

Online Supplement for:

Meador et al. Breastfeeding in Children of Women on Antiepileptic Drugs: Cognitive Outcomes at Age 6 Years. JAMA Pediatr. 2014 Jun 16. doi: 10.1001/jamapediatrics.2014.118. [Epub ahead of print] PMID: 24934501

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eTable 1. Pregnancy average AED dose comparing breastfed to non-breastfed for each AED for the n=177 mothers in the primary analysis.

AED Group	Breastfed	N	Pregnancy Average AED Dose (mg)	95% CIs	p-value for comparison of Breastfed to Non-breastfed
Carbamazepine	Yes	22	750	575 : 925	0.36
	No	24	851	704 : 999	
	ALL	46	803	693 : 913	
Lamotrigine	Yes	27	511	422 : 600	0.93
	No	33	505	412 : 598	
	ALL	60	508	445 : 571	
Phenytoin	Yes	16	379	334 : 423	0.56
	No	20	404	327 : 480	
	ALL	36	393	348 : 438	
Valproate	Yes	11	998	667 : 1329	0.37
	No	24	1235	900 : 1570	
	ALL	35	1160	915 : 1406	

AED=antiepileptic drug; CIs=confidence intervals

eTable 2. Adjusted means (95% CIs) for age-6 cognitive domains by AED comparing breastfed vs. non-breastfed children.*

	N Breastfed	N Not Breastfed	Breastfed	Not Breastfed
Verbal Index	79	102	105 (103:108)	102 (100:104)
CBZ	23	24	109 (105:114)	104 (100:108)
LTG	27	34	109 (105:113)	107 (103:111)
PHT	17	20	105 (100:110)	103 (99:108)
VPA	12	24	98 (91:105)	92 (87:97)
Non-verbal Index	79	103	105 (103:108)	104 (102:106)
CBZ	23	25	102 (97:107)	103 (99:108)
LTG	27	34	112 (109:115)	109 (106:111)
PHT	17	20	104 (100:108)	107 (103:110)
VPA	12	24	102 (94:109)	99 (94:104)
Memory Index	78	96	103 (99:107)	100 (96:104)
CBZ	23	23	106 (98:115)	105 (97:114)
LTG	27	33	112 (106:118)	105 (99:111)
PHT	17	19	97 (88:106)	104 (95:112)
VPA	11	21	95 (84:106)	89 (80:97)
Executive Index	78	99	105 (102:107)	104 (101:106)
CBZ	23	24	104 (99:109)	106 (101:111)
LTG	27	32	110 (107:114)	107 (104:110)
PHT	17	20	97 (92:102)	107 (103:112)
VPA	11	23	105 (98:112)	97 (92:102)
BRIEF (parent)	68	89	103 (101:106)	101 (99:104)
CBZ	22	19	99 (95:104)	103 (98:108)
LTG	26	30	102 (97:107)	99 (95:104)
PHT	9	18	106 (98:115)	99 (93:104)
VPA	11	22	109 (101:117)	106 (100:111)

*Adjusted for maternal IQ, AED group, AED dose, periconceptional folate, and breastfeeding.
CIs=confidence intervals; AED=antiepileptic drug, CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate.

eTable 3. Results from Analysis of Sensitivity of Results to Unmeasured Covariates.^A

D ^B	G ^C	B ^D	95% Confidence Interval for B
Difference Between Breastfed and Non-Breastfed in Unobserved Covariate	Coefficient of Unobserved Covariate in Regression Model	Estimated Effect of Breastfeeding Taking into Account the Unobserved Covariate	
-0.8	-6	-0.8	(-4.8 : 3.2)
	-4	0.8	(-3.2 : 4.8)
	-2	2.4	(-1.6 : 6.4)
-0.4	-6	1.6	(-2.4 : 5.6)
	-4	2.4	(-1.6 : 6.4)
	-2	3.2	(-0.8 : 7.2)
0.4	-6	6.4	(2.4 : 10.4)
	-4	5.6	(1.6 : 9.6)
	-2	4.8	(0.8 : 8.8)
0.8	-6	8.8	(4.8 : 12.8)
	-4	7.2	(3.2 : 11.2)
	-2	5.6	(1.6 : 9.6)

- A. The sensitivity analysis follows methods outlined in Yin et al²⁶ and Rosenbaum.²⁷ Sensitivity of the estimated effect of breastfeeding to the existence of an unmeasured covariate was assessed as follows: the unmeasured covariate was assumed to be continuous and to follow a standard normal distribution. Yin et al²⁶ and Rosenbaum²⁷ show that the effect of adding the unmeasured covariate to the primary model is: $B = B^* - G \times D$
Here, B^* is the estimated breastfeeding effect from the primary model without taking into account the unmeasured covariate. In our analysis, $B^* = 4$ IQ points with 95% confidence interval = (0 : 8). D, G and B are explained in the footnotes below.
- B. D is the mean difference between the breastfed and non-breastfed groups in the unobserved covariate. A hypothetical range for D was determined by considering all continuous covariates in the dataset, standardizing them according to a standard normal distribution, and looking at the mean differences between the breastfed and non-breastfed groups. The range for D includes and extends beyond the maximum and minimum differences observed in the data.
- C. G is the hypothetical effect of the unobserved covariate in the regression model after it has been added to the primary model, which includes the breastfeeding variable and the other observed covariates. A range for G was determined by adding the standardized continuous observed covariates to the primary model. The range for G includes and extends beyond the maximum and minimum estimated effects obtained in this way. Only negative values for G are considered in this table since the corresponding positive values result in values for B that are already included in the table.
- D. B is the effect of breastfeeding after adding the unmeasured covariate to the primary model. Note that most effects are positive as in our primary analysis. Negative effects have confidence intervals that include zero.

eTable 4. Summary of missing data for age 6 IQ and for breastfeeding by AED group.

AED Group	N	Missing Age 6 IQ n (%)	Missing Breastfeeding n (%)	Missing Either n (%)
Carbamazepine	92	32 (35)	20 (22)	45 (49)
Lamotrigine	99	25 (25)	18 (18)	38 (38)
Phenytoin	55	15 (27)	4 (7)	18 (33)
Valporate	62	13 (21)	17 (27)	26 (42)
ALL AEDs	308	85 (28)	59 (19)	127 (41)
p-value for difference across groups (Chi- square test)		0.26	0.042	0.24

AED=antiepileptic drug

eTable 5. Summary of missing Age 6 IQ data by breastfeeding status.

Breastfeeding Status	N	Missing Age 6 IQ n (%)
YES	102	24 (24)
NO	147	44 (30)
Breastfeeding Data Missing	59	17 (29)
ALL	308	85 (28)
p-value for difference across groups (Chi-square test)		0.52

eTable 6. Results from Repeated Measures Model: Estimated Means by Age and Breastfeeding Status.*

	Breastfed Mean (CI) n	Not Breastfed Mean (CI) n	Mean Difference (CI)	P Value
Age 2	95 (92 : 99) n=78	91 (88 : 94) n=102	5 (0 : 9)	0.063
Age 3	100 (97:104) n=83	96 (93 :99) n=115	4 (-1 : 9)	0.085
Age 4.5	108 (104:111) n=74	101 (98:104) n=103	7 (2 : 11)	0.007
Age 6	108 (105:111) n=78	103 (100:105) n=103	5 (2 : 9)	0.003
All Ages	103 (100:106)	98 (95:100)	5 (1 : 9)	0.007

* To assess whether results were similar across all ages when IQ was measured, a repeated measures model was estimated using all available data at ages 2, 3, 4.5 and 6. This model incorporated within-subject correlations over time and included child age along with breastfeeding status, maternal IQ, AED, folate and standardized dose as covariates. At each age, adjusted means were compared for breastfed vs. non-breastfed children. 229 children had breastfeeding information and testing data available from at least one time point; 97 (42%) were breastfed and 132 (58%) were non-breastfed.