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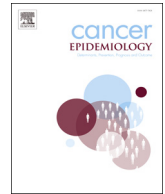
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# Parental occupational organic dust exposure and selected childhood cancers in Denmark 1968–2016

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## ABSTRACT

**Background:** Parental occupational exposures are suggested as contributing causes of childhood cancer.

**Methods:** Children age  $\leq 19$ , born in Denmark and diagnosed with leukemia, central nervous system (CNS) cancers and likely prenatally initiated cancers [hepatoblastoma, medulloblastoma, Wilms tumor (neuroblastoma), neuroblastoma, retinoblastoma and acute lymphoid leukemia]  $n = 4268$  were identified using Danish registries. We randomly selected twenty-five controls per case matched on birth year and sex. Parents and their employment histories were extracted from nationwide registries. We examined occupational dust exposures perinatally and postnatally in both parents. Odds ratios (ORs) and 95 % confidence intervals (95 % CI) were estimated using conditional logistic regression.

**Results:** Maternal wood dust exposure from birth to diagnosis was associated with increased risks of leukemia (OR 1.44, 95 % CI 1.08–1.94) and acute myeloid leukemia (OR 2.14, 95 % CI 1.13–4.03); exposure to paper dust was associated with CNS cancer (OR 2.28, 95 % CI 1.22–4.2). Paternal exposure to wood dust was associated with astrocytoma in both periods (OR 1.43, 95 % CI 1.05–1.96 and 1.42, 1.09–1.86, respectively) and CNS cancer (OR 1.24, 95 % CI 1.00–1.53) in the perinatal period. The increased risk observed for potentially prenatally-initiated cancers in relation to wood was driven by ORs for neuroblastoma (1.54, 95 % CI 1.03–2.29) and hepatoblastoma (2.41, 95 % CI 0.99–5.88). An OR of 2.58 (95 % CI 1.10–6.05) for CNS cancer was associated with both parents working in textile industries postnatally.

**Conclusion:** The study suggests that parental exposure to wood dust may increase risk of specific childhood cancers.

## 1. Introduction

Little is known about the etiology of many types childhood cancers besides genetic syndromes and new mutations. Parental exposures, especially around pregnancy, have been suggested as a contributing factor of childhood cancers. Several parental occupations and exposures are well-established causes of cancer in adults, but potential risks for the offspring have not received the same attention in research studies. Previous studies have investigated the effect of parental exposures to organic dusts in relation to several childhood cancers [1–5]. Mechanisms are not clear, but generally, the potential effects are thought to be either direct or indirect exposure of the child through inadvertent transfer of substances from work to the child or through transmission across the placenta [6]. Further, mutations or epigenetic alternations in sperm have also been suggested as a possible mechanism [7].

Employment in industries involving exposure to organic dusts such as wood, textile, and paper has been investigated by the International Agency for Research on Cancer (IARC) for its carcinogenic potential and categorized as human carcinogen (group 1) [8,9], possibly carcinogenic to humans (group 2B) [10], and as not classifiable as to its carcinogenicity to humans (group 3), respectively [11]. Childhood cancers were not evaluated due to the small number of studies available at the time of the IARC classification. However, several subsequent studies have found increased risks of leukemia and some also for central nervous system (CNS) cancers, in particular in relation to wood exposures [1–4,12], while studies are lacking on textile and paper exposures.

Even though working in paper industries is not categorized as carcinogenic (IARC group 3) in IARC's relatively old evaluation there are some overlaps in exposure with wood industries and we have chosen to include this exposure.

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We used Danish registers of high validity [13–16] and completeness to investigate whether offspring of mothers and fathers working in industries where organic dust exposure occurs, have increased risk of leukemia, central nervous system cancers and cancers thought to have originated before birth i.e. likely prenatally initiated cancers.

## 2. Methods

### 2.1. Ascertainment of cases and controls

The Danish Cancer Registry was founded in 1942 and contains both personal information such as date of birth and sex as well as tumor characteristics [13]. Before 1978 diagnoses were classified using a conversion system from the original notification forms to a Danish modification of International Classification of Disease, Revision 7 (ICD-7); a converted version of ICD-10 until 2003 and subsequently ICD-10 [13] while topography and morphology were kept according to International Classification of Childhood Cancer (ICCC) revisions 1 (ICCC-1) and 3 (ICCC-3) [17,18].

The unique 10-digit personal identifier, the CPR-number, given to all Danish residents, establishes each person in the registry. The number is designated by the Civil Registration System, founded in 1968, and used by all registries in Denmark, thereby securing correct linkages and prevents counting the same case more than once. It stores present and historical information on parents, spouses, children, siblings, and vital status. Further, it is updated daily and information includes emigration or death [15].

All children born in Denmark between 1968–2013 and diagnosed with cancer during 1968–2016 were identified for this study with International Classification of Childhood Cancer (ICCC-1 and ICC-3) (See Supplementary Table 2 for ICC-3 codes). Children diagnosed with leukemia, CNS cancers or likely prenatally initiated cancers ( $n = 4268$ ) were included in the study. Twenty-five controls per case alive and free of cancer at time of diagnosis of the index child, matched on year of birth and sex, were randomly selected from the Civil Registration System. In order to retrieve parental employment history perinatally, children born outside Denmark were excluded.

Finally, in order to minimize the possibility that cancers were caused by genetic syndromes, we were able to identify children with neurofibromatosis (0.08 %), retinoblastoma (0.05 %) and children born with Down syndrome (0.07 %), who are known to have increased risks of ALL. Exclusion of these few children only changed results minimally and therefore they were included in analysis. We also tried to exclude children with more than one tumor, but again minimal changes were found and thus the children were kept in analysis.

### 2.2. Parental employment history

We identified biological mothers in the Medical Birth Registry from 1972 and onwards. In addition, the Civil Registration System holds information on family relationships allowing us to identify both parents.

Parental employment history was obtained through linkage to the Supplementary Pension Fund Registry, where membership is mandatory for all employees in Denmark. This registry was founded in 1964 and contains information on start and end dates of employment exceeding nine hours a week for workers ages 18–66 years, and from 1978 also ages 16–17 years. The employee is identified using the CPR-number while the employer is identified using an eight-digit company number assigned to each company for tax purposes based on the most important economic activity. The company number was updated during the study period so in order to limit misclassification, we converted industry codes to the original Danmarks Statistik Erhvervsgrupperingskode 1977, DSE-77 code [14].

Parents with no employment history were excluded to make the comparison between groups more uniform and this exclusion only

changed estimates marginally. We examined 1) the perinatal period, and 2) from birth to diagnosis. For mothers, the perinatal employment histories were restricted to one year before birth until one year after birth to capture pregnancy and lactation periods, while paternal employment history one year before birth to birth reflected the period of spermatogenesis. Further, for both parents, we examined the period from birth until diagnosis as one may inadvertently bring home dust from work on clothing and thereby expose the index child [19].

We used different methods to define parental occupational exposure to organic dusts. To determine industries in which workers were exposed to wood, we used the job titles stated in an established job-exposure matrix (NOCCA-JEM) adapted to Danish working conditions by expert opinions based on workplace measurements from the five Nordic countries (NOCCA-DANJEM) [20]. Textile and paper industries were not available in the NOCCA-DANJEM, so these were identified by an expert on the working environment, JH. The included industries are gathered in the Supplementary Table 3.

### 2.3. Covariates

From the Civil Registration System we gathered and categorized the following variables: Family socioeconomic status (SES), birth order (1, 2, and 3 or later), parity at the time of diagnosis (index date) of the child (1, 2, and 3 or more children), maternal and paternal age at the time of birth of the index child ( $< = 25, 26–28, 29–33,$  and 34 years or older), and birth place of the index child in Denmark (rural, small town, and urban) (15). We categorized urban as being the three largest cities in Denmark with populations above 200,000, small towns as “Other Cities” and remaining categories as rural, in order to adjust for potential regional differences as background exposures in these parts of Denmark the country may have influenced exposure of the index children.

Parents were assigned SES, defined as the highest level of education based on the job title obtained from the income tax reform. Categorization of SES on the family level was defined as the highest SES level of either parent and was based on the definition by the Danish Institute for Social Sciences as academics or executive managers, higher education of intermediate duration, higher education of shorter duration, skilled work, unskilled work and unknown [21]. As around 19–23 % of parents had unknown SES, we also carried out analyses for only parents with known SES but estimates changed less than 15 %.

Since parental smoking is suggested as a potential risk factor for some childhood cancers [22], we retrieved information on maternal smoking during pregnancy from the Medical Birth Registry, which was established in 1973 and information was initially gathered by midwives and from 1993 by hospitals [23]. Maternal smoking status at first visit with a midwife was available from 1991 and from more elaborate information on cigarettes per day we dichotomized information to no/yes. Mothers with no information on smoking status were excluded from analysis.

### 2.4. Statistical analyses

We performed analyses on parental exposure to the chosen types of organic dusts when data allowed (i.e. more than five exposed cases of a specific diagnoses) in relation to our selected childhood cancers. Parental occupation or exposure was classified as ever employed in the industry of interest during the period of interest vs. no employment. We examined all the selected cancers combined and individually. Risks were estimated for mothers and fathers separately by calculating Odds Ratios (ORs) and their corresponding 95 % confidence intervals (95 % CI). In addition, when feasible (i.e. number of exposed cases exceeded five), we examined risk estimates when both parents were employed in the same overall industry. Further, the two time periods (i.e. the perinatal periods and from birth to diagnosis) were estimated separately. As risk estimates changed less than 10 %, we left out the previously mentioned potential covariates from regression analyses. Excluding

**Table 1**  
Characteristics of population in the perinatal period.

|   | Leukemia               |      |                    |      |                        |      |                    |      | CNS                 |      |                     |      |                     |      |                       |      |
|---|------------------------|------|--------------------|------|------------------------|------|--------------------|------|---------------------|------|---------------------|------|---------------------|------|-----------------------|------|
|   | Mothers                |      |                    |      | Fathers                |      |                    |      | Mothers             |      |                     |      | Fathers             |      |                       |      |
|   | Controls<br>n = 39,107 |      | Cases<br>n = 1,673 |      | Controls<br>n = 44,255 |      | Cases<br>n = 1,811 |      | Cases<br>n = 22,064 |      | Controls<br>n = 926 |      | Cases<br>n = 24,780 |      | Controls<br>n = 1,003 |      |
|   | N                      | %    | n                  | %    | n                      | %    | n                  | %    | n                   | %    | n                   | %    | n                   | %    | n                     | %    |
| <b>Child's sex</b>                          |                        |      |                    |      |                        |      |                    |      |                     |      |                     |      |                     |      |                       |      |
| Boy   | 21,930                 | 56.1 | 922                | 55.1 | 24,627                 | 55.6 | 1,004              | 55.4 | 11,703              | 53.0 | 495                 | 53.5 | 13,149              | 53.1 | 534                   | 53.2 |
| Girl  | 17,177                 | 43.9 | 751                | 44.9 | 19,628                 | 44.4 | 807                | 44.6 | 10,361              | 47.0 | 431                 | 46.5 | 11,631              | 46.9 | 469                   | 46.8 |
| <b>Birth order</b>                          |                        |      |                    |      |                        |      |                    |      |                     |      |                     |      |                     |      |                       |      |
| First                                       | 17,919                 | 45.8 | 780                | 46.6 | 19,178                 | 43.3 | 796                | 44.0 | 10,198              | 46.2 | 440                 | 47.5 | 10,870              | 43.9 | 452                   | 45.1 |
| Second                                      | 14,590                 | 37.3 | 621                | 37.1 | 16,876                 | 38.1 | 689                | 38.0 | 8,257               | 37.4 | 348                 | 37.6 | 9,474               | 38.2 | 385                   | 38.4 |
| Third or later                              | 6,598                  | 16.9 | 272                | 16.3 | 8,201                  | 18.5 | 326                | 18.0 | 3,609               | 16.4 | 138                 | 14.9 | 4,436               | 17.9 | 166                   | 16.6 |
| <b>Family socioeconomic status</b>          |                        |      |                    |      |                        |      |                    |      |                     |      |                     |      |                     |      |                       |      |
| Academics                                   | 3,900                  | 10.0 | 167                | 10.0 | 44,120                 | 10.0 | 172                | 9.5  | 2,226               | 10.1 | 105                 | 11.3 | 2,421               | 9.8  | 111                   | 11.1 |
| Middle education                            | 5,554                  | 14.2 | 234                | 14.0 | 5,748                  | 13.0 | 244                | 13.5 | 3,268               | 14.8 | 127                 | 13.7 | 3,374               | 13.6 | 128                   | 12.8 |
| Shorter education                           | 5,909                  | 15.1 | 226                | 13.5 | 6,145                  | 13.9 | 231                | 12.8 | 3,626               | 16.4 | 153                 | 16.5 | 3,731               | 15.1 | 159                   | 15.9 |
| Skilled                                     | 9,667                  | 24.7 | 430                | 25.7 | 11,206                 | 25.3 | 469                | 25.9 | 5,973               | 27.1 | 235                 | 25.4 | 6,851               | 27.6 | 262                   | 26.1 |
| Unskilled                                   | 5,384                  | 13.8 | 234                | 14.0 | 6,583                  | 14.9 | 274                | 15.1 | 3,038               | 13.8 | 120                 | 13.0 | 3,803               | 15.3 | 143                   | 14.3 |
| Unknown                                     | 8,693                  | 22.2 | 382                | 22.8 | 10,161                 | 23.0 | 421                | 23.2 | 3,933               | 17.8 | 186                 | 20.1 | 4,600               | 18.6 | 200                   | 19.9 |
| <b>Parental age at birth of index child</b> |                        |      |                    |      |                        |      |                    |      |                     |      |                     |      |                     |      |                       |      |
| < = 25                                      | 10,086                 | 25.8 | 388                | 23.2 | 6,250                  | 14.1 | 229                | 12.6 | 6,187               | 28.0 | 265                 | 28.6 | 3,740               | 15.1 | 152                   | 15.2 |
| 26-28                                       | 8,985                  | 23.0 | 397                | 23.7 | 8,392                  | 19.0 | 343                | 18.9 | 5,254               | 23.8 | 242                 | 26.1 | 5,052               | 20.4 | 210                   | 20.9 |
| 29-33                                       | 12,933                 | 33.1 | 560                | 33.5 | 15,314                 | 34.6 | 636                | 35.1 | 7,062               | 32.0 | 276                 | 29.8 | 8,703               | 35.1 | 375                   | 37.4 |
| > = 34                                      | 7,103                  | 18.2 | 328                | 19.6 | 14,299                 | 32.3 | 603                | 33.3 | 3,561               | 16.1 | 143                 | 15.4 | 7,285               | 29.4 | 266                   | 26.5 |
| <b>Childs birth place</b>                   |                        |      |                    |      |                        |      |                    |      |                     |      |                     |      |                     |      |                       |      |
| Urban                                       | 12,765                 | 32.6 | 525                | 31.4 | 14,617                 | 33.0 | 584                | 32.2 | 6,997               | 31.7 | 317                 | 34.2 | 7,968               | 32.2 | 338                   | 33.7 |
| Small town                                  | 12,328                 | 31.5 | 523                | 31.3 | 14,312                 | 32.3 | 568                | 31.4 | 7,234               | 32.8 | 285                 | 30.8 | 8,239               | 33.2 | 318                   | 31.7 |
| Rural                                       | 14,014                 | 35.8 | 625                | 37.4 | 15,326                 | 34.6 | 659                | 36.4 | 7,833               | 35.5 | 324                 | 35.0 | 8,573               | 34.6 | 347                   | 34.6 |
| <b>Number of children by mother</b>         |                        |      |                    |      |                        |      |                    |      |                     |      |                     |      |                     |      |                       |      |
| 1   | 8,079                  | 20.7 | 365                | 21.8 |                        |      |                    |      | 3,921               | 17.8 | 186                 | 20.1 |                     |      |                       |      |
| 2   | 19,699                 | 50.4 | 849                | 50.7 |                        |      |                    |      | 11,330              | 51.4 | 461                 | 49.8 |                     |      |                       |      |
| 3 or more                                   | 11,329                 | 29.0 | 459                | 27.4 |                        |      |                    |      | 6,813               | 30.9 | 279                 | 30.1 |                     |      |                       |      |

|   | Prenatal cancers <sup>a</sup> |      |                    |      |                        |      |                    |      |
|---|-------------------------------|------|--------------------|------|------------------------|------|--------------------|------|
|   | Mothers                       |      |                    |      | Fathers                |      |                    |      |
|   | Controls<br>n = 52,357        |      | Cases<br>n = 2,242 |      | Controls<br>n = 59,320 |      | Cases<br>n = 2,448 |      |
|   | n                             | %    | n                  | %    | n                      | %    | n                  | %    |
| <b>Child's sex</b>                          |                               |      |                    |      |                        |      |                    |      |
| Boy   | 29,858                        | 57.0 | 1,279              | 57.0 | 33,607                 | 56.7 | 1,393              | 56.9 |
| Girl  | 22,499                        | 43.0 | 963                | 43.0 | 25,713                 | 43.3 | 1,055              | 43.1 |
| <b>Birth order</b>                          |                               |      |                    |      |                        |      |                    |      |
| First                                       | 24,015                        | 45.9 | 1,051              | 46.9 | 25,670                 | 43.3 | 1,079              | 44.1 |
| Second                                      | 19,497                        | 37.2 | 834                | 37.2 | 22,673                 | 38.2 | 936                | 38.2 |
| Third or later                              | 8,845                         | 16.9 | 357                | 15.9 | 10,977                 | 18.5 | 433                | 17.7 |
| <b>Family socioeconomic status</b>          |                               |      |                    |      |                        |      |                    |      |
| Academics                                   | 5,254                         | 10.0 | 238                | 10.6 | 5,879                  | 9.9  | 247                | 10.1 |
| Middle education                            | 7,405                         | 14.1 | 323                | 14.4 | 7,669                  | 12.9 | 335                | 13.7 |
| Shorter education                           | 8,019                         | 15.3 | 299                | 13.3 | 8,346                  | 14.1 | 317                | 12.9 |
| Skilled                                     | 13,045                        | 24.9 | 562                | 25.1 | 15,109                 | 25.5 | 628                | 25.7 |
| Unskilled                                   | 7,065                         | 13.5 | 307                | 13.7 | 8,784                  | 14.8 | 366                | 15.0 |
| Unknown                                     | 11,569                        | 22.1 | 513                | 22.9 | 13,533                 | 22.8 | 555                | 22.7 |
| <b>Parental age at birth of index child</b> |                               |      |                    |      |                        |      |                    |      |
| < = 25                                      | 13,539                        | 25.9 | 543                | 24.2 | 8,415                  | 14.2 | 304                | 12.4 |
| 26-28                                       | 11,970                        | 22.9 | 519                | 23.1 | 11,294                 | 19.0 | 473                | 19.3 |
| 29-33                                       | 17,195                        | 32.8 | 749                | 33.4 | 20,439                 | 34.5 | 879                | 35.9 |
| > = 34                                      | 9,653                         | 18.4 | 431                | 19.2 | 19,172                 | 32.3 | 792                | 32.4 |
| <b>Childs birth place</b>                   |                               |      |                    |      |                        |      |                    |      |
| Urban                                       | 17,028                        | 32.5 | 732                | 32.6 | 19,458                 | 32.8 | 826                | 33.7 |
| Small town                                  | 16,669                        | 31.8 | 701                | 31.3 | 19,412                 | 32.7 | 775                | 31.7 |
| Rural                                       | 18,660                        | 35.6 | 809                | 36.1 | 20,450                 | 34.5 | 847                | 34.6 |
| <b>Number of children by mother</b>         |                               |      |                    |      |                        |      |                    |      |
| 1   | 12,812                        | 24.5 | 577                | 25.7 |                        |      |                    |      |
| 2   | 25,749                        | 49.2 | 1,101              | 49.1 |                        |      |                    |      |
| 3 or more                                   | 13,796                        | 26.3 | 564                | 25.2 |                        |      |                    |      |

<sup>a</sup> Hepatoblastoma, medulloblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma and acute lymphoid leukemia.

children with more than one tumor and children with Down syndrome and running analysis again demonstrated only very minor changes to result estimates.

We performed sensitivity analysis on maternal smoking status from 1991 to 2016, but no evidence of confounding nor effect modification was observed.

Statistical analyses were carried out using Stata 14.2 (StataCorp, College Station, TX, USA).

The study was approved by the Danish Data Protection Agency ref. No. 2008-41-2639, 2014-41-3174. As only register-based information was used, no individual consent was needed.

### 3. Results

More leukemia cases had an older mother at birth, were born in rural areas, and were only children, compared to control children (Table 1). CNS cases were more likely to be born as the third or later child, have parents with high SES, born in an urban area, or be an only child, compared to healthy controls (Table 1).

For offspring of mothers employed in wood industries in the perinatal period, a slightly increased risk of leukemia and ALL was found, while increased but low point estimates were found for employment in textile industries during the perinatal period. A low number of exposed cases did not allow for meaningful analysis of offspring with maternal employment in paper industries (Table 2). During the period from birth to diagnosis we observed increased ORs for children with maternal employment in wood industries for leukemia, ALL and AML, while employment in paper industries was associated with increased risk of all our selected diagnoses combined, probably driven by increased risks of CNS cancer (Table 3).

For children whose fathers worked during the perinatal period, we observed an increased risk of all selected diagnoses combined driven by astrocytoma and likely prenatally initiated childhood cancers in wood industries (Table 4). We also found an increased risk of astrocytoma and ALL for wood and elevated estimates for paper exposure with wide confidence intervals in the perinatal period. In addition, we found increased risks of cancer types likely initiated prenatally in offspring of fathers working in industries with wood and paper dust exposures (Table 4). This increase for so-called prenatal cancers was primarily driven by hepatoblastoma and neuroblastoma, though CI's included 1 for the former diagnosis (Table 5).

For children whose fathers worked from birth to diagnosis significantly increased ORs were seen for all diagnoses combined, driven by CNS cancers and astrocytoma for wood employment (Table 6).

**Table 2**

Odds Ratios (OR) and 95 % confidence intervals (95 % CI) for childhood cancers in offspring of mothers working in industries with exposure to wood, paper and textile one year before birth to one year after birth.

|   | Wood   |                  | Paper |                  | Textile  |                  |
|---|--------|------------------|-------|------------------|----------|------------------|
|   | n      | OR (95 % CI)     | n     | OR (95 % CI)     | n        | OR (95 % CI)     |
| Leukemia                                  | 28/484 | 1.37 (0.93–2.02) | *     | –                | 48/1,016 | 1.10 (0.82–1.49) |
| Acute lymphoblastic leukemia              | 23/379 | 1.44 (0.94–2.21) | *     | –                | 37/777   | 1.10 (0.78–1.55) |
| Acute myeloid leukemia                    | *      | –                | *     | –                | 8/165    | 1.11 (0.54–2.31) |
| Central nervous system cancer             | 11/281 | 0.91 (0.50–1.68) | *     | –                | 21/635   | 0.78 (0.50–1.22) |
| Astrocytoma                               | 7/149  | 1.12 (0.52–2.42) | *     | –                | 9/342    | 0.61 (0.31–1.19) |
| Medulloblastoma                           | *      | –                | *     | –                | 6/148    | 0.95 (0.41–2.19) |
| Ependymoma                                | *      | –                | *     | –                | *        | –                |
| Prenatally-initiated cancers <sup>a</sup> | 28/650 | 1.03 (0.70–1.50) | 6/161 | 0.89 (0.39–2.02) | 60/1,384 | 1.03 (0.79–1.35) |
| Selected cancers combined <sup>b</sup>    | 42/961 | 1.03 (0.75–1.41) | 8/236 | 0.81 (0.40–1.65) | 86/2,110 | 0.97 (0.78–1.21) |

\* n < 5

<sup>a</sup> Hepatoblastoma, medulloblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma and acute lymphoid leukemia.

<sup>b</sup> Acute lymphoid leukemia, acute myeloid leukemia, astrocytoma, medulloblastoma, ependymoma, hepatoblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma.

Investigating both parent employed in the same type of industry, we found an increased OR 2.58 (95 % CI: 1.10–6.05) of CNS cancers in children whose mother and father worked for the textile industry (Supplementary Table 1). Controlling for birth place of the index child showed overlapping CIs (results not shown).

Sensitivity analyses comparing results with, and without children with maternal smoking data indicated no substantive differences, and results did not differ by smoking status when analyses were restricted to children with maternal smoking information. (results not shown).

### 4. Discussion

This register-based case-control study of childhood cancer suggested that leukemia and AML in offspring was associated with maternal wood exposure, while CNS cancer was associated with maternal paper exposure in the period from birth to diagnosis. Children with paternal exposure to wood dust in the perinatal period had an elevated risk of ALL, astrocytoma and prenatal cancers, while the period from birth to diagnosis was associated with increased risks of CNS cancers and astrocytomas. This present study adds to the literature by having estimated the risk of leukemia, CNS cancers and cancers with a presumed prenatal origin in offspring of both mothers and fathers occupationally exposed to specific organic dusts.

Previous studies investigating childhood leukemia in relation to maternal wood exposure displayed discrepant results [1,2,24,25], yet one study has reported increased risks consistent with our results [2]. For offspring whose fathers were employed in wood industries, several studies have found insignificantly increased risks of ALL [1,26,27] yet the largest study reported null results [4]. Inconsistent results were found for textile and paper industries [1,3,4,28,29]. Few studies explored CNS cancers and generally didn't support our results demonstrating increased risks, however, few other studies stratified by CNS cancer type and none for wood exposures [1,3,5,30–33]. For the likely prenatally initiated childhood cancers, the increased risk after paternal perinatal employment in wood industries was driven by hepatoblastoma and neuroblastoma. To our knowledge no studies exist on the former diagnosis, while two studies reported positive non-significant associations on the latter [34,35].

Wood dust exposures are complex depending on the type of wood used, whether one is working with natural or composite wood, which task is performed, the machinery and use of personal protective equipment. Various complex exposures and potential carcinogens besides wood dusts are encountered in wood related industries including arsenic, solvents, pesticides, bacteria and fungi [36].

**Table 3**

Odds Ratios (OR) and 95 % confidence intervals (95 % CI) for childhood cancers in offspring of mothers working in industries with exposure to wood, paper and textile from birth to diagnosis.

|   | Wood     |                         | Paper  |                         | Textile   |                  |
|---|----------|-------------------------|--------|-------------------------|-----------|------------------|
|   | n        | OR (95 % CI)            | n      | OR (95 % CI)            | n         | OR (95 % CI)     |
| Leukemia                                  | 49/825   | <b>1.44 (1.08–1.94)</b> | 10/188 | 1.30 (0.68–2.46)        | 55/1,320  | 0.98 (0.74–1.29) |
| Acute lymphoblastic leukemia              | 35/627   | 1.35 (0.95–1.91)        | 7/151  | 1.13 (0.53–2.43)        | 41/1,010  | 0.95 (0.69–1.30) |
| Acute myeloid leukemia                    | 11/128   | <b>2.14 (1.13–4.03)</b> | 1/24   | 0.96 (0.13–7.10)        | 11/227    | 1.13 (0.60–2.11) |
| Central nervous system cancer             | 17/563   | 0.73 (0.45–1.19)        | 11/120 | <b>2.28 (1.22–4.26)</b> | 31/826    | 0.91 (0.63–1.31) |
| Astrocytoma                               | 10/318   | 0.78 (0.41–1.47)        | 5/73   | 1.71 (0.68–4.27)        | 14/457    | 0.74 (0.43–1.27) |
| Medulloblastoma                           | *        | –                       | *      | –                       | 8/203     | 0.95 (0.46–1.96) |
| Ependymoma                                | *        | –                       | *      | –                       | *         | –                |
| Prenatally-initiated cancers <sup>a</sup> | 40/1,008 | 0.95 (0.69–1.32)        | 12/239 | 1.24 (0.69–2.23)        | 65/1,639  | 0.95 (0.73–1.22) |
| Selected cancers combined <sup>b</sup>    | 67/1,640 | 0.99 (0.77–1.27)        | 23/368 | <b>1.56 (1.02–2.38)</b> | 102/2,572 | 0.95 (0.77–1.16) |

\* n < 5

<sup>a</sup> Hepatoblastoma, medulloblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma and acute lymphoid leukemia.

<sup>b</sup> Acute lymphoid leukemia, acute myeloid leukemia, astrocytoma, medulloblastoma, ependymoma, hepatoblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma.

Two studies supported our finding of an increased risk of astrocytoma in the perinatal period though both were based on few exposed cases [31,37]. However, other studies on this topic in regards to any cancer type have been few, and have found varying results [3,4,27,28,37–40]. As the studies report on many different job titles and industries from various countries and therefore encompass different tasks and exposures, this may explain the discrepant results. Another explanation may be the use of personal protective equipment and other hygiene installments differ between countries and study populations, which no studies accounted for. However, the Danish industry guidelines for construction, carpentry and joining state that personal protective equipment must be used during exposure to dusts and that machinery must be kept clean and equipped with suction devices to minimize exposure [41,42]. Thus, if a true effect exists we may be observing lower effect estimates than studies elsewhere.

To our knowledge, no other studies have examined risk of cancer in offspring when both parents have worked in organic dust industries. These results must be interpreted carefully and further studies on the subject are needed.

As pregnant women in Denmark may have maternity leave from up to eight weeks before the expected birth, the exposures that we examined best represent the early to mid-pregnancy period. Postnatal leave and thus duration of exposure varied during the study period

[43]. To our knowledge, no studies have investigated whether substances from these complex industries have even been transferred from mother to child either through the placenta or through breast milk. Fathers were not entitled to prenatal leave but from 1983, fathers were able to take between 2–20 weeks of leave postnatally depending on existing regulations during specific time periods, yet a report showed that fathers took 19 days of paternity leave in 2003 increasing to 30 days in 2013 [43]. Thus, only minor effects on results are expected due to paternity leave.

Our results may be explained by new mutations in the offspring or transfer of substances from the workplace directly to the child after birth. Another possible biological mechanism is epigenetic changes although our chosen exposures have not been investigated with regards to the possibility of transgenerational effects. For mothers, substances may be transferred to the offspring through the placenta or via lactation [44]. For fathers, studies on these specific exposures and outcomes are lacking, but as spermatogenesis continues throughout life exposures may accumulate in the sperm and epigenetic changes may be transferred to the offspring in this manner [7]. Still, the exact role of these mechanisms remains unclear as mostly animal studies and few observational human studies have been carried out. Studies found DNA damage in wood workers but this may have been influenced by the abovementioned factors [45,46]. Whether or not such damages affect

**Table 4**

Odds Ratios (OR) and 95 % confidence intervals (95 % CI) for childhood cancers in offspring of fathers working in industries with exposure to wood, paper and textile one year before birth to birth.

|   | Wood      |                         | Paper  |                  | Textile |                  |
|---|-----------|-------------------------|--------|------------------|---------|------------------|
|   | n         | OR (95 % CI)            | n      | OR (95 % CI)     | n       | OR (95 % CI)     |
| Leukemia                                  | 119/2,586 | 1.14 (0.94–1.38)        | 17/350 | 1.22 (0.75–1.99) | 13/439  | 0.74 (0.42–1.29) |
| Acute lymphoblastic leukemia              | 95/1,956  | 1.20 (0.97–1.49)        | 14/277 | 1.28 (0.74–2.19) | 11/351  | 0.78 (0.43–1.43) |
| Acute myeloid leukemia                    | 20/420    | 1.16 (0.73–1.86)        | *      | –                | *       | –                |
| Central nervous system cancer             | 71/1,469  | 1.20 (0.94–1.54)        | 9/196  | 1.11 (0.57–2.18) | 10/232  | 1.09 (0.57–2.06) |
| Astrocytoma                               | 45/796    | <b>1.43 (1.05–1.96)</b> | 6/108  | 1.37 (0.60–3.13) | *       | –                |
| Medulloblastoma                           | 12/349    | 0.83 (0.46–1.51)        | *      | –                | *       | –                |
| Ependymoma                                | 7/208     | 0.81 (0.38–1.76)        | *      | –                | *       | –                |
| Prenatally-initiated cancers <sup>a</sup> | 171/3,421 | <b>1.23 (1.05–1.45)</b> | 24/473 | 1.26 (0.83–1.90) | 22/607  | 0.90 (0.59–1.38) |
| Selected cancers combined <sup>b</sup>    | 254/5,171 | <b>1.22 (1.07–1.39)</b> | 33/695 | 1.17 (0.83–1.67) | 30/855  | 0.87 (0.61–1.26) |

\* n < 5

<sup>a</sup> Hepatoblastoma, medulloblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma and acute lymphoid leukemia.

<sup>b</sup> Acute lymphoid leukemia, acute myeloid leukemia, astrocytoma, medulloblastoma, ependymoma, hepatoblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma.

**Table 5**

Odds Ratios (OR) and 95 % confidence intervals (95 % CI) for likely prenatally-initiated childhood cancers in offspring of fathers working in industries with exposure to wood, paper and textile from one year before birth to birth.

|                              | Wood      |                         | Paper  |                  | Textile |                  |
|------------------------------|-----------|-------------------------|--------|------------------|---------|------------------|
|                              | n         | OR (95 % CI)            | n      | OR (95 % CI)     | n       | OR (95 % CI)     |
| Prenatally-initiated cancers | 171/3,421 | <b>1.23 (1.05–1.45)</b> | 24/473 | 1.26 (0.83–1.90) | 22/607  | 0.90 (0.59–1.38) |
| Acute lymphoblastic leukemia | 95/1,302  | 1.20 (0.97–1.49)        | 14/277 | 1.28 (0.74–2.19) | 11/351  | 0.78 (0.43–1.43) |
| Medulloblastoma              | 12/349    | 0.83 (0.46–1.51)        | *      | –                | *       | –                |
| Wilms tumor (nephroblastoma) | 19/380    | 1.17 (0.72–1.89)        | 5/50   | 2.34 (0.92–6.04) | *       | –                |
| Neuroblastoma                | 28/444    | <b>1.54 (1.03–2.29)</b> | *      | –                | *       | –                |
| Hepatoblastoma               | 6/71      | 2.41 (0.99–5.88)        | *      | –                | *       | –                |
| Retinoblastoma               | 11/221    | 1.32 (0.70–2.48)        | –      | –                | *       | –                |

\* n < 5

the offspring's risk of childhood cancer is unknown.

Paternal, but not maternal employment in these industries was associated with increased risk of likely prenatally-initiated childhood cancers, suggesting that the timing of exposure may be more relevant for fathers, and that different mechanisms may be involved, [6]. It was not possible to examine the relevance of specific exposure periods (trimesters), due to a relatively low number of exposed cases and because parents changed jobs infrequently during the perinatal period.

It was not possible to identify other of the most common childhood cancer syndromes besides neurofibromatosis, retinoblastoma and Down syndrome. Yet, we excluded children with more than one tumor and those diagnosed with these syndromes. Minute changes to results were found and thus did not alter direction of results or conclusion.

Limitations in our study may also have affected results. The same weight was assigned to all parents regardless of employment time which may have led to underestimation or overestimation of results depending on whether parents were employed long or short period of time. Working conditions have presumably improved during the study period, yet it was not possible to identify specific historical changes and investigate their potential effect on risk estimates. In addition, investigation of a possible dose-response relationship was not feasible due to low numbers of exposed cases, conversion of job titles to industry codes and uncertainty regarding each person's actual exposure. Therefore, we assumed same level of exposure across all industries, ignoring the possible variability between industries and workers. This would have led to an attenuation of the risk towards the null. Common to employment in wood, paper and textile industries is that exposure

levels depend, among other parameters, on the use of personal protective equipment, the type of task performed, and the type of machinery involved, all of which may have changed during the study period. As we used record-based exposure data based on industry codes, it was not possible to take individual exposure into account or address within worker variability. This would lead to non-differential misclassification, causing an underestimation of results.

Finally, it is possible that participants may have been exposed domestically to wood dusts or perhaps textile dusts. Regarding wood dusts, we have partially controlled for this using child's birth place, the inclusion of which did not change effect estimates, and a sensitivity analysis by place of birth did not show meaningful difference in risk. Regarding textile dusts, domestic exposures are possible but these would be rather limited compared to full time employment exposures.

Another limitation is the lack of information on maternal smoking status from 1968 to 1990 as no such records were available. However, inclusion of maternal smoking information in sensitivity analyses changed results only marginally. Finally, we had no information on paternal smoking. We conducted multiple comparisons in this study, but opted not to perform statistical corrections to account for this, preferring instead to interpret results with caution and within the context of other relevant studies [47].

Our study has several strengths. We used a nationwide and validated register to identify childhood cancer cases to reduce the risk of case misclassification [13,16]. These registries also reduced the potential for selection bias. Further, we included children < = 19 years to increase power of our risk estimation. There has not been evidence to

**Table 6**

Odds Ratios (OR) and 95 % confidence intervals (95 % CI) for childhood cancers in offspring of fathers working in industries with exposure to wood, paper and textile from birth to diagnosis.

|   | Wood      |                         | Paper  |                  | Textile  |                  |
|---|-----------|-------------------------|--------|------------------|----------|------------------|
|   | n         | OR (95 % CI)            | n      | OR (95 % CI)     | n        | OR (95 % CI)     |
| Leukemia                                  | 156/3,489 | 1.10 (0.93–1.30)        | 22/505 | 1.07 (0.70–1.65) | 22/640   | 0.84 (0.55–1.30) |
| Acute lymphoblastic leukemia              | 115/2,619 | 1.07 (0.88–1.30)        | 17/390 | 1.08 (0.66–1.77) | 18/486   | 0.91 (0.56–1.46) |
| Acute myeloid Leukemia                    | 31/584    | 1.32 (0.90–1.95)        | *      | –                | *        | –                |
| Central nervous system cancer             | 101/2,067 | <b>1.24 (1.00–1.53)</b> | 13/305 | 1.03 (0.59–1.80) | 17/374   | 1.12 (0.68–1.82) |
| Astrocytoma                               | 63/1,144  | <b>1.42 (1.09–1.86)</b> | 8/170  | 1.15 (0.56–2.36) | 7/215    | 0.78 (0.37–1.68) |
| Medulloblastoma                           | 18/467    | 0.96 (0.59–1.56)        | 5/74   | 1.60 (0.64–4.00) | 5/88     | 1.45 (0.58–3.61) |
| Ependymoma                                | 15/272    | 1.35 (0.78–2.36)        | *      | –                | *        | –                |
| Prenatally-initiated cancers <sup>a</sup> | 195/4,276 | 1.12 (0.96–1.30)        | 28/617 | 1.12 (0.77–1.65) | 32/767   | 1.02 (0.71–1.45) |
| Selected cancers combined <sup>b</sup>    | 319/ 6746 | <b>1.17 (1.04–1.32)</b> | 41/963 | 1.05 (0.76–1.43) | 48/1,207 | 0.97 (0.72–1.30) |

\* n < 5

<sup>a</sup> Hepatoblastoma, medulloblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma and acute lymphoid leukemia.

<sup>b</sup> Acute lymphoid leukemia, acute myeloid leukemia, astrocytoma, medulloblastoma, ependymoma. Hepatoblastoma, Wilms tumor (nephroblastoma), neuroblastoma, retinoblastoma.

suggest that late adolescent leukemias and astrocytoma have a distinct etiology compared to earlier life cancers; it is likely the majority of prenatally-initiated childhood cancers are diagnosed prior to age 10 years so the sample size is unlikely to have changed by the inclusion of cases in older adolescence. Also, we used validated registries of high completeness to identify mothers and fathers [15] and their employment histories through a mandatory pension fund [14].

## 5. Conclusion

Our study suggested that maternal and paternal exposure to organic dusts may increase the risk of certain childhood cancers in offspring; further studies are warranted.

## 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. JEJ 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.

## Declaration of Competing Interest

None declared.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2020.101667>.

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