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REVIEW

Association Between Petroleum Compounds Exposure and Risk of Childhood Leukemia: A Systematic Review

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Abstract: Childhood leukemia remains a critical public health concern, necessitating comprehensive evaluations of environmental risk factors. This systematic review aims to evaluate the epidemiological evidence regarding the relationship between combined oil exposure during pregnancy and childhood and an increased risk of childhood leukemia, thereby contributing to improved overall childhood health. The review focused on children diagnosed with leukemia. Following the guidelines set forth by the Cochrane Handbook for Systematic Reviews of Interventions' instructions, we conducted a systematic review. Three databases (PubMed, Google Scholar, and Medline) were thoroughly searched to find research that was up to May 31, 2025. Two independent reviewers screened the literature by using Covidence software. The methodological quality and potential for bias in each included case-control and cohort study were systematically evaluated using the Quality Assessment Tool integrated within Covidence software. We assessed the overall quality of evidence using AMSTAR 2, a widely used instrument for critically appraising systematic reviews. In total, 13 studies were included in this review: 11 case-control and 2 cohort studies with an overall sample size of 2,808,870 individuals. Four studies indicated a statistically significant association between maternal and paternal exposure to "gasoline, benzene, diesel exhaust, oil, mineral oil, and gas" and an increased likelihood of childhood leukemia. One study indicated that the association with petrol compound exposure appeared stronger for acute myeloid leukemia (AML) than for acute lymphoblastic leukemia (ALL). Multiple studies reported positive associations between different petroleum compound exposures and childhood leukemia. In conclusion, the current review pointed toward an association between exposure to petrol compounds and a higher risk of childhood leukemia. Therefore, we recommend implementing stricter environmental regulations on benzene emissions and establishing evidence-based safety buffer zones between petrol stations and residential areas. Furthermore, routine air quality monitoring near these sites is essential to safeguard pediatric health.

Keywords: acute lymphoblastic leukemia, acute myeloid leukemia, gas station, pediatric leukemia, petrol station

Introduction

This study investigates the relationship between exposure to petroleum compounds and the risk of childhood leukemia (CL), which is a group of tumors that start in the bone marrow and has a significant effect on the blood and lymphatic systems of young people. In 2022, about 64,566 new cases of leukemia were found in children aged 0 to 14 around the world, which represents 31.9% of all childhood cancers. This disease caused about 23,833 deaths in this age group, which is 30.9% of all childhood cancer deaths. This shows that it is one of the main causes of cancer deaths in children despite the fact that major therapeutic advances have significantly increased survival rates over the past few decades.[1]

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Geodemographic factors have a significant impact on the incidence of CL. While the prevalence of acute lymphoblastic leukemia (ALL) is approximately 3–4 cases per 100,000 children annually, acute myeloid leukemia (AML) is less common in wealthier countries, occurring at 0.5–1 cases per 100,000 children annually. Because of factors like limited access to healthcare and diagnostic capabilities, incidence rates are higher in developing nations. For example, 2.25 cases of ALL per 100,000 children under the age of fifteen were reported to occur on average each year in Iran.[2]

Childhood leukemia was the most common cancer diagnosed in Egypt among children ages 0–14, with 1362 new cases reported in 2022. This number accounted for 26.7% of all pediatric cancer diagnoses in the nation. Additionally, in Egypt during the same year, leukemia accounted for 493 deaths, or 24.5% of all childhood cancer deaths, making it the leading cause of cancer-related deaths in this age group.[3]

Understanding the epidemiological patterns of childhood leukemia is crucial, as evidenced by the rising prevalence of the disease seen worldwide in recent decades. Changes in environmental exposures, improvements in diagnostic methods, or other factors that are still being studied could be the cause of this increase.[3,4]

ALL and AML are the two most common subtypes of childhood leukemia.[4] Less frequently occurring subtypes of CL include mixed lineage leukemia (MLL), juvenile myelomonocytic leukemia (JMML), and chronic myeloid leukemia (CML). Regarding specific subtypes and age of onset, ALL usually manifests between the ages of two and five, whereas AML is more frequently observed in infants and teenagers.[5]

Emerging data pointed to the role of environmental factors in the development of childhood leukemia. Exposure to ionizing radiation is a known risk factor.[6] However, several studies have also linked the disease to other environmental exposures, such as air pollution, pesticides, and parental smoking.[7,8] Notably, studies suggest that the interaction of genetic variations and environmental exposures may alter the risk of ALL in children.[9] Particularly, air pollution contains a complex mixture of known or suspected carcinogens, such as formaldehyde, 1,3-butadiene, and benzene.[4]

Abundant sources, including automobile emissions, gas stations, and industrial operations, can produce these pollutants. The duration and timing of exposure during critical developmental stages, including pregnancy and the first few months of life, may have a particularly significant impact on the risk of leukemia.[10]

Gas stations are ubiquitous in urban areas, providing essential services while simultaneously releasing hazardous volatile organic compounds (VOCs) such as benzene, toluene, ethylbenzene, and xylene (BTEX), which serve as the primary chemical markers of petroleum-related environmental pollution. These compounds are released into the atmosphere during the storage, distribution, and combustion of gasoline, as well as through evaporative emissions at refueling stations. Besides, underground leaks pose long-term threats to soil and groundwater quality.[10]

Chronic exposure to petroleum-related pollutants is linked to a broad spectrum of adverse health outcomes. Residents near high-traffic areas and gas stations face increased rates of respiratory morbidity—including childhood asthma and reduced lung capacity—alongside neurological impairments such as chronic headaches and cognitive delays. Furthermore, long-term exposure elevates the risk of cardiovascular diseases and adverse birth outcomes, such as low birth weight and preterm delivery.[8–11]

Among petroleum-related pollutants, benzene is of paramount concern; it is classified by the International Agency for Research on Cancer (IARC) as a Group 1 human carcinogen due to its well-documented hematotoxic and myelotoxic properties. Identifying these specific environmental factors is critical for pinpointing communities at higher risk for CL and establishing safer urban planning guidelines.[10,11]

Localized zones of greater exposure are created by the concentration of benzene and other VOCs being higher in the immediate vicinity of gas stations. Children's higher respiratory rates and developing bodies may make them particularly vulnerable to the harmful health effects of environmental contaminants. Benzene can induce leukemia through various mechanisms, including interfering with the immune system, damaging DNA, and disrupting bone marrow function. While occupational exposure in industries like petrochemicals is a known risk factor, even low-level environmental exposure to benzene can be harmful, especially to vulnerable populations like young children. Many studies have looked at the possible connection between residential proximity to gas stations and childhood leukemia, as it has been associated with an increased risk of leukemia, especially AML.[4,11]

However, the results are diverse, with some studies indicating an increased risk, while others show no association. A 2015 meta-analysis by Filippini et al indicated that living close to petrol stations might be a risk factor for childhood

leukemia.[12] This study, examining residential exposure to traffic-related pollutants including benzene near roads and petrol stations, found a correlation between ambient traffic pollution exposure and an elevated risk of the disease. Likewise, a multicenter case-control study conducted at a hospital found a correlation between acute childhood leukemia and residences close to gas stations and auto repair shops.[13] Living close to gas stations was also linked to an increased risk of childhood leukemia, according to another meta-analysis.[14]

Notably, a study by Malavolti et al even suggested an exposure–response relationship, where the risk of leukemia increased with the number of nearby gas stations.[15] On the other hand, a UK study did not find a statistically significant risk of childhood leukemia for those living within 100 meters of a fuel station.[16] Furthermore, there was no proof of a higher risk of leukemia in kids who lived near gas stations, according to a study by Mazzei et al.[17]

The release of benzene, which Snyder's review (2012) confirmed, contributes to leukemia development by damaging bone marrow and makes the possible biological link between proximity to a gas station and leukemia plausible.[18] Furthermore, the Taiwanese study's findings demonstrated a substantial exposure-response association between exposure to traffic exhaust pollution and young children's risk of leukemia,[19] which supports worries about genetic harm from benzene exposure expressed by Lev Bar-Or et al.[20] Additionally, the risk of childhood leukemia may also be raised by parental occupational exposures to chemicals like benzene.[21–23]

This complexity highlights the challenge in investigating the association between the exposure to petrol compounds and the development of childhood leukemia. However, previous systematic reviews[8,12,23] were either based primarily on case-control studies, which are not the highest form of evidence because they are retrospective, making it difficult to establish the temporal relationship, and thus typically rank lower on the evidence hierarchy than cohort studies, or they implemented an unspecific cohort study that included a wide variety of exposures in addition to petroleum compounds and outcomes other than leukemia.

Therefore, the current systematic review was conducted to synthesize the impact of a wide range of petroleum compound exposures from two cohorts with a large sample size and eleven case-control studies that have specific exposure (petroleum compounds) and outcome (childhood leukemia). Moreover, the present review included one study from Middle East countries (Iran) which enhanced the generalizability of the results. This review aims to evaluate the epidemiological evidence regarding the relationship between combined oil exposure during pregnancy and childhood and an increased risk of childhood leukemia. The findings could deepen the understanding of the link between petroleum compound exposure and childhood leukemia. Furthermore, they provide a framework for developing evidence-based health policies and prioritizing research into the environmental factors that impact pediatric health.

Methodology

Study Registration

We conducted a systematic review based on the principles of the Cochrane Handbook for Systematic Reviews of Interventions and reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 Checklist (https://www.prisma-statement.org/prisma-2020-checklist) as shown in Supplementary Table S1. The project was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD420251064678.

Eligibility Criteria

For this systematic review, studies were included based on the following criteria: Population: Studies focusing on children who diagnosed at age 0–24 years diagnosed with leukemia (as the latent phase for some leukemia types can last anywhere from five to ten years before the illness shows symptoms), Exposure & Outcome: Investigations into the association between exposure to petroleum compounds and the incidence of leukemia, Publication Format: Full-text studies published in English, and Study Design: Cohort studies, case-control, and cross-sectional. Studies were excluded if they met any of the following criteria: Population: Studies involving adult or animal subjects, Data Availability: Studies with inadequate or incomplete data, and Study Design: Qualitative studies, case series, and narrative reviews.

Information Sources and Search Strategy

The study search sources were PubMed, Google Scholar, and Medline. We searched those published up to May 31, 2025, conducted on humans, with case-control, cohort, or cross-sectional designs, and written in English. All Medical Subject Headings (MeSH) terms, as well as the text words for each topic in the search, were used in the literature search approach combined with "OR" and "AND". The following combination of keywords and Medical Subject Heading (MeSH) search terms associated with Boolean operators was used to search all databases indexed within PubMed: (((Children [MeSH Subheading]) OR (Maternal [MeSH Subheading])) AND (Petroleum compounds [MeSH Subheading]) AND ((Acute Lymphoblastic Leukemia [MeSH Subheading]) OR (Childhood ALL [MeSH Subheading]) OR (Acute Myeloid Leukemia [MeSH Subheading]))). The retrieved studies were exported to the Mendeley citation manager. The final folder of retrieved studies was exported to Covidence software as a Research Information System (RIS) document.

Selection Process

Two independent reviewers, Dr. Hossam Soliman (HS) and Dr. Mohamed Fakhry Hussein (MFH), screened the literature. Disagreements were resolved through consensus, with a third reviewer, Mohamed Hossam Mohamed (MHM), consulted if needed. The screening process involved two stages: assessing abstracts and titles, followed by full-text review, both conducted using Covidence software.

Data Collection Process and Data Items

After finalizing the selection of studies for inclusion in the review, (HS) had extracted data from all of them, and the other reviewer (MFH) checked them. This extracted information, encompassing author, publication year, country, study design, participant details (age, gender, and number), and descriptions of measures and measured outcomes, was then recorded in the "Table of Study Characteristics (Table 1).

Study Risk of Bias Assessment

The methodological quality and potential for bias in each included case-control and cohort study were systematically evaluated using the Quality Assessment Tool integrated within Covidence software. This assessment considered several key domains, including the risk of selection bias (eg, due to sampling methods, differential case and control ascertainment like Berksonian bias, or non-response), information bias (such as recall bias regarding past exposures or issues with accurate and consistent ascertainment of both exposure to petrol compounds and the outcome of childhood leukemia), and confounding bias (evaluating the adequacy of control for known confounders like socioeconomic status or other environmental factors and the appropriateness of matching criteria, including the number of controls per case). Additionally, the assessment addressed potential reporting bias (specifically, incomplete outcome data) and the overall transparency and completeness of reporting that might indicate selective reporting or other methodological weaknesses. Each study was ultimately categorized as having a high, some, or low risk of bias, based on a comprehensive consideration of these factors.

Certainty Assessment

We assessed the overall quality of evidence using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews), a widely used instrument for critically appraising systematic reviews.[34] While published in 2007, we applied a published version of its 16-items checklist to our review of non-randomized studies. Specifically, we included 13 items appropriate for a review of non-randomized designs and excluded three items related to meta-analysis (items 11, 12, and 15) (the full checklist was included in Supplementary Figure S1). The prioritized domains from the AMSTAR 2 checklist were: inclusion criteria for the review include the components of PICO (item 1), protocol registered before commencement of the review (item 2), study designs were identified in the review (item 3) adequacy of the literature search (item 4), study selection was duplicate (item 5), extraction of data was duplicate (item 6), Justification for excluding individual studies (item 7), descriptions of included studies (item 8), risk of bias from individual studies being included in the review was assessed (item 9), reporting of funding sources in case of their existence (item 10), Risk of bias was included in the results section (item 13), explanation of different results from the review (item 14), and reporting the conflict of interests (item 16).

Table 1 Summary Findings of the Review Studies (N= 13 Studies)

No	C. Author and Year of Publication	Country	Study Design	Population Description	Inclusion Criteria	Exclusion Criteria	Method of Recruitment of Participants	Total Number of Participants	Outcome (OR) or (HR)
1	Norzaee et al, 2024[24]	Iran	Case control study	428 cases of juvenile lymphoma and leukemia (2016–2021), as well as a control group of 428 Tehran-based children ages 1–15. Healthy children receiving routine checkups or visiting the pediatric clinic for non-blood-related conditions, such as fractures, osteoarticular disorders, trauma, injuries, gastrointestinal disorders, infections, and poisoning, comprised the controls, who were selected at random.	Those under the age of 15 at the time of diagnosis who had lived in the same residence for at least a year prior to the diagnosis date	Children with Down syndrome, those whose individual-level data was lacking, and those whose file did not include their geographic address.	Clinic patients	856	Leukemia with exposure to gas stations within 100 meters had an OR of 2.15 (95% CI = 1.00–4.63). For children with leukemia living within 100 meters of the closest highway, the odds ratio (OR) was around 1.87 (95% CI = 1.00–3.49).
2	McKenzie et al, 2025,[11]	United States	Case control study	451 children diagnosed with ALL between 1992 and 2019 who were between the ages of 2 and 9 were chosen as cases. In accordance with birth month, year, and ethnicity (Hispanic or not), controls were paired with cases and given a reference date that coincided with the date of the matched case's ALL diagnosis. 2,706 kids were chosen as controls based on these standards.	I. A verified diagnosis of ALL inside the CCCR from 2002 to 2021 ii. No prior cancer diagnosis of any type submitted to the CCCR	Children with baby ALL whose etiology is different from that of childhood ALL should not be included. Do not include ALL related to the prior cancer therapy. All cases lacking a Colorado birth certificate should be excluded.	The Colorado birth registry and the Colorado Central Cancer Registry (CCCR)	3157	In comparison to the referent group, the low, medium, and high intensity-adjusted inverse distance weight (IA-IDW) groups showed a 62% [OR = 1.62; 95% CI), 84% (OR =1.84; 95% CI, 1.35–2.48), and 100% (OR = 2.00; 95% CI, 1.14–3.37) increase in ALL risk for children living within 5 km of an O&G well site. For low, medium, and high IA-IDW groups, the increase in ALL risk within 13 km was 59% (OR = 1.59; 95% CI, 1.03–2.37), 40% (OR = 1.40; 95% CI, 1.09–1.80), and 164% (OR = 2.64; 95% CI, 1.80–3.86), respectively.

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Table 1 (Continued).

No	C. Author and Year of Publication	Country	Study Design	Population Description	Inclusion Criteria	Exclusion Criteria	Method of Recruitment of Participants	Total Number of Participants	Outcome (OR) or (HR)
3	Kirkeleit et al, 2018[25]	Norway	Cohort study	From 1999 to 2008, participants were gathered from all throughout Norway. A postal invitation prior to a standard ultrasound examination, which was available to all pregnant women in Norway at 17 weeks of gestation, was used to recruit pregnant women (index persons) during this time. There are now 94,428 mothers and 113,754 children in the cohort. Results of the cancer ascertainment By connecting with the Cancer Registry of Norway, incident cancer cases in the offspring cohort were found up until December 31, 2014. Childhood leukemia was the primary result (n = 70). There are 94,428 mothers and 113,754 children in the cohort.	In Norway, pregnant women are 17 weeks early in their pregnancy.		Mail	208182	Exposure to "gasoline or exhaust" during pregnancy was linked to a higher incidence of acute lymphatic leukemia (HR = 2.71; 95% CI: 0.97, 7.58) and juvenile leukemia (HR = 2.59; 95% CI: 1.03, 6.48). After controlling for maternal smoking, the connection remained unchanged.
4	Yu et al, 2006[26]	Taiwan	Case control study	Between November 1997 and June 2003, 171 leukemia cases were diagnosed, and 410 controls who were matched for age and sex were enlisted.			Registry	581	For the younger age range, no general association was found.

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5	McKenzie et al, 2017[27]	United States	Case control study	975 children in the registry who were diagnosed with cancer between the ages of 0 and 24 and who lived in rural Colorado at the time of diagnosis made up the study population. To account for a potential 10-year latency interval between childhood exposures prior to the age of 15 and the beginning of cancer, subjects between the ages of 15 and 24 were included in the study. There were 528 individuals in the control group.	Age range for cancer diagnosis: 0–24 years		The Colorado Central Cancer Registry (CCCR)	1503	After controlling for age, race, gender, income, and elevation in model 1, children with ALL were more than twice as likely as controls to reside within 16.1 kilometers of an active oil and gas well during the latency period (p for trend = 0.22). The likelihood of living in the inverse distance weight (IDW) well count textile was 4.3 (95% CI: 1.1 to 16) times higher for children with ALL aged 5–24 years than for controls, and there was a monotonic increase in IDW well count textiles (p for trend = 0.035).
6	Heck et al, 2014[28]	United States	Case control study	Between 1990 and 2007, 69 instances involving children under the age of six were registered in the California Cancer Registry. and 2994 Controls were randomly chosen from California birth certificates for the same time period (20:1 matching), frequency-matched by year of birth to all children cancer cases in the parent APCC cohort.	Californian children under the age of six	Their home residence was listed as being outside of California, and their birth certificates lacked information on gestational age.	California Cancer Registry from 1990 to 2007 and Controls, who were randomly chosen from California birth certificates for the same time period and frequency-matched by year of birth of all childhood cancer cases in the parent APCC research (20:1 matching)	3063	Exposure to benzene during the third trimester raised the risk of AML and ALL (OR 1.75, 95% CI 1.04, 2.93) and (OR = 1.50, 95% CI 1.08, 2.09), respectively.

(*Continued*)

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Table 1 (Continued).

No	C. Author and Year of Publication	Country	Study Design	Population Description	Inclusion Criteria	Exclusion Criteria	Method of Recruitment of Participants	Total Number of Participants	Outcome (OR) or (HR)
7	Lagorio et al, 2013[29]	Italy	Case control study	The Association of Pediatric Hematology and Oncology's national registry was used to identify 108 childhood leukemia cases from seven Italian provinces that were diagnosed between July 2000 and December 2001. A random selection of 194 controls who were matched to cases (2:1 ratio) based on gender, date of birth, and region was made from population lists.	Leukemia in children, ages 2–12		Clinic patients	202	While there was no difference in ambient benzene levels between participant and non-participant cases (OR=0.95; 95% CI 0.82 to 1.09), benzene concentrations close to the homes of full-participant controls were significantly lower than those close to the homes of partial-participants (OR=0.88; 95% CI 0.80 to 0.97), controlling for gender, age, season, and place of residence.
8	Harrison et al, 1999[16]	UK	Case control study	251 Controls of solid cancer and benign neoplasm, and 130 leukemia cases. We examined data for children aged 0 to 15 who were diagnosed between 1990 and 1994 from the West Midlands Cancer Intelligence Unit.	Children aged 0 to 15 who received diagnoses between 1990 and 1994 were used.		Information from the Cancer Intelligence Unit in the West Midlands	381	The odds ratios for people who lived within 100 meters of a major road or a petrol station were 1.61 (95% CI 0.90 to 2.87), and 1.99 (95% CI 0.73 to 5.43), respectively.
9	Brosselin et al,2009[30]	France	Case control study	There were 1681 controls and 765 acute leukemia cases. Cases and population controls were frequency matched by gender and age.	Children under the age of fifteen.		Telephone, Standardized telephone interviews with the mothers were used to gather data.	2446	Living close to a gas station was substantially linked to acute leukemia (OR 1.9, 95% CI 1.2 to 3.0).

10	Tamayo-Uria et al, 2018[31]	Spain	Case control study	1061 children between the ages of 0 and 14 were diagnosed with leukemia. The study comprised five autonomous regions: the Autonomous Region of Madrid, the Basque Country, Aragon, Navarre, and Catalonia. The study period ran from 1996 to 2011.6447 Controls were matched to cases in a 6:1 ratio by sex, year of birth, and autonomous region of residency.	Non-inclusion of individual data		For cases, see the Spanish Registry of Childhood Tumors (RETI-SEHOP). For the control group, a random incidence density sample was taken from the entire Birth Registry of the Spanish Statistical Office (Instituto Nacional de Estad Ãstica, or INE) from the at-risk population.	7508	The odds of residing less than 50 meters from the busiest motorways were more than three times higher for pediatric leukemia cases than for controls (OR = 2.90; 95% CI = 1.30–6.49). While estimates for patients with the same address at birth and at diagnosis were lower (OR = 2.40; 95% CI = 0.70–8.30), those for acute lymphoid leukemia (ALL) were somewhat higher (OR = 2.95; 95% CI = 1.22–7.14).
11	Steffen et al, 2004[13]	France	Case control study	There were 285 controls and 280 leukemia cases. Four hospitals—Nancy, Lille, Lyon, and Paris—were found to have cases. Sex, age, center, and ethnic origin were used to frequency match the cases and controls. The inclusion of both cases and controls, as well as the local frequency matching based on age and sex, was handled by the same interviewer in each center. Participation in the study was requested from all mothers of qualifying cases or controls who were present during the interviewers' working hours. Children under the age of 15 who lived in the same vicinity as cases and were admitted for acute illnesses, primarily traumatic (51%) and non-traumatic (34%) orthopedic conditions, served as controls.	Children between the ages of 0 and 14 at the time of diagnosis were required to have a new diagnosis of acute leukemia (AL) between January 1, 1995, and December 31, 1999, in order to be eligible for the study. The diagnosis was made using immunophenotype and cytology.	Cases of acute leukemia following treatment were not included.	Clinic patients	565	Living next to a gas station or repair shop as a child was linked to an increased risk of childhood leukemia (OR 4.0, 95% CI 1.5 to 10.3), with a trend in duration. Adjusting for potential confounding factors did not change the association, which seemed especially robust for acute non-lymphocytic leukemia (OR 7.7, 95% CI 1.7 to 34.3).

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Table 1 (Continued).

No	C. Author and Year of Publication	Country	Study Design	Population Description	Inclusion Criteria	Exclusion Criteria	Method of Recruitment of Participants	Total Number of Participants	Outcome (OR) or (HR)
12	Miligi et al, 2013[32]	Italy	Case control study	There were 1044 controls, 97 NHL cases, and 83 cases of acute childhood leukemia.	Age 0–14 years old		The Association of Pediatric Hematology and Oncology (AIEOP), an Italian network of childhood cancer facilities, is linked to the pediatric oncology centers where cases were recruited. When a kid is initially hospitalized as an inpatient or outpatient to any AIEOP unit, all pediatric neoplasm cases in children ages 0–14 are documented. For every case of childhood leukemia, two controls were randomly selected from the local population in each location. These controls were matched for gender, birthdate, and place of residence.	1824	Paternal exposure to diesel exhaust (OR 1.4., 95% CI 1.1 to 1.9), lead exposure (OR 1.4), and mineral oils (OR 1.7, 95% CI 1.1 2.4) was linked to an increased risk of childhood leukemia, as was maternal exposure to aliphatic (OR 4.3, 95% CI 1.8–10.4) or aromatic hydrocarbons (OR 3.8, 95% CI-1.6–9.2) during the preconception period.
13	Spycher et al, 2017[33]	Switzerland	Cohort Study	Children under 16 in the 1990 and 2000 national censuses Mother: 1,050,637 Male: 1,527, 965	Only kids with a birth certificate	Offspring born overseas Prior to admission, children were diagnosed with cancer.	We included children under 16 from national censuses in Switzerland (1990, 2000) as part of a census-based cohort research. Parental occupational exposure to benzene was evaluated using a unique job exposure matrix (BEN-JEM) based on the International Classification of Occupations 1988 (ISCO-88).	2,578, 602	Risk of ALL (1.88, 1.16–3.04) and childhood leukemia (hazard ratio 1.73, 95% CI 1.12–2.67)

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The overall confidence in the results of this systematic review was rated as: High: No or only one non-critical weakness, and the systematic review provided an accurate and thorough summary of the available research addressing the topic, Moderate: More than one non-critical weakness, but no critical flaws. It likely provided an accurate summary of the available studies included in the evaluation, Low: One major flaw, with or without non-critical weaknesses, and Critically Low: The review had a critical flaw and may not offer an accurate and thorough assessment of the available papers, more than one major flaw, with or without non-critical weaknesses.

Results

Study Selection

The initial search across three electronic databases—Medline, Google Scholar, and PubMed—yielded 68 relevant studies (Supplementary Table S2). After automatically removing duplicates using Covidence software, 53 unique studies remained for title and abstract screening.

Following this initial screening, 16 studies were excluded, leaving 37 studies for full-text review. The full-text screening process led to the exclusion of an additional 24 studies, resulting in 13 studies ultimately included in this review. Of these, 11 were case-control studies (n=11),[11,13,16,24,26–32] and two were cohort studies (n=2).[25,33] The complete study selection process is illustrated in the PRISMA flow diagram (Figure 1).

Study Characteristics

Table 1 presents the characteristics of the 13 included studies, which were conducted across various countries: Iran, Norway, India, the United Kingdom (UK), Switzerland, France, Taiwan, Italy, and the United States of America (USA). Of these, 11 were case-control studies and two were cohort studies. The total number of participants across all included studies was substantial, reaching 2,808,870 individuals. This figure comprised 22,086 participants from case-control studies and 2,786,784 from the two cohort studies.

Regarding exposure assessment, four observational studies have identified maternal exposure to petrol compounds as a predictor for leukemia incidence.[25,28,32,33] The remaining studies focused on assessing children's direct exposure to petrol and gas compounds in relation to leukemia development. All reviewed studies covered a wide pediatric age range, from 0 to 18 years old. For outcome reporting, the association between petrol compound exposure and leukemia development was primarily presented as odds ratios (ORs) in 11 studies, while the two cohort studies reported hazard ratios (HRs).

Risk of Bias in Included Studies

The quality and potential for bias in the 13 included studies (11 case-control and two cohort studies), presented in Supplementary Table S3, were rigorously assessed using a modified Covidence quality assessment tool. This evaluation identified several areas of concern: Three studies were deemed at high risk for Berksonian bias[13,16,24] because their controls were drawn from healthcare settings, potentially limiting their representativeness of the general population. Additionally, three studies raised high concerns regarding the adequate identification and control of confounding factors, as well as the presence of response bias.[16,29,30] Furthermore, two studies[16,24] lacked clear identification of their matching criteria and participant selection methods. In total, four studies were identified as having overall high bias concerns.[16,24,26,29]

Findings and Certainty of Evidence

Table 1 summarizes the findings on the association between exposure to petrol compounds and the risk of childhood leukemia. Our analysis focused on several key parameters:

Findings of Studies Examining the Association Between Maternal Exposure and an Increased Likelihood of Childhood Leukemia

Four studies[25,28,32,33] indicated a statistically significant positive association between maternal and paternal exposure to "gasoline, benzene, diesel exhaust, oil, mineral oil, and gas" and an increased likelihood of childhood leukemia. The results from two studies found increased risk of childhood leukemia from maternal exposure to benzene with ORs 1.75 (95% CI 1.04, 2.93) and OR = 1.50, (95% CI 1.08, 2.09) for of AML and ALL, respectively, regarding the first study and

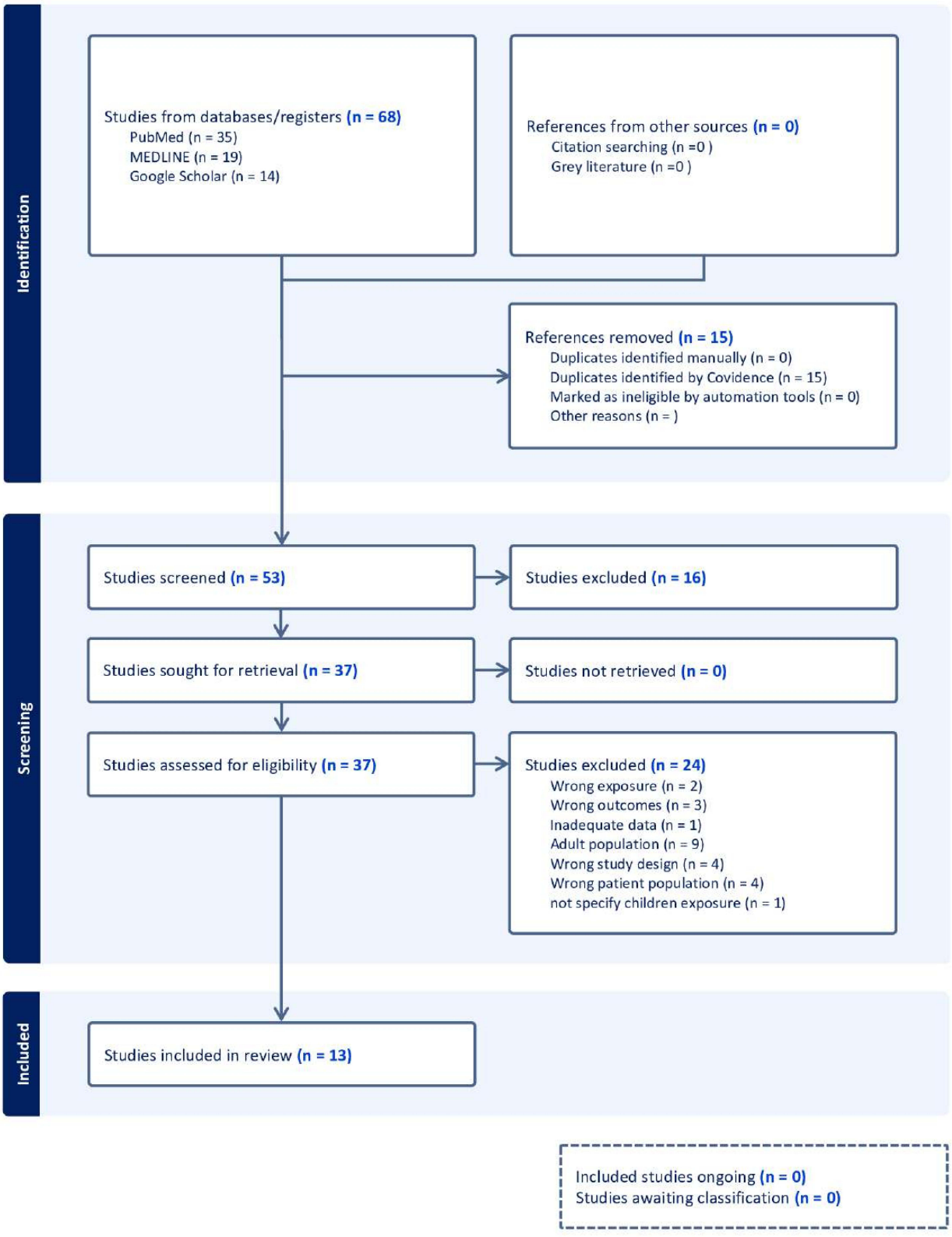

Figure 1 PRISMA diagram flow illustrating the selection process of the included studies (n=13 studies).

with OR =1.4, (95% CI 1.1 to 1.9) from exposure to diesel exhaust in the second study.[28,32] The other two cohort studies demonstrated that exposure to "gasoline or exhaust" during pregnancy was linked to a higher incidence of acute lymphatic leukemia (HR = 2.71; 95% CI: 0.97, 7.58) and juvenile leukemia (HR = 2.59; 95% CI: 1.03, 6.48) for the first study and that paternal exposure increased the risk of ALL (1.88, 1.16–3.04) and childhood leukemia (hazard ratio 1.73, 95% CI 1.12–2.67) in the second study.[25,33]

Association Between Exposure and to Oil, Gas Wells, and Busy Motorways, and ALL

Three studies[11,27,31] looked at exposure to major roadways, gas and oil well sites, and gas stations. Across exposure intensity groups, the first study found that children living within 5 km of an oil and gas well site was linked to higher odds of ALL: OR = 1.62 (95% CI 0.96–2.62) for low intensity, OR = 1.84 (95% CI 1.35–2.48) for medium intensity, and OR = 2.00 (95% CI 1.14–3.37) for high intensity in comparison to the referent group and those within 13 km. Furthermore, it demonstrated an increase in ALL risk of 59% (OR = 1.59; 95% CI, 1.03–2.37), 40% (OR = 1.40; 95% CI, 1.09–1.80), and 164% (OR = 2.64; 95% CI, 1.80–3.86) for low, medium, and high IA-IDW groups, respectively.[11] According to the second one, it was found that children with ALL were more than twice as likely as controls to reside within 16.1 kilometers of an active oil and gas well during the latency period (p for trend = 0.22). The likelihood of living in the inverse distance weight (IDW) well count textile was 4.3 (95% CI: 1.1 to 16) times higher for children with ALL aged 5–24 years than for controls, and there was a monotonic increase in IDW well count textiles (p for trend = 0.035).[27] Regarding the third study, the odds of living less than 50 meters from the busiest roads were more than three times higher for children with ALL than for controls (OR = 2.90; 95% CI = 1.30–6.49).[31]

Association Between Proximity to Petrol Stations and CL

Two case-control studies[13,30] found elevated risk of childhood leukemia with for participants whose residences were in close proximity to gas stations and repair garages or petrol stations compared to the control group. The first study indicated that Living next to a gas station or repair shop as a child was linked to an increased risk of childhood leukemia (OR 4.0, 95% CI 1.5 to 10.3), with a trend in duration. Adjusting for potential confounding factors did not change the association, which seemed especially robust for acute non-lymphocytic leukemia (OR 7.7, 95% CI 1.7 to 34.3).[13] Moreover, living close to a gas station was substantially linked to acute leukemia (OR 1.9, 95% CI 1.2 to 3.0) in the second study.[30]

Risk for ALL vs AML Subtypes

The findings from one study indicated that the association with petroleum compound exposure appeared stronger for AML than for ALL, with odds ratios OR = 1.75 (95% CI 1.04–2.93), and OR = 1.50 (95% CI 1.08–2.09), respectively.[28]

Certainty of the Evidence

The overall quality of evidence, assessed using AMSTAR 2, indicated a moderate level of certainty for the findings of this systematic review.

Discussion

Our aim was to critically evaluate the existing body of epidemiological evidence regarding the association between individual exposure to petrol compounds and the development of childhood leukemia. On the basis of this aim, we ran a systematic review with 13 studies included to synthesize the results. The results of this study indicate a statistically significant association between exposure to petroleum compounds and the development of childhood leukemia. This finding aligns with the a previous meta-analysis which found a summary relative risk of leukemia of 2.42 (95% confidence interval: 1.51, 3.89) for children who reside in close proximity to gasoline stations, which suggests the need for leukemia screening on a wide scale for children who reside in close proximity to petrol stations, gas and oil sites, and petrochemical compounds.[14] Moreover, the current study findings regarding ALL and AML were aligned with those of a previous systematic review, which indicated a stronger association was observed for AML compared to ALL.[12] This supports the hypothesis that exposure to pollutants emitted from petrol stations, particularly benzene, contributes to leukemogenesis in children and indicates the demand for further studies regarding the dose-response relationship, which could strengthen the evidence for a causal association. The results contribute insights with regard to the role of

environmental pollutants in the development of acquired genetic mutations that occur in blood cells. However, the review findings regarding maternal exposure were in contrast to an American case-control study of children aged 10 years and under in Los Angeles County, which found no increased risk of childhood leukemia associated with paternal exposure to petrol compounds.[35] The inconsistencies may be due to differences in study design, exposure assessment methods, control for confounding factors, and population characteristics.

This study has various strengths. First, two independent reviewers selected research and assessed its quality. Second, the study's goal was to look at both maternal and childhood exposures, as opposed to earlier research that only looked at one. Moreover, the exposure to petrol compounds includes several categories such as petrol stations, oil and gas sites, busy roads, and the petrochemical industry. The large sample size of cohort designs allows for a robust conclusion regarding the relationship between exposure to petroleum chemicals and childhood leukemia risk. The use of full residence details enables a more precise assessment of gas and petrol stations, exposure throughout critical times of childhood development. Moreover, geographical analysis based on official registries is a sophisticated way to analyze exposure and discover spatial trends. However, the study has some limitations. The quality assessment of the review papers found that four of them had bias concerns, which could affect the interpretation of the findings. The studies were carried out in Italy, Iran, the United States, the United Kingdom, Norway, Taiwan, France, and Spain; this may limit generalizability because populations in other nations may have distinct genetic and behavioral traits. Last, this synthesis comprised only articles published in English.

Conclusion

The current study reported an association between exposure to petroleum compounds and a higher risk of childhood leukemia. The relationship was stronger for AML compared to ALL. These findings serve as a critical evidence base for urban planners and public health officials, who should consider implementing stricter zoning regulations and mandatory safety buffer zones between residential areas and petrol stations to mitigate environmental benzene exposure. For practitioners, this study highlights the importance of incorporating environmental history into pediatric health assessments, particularly for children living in high-traffic or industrial corridors. Additionally, future long-term studies will be necessary to evaluate the lasting health effects of living close to petrol stations and to clarify the underlying biological mechanisms and genetic susceptibilities that enhance the disease development following petroleum exposure.

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Disclosure

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