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Developmental outcomes at age four following maternal antiepileptic drug use

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ABSTRACT

We investigated whether prenatal antiepileptic drug (AED) exposure was associated with adverse outcomes in the Before School Check (B4SC) assessments, particularly the assessments measuring neurodevelopment. Children exposed to AEDs were identified by linking women dispensed AEDs in the Pharmaceutical Collection to births recorded on the National Minimum Dataset (NMDS). Multinomial logistic regression was used to estimate adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) for outcomes of the parent-completed Parental Evaluation of Developmental Status (PEDS) questionnaire and Strengths and Difficulties Questionnaire (SDQ), after adjusting for gender, ethnicity, and socioeconomic deprivation. Between 2012 and 2016, 606 children with a mother who had been dispensed one or more AEDs during pregnancy had taken part in the B4SC. Prenatal exposure to sodium valproate (n = 161) or lamotrigine (n = 149) monotherapy was associated with an increased risk of having an abnormal SDQ — parent-completed (SDQP) score, ≥17 — indicating emotional or behavioral concerns (9.32% of children exposed to sodium valproate monotherapy had an abnormal score; aRR: 2.11; 1.23–3.63; lamotrigine 8.05%; aRR: 2.21; 1.21–4.02). Prenatal exposure to carbamazepine monotherapy (n = 201) was not associated with an increased risk of having an abnormal total SDQP score but was associated with increased risks in the individual domains of the SDQP. Prenatal exposure to AED polytherapy (n = 57) was associated with the highest risk of abnormal SDQP scores (17.54% of children exposed to polytherapy had abnormal scores; aRR: 2.75; 1.25–6.02). Prenatal exposure to sodium valproate and lamotrigine is associated with an increased risk of concerns about emotional and behavioral development being reported by parents in a neurodevelopmental screening program. Additional investigation is required into why significant differences between AEDs were not seen in this study.

1. Background

The link between antiepileptic drug (AED) use and congenital malformations is well established with evidence showing a two- to threefold increased risk of major congenital malformations following in utero exposure to AEDs, compared with the general population [1]. This risk is further increased following exposure to more than one AED during pregnancy [1]. Despite these risks, women with epilepsy and bipolar disorder typically continue treatment with AEDs during pregnancy to avoid the serious maternal and fetal risks associated with recurrent seizures or mood episode recurrence [2–4].

Studies have assessed the neurodevelopmental effects of sodium valproate using objective measures such as intelligence quotient (IQ) tests [5], the diagnosis of a neurodevelopmental disorder [6], or school performance results, [7] and found an elevated risk of long-term neurodevelopmental effects in children following maternal use of sodium valproate, particularly reduced verbal IQ and autism spectrum disorders [5,6,8]. The same association has not been shown consistently with other AEDs such as carbamazepine and lamotrigine [6,7].

A small number of studies have investigated the effect of prenatal sodium valproate exposure on emotional and behavioral development [9–12]. However, the neurodevelopmental effects of other AEDs are not as well studied nor are their effects when used for conditions other than epilepsy. New Zealand has a nationwide health and development screening program, the Before School Check (B4SC), which assesses 4-year-olds prior to school entry. In addition to measuring vision, hearing, height, and weight, children are screened for their emotional and physical development with two questionnaires, the Parental Evaluation of Development Status (PEDS) tool and the Strengths and Difficulties Questionnaire (SDQ), which is completed by parents and teachers. Depending on the outcomes of the assessments, children may be referred to other secondary care services. Participation in the B4SC program is voluntary, and assessments are done in community-based clinics and visits to childcare centers. The data are collected and stored in a secure national database managed by the Ministry of Health.

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Between 2012 and 2016, 89% of all eligible four-year-olds participated in the program making it a unique collection of data covering the psychosocial development of New Zealand 4-year-olds [13].

We aimed to conduct a database-linking cohort study to investigate whether prenatal AED exposure was associated with adverse outcomes in the B4SC assessments, particularly the assessments measuring neurodevelopment.

2. Methods

This retrospective nationwide cohort study uses three of New Zealand's administrative databases;: the Pharmaceutical Collection, the National Minimum Dataset (NMDS; hospital events), and the B4SC database. Every New Zealander has a unique National Health Index (NHI) code, an alphanumeric identifier that is used in all interactions with the health system over their life. This code makes it possible to link an individual's health data across a range of databases. By combining the births recorded on the NMDS, the medicines recorded in the Pharmaceutical Collection and the information included in the B4SC database, we can identify the children exposed to AED in utero and then assessed by the B4SC program.

Accurate recording of NHI numbers began in 2008, and the B4SC program was launched nationwide in 2010, therefore, our sample population were children who were exposed to an AED between 2008 and 2012 and who had a B4SC assessment between 2012 and 2016. The comparator group was all other children who had a B4SC in the study period.

The study was approved by the University of Otago Human Research Ethics Committee (HD17/003).

2.1. AED exposure

Information about AED exposure was obtained from the Pharmaceutical Collection database. In New Zealand, this covers all community-dispensed AEDs but does not record AEDs dispensed in hospitals. We defined AED exposure as any redeemed prescription of an antiepileptic drug belonging to the Anatomical Therapeutic Chemical (ATC) class N03A (antiepileptic), which included carbamazepine, lamotrigine, levetiracetam, sodium valproate, and topiramate, from January 2008 to December 2012. The exposure window was defined as nine months before the day a birth was recorded on the NMDS. A child was defined as being exposed to AED monotherapy if only one type of AED was prescribed during the exposure window and defined as exposed to AED polytherapy if more than one type of AED was dispensed during the exposure window.

2.2. B4SC outcomes

Registered nurses or nurse practitioners undertake the B4SC throughout New Zealand in different locations depending on the needs of the community, for example, preschools, doctors' clinics, and other community venues such as churches and marae (a sacred and traditional Maori area and meeting house). In addition to measuring vision and hearing using sweep audiometry, tympanometry, and distance visual acuity, height and weight measurements are taken, and children are screened for their behavioral, emotional, and physical development with two questionnaires, the SDQ and PEDS [14]. The B4SC uses the PEDS questionnaire to screen for developmental delays and behavioral problems in children. This questionnaire asks parents ten general questions about behavior, development, speech and language, and motor skills to assign children to pathways A, B, C, D, or E depending on the number of parental concerns. Pathway A is two or more significant developmental concerns, pathway B is one significant concern, pathway C is one nonsignificant concern, pathway D is parental communication difficulties, and pathway E is no concerns [15]. The PEDS questionnaire detects children with disabilities across different age groups with a sensitivity of 74–79% and specificity of 70–80% [16].

The SDQ is a brief questionnaire for parents and early childhood teachers comprising five important domains of child psychopathology, including emotional symptoms, conduct problems, hyperactivity–inattention, and peer problems. The SDQ is scored using a 3-point Likert scale where 0 = not true, 1 = somewhat true, and 2 = certainly true; several questions are reverse scored [17]. The resultant SDQ scores can be used as continuous variables but are often classified into the categories normal, borderline, and abnormal. For example, for total difficulties with a parent as the informant (SDQ — parent-completed (SDQP)), normal is a score of 0–13, borderline is 14–16, and abnormal is 17–40. The SDQ has high specificity (94%) and moderate sensitivity (63%) when completed by parents and teachers [18] but poorer sensitivity when only completed by parents (approximately 30% across the different domains) [19].

2.3. Covariate information

Maternal characteristics were obtained from the linked NMDS and Pharmaceutical Collection datasets, including age, smoking status, and AED therapy. Available information on covariates of children having a B4SC assessment included gender, ethnicity, and socioeconomic deprivation (measured as quintiles — 1 being least deprived to 5 being most deprived).

2.4. Statistical analysis

Stata statistical software, version 15 (Statacorp LLC) was used to analyze the data. Baseline maternal and study population characteristics were compared using Pearson's chi-squared tests. Multinomial logistic regression models were used to estimate adjusted risk ratios (aRRs) for SDQP scores, PEDS outcomes, and vision and hearing outcomes in children prenatally exposed to AEDs compared with the reference group of children who were not prenatally exposed to AEDs. The models were adjusted for gender, ethnicity, and socioeconomic deprivation. Outcomes for children exposed to individual AEDs and to AED monotherapy and polytherapy were also compared in this way. Hypothesis tests were performed using 95% confidence intervals (CIs) for aRRs, with the level of significance being set at two-sided p-values <0.05. No adjustment was made for multiple comparisons.

3. Results

3.1. Children with prenatal exposure to AEDs

Between 2008 and 2012, 765 children were exposed to AEDs during pregnancy. Of those, 606 (79.2%) had a B4SC and 159 infants prenatally exposed to AEDs did not have a B4SC. Maternal characteristics did not determine the likelihood of a child having a B4SC or not (Table 1). When comparing children who did have a B4SC at age four with those that did not, there was no significant difference in the age or smoking

Table 1
Maternal characteristics of children exposed to AEDs during pregnancy according to B4SC status.

Maternal characteristics	B4SC n = 606	No B4SC n = 159	p-Value
Age of mother (years): mean (SD)	29.2 (6.21)	29.0 (6.53)	0.836
	n (%)	n (%)	
Smoking listed in notes	37 (6.11)	15 (9.43)	0.138
AED:			
Sodium valproate	194 (32.01)	59 (37.11)	0.224
Carbamazepine	241 (39.77)	55 (34.59)	0.233
Lamotrigine	182 (30.03)	42 (26.42)	0.372
Levetiracetam	10 (1.65)	5 (3.14)	0.226
Polytherapy	57 (9.41)	16 (10.1)	0.792

Abbreviations: B4SC, Before School Check; AED, antiepileptic drugs; SD, standard deviation.

Table 2
Demographics of the B4SC study cohort.

Characteristics	n (%)	n (%)	p-Value
	No AED n = 286,966	AED n = 606	
Gender			
Male	147,538 (51.41)	326 (53.60)	0.241
Female	139,428 (48.59)	280 (46.20)	
Ethnicity			
European and other	153,729 (53.57)	353 (58.25)	<0.001
NZ Maori	66,296 (23.10)	183 (30.20)	
Pacific	29,003 (10.11)	49 (8.09)	
Asian/Indian	33,452 (11.66)	14 (2.31)	
MELAA	4486 (1.56)	7 (1.16)	
Quintile (measure of socioeconomic deprivation):			
1 — least deprived	55,066 (19.19)	74 (12.21)	<0.001
2	53,068 (18.49)	92 (15.18)	
3	52,626 (18.34)	108 (17.82)	
4	55,020 (19.17)	149 (24.59)	
5 — most deprived	69,042 (24.06)	182 (30.03)	
Missing data	2144 (0.75)	1 (0.17)	0.0980

Abbreviations: B4SC, Before School Check; AED, antiepileptic drugs; MELAA, Middle Eastern/Latin American/African.

status of the mother, in the type of AED dispensed, or whether they were dispensed AED polytherapy (Table 1).

During the study period, 286,966 children not prenatally exposed to AEDs had a B4SC check. Children with prenatal exposure to AEDs were more likely to be Maori and less likely to be Asian/Indian. They were also more likely to be living in the most deprived areas (quintiles 4 and 5) compared with children who were not prenatally exposed to AEDs (Table 2).

3.2. B4SC check outcomes

Of the 606 children who had any prenatal exposure to AEDs, 39 (6.44%) had parents report two or more significant concerns about their global development in the PEDS assessment, 48 (7.98%) were referred, and 46 (7.59%) were already under care. In comparison, 4.78% of children not exposed to AEDs had parents report two or more significant concerns about their global development in the PEDS assessment, 5.54% of children were referred, and 3.74% of children were already under care. After adjusting for gender, ethnicity, and socioeconomic deprivation, children with maternal exposure to any AED had an increased risk of having two or more significant developmental concerns (aRR: 1.50; 95% CI: 1.08–2.06), an increased risk of being referred for developmental concerns (aRR: 1.53; 95% CI: 1.13–2.08), and were more likely to be already under specialist pediatric care (aRR: 2.25; 95% CI: 1.65–3.07) compared with children not exposed to AEDs. In the SDQP assessment, 51 children (8.42%) of those prenatally exposed to AEDs had parents report significant concerns about emotional or behavioral development (SDQP score ≥17), 39 children (6.44%) were referred, and 24 children (3.96%) were already under care. In the comparison population of children not exposed to AEDs, 3.79% had an abnormal SDQP score, 3.67% were referred, and 1.47% were already under care. When compared with children with no prenatal exposure to AEDs, any prenatal AED exposure was associated with an increased risk of an abnormal SQDP score indicating parental concerns about emotional and behavioral development (aRR: 2.06; 95% CI: 1.53–2.76), an increased risk of being referred for these concerns (aRR: 1.72; 95% CI: 1.24–2.41), and an increased likelihood of already being under specialist care (aRR: 2.76; 95% CI: 1.82–4.19). Children prenatally exposed to AEDs were two times more likely to have abnormal scores for the conduct and hyperactivity domains of the SDQP than children not exposed to AEDs. Prenatal exposure to AEDs was not significantly associated with an increased risk of being referred for further hearing or vision assessment (Table 3).

Among the 606 children prenatally exposed to AEDs, 549 (90.59%) were exposed to monotherapy and 57 (9.41%) were exposed to polytherapy. Among those exposed to monotherapy, 161 were exposed to sodium valproate, 149 to lamotrigine, 201 to carbamazepine, 10 to levetiracetam, and 28 to topiramate. Among the 161 children exposed to sodium valproate monotherapy, 13 children (8.07%) had parents report two or more significant concerns about their development, 10 children (6.21%) were referred, and 15 children (9.32%) were already under care. In the SDQP assessment, 15 children (9.32%) exposed to sodium valproate monotherapy had abnormal total SDQP scores, and 11 children (6.83%) were referred. Among the children exposed to lamotrigine monotherapy, 8 children (5.37%) had two or more significant developmental concerns reported by parents in the PEDS assessment, and 9 children (6.04%) were referred. In the SDQP assessment, 12 children

Table 3
B4SC outcomes among children with and without prenatal exposure to AEDs.

Outcome	n (%)	n (%)	Crude RR (95% CI)	aRR (95% CI)[a]
	No AEDs (n = 286,966)	AEDs (n = 606)		
PEDS				
Pathway A — ≥2 concerns	13,731 (4.78)	39 (6.44)	**1.54 (1.12–2.15)**	**1.50 (1.08–2.06)**
Referred	15,903 (5.54)	48 (7.92)	**1.73 (1.28–2.35)**	**1.53 (1.13–2.08)**
Already under care	10,736 (3.74)	46 (7.59)	**2.46 (1.81–3.35)**	**2.25 (1.65–3.07)**
SDQP				
Score ≥17	10,887 (3.79)	51 (8.42)	**2.34 (1.76–3.12)**	**2.06 (1.53–2.76)**
Referred	10,536 (3.67)	39 (6.44)	**2.02 (1.45–2.81)**	**1.72 (1.24–2.41)**
Already under care	4218 (1.47)	24 (3.96)	**3.11 (2.05–4.70)**	**2.76 (1.82–4.19)**
Emotion ≥4	22,852 (7.96)	68 (11.22)	**1.46 (1.13–1.88)**	**1.40 (1.08–1.80)**
Conduct ≥5	17,680 (6.16)	77 (12.71)	**2.22 (1.74–2.82)**	**1.95 (1.53–2.49)**
Hyperactivity ≥7	11,841 (4.13)	54 (8.91)	**2.27 (1.72–3.01)**	**2.01 (1.52–2.67)**
Peer problems ≥4	19,420 (6.77)	56 (9.24)	**1.40 (1.07–1.85)**	**1.36 (1.03–1.79)**
Hearing				
Referred	15,657 (5.46)	36 (5.94)	1.12 (0.80–1.58)	1.05 (0.75–1.48)
Already under care	10,184 (3.55)	36 (5.94)	**1.73 (1.23–2.42)**	**1.55 (1.10–2.18)**
Vision				
Referred	19,156 (6.68)	48 (7.92)	1.23 (0.91–1.65)	1.24 (0.92–1.67)
Already under care	9866 (3.44)	33 (5.45)	**1.64 (1.15–2.33)**	**1.57 (1.10–2.23)**

NB: bold font indicates statistical significance.
Abbreviations: B4SC, Before School Check; AED, antiepileptic drugs; PEDS, Parental Evaluation of Developmental Status; SDQP, Strengths and Difficulties Questionnaire — parent-completed; RR, relative risk.
[a] Adjusted for gender, ethnicity and socioeconomic deprivation.

(8.05%) had abnormal total SDQP scores, and 10 children (6.71%) were referred. Among the children exposed to carbamazepine monotherapy, 15 children (7.46%) had parents report two or more concerns about their development, and 23 children (11.44%) were referred. In the SDQP assessment, 14 children (6.97%) with prenatal carbamazepine exposure had an abnormal score, and 12 children (5.97%) were referred.

After adjusting for gender, ethnicity, and socioeconomic deprivation, children exposed to sodium valproate or lamotrigine monotherapy were significantly more likely to have an abnormal total SDQP score than children not prenatally exposed to any AEDs (sodium valproate aRR: 2.11; 95% CI: 1.23–3.63 and lamotrigine aRR: 2.21; 95% CI: 1.21–4.02). Comparing children exposed to sodium valproate monotherapy with those exposed to lamotrigine or carbamazepine monotherapy revealed no significant differences in the risk of parents reporting concerns in the PEDS or SDQP assessments. Children prenatally exposed to carbamazepine monotherapy were only significantly more likely to be referred following the PEDS assessment (aRR: 2.04; 95% CI: 1.29–3.21) compared with no AED exposure. Other assessments did not reveal significant differences between children exposed to carbamazepine monotherapy and those with no exposure to AEDs, however, they did have increased risks of abnormal scores in the conduct, hyperactivity, and peer problem domains of the SDQP. Comparing carbamazepine monotherapy to lamotrigine monotherapy did not reveal any significant differences in the B4SC outcomes (Table 4). One child exposed to levetiracetam monotherapy was already under specialist care in the PEDS assessment, and one was referred following the SDQP assessment. Of the 28 children exposed to topiramate monotherapy, one was referred and two were under care in the PEDS assessment and none had concerning SDQP outcomes. Adjusted risk ratios were not calculated because of the small numbers of children prenatally exposed to levetiracetam or topiramate monotherapy.

Children exposed to AED polytherapy had an increased risk of having an abnormal SDQP score compared with children exposed to AED monotherapy (aRR: 2.75; 95% CI: 1.25–6.02). They were also significantly more likely to be already under care for concerns in the SDQP childhood development domain (aRR: 4.27; 95% CI: 1.61–11.39) (Table 5).

3.3. Sibling analysis

Of the 606 children exposed to an AED who had a B4SC, 478 were the only child assessed (i.e., no sibling in the dataset). There were 60 sibling pairs and two sets of three siblings and two children appearing from one set of three siblings (one sibling had not had a B4SC). After excluding siblings and rerunning the analysis of outcomes following any exposure to AEDs, we found that associations largely stayed the same except in

Table 4
B4SC outcomes among children exposed to individual AED monotherapy compared with children unexposed to AEDs during pregnancy.

	n (%)	Reference group: children unexposed to AEDs	Sodium valproate vs lamotrigine	Sodium valproate vs carbamazepine
Monotherapy AED exposure outcomes		aRR[a]	aRR[a]	aRR[a]
Sodium valproate	161 (82.99[b])			
PEDS				
Pathway A — ≥2 concerns	13 (8.07)	1.53 (0.83–2.80)	1.21 (0.47–3.13)	0.99 (0.47–2.11)
Referred	10 (6.21)	1.20 (0.62–2.32)	0.75 (0.29–1.95)	0.51 (0.24–1.07)
Under care	15 (9.32)	**2.81 (1.61–4.89)**	0.74 (0.34–1.64)	1.60 (0.72–3.50)
SDQP				
Score ≥17	15 (9.32)	**2.11 (1.23–3.63)**	1.08 (0.50–2.32)	1.60 (0.80–3.17)
Referred	11 (6.83)	1.78 (0.95–3.34)	0.87 (0.34–2.17)	1.21 (0.55–2.70)
Under care	7 (4.35)	**3.01 (1.39–6.52)**	0.69 (0.25–1.88)	1.98 (0.69–5.68)
Emotion ≥4	19 (11.80)	1.46 (0.90–2.36)	1.33 (0.69–2.56)	1.49 (0.83–2.69)
Conduct ≥5	20 (12.42)	**1.87 (1.17–3.00)**	0.86 (0.45–1.66)	1.17 (0.66–2.09)
Hyperactivity ≥7	10 (6.21)	1.35 (0.71–2.58)	0.67 (0.31–1.42)	0.89 (0.45–1.76)
Peer problems ≥4	10 (6.21)	0.87 (0.46–1.67)	1.18 (0.50–2.78)	0.74 (0.39–1.41)
Lamotrigine	149 (81.87[b])			
PEDS				
Pathway A — ≥2 concerns	8 (5.37)	1.15 (0.56–2.38)		
Referred	9 (6.04)	1.26 (0.63–2.51)		
Under care	12 (8.05)	**2.42 (1.31–4.45)**		
SDQP				
Score ≥17	12 (8.05)	**2.21 (1.21–4.02)**		
Referred	10 (6.71)	**2.00 (1.04–3.85)**		
Under care	6 (4.03)	**2.97 (1.30–6.80)**		
Emotion ≥4	15 (10.07)	1.31 (0.77–2.25)		
Conduct ≥5	19 (12.75)	**2.17 (1.34–3.54)**		
Hyperactivity ≥7	13 (8.72)	**2.15 (1.21–3.81)**		
Peer problems ≥4	7 (4.70)	0.73 (0.34–1.57)		
Carbamazepine	201 (83.40[b])		Lamotrigine vs carbamazepine	
PEDS			aRR	
Pathway A — ≥2 concerns	15 (7.46)	1.64 (0.95–2.82)	0.84 (0.37–1.92)	
Referred	23 (11.44)	**2.04 (1.29–3.21)**	0.69 (0.33–1.45)	
Under care	9 (4.48)	1.25 (0.63–2.46)	2.25 (0.96–5.31)	
SDQP				
Score ≥17	14 (6.97)	1.61 (0.93–2.80)	1.56 (0.77–3.17)	
Referred	12 (5.97)	1.44 (0.79–2.61)	1.37 (0.60–3.13)	
Under care	4 (1.99)	1.26 (0.47–3.43)	2.90 (0.96–8.70)	
Emotion ≥4	20 (9.95)	1.19 (0.75–1.90)	1.15 (0.61–2.16)	
Conduct ≥5	25 (12.44)	**1.83 (1.20–2.80)**	1.26 (0.70–2.29)	
Hyperactivity ≥7	17 (8.46)	**1.83 (1.11–3.02)**	1.16 (0.60–2.24)	
Peer problems ≥4	25 (12.44)	**1.79 (1.18–2.74)**	0.70 (0.35–1.41)	

NB: bold font indicates statistical significance.
Abbreviations: B4SC, Before School Check; AED, antiepileptic drugs; PEDS, Parental Evaluation of Developmental Status; SDQP, Strengths and Difficulties Questionnaire — parent-completed; RR, relative risk.
[a] Adjusted for gender, ethnicity, and socioeconomic deprivation.
[b] Percentage of children exposed to each AED as monotherapy.

Table 5
B4SC outcomes among children exposed to AED monotherapy and polytherapy.

Outcome	n (%) AED monotherapy (n = 549)	n (%) AED polytherapy (n = 57)	AED monotherapy vs AED polytherapy aRR (95% CI)[a]
PEDs			
Pathway A — ≥2 concerns	36 (6.56)	6 (10.53)	1.89 (0.72–4.99)
Referred	43 (7.83)	5 (8.77)	1.11 (0.40–3.09)
Already under care	39 (7.10)	7 (12.28)	2.11 (0.84–5.30)
SDQP			
Score ≥ 17	41 (7.47)	10 (17.54)	**2.75 (1.25–6.02)**
Referred	34 (6.19)	5 (8.77)	1.35 (0.48–3.84)
Already under care	17 (3.10)	7 (12.28)	**4.27 (1.61–11.39)**
Emotion ≥4	55 (10.02)	13 (22.81)	**2.44 (1.23–4.85)**
Conduct ≥5	67 (12.20)	10 (17.54)	1.35 (0.64–2.84)
Hyperactivity ≥7	42 (7.65)	12 (21.05)	**2.99 (1.46–6.12)**
Peer problems ≥4	45 (8.20)	11 (19.30)	**2.43 (1.16–5.11)**
Hearing			
Referred	29 (5.28)	7 (12.28)	**3.10 (1.25–7.72)**
Already under care	29 (5.28)	7 (12.28)	**2.82 (1.12–7.12)**
Vision			
Referred	41 (7.47)	7 (12.28)	2.19 (0.90–5.33)
Already under care	24 (4.37)	9 (15.79)	**4.63 (1.94–11.05)**

NB: bold font indicates statistical significance.
Abbreviations: B4SC, Before School Check; AED, antiepileptic drugs; PEDs, Parental Evaluation of Developmental Status; SDQP, Strengths and Difficulties Questionnaire — parent-completed; RR, relative risk.
The three most common polytherapy AED combinations included carbamazepine and lamotrigine; carbamazepine and sodium valproate, and sodium valproate and lamotrigine (accounting for 74% of the polytherapy combinations). Other combinations included carbamazepine and topiramate, sodium valproate and levetiracetam, sodium valproate and topiramate, and lamotrigine and levetiracetam.
Triple AED therapy includes the following: carbamazepine, levetiracetam, and sodium valproate; lamotrigine, levetiracetam, sodium valproate; carbamazepine, lamotrigine, and sodium valproate.
[a] Adjusted for gender, ethnicity, and socioeconomic deprivation.

one case where the association was weaker (PEDS pathway A; aRR: 1.38; p = 0.092; 95% CI: 0.95–2.00). This suggests that although the sibling effect appears to be small, we cannot exclude it completely.

4. Discussion

In this nationwide record-linkage cohort study, compared with children not prenatally exposed to AEDs, children prenatally exposed to AEDs were at an increased risk of having developmental concerns reported by parents. Maternal monotherapy with sodium valproate or lamotrigine was associated with an increased risk of abnormal total SDQP scores, but carbamazepine monotherapy was not. Prenatal exposure to AED polytherapy was associated with an increased risk of abnormal SDQP scores compared with monotherapy exposure. While children prenatally exposed to AEDs had elevated risks of developmental concerns compared with children not exposed to AEDs, the prevalence of concerns for these children was below 15% across all neurodevelopmental domains measured in the B4SC, except for children exposed to AED polytherapy, where in some cases, absolute risks exceeded 20%.

Maternal use of AEDs was associated with an increased risk of having an abnormal total SDQP score, indicating parental concerns about behavioral and emotional development. The risk of abnormal scores in the conduct and hyperactivity domains of the SDQP was twice that of children not prenatally exposed to AEDs. Only a small number of studies have investigated the effect of prenatal AED exposure on preschool emotional and behavioral development [10–12]. This study agrees with the results of Kjaer et al., who used the SDQ to measure the association between maternal epilepsy, AED use, and behavioral problems in preschool children [12]. They found that prenatal exposure to AEDs was associated with an increased likelihood of abnormal SDQ scores and that AED exposure was especially associated with abnormal scores for the hyperactivity and conduct domains [12].

In comparison to the SDQP, which specifically assesses concerns about emotional and behavioral development, the PEDS questionnaire is a more global assessment of a child's development and may identify concerns about a child's behavior, speech and language, or fine and gross motor skills. Language delays, as seen in other studies after prenatal sodium valproate exposure [20], may be the type of problem identified by parents in the PEDS questionnaire. In the current study, we found that prenatal exposure to any AED was associated with an increased risk of having developmental concerns identified by parents in the questionnaire, however, elevated risks were not as large as they were for the SDQP assessment.

Similar to findings by Thomas et al. [21], we found that when comparing AEDs with each other, differences in developmental outcomes following prenatal exposure to the three most commonly used AEDs did not reach significance. In particular, exposure to sodium valproate was associated with worse neurodevelopmental outcomes compared with no exposure to AEDs, but risk ratios were similar for lamotrigine. Compared with no prenatal AED exposure, prenatal exposure to carbamazepine monotherapy was not associated with a significantly increased risk of abnormal neurodevelopment. This contrasts with other studies that have used objective measures of cognitive performance and consistently reported neurodevelopmental delay following prenatal sodium valproate exposure but have not always shown adverse neurodevelopmental outcomes following prenatal exposure to other AEDs. They have found increased rates of autism and Attention Deficit Hyperactivity Disorder (ADHD), a lower IQ, delayed motor development, and an increased risk of additional education needs following maternal sodium valproate use [5,6,22–24]. Adab et al. found that 30% of children exposed to sodium valproate monotherapy had additional education needs compared with only 3% and 6.5% of those exposed to carbamazepine and lamotrigine respectively [23]. This is also supported by a number of studies that have consistently found sodium valproate to be associated with poorer neurodevelopmental outcomes when compared with lamotrigine and carbamazepine [5,6,9,10,25,26].

Other studies have shown that AED polytherapy is associated with the greatest risk of adverse outcomes for infants exposed, and for that reason, AED polytherapy is often excluded from studies investigating neurodevelopmental outcomes [5,22,27]. We included AED polytherapy data and our results appear to confirm this; the risk of abnormal scores in the SDQP was highest for children exposed to AED polytherapy and were up to three to four times that of AED monotherapy exposure.

4.1. Strengths

Deriving data from the whole population limits loss to follow-up of the study subjects. In addition, it allows the capture of data from all children prenatally exposed to AEDs rather than only those born to mothers with epilepsy. Our study captures screening information, therefore potentially revealing mild to moderate difficulties that may not meet the criteria for diagnosis of a neurodevelopmental disorder. Other studies have investigated the effect of prenatal exposure to AEDs using a diagnosis of a neurodevelopmental disorder or the requirement for additional education needs and found only sodium valproate to be detrimental to neurodevelopment [6,23] whereas it is possible that more subtle changes in neurodevelopment occur with other AEDs.

4.2. Limitations

The NMDS does not provide reliable diagnosis information, therefore, we do not have a control group of children from mothers who had the same indication but were not treated with an AED so we cannot exclude confounding by indication. In this case, it is possible that differences between sodium valproate and other AEDs seen in other studies, which only include women with epilepsy, are mitigated when they are

used for other conditions. Lamotrigine is commonly used in the management of bipolar disorder. Children of mothers with bipolar disorder have an increased risk of developmental and behavioral problems [28,29] and this is possibly why such large differences in the SDQP and PEDS were not seen in this study. Elkjaer et al. found that prenatal sodium valproate exposure was associated with worse outcomes in sixth grade Danish language tests, but when they separated the children by maternal diagnosis, differences between z-scores in sixth grade Danish language tests only remained significant for women without epilepsy treated with sodium valproate [7]. In another study, increased risks of childhood autism and autism spectrum disorder were found in children prenatally exposed to sodium valproate with hazard ratios further elevated in children whose mothers did not have an epilepsy diagnosis [30]. Results would be biased if mothers with epilepsy or other psychiatric disorders are more likely to rate their child as having worse behavior than mothers without these conditions, either because they were less able to cope with their children or because of knowledge of prenatal AED exposure. This is why ideally, the teacher-rated SDQ is used in conjunction with the parent-rated SDQ as teachers have other children to compare these children with. Kjaer et al. used the parent-completed SDQ and found that AED exposure was associated with poorer scores on the SDQP [12]. They had also used the SDQ in another study where they assessed the behavior of children among children of mothers with depression and found no association between prenatal antidepressant exposure and poorer SDQ scores [31].

There are a number of covariates that are not available in this dataset but have been shown to be predictors of behavioral or cognitive problems in children. These include genetic or medical conditions (e.g., epilepsy, hypoxic birth injury, and congenital malformations), family history of behavioral or cognitive problems, parental IQ, or gestational age [32]. Exposure to other teratogens, such as alcohol, during pregnancy is also a risk factor for neurodevelopmental problems and is not captured accurately because of recall or reporting bias [33].

Teratogenicity of AEDs is also influenced by dose [34], and because we had incomplete dosage information, we were unable to investigate dose effects of AEDs on neurodevelopment. This is a particular concern for sodium valproate, where a number of studies have found that a high dose of sodium valproate (>1000 mg/day) has the most detrimental effect on neurodevelopment [10,11]. We also did not have access to any therapeutic drug monitoring information for the mothers of the children exposed to AEDs, where there can be large increases in the clearance of some AEDs (e.g., lamotrigine, levetiracetam) during pregnancy with an associated significant decline in the serum concentration [35,36]. However, previous research has suggested that therapeutic drug monitoring is not often utilized in New Zealand [37], and it is unclear whether changes in clearance of AEDs are linked to adverse outcomes for children [38]. Recent studies have found that folic acid supplementation has a protective effect on neurodevelopment of children prenatally exposed to AEDs [39,40]. However folic acid is available over-the-counter in New Zealand, making it difficult to ascertain whether women were taking folic acid before or during the early stages of pregnancy.

Compared with the unexposed children, a larger proportion of children exposed to AEDs did not have a B4SC, and if this was because children with significant developmental needs were not assessed by the B4SC, then this could mask some of the detrimental effects of AED exposure. Burakevych et al. compared a comprehensive neurodevelopmental assessment with the B4SC screening questionnaires and found that children who were not screened in the B4SC had a higher incidence of cognitive and behavioral problems in the comprehensive assessment [41]. Because of the nature of the information contained in these datasets and the method used to determine an exposure window, it is possible that there is some misclassification of exposure if gestational periods did not last nine months or when there was tapering of AEDs.

Using administrative data assumes that pregnant women take the medicine as prescribed, at the time it is dispensed or take it at all, however, studies investigating the correlation between self-reported medicine use and administrative data have found a good correlation for chronic conditions such as epilepsy [42]. Particularly, high rates of compliance have been reported for pregnant women taking AEDs [43], making misclassification unlikely.

5. Conclusion

Prenatal exposure to sodium valproate and lamotrigine is associated with an increased risk of concerns about emotional and behavioral development being reported by parents in a neurodevelopmental screening program. Exposure to AED polytherapy was associated with the highest risk.

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Author contributions

NR and AS have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis or interpretation of data: NR and AS.

Drafting the manuscript: NR.

Critical revision of the manuscript for important intellectual content: All authors.

Conflicts of interest disclosures

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