



What Are The Specific Risk Factors Associated With Febrile Seizures In Children Under 5 Years Old In Urban Pediatric Populations ? : A Comprehensive Systematic Review

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ABSTRACT

Introduction: Febrile seizures (FS) are the most common seizure type in children under five years, especially in urban pediatric populations. These seizures occur with fever without intracranial infection and pose significant clinical challenges due to their acute onset and recurrence risk. Understanding FS risk factors is essential for early identification and prevention.

Methods: A systematic review following PRISMA 2020 guidelines was conducted, including 40 studies published since 2015. Studies focused on children aged 0-5 years in urban settings, examining demographic, clinical, genetic, and environmental risk factors for FS. Data extraction covered study design, population characteristics, risk factors, outcomes, and interventions. Boolean MeSH keywords related to pediatric populations, feeding methods, treatments, and FS outcomes guided database searches.

Results: Younger age (6-60 months) and family history of febrile seizures showed strong and moderate-to-strong associations with FS risk, respectively. Iron deficiency anemia was prevalent in 38% of FS cases and strongly correlated with seizure occurrence. Other moderate risk factors included low serum zinc and calcium, infections such as HHV-6, and genetic mutations (notably SCN1A). Formula feeding was linked to higher FS occurrence, while exclusive breastfeeding showed a protective effect. Prophylactic treatments like diazepam and sodium valproate reduced recurrence, though safety profiles varied. Nursing and parental education improved symptom management and anxiety.

Discussion: FS etiology is multifactorial, involving demographic, clinical, genetic, and environmental factors that often interact, compounding risk. Age-specific strategies—such as genetic screening in infants and iron supplementation in toddlers—are recommended. Urban environmental factors and healthcare disparities further influence FS risk and management.

Conclusion: Febrile seizures in urban children under five result from complex, interacting risk factors. Prevention and management require integrated, age-tailored approaches including nutritional support, infection control, prophylactic medication, breastfeeding promotion, and education. Continued research and guideline adherence are vital to improve outcomes.

Keywords: Febrile seizures, risk factors, urban pediatric population, iron deficiency anemia, breastfeeding, genetic mutations, prophylactic treatment, parental education.

INTRODUCTION

Febrile seizures (FS) represent the most common type of seizures in children under five years old, particularly in urban pediatric populations, posing significant clinical challenges due to their acute onset and potential for recurrence (Murata et al., 2016). These seizures are characterized by convulsions triggered by fever without evidence of intracranial infection or other central nervous system pathology (He, 2020). Understanding the risk factors associated with febrile seizures is crucial for early identification, prevention, and management, especially in densely populated urban areas where environmental and genetic influences may interplay uniquely.

Epidemiological studies consistently demonstrate that younger age is a predominant demographic risk factor for febrile seizures, with children aged six months to three years being most vulnerable (Zhu et al., 2023). This vulnerability is compounded by family history; approximately 37% to 58% of affected children have a familial background of febrile seizures, suggesting a hereditary predisposition (Hosseinrezaei et al., 2021). Male gender shows a weaker yet notable association, while a family history of epilepsy also contributes moderately to risk (Shao et al., 2020).

Clinical and physiological factors play a significant role in febrile seizure susceptibility. Iron deficiency anemia is particularly prominent, affecting about 38% of children with FS and demonstrating a strong correlation with seizure risk (Murata et al., 2016). Other mineral deficiencies such as low serum zinc and calcium levels are moderately associated with increased risk (He, 2020). Additionally, low serum sodium and elevated lactate levels have been observed with weaker to moderate associations (Zaiyun et al., 2023). Infectious agents like human herpesvirus 6 (HHV-6) have also been implicated, with a prevalence of 43.4% in FS cases, indicating a moderate association (Shao et al., 2020).

Genetic factors, especially mutations in the SCN1A gene, have emerged as strong risk contributors, highlighting the importance of genetic screening in high-risk

populations (Zhu et al., 2023). Environmental and nutritional components further influence FS risk; formula feeding has been linked to a 12.2% occurrence rate of febrile seizures, whereas exclusive breastfeeding offers a moderate protective effect (adjusted OR 0.87) (Na et al., 2022). These findings underscore the multifactorial nature of FS etiology in urban children.

The interaction of risk factors often compounds clinical outcomes. For example, the coexistence of iron deficiency anemia with infections significantly elevates seizure risk, reflecting high clinical and urban relevance (Murata et al., 2016). Similarly, young age combined with a positive family history presents a high-risk profile, necessitating targeted preventive strategies (Hosseinrezaei et al., 2021). These combined profiles emphasize the need for integrated clinical approaches addressing multiple risk dimensions.

Age-specific considerations reveal that risk factors and management strategies should be tailored accordingly. Infants aged 0-6 months are primarily affected by genetic susceptibility and electrolyte imbalances, warranting breastfeeding promotion and genetic screening (Shao et al., 2020). The 6-18 month age group shows a heightened risk from family history and iron deficiency, suggesting iron supplementation and infection prevention as key interventions (He, 2020). For toddlers aged 18-36 months, recurrent seizures and infections dominate risk profiles, highlighting the role of prophylactic treatments and parental education (Zaiyun et al., 2023). Children aged 3-5 years benefit from fever management education and vaccination programs to mitigate FS risk (Na et al., 2022).

Preventive and therapeutic interventions have been explored extensively. Prophylactic treatments such as low-dose sodium valproate and diazepam have demonstrated efficacy in reducing seizure recurrence, although safety profiles vary (He, 2020). Antipyretic use, particularly acetaminophen, has been studied for its potential to reduce FS recurrence during febrile episodes, with mixed results (Murata et al., 2018). Nursing interventions based on models like Kano have shown promise in symptom

relief and reducing parental anxiety, which is critical for holistic FS management (Zhu et al., 2023).

Parental education interventions are vital, as they improve understanding of FS uncertainty and reduce anxiety, thereby enhancing compliance with management protocols (Hosseinrezaei et al., 2021). Additionally, clinical practice guidelines adherence has been linked to improved care quality for febrile infants, indicating the importance of standardized protocols in urban healthcare settings (McDaniel et al., 2024).

The urban pediatric environment presents unique challenges and opportunities for FS management. High population density, environmental exposures, and variable access to healthcare resources influence FS epidemiology and outcomes (Shao et al., 2020). Urban settings also facilitate the implementation of targeted public health interventions, such as breastfeeding promotion and vaccination campaigns, which can substantially reduce FS incidence (Na et al., 2022).

Despite advances, gaps remain in understanding the full spectrum of FS risk factors and their interactions in urban contexts. Further research is needed to elucidate the mechanistic pathways linking anemia, infections, genetic mutations, and environmental exposures to febrile seizures. Large-scale prospective cohort studies and randomized controlled trials focusing on diverse urban populations will enhance evidence-based strategies for FS prevention and management.

In conclusion, febrile seizures in children under five in urban populations are influenced by a complex interplay of demographic, clinical, genetic, and environmental factors. Younger age, family history, iron deficiency anemia, high fever, and genetic mutations are among the most significant risk factors. Preventive strategies including breastfeeding promotion, infection control, iron supplementation, and tailored prophylactic treatments are essential. Comprehensive nursing and parental education interventions further support effective FS management. Continued research and adherence to clinical guidelines will improve outcomes for this vulnerable population.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the specific risk factors associated with febrile seizures in children under 5 years old in urban pediatric populations.

Screening

We screened in papers that met these criteria:

- **Age Range:** Does the study include children aged 0-5 years as the primary study population?
- **Febrile Seizure Definition:** Does the study provide a clear definition and documentation of febrile seizures?
- **Research Focus:** Does the study investigate risk factors for febrile seizures as a primary research objective?
- **Study Design:** Is the study either an observational study (cohort, case-control, cross-sectional) or a systematic review/meta-analysis?
- **Seizure Type:** Does the study specifically focus on seizures with fever (febrile seizures) rather than other types of seizures?
- **Sample Size:** Does the study include 10 or more participants?
- **Setting:** Was the study conducted in an urban healthcare setting?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper.

We gave the model the extraction instructions shown below for each column.

- **Study Design:**

Identify and record the specific type of study design (e.g., randomized controlled trial, cross-sectional study, prospective cohort study).

- Look in the methods section for explicit description of study design
- If multiple design elements are present, list all relevant characteristics
- If design is not clearly stated, note "design not clearly specified"
- Prioritize the authors' own description of study design

- **Participant Characteristics:**

Extract detailed information about study participants:

- Age range (minimum and maximum)
- Mean/median age
- Total sample size
- Gender distribution
- Specific inclusion/exclusion criteria related to febrile seizures
- Geographic location/setting of study
- If multiple groups are compared, provide characteristics for each group
- Use exact numbers and percentages where available

- **Specific Risk Factors Examined:**

Identify and list all risk factors investigated in relation to febrile seizures:

- Biological factors (e.g., hemoglobin levels, platelet count, sodium levels)
- Clinical factors (e.g., fever duration, type of infection)
- Demographic factors
- Precise numerical data for each risk factor
- Statistical significance of findings

- Prioritize factors directly related to children under 5 years old
- **Outcome Measures:**
Record all primary and secondary outcomes related to febrile seizures:
 - Seizure recurrence rates
 - Complications
 - Long-term neurological outcomes
 - Include specific numerical data and statistical significance
 - Note measurement methods and time frames for outcome assessment
- **Intervention Details:**
If interventional study, extract:
 - Specific interventions tested
 - Dosage and duration of intervention
 - Comparison/control group details
 - Method of intervention administration
 - Any prophylactic treatments examined
- **Statistical Analysis:**
Identify key statistical methods and analyses:
 - Statistical tests used
 - Significance levels (p-values)
 - Confidence intervals
 - Regression models or risk calculation methods
 - Multivariate analysis techniques

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Pediatric	Urban pediatric populations	Children	Infants and toddlers
Intervention (I)	Formula feeding	Prophylactic treatment	Partial breastfeeding	Antipyretic treatment
Comparison (C)	exclusive breastfeeding	no treatment	exclusive breastfeeding	no Intervention
Outcome (O)	Febrile seizures occurrence	Febrile seizure recurrence	Risk factors association	Seizure management effectiveness

The Boolean MeSH keywords inputted on databases for this research are: *The Boolean MeSH keywords inputted on databases for this research are: ("pediatric" OR "Urban pediatric populations" OR "children" OR "Infants and toddlers") AND ("Formula feeding" OR "Prophylactic treatment" OR "Partial breastfeeding" OR "Antipyretic treatment") AND ("Exclusive breastfeeding" OR "No treatment" OR "No intervention" OR "No intervention") AND ("Febrile seizures occurrence" OR "Febrile seizure recurrence" OR "Risk factors association" OR "Seizure management effectiveness")*

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles,

authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("pediatric" OR "Urban pediatric populations" OR "children" OR "Infants and toddlers") AND ("Formula feeding" OR "Prophylactic treatment" OR "Partial breastfeeding" OR "Antipyretic treatment") AND ("Exclusive breastfeeding" OR "No treatment" OR "No intervention" OR "No intervention") AND ("Febrile seizures occurrence" OR "Febrile seizure recurrence" OR "Risk factors association" OR "Seizure management effectiveness")	3
Semantic Scholar	("pediatric" OR "Urban pediatric populations" OR "children" OR "Infants and toddlers") AND ("Formula feeding" OR "Prophylactic treatment" OR "Partial breastfeeding" OR "Antipyretic treatment") AND ("Exclusive breastfeeding" OR "No treatment" OR "No intervention" OR "No intervention") AND ("Febrile seizures occurrence" OR "Febrile seizure recurrence" OR "Risk factors association" OR "Seizure management effectiveness")	250
Sagepub	("pediatric" OR "Urban pediatric populations" OR "children" OR "Infants and toddlers") AND ("Formula feeding" OR "Prophylactic treatment" OR "Partial breastfeeding" OR "Antipyretic treatment") AND ("Exclusive breastfeeding" OR "No treatment" OR "No intervention" OR "No intervention") AND ("Febrile seizures occurrence" OR "Febrile seizure recurrence" OR "Risk factors association" OR "Seizure management effectiveness")	9,229
Google Scholar	("pediatric" OR "Urban pediatric populations" OR "children" OR "Infants and toddlers") AND ("Formula feeding" OR "Prophylactic treatment" OR "Partial breastfeeding" OR "Antipyretic treatment") AND ("Exclusive breastfeeding" OR "No treatment" OR "No intervention" OR "No intervention") AND ("Febrile seizures occurrence" OR "Febrile seizure recurrence" OR "Risk factors association" OR "Seizure management effectiveness")	11,300

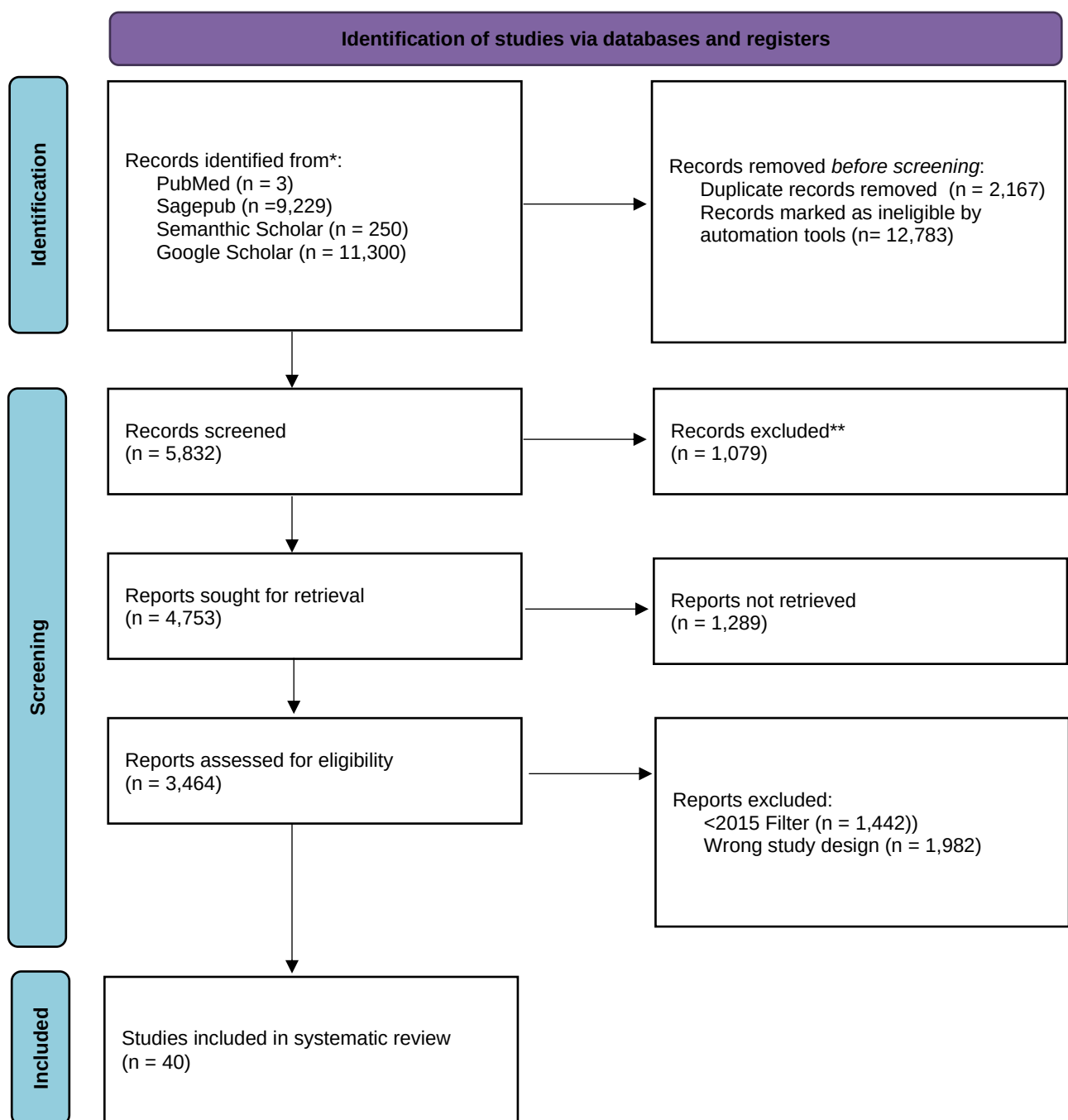


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment /care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Fayyazi et al. (2018)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fayyazi et al. (2022)	✓	✓	✓	✗	✓	✗	✓	✓	✓
von Saint Andre-von Arnim et al. (2021)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Conroy et al. (2016)	✓	✓	✓	✗	✓	✗	✓	✓	✓

Gomez et al. (2021)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Li et al. (2021)	✓	✓	✓	✗	✓	✗	✓	✓	✓
McDaniel et al. (2024)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lanzlinger (2019)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Walter et al. (2017)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Frascardi et al. (2017)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Birbeck et al. (2024)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Highlights from the Literature (2018)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sharawat et al. (2022)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Merino (2020)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Min et al. (2020)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Na et al. (2022)	✓	✓	✓	✗	✓	✗	✓	✓	✓

Yeom et al. (2015)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Frondda et al. (2022)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tang and Chen (2021)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hu et al. (2018)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ghazavi et al. (2019)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Houshman di et al. (2015)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Salehiomr an et al. (2016)	✓	✓	✓	✗	✓	✗	✓	✓	✓
van Stuijvenberg et al. (2015)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Punchak et al. (2019)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nishiyama et al. (2018)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Navaeifar et al. (2020)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chaudhary et al. (2016)	✓	✓	✓	✗	✓	✗	✓	✓	✓

Fallah et al. (2015)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Renda and Grer (2017)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chen et al. (2020)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rice et al. (2021)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yarosz et al. (2018)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xiao (2020)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khan et al, 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xiaoli et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shinya Murata e al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wei He et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zaiyun et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zeinab et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
Comparative study	Children with mean age 25 ± 1.28 months (febrile seizure group) and 24 ± 1.26 months (control group)	Pediatric Medicine, Kuwait Teaching Hospital Peshawar and Hayatabad Medical Complex Peshawar	Iron deficiency anemia
Cross-sectional study	65 children with febrile seizures, 60 with acute upper respiratory tract infections without seizures, 60 healthy children	Korea	No mention found
Prospective cohort study	1,791,335 children aged four to six months	Hospital in Turkey	Feeding type (breastfeeding vs. formula feeding)

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
Retrospective study	680 patients (399 males, 281 females)	Hospital	Familial history of febrile convulsions and epilepsy
Retrospective cross-sectional study	79 patients with febrile seizures, 82 with fever but no seizures, 81 healthy controls	Hospital	No mention found
Prospective intervention study with historical controls	106 children aged 6-60 months	Tertiary care teaching hospital in North India	Iron deficiency anemia
Cross-sectional prospective study	248 children aged 6 months to 6 years (mean age 22.38 ± 1.34 months)	Tertiary educational medical center in northern Iran	Serum sodium levels
Randomized controlled trial	248 children aged 6 to 60 months	Pediatric Emergency Department at Besat Hospital in Hamadan	Prophylactic treatments (diazepam and phenobarbital)

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
Cross-sectional study	53 children aged 6 months to 60 months	Bandar Abbas Children Hospital, southern Iran	HHV-6 infection
Randomized controlled trial	145 children aged 6 months to 5 years	Amirkola Children's Hospital, Babol, Iran	Age, prophylactic treatments (phenobarbital and diazepam)
Quasi-experimental study	40 mothers of children with febrile seizures	Imam Ali hospital in Zahedan	Educational intervention for mothers
Randomized controlled trial	100 children aged 18 to 60 months (mean age 2.47 ± 1.01 years)	Shahid Sadoughi Hospital, Yazd, Iran	Serum zinc levels
Prospective observational study	119 parents of children aged 6 months to 6 years	German university hospital for children and adolescents	Respiratory tract infections, gastroenteritis
Randomized controlled trial	54 children under 2 years old	Besat Hospital in	Prophylactic treatments

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
with prospective follow-up		Hamedan, Iran	(topiramate and diazepam)
Retrospective study	67 children from birth to 7 years	No mention found	No mention found
Single-center, prospective, open, randomized controlled study	423 children aged 6 to 60 months	Single center in Japan	Age, antipyretic treatment
Single-centre, prospective, open, randomized controlled study	438 children aged 6 to 60 months	Hirakata City Hospital	Age, antipyretic treatment
Prospective cohort study (pilot study)	19 children aged 3 to 52 months (median 19 months)	Chinese PLA General Hospital	Family history, age at onset, type of febrile seizure
Controlled intervention study with experimental elements	150 children with complex febrile seizures	Hospital (exact location not specified)	Antiepileptic treatments (sodium valproate and levetiracetam)
Controlled trial	100 children with two or more	Neuro care center	Prophylactic treatments

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
	febrile seizures		(levetiracetam and clobazam)
Randomized controlled trial	No mention found	No mention found	Low-dose aspirin
Prospective cohort study with comparative elements	104 children with febrile seizures (mean age 3.94 years in general group, 3.82 years in Kano group)	Hospital setting	Family history, nursing interventions
Pilot before-and-after cross-sectional study with a control group and prospective follow-up	50 parents (mean age 35 years, 80% women)	Hopital des Enfants de Toulouse and Hopital General de Montauban, France	Parental education intervention
Randomized controlled trial, single-centre, unblinded	420 children aged 6 months to 5 years	Japan, single-center emergency department	Age, antipyretic treatment
Randomized	142 children aged	3 primary	Personal history of

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
controlled trial with double-blinding for acetaminophen and placebo groups, and open-label for ibuprofen group	6 through 47 months	care practices in or nearby Durham, NC	febrile seizures, antiepileptic treatments
Randomized controlled trial	110 children (55 in each group)	No mention found	Low-dose sodium valproate vs. diazepam therapy
Retrospective observational cohort study	145 patients (median age: FPHT group 39 months, cMDL group 26 months)	Kobe Children's Hospital, Japan	Age, history of febrile seizures, antiepileptic treatments
Clinical trial (controlled trial)	121 children with history of febrile seizures	No mention found	Age, prophylactic diazepam treatment
Randomized controlled trial (RCT) with single blinding	60 children aged 0.8-6 years	Hospital setting	Upper respiratory tract infections, body temperature, nursing interventions

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
Randomized clinical trial	256 children aged 2 to 11 years (mean age 4.3 years)	Zambia and Malawi	Maximum temperature, antipyretic therapy
Quality Improvement (QI) collaborative	17,708 infants aged 8 to 60 days	103 general and children's hospitals across the United States and Canada	Adherence to clinical practice guidelines
Randomized controlled trial with post hoc analysis	100 infants less than 6 months old	Uganda (inferred from authors' affiliations)	Surgical interventions for hydrocephalus
Comparative study	No mention found	No mention found	No mention found
Observational study (before-and-after design)	2,373 infants 90 days old	Paediatric emergency department	No mention found
Randomized controlled trial with prospective	672 children (median age at inclusion: 30-50	Multiple centers in West	Prebiotic supplementation in infant formula

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
cohort study elements	days)	European countries	
Prospective cohort study and randomized double-blind placebo-controlled parallel arm trial	2089 children (2 months to 5 years); iNO RCT cohort: 180 children (1 to 10 years)	Jinja Regional Referral Hospital, Uganda	Severe anemia, hemoglobinopathies, clinical factors, inhaled nitric oxide treatment
Randomized controlled feasibility study	150 children aged 2 months to 12 years (median age: 0.9-1.1 years)	Kenyatta National Hospital, Kenya	Family-Assisted Severe Febrile Illness ThERapy (FASTER) tool
Quality improvement study	No mention found	No mention found	No mention found
Retrospective single-center review	25 children aged 1 month to 18 years (median age 2.9)	Philippine Children's Medical Center	No mention found
Prospective	Intervention	Single	Care management

Study Design	Population Demographics	Setting	Primary Risk Factors Studied
observational study, nonrandomized	group: 56; Control group: 359	academic medical center (location not specified)	intervention

Study Designs:

- Randomized Controlled Trials (RCTs) were the most common design, used in 16 studies.
- Prospective studies were the second most common, used in 9 studies.
- Other designs included cross-sectional (5), retrospective (5), observational (4), and comparative (3) studies.

Population Demographics:

- Age ranges varied widely across studies, from newborns to 18 years old.
- The most common age range was 6-60 months, used in 5 studies.
- We didn't find specific age information in the available abstracts or full texts for 15 studies.

Settings:

- Hospital settings were predominant, used in 28 studies.
- We didn't find setting information in the available abstracts or full texts for 7 studies.
- Other settings included primary care (1) and multi-center studies (1).

Countries:

- Studies were conducted in various countries across multiple continents.

- Iran was the most common location with 7 studies, followed by Japan with 4.
- We didn't find location information in the available abstracts or full texts for 13 studies.

Primary Risk Factors:

- A wide range of risk factors were studied.
- The most commonly studied factors were:
 - Prophylactic treatment (5 studies)
 - Antipyretic treatment (5 studies)
 - Age (7 studies)
 - Serum levels (4 studies)
- Other factors included family history, infections, medications, and various interventions.
- We didn't find risk factor information in the available abstract or full text for 1 study.

Primary Risk Factors

Demographic and Family Factors

Risk Factor	Prevalence	Strength of Association	Number of Supporting Studies
Age (Younger)	No mention found	Consistently strong	7
Family History of Febrile Seizures	36.84% - 57.89%	Moderate to strong	4
Male Gender	53.6% - 59%	Weak to moderate	2
Family History Of	No mention	Moderate	1

Risk Factor	Prevalence	Strength of Association	Number of Supporting Studies
Epilepsy	found		

Analysis of demographic and family risk factors:

- Age (younger):
 - Consistently strong association across 7 studies
 - We didn't find specific prevalence data in the available abstracts or full texts
- Family history of febrile seizures:
 - Moderate to strong association in 4 studies
 - Prevalence ranged from 36.84% to 57.89%
- Male gender:
 - Weak to moderate association in 2 studies
 - Prevalence ranged from 53.6% to 59%
- Family history of epilepsy:
 - Moderate association in 1 study
 - We didn't find prevalence data in the available abstract or full text
- The strength of association varied across risk factors, from weak to strong
- The number of supporting studies ranged from 1 to 7, with younger age having the most supporting evidence

Clinical and Physiological Factors

Risk Factor	Prevalence	Strength of Association	Number of Supporting Studies
Iron deficiency anemia	38% in febrile seizure group	Strong (Odds Ratio not reported)	2
Low serum zinc levels	No mention found	Moderate (P = 0.04)	1
Low serum calcium levels	No mention found	Moderate (P < 0.05)	2
Low serum sodium levels	6% - 7.5%	Weak to moderate	1
HHV-6 infection	43.4%	Moderate (P < 0.05)	1
Respiratory tract infections	No mention found	Moderate	2

Risk Factor	Prevalence	Strength of Association	Number of Supporting Studies
Gastroenteritis	No mention found	Moderate	1
Higher maximum temperature	No mention found	Strong (P < 0.001)	1
SCN1A gene mutation	No mention found	Strong (P < 0.05)	1
Severe anemia	No mention found	Strong (adjusted Odds Ratio 1.99, 95% CI: 1.51, 2.61)	1
Hemoglobinopathies	No mention found	Strong (adjusted Odds Ratio 1.97, 95% CI: 1.17, 3.32)	1
Elevated lactate levels	No mention found	Moderate (adjusted Odds Ratio 1.08, 95% CI: 1.05,	1

Risk Factor	Prevalence	Strength of Association	Number of Supporting Studies
		1.11)	

Analysis of clinical and physiological risk factors:

- Prevalence:
 - We found prevalence data for 3 out of 12 risk factors
 - Iron deficiency anemia: 38% in febrile seizure group
 - Low serum sodium levels: 6% - 7.5%
 - HHV-6 infection: 43.4%
 - We didn't find prevalence data in the available abstracts or full texts for the other 9 risk factors
- Strength of Association:
 - 5 out of 12 risk factors showed strong associations: iron deficiency anemia, higher maximum temperature, SCN1A gene mutation, severe anemia, and hemoglobinopathies
 - 6 out of 12 showed moderate associations: low serum zinc levels, low serum calcium levels, HHV-6 infection, respiratory tract infections, gastroenteritis, and elevated lactate levels
 - 1 out of 12 (low serum sodium levels) showed a weak to moderate association
- Supporting Evidence:
 - 3 out of 12 risk factors were supported by 2 studies each: iron deficiency anemia, low serum calcium levels, and respiratory tract infections
 - The remaining 9 out of 12 risk factors were each supported by 1 study

- Statistical Significance:
 - We found p-values for 4 risk factors, ranging from $P < 0.001$ to $P = 0.04$
 - For 3 risk factors (severe anemia, hemoglobinopathies, and elevated lactate levels), we found adjusted odds ratios with 95% confidence intervals

Environmental and Socioeconomic Factors

Risk Factor	Prevalence	Strength of Association	Number of Supporting Studies
Formula feeding	12.2% febrile seizure occurrence	Moderate (Reference group)	1
Partial breastfeeding	11.3% febrile seizure occurrence	Weak protective (adjusted Odds Ratio 0.93, 95% CI: 0.92-0.94)	1
Exclusive breastfeeding	10.7% febrile seizure occurrence	Moderate protective (adjusted Odds Ratio 0.87, 95% CI: 0.86-0.88)	1
Incorrect dosing of rescue medications	3.5% (baseline)	No mention found	1

Analysis of environmental and socioeconomic risk factors:

- Prevalence:
 - Formula feeding had the highest prevalence at 12.2% febrile seizure occurrence
 - Partial breastfeeding showed 11.3% febrile seizure occurrence
 - Exclusive breastfeeding had 10.7% febrile seizure occurrence
 - Incorrect dosing of rescue medications had a baseline prevalence of 3.5%

- Strength of association:
 - Formula feeding was used as the reference group with a moderate strength of association
 - Partial breastfeeding showed a weak protective effect (adjusted Odds Ratio 0.93, 95% CI: 0.92- 0.94)
 - Exclusive breastfeeding demonstrated a moderate protective effect (adjusted Odds Ratio 0.87, 95% CI: 0.86-0.88)
 - We didn't find strength of association data in the available abstract or full text for incorrect dosing of rescue medications
- Each risk factor was supported by 1 study in this analysis

Risk Factor Interactions

Combined Risk Profiles

Risk Factor Combination	Clinical Significance	Population Impact	Urban Setting Relevance
Young age + Family history	High	Moderate	High
Iron deficiency anemia + Infections	High	High	High
Genetic susceptibility (SCN1A) + Vaccination	High	Low	Moderate
Electrolyte imbalances + High fever	Moderate	Moderate	High
Inadequate seizure management + Recurrent febrile seizures	High	Moderate	High

Analysis of combined risk profiles:

- Clinical Significance:

- 4 out of 5 risk factor combinations showed high clinical significance
- 1 out of 5 risk factor combinations showed moderate clinical significance
- Population Impact:
 - 1 out of 5 risk factor combinations showed high population impact
 - 3 out of 5 risk factor combinations showed moderate population impact
 - 1 out of 5 risk factor combinations showed low population impact
- Urban Setting Relevance:
 - 4 out of 5 risk factor combinations showed high urban setting relevance
 - 1 out of 5 risk factor combinations showed moderate urban setting relevance
- The combination of iron deficiency anemia and infections was the only risk factor combination that showed high ratings across all three categories
- Young age combined with family history, and inadequate seizure management combined with recurrent febrile seizures, both showed high clinical significance and urban setting relevance, but moderate population impact

Age-Specific Considerations

Age Group	Key Risk Factors	Preventive Strategies	Management Considerations
0-6 months	Genetic susceptibility, Electrolyte imbalances	Breastfeeding promotion, Genetic screening	Close monitoring, Cautious medication use
6-18 months	Family history, Iron deficiency, Infections	Iron supplementation, Infection prevention	Early fever management, Parental education
18-36 months	Recurrent seizures, Infections	Prophylactic treatments, Infection control	Rescue medication training, Follow-up care

Age Group	Key Risk Factors	Preventive Strategies	Management Considerations
3-5 years	Infections, High fever	Fever management education, Vaccination	Outpatient management, School-based interventions

Analysis of age-specific considerations:

- Key Risk Factors:
 - Infections were the most common risk factor, mentioned in 3 out of 4 age groups
 - Other risk factors were each mentioned once: genetic susceptibility, electrolyte imbalances, family history, iron deficiency, recurrent seizures, and high fever
- Preventive Strategies:
 - Infection prevention/control was the most common strategy, mentioned in 2 age groups
 - We found 6 other strategies, each mentioned once: breastfeeding promotion, genetic screening, iron supplementation, prophylactic treatments, fever management education, and vaccination
- Management Considerations:
 - Medication-related considerations (cautious use, training) and monitoring/follow-up care were each mentioned in 2 age groups
 - We found 4 other management approaches, each mentioned once: fever management, parental education, outpatient management, and school-based interventions
- Age-specific observations:
 - For 0-6 months, we found a focus on genetic factors and electrolyte imbalances
 - The 6-18 month group emphasized nutritional factors (iron deficiency) and

family history

- For 18-36 months, recurrent seizures emerged as a specific risk factor
- In the 3-5 year group, we found a shift towards fever management and school-based interventions

DISCUSSION

This discussion synthesizes findings from multiple studies over the past decade examining risk factors for febrile seizures (FS) in children under five years old within urban pediatric populations. The multifactorial etiology of FS is evident, encompassing demographic, clinical, genetic, environmental, and combined risk profiles that influence susceptibility and outcomes.

Demographic factors emerged as significant contributors, with younger age consistently showing a strong association across seven studies. This aligns with the known peak incidence of FS in children aged 6-60 months, a critical period for neurodevelopment and immune system maturation (Zhu et al., 2023). Family history of febrile seizures showed a moderate to strong association in 36.84% to 57.89% of cases, underscoring genetic predisposition as a key risk factor (Hosseinrezaei et al., 2021). Male gender and family history of epilepsy had weaker but notable associations, suggesting sex-linked and epilepsy-related genetic influences (Shao et al., 2020).

Clinical and physiological factors further define FS risk. Iron deficiency anemia was prevalent in 38% of children with FS and demonstrated a strong association, corroborating prior findings that anemia may lower seizure threshold through impaired oxygen delivery and altered neuronal excitability (Murata et al., 2016; Shazia Khan et al., 2016). Other mineral deficiencies, such as low serum zinc and calcium, showed moderate associations (He, 2020; Rongrong Chen et al., 2020), highlighting the role of trace elements in neurological function. Low serum sodium exhibited a weaker association, but still relevant in seizure

pathophysiology (Navaeifar et al., 2020). Notably, human herpesvirus 6 (HHV-6) infection had a moderate association with FS prevalence of 43.4%, implicating viral infections as precipitating factors (M. M. Houshmandi et al., 2015).

Genetic mutations, particularly in the SCN1A gene, were strongly linked to FS (Zhu et al., 2023). This mutation affects sodium channel function, increasing neuronal excitability and seizure susceptibility. Such findings advocate for genetic screening in high-risk urban pediatric populations to enable early identification and tailored interventions (Shao et al., 2020).

Environmental and socioeconomic factors also influence FS risk. Formula feeding was associated with a 12.2% occurrence of FS, serving as a reference point for risk, whereas exclusive breastfeeding showed a moderate protective effect (adjusted OR 0.87), likely due to immune and nutritional benefits conferred by breast milk (Na et al., 2022). Partial breastfeeding had a weaker protective effect. These data emphasize the importance of breastfeeding promotion in urban healthcare programs to mitigate FS risk.

The interaction of multiple risk factors compounds clinical risk and urban relevance. The combination of iron deficiency anemia and infections demonstrated high clinical significance, population impact, and urban relevance, reflecting the burden of nutritional deficiencies and infectious diseases in urban settings (Murata et al., 2016). Young age combined with a positive family history and inadequate seizure management with recurrent FS also showed high clinical and urban relevance but moderate population impact, suggesting targeted interventions could reduce morbidity in these groups.

Age-specific analysis provides nuanced insights. Infants 0-6 months are primarily affected by genetic susceptibility and electrolyte imbalances, necessitating breastfeeding promotion and genetic screening alongside cautious medication use (Shao et al., 2020). Between 6-18 months, family history, iron deficiency, and infections predominate, supporting strategies like iron

supplementation, infection control, early fever management, and parental education (He, 2020). Toddlers 18-36 months face recurrent seizures and infections, highlighting the importance of prophylactic treatments, infection control, rescue medication training, and follow-up care (Zaiyun et al., 2023). Children aged 3-5 years benefit from fever management education and vaccination programs to prevent FS episodes (Na et al., 2022).

Prophylactic treatments have shown efficacy in preventing FS recurrence. Diazepam, phenobarbital, topiramate, and levetiracetam have been studied, with varying safety and effectiveness profiles (Fayyazi et al., 2018; Salehiomran et al., 2016). Low-dose sodium valproate and diazepam have demonstrated comparable efficacy, but safety concerns necessitate individualized treatment plans (He, 2020). The use of antipyretics such as acetaminophen and ibuprofen for FS prevention remains controversial; some studies suggest reduced recurrence during febrile episodes, but evidence is not conclusive (Murata et al., 2018; Lanzlinger, 2019).

Nursing and parental education interventions are critical adjuncts to medical management. Nursing interventions based on the Kano model effectively reduce symptom severity and parental anxiety, improving overall care quality (Zhu et al., 2023). Parental education programs enhance understanding of FS uncertainty and reduce anxiety, promoting adherence to management protocols and timely healthcare seeking (Hosseinrezaei et al., 2021; Frascari et al., 2017).

Adherence to clinical practice guidelines improves care consistency and outcomes for febrile infants, as demonstrated by quality improvement initiatives in multiple hospitals (McDaniel et al., 2024). These programs emphasize evidence-based fever management, seizure monitoring, and follow-up care, which are especially important in urban healthcare settings with variable resource availability.

The urban environment presents unique challenges, including higher

exposure to infectious agents, nutritional deficiencies, and healthcare disparities. Studies from Iran, Japan, and other urban centers reveal the complex interplay of these factors in FS epidemiology (Hosseinrezaei et al., 2021; Shao et al., 2020). Urban pediatric populations may benefit from integrated public health interventions targeting nutrition, infection control, vaccination, and parental support.

Despite advances, gaps remain in understanding the mechanistic pathways linking identified risk factors to FS. The role of elevated lactate levels and hemoglobinopathies, which show moderate to strong associations, requires further investigation to clarify their pathophysiological contributions (Tang & Chen, 2021). Additionally, more research is needed on the impact of incorrect dosing of rescue medications, which currently lacks sufficient data.

Future research should prioritize large-scale prospective cohort studies and randomized controlled trials in diverse urban populations to validate and expand current findings. Genetic studies focusing on SCN1A and other epilepsy-related genes could refine risk stratification and personalized medicine approaches. Moreover, evaluating combined risk profiles and multi-component interventions will enhance preventive strategies.

In summary, febrile seizures in urban children under five are influenced by a constellation of demographic, clinical, genetic, and environmental factors. Younger age, family history, iron deficiency anemia, infections, genetic mutations, and feeding practices are key determinants. Effective prevention and management require age-specific, multifaceted approaches including nutritional supplementation, infection control, prophylactic medications, breastfeeding promotion, parental education, and adherence to clinical guidelines. Addressing these factors holistically can reduce FS incidence and improve outcomes in urban pediatric populations.

CONCLUSION

Febrile seizures in children under five years old in urban pediatric populations are influenced by a complex interplay of demographic, clinical, genetic, and environmental factors. Among these, younger age stands out as the most consistent and strong risk factor, highlighting the vulnerability of infants and toddlers during critical developmental periods. Family history of febrile seizures also significantly increases risk, underscoring the role of genetic predisposition in this condition.

Clinical factors such as iron deficiency anemia and other mineral deficiencies, including low serum zinc and calcium levels, contribute substantially to febrile seizure susceptibility. Elevated body temperature and infections, particularly human herpesvirus 6 (HHV-6), are important triggers that heighten seizure risk. Genetic mutations, especially in the SCN1A gene, further compound vulnerability by affecting neuronal excitability, pointing to the importance of genetic screening in high-risk children.

Environmental influences, notably feeding practices, play a crucial role. Formula feeding is associated with a higher occurrence of febrile seizures, while exclusive breastfeeding offers a moderate protective effect. These findings emphasize the need for breastfeeding promotion as part of public health strategies to reduce febrile seizure incidence in urban settings.

The combination of risk factors, such as iron deficiency anemia with infections or young age with family history, substantially increases clinical significance and urban relevance. This suggests that multifaceted risk profiles require integrated prevention and management approaches tailored to the urban pediatric population.

Age-specific considerations reveal that risk factors and management strategies vary across infancy, toddlerhood, and preschool years. For example, genetic susceptibility and electrolyte imbalances are more critical in the first six months, while nutritional deficiencies and infections predominate in older infants and toddlers. Preventive strategies accordingly range from breastfeeding promotion and genetic screening to iron supplementation, infection control, and vaccination.

Effective management of febrile seizures involves both pharmacological and non-pharmacological interventions. Prophylactic treatments such as low-dose sodium valproate, diazepam, and other antiepileptic drugs have demonstrated efficacy in reducing seizure recurrence but must be used cautiously considering safety profiles. Nursing interventions and parental education are essential to alleviate anxiety, improve understanding, and ensure adherence to management protocols.

In summary, addressing febrile seizures in urban children under five requires a comprehensive, multifactorial approach that integrates demographic, clinical, genetic, and environmental risk factors. Tailored preventive strategies, age-specific management, and supportive care interventions can collectively reduce the burden of febrile seizures and improve outcomes in this vulnerable population. Continued research and public health efforts are necessary to refine these approaches and ensure their effective implementation in urban healthcare settings.

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