Title

Parental occupational exposure to diesel engineexhaust in relation to childhood leukaemia andcentral nervous system cancers: a register-basednested case-control study in Denmark 1968–2016

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Abstract

Objectives Using nationwide register data, we investigated the association between maternal and paternal perinatal employment in industries with exposure to diesel engine exhaust and risk of leukemia and central nervous system (CNS) cancers, including certain subtypes.

Methods Children aged <=19 years old and diagnosed with childhood cancer from 1968–2016 were identified in the Danish Cancer Registry and 25 randomly selected cancer free controls per case were matched by age and sex. Parents were identified in the Danish Civil Registration System and employment histories were retrieved from a nationwide mandatory pension fund. The probability of exposure to diesel engine exhaust was assessed using a validated job exposure matrix. Conditional logistic regression was used for estimation of odds ratios (OR), including their 95% confidence intervals (95% CI).

Results Maternal employment in industries with diesel engine exhaust exposure was associated with an increased risk of CNS cancers (OR 1.31, 95% CI 0.99–1.74) and of astrocytoma (OR 1.49, 95% CI 1.04–2.14) in offspring. The highest OR for these cancers were seen for mothers with highest probability of exposure to diesel engine exhaust. For fathers, ORs for cancers under study were close to one. No increased risks of leukemias were found for neither mothers nor fathers employed in diesel industries.

Conclusions Risks were increased for CNS and astrocytoma for maternal employment in industries with diesel engine exhaust.

Key terms: Childhood cancer, parental occupational exposure, diesel engine exhaust, register-based study, job-exposure matrix

What is already known about this subject?

Studies have been conducted on primarily paternal exposure to diesel engine exhaust and they display discrepant results for childhood leukemia and for central nervous system cancers. However, exposure assessment is complicated by grouping of various exposure sources and job titles making comparisons difficult.

What are the new findings?

This register-based study found that maternal employment in industries with exposure to diesel engine exhaust is associated with CNS cancers, in particular astrocytoma, and indicates a dose-response relationship for the latter. No increases were seen after paternal exposure.

How might this impact on policy or clinical practice in the foreseeable future?

Studies on various effects of exhaust is important and especially a distinction between diesel engine exhausts and petrol exhausts, as policy makers may introduce regulations on these matters.

Introduction

Although childhood cancer is rare, it is estimated that more than 300,000 children under the age of 20 were diagnosed with cancer worldwide between 2001-2010. (1)

Little is known about the etiology of childhood cancers, yet, aside from new mutations or genetic syndromes, parental occupational exposures are suggested as contributing factors (2). Effects from maternal exposures can happen either before conception, during pregnancy through direct or indirect exposure of the womb or after birth through breastfeeding (3). For paternal exposures, effects may take place through epigenetic changes transferred by the sperm (4) or new mutations among other mechanisms.

Diesel engine exhaust consists of a complex mixture of gases and particles, is common in several industries and has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC) (IARC group 1). IARC considered whether diesel exhaust may be a cause of childhood cancers, but a conclusion was not reached due to the small number of studies available (5).

Older studies have primarily investigated exposures arising across industries such as hydrocarbons or polycyclic aromatic hydrocarbons (PAH), or industries where workers presumably are exposed to exhausts. Larger studies are needed focusing on exhausts, which includes a broad mixture of chemicals, and differentiating between various types of exhaust. Generally, results are based on few exposed cases and display inconsistent results for leukemia and central nervous system cancers for both maternal and paternal exposures and employment in relevant industries (6-11). While there is a growing literature on ambient exposure to traffic pollution and childhood cancer, no studies have reported on diesel specifically. Notably, however, studies of leukemia in relation to ambient traffic exposure have found higher effect estimates in Europe compared to the US (12), and Europe has a much higher proportion of diesel cars registered (in 2008, 58% of cars in the EU vs. <3% in the US) (13).

Retrospective assessment of parental occupational exposures is methodologically difficult in epidemiological studies. As population-based occupational information is not available in many countries, exposure assessments have most often been based on interviews, questionnaires and sometimes proxy informants e.g. mothers reporting the fathers' exposure or tasks. Though several studies used expert assessment to evaluate exposure, the use of proxy informants may have caused recall bias.

In this relatively large case-control study for these rare cancers, we explored the association between exposure to diesel engine exhaust in both mothers and fathers and risk of childhood cancer in offspring. We used registry-based data on employment history and a job exposure matrix and validated cancer registry-based diagnoses.

Methods and material

Cases ascertainment and control selection

Cancer cases aged <=19 years and diagnosed with leukemia (n= 2,039) and CNS cancers (n= 1,141) were identified in the Danish Cancer Registry in the period 1968-2016. Subtypes of childhood cancer (acute lymphoblastic leukemia, acute myeloid leukemia, astrocytoma, medulloblastoma), as well as prenatal cancers (n= 2,737), thought to have originated in utero [i.e. acute lymphoblastic leukemia, Wilms tumor (nephroblastoma), medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma] (14, 15) were also included and grouped together. The Danish Cancer Registry was established in 1942 and contains information on morphology, topography, sex, and age at diagnosis, which is subjected to quality control and is updated regularly (16). Diagnosis was based on a Danish modification of the International Classification of Diseases, Revision 7 (ICD-7) before 1978 from reporting forms, a converted version of ICD-7 to ICD-10 until 2004 and subsequently ICD-10, while morphology and topography was recorded according to ICCC-1 and ICCC-3 (16).

A unique 10-digit personal identifier, the CPR-number, is given to all Danish residents in Denmark and is used in all registries in the country. This secures correct linkages and avoiding multiple counts of same case. The CPR-numbers are confined to the Civil Registration System, which was established in 1968; it contains and continuously updates information on parents, children, spouses, and vital status. This registry was used to randomly select and match twenty-five controls per case based on age, sex and vital status at diagnosis date of the matched case (index date) (17).

Parental employment histories

Through record linkages, parents were identified in the Civil Registration System. Employment histories of the mothers and fathers were obtained through the Supplementary Pension Fund, including mandatory membership for all employees. Records hold information on the employee (CPR-number and name), the start and end of each employment, and a unique 8-digit company number. Companies have been classified into industry code “Danmarks Statistiks Erhvervsgrupperingskode”, DSE-77, corresponding to an extended version of the International Standard Industrial Classification of all Economic Activities from 1968. All information is kept even if a worker has emigrated or died or the company closed (18). Mothers and fathers lacking employment records, e.g. due to employment less than 9 hours a week, being self-employed or being unemployed, were excluded in order to increase the comparability of included parents, i.e. all employees during relevant period of time. For mothers, exposure time was restricted to employment periods one year before to one year after birth in order to capture both the preconception and lactation periods. For fathers, exposure time was restricted to employment one year before birth to capture the period of spermatogenesis. Only parents with employment history during the period of interest were included in the study.

Parental occupational exposure to diesel engine exhaust was assessed by linkage between the DSE-77 codes and the Nordic Occupational Cancer Study job exposure matrix (NOCCA-JEM) for Denmark (NOCCA-DANJEM). The overall NOCCA-JEM was developed by a group of Nordic occupational exposure experts based on the template of the Finnish job exposure matrix and included the time periods of 1960–1974, 1975–1984 and 1985–1994 (19). The NOCCA-DANJEM was converted to the population of Denmark on the basis of measurements of diesel exposures obtained in Finland and Denmark and further adapted to Danish conditions. The NOCCA-DANJEM was used to examine ever/never employment in industries with diesel engine exhaust exposure and probability of exposure, which was categorized into two groups: parents having a 5 to 50% probability of exposure in jobs with diesel exposure and parents with ≥50% probability of exposure. Further, we examined relative risks during the available time periods adjusted to our study period while assuming no change in exposure after 1994.

Covariates

Selection of confounders was based on the availability of covariates based on which factors were investigated by other papers (20-24). Potential confounders included information on socioeconomic status (SES) at the family level, reproductive factors (parental age at birth, birth order, and parity), and, geography (place of residence at the time of birth of index child), with covariates obtained from the Civil Registration System (17). Maternal smoking status, as collected at the first midwife consultation, was considered as a confounding variable and was obtained from the Medical Birth Registry. This registry was established and computerized since 1973 and information was gathered by midwives until 1996 and from then on by hospitals. The registry has undergone revisions, and therefore maternal smoking status is available from 1991 to 2016 (25).

SES was based on the last known job title, primarily available from income tax forms and was categorized into six groups corresponding to the definition made by the Danish Institute of Social Sciences, including academics or executive managers reflecting the highest status group, higher education of intermediate duration, higher education of shorter duration, skilled work, unskilled work and unknown (26). Categories for place of residence at time of birth of the index child included rural, small town, or urban areas in Denmark, while reproductive and geographical factors were categorized as follows: maternal and paternal age at birth (≤25, 26-28, 29-33, and ≥34), birth order (first, second, and third or later) and parity (1, 2, and 3 or more). Lastly, maternal smoking status was categorized as no/yes.

Statistical analyses

Conditional logistic regression for matched case-control sets was used to estimate the relative risk of childhood cancers in offspring of parents exposed to diesel exhaust, using odds ratios (OR) and their corresponding 95% confidence intervals (95% CIs). Analyses were conducted separately for mothers and fathers, and we additionally examined whether diesel exposure in both parents was related to higher risk of selected childhood cancers compared to children who had no exposed parents. Analyses were not carried out if the number of exposed cases was less than five.

The impact of potential confounders for examined childhood cancers, including SES, reproductive factors and geography, was tested. Various models were investigated including models where we removed each factor one by one. Since the exposure-outcome association measure changed less than 10% when these factors were included, they were not considered confounders and based on this we chose to only display the unadjusted model.

Since smoking was suggested as a risk factor for some childhood cancers (23, 27), we conducted a sensitivity analysis exploring the effect of maternal smoking for diagnoses with sufficient numbers. Stata 14.2 (StataCorp, College Station, TX, USA) was used for all statistical analyses. All p-values were two-sided.

The Danish Data Protection agency approved this study, ref. No. 2008-41-2639, 2014-41-3174. As only register-based information was used, no personal consent was needed.

Results

Regarding population characteristics, cases and controls differed only marginally (Table 1).

For maternal employment in industries with exposure to diesel engine exhaust, a modestly increased risk of CNS cancers (OR 1.31, 95% CI 0.99–1.74), particularly astrocytoma (OR 1.49, 95% CI 1.04–2.14) was observed in offspring. For other subtypes of CNS only marginally increased ORs were observed based on relatively few exposed cases. No increases were observed for leukemia or prenatal cancers (Table 2). The effects of maternal diesel engine exhaust exposure generally seemed to be larger during the first study period of 1968-1974 compared to the other study periods in which no effect was found except for astrocytoma (Supplementary table 1).

For fathers, no deviations from unity were observed (Table 3). No clear pattern was found when investigating paternal exposure to diesel engine exhaust in the three available time periods based on information from the NOCCA-DANJEM (Supplementary table 2). When both parents were exposed estimates of selected cancers did not differ compared to non-exposed parents (Table 4).

Results from our sensitivity analysis including maternal smoking did not differ significantly compared to risk estimates in our main analysis (results not shown).

Discussion

This nationwide register-based study of childhood cancers diagnosed over almost 50 years in Denmark showed that maternal occupational exposure to diesel exhaust was associated with an increased relative risk of CNS tumors and astrocytomas in offspring overall and the highest OR was observed in the group with the highest probability of exposure. Also, an indication of a stronger effect of maternal employment in our selected industries in the early study period on the cancers investigated was found. For fathers, no significant associations were observed. Thus, our results are in contrast to the literature on ambient exposure to traffic pollution and childhood cancer, which largely has reported increases in leukemia with less clear increases in CNS cancers and especially astrocytoma though some studies report positive associations (28-31). The ambient traffic pollution studies include emissions from all on-road sources which can include substantial emissions from non-diesel cars. Hence, our findings suggest that the unique constituents of diesel may appear relevant for astrocytomas specifically.

Although biological mechanisms for transmission of parental exposure to children are still poorly understood, perhaps maternal exposure may be of greater importance in relation to childhood cancer than paternal exposure since we only observed increased risks for maternal exposure rather than when both parents were exposed.

Occupational maternal exposure to diesel exhaust has been linked to specific genetic mutations found in cord blood (32, 33). Timing of parental exposure in relation to conception and pregnancy has been investigated by several studies (9, 11, 34, 35). Further, postnatal environmental exposures are also proposed as a contributing factor for childhood cancers and in some industries substances parents may inadvertently be transferred to the child on clothes, hair etc. These different mechanisms may explain the observed cancer susceptibility in children of mothers exposed to diesel exhaust in our study. Due to the relatively small number of exposed mothers, along with that mothers were unlikely to change jobs in the perinatal period, we were not able to distinguish between effects of maternal exposure before conception, during gestation, and after birth. However, we were able to investigate different study periods defined by the NOCCA-DANJEM, which indicated that effects were larger for maternal employment in the selected industries during the early study period compared to the two later periods. Perhaps this can be attributed to protection devises used in the later time periods.

The proportion of Danish women participating in the workforce has remained stably high during the study period (36). The ten most common industries for female employment with exposure to diesel engine exhaust (Supplementary table 5) were often characterized as being in the lower exposed category (probability of exposure under 50%). This distribution of industries remained stable throughout the three available JEM-periods. We found the same pattern for paternal employment. Since we found increased risks of cancer in off for maternal employment not neither for paternal employment nor combined maternal and paternal employment, this suggests that perhaps different underlying biological mechanisms are at play. Only few studies of epigenetic effect on cancer in humans have been conducted, yet it is a hypothesis that remains to be fully examined. As only few cases had both maternal and paternal exposure, results must be interpreted carefully.

Several changes may have occurred during the study period. Information on benzene contents, which has been linked with childhood AML (37) in diesel during the early time period investigated was not available for Denmark. However, gasoline contained around 1 % weight/weight benzene during the late 1960’s and early 1970’s in Denmark (38) and may have contained various potentially carcinogenic substances such as sulphur or lead. Since exposure to diesel engine exhaust and gasoline exhaust may have overlapped, we cannot rule out that mothers have also been exposed to benzene and that this contributed to the observed results, at least until 1974, after which benzene was largely phased out of Danish workplaces. Analyses of maternal employment in relation to JEM periods showed increased risks for CNS cancer and astrocytoma before 1975 and and lower point estimates observed after 1975, indicating that certain substances in the former period may contribute to these findings. However, we would not have expected this to lead to an increased risk of CNS cancers as seen, but rather leukemia cases.

To our knowledge, no other studies have investigated various time periods in relation to maternal employment.

Previous studies on maternal perinatal exposure to diesel engine exhaust are few and display inconsistent results and they have been conducted on a relatively small number of cancers and exposed mothers (6, 8, 10, 11). More studies have examined fathers employed in occupations and industries with exposure to diesel engine exhausts in relation to both leukemia and CNS cancer risk in offspring but they also show inconsistent results (7, 8, 35, 39-41), yet some larger studies had increased ORs (6, 11, 34, 42). The largest studies were performed in England from 1962–2006 using exposure assessment from job titles in birth registration forms (43, 44) and did not find a positive association for fathers with leukemia or overall CNS cancers, which is consistent with our findings. Several other previous studies typically used interviews and self-administered questionnaires when assessing exposure to diesel exhaust in parents, which might be prone to recall or participation biases, with recall bias potentially causing exposure misclassification leading to an overestimation of the true association (6, 9, 10, 34, 41) yet some studies evaluated exposure using expert assessment or JEMs. In addition, studies covered various grouping of job titles, industries or exposures and also investigated different time periods further complicating comparisons.

However, there are limitations in our study. As laws on maternity leave from 1960 gave all women the right to leave work up to eight weeks prior to births, this may mean that we, at least for a subgroup of mothers, only investigated the potential effects of employment in diesel engine exhaust industries in the first two-thirds of pregnancy. The period of leave postnatally changed during the study period.

Since paternity leave is granted after birth, this would not have affected results in our study (36).

Further, NOCCA-DANJEM assumes uniform exposure across industries and cannot determine individual exposures, which might have induced exposure misclassification leading to an attenuation of the OR towards the null. Further, we assumed that exposure was the same throughout the study period, which might have led to exposure misclassification.

The composition of exhaust depends, among other parameters, on the types of engines, the types of vehicles and the technologies controlling the composition of the exhaust, which has all changed during the study period (5). Yet it was not possible to pinpoint exact times for implementation of changes possibly affecting exposures in order to conduct further sub analyses, as turnover of on-road vehicles may take many years. We did, however, use the time periods specified in the NOCCA-DANJEM as a proxy for changes in exposures during the study period. In addition, a distinction between diesel and gasoline exhaust exposure was not possible and exposures likely overlap. Lastly, many different occupations are exposed to diesel engine exhaust at different levels, and protective factors such as air filters and wind direction also influence the level of exposure, further complicating exposure assessment and potentially introducing misclassification (5). Further, individual domestic and environmental exposure to diesel exhaust could not be accounted for, which may have induced bias if cases live in locations with higher or lower ambient exposures than controls. In addition, ambient air pollution may affect exposure but home air pollution exposure information was not available for us to investigate further. Nevertheless, these effects may have been limited; when controlling for our geography variable as a proxy for domestic exposure at birth, risks were not affected. Also, a Danish study investigating air pollution found increased risks of Hodgkin lymphoma but no other types of childhood cancers, thus supporting our results(29). It it also possible that unknown factors have impacted results why it would have been interesting to perform a neughbourhood cluster analysis, but data was not available for this.

Still, there are several strengths to our study. We were able to identify a large number of childhood cancer cases from the Danish Cancer Registry. In addition, we could also identify a relatively large percentage of both mothers (100%) and fathers (99.4%) and their full job history using updated nationwide registries with high coverage and validity (16-18). Further, using a validated JEM this is one of the first studies to have specifically targeted diesel exposure in both parents combined when examining associated childhood cancers. By prospective collection of occupational data linked to the JEM, recall bias was avoided. Lastly, the proportion of women employed in the Danish workforce has remained stably high since the 1960's and 1970's with more than 70% employed outside the home.

Conclusion

Policymakers concerned about the health and environmental effects of occupational exposures can shape policies encouraging or discouraging the use of diesel vehicles. Hence it remains important in research studies to differentiate the risks incurred from diesel exposures from the risks from gasoline. Our study does lend some support to the hypothesis that maternal exposure to diesel engine exhaust may increase the risk of CNS cancers and the specific subtype astrocytoma in offspring. However, large epidemiological studies exploring the association between paternal and especially maternal exposure to diesel exhaust and childhood cancers are warranted, including studies of environmental models that can differentiate the two exposures.

Conflicts of interest

None declared.

Contributors

JV performed programming of data, analyses, participated in interpretation of results and wrote the manuscript. KS participated in the interpretation of results and critically reviewed the manuscript. JEH was a key participant in the design of the study, interpretation of results and critical review of the manuscript. JH was a key participant in designing the study, collection of data, programming of data, interpretation of results, and supervised the writing of the manuscript.

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Tables

Table 1 Characteristics of the population

	Leukemia								Acute lymphoblastic leukemia							
	Mothers				Fathers				Mothers				Fathers			
	Cases n= 1,673		Controls n= 39,107		Cases n= 1,811		Controls n= 44,255		Cases n= 1,304		Controls n= 30,185		Cases n= 1,397		Controls n= 34,022	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%
Child's sex																
Boy	922	55.1	21,930	56.1	1,004	55.4	24,627	55.6	745	57.1	17,456	57.8	799	57.2	19,545	57.4
Girl	751	44.9	17,177	43.9	807	44.6	19,628	44.4	559	42.9	12,729	42.2	598	42.8	14,477	42.6
Child's age at diagnosis																
0-4	728	52.7	16,778	51.9	774	51.8	18,997	52.0	440	34.4	10,119	34.2	591	51.6	14,430	51.8
5-9	321	23.2	7,679	23.8	358	23.9	8,595	23.5	529	41.4	12,315	41.6	310	27.1	7,482	26.8
10-14	186	13.5	4,233	13.1	199	13.3	4,792	13.1	187	14.6	4,242	14.3	147	12.8	3,497	12.5
15-19	146	10.6	3,622	11.2	164	11.0	4,160	11.4	123	9.6	2,955	10.0	97	8.5	2,462	8.8
Birth order																
First	780	46.6	17,919	45.8	796	44.0	19,178	43.3	287	22.0	6,055	20.1	624	44.7	14,735	43.3
Second	621	37.1	14,590	37.3	689	38.0	16,876	38.1	660	50.6	15,429	51.1	521	37.3	12,957	38.1
Third or later	272	16.3	6,598	16.9	326	18.0	8,201	18.5	357	27.4	8,701	28.8	252	18.0	6,330	18.6
Family																

socioeconomic status																
Academics	167	10.0	3,900	10.0	172	9.5	4,412	10.0	137	10.5	3,018	10.0	137	9.8	3,417	10.0
Middle education	234	14.0	5,554	14.2	244	13.5	5,748	13.0	187	14.3	4,266	14.1	193	13.8	4,391	12.9
Shorter education	226	13.5	5,909	15.1	231	12.8	6,145	13.9	176	13.5	4,571	15.1	181	13.0	4,739	13.9
Skilled	430	25.7	9,667	24.7	469	25.9	11,206	25.3	334	25.6	7,463	24.7	361	25.8	8,604	25.3
Unskilled	234	14.0	5,384	13.8	274	15.1	6,583	14.9	183	14.0	4,166	13.8	210	15.0	5,033	14.8
Unknown	382	22.8	8,693	22.2	421	23.2	10,161	23.0	287	22.0	6,701	22.2	315	22.5	7,838	23.0
Parental age at birth of the index child																
<=25	388	23.2	10,086	25.8	229	12.6	6,250	14.1	299	22.9	7,678	25.4	162	11.6	4,743	13.9
26-28	397	23.7	8,985	23.0	343	18.9	8,392	19.0	309	23.7	6,922	22.9	264	18.9	6,465	19.0
29-33	560	33.5	12,933	33.1	636	35.1	15,314	34.6	436	33.4	10,071	33.4	505	36.1	11,745	34.5
>=34	328	19.6	7,103	18.2	603	33.3	14,299	32.3	260	19.9	5,514	18.3	466	33.4	11,069	32.5
Childs birthplace																
Urban	525	31.4	12,765	32.6	584	32.2	14,617	33.0	419	32.1	9,766	32.4	465	33.3	11,135	32.7
Small town	523	31.3	12,328	31.5	568	31.4	14,312	32.3	403	30.9	9,499	31.5	430	30.8	10,981	32.3
Rural	625	37.4	14,014	35.8	659	36.4	15,326	34.6	482	37.0	10,920	36.2	502	35.9	11,906	35.0
Number of children																
1	365	21.8	8,079	20.7					287	22.0	6,055	20.1				

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2	849	50.7	19,699	50.4	660	50.6	15,429	51.1
3 or more	459	27.4	11,329	29.0	357	27.4	8,701	28.8
Maternal smoking during pregnancy 1991-2015								
No	601	75.1	13,691	75.3	475	74.9	10,683	75.2
Yes	164	20.5	3,683	20.2	130	20.5	2,869	20.2
Unknown	35	4.4	818	4.5	29	4.6	652	4.6

Table 1 Characteristics of the population

	Acute myeloid leukemia								CNS							
	Mothers				Fathers				Mothers				Fathers			
	Cases n= 264		Controls n= 6,171		Cases n= 287		Controls n= 6,957		Cases n= 926		Controls n= 22,064		Cases n= 1,003		Controls n= 24,780	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%
Child's sex																
Boy	254	96.2	5,876	95.2	135	47.0	3,239	46.6	495	53.5	11,703	53.0	534	53.2	13,149	53.1
Girl	10	3.8	295	4.8	152	53.0	3,718	53.4	431	46.5	10,361	47.0	469	46.8	11,631	46.9
Child's age at diagnosis																
0-4	117	46.2	2,610	44.0	118	48.6	2,899	49.3	277	36.4	6,222	34.2	287	34.8	7,009	34.3
5-9	34	13.4	920	15.5	34	14.0	813	13.8	227	29.9	5,559	30.5	252	30.5	6,201	30.3
10-14	43	17.0	1,019	17.2	41	16.9	949	16.1	143	18.8	3,571	19.6	159	19.3	3,994	19.5
15-19	59	23.3	1,388	23.4	50	20.6	1,223	20.8	113	14.9	2,851	15.7	127	15.4	3,235	15.8
Birth order																
First	116	43.9	2,851	46.2	117	40.8	3,049	43.8	440	47.5	10,198	46.2	452	45.1	10,870	43.9
Second	106	40.2	2,330	37.8	118	41.1	2,664	38.3	348	37.6	8,257	37.4	385	38.4	9,474	38.2
Third or later	42	15.9	990	16.0	52	18.1	1,244	17.9	138	14.9	3,609	16.4	166	16.6	4,436	17.9
Family socioeconomic status																
Academics	24	9.1	609	9.9	26	9.1	669	9.6	105	11.3	2,226	10.1	111	11.1	2,421	9.8
Middle	40	15.2	881	14.3	41	14.	934	13.	12	13.	3,268	14.	12	12.		

education						3		4	7	7		8	8	8	3,374	13.6
Shorter education	34	12.9	949	15.4	30	10.5	977	14.0	153	16.5	3,626	16.4	159	15.9	3,731	15.1
Skilled	58	22.0	1,562	25.3	68	23.7	1,778	25.6	235	25.4	5,973	27.1	262	26.1	6,851	27.6
Unskilled	37	14.0	858	13.9	46	16.0	1,071	15.4	120	13.0	3,038	13.8	143	14.3	3,803	15.3
Unknown	71	26.9	1,312	21.3	76	26.5	1,528	22.0	186	20.1	3,933	17.8	200	19.9	4,600	18.6
Parental age at birth of the index child																
<=25	62	23.5	1,690	27.4	44	15.3	1,023	14.7	265	28.6	6,187	28.0	152	15.2	3,740	15.1
26-28	60	22.7	1,460	23.7	53	18.5	1,355	19.5	242	26.1	5,254	23.8	210	20.9	5,052	20.4
29-33	86	32.6	1,953	31.6	92	32.1	2,436	35.0	276	29.8	7,062	32.0	375	37.4	8,703	35.1
>=34	56	21.2	1,068	17.3	98	34.1	2,143	30.8	143	15.4	3,561	16.1	266	26.5	7,285	29.4
Childs birthplace																
Urban	75	28.4	2,045	33.1	82	28.6	2,340	33.6	317	34.2	6,997	31.7	338	33.7	7,968	32.2
Small town	87	33.0	1,973	32.0	94	32.8	2,260	32.5	285	30.8	7,234	32.8	318	31.7	8,239	33.2
Rural	102	38.6	2,153	34.9	111	38.7	2,357	33.9	324	35.0	7,833	35.5	347	34.6	8,573	34.6
Number of children																
1	55	20.8	1,348	21.8					186	20.1	3,921	17.8				
2	135	51.1	2,998	48.6					461	49.8	11,330	51.4				
3 or more	74	28.0	1,825	29.6					27	30.	6,813	30.				

					9	1		9
Maternal smoking during pregnancy 1991-2015								
No	86	74.8	1,968	75.5	268	70.3	6,300	72.8
Yes	23	20.0	521	20.0	89	23.4	1,956	22.6
Unknown	6	5.2	116	4.5	24	6.3	401	4.6

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Table 1 Characteristics of the population

	Astrocytoma								Ependymoma							
	Mothers				Fathers				Mothers				Fathers			
	Cases n=503		Controls n= 12,210		Cases n=548		Controls n= 13,644		Cases n= 136		Controls n= 3,112		Cases n=142		Controls n= 3,490	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Child's sex																
Boy	244	48.5	5,903	48.3	263	48.0	6,578	48.2	79	58.1	1,766	56.7	83	58.5	1,986	56.9
Girl	259	51.5	6,307	51.7	285	52.0	7,066	51.8	57	41.9	1,346	43.3	59	41.5	1,504	43.1
Child's age at diagnosis																
0-4	131	28.2	2,965	26.1	136	29.6	3,302	29.1	59	46.5	1,339	46.6	64	54.7	1,538	53.2
5-9	150	32.3	3,647	32.1	147	32.0	3,593	31.7	29	22.8	628	21.8	21	17.9	494	17.1
10-14	102	21.9	2,675	23.5	97	21.1	2,474	21.8	21	16.5	459	16.0	14	12.0	370	12.8
15-19	82	17.6	2,082	18.3	79	17.2	1,965	17.3	18	14.2	450	15.6	18	15.4	487	16.9
Birth order																
First	237	47.1	5,639	46.2	247	45.1	5,980	43.8	68	50.0	1,454	46.7	66	46.5	1,571	45.0
Second	188	37.4	4,548	37.2	204	37.2	5,196	38.1	46	33.8	1,166	37.5	50	35.2	1,326	38.0
Third or later	78	15.5	2,023	16.6	97	17.7	2,468	18.1	22	16.2	492	15.8	26	18.3	593	17.0
Family socioeconomic status																
Academics	52	10.3	1,225	10.0	51	9.3	1,333	9.8	16	11.8	330	10.6	18	12.7	358	10.3
Middle	67	13.3	1,788	14.6	69	12.	1,835	13.	21	15.	502	16.	19	13.	496	14.

education						6		4		4		1		4		2
Shorter education	89	17.7	2,027	16.6	95	17.3	2,065	15.1	23	16.9	509	16.4	24	16.9	527	15.1
Skilled	120	23.9	3,274	26.8	137	25.0	3,683	27.0	36	26.5	812	26.1	40	28.2	970	27.8
Unskilled	65	12.9	1,687	13.8	79	14.4	2,109	15.5	12	8.8	439	14.1	14	9.9	535	15.3
Unknown	110	21.9	2,209	18.1	117	21.4	2,619	19.2	28	20.6	520	16.7	27	19.0	604	17.3
Parental age at birth of the index child																
<=25	138	27.4	3,374	27.6	78	14.2	2,020	14.8	43	31.6	928	29.8	22	15.5	527	15.1
26-28	134	26.6	2,917	23.9	104	19.0	2,765	20.3	36	26.5	719	23.1	33	23.2	731	20.9
29-33	155	30.8	3,927	32.2	215	39.2	4,822	35.3	37	27.2	1,007	32.4	56	39.4	1,236	35.4
>=34	76	15.1	1,992	16.3	151	27.6	4,037	29.6	20	14.7	458	14.7	31	21.8	996	28.5
Childs birthplace																
Urban	174	34.6	3,873	31.7	186	33.9	4,374	32.1	42	30.9	1,017	32.7	43	30.3	1,165	33.4
Small town	153	30.4	3,918	32.1	173	31.6	4,459	32.7	44	32.4	1,049	33.7	47	33.1	1,188	34.0
Rural	176	35.0	4,419	36.2	189	34.5	4,811	35.3	50	36.8	1,046	33.6	52	36.6	1,137	32.6
Number of children																
1	97	19.3	1,981	16.2					36	26.5	702	22.6				
2	245	48.7	6,351	52.0					64	47.1	1,520	48.8				
3 or more	161	32.0	3,878	31.8					36	26.5	890	28.6				
Maternal																

smoking during pregnancy								
No	151	69.9	3,639	73.5	36	70.6	783	73.1
Yes	51	23.6	1,071	21.6	12	23.5	236	22.0
Unknown	14	6.5	239	4.8	3	5.9	52	4.9

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Table 1 Characteristics of the population

	Medulloblastoma								Prenatal cancers							
	Mothers				Fathers				Mothers				Fathers			
	Cases n=222		Controls n= 5,184		Cases n=242		Controls n= 5,864		Cases n= 2,242		Controls n= 52,357		Cases n= 2,448		Controls n= 59,320	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Child's sex																
Boy	141	63.5	3,228	62.3	152	62.8	3,657	62.4	1,279	57.0	29,858	57.0	1,393	56.9	33,607	56.7
Girl	81	36.5	1,956	37.7	90	37.2	2,207	37.6	963	43.0	22,499	43.0	1,055	43.1	25,713	43.3
Child's age at diagnosis																
0-4	75	36.8	1,633	34.2	75	39.1	1,857	38.9	1,195	59.0	27,602	58.4	1,289	61.8	31,323	61.8
5-9	80	39.2	1,916	40.2	70	36.5	1,760	36.9	486	24.0	11,529	24.4	476	22.8	11,496	22.7
10-14	32	15.7	740	15.5	30	15.6	702	14.7	218	10.8	4,993	10.6	199	9.5	4,719	9.3
15-19	17	8.3	481	10.1	17	8.9	451	9.5	125	6.2	3,133	6.6	122	5.8	3,117	6.2
Birth order																
First	110	49.5	2,382	45.9	111	45.9	2,537	43.3	1,051	46.9	24,015	45.9	1,079	44.1	25,670	43.3
Second	89	40.1	1,947	37.6	103	42.6	2,259	38.5	834	37.2	19,497	37.2	936	38.2	22,673	38.2
Third or later	23	10.4	855	16.5	28	11.6	1,068	18.2	357	15.9	8,845	16.9	433	17.7	10,977	18.5
Family socioeconomic status																
Academics	32	14.4	516	10.0	35	14.5	553	9.4	238	10.6	5,254	10.0	247	10.1	5,879	9.9
Middle	30	13.	732	14.	29	12.0	785	13.4	323	14.	7,405	14.	335	13.	7,669	12.

education		5		1						4		1		7		9
Shorter education	33	14.9	828	16.0	32	13.2	865	14.8	299	13.3	8,019	15.3	317	12.9	8,346	14.1
Skilled	55	24.8	1,432	27.6	60	24.8	1,663	28.4	562	25.1	13,045	24.9	628	25.7	15,109	25.5
Unskilled	31	14.0	694	13.4	38	15.7	876	14.9	307	13.7	7,065	13.5	366	15.0	8,784	14.8
Unknown	41	18.5	982	18.9	48	19.8	1,122	19.1	513	22.9	11,569	22.1	555	22.7	13,533	22.8
Parental age at birth of the index child																
<=25	62	27.9	1,422	27.4	1	0.4	46	0.8	543	24.2	13,539	25.9	304	12.4	8,415	14.2
26-28	59	26.6	1,253	24.2	122	50.4	2,443	41.7	519	23.1	11,970	22.9	473	19.3	11,294	19.0
29-33	65	29.3	1,632	31.5	78	32.2	2,202	37.6	749	33.4	17,195	32.8	879	35.9	20,439	34.5
>=34	36	16.2	877	16.9	41	16.9	1,173	20.0	431	19.2	9,653	18.4	792	32.4	19,172	32.3
Childs birthplace																
Urban	73	32.9	1,604	30.9	77	31.8	1,854	31.6	732	32.6	17,028	32.5	826	33.7	19,458	32.8
Small town	70	31.5	1,731	33.4	78	32.2	1,981	33.8	701	31.3	16,669	31.8	775	31.7	19,412	32.7
Rural	79	35.6	1,849	35.7	87	36.0	2,029	34.6	809	36.1	18,660	35.6	847	34.6	20,450	34.5
Number of children																
1	46	20.7	1,003	19.3					577	25.7	12,812	24.5				
2	121	54.5	2,634	50.8					1,101	49.1	25,749	49.2				
3 or more	55	24.8	1,547	29.8					564	25.2	13,796	26.3				
Maternal																

smoking during pregnancy 1991-2015								
No	62	67.4	1,522	70.8	788	73.1	18,104	75.4
Yes	23	25.0	536	24.9	240	22.3	4,876	20.3
	7	7.6	91	4.2	50	4.6	1,042	4.3

Table 2 Unadjusted Odds Ratios (OR) and 95% confidence interval (95% CI) for offspring of mothers exposed to diesel engine exhaust in the year before birth to the year after birth of index child

	Overall exposure to diesel engine exhaust			Probability of exposure to diesel engine exhaust under 50 %		Probability of exposure to diesel engine exhaust over 50 %	
	Total cases and controls n	Exposed cases and controls n	OR (95% CI)	Exposed cases and controls n	OR (95% CI)	Exposed cases and controls n	OR (95% CI)
Leukemia	1,643/38,915	80/1,775	1.06 (0.84–1.34)	68/1,503	1.76 (0.83–1.37)	12/272	1.01 (0.56–1.81)
Acute lymphoblastic leukemia	1,280/30,035	62/1,362	1.07 (0.82–1.39)	55/1,157	1.12 (0.85–1.48)	7/205	0.79 (0.37–1.68)
Acute myeloid Leukemia	260/6,141	10/295	0.76 (0.40–1.44)	8/246	0.74 (0.36–1.51)	*	–
Central nervous system cancer	913/21,944	55/1,027	1.32 (0.99–1.75)	44/863	1.24 (0.91–1.70)	11/164	1.75 (0.94–3.26)
Astrocytoma	491/12,142	34/579	**1.52 (1.06–2.18)**	28/494	1.44 (0.97–2.15)	6/85	1.97 (0.84–4.58)
Medulloblastoma	222/5,150	11/229	1.09 (0.59–2.03)	9/190	1.08 (0.55–2.13)	*	–
Ependymoma	135/3,098	8/153	1.20 (0.57–2.51)	6/126	1.06 (0.46–2.48)	*	–
Prenatal cancers [a]	2,205/52,110	102/2,304	1.05 (0.85–1.28)	92/1,948	1.12 (0.90–1.39)	10/356	0.66 (0.35–1.24)

Table 3 Unadjusted Odds Ratios (OR) and 95% confidence interval (95% CI) for offspring of fathers exposed to diesel engine exhaust in the year before birth to the birth of index child

	Overall exposure to diesel engine exhaust			Probability of exposure to diesel engine exhaust under 50 %		Probability of exposure to diesel engine exhaust over 50 %	
	Total cases and controls n	Exposed cases and controls n	OR (95% CI)	Exposed cases and controls n	OR (95% CI)	Exposed cases and controls n	OR (95% CI)
Leukemia	1,806/44,178	480/11,775	0.99 (0.89–1.11)	342/8,488	0.98 (0.87–1.11)	138/3,287	1.03 (0.86–1.23)
Acute lymphoblastic leukemia	1,393/33,962	373/9,025	1.01 (0.89–1.14)	267/6,518	1.00 (0.87–1.14)	106/2,507	1.04 (0.84–1.27)
Acute myeloid Leukemia	287/6,941	75/1,883	0.95 (0.73–1.25)	54/1,376	0.94 (0.69–1.27)	21/507	0.99 (0.62–1.56)
Central nervous system cancer	1,000/24,741	263/6,658	0.97 (0.84–1.12)	189/4,836	0.95 (0.81–1.12)	74/1,822	1.00 (0.78–1.27)
Astrocytoma	546/13,624	142/3,672	0.95 (0.78–1.16)	97/2,702	0.88 (0.70–1.10)	45/970	1.15 (0.84–1.58)
Medulloblastoma	242/5,853	72/1,579	1.14 (0.86–1.51)	55/1,145	1.20 (0.87–1.63)	17/434	0.98 (0.59–1.63)
Ependymoma	142/3,487	29/940	0.70 (0.46–1.06)	20/664	0.69 (0.43–1.12)	9/276	0.72 (0.36–1.43)
Prenatal cancers [a]	2,438/59,217	652/15,777	1.00 (0.92–1.10)	472/11,484	1.00 (0.90–1.10)	180/4,293	1.03 (0.88–1.20)

Table 4 Odds ratios (OR) and 95% confidence intervals (95% CI) for offspring of both mothers and fathers exposed to diesel engine exhaust

	Total cases and controls n	Exposed cases and controls n	OR (95% CI)
Leukemia	1,104/25,410	30/711	0.96 (0.66–1.40)
Acute lymphoblastic leukemia	868/19,623	26/535	1.09 (0.72–1.63)
Central nervous system cancer	587/14,243	19/414	1.14 (0.71–1.84)
Astrocytoma	316/7,866	12/231	1.38 (0.75–2.53)
Medulloblastoma	144/3,366	5/96	1.20 (0.47–3.05)
Prenatal cancers [a]	1,497/33,997	45/942	1.06 (0.78–1.44)

a Acute lymphoblastic leukemia, Wilms tumor (nephroblastoma), medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma

Referent group is non exposed parents

Supplementary table 1 Odds Ratios (OR) and 95% confidence interval (95% CI) for offspring of mothers exposed to diesel engine exhaust in the year before birth to the year after birth of index child for various time periods defined by the job-exposure matrix NOCCA-DANJEM

	1968–1974			1975–1984			1985–2015		
	Total cases and controls n	Exposed cases and controls n	OR (95% CI)	Total cases and controls n	Exposed cases and controls n	OR (95% CI)	Total cases and controls n	Exposed cases and controls n	OR (95% CI)
Leukemia	252/6,038	17/311	1.27 (0.76–2.13)	347/8,325	10/316	0.78 (0.41–1.47)	1,044/24,552	53/1,148	1.08 (0.81–1.44)
Acute lymphoblastic leukemia	185/4,439	12/223	1.29 (0.70–2.37)	278/6,515	8/238	0.80 (0.39–1.65)	817/19,081	42/901	1.09 (0.79–1.50)
Acute myeloid Leukemia	42/974	*	-	56/1,415	*	-	162/3,752	6/172	0.78 (0.34–1.80)
Central nervous system cancer	137/3,290	14/173	**2.14 (1.19–3.84)**	247/6,017	11/235	1.13 (0.61–2.10)	529/12,637	30/619	1.18 (0.81–1.73)
Astrocytoma	64/1,609	7/82	**2.59 (1.12–5.99)**	137/3,337	9/138	1.51 (0.75–3.06)	290/7,196	18/359	1.31 (0.80–2.14)
Medulloblastoma	39/808	*	-	55/1,362	*	-	128/2,980	5/139	0.80 (0.32–1.98)
Ependymoma	22/510	*	-	34/841	*	-	79/1,747	6/88	1.61 (0.68-3.85
Prenatal cancers[a]	316/7,843	20/371	1.35 (0.84–2.17)	494/11,994	20/468	1.07 (0.67–1.69)	1,395/32,273	62/1,465	0.97 (0.75–1.26)

*n<5

a Acute lymphoblastic leukemia, Wilms tumor (nephroblastoma), medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma

Supplementary table 2 Odds Ratios (OR) and 95% confidence interval (95% CI) for offspring of fathers exposed to diesel engine exhaust the year before birth to birth of index child for various time periods defined by the job-exposure matrix NOCCA-DANJEM

	1968–1974			1975–1984			1985–2015		
	Total cases and controls n	Exposed cases and controls n	OR (95% CI)	Total cases and controls n	Exposed cases and controls n	OR (95% CI)	Total cases and controls n	Exposed cases and controls n	OR (95%
Leukemia	337/8,160	102/2,267	1.11 (0.88–1.41)	380/9,180	99/2,638	0.87 (0.69–1.10)	1,089/26,838	279/6,870	1.00 (0.8 1.15)
Acute lymphoblastic leukemia	246/5,964	80/1,660	1.23 (0.94–1.62)	297/7,148	82/2,060	0.94 (0.73–1.23)	850/20,850	211/5,305	0.97 (0.8 1.13)
Acute myeloid leukemia	56/1,303	14/377	0.82 (0.44–1.52)	64/1,567	13/444	0.65 (0.35–1.21)	167/4,071	48/1,062	1.14 (0.8 1.61)
Central nervous system cancer	176/4,348	39/1,234	0.72 (0.50–1.03)	261/6,628	73/1,846	1.01 (0.76–1.33)	563/13,765	151/3,578	1.03 (0.8 1.25)
Astrocytoma	85/2,097	19/584	0.76 (0.45–1.28)	147/3,658	39/1,032	0.92 (0.63–1.33)	314/7,869	84/2,056	1.02 (0.7 1.32)
Medulloblastoma	45/1,082	14/321	1.07 (0.56–2.05)	58/1,532	21/438	1.41 (0.82–2.46)	139/3,239	37/820	1.05 (0.7 1.54)
Ependymoma	29/690	*	–	35/903	7/231	0.74 (0.32–1.71)	78/1,894	19/514	0.88 (0.5 1.48)
Prenatal cancers[a]	440/10,559	136/2,975	1.13 (0.92–1.39)	548/13,327	158/3,814	1.01 (0.84–1.22)	1,450/35,331	358/8,988	0.95 (0.8 1.08)

*n<5

a Acute lymphoblastic leukemia, Wilms tumor (nephroblastoma), medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma

Supplementary table 3 Adjusted Odds Ratios (OR) and 95% confidence interval (95% CI) for offspring of mothers exposed to diesel engine exhaust in the year before to the year after the birth of index child

	Leukemia	Acute lymphoblastic leukemia	Acute myeloid leukemia	Central nervous system	Astrocytoma	Medulloblastoma	Ependymoma	Prenatal cancers[a]
Exposure to diesel engine exhaust	1.04 (0.83-1.31)	1.05 (0.81-1.37)	0.78 (0.41-1.49)	1.32 (0.99-1.75)	**1.49 (1.04-2.15**)	1.13 (0.60-2.11)	1.15 (0.55-2.42)	1.03 (0.84-1.27)
Socioeconomic status at the family level								
Academics and high self employed	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Middle long education"	1.00 (0.81-1.22)	0.98 (0.78-1.23)	1.18 (0.70-1.99)	0.82 (0.62-1.07)	0.86 (0.59-1.25)	0.66 (0.39-1.11)	0.85 (0.43-1.67)	0.98 (0.82-1.16)
Shorter education	0.91 (0.74-1.12)	0.86 (0.68-1.09)	1.00 (0.58-1.71)	0.86 (0.67-1.12)	0.99 (0.70-1.42)	0.63 (0.38-1.05)	0.85 (0.44-1.65)	0.84 (0.70-1.00)
Skilled worker	1.08 (0.89-1.30)	1.02 (0.83-1.26)	1.06 (0.64-1.74)	0.81 (0.63-1.03)	0.83 (0.59-1.18)	0.62 (0.39-0.99)	0.82 (0.44-1.53)	0.98 (0.83-1.15)
Unskilled worker"	1.07 (0.87-1.32)	1.01 (0.80-1.28)	1.28 (0.74-2.19)	0.79 (0.60-1.04)	0.88 (0.59-1.29)	0.73 (0.43-1.24)	0.47 (0.21-1.03)	0.99 (0.83-1.18)
Unknown"	1.06 (0.86-1.31)	0.94 (0.75-1.19)	**1.90 (1.11-3.23)**	0.93 (0.70-1.22)	1.14 (0.78-1.67)	0.63 (0.37-1.10)	0.88 (0.43-1.81)	0.95 (0.80-1.14)
Parental age	**1.02 (1.01-1.03)**	1.02 (1.00-1.03)	**1.05 (1.02-1.09)**	0.98 (0.97-1.00)	0.99 (0.97-1.01)	1.00 (0.96-1.04)	0.96 (0.92-1.01)	**1.01 (1.00-1.02)**
Number of children by mother prior to diagnosis								
1 child	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
2 children	0.96 (0.82-1.12)	0.90 (0.75-1.07)	1.16 (0.75-1.79)	0.86 (0.69-1.06)	0.78 (0.58-1.05)	1.04 (0.67-1.62)	0.79 (0.44-1.39)	0.94 (0.82-1.08)

3 or more children	0.91 (0.73-1.14)	0.86 (0.67-1.10)	1.04 (0.59-1.83)	0.91 (0.69-1.20)	0.89 (0.62-1.29)	1.08 (0.61-1.91)	0.59 (0.27-1.30)	0.93 (0.76-1.14)
Birth order								
First born	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Second born	0.94 (0.82-1.07)	0.94 (0.81-1.10)	0.91 (0.63-1.30)	1.10 (0.92-1.31)	1.11 (0.87-1.41)	0.98 (0.68-1.40)	1.11 (0.66-1.86)	0.98 (0.86-1.11)
Third born or later	0.89 (0.70-1.12)	0.91 (0.70-1.19)	0.79 (0.44-1.43)	1.02 (0.76-1.38)	1.00 (0.67-1.49)	0.57 (0.30-1.10)	1.80 (0.77-4.24)	0.90 (0.73-1.12)
Childs birth place								
Urban	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Small town	1.06 (0.94-1.20)	1.02 (0.88-1.18)	1.25 (0.91-1.72)	0.88 (0.74-1.04)	0.89 (0.71-1.11)	0.95 (0.67-1.34)	0.99 (0.63-1.54)	1.00 (0.90-1.12)
Rural	1.11 (0.98-1.26)	1.07 (0.93-1.23)	1.29 (0.94-1.77)	0.92 (0.78-1.09)	0.89 (0.71-1.11)	1.03 (0.74-1.45)	1.19 (0.76-1.84)	1.03 (0.93-1.14)

a Acute lymphoblastic leukemia, Wilms tumor (nephroblastoma), medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma

Supplementary table 4 Adjusted Odds Ratios (OR) and 95% confidence interval (95% CI) for offspring of fathers exposed to diesel engine exhaust in the year before birth to the birth of index child

	Leukemia	Acute lymphoid leukemia	Acute myeloid leukemia	Central nervous system	Astrocytoma	Medulloblastoma	Ependymoma	Prenatal cancers[a]
Exposure to diesel engine exhaust	0.99 (0.89-1.10)	1.01 (0.89-1.14)	0.95 (0.72-1.25)	0.98 (0.84-1.13)	0.96 (0.78-1.17)	1.18 (0.88-1.57)	0.71 (0.47-1.08)	1.00 (0.92-1.10)
Socioeconimic status at the family level								
Academics and high self employed	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Middle long education"	1.10 (0.90-1.34)	1.12 (0.89-1.40)	1.11 (0.67-1.84)	0.82 (0.63-1.07)	1.00 (0.69-1.45)	**0.56 (0.34-0.94)**	0.70 (0.36-1.36)	1.06 (0.89-1.25)
Shorter education	0.98 (0.80-1.20)	0.98 (0.78-1.23)	0.78 (0.45-1.33)	0.92 (0.72-1.19)	1.23 (0.87-1.75)	**0.55 (0.33-0.90)**	0.81 (0.43-1.53)	0.92 (0.77-1.09)
Skilled worker	1.10 (0.92-1.32)	1.08 (0.88-1.33)	0.97 (0.60-1.55)	0.83 (0.66-1.05)	1.01 (0.72-1.41)	**0.52 (0.33-0.81)**	0.76 (0.42-1.36)	1.02 (0.87-1.19)
Unskilled worker"	1.11 (0.91-1.35)	1.09 (0.87-1.37)	1.13 (0.68-1.86)	0.81 (0.63-1.06)	1.00 (0.69-1.44)	0.68 (0.41-1.10)	0.47 (0.23-0.98)	1.04 (0.88-1.23)
Unknown"	1.16 (0.95-1.42)	1.07 (0.85-1.34)	1.66 (1.00-2.77)	0.90 (0.69-1.17)	1.21 (0.83-1.76)	**0.57 (0.34-0.96)**	0.76 (0.38-1.51)	1.02 (0.86-1.21)
Parental age	1.02 (1.01-1.03)	**1.02 (1.01-1.03)**	1.02 (1.00-1.05)	0.99 (0.98-1.00)	1.00 (0.98-1.02)	0.98 (0.95-1.01)	0.97 (0.94-1.01)	**1.01 (1.00-1.02)**
Number of children by mother								
1 child	1.00 1.00-1.00	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
2 children	0.99 (0.85-1.16)	0.97 (0.82-1.16)	0.98 (0.64-1.49)	0.88 (0.71-1.09)	0.82 (0.61-1.09)	0.99 (0.65-1.52)	0.96 (0.54-1.69)	0.97 (0.85-1.11)
3 or more children	0.93 (0.76-1.15)	0.90 (0.71-1.15)	0.91 (0.53-1.55)	0.93 (0.71-1.22)	0.95 (0.67-1.36)	0.83 (0.48-1.46)	0.85 (0.40-1.82)	0.91 (0.75-1.11)
Birth order								
First born	1.00 1.00	1.00 (1.00-	1.00 (1.00-	1.00 (1.00-	1.00 (1.00-	1.00 (1.00-	1.00 (1.00-	1.00 (1.00-

	1.00	1.00)	1.00)	1.00)	1.00)	1.00)	1.00)	1.00)
Second born	0.95 (0.84-1.08)	0.93 (0.80-1.07)	1.12 (0.80-1.57)	1.05 (0.89-1.24)	1.03 (0.82-1.29)	1.10 (0.78-1.54)	0.97 (0.59-1.59)	0.98 (0.87-1.10)
Third born or later	0.92 (0.75-1.14)	0.92 (0.72-1.18)	1.07 (0.63-1.80)	0.96 (0.73-1.25)	0.91 (0.64-1.30)	0.75 (0.41-1.37)	1.41 (0.64-3.10)	0.96 (0.79-1.17)
Childs birth place								
Urban	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Small town	1.00 (0.89-1.12)	0.95 (0.83-1.08)	1.18 (0.86-1.60)	0.94 (0.80-1.10)	0.92 (0.75-1.14)	1.03 (0.74-1.43)	1.12 (0.73-1.72)	0.95 (0.86-1.05)
Rural	1.10 (0.97-1.23)	1.04 (0.91-1.18)	1.33 (0.98-1.79)	0.97 (0.83-1.1)	0.93 (0.75-1.15)	1.11 (0.80-1.54)	1.30 (0.84-1.99)	0.99 (0.90-1.10)

a Acute lymphoblastic leukemia, Wilms tumor (nephroblastoma), medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma

Supplementary table 5 The ten most common industries with exposure to diesel engine exhaust for mothers and fathers of children diagnosed with leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, central nervous system cancer, astrocytoma, medulloblastoma, ependymoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma, and hepatoblastoma

Mothers				Fathers			
	Exposed controls n	Exposed cases n	Exposed total n		Exposed controls n	Exposed cases n	Exposed total n
29011. Clay and gravel pits, also stone quarries	417	14	431	71142. Moving businesses	5,099	222	5,321
29013. Limestone and chalk quarries	404	14	418	71163. #Fire brigade	2,748	128	2,876
29030. Extraction of salt	326	16	342	71211. Shipping companies	2,564	89	2,653
29090. Other nonmetallic raw materials extraction in general	288	10	298	71212. Ferry operations	1,715	56	1,771
35401. Asphalt factories	271	9	280	71232. Harbours	1,174	37	1,211
38210. Manufacture of engines (except for electric motors and marin	220	19	239	71233. Loading and unloading contractors (stevedores), etc.	1,05	50	1,1
38220. Manufacture of agricultural machinery and accessories	208	13	221	83241. Consulting engineers	1,022	30	1,052
38231. Manufacture of machinery for wood-working	196	11	207	91020. Police	1,007	40	1,047
38232. Manufacture of machinery for metal-working	151	7	158	29011. Clay and gravel pits, also stone quarries	947	39	986
38233. Manufacture of foundry machinery and machines for rolling me	137	8	145	29012. Stone fishers (who fish up stones from sea bottom)	952	33	985