Original Article

# Environmental Risk Factors for Pediatric Acute Leukemia: Methodology and Early Findings

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## Abstract

**Background:** Acute leukemia is the most common type of malignancy in children, and no major environmental risk factors have been identified relating to its pathogenesis. This study has been conducted with the aim for identifying risk factors associated with this disease. **Methods:** This study was conducted in 2016–2020 among children aged <15 years residing in Isfahan Province, Iran. Children with newly diagnosed Acute lymphoblastic leukemia, including Acute myeloid leukemia (ALL and AML) were considered a case group. The control group was selected among children hospitalized in orthopedic and surgery wards in the same region. Demographic data, parental occupational exposures and educational level, maternal obstetric history, type of feeding during infancy and parental smoking habits, exposure to pesticides, and hydrocarbons besides dietary habits (using a food frequency questionnaire) were evaluated. **Results:** Overall, 497 children (195 cases and 302 controls) completed the survey. In the initial analysis, there was no significant difference between case and control groups about type of milk feeding ($P$ = 0.34) or parental age ($P$ = 0.56); however, an association between mothers' education and increased risk for ALL was observed ($P$ = 0.02). **Conclusions:** The results of this study can be helpful in better understanding the environmental risk factors involved in the incidence of acute leukemia. Future publications based on the analysis of the database created in the present study can lead to recognizing these factors. In addition, evaluating the effect of these factors on treatment outcomes is an important step in reducing the burden of the disease.

**Keywords:** *Epidemiology, hematology, leukemia, pediatrics*

## Introduction

Acute leukemia is the most prevalent pediatric cancer globally and in Iran, comprising around 30% of all malignancies diagnosed in children younger than 15 years old worldwide.[1,2] During childhood, acute lymphocytic leukemia (ALL) is more common than acute myelogenous leukemia (AML) and accounts for approximately three-quarters of all childhood leukemia, which accounts for about 12% of all leukemias. The incidence of ALL children is three to four cases per 100,000 per year in children younger than 15 years, with a peak incidence at approximately 2–5 years of age.[3] The incidence of childhood AML is 7.6 per 1,000,000[4] with a peak incidence in infants.[5] The overall incidence of childhood leukemia has been rising for decades.[4,6,7]

With genetic predispositions having been associated with only 5% of cases, there is strong evidence indicating the important role of environmental factors in the etiology of acute leukemia.[3,8,9] In the past two decades, several studies have focused on evaluating possible associations between childhood acute leukemia and lifestyle, infectious, or environmental factors. Ionizing radiation has been suggested as an environmental factor contributing to the development of childhood acute leukemia. The degree of associated risk is related to the dose of radiation, the duration of exposure, and the age at the time of exposure.[3,6,10] Studies have investigated the association between paternal ionizing radiation (before conception) and childhood leukemia[11] as well as the relationship between in utero exposure

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**How to cite this article:** Nematollahi P, Arabi S, Mansourian M, Yousefian S, Moafi A, Mostafavi SN, *et al.* Environmental risk factors for pediatric acute leukemia: Methodology and early findings. Int J Prev Med 2023;14:103.

**Access this article online**

**Website:** www.ijpvmjournal.net/www.ijpm.ir

**DOI:** 10.4103/ijpvm.ijpvm_348_22

**Quick Response Code:**

with diagnostic X-ray and childhood leukemia.[12] Some studies have confirmed an increased risk for childhood leukemia in patients who had received radiotherapy for benign diseases[3] while others have not detected such a risk.[13] A meta-analysis study has found non-ionizing electromagnetic field (EMF) to be linked with childhood cancer.[14] Hydrocarbons are organic compounds that are routinely found in many household and industrial products. The most widely recognized hydrocarbon is benzene, which is a known human carcinogen and has a documented relationship with leukemia, particularly AML.[3] One of the sources of benzene is traffic-related air pollution, the relationship of which with childhood AML has been observed in a study by Houot *et al*.[15]

It has also been observed that exposure to second-hand cigarette smoke of the parents also has associations with childhood leukemia[3] as well as prognostic value in ALL patients.[16] Pesticide,[17] chemicals,[18] parental occupation,[19] and residential proximity to gasoline stations or roads with heavy traffic[20,21] have been weakly or controversially associated with childhood leukemia. Studies have also shown that indoor chemical air pollution creates a two-fold increase in ALL when comparing those with the highest and lowest amounts of pollution.[22] Furthermore, a number of researchers have found an association between children's diet and the risk of pediatric cancer.[23,24] It is of note that similar studies have been conducted in Iran as well, concluding that exposure to pesticides, EMF, and vitamin D deficiency could be associated with pediatric leukemia.[25-27]

Considering that acute leukemia is the most common malignancy in children and no comprehensive study has been conducted on its environmental risk factors in our region, we decided to evaluate several potential demographic and environmental risk factors of pediatric acute leukemia, including lifestyle, nutritional factors, and infectious disease in a hospital-based study.

## Methodology

### Study design and ethics

This main body of our projects consists of a case-control study with a number of variables followed as a prospective cohort study, which was conducted between 2016 and 2020 among children aged <15 years in Isfahan province, Iran. Two trained interviewers from Omid hospital's healthcare staff were responsible for identifying and recruiting the cases and controls, interviewing them, and following up on the blood, urine, and other laboratory tests. They also interviewed one of each subject's parents in a structured interview using a designed checklist focused on gathering the necessary data in accordance with the aims of the study (explained in detail in the following "data collection" section). All cases and controls were interviewed in the hospital in a peaceful environment, with questions read to parents using simple vocabulary and documented exactly by the interviewer. The process was supervised and controlled by the project principal investigator thoroughly, correcting and providing necessary feedback when needed. Through the specific computer program designed for the purposes of this project, to gather data with more accuracy and efficacy, all the patients' information was entered in the checklist using personal computers and then extracted to the database of the application.

In addition, we intend to investigate the effect of several quantitatively measured environmental factors on patient survival and disease relapse. After induction therapy, when complete remission was achieved, the cases will be followed up for at least 24-month observation. The decision on the outcome will be based upon the relapse of the central nervous system, bone marrow, testicle, and death. A schematic representation of the current study is shown in Figure 1.

Study protocols were reviewed and approved by the Research and Ethics Council of Isfahan University of Medical Sciences (Project Number: 196087, The ethics code IR.MUI.REC.1396.1.087). After a complete explanation of the study objectives and protocols, written informed consent and verbal consent were obtained from the parents and children, respectively.

### Population

The cases were chosen from children recently diagnosed with childhood acute leukemia who had been referred

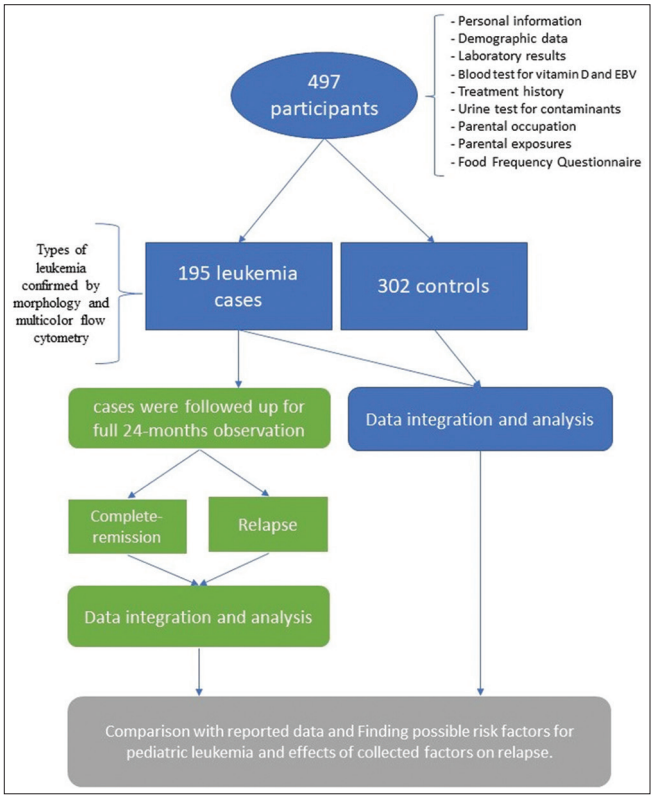


**Figure 1: Schematic representation of the current study**

to Omid Hospital, affiliated with Isfahan University of Medical Sciences. Inclusion criteria for participation in the study were: age less than 15 years, a new and definite diagnosis of acute leukemia confirmed by morphology and multicolor flow cytometry in the case group, and having informed consent for participation in the study. The control group was randomly selected among children hospitalized in the orthopedic or surgery wards of the Imam Hussein pediatric hospital, also located in Isfahan and affiliated with Isfahan University of Medical Sciences, during the same period and adjusted for age.

Exclusion criteria included refusal to participate, participant death before blood and urine sampling in the case group, patients who received any blood product before blood and urine sampling, stepchildren (due to the unavailability of information about peripartum and infancy), and known cases of genetic predisposition to hematologic malignancies.

### Data collection

Data were gathered by trained hospital staff under the supervision of the primary investigator, as mentioned, using a checklist and laboratory tests. The checklist included two parts. first being designed based on previously correlated demographic data and pediatric acute leukemia environmental risk factors, including those with more questionable and controversial evidence. The second part was a validated semi-quantitative food frequency questionnaire (FFQ) containing 168 food items and was used to assess usual dietary intake over the past year. The first part of the checklist included: demographic data (including age, gender, weight, height, birth weight, and parental age); parental occupational exposures (and risk stratification based on exposures to chemicals, EMFs, and ionizing radiation); parental educational level; maternal obstetric history (including histories of abortion, infertility, and method of delivery); type of feeding during infancy; and parental smoking habits. In addition, exposure to infection (such as season of birth and kindergarten attendance) and ionizing radiation (using the history of acute conditions requiring diagnostic imaging) as well as exposure to pesticides and hydrocarbons/benzene (evaluated using both urine sample analysis and proximity to agricultural farms and gas stations using Google Maps) were also evaluated.

As for the second part, a validated semi-quantitative FFQ containing 168 food items was used to assess usual dietary intake over the past year. For each food item, participants answered how frequently they consumed the food in the past year, and the portion sizes for food items were determined according to the most commonly consumed portion size for each food item among the Iranian general population. Then, foods were converted into their ingredients, and their amounts were calculated into grams per day. The Nutritionist 4 (Version 7; N-squared computing, OR USA) software (NUT 4), which was modified for Iranian foods, was used to calculate the individual composition in energy, macronutrients, and micronutrients of the included foods with focus on possible dietary risk factors of pediatric acute leukemia based on literature. Using an excel file designed with N4 software, the nutrients amount related to each participant were measured.

### Laboratory measurements

In terms of laboratory data, 6 mL of venous blood was drawn before receiving any blood product or treatment. All serum samples were evaluated for 25(OH) Vitamin D3 and Epstein-Barr virus (EBV) antibody (anti-EBV-CA IgG) assay at the Clinical Chemistry Laboratory of Omid Hospital.

The Euroimmun anti-EBV-CA ELISA (IgG) kit (EUROIMMUN Medizinische Labordiagnostika AG) was used for the quantitative determination of IgG antibodies to EBV (recombinant) viral capsid antigen (EBV-VCA IgG) in human serum by indirect enzyme immunoassay. Moreover, 25(OH)D3 was measured via high performance liquid chromatography based on manufacturing instruction (©RECIPE-Chemicals GmbH).

Furthermore, 25 mL urine samples were collected from cases and controls during hospitalization for urine creatinine, benzene metabolites, and organochlorine pesticides to be measured. Benzene metabolites and organochlorine pesticides were analyzed by gas chromatography-mass spectrometer based on manufacturing instructions. Reagents including: trans, trans-Muconic Acid (tt-MA) and N-Methyl-N-(Trimethylsilyl) trifluoroacetamide (MSTFA) were purchased from Sigma-Aldrich, USA and methanol, tetrahydrofuran (THF), chloroform, and hydrochloric acid were purchased from Merck, Germany.

### Statistical analysis and bias

Continuous variables were tested for normality with the Kolmogorov–Smirnov test. Mean and standard deviations (SD) were calculated for normally distributed variables. Median and interquartile ranges were analyzed for non-normal variables. The number/percent of participants for each categorical variable was calculated. The Chi-square tests examined the significance of differences between groups. Various primary risk factors were compared between cases and controls by parametric or non-parametric two independent groups to find any significant association with leukemia. *P* value less than 0.05 was considered significant. The data were analyzed with SPSS software (version 24:0).

## Results

Overall, 497 children under 15-year-old completed the survey (195 cases and 302 controls; participation rate: 98%). The recruited individuals consisted of 172 (34.6%) girls and 325 (65.4%) boys. The mean age of participants

was 60.59 (±43.43) months in the case group and 86.05 months (±47.03) in the control group. It should be noted that among the case group, 177 (90.76%) subjects were diagnosed with ALL and 18 (9.23%) with AML. Table 1 shows detailed demographic data, including birth weight, parents' age, and other aforementioned variables. In the initial analysis, there was no significant difference between the case and control groups about type of milk feeding ($P$ = 0.34) and parental age ($P$ = 0.56); however, an association between mothers› education and increased risk for ALL was observed ($P$ = 0.02).

## Discussion

Acute lymphoblastic leukemia is the most common malignant disease in children (1). This study has been conducted with the aim of identifying of risk factors associated with this disease. The environmental risk factors we evaluate in this article include some of the more researched as well as controversial factors, including infectious agents, ionizing and nonionizing radiation, chemicals, pesticides, passive smoking, nutrition, and demographic variables.

### Previous experiences

Current evidence suggests that pediatric leukemias have multifactorial etiologies; however, epidemiologic associations of 90% of cases remain opaque.[28] The investigation of pediatric leukemia requires evaluating various factors in conjugation with one another to reduce confounding factors. Up until now, investigations of environmental factors on leukemia have been limited to a few factors at a time. In some of the previous studies, childhood ALL was more common in urban areas than in rural ones,[29] associated mainly with higher traffic pollution and proximity to industrial centers.[30] In contrast with previously published findings in Taiwan, Australia, Greece, Sweden, and the United States, studies in the United Kingdom revealed a higher incidence of childhood ALL in rural areas,[29] explained by working in farming and thus greater childhood exposure to pesticides in rural areas.[30] The incidence of ALL among white boys aged 0–4 years in rural areas was 29% lower than among their urban counterparts; however, such a rural-urban gradient was not detected among white girls.[29] In the current study, the distribution of patients in rural and urban areas was examined, and there was no rural–urban gradient with respect to ALL incidence.

A recent meta-analysis of 18 studies found a high risk of ALL in those with a birth weight of over 4000 grams. In addition, the risk increased 14% for each 1000 grams increase in birth weight.[31]

**Table 1: Characteristics of case and control subjects**

| Characteristics | Case ($N$=195) $N$ or Mean±SD (%) | Control ($N$=302) $N$ or Mean±SD (%) | $P$ |
|---|---|---|---|
| Male, N (%) | 115 (58%) | 210 (69%) | 0.01 |
| Age, Months (Mean±SD) | 60.59±43.43 | 86.05±47.03 | 0.08 |
| Height, cm (Mean±SD) | 108.73±30.01 | 119.28±25.24 | 0.001 |
| Body mass index, kg/m$^2$ (Mean±SD) | 24.27±10.87 | 20.01±5.25 | 0.27 |
| Breastfeeding pattern | | | |
| Exclusive breastfeeding | 163 (83%) | 239 (79%) | 0.34 |
| Non-exclusive breast milk feeding | 21 (11%) | 35 (11%) | |
| Pure milk powder | 11 (6%) | 28 (10%) | |
| Living in city, $N$ (%) | 169 (86%) | 276 (91%) | 0.44 |
| Birth weight, g (Mean±SD) | 3210.91±754.38 | 2995.30±573.35 | 0.05 |
| Maternal age, years (Mean±SD) | 27.82±4.80 | 27.48±5.48 | 0.81 |
| paternal age, years (Mean±SD) | 32.34±5.35 | 32.02±5.68 | 0.56 |
| Leukemia types | | | |
| ALL $n$ (%) | 177 (90.76%) | | |
| AML $n$ (%) | 18 (9.23%) | | |
| Mother's occupation | | | 0.02 |
| House wife, $N$ (%) | 157 (80.7%) | 258 (85.3%) | |
| Workers, $N$ (%) | 38 (19.3%) | 44 (14.7%) | |
| Maternal education | | | 0.02 |
| Illiterate, $N$ (%) | 9 (4.9%) | 4 (1.3%) | |
| Primary school, $N$ (%) | 15 (7.9%) | 10 (3.4%) | |
| Diploma, $N$ (%) | 120 (61.7%) | 186 (61.7%) | |
| University Degree, $N$ (%) | 51 (25.5%) | 102 (33.6%) | |
| Father's occupation | | | 0.34 |
| High risk, $N$ (%) | 37 (19%) | 64 (21%) | |
| Low risk, $N$ (%) | 64 (21%) | 238 (79%) | |

Researchers believe the association to be a result of the high rate of cell proliferation, leading to an increased risk of malignant transformation.[32] Furthermore, the Childhood Leukemia International Consortium has recently done a pooled analysis of case-control studies, showing that accelerated fetal growth is associated with an increased risk of ALL.[33] However, we did not reach such an association, similar to what was described by other investigators.

Some studies revealed older maternal age as a risk factor for ALL, likely due to the gametes' long-term exposure to environmental agents.[33,34] Older paternal age was also associated with increased risk for childhood ALL and was mostly observed among children aged 1–5 years.[34,35] A meta-analysis using primary data from other studies confirmed the increased risk for childhood ALL with advancing paternal age, but not with maternal age.[34] Notably, such an association was not observed for AML.[36] Our study does not support the existence of a link between advanced maternal or paternal age with the risk of childhood leukemia.

The association between the maternal education rate and the risk of ALL is also a matter of controversy. Some studies have been unable to detect a significant difference between the mother's education and the risk of ALL,[32] while a recent study that analyzed ALL and maternal education in Egyptian children observed an association between a high educational level and ALL risk.[33] We found an association between mothers' education and increased risk for ALL development when mothers had an education under the level of Diploma (Illiterate or primary school) and decreased risk in those with a university level education. Hence, we are of the opinion that maternal educations can be used as a proxy variable for socioeconomic indicator level and might reflect the social environment experienced by participants.

In our study, like many others, parental occupational exposure has been established as a cause of childhood leukemia.[37] Exposure classification is very critical, with the exposures being caused by specific physical or chemical agents in the workplace that reach the parent.[37] In our study, an increased risk of ALL was observed in children whose mothers worked a job outside their homes compared to those who had housewife mothers. On the contrary, for those children who had fathers with a job, the risk was lower in comparison with participants with unemployed fathers. To explain such an observation, we could suggest that mothers' occupational effects can be related to exposures, but the paternal occupational effect is probably confounded by socioeconomic level. Notably, positive associations have been observed with maternal employment in specific jobs, such as teachers and cleaners.[38] Maternal exposures to occupational hazards were addressed in rather few studies, primarily because of the rarity of situations in which mothers had to work in potentially hazardous workplaces.[37] Corresponding positive associations with paternal jobs were reported in clerks, farmers, and employees in office equipment production.[38] Hemminki *et al*.[39] found a higher total cancer risk associated with having parents working as a pharmacist, farmer, baker, or in the food industry. With regards to vitamin D, children with cancer may be at increased risk of vitamin D deficiency due to side effects that are induced by both the disease and various treatments.[40] The prevalence of 25(OH)D deficiency and insufficiency in children diagnosed with hematological malignancies was 24% and 39.5%, respectively.[41]

Therefore, based on the cited studies, various environmental and genetic factors can be associated with the prevalence of pediatric hematological malignancies. It is of note that in the current study, all the environmental factors mentioned in the previous studies were examined together as much as possible. Moreover, we decided to evaluate the possible prognostic value of said factors on relapse and survival amongst children with ALL and AML. It could be possible that the exogenous factors will be used alongside the known risk factors to aid prognostic models.[42]

While we provide a vast amount of information on environmental factors, there are limitations to this study. First, the current study is a single institution study, which could lead to a selection bias. Furthermore, due to limited access to genetic tests as well as financial constraints, genetic evaluation was not performed in the present study.

## Our approach

Acute leukemia is the most frequent malignancy in childhood. Despite many advances in the treatment of childhood leukemia, its etiology remains indeterminate. As a result, identifying risk factors for childhood leukemia (e.g. environmental, genetic, infectious) is critical in the path to reducing the total burden of the disease. Some environmental risk factors, including exposure to benzene and ionizing radiation, are proven to have strong associations with the development of childhood acute leukemia (38). In the present study, we tried to examine a plethora of variables likely to affect the incidence of leukemia in children. Examining various factors together makes it possible to limit the influence of confounding factors. The major strengths of this study are the large sample size and the nationwide design of the study, which ensure the representativeness of the findings. Additionally, high-quality control throughout the process of data collection was the other strength of this study.

## What can we expect in the future

The etiology of acute leukemia is not fully determined, and in the majority of those diagnosed, no definite cause can be ascertained. This study, besides those with similar aims, can determine probable environmental risk factors for acute leukemia, which might, in the future, enable us to utilize

efficacious and efficient changes in lifestyle as a route to decrease the incidence of the disease. We are of the opinion that determining the exogenous factors of acute leukemia in pediatrics could be helpful in reducing its incidence. Future publications based on the analysis of the database created in the present study can lead to recognizing these factors. In addition, evaluating the effect of these factors on treatment outcomes is an important step in reducing the burden of the disease.

## Summary

In the current study, potential risk factors and their relationship with the incidence of childhood acute leukemia were investigated. Our approach covers major topics of importance such as infectious agents, ionizing and non-ionizing radiation, chemicals, pesticides, passive smoking, nutrition, and demographic variations. The results of our study can be helpful in better understanding the environmental risk factors involved in the incidence of acute leukemia.

### Availability of data and materials

The data sets used and analyzed during the current study are not publicly available. They are available from the corresponding author on reasonable request.

### Financial support and sponsorship

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors. This research is funded by the Isfahan University of Medical Sciences.

### Conflicts of interest

There are no conflicts of interest.

**Received:** 19 Oct 22 **Accepted:** 16 Feb 23
**Published:** 28 Aug 23

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