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Parental occupational exposure to pesticides, animals and organic dust and risk of childhood leukemia and central nervous system tumors: Findings from the International Childhood Cancer Cohort Consortium (I4C)

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Abbreviations: ALL: acute lymphoblastic leukemia; ALSPAC: Avon Longitudinal Study of Parents and Children; AML: acute myeloid leukemia; CI: Confidence Interval; CNS: central nervous system; CBT: childhood brain tumors; DNBC: Danish National Birth Cohort; HR: hazard ratio; I4C: International Childhood Cancer Cohort Consortium; ISCO-88: International Standard Classification of Occupations-1988; JEM: job exposure matrix; JPS: Jerusalem Perinatal Study; MoBa: Norwegian Mother and Child Cohort Study; TIHS: Tasmanian Infant Health Study
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Parental occupational exposures to pesticides, animals and organic dust have been associated with an increased risk of childhood cancer based mostly on case–control studies. We prospectively evaluated parental occupational exposures and risk of childhood leukemia and central nervous system (CNS) tumors in the International Childhood Cancer Cohort Consortium. We pooled data on 329,658 participants from birth cohorts in five countries (Australia, Denmark, Israel, Norway and United Kingdom). Parental occupational exposures during pregnancy were estimated by linking International Standard Classification of Occupations-1988 job codes to the ALOHA+ job exposure matrix. Risk of childhood (<15 years) acute lymphoblastic leukemia (ALL; $n = 129$), acute myeloid leukemia (AML; $n = 31$) and CNS tumors ($n = 158$) was estimated using Cox proportional hazards models to generate hazard ratios (HR) and 95% confidence intervals (CI). Paternal exposures to pesticides and animals were associated with increased risk of childhood AML (herbicides HR = 3.22, 95% CI = 0.97–10.68; insecticides HR = 2.86, 95% CI = 0.99–8.23; animals HR = 3.89, 95% CI = 1.18–12.90), but not ALL or CNS tumors. Paternal exposure to organic dust was positively associated with AML (HR = 2.38 95% CI = 1.12–5.07), inversely associated with ALL (HR = 0.55, 95% CI = 0.31–0.99) and not associated with CNS tumors. Low exposure prevalence precluded evaluation of maternal pesticide and animal exposures; we observed no significant associations with organic dust exposure. This first prospective analysis of pooled birth cohorts and parental occupational exposures provides evidence for paternal agricultural exposures as childhood AML risk factors. The different risks for childhood ALL associated with maternal and paternal organic dust exposures should be investigated further.

What's new?

Exposure to agricultural contaminants and animals has been associated with an increased risk of childhood leukemia and other cancers in the children of agricultural workers. However, most of those data have come from retrospective, case–control studies. In this large, international, prospective study, the authors found that the children of men exposed to pesticides, animals, or organic dust all had a significantly increased risk of AML, but not of ALL or CNS tumors. These novel findings regarding paternal exposure should be verified with further studies.

Introduction

Parental occupational exposure to pesticides and childhood cancer risk has been studied for decades but almost exclusively through retrospective case–control studies, which may be subject to recall and selection bias. Occupational exposure to pesticides in one or both parents has been consistently associated with childhood leukemia in the offspring. A meta-analysis of 26 case–control studies and five cohorts found that maternal occupational pesticide exposure during pregnancy increased risk of childhood leukemia, but there were no associations with paternal pesticide exposures.[1] However, a pooled analysis of 13 case–control studies found increased risk of leukemia with occupational pesticide exposure in both parents.[2] Fewer studies have examined the association between parental occupational exposure to pesticides and childhood central nervous system (CNS) tumors, with most focusing on the most common type, childhood brain tumors (CBT). Positive associations between occupational exposure to pesticides in either parent and CBT were found in a systematic review and meta-analysis of 16 case–control studies;[3] however, there was significant heterogeneity across studies.

Parental exposure to animals and childhood cancer has not been as well studied, but there is suggestive evidence for a positive association between maternal prenatal occupational exposure to farm animals (pigs, horses and poultry) and childhood CBT,[4–7] and largely null findings for occupational farm animal exposure to either parent and childhood leukemia based on three case–control studies.[7–9] Organic dust exposures occur across a broad range of occupations, although the frequency and intensity of exposure is high in agricultural tasks such as handling grain or working in confined animal operations.[10] Although parental occupational exposure to organic dust and childhood cancer has not been previously studied, results from studies of occupations with high exposure to organic dusts from animal, plant or microbial origin including grain handlers, bakers, textile workers and wood workers provided mixed findings for childhood leukemia and CNS tumors.[1,6–9,11–15]

Agricultural occupations comprise a variety of tasks such as planting and harvesting crops, mixing and applying pesticides, caring for farm animals and maintaining machinery and buildings, which result in exposures to pesticides, dusts, endotoxins, viruses, diesel exhaust and solvents. Although the etiology is unclear, several plausible mechanisms may explain increased risk of cancers in children whose parents work in occupations with these exposures, including germ cell damage prior to pregnancy and DNA damage and immune dysregulation from *in utero* and early life exposures.[16]

The aim of our study was to prospectively evaluate parental occupational exposures to pesticides, animals and organic dusts during pregnancy and risk of any childhood leukemia, the leukemia subtypes acute lymphoblastic leukemias (ALL) and acute myeloid leukemias (AML), and CNS tumors in their offspring using data pooled from five birth cohorts participating in the International Childhood Cancer Cohort Consortium (I4C).

Materials and Methods

Cohort follow-up and cancer ascertainment

The I4C was established to examine the etiology of childhood cancers by pooling prospectively collected data that would otherwise be underpowered to address these outcomes.[17,18] For the current study, parental and infant data were pooled on 329,658 families from five I4C birth cohorts that collected parental occupation on both parents during the pregnancy: the Avon Longitudinal Study of Parents and Children (ALSPAC, UK),[19,20] the Danish National Birth Cohort (DNBC, Denmark), the Jerusalem Perinatal Study (JPS, Israel), the Norwegian Mother and Child Cohort Study (MoBa, Norway) and the Tasmanian Infant Health Study (TIHS, Australia). DNBC and MoBa provided data for all cases and a 10% random sample of their cohorts. Details about the participating cohorts, including references, informed consent procedures, data provided to a central data coordinating center and harmonization strategies have been described.[18,21]

Children in the ALSPAC and JPS cohorts were followed through 15 years of age or were censored at date of cancer diagnosis or death. The DNBC and MoBa cohorts have been followed to the point of last linkage to the national cancer registries in Denmark and Norway, respectively, on December 31, 2014, and continued follow up through age of 15 years is ongoing. Noncases in TIHS were assumed to be followed to the last date of diagnosis of the most recent case in the Tasmanian Cancer Registry (September 28, 2008), when the youngest child was 13 years old.

Childhood cancers (<15 years of age) were ascertained by linkage to national registries for ALSPAC, DNBC, JPS and MoBa and the Tasmanian Cancer Registry for TIHS. Tumors were classified using the International Classification of Diseases (ICD)-O, Third Edition, morphology codes and the third revision of the 1996 International Classification of Childhood Cancers into leukemias (C42), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and CNS tumors (C70–C72 and C75.1–C75.3).[22] CNS cases were primarily CBT (>80%) and included benign tumors. CNS tumors were not identified in ALSPAC due to data protection rules, therefore analyses of CNS only included four cohorts; no AML cases occurred in ALSPAC. After excluding nonsingleton births and children with Down Syndrome, the pooled data included 168 leukemias, 129 ALL, 32 AML and 154 CNS tumor cases (Table 1).

Parental occupational exposure

Parental occupation was obtained at gestational weeks 12, 15 and 18 for DNBC, MoBa and ALSPAC, respectively, around the time of birth for JPS and around day four after birth for TIHS. Jobs were coded using 1990 Standard Occupational Classification (SOC90) for ALSPAC, the Danish version of the 1988 International Standard Classification of Occupations (ISCO-88) for DNBC, study-specific codes for JPS, the Norwegian version of ISCO-88 for MoBa and the 1986 Australian Standard Classification of Occupations for TIHS.

Occupational data from each cohort were harmonized to the ISCO-88 four-digit classification and linked to the ALOHA job exposure matrix (JEM) to assign organic dust exposure.[23] An extension of the JEM, ALOHA+, was used to assign exposure to pesticides overall and to fungicides, herbicides and insecticides (Supporting Information Table S1). These JEMs were developed by industrial hygienists (HK and RV) to classify jobs by their level of exposure to pesticides and organic dusts (based on intensity and probability of exposure combined) into categories of 0 = no exposure, 1 = low exposure and 2 = high exposure. ISCO-88 jobs were also classified by their potential exposure to animals (any/none; Supporting Information Table S2). Jobs with high organic dust exposure included agricultural jobs and a range of other occupations, which differed in prevalence between mothers and fathers (Supporting Information Tables S3 and S4).

Covariates and potential confounders

Covariates that have been associated with childhood leukemia or CNS tumors, and were available for at least four of the cohorts, were assessed as potential confounders. For mothers, these included: age at time of the index child's birth (years), years of education (<12/≥12 years), any smoking during pregnancy (yes/no), any alcohol intake during pregnancy (yes/no) and exposure to passive smoking in home either by her partner or by other household member(s) (yes/no). Paternal factors included age at time of the index child's birth (years) and years of education (<12/≥12 years). Children's characteristics and exposures linked with childhood leukemia or CNS tumors included sex, birth order (e.g., first born [yes/no]), breastfeeding (ever/never in the first 6 months) and birth weight (g).

Missing data for these variables ranged from 0% to 35% across the cohorts as has been described previously.[18] Chained multiple imputation was used to impute 20 complete datasets. Truncated linear regression was used to impute missing paternal age with lower and upper limits set at the minimum and maximum of nonmissing observations across all cohorts. We imputed dichotomous variables (first born, maternal education, paternal education, maternal smoking, passive smoking, maternal alcohol use and breastfeeding) using logistic regression. Maternal age, birth weight, child's sex, cohort, cancer status and maternal and paternal exposure to organic dusts (the most common occupational exposure) were covariates in these models.

The criteria for retaining covariates in the models was their association with risk of one or more of the cancers ($p < 0.10$) or a change in the childhood cancer hazard ratios (HR) by more than 10%. Maternal age and paternal age were associated with each of the cancer outcomes ($p < 0.10$) and were included in final models of maternal and paternal exposures, respectively. Maternal and passive smoking and maternal alcohol intake during pregnancy were only available in four of the five cohorts (JPS had limited or missing data for these variables). When we examined smoking and alcohol as covariates in our models, they did not change the hazard ratios >10% for childhood leukemia,

Table 1. Descriptive characteristics of the five International Childhood Cancer Cohort Consortium (I4C) cohorts included in the pooled analysis

	ALSPAC	DNBC	JPS	MoBa	TIHS	Total
Recruitment years	1991–1992	1996–2002	1964–1976	1999–2009	1987–1995	1964–2009
Singleton live births with no Down syndrome	13,664	9,362[1]	87,856	10,567[1]	9,362	130,916[2]
Years of follow-up Mean (range)	14.9 (1.3–15.0)	13.8 (0.01–15.0)	14.9 (0.01–15.0)	9.3 (0.04–15.0)	14.7 (0.02–15.0)	14.4 (0.01–15.0)
Total cancer cases	22	191	162	190	24	589
Leukemia	3	61	38	62	4	168
Acute lymphoblastic leukemia (ALL)	3	44	30	49	3	129
Acute myeloid leukemia (AML)	0[3]	14	7	10	1	32
Childhood central nervous system (CNS) tumors	–[3]	59	33	57	5	154
Maternal age (years) Mean ± SD	27.9 ± 5.0	30.5 ± 4.3	27.6 ± 5.7	30.2 ± 4.6	23.6 ± 4.4	27.8 ± 5.5
Mother completed 12 or more years of education, *n* (%)	4,286 (35.3)	4,388 (62.3)	36,568 (42.4)	7,594 (79.6)	1,690 (18.1)	54,526 (44.4)
Maternal prenatal smoking *n* (%)	3,561 (29.6)	2,365 (25.3)	–[4]	925 (11.2)	5,023 (53.7)	11,874 (30.6)
Passive smoking at home, prenatal, *n* (%)	5,362 (45.4)	2,712 (31.3)	–[4]	782 (8.5)	5,242 (56.1)	14,098 (36.2)
Paternal age (years) Mean ± SD	30.7 ± 5.7	32.7 ± 5.2	31.6 ± 6.8	32.7 ± 5.3	26.5 ± 5.6	31.3 ± 6.6
Father completed 12 or more years of education, *n* (%)	5,151 (44.2)	2,908 (44.8)	40,257 (46.9)	5,855 (85.9)	1,624 (19.1)	55,795 (46.8)
Child's sex, male, *n* (%)	7,052 (51.6)	4,774 (51.0)	45,294 (51.5)	5,315 (50.3)	6,673 (71.3)	69,108 (52.8)
Birthweight, g Mean ± SD	3,410 ± 551	3,586 ± 567	3,272 ± 523	3,604 ± 562	3,195 ± 750	3,330 ± 565
First born, *n* (%)	5,500 (40.7)	3,112 (33.2)	25,476 (29.2)	4,744 (44.8)	4,387 (46.9)	41,226 (32.0)
Breastfed, *n* (%)	8,211 (75.5)	4,512 (63.3)	–[4]	8,183 (77.3)	5,251 (60.6)	26,157 (70.2)

Percentages of characteristics are among those with nonmissing data.
[1]The DNBC and MoBa cohorts provided all cases and 10% random sample of the cohorts. The total number of live births for DNBC and MoBa was 96,860 and 108,847, respectively.
[2]The total number of live births for the full cohorts (including all participants of DNBC and MoBa) was 380,445.
[3]CNS information were not provided by ALSPAC due to data protection/IRB issues associated with small numbers and there were no cases of AML found in this cohort.
[4]Smoking and Breastfeeding data was limited or only collected on a small subset of the JPS cohort and thus was considered missing.

ALL, AML or CNS tumors. Adjustment for other maternal and paternal factors also did not change the hazard ratios and were not included in final models. We included child's sex in the final models to adjust for the sex differences in cancer incidence.[24]

Statistical analysis

We used Cox proportional hazards models to generate hazard ratios (HR) and 95% confidence intervals (CI) for childhood leukemia, ALL, AML and CNS tumors in relation to JEM-based maternal and paternal exposures separately. Models were run for each imputed dataset and results were summarized using the SAS MIANALYZE procedure. All models were stratified by cohort to allow each cohort to have a different baseline hazard and were weighted to account for the 10% sample in the DNBC and MoBa cohorts. Organic dust was the most common exposure and was analyzed for both mothers and fathers (none, low and high). Pesticides (overall and by type: herbicide, insecticide, fungicide) and animal exposures were modeled as any *vs.* none due to small numbers and only evaluated among fathers due to the low prevalence of exposure among mothers (Supporting Information Table S5). All jobs with pesticide or animal exposure had organic dust exposure. Therefore, to clarify associations for organic dust among fathers, we examined organic dust stratified by pesticide exposure using a common reference group with no pesticide or dust exposure. Due to the high correlation between paternal animal and pesticide exposures (Spearman rho = 0.89) we did not conduct stratified analyses by animal exposure, which was slightly less common. We computed *p* values for multiplicative interaction by comparing nested models with and without the interaction terms for the paternal organic dust models.

The proportional hazards assumption was met in all our models. SAS, Version 9.3 (SAS Institute Inc., Cary, NC) was used to conduct all analyses.

Results

Characteristics of mothers, fathers and the children by cohort are presented in Table 1. The distribution of children's sex was similar across all cohorts (about 50%), apart from TIHS which had a larger proportion of males (71%), which was due to the study design focused on children at highest risk for sudden infant death syndrome. Mean maternal and paternal age were the lowest in TIHS (mothers = 23.6 ± 4.4, fathers = 26.5 ± 5.6) and highest in DNBC (mothers = 30.5 ± 4.3, fathers = 32.7 ± 5.2) and MoBa (mothers = 30.2 ± 4.6, fathers = 32.7 ± 5.3). Other covariates were similar across the cohorts.

Pesticides

Prevalence of all the parental occupational exposures evaluated was higher in fathers compared to mothers (Supporting Information Table S5). Pesticide exposure among fathers (4.0%) was four times that among mothers (1.0%) and did not vary substantially by pesticide type. Pesticide exposure among fathers was lowest in ALPSAC (1.1%) and highest in DNBC (6.1%). Paternal exposures to fungicides, herbicides and insecticides were highly correlated; 82% of fathers with pesticide exposure overall had exposure to all three of these pesticide types. Paternal occupational exposure to pesticides was primarily from agricultural jobs (>85% jobs with pesticide exposure) but also included transport laborers and freight handlers (6%) and wood treaters and wood processing workers (4%).

Based on few exposed cases, father's exposure to pesticides (all types combined) was not associated with childhood leukemia overall (HR = 0.92, 95% CI = 0.43–1.97), ALL (HR = 0.51, 95% CI = 0.16–1.62), or CNS tumors (HR = 0.71, 95% CI = 0.29–1.75) (Table 2). For AML, we observed borderline significant positive associations with paternal exposure to herbicides (HR = 3.22, 95% CI = 0.97–10.68) and insecticides (HR = 2.85, 95% CI = 0.99–8.23). Risk was also elevated for AML with exposure to total pesticides (HR = 2.62, 95% CI = 0.91–7.55) and fungicides (HR = 2.59, 95% CI = 0.78–8.56). AML cases with paternal pesticide exposure occurred only in the DNBC and JPS cohorts.

Animals

Paternal exposure to animals was 3.2% overall and ranged from 0.2% in ALSPAC to 4.0% in JPS. Paternal animal exposure was associated with increased risk of AML (HR = 3.89, 95% CI = 1.18–12.90) but was not associated with ALL or CNS tumors. Occupational exposure to animals was highly correlated with pesticide exposure; 80% of fathers who had either of these exposures were exposed to both.

Organic dust

Organic dust exposure was more common than pesticide or animal exposures (mothers: 10%; fathers: 15%) but varied considerably between cohorts. Among mothers, the prevalence ranged from 5% in JPS to 25% in DNBC; whereas among fathers, prevalence ranged from 11% in ALSPAC to 25% in TIHS. Maternal exposure to organic dust was not significantly associated with ALL (HR = 1.36, 95% CI = 0.87–2.14) or CNS tumors (HR = 1.35, 95% CI = 0.90–2.03) and there were insufficient cases to assess risk of AML (1 exposed case). Paternal occupational exposure to organic dust was associated with an increased risk of AML (HR = 2.38, 95% CI = 1.12–5.07) and inversely associated with ALL (HR = 0.55, 95% CI = 0.31–0.99). There was no association between paternal dust exposure and risk of CNS tumors (Table 3).

We examined fathers' occupational exposure to organic dust stratified by pesticide exposure (Table 4). We observed a significantly increased risk of AML in children of fathers occupationally exposed to organic dust who also had pesticide exposure (HR = 3.07, 95% CI = 1.03–9.10), and an elevated risk among fathers exposed to dust but without pesticide exposure (HR = 2.12, 95% CI = 0.88–5.12; p-interaction = 0.98). Exposure to organic dust was inversely associated with ALL among those with and without pesticide exposures (HR = 0.48 95% CI = 0.15–1.50 and HR = 0.59, 95% CI = 0.31–1.14, respectively; p-interaction = 0.99). Paternal organic dust exposure was not associated with CNS tumors regardless of pesticide exposure.

Discussion

In our large pooled analysis of five international birth cohort studies, we found increased risk of AML associated with paternal occupational exposure to pesticides during pregnancy but found no associations with ALL or CNS tumors. Paternal occupational exposure to animals and organic dust was also associated with increased risk of AML. When stratified by pesticide exposure, the association for organic dust was stronger among those with both organic dust and pesticide exposures than with organic dust alone. Paternal organic dust exposure was inversely associated with ALL, regardless of pesticide exposure, but was not associated with CNS tumors. Maternal exposure to organic dust was not significantly associated with ALL or CNS tumors.

To the best of our knowledge, this is the first report of an increased risk of childhood AML associated with these paternal occupational exposures. However, AML has been associated with maternal pesticide exposures and other parental occupational exposures, especially benzene and other solvents,[25–27] as well as certain chemotherapy drugs.[28] Like many pesticides, these exposures may cause chromosomal alterations and mutations.[29] Our finding of an inverse association between paternal organic dust exposure and ALL is novel but the biologically plausibility for this association is unclear.

Paternal exposure to pesticides and animals

Our novel findings for paternal pesticide exposure and AML and lack of association with ALL differ from most prior studies. A meta-analysis of 10 case–control studies found no association between paternal pesticide exposures and AML or ALL.[27] A pooled analysis of 13 international case–control studies found no association with paternal pesticide exposure and AML, but found a modest increased risk of ALL.[2] In contrast to the null

Table 2. Associations between father's occupational pesticide and animal exposure and childhood leukemia and CNS cancers in pooled data from five cohorts

Exposure	Diagnostic group	Exposure level	Cases	Hazard ratio[1]	95% CI	
Total pesticides	Any leukemia	None	130	Ref		
		Any	7	0.92	0.43	1.97
	ALL	None	101	Ref		
		Any	3	0.51	0.16	1.62
	AML[2]	None	25	Ref		
		Any	4	2.62	0.91	7.55
	CNS[2]	None	118	Ref		
		Any	5	0.71	0.29	1.75
Fungicides	Any leukemia	None	131	Ref		
		Any	6	1.05	0.46	2.39
	ALL	None	101	Ref		
		Any	3	0.70	0.22	2.17
	AML[2]	None	26	Ref		
		Any	3	2.59	0.78	8.56
	CNS[2]	None	119	Ref		
		Any	4	0.76	0.28	2.05
Herbicides	Any leukemia	None	131	Ref		
		Any	6	1.36	0.60	3.10
	ALL	None	101	Ref		
		Any	3	0.89	0.28	2.82
	AML[2]	None	26	Ref		
		Any	3	3.22	0.97	10.68
	CNS[2]	None	120	Ref		
		Any	3	0.71	0.23	2.25
Insecticides	Any leukemia	None	131	Ref		
		Any	6	0.85	0.38	1.94
	ALL	None	102	Ref		
		Any	2	0.37	0.09	1.50
	AML[2]	None	25	Ref		
		Any	4	2.86	0.99	8.23
	CNS[2]	None	118	Ref		
		Any	5	0.78	0.32	1.91
Animals	Any leukemia	None	163	Ref		
		Any	5	1.24	0.51	3.02
	ALL	None	127	Ref		
		Any	2	0.64	0.16	2.60
	AML[2]	None	29	Ref		
		Any	3	3.89	1.18	12.90
	CNS[2]	None	150	Ref		
		Any	4	1.05	0.39	2.84

[1]Adjusted for child's sex and paternal age. All models were stratified by cohort to allow each cohort to have a different baseline hazard. DNBC and MoBa provided all childhood cancer cases and a 10% random sample of their cohorts. These data were weighted to represent the entire cohorts.
[2]CNS tumor analyses were conducted with four cohorts, ALPSAC did not provide data on CNS tumor cases due to data protection/IRB issues associated with small numbers and there were no cases of AML found in this cohort.

finding in our study for CNS tumors, a meta-analysis of 16 case–control and five cohort studies of parental occupational exposure to pesticides and CBT found positive associations for parental prenatal exposure (one or both parents).[3]

Parental occupational contact with animals is hypothesized to be a risk factor for childhood cancer due to exposure to zoonotic viruses and other microbes. However, in contrast to our finding of an increased risk of AML with paternal animal

Table 3. Associations between parental occupational exposure to organic dust and childhood leukemia and CNS cancers in pooled data from five cohorts

Exposure	Diagnostic group	Exposure level	Mothers				Fathers			
			Cases	Hazard ratio[1]	95% CI		Cases	Hazard ratio[2]	95% CI	
Organic dust	Any leukemia	None	114	Ref			112	Ref		
		Low	28	1.05	0.69	1.61	15	0.81	0.47	1.40
		High	1	0.68	0.08	4.86	10	0.96	0.51	1.87
		Any	29	1.04	0.68	1.58	25	0.87	0.56	1.35
	ALL	None	83	Ref			91	Ref		
		Low	26	1.37	0.87	2.17	7	0.46	0.21	1.00
		High	1	0.95	0.13	6.85	6	0.72	0.32	1.65
		Any	27	1.36	0.87	2.14	13	0.55	0.31	0.99
	AML[2]	None	28	Ref			18	Ref		
		Low	1	0.14	0.02	1.07	7	2.39	0.99	5.78
		High	0	–	–	–	4	2.44	0.82	7.21
		Any	1	0.14	0.02	1.07	11	2.38	1.12	5.07
	CNS[3]	None	101	Ref			99	Ref		
		Low	31	1.35	0.89	2.05	17	1.04	0.62	1.75
		High	2	1.49	0.37	6.06	7	0.79	0.37	1.71
		Any	33	1.35	0.90	2.03	24	0.96	0.61	1.50

All models were stratified by cohort to allow each cohort to have a different baseline hazard. DNBC and MoBa provided all childhood cancer cases and a 10% random sample of their cohorts. These data were weighted to represent the entire cohorts.
[1]Adjusted for child's sex and maternal age.
[2]Adjusted for child's sex and paternal age.
[3]CNS tumor analyses were conducted with four cohorts, ALPSAC did not provide data on CNS tumor cases due to data protection/IRB issues associated with small numbers and there were no cases of AML found in this cohort.

Table 4. Associations between father's exposure to organic dust and childhood leukemia and CNS stratified by exposure to pesticides in pooled data from five cohorts

Diagnostic group	Exposure	Organic dust exposure	Cases	Hazard ratio[1]	95% CI	
Any leukemia	No pesticides	None	112	Ref		
		Any	18	0.87	0.53	1.44
	Any pesticides	None	0	–	–	–
		Any	7	0.89	0.42	1.92
ALL	No pesticides	None	91	Ref		
		Any	10	0.59	0.31	1.14
	Any pesticides	None	0	–	–	–
		Any	3	0.48	0.15	1.50
AML[2]	No pesticides	None	18	Ref		
		Any	7	2.12	0.88	5.12
	Any pesticides	None	0	–	–	–
		Any	4	3.07	1.03	9.10
CNS tumors[2]	No pesticides	None	99	Ref		
		Any	19	1.05	0.64	1.72
	Any pesticides	None	0	–	–	–
		Any	5	0.72	0.29	1.76

All models were stratified by cohort to allow each cohort to have a different baseline hazard. DNBC and MoBa provided all childhood cancer cases and a 10% random sample of their cohorts. These data were weighted to represent the entire cohorts.
[1]Adjusted for child's sex and paternal age.
[2]CNS tumor analyses were conducted with four cohorts, ALPSAC did not provide data on CNS tumor cases due to data protection/IRB issues associated with small numbers and there were no cases of AML found in this cohort.

exposure, previous studies have found no associations with ALL or AML.[7–9,30] We found no association between paternal contact with animals and CNS tumors, whereas a registry-based case–control study in Great Britain and a registry-based cohort study in Norway observed significant positive associations with paternal occupational contact with animals based on the father's occupation at the time of birth.[6,30] Similarly, maternal prenatal contact with animals was associated with increased risk of CBT in pooled analyses.[4] Differences between our findings and those of previous studies may be due to differences in study populations, pesticide and animal exposures, study design or limited power of our study to detect some associations.

Maternal and paternal exposures to organic dust

To the best of our knowledge, parental occupational exposure to organic dust has not been previously studied in relation to childhood leukemia or CNS tumors using a JEM. However, several occupations with substantial organic dust exposure have been evaluated. Maternal occupations with exposure to textile dust (i.e., sewing machinist, menders and embroiders) or wood dust were not associated with childhood leukemia and CNS cancers in a case–control study in the UK;[7] however, positive associations were found between mothers working in the textile industry and childhood leukemia in a Dutch case–control study and CNS tumors in a Danish case–control study.[9,13] Strong positive associations were also observed for maternal occupational exposure to dust comprised of cotton, wool and synthetic fibers and childhood ALL in a Spanish case–control study.[15] Maternal occupations with these dust exposures were uncommon in our study and we had limited power to evaluate risk for high-dust exposure. Nursing and healthcare occupations with low-dust exposure were the most common among mothers, while agricultural and craft-related occupations with high-dust exposure were most common among fathers.

Our findings of a positive association between paternal organic dust exposure and AML and an inverse association with ALL differ from previous studies of specific types of occupational dust exposure. Among three leukemia case–control studies in the UK and US, and a Swedish cohort study estimating paternal occupational textile exposure, only one assessed risk of AML and no associations were found with either leukemia subtype.[7,8,11,12] Associations between paternal occupational exposure to wood dust and childhood leukemia were also null in two case–control studies,[7,9] whereas a twofold increased risk was found in the Swedish cohort study.[11] While our study found no association between paternal organic dust exposure and CNS tumors, a UK case–control study found an inverse association with paternal wood dust exposure;[7] however, no associations were observed in two other case–control studies or cohort study.[6,7,11] The inverse association with ALL we observed was present in jobs with and without pesticide exposure suggesting that the inverse association we observed with pesticide exposures may be due to organic dust. Organic dusts are complex mixtures containing microbes, allergens and other plant and animal material. Early life exposure to these agents through the para-occupational route of exposure may be relevant since microbial exposures in early life and surrogates of those exposures such as later birth order and early daycare attendance have been hypothesized to show an inverse association with childhood ALL.[16,31]

Strengths and limitations

A strength of our study was the prospective study design, which minimized recall and selection biases. We had the ability to examine potential confounders such as parental smoking, birth weight and breastfeeding; however, we did not identify any factors that impacted the relationships between our exposures of interest and childhood cancer outcomes. The use of the ALOHA + JEM and standardized occupational codes allowed us to examine several occupational exposures based on job titles across the cohorts and reduced the likelihood of recall bias arising from asking about specific occupational exposures.[32]

By pooling data from five cohorts, we were able to study the uncommon outcome of childhood cancer, although we had limited power to examine rare childhood cancers and the histological subtypes of leukemias and CNS tumors for which there is evidence of etiologic heterogeneity.[1,3] The population-based cohorts included in our pooled analysis had a fairly low prevalence of pesticide and animal exposures and we were not able to evaluate risk associated with maternal exposures. Although we observed statistically significant associations for paternal exposures to animals and organic dust and AML, our risk estimates were based on small numbers of exposed cases and were imprecise. In addition, the occupational exposure categories were composed of many different pesticides and types of organic dusts that may differ in their toxicity and potential biological effects, which would likely lead to heterogeneity in risk estimates between these individual exposures.

Our use of JEMs will likely have introduced some nondifferential misclassification of parental occupational exposures since we were not able to assess specific job tasks. In a large case–control study of ALL, Gunier *et al.*[33] identified occupational pesticide exposure misclassification in 9.4% of fathers and 2.6% of mothers when using a JEM compared to job modules; however, this study showed high specificity with the JEM for both maternal (98%) and paternal (90%) assessments, which is important in reducing the likelihood of bias from exposure misclassification when exposure prevalence is low. Additionally, our JEM did not account for changes in these occupational exposures over the different time periods of our cohorts or regional differences in exposures; however, the two Nordic cohorts contributing the most person-years and cases (DNBC and MoBa) were conducted in a similar time frame and would be likely to have more similar exposures for many of the same jobs.

In addition to the exposures we estimated, parents might have had additional occupation-related exposures that were not accounted for in our analysis. For example, farmers who were exposed to pesticides may have also been exposed to

diesel exhaust fumes from farm equipment, for which parental occupational exposure has been associated with increased risk of childhood leukemia.[34] It is also expected that the use of personal protective equipment for pesticide application is not uniform within or between the countries and has improved over time. In addition to uncertainty surrounding specific exposures, we had limited information on duration of employment and employment history although jobs during pregnancy were likely representative of prenatal and postnatal time periods. Furthermore, although our exposure assessment was limited to the pregnancy, there is evidence that pregnancy is a critical window of exposure for childhood cancer; however, future studies should evaluate other occupational time periods (prior to conception, during infancy, etc.) to further understand these relationships.

Conclusions

In this pooled analysis of five birth cohorts based on more than 320,000 pregnancies, paternal occupational exposures to pesticides, animals and organic dust were associated with an increased risk of childhood AML. To the best of our knowledge, this is the first time these paternal exposures have been associated with increased risk of AML. Paternal organic dust exposure was inversely associated with ALL, whereas paternal exposures to organic dust, animals and pesticides were not associated with childhood CNS tumors. We found no significant associations between maternal occupational exposure to organic dust and any of the childhood cancer outcomes that we evaluated; we were unable to evaluate maternal exposure to pesticides and animals. Risk of ALL differed for maternal and paternal organic dust exposures likely due to the different types of occupations with these exposures and should be investigated further. Our findings need to be followed up in larger studies to further investigate animal exposures including the type and number of animals raised, type and components of organic dust and specific pesticide active ingredients to determine which exposures may contribute to childhood cancer risk.

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Disclaimer

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