

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009;360:1597-605.

Web Supplemental Appendix for NEAD 3 Year Old IQ Study: 4 tables & 5 figures

Web Table 1. Age 3 IQ Regression Model Results for the Primary Analysis of the Intent-To-Treat Group (n=309).^A

	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Significant Variables in Primary Model		
AED Group (4 levels, p-value only) ^D	.007	.02
Maternal IQ^D	0.4 (0.3, 0.5); p<.001	p<.001
Maternal Age^D	1.0 (0.6, 1.3); p<.001	p<.001
Standardized Dose^{D,E}	-0.1 (-0.2, 0.0); p=.13	p=.02
Gestational Age^D	1.3 (0.3, 2.2); p=.008	p=.01
Preconception Folate Use^D	9.1 (4.9, 13.4); p<.001	p=.02
Non-significant Variables When Added to Primary Model		

	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Epilepsy Etiology^F (3 levels, p-value only)	.36	.77
Epilepsy Type: Localization Related	0.4 (-4.1, 4.8); p=.87	.71
Epilepsy Type: Idiopathic Generalized	-2.1 (-6.8, 2.5); p=.37	.51
Epilepsy Type: Generalized Tonic Clonic Seizures^G	5.2 (-2.9, 13.4); p=.20	.65
No Convulsions During Pregnancy (3 levels, p-value only) ^H	.02	.72
> 5 Convulsions During Pregnancy (3 levels, p-value only) ^H	.03	.27
Education^I	9.9 (5.2, 14.6); p<.001	.56
Employment	6.1 (1.6, 10.6); p=.008	.31
Race (4 levels, p-value only)^J	.002	.22
Socioeconomic Status^K	2.6 (1.8, 3.5); p<.001	.26
USA vs. UK Site	-0.2 (-4.7, 4.4); p=.94	.89

	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Alcohol Use	2.6 (-5.5, 10.8); p=.53	.63
Tobacco Use	-5.6 (-12.3, 1.1); p=.10	.80
Birth Weight	4.7 (1.4, 8.0); p=.005	.49
Wanted vs. Unwanted Pregnancy	10.3 (4.2, 16.3); p<.001	.61
Breastfed (3 levels, p-value only)^H	.004	.55
Prior Pregnancy Complications	-0.0 (-4.6, 4.5); p=.99	.98
Prior Pregnancy Birth Defects	-2.6 (-10.5, 5.4); p=.53	.55
Complications During Current Pregnancy	-1.0 (-5.3, 3.4); p=.67	.88
Compliance (missed AED doses) (3 levels, p-value only)^H	.10	.50

^A Age 3 IQ imputed for 77 children without age 3 assessments from the original 309 live births (1 died from severe heart malformation, 6 enrolled from the UK study after 3 years/old, 31 withdrew prior to age 3, and 39 did not present for testing). ^B Estimated regression coefficient (non-ordered categorical variables have only p value), 95% CI = 95% Confidence Intervals; ^C Model includes AED, maternal IQ, maternal age,

standardized AED dose, gestational age, and preconception folate; ^D Variables in primary model; ^E Standardized dose for pregnancy average (see Methods); ^F Three epilepsy types: localization related, idiopathic generalized, & generalized tonic clonic unknown if partial or generalized; ^G Unknown if idiopathic generalized or secondary generalized localization related; ^H Three categories (yes, no, not reported); ^I Education \leq or $>$ high school; ^J Four categories: Caucasian, Black, Hispanic, other; ^K Hollingshead Index.¹⁰

Web Table 2. Age 3 IQ Regression Model Results for Age 2 & 3 Completers Sample (n=258).^A

VARIABLE	Coefficient ^B (95% CIs) and p-value for variable alone, unadjusted	P-value for Variable in Model ^C
Significant Variables in Primary Model		
AED Group (4 levels, p-value only) ^D	.003	.02
Maternal IQ ^D	0.4 (0.3, 0.5); p<.001	<.001
Maternal Age ^D	1.0 (0.6, 1.3); p<.001	.002
Standardized Dose ^{D, E}	-0.1 (-0.2, 0.0); p=.17	.02
Gestational Age at Birth ^D	1.2 (0.3, 2.2); p=.01	.01
Preconception Folate Use ^D	9.2 (4.8, 13.7); p<.001	.02
Non-significant Variables When Added to Primary Model		
Epilepsy Type ^F (3 levels, p-value only)	p=.44	.67
Epilepsy Type: Localization Related	0.5 (-4.2, 5.1); p=.84	.73

VARIABLE	Coefficient ^B (95% CIs) and p-value for variable alone, unadjusted	P-value for Variable in Model ^C
Epilepsy Type: Idiopathic Generalized	-2.1 (-6.9, 2.8); p=0.40	.44
Epilepsy Type: Generalized Tonic Clonic Seizures ^G	4.8 (-3.6, 13.2); p=.26	.52
No Convulsions During Pregnancy (3 levels, p-value only) ^H	.02	.62
> 5 Convulsions During Pregnancy (3 levels, p-value only) ^H	.03	.19
Education ^I	10.8 (6.0, 15.7); p<.001	.45
Employment	6.2 (1.6, 10.8); p=.008	.30
Race (4 levels, p-value only) ^J	<.001	.08
Socioeconomic Status ^K	2.8 (1.9, 3.7); p<.001	.26
USA vs. UK Site	-1.0 (-5.9, 3.9); p=.70	.98

VARIABLE	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	P-value for Variable in Model^C
Alcohol Use	3.9 (-4.7, 12.4); p=.38	.51
Tobacco Use	-6.6 (-13.7, 0.5); p=.07	.69
Birth Weight	4.7 (1.4, 8.0); p=.006	.44
Wanted vs. Unwanted Pregnancy	10.4 (4.0, 16.8); p=.001	.60
Breastfed (3 levels, p-value only)^H	.003	.50
Prior Pregnancy Complications	-0.0 (-4.8, 4.7); p=.99	.91
Prior Pregnancy Birth Defects	-3.4 (-11.6, 4.8); p=.42	.48
Complications During Current Pregnancy	-1.0 (-5.6, 3.6); p=.67	.94
Compliance (missed AED doses) (3 levels, p-value only)^H	.12	.37

^A Age 3 IQ imputed for 26 children with 2 year assessments only; ^B Estimated regression coefficient (non-ordered categorical variables have only p value), 95% CI = 95% Confidence Intervals; ^C Model includes AED, maternal IQ, maternal age, standardized AED dose, gestational age, and preconception folate; ^D Variables in primary model; ^E Standardized dose for pregnancy average (see Methods); ^F Three epilepsy types: localization related, idiopathic generalized, generalized tonic clonic unknown if partial or generalized; ^G Unknown if idiopathic generalized or secondary generalized localization related; ^H Three categories (yes, no, not reported); ^I Education \leq or $>$ high school; ^J Four categories: Caucasian, Black, Hispanic, other; ^K Hollingshead Index¹⁰

Web Table 3. Age 3 IQ Regression Model Results for Age 3 Completers Sample (n=232).^A

VARIABLE	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Significant Variables in Primary Model		
AED Group (4 levels, p-value only) ^D	.002	.01
Maternal IQ^D	0.4 (0.3, 0.5); p<.001	<.001
Maternal Age^D	1.1 (0.7, 1.4); p<.001	<.001
Standardized Dose^{D, E}	-0.1 (-0.2, 0.0); p=.23	.03
Gestational Age at Birth^D	1.3 (0.3, 2.3); p=.01	.02
Preconception Folate Use^D	9.1 (4.6, 13.6); p<.001	.02
Non-significant Variables When Added to Primary Model		
Epilepsy Etiology^F (3 levels, p-value only)	.21	.33
Epilepsy Type: Localization Related	2.1 (-2.6, 6.8); p=.37	.32

VARIABLE	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Epilepsy Type: Idiopathic Generalized	-3.9 (-8.8, 1.0); p=.11	.14
Epilepsy Type: Generalized Tonic Clonic Seizures^G	4.7 (-3.7, 13.1); p=.27	.55
No Convulsions During Pregnancy (3 levels, p-value only)^H	.02	.91
> 5 Convulsions During Pregnancy (3 levels, p-value only)^H	.03	.26
Education^I	11.4 (6.5, 16.3); p<.001	.36
Employment	7.2 (2.5, 11.9); p=.003	.26
Race (4 levels, p-value only)^J	<.001	.06
Socioeconomic Status^K	2.8 [(1.9, 3.7); p<.001	.30
USA vs. UK Site	-1.2 (-6.1, 3.7); p=.64	.98
Alcohol Use	3.2 (-5.5, 11.8); p=.47	.79
Tobacco Use	-7.6 (-14.7, -0.5); p=.04	.62

VARIABLE	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Birth Weight	4.1 (0.6, 7.5); p=.02	.84
Wanted vs. Unwanted Pregnancy	10.1 (3.7, 16.5); p=.002	.80
Breastfed (3 levels, p-value only)^H	.005	.66
Prior Pregnancy Complications	1.0 (-3.8, 5.9); p=.67	.93
Prior Pregnancy Birth Defects	-3.0 (-11.4, 5.4); p=.48	.49
Complications During Current Pregnancy	0.3 (-4.4, 4.9); p=.91	.62
Compliance (missed AED doses) (3 levels, p-value only)^H	.13	.42

^A Only the 232 children with IQ assessment at age 3 included in this analysis.

^B Estimated regression coefficient (non-ordered categorical variables have only p

value), 95% CI = 95% Confidence Intervals; ^C Model includes AED, maternal IQ,

maternal age, standardized AED dose, gestational age, and preconception folate; ^D

Variable included in primary model; ^E Standardized dose for pregnancy average (see

Methods); ^F Three epilepsy types: localization related, idiopathic generalized, &

generalized tonic clonic unknown if partial or generalized; ^G Unknown if idiopathic
generalized or secondary generalized localization related; ^H Three categories (yes,
no, not reported); ^I Education \leq or $>$ high school; ^J Four categories: Caucasian, Black,
Hispanic, other; ^K Hollingshead Index.¹⁰

Web Table 4. Regression Model Results for Age 2 Sample (n=187).^A

VARIABLE	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Variables in Primary Model		
AED Group (4 levels, p-value only) ^D	.03	.08 ^A
Maternal IQ^D	0.4 (0.2, 0.5); p<.001	<.001
Maternal Age^D	0.9 (0.4, 1.4); p<.001	.04
Standardized Dose^{D, E}	-0.1 (-0.3, -0.0); p=.03	.006
Gestational Age at Birth^D	1.0 (-0.1, 2.1); p=.07	.05
Preconception Folate Use^D	9.8 (4.7, 14.9); p<.001	.04
Other Variables		
Epilepsy Etiology^F (3 levels, p-value only)	.006	.03^A
Epilepsy Type: Localization Related	-3.7 (-9.1, 1.6); p=.17	.57
Epilepsy Type: Idiopathic Generalized	-0.9 (-6.6, 4.8); p=.76	.29

VARIABLE	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Epilepsy Type: Generalized Tonic Clonic Tonic Seizures^G	16.4 (6.4, 26.4); p=.002	.008^A
No Convulsions During Pregnancy (3 levels, p-value only)^H	.18	.49
> 5 Convulsions During Pregnancy (3 levels, p-value only)^H	.48	.56
Education^I	12.0 (6.4, 17.5); p<.001	.37
Employment	0.9 (-4.6, 6.4); p=.74	.48
Race (4 levels, p-value only)^J	.02	.89
Socioeconomic Status^K	2.6 (1.5, 3.6); p<.001	.79
USA vs. UK Site	-1.1 (-10.5, 8.2); p=.81	.60
Alcohol Use	-0.6 (-12.9, 11.6); p=.92	.92
Tobacco Use	-8.8 (-18.7, 1.0); p=.08	.96
Birth Weight	5.4 (1.6, 9.2); p=.005	.08
Wanted vs. Unwanted Pregnancy	13.7 (6.6, 20.7); p<.001	.26
Breastfed (3 levels, p-value only)^H	.004	.38

VARIABLE	Coefficient^B (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model^C
Prior Pregnancy Complications	-4.0 (-9.4, 1.4); p=0.15	.05
Prior Pregnancy Birth Defects	-0.3 (-10.6, 10.0); p=.96	.85
Complications During Current Pregnancy	-3.3 (-8.5, 2.0); p=.22	.42
Compliance (missed AED doses) (3 levels, p-value only)^H	.30	.64

^A Only the 187 children with cognitive assessment at age 2 with the Bayley Scales of Infant Development were included in this analysis. Although there was only a trend for AED group in this initial analysis, the effects of epilepsy types were due to higher child IQs in the small Generalized Tonic Clonic Seizure (GTCS) group (n=13) with mean (CIs) = 108 (96:120) compared to partial seizure = 92 (88:95) and generalized seizures = 92 (88: 97). Re-analysis of data deleting GTCS group revealed no significant effects of epilepsy types, but significant effects of maternal IQ (F = 12.95, 1 df, p=.0004), age (F=4.3, 1 df, p=.04), dose (F=6.1, 1 df, p=0.01), folate (F=4.0, 1 df, p=.05) and AED x dose interaction (F = 3.0, 3 df, p=.03). Only valproate dose correlated with IQ (r=-0.59, p=.0009 without GTCS; r=-0.58, p=.0009 with GTCS). Age 2 and 3 IQs were highly correlated (r=.70; p<.0001) in children who completed both (n=161); ^B Estimated

regression coefficient (non-ordered categorical variables have only p value), 95% CI = 95% Confidence Intervals; ^C Model was the same as the primary analysis and included AED, maternal IQ, maternal age, standardized AED dose, gestational age, and preconception folate; ^D Variable included in primary model; ^E Standardized dose for pregnancy average (see Methods); ^F Three epilepsy types: localization related, idiopathic generalized, & generalized tonic clonic unknown if partial or generalized; ^G Unknown if idiopathic generalized or secondary generalized localization related; ^H Three categories (yes, no, not reported); ^I Education \leq or $>$ high school; ^J Four categories: Caucasian, Black, Hispanic, other; ^K Hollingshead Index.¹⁰

Web Figure Legends.

Web Figure 1. Means and 95% confidence intervals (horizontal lines) for child IQ as a function of subgroup defined by VPA group membership (VPA vs. Non VPA, i.e., other 3 AEDs) and propensity score subgroup¹⁸ (above-median vs. below-median). The below-median group was further subclassified by epilepsy type (see Statistical Analysis).

Web Figure 2. Means and 95% confidence intervals (horizontal lines) for child IQs as a function of maternal age and AED group. Low maternal age is below median for all mothers (30.7 years), and high maternal age is above median. Child IQs are adjusted for factors in the primary model except maternal age. In this and subsequent figures, the vertical line is the mean IQ across all children, the middle of the boxes on the horizontal lines are means for the subgroups, and the box size depicts sample size.

Web Figure 3. Means and 95% confidence intervals (horizontal lines) for child IQ as a function of USA vs. UK site and AED group. Child IQs are adjusted for factors in the primary model.

Web Figure 4. Means and 95% confidence intervals (horizontal lines) for child IQ as a function of breastfeeding and AED group. Child IQs are adjusted for factors in the primary model.

Web Figure 5. Relationships of child IQ - mother IQ differences vs. dose (pregnancy average) for the four AEDs. Correlations (r values) and p values given for each AED group. Only valproate exhibited a significant dose effect. Based on the intent-to-treat sample (n=309). Seventy-seven child IQ values were imputed (see Statistical Analysis).

Web Figure 1.

Propensity Score Subgroup

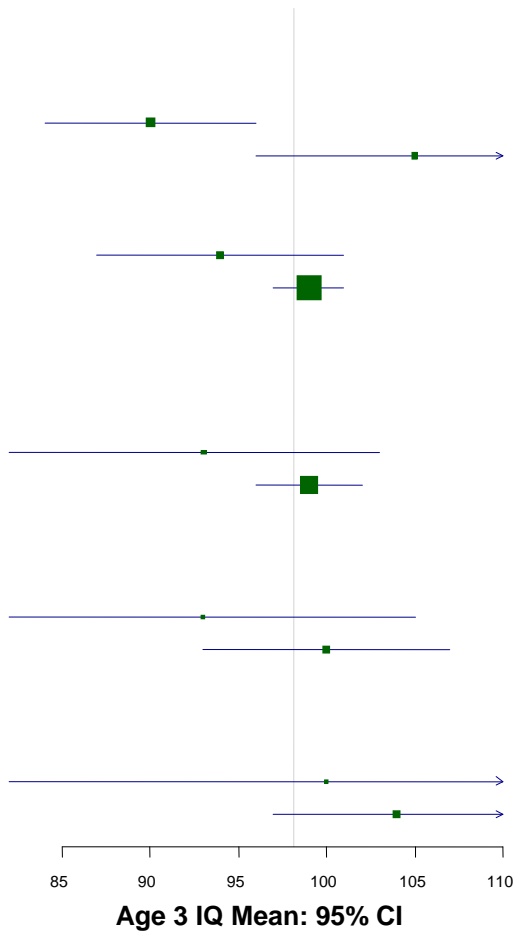
	N	Mean IQ
Above-Median		
Valproate	30	90
Non-Valproate	17	105

	N	Mean IQ
Below-Median		
Valproate	31	94
Non-Valproate	231	99

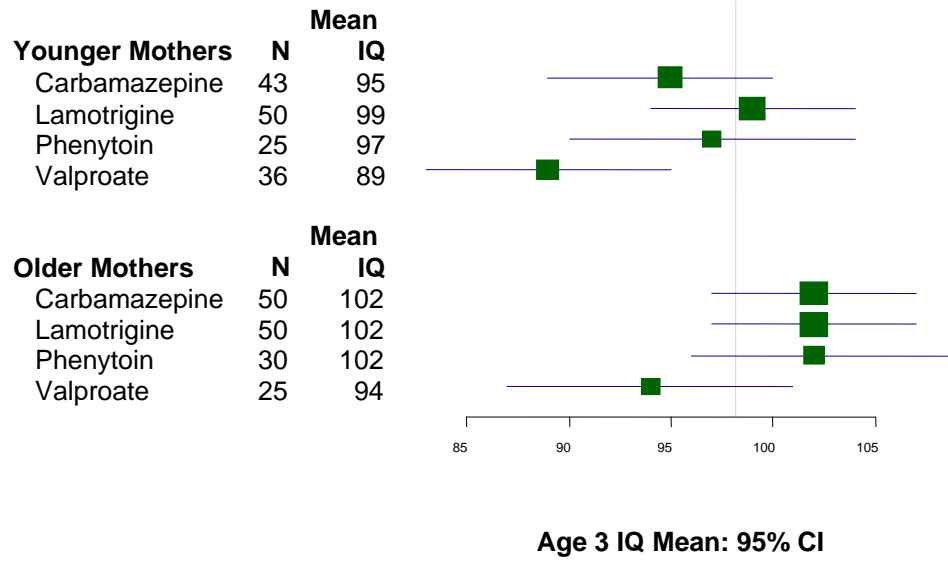
	N	Mean IQ
Below-Median: Localization-related Epilepsy		
Valproate	13	93
Non-Valproate	174	99

	N	Mean IQ
Below Median: Idiopathic Generalized Epilepsy		
Valproate	14	93
Non-Valproate	39	100

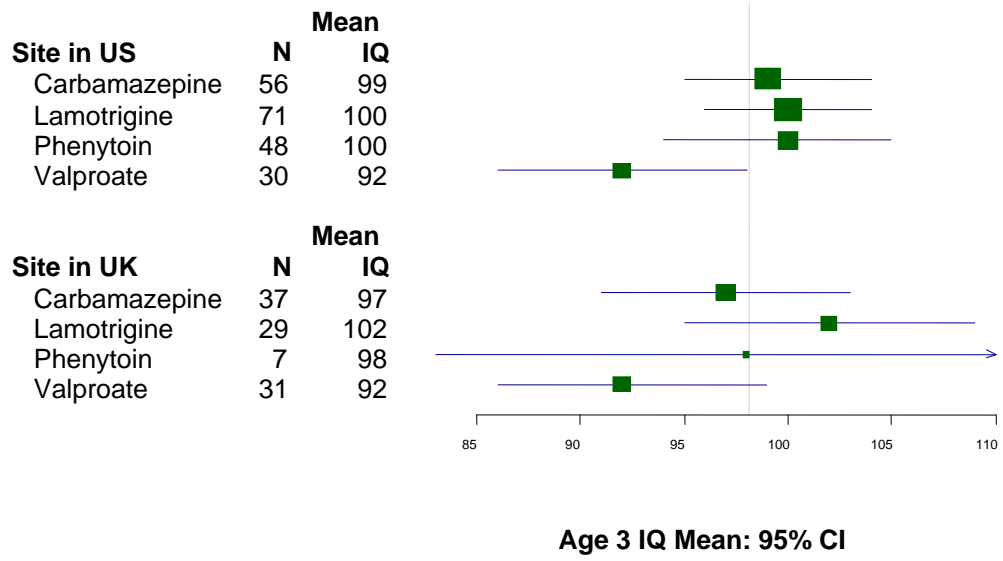
	N	Mean IQ
Below Median: Generalized Tonic-Clonic Epilepsy		
Valproate	4	100
Non-Valproate	18	104



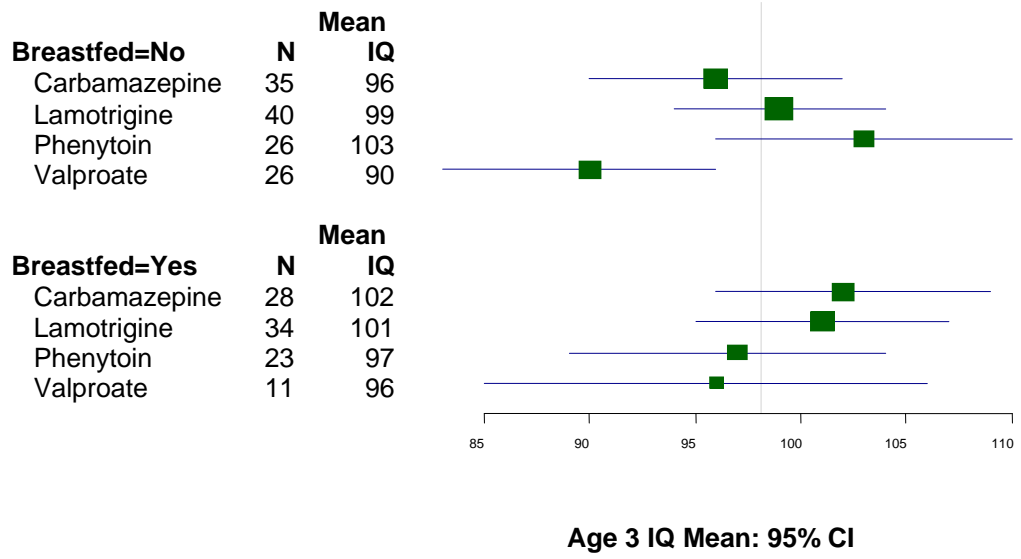
Web Figure 2.



Web Figure 3.



Web Figure 4.



Web Figure 5.

