THE LANCET Neurology

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Meador KJ, Baker GA, Browning N, et al, for the NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; published online Jan 23. http://dx.doi.org/10.1016/S1474-4422(12)70323-X.

SUPPLEMENTARY WEB APPENDIX

Meador et al., Fetal Antiepileptic Drug Exposure: Prospective Observational Study of Cognitive Outcomes at Age 6 Years.

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Table A1. Results for linear regression analysis with age 6 IQ as dependent variable for Total-Enrolled (n=311 children) and Age-6-Completer Analysis (n=224 children).[A]

Age 6 Total-Enrolled Analysis[B] (R^2 = 30%; average R^2 over all imputed data sets)				
Effect	**F value**	**Df** [C]	**Coefficient (CI)** [D]	**p value**
AED[E] (4 groups)	7·3	3	N/A	<0·0001
Carbamazepine	10.4	1	7.44 (2.88 : 12.01)	0.0015
Lamotrigine	19.4	1	10.46 (5.77 : 15.16)	<0.0001
Phenytoin	13.2	1	10.33 (4.74 : 15.93)	0.0003
Maternal IQ[F]	37·5	1	0·30 (0·21 : 0·40)	<0·0001
Periconceptional Folate	11·4	1	5·92 (2·46 : 9·37)	0·0009
Standardized Dose[G]	7·7	1	-0·12 (-0·21 : -0·04)	0·0060
Gestational Age[H]	4·2	1	0·78 (0·03 : 1·52)	0·0413
Age-6-Completer Analysis (R^2 = 30%)				
Effect	**F value**	**df** [B]	**Coefficient (CI)** [C]	**p value**
AED[E] (4 groups)	7·4	3	N/A	<0·0001
Carbamazepine	11.2	1	7.99 (3.28 : 12.70)	0.0010
Lamotrigine	18.7	1	10.09 (5.50 : 14.67)	<0.0001
Phenytoin	14.6	1	10.61 (5.14 : 16.09)	0.0002
Maternal IQ[F]	34·3	1	0·30 (0·20 : 0·41)	<0·0001
Periconceptional Folate	8·6	1	5·19 (1·71 : 8·66)	0·0037
Standardized Dose[G]	5·2	1	-0·10 (-0·19 : -0·01)	0·0233
Gestational Age[H]	3·5	1	0·74 (-0·04 : 1·51)	0·0616

[A] In addition to the analyses of maternal and baseline covariates noted elsewhere, the following analyses were conducted to determine the potential effect of other factors on the results. Paternal IQ was related to child IQ (r=0·27, p=0·003) and maternal IQ (r=0·37, p<0·0001). When maternal IQ was replaced by paternal IQ in the model, paternal IQ was a significant predictor of child IQ (F=4·43, p=0·037. R-squared=0.39), and the AED differences were unchanged. For same subsample, paternal effects were less than maternal IQ (F=13·10, p=0·0004, R-squared=0.43). Since less IQ data were available for fathers (n=157 total enrolled; n=119 age 6 cohort) than for mothers (n=305 total enrolled; n=221 age 6 cohort), maternal IQ was used for the analyses.

The number of children who had major congenital malformations (n=16) in the Total Enrolled sample differed across AEDs with greater malformations in the valproate group. The number of children who had major congenital malformations (n=11) in the Completer sample did not differed across AEDs. In the Total Enrolled sample, the number of children who were premature (n=30 with gestational age at birth <37 weeks), or developed epilepsy (n=14) did not differ statistically across AED groups. When the children with malformations, prematurity or epilepsy were deleted and the analyses re-run, the IQ differences across AEDs were not altered. There were 6 pairs of twins (3 for phenytoin, and 1 each for the other AEDs); when one child from each pair were deleted and the analyses re-run, the results were unchanged. Child gender (53% female overall) did not differ across AED groups (Chi Square = 5·01, p=0·17) and did not differ for the ITT vs. age 6 completers (Fisher's exact, p=0·20).

[B] Variables used to impute missing Age 6 outcome data included: Age 2 BSID, DAS at ages 3 and 4·5, maternal IQ, AED dose, folate, gestational age, unwanted pregnancy (yes/no), maternal age, convulsions during pregnancy (yes/no), employment status, US/UK site, years of maternal education and socioeconomic status.

[C] df = degrees of freedom.

[D] CI = 95% confidence intervals.

[E] AED = antiepileptic drug.

[F] Because different measures were used to estimate maternal IQ, a covariate for type of maternal IQ measure was added to the primary model; this covariate was non-significant (p=0·39). In addition, re-analysis of the age 6 completer group analysis using only those with maternal TONI measure yielded results similar to the original analyses.

[G] See Appendix Figure A2 for dose correlations for individual AEDs. Therapeutic dosages (mg/day) vary across AEDs, so doses were standardized to allow comparisons across AEDs; ranges within each AED total-enrolled group were used in calculation: 100 × (observed dose – minimum dose) ÷ range of doses (i.e., maximum – minimum).[1]
[H] Gestational age at birth. Note that gestational age at enrollment did not differ across AEDs and was not significant in the analyses of child IQ (also see Table 1).

Table A2. Demographics and IQ results for mothers of 225 children with IQ at 6 years.

Antiepileptic Drug	**Carbamazepine**	**Lamotrigine**	**Phenytoin**	**Valproate**	**Total** [A]	**Missing** [B]
Mothers (n)	61	73	39	48	221	84
Mean Maternal IQs (95% CI)	100 (96:104)	102 (99:106)	94 (88:99)	95 (91:100)	99 (96:101)	96 (92:99)
Mean Maternal Ages (95% CI)	31 (30:32)	31 (30:32)	30 (28:32)	28 (27:30)	30 (30:31)	29 (27:30)
Mean Dose mg/day [C] **(95% CI)**	749 (650:848)	468 (410:525)	387 (345:429)	1054 (868:1240)	N/A	N/A
Standardized Dose [D] **(95% CI)**	31 (27:35)	36 (31:41)	47 (41:53)	27 (21:32)	34 (32:37)	36 (31:40)
Gestational Age at Enrollment, weeks (95% CI)	18 (16:20)	17 (15:19)	19 (16:22)	17 (15:20)	18 (17:19)	19 (17:20)
Gestational Age at Birth, weeks (95% CI)	39 (38:39)	39 (39:40)	39 (38:39)	39 (39:40)	39 (39:39)	39 (38:39)
Years of Maternal Education (95% CI)	14 (14:15)	15 (14:16)	13 (12:14)	13 (12:14)	14 (14:14)	14 (13:14)
Enrolled at UK Site n(%)	32 (52)	23 (32)	7 (18)	28 (58)	90 (41)	15 (18)
Periconceptional Folate n (%)	34 (56)	46 (63)	19 (49)	31 (65)	130 (59)	44 (52)
Alcohol use [E] **n (%)**	6 (10)	5 (7)	1 (3)	4 (8)	16 (7)	8 (10)
Epilepsy Types [F] n (%)						
Localization Related	52 (85)	39 (53)	31 (80)	10 (21)	132 (60)	52 (62)
Idiopathic Generalized	5 (8)	26 (36)	4 (10)	33 (69)	68 (31)	29 (34)
GTCS	4 (7)	8 (11)	4 (10)	5 (10)	21 (10)	3 (4)
Convulsions [G] n (%)						
None	50 (89)	49 (74)	30 (81)	36 (77)	165 (80)	60 (86)
>5 Convulsions	2 (4)	0 (0)	2 (4)	1 (3)	5 (3)	3 (3)
Race/Ethnicity n (%)[H]						
Caucasian	54 (88)	65 (89)	23 (59)	44 (92)	186 (84)	59 (70)
Black	2 (3)	1 (1)	3 (8)	1 (2)	7 (3)	7 (8)
Hispanic	3 (5)	3 (4)	12 (31)	1 (2)	19 (9)	12 (14)
Other	2 (3)	4 (6)	1 (3)	2 (4)	9 (4)	6 (7)

n = number, % = percent, 95% CIs = 95% confidence intervals, N/A = non-applicable, GTCS = generalized tonic clonic seizures.
[A] Totals for mothers with children tested at age 6. Note there were 6 twin pairs, so a total of 224 children. Reasons for absence of age 6 test results included early terminations and missing scheduled testing within assessment window.
[B] Missing = mothers for whom their children who have missing age 6 year IQ scores.
[C] Average dose for whole pregnancy.
[D] Therapeutic dosages (mg/day) vary across AEDs, so doses were standardized to allow comparisons across AEDs; ranges within each AED total-enrolled group were used in calculation: 100 × (observed dose – minimum dose) ÷ range of doses (i.e., maximum – minimum).[1]
[E] Any alcohol use during pregnancy (yes/no)
[F] Epilepsy types: Localization Related (includes cryptogenic and symptomatic); Idiopathic Generalized (includes absence, juvenile myoclonic, genetic, and other idiopathic generalized not otherwise classified); GTCS = generalized tonic clonic seizures (unknown if generalized or secondary generalized).
[G] Convulsions = number (%) of mothers without convulsions or >5 during pregnancy. Seizure frequency during pregnancy not reported for n=14 mothers.
[H] Race/ethnicity was self reported for listed categories, and obtained to assess possible contributions to outcomes.

Table A3. Adjusted mean[A] cognitive scores and % with marked (<70 score) or mild (<85 score) intellectual impairment for each antiepileptic drug (AED) across ages for all children tested and for those tested on the Differential Abilities Scales (DAS) at each age of 3, 4·5 and 6); this group was chosen since the children were all tested on the same measure at the three ages.[B]

All Available Children[C]						
Age	**Measure**	**Carbamazepine**	**Lamotrigine**	**Phenytoin**	**Valproate**	**All AEDs**
2	BSID	93 n=48	95 [D] n=68	95 [D] n=42	88 [D] n=29	93 n=187
	% <70	12%	9%	12%	24%	13%
	% <85	31% [D]	16% [D]	40% [D]	41% [D]	27%
3	IQ	99 [D] n=66	101 [D] n=76	99 [D] n=42	91 [D] n=46	99 n=230
	% <70	4%	3%	5%	13%	6%
	% <85	20% [D]	12% [D]	31% [D]	37% [D]	23%
4.5	IQ	106 [D] n=54	108 [D] n=73	105 [D] n=43	95 [D] n=39	104 n=209
	% <70	4% [D]	0% [D]	0% [D]	10% [D]	3%
	% <85	11%	8%	9%	15%	10%
6	IQ	105 [D] n=61	108 [D] n=74	107 [D] n=40	98 [D] n=49	105 n=224
	% <70	2%	0%	0%	4%	1%
	% <85	8% [D]	3% [D]	5% [D]	16% [D]	8%
Children with Cognitive Assessment at All Three Ages of 3, 4.5 and 6 [C]						
Age	**Measure**	**CBZ**	**LTG**	**PHT**	**VPA**	**All AEDs**
2	BSID	95 n=28	97 n=52	98 n=28	89 n=19	96 n=127 [B]
	% <70	7%	6%	7%	21%	9%
	% <85	14%	12%	25%	32%	18%
3	IQ	101 [D] n=43	102 [D] n=61	102 [D] n=33	92 [D] n=33	100 n=170
	% <70	0%	3%	0%	9%	3%
	% <85	19%	13%	21%	36%	21%
4.5	IQ	109 [D] n=43	109 [D] n=61	108 [D] n=33	96 [D] n=33	106 n=170
	% <70	2% [D]	0% [D]	0% [D]	12% [D]	3%
	% <85	9%	8%	3%	12%	8%
6	IQ	107 [D] n=43	110 [D] n=61	110 [D] n=33	99 [D] n=33	107 n=170
	% <70	2%	0%	0%	0%	1%
	% <85	9% [D]	2% [D]	0% [D]	15% [D]	6%

[A] Means adjusted in repeated measure model for: maternal IQ, maternal age, dose, gestational age and folate.
[B] Because of the later merger of US and UK sites, there were less children tested at age 2. So, this analysis assessed the cohort in which children were tested at all three later ages (i.e., 3, 4·5, and 6), which all employed the same measure (i.e., DAS). The children also tested at age 2 on Bayley Scales of Infant Development (BSID) in this cohort are included for comparison.
[C] Age 6 IQ was correlated with age 2 BSID ($r = 0{\cdot}59$, $p<0{\cdot}0001$), age 3 DAS IQ ($r = 0{\cdot}72$, $p<0{\cdot}0001$), and age 4·5 DAS ($r = 0{\cdot}77$, $p<0{\cdot}0001$). These correlations were also significant when examined for each AED (age 6 compared to age 2 ($r=0{\cdot}39$ to $0{\cdot}71$), age 3 ($r=0{\cdot}62$ to $0{\cdot}77$), and age 4·5 ($r=0{\cdot}68$ to $0{\cdot}78$)).
[D] Significant differences across AEDs in IQ or % with reduced cognitive scores. Comparisons of DAS IQs for valproate to each AED (i.e., carbamazepine, lamotrigine, phenytoin) are significantly worse for valproate at each age (i.e., 3, 4·5, 6). Comparisons of BSID for valproate to each AED at each age 2 are significantly worse for valproate vs. lamotrigine and phenytoin.

Table A4. Periconceptional Folate Dose and IQ for Completers. See footnote for analyses.*

Dose	n (%)	IQ	CIs	p value
0	91 (41%)	102	99-105	NA
>0 – 0.4 mg	6 (3%)	105	95-115	0.54
0.4 – 1.0 mg	29 (13%)	109	105-114	0.008
>1.0 – 4.0 mg	42 (19%)	107	103-111	0.03
>4.0 mg	53 (24%)	107	103-110	0.04

CIs = 95% confidence intervals.
*Periconceptional folate was categorized as 0mg, >0mg to ≤0·4mg, >0·4 to 1·0mg, >1·0mg to <4·0mg, and ≥4·0mg per day. Higher folate dose was used in the valproate group vs. other AEDs (p=0·01). When valproate was excluded and folate dose categories analyzed in the linear regression model, higher periconceptional folate dose was significant (F=2·44, p=0·049).

Table A5a. Results for mixed model analysis with repeated measures for child IQ at ages 2, 3, 4·5 and 6 year with child IQs as dependent variables for all available children and for those children with testing at all there ages of 3, 4·5 and 6..

All Available Children			
Effect	**F value**	**df [A]**	**p value**
AED [B,C] (4 groups)	6·7	3	0·0002 [C]
Age at Testing [D]	47·5	3	<0·0001 [D]
AED X Test Age	0·70	9	0·7079
Maternal IQ [E]	35·3	1	<0·0001 [E]
Maternal Age [F]	6·4	1	0·0123 [F]
Gestational Age [G]	7·0	1	0·0086 [G]
Periconceptional Folate [H]	8·2	1	0·0045 [H]
Standardized Dose [I]	10·4	1	0·0014 [J]
Children with Cognitive Assessment at All Three Ages of 3, 4.5 and 6			
Effect	**F Value**	df [A]	**p value**
AED [B,C]	6.15	3	0.0005
Age at Testing [D]	35.60	3	<.0001
AED*Test Age	0.65	9	0.7523
Maternal IQ [E]	27.55	1	<.0001
Maternal Age [F]	4.45	1	0.0365
Gestational Age [G]	4.17	1	0.0429
Periconceptional Folate [H]	5.59	1	0.0192
Standardized Dose [I]	3.68	1	0.0568

[A] df = degrees of freedom.
[B] AED = antiepileptic drug.
[C] Valproate was significantly worse than each of the other AEDs at each age except carbamazepine at age 2.
[D] Mean IQs in children were higher at older test ages.
[E] Higher maternal IQ was associated with higher child IQ.
[F] IQs in children of very young mothers were lower than other children.
[G] Older gestational age was associated with higher child IQ.
[H] Periconceptional folate use was associated with higher child IQ.
[I] Therapeutic dosages (mg/day) vary across AEDs, so doses were standardized to allow comparisons across AEDs; ranges within each AED total-enrolled group were used in calculation: 100 × (observed dose – minimum dose) ÷ range of doses (i.e., maximum – minimum).[1]
[J] Higher AED dose was associated with higher child IQ.

Table A5b. Mixed model coefficient estimates for cohorts with All Children Available and for Children with Cognitive Assessment at All Three Ages of 3, 4.5 and 6

All Available Children				
Effect	**Estimate**	**Pr > |t|**	**Lower Limit of 95% CI**	**Upper Limit of 95% CI**
Intercept	26.5504	0.0640	-1.5569	54.6578
Carbamazepine	6.6767	0.0048	2.0535	11.2999
Lamotrigine	10.1326	<.0001	5.6348	14.6305
Phenytoin	9.4386	0.0006	4.0957	14.7815
Age=2	-9.9909	0.0002	-15.2143	-4.7675
Age=3	-7.1833	0.0001	-10.8038	-3.5628
Age=4.5	-2.6671	0.1406	-6.2200	0.8857
Carbamazepine*Age=2	-1.8837	0.5800	-8.5767	4.8093
Carbamazepine*Age=3	1.8812	0.4388	-2.8955	6.6579
Carbamazepine*Age=4.5	4.0144	0.0929	-0.6730	8.7018
Lamotrigine*Age=2	-2.7393	0.3936	-9.0511	3.5726
Lamotrigine*Age=3	0.009959	0.9966	-4.6007	4.6206
Lamotrigine*Age=4.5	2.5040	0.2678	-1.9357	6.9438
Phenytoin*Age=2	-2.0312	0.5663	-8.9960	4.9336
Phenytoin*Age=3	-1.1474	0.6700	-6.4425	4.1476
Phenytoin*Age=4.5	0.6235	0.8063	-4.3780	5.6249
Maternal IQ	0.2828	<.0001	0.1891	0.3765
Maternal Age	0.3623	0.0123	0.07941	0.6453
Gestational Age	0.8824	0.0086	0.2262	1.5386
Folate	4.7060	0.0045	1.4690	7.9431
Standardized Dose	-0.1289	0.0014	-0.2076	-0.05019

Children with Cognitive Assessment at All Three Ages of 3, 4.5 and 6				
Effect	**Estimate**	**Pr > |t|**	**Lower Limit of 95% CI**	**Upper Limit of 95% CI**
Intercept	32.4399	0.0429	1.0488	63.8310
Carbamazepine	8.0327	0.0027	2.8297	13.2358
Lamotrigine	11.1050	<.0001	6.1259	16.0841
Phenytoin	11.3342	0.0001	5.5778	17.0905
Age=2	-9.3160	0.0022	-15.2318	-3.4002
Age=3	-6.8485	0.0017	-11.0843	-2.6127
Age=4.5	-2.5152	0.2171	-6.5240	1.4937
Carbamazepine*Age=2	-0.9626	0.8055	-8.6703	6.7451
Carbamazepine*Age=3	1.5694	0.5828	-4.0619	7.2007
Carbamazepine*Age=4.5	4.3058	0.1126	-1.0237	9.6354
Lamotrigine*Age=2	-3.7081	0.2978	-10.7189	3.3027
Lamotrigine*Age=3	-1.3318	0.6176	-6.5900	3.9264
Lamotrigine*Age=4.5	1.8102	0.4736	-3.1662	6.7866
Phenytoin*Age=2	-2.6404	0.5065	-10.4727	5.1920
Phenytoin*Age=3	-1.2727	0.6754	-7.2631	4.7176
Phenytoin*Age=4.5	0.03030	0.9916	-5.6390	5.6996
Maternal IQ	0.2615	<.0001	0.1631	0.3599
Maternal Age	0.3562	0.0365	0.02266	0.6898
Gestational Age	0.7578	0.0429	0.02467	1.4909
Folate	4.3614	0.0192	0.7201	8.0027
Standardized Dose	-0.08515	0.0568	-0.1728	0.002498

Table A6. Results for linear regression analysis with age 6 Verbal and Non-verbal Index scores [A] as dependent variable (n=224 children).

Verbal Index B (R2 = 37%; average R2 over all data sets)		
Effect	**Coefficient (CI) [C]**	**p value**
AED [D,E] (4 groups)	N/A [F]	0·0002
Carbamazepine	7.44 (3.30 : 11.58)	0.0005
Lamotrigine	8.09 (4.10 : 12.08)	<0.0001
Phenytoin	8.79 (3.96 : 13.63)	0.0004
Maternal IQ	0·29 (0·20 : 0·39)	<0·0001
Maternal Age	0·43 (0·16 : 0·70)	0·0022
Race/Ethnicity [G] (4 groups)	N/A [F]	0·0086
Black	-10.13 (-18.45 : -1.81)	0.0173
Hispanic	-6.77 (-12.44 : -1.11)	0.0193
Other	-5.80 (-13.03 : 1.42)	0.1148
Non-verbal Index [H] (R^2 = 16%)		
Effect	**Coefficient (CI) [C]**	**p value**
AED [D,I] (4 groups)	N/A [F]	0·0049
Carbamazepine	3.42 (-0.44 : 7.28)	0.0818
Lamotrigine	6.74 (3.00 : 10.48)	0.0005
Phenytoin	4.87 (0.60 : 9.15)	0.0257
Maternal IQ	0·15 (0·07 : 0·23)	0·0003
Gestational Age	0·85 (0·23 : 1·48)	0·0073

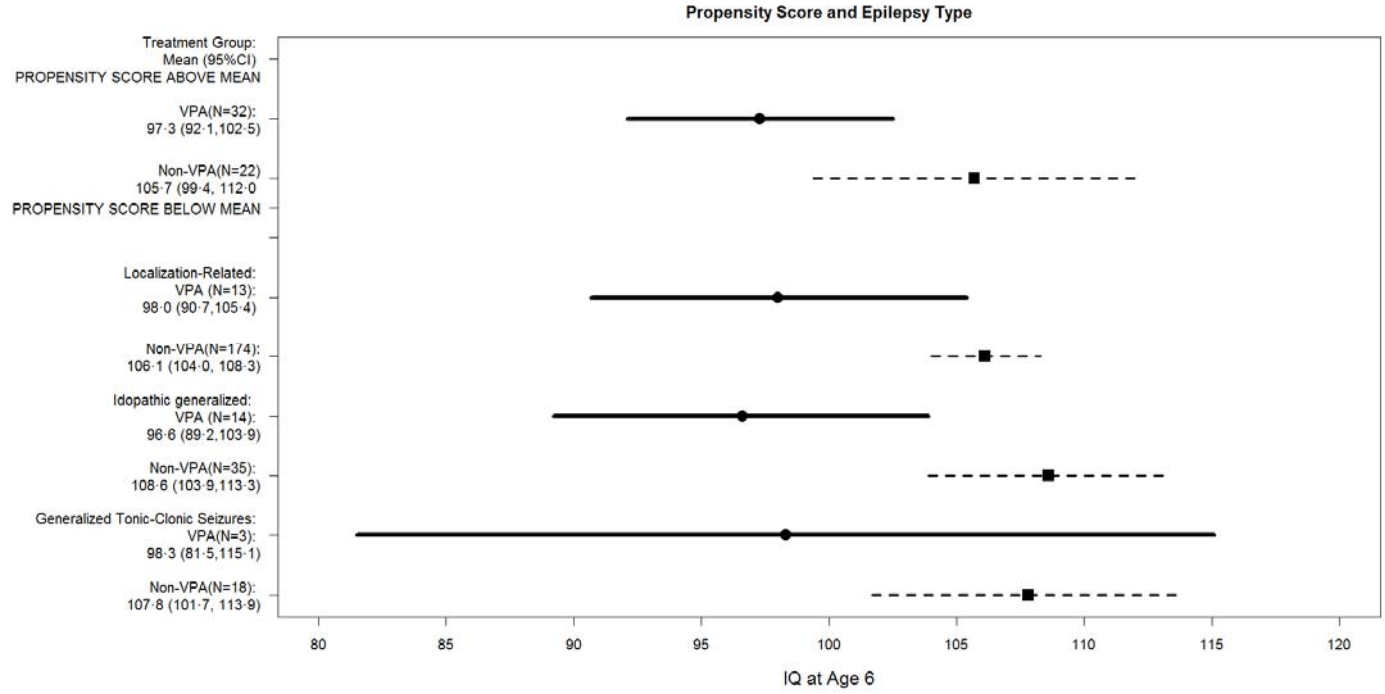
A Index scores were calculated for each subject with available non-missing subtests for that subject.
B The Verbal Index was created by averaging the standard scores (mean = 100; standard deviation =15) from the Word Definition and Similarities subtests of the Differential Abilities Scales (DAS),[2] the Expressive One-Word Picture Vocabulary Test,[3] and the Phonological Processing, Comprehension of Instructions and Sentence Repetition subtests from the Developmental Neuropsychological Assessment (NEPSY).[4]
C CI = 95% Confidence Interval.
D AED = antiepileptic drug.
E Verbal Index: valproate worse than carbamazepine (p=0·0005), lamotrigine (p=0·0003), and phenytoin (p=0·0005)·
F N/A = non-applicable.
G Race/ethnicity has 4 categories (Caucasian non-hispanic, Black non-hispanic, Hispanic, and Other).
H The Non-verbal Index was created by averaging the standard scores from the Pattern Construction, Matrices, and Recall of Designs subtests of the Differential Abilities Scales (DAS),[2] the Arrows subtest from the NEPSY,[4] and the Developmental Test of Visual Motor Integration.[5]
I Non-verbal Index: valproate worse than lamotrigine (p=0·0015 with trends toward worse than carbamazepine (p=0·0818) and phenytoin (p=0·0514).

Table A7. Results for linear regression analyses General Memory Index, Executive Index from NEPSY, and Parent Index from the BRIEF at age 6 years as dependent variables. Means are adjusted for maternal IQ, dose, maternal age, gestational age, race/ethnicity, alcohol use, years of maternal education.

General Memory Index [A] (R^2 = 22%; average R^2 over all data sets)		
Effect	**Coefficient (CI)** [B]	**p value**
AED [C] (4 groups)	N/A [D]	0·0006
Carbamazepine	11.79 (5.17 : 18.41)	0.0005
Lamotrigine	13.36 (6.82 : 19.89)	<0.0001
Phenytoin	8.74 (1.06 : 16.42)	0.0260
Maternal IQ	0·25 (0·11 : 0·39)	0·0004
Alcohol Use	-11·51 (-20·36 : -2·66)	0·0110
Maternal Age	0·59 (0·16 : 1·03)	0·0076
Standardized Dose [E]	-0·13 (-0·26 : -0·01)	0·0373
NEPSY Executive Index [F] (R^2 = 16%)		
Effect	**Coefficient (CI)** [B]	**p value**
AED [C] (4 groups)	N/A [D]	0·0185
Carbamazepine	4.53 (0.51 : 8.54)	0.0273
Lamotrigine	6.04 (2.14 : 9.94)	0.0026
Phenytoin	2.40 (-2.01 : 6.81)	0.2844
Maternal IQ	0·09 (0·01 : 0·18)	0·0309
Gestational Age	1·09 (0·45 : 1·74)	0·0010
Maternal Age	0·30 (0·03 : 0·56)	0·0269
BRIEF [G] (R^2 = 4%)		
Effect	**Coefficient (CI)** [B]	**p value**
AED [C] (4 groups)	N/A [D]	0·1942
Carbamazepine	-3.84 (-8.59 : 0.91)	0.1126
Lamotrigine	-4.66 (-9.27 : -0.04)	0.0479
Phenytoin	-5.14 (-11.04 : 0.75)	0.0868
Standardized Dose [E]	0·10 (0·01 : 0·19)	0·0297

[A] The General Memory Index (GMI) standard score from the Children's Memory Scale[6] represents general memory functioning. GMI is generated by combining the immediate and delayed Verbal and Visual Indexes. Means are adjusted for maternal IQ, dose, maternal age, and alcohol use.
[B] 95% Confidence Interval.
[C] AED = antiepileptic drug.
[D] N/A = not applicable.
[E] Therapeutic dosages (mg/day) vary across AEDs, so doses were standardized to allow comparisons across AEDs; ranges within each AED total-enrolled group were used in calculation: 100 × (observed dose – minimum dose) ÷ range of doses (i.e., maximum – minimum).[1]
[F] The Executive Index was created by averaging the standard scores from the Tower, Verbal Fluency, and Visual Attention subtests from the Developmental Neuropsychological Assessment (NEPSY).[4] Means are adjusted for maternal IQ, gestational age, and maternal age.
[G] The BRIEF Parent Index from the Behavioral Rating Inventory of Executive Function (BRIEF)[7] represents global executive functions as rated by the child's parent. As such, it incorporates all eight clinical scales. Means are adjusted for dose.

Figure A1. Forest plot of IQ scores (means and 95% confidence intervals) by propensity score subgroup and epilepsy type. Subgroups include: VPA = valproate (solid lines), and Non-VPA = the other three AEDs (dashed lines).*



* Propensity scores are predicted probabilities of receiving a treatment given baseline covariates.[8,9] Subjects with similar propensity score values are considered to be balanced with respect to their observed covariates. Variables related to valproate group membership (i.e., maternal age and education, dose, US/UK site and epilepsy type) were predictors in the propensity score model along with variables significantly related to age 6 IQ.[9] Predictors in the propensity score model included dose, folate, maternal IQ, age and education, gestational age, convulsions during pregnancy (yes/no), employment status, socioeconomic status, unwanted pregnancy (yes/no), US/UK site, epilepsy type, and whether or not the child was breastfed. Given the resulting distributions of estimated propensity scores in the two groups (valproate and non-valproate), subjects were partitioned into two subgroups depending on whether their estimated propensity score was above or below the mean estimated propensity score for subjects taking valproate. Within each propensity score subgroup, mean IQ outcomes were compared between the valproate group and non-valproate group using least squares means from linear regression models that controlled for covariates included in the primary analysis model. The below-mean propensity group was further classified by epilepsy type (localization-related, idiopathic generalized or generalized tonic-clonic) to remove residual imbalances in this covariate. Within each of the four resulting subgroups, covariates were balanced between the valproate and non-valproate groups ($p > 0{\cdot}05$, t-test for continuous variables or chi-square test for categorical variables), permitting us to compare mean IQ outcomes between the groups using forest plots.

Figure A2. Mean cognitive scores (i.e., BSID & IQ) across ages 2, 3, 4.5, and 6 years.

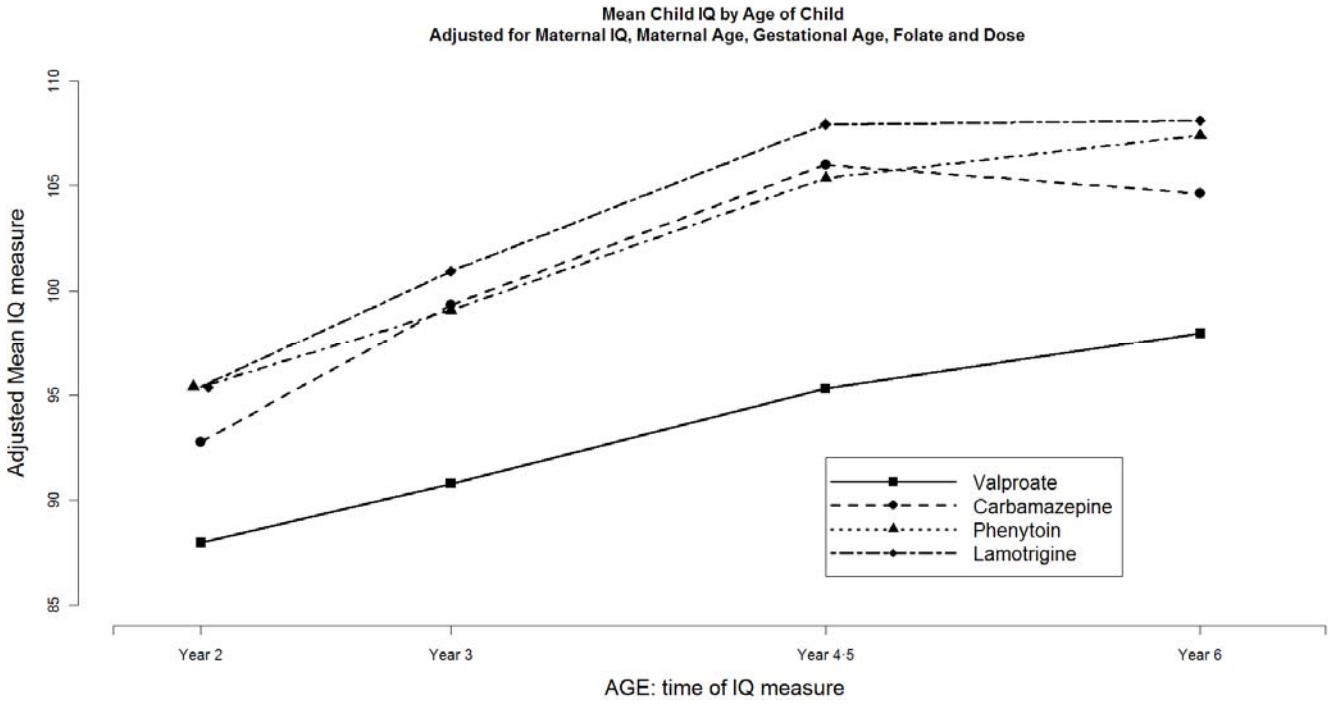
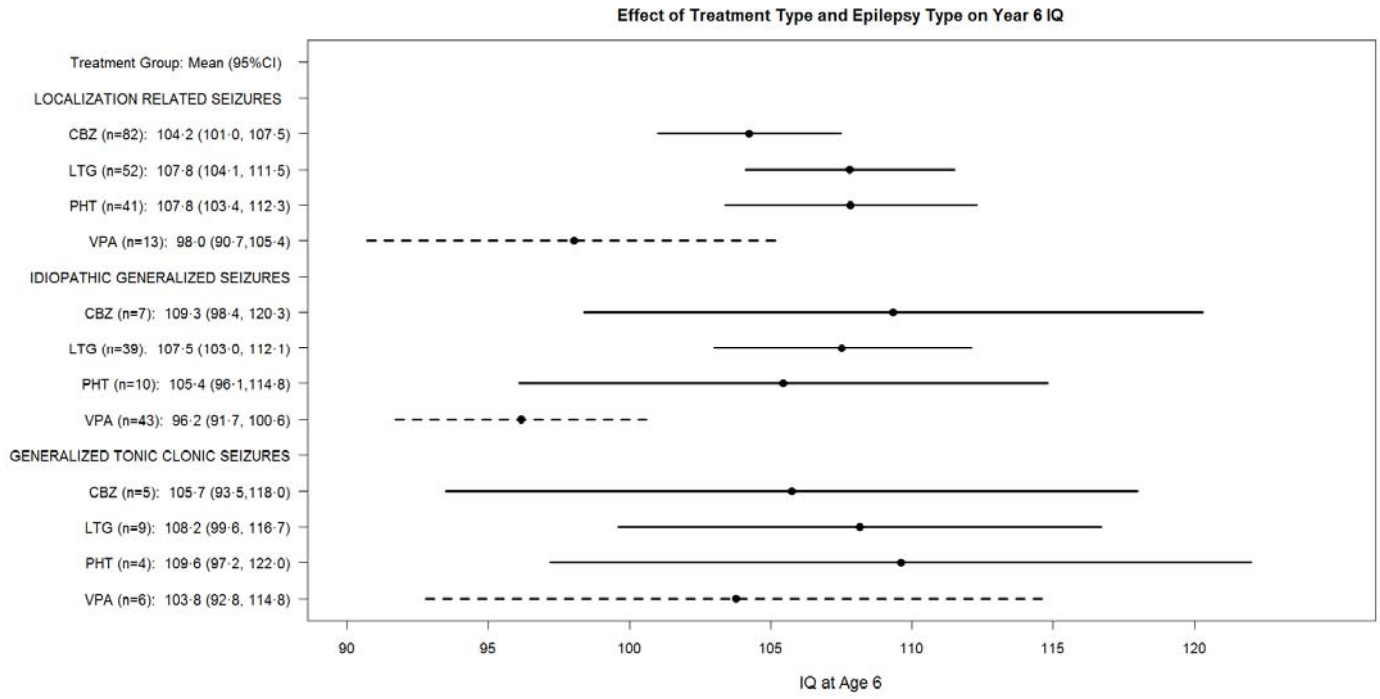


Figure A3. Forest plot of child IQ vs. type of maternal epilepsy* by antiepileptic drug. CBZ = carbamazepine, LTG = lamotrigine, PHT = phenytoin, VPA = valproate. Means and 95% confidence intervals depicted (dashed lines for VPA and solid lines for other drugs).



*Epilepsy types: Localization Related (includes cryptogenic and symptomatic); Idiopathic Generalized (includes absence, juvenile myoclonic, genetic, and other idiopathic generalized not otherwise classified); GTCS = generalized tonic clonic seizures (unknown if generalized or secondary generalized).

Determination of Socioeconomic Status.
Socioeconomic status was determined by the Hollingshead four factor index of social status.[10]

Description of Maternal IQ Testing.
USA and UK investigators collaborated during design of separate studies that were later combined, resulting in different maternal IQ measures: Test of Non-verbal Intelligence-3rd Edition (TONI-3)[11] in 267 mothers (67 UK), Wechsler Abbreviated Scale of Intelligence (WASI)[12] in 20 (all UK), and National Adult Reading Test (NART)[13] in 17 (all UK). The three maternal IQ measures are all based on a standardized scale with a mean of 100 and standard deviation of 15. These measures are strongly correlated to each other. Analyses considering the different maternal IQ tests do not alter the results.

Determination of Handedness.
Of the 225 children assessed at age 6, handedness information was available for 215 of them. Verbal and Non-verbal Indexes were derived from subscores of the Differential Abilities Scales (DAS)[4] and the Developmental Neuropsychological Assessment (NEPSY),[6] and also the Expressive One-Word Picture Vocabulary Test,[5] and the Developmental Test of Visual Motor Integration (DTVMI).[7] Handedness was assessed in 167 children by a 7-item modification of the Edinburgh Handedness Inventory.[14] Hand performance was assessed for writing, drawing, ball throwing, scissor cutting, brushing teeth, eating with a spoon, and opening a box. A handedness index was calculated using ((R – L) / (R + L) X 100. A score > 40 was classified as right handed. In another 48 children, handedness was determined by hand use on the Grooved Pegboard or DTVMI. Handedness results were compared to handedness information from 187 normal six year old children in the standardization sample of the Wechsler Intelligence Scale for Children (WISC-4).[15] Handedness was analyzed using logistic regression models with binary handedness (right vs. non-right) as the outcome variable. Predictor variables were pregnancy average AED dose and group membership (four NEAD AED groups and WISC-4 standardization sample) as predictor variables. Dose was not included in the model, which compared the NEAD groups to the standardization sample. Gender of child, race, maternal education level and age of child at testing were also investigated for inclusion in the logistic regression models, but they were not significant predictors of the outcome.

References Related to Periconceptional Folate.
Two studies referenced in the manuscript are relisted here,[16,17] and seven additional studies are referenced here.[18—23] All of these studies found positive effects of periconceptional folate on cognition except one.[23]

References Related to Cognitive Deficits Associated with Fetal AED Exposure.
Two systematic reviews referenced in the manuscript are relisted here,[24,25] and nine additional studies published since the last systematic review or not included in these prior reviews are referenced here.[26—34] No prior studies were found examining fetal AED effects on handedness, and only our prior study discussed AED effects on cerebral lateralization.[35]

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