88. We thereafter converted the ISCO-88 codes to ISCO-68. As ISCO-68 is more detailed (5 digits) than ISCO-88 (4 digits), we sometimes had several plausible ISCO-68 codes for one ISCO-88 code. In that case, we either chose a 3-digit ISCO-68 code or when many 3-digit ISCO-68 codes were possible we chose the most similar ISCO-68 job description text (in 3- or 5-digit code) to the

national classification. The DOM–JEM includes exposure estimates for 2-, 3-, 4-, and 5-digit ISCO-68 codes.

Statistical analyses

Unconditional logistic regressions were fitted and odds ratios (OR) and 95 % confidence intervals (CI) were computed to assess the association between occupational exposure and CNS tumor. Three statistical models were run. The first model (OR1) was adjusted only for the matching variables: age, sex, and country. The others were as follows: OR2 which additionally adjusted for child's - year of birth; OR3 which additionally adjusted for parental educational level. ORs and 95 % CI were computed for each exposure using a dichotomous variable (never/ever exposed), and also an ordinal variable for intensity of exposure (never/low/high).

Further, analyses by histological subgroups (astrocytoma; CNS embryonal tumor (mainly medulloblastoma); ependymoma; other) were performed by selecting only cases from the same subgroup and all the controls available. A meta-analysis was performed to assess the heterogeneity in risk between the three datasets. We estimated I^2, which reflected the percentage of total variation across studies due to heterogeneity, and visualized the results using forest plots. An I^2 of 25, 50, and 75 % was considered as low, moderate, and high heterogeneity, respectively [25].

Qualitative variables were reported as numbers and percentages, and the quantitative variables as means with their standard deviations (SD). Qualitative variables were compared using a chi-squared or fisher test, and quantitative variables were compared using a fisher test (equality of variances). Exposure–response trends were assessed by applying a logistic regression model including the ordinal variable. All p values <0.05 were considered as significant.

Statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA), and the metan command from Stata version 12.1 (StataCorp LP, College Station, TX) for the meta-analysis.

Results

Characteristics of the population

Our pooled sample consisted of 1,361 cases and 5,500 controls as shown in Table 2. Overall, 54.5 % were boys. The mean age at diagnosis/recruitment was 5.6 years among cases and was 6.0 years among controls. The parental mean age at birth of the child was 28.1 years for mothers and 31.0 years for fathers, and did not differ significantly between cases and controls. The children's years of birth ranged from 1974 to 2005. Paternal and maternal educational levels were significantly different between cases and controls, with more parents who reached tertiary education among the controls ($p < 0.0001$). Overall, 446 cases (32.8 %) were astrocytomas; 374 cases (27.5 %) were CNS embryonal tumors, and 152 (11.2 %) were ependymomas. The German and UK studies followed this pattern, while the French study comprised more embryonal tumors (47.9 %) than astrocytomas (12.4 %). The reason is that the French study included only cases with malignant CNS tumors, which excluded most astrocytomas.

Chromium and nickel were highly correlated among paternal and maternal occupational exposure (Spearman coefficients: 0.86 and 0.82, respectively), so we merged them (either/or) to a new exposure variable named metals.

CNS tumor risk in relation to parental occupational exposure

Table 3 shows the associations between CNS tumor risk and paternal exposure to PAH, DME, asbestos, crystalline silica, and metals. Adjustment for the year of birth of the child (OR2) or parental educational level (OR3) did not change the results (data not shown); hence, we present only the OR1 adjusted for sex, age, and country in the subsequent tables. Paternal exposure to PAH around conception was associated with a moderate non-significant increased risk of CNS tumors (OR 1.22, 95 % CI 0.98–1.52). Paternal exposure to asbestos around conception was associated with a non-significant slightly increased risk of CNS tumors (OR 1.12, 95 % CI 0.95–1.32), while exposure to asbestos around diagnosis showed an odds ratio close to 1 (OR 1.05, 95 % CI 0.84–1.32). However, the odds ratios for paternal exposure to asbestos both around conception and around diagnoses tended to be higher among fathers exposed to high levels of asbestos compared to low levels, but the odds ratios were not significantly elevated. Paternal exposure to metals around conception was not associated with a significantly increased risk of CNS tumors (OR 1.18, 95 % CI 0.96–1.46).

Table 4 presents the associations between CNS tumor risk and maternal exposure to PAH, DME, asbestos, crystalline silica, and metals. Since there were very few mothers who were exposed to high levels, we only presented the never/ever exposed categories for maternal exposure. Very few mothers were exposed to crystalline silica and metals. Overall none of the maternal exposures were associated with CNS tumors.

Tables 5 and 6 present the CNS tumor risk associated with the selected exposures by histological subgroups. For paternal occupational exposure to PAH around conception, a small non-significant increased risk was seen in

Table 2 Characteristics of the study population

Characteristics of the population	Controls $n = 5{,}500$ (% or SD)	Cases $n = 1{,}361$ (% or SD)	Overall $n = 6{,}861$ (% or SD)	p[a]
Study				<0.0001
Germany (1988–1994)	2,458 (44.7)	466 (34.2)	2,924 (42.6)	
France (2003–2004)	1,681 (30.6)	209 (15.4)	1,890 (27.5)	
UK (1991–1996)	1,361 (24.7)	686 (50.4)	2,047 (29.8)	
Sex				0.54
Boys	3,005 (54.6)	731 (53.7)	3,736 (54.5)	
Girls	2,495 (45.4)	630 (46.3)	3,125 (45.5)	
Age at diagnosis/recruitment				<0.0001
0–4 years	2,618 (47.6)	554 (40.7)	3,172 (46.2)	
5–9 years	1,726 (31.4)	502 (36.9)	2,228 (32.5)	
10–14 years	1,156 (21.0)	305 (22.4)	1,461 (21.3)	
Age at diagnosis/recruitment, mean (SD)	5.6 (4.1)	6.0 (4.0)	5.7 (4.1)	0.15
Maternal age at birth, mean (SD)	28.3 (4.9)	27.5 (4.9)	28.1 (4.9)	0.62
Missing data	12 (0.0)	4 (0.0)	16 (0.0)	
Paternal age at birth, mean (SD)	31.2 (5.8)	30.3 (5.8)	31.0 (5.8)	1.00
Missing data	159 (0.0)	61 (0.0)	220 (0.0)	
Parental educational level				
Fathers				<0.0001
Did not complete secondary school	2,155 (39.2)	468 (34.4)	2,623 (38.2)	
Completed secondary education	1,291 (23.5)	395 (29.0)	1,686 (24.6)	
Completed tertiary education	1,622 (29.5)	379 (27.9)	2,001 (29.2)	
Missing data	432 (7.8)	119 (8.7)	551 (8.0)	
Mothers				<0.0001
Did not complete secondary school	1,849 (33.6)	467 (34.3)	2,316 (33.7)	
Completed secondary education	1,938 (35.2)	558 (41.0)	2,496 (36.4)	
Completed tertiary education	1,577 (28.7)	308 (22.6)	1,885 (27.5)	
Missing data	136 (2.5)	28 (2.1)	164 (2.4)	
Histological subgroups				
Astrocytomas	–	446 (32.8)		
CNS embryonal tumors[b]	–	374 (27.5)		
Ependymomas	–	152 (11.2)		
Other	–	389 (28.6)		

[a] p value for the difference between cases and controls

[b] PNET and medulloblastoma included

CNS embryonal tumors (OR 1.36, 95 % CI 0.95–1.95) and for the "other" category (OR 1.38, 95 % CI 0.98–1.95), whereas for paternal occupational exposure to metals, the association was restricted to astrocytoma (OR 1.26, 95 % CI 0.90–1.76) and CNS embryonal tumors (OR 1.36, 95 % CI 0.95–1.93). However, the ORs were all non-significant. Paternal exposure to asbestos around conception was significantly associated with the risk of "other" CNS tumors (OR 1.32, 95 % CI 1.01–1.70). For maternal exposures during pregnancy, no significant association was seen.

Results of the meta-analysis

No heterogeneity in risk was found between the three countries for paternal occupational exposure to PAH, DME, crystalline silica, and metals, and maternal occupational exposure to PAH, asbestos, crystalline silica, and metals (all $I^2 < 25$ %). Paternal exposure to asbestos showed moderate heterogeneity in risk between the three countries ($I^2 = 59.5$ %). The German study showed a significant increased risk of CNS tumors, opposite to the French study (Fig. 1). In the French study, there was a

Table 3 Childhood brain tumors associated with occupational paternal exposure

	Around time of conception				Around time of diagnosis			
	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI
Exposure to PAH								
Not exposed	1,241	5,076	1.00	Reference	1,269	5,125	1.00	Reference
Exposed	120	424	1.22	[0.98–1.52]	92	375	1.07	[0.84–1.36]
Low	110	388	1.22	[0.97–1.53]	83	338	1.07	[0.83–1.38]
High	10	36	1.20	[0.58–2.48]	9	37	1.05	[0.49–2.22]
Exposure to DME								
Not exposed	1,185	4,700	1.00	Reference	1,199	4,739	1.00	Reference
Exposed	176	800	0.89	[0.74–1.07]	162	761	0.90	[0.74–1.08]
Low	169	758	0.90	[0.75–1.08]	160	731	0.92	[0.76–1.11]
High	7	42	0.67	[0.29–1.52]	2	30	0.32	[0.08–1.38]
Exposure to asbestos								
Not exposed	1,117	4,710	1.00	Reference	1,233	5,191	1.00	Reference
Exposed	244	790	1.12	[0.95–1.32]	128	309	1.05	[0.84–1.32]
Low	221	722	1.10	[0.92–1.30]	115	287	1.01	[0.80–1.28]
High	23	68	1.42	[0.87–2.32]	13	22	1.61	[0.79–3.26]
Exposure to silica								
Not exposed	1,276	5,135	1.00	Reference	1,294	5,151	1.00	Reference
Exposed	85	365	0.96	[0.74–1.23]	67	349	0.84	[0.64–1.10]
Low	77	332	0.96	[0.74–1.25]	64	328	0.85	[0.64–1.12]
High	8	33	0.92	[0.41–2.03]	3	21	0.69	[0.20–2.37]
Exposure to metals								
Not exposed	1,232	5,074	1.00	Reference	1,258	5,108	1.00	Reference
Exposed	129	426	1.18	[0.96–1.46]	103	392	1.05	[0.83–1.32]
Low	114	372	1.22	[0.97–1.53]	92	343	1.10	[0.86–1.40]
High	15	54	0.96	[0.53–1.74]	11	49	0.75	[0.38–1.47]

[a] OR1 is adjusted for the matching variables: age, sex, and country

Table 4 Childhood brain tumors associated with occupational maternal exposure

	During pregnancy				Around time of diagnosis			
	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI
Exposure to PAH								
No	1,329	5,367	1.00	Reference	1,327	5,373	1.00	Reference
Yes	32	133	0.91	[0.61–1.35]	34	127	0.84	[0.57–1.25]
Exposure to DME								
No	1,343	5,382	1.00	Reference	1,336	5,368	1.00	Reference
Yes	18	118	0.81	[0.49–1.35]	25	132	0.90	[0.58–1.40]
Exposure to asbestos								
No	1,337	5,398	1.00	Reference	1,355	5,480	1.00	Reference
Yes	24	102	1.03	[0.65–1.63]	6	20	0.70	[0.28–1.77]
Exposure to silica								
No	1,353	5,445	1.00	Reference	1,353	5,442	1.00	Reference
Yes	8	55	0.69	[0.33–1.47]	8	58	0.68	[0.32–1.45]
Exposure to metals								
No	1,356	5,485	1.00	Reference	1,360	5,487	1.00	Reference
Yes	5	15	1.32	[0.47–3.75]	1	13	0.27	[0.03–2.11]

[a] OR1 is adjusted for the matching variables: age, sex, and country

Table 5 Risk of childhood brain tumors associated with paternal occupational exposure around conception, according to main histological subgroups

	Astrocytoma				Embryonal tumors				Ependymomas				Others			
	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI
Exposure to PAH																
Not exposed	412	5,076	1.00	Reference	338	5,076	1.00	Reference	142	5,076	1.00	Reference	349	5,076	1.00	Reference
Exposed	34	424	1.09	[0.75–1.58]	36	424	1.36	[0.95–1.95]	10	424	0.88	[0.46–1.69]	40	424	1.38	[0.98–1.95]
Exposure to DME																
Not exposed	388	4,700	1.00	Reference	322	4,700	1.00	Reference	134	4,700	1.00	Reference	341	4,700	1.00	Reference
Exposed	58	800	0.90	[0.67–1.21]	52	800	0.94	[0.69–1.28]	18	800	0.80	[0.48–1.31]	48	800	0.85	[0.62–1.16]
Exposure to asbestos																
Not exposed	369	4,710	1.00	Reference	314	4,710	1.00	Reference	126	4,710	1.00	Reference	308	4,710	1.00	Reference
Exposed	77	790	0.98	[0.75–1.28]	60	790	1.07	[0.80–1.43]	26	790	1.15	[0.74–1.78]	81	790	1.32	[1.01–1.70]
Exposure to silica																
Not exposed	416	5,135	1.00	Reference	347	5,135	1.00	Reference	148	5,135	1.00	Reference	365	5,135	1.00	Reference
Exposed	30	365	1.04	[0.69–1.55]	27	365	1.10	[0.73–1.66]	4	365	0.38	[0.14–1.04]	24	365	0.95	[0.62–1.46]
Exposure to metals																
Not exposed	400	5,074	1.00	Reference	336	5,074	1.00	Reference	140	5,074	1.00	Reference	356	5,074	1.00	Reference
Exposed	46	426	1.26	[0.90–1.76]	38	426	1.36	[0.95–1.93]	12	426	1.02	[0.56–1.86]	33	426	1.02	[0.70–1.48]

lower prevalence of exposure to asbestos: 5.6 % versus 18.3 % in Germany and 21.2 % in the UK ($p < 0.05$).

Maternal occupational exposure to DME showed moderate heterogeneity in risk between the three countries ($I^2 = 69.7$ %). Only the UK study presented a positive association, although non-significant (Fig. 2).

Discussion

Our study, using a large pooled sample of children with CNS tumors and controls from three European case–control studies and a general population JEM to estimate parental occupational exposures, showed that paternal occupational exposures to PAH, metals, and asbestos were associated with a marginally increased risk of CNS tumors, although not statistically significant. No increased risks of CNS tumors were found for paternal exposure to DME and crystalline silica, and maternal exposure to PAH, DME, asbestos, crystalline silica, and metals.

One of the strengths of our study was the large sample size, attempting to get more precise risk estimates and more power to detect an association, even if moderate. It also permitted a more detailed analysis by histological subgroups; this is important because there may exist different risk factors and aetiologies for each tumor subtype [26]. Furthermore, cases were identified by nationwide registries of childhood cancer in the German and French studies, and in UK study, they were recruited by treatment centers with cross-checks against regional and national cancer registries. These methods meant to be comprehensive, even if some cases of CNS tumors who were not seen by pediatric oncologists or who were treated in adult clinics may have been missed [27]. For the French study, it has to be noted that they recruited only the malignant CNS tumors, so that the astrocytomas, which are mostly benign tumors, are underrepresented. Another strength was that we had a relatively high participation rate in the three studies. Moreover, using a general population JEM to assess exposures presented some benefits in comparison with the following: (1) self-reported exposure, because of recall bias and differential misclassification if the parents of the cases would be more likely to report having been exposed than the parents of the controls [28]; (2) expert assessment, which depends on each expert's-specific background and is difficult to standardize across studies, and which would require exposure-specific questionnaire. The DOM–JEM assigns exposure blinded to disease status and in the same way across countries.

On the other hand, using a general population JEM did not allow us to take into account specific tasks performed by the parents at work and potential country differences, which may imply differences in levels of exposure. This

Table 6 Risk of childhood brain tumors associated with maternal occupational exposure during pregnancy, according to main histological subgroups

	Astrocytoma				Embryonal tumors				Ependymomas				Others			
	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI	Cases	Controls	OR1[a]	95 % CI
Exposure to PAH																
Not exposed	436	5,367	1.00	Reference	368	5,367	1.00	Reference	148	5,367	1.00	Reference	377	5,367	1.00	Reference
Exposed	10	133	0.81	[0.41–1.58]	6	133	0.62	[0.27–1.42]	4	133	1.03	[0.37–2.83]	12	133	1.19	[0.65–2.17]
Exposure to DME																
Not exposed	442	5,382	1.00	Reference	371	5,382	1.00	Reference	149	5,382	1.00	Reference	381	5,382	1.00	Reference
Exposed	4	118	0.71	[0.26–1.99]	3	118	0.44	[0.14–1.39]	3	118	1.14	[0.35–3.64]	8	118	1.19	[0.57–2.47]
Exposure to asbestos																
Not exposed	440	5,398	1.00	Reference	366	5,398	1.00	Reference	150	5,398	1.00	Reference	381	5,398	1.00	Reference
Exposed	6	102	0.80	[0.34–1.87]	8	102	1.40	[0.67–2.93]	2	102	0.86	[0.21–3.55]	8	102	0.99	[0.47–2.05]
Exposure to silica																
Not exposed	446	5,445	1.00	Reference	372	5,445	1.00	Reference	150	5,445	1.00	Reference	385	5,445	1.00	Reference
Exposed	0	55	–	–	2	55	0.67	[0.16–2.76]	2	55	1.56	[0.37–6.51]	4	55	1.05	[0.38–2.93]
Exposure to metals																
Not exposed	445	5,485	1.00	Reference	373	5,485	1.00	Reference	152	5,485	1.00	Reference	386	5,485	1.00	Reference
Exposed	1	15	1.04	[0.13–8.35]	1	15	1.08	[0.14–8.28]	0	15	–	–	3	15	2.74	[0.78–9.63]

may have led to non-differential exposure misclassification, which usually leads to an attenuation of the OR toward the null [29]. We were also not able to take into account the duration of exposure and its intensity across time, as we only have exposure at specific periods (i.e., around time of conception/pregnancy/diagnosis). It would have been interesting if we consider that longer and higher exposure could increase the risk of cancer. Furthermore, our risk estimates did not take into account the potential exposure of the parents and their children at home, which could have led to misclassification bias. Moreover, we recoded the job codes in the German and UK studies first to ISCO-88 and then to ISCO-68 in order to apply the DOM–JEM. Hence, we might have introduced further exposure misclassification, as codes in different classifications do not always match well. We made an attempt to assess the impact of using 3-digit ISCO-68 codes rather than 5-digit ISCO-68 codes based on the French data, where the assignment in 5-digit codes can be converted to less precise 3-digit codes. Prevalence of exposure among controls subjects was not different (for asbestos: 12 vs. 12 %, $p = 0.38$; for PAH: 7 vs. 8 %, $p = 0.17$) except for the assignment of exposure to metals (5 vs. 7 %, $p = 0.05$). Although the prevalence of metal exposure changed, this change was similar among cases and controls so it would not substantially change the risk estimate of CNS tumors in relation to metal exposure. Furthermore, we cannot rule out some unmeasured confounders; however, as few risk factors of CNS tumors are established, it is not obvious what could confound the investigated associations. Finally, we cannot exclude that our multiple comparisons could have led to a statistically significant result only due to chance.

Our finding about paternal occupational exposure to PAH was consistent with Cordier et al., who found an increased risk of childhood brain tumor with paternal occupational exposure to PAH before conception, as well as with paternal smoking [13]. It has also been demonstrated by Gaspari et al. [30] that occupational exposure to PAH is significantly associated with DNA adducts in the sperm, which could be a sign of severe DNA damage, and may explain how exposure impact on the risk of cancer in the child.

The slight positive association we found between paternal occupational exposure around conception and diagnosis to asbestos and risk of CNS tumors was also reported in a study from Feingold et al., who studied occupational exposure during the year prior to child's birth, although not significant (OR 1.7, 95 % CI 0.6–5.3) [16]. The highest effect among fathers exposed to high levels of asbestos also strengthens this finding. The risk estimate was highest in the German study. This is the oldest study, which could imply higher exposure levels and less protective measures against occupational exposure to asbestos

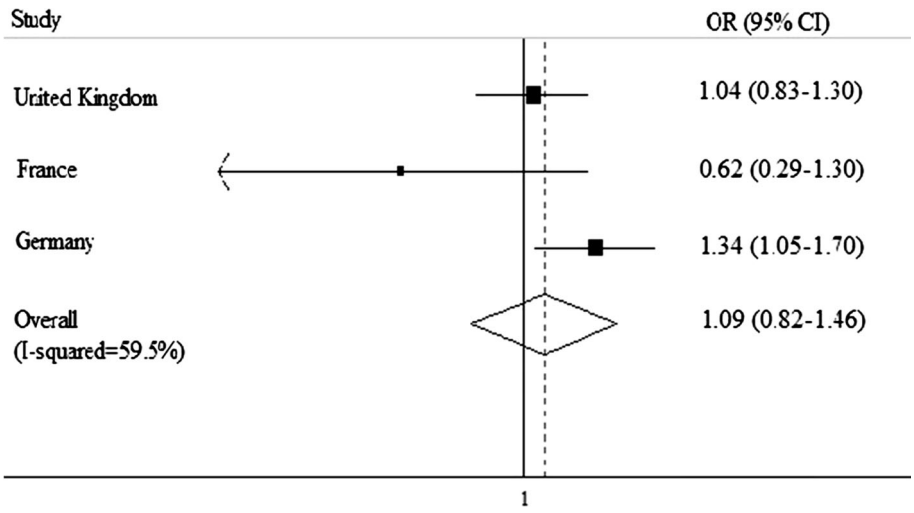

Fig. 1 Forest plot for paternal occupational exposure to asbestos, by country

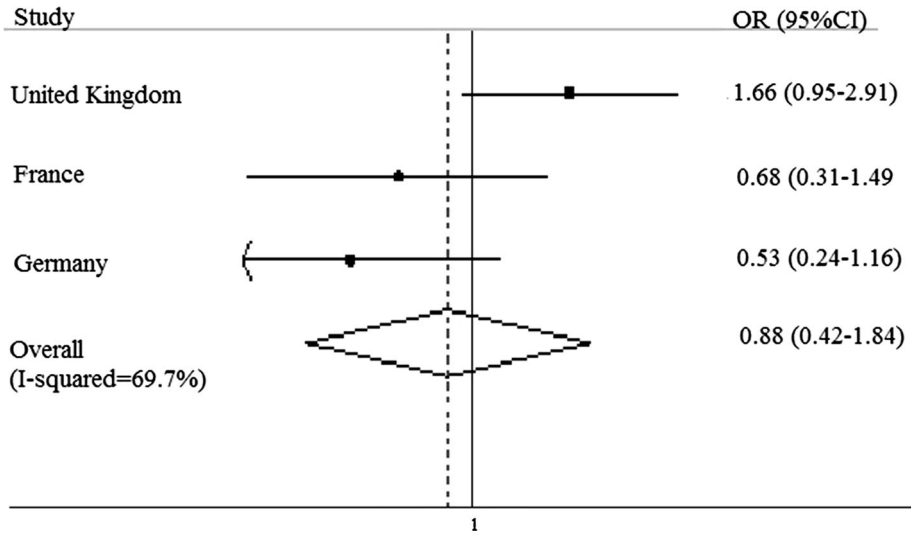

Fig. 2 Forest plot for maternal occupational exposure to DME, by country

in the late 1970s to early 1990s when those children were born; asbestos was banned in Germany in 1993 [21]. Our finding about the paternal exposure to asbestos may be explained by the fact that fathers can bring back home asbestos fibers on their clothes or hair [31]. A cohort study of adults living in Wittenoom during their childhood, Western Australia, which was a town surrounded by asbestos mines and mills, has shown that there was an increased risk of brain tumor among both men and women, although it was non-occupational exposure and the number of cases were small (5 and 4 brain tumor cases for men and women, respectively) [32]. Moreover, one study from Pan et al. [33] found that exposure to asbestos could be possibly associated with adult brain tumor, as well as one case report about a man exposed to asbestos at work for years diagnosed with a malignant astrocytoma, with asbestos fibers found in the brain [34]. We have at present no biological evidence of a link between parental occupational exposure to asbestos and childhood CNS tumors, and adult tumors differ markedly from those diagnosed in children.

We observed a non-significant positive association between paternal occupational exposure to metals and the risk of CNS tumors. Previous findings from an USA population-based case–control study suggested a non-significant association between childhood brain cancer and paternal occupational exposure to nickel during the year prior to the birth of the child (OR 1.7, 95 % CI 0.5–5.8) but no association with chromium (OR 0.8, 95 % CI 0.3–2.8); however, their sample was small, with 5 and 9 exposed cases for these agents, respectively [16], and we would like to notice that our analyses done with nickel and chromium separately did not lead to different results. Another study from Feychting et al. [10] did not show any association with paternal occupational exposure to chromium/nickel

before conception (OR 0.26, 95 % CI 0.04–1.85), but only one case was exposed. We are not aware of any potential physiopathological mechanism to explain how exposure to metals could have an impact on CNS tumor risk. The association has not been reported before in the literature; hence, we cannot exclude the role of an unknown confounder, or a chance finding.

Peters et al. [14] showed a somewhat increased risk of childhood brain tumors for maternal exposure to diesel exhaust any time before birth (OR 1.77, 95 % CI 0.96–3.26) in a study including 293 cases and 935 controls. We could not replicate this finding; a potential explanation could be that they assessed exposure to DME more precisely, based on the job characteristics by a priori exposure rules and not job titles alone. Nevertheless, DME also contain PAH, and we found a non-significant positive association between paternal exposure to PAH and childhood CNS tumor risks.

Parental social class could also be a confounder. Keegan et al. [35] reported that the risk of astrocytoma and other gliomas increased with higher social class in a study based on the National Registry of Childhood Tumors in Great Britain. However, using parental educational level as a proxy of social class in our study did not change the results. Social class is linked to job titles and thus to occupational exposures, so if high social class would be associated with increased risk of CNS tumors in our data, we would expect reduced odds ratios for the exposures we studied, because these exposures are more frequent among workers in lower social classes.

In conclusion, our study showed weak evidence of a modest association between paternal occupational exposure to PAH and CNS tumor risk. For PAH, this is consistent with previous studies, but altogether there are still too few to allow firm conclusions. Our findings regarding an association between CNS tumor risk and parental exposure to asbestos are intriguing but need to be confirmed in further investigations. The positive association between paternal exposure to metals and CNS tumor risk has to be interpreted with care, as there is little evidence from other studies. As there are still so many unknown risk factors in childhood CNS tumors and explanation of plausible biological mechanisms between occupational exposure and CNS tumor risk still remains sparse, opportunities of either experimental studies or larger epidemiological studies could provide further important results.

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Conflict of interest None.

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