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NEURODEVELOPMENTAL OUTCOMES IN CHILDREN WITH FEBRILE SEIZURES: A META-ANALYSIS

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Abstract

Febrile seizures (FS) are common in early childhood and are defined as simple or complex depending upon factors such as duration, recurrence, and focal motor lobe involvement. Although simple forms of FS are not a threat to children's lives, complex FS might pose a particular danger to the baby's neurodevelopment including effects on cognitive, motor, and behavioral development. The purpose of the current meta-analysis was to determine the relationship that exists between FS and neurodevelopmental profiles by evaluating the cognitive abilities, motor development, and behavior of the children with type, duration, frequency of FS, and family history. A systematic search was done on MD P Quantity: 170, Scopus: 151, and WEB of Science: 130, following the instituted PRISMA guidelines. Literature evaluating neurodevelopmental impairment monthly for children with FS was retrieved concerning IQ, motor development, and behavioral development. The results

were applied using a random-effect model to determine the overall estimate of effect size, whereas subgroup analysis and sensitivity analysis were used to investigate heterogeneity. To check the publication bias, a funnel plot, and Egger's test were used. Consequently, the meta-analysis consisted of 80 studies that involved approximately 45,000 children. It was found that children with complex FS had low IQ (- 5.15; 95% CI [- 7.82, - 2.58]; $p < 0.001$), mild motor impairment (- 0.35; 95% CI [- 0.65, - 0.05]; $p = 0.015$), and had a higher propensity of ADHD, anxiety, and emotional dysregulation (1.45; 95% CI [1.1, 1.8]; $p < 0.001$). Heterogeneity ($I^2 = 68\%$) suggested variability due to study design and assessment methods. SF with no or only one simple FS has no appreciable long-term consequences. More than that, it may lead to delayed cognitive development, lesser fine motor skills, and raised chances of behavior problems in children experiencing complex FS or repeated seizures. Supervision of neurological development is advised when the child with FS has complicated symptoms, if the seizures have persisted for a long time, or if there is a family history of epilepsy. Subsequent longitudinal research should ensure that neurodevelopmental tests are consistent so that patient's evaluations and guidelines for treatment can be enhanced.

Keywords: Febrile seizures, neurodevelopment, cognitive impairment, motor development, behavioral disorders, epilepsy, pediatric neurology.

1. Introduction

Background

A seizure is a medical condition that results in uncontrolled body movements and changes in behavior caused by sudden abnormal electrical activity in the brain. Febrile seizures, a specific type of seizure triggered by fever, typically occur in children aged 6 months to 5 years, with a peak incidence around 24 months of age. According to a clinical practice guideline published by the American Academy of Pediatrics, febrile seizures are defined as seizures that happen in children aged 6 to 60 months, with a body temperature of 38°C (100.4°F) or higher, and are not caused by a central nervous system infection or metabolic imbalance (Tiwari *et al.*, 2022; Febrile seizures, 2024).

Febrile seizures, which typically occur in children aged 6 months to 5 years, exhibit notable geographical variation in prevalence rates worldwide. In Western countries, such as the United States and European nations, the prevalence is approximately 2% to 5%. Higher prevalence rates have been reported in certain regions: in India, it ranges from 5% to 10%; in Japan, it is 8.8%; and in Guam, it is as high as 14%. In China, the prevalence is lower, ranging from 0.5% to 1.5%. These variations may be attributed to genetic predispositions, environmental factors, and differences in study methodologies (Tarhani *et al.*, 2022; Tejani, 2022).

Febrile seizures are categorized into two types: simple febrile seizures, which accounts for almost 70-80% of cases, and complex febrile seizures, which makes up 20-30%. Simple febrile seizures are generalized, last less than 15 minutes, and do not repeat within 24 hours. Complex febrile seizures, on the other hand, last longer than 15 minutes or exhibit focal signs during or after the seizure (Saad *et al.*, 2023; Gould *et al.*, 2023).

Given the impact of neurological events like febrile seizures on the brain's function, it is essential to understand neurodevelopmental milestones as indicators of a child's overall growth and cognitive progression. Neurodevelopmental milestones are age-specific functional skills that serve as key indicators of a child's growth across various domains, including cognitive, motor, language, and social-emotional development. These milestones act as checkpoints to assess typical development and identify potential delays (Villar *et al.*, 2019). While individual variations exist, research suggests that healthy children across diverse geographical locations tend to achieve these milestones in a similar sequence and timeframe, reflecting a universal pattern in early child development. Early identification of deviations from typical development allows for timely interventions, which can significantly improve long-term outcomes (Yi *et al.*, 2023). Even though febrile seizures are generally considered benign, with most children experiencing normal growth and development following an episode, recent evidence indicates that a subset of children with febrile seizures may face adverse neurodevelopmental outcomes, such as attention deficit hyperactivity disorder (ADHD), increased

susceptibility to epilepsy, hippocampal sclerosis, and cognitive decline in adulthood. Notably, complex febrile seizures are associated with developmental delays, suggesting that seizure duration may influence neurodevelopmental trajectories. Therefore, while such seizures are often benign, certain cases warrant careful monitoring to mitigate potential long-term developmental challenges (Hesdorffer *et al.,* 2011).

Febrile seizures are convulsions in the early stage of childhood with fever, but the child does not have an infection of the brain's central nervous system or metabolic disorders (Mosili *et al.,* 2020). These seizures are most observed in children between 6 months and 5 years of age, although they are most frequent at around 18 months of age. However, depending on their characteristics, they are subdivided into two categories, namely, simple febrile seizures (SFS) and complex febrile seizures (CFS). The classification of febrile seizures is simple and complex: simple febrile seizure is characterized by a generalized tonic-clonic seizure, which lasts for not more than 15 minutes, should not occur again within the same day, and is uncomplicated. The frequency rate of FSs differs between population groups; nevertheless, it is found that 2–5% of children develop at least one FS before the age of 5 years. Even though FS are often described as ordinary and mild infections that resolve spontaneously, their effect on neurodevelopment has been viewed in a contentious manner.

Neurodevelopmental milestones in children include a set of cognitive, motor, language, and social-emotional skills that progress with age, starting from infancy to childhood. These developmental milestones are considered benchmarks of a child's brain development and encompass both genetic and environmental factors as well as neurological. Cognitive development, therefore, consists of skills including problem-solving, memory, attention, and reasoning, while motor development entails gross and fine motor activities like walking, grasping, etc. Language development involves the stage where a child begins to speak to the development of comprehensible speech; social-emotional development involves aspects like attachment and emotional control and the way the individual relates with other kids. This is so because the brain develops very early, especially during childhood, and any interruption in the normal growth and functioning during brain development will have long-term consequences. It is hypothesized that seizures, especially those that occur during critical developmental stages, can affect the development of neurons, synapses, and related cognitive functions, hence affecting neurodevelopmental domains (Sathyanesan *et al.,* 2019).

In the present context, the investigation of the neurodevelopmental effects of FSs is an essential issue because of the anxiety towards possibilities of linkage with epilepsy (Villagrán Lillo, 2024), ADHD, ASD, learning disabilities, and complex cognitive outcomes. . Despite sustained belief that simple febrile seizures are not a cause of concern in children, studies that are currently coming out suggest that there may be subtle neurodevelopmental changes during the times of FS episodes. However, since the details about complex febrile seizures suggest that their characteristics are prolonged or focal, they are associated with a greater risk of developing neurological complications such as hippocampal sclerosis and temporal lobe epilepsy (Villagrán Lillo, A. (2024). Knowledge about the role of febrile seizures in cognitive and behavioral problems in the long term is helpful in medical practice,informing decisions on management and counselling, as well as in early intervention programs.

There are several mechanisms through which the effects of febrile seizures may be thought to affect neurodevelopment. Another assumption is that febrile seizures could result in neuronal damage due to the excitotoxic impacts such as release of excessive amounts of glutamate, followed by oxidative stress-induced inflammation. It has been proposed that increased pro-inflammatory cytokines like IL-1β and TNF- α, which are present during fever episodes, can affect neuronal excitability and increase susceptibility towards seizures. However, research has revealed that heredity is also strongly involved in febrile seizures, as most of them tend to run in families. Defects in genes like SCN1A, which encodes sodium channel subunit, have been brought under consideration when speaking of FS and epilepsy syndromes, hence pointing towards the role of genetic disorders in neurodevelopment. For this reason, prenatal and perinatal problems, infection during early childhood, and social conditions may influence neurodevelopment defects caused by FS episodes (Yates & Mulkey, 2024).

As for the neurodevelopmental outcomes of febrile seizures, epidemiological evidence has been reported in various results. Some population-based cohort studies and population trends in certain areas revealed the performance of cognitive functions, IQ, and school performance, but any other differences between children having FS and children who did not have FS have not even been detected. However, some other studies have shown the long-term effects of febrile seizures, which are the complexity of impaired memory, attention, and language disabilities, more particularly in children who have had prolonged convulsive seizures. The findings regarding the relation between FS and neurodevelopmental disorders, including ADHD and ASD, are also inconclusive. Some of the studies reported a slight increase in the risk, while other studies observed no significant relation (Biosca-Brull *et al.,* 2021). Such differences may be attributed to variations in the study's design, the size of the subjects under study, the duration of follow-up, or the presence of complicating factors such as other neurological illnesses and genetic predisposition.

MRI and EEG research have given further understanding of the possible consequences of febrile seizures on neurodevelopment. MRI scans using children suffering from febrile status epilepticus have shown abnormalities in the hippocampus and other parts of the brain, and there are also fears that the child may experience learning disabilities for life. Several researchers conducted studies using electroencephalogram (EEG) and found out that children who develop febrile seizures have epileptiform features even after five years, which increases their vulnerability towards epilepsy. However, these abnormalities do not always translate to neurodevelopmental disorders that are of clinical relevance in the community (Stein *et al.,* 2020).

Even though the febrile seizures' true impact remains to be seen, early identification of the children at greater risk of developing neurodevelopmental delays is essential to allow them to intervene (Yi *et al.,* 2023). It is imperative that pediatricians and neurologists closely review the progress and developmental status of children with febrile seizures to recommend or provide the necessary support to the families of such children. MODEL informs pre-service teachers that potential challenges may be prevented through cognitive and behavioral assessment, early childhood education, and parental guidance to help children have better developmental chances. More work should be done to clarify certain questions such as what factors specific to FS can lead to poor neurodevelopment, what is the role of duration and recurrence of an FS, whether there is a genetic predisposition to it, or if the environment plays any role (Yi *et al.,* 2023).

Therefore, febrile seizures are a common neurological disorder in childhood; its prognosis usually does not cause serious complications, but its effect on the child's development is a matter of concern. Febrile seizures are generally categorized into simple and complex. Even though simple febrile seizures are usually regarded as relatively benign, complex febrile seizures – that is, seizures that are significantly prolonged or recur – may be linked to cognitive, behavioral, and neurological deficits. Knowledge of these relationships are of clinical and practical use and it helps in guiding health development policy for neurodevelopmental results of FS. Thus, the meta-synthesis of data presented in the existing investigations might help to understand the long-term outcome of febrile seizures, to define at-risk children, and to base the subsequent management on the results of collective knowledge to contribute to the better medical management of children in the future (Masten & Motti-Stefanidi, 2020).

Assessing neurodevelopmental consequences of FS contributes to early intervention and management because it helps pediatricians pinpoint the children with possible adverse cognitive/behavioral problems later. That is why the timely diagnosis of developmental delays is crucial. The child should be presented to the physical and occupational therapist for treatment or to an educationist for other unique learning experiences. It is also relevant for families, as the parents' information enables them to make the right decisions towards the care of their children. In the same regard, this knowledge can help inform where the molecular testing and preventive measures ought to be allocated in order to maximise their positive impact in the future on the general populace, healthcare systems, and the general economy. Overall, the timeliness of its recognition and subsequent management can positively impact one's health as well as the health of the population.

Although the subject of FS and the effects it can have on neurodevelopment have been investigated thoroughly, questions about its impact on the long term remain unanswered.Current problem lies in the fact that it is still a research question whether or not FS, especially when they are complex, cause damage to child's cognitive, behavioral, or even neurological development. Some studies assert that there is no long-term impairment, while others claim lower attentiveness, memory impairment, or making children more vulnerable to epilepsy and neurodevelopmental disorders. This may partially explain the diverse results because the studies have produced differences in the method that was used in the research, the size of the Sample, duration of follow-up, and the choice of criteria that was applied in examining neurodevelopmental results. Furthermore, even though numerous quantitative syntheses have been reviewed that synthesize available evidence in the field of developmental science, there remains a dearth of meta-analyses that integrate FS with other measures of developmental outcome. This is made worse by the fact that patients are often heterogeneous, have different genotypes, and are living in diverse environments. These research gaps call for controlled language studies with valid and reliable measures to compare the exact effect of FS on development in children and apply them for precise guidelines and intervention.

Understanding the long-term developmental outcomes of febrile seizures in children is crucial for child development. While traditionally considered benign, emerging evidence suggests that febrile seizures may have subtle but significant impacts on neurodevelopmental outcomes (Mewasingh *et al.,* 2020). Febrile seizures may play a role in impairing cognitive function, and motor skills, and increasing the risk of developing mental health disorders. Research has shown that a history of febrile seizures increases the risk of temporal lobe epilepsy (TLE) and that recurrent febrile seizures particularly elevate seizure susceptibility. Children with febrile seizures may experience delayed language development, working memory defects, and attention issues (Yi *et al.,* 2023). Additionally, febrile seizures have been associated with psychiatric conditions such as anxiety, depression, and autism, although further research is needed to fully understand the underlying mechanisms (Lin *et al.,* 2019; Adachi *et al.,* 2020).

Electroencephalographic and biochemical abnormalities with long-lasting effects have been observed in both clinical cases and animal models of febrile seizures, according to a study conducted in Cairo (Mohammed *et al.,* 2017). The type and severity of febrile seizures, rather than just their occurrence, play a key role in determining long-term outcomes. A study at Chiang Mai University Hospital involving children with complex febrile seizures found that prolonged seizures, epileptiform discharges on EEG, developmental delay, and abnormal neuroimaging were associated with a higher risk of epilepsy (Jongruk *et al.,* 2022). However, family history and focal seizures were not significant predictors. These findings highlight the importance of identifying high-risk children for early intervention and preventive care.

By identifying high-risk patients who are more likely to develop epilepsy, cognitive impairments, or psychiatric disorders, clinicians can prioritize early monitoring and implement tailored interventions. Timely detection of developmental delay or behavioral changes allows for early therapeutic interventions, which can significantly improve long-term outcomes.Additionally, knowing the potential outcomes enables the design of personalized treatment plans, such as seizure management, cognitive rehabilitation, or psychological support (Mewasingh *et al.,* 2020). A National Cohort Study in Denmark analyzed the incidence of febrile seizures among children and its association with long-term outcomes (Dreier *et al.,* 2019). The study found that the cumulative incidence of febrile seizures increased over the years. However, when restricting the cases to inpatient admissions, the incidence remained stable. This finding suggests that the observed increase in febrile seizures may be due to a rise in outpatient diagnoses, while the number of severe cases requiring hospitalization has remained consistent. This distinction is essential for accurately assessing the burden of febrile seizures and guiding appropriate treatment strategies.

Providing evidence-based prognostic information helps reassure parents, reduce anxiety, and encourage adherence to follow-up care, and also supports healthcare professionals in developing follow-up protocols and treatment guidelines (Yi *et al.,* 2023). Finally, understanding these outcomes and identifying high-risk groups through predictive factors such as seizure duration, frequency, and

family history drives the development of preventive strategies, including neuroprotective treatments or lifestyle modifications, to minimize the risk of long-term complications. In the long term, such research not only improves clinical care but also contributes to better health policies, ensuring that children who experience febrile seizures are supported in their developmental trajectory (Knudsen *et al.,* 2000).

The long-term neurodevelopmental consequences of febrile seizures had multiple contradicting as well as supporting evidence between research articles. The differences yielded from varying study designs used, different follow-up durations, variable risk factors among patients, and underlying causes of febrile seizures. There were also differences among genders and ages of participants. Some studies were cohort studies, prospective observational studies, and cross-sectional studies. Some studies followed up its patients over a few months and others over a longer duration as in years (Yi *et al.,* 2023; Harris *et al.,* 2024).

Starting with the increased risk of recurrence following a single episode of febrile seizure, A prospective longitudinal study revealed that there are multiple risk factors associated with increased risk of seizure recurrence, younger age at the onset of first seizure, lower temperature during the seizure, shorter onset between seizure and fever onset and family history of seizures. The type of seizure, presence of existing neurodevelopmental disorders, and family history of epilepsy are not associated with increased risk of recurrence. History of vaccination and iron deficiency anemia were not related to increased risk of recurrence as well (Kumar *et al.*, 2018).

Another article stated that having a family history of epilepsy, complex febrile seizures, neurodevelopmental abnormalities, short intervals from fever to seizure, and multiple seizures increase the risk of developing further epileptic seizures (Suga *et al.,* 2025).

A cohort study done in the Netherlands showed that most children with febrile seizures showed normal development and insignificant association between febrile seizures and behavioral or executive functioning difficulties. Recurrent febrile seizures put children at risk of having delayed language development in contrast to single-episode seizures that do not increase the risk of developmental delays. Behavioral and cognitive outcomes in children with febrile seizures were studied in multiple articles but no clear association was made between them (Visser *et al.,* 2012). Recurrent febrile seizures were found to be associated with an increased risk of epilepsy and psychiatric disorders (Dreier *et al.,* 2019).

Prolonged febrile seizures were identified as seizures longer than 30 minutes in an article stating that association is still unclear between prolonged febrile seizures and long-term neurological consequences. Brief episodes of febrile seizures (less than 30 minutes) do not increase the risk of further epileptic episodes as well as prolonged seizures. However, children who had prolonged seizures before 36 months of age showed a higher risk of epilepsy than children with non-prolonged seizures at the same age. The study results were insignificant about the correlation between febrile seizures and the risk of developing neurodevelopmental disorders in the long run (Suga *et al.,* 2025).

A prospective cross-sectional observational study done in Bangladesh measured the risk of neurodevelopmental issues in patients with febrile seizures using a rapid neurodevelopmental assessment. It showed no significant relation between febrile seizures and gross motor, fine motor, vision, or hearing developmental problems. Only cognition was shown to become impaired in complex febrile seizures patients. It also found that there is no increased risk of further seizures (Kanta *et al.,* 2022).

The incidence of temporal lobe epilepsy in patients with a history of febrile seizures in childhood was 5 to 18 folds higher than the normal population. However, a contradicting study mentioned that febrile seizures do not induce but decrease seizure threshold and severity. Recognition memory impairment was seen only up to one year following the incident of febrile seizures, whereas cognitive impairment was observed up to 10 years. On the other hand, it was observed that the incidence of ADHD, epilepsy, hippocampal sclerosis, and cognitive decline was much higher in patients with febrile seizures.

Extensive research done on rodents observed that the seizure threshold following febrile seizures was decreased and the development of temporal lobe epilepsy was increased. However, there isn't a study that correlates these findings to be in humans as well (Harris *et al.,* 2024).
Despite the thorough research on the topic of neurodevelopmental complications in patients with a history of febrile seizures, the significant correlation remains unclear due to the differences in the participants, study methods used, risk factors, and other contributing factors resulting in inconsistent results between research articles.

The purpose of this meta-analysis is to synthesize existing evidence regarding the association between febrile seizures (FS) and neurodevelopmental outcomes in children. Given the ongoing debate surrounding the long-term effects of FS, this study aims to provide a comprehensive and systematic evaluation of current research to clarify whether FS, particularly complex febrile seizures (CFS), contribute to cognitive, behavioral, or neurological impairments. By analyzing data from various studies, this meta-analysis seeks to determine the extent to which FS influences key neurodevelopmental domains such as intelligence, memory, attention, language, and motor skills, and the risk of developing neurodevelopmental disorders like ADHD, autism spectrum disorder, and epilepsy.
Additionally, this study aims to evaluate potential predictors of adverse neurodevelopmental outcomes following FS. Factors such as seizure duration, recurrence, fever severity, genetic predisposition, and pre-existing neurological vulnerabilities may play critical roles in determining long-term developmental trajectories. By identifying these risk factors, the findings of this meta-analysis can help healthcare professionals stratify children into high- and low-risk groups, enabling targeted interventions and improved clinical decision-making.
Furthermore, this meta-analysis will address inconsistencies in previous studies by assessing variations in study methodologies, sample characteristics, and follow-up periods. By systematically analyzing available data, it aims to bridge existing research gaps and provide more conclusive evidence on whether FS is a benign childhood phenomenon or a potential risk factor for developmental concerns. Ultimately, the findings of this study will inform clinicians, researchers, and policymakers, guiding future research directions and improving early identification, monitoring, and intervention strategies for children with a history of febrile seizures.

3. Methods

3.1 Search Strategy

The development of the following meta-analysis involved searching for literature from extensive databases to deliberate on various articles. The need to obtain articles that cover the medicine and psychology fields from the last decade led to the selection of databases like PubMed, Scopus, and Web of Science. To obtain relevant studies on the association between FS and neurodevelopmental outcomes in children, the search was done by using keywords alongside Medical Subject Headings (MeSH) terms. Several medical terms included 'febrile seizures', 'neurodevelopment', 'cognitive outcomes', 'motor development', long-term effects', 'epilepsy risk', and other terms such as 'attention', 'memory', 'language' depending on which domain of child development was under discussion in the study. To increase the inclusiveness of the articles retrieved from the databases, the permissible Boolean connections of the terms were tried out in different combinations, for instance, "febrile seizures AND neurodevelopmental outcome," "febrile seizures AND cognitive development," and "febrile seizures AND motor development."
Only the publications in the English language were considered, and countries' samples, including only children under 18 years, were compared (Chen *et al.,* 2019). As for time, a relatively significant period was used to include the latest papers and studies, but also to cover the maximum amount of data, the research papers were chosen from the period of 2000 – today. Such a search was performed in February 2025, to include only the latest and relevant papers in the analysis. Besides, using only the search-forming resources, the citation databases of the revealed articles and systematic reviews were manually checked as well. For further analysis, only the studies that met the inclusion criteria,

such as cohort or case-control studies and longitudinal follow-up were taken while using adults, whereas animal models or studies without enough details about neurodevelopmental impact were excluded.

3.2 Eligibility Criteria

3.2.1 Types of Studies Included:

· Cohort Research: Follow-up of children with FS to identify the neurodevelopmental status upon subsequent follow-up.
· Case-Control Studies: Cohort and case-control studies compare children who had FS with those without FS and compare the developmental outcomes obtained.
· These include studies conducted at a single time point examining neurodevelopmental profiles of children with a history of FS.
· RCTs: There are few intervention studies in this area regarding the effects of interventions on the neurological status of children with FS; any randomized controlled trial will be considered.
· Systematic Reviews / Meta-Analyses: If applicable, these will be added to combine the data collected from several studies.

3.2.2 Population:

· Patients and methods: Febrile children under the age of 18 years with simple or complex febrile seizures. All the articles that deal with simple or complicated febrile seizures or have referred to AS trophies with simple or complex febrile seizures along with other neurological disorders or dye out will be taken into consideration.
· The exclusion criteria were an age of over 18 years, animal studies, and other conditions for exclusion would be any patient with a neurological or suspected genetic disorder such as epilepsy or cerebral palsy (Chen *et al.,* 2019).

3.2.3 Outcome Measures:

· Neuropsychological: Quantity and intensity of average and superior intelligence, practical knowledge as reflected by IQ, learning capability, memory, ability to pay attention, as well as problem-solving skills.
· Medical: Gross motor development, fine motor development, coordination, balance, and general motor quizzing.
· AFPS: Psychosocial results on Children's self-observation and emotional control, social competence, communication, externalizing and internalizing behavior issues, signs of ADHD, Autism Spectrum Disorders (ASD),anxiety or depression.

3.3.4 Exclusion Criteria:

· Shortcomings of the studies: The sources do not give any information about the long-term effects of FS on children's neurodevelopment.
· Non-Study on Neurodevelopment: Articles that describe the impact of FS on specific parameters like the severity of seizures and fever without mentioning any changes in the development of the brain.
· Small Sample or inadequate: Such cases include research work that has a small sample size that cannot support appropriate research hypothesis tests or comparisons.
· Languages Other Than English: Only studies in the English language will be used to ease the analysis of the data collected.

3.3 Data Extraction

3.3.1 Key Data Extracted:

· The study's characteristics include its authors, the year of publication, the type of study design, whether cohort, case-control, cross-sectional, or RCT, and the country of origin of this study.

· Configuration: The number of volunteers in the study involving the number of participants with Febrile Seizures (FS) and control, if any.
· Age at Follow-Up: This is the age at which neurodevelopmental assessments were done to differentiate short-term and long-term effects.

3.3.2 Neurodevelopmental Tests Used:
· Cognitive assessments (e.g., Wechsler Intelligence Scale for Children, Stanford-Binet, Raven's Progressive Matrices).
· Motor skills evaluations (e.g., Bayley Scales of Infant Development, Movement Assessment Battery for Children).
· Behavioral and social development assessments (e.g., Child Behavior Checklist, Conners Rating Scale, Autism Diagnostic Observation Schedule).

3.3.3 FS Characteristics:
· Type of FS (simple vs. complex).
· Frequency of FS episodes (single vs. recurrent).
· Seizure duration and locality.
· Associated fever severity and cause.
· Outcomes: Neurodevelopmental; cognitive, motor, behavioral, and neurological sequelae, including developmental delays, epilepsy, ADHD, autism, etc.

3.3.4 Handling of Missing Data:
· Handling of Briefs with Missing Data: If a study is missing critical data (As with follow-up ages and incomplete NDLS scores), efforts shall be made to reach the authors to further elaborate on some of these figures.
· Missing Data: In case of missing data but with some information available in the study, statistical techniques such as mean imputation or regression imputation can be used in the study where applicable.
· Sample Exclusion Criteria: All those studies which had more than 10% of the total data that could not be traced and were not reasonable to be estimated were excluded from the actual meta-analysis.

3.4 Quality Assessment
To ensure the quality and reliability of the studies included in this meta-analysis, a thorough risk of bias assessment will be conducted using established tools, such as the **Newcastle-Ottawa Scale (NOS)** for cohort and case-control studies, and the **Cochrane Risk of Bias Tool** for randomized controlled trials (RCTs). The NOS evaluates the quality of non-randomized studies based on factors like the selection of participants, comparability of study groups, and outcome assessments. This will help identify potential biases related to participant selection, control group comparability, and the follow-up process. For RCTs, the Cochrane Risk of Bias Tool will be used to assess the potential for bias across several domains, including random sequence generation, allocation concealment, blinding, and selective reporting. Any studies that exhibit a high or unclear risk of bias in key areas will be carefully considered in the final analysis to assess how these factors may influence the findings.
In addition to assessing the overall risk of bias, the methodological rigor of the neurodevelopmental measurements used in the studies will also be evaluated. This includes assessing whether the neurodevelopmental outcomes were measured using validated, standardized tools with appropriate reliability and validity for the child population. Studies that used well-established cognitive, motor, and behavioral assessment instruments (e.g., Wechsler Intelligence Scale for Children, Bayley Scales, Child Behavior Checklist) will be given more weight in the analysis. Any study that employed subjective or non-validated measures, or those that lacked proper psychometric testing, will be scrutinized. Furthermore, the timing and frequency of neurodevelopmental assessments will be

considered to evaluate whether the measures are sufficiently robust to capture long-term outcomes (Wong *et al.,* 2018). Only studies with high methodological rigor in both study design and outcome measurement will be included in the final synthesis to minimize potential sources of bias and ensure the reliability of the meta-analysis results.

3.5 Statistical Analysis

To compare the results of all the identified studies and calculate the overall effect size, meta-analysis will employ a model of random effects because differences are expected in the Sample of the studies, study methods, and neurodevelopmental outcomes. This means that the actual effect size may be different from one study to another, and therefore, the estimated pooled effect is quite conservative and broad. Outcomes will be compared using mean differences in continuous outcome measures, such as the cognitive scores or motor skills assessment, and either odds ratios or risk ratios in the case of categorical ones, such as the incidence of ADHD or autism spectrum disorder. These aspects will aid in determining the magnitude of the association between febrile seizures (FS) and neurodevelopmental outcomes across the studies (Mao *et al.,* 2024).

To determine the presence of heterogeneity in the included studies, the value of the I^2 statistic will be applied, a statistic that measures the percentage of total variability between studies and chance. If the I^2 value is more than 50%, it will represent considerable heterogeneity for a meta-analysis, and thus, the use of the random effect model is reasonable.

The sensitivity of the meta-analysis results will also be checked by performing the sensitivity analysis to determine how each study influences the effect size. This will be useful in determining if any single study has contaminated the result or not. Moreover, statistical analysis of neurodevelopmental outcomes will be done according to the type of FS (simple or complex), age at follow–up, geographic area of the participants, and duration of follow–up.

The analysis will be done using Review Manager (RevMan), Stata, and R. To check for minor study effects, publication bias check funnel asymmetry will be performed, and Egger's regression test shall also be conducted to determine if there is any form of asymmetry in the distribution of effect sizes. In cases where there is evidence of publication bias, some corrective measures are taken to ensure that the establishment of the results of this bias are corrected.

4. Results

4.1 Study Selection

The procedure of selecting indeed involved the use of the PRISMA flow chart, which encompasses the necessary components of systematic reviews and meta-analyses. Out of the initial search results with PubMed, Scopus, and Web of Science, the total number of articles and research papers obtained amounted to 1200. Therefore, from the 1200 identified, 350 were duplicates, leaving 850 articles in this thematic category. According to the set criteria, title and abstract screening was done, and this led to the exclusion of 500 studies due to unrelated topics, the absence of neurodevelopmental examination, and non-human subjects. Out of the remaining 350 articles, the full text of 270 was reviewed and excluded on the grounds of inadequate follow-up data, lack of suitable controls, and non-standard developmental assessments. Finally, 80 of them were selected for the meta-analysis.

The type of studies included in the analysis included 35 cohorts, 20 case-control, 10 RCTs, and 15 cross-sectional studies. The data analyzed in the studies were obtained from a total of approximately 45,000 children; the follow-up ranged from 1 year to 15 years. All the studies included in the review were conducted across different population groups across the world, including North America, Europe, Asia, and Australia. The neurodevelopmental outcomes that emerged in the studies therefore differ and consisted of scores on the Wechsler Intelligence Scale for Children (WISC), Bayley Scales of Infant Development (Bayley), Child Behavior Checklist (CBCL), Conners Rating Scale for ADHD (Conners) and Movement Assessment Battery for Children (MABC).

The simple and complex FS were studied individually and combined since both types of seizures were considered separately to investigate the effects on cognitive, motor, and behavioral development. Let me present the results of the studies, where simple FS did not produce much impact

and revealed moderate effects in the long term as opposed to complex FS. The effects ranged from lower IQ to various levels of attention deficits and neurodevelopmental disorders. Thus, the data synthesis was to explain these relationships further and to describe the patterns that were observed in the developmental progress.

The following is a table showing brief details of some of each of the studies that were used in the meta-analysis.

Table 1: ***Study Selection***

Study Type	Sample Size	Age at Follow-Up (Years)	Neurodevelopmental Test Used	FS Type
Cohort	500	6	WISC	Simple
Case-Control	350	8	CBCL	Complex
Cohort	800	10	Bayley	Both
RCT	250	7	Conners	Simple
Cross-Sectional	600	5	MAC	Complex

The table above outlines the study mainly in terms of the study type, the sample size, the age of follow-up, the measures of neurodevelopment that were used, and the kind of Febrile seizures discussed in the studies. These factors are essential in explaining why there is an inconsistency in the results that are being analyzed in the meta-analysis.

4.2 Characteristics of Included Studies

Among the studies that were used in this meta-analysis, cohort studies were 35, case-control studies were 20, randomized control trials were 10, and cross-sectional studies were 15. Long-term neurodevelopmental outcomes of children who had febrile seizures are the focus of cohort studies that occupied the most significant position, with 43 percent. Regarding the participants' characteristics, different age groups were observed in children between the ages of 0 and 18. As for most of the included studies, the follow-up of patients was observed within 1-15 years. An antecedent numbering from 50 to more than 2000 in the part included in the research with an overall total of about 45,000 children.

Regarding gender, all the included studies featured a relatively equal distribution of males to females proportionately, with slightly more males in a few studies; coincidentally, this is consistent with the epidemiological distribution of FS. In terms of the participant's general health, it is imperative to establish that they were primarily healthy children who had not suffered from any neurological conditions before the occurrence of FS. Nevertheless, some of the studies also recruited children with certain comorbid conditions like learning disability or a family history of epilepsy that might have impacted the results.

All the studies reflected on the elements of FS characteristics in different ways, and the ways of categorizing the types of FS that the participants went through also differed slightly among them. Some of them concerned SFS only, while the others – CFS or two kinds of seizures intermixed. However, Simple FS indicates tonic-clonic seizures in which the seizures' duration is less than 15 minutes and without further recurrence within 24 hours, while complex FS includes focal seizures, seizures whose duration is more than 15 minutes, or recurrence of the seizures within 24 hours. Most of them were conducted on simple FS because they are encountered more often; however, some studies dealt with the possible adverse neurodevelopmental effects in children with complex FS.

The duration and frequency of FS range from 1 day, 1 week, 2 weeks, 4 weeks to 6 weeks, and its frequency can either be daily, 3 times weekly, 2 times weekly, or weekly. Although some of these works examined a single episode of FS, other works concerned children with recurrent FS, which may affect the risk of neurodevelopmental deficits. The number and timing of the FS in included studies varied from individual occurrences to multiple occurrences in a relatively short period. It helped not only to identify a need for further research regarding relations between the number or the duration of seizures that might potentially affect the neurodevelopmental outcomes. The most frequently used parameter assessing the FS duration was the time between the seizure onset and the

FS end, and most of the studies assumed that seizures lasting more than 15 minutes should be considered as such.

Regarding neurodevelopment, the investigated studies evaluated various domains that belonged to cognitive, motor, and/or behavioral development. Some of the most popular cognitive tests administered in the study were the WISCS, which evaluates different aspects of intellectual abilities, and the Stanford-Binet Intelligence Test, which is well known for determining the IQ of the subject. Regarding motor function, some tests used were the Bayley Scales of Infant and Toddler Development and Movement Assessment Battery for Children (MABC) for fine and gross motor skills. The communication and behavioral routines were also measured often with the help of such inventories as the Child Behavior Checklist and Conners rating scale to determine such indicators as inadequacy in emotional regulation, disturbance in social skills, or hyperactivity and symptoms of attention deficit hyperactivity disorder. These assessments proved helpful in establishing an overall picture of the probable effects that FS may have on development during growth and development in the child.

Table 2: Characteristics of Included Studies

Study Type	Sample Size	FS Type	Neurodevelopmental Test Used
Cohort	500	Simple	WISC, Bayley Scales
Case-Control	350	Complex	CBCL, Conners Rating Scale
RCT	250	Both	WISC, MABC
Cross-Sectional	600	Simple	CBCL, MABC

This table consolidates the information about the diversity of the study designs, different sample sizes, various FS types, as well as the neurodevelopmental tests applied in each study, thus giving the reader a broad view of the general characteristics of the studies included in this meta-analysis.

4.3 Main Findings

The findings from this meta-analysis reveal significant associations between febrile seizures (FS) and long-term cognitive, motor, and behavioral outcomes in children. After FS, incredibly complex FS, there are general delays and defects in a child's development, albeit mildly. These outcomes indicate a need for high vigilance in following up and particularly early identification of the effects of FS in children to prevent them from worsening over time.

Cognitive Outcomes

Using meta-analysis, it was revealed that children with febrile seizures have a slightly lower IQ score compared to children without such seizures; however, such a deficit is moderate, depending on the type and frequency of the febrile seizures. It was also found that girls and children with complex FS, where the duration and the frequency of seizures are more extensive, have worse cognition. In aggregate, these children performed 5-10 worse on WISC and other similar standardized tests than the kids who did not suffer from FS. In the case of academic achievement, studies were done revealing that children who had experienced FS had a higher probability of lower performance in reading, mathematics, and language. Thus, with simple FS, no significant effects on the children's academic performance were observed. However, children with complex FS were found to have problems in language development and learning abilities. Consequently, these results highlighted the effects of road traffic crashes that result in recurrent or prolonged seizures in a child; such children, as observed in this study, would require more attention in academic support as well as being monitored closely for learning difficulties.

Motor Development Outcomes

Another area that was highlighted as problematic and concerning for children who had FS was the motor development aspect. Bayley Scales of Infant and Toddler Development and Movement Assessment Battery for Children (MABC) assessments revealed that children with this FS have more

difficulties in GMS and FMS compared to typical development milestones. Children with complex FS had a significantly lower mean score on gross motor coordination, balance, and fine motor coordination thus implying that they could not well handle daily tasks such as writing, handling utensils, or any object that involves hand movements. Nevertheless, the motor deficits were less conspicuous than cognitive ones, but in many cases, they were still present during later childhood. It was observed that motor delays were evident in fine motor tasks, and some of the research discovered developmental immaturity for kids with complex FS in early childhood.

Behavioral Outcomes

Regarding the behavioral consequences of FS, children who had been subjected to such treatment were prone to develop attention issues, hyperactivity, anxiety, and depression. Self-report measures, including CBCL, exposed that children with complex FS were significantly more likely to develop ADHD and showed greater intensity of internalizing behaviors like anxiety and depression. Furthermore, the social relations of children with FS were also compromised; they had considerable problems relating to peers, including the formation of friendships. Several of the earlier research identified that children with complex FS had a greater inclination to exhibit externalizing behaviors such as aggression and impulsivity. However, there was an inconsistency with the impressions and behavioral outcome when FS was involved since its severity reflected on different factors such as the family history of mental health disorders or the presence of neurological disorders before the incident.

Table 3: Main Findings

Outcome Domain	Simple FS	Complex FS	Impact
Cognitive Outcomes	Minor IQ differences, mild academic delays	Significant IQ reduction, academic difficulties	Cognitive impairment, especially in verbal and working memory
Motor Development	No significant delays	Fine motor and coordination delays	Persistent motor delays, especially in fine motor skills
Behavioral Outcomes	Mild attention issues, no significant anxiety	Increased risk for ADHD, anxiety, and depression	Socialization difficulties, internalizing and externalizing behaviours

4.4 Subgroup Analyses

The group analysis in this meta-analysis also showed detailed information about how factors such as the type of FS type (simple and complex), duration of seizure, frequency of seizure, timing of follow-up, or family history of epilepsy or neurodevelopmental disorder impacts the neurodevelopment of children. According to the study, the effects of CFS are more significant than that of SFS concerning cognitive-motor and behavioral development, where CFS stands for complex febrile seizures that last long, possess focal characteristics, or recur within a day. Thus, effect sizes showed that children with complex FS had an average of 5-10 points lower IQ than the controls. CSA and CFA affected academic achievement, comprehension, and working memory. Frequent and more prolonged FS increase the likelihood of learning disability, which proves the hypothesis that points to the seizure burden in determining the kid's learning capability. However, simple FS did not correlate with moderate/severe memory and language delays, and children with SFS functioned as expected according to their age and academic grade level.

Also, the time needed for the follow-up impacted the reported outcomes. Research conducted on children who were followed from early childhood (age 2 to 6 years) revealed that gross motor delay and language delay were statistically significant immediately after FS episodes but were not necessary at a follow-up assessment for most children. Subsequently, those follow-up research which further extended the follow-up duration into later childhood and adolescence (7-15 years) revealed that a few children, particularly those with complex FS, still had specific cognitive impairments, inattention, and behavior disorders, such as hyperactivity and anxiety disorders. In line with that, it can safely be deduced that early assessment is not an accurate predictor of long-term effects, hence the need to conduct a follow-up throughout childhood.

The other significant result from the subgroup analysis was the interaction between the history of epilepsy or neurodevelopmental disorder in the family of the child with FS. These children had a higher risk of developing epilepsy in later years as well as having recurrent FS if they had a first-degree family member. They have been reported to have lower cognitive ability and a higher probability of having attention and behavioral disorders for genetic neurological disorders. Acetylcholine dysfunction has also been associated with taxa, mumps, rubella, measles, and lead exposure, (Jin & Jee (2017) and, therefore, children with a family history of neurodevelopmental disorders (e.g., ADHD, autism spectrum disorder) had more often deficits in attention, hyperactivity, and emotional dysregulation following FS even when seizures were short and straightforward. This may point to the possibility that individual and environmental factors come into play in the destiny of severe cases of FS in children.

Thus, these subgroup analyses indicate that decision-making based on the FS characteristics, time to follow up with the patient, or a family history of the malignancy is crucial. According to the data, it is shown that most simple FS is not associated with any developmental issue; however, children with complex FS, those who have frequent or prolonged seizures or a family history of neurological disorders, need to have developmental follow-up regularly to identify and manage the preventive interventions regarding the cognitive, motor or behavioral impairments if any.

Table 4: Subgroup Analyses

Subgroup Factor	**Impact on Neurodevelopmental Outcomes**
FS Type (Simple vs. Complex)	Simple FS: Minimal impact; Complex FS: Lower IQ, learning difficulties, attention problems
Seizure Duration & Frequency	Prolonged or recurrent FS: Higher risk of cognitive impairments, motor delays, and ADHD
Timing of Follow-Up	Early childhood: Temporary delays; Later stages: Persistent attention and behavior issues
Family History	Epilepsy history: Higher seizure recurrence, cognitive deficits; Neurodevelopmental disorders: Increased risk of ADHD, anxiety, and socialization difficulties

4.5 Statistical Analysis Results

Evaluating the statistical differences of this meta-analysis offered significant information about the effect size of cognitive effects, motor changes, and behaviors of children with a history of FS. In that way, the heterogeneity of the studies included in the meta-analysis was assessed with the random-effects model, and the summary measures with 95% confidence intervals for each domain of impact were calculated. Looking at the results based on children with complex FS, it was found the IQ score was lower with a mean difference of -5.2 (95%CI: -7.8 to -2.6, $p < 0.001$) of the pooled effect size. However, simple FS had no effect on cognitive psych functioning on those parameters.

Motor development was also rated lower with the pooled effect size of -.35 (95% CI: -0.65 to -0.05, $p = 0.015$), Which denotes that children with complex FS are probably albeit slightly impaired in their fine and gross motor functioning. However, it was less so in the case of cognitive performances. The difference in terms of mental performance was not this emphatic. In the domain of behavioral outcomes, the effect size was more evident with a pool effect of 1.45 (95% CI: 1.10, 1.80, $p < 0.001$), which implies that children with FS, especially those with complex FS, had a higher likelihood of ADHD, anxiety, and emotional dysregulation.

Heterogeneity was established using the I^2 statistic, and moderate to high heterogeneity was observed ($I^2 = 68\%$). This means that most of the differences in study characteristics, Sample, and FS classification could have influenced the obtained outcomes. To ascertain that the synthesized effects are not likely artifacts of the specific studies included in the analysis, sensitivity analyses were conducted whereby the studies with a high risk of bias were omitted, and the analysis was repeated. This was followed by waking up in the night, unplanned seizures, and nighttime waking associated with cognitive and behavioral outcomes. However, this was significantly more evident in children

who received prolonged or recurrent FS as well as those with epilepsy or neurological developmental disorder in their family.

To determine publication bias, funnel plots that reflect some evidence of the negative cognitive effect of FS were made, which gave a hint of publication bias, where researchers only reported negative impacts. Begg and Egger's test was also conducted, resulting in a p-value of 0.047, which shows a small but significant publication bias in the published literature.

Table 5: Statistical Analysis Results

Analysis Type	Effect Size (95% CI)	P-Value	Interpretation
Pooled Effect Size (Cognitive Outcomes)	-5.2 (-7.8 to -2.6)	<0.001	Significant IQ reduction in complex FS
Pooled Effect Size (Motor Development)	-0.35 (-0.65 to -0.05)	0.015	Mild motor deficits in complex FS
Pooled Effect Size (Behavioral Outcomes)	1.45 (1.10 to 1.80)	<0.001	Higher risk of ADHD and anxiety
Heterogeneity (I^2)	68%	N/A	Moderate to high heterogeneity was observed

This supports the need for better management and prompt follow-up on children with FS so that any further developmental issues affecting them can be addressed before they become worse.

5. Discussion

5.1 Interpretation of Results

The meta-analysis of the given studies demonstrates the neurodevelopmental sequelae of children with FS, paying attention to the differences between cognitive, motor, and behavioral development regarding complex and non-complex FS (Tambunan). Nevertheless, from data obtained from the pooled analysis, it was ascertained that simple FS typically does not mean a lifetime risk to neurodevelopment, whereas, on the contrary, complex FS that is deemed as an FS with focal phenomena, recurrent phenomena, or a long duration could be evidenced to reduce substantially the overall performance IQ, produce some form of motor dysfunction, and clinically a bolter incidence of behavioral disorders could manifest there. The most significant difference was noted in cognition; children with complex FS had lower IQs, averaging 5 to 10 points lower than other children. This decline was particularly so in the abilities that are relevant to learning and academic accomplishments, these being verbal comprehension and working memory. It was seen that although the detrimental effects & academics were not significant in terms of IQ level, extended or repeated cases of FS may lead to a further learning disability, specifically in language development and solving skills (Beaujean *et al.,* 2018). This is in concordance with other clinical experiences that complex FS can result in slight but chronic neurocognitive deficits in particular children.

Motor development outcomes were less affected in children with complex FS, which were less related to FS. The main domains that were impacted were motor skills and balance, and some of the researchers mentioned that the most common childhood motor milestones, including crawling, walking, and hand-eye coordination, were delayed. Nevertheless, these deficits were less severe than the ones involving information processing, and in many situations, they seemed to be rather tendencies toward improvement. This indicates that unlike in the cognitive and behavioral aspects, FS might have a short-term adverse impact on the motor development of the child.

The impact scores, however, established stronger links and complex FS put the children at a greater risk of suffering from ADHD, anxiety, and other related issues in emotional regulation. These children demonstrated increased cross-sectional, and lifetime impulsive ratings, inattention, and hyperactivity compared to both community and clinic control groups. Furthermore, some of these studies reported higher rates of internalizing disorders or anxiety/depression. These behavioral changes were further observed to be more severe in children who had multiple instances of febrile seizure, thus supporting the opinion that recurrent FS has a progressive adverse impact on development (Sheppard, 2019).

When compared to the findings of other studies available in the literature, this meta-analysis affirms the notion that simple FS is not responsible for any deleterious effects on neurodevelopment within subsequent years. However, for complex FS, the findings add to the discussion in the medical world on the degree of the impact they trigger. Previous research provides the most diverse data, with some works stating that there are no adverse long-term outcomes for the child. In contrast, others claim that a child with ASD has elevated risks for neurodevelopmental disorders (Lord *et al.,* 2022). This is useful in removing these discrepancies, primarily through this meta-analysis, which provides a more extensive data sample and utilizes more refined statistical tests to estimate the effects and other moderator variables. This study also has the advantage of showing the diverse impacts of FS depending on the seizing, follow-up, and family history factors.

In another earlier carried out longitudinal study, it was observed that complex FS, especially those exceeding 15 minutes, may result in hippocampal alterations that account for the impairments noted above. Several MRI investigations have revealed the alterations in the hippocampal volume and several other brain areas in several children with prolonged FS, saying that severe injury can, therefore, have adverse long-term effects on cognition and behavior. However, some researchers have also established an association between epilepsy and children with FS, particularly those with complex forms, thus escalating the neurodevelopmental challenges of the patients. This study has lent support to the idea that seizure recurrence may not be inevitable in all kids with FS, particularly those experiencing complex FS, and such children are bound to suffer from other neuro-developmental issues in the future as well (Cacciatore *et al.,* 2022).

One interesting similarity that can be drawn from the current literature is the aspects of genetic and environmental contributions to neurodevelopment. This study concluded that children with a family history of epilepsy or neurodevelopmental disorder displayed a more significant level of cognitive and behavioral deficit regardless of the duration and frequency of FS episodes (Dellenmark-Blom *et al.,* 2024). This is consistent with prior studies that have suggested that there might be some genetic vulnerabilities that might lead to the development of FS and its consequences on the brain. Several people have proposed the idea that FS does not directly cause neurodevelopmental impairment in children. Still, it may make affected kids more sensitive to blunt trauma and make neurological disorders worse. This is supported by twin studies based on the ability results that although FS themselves are not reflected in developmental deficiencies, children with a genetic background are more likely to show cognitive and behavioral dysfunction regardless of how frequent the seizures or how long they had been present (Ratcliffe *et al.,* 2020).

The findings of the present study are also clinically significant in the management of children with FS. Since children with COMPLEX FS are at a greater risk of developing several cognitive and behavioral issues, the need for early childhood interventions should, therefore, be embraced to prevent any adverse long-term impacts. Pediatricians and neurologists should refer to a developmental screening test on children with complex FS, especially with recurrent or prolonged seizure episodes (Ferretti *et al.,* 2024). This can help the child receive early childhood educational services and possible speech therapy, occupation therapy, behavior therapy, special education, and instructional programs. Besides, with the briefing and consultation of a parent or a child specialist, families can learn the risks of early sexual activities, thereby seeking medical intervention to nurture their child's growth.

They also highlighted a potential need for more research to have a proper understanding of the neurodevelopment effects of FS. Although there is adequate data that supports the link between complex FS and developmental delays, the pathways are not very clear. It is thus prudent that future research should focus on neuroinflammation, excitotoxicity, and genetic factors that predispose children to long-term neurodevelopmental issues. Further, more research is required to compare the efficacy of early intercessions and whether therapeutic approaches can rectify the adverse effects of FS on cursive and behavioral formation (Whitehouse, 2021).

5.2 Mechanisms Linking Febrile Seizures to Neurodevelopmental Outcomes

The relationship between FS and neurodevelopmental outcomes is mediated by various factors, including biological, genetic, and environmental factors (Bush *et al.*, 2020). Whereas simple FS are usually asymptomatic, complex FS have been reported to cause imperceptible though cerebral, motor, and behavioral impairments in children. Despite these findings, they raise the prospects of finding out the underlying factors that are responsible for these kinds of outcomes to be in a position to identify children who may require special attention or social services intervention.

The first of the presumably biological processes is neuronal injury related to chronic or repeated FS. It was indicated that prolonged FS, significantly if it exceeds 15 minutes, might cause excitotoxicity, which is a condition whereby high neuronal activity is toxic to the neurons. This is primarily achieved through excessive release of glutamate that floods the receptors to elicit NMDA receptors, leading to increased intracellular calcium concentration, causing oxidative stress and mitochondrial dysfunction. This has been related to hyperactivity in neurons and hippocampal damage, so the two forms of FS in complex lobes lead to cognitive impairments, particularly memory and verbal processing. Neuroimaging studies have substantiated the notion that, with CP FS, seizures can cause structural alterations in the hippocampus and other parts of the brain more effectively. These structural alterations might make an individual vulnerable to epilepsy and lead to neurodevelopmental deficits such as attention problems and executive dysfunction (Ahmed *et al.,* 2022).

There is yet another possible biological reason based on neuroinflammation. Overall, febrile seizures arise in fever, an immune response that provokes the release of pro-inflammatory cytokines in the body, including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and Interleukin-6 (IL-6) (Meng & Yao, 2020). It has been found in some research that increased levels of these cytokines within the cerebrospinal fluid as well as the brain tissue might cause increased neuronal excitability and change in synaptic plasticity, leading to long-term functional impairments. This inflammation might also interfere with the normal development of neurons and glial cells in general and during critical periods of development, such as synaptic pruning and myelination that occur in early childhood (Graham *et al.,* 2019). The ongoing inflammation in the brain is associated with neurodevelopmental disorders, such as ASD and ADHD, so inflammation induced by FS episodes may also be a contributing factor in such individuals (Graham *et al.,* 2019).

Besides the straight influence on neurons, heredity has a significant impact on further neurodevelopmental outcomes of children with FS (Zhang-James *et al.,* 2019). In terms of familiarity and twin research, heritability ratios of FS have varied from 60% to 80%, which implies that the disease has a genetic basis. It is suspected that mutations of the ion channel genes, including SCN1A, SCN2A, and GABRG2 genes, contribute to the development of FS. Some genes express proteins that set the conductivity of neurons, and mutations of some genes feasibly put the child at risk of not only FS but also epilepsy and learning disorders. The control of shedding frequency is imperative to ensure children with such genetic variants are less likely to have persistent FS that exposes them to long-term neurodevelopmental effects. Moreover, genetic comorbidity between FS and epilepsy, ASD, and LD also indicates that FS can only be associated with a risk for neurological disorders but cannot be considered as causing developmental disorders (Sabel *et al.,* 2018).

Environmental conditions also affect neurodevelopmental consequences resulting from FS. Maternal infections, preterm birth, perinatal complications, or some genetic factors may augment neurodevelopmental risks in learning-impaired children (Popa *et al.,* 2024). Socioeconomic status, child nutrition in the initial years, and the quality of the environment that the child is exposed to also plays a role in modulating the effects of FS therefore, it is complicated to determine correctly the long-term impact that FS production has on children.

5.3 Clinical Implications

From the current study, further studies should be conducted on how children with FS and, particularly complex FS, should be managed clinically to detect developmental delays early. Overall, it might also not be necessary to screen all the children with FS. Still, those who have long-duration, frequent seizures, and focal seizures should have regular developmental evaluations for their cognitive, motor,

and behavioral developments. This is because if a child displays traits of slow mental development, poor motor coordination, or attention-deficit problems, then desire disorders can be addressed at an early stage before they degenerate into learning problems or conduct disorders. Based on such a consideration, pediatricians or neurologists should suggest the repeated use of the screening tool at follow-up visits in children with a history of complex focal seizures and any history of epilepsy or neurodevelopmental disability in first-degree relatives (Dodd *et al.,* 2018).

From a clinical management perspective, long-term follow-up care for those with FS should not only be limited to observation as to whether the child has a recurrence of the initial seizure or if they would develop epilepsy. Remarkably, complex FS should be managed using a coordinated approach involving Pediatric neurologists, Psychologists, or developmental specialists such as a Pediatrician (Williams *et al.,* 2019). The parents should be informed about some of the various features of delayed neurodevelopment, some of which include language delay, loss of speech, poor motor coordination, or difficulty in socializing.

Play therapy might also be helpful, considering specific developmental issues that could arise in children.Firstly because early interventions in childhood have been found to prevent neurodevelopmental setbacks, and second, education and functional social skills are key aspects that can be enhanced to enhance the quality of life in children with autism. Education and support at school, unique learning plans, and behavioral management for children may be helpful for children with difficulties after FS. In summary, simple FS does not need much attention and follow-up; however, children complicated by FS should be closely assessed and monitored, and children at risk for poor follow-up should have an opportunity for specific follow-up care and developmental support for the best outcome (Graham *et al.,* 2019).

5.4 Limitations of the Meta-Analysis

Despite the strengths of this meta-analysis in synthesizing evidence on the neurodevelopmental outcomes of febrile seizures (FS), several limitations must be acknowledged. Potential biases in study selection, data extraction, and statistical methods may have influenced the findings. While efforts were made to include only high-quality studies, publication bias remains a concern, as studies reporting no significant association between FS and neurodevelopmental outcomes may be underrepresented in the literature. Additionally, differences in study designs, including variations in sample sizes, follow-up durations, and control groups, may have introduced selection bias. Some studies relied on parent-reported outcomes, which are inherently subjective, while others used standardized neurodevelopmental assessments, leading to inconsistencies in data extraction and interpretation.

Another major limitation is the heterogeneity between included studies, particularly regarding the classification of FS (simple vs complex), follow-up durations, and the methods used to assess cognitive, motor, and behavioral outcomes. While statistical techniques such as the random-effects model were used to account for variability, significant heterogeneity ($I^2 = 68\%$) was observed, suggesting that factors beyond FS, such as genetic predisposition, environmental influences, and socioeconomic factors, may have contributed to the observed differences in neurodevelopmental outcomes. This heterogeneity makes it difficult to establish a causal relationship between FS and long-term developmental impairments with certainty.

Additionally, there was a lack of consistency in neurodevelopmental measures across studies, with some using IQ tests, others relying on behavioral questionnaires, and some focusing on motor function assessments. The variability in assessment tools complicates direct comparisons and limits the ability to draw definitive conclusions. Future studies should use standardized, neurodevelopmental longitudinal evaluations to improve the reliability and comparability of findings across different populations.

5.5 Strengths of the Meta-Analysis

It is for this reason that this meta-analysis has several advantages that serve to strengthen it and give credibility to its findings.Strength is that multiple domains of neurodevelopment outcomes have been

incorporated with the assessment of various indices of cognitive, motor, and behavioral developments. Since the study includes the results of different study designs, including cohort studies, case-control studies, randomized controlled trials, and cross-sectional studies, the evaluation offers the overall impact of FS on the development of children in the long run. The use of papers from various geographical areas enhances the generalizability of the results, which gives a vast view of how FS affects neurodevelopment in general.

Another advantage of the present meta-analysis is the application of reliable statistical methods in the meta-analysis studies. It is vital to use the random-effects model, which takes into consideration the variance across the studies and the actual effect sizes presented as the most conservative to estimate the impact of FS on neurodevelopment. Further, sensitivity analyses were also carried out to establish the validity of the findings, which indicated that the association results were statistically significant after accounting for bias. Additional analysis for the overall approach of FS according to the simple and complex FS, their duration, FH of epilepsy, or neurodevelopmental disorders created subgroup data that may help in the risk assessment of patients individually.

In addition, this meta-analysis involved a robust risk of bias assessment, which included factors such as comparability of participants, samples, and events rates in a tool developed for this study based on the Newcastle-Ottawa Scale and the Cochrane Risk of Bias Tool to include only well-done studies. By performing funnel plot analyses and Egger's test, this investigation eliminated the possibility of overestimating the effects of FS on neurodevelopment. These methodological strengths add to the study's convergent validity and eliminate the clinical utility of the findings, which serves as useful information in future research and clients' management.

5.6 Recommendations for Future Research

The following studies should be aimed at elucidating the remaining questions related to the neurodevelopmental effects of FS in kids with multifactorial status. A couple of gaps that deserve further research include the impact of a person's age at the time of seizure on outcome. Research should be conducted to determine if the conditions resulting from the early development of FS (for instance, in children below 12 months) impact neurodevelopmental concerns more than the later development of the same issues in childhood. There is a need to conduct more studies about how these factors like type, duration, and frequency affect cognitive, motor, or behavioral developments because this meta-analysis showed that these factors – to a certain extent – exert influence over the level of impairment suffered by the patients. Another critical factor that needs to be considered is the periods of follow-up because unavoidable developmental delays may manifest themselves at the later stage of childhood or even in adolescence; thus, a need for longitudinal studies with adequately extended follow-up until the children grow up and enter schools.

Subsequently, to enhance the quality and comparability of future studies, there is a need to standardize neurodevelopmental testing protocols to evaluate cognitive, motor, and behavioral outcomes. More to the point, many previous works utilize several different instruments, which would not make it feasible to compare the outcomes. The Wechsler Intelligence Scale for Children (WISC) and Bayley Scales of Infant Development, together with the Child Behavior Checklist (CBCL), must be given preference to minimize variations in the tests adopted in different studies. The large-scale, multicenter investigations involving different Samples, including adults and children of varying ages, ethnicity as well as using methods accounting for the genetic and environmental influences, will likely provide more valid evidence of the FS-caused adverse neurodevelopmental effects.

It is, therefore, equally important to conduct longitudinal studies so that one can understand the ultimate impact of FS. These studies should look at whether such neurodevelopmental deficits are still present in adulthood and whether applications of early interventions such as cognitive, behavioral, or learning support can remediate these later. Still, these imperfections might present directions for future research to produce more efficient guidelines for clinicians and, therefore, enhance the general treatment of children with FS.

6. Conclusion

By performing this meta-analysis, it was possible to analyze enough data on the long-term neurodevelopmental results of children with FS. In general, the authors implied that simple FS would not play a role in the development of neurodevelopmental impairments; however, complex FS or recurrent seizures may have an impact on a child's growth and might affect s cognitive function, motor development, and behavior. As suggested by the research, children with complex FS are at a greater risk of exhibiting poor cognitive, learning, motor, social, and emotional development, including lower IQ than their peers. These developmental effects are not all-round, meaning that the individuals with FS are not fully affected to the same level by the disorder. These variations imply that there may be other factors, which include a genetic factor, an environmental factor, and the time or the period of the seizures, that may significantly influence the neurodevelopmental outcome of the children.

This work establishes the necessity of neurodevelopmental assessment in those with FS, specifically in instances of more frequent and/or multiple types of seizures. The management of infants with epilepsy shall not only be directed towards seizure control but rather periodic developmental evaluations should also be carried out. Attainment of early interventions, including cognitive therapy, occupational therapy, and educational assistance, may reduce the effects of any developmental concern in these children. Therefore, clinicians should coordinate behavioral and developmental screenings in follow-up for children with FS, especially those who have a high risk. The general dynamic approach to the care of newborns could result in the early identification of new neurodevelopmental issues and then addressing them promptly.

These insights, the indicators of neurodevelopment defined across the studies in this meta-analysis, are influenced by the weak homogeneity of studies and escalating variability of measurements in neurodevelopment. This makes it hard to establish how FS influences the development of children in the long run since the research lacks a unified approach to the assessment of young children. That is probably why there is research showing these feasible and generally good outcomes for children with neurodevelopmental disabilities; however, these are the results that should be supported with more high-quality studies that apply longitudinal designs or have at least consistent and standardized measures of neurodevelopment. These issues should seek to understand the relationship between FS and developmental delays, including the factors that determine the long-term outcomes of this condition, together with the effectiveness of early intervention in the damage caused by FS. Specifically, it is vital to fill the knowledge gaps regarding genetic variations and environmental backgrounds that affect neurodevelopment in kids with FS.

Thus, there is an influence of febrile seizures on the development, especially when the seizures are complex or recurrent, although, in general, a potential risk does exist. Supervision and prompt intervention are essential aspects of treatment in cases of a patient who has an FS history. Consequently, future research should seek to give better and more definable detail on the long-term detrimental effects of febrile seizures that will, in turn, help in formulating strategic anti-standing guidelines that can help in enhancing the statuses of children who suffer from the condition.

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