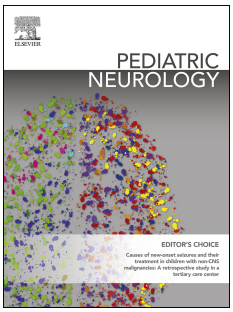

Antiseizure prescription for children with severe congenital heart defects and children with gastrointestinal anomalies

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Antiseizure prescription for children with severe congenital heart defects and children with gastrointestinal anomalies

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Short title: epilepsy in gastrointestinal malformations

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Antiseizure prescription for children with severe congenital heart defects and children with gastrointestinal anomalies

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Abstract

Background:

Children with congenital anomalies are at an increased risk of developing epilepsy, but the relative risk for specific anomaly subtypes remains underexplored. This study aims to estimate the risk of epilepsy, as indicated by antiseizure medication (ASM) prescriptions, among children with various congenital anomalies compared to children without anomalies.

Methods:

We utilized data from six European regions participating in the EUROCAT registries, covering births from 2000 to 2015. Children with major congenital anomalies, classified by International Classification of Diseases (ICD) codes, were compared to a reference population without anomalies. Epilepsy was identified based on >1 ASM prescription within a year. Relative risks (RRs) were calculated using mixed-effects models to account for registry-specific variations.

Results:

The study included 60,662 children with anomalies and 1,722,912 reference children, with a mean follow-up of 5.5 years. By age 5, ASM prevalence was 17.8 per 1,000 in anomaly groups and 2.0 per 1,000 in reference children. The highest RRs were observed in children with central nervous system (CNS) anomalies, including anomalies of the corpus callosum, severe microcephaly, and hydrocephalus. Comparable RRs were found in children with severe congenital heart defects (CHD) and gastrointestinal anomalies, primarily driven by diaphragmatic hernia.

Conclusion:

Children with congenital anomalies have a significantly higher risk of epilepsy, with CNS, chromosomal, severe CHD, and diaphragmatic hernia being key contributors. This study highlights the importance of tailored monitoring and early intervention for high-risk groups to improve neurological outcomes.

Keywords : Congenital anomalies, Epilepsy, Antiseizure medication, EUROCAT, Pediatric neurology

List of abbreviations

ASM: Antiseizure Medication

CA: Congenital Anomaly

CHD: Congenital Heart Defect

CI: Confidence Interval

CNS: Central Nervous System

CPM: Cardiopulmonary Bypass

DS: Down Syndrome

ECMO: Extracorporeal Membrane Oxygenation

EUROCAT: European Network for the Surveillance of Congenital Anomalies

EUROlinkCAT: European Linkage of Congenital Anomalies to Health Care Data

ICD: International Classification of Diseases

PHTN: Pulmonary Hypertension

RACHS: Risk Adjustment for Congenital Heart Surgery

RR: Relative Risk

SD: Standard Deviation

Background

Childhood epilepsy is a chronic condition that may have a long-term impact on health and well-being. The spectrum of the condition ranges from benign, self-limiting epilepsy to early-onset, medication-resistant epilepsy with poor long-term outcomes [1, 2]. Childhood epilepsy has been reported with a cumulative incidence of 0.23% at 3 years of age [2], 0.38% at 5 years [3] and 0.66% at 10 years of age [2-4]. Studies from the Nordic countries and UK have shown a decrease over time in the incidence of childhood epilepsy in younger children [3, 5].

Congenital cerebral anomalies are a known risk factor for epilepsy [6] and are often associated with early onset epilepsy with a poor prognosis [2]. While it is unsurprising that central nervous system (CNS) anomalies are associated with an increased risk of epilepsy, it is noteworthy that this is also the case for many major non-CNS anomalies [6]. For example, children born with congenital heart defects (CHD) [7, 8] have an adjusted odds ratio for epilepsy at around 2.4 compared to those without congenital anomalies [9]. Some studies are biased as they only include children with an anomaly born to mothers with known epilepsy, rather than all children with the given anomaly [10]. Most research attention focuses on whether maternal epilepsy +/- antiseizure medication (ASM) treatment affects the risk of being born with a congenial anomaly [11-14].

The European network for surveillance of congenital anomalies (EUROCAT) comprises population-based congenital anomaly registries in 23 countries covering more than 1.7 million (29%) of European births per year [15]. To investigate the survival and morbidity of children born with major congenital anomalies, members of the EUROCAT registries initiated the EUROlinkCAT project. The goal was to link data on children with congenital anomalies from EUROCAT registries to electronic health care databases including prescription databases [16]. The power of database linkage is exemplified through its ability to provide a comprehensive understanding of the healthcare journey for children with congenital anomalies. By linking congenital anomaly registries with hospital and prescription data across Europe, the project offers invaluable insights into medication usage, treatment efficacy, and long-term health outcomes in this vulnerable population [17-21].

By using >1 prescription of ASM as a proxy for an epilepsy/seizure diagnosis we aim to provide estimates of the relative risk (RR) of developing epilepsy for children with specific isolated congenital anomalies compared to children without congenital anomalies.

Methods

In this study, we used data from six EUROCAT registries across five European countries, as detailed in Table 1. Our inclusion criteria encompassed all children born alive with major congenital anomalies (referred to as EUROCAT children) from January 1, 2000, or from the first year where good quality linkage data could be obtained, until December 31, 2015, or the final year data were available if earlier. We had at least 1-year follow-up for all children. Additionally, we included all live-born children without congenital anomalies (reference children) born in the same time period and from the same populations as EUROCAT children. The Tuscany, Italy, registry only contributed a 10% random sample of the reference population, matched on the child's birth year and sex.

The EUROCAT children were all those registered in EUROCAT databases diagnosed with major congenital anomalies within 1 year of birth, as defined by EUROCAT [22]. The classification of congenital anomalies (CAs) followed the EUROCAT anomaly subtype, utilizing the International Classification of Diseases (ICD), Ninth or Tenth Revision—British Paediatric Association (ICD9-BPA or ICD10-BPA) coding system. Anomalies were coded using ICD-9 codes starting with 74–75, and Q-chapter codes in ICD-10. Children presenting solely with minor anomalies, which are characterized by limited medical, functional, or cosmetic impact as per EUROCAT definitions, were excluded from the analysis. Anomalies for inclusion were selected based on a livebirth prevalence of ≥ 1.75 per 10,000 births [16], additionally the release of small numbers (<5) was not allowed for some of the registries therefore we do not have data on all EUROCAT anomalies. Only children with isolated anomalies were included in the study. For those where data was available, CAs were grouped by organ systems as outlined below.

Severe CHD: As previously described in detail [18], all diagnoses of common arterial truncus, double-outlet right ventricle, transposition of the great arteries, single ventricle, atrioventricular septal defect, tetralogy of Fallot, pulmonary atresia, tricuspid atresia or stenosis, Ebstein anomaly, hypoplastic right heart syndrome, aortic valve atresia or stenosis, mitral valve anomalies, hypoplastic left heart, coarctation of the aorta, interrupted aortic arch, and total anomalous pulmonary venous return.

Gastrointestinal: All diagnoses of esophageal atresia, ano-rectal atresia & stenosis, diaphragmatic hernia and gastroschisis.

Central nervous system (CNS) anomalies: All diagnoses of anomalies of corpus callosum, craniosynostosis, hydrocephalus, severe microcephaly (< -3 SD) and Spina Bifida.

Chromosomal anomalies: These include trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome), as well as sex chromosome anomalies such as Turner syndrome (45, X) and Klinefelter syndrome (47, XXY). Additionally, triploidy, Cri du chat syndrome (5p deletion), DiGeorge (22.q11.1), Noonan and other unbalanced structural chromosomal anomalies (e.g., deletions, duplications, translocations) are included [22].

Classification of medication: ASM was defined as all medications included in the ATC system [23] beginning with N03. To identify children with ongoing antiseizure treatment, we required more than one prescription (refill) for any antiseizure medication within a 12-month period. This criterion captures children receiving continued pharmacologic management for epilepsy, while excluding those with only a single prescription, which may reflect short-term or acute symptomatic treatment. This operational definition does not replicate the clinical definition of epilepsy, which requires recurrent unprovoked seizures or a diagnosed epilepsy syndrome as defined by the International League Against Epilepsy [24], but provides a pragmatic and consistent proxy suitable for population-based registry analyses. For further methodological details, see [19, 25].

Statistical Methods

In each registry all children with at least two prescriptions of an ASM during a year were identified and the annual prevalence within each registry was defined as the number of children with >1 ASM prescription in that year of age divided by the person years of observation of children of the same age. This was done for each individual year of age from birth up to their tenth birthday (if available). The combined prevalence across all registries was calculated using mixed effects general linear models assuming a binomial distribution with the person years as the exposure and the registries were modelled as random effects. These results were compared to those obtained by summing all the data across the registries (ignoring any registry specific effects). The results were very similar, so the aggregated data was used to estimate the relative risks of having an ASM prescription in those children who had a specified anomaly compared to the reference children.

Results

Data Collection and Demographics: The dataset with data from six European regions included a total of 60,662 children diagnosed with major congenital anomalies ('EUROCAT children'), providing a broad spectrum of conditions for analysis. Additionally, the study included 1,722,912 reference children, representative of the general population. The mean time of follow-up after birth was 5.5 years (Table 1). Overall, the prevalence of having >1 ASM by the age of 5 was 17.8 per 1,000 (95% Confidence Interval (CI) 16.6 – 19.2)) in EUROCAT children and 2.0 per 1,000 (95% CI 1.9 – 2.1) in reference children.

Incidence of prescriptions with age: For both EUROCAT children and reference children we observed increasing prescription of ASM with age (Fig 1).

Prevalence according to organ system involved: Children with CNS anomalies had the highest prescription rates. A comparison of children diagnosed with gastrointestinal malformations and those with severe CHD revealed that both groups exhibited comparable prescription rates, with a similar increase in risk as age advanced (Fig 1).

Anomaly subtypes: The CNS anomalies that conferred the highest risk of being prescribed ASM were anomalies of the corpus callosum, severe microcephaly and hydrocephaly. The relative risk of prescription for children with chromosomal anomalies were on par with that of children with CNS anomalies. Children with non-severe CHDs such as ventricular septal defects or patent arterial ducts have lower relative risks, although still around double that of reference children. Those with congenital anomalies of the urinary system had low relative risks, as did cleft palate (Fig 2). The high rates in children with gastro-intestinal anomalies is partly explained by children with diaphragmatic hernia (Fig 2). Only 10% of children with gastro-intestinal anomalies had diaphragmatic hernia, yet they accounted for 70% of all prescriptions in this category. For some anomalies, such as limb anomalies and hypospadias, the risk of epilepsy is low, but still higher than for reference children.

Discussion

This study provides a comprehensive analysis of the risk of prescribing for epilepsy/seizures in children with congenital anomalies, utilizing a large, multi-country dataset from the EUROCAT registries. Our findings underscore the significant association between various congenital anomalies and the increased likelihood of epilepsy, as indicated by >1 prescription for epilepsy.

The observed increase in ASM prescriptions with age among both EUROCAT children and reference children aligns with previous research indicating a progressive risk of epilepsy as children grow older [2-4]. This trend is particularly pronounced in children with congenital anomalies, suggesting that some unifying trajectory of these children may predispose them to a higher risk of neurological complications, including epilepsy. Interestingly, the parity in prescription rates between children with gastrointestinal malformations and those with severe CHD suggests that the risk of epilepsy in these groups is more closely aligned than previously understood. Notably, the increased risk of epilepsy in children with gastrointestinal malformations was predominantly driven by those diagnosed with diaphragmatic hernia. Diaphragmatic hernia stands out from the other gastrointestinal malformations in that the pathophysiology is not restricted to the gastrointestinal

tract, but is also characterized by pulmonary hypoplasia and pulmonary hypertension (PHTN) [26]. The PHTN associated with diaphragmatic hernia can lead to shunting, hypercapnia and cardiac dysfunction [27], in addition PHTN severity is one of the main predictors of mortality [28]. The cardiovascular complications linked to diaphragmatic hernia are the primary reason it is the most common indication for extracorporeal membrane oxygenation (ECMO) in neonates [29]. In addition to perioperative factors such as surgical complexity and ECMO use, recent studies have shown that children with CHD may already exhibit cerebral injury before surgery. Preoperative neuroimaging has demonstrated both ischemic and white-matter lesions suggestive of pre- and perinatal brain injury, which may predispose these children to later development of epilepsy [30, 31]. In children with severe CHD, it is well established that that the main determinant of perioperative clinical seizures is the surgical treatment complexity, as identified by higher RACHS scores (Risk Adjustment for Congenital Heart Surgery, see [32]), the need for delayed sternal closure and time on ECMO [30]. In a recent study using continuous electroencephalographic monitoring authors identified seizures in 8% of neonates after cardiac surgery with cardiopulmonary bypass (CPM) [33]. Moreover, for those born with severe CHD the risk of epilepsy increased with additional surgical procedures [8]. The median number of surgeries in the first 5 years of life is actually higher for children with esophageal atresia than for children with diaphragmatic hernia [34]. It is tempting to speculate that a common unifying feature between the epilepsy risk experienced by children with severe CHD and diaphragmatic hernia is that these conditions often result in compromised hemodynamics and respiratory function requiring intensive care treatment and sometimes ECMO — all of which are known risk factors for neurological impairment and seizure development. This interpretation is in line with data from a recent Australian study [35] looking development of cerebral palsy. Broadly, congenital anomalies in two organ systems appear to be on the causal pathway to CP – those are cerebral and cardiac anomalies. Interestingly, while cerebral anomalies seem to directly contribute to CP development through cortical malformations, MRI findings in patients with cardiac defects suggest central nervous system damage resulting from perinatal or postnatal insults. As pointed out previously, this might well reflect complications related to surgical/intensive care management, rather than

the CA per se [36]. Similarly, in diaphragmatic hernia, multiorgan dysfunction and hypoxic injury during the neonatal period may lead to acquired brain injury that contributes to later epilepsy. Thus, while shared developmental pathways cannot be excluded, our findings are more likely to reflect the cumulative effect of acquired brain injury and critical illness in these high-risk groups. Future studies combining neuroimaging and longitudinal neurological follow-up will be essential to disentangle these mechanisms.

Children with Down syndrome (DS) have increased risk of epilepsy in their entire lifespan, with a peak incidence in childhood at around 2 years of age and again in late adulthood [37]. In our study we also report high RRs for ASM prescription for chromosomal disorders as a group, and specific conditions such as Turner and Down syndrome. This is in-line with previous reports [38]; unfortunately, we do not have data on whether or not these children with chromosomal disorders have undergone surgery.

One of the significant strengths of this study lies in its population-based design, which provides a robust and representative dataset for analyzing the risk of epilepsy in children with congenital anomalies. By utilizing data from multiple EUROCAT registries covering a substantial portion of European births, we achieved a comprehensive and diverse sample that enhances the generalizability of our findings. This population-based approach reduces selection bias and allows for a more accurate assessment of the true association between congenital anomalies and the risk of epilepsy. Additionally, the linkage of congenital anomaly registries with electronic health care databases, including prescription databases, offered a unique opportunity to track medication usage and treatment patterns in this vulnerable population, providing valuable insights into the healthcare journey of these children. An important limitation is that we have used prescription of ASM as a proxy of epilepsy rather than the clinical diagnostic criteria [24], this could possibly lead us to underestimate the true incidence of seizures in the cohort if a significant proportion of children with epilepsy (defined generally as 2 or more seizures) are not started on pharmacological treatment. It should be noted that our definition of epilepsy—based on more than one ASM prescription within a year—refers to repeated prescription events (of a single ASM type) rather than the use of multiple ASM types. This approach ensures that children with ongoing antiseizure treatment are captured, while minimizing inclusion of those who

received a single, short-term prescription for acute symptomatic seizures. Our definition therefore reflects treated epilepsy rather than all cases meeting the clinical diagnostic criteria. Current clinical guidelines, including those from the International League Against Epilepsy, recommend initiating long-term ASM therapy only after recurrent unprovoked seizures or when the risk of recurrence is high due to an identifiable underlying etiology [24]. Consequently, our approach is likely to capture children with established or high-risk epilepsy, while excluding those treated acutely after a single provoked seizure. This supports the validity of using repeated ASM prescriptions as a pragmatic indicator of epilepsy in large-scale registry studies. Children could also have seizure episodes in relation to acute illness, i.e. febrile convulsions so that could potentially lead to over-estimation if ASM are commenced. It has previously been shown that the proportion of young children with a prescription of ASM for non-seizure indication is low compared to older children and young adults as such we are unlikely to overestimate the true epilepsy incidence [3, 39]. Another limitation is that, although information on gestational age and birth weight is available within the EUROlinkCAT framework, these variables were not included in the present analysis because stratification by both congenital anomaly subtype and preterm birth would have produced numbers too small to report. Preterm birth and low birth weight are well-known risk factors for seizures and epilepsy and likely contribute to the overall risk observed in children with congenital anomalies. In a previous EUROlinkCAT study including more than 1.7 million children without congenital anomalies, preterm birth was associated with a twofold higher relative risk of receiving antiseizure medication up to 10 years of age, compared with term birth [19]. These findings suggest that preterm birth does not account for the increased risk of epilepsy among children with congenital anomalies.

Conclusion

This population-based study highlights the significant association between congenital anomalies and the risk of epilepsy, as indicated by the prescription of ASM. Our findings suggest that children with specific congenital anomalies are at an increased likelihood of developing epilepsy, and this risk increases with age,

especially in those with central nervous system disorders. Notably, our study reveals a surprising similarity in the prescription rates of ASM between children with sCHD and gastrointestinal anomalies, with diaphragmatic hernia being the predominant driver of risk in the latter group. This suggest that the cardiovascular complications of both severe CHD and diaphragmatic hernia may be a unifying pathway for the development of epilepsy. Notably, our study reveals a surprising similarity in ASM prescription rates between children with severe CHD and gastrointestinal anomalies, with diaphragmatic hernia being the predominant driver in the latter group. We hypothesize that this may relate to shared exposures to critical illness and acquired brain injury (pre-, peri-, and postprocedural), rather than a single definitive causal pathway.

Conflict of Interest

None to declare.

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Table 1: Overview of participating registries, number of births, and mean follow-up duration for children with congenital anomalies and reference children.

	Any Anomaly		Reference Children	
Region	Number of children born	Average length follow-up (yrs)	Number of children born	Average length follow-up (yrs)
Fyn, Denmark	1789	7,2	72,290	7,3
Finland	32,926	6,7	755,923	7,2
Emilia Romagna, Italy	5499	4,2	250,829	4,6
Tuscany, Italy*	3048	4,4	16,844	4,4
Valencian Region, Spain	4281	3,4	223,760	3,6
Wales, UK	13,119	7,0	403,266	6,7
Total	60,662		1,722,912	

* The Tuscany registry contributed a 10% random sample of the reference population

Figures

Figure 1: Prevalence and 95% confidence intervals (provided on the last point only) for prescription of antiseizure medication for children with congenital anomalies and reference children. All anomalies are isolated.

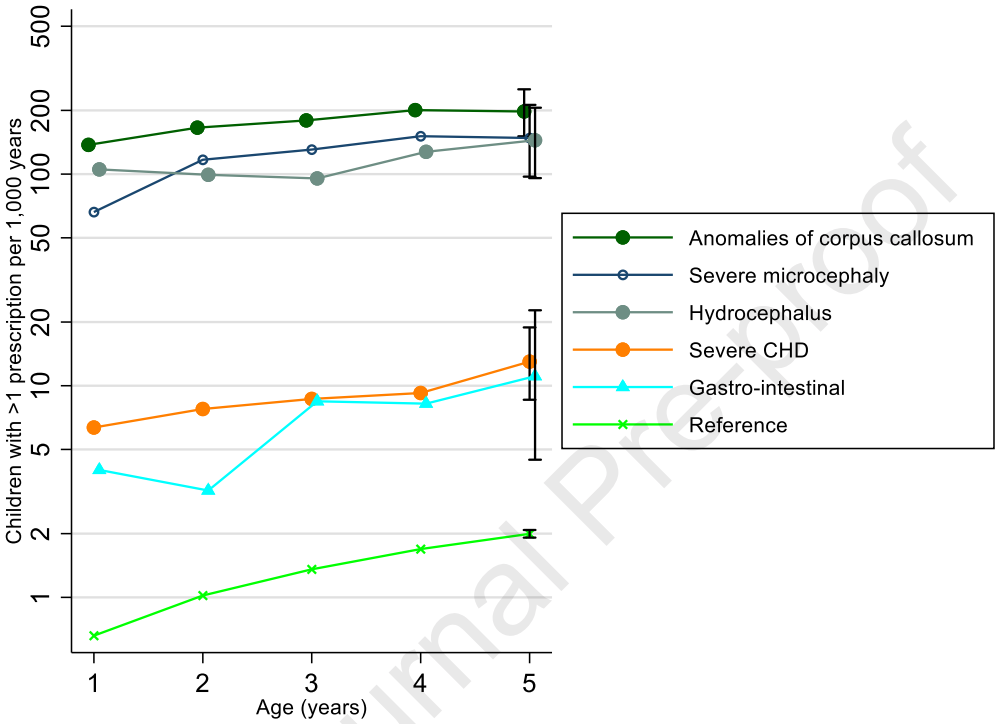
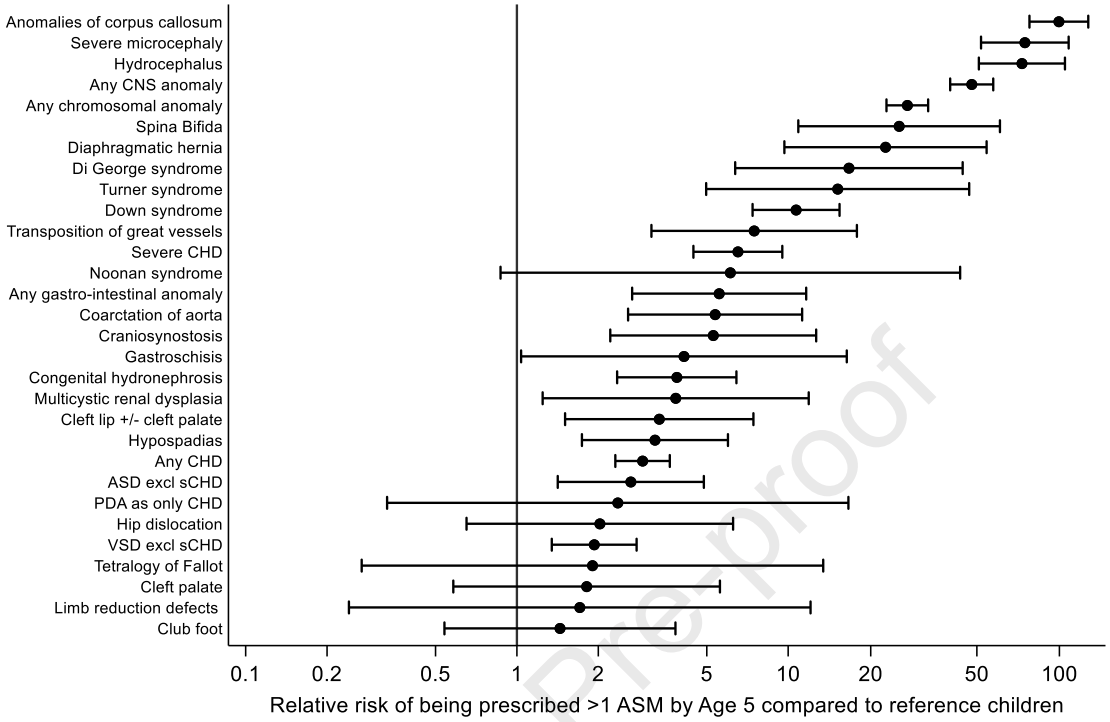


Figure 2: Relative risk of being prescribed antiseizure medication for children with selected isolated congenital anomalies compared to reference children.



Highlights

- Similar seizure risk in children with gastrointestinal malformations and severe CHD.
- Risk in gastrointestinal anomalies driven by congenital diaphragmatic hernia.
- Antiseizure medication prescriptions increase with age in all groups.
- CNS anomalies have a higher seizure risk than non-CNS anomalies.
- Isolated anomalies increase seizure medication risk ninefold compared to no anomalies.

Conflict of Interest Statement:

We, the undersigned authors, hereby declare that there are no conflicts of interest to report in relation to the manuscript titled "Converging paths: similar antiseizure prescription rates for children with severe congenital heart defects and children with gastrointestinal anomalies" This statement confirms that there are no financial, personal, or professional affiliations or relationships that could be perceived as potential sources of bias or conflict of interest affecting any aspect of our study.

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