Received: 7 March 2023 | Revised: 27 June 2023 | Accepted: 29 June 2023

DOI: 10.1111/epi.17709

Epilepsia™

RESEARCH ARTICLE

Neurodevelopment of babies born to mothers with epilepsy: A prospective observational cohort study

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Funding information
National Institute for Health Research (NIHR). Research Trainees Coordinating Centre, Grant/Award Number: PDF-2013-06-041

Abstract

Objective: Despite widespread monotherapy use of lamotrigine or levetiracetam during pregnancy, prospectively collected, blinded child development data are still limited. The NaME (Neurodevelopment of Babies Born to Mothers With Epilepsy) Study prospectively recruited a new cohort of women with epilepsy and their offspring for longitudinal follow-up.

Methods: Pregnant women of <21 weeks gestation ($n = 401$) were recruited from 21 hospitals in the UK. Data collection occurred during pregnancy (recruitment, trimester 3) and at 12 and 24 months of age. The primary outcome was blinded assessment of infant cognitive, language, and motor development on the Bayley Scales of Infant and Toddler Development (3rd edition) at 24 months of age with

[†]See Appendix 1 for all members of the NaME Study Group.

supplementary parent reporting on the Vinelands Adaptive Behavior Scales (2nd edition).

Results: There were 394 live births, with 277 children (70%) completing the Bayley assessment at 24 months. There was no evidence of an association of prenatal exposure to monotherapy lamotrigine (−.74, SE = 2.9, 95% confidence interval [CI] = −6.5 to 5.0, $p = .80$) or levetiracetam (−1.57, SE = 3.1, 95% CI = −4.6 to 7.7, $p = .62$) with poorer infant cognition, following adjustment for other maternal and child factors in comparison to nonexposed children. Similar results were observed for language and motor scores. There was no evidence of an association between increasing doses of either lamotrigine or levetiracetam. Nor was there evidence that higher dose folic acid supplementation (≥5 mg/day) or convulsive seizure exposure was associated with child development scores. Continued infant exposure to antiseizure medications through breast milk was not associated with poorer outcomes, but the number of women breastfeeding beyond 3 months was low.

Significance: These data are reassuring for infant development following in utero exposure to monotherapy lamotrigine or levetiracetam, but child development is dynamic, and future follow-up is required to rule out later emerging effects.

KEYWORDS

antiseizure medication, development, epilepsy, pharmacovigilance, pregnancy

1 | INTRODUCTION

The prescribing of medications to women with epilepsy involves a balance between optimizing maternal health and minimization of the risk to the fetus.[1] In utero exposure to certain antiseizure medications (ASMs) is associated with an increased risk to child neurodevelopment.[2–4] Both valproate and phenobarbital convey an increased risk of neurodevelopmental difficulties, including reduced intelligence quotient (IQ)[5–9] and language functioning,[10,11] with an increased rate of autistic spectrum disorder[12–14] and attention-deficit/hyperactivity disorder[15] for valproate exposure. Recently, evidence of neurodevelopmental risk following topiramate has also been presented.[16,17] Prescribing practices have shifted in the past two decades, and use of lamotrigine and levetiracetam has increased internationally.[1] Excluding higher doses of lamotrigine, prenatal exposure to these two medications in monotherapy does not appear to be associated with a significantly increased risk of major congenital anomalies,[18,19] but the evidence pertaining to longer term child health and neurodevelopmental outcomes remains incomplete.

Assessments in infancy of children prenatally exposed to lamotrigine or levetiracetam have demonstrated better neurodevelopmental trajectories across infancy and childhood in comparison to children exposed to valproate.[5–7,9,20–25] However, comparisons to groups against unexposed control children, utilizing a fully prospective methodology with objective, blinded assessments of early infant development, are limited,[20,21,26] with only the MONEAD study being of adequate size to detect more moderate effect sizes or to consider the influence of dose.[26]

Key Points

- Early child development for children exposed to lamotrigine or levetiracetam monotherapy is not different from unexposed children
- Dose of either lamotrigine or levetiracetam was not associated with child outcomes
- Taking ≥5 mg/day of folate was not associated with improved developmental outcomes
- There was no negative impact of breastfeeding, although rates were lower than in the general population
- Observations of the children during the assessment contributed significantly to the variance in the analysis

The MONEAD study demonstrated that language development at 2 years of age was not influenced by exposure to lamotrigine or levetiracetam per se, but did report signals of a dose-related impact on other areas of infant development.[26] This was most notable for childhood motor functioning following levetiracetam exposure.

Although population level health care database-derived data have demonstrated no increased risk of diagnosed autistic spectrum disorder[13,14,16] or attention-deficit/hyperactivity disorder[15,16] in comparison to nonexposed children for lamotrigine or levetiracetam, parental ratings highlight possible concerns about aspects of social and language development for lamotrigine.[27–30] Questions therefore remain over the neurodevelopmental outcome of children exposed to lamotrigine or levetiracetam prenatally, particularly in comparison to children unexposed to ASMs.

2 | MATERIALS AND METHODS

The Neurodevelopment of Babies Born to Mothers With Epilepsy (NaME) Study is a prospective, longitudinal study with the aim of investigating neurodevelopment after prenatal exposure to ASMs. Pregnant women with a diagnosis of epilepsy were recruited from 21 hospitals across the North West and North East of England and from Northern Ireland, prior to 21 weeks gestation. Eligible women living in these regions who enrolled in the UK Epilepsy and Pregnancy Register were also invited to participate.

Women with epilepsy on ASMs (monotherapy or polytherapy) and those with no ASM use were eligible for inclusion. Treatment was classed as polytherapy where two or more ASMs were used at any point during gestation even for a short period. The prescribed dose of the ASMs was collected at recruitment and then again at ≥32 weeks gestation. The possibility of relationship with dose was investigated for the two commonest monotherapy ASMs, lamotrigine and levetiracetam.

Women were excluded if they had a significant level of learning disability (e.g., unable to live independently), had another acute or chronic health condition for which they were taking a concomitant medication (non-ASM) with a known teratogenic profile (e.g., isotretinoin, warfarin, mycophenolate), or already had a live born child in the study. Recruitment ran from August 2014 through to March 2016. Individual ASM groups were adequately powered to detect a medium–large effect size (defined as ≥10 points on the Bayley Scales of Infant and Toddler Development) with 80% power and an overall significance level of .05 ($n \geq 48$), assuming a pooled SD of 15 for the primary domains.[29]

Recruitment was undertaken by the local clinical care team and the UK National Institute for Health Research (NIHR) Local Clinical Research Networks (LCRN). Family demographic information and maternal health including epilepsy information were recorded prospectively from both medical records and maternal interviews at recruitment. Telephone interviews after 32 weeks of gestation documented maternal health, seizure status, and treatment changes including dose. Birth or fetal outcome, including information on congenital anomalies, was taken from hospital records. Once the maternofetal outcome information had been recorded, participant research files were transferred to the lead hospital site (Manchester, UK), from where the postnatal follow-up visits were coordinated.

At 12 months (=/+3 months) mothers were contacted by telephone to complete the Vinelands Adaptive Behavior Scales, 2nd edition (Vinelands Scales)[31] and a brief set of questions about the child's health. The Vinelands Scales are a widely used semistructured interview in which respondents answer questions about a child's development in the areas of communication, daily living, socialization, and motor development. Raw scores were converted into age-adjusted standard scores (mean = 100, SD = 15).[27] The Vinelands has been demonstrated to be sensitive to the pattern of difficulties that can be associated with in utero exposure to ASMs[17,32] and was conducted by one of three interviewers blinded to the exposure group. Breastfeeding information was collected from maternal report at 12 months or at the 24-month visit, if contact had not been made at 12 months. Duration of breastfeeding was collected as number of weeks, but due to the small numbers of women breastfeeding was coded as "none," "<3 months," or "≥3" months for analysis.

At 24 months (=/+6 months), home visits were undertaken where the brief health questions and Vinelands Scales were readministered. The Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley Scales),[33] which was the primary study outcome, was completed with the child. The Bayley Scales offer objective, standardized measurement of child development across the domains of cognitive, language (receptive and expressive skills), and motor (fine and gross skills). Administration of the Bayley Scales was limited to two blinded assessors (R.L.B., C.J.) who had extensive neuropsychological assessment experience. Observations were made during the assessment as to emerging handedness preference on the fine motor tasks, and engagement level was rated as either good (child's engagement was high), adequate (efforts were needed at points of the assessment to keep the child engaged), or poor (child's performance was not representative due to poor engagement). Invalid scores due to poor engagement or other reasons were excluded

(Figure S1). Raw scores were generated for each of the subscales (cognitive, receptive language, expressive language, gross motor, fine motor) and converted into norm-based scale scores (range = 1–19, mean = 10, SD = 3). Scale scores were then converted into standardized composite scores (mean = 100, SD = 15).[33] A score of <85 is considered to be below average (1.5 SD from the normative sample mean), but due to evidence that the current 3rd edition of the Bayley Scales is subject to overestimation,[34] NaME cohort and domain-specific metrics were calculated at 1.5 SD as the cutoff for a below average performance. Participating mothers completed the Wechsler Abbreviated Scale of Intelligence, 2nd edition[35] to inform on parental cognitive ability level.

Up-to-date addresses were sought from the participants' family doctor at each assessment point. Where home visits could not be completed in a single session (e.g., due to tiredness), follow-up appointments were arranged. Written feedback regarding the child's performance on the Bayley Scales was provided to family doctors and copied to the mother.

Both the scoring of the Vineland Scales and the Bayley Scales and all data entries were double-checked to minimize scoring and data entry errors. Epilepsy history was reviewed by a neurologist (E.C.) and categorized as a focal syndrome, generalized syndrome, unclassified syndrome with generalized seizures, or unclear. Congenital anomaly data were reviewed by a clinical geneticist (J.C-S.) blinded to ASM exposure for categorization.

The study was preregistered (International Standard Randomised Controlled Trial Number (ISRCTN) 98260309), and ethical approval was obtained for the study (Integrated Research Application System (IRAS) number 143279). Each participating woman provided written consent.

2.1 | Statistical analysis

Data analysis was conducted in SPSS version 25 and R version 4.2.0. Demographic and background information was summarized using mean and SD for continuous normally distributed data, and proportion for frequency or categorical data. Unadjusted comparisons between completers and noncompleters were conducted using *t*-tests and chi-squared tests, respectively.

The primary outcome measurement (Bayley Scales) and secondary outcomes measurement (Vinelands Scales) were continuous and normally distributed. Univariate regression analyses were conducted to investigate the potential relationship between parental demographic, maternal health, and exposure variables with the specific domains of the Bayley Scales (cognitive, language, motor) and the Vinelands Scales (adaptive behavior composite). Variables considered for univariate analysis were determined based on clinical judgment, to reduce the number of potential variables (see Table 4 footnote for all considered variables). Variables with a statistical significance < .2 were entered into the multiple linear regression models bespoke to each of the Bayley Scales domains. In the multiple regression analyses, ASM group was entered a priori with other variables entered using backward selection; final models are reported. Dose investigations followed the above procedure but were restricted to women taking either monotherapy lamotrigine or monotherapy levetiracetam. Third trimester dose was used due to the rapid development occurring within the fetal brain in this period. Following a visual inspection using scatterplots, a linear regression model was then fitted for each developmental domain assessing the linear association between dose and Bayley Scales score. For completeness, the linear regression was repeated adjusting for all variables that were included in the final regression models for the main analysis.

2.2 | Sensitivity analyses

Statistically significant differences between completers and noncompleters were assessed to investigate the extent to which these biased findings. This was done using a propensity score to assess the probability of the Bayley Scale being completed. All variables in Tables 1 and 2 with statistically significant differences between completers and noncompleters were considered as possible candidate predictors in the propensity score model. Complete case analysis was used. As a result, use of folic acid was dropped as a potential predictor, as all but two of 354 complete cases used folic acid. The propensity score was used to derive an inverse probability weight to be used in the linear regression models. The final models for each component of the Bayley Scales were refit with the inclusion of inverse probability weights to assess the impact of noncompletion of the Bayley assessment.

3 | RESULTS

Four hundred and four pregnant women with epilepsy were recruited (mean gestational timepoint = 18 weeks, range = 6–21 weeks) from neurology and obstetric clinics in the North West (61%) and North East (36%) of England and Northern Ireland (.5%) and from new recruits into the UK Epilepsy and Pregnancy Register who

TABLE 1 Maternal and paternal demographic information by ASM exposure group.

		Main ASM groups						Completer information		
	Total cohort, $N = 401$	**No ASM, $n = 80$**	**LTG, $n = 106$**	**LEV, $n = 70$**	**CBZ, $n = 27$**	**Polytherapy, $n = 95$**	**Other monotherapy, $n = 23$**	**Completers, $n = 277$[a]**	**Non-completers, $n = 124$**	***p***
Maternal background demographics										
Maternal age at birth, years, mean (SD)	30.1 (5.6)	29.5 (5.5)	30.7 (5.3)	29.2 (5.7)	32.9 (6.1)	30.1 (5.6)	31.6 (5.1)	30.7 (5.5)	28.7 (5.7)	.001
Married/cohabiting, *n* (%)	332 (82.8%)	65 (81.3%)	90 (84.9%)	58 (82.0%)	25 (92.6%)	77 (81.1%)	17 (73.9%)	233 (84.1%)	99 (79.8%)	.182
Lower SES, *n* (%)[b]	269 (67.1%)	58 (72.5%)	76 (71.7%)	48 (68.6%)	14 (51.9%)	57 (60%)	16 (69.6%)	176 (63.5%)	93 (75%)	.001
Ethnicity, White British, *n* (%)	365 (91.0%)	71 (88.8%)	97 (91.5%	63 (90.0%)	23 (85.2%)	89 (93.7%)	22 (95.7%)	255 (92.1%)	110 (88.7%)	.057
Higher education, *n* (%)[c]	178 (44.4%)	37 (46.3%)	44 (41.5%)	35 (50%)	13 (48.1%)	43 (45.3%)	6 (26.1%)	146 (82%)	130 (59%)	<.001
Maternal FSIQ, mean (SD)[d]	93.93 (13.75)	93.56 (13.11)	95.54 (13.95)	94.55 (14.10)	98.80 (11.68)	91.00 (13.74)	91.36 (15.39)	93.93 (13.75)	N/A[e]	N/A
Employed, *n* (%)[f]	265 (66.1%)	57 (71.3%)	75 (70.8%)	42 (60.0%)	17 (63.0%)	60 (63.2%)	14 (60.9%)	203 (73.3%)	62 (50.0%)	<.001
Managerial level, *n* professional status (%)	109 (27.2%)	23 (28.8%)	33 (31.1%)	17 (24.3%)	10 (37.0%)	19 (20.0%)	7 (30.4%)	19 (20.0%)	34 (27.4%)	.538
Mental health condition, *n* (%)	76 (19.0%)	18 (22.5%)	20 (18.9%)	12 (17.1%)	6 (22.2%)	16 (16.8%)	4 (17.4%)	44 (15.9%)	32 (25%)	.015
Family history, *n* (%)										
Birth defects	56 (14.0%)	12 (15.0%)	15 (14.2%)	7 (10.0%)	4 (14.8%)	14 (14.7%)	4 (17.4%)	33 (11.9%)	32 (25%)	.015
Learning difficulties	66 (16.5%)	18 (22.5%)	18 (17.0%)	8 (11.4%)	9 (33.3%)	7 (7.4%)	6 (26.1%)	44 (15.9%)	23 (18.5%)	.053
Developmental disorders	42 (10.5%)	8 (10.0%)	10 (9.4%)	14 (20.0%)	3 (11.1%)	5 (5.3%)	2 (8.7%)	34 (12.3%)	8 (6.5%)	.052
Epilepsy	129 (32.2%)	23 (28.8%)	39 (36.8%)	21 (30.0%)	9 (33.3%)	29 (30.5%)	8 (34.8%)	88 (68%)	41 (69%)	.451
Maternal epilepsy										
Epilepsy type, *n* (%)										
Focal epilepsy	116 (28.9%)	24 (30.0%)	27 (25.5%)	19 (27.1%)	9 (33.3%)	34 (35.8%)	3 (13.0%)	84 (30.3%)	32 (25.8%)	.212
Generalized epilepsy	125 (31.2%)	18 (22.5%)	24 (22.6%)	32 (45.7%)	7 (25.9%)	35 (36.8%)	9 (39.1%)	86 (31.0%)	39 (31.5%)	.512
Unclassified with GTCS	103 (25.7%)	25 (31.3%)	35 (33.0%)	13 (18.6%)	9 (33.3%)	14 (14.7%)	7 (30.4%)	68 (24.5%)	35 (28.2%)	.255
Unclear	57 (14.2%)	13 (16.3%)	20 (18.9%)	6 (8.6%)	2 (7.4%)	12 (12.6%)	4 (17.4%)	39 (14.1%)	18 (14.5%)	.510

(Continues)

TABLE 1 (Continued)

		Main ASM groups						Completer information		
	Total cohort, *N* = 401	**No ASM, *n* = 80**	**LTG, *n* = 106**	**LEV, *n* = 70**	**CBZ, *n* = 27**	**Polytherapy, *n* = 95**	**Other monotherapy, *n* = 23**	**Completers, *n* = 277[a]**	**Non-completers, *n* = 124**	***p***
Onset age, *n* (%)										
0–12 years	144 (35.09%)	39 (48.8%)	28 (26.4%)	22 (31.4%)	9 (33.3%)	38 (40.0%)	8 (34.8%)	98 (35.4%)	46 (37.1%)	.432
13–18 years	132 (32.9%)	23 (28.8%)	36 (34.0%)	22 (31.4%)	7 (25.9%)	34 (35.8%)	10 (43.5%)	92 (33.2%)	40 (32.3%)	.454
>19 years	123 (30.7%)	18 (22.5%)	42 (39.6%)	25 (35.7%)	11 (40.7%)	22 (23.2%)	5 (21.7%)	85 (30.7%)	38 (30.6%)	.528
ASM dose, mg/day, mean (range)[g]	N/A	N/A	293 (50–800)	1798 (250–4250)	737 (200–2500)	N/A	N/A	-	-	-
Paternal background demographics										
Paternal age, years, mean, SD	34.54 (7.188)	35.12 (8.773)	34.99 (6.885)	33.42 (7.194)	36.63 (6.211)	33.89 (6.560)	34.53 (7.46)	34.54 (7.19)	N/A[e]	-
Higher education, *n* (%)[c]	106 (26.4%)	21 (26.3%)	26 (24.5%)	16 (22.9%)	7 (25.9%)	31 (32.6%)	5 (21.7%)	106 (28.3%)	N/A[e]	-

Note: Statistical comparisons between completers and non-completers were based on *t*-tests for normally distributed variables with nonparametric analyses for continuous variables that were nonnormally distributed (such as gestational age at birth), and chi-squared tests for categorical variables.

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; FSIQ, full-scale intelligence quotient; GTCS, generalized tonic–clonic seizures; LEV, levetiracetam; LTG, lamotrigine; N/A, not available; SES, socioeconomic status.

[a]Completed the 24-month assessment.

[b]Lower SES defined by postcode as the bottom two quartiles of the UK National Office for Statistics.

[c]Higher education was defined as greater than compulsory education.

[d]FSIQ measured using the Wechsler Abbreviated Intelligence Scales, 2nd edition, two-subtest version.

[e]N/A for noncompleters as completed at the 24-month check.

[f]Employed was defined as full- or part-time work, any hours.

[g]Trimester 3 ASM dose.

TABLE 2 Pregnancy information and immediate birth outcomes and breastfeeding by ASM exposure group.

		ASM group						Completer information		
	Total cohort, $N = 401$	No ASM, $n = 80$	LTG, $n = 106$	LEV, $n = 70$	CBZ, $n = 27$	Polytherapy, $n = 95$[a]	Other monotherapy, $n = 23$	Completers, $n = 277$	Non-completers, $n = 124$	p
Pregnancy, n (%)										
Folic acid	376 (93.8%)	67 (83.8%)	102 (96.2%)	69 (98.6%)	26 (96.3%)	91 (95.8%)	21 (91.3%)	264 (95.3%)	112 (90.3%)	.036
Before conception	184 (45.9%)	19 (23.8%)	54 (50.9%)	37 (52.9%)	18 (66.7%)	49 (51.6%)	7 (30.4%)	152 (82.1%)	32 (17.4%)	<.001
Folic acid > 5 mg/day	275 (68.6%)	19 (23.8%)	88 (83%)	57 (81.4%)	23 (85.2%)	72 (75.8%)	16 (69.6%)	199 (71.8%)	76 (61.3%)	.080
Smoking	67 (16.7%)	15 (18.8%)	17 (16.0%)	9 (12.9%)	5 (18.5%)	17 (17.9%)	4 (17.4%)	36 (13.0%)	31 (25%)	.003
Alcohol consumption	20 (5.0%)	3 (3.8%)	7 (6.6%)	5 (7.1%)	2 (7.4%)	3 (3.2%)	0 (.0%)	16 (5.8%)	4 (3.2%)	.198
Change in use										
No alteration	135 (33.7%)	23 (28.8%)	39 (36.8%)	18 (25.7%)	10 (37.0)	39 (41.1%)	3 (13.0%)	100 (36.1%)	35 (28.2%)	.084
Before conception	69 (17.2%)	41 (51.3%)	50 (47.2%)	16 (22.9%)	7 (25.7%)	14 (14.7%)	7 (30.4%)	51 (18.4%)	18 (14.5%)	.221
During pregnancy	182 (45.4%)	15 (18.8%)	14 (13.2%)	31 (44.3%)	10 (37.0)	37 (38.9%)	14 (60.9%)	114 (41.2%)	68 (54.8%)	.006
Seizure during pregnancy										
Yes	158 (39.4%)	11 (13.8%)	45 (42.5%)	25 (35.7%)	10 (37.0%)	58 (61.1%)	9 (39.1%)	111 (40.1%)	47 (37.9%)	.406
1–4 seizures	56 (14.0%)	5 (6.3%)	19 (17.9%)	9 (12.9%)	5 (18.5%)	16 (16.8%)	2 (8.7%)	35 (13.0%)	20 (16.1%)	.236
>5 seizures	102 (25.4%)	6 (7.5%)	26 (24.5%)	16 (22.9%)	5 (18.5%)	42 (44.2%)	7 (30.4%)	75 (27.1%)	27 (21.8%)	.168
Convulsive										
Yes	97 (24.4%)	4 (5.0%)	28 (26.4%)	18 (25.7%)	2 (7.4%)	39 (41.1%)	6 (26.1%)	66 (24.1%)	30 (24.2%)	.546
>5 Seizures	32 (8.0%)	1 (1.3%)	9 (8.5%)	6 (8.6%)	0 (0%)	14 (14.7%)	2 (8.7%)	20 (7.2%)	12 (9.7%)	.261
Birth outcome data										
Birth outcomes										
Gestational age, mean (SD)	38.5 (2.2)	38.6 (2.3)	38.3 (2.5)	38.8 (2.2)	38.4 (1.9)	39.0 (1.8)	38.3 (3.4)	38.7 (1.9)	38.0 (2.9)	
Preterm birth, n (%)[b]	48 (12%)	11 (13.8%)	15 (14.2%)	7 (10%)	3 (11.1%)	10 (10.5%)	2 (8.7%)	27 (9.7%)	21 (16.9%)	
Live birth, n (%)[c]	391 (97.5%)	77 (96.3%)	105 (99.1%)	70 (100%)	26 (96.3%)	94 (98.9%)	19 (82.6%)	277 (100%)	114 (91.9%)	
Gender, n girls (%)	198 (49.4%)	32 (40%)	54 (50.9%)	42 (60%)	13 (48.1%)	47 (49.5%)	10 (43.5%)	135 (48.7%)	63 (50.8%)	
Birth weight,g, mean (SD)	3243.35 (611.8)	3217.1 (567.9)	3224.9 (676.0)	3238.4 (550.6)	3249.4 (681.2)	3285.0 (561.5)	3264.74 (797.4)	3289.1 (601.2)	3133.1 (625.9)	
Small for gestation, n (%)[d]	48 (12%)	13 (16.3%)	13 (12.3%)	6 (8.6%)	1 (11.1%)	10 (10.5%)	1 (4.3%)	32 (11.6%)	16 (12.9%)	

(Continues)

TABLE 2 (Continued)

		ASM group						Completer information		
	Total cohort, *N* = 401	**No ASM, *n* = 80**	**LTG, *n* = 106**	**LEV, *n* = 70**	**CBZ, *n* = 27**	**Polytherapy, *n* = 95[a]**	**Other monotherapy, *n* = 23**	**Completers, *n* = 277**	**Non-completers, *n* = 124**	***p***
Neonatal complications, *n* (%)	78 (19.5%)	15 (18.8%)	23 (21.7%)	14 (20%)	5 (18.5%)	19 (20.0%)	2 (8.7%)	56 (20.2%)	111 (89.5%)	
Special care admission, *n* (%)	51 (12.7%)	6 (7.5%)	20 (18.9%)	8 (11.4%)	3 (11.1%)	12 (12.6%)	2 (8.7%)	34 (12.3%)	17 (13.7%)	
Congenital anomaly, *n* (%)										
Any anomaly	32 (8%)	4 (5%)	11 (10.4%)	4 (5.7%)	3 (11.1%)	8 (8.4%)	2 (8.7%)	25 (9%)	7 (5.6%)	
Major[e]	15 (3.7%)	3 (3.8%)	3 (2.8%)	2 (2.9%)	2 (7.4%)	4 (4.2%)	1 (4.3%)	10 (3.6%)	5 (4.0%)	
Minor	15 (3.7%)	1 (1.3%)	8 (7.5%)	2 (2.9%)	1 (3.7%)	2 (2.1%)	1 (4.3%)	13 (4.7%)	1 (1.6%)	
Unclear	2 (.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2.1%)	0 (.0%)	2 (.7%)	0 (0%)	
Breastfeeding duration, *n* (%)										
None	165 (41.1%)	17 (21.3%)	46 (43.4%)	24 (34.3%)	11 (40.7%)	39 (41.1%)	2 (8.7%)	121 (66.8%)	27 (21.8%)	
<3 months	70 (17.%)	12 (15%)	18 (17.0%)	14 (20%)	6 (22.2%)	19 (20%)	1 (4.3%)	64 (23.1%)	6 (4.8%)	
≥3 months	93 (23.2%)	27 (33.8%)	21 (19.8%)	20 (28.6%)	9 (33.3%)	15 (15.8%)	1 (4.3%)	80 (28.9%)	13 (10.5%)	
Not known[f]	90 (22.4%)	24 (30.0%)	21 (19.8%)	12 (17.1%)	1 (3.7%)	22 (23.2%)	10 (43.5%)	-	-	

Note: Statistical comparisons between completers and noncompleters were based on *t*-tests for normally distributed variables with nonparametric analyses for variables with a nonnormative distribution (i.e., binary outcomes for those with a skewed distribution, such as gestational age at birth), and chi-squared tests for categorical variables.

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine.

[a]Includes nine polytherapy cases including valproate.

[b]Gestational age < 37 weeks.

[c]Two first trimester miscarriages, one second trimester miscarriage, four intrauterine deaths, two deaths in the neonatal period, and one child death at 13 months.

[d]Calculated using gender-specific scales (Mothers and Babies: Reducing Risk through Audits and Confidential Enquires across the UK (MBRRACE UK).

[e]A major congenital anomaly was one that required significant surgical or other intervention, and that had substantial impact on the daily functioning of the child.

[f]Rates of missing data are high due to collection at 12 or 24 months.

resided in these regions (3%). Three cases required exclusion (Figure S1).

Complete demographic data for the cohort are presented in Tables 1 and 2. Of relevance for child neurodevelopment, 178 (44%) participating mothers had completed more than the UK compulsory education, 265 (66%) were in employment at the time of the pregnancy, and 269 (67%) resided within the UK's lower socioeconomic areas. All participants were taking ASMs for the treatment of epilepsy and most commonly were diagnosed with a syndrome featuring generalized seizures ($n = 228$, 57%). One hundred eighteen women (29%) reported additional health conditions, and 76 (19%) reported having a mental health condition. One hundred fifty women (39%) experienced seizures of any type during pregnancy, with 97 (24%) experiencing one or more convulsive seizures. Rate of nicotine use recorded was 17% ($n = 67$) and of alcohol use only 5% ($n = 20$); 46% of participating women made alterations to their habits prior to confirmation of pregnancy.

3.1 | Birth and physical developmental outcomes

The child's birth and health data are presented in Table 2. There were seven miscarriages or fetal deaths in utero following enrollment, with 394 live births. Preterm birth occurred in 48 women (12%), and gender-specific small for gestational age (SGA) was observed in 48 (12%). Although topiramate exposure was only present for 12 children, four (24%) were SGA. The rate of major congenital anomalies in the cohort was slightly elevated above the UK average of 2.3%[36] at 3.7% ($n = 15$); two cases were associated with in utero valproate exposure. Four child postnatal deaths (1%) were reported within the cohort, spanning different exposure groups.

3.2 | Development at 1 year of age

Two hundred eighty-three (73%) completed the Vinelands interview when their child was 12 months old. Forty-two (18%) of the mothers were concerned about their child's development, most frequently language and/or motor developmental progress, and there was no difference in the frequency of these concerns between those taking an ASM and those not. Mean scores on the Vinelands Scales were comparable across all the exposed and control groups (Table S1). Being born prematurely was influential on Vinelands scores, but other demographic and maternal health variables and specific ASM exposures were not (data not shown).

3.3 | Development at 2 years of age

Two hundred seventy-seven (70%) children were assessed at 2 years of age for the primary outcome. Families who completed this visit were more likely to have had a mother in work at the time of her enrollment into the study, had a higher socioeconomic status, reported higher levels of parental education, were less likely to smoke, and had increased rates of self-reported mental health difficulties (Tables 1 and 2). There were no statistically significant differences in mean doses of lamotrigine (mean = 290 mg/day vs. 256 mg/day, $p = .284$) and levetiracetam (mean = 1476 mg/day vs. 1643 mg/day, $p = .626$) across completers and noncompleters.

Most Bayley assessments were completed in one home visit, with 22 (8%) requiring follow-up to achieve better engagement. Observations on the fine motor tasks highlighted emerging handedness to be left in 13% ($n = 35$) and unclear in 20% ($n = 34$).

There were no significant differences in the mean cognitive, language, or motor developmental scores by specific ASM monotherapy exposure type when compared to the no ASM exposure control group (Table 3, Figure 1) and following the adjustment for influential demographic and health variables (Table 4). Comparable developmental scores were achieved for the groups exposed to lamotrigine monotherapy and levetiracetam monotherapy (Table 3). There was no statistically significant evidence of an association between dose of lamotrigine or levetiracetam and cognitive, language, or motor scores (Figure 2). This remained the case when the analysis was adjusted for other variables.

Bayley Scales score distributions across the indices did not suggest a small subgroup with a poorer performance (i.e., a bimodal distribution) in any of the ASM-exposed groups. The prevalence of a "below average" performance (>1.5 SD below the cohort mean) across the developmental domains ranged from 4% to 9% of those in the no ASM group, ranged from 3% to 10% of those exposed to lamotrigine, and was consistently 10% of those exposed to levetiracetam. The highest rate of below average performance was seen in the polytherapy group (valproate cases excluded), where 22% ($n = 13$) of cases exhibited poorer language development (Table 3).

We found no evidence that maternal epilepsy type or seizure exposure (convulsive vs. nonconvulsive, seizures vs. no seizures) was associated with child developmental scores, including experiencing five or more generalized tonic–clonic seizures. Maternal IQ, socioeconomic status, further education, employment status, gestational age, birth weight, child gender, being the oldest or only child, and the child's assessment engagement were associated with one or more developmental domain (Table 4).

TABLE 3 Mean scores (adjusted and unadjusted) and rates of below average developmental score for the primary outcome measure at 24 months.

	Total cohort, $N=272$[a]	No ASM, $n=48$	Monotherapy exposure groups				Polytherapy exposure groups	
			LTG, $n=73$	LEV, $n=51$	CBZ, $n=21$	Other, $n=11$[b]	Polytherapy total, $n=68$	Polytherapy no VPA, $n=60$
Cognitive[c]								
Mean (SD)	102.1 (13.1)	103.2 (13.3)	102.8 (12.1)	102.9 (16.6)	104.8 (15.5)	103.2 (12.7)	98.8 (9.7)	98.5 (10.1)
Below average score, *n* (%)[d]	16 (9%)	2 (4%)	2 (3%)	5 (10%)	2 (10%)	1 (9%)	4 (6%)	4 (7%)
Language								
Mean (SD)	104.0 (17.2)	105.3 (16.8)	106.1 (15.3)	105.1 (18.5)	105.5 (20.3)	104.3 (17.1)	99.6 (17.4)	99.5 (18.0)
Below average score, *n* (%)[d]	29 (11%)	3 (7%)	4 (6%)	5 (10%)	2 (10%)	2 (18%)	13 (20%)	13 (22%)
Receptive, mean (SD)	10.9 (3.0)	10.7 (3.1)	11.4 (2.7)	11.0 (3.0)	11.3 (3.0)	11.5 (3.5)	10.4 (3.2)	10.3 (3.4)
Expressive, mean (SD)	10.3 (3.2)	10.6 (3.5)	10.6 (2.9)	10.6 (3.4)	10.6 (4.2)	9.9 (2.7)	9.4 (3.0)	9.5 (3.1)
Motor								
Mean (SD)	102.6 (13.3)	103.1 (13.2)	102.2 (12.5)	106.3 (15.7)	105.4 (19.7)	98.9 (10.5)	99.6 (9.5)	99.1 (9.6)
Below average score, *n* (%)[d]	30 (11%)	4 (9%)	7 (10%)	5 (10%)	2 (17%)	2 (18%)	9 (14%)	9 (16%)
Fine, mean (SD)	10.7 (2.3)	10.6 (2.5)	10.6 (1.9)	11.3 (2.6)	11.3 (2.9)	10.3 (2.0)	10.4 (1.9)	10.3 (1.8)
Gross, mean (SD)	10.1 (2.7)	10.3 (2.7)	10.0 (2.7)	10.8 (3.2)	10.5 (4.0)	9.4 (2.1)	9.4 (1.8)	9.6 (2.1)

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; VPA, valproate.

[a]Two hundred seventy-seven children were seen for the assessment at 24 months, but in six cases completion of the Bayley Scales was not possible or the child had a medical condition associated with poorer developmental outcome and was therefore excluded.

[b]"Other" comprises exposure to topiramate ($n=4$), gabapentin ($n=1$), phenobarbital ($n=1$), ethosuximide ($n=1$), and valproate ($n=4$).

[c]Completion numbers vary by domain completed.

[d]Calculated based on the domain mean and SD: cognitive ≤ 88, language ≤ 86, and motor ≤ 88.

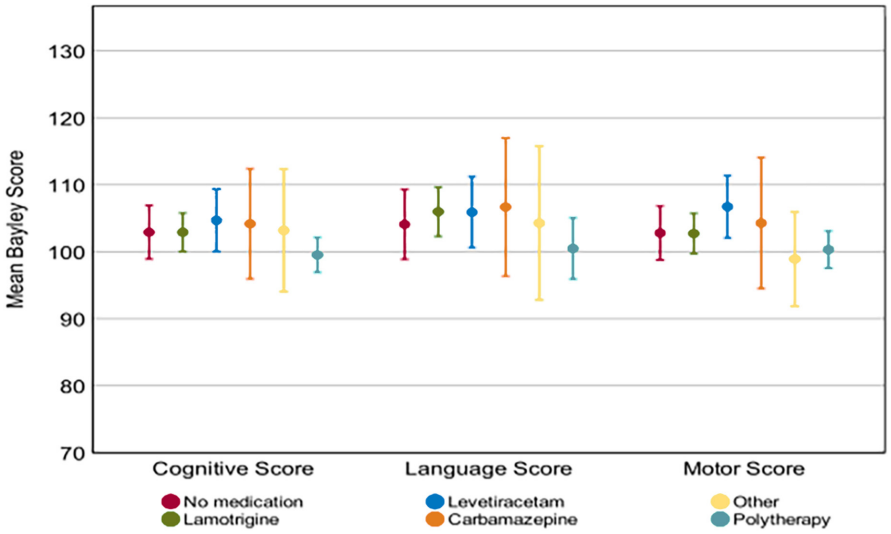

FIGURE 1 Bayley mean scores (unadjusted) by exposure group for each Bayley Scales domain.

Despite low levels of use, nicotine exposure was negatively associated with child language and motor development. Sensitivity analyses with the removal of children with major congenital anomalies and twin pregnancies did not alter the results.

Vineland Scales scores at 24 months replicated the earlier findings at 12 months, with no association between ASM exposure and parent ratings of development in the areas of communication, daily living, socialization, and motor skills (Table S1).

3.4 | Folate supplementation

During pregnancy, 94% of women in the overall cohort (completers and noncompleters) took folic acid supplements; however, only 46% ($n = 184$) took these prior to conception. Early initiation of folic acid was lowest in the no treatment group (24%) and highest in those taking carbamazepine (67%). We found no statistical evidence that the time of starting or the dose of folate used (<5 mg/day or ≥5 mg/day) was associated with the mean Bayley Scales scores for any domain in the adjusted analyses (Figure 3A).

3.5 | Breastfeeding

Breastfeeding data were available from 312 women. Initiation of breastfeeding (any duration) was undertaken by 165 (56%) women (51% in the ASM exposed and 68% in the no ASM group). Only 80 (29%) participating women continued to breastfeed past 3 months. No negative effect of continued ASM exposure through breastfeeding was observed across cognitive development (breastfed adjusted mean = 103.5, 95% confidence interval [CI] = 101.4–105.6 vs. not breastfed 100.5, 95% CI = 98.1–102.9), language development (breastfed adjusted mean = 105.4, 95% CI = 102.6–108.2 vs. not breastfed 102.8, 95% CI = 99.6–105.9), and motor development (breastfed adjusted mean = 104.9, 95% CI = 102.7–107.2 vs. not breastfed 100.5, 95% CI = 98.0–102.7; Table 4) or in terms of duration of <3 or >3 months (Figure 3B).

3.6 | Sensitivity analysis

The sensitivity analysis using the propensity score provided results (Table S2) that were similar to the main regression models, with similar effect sizes, directions, and conclusions. Of note is the change in direction for the carbamazepine effect on the Bayley motor score in this sensitivity analysis (−1.1 to 1.1; Table 4, Table S2), although the effect size is small and the association was not statistically significant in either analysis. The propensity score models used to weight the multiple regression models (using the inverse probability weights method) are shown for each component of the Bayley Scales in Table S2.

4 | DISCUSSION

The NaME Study cohort is reflective of the changes in UK ASM prescribing patterns,[37] with lamotrigine and levetiracetam monotherapy the most frequently used.

Although the literature in this area has been slowly accumulating, studies have so far been limited by retrospective recruitment to follow-up,[22,23,30] small cohorts of monotherapy lamotrigine and levetiracetam,[20,28] unblinded assessments,[27–30] or lack of an unexposed control group.[6,9] The NaME Study design, which addresses these methodological limitations, demonstrates early

TABLE 4 Multiple regression model results for child performance on the cognitive, language, and motor domains of the Bayley Scales of Infant and Toddler Development, 3rd Edition.

					95% CI	
	Estimate	SE	*t* value	Pr (>|t|)	2.50%	97.50%
Bayley cognitive score						
(Intercept)	74.43	8.12	9.165	<.001	58.409	90.446
Lamotrigine	−.74	2.899	−.255	.799	−6.458	4.978
Levetiracetam	1.57	3.111	.504	.615	−4.569	7.704
Carbamazepine	1.532	3.863	.396	.692	−6.089	9.152
Other monotherapy	.689	4.574	.151	.880	−8.333	9.712
Polytherapy	−4.285	3.035	−1.412	.160	−10.272	1.702
SES[a]	−3.094	1.723	−1.796	.074	−6.492	.305
Higher education[b]	3.544	1.957	1.811	.072	−.317	7.405
Maternal IQ[c]	.143	.076	1.898	.059	−.006	.293
Folate supplementation (<5 mg/day vs. ≥5 mg/day)[d]	−3.601	2.485	−1.449	.149	−8.503	1.301
Child gender (male/female)[e]	4.331	1.659	2.611	.010	1.059	7.603
Oldest child (no/yes)[f]	4.073	1.650	2.468	.014	.817	7.328
Child assessment engagement (adequate/good)[g]	−8.327	2.144	−3.883	<.001	−12.556	−4.097
Birth weight (g)	.005	.001	3.164	.002	.002	.008
Bayley language score						
(Intercept)	44.265	22.247	1.990	.048	.403	88.128
Lamotrigine	−.405	2.944	−.138	.891	−6.210	5.399
Levetiracetam	−2.347	3.217	−.730	.466	−8.690	3.995
Carbamazepine	−1.794	4.098	−.438	.662	−9.873	6.286
Other monotherapy	.455	5.033	.090	.928	−9.468	10.379
Polytherapy	−5.240	3.203	−1.636	.103	−11.555	1.075
SES[a]	−4.267	2.058	−2.074	.039	−8.324	−.210
Maternal IQ[c]	.370	.077	4.778	<.001	.217	.523
Employment status (nonprofessional vs. professional)[h]	−4.999	2.501	−1.999	.047	−9.930	−.069
Tobacco use (no/yes)[i]	−6.129	3.054	−2.007	.046	−12.149	−.108
Seizures during pregnancy (no/yes)[i]	−4.863	2.066	−2.353	.020	−8.936	−.789
Gestational age (weeks)	.899	.535	1.680	.094	−.156	1.954
Child gender (male/female)[e]	5.413	1.919	2.820	.005	1.629	9.197
Neonatal complications (no/yes)[i]	−3.423	2.496	−1.371	.172	−8.345	1.498
Malformation (no/yes)[i]	−6.835	3.495	−1.955	.052	−13.726	.057
Oldest child (no/yes)[f]	5.327	1.969	2.706	.007	1.445	9.209
Child assessment engagement (adequate/good)[g]	−16.581	2.441	−6.793	<.001	−21.393	−11.768
Bayley motor score						
(Intercept)	94.510	6.675	14.159	<.001	81.349	107.670

TABLE 4 (Continued)

	Estimate	SE	*t* value	Pr (>|t|)	95% CI	
					2.50%	97.50%
Lamotrigine	−3.127	2.457	−1.272	.205	−7.972	1.718
Levetiracetam	.533	2.631	.203	.840	−4.654	5.720
Carbamazepine	1.115	3.598	.310	.757	−5.979	8.209
Other monotherapy	−5.343	4.133	−1.293	.198	−13.493	2.806
Polytherapy	−4.941	2.533	−1.950	.053	−9.936	.054
SES[a]	−3.902	1.758	−2.220	.028	−7.367	−.437
Maternal IQ[b]	.145	.065	2.245	.026	.018	.273
Tobacco use (no/yes)[i]	−5.136	2.615	−1.964	.051	−10.292	.021
Child gender (male/female)[e]	2.613	1.596	1.637	.103	−.534	5.760
Child assessment engagement (adequate/good)[g]	−11.927	2.183	−5.463	<.001	−16.232	−7.623

Note: Lamotrigine, levetiracetam, and carbamazepine exposures were monotherapy cases only. For exposure groups, the reference group is the unexposed children. Variables were selected through univariate regression analysis for each specific developmental domain. Variables considered were maternal age, employment type (maternal or paternal professional employment), higher education, maternal IQ, family history of developmental problems, epilepsy type, seizure exposure, convulsive seizure exposure, folate use, folate dose (≥5 mg/day), folate start (prior to conception vs. later in gestation), tobacco use, alcohol use, paternal age, paternal higher education. Child factors were gestational age at birth, preterm birth, birth weight, neonatal complications, physical malformation, child gender, oldest child, breastfed (any duration), breastfed (≥3 months). In the multiple regression model, antiseizure medication exposure was entered a priori, other variables by backward selection.

Abbreviations: CI, confidence interval; IQ, intelligence quotient; SES, socioeconomic status.

[a]SES marker (nonprofessional employment [reference] vs. professional employment).

[b]Compulsory education up to 16 years of age [reference] versus further education.

[c]Two-scale Wechsler Abbreviated Scale of Intelligence II.

[d]Folic acid supplementation of <5 mg/day as the reference.

[e]Males as the reference.

[f]Not oldest child as the reference.

[g]Engagement rated by blinded researcher at home visits (adequate [reference] vs. good).

[h]Employment (no employment [reference] vs. full- or part-time employment).

[i]No as the reference value.

developmental trajectories consistent with children not exposed to an ASM for children exposed to monotherapy lamotrigine or levetiracetam.

No evidence of dose-associated outcomes was seen for either lamotrigine or levetiracetam exposure. In contrast to the MONEAD Study Group,[26] this study did not find poorer motor development in the children exposed to higher doses of levetiracetam. However, our data were limited to prescribed dose, rather than ASM blood levels, which were utilized in the MONEAD investigations.

The NaME Study was, however, consistent with the MONEAD Study in that it did not replicate the results of a questionnaire study that observed poorer early language development in the children exposed to lamotrigine in utero.[28] Although polytherapy exposure was not found to be statistically associated with lower development mean scores, higher rates of a below average performance were observed for language development, and further investigation is required considering this and other recent data.[16] The results of this study in conjunction with the MONEAD study[22] are overall reassuring for infant development following exposure to lamotrigine or levetiracetam monotherapies; however, caution in extrapolating those findings into later childhood is required, as child neurodevelopment is dynamic and brain development continues to expand rapidly through to early adulthood. Thus, later effects may emerge once the expected development of cortical functioning occurs.

At 24 months of age, child development was positively influenced by higher maternal IQ, education level, and socioeconomic level as well as child factors such as being the first child in the family or being female, consistent with results in general child developmental studies. Rating of child engagement level during the assessment was the strongest influencing variable. This rating (good, adequate, poor) reflects testing behavior, and it is hypothesized to represent immature behavioral regulation, attention, and reciprocity skill development. Such observations should be considered in future research studies investigating infant development following ASM exposure.

Exposure to ASMs via breast milk was not associated with poorer outcomes for children exposed both in utero

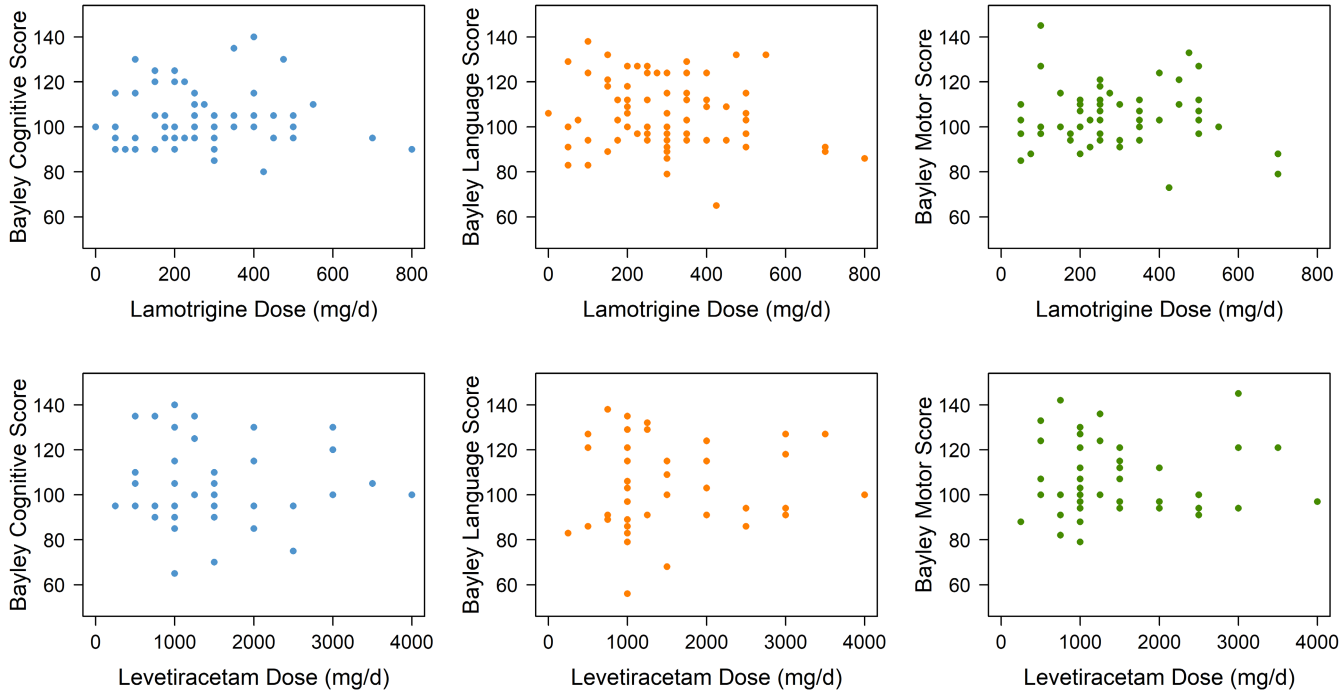

FIGURE 2 The relationship between levetiracetam dose and each domain of the Bayley Scales for lamotrigine (monotherapy)-exposed children and levetiracetam (monotherapy)-exposed children.

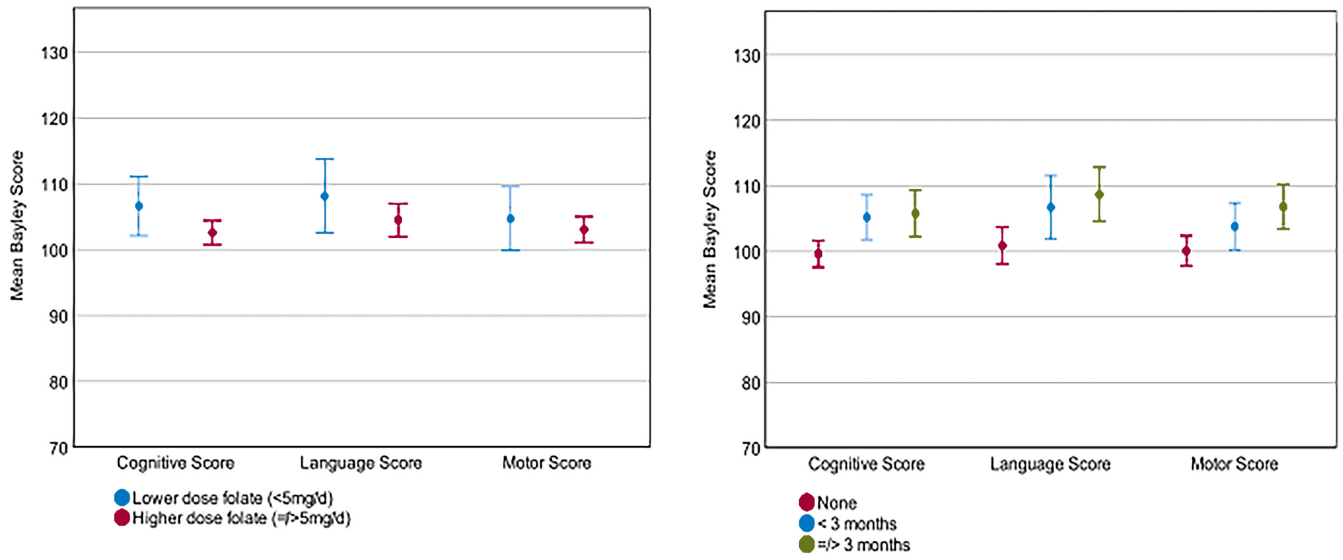

FIGURE 3 Mean Bayley scores by (A) folate supplementation dose (<5 mg/day or ≥5 mg/day) and (B) duration of breastfeeding (<3 months, ≥3 months).

and via breast milk versus those exposed in utero only, but our power to investigate this was limited due to rates of breastfeeding below the UK average of 72%.[38] Anecdotal reports during data collection were that concerns about prolonging the ASM exposure had influenced decisions not to breastfeed. Although there are limited data regarding child outcomes following ASM exposure through breast milk in addition to exposure in the womb,[1] the levels of both lamotrigine and levetiracetam in breast milk are lower than maternal blood concentrations.[39]

Maternal epilepsy variables including epilepsy type and exposure to seizures were not independently associated with child developmental outcome. Adab et al.[24] observed an increased risk to child verbal IQ of five or more generalized seizures during pregnancy; however, our study and other prospective observational cohort studies[6,7,26] have

failed to replicate this association. Uncontrolled generalized seizures can pose a threat to maternal health and in some cases the life of the mother and fetus,[40] but robust evidence of a direct impact on child neurodevelopmental outcomes from five or more generalized seizures is lacking.

Folic acid supplementation was not associated with Bayley Scales scores at 2 years of age, but most women had at least some supplementation. Mean scores of children exposed to ≥5 mg/day did not differ from those whose mothers took lower supplementation levels. Concerningly, fewer than half the cohort initiated folic acid supplementation prior to conception, with similar low rates of preconception adjustment of alcohol consumption, suggesting many women are not planning pregnancy according to current UK guidelines.[41]

Strengths of this study include its prospective design and per protocol, blinded assessments with instruments with proven ability to detect developmental deviations following in utero exposures. Importantly, the primary outcome assessments were administered by just two highly trained assessors to limit interrater bias. Additionally, inclusion of the Vinelands parent interview meant that there was an additional perspective on the child's development, which provides a more functional evaluation of skills relevant to everyday living. Observations of the level of engagement of the child were strongly associated with child score. Child development data were obtained at both 12 and 24 months. Children with conditions likely to be associated with poorer developmental outcome were excluded from the analysis. Finally, adjustment for a wide range of demographic, maternal background, and health data was undertaken, and propensity score modeling considered the impact of those lost to follow-up.

There are four primary limitations to this study that should be considered. First, the 2-year-old assessments were only completed in 70% of live births. Most noncompleters were lost to follow-up; they were more frequently younger mothers from lower socioeconomic areas who had lower formal education, and this could have biased the cohort toward improved child outcomes. However, sensitivity analysis using propensity score weighting did not alter the direction of the results. This completion rate is comparable to previous studies using primary data collection[7] and in some cases those with a secondary use of data approach.[42] Second, this study was limited by its lack of biological samples. ASM levels are not routinely taken in a standardized manner in the UK, and sample collection was not funded as part of this study. Breastfeeding data were based on maternal report rather than analyzed milk samples. However, with so few data available currently regarding breastfeeding and child neurodevelopment in this context, these data remain important. Third, the size of the individual ASM groups means that we were only able to rule out medium to large effect sizes and were not highly powered to assess association between dose of ASM and Bayley Scales score, and therefore the results are exploratory in nature. Finally, we were not able to provide insight into the optimal level of folate supplementation, with >70% of the cohort being prescribed 5 mg/day, and this requires future investigation.

5 | CONCLUSIONS

Infant cognitive, language, and motor development at 2 years of age was not influenced by prenatal exposure to either lamotrigine or levetiracetam monotherapy. Further longitudinal follow-up of this cohort will take place at 8 years of age to investigate more complex child cognitive, social, motor, and behavioral functioning that develops as the children age.

AUTHOR CONTRIBUTIONS

Rebecca L. Bromley and Jill Clayton-Smith contributed to study conception, design, funding, data acquisition, analysis, drafting of the manuscript, and final approval for publication. Philip Bullen, Teresa Kelly, John Craig, Amy Ingham, Beth Irwin, Cerain Jackson, Sarah Rushton, and Janine Winterbottom contributed through data acquisition and manuscript revisions. Ellen Campbell contributed to data acquisition, data review, and manuscript revisions. James Morrow, Amanda Wood, and Laura M. Yates contributed to study design, funding, data acquisition, and manuscript revisions. David M. Hughes conducted the data analysis and drafting/reviewing of the manuscript. Marta García-Fiñana contributed to study design, funding, data analysis, and manuscript revisions.

ACKNOWLEDGMENTS

The authors are grateful to all the women and children who participated in the study and to the health professionals who recruited them. This work was supported through the Department of Health NIHR LCRN. We are grateful to the Manchester University Hospital NHS Foundation Trust Genetics LCRN Team for supporting this work above and beyond their initial remit, and to Lauren Riley for data support. We would finally like to acknowledge the NaME Study Steering and Public and Patient Input representatives: Nicole Crosby-McKenna, Janet Williams, Amanda Jolly, Sarah Marshall, Stewart Rust, Stuart Ingram, Janine Winterbottom, Rebecca Bromley, and Jill Clayton-Smith.

FUNDING INFORMATION

This study is funded by the NIHR Post Doctoral Fellowship Scheme (NIHR PDF-2013-06-041). The

views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

R.L.B. has served on an expert advisory board for women's health funded by UCB Pharma, with funds going to her institution. L.M.Y. provided consultancy for Sanofi Genzyme South Africa on two occasions in 2021 relating to genetic testing in Gaucher disease and a conference lecture on genetic testing in cardiac clinics. B.I. has received sponsorship to attend meetings and honoraria for presentations from Eisai, UCB, and Sanofi Aventis. J.C. has received grants to undertake research as part of the UK Epilepsy and Pregnancy Register and honoraria for giving lectures from UCB Pharma, GlaxoSmithKline, Janssen-Cilag, Sanofi Aventis, and Eisai. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bromley RL, Bullen P, Campbell E, Craig J, Ingham A, Irwin B, et al. Neurodevelopment of babies born to mothers with epilepsy: A prospective observational cohort study. Epilepsia. 2023;00:1–18. https://doi.org/10.1111/epi.17709

APPENDIX

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