Original Article

Childhood cancer risk in offspring of parents occupationally exposed to dusts: A register-based nested case-control study from Sweden of 5 decades

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BACKGROUND: Some largely inconsistent associations between parental occupational dust exposure and childhood cancer have been reported, with maternal exposures inadequately studied. The authors examined whether maternal or paternal occupational exposure to animal, wood, textile, or paper dust around a child's birth was associated with an increased risk of childhood cancer, both overall and by type (leukemias, lymphomas, central nervous system tumors, and other cancers). **METHODS:** In this nationwide, register-based, case-control study, children who were diagnosed with cancer from 1960 to 2015 were compared with up to 25 matched controls regarding maternal and paternal occupational dust exposure (9653 cases in maternal analyses and 12,521 cases in paternal analyses). Exposures were assessed using a job-exposure matrix and occupational information from census and register data. By using conditional logistic regression models, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. **RESULTS:** Neither maternal nor paternal occupational exposure to animal, wood, textile, or paper dust was associated with childhood cancer overall, leukemias, or central nervous system tumors. Maternal, but not paternal, wood dust exposure was associated with an increased risk of lymphoma (OR, 1.42; 95% CI, 1.10-1.84), particularly non-Hodgkin lymphoma (OR, 2.03; 95% CI, 1.21-3.40). **CONCLUSIONS:** The current study did not confirm the associations reported previously but is the first to suggest a link between maternal occupational exposure to wood dust around pregnancy and lymphoma in the offspring. *Cancer* 2022;128:1637-1648. © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: case-control studies, childhood cancer, dust, job-exposure matrix, parental occupational exposure, registries, Sweden.

INTRODUCTION

Cancer is a leading cause of mortality and suffering during childhood and young adulthood despite recent advancements in diagnosis and treatment.[1,2] Malignant primary tumors affect approximately 15 to 20 in 100,000 children younger than 15 years in Sweden, with most diagnoses being hematopoietic and central nervous system (CNS) tumors.[2,3] Although the etiology of most of malignant tumors is yet to be elucidated, environmental insults during conception, fetal life, and early infancy have been suggested as potential causes of cancer in this age group.

Inhalation, skin absorption, and ingestion of animal, wood, textile, and paper dusts in the work environment are hazardous for the exposed individual and have been linked to several adverse health effects, including cancer.[4,5] However, the carcinogenic effects in the offspring of exposed parents are less clear. Theoretically, occupational dust exposure in mothers may affect the ovum before or during conception, the fetus through direct passage from the placenta, and the infant during the perinatal and postnatal periods through breastfeeding. Similarly, paternal exposure at preconception may lead to spontaneous mutations in the sperm.

Results of epidemiologic studies concerned with the role of dust on childhood cancer occurrence have been conflicting. Maternal exposure to wood dust was associated with a higher risk of leukemia, and paper and animal dusts were associated with a higher risk of CNS tumors in 2 Danish studies,[6,7] but not in a pooled analysis of international cohorts.[8] Similarly, some studies reported associations between paternal exposure to animal and other organic dusts and leukemias and CNS tumors,[6-11] but those results were not replicated by others.[6,8] The small number of exposed cases and the

differences in exposure ascertainment methods are some of the factors that might explain the discordance among previous findings.

By using Swedish population-based register data spanning over 5 decades and applying the Swedish job-exposure matrix (SWEJEM) to parental occupational information, our objective was to examine whether occupational exposure to animal, wood, textile, or paper dust in mothers or fathers was associated with a higher risk of childhood cancer, both overall and by type.

MATERIALS AND METHODS

Childhood Cancer Cases and Noncancer Controls

We conducted a register-based, case-control study nested in the child population of Sweden. We identified all children born between 1960 and 2014 in Sweden who had a first cancer diagnosis from birth to age 19 years or younger registered in the Cancer Register between 1960 and 2015. The Cancer Register was established in 1958 and holds information on primary tumors, with mandatory reporting by the treating physician and separately by pathologists/cytologists or radiologists.[12] After the exclusion of children with benign non-CNS tumors (for details, see Supporting Methods), childhood cancer diagnoses were classified according to the *International Classification of Childhood Cancer*, third edition, as leukemias, lymphomas, CNS tumors, and other cancer types.[13]

At the time of each child's cancer diagnosis (cases), up to 25 children without a history of cancer in the Cancer Register were randomly selected from the Total Population Register (controls) and individually matched to cases on birth year and sex. We excluded cases and controls who had a diagnosis of Down syndrome or cancer-predisposing neurocutaneous syndromes (eg, neurofibromatosis type 1 and 2, tuberous sclerosis) identified in the Medical Birth Register (MBR) (data available starting 1973) and the National Patient Register (established in 1964), with nationwide coverage of inpatient and outpatient care since 1987 and 2001, respectively,[14] or in the Cause of Death Register (data available starting 1952).[15] A study flowchart detailing all exclusions is available in the online Supporting Information (see Supporting Fig. 1).

Parental Occupational Exposure to Dusts

Biologic mothers and fathers of cases and controls were identified through the Multi-Generation Register, which links individuals born from 1932 and registered in Sweden at any time since 1961 to their parents. The register has nearly complete coverage for individuals born in Sweden.[16]

Maternal and paternal occupation around the time of a child's birth was obtained from 2 sources. For children born before 1997, parental occupation was retrieved from 6 censuses conducted by Statistics Sweden between 1960 and 1990. Occupations in censuses were codified using a census-specific, 3-digit code based on the Nordic Classification of Occupations, a coding scheme adapted from the 1958 International Standard Classification of Occupations (ISCO).[17] For cases and controls born 1997 and later, parental employment data were obtained from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA).[18] Data on occupation were available annually since 2001 and were codified using the 1996 Swedish Standard for Classification of Occupations, a 3-digit, hierarchical classification system adapted from the 1988 European International Standard Classification of Occupations.[19] Occupational codes in LISA are missing for approximately 5% of the employed.[18]

Because occupational history in Sweden was not available before 2001 on an annual basis, a scheme was devised to obtain the most accurate parental occupation from the census closest to a child's birth (Fig. 1). We excluded cases and controls from the main analyses when occupational information was missing for a parent—either because of unemployment or because data were missing in censuses or LISA—or if a parent had an unclassified occupation (33%/29% and 12%/12% of cases/controls in maternal and paternal analyses, respectively) (see Supporting Fig. 1). Ninety percent of childhood cancer cases in the maternal analyses were also included in the paternal analyses, whereas 69% of cases in the paternal analyses overlapped with cases in the maternal analyses.

We used a job-exposure matrix that was developed for Swedish working conditions, the SWEJEM, to assess parental occupational exposures to 4 types of inhalable dusts: 1) animal (from live animals or animal hair), 2) wood (from various softwoods and hardwoods), 3) textile (from treated natural materials used in garments), and 4) paper (from pulp, newsprint, printing paper, soft papers, or cardboard). The SWEJEM is based on the well established Finnish job-exposure matrix, which was designed for register-based studies and has been extensively validated and used.[20,21] The SWEJEM was adapted to Swedish working conditions by local experts and was extended to cover a longer period (1945-2018). The SWEJEM specifies the probability and level (air concentration) of occupational exposure, expressed as the 8-hour weighted average, and is calendar period-specific, capturing changes in exposure probability and level
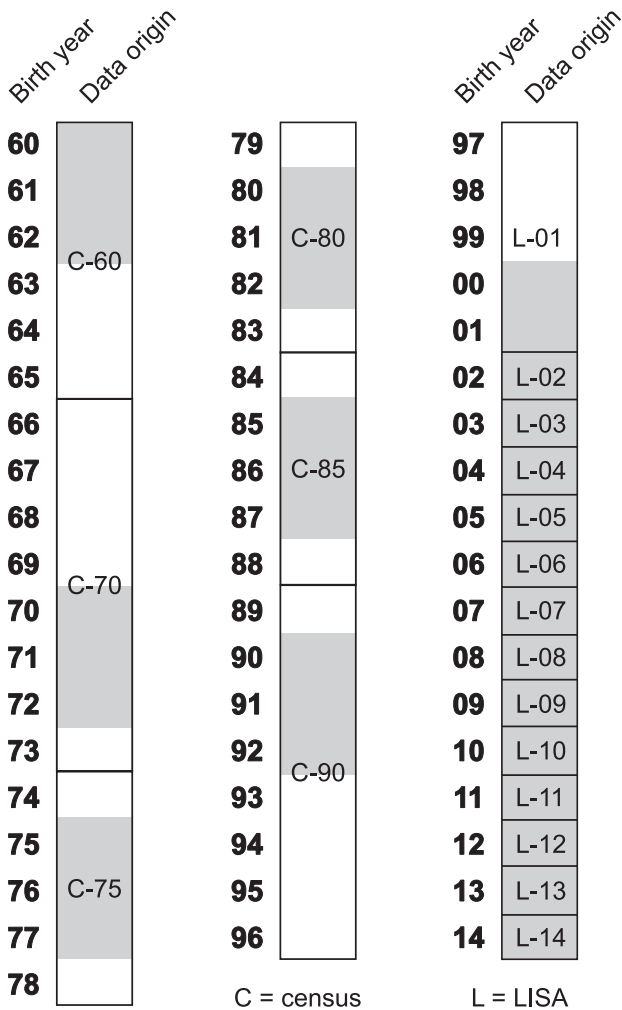
Figure 1. The origin of parental occupational data is illustrated according to a child's birth year. C indicates a census, and L indicates the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) followed by the year of data collection. Gray-shaded years indicate those close to a census or when LISA data were available on an annual basis. Children born during these years were included in a sensitivity analysis in which it was assumed that misclassification of dust exposures through occupation were lower.

the probability times the level of exposure among parents of controls, we grouped occupations into those of higher exposure (greater than or equal to the median) or lower exposure (lower than the median). Occupations in each exposure group are listed in the Supporting Methods.

Other Variables
We collected information on several potential confounders and other variables from various sources. A child's age, sex, region of residence at diagnosis (grouped into 6 health care regions, all highly urbanized with little variation throughout the study period[22]), birth order (first, subsequent birth, or missing), and a parent's birth date and country of birth (Sweden or other) were obtained from the Total Population Register. From censuses and LISA, we retrieved data on parental education ($\leq$9, 10-12, or $\geq$13 years of education or missing). Missing educational level in a census closest to a child's birth (Fig. 1) was imputed from the nearest census or from LISA. In addition, we retrieved an indicator of socioeconomic status based on employment and income from censuses and LISA. We further grouped socioeconomic classes into blue-collar worker, lower level white-collar worker, upper level white-collar worker, or unclassified/unknown (for details and codes, see Supporting Methods).

Because parental history of cancer before a child's birth might have confounded employment choice and the risk of cancer in the offspring, we sought information on parental cancer history from the Cancer Register. Finally, we used self-reported maternal first-trimester smoking (yes, no, or missing) in the MBR as a proxy for parental lifestyle factors. Maternal smoking data were available for children born 1982 and later.

Statistical Analysis
All analyses were conducted separately for maternal and paternal occupational exposures. Descriptive statistics on sociodemographic information of children and their parents were presented according to case/control status and parental exposure to occupational dusts.

We used conditional logistic regression models estimating odds ratios (ORs) and 95% confidence intervals (CIs) to examine the risk of childhood cancer, both overall and separately for leukemias, lymphomas, CNS tumors, and other cancers combined, associated with maternal or paternal occupational exposure to animal, wood, textile, or paper dust. Models were inherently adjusted for the matching variables birth year and sex of the child and were further adjusted for a child's region of residence at diagnosis, birth order, maternal or paternal (depending

as occupations evolve (over 12 distinct time periods). Parents' occupational information from the censuses or LISA around the time of conception or pregnancy was linked to the exposure information in SWEJEM.

In main analyses, exposure to each dust was dichotomized into any exposure versus no exposure. Parents with occupations for which either the calendar period probability or level of exposure was zero were considered unexposed. In a secondary analysis, we examined exposure to occupational dusts in a categorical fashion, comparing higher or lower exposure versus no dust exposure. On the basis of the study-wide median of the product of

on the analysis) country of birth, age, education, and history of cancer at the child's birth. We adjusted all models for parental education as a proxy for socioeconomic status and conducted a separate analysis restricted to parents who were blue-collar workers to account for potential residual confounding. To replicate findings reported in previous studies, we also estimated associations for specific cancer subtypes, including acute lymphoid leukemia, myeloid leukemias (and myeloprolifetarive and myelodysplastic syndromes), Hodgkin and non-Hodgkin lymphomas, ependymoma, and astrocytoma (including other gliomas).

In a secondary analysis, we examined exposure to parental occupational dusts by level of exposure, comparing higher and lower exposure versus no exposure to a specific dust. To avoid unstable results from logistic models, we reported associations in which ≥5 exposed cases or controls were available for each analysis. Estimates from adjusted models were very similar to those from crude models, thus only the former were presented. Observations with missing data on covariates (birth order, parental education, and maternal first-trimester smoking used in a sensitivity analysis) were included in all analyses, with missing values marked as a separate category.

We conducted several sensitivity analyses to test the robustness of our findings. First, to reduce potential misclassification of occupational exposures and other confounding variables, we restricted our analyses to children born around a census year or from 2000 onward, when employment history could be evaluated annually in LISA (Fig. 1). Because some parents' occupations could only be ascertained from a census conducted after the child's birth, we ran an analysis restricted to cases and controls whose parents' occupations could be retrieved before or at birth. In a separate analysis, we considered as exposed only parents working in an occupation for which the probability of exposure was ≥5% in the SWEJEM. Second, we further adjusted our analyses for maternal first-trimester smoking, a potential confounder for which we had self-reported data from the MBR for children born 1982 and later. Third, because the study period was long and occupational exposures as well as data sources evolved, we stratified analyses by study period (children born 1960-1996 [census data] and 1997-2014 [LISA data]). Finally, to test whether the exclusion of unemployed parents led to selection bias, we included them in an analysis regarding their child as being unexposed to occupational dusts.

Data were managed and analyzed using SAS software version 9.4 (SAS Institute Inc). Plots were created with *ggplot2* version 3.3.5[23] for R version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

Sociodemographic Characteristics of Children and Their Parents

In total, 9653 children diagnosed with a childhood cancer were matched to 172,194 controls who had an employed mother and 12,521 children diagnosed with cancer were matched to 274,434 controls who had an employed father around the time of birth were included in the analyses. Sociodemographic characteristics of the children and their parents are presented in Table 1. No notable difference in any characteristic was identified between cases and controls. Briefly, the mean age at cancer diagnosis was approximately 9 years, and there was a slight majority of males (54%) in both maternal and paternal analyses. Cancer types by age group are presented in Supporting Table 1. One-half of children were born before 1990 and 1984 in maternal and paternal analyses, respectively. On average, parents were aged 30 years at their child's birth, ≥90% were born in Sweden, and most had completed at least secondary education.

Mothers of both cases and controls were more likely to be employed in blue-collar or lower level white-collar occupations, whereas >50% of fathers were blue-collar workers (Table 1). As shown in Supporting Table 2, lower education and employment in blue-collar jobs were generally more common in parents who were exposed to dusts than in those who were unexposed. Occupational titles contributing to each exposure group are listed in Supporting Table 3.

Parental Occupational Exposure to Dusts and the Risk of Childhood Cancer Overall

The proportions of exposed parents of either cases or controls to any of the dusts examined were generally low (Table 2). Among mothers, the highest proportion of those who were exposed was observed for paper and wood dusts (4%-5%), and the lowest was observed for animal dust (1%); whereas approximately 7% to 8% of fathers were exposed to wood, and 2% were exposed to textile dust. Overall, neither maternal nor paternal exposure to animal, wood, textile, or paper dust was associated with higher odds of childhood cancer in the offspring (Table 2). Adjustment for confounders and restriction of the analysis to blue-collar worker parents did not materially change any of our findings (see Supporting Table 4).

TABLE 1. Demographic, Parental, and Other Characteristics of the Childhood Cancer Cases and Their Matched Controls Born in Sweden (1960-2014)

Characteristic	Maternal Analysis		Paternal Analysis	
	No. of Cases (%)	No. of Controls (%)	No. of Cases (%)	No. of Controls (%)
Children				
No.	9653	172,194	12,521	274,434
Age at cancer diagnosis/matching: Mean ± SD, y	8.7 ± 6.3	8.5 ± 6.3	9.1 ± 6.3	9.2 ± 6.3
Sex				
Female	4461 (46.2)	79,476 (46.2)	5774 (46.1)	126,541 (46.1)
Male	5192 (53.8)	92,718 (53.8)	6747 (53.9)	147,893 (53.9)
Region of residence at diagnosis				
Stockholm-Gotland	2075 (21.5)	35,973 (20.9)	2469 (19.7)	52,942 (19.3)
Uppsala-Örebro	1910 (19.8)	37,139 (21.6)	2596 (20.7)	61,017 (22.2)
West	1853 (19.2)	32,899 (19.1)	2446 (19.5)	52,421 (19.1)
South	1710 (17.7)	29,595 (17.2)	2207 (17.6)	47,417 (17.3)
Southeast	1146 (11.9)	19,272 (11.2)	1486 (11.9)	31,686 (11.5)
North	959 (9.9)	17,316 (10.1)	1317 (10.5)	28,951 (10.5)
Birth year: Median [IQR]	1988 [1977-1997]	1990 [1982-1998]	1984 [1972-1994]	1983 [1972-1993]
Birth order				
First-born	4515 (46.8)	76,895 (44.7)	5299 (42.3)	112,962 (41.2)
Subsequent birth	5138 (53.2)	95,299 (55.3)	7211 (57.6)	161,441 (58.8)
Missing	—	—	11 (0.1)	31 (0.0)
Parents				
Age at child's birth: Mean ± SD, y	28.8 ± 5.2	29.0 ± 5.1	31.4 ± 6.1	31.3 ± 6.1
Country of birth				
Sweden	8738 (90.5)	156,456 (90.9)	11,343 (90.6)	247,145 (90.1)
Other	915 (9.5)	15,738 (9.1)	1178 (9.4)	27,289 (9.9)
Education, y				
≤9	2367 (24.5)	38,139 (22.1)	4112 (32.8)	92,937 (33.9)
10-12	4660 (48.3)	84,899 (49.3)	5692 (45.5)	124,563 (45.4)
≥13	2594 (26.9)	48,459 (28.1)	2600 (20.8)	54,530 (19.9)
Missing	32 (0.3)	697 (0.4)	117 (0.9)	2404 (0.9)
Socioeconomic class				
Blue-collar worker	3717 (38.5)	69,875 (40.6)	6734 (53.8)	146,594 (53.4)
Lower level white-collar worker	3698 (38.3)	61,168 (35.5)	2980 (23.8)	66,031 (24.1)
Upper level white-collar worker	995 (10.3)	18,432 (10.7)	1631 (13.0)	34,390 (12.5)
Unclassified/unknown	1243 (12.9)	22,719 (13.2)	1176 (9.4)	27,419 (10.0)
History of cancer at child's birth	235 (2.4)	4114 (2.4)	66 (0.5)	837 (0.3)
Maternal first-trimester smoking[a]	N = 6456	N = 129,286	N = 6859	N = 148,587
Yes	1043 (16.2)	21,583 (16.7)	1128 (16.4)	25,377 (17.1)
No	4833 (74.9)	96,821 (74.9)	5085 (74.1)	109,865 (73.9)
Missing	580 (9.0)	10,882 (8.4)	646 (9.4)	13,345 (9.0)

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a]This variable was assessed in children born in 1982 or later when data in the Medical Birth Register became available.

Relative Risks by Cancer Type

We found no association between maternal exposures and leukemias, CNS tumors, and non-CNS solid tumors (Table 2). Maternal exposure to wood dust was associated with a 42% higher odds of lymphoma in the offspring (adjusted OR, 1.42; 95% CI, 1.10-1.84), and the association appeared to be stronger for non-Hodgkin lymphomas (OR, 2.03; 95% CI, 1.21-3.40) (see Supporting Table 5). Point estimates of approximately 1.2 were observed for maternal animal, textile, and paper dust exposure and lymphoma, but the CIs were wide. Restricting our analyses to mothers who were employed in blue-collar jobs resulted in stronger associations for lymphoma (eg, OR, 1.53 [95% CI, 1.07-2.20] for wood dust; OR, 1.78 [95% CI, 0.99-3.21] for

animal dust) (see Supporting Table 4). We also found an OR of 1.54 (95% CI, 0.98-2.41) for paternal exposure to animal dust and myeloid leukemias (see Supporting Table 5), but there were no increased risks of total leukemia or other cancer types (Table 2).

Relative Risks by Level of Parental Occupational Exposure to Dusts

We did not observe any increased risk of childhood cancer associated with either higher or lower maternal or paternal exposure to dusts and childhood cancer, either overall or for leukemias, CNS tumors, or other cancers (Table 3). For lymphomas, we found an association between higher maternal exposure to wood dust (OR, 1.44; 95% CI, 1.11-1.87) (Table 3) and lower exposure to paper dust

TABLE 2. Odds Ratios of Childhood Cancer, Overall and by Type, in Children Born in Sweden (1960-2014) Associated With Maternal or Paternal Occupational Exposure to Animal, Wood, Textile, or Paper Dust

	Maternal Analysis			Paternal Analysis		
Variable	No. of Exposed Cases (%)	No. of Exposed Controls (%)	Adjusted OR [95% CI][a]	No. of Exposed Cases (%)	No. of Exposed Controls (%)	Adjusted OR [95% CI][a]
Any cancer						
No. of children	9653	172,194		12,521	274,434	
Animal dust	138 (1.4)	2383 (1.4)	0.99 [0.83-1.18]	384 (3.1)	9103 (3.3)	0.92 [0.83-1.02]
Wood dust	421 (4.4)	7263 (4.2)	1.03 [0.93-1.14]	901 (7.2)	20,525 (7.5)	0.96 [0.90-1.03]
Textile dust	254 (2.6)	4463 (2.6)	0.96 [0.84-1.09]	238 (1.9)	5819 (2.1)	0.89 [0.78-1.02]
Paper dust	440 (4.6)	8209 (4.8)	0.94 [0.85-1.04]	566 (4.5)	12,667 (4.6)	0.99 [0.91-1.08]
Leukemias						
No. of children	2571	46,518		3245	70,789	
Animal dust	42 (1.6)	652 (1.4)	1.13 [0.82-1.55]	95 (2.9)	2222 (3.1)	0.92 [0.74-1.13]
Wood dust	107 (4.2)	1991 (4.3)	0.95 [0.78-1.16]	239 (7.4)	5438 (7.7)	0.95 [0.83-1.09]
Textile dust	64 (2.5)	1218 (2.6)	0.88 [0.68-1.14]	64 (2.0)	1607 (2.3)	0.86 [0.67-1.11]
Paper dust	108 (4.2)	2213 (4.8)	0.84 [0.68-1.02]	128 (3.9)	3205 (4.5)	0.88 [0.73-1.05]
Lymphomas						
No. of children	1160	20,350		1529	33,650	
Animal dust	20 (1.7)	282 (1.4)	1.19 [0.75-1.88]	49 (3.2)	1165 (3.5)	0.92 [0.69-1.24]
Wood dust	69 (5.9)	874 (4.3)	1.42 [1.10-1.84]	97 (6.3)	2360 (7.0)	0.90 [0.73-1.11]
Textile dust	35 (3.0)	520 (2.6)	1.14 [0.80-1.61]	33 (2.2)	653 (1.9)	1.10 [0.77-1.56]
Paper dust	66 (5.7)	1004 (4.9)	1.17 [0.90-1.53]	80 (5.2)	1572 (4.7)	1.11 [0.88-1.41]
CNS tumors						
No. of children	2450	43,801		3238	71,133	
Animal dust	33 (1.3)	581 (1.3)	0.95 [0.66-1.36]	101 (3.1)	2317 (3.3)	0.95 [0.77-1.16]
Wood dust	104 (4.2)	1912 (4.4)	0.99 [0.81-1.21]	245 (7.6)	5377 (7.6)	0.99 [0.87-1.14]
Textile dust	56 (2.3)	1157 (2.6)	0.84 [0.64-1.11]	54 (1.7)	1508 (2.1)	0.78 [0.59-1.02]
Paper dust	109 (4.4)	2180 (5.0)	0.90 [0.74-1.10]	159 (4.9)	3344 (4.7)	1.06 [0.90-1.25]
Other tumors						
No. of children	3472	61,525		4509	98,862	
Animal dust	43 (1.2)	868 (1.4)	0.84 [0.62-1.15]	139 (3.1)	3399 (3.4)	0.90 [0.75-1.07]
Wood dust	141 (4.1)	2486 (4.0)	1.00 [0.84-1.19]	320 (7.1)	7350 (7.4)	0.97 [0.86-1.09]
Textile dust	99 (2.9)	1568 (2.5)	1.04 [0.84-1.28]	87 (1.9)	2051 (2.1)	0.93 [0.75-1.16]
Paper dust	157 (4.5)	2812 (4.6)	0.98 [0.82-1.15]	199 (4.4)	4546 (4.6)	0.98 [0.85-1.13]

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio.
[a]ORs and corresponding CIs were estimated using conditional logistic regression models inherently adjusted for the matching variables child's birth year and sex and further adjusted for child's region of residence at diagnosis, birth order, parental (maternal or paternal, depending on the analysis) country of birth, age, education, and history of cancer at their child's birth.

(OR, 1.45; 95% CI, 1.03-2.05). Mothers with lower exposure to wood dust were too few to allow for a reliable estimation of the ORs for lymphomas.

Sensitivity Analyses

Results from sensitivity analyses for maternal and paternal exposures are presented in Figures 2 and 3, respectively, and Supporting Tables 6 and 7, respectively. Although a smaller sample size resulted in greater uncertainty, our findings did not deviate considerably from those in the main analysis. The association between maternal exposure to wood dust and childhood lymphomas persisted in most sensitivity analyses but was somewhat attenuated when we restricted the analysis to children born close to a census or when LISA data were available yearly to reduce exposure misclassification (OR, 1.23; 95% CI, 0.85-1.79). The inclusion of unemployed parents in the

analyses as unexposed did not alter any of our estimates (see Supporting Table 8).

DISCUSSION

In this large, register-based, case-control study of childhood cancer cases spanning >5 decades, we found no indication that maternal or paternal occupational exposure to animal, wood, textile, or paper dusts around the time of birth was associated with a higher risk of childhood cancer in the offspring, either overall or specifically for leukemia and CNS tumors. However, we found a 42% increased risk of lymphoma among children of mothers who were exposed to wood dust and possibly to other organic dusts, although the CIs for the latter were wide. Associations for lymphoma were generally stronger for children of mothers classified as blue-collar workers. Several sensitivity analyses aiming

TABLE 3. Odds Ratios of Childhood Cancer, Overall and by Type, Associated With Higher or Lower Versus No Parental Occupational Exposure to Dusts

| | Maternal Analysis | | | | Paternal Analysis | | | |
| | Higher Exposure | | Lower Exposure | | Higher Exposure | | Lower Exposure | |
Variable	No. of Exposed Cases/Controls	Adjusted OR (95% CI)[a]	No. of Exposed Cases/Controls	Adjusted OR (95% CI)[a]	No. of Exposed Cases/Controls	Adjusted OR (95% CI)[a]	No. of Exposed Cases/Controls	Adjusted OR (95% CI)[a]
Any cancer								
Animal dust	69/1032	0.96 (0.75-1.22)	69/1351	1.03 (0.80-1.31)	249/6191	0.88 (0.77-1.00)	135/2912	1.00 (0.84-1.19)
Wood dust	414/7003	1.05 (0.95-1.17)	7/260	0.49 (0.23-1.04)	438/10,184	0.96 (0.87-1.06)	463/10,341	0.97 (0.88-1.06)
Textile dust	166/2935	0.94 (0.80-1.11)	88/1528	0.99 (0.80-1.23)	137/3357	0.90 (0.75-1.06)	101/2462	0.88 (0.72-1.08)
Paper dust	250/4421	0.92 (0.80-1.04)	190/3788	0.98 (0.84-1.13)	303/6906	0.97 (0.86-1.09)	263/5761	1.02 (0.90-1.15)
Leukemias								
Animal dust	18/239	1.07 (0.66-1.74)	24/413	1.18 (0.78-1.80)	54/1426	0.81 (0.61-1.07)	41/796	1.09 (0.80-1.50)
Wood dust	106/1915	0.98 (0.80-1.20)	<5/76	Not estimable	105/2515	0.92 (0.75-1.12)	134/2923	0.98 (0.82-1.18)
Textile dust	38/790	0.78 (0.56-1.09)	26/428	1.07 (0.72-1.60)	34/910	0.81 (0.58-1.15)	30/697	0.92 (0.64-1.34)
Paper dust	64/1196	0.85 (0.66-1.11)	44/1017	0.81 (0.60-1.11)	61/1774	0.75 (0.58-0.97)	67/1431	1.03 (0.80-1.32)
Lymphomas								
Animal dust	11/146	1.10 (0.59-2.05)	9/136	1.31 (0.66-2.59)	35/835	0.92 (0.65-1.30)	14/330	0.93 (0.54-1.59)
Wood dust	68/849	1.44 (1.11-1.87)	<5/25	Not estimable	49/1331	0.82 (0.61-1.10)	48/1029	0.99 (0.74-1.34)
Textile dust	22/340	1.10 (0.71-1.71)	13/180	1.20 (0.68-2.12)	19/373	1.09 (0.69-1.75)	14/280	1.10 (0.64-1.89)
Paper dust	28/493	0.93 (0.63-1.38)	38/511	1.45 (1.03-2.05)	41/818	1.10 (0.80-1.51)	39/754	1.13 (0.82-1.57)
CNS tumors								
Animal dust	16/260	0.84 (0.50-1.41)	17/321	1.07 (0.66-1.76)	69/1598	0.95 (0.74-1.21)	32/719	0.95 (0.67-1.37)
Wood dust	102/1853	1.00 (0.81-1.23)	<5/59	Not estimable	123/2654	1.02 (0.85-1.23)	122/2723	0.96 (0.80-1.17)
Textile dust	38/750	0.88 (0.63-1.23)	18/407	0.77 (0.48-1.24)	32/862	0.81 (0.57-1.16)	22/646	0.73 (0.47-1.12)
Paper dust	66/1154	0.95 (0.74-1.23)	43/1026	0.83 (0.61-1.14)	84/1809	1.03 (0.83-1.29)	75/1535	1.09 (0.86-1.38)
Other tumors								
Animal dust	24/387	0.90 (0.59-1.37)	19/481	0.78 (0.49-1.24)	91/2332	0.86 (0.69-1.07)	48/1067	0.97 (0.72-1.30)
Wood dust	138/2386	1.02 (0.85-1.21)	<5/100	Not estimable	161/3684	0.99 (0.84-1.17)	159/3666	0.95 (0.80-1.12)
Textile dust	68/1055	1.05 (0.81-1.35)	31/513	1.03 (0.71-1.48)	52/1212	0.96 (0.72-1.26)	35/839	0.91 (0.64-1.27)
Paper dust	92/1578	0.94 (0.75-1.16)	65/1234	1.04 (0.80-1.34)	117/2505	1.04 (0.86-1.26)	82/2041	0.90 (0.72-1.13)

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio.

[a] ORs and corresponding CIs were estimated using conditional logistic regression models inherently adjusted for the matching variables child's birth year and sex and further adjusted for child's region of residence at diagnosis, birth order, parental (maternal or paternal, depending on the analysis) country of birth, age, education, and history of cancer at their child's birth. Models with <5 exposed cases or controls were not run and were marked as *not estimable*.
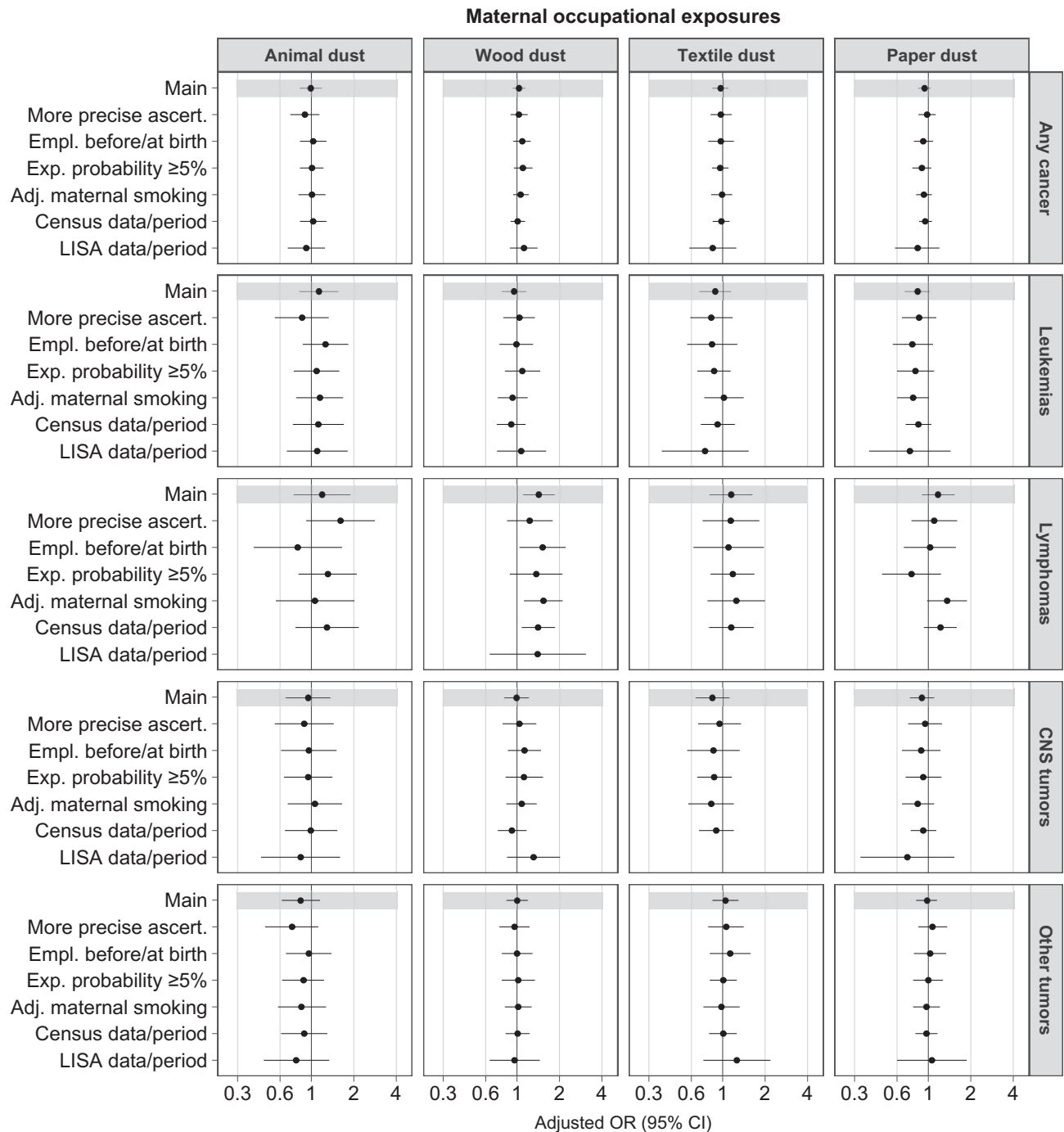
Figure 2. Plots show adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) (error bars) of childhood cancer, overall and by type, associated with maternal occupational exposure to dusts from main and sensitivity analyses. Main refers to results from the main analysis (see Table 2), and more precise ascertainment (ascert.) refers to restriction to children born close to a census or when Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) data were available yearly. Employment (Empl.) before/at birth included only children of mothers whose occupation could be ascertained before or at the year of their birth. Exposure (Exp.) probability ≥5% refers to a sensitivity analysis in which exposed individuals were mothers with an occupation for which the calendar period specific probability of exposure in the job-exposure matrix was ≥5%. Estimates from analyses with <5 exposed cases are not presented. Adj. indicates adjusted; CNS, central nervous system.
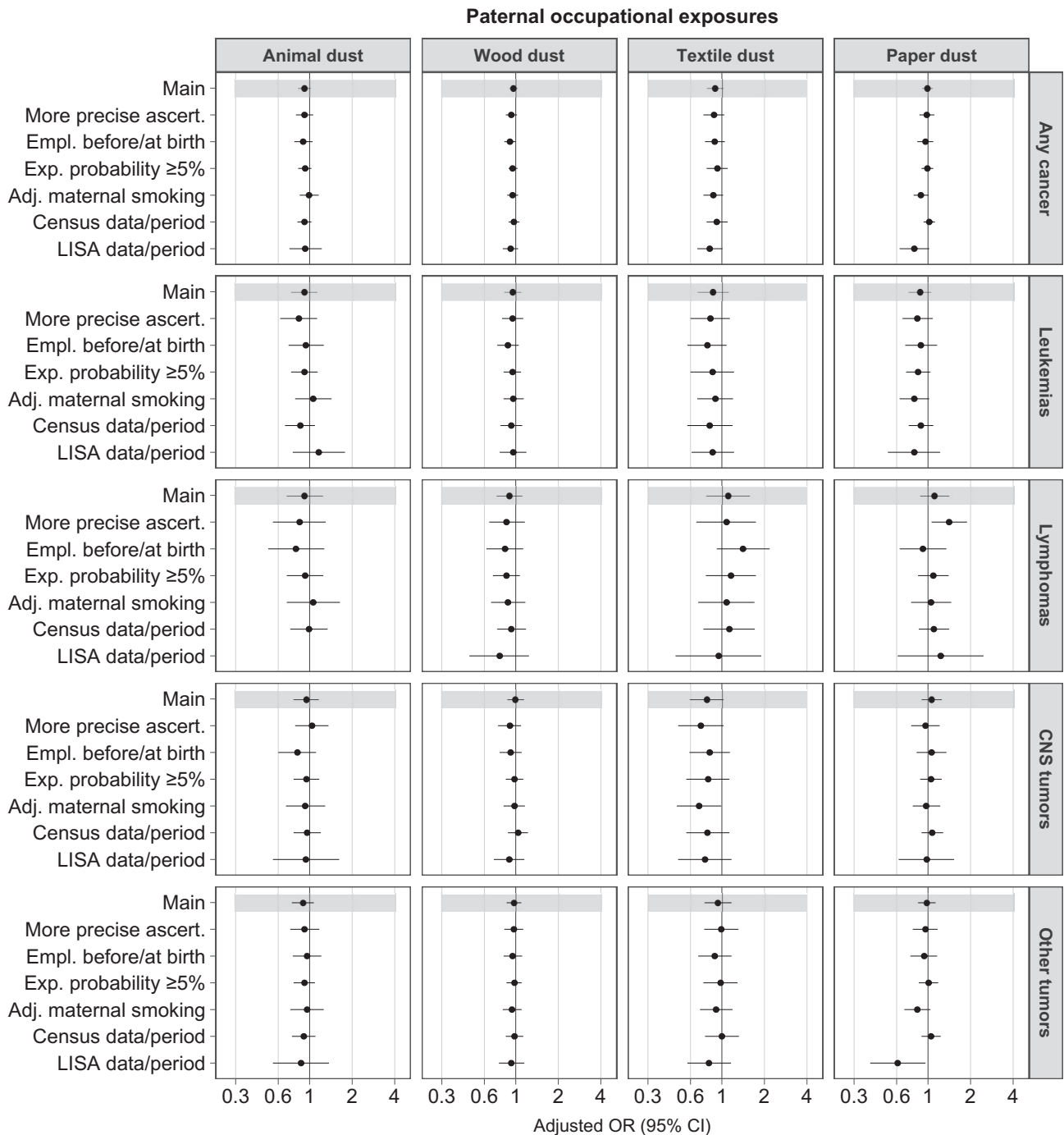
Paternal occupational exposures

Figure 3. Plots show adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) (error bars) of childhood cancer, overall and by type, associated with paternal occupational exposure to dusts from main and sensitivity analyses. Main refers to results from the main analysis (see Table 2), and more precise ascertainment (ascert.) refers to restriction to children born close to a census or when Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) data were available yearly. Employment (Empl.) before/at birth included only children of fathers whose occupation could be ascertained before or at the year of their birth. Exposure (Exp.) probability ≥5% refers to a sensitivity analysis in which exposed individuals were fathers with an occupation for which the calendar period specific probability of exposure in the job-exposure matrix was at ≥5%. Estimates from analyses with <5 exposed cases are not presented. Adj. indicates adjusted; CNS, central nervous system.

to address exposure misclassification did not alter our interpretations.

This is the first study to report a 42% increased risk of lymphoma associated with maternal occupational exposure to wood dust, an association that was specific to non-Hodgkin lymphoma (OR, 2.0 vs 1.1 for Hodgkin lymphoma). Few previous studies have reported results specifically for lymphoma. An imprecise estimate of a 40% increased risk of non-Hodgkin lymphoma among children of a few mothers who reported being exposed to wood dust during preconception was indicated in the UK Childhood Cancer Study.[24] Some smaller studies did not suggest any such link.[25,26] In our study, the association between wood dust exposure and lymphoma persisted when we required an exposure probability of ≥5% or required parental occupation to be ascertained at birth or earlier. In addition, the results were slightly stronger when we restricted the analysis to blue-collar mothers to better account for residual confounding by socioeconomic status. However, we observed a lower OR (1.2) when we restricted the analysis to children whose mothers' occupational information could be assessed with greater precision; that is, for those born close to a census year or from 2000 or later, when annual data were available in LISA. Few mothers were classified as having lower exposure to wood dust, thus we could not examine its potency. The OR did not vary considerably by study period or source for occupational data (census data [1960-1996] vs LISA data [1997-2014]), although we should note that only 7 exposed cases contributed to the latter period, resulting in lower precision.

Little is known about the biologic mechanisms behind wood dust exposure around the time of pregnancy and (non-Hodgkin) lymphoma. Wood dust is a potent carcinogen[27] and has been linked in exposed adults to non-Hodgkin lymphomas in some,[28,29] but not all,[30] studies. Findings from animal studies also suggest that exposure to wood dust may result in germline mutations.[5] It remains unclear, however, whether wood particles or solvents used for wood treatment and preservation (eg, formaldehyde) might be responsible for those mutations. In our data, we could not establish whether exposure during the preconception, perinatal, and/or postnatal periods was critical. The role of maternal wood dust exposure, and possibly other dust exposure, on lymphoma occurrence in the offspring merits further investigation with epidemiologic and experimental data.

We did not identify any indications of higher risks of other cancer types because of maternal occupational exposure to dusts. Several such associations were suggested in smaller studies, including higher risks of CNS tumors in children of mothers exposed to animal or organic dusts (OR, 1.4-2.6),[7,8,31,32] leukemia and wood (OR, 1.4)[6] or textile (OR, 1.2)[33] dust exposure, and retinoblastoma and animal dust exposure in mothers (OR, 2.7).[7] Similarly, several associations between paternal dust exposure and the risk of childhood cancer were reported in previous studies. Paternal animal dust exposure was associated with a higher risk of CNS tumors (OR 1.4)[9] and acute myeloid leukemia (hazard ratio, 3.9 based on 3 exposed cases)[8] in UK and multicountry data, but not Danish data.[7] In addition, a 40% to 50% increased risk was found for astrocytoma and neuroblastoma associated with paternal wood dust exposure in Denmark.[6] None of these associations were replicated in our data except for paternal animal dust exposure and myeloid leukemias (OR, 1.5). We also could not replicate our previous finding of an increased risk of leukemia in children of fathers exposed to wood dust in Sweden,[34] which was based on 14 exposed cases compared with 239 in the current study.

Disentangling the reasons behind different findings among studies is challenging for several reasons. Various sources were used to ascertain occupational exposure to each dust, with data on employment originating from interviews in some studies or from registers and censuses in others. Job-exposure matrices were used in some studies, whereas a qualitative assessment of occupational codes to isolate the likely exposed was performed by experts in other investigations. Furthermore, occupations and exposure levels associated with them may differ considerably even among neighboring countries (eg, Sweden and Denmark).[35] Other factors, including study period, age of included children, cancer ascertainment and subclassification, parental leave practices, and the small number of exposed parents in most of studies, combined with multiple statistical testing, could explain some of the inconsistencies among studies.

A wide range of crucial changes that occurred during the long study period might have influenced our findings in various ways. Changes in the occupational market and tasks, improvement of socioeconomic status, and advances in knowledge that led to the regulation of safety standards have all contributed to a significant reduction in exposure to certain carcinogenic and mutagenic dusts.[36] Therefore, an attenuation of the associations, if any, would have been expected after the 2000s in our study. Despite expectations, we did not identify any differences between the 2 study periods beyond some random variation suggesting that some risks are contemporary, and further research is warranted.

Certain limitations of this study are of note. Although data on occupation were retrieved from established sources, some misclassification of parental occupational exposure is to be expected because of the unavailability of yearly data for the early study period and some coding inaccuracies or missingness in the data. Moreover, because occupational data were available at best on a yearly basis, we could not define precise exposure windows in relation to a child's conception. Therefore, we cannot exclude the possibility that some children were directly exposed to some dusts longer after birth. In addition, we could not distinguish among specific tasks within an occupational title in the SWEJEM, hence true exposure for some parents is likely to have been underestimated or overestimated in this study. However, sensitivity analyses designed to mitigate some of this bias yielded results that were largely similar those of the main analysis. In addition, because occupational transitions were limited particularly during the early study period,[37] the sparsity of occupational data during that period is unlikely to have considerably affected exposure ascertainment. Importantly, because employment history was not based on recall and, in most cases, was collected before a child's cancer diagnosis, exposure misclassification was likely nondifferential.

Attributing risks to a single exposure was challenging because some exposures in the workplace co-occur. As shown in Supporting Table 9, 61% of mothers exposed to wood dust were also exposed to paper dust, and 54% of those exposed to paper dust were simultaneously exposed to wood dust. Although adjustment for concomitant dust exposures had no effect on the association between wood dust and lymphoma (data not shown), we cannot exclude the possibility that other agents (eg, pesticides or silica dust) might have contributed to some of the associations.

There are several strengths to our register-based study. We were able to capture virtually all first malignant cancers in children and adolescents younger than 20 years in Sweden since the 1960s. We also were able to avoid recall bias and reduce the possibility of unmeasured confounding. In addition, the use of a locally developed job-exposure matrix allowed for a more accurate and period-specific investigation of occupational exposures. We believe our findings are generalizable to populations that have a similar occupational environment with generally low exposure levels (eg, for farm workers, animal dust exposure was one-tenth that of the Swedish occupational exposure limit value of 0.1 mg/m^3).

In summary, in this large Swedish register-based study, we found no association between maternal or paternal occupational exposure to animal, wood, paper, or textile dust and cancer overall, leukemias, or CNS tumors in the offspring. These findings did not confirm the associations reported in some previous studies. However, we observed a moderately increased risk of lymphoma, particularly of the non-Hodgkin type, in children of mothers who were exposed primarily to wood dust through their occupation. Paternal wood or other dust exposure around a child's birth did not confer any increased risk for lymphoma.

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Marios Rossides reports nonpromotional speaker fees from Teva outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS
Marios Rossides: Conceptualization, methodology, software, formal analysis, visualization, writing–original draft, and writing–review and editing. **Christina-Evmorfia Kampitsi:** Conceptualization and writing–review and editing. **Mats Talbäck:** Resources, data curation, and writing–review and editing. **Pernilla Wiebert:** Conceptualization, resources, and writing–review and editing. **Maria Feychting:** Conceptualization, methodology, supervision, funding acquisition, and writing–review and editing. **Giorgio Tettamanti:** Conceptualization, data curation, writing–review and editing.

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