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Parental occupational exposure to combustion products, metals, silica and asbestos and risk of childhood leukaemia: Findings from the Childhood Cancer and Leukaemia International Consortium (CLIC)

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A R T I C L E I N F O

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A B S T R A C T

Parental occupational exposures around conception (father) or during pregnancy (mother) have been hypothesized as potential predisposing factors for childhood leukaemia. We investigated parental exposure to several known occupational carcinogens and childhood leukaemia risk. We conducted a pooled analysis using case-control data from four European countries (3362 childhood leukemia cases and 6268 controls). Parental occupational exposures to polycyclic aromatic hydrocarbons (PAH), diesel engine exhaust (DEE), chromium, nickel, crystalline silica, and asbestos were assessed by a general population job-exposure matrix. We estimated odd ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression models for all childhood leukaemia combined, by leukaemia type (ALL and AML) and by ALL subtype (B-lineage and T-lineage). We found an association between high paternal occupational exposure to crystalline silica and childhood ALL (OR 2.20, CI 1.60–3.01) with increasing trend from no exposure to high exposure ($P = <0.001$), and also for AML (OR 2.03, CI 1.04–3.97; *P for trend* = 0.008). ORs were similar for B- and T-lineage ALL. For ALL, ORs were also slightly elevated with wide confidence intervals for high paternal occupational exposure to chromium (OR 1.23, CI 0.77–1.96), and DEE (OR 1.21, CI 0.82–1.77). No associations were observed for paternal exposures to nickel, PAH and asbestos. For maternal occupational exposure we found several slightly elevated odds ratios but mostly with very wide confidence intervals due to low numbers of exposed mothers. This is a first study suggesting an association between fathers' occupational exposure to crystalline silica and an increased risk of childhood leukaemia in their offspring. As this association was driven by certain occupations (field crop farmers and miners) where other potentially relevant exposures like pesticides and radon may also occur, more research is

Abbreviations: ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; CI, Confidence Interval; CLIC, Childhood Cancer and Leukaemia International Consortium; ESCALE, Epidemiological Study on Childhood Cancer and Leukemia; GCCR, German Childhood Cancer Registry; ISCO, International Standard Classification for Occupation; JEM, Job Exposure Matrix; NARECHEM-ST, Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors; SETIL, Studio sulla Eziologia dei Tumori Infantili Linfoemopoietici.

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needed to confirm our findings of an association with crystalline silica, and if so, mechanistic studies to understand the pathways.

1. Introduction

Leukaemia is the most common cancer diagnosis among children aged 0–14 years (Namayandeh et al., 2020). The main subtypes of leukaemia are acute lymphoblastic leukaemia (ALL) which accounts for ~80% of leukaemia and acute myeloid leukaemia (AML) ~17% (Schüz and Erdmann, 2016). Chronic leukaemia and other leukaemia subtypes occur very rarely at young age. For a large number of European countries, North America and Australia, a gradual increase in the incidence of childhood leukaemia has been observed since the mid-1970s (Siegel et al., 2020; Youlden et al., 2020). At the same time, the 5-year overall survival has greatly increased in high-income countries over the past decades, from 60% to approximately 90% (Sant et al., 2014; Bonaventure et al., 2017).

Although a growing body of research has targeted a broad range of potentially aetiologic factors, including perinatal factors, family and parental lifestyle factors, as well as environmental and occupational exposures (Schüz and Erdmann, 2016; Onyije et al., 2022), the aetiology of childhood leukaemia remains poorly understood and primary prevention measures are largely lacking. There have been numerous studies on parental occupational exposures for instance including pesticides and solvents (e.g., benzene) attracting scientific interest as potential predisposing factors for childhood leukaemia, with already around 50 studies published before the late 1990s (Colt and Blair, 1998). The biological rationale for those hypotheses is the development of childhood ALL in general, which commonly occurs as a result of two genetic "hits" with the first occurring in utero (or before conception), often a chromosomal translocation generating a pre-leukemic fusion gene and the second often point mutations, deletions and duplications with a number of pre- and post-natal environmental exposures been suggested. Therefore parental exposures are candidate events for those first "hits" (Greaves, 2018; Tebbi, 2021; Kosik et al., 2017). Few studies reported associations between parental occupational exposure to combustion products including polycyclic aromatic hydrocarbons (PAH) and diesel engine exhaust (DEE) (Miligi et al., 2013; Reid et al., 2011; McKinney et al., 2003) and the risk of childhood leukaemia, while others did not find an association (Reid et al., 2011; Volk et al., 2019; Feychting et al., 2001). Similarly, observations were inconsistent for the association with parental occupational exposure to metals (chromium VI and nickel) (Miligi et al., 2013; Feychting et al., 2001). There is only one study to date on parental occupational exposure to asbestos and childhood leukaemia, where they reported no association (Feychting et al., 2001). Main limitation of most studies is their small sample size and therefore insufficient statistical power to detect presumably modest associations. Comparing results from individual studies is often hampered by their differing methods in collecting and analysing exposure.

To date, no parental exposure has been clearly established as a leukaemia risk for the offspring, but there's also few factors that can be clearly ruled out, especially among those being known carcinogens in adults. We studied the association between parental occupational exposure to asbestos, crystalline silica, PAH, DEE and metals, which are known lung carcinogens in adults, and the risk of childhood leukaemia in their offspring using data of the Childhood Cancer and Leukaemia International Consortium (CLIC) (Metayer et al., 2013). With this approach we address previous limitations of small sample sizes by pooling four case-control studies from different countries and of exposure heterogeneity by using collected parental occupational histories to assign exposure in the same way.

2. Methods

2.1. Study design and participants

CLIC is a multinational collaboration of researchers interested in the aetiology of childhood leukaemia. It was established in 2007, with the overall aim to overcome the limitations of single epidemiological studies (Metayer et al., 2013). In the present pooled analysis, we included four case–control studies from France, Germany, Greece and Italy, which all had comprehensive parental occupational data around the time of conception (in text or coded according to the International Standard Classification of Occupations (ISCO) 1968) available. In total, our study population included 3362 childhood leukaemia cases and 6268 controls (Table 1). Of the 3362 leukaemia cases, 2986 had ALL (2573 were of B-lineage, 340 of T-lineage, and 73 unknown) and 376 children had AML. We excluded 42 (1.2%) cases and 1 (0.02%) control with Down syndrome, a condition known to considerably increase the risk of developing childhood leukaemia (Hasaart et al., 2021), leaving 3320 cases and 6267 controls for the analyses. The cases had been diagnosed between 1988 and 2012, depending on the individual study, and were identified from national population-based cancer registries (Metayer et al., 2013). Control subjects were recruited from population registries, same hospitals as cases, or by using random digit dialling, see Table 1. Cases and controls were <15 years of age at date of diagnosis (Table 2).

2.2. Data collection

All studies made comprehensive assessments of potential risk factors and confounders (Metayer et al., 2013). In our study we used information on parental occupations around the time of conception and information on potential confounders such as sex, age, birth weight and parental education collected using standardised self-administered questionnaires, telephone or face-to-face interviews. Controls were population-based in the French (ESCALE, 2003–2004), German (GCCR, 1988–1994) and Italian (SETIL, 1998–2001) studies (i.e. randomly drawn from population registers (Germany, Italy), representative sample of telephone subscribers (France)), while in the Greek study controls were selected from the hospital (paediatric patients with infectious and parasitic diseases). Controls were matched to cases on age and gender in all four studies, and additionally by district in Italy and Germany. Frequency-matching for sampling was used in France and Greece, while Germany and Italy used individual matching that was however broken up for analysis with adjustment for the matching factors (Metayer et al., 2013; Amigou et al., 2011). We categorised covariates such as age, and parental educational level according to standard categorizations previously used across CLIC studies (Talibov et al., 2019). The time periods of interest were the year before conception for both parents and during pregnancy for the mother. For the father and mother, we identified the job held at conception, calculated from the date of birth of the child and the information on gestational age (except for France, see footnote Table 1). For the mother we also identified the job held longest during pregnancy (before going on maternity leave). As for mothers there was too little difference between the jobs before conception and during pregnancy, we present only the results for the exposure during pregnancy (data not shown). Parental occupations recorded as free text in the German study was first translated to English language and later coded to ISCO 1968. Occupational data from other studies were already coded in ISCO-68 format (Table 1).

Details of data collection for the 4 included studies and methods for the evaluation of parental occupational pesticide exposure and the risk of childhood leukemia in the offspring are reported elsewhere (Bailey

Table 1
Characteristics of studies included in the CLIC pooled analysis of parental occupational exposure to combustion products (PAH and DEE), metals (chromium and nickel), silica and asbestos and risk of childhood leukaemia.

Country, study (years of case accrual)	Cases		Controls				
	Source	N	Source	N	Source of occupational history data	Time period(s) of interest	Original occupational coding
France, ESCALE (2003–2004)	Population-based cancer registry (nationwide).	ALL = 648 AML = 101	Population quotas by age, sex and region (nationwide)	1,681	Telephone interview	During pregnancy†	ISCO 1968
Germany, GCCR (1988–1994)	Population-based German Childhood Cancer Registry (nationwide)	ALL = 773 AML = 130	Regional population registries (all regional registries combined have national coverage)	2,458	Self-administered questionnaire, telephone interview	Around conception and during pregnancy	Original German job text was translated to English and coded to ISCO 1968
Greece, NARECHEM-ST (1996–2011)	Hospital-based cancer registry (nationwide)	ALL = 964 AML = 113	Hospital	1,085	Telephone interview	One year before birth and during pregnancy	ISCO 1968
Italy, SETIL (1998–2001)	Clinical cancer registry (nationwide)	ALL = 601 AML = 32	Population-based National Health Service Registry (nationwide)	1,044	Face-to-face interview	One year before conception and during pregnancy	ISCO 1968

†France ESCALE, paternal exposure during pregnancy was used as a proxy for exposure around conception as these data were not available.
Abbreviations: ESCALE: Etude Sur les Cancers et les Leucémies de l, Enfant, GCCR: German Childhood Cancer Registry, NARECHEM-ST: Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors, SETIL: Studio sulla Eziologia dei Tumori Infantili Linfoemopoietici.

et al., 2014).

2.3. Exposure assessment

We investigated parental occupational exposure to the known carcinogens PAH, DEE, chromium VI, nickel, crystalline silica, and asbestos around conception for fathers and during pregnancy for mothers using DOM-JEM. DOM-JEM was created by three occupational exposure experts (H.K., R.V., and S.P.) and is an expert-based general population job-exposure matrix (JEM) for exposure to lung carcinogens asbestos, crystalline silica, DEE, PAH, chromium and nickel assigning 0 = no exposure, 1 = low exposure or 2 = high exposure for every single 5-digit standard occupational ISCO-68 code, developed for a consortium of lung cancer case-control studies (Peters et al., 2011) but applicable to other outcomes where the same agents are potential risk factors. As a consequence, however, the occupational exposures studied in the parents of children with leukaemia in the present study are all known lung carcinogens in adults, but some of them are known to cause also other types of cancers in adults.

2.4. Statistical analysis

Firstly, we pooled the individual level data from the four CLIC case–control studies and estimated odd ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression models. In our main analysis, we assessed the association between parental occupational exposure to PAH, DEE, chromium, nickel, crystalline silica and asbestos, and the risk of childhood leukaemia by leukaemia types (ALL and AML). Afterwards we assessed the same associations by ALL subtype (B-lineage and T-lineage). In sub-analysis, we stratified the analyses of ALL by child's age (<1, 1–6 and ≥7 years old) at diagnosis. All models were adjusted for the child's age and sex, and study (OR1), and the main model with additional adjustment for highest-level education of either parent (OR2) in view of the fact that this type of occupational exposures are more frequent in elementary jobs, which are correlated with educational level. Pesticide exposure around the time of conception, maternal age and birth weight were also considered as a potential confounders, but were not retained in the final model because they did not impact the ORs for the exposures of interest (Bailey et al., 2014). Log-linear trends in ORs across the no, low, and high exposure categories were examined by treating the level of exposure as an ordinal variable in the logistic regression model, for paternal exposures only. Maternal occupational exposures were categorised into ever versus never exposed due to low numbers of exposed mothers.

Secondly, we conducted random effects *meta*-analyses in order to evaluate heterogeneity between studies by leukaemia type, and ALL subtypes. Heterogeneity was considered as "no heterogeneity" when I^2 was 0%, "probably unimportant" when I^2 was 1–35%, "moderate" when I^2 was 36–55%, "substantial" when I^2 was 56–70% and "considerable" when I^2 was 71–100% (Lin et al., 2020). All analyses were performed in Stata®, version 14.0. (Stata® statistical software, College Station, TX, USA).

3. Results

ALL was more often diagnosed in boys (57%) than in girls (43%). For AML the distribution was 51% and 49% for boys and girls, respectively. More than half of the ALL cases were diagnosed in children aged 1–4 years (53%), while the age distribution of children with AML was more dispersed (Table 2). Mothers of controls had more often higher completed educations than mothers of cases. Job histories were available for a high 97% of fathers; the proportion is also high among mothers, albeit slightly lower than in fathers, because we conservatively treated situations as missing when it was not entirely clear whether the mother had no job or the information was missing.

Table 2
Selected sociodemographic characteristics of the study population of the pooled analysis by case-control status.

Participants' characteristics	ALL		AML			
	Cases		Cases		Controls	
Child's characteristics						
Sex	**N**	**%**	**N**	**%**	**N**	**%**
Boy	1678	56.8	186	51.2	3505	55.9
Girl	1279	43.3	177	48.8	2762	44.1
Age at diagnosis						
<1	62	2.1	40	11.0	392	6.3
1–4	1578	53.3	130	35.8	2798	44.7
5–9	913	30.8	104	28.7	1921	30.7
10–14	408	13.8	89	24.5	1156	18.5
Year of birth						
≤1980	53	1.8	18	4.8	234	3.7
1981–1990	726	24.6	103	27.6	1931	30.8
1991–2000	1644	55.6	166	44.5	3073	49.1
>2000	534	18.1	86	23.1	1029	16.4
Parental characteristics						
Paternal highest level of education						
Did not completed secondary education	934	31.6	125	34.4	1611	25.7
Completed secondary education	1260	42.6	143	39.4	2746	43.8
Tertiary education	671	22.7	76	20.9	1635	26.1
Missing	92	3.1	19	5.2	275	4.4
Maternal highest level of education						
Did not completed secondary education	848	28.7	100	27.6	1361	21.7
Completed secondary education	1334	45.1	164	45.2	3137	50.0
Tertiary education	731	24.7	88	24.2	1641	26.1
Missing	42	1.4	11	3.0	128	2.0
Paternal job history available						
Yes	2865	96.9	350	96.4	6085	97.1
No	92	3.1	13	3.5	182	2.9
Maternal job history available						
Yes	2957	93.1	372	96.4	6225	93.9
No	24	6.9	4	3.6	43	6.1
Histological subtype						
ALL B-lineage	2545	86.1				
ALL T-lineage	339	11.5				
Unknown	73	2.4				
Total	**2957**		**363**		**6267**	

3.1. Parental occupational exposures in relation to childhood leukaemia risk in the offspring

For ALL, we observed slightly elevated ORs with wide confidence intervals overlapping unity in paternal exposure to chromium (OR 1.23, CI 0.77–1.96) and DEE (OR 1.21, CI 0.82–1.77) around conception (Table 3). Paternal exposure to high levels of crystalline silica around conception was associated with an increased risk of childhood ALL (OR 2.20, CI 1.60–3.01). We found no association with nickel, PAH, asbestos and low silica exposures.

In analyses by ALL subtype, we observed for ALL B-lineage similar results as in the main results for children whose fathers were exposed to high levels of crystalline silica. There was again slightly elevated ORs in children whose fathers were exposed to high levels of DEE (OR 1.40, CI 0.95–2.06). Regarding ALL T-lineage, paternal occupational exposure to PAH, DEE, nickel, chromium and asbestos around conception were not associated with the disease. However, we observed somewhat elevated risks for fathers low exposure to crystalline silica (OR 1.34, CI 0.92–1.94, low exposure; OR 1.75, CI 0.90–3.42, high exposure) and ALL T-lineage in their children with an increasing linear trend from no exposure to high exposure (p = <0.021).

For AML we did not observe any association between paternal occupational exposure to PAH, DEE, nickel and asbestos around conception (Table 3), although an increased risk (OR 1.46, 1.03–2.07) in children whose fathers were exposed to low levels of chromium. This association was however attenuated when we adjusted for educational level (OR 1.29, CI 0.89–1.86). Paternal exposure to high levels of crystalline silica was associated with risk of childhood AML (OR 2.03, CI 1.04–3.97) with a linear trend of P = 0.008 by increasing categories of exposure.

In maternal occupational exposure we found a few raised odds ratios with AML but mostly with very wide confidence intervals due to low prevalence of exposure among mothers (Table 3). Results for the subtypes of ALL B and T-lineage in association with maternal occupational exposure did not differ from those of the main analysis

Stratified analysis by child's age at diagnosis did not reveal different results than those from the main analysis for both paternal and maternal occupational exposures and childhood ALL and by ALL subtype (B-lineage and T-lineage) (Appendix Tables 1–4).

3.2. Heterogeneity of results by study

The heterogeneity between the studies by level of exposure (low and high) for each leukaemia type is displayed in Appendix Figs. 1–4 for paternal exposures, and in Appendix Fig. 5 for maternal occupational exposures in relation to ALL in the offspring. Most study-specific odd ratios had wide confidence intervals. For ALL low exposures (Appendix Fig. 1) no "considerable" heterogeneity was observed across studies for chromium and DEE, but moderate heterogeneity for nickel and asbestos. For ALL high exposures (Appendix Fig. 2) we observed "considerable" heterogeneity in paternal occupational exposure to high levels of crystalline silica ($I^2 = 74\%$, p-value < 0.01) with odds ratios ranging from 0.26 (France), to 1.22 (Italy), to 1.64 (Germany) and 3.54 (Greece). For AML low exposures (Appendix Fig. 3), we observed "substantial" heterogeneity for DEE ($I^2 = 65\%$, p-value 0.03), while for high exposures there was no substantial heterogeneity.

We did not observe any "substantial" heterogeneity in the risk of childhood ALL for maternal occupational exposure to all agents considered (Appendix Fig. 5).

4. Discussion

In this pooled analysis of four European case-control studies on childhood leukaemia including 3320 cases and 6267 controls, we analysed associations between parental occupational exposure to the known carcinogens PAH, DEE, chromium, nickel, crystalline silica, and asbestos and leukaemia in their offspring. We did not find any evidence of an association between paternal exposures (low and high) to PAH, chromium, DEE and asbestos in either ALL or AML. We found a positive association between paternal occupational exposure to crystalline silica and childhood leukaemia: paternal high exposure to crystalline silica was associated with ALL, ALL subtypes, as well as when stratified by age groups <1, 1–6 and ≥7 years old, but exposure to lower levels was not associated with ALL. The *meta*-analysis showed evidence of high heterogeneity between studies for the association of ALL and paternal exposure to high levels of crystalline silica, with country-specific ORs ranging from 0.26 (France), to 1.22 (Italy), 1.64 (Germany) and 3.54 (Greece). For AML, both low and high exposure to crystalline silica were associated with increased risks, with no marked heterogeneity across countries. We observed no elevated risks for maternal exposures.

The OR of 1.21(CI 0.82–1.77) observed for paternal occupational exposure to DEE and risk of childhood ALL was lower than the ORs in previous studies (Miligi et al., 2013; Reid et al., 2011). Reid et al. (2011)

Table 3
Estimated risk of acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) in the offspring following parental occupational exposure to combustion products (PAH and DEE), metals (chromium and nickel), crystalline silica and asbestos in a pooled analysis of Childhood Leukaemia International Consortium (CLIC) studies.

		ALL					AML			
Exposures	**Cases/Controls**	**OR1***	**95 %CI**	**OR2****	**95 %CI**	**Cases/Controls**	**OR1***	**95 %CI**	**OR2****	**95 %CI**
Paternal exposure around conception										
Chromium										
Never	2584/5568	1.00	Ref.	1.00	Ref.	305/5568	1.00	Ref.	1.00	Ref
Low	250/459	1.04	0.88–1.23	0.98	0.82–1.16	41/459	1.46	1.03–2.07	1.29	0.89–1.86
High	30/54	1.32	0.84–2.09	1.23	0.77–1.96	3/54	1.19	0.37–3.88	1.13	0.35–3.71
Test for trend, *P* value		0.28		0.63			0.05		0.20	
Nickel										
Never	2725/5765	1.00	Ref.	1.00	Ref.	329/5765	1.00	Ref.	1.00	Ref
Low	109/259	0.88	0.69–1.11	0.84	0.66–1.06	17/259	1.13	0.68–1.88	0.96	0.55–1.65
High	30/56	1.22	0.77–1.92	1.12	0.70–1.78	3/56	1.06	0.32–3.45	0.93	0.28–3.08
Test for trend, *P* value		0.85		0.58			0.68		0.96	
PAH										
Never	2615/5561	1.00	Ref.	1.00	Ref.	321/5561	1.00	Ref.	1.00	Ref
Low	221/452	1.03	0.87–1.22	1.00	0.84–1.19	24/452	0.97	0.63–1.49	0.86	0.55–1.35
High	28/68	0.72	0.46–1.14	0.71	0.45–1.12	4/68	0.90	0.32–2.51	0.61	0.19–1.99
Test for trend, *P* value		0.53		0.33			0.80		0.46	
DEE										
Never	2310/5024	1.00	Ref.	1.00	Ref.	281/5024	1.00	Ref.	1.00	Ref
Low	511/976	1.07	0.94–1.20	1.03	0.91–1.16	65/976	1.21	0.91–1.61	1.08	0.80–1.45
High	43/81	1.24	0.85–1.82	1.21	0.82–1.77	3/81	0.81	0.25–2.59	0.76	0.24–2.46
Test for trend, P value		0.14		0.36			0.31		0.62	
Crystalline Silica										
Never	2530/5603	1.00	Ref.	1.00	Ref.	304/5603	1.00	Ref.	1.00	Ref
Low	227/401	1.11	0.94–1.33	1.04	0.87–1.24	34/401	1.51	1.04–2.20	1.38	0.94–2.03
High	106/74	2.29	1.67–3.12	2.20	1.60–3.01	11/74	2.27	1.17–4.39	2.03	1.04–3.97
Test for trend, *P* value		<0.001		<0.001			0.001		0.008	
Asbestos										
Never	2395/5122	1.00	Ref.	1.00	Ref.	301/5122	1.00	Ref.	1.00	Ref
Low	409/817	1.11	0.97–1.27	1.06	0.93–1.21	37/817	0.85	0.59–1.21	0.75	0.52–1.09
High	60/142	0.89	0.65–1.21	0.84	0.61–1.15	11/142	1.28	0.68–2.42	1.12	0.57–2.18
Test for trend, *P* value		0.48		0.99			0.89		0.46	
Maternal exposure during pregnancy										
Chromium										
Never	2921/6203	1.00	Ref.	1.00	Ref.	358/6203	1.00	Ref.	1.00	Ref
Ever	9/15	1.07	0.45–2.50	1.01	0.43–2.37	2/15	1.97	0.43–8.98	0.97	0.12–7.67
Nickel										
Never	2,922/ 6204	1.00	Ref.	1.00	Ref.	358/6204	1.00	Ref.	1.00	Ref
Ever	8/14	1.01	0.41–2.46	0.96	0.39–2.35	2/14	2.07	0.45–9.54	1.01	0.12–8.08
PAH										
Never	2852 /6099	1.00	Ref.	1.00	Ref.	348/6099	1.00	Ref.	1.00	Ref
Ever	78/119	1.19	0.89–1.61	1.13	0.84–1.53	12/119	1.75	0.94–3.25	1.54	0.81–2.94
DEE										
Never	2846 /6056	1.00	Ref.	1.00	Ref.	351/6056	1.00	Ref.	1.00	Ref
Ever	84/162	0.97	0.74–1.28	0.92	0.70–1.22	9/162	0.89	0.45–1.78	0.86	0.43–1.72
Crystalline Silica										
Never	2888/6145	1.00	Ref.	1.00	Ref.	353/6145	1.00	Ref.	1.00	Ref
Ever	42/73	1.08	0.73–1.60	1.00	0.67–1.48	7/73	1.54	0.69–3.42	1.42	0.63–3.17
Asbestos										
Never	2875/6127	1.00	Ref.	1.00	Ref.	354//6127	1.00	Ref.	1.00	Ref
Ever	55/91	1.20	0.85–1.70	1.17	0.83–1.66	6/91	1.20	0.51–2.79	1.17	0.50–2.74

*Adjusted for child's age and sex, and study.
**Adjusted for child's age and sex, study and highest level of education of either parent.

reported an association (OR 1.34, CI 1.01–1.78) in children whose fathers were exposed to exhausts (diesel, petrol, and others) around conception and the risk childhood ALL in a population-based case–control study with 416 cases and 2071 controls conducted in Australia. The parents of these children had worked in specific jobs and industries of interest, they were telephoned, and trained interviewers used job-specific modules (JSMs) to ask them further detailed questions about the tasks they undertook in that job to ascertain the type, frequency, and level of exposure. An expert reviewed the job history and answers to the additional questions to assess exposure. The reviewer was blinded to the case/control status, and assigned a likelihood of exposure and rated the level of exposure as high, medium, or low. Similarly, Miligi et al. reported an association OR 1.6, CI 1.2–2.1 between paternal exposure to DEE one year before conception and the risk of childhood ALL, based on the same data we used for Italy in the present CLIC pooled analysis (Miligi et al., 2013). They also reported an OR 1.3, CI 1.0–1.8 in paternal exposure to PAH and childhood ALL. However, this was in contrast with the current study, as we did not find any association for paternal exposure to high levels of PAH and the risk of childhood ALL. Miligi and co-authors used job specific questionnaires for more detailed information on potential exposures with subsequent expert ratings of 'probability' and 'intensity' to assign exposure to a list of agents. The different approaches to assign parental occupational exposures (JEM versus expert-based individual assessments) might explain the somewhat different results.

Furthermore, the slightly elevated risk we observed in both paternal and maternal occupational exposure to chromium and childhood ALL was also lower than those of Miligi and co-authors (Miligi et al., 2013). We found no association between paternal and maternal occupational exposure to asbestos and confirmed Feychting et al. (2001) study that also found no association with paternal exposure to asbestos.

In our analysis, we observed a two-fold increased risk of childhood leukaemia (in ALL, AML and ALL B and T-lineage) in children whose fathers were exposed to high levels of crystalline silica in their workplaces. This association was mainly driven by agricultural field crop workers in Greece and, to lesser extent, in Italy and by miners in Germany (Appendix Fig. 2). To our knowledge, no previous studies have evaluated the association between parental occupation exposure to crystalline silica and the risk of childhood leukaemia. It could still be other exposures occurring simultaneously creating a spurious association with silica exposure. For miners this could be exposure to radon and ionizing radiation (Taeger et al., 2006). For the crop farmers exposure to pesticides will have been a co-exposure (Appendix Tables 4 and 5). Indeed there are some evidence for an association between paternal occupational pesticide exposure and childhood ALL risk, but the observed association with paternal pesticide exposure was substantially weaker than the one we observed with silica (Bailey et al., 2014). There is no plausible hypothesized mechanism by which paternal exposures to crystalline silica at the workplace could cause childhood leukaemia in the offspring. Therefore, our results need to be replicated in other epidemiological studies.

The major strength of this study is the use of high-quality data from regional and nationwide cancer registries in the different countries involved. Another strength is the detailed coding of occupational data (5-digit ISCO-68) and the semi-quantitative exposure based on a job-exposure matrix that will not have suffered from differential reporting bias. It was also designed according to exposure time windows (fathers around time of conception and mothers during pregnancy). Furthermore, we investigated leukaemia sub-types and stratified by child's age at diagnosis.

Our study has also several limitations, some inherent in the design and conduct of those types of studies. First, selection bias cannot be ruled out as not everyone invited to participate did finally participate; in controls, mothers with higher education were slightly more likely to participate, which could lead to an under-representation of blue-collar workers in our study alongside an underestimation of exposure in controls. This may have led to an inflation of the observed associations. Second, use of a JEM inevitably leads to some non-differential exposure misclassification, as not all workers in a certain job category are exposed equally and the JEM was not developed specifically for our study population. That windows of exposure assessment were not identical across our studies may have added to this misclassification bias. This type of bias is usually leading to an underestimation of the observed association, if there is one. Job modules have been proposed to lead to less misclassification (Gunier et al., 2017), but those were not collected in all the individual studies. Third, albeit all our efforts to harmonize information collected in the four studies to the extent possible, they remain independently conducted studies from different time periods with somewhat differing methodology. Finally, we carried out several analyses but did not formally adjust for multiple testing, as commonly done in observational studies, so some observations may be due to chance.

5. Conclusion

In conclusion, our study suggests a possible association between paternal occupational exposure to high levels of crystalline silica around conception and the risk of childhood leukaemia. However, these results should be interpreted with caution. If confirmed, this is highly relevant for primary prevention measures, as occupational exposures can often be reduced either through regulations or advice to parents preparing for conception to avoid exposures to hazardous chemicals. For other exposures, we did not see compelling evidence for associations. Low prevalence of maternal exposures precluded informative risk estimates for maternal exposures in this large-scale study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributors

AO and JS conceived the study. FMO drafted the manuscript. AO and JS verified the data. FMO provided the analysis, AO, FE, CM, EP, JC, LM, AB, SP, HK, and JS reviewed the manuscript, provided advice on methods and interpreted results. All other authors contributed data, developed exposure assessment tool, and reviewed the manuscript.

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Appendix A. Supplementary material

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