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Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: Findings from the Childhood Leukemia International Consortium

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Abstract

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Maternal occupational pesticide exposure during pregnancy and/or paternal occupational pesticide exposure around conception have been suggested to increase risk of leukemia in the offspring. With a view to providing insight in this area we pooled individual level data from 13 case-control studies participating in the Childhood Leukemia International Consortium (CLIC). Occupational data were harmonized to a compatible format. Pooled individual analyses were undertaken using unconditional logistic regression. Using exposure data from mothers of 8,236 cases, and 14,850 controls, and from fathers of 8,169 cases and 14,201 controls the odds ratio (OR) for maternal exposure during pregnancy and the risk of acute lymphoblastic leukemia (ALL) was 1.01 (95% confidence interval (CI) 0.78, 1.30) and for paternal exposure around conception 1.20 (95% 1.06, 1.38). For acute myeloid leukemia (AML), the OR for maternal exposure during pregnancy was 1.94 (CI 1.19, 3.18) and for paternal exposure around conception 0.91 (CI 0.66, 1.24.) based on data from 1,329 case and 12,141 control mothers, and 1,231 case and 11,383 control fathers. Our finding of a significantly increased risk of AML in the offspring with maternal exposure to pesticides during pregnancy is consistent with previous reports. We also found a slight increase in risk of ALL with paternal exposure around conception which appeared to be more evident in children diagnosed at the age of five years or more and those with T cell ALL which raises interesting questions on possible mechanisms.

Keywords

pesticide; occupation; leukemia; childhood; pooled analysis; meta-analysis

Introduction

Little is known about the etiology of childhood leukemia and its main sub-types, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) but it is likely that they are attributable to a mixture of genetic and environmental factors,[1] which may vary by disease sub-type, or for ALL, by immunophenotype. Most cases occur before the age of five years, although T cell ALL is seen mainly in slightly older children. Some of the most common chromosomal translocations seen in both sub-types of ALL[2, 3] and AML[4] may be of prenatal origin, suggesting a role for parental exposures. Individual studies rarely have the power to investigate potential risk factors by sub-type and/or immunophenotype, especially for uncommon exposures. To help overcome this, we pooled individual data from studies in the Childhood Leukemia International Consortium (CLIC), a multi-national collaboration of case-control studies of childhood leukemia.[5] The focus of these analyses was parental occupational exposures to pesticides.

The term ‘pesticide’ covers a large, heterogeneous group of chemicals used to control insects, weeds, fungi and other pests. The active ingredients of each chemical may have different mutagenic, carcinogenic or immunotoxic properties. More than 20 individual pesticides have been classified as, at least ‘probable or possible’ human carcinogens by the International Agency for Research on Cancer.[6] Exposure of the father before conception could result in germ cell damage, while maternal exposure during pregnancy can result in fetal exposure, as demonstrated by pesticide residuals found in umbilical cord blood and meconium.[7] Prenatal exposure to certain insecticides, has been associated with

translocations found in children with AML.[8, 9] Propoxur, has been associated with t(8;21) translocations in cord blood[9] and permethrin has been associated with a 11q23 translocation in a case report of congenital AML,[8] thus suggesting that maternal pesticide exposure around pregnancy could result in chromosome translocations in the offspring. Maternal pre-natal occupational pesticide exposures have been examined in two recent meta-analyses,[10, 11] with both reporting an increased risk of all leukemias, as well as of leukemia sub-types. However, the estimates for ALL and AML were based on five or fewer studies because most studies in the overall analyses did not report risk by leukemia sub-type, and none reported by immunophenotype. Pre-conceptional paternal occupational exposure has also been suggested as a risk factor in individual studies of ALL[12] and AML.[13]

The aim of the current analyses was to investigate whether parental occupational pesticide exposure in the prenatal period increased the risk of ALL or AML in the offspring. We also aimed to investigate whether the relationship varied by immunophenotype of ALL. For these analyses, we used all CLIC studies that had relevant data available in 2012, that is, 13 studies (12 with ALL cases and 10 with AML cases) that were conducted in North America, Europe and Australasia over a 30 year period.

Methods

Original data were requested from each of the participating studies including demographics, disease sub-types, potential covariates, variables used for control selection or matching and occupational pesticide exposure assessments for both parents. A summary of study design and participant details, including inclusion criteria, has already been published[5] and the characteristics of each study as well as participation fractions (based on information available from published studies or obtained directly from study personnel) are listed in Table 1. Definition of the participation fraction varied across studies. In most cases, the studies were conducted on a nationwide or region-wide basis and thus they included a mixture of urban and rural subjects. All studies were approved by the relevant institutional or regional ethical committees.

Original occupational exposure data

The time periods of interest were the year before conception for fathers and during the pregnancy for the mother. However, the included studies had data for differing periods around conception or only during pregnancy in some (Table 1). In four studies, data for jobs in the time periods were extracted from the provided work history.

Occupational data were provided in three main formats (Table 1); 1) Eight studies (France: Adele and Escale; Greece Nationwide Registry for Childhood Haematogical Malignancies (NARECHEM) 1993–1994 and 1996–2011; Germany; United Kingdom Childhood Cancer Study (UKCCS); US Northern California Childhood Leukemia Study (NCCLS); US Children’s Oncology Group (COG)-E15 provided jobs coded using an occupational coding system, which needed to have pesticide exposure assigned; 2) Four studies provided data in which jobs in the relevant time periods had already been assessed for pesticide exposure and exposure assigned (Australia, Canada, Italy, New Zealand) and 3) One study (US COG-E14)

provided detailed pesticide questionnaire data which needed to be collated to a single exposure variable.

Development of a Job Exposure Matrix (JEM)

The assessments from two of the studies, Australia[14] and Canada[15], were used to develop a JEM to assign the likelihood of pesticide exposure for the studies with job title codes. Both of these studies use the expert assessment method to assess occupational pesticide exposure.[16] In this method a full job history is taken, and job specific questionnaires are asked about each relevant job (for example an orchardist would be asked the Farmer questions while a sports field manager would be asked the Gardener questions). The answers to these questions are reviewed on an individual level by experts, such as industrial hygienists or chemists, who determine whether the person was likely to be exposed to pesticides in that job. For each job title in International Standard Classifications of Occupation (ISCO)-2008 (08)[17] we determined what proportion of the jobs in the Australian data were assessed as being exposed to pesticides. All job codes were then assigned to a category relating to the certainty of pesticides exposure as follows; 1) Job codes where 70% or more people (males and females combined) with the ISCO-08 code had been assessed as exposed to pesticides ('High likelihood of pesticide exposure'); 2) Job codes where 25% ≤ 70% were assessed as exposed ('Moderate likelihood of exposure'); 3) Job codes where 10 ≤25% were exposed ('Limited likelihood of exposure') and 4) Job codes where less than 10% were exposed ('No or minimal likelihood of pesticide exposure' (Reference Group)). ISCO-08 jobs codes that were rare or not used in the Australian dataset were identified and these were assigned an exposure category by an occupational epidemiologist (LF). Modifications to the exposure categories were made after doing similar comparisons of expert assessment and jobs coding from the Canadian study.[18] The final exposure codes in the JEM were then assigned to equivalent ISCO-88 codes and hence to jobs in the other occupational classification systems using conversion tools (Table 1)[19–23]. In the case of 'many to one' or 'one to many' matches to job codes across systems, a judgment was made of the exposure category that best fitted the original job code description. Rather than assigning an exposure category to all codes in each of the coding systems, other than ISCO-08 or ISCO-88, matches were only found for those that appeared in any of the datasets. A full list of the job codes which were categorized as highly likely to be occupationally exposed in each of the occupational coding systems is found in Supplementary Table 1. Finally, we compared the job titles in the 'High likelihood of pesticide exposure' category to a list of jobs involving possible pesticide exposure based on a literature search of the topic. Because of likely heterogeneity across studies in pesticide usage patterns, we did not attempt to differentiate between types of pesticides.

Harmonisation of occupational data from other studies

Among the four studies where pesticide exposure had already been assigned, three (Canada, Italy and New Zealand) had assigned pesticide exposure as yes or no. These categories in the Italian study were derived from the assessment of the probability and intensity of exposure,[24] while those in the New Zealand data were derived from detailed assessment. In order to pool with the studies for which we used the JEM, we coded exposed subjects the same as the 'High likelihood of pesticide exposure' category and non-exposed the same as

the ‘No or minimal likelihood of pesticide exposure’ category. In the Australian study which assigned more levels of exposure, we coded those with ‘probable high/medium exposure’ the same as the ‘High likelihood of pesticide exposure’ category, and ‘probable low exposure and possible low/medium/high exposure’ the same as the ‘Moderate likelihood of exposure’ category and those assessed as not exposed the same as the ‘No or minimal likelihood of pesticide exposure’ category (Table 1).

US COG-E14 had collected data about exposure to individual pesticides. These data were collated into a single ‘any pesticide exposure’ for each time period, with four levels of exposure (in order to be comparable to the studies for which we used the JEM), based on the information about total contact time with pesticides.

Statistical analyses

Two analytic approaches were taken which both used the final exposure measure. Firstly, study-specific odds ratios (ORs) of ALL and AML and exposure to pesticides were estimated and included in meta-analyses in order to identify heterogeneity between the studies. Secondly, as main approach, individual data were pooled in a single dataset and the pooled ORs estimated. Because the final exposure measure was an imprecise approximation of occupational exposure, the main focus of both the meta-analysis and pooled analyses was to contrast the OR between Exposure Category 1 (‘High likelihood of pesticide exposure’) to the Reference Category 4 (‘No or minimal likelihood of pesticide exposure’) for both the study specific and pooled analyses. While those with other exposure categories were included in the analyses, a trend across categories response was not investigated and results from ‘Moderate likelihood of exposure’ and ‘Limited likelihood of exposure’ categories are only shown in a supplementary table. ALL and AML were analyzed separately and where possible, subgroup analysis were undertaken by ALL immunophenotypes and by type of occupational assessment.

The Escale study only had paternal exposure data for the time period during pregnancy so this was used as a proxy for before conception exposure.

Generating and meta-analyzing study-level ORs from individual-level data and meta-analyses from published studies

Unconditional logistic regression (SAS version 9.2, SAS Institute Inc, Cary, NC, USA) was used to estimate ORs and 95 percent confidence intervals (95% CIs) for occupational pesticide exposures in mothers during pregnancy and for fathers before conception. All models included child’s age and sex and additional study-specific matching variables. This approach was used to optimize the number of available cases and controls.[25] The following variables were considered *a priori* to be potential confounders or independent competing factors (birth order, birth weight (in studies where data were readily available), ethnicity, maternal age group and education (for maternal analyses) and paternal age group and education (for paternal analyses)). Maternal and paternal education were the only common socio-economic level indicators that were available in all studies, albeit in different formats. Factors that were independently associated with both the exposure and outcome were retained in the final models. The study-specific ORs were combined in a meta-analysis in

Stata version 11.2 (StataCorp LP, College Station Texas, USA, 2009), using the random effects model (to acknowledge the between study heterogeneity, such as in terms of study designs, occupational assessment methods, and pesticide use across countries and time[26]). Summary ORs, 95% CIs, I^2 statistics (a measure of the variation across studies that is not due to chance)[27] and forest plots were produced. Studies without any cases or controls in the 'High likelihood of pesticide exposure' were not included in the meta-analyses.

Finally, we identified additional published papers or other theses that had been included in recent meta-analyses[11, 28] (supplemented by information from one of the authors (personal communication, D Wigle April 2013)) of maternal occupational pesticide exposure and the risk of ALL[29–34] or AML[13, 29, 31] or paternal exposure and risk of ALL[12, 30, 32–38] or AML[13, 36–38] of studies not being part of CLIC The search strategies of all these meta-analyses can be found in the supplementary material. Using one of these search strategies,[10] we searched PubMed (National Library of Medicine, Bethesda, MD) to identify papers of maternal occupational pesticide exposure and the risk of ALL[14, 39], or AML[39] or paternal exposure of both sub-types[40] published January 2009 to 31 October 2013. We extracted the relevant OR from each of these studies to calculate summary ORs (as described above) with the results from the individual CLIC studies, after excluding studies which had an overlap of data with the CLIC studies,[12, 14, 30, 38, 41] did not specify which parent was exposed[35, 36] or did not provide an overall pesticide exposure variable.[34] Another published study[37] was excluded as it was a subset of the UK National Registry of Childhood Tumours (NRCT) study.[40] One of the CLIC studies, the UKCCS, was also a subset of the NRCT study and was thus excluded from the meta-analyses of the CLIC and other published studies.

Pooled analyses of individual-level data

Unconditional logistic regression (SAS version 9.2, SAS Institute Inc, Cary, NC, USA) was used to estimate pooled OR and 95% CI for occupational pesticide exposures in mothers during pregnancy and for fathers before conception. All models included the child's age and sex, year of birth group (grouped into five approximately equal time periods), ethnicity (Caucasian, European or White versus the rest) and a variable denoting the study of origin. The following variables were tested to determine whether they were independently associated with both the exposure and outcome: Birth order, birth weight (for the subset of studies where data were readily available), the relevant parent's age group and education (recoded into three groups: secondary education not completed, completed secondary education, and tertiary education), and study-specific matching variables (by allocating all the other studies the same dummy value for each variable); of these, only maternal or paternal education was retained. As children with Down syndrome have higher rates of leukemia than other children, analyses were repeated, excluding these children.

Results

Data were obtained from 12 studies for 8,835 ALL cases and from 10 studies for 1,357 AML cases (Table 2). There were 15,486 controls from studies with ALL cases and 12,443 from those with AML cases. The same controls were used for ALL and AML cases if the original study included both types of leukemia. Most studies recruited children under the age

of 15, except one study that included children up to the age of 10 years (Italy) and one study of AML that included children up to the age of 18 years (US COG-E14). Maternal occupational data were available for 93.2% of ALL cases, 95.9% ALL controls, 97.9% of AML cases, 97.6% of AML controls and paternal occupational data for 92.5%, 91.7 %, 90.6%, and 91.5%, respectively (Table 2). These rates reflect missing occupational data from the original studies, for example, most studies had fewer fathers participating than mothers. The table showing the demographic characteristics of the total sample and the individual studies is provided as Supplementary Table 2.

Meta-analyses of CLIC studies

Twelve CLIC studies were included in the meta-analysis of parental occupational pesticide exposures and the risk of ALL in the offspring. There were 8,236 cases and 14,850 controls in the meta-analysis of maternal exposure and 8,157 cases and 14,201 controls in that of paternal exposures. Further details about each study are in Supplementary Table 3. The summary OR for maternal exposure and the risk of ALL in the offspring was 1.03 (95% CI 0.77, 1.38) with little evidence of heterogeneity among the ORs (Table 3). The summary OR for paternal occupational exposure and the risk of ALL in the offspring was 1.22 (95% CI 0.94, 1.58) with high heterogeneity (I^2 = 68.7%) (Table 3). When the paternal analyses were stratified by the type of occupational data, high heterogeneity was only seen in studies for which coded job titles were used to assign occupational assessment (summary OR 1.28, 95% CI 0.89, 1.85, I^2 = 77.5%) and not among studies where pesticide assessment was based on more detailed questions or assessment (summary OR 1.15, 95% CI 0.84, 1.57, I^2 = 20.1%) (results not otherwise shown).

When individual studies were omitted in turn from the meta-analyses, the summary estimate changed by less than eight percent (OR scale). The summary estimates were higher for T cell ALL than B cell ALL (Table 3) for both maternal and paternal exposures, but the estimates for T cell ALL were based on smaller numbers of cases.

As only studies with any cases in the ‘High likelihood of pesticide exposure’ category were included in the AML meta-analyses, 895 cases and 5,428 controls from five studies were included for maternal exposures, and 1,184 cases and 10,863 controls from eight studies for paternal exposures. Further details about each study are in Supplementary Table 4. The summary ORs for maternal and paternal occupational pesticide exposures and the risk of AML in the offspring were 2.69 (95% 1.49, 4.86) and 1.12 (95% CI 0.72, 1.70), respectively with little or low heterogeneity among the ORs (Table 3). When individual studies were removed one by one, the summary estimates for maternal exposure changed by up to 26% while those for paternal exposure changed by less than 11%.

Meta-analyses of CLIC studies together with previously published papers—For the combined meta-analyses of the CLIC data and previous published papers of ALL we added estimates from six additional studies for the investigation of maternal exposure[29, 31–33, 39, 42] and three for those of paternal exposure[32, 33, 40, 40], while those of AML contained estimates from an additional four studies for maternal exposure[13, 29, 31, 39] and three for paternal exposure,[13, 31, 40] but excluded one of the CLIC studies from the

paternal analyses. The resulting summary ORs for maternal exposures during pregnancy and paternal exposures around conception and the risk of ALL in the offspring were 1.35 (95% CI 0.96, 1.89, I^2 =43.0%) (Supplementary Figure 1) and 1.23 (95% CI 0.99, 1.53 I^2 =68.3%) (Figure 1) respectively. The summary estimates for maternal and paternal exposures respectively and the risk of AML in the offspring were 3.30 (95% CI 2.15, 5.06, I^2 =0.0%) (Figure 2) and 1.14 (95% CI 0.88, 1.49 I^2 =24.0%) (Supplementary Figure 2).

Pooled analyses of individual data from CLIC studies

The analyses for ALL included 12 studies (8,236 case mothers, 14,850 control mothers, 8,169 case fathers and 14,201 control fathers). No association was seen with maternal occupational pesticide exposure during pregnancy and the risk of ALL (OR 1.01, 95% CI 0.78, 1.30) (Table 4). There was no difference in the OR when the analyses were stratified by type of occupational assessment, or immunophenotype (Table 4).

The OR for paternal occupational pesticide exposure and the risk of ALL in the offspring was 1.20 (95% CI 1.06, 1.38) (Table 4). The risk of ALL related to exposure appeared to be stronger in children diagnosed at five years or older than for those diagnosed earlier (p value for the interaction 0.07). When the analyses were stratified by both immunophenotype and age at diagnosis, the ORs for B cell and T cell ALL were 1.04 (95% CI 0.85, 1.25) and 1.16 (95% CI 0.65, 2.09) in children aged under five years, and 1.39 (95% CI 1.12, 1.71) and 1.55 (95% CI 1.07, 2.25), respectively in children aged five years or more (results not shown). There was little difference in the OR when the analyses were stratified by type of occupational assessment (Table 4).

The analyses for AML included 10 studies (1,329 case mothers, 12,141 control mothers, 1,231 case fathers and 11,383 control fathers). The OR for maternal occupational exposure during pregnancy was 1.94 (95% 1.19, 3.18) (Table 4). While there was little variation by age at diagnosis, the OR varied by whether the exposure assessment was based on job codes or another method. One study (US, COG-E14) contributed nearly 50% of the cases for this analysis; when this study was excluded, the resulting pooled OR was 1.51 (95% CI 0.83, 2.74). No association was seen with paternal occupational exposure around the time of conception (OR 0.91, 95% CI 0.66, 1.24), or when these analyses were stratified by type of occupational assessment or age at diagnosis (Table 4).

When all the analyses for ALL and AML were rerun excluding children with Down syndrome (103 ALL cases and six controls, 89 AML cases and four controls), there was little change in the results and there was also little difference when they were stratified by the birth year group (data not shown). The estimates for paternal exposure and for maternal exposure changed little when adjusted for the exposure level of the other parent. Few cases (0.9 % of ALL cases and 0.7% of AML cases) and 0.6% of controls had both parents in the ‘High likelihood of pesticide exposure’ group. The ORs for ALL and AML in the offspring with both parents being exposed compared to both parents being unexposed were 1.29 (95% CI 0.90, 1.85) and 1.43 (95% CI 0.67, 3.08), respectively (results not tabulated).

Discussion

Our findings suggest that it may be important to investigate occupational exposure to pesticides by sub-type of leukemia as the findings for ALL were different from those for AML for both maternal and paternal exposure. For maternal occupational exposures to pesticides during pregnancy, we found a significantly increased risk of AML using pooled data from 10 international case-control studies in the offspring, although the findings lacked precision when the largest study was excluded, while no increased risk of ALL was found using data from 12 studies. For paternal occupational pesticide exposures around the time of conception, we found about a 20% increased risk of childhood ALL in the analyses of pooled data from 12 international case-control studies, but no association with AML using data from 10 studies.

Our observations for maternal exposure and the risk of AML are consistent with previously published studies[13, 29, 31, 39] with additional support provided by studies implicated the use of pesticides by the mother in the home environment during pregnancy as a risk factor for AML in the offspring.[13, 43]

The finding for maternal exposure and ALL is at odds with the elevated risk reported in two previous meta-analyses.[10, 11] and a recent Brazilian study.[39] The disparity with other previous literature appears to be due mainly to the findings of four studies, which all had <200 cases and reported ORs for exposures during pregnancy of greater than 2.5.[29, 31, 33, 39] One of these was conducted in China[31] and another in Japan[33] The definition of pesticide exposure was based on maternal recall of pesticide exposure in the Chinese study,[31] while in the hospital–based Japanese study,[33] it was defined as working in an agricultural industry. The other two studies[29, 39] were restricted to ALL diagnosed either before 18 months[29] or two years of age.[39] The first of these was an international study obtaining information about maternal occupational exposures during an interview, but may have included non-occupational exposures in some countries.[29] The other was a hospital-based case-control Brazilian study in which mothers were asked about exposure to agricultural pesticides.[39] On the other hand, all the CLIC studies were conducted in predominantly Caucasian populations and included children under 15 years and the exposure was restricted to occupational exposures, thus the difference in the findings could be explained by a mixture of factors; differing distributions of cytogenetic sub-types between the populations,[44] or age groups[45] as susceptibility to pesticides could be restricted to certain cytogenetic sub-types, or related to the definitions of exposure. The findings could also reflect differences in the types of pesticides used and the protection measures used during pesticide application. However, we have insufficient information to speculate on these issues.

It is biologically plausible that maternal occupational pesticide exposure could increase the risk of either sub-type of leukemia in the offspring as there is evidence that some pesticides cross the placental blood barrier, thus resulting in fetal exposure.[7] However, to the best of our knowledge, while there have been several case reports of translocations associated with AML being found in either in cord blood or soon after delivery, following maternal insecticide exposure during pregnancy,[8, 9] there are no such evidence for translocations associated with ALL.

For paternal exposures, the increased risk is consistent with two[32, 33] of three previous studies,[34, 35, 42] as well as those of the participating Canadian study, [12] but different from the UK NRCT study[42] which reported an OR of 1.00 (95% CI 0.86, 1.33)

Our findings for paternal exposure and the risk of ALL in the offspring raise some interesting issues as the association appears stronger in older children and those with T cell ALL. T cell ALL generally occurs between the ages of six to eight years of age while precursor B cell (the vast majority of B cell lineage cases) is mainly seen in children aged less than five years. Despite this, there is still evidence that T cell ALL can originate in the prenatal period,[3] and thus damage to paternal germ cells could play a role, albeit with a long latency.

However, our findings also suggested the association between paternal pesticide exposure and B cell ALL was more pronounced in older children. Another possible explanation for our findings is that paternal occupational pesticide exposure around conception is a proxy measure for either paternal exposure during the child's early years or for exposure of the child by living on or close to a farm, but we do not have the data to investigate this theory. Exposed parents can track pesticides back into the home such as on shoes and on hands,[46] or homes and play areas can be contaminated by air drift from pesticide spraying,[47] thus higher levels of pesticide residues have been detected on children's hands and in house dust in farmhouses than others.[46] In one of the CLIC studies, US NCCLS, children who lived in homes where chlorthal (a potentially carcinogenic agricultural herbicide) was detected in carpet dust had an increased risk of ALL.[48]

Consistent with previous studies,[13, 40] we found no association between paternal occupational pesticide exposure and the risk of AML in the offspring in the pooled analyses.

The major strength of our investigation was the large sample size, which allowed us to investigate exposure by sub-type of leukemia in more detail than in previous individual studies; and access to the original data allowing better harmonization of exposure variables and their categorization as compared to literature-based meta-analyses.

However, there were also major limitations with respect to our investigations. Notably, the occupational exposure data were available in many forms. In order to harmonize the data, a crude measure of exposure was developed. For most studies, we had only job title information coded in different formats. It is unlikely that all people with the same job code would have the same level of exposure, or that pesticide exposure levels would have been similar across all the study populations (North America, Europe and Australasia) and over time (30 years). The size of farms, the crops grown and the animals raised would have varied across studies and the types and extent of pesticide handled may have varied by gender. The proportion of controls classed as exposed to pesticides varied by study, which may reflect true differences in exposure to pesticides, for example between countries, or weaknesses in the exposure measure. Despite these limitations, the estimates obtained for ALL using studies that had used coded job titles were similar to the three studies (Australia, Canada and Italy) that used expert occupational assessment. No such comparison was possible for AML as only the Italian study included cases of AML. This study only assigned exposure to

agricultural pesticides, but this was considered an adequate proxy for any occupational pesticide exposure.[49] In addition, most of the job titles in our 'High likelihood of pesticide exposure' category were agriculture or farm-related.

Our study has the same limitation as most previous research of this topic, that is, the inability to define exposure by type of pesticide. By combining all pesticide exposure into a single measure of general pesticide exposure, we may have diluted the effect of different pesticides and introduced non-differential misclassification. If we could have defined pesticides more specifically, we may still not have not been able to address the issue of exposure to multiple types of pesticides as exposed individuals commonly use more than one type.[12]

We developed the JEM using data from Australia and Canada, but applied it to US and European studies, which raises questions about the validity of the JEM in other settings. However, to the best of our knowledge, our choices of 'High likelihood of exposure' job codes are in line with other published literature.

In all of the studies, data were collected using structured questionnaires that focused on jobs instead of exposures in attempts to minimize recall bias. Nonetheless, this would not remove the potential for cases to think more deeply about jobs held.

Although our investigation focused on the exposure time-windows of around conception or pregnancy, occupational exposure is likely to have extended over a wider time period. Among mothers, there was a high correlation (Spearman P 0.884) with maternal exposures around conception and during pregnancy with over 98.5 % of women having the same exposure code in studies with both time periods. This also means that the risks we observed may also apply to a broader period of time, such as before conception or during the child's early years. Most occupational pesticide exposures occur in farming or agriculture,[49] and the children of exposed parents may have been exposed around the home to agricultural pesticides, such as through spray drift.[47] Another limitation was that there were few parents, especially women in the 'High likelihood of pesticide exposure' category, which made some estimates imprecise, despite the sample size.

In conclusion, we found an increased risk of AML in the offspring following maternal occupational pesticide exposure during pregnancy. We also found that the risk of ALL increased slightly with paternal occupational pesticide exposure around conception. More information is needed by pesticide type and about the use of protective measures during application before any recommendations are made in relation to pesticide use in the workforce and the risk of childhood leukemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The UKCCS was conducted by 12 teams of investigators (ten clinical and epidemiological and two biological) based in university departments, research institutes, and the National Health Service in Scotland. Its work is coordinated by a management committee. Further information can be found on the web-site www.ukccs.org.

COG: The E14 and E15 cohorts of the Children's Oncology Group was identified by CCG (Children's Cancer Group) principle and affiliate member institutions. Further information can be found on the web-site: http://www.curesearch.org/.

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Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
Aus-ALL	Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children
CI	Confidence interval
CLIC	Childhood Leukemia International Consortium
COG	Childhood Oncology Group (Children's Cancer Group)
ESCALE	Epidemiological Study on childhood Cancer and Leukemia
GCCR	German Childhood Cancer Registry
ISCO	International Standard Classification for Occupation
JEM	Job Exposure Matrix
NARECHEM	Nationwide Registration for Childhood Haemotological Malignancies
NCCLS	Northern California Childhood Leukemia Study (USA)
NEC	Not else classified
NZCCS	New Zealand Childhood Cancer Study
OR	Odds ratio

RDD	random digit dialling
UKCCS	United Kingdom Childhood Cancer Study

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Novelty and Impact statement

Parental occupational pesticide exposure before birth may be a risk factor for childhood leukemia. Using pooled individual level occupational pesticide exposure data from 13 case- control studies (over 8,000 acute lymphoblastic leukemia (ALL) cases and 14,000 controls, and 1,200 acute myeloid leukemia (AML) cases and 12,000 controls), we found an increased risk of AML with maternal exposure during pregnancy and a slightly increased risk of ALL with paternal exposure around conception.

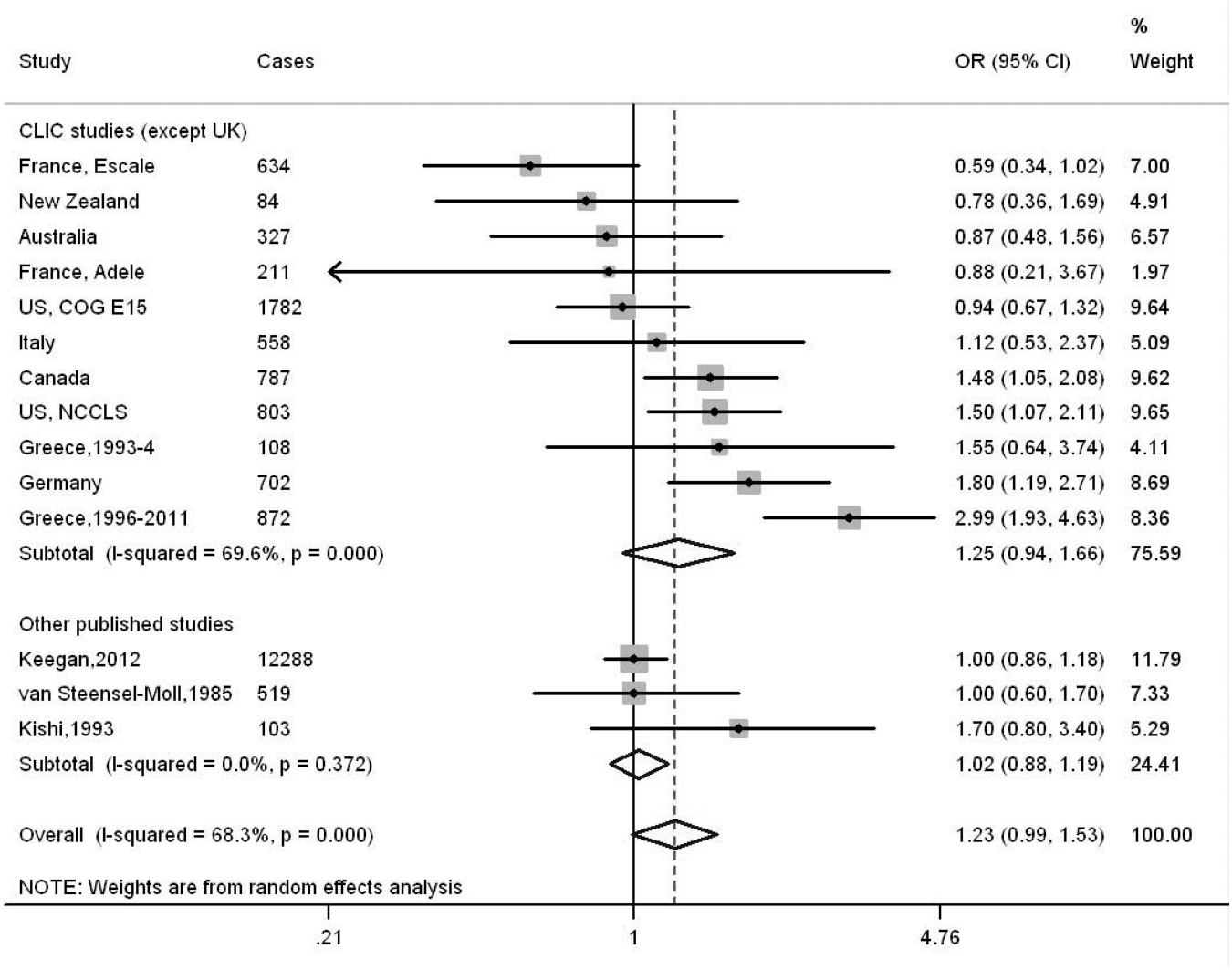

Figure 1.

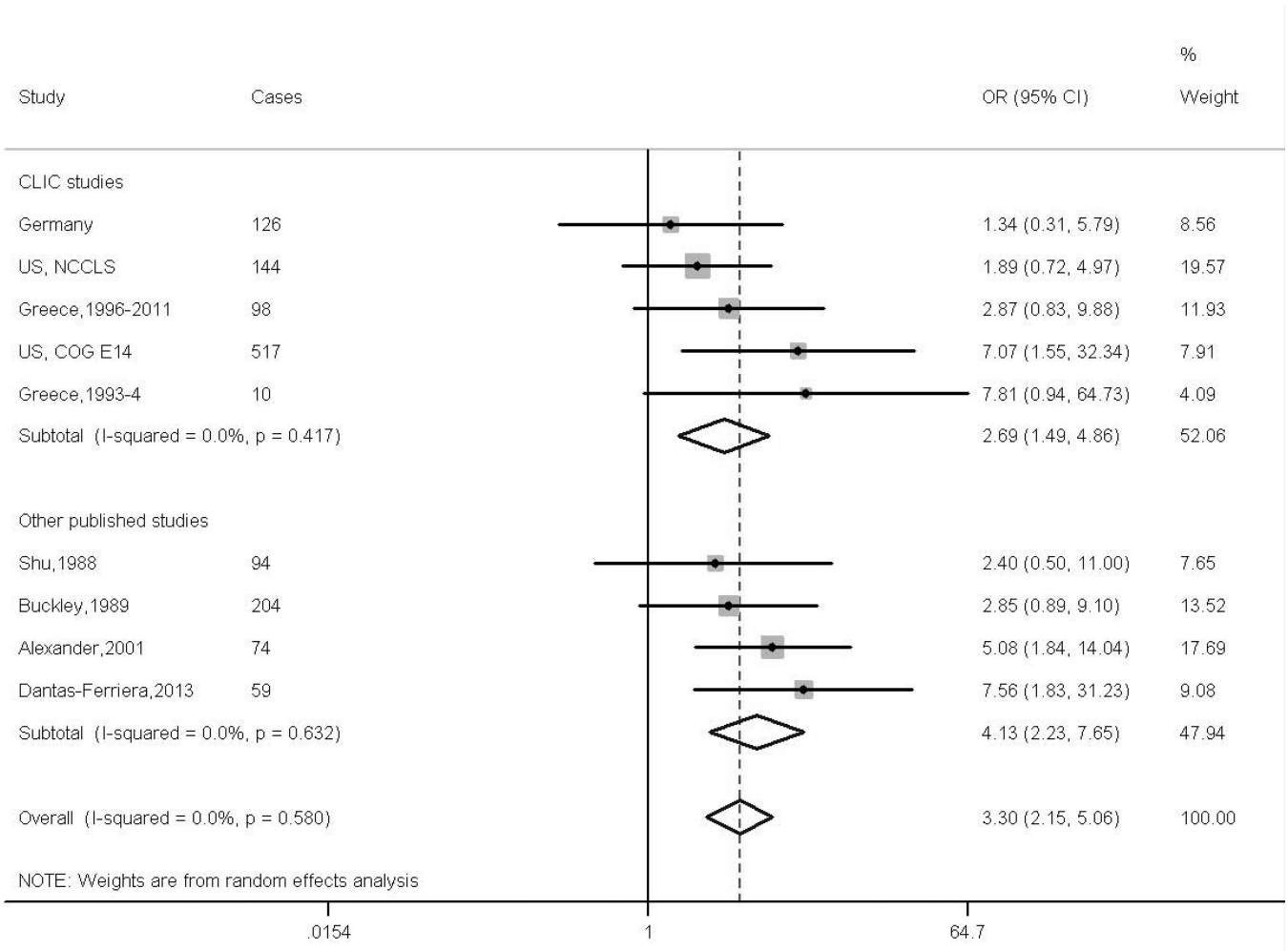

Figure 2.

Table 1

Selected characteristics including occupational exposure assessment of the 13 studies in the CLIC pooled analyses of parental occupational pesticide exposure and the risk of leukemia in the offspring

Country, Study (years of case accrual)	Method of occupational assessment	Case			Control			Time period(s) of interest[a]	Scope of assessment	Final exposure variable[b]	Prevalence of 'High likelihood of pesticide exposure' amongst controls		Source of conversion tool to other Occupational Classifications (where applicable)
		Source	Participation[c]	N[d]	Source	Participation[c]	N[d]				Mothers	Fathers	
1. Use of an Occupational Classification System													
France, ADELE (1993–1999)	ISCO 1988	Hospitals	95%	ALL: 240 AML: 36	Hospitals (same as cases)	99%	288	Extracted from work history (start & end year of each job) 1. Main year before conception (defined as the year of the mid point of the year before conception) 2. Main year of pregnancy (defined as the year of the midpoint of the pregnancy)	All jobs held in time periods	4 level 1. 'High likelihood of pesticide exposure' 2. 'Moderate likelihood of exposure' 3. 'Limited likelihood of exposure' 4 = 'No or minimal likelihood of pesticide exposure'	0.4	1.7	Correspondence Table ISCO 08 to ISCO 88[19]
Greece, NARECHEM (1993–1994)	ISCO 1988	Nationwide hospital cancer registry	100%	ALL; 140 AML: 13	Hospital	96%	300	1.One year before birth 2.During pregnancy	All jobs held in time periods	As above	2.9	9.8	Correspondence Table ISCO 08 to ISCO 88[19]
France ESCALE (2003–2004)	ISCO 1968	Population-based cancer registry (nationwide)	91%	ALL: 648 AML: 101	Population quotas by age, sex, region (nationwide)	71%	1681	1.During pregnancy[e]	Main job in time period	As above	0.8	4.3	Correspondence Table ISCO 68 to ISCO 88[20]
Greece, NARECHEM (1996–2010)	ISCO 1968	Nationwide hospital cancer registry	83%	ALL: 964 AML: 113	Hospital	96%	1085	1. One year before birth 2. During pregnancy	All jobs held in time periods	As above	1.1	3.0	Correspondence Table ISCO 68 to ISCO 88[20]
Germany, GCCR (1988–1994)	Germany, Bundesgentur fur Abeit Wirtschaftsklasse 1988	Population-based cancer registry (nationwide)	82%	ALL: 751 AML: 130	Population-based registry (community based but complete nationwide coverage)	71%	2458	1. Conception 2. During pregnancy	Main job in time periods	As above	1.2	3.0	Correspondence Table to ISCO 88 obtained from Federal Statistical Office, Germany[21]
UK, UKCCS (1991–1996)	UK, Standard Occupational Classification 1990	Population-based tailored referral systems	93%	ALL: 1461 AML: 248	GP registries (nationwide)	64%	3448	1. Around conception 2. During pregnancy	All jobs held in time periods	As above	0.3	2.4	Correspondence Table to ISCO 88 obtained from Office for National Statistics, UK[22]
US, NCCLS (1995–2008)	US, Census Occupational Classification Codes,1990	Hospitals	86%	ALL: 840 AML: 145	Birth registry (state wide)	68%	1226	Extracted from work history (start and end month, year of each job) 1. Year before conception 2. During pregnancy	All jobs held in time periods	As above	2.0	8.3	Correspondence Tables obtained from the National Crosswalk Center[23] between 1990 Census to 2000 Census codes and 2000 Census codes to ISCO 88
US, COG-E15 (1989–1993)	US, Department of Labor Dictionary of Occupational Titles (4th ed., rev. 1991)	Children's Cancer Group clinical trials	87%	ALL: 1914	RDD	70%	1987	Extracted from work history (start and end month, year of each job) 1. Year before conception 2. During pregnancy	All jobs held in time periods	As above	1.1	4.2	Correspondence Tables obtained from the National Crosswalk Center[23] between DOT to 2000 Census codes and 2000 Census codes to ISCO 88
2. Pesticide exposure already assigned													
Australia, Aus-ALL (2003–2007)	Answers to initial structured questionnaire and follow-up job specific interview reviewed by expert[14]	Hospitals (nationwide)	75%	ALL: 389	RDD	64% of agreed controls	876	1. One year before birth	All jobs held in time period	3 level: 1 = medium/high exposure 2 = low exposure 4 = not exposed	0.2	5.5	
Canada, Quebec (1980–2000)	Answers to initial structured interview and follow-up job specific questions reviewed by expert[12, 16]	Hospitals (province wide)	93%	ALL: 790	Health Insurance file population-based registry (province-wide)	86%	790	1. Two years before conception 2. During pregnancy	All jobs held in time periods	2 level: 1 = exposed 4 = not exposed	4.4	7.9	

Country, Study (years of case accrual)	Method of occupational assessment	Case			Control			Time period(s) of interest[a]	Scope of assessment	Final exposure variable[b]	Prevalence of 'High likelihood of pesticide exposure' amongst controls		Source of conversion tool to other Occupational Classifications (where applicable)
		Source	Participation[c]	N[d]	Source	Participation[c]	N[d]				Mothers	Fathers	
Italy, SETIL (1998–2001)	Answers to initial structured interview and follow-up job specific questions reviewed by experts[24] (restricted to agricultural pesticides)	Nationwide clinical database	91%	ALL: 601 AML: 32	Population-based National Health Service Registry	69%	1044	1. One year before conception 2. During pregnancy	All jobs held in time periods	2 level: 1 = exposed 4 = not exposed	0.4	1.9	
New Zealand, NZCCS (1990–1993)	Exposure assignment based on detailed questionnaire and interview about pesticide exposures in each job	Registry (nationwide)	92%	ALL: 97 AML: 22	Birth registry (nationwide)	69%	303	1. Two years before birth 2. During pregnancy	All jobs held in time periods	2 level: 1 = exposed 4 = not exposed	1.3	18.0	
3. Pesticide exposure data collected, but exposure not assigned													
US, COG-E14 (1988–1993)	Detailed questionnaire about each type of pesticide use in each job	Children's Cancer Group clinical trials	76%	AML: 517	RDD	72%	610	Extracted from work history (start and end month, year of each job) 1. Year before conception 2. During pregnancy	All jobs held in time periods	4 level: Tertiles of exposure[f] 1 = 'High' 2 = 'Medium' 3 = 'Low' 4 = unexposed	0.3	5.2	

[a] The time periods of interest were 1. Around conception for the father and 2. During pregnancy for the mother.

[b] In the final pooling process, a 4 level variable was used, but levels 2 and or 3 were empty for studies with less than 4 categories.

[c] Participation fractions are based on information available from published studies or obtained directly from study personnel. Definition of the participation fraction may vary across studies.

[d] Occupational histories were available for more than 90% of parents. The numbers of mothers and fathers with occupational histories are in Supplementary Table 2.

[e] In France ESCALE, paternal exposure during pregnancy was used as a proxy for paternal exposure at conception as these data were not available.

[f] Based on tertiles of the total time any pesticide was in the air the subject or on the skin/clothing during time period among exposed control mothers and fathers.

ISCO: International Standard Classification for Occupation
RDD: random digit dialing

Table 2

Key demographic characteristics of participants in the 13 studies in the CLIC pooled analyses of parental occupational pesticide exposure and the risk of leukemia in the offspring

	ALL (12 studies)				AML (10 studies)			
	Case (n= 8835)		Control[a] (n = 15486)		Case (n= 1357)		Control[b] (n= 12443)	
	n	%	n	%	n	%	n	%
Sex								
Boy	4972	*56.3*	8634	*55.8*	713	*52.5*	6928	*55.7*
Girl	3863	*43.7*	6852	*44.2*	644	*47.5*	5515	*44.3*
Age (years)[c]								
0–1	958	*10.8*	2272	*14.7*	376	*27.7*	2000	*16.1*
2–4	4109	*46.5*	6156	*39.8*	259	*19.1*	4610	*37.0*
5–9	2570	*29.1*	4507	*29.1*	313	*23.1*	3526	*28.3*
10–14	1198	*13.6*	2551	*16.5*	342	*25.2*	2231	*17.9*
15–17	0	*0.0*	0	*0.0*	67	*4.9*	76	*0.6*
Year of birth								
1970–1978	294	*3.3*	395	*2.6*	151	*11.1*	289	*2.3*
1979–1987	2555	*28.9*	4318	*27.9*	426	*31.4*	2943	*23.7*
1988–1996	3927	*44.5*	7226	*46.7*	578	*42.6*	6350	*51.0*
1997–2005	1936	*21.9*	3394	*21.9*	175	*12.9*	2710	*21.8*
2006–2011	123	*1.4*	153	*1.0*	27	*2.0*	151	*1.2*
Child has Down Syndrome								
Yes	103	*1.2*	6	*0.0*	89	*6.6*	4	*0.0*
Maternal education								
Did not finish secondary education	2327	*26.3*	3950	*25.5*	322	*23.7*	3479	*28.0*
Completed secondary education	3859	*43.7*	6619	*42.7*	664	*48.9*	5098	*41.0*
Tertiary education	2588	*29.3*	4756	*30.7*	358	*26.4*	3706	*29.8*
Missing	61	*0.7*	161	*1.0*	13	*1.0*	160	*1.3*
Paternal education								
Did not finish secondary education	2420	*27.4*	4266	*27.5*	349	*25.7*	3847	*30.9*

	ALL (12 studies)				AML (10 studies)			
	Case (n= 8835)		Control[a] (n = 15486)		Case (n= 1357)		Control[b] (n= 12443)	
	n	%	n	%	n	%	n	%
Completed secondary education	3341	*37.8*	5400	*34.9*	559	*41.2*	4095	*32.9*
Tertiary education	2579	*29.2*	4757	*30.7*	348	*25.6*	3708	*29.8*
Missing	495	*5.6*	1063	*6.9*	101	*7.4*	793	*6.4*
Maternal occupational pesticide exposure data during pregnancy available	8236	*93.2*	14850	*95.9*	1329	*97.9*	12141	*97.6*
Paternal occupational pesticide exposure data around conception available	8169	*92.5*	14201	*91.7*	1231	*90.7*	11383	*91.5*
Occupational pesticide exposure data available for both parents	7679	*86.9*	13704	*88.5*	1210	*89.2*	11184	*89.9*

[a] Includes controls from all studies with ALL cases (that is, all studies except US, COG-E15).

[b] Includes controls from all studies with AML cases (that is, all studies except Australia, Aus-ALL, Canada, Quebec and US, US, COG-E14)).

[c] Age groups are based on the child's age at the censoring date. For case, this was the date at diagnosis and for controls, it was the date that the study investigators nominated (either the date of recruitment or the date of the questionnaire return).

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Table 3

Summary ORs from Meta-analyses of parental occupational exposures to pesticides and the risk of leukaemia in the offspring

Leukemia Type	Mother during pregnancy					Father around conception				
	Study N	Total N Case/control	Summary OR (95% CI)[a, b]	I^2	Maximum percentage difference when individual studies removed in turn	Study n	Total N Case/control	Summary OR (95% CI)[a, b]	I^2	Maximum percentage difference when individual studies removed in turn
ALL	12	8236/14850	1.03 (0.77, 1.38)	11.2	8.4	12	8157/14201	1.22 (0.94, 1.58)	68.7	7.8
B Cell	12	6529/14850	1.04 (0.78, 1.38)	0.0	7.7	12	6449/14201	1.14 (0.85, 1.54)	71.4	10.1
T Cell	7[c]	526/10726	1.66 (0.88, 3.14)	0.0	25.8	10[c]	784/13681	1.86 (1.34, 2.58)	5.4	10.3
AML	5[c]	895/5428	2.69 (1.49, 4.86)	0.0	23.9	8[c]	1184/10863	1.12 (0.72, 1.70)	32.2	10.8

[a] The random effects model was used to calculate the summary OR

[b] OR comparing Category 1 (High likelihood of pesticide exposure) to Reference Category 4 (No or minimal likelihood of pesticide exposure)

[c] Studies without any cases in Category 1 (High likelihood of pesticide exposure) were not included in the meta-analysis.

Table 4

Pooled OR (95% CI) for the association between parental occupational exposures to pesticides and the risk of leukaemia in the offspring: Overall and by subgroups

	Maternal exposures during pregnancy			Paternal exposures around conception		
	Total N Case/Controls	**% in High likelihood of exposure category**	**OR[a,b] (95% CI)**	**Total N Case/Controls**	**% in High likelihood of exposure category**	**OR[b,c] (95% CI)**
1. ALL						
Overall	8236/14850	1.3/1.1	1.01 (0.78, 1.30)	8169/14201	5.5/4.3	1.20 (1.06, 1.38)
Age at diagnosis						
0–1 years	880/2192	1.1/0.6	1.20 (0.50, 2.88)	895/2156	4.8/3.3	1.18 (0.77, 1.79)
2–4 years	3832/5906	0.9/1.0	0.74 (0.48, 1.14)	3842/5666	4.9/4.5	1.02 (0.83, 1.24)
5 or more years	3524/6752	1.8/1.2	1.18 (0.84, 1.67)	3432/6379	6.4/4.3	1.38 (1.13, 1.67)
			Interaction *p* value = 0.33			Interaction *p* value = 0.07
Immunophenotype						
B-lineage cases	6529/14850	1.3/1.1	1.00 (0.76, 1.31)	6448/14201	5.6/4.3	1.19(1.03, 1.37)
T-lineage cases	841/14850	1.4/1.1	1.07 (0.58, 1.97)	818/14201	6.1/4.3	1.42 (1.04, 1.94)
Type of occupational assessment						
Expert assessment[d]	1755/2676	2.1/1.5	0.90 (0.57, 1.43)	1672/2510	7.0/4.8	1.24 (0.95, 1.63)
Assessment based on coded job titles[e]	6384/11871	1.1/0.9	1.06 (0.78, 1.45)	6413/11407	5.0/3.8	1.22 (1.05, 1.43)
2. AML						
Overall	1329/12141	1.8/0.8	1.94 (1.19, 3.18)	1231/11383	4.5/4.0	0.91 (0.66,1.24)
Age at diagnosis						
Less than 5 years	627/6491	1.6/0.7	1.92(0.86, 4.28)[d]	585/6114	3.9/3.8	0.84 (0.52, 1.37)[e]
5 or more years	702/5650	2.0/1.0	1.96 (1.02, 3.77)[d]	646/5269	5.0/4.2	0.97 (0.64, 1.49)[e]
			Interaction *p* value =0.52			Interaction *p* value = 0.72
Type of occupational assessment						
Assessment not based on coded job titles[f]	569/1929	1.9/0.5	3.83 (1.29, 11.34)	511/1776	5.3/5.4	1.05 (0.62, 1.77)
Assessment based on coded job titles[g]	760/10212	1.7/0.9	1.63 (0.90, 2.98)	1201/10409	4.3/4.2	0.85 (0.62, 1.18)

[a]Adjusted for age, sex, birth year group, ethnicity, study and maternal education

[b] OR comparing Category 1 (High likelihood of pesticide exposure) to Reference Category 4 (No or minimal likelihood of pesticide exposure)

[c] Adjusted for age, sex, birth year group, ethnicity, study and paternal education

[d] Australia (Aus-ALL), Canada (Quebec), Italy(SETIL) (Agricultural pesticides only)

[e] France (ADELE & ESCALE), Greece (NARECHEM 1993–1994 & 1996–2011), Germany (GCCR), UK (UKCCS), US (COG -E15). See Table 1 for details of the Occupational coding system.

[f] Italy(SETIL) (Agricultural pesticides only), New Zealand (NZCCS), US (COG (COG-E14).

[g] France (ADELE & ESCALE), Greece (NARECHEM 1993–1994 & 1996–2011), Germany (GCCR), UK (UKCSS). See Table 1 for details of the Occupational coding system.

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