Cancer Epidemiology 58 (2019) 146–152

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Maternal prenatal exposure to environmental factors and risk of childhood acute lymphocytic leukemia: A hospital-based case-control study in China

Yiran Wang[a,1], Pan Gao[a,1], Ge Liang[a], Ningning Zhang[a], Chunmei Wang[b], Yingchao Wang[b], Luting Nie[a], Xuewei Lv[a], Wenjing Li[a], Qianqian Guo[a], Xiaowen Jiang[a], Jie Lu[a,*]

[a] Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, Zhengzhou, Henan Province, China
[b] Department of Pediatrics, The First Affiliated Hospital Of Zhengzhou University, Zhengzhou, Henan Province, China

ARTICLE INFO

Keywords:
Childhood
Acute lymphocytic leukemia
Maternal
Prenatal
Case-control study
Risk factors

ABSTRACT

Objective: To investigate an association between maternal prenatal exposure to several environmental factors and risk of childhood acute lymphocytic leukemia (ALL), and the possible interactions in the Chinese population.

Methods: 345 cases with ALL and their 1:1 age, gender, residence region matched controls aged 0–15 years were recruited from four hospitals in Henan Province from 2014 to 2016. Information was collected by interviews using a questionnaire. Unconditional logistic regression adjusted for age, gender, residence region and relevant confounders was carried out to generate the odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Our data indicate that maternal prenatal exposure to interior housing renovation (adjusted OR: 2.98, 95% CI: 1.51–5.86) or pesticides (adjusted OR: 1.48, 95% CI: 1.67–2.28) increased the risk of childhood ALL. Various subgroup analyses stratified by child's gender, age at diagnosis and other factors also supported these results. However, no interaction was detected between exposure to internal housing renovation and pesticides using an additive model. No significant links between maternal exposures to, environmental tobacco smoking (ETS), antipyretic analgesia intake, or viral infectious diseases with risk of ALL were detected.

Conclusion: Findings in our study are in line with the existing literatures, which support the hypothesis that maternal prenatal exposure to interior housing renovation and pesticides are risk factors for childhood ALL. Notably, we found no interaction between these two risk factors, these findings may inform prevention and early detection strategies.

1. Introduction

The number of newly diagnosed leukemia cases in children aged 0–15 years is about 15,000 ~ 20,000 each year in China, making it the most common cancer in children. More than 90% of the cases are acute leukemia (AL) and approximately 80% of cases of AL are acute lymphocytic leukemia (ALL) [1–4]. Childhood leukemia is assumed to be a multi-factorial disease that occurs when genetic and environmental factors interact in a multistage sequence. Even though new genetic risk factors are still likely to be discovered, only a small fraction (less than 10%) can be attributed to the influence of genetics [5,6]. It is probable that environmental, infectious and dietary exposures [7] play a significant role in the etiology of childhood leukemia.

The presence at birth of “pre-leukemic” genetic signatures combined with the young age of onset suggests that childhood leukemia occurs within two time frames, prenatal initiating events that induce some cellular changes, and postnatal genetic and epigenetic events that allow the emergence of acute disease. Several U.S. studies [8–10] using newborn blood spots showed that several translocations commonly found in leukemia were detected with clear presence of the mutations, including t(12;21) *ETV6-RUNX1*, t(8;21) *RUNX1-MTG8*, inv(16) *CBFB-MYH11*. Epidemiologic evidence suggests that peak incidence for ALL in children are 2 ~ 5 years old which implies that prenatal events caused by parental exposures to risk factors may be critical to the development of childhood leukemia.

Identifying environmental factors may inform prevention and early detection strategies. Our goal in this study was to identify the role of maternal prenatal exposures in the etiology of childhood ALL. Established studies including those from the pooled analyses and meta-analyses have investigated some exposures for childhood ALL, for

* Corresponding author at: Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, No. 100 Science Avenue, Zhengzhou City, 450001, China.
E-mail address: hanyaa800@zzu.edu.cn (J. Lu).
[1] Yiran Wang and Pan Gao contributed equally to this manuscript.

https://doi.org/10.1016/j.canep.2018.11.005
Received 29 November 2017; Received in revised form 21 September 2018; Accepted 13 November 2018
Available online 20 December 2018

example indoor environmental pollution [11–13], pesticides [14–16] and parental smoking [17,18], but little of the existing literature comes from China or other Asian countries. Meanwhile, recent studies lacked analysis of the possible interactions among environmental factors. Therefore, using a hospital-based case-control study, we sought to identify several possible maternally-related risk behaviors or environmental exposures before and during pregnancy for childhood ALL, including maternal exposure to interior housing renovation, pesticides, environmental tobacco smoking (ETS), antipyretic analgesia intake, and viral infectious diseases. We also address the possible interactions among these environmental factors.

2. Methods

2.1. Participants

We conducted a hospital-based case-control study at the College of Public Health, Zhengzhou University between May 1st, 2014 and December 31st, 2016. In this study, 357 eligible cases with childhood ALL were recruited from the First Affiliated Hospital 199 (55.7%), the Third Affiliated Hospital of Zhengzhou University 40 (11.2%), Children's Hospital of Zhengzhou 66 (18.5%) as well as Henan Cancer Hospital 52 (14.6%). Cases were contacted when they were undergoing chemotherapy at the Pediatric Hematology-Oncology Ward. Eligibility was based on a diagnosis of childhood ALL in the past 12 months by bone marrow cytology examination. The 361 hospital-based controls were selected from the same hospitals during approximately the same time (± 1 week), and frequency matched to cases on age (± 1 years), gender and residence region. To reduce the potential selection bias, controls were selected from pediatric patients among children who diagnosed with various diseases other than hematological diseases or tumors, namely, respiratory infectious diseases 123 (34.1%), digestive diseases 91 (25.2%), neurological diseases 62 (17.2%), traumatic rehabilitation exercises after fraction 46 (12.7%), and cardiovascular diseases 39 (10.8%). Our case and control eligibility criteria included: 1) resident in Henan before diagnosis/reference date for at least one year; 2) aged 0–15 years at case diagnosis or at the recruited date for controls; 3) not diagnosed with other blood system diseases or cancer; 4) not diagnosed with immune-related diseases, mental disease or severe liver disease (increased ALT > 3 times of the normal upper limit) or kidney disease (urine protein/creatinine ≥1 mg/g, creatinine or albumin/urine protein ≥ 600 mg/g); 5) not diagnosed with Down Syndrome or other congenital anomalies. The exclusion criteria for cases and controls included: 1) incomplete clinical data; 2) nonresidents of Henan province. The Ethics Committee of the Zhengzhou University approved this study, and the parents or guardians of participants signed the informed consent form before participating the study.

2.2. Data collection

A specially designed and standardized questionnaire was used to collect information on child and parental socio-demographic characteristics, child birth characteristics and environmental exposures potentially associated with childhood ALL. Trained interviewers administered the questionnaire during interviews with the children's direct guardians. We obtained information on the child's birth weight, delivery mode, and maternal and paternal age at delivery from their birth certificate cards or vaccination cards and also collected related medical data, such as age at diagnosis, the leukemia subtype, and the result of immunological examination from their medical records in the hospital. In order to address potential sources of recall bias and reporting bias in the interview, we used cue cards to facilitate the interviewers' recall of various exposures. We also set up some associated questions before and after the questionnaire to examine possible recall bias. To ensure the reliability of the information, we routinely examined the questionnaires on the survey day and checked for missing items and logical errors. When data was found to be inconsistent, we would list the numbers of the questionnaires, record names, variable names and error categories to facilitate future checks and corrections.

2.3. Data management

In this study, we evaluated five maternally-related suspected risk factors, including exposure to interior housing renovation, pesticides, ETS, antipyretic analgesia intake and viral infectious diseases. All information was self-reported by participants and restricted to the period of 6 months before and during maternal pregnancy. Interior housing renovation was elicited by the questions: "Did you make interior housing renovation or buy new furniture 6 months before or during the pregnancy?", the participants who selected "Yes" were further asked: "When did you renovate your house and when did you/your wife move into the newly renovated house?", "What materials did you use for the wall decoration or floor construction in your renovation?", "What kinds of new furniture did you buy for your house?". The response was classified as a dichotomous variable; "exposed" was assigned if the answers obtained indicated that the mother was living in the house which was renovated with one or more of the following materials [19]: fresh paint, wall paper, laminated flooring, or new furniture, as well as the move-in time was within six months of the renovation. Others were assigned as "not exposed". Exposure to pesticides was defined as mother's direct contact with insecticides or herbicides in their occupational or residential settings. The questions asked were: "Did you / your wife work regularly with pesticides along with did you / your wife work in common agricultural occupations such as farmer, ranch worker, groundskeeper, garden nursery worker, or pesticide applicator?" [20]. The questions also addressed a mothers' home pesticide use: "Did you / your wife regularly use pesticides in your home or your garden?" If the answers were "Yes", they would be followed by "What kinds of insecticides, herbicides or other chemicals did you use?" [21]. Regarding cigarette smoking, mothers were categorized as active smokers if they had smoked more than 1 cigarette per day, or as exposed to second-hand smoking if they had stayed in a smoking room more than 15 min per day for at least a year. After a preliminary analysis of the data, we found that only three mothers were self-reported active smokers, therefore, we combined the status of mother active smoking and exposure to second-hand smoking as maternal exposure to ETS, and created it as a dichotomous variable: not exposed, exposed. Antipyretic analgesics intake was defined as whether the mother had a history of taking antipyretic analgesics. Viral infectious diseases referred to whether mother had been diagnosed with rubella, measles, cytomegalovirus, toxoplasma infection, but not including common viral infections like colds and influenza.

2.4. Ascertainment of covariates

In the statistical analyses, the child-related variables, the parent-related variables, maternal age at diagnosis and educational level were considered as covariates. The child-related variables included residence region, household per capita annual income, birth order (one, two, three or more), birth weight (normal defined as 2500 g ~ 4000 g, abnormal defined as < 2500 g or > 4000 g), delivery mode, familial history of leukemia or other cancer and exposure to pesticides. The data on exposure was collected within one year before diagnosis (cases) or recruitment (controls). We grouped self-reported household per capita annual income into three levels based on the official poverty line defined by the Organization for Economic Co-operation and Development (OECD-50 limit) [22] for a low income level and the 2016 urban (≥ 25,576 Yuan per year) or rural (≥10,853 Yuan per year) per capita income in Henan Province for a high income level.

The parent-related variables included parental age at delivery (21 ~ 25, 26 ~ 30, 31 ~ 35, and > 35 years), parental educational level (middle school or below, high school, and university), paternal

exposure to pesticides and paternal heavy alcohol drinking. Information was restricted to the period of six months before pregnancy. Paternal heavy alcohol drinking was defined as a person who consumed 38 percent and above liquor, or the amount of alcohol equivalent to red wine or beer, 100 g per day, at least 3 days per week and had done so far more than six months.

2.5. Statistical analysis

Baseline information comparisons between cases and controls were conducted with a *t*-test, Wilcoxon rank-sum test or the Chi-square test. Considering that there still were nonmatching variables between cases and controls apart from age, gender, and residence region, we carried out unconditional logistic regression models to evaluate the association between maternal exposures and the risk of childhood ALL. Collinearity between potential confounding variables was examined using Spearman rank-order correlation for continuous variables or Chi-square test for category variables. We generated odds ratios (*OR*s) and 95% confidence intervals (*CI*s) after adjusting for child's age, gender, residence region, birth weight, delivery mode, household per capita annual income, familial history of leukemia and other cancer, exposure to pesticides, parental age at delivery, parental educational level, along with paternal exposure to pesticides, paternal cigarette smoking and paternal heavy alcohol drinking.

We conducted subgroup analyses stratified by the child's gender, age at diagnosis, residence region, birth weight, delivery mode and household per capita annual income in childhood ALL. We also used an additive model to test for possible biological interactions on a multiplicative scale, *OR* was calculated for each category after adjustment for covariates, the interaction effect was defined as departure from additivity of absolute effects, and excess *OR* caused by interaction. We calculated Relative Excess Risk of Interaction (*RERI*) as follows: $RERI = OR(a^+b^+)\text{-}OR(a^-b^-)\text{-}OR(a^+b^-)+1$, where $OR(a^+b^+)$ denotes *OR* among those exposed to both factors and $OR(a^-b^-)$ is used as reference category ($OR = 1.0$).

All statistical analyses were performed using IBM software SPSS (version 21, Chicago, IL, USA). All statistical tests were two-tailed and considered to be significant at P value less than 0.05.

3. Results

357 cases with childhood ALL and 361 hospital-based controls signed the informed consent to participate this study. Twelve cases were excluded because they were complicated with nephroblastoma (n = 2), hepatoblastoma (n = 2), or neuroblastoma (n = 1), or missing essential variables (n = 7). Sixteen controls were excluded with immune-related diseases (n = 7), liver disease (n = 6), kidney disease (n = 2) or mental disease (n = 1) based on our exclusion criteria. Therefore, 345 cases and 345 controls were included in the analysis.

Among these participants, the number of interviews with mothers, fathers and other guardians were 294 (85.2%), 34 (9.9%) and 17 (4.9%) in cases, and 290 (84.1%), 42 (12.2%), and 13 (3.7%) in controls.

3.1. Baseline characteristics of cases and controls

Demographic and socioeconomic characteristics of participants as well as their parents by case-control status are reported in Table 1. As only six mothers were exposed to occupational pesticides, we only present the results for home pesticides exposure. Males constituted 216 (62.6%) of cases and 205 (59.4%) of controls. The median age at diagnosis of cases and controls was 6.5 and 6.0 years old respectively, and the range of age was (2.5–15) in cases and (2.8–15) in controls. No difference in gender or age at diagnosis was observed between cases and controls (all $P > 0.05$), indicating that matching was effective. The proportion of cesarean sections in cases 104 (30.1%) was lower than

Table 1
Demographic and socioeconomic characteristics for 345 cases and 345 controls in a hospital-based study of childhood acute lymphocytic leukemia.

		Cases (%) N = 345	Controls (%) N = 345	*P*-value
Child	age at diagnosis (years old)	6.53(3.6,8.9)	6.09(3.5,8.0)	0.106
	gender			0.391
	Male	216(62.6)	205(59.4)	
	Female	129(37.4)	140(40.6)	
	residence region			0.140
	Urban	100(29.0)	118(34.2)	
	Rural	245(71.0)	227(65.8)	
	household per capita annual income			0.001
	Low	149(43.2)	60(17.4)	
	Middle	94(27.2)	51(14.8)	
	High	102(29.6)	234(67.8)	
	birth order			0.036
	one	182(52.8)	152(44.1)	
	two	115(33.3)	147(42.6)	
	three or more	48(13.9)	46(13.3)	
	birth weight(g)			0.076
	< 2500	26(7.5)	19(5.5)	
	2500 ~ 4000	278(80.6)	299(86.7)	
	> 4000	41(11.9)	27(7.8)	
	delivery mode			0.003
	Natural delivery	241(69.9)	203(58.8)	
	Cesarean section	104(30.1)	142(41.2)	
	familial history of leukemia and other cancer			0.816
	No	304(88.1)	302(87.5)	
	Yes	41(11.9)	43(12.5)	
	exposure to pesticides			0.480
	No	301(87.2)	307(89.0)	
	Yes	44(12.8)	38(11.0)	
Maternal	age at delivery(years old)			0.710
	21 ~ 25	112(32.4)	113(32.9)	
	26 ~ 30	148(42.9)	143(41.4)	
	31 ~ 35	83(24.1)	84(24.3)	
	> 35	2(0.6)	5(1.4)	
	education level			0.010
	Middle school or below	249(72.2)	221(64.1)	
	High school	76(22.0)	83(24.1)	
	University	20(5.8)	41(11.9)	
	interior housing renovation			0.001
	No	306(88.7)	330(95.7)	
	Yes	39(11.3)	15(4.3)	
	home exposure to pesticides			0.001
	No	250(72.5)	289(83.8)	
	Yes	95(27.5)	56(16.2)	
	exposure to ETS			0.105
	No	211(61.2)	190(55.1)	
	Yes	134(38.8)	155(44.9)	
	antipyretic analgesia intake			0.088
	No	293(84.9)	308(89.3)	
	Yes	52(15.1)	37(10.7)	
	viral infectious diseases			0.362
	No	341(98.8)	338(98.0)	
	Yes	4(1.2)	7(2.0)	
Paternal	age at delivery(years old)			0.921
	21 ~ 25	65(18.9)	70(20.3)	
	26 ~ 30	154(44.6)	153(44.4)	
	31 ~ 35	118(34.2)	116(33.6)	
	> 35	8(2.3)	6(1.7)	
	education level			0.001
	Middle school or below	246(71.3)	225(65.2)	
	High school	79(22.9)	70(20.3)	
	University	20(5.8)	50(14.5)	
	cigarette smoking			0.761
	No	175(50.7)	179(51.9)	
	Yes	170(49.3)	166(48.1)	
	heavy alcohol drinking			0.648
	No	163(47.2)	169(49.0)	
	Yes	182(52.8)	176(51.0)	
	exposure to pesticides			0.056

(*continued on next page*)

Table 1 (*continued*)

	Cases (%) $N = 345$	Controls (%) $N = 345$	*P*-value
No	253(73.3)	292(84.6)	
Yes	92(26.7)	53(15.4)	

Interior housing renovation (live in the newly-renovation rooms which were renovated with fresh paint, wall paper, laminated flooring, or new furniture, and the move-in time was within six months of the renovation); home exposure to pesticides (contact with insecticides or herbicides at home); exposure to ETS (mothers smoked more than 1 cigarette per day or exposure to second-hand smoking if they had stayed in a smoking room more than 15 min per day for at least a year); viral infectious diseases (rubella, measles, cytomegalovirus, toxoplasma infection-); household per capita annual income[classified based on the official poverty line defined by the Organization for Economic Co-operation and Development(OECD-50 limit) for a low income level and the 2016 urban (≥25,576 Yuan per year) or rural (≥10,853 Yuan per year) per capita income in Henan Province for a high income level].

that of controls 142 (41.2%) ($\chi^2 = 9.12$, $P = 0.003$). The level of household per capita annual income in controls was statistically significantly higher than that of the cases ($Z = 9.85$, $P = 0.001$). Birth order in cases and controls shows a significant difference ($\chi^2 = 6.646$, $P = 0.036$). Mother's education level in cases was lower than in controls ($Z = 2.59$, $P = 0.005$). All other considered characteristics tested with no difference between cases and controls (all $P > 0.05$).

3.2. Association between maternally-related exposures and the risk of childhood ALL

Table 2 showed the results from the analysis based on the cases of childhood ALL. Maternal exposures to interior housing renovation (adjusted *OR*: 2.98, 95% *CI*: 1.51–5.86, $P = 0.002$) and home exposure to pesticides (adjusted *OR*: 1.48, 95% *CI*: 1.68–2.28, $P = 0.016$) increased the risk of childhood ALL. However, no significant association was identified between maternal exposure to ETS, antipyretic analgesia intake, or viral infectious diseases and risk of childhood ALL. The subgroup analyses supported the conclusion that maternal exposure to interior housing renovation or to pesticides increased the risk of childhood ALL even after adjustment for covariates. The results were more pronounced in stratification when the gender was male, age at diagnosis was < 5 years, residence region was rural, birth weight was abnormal, delivery mode was cesarean section or household per capita annual income was low (Fig. 1, Fig. 2). The subgroup analyses did not provide evidence of effect modification by gender, age at diagnosis, residence region or other characteristics. Table 3 also showed the maternal exposure to individual specific environmental risk factors and the risk of childhood ALL. The *RERI* and 95% *CI* in childhood ALL was 2.06 (−3.52, 7.29) and indicated that no interaction was detected between maternal exposure to interior housing renovation and pesticides, based on the additive model.

Table 2
ORs and 95%CIs for maternal prenatal exposure to environmental factors and the risk of childhood acute lymphoblastic leukemia.

	Cases *n*(%)	Controls *n*(%)	Model
interior housing renovation			
No	306(88.7)	330(95.7)	1.00(ref)
Yes	39(11.3)	15(4.3)	2.98(1.51–5.86)
P-value			0.002
home exposure to pesticides			
No	250(72.5)	289(83.8)	1.00(ref)
Yes	95(27.5)	56(16.2)	1.48(1.67–2.28)
P-value			0.016
exposure to ETS			
No	211(61.2)	190(55.1)	1.00(ref)
Yes	134(38.8)	155(44.9)	0.82(0.58–1.14)
P-value			0.243
antipyretic analgesia intake			
No	293(84.9)	308(89.3)	1.00(ref)
Yes	62(15.1)	37(10.7)	1.55(0.93–2.57)
P-value			0.088
viral infectious diseases			
No	341(98.8)	338(98.0)	1.00(ref)
Yes	4(1.2)	7(2.0)	0.72(0.19–2.75)
P-value			0.636

Model: adjusted for child's age, gender, residence region, birth weight, delivery mode, household per capita annual income, familial history of leukemia or other cancer, exposure to pesticides, parental age at delivery, parental educational level, paternal exposure to pesticides, paternal cigarette smoking and paternal heavy alcohol drinking.

4. Discussion

We found that maternal prenatal exposure to interior housing renovation or maternal prenatal exposure to pesticides was associated with higher risk of childhood ALL, and our various subgroup analyses supported the results. No interaction was detected between the exposure to internal housing renovation and home exposure to pesticides. However, maternal exposures to ETS, antipyretic analgesia intake, or viral infectious diseases were not the significant risk factors for childhood ALL in this analysis.

4.1. Exposure to interior housing renovation

Interior housing renovation is very common activity in present-day China. Because most houses or apartments purchased for residence are roughcast, which they need to be renovated by constructing the floor, decorating the wall, as well as purchasing new furniture before moving in. In addition, an increasing number of people renovate their older houses. Notably, as an old custom in China, newlyweds usually buy a new house which needs to be renovated before they get married, and the new couples will have their first baby within the first few years of moving in. Thus, a large proportion of expectant parents would be exposed to the indoor environmental pollution. Our data showed that the proportions of maternal exposure to interior housing renovation during the period of 6 months before and during pregnancy in cases and controls was 11.3% and 4.3% respectively. The maternal exposure to interior housing renovation were associated with increased risk of childhood ALL (adjusted *OR*: 2.98, 95% *CI*: 1.51–5.86). For different types of house renovation, maternal individual exposure to painting (adjusted *OR*: 4.19, 95% *CI*: 2.60–6.77), flooring (adjusted *OR*: 3.13, 95% *CI*: 2.17–4.49), new furniture (adjusted *OR*: 2.98, 95% *CI*: 2.04–4.36) increased the risk of ALL (Table 3). Previous studies tended to explain the association ALL with certain chemicals [(formaldehyde, NO_2, volatile organic compounds (VOC)] or renovation materials (paint) [23]. In a China hospital-matched case-control study, Gao et al. found that higher concentrations of NO_2 (*OR*: 5.87, 95% *CI*: 2.25–15.30), and benzene (*OR*: 2.56, 95% *CI*: 1.04–6.28) caused by interior housing renovation were related to childhood AL [11]. In a Swiss census-based cohort study, Spycher et al. found maternal exposure to benzene in paints was associated with an increased risk of ALL (*OR*: 1.88, 95% *CI*: 1.16–3.04), and effects were stronger for maternal exposure during pregnancy (*OR*: 2.06, 95% *CI*: 1.51–2.81) than for preconception exposure (*OR*: 1.32, 95% *CI*: 0.84–2.08) [24]. Notably, in a pooled analysis of 8 studies from the Childhood Leukemia International Consortium (CLIC), Bailey et al. indicated that maternal exposure to home paint during the period of 1–3 months before conception (*OR*: 1.54, 95% *CI*: 1.28–1.85) or during the period of pregnancy (*OR*: 1.14, 95% *CI*: 1.04–1.25) increased the risk of ALL [12]. But, in a case-control study of incident childhood leukemia (all subtypes) diagnosed at nine pediatric oncology centers in 35 California counties from 1995 to 2008, the results found that only construction in the home

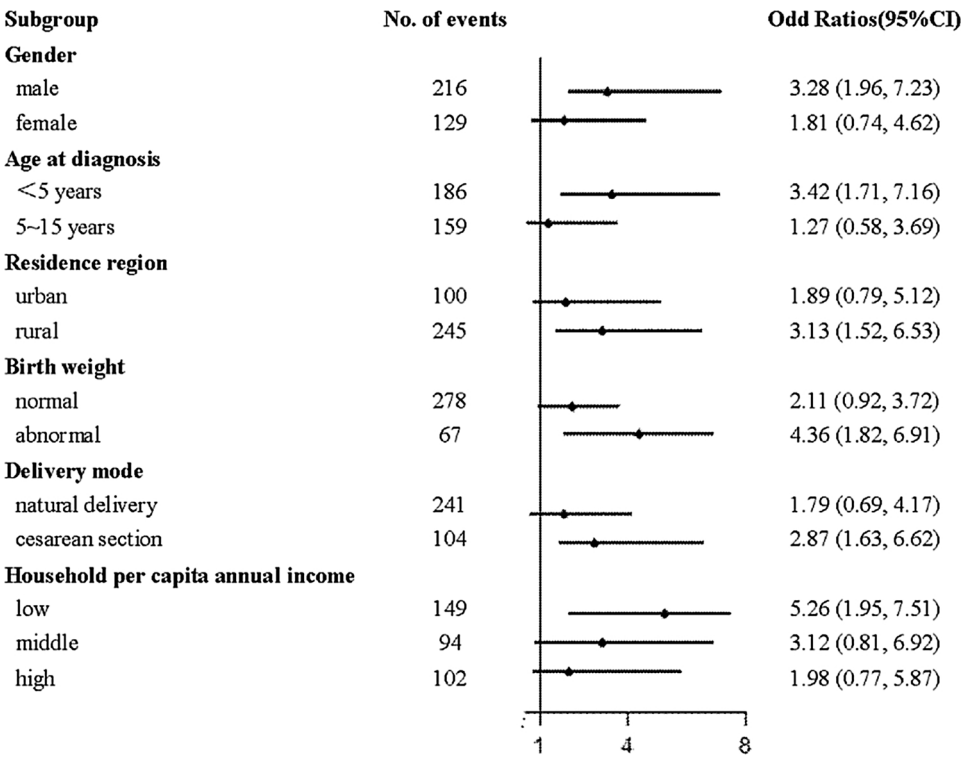

Fig. 1. Subgroup analysis of the association between maternal prenatal exposure to interior housing renovation and risk of childhood acute lymphoblastic leukemia (ALL) according to potential risk factors. (All covariates were child's familial history of leukemia and other cancer, child's exposure to pesticides, parental age at delivery, parental education level and paternal heavy alcohol drinking. The reference group was no-exposure to interior housing renovation. Horizontal lines represent 95% confidence intervals.).

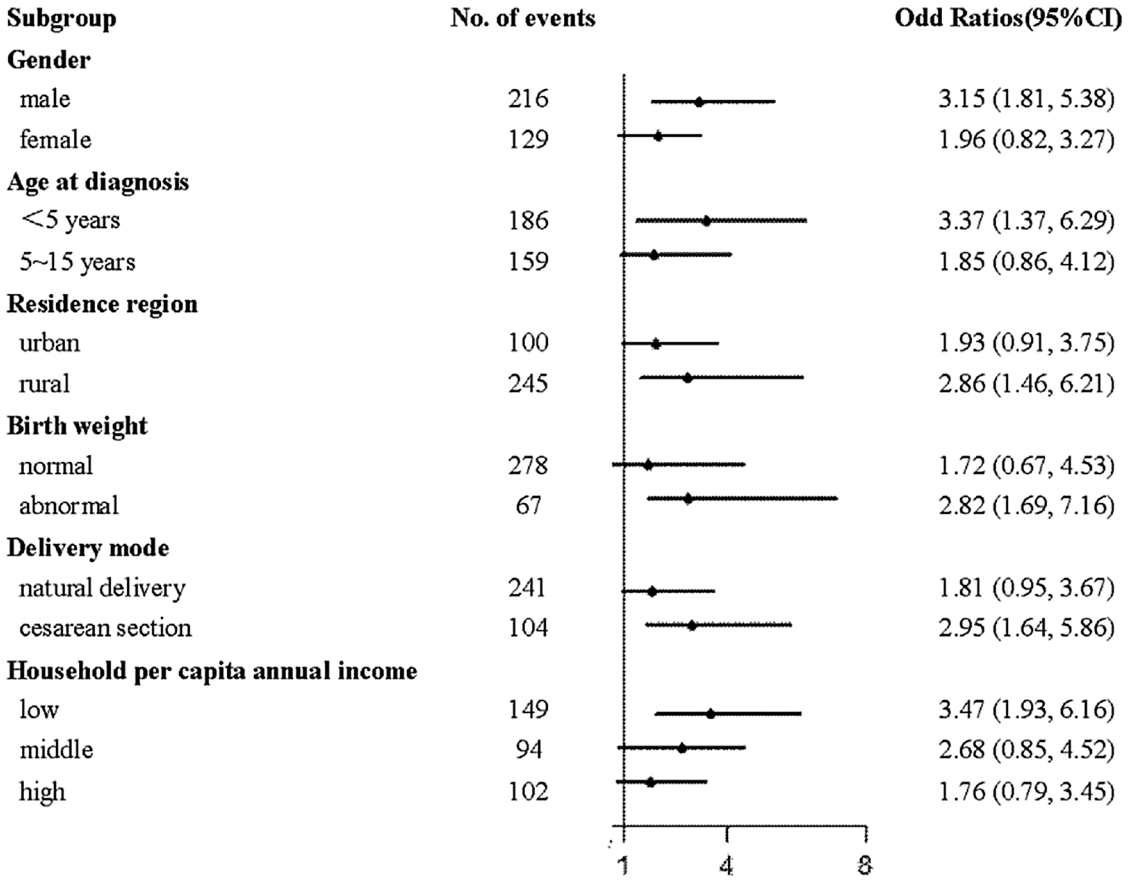

Fig. 2. Subgroup analysis of the association between maternal prenatal exposure to pesticides and risk of childhood acute lymphoblastic leukemia (ALL) according to potential risk factors. (All covariates were child's familial history of leukemia and other cancer, child's exposure to pesticides, parental age at delivery, parental education level and paternal heavy alcohol drinking. The reference group was no-exposure to pesticides. Horizontal lines represent 95% confidence intervals.).

Table 3
ORs and 95% CIs for maternal exposure to individual specific environmental factor and the risk of childhood acute lymphoblastic leukemia.

variable	Cases *n*(%)	Controls *n*(%)	Model
Interior housing renovation			
painting			
No	256(74.2)	311(90.1)	1.00(ref)
Yes	89(25.8)	34(9.9)	4.19(2.60–6.77)
P-value			0.000
flooring			
No	180(52.2)	260(75.4)	1.00(ref)
Yes	165(47.8)	85(24.6)	3.13(2.17–4.49)
P-value			0.000
new furniture			
No	71(20.6)	144(41.7)	1.00(ref)
Yes	274(79.4)	201(58.3)	2.98(2.04–4.36)
P-value			0.000
home exposure to pesticides			
insecticides			
No	149(43.2)	294(85.2)	1.00(ref)
Yes	196(56.8)	67(14.8)	7.66(5.13–11.46)
P-value			0.000
herbicides			
No	89(25.8)	215(62.3)	1.00(ref)
Yes	256(74.2)	130(37.7)	5.19(3.59–7.49)
P-value			0.000

Model: adjusted for child's age, gender, residence region, birth weight, delivery mode, household per capita annual income, familial history of leukemia or other cancer, exposure to pesticides; parental age at delivery, parental educational level, paternal exposure to pesticides, paternal cigarette smoking and paternal heavy alcohol drinking.

between birth and diagnosis was associated with a significant increase in ALL risk(*OR*: 1.52, 95% *CI* : 1.14–2.02), no other remodeling activities were detected in the main analysis [13]. Since studies used varying definition of the exposed variable, different time-windows, different control recruitment methods and adjustment for different sets of covariates, the direct comparison of ORs between studies is challenging. In this study, we used renovation activity as the tested variable unlike the previous studies. We believe that indoor environmental pollution caused by interior housing renovation is complicated, it usually inevitably contains many types of hazardous substances, such as the organic solvents benzene, formaldehyde from home paint, laminated flooring and new furniture, and other substances which cannot be identified. It is difficult to attribute the mixed effects to one or two special components. In addition, the timing of renovation is also important; a study [23] showed that the VOCs level released from building materials and solvent-based paints was variable at different renovation times, it was found with the highest levels in the newly renovated houses. Therefore, we thought it was more suitable to use "renovation activity" as a comprehensive variable to encompass the indoor pollution caused by interior housing renovation. In addition, it was more convenient to use "renovation activity" as a predictor index of risk to childhood ALL.

4.2. Exposure to pesticides

Our study indicated that maternal home exposure to pesticides was associated with increased risk of childhood ALL (adjusted *OR*: 1.48, 95% *CI*: 1.67–2.28). The terms "pesticides" cover a large, heterogeneous group of chemicals and applies in various ways, such as: insecticides used at home, on pets, or for garden crops and herbicides used as "weed killers" [14]. In this study, we defined the tested variable as the contact with pesticides (insecticides or herbicides) in residential and occupational settings, which was a general exposure that included a loosely related group of environmental exposures that shared characteristic chemical signatures. Maternal exposed to pesticides at work can also track chemicals back to homes on their shoes, clothing, and skin, potentially exposing their families, and the active ingredients of each chemical in pesticides may have different mutagenic, carcinogenic or immunotoxic properties. In our data, as only six mothers were exposed to occupational pesticides, so we just analyzed for home exposure to pesticides. The result indicated that both insecticides and herbicides increased the risk of ALL. Our finding was consistent with the previous literatures, especially for those using pooled analyses [15,16,25], supported that there is likely to be a positive association between pesticide exposure and childhood ALL. Bailey et al. carried out a pooled analysis of 12 studies from CLIC, in which they found that *OR* for ALL associated with home pesticide exposure shortly before conception and during pregnancy were 1.39(95% *CI*: 1.25–1.55) (using 2785 cases, 3635 controls), and 1.43(95% *CI*:1.32- 1.54) (using 5055 cases, 7370 controls) [25]. The systematic review and meta-analysis made by Turner MC et al. [16] revealed that the exposure to unspecified residential pesticides during pregnancy held a significant and positive association with childhood ALL when combining results from 11 studies (*OR* = 2.04; 95% *CI*, 1.54–2.68), indoor use of unspecified pesticides (*OR* = 1.86; 95% *CI*, 1.25–2.77); the exposure to residential insecticides during pregnancy was associated with a significant increase in risk of childhood ALL when combining the results from eight studies (*OR* = 2.14; 95% *CI*, 1.83–2.50). Another systematic review and meta-analysis combining 13 case-control studies made by Van Maele-Fabry G [15] gave the similar results, in which they revealed that exposure during and after pregnancy was positively associated with childhood leukemia, with the strongest risk for exposure during pregnancy (*mRR*: 2.19, 95% *CI*: 1.92–2.50). All these findings support the assumption that residential pesticide exposure may be a contributing risk factor for childhood ALL. But, as a retrospective study, harmful substances released by maternal home exposure to pesticides are complex and changeable, it is hard to specify a single or multiple chemicals as causative agents, so there was concern that assessment of exposure lacked a recognized quantitative standard.

No interaction between maternal prenatal exposure to interior housing renovation and pesticides was found in this study, and when multiple risk factors interact with childhood ALL, the effect is equivalent to the sum of the independent effects of the two factors.

4.3. Exposure to ETS, antipyretic analgesia intake, viral infectious diseases

Maternal prenatal exposure to cigarette smoking is also a suspected risk factor and has received a lot of attention. Our study took ETS as the tested variable and did not support the hypothesis that maternal prenatal exposure to ETS increases the risk of childhood ALL. In a French national registry-based case-control study, Rudant et al. reported that they did not observe an association between maternal smoking and childhood AL (*OR*: 1.2, 95% *CI*: 0.9–1.5) [17]. However, in a Brazil hospital-based multicenter case-control study, Ferreira et al. found that in mothers who reported to have smoked 20 or more cigarettes during pregnancy, an adjusted *OR* = 5.28 (95% *CI*: 1.40–19.95) for ALL was observed [18]. The inconsistencies in findings on maternal exposure to ETS and risk of childhood leukemia might be related to the comparability of cases. We did not find an association between maternal exposure to antipyretic analgesia intake, or viral infectious diseases with an increased incidence of childhood ALL. In a Brazil hospital-based case-control study, Couto et al. showed that acetaminophen use during the first trimester of pregnancy showed an *OR* = 0.39 (95% *CI*: 0.17–0.93) for ALL [26]. In an Indian case-control study, Kumar et al. concluded that the difference was not statically significant between history of infection (*P* = 0.696) and childhood AL during pregnancy [27]. Since related studies are rare, further validation for these factors is warranted in larger studies or in pooled analyses.

The main strengths of the present study are the relatively large sample size and adjustment for various covariates in the analysis. But several limitations of the study should be noted. Firstly, in an interview-

based case-control study, the median age of cases, controls in our study was 6.5 and 6.0 years old respectively, leaving a long time interval between the exposure period and the interview. Case groups may be more prone to reporting excessive environmental exposures association with diseases, so recall bias and reporting bias are always a concern. Secondly, as a hospital-based case-control study, the introduction of selection and information biases cannot be disregarded. The selected controls were recruited among children of similar ages to cases who were diagnosed with various diseases. However, despite the cases and controls being of matching age, gender and residence region, some factors like caesarean section, education level, household per capita annual income could still differ between groups, leading to unrecognized selection bias. In addition, the high proportion of caesarean section also reflected the higher SES status, namely that people can alleviate concern for household and medical expenses when income and education is relatively good, and have greater access to get more medical resources. It is very hard to balance all these factors in the process of recruiting cases and controls. In addition, according to the design of the study, the controls were hospital-based and not selected randomly from the population, raising the problem of under-representation, and could lead to a higher proportion of participants reporting exposure to some risk factors, we have designed to use an unconditional logistic regression model to adjust for some important covariates, including socio-economic status (SES), to decrease the effects of selection bias. Thirdly, by virtue of its case-control design, we had to rely on questionnaires to retrospectively obtain environmental exposure data rather than biomarkers, the concern exposure lacked an established quantitative standard. We also lacked details on the time-period of exposure and the frequency and dose of exposure data. To harmonize the data, a crude measure of exposure was developed in our study. In particular, given the retrospective nature of the assessment procedure and the uncertainties of the underlying data sources, the assignments of jobs to specific exposure groups necessarily involved subjective judgment, and analysis based on exposure groups might have been affected by misclassification. Finally, because of the large number of combinations of risk factors by childhood leukemia subtypes, some of the risk estimates were based on small numbers and some might be statistically significant simply by chance alone. Our findings need to be replicated by other investigations in the future with larger sample sizes.

5. Conclusions

In conclusion, findings in our study are in line with the existing literatures, which support the hypothesis that maternal prenatal exposure to interior housing renovation and pesticides are risk factors for childhood ALL. Notably, we found no interaction between these two risk factors. Future validation of these findings is warranted in larger case-control studies in different countries and in pooled analyses, especially in cohort studies, and will help in inform prevention and early detection strategies for childhood AL.

Author contributions

Jie Lu contributed to the conception and design, review and revision of the manuscript, as well as study supervision. Yiran Wang, Pan Gao contributed equally, including the collection, analysis and interpretation of data, writing, review, and revision of the manuscript. Ge Liang and Ningning Zhang contributed to the collection of data, part of the statistical analysis. Chunmei Wang, Yingchao Wang contributed to the recruitment and management of participants, and quality control. Luting Nie, Xuewei Lv, Wenjing Li, Qianqian Guo and Xiaowen Jiang contributed to the management of participants, and collection of the data. All authors read and approved the final manuscript. We are deeply grateful to all participants who took part in this study.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

This research was supported by the Department of Science and Technology (No. 162300410239; No. 172102310194) and the Department of Education (No. 18B330003). Thank you.

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