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Relationship of Child IQ to Parental IQ and Education in Children with Fetal Antiepileptic Drug Exposure

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Abstract

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Conflict of Interest Statement

Dr. Meador reports receiving research support from McKnight Brain Institute, MCG Foundation, GlaxoSmithKline, Eisai Medical Research, Myriad Pharmaceuticals, Marinus Pharmaceuticals, NeuroPace, SAM Technology, and UCB Pharma; and also serves on the Professional Advisory Board for the Epilepsy Foundation and the editorial boards for *Epilepsy and Behavior*, *Epilepsy Currents*, *Epilepsy.com*, *Neurology*, and *Journal of Clinical Neurophysiology*. Dr. Baker reports serving on paid advisory boards, receiving lecture fees from Pfizer, UCB, and Janssen, receiving grant support from Sanofi-Aventis and Pfizer, and has served as an expert witness in litigation related to neurodevelopment effects of antiepileptic drugs. Dr. Clayton-Smith is journal editor for *Clinical Dysmorphology* and has served as an expert witness in litigation related to neurodevelopment effects of antiepileptic drugs. Dr. Combs-Cantrell reports receiving lecture fees from GlaxoWellcome. Dr. Kalayjian reports receiving lecture fees from GlaxoSmithKline and Ortho-McNeil, and grant support from Marinus and Medical College of Georgia. Dr. Kanner reports receiving lecture fees from GlaxoSmithKline, Ortho-McNeil, Pfizer, and UCB, consulting fees or paid advisory boards from GlaxoSmithKline, Ortho-McNeil, Valeant Laboratories, and UCB, and grant support from GlaxoSmithKline and Novartis. Dr. Liporace reports receiving lecture fees from UCB Pharma, and also is a member of the Professional Board of Epilepsy Foundation of Eastern PA. Dr. Pennell has received grant support from NIH, CDC, Milken Family Foundation, UCB Pharma and Marinus Pharmaceuticals; and serves on the Professional Advisory Board for the Epilepsy Foundation, the Board of Directors for the American Epilepsy Society, and the editorial boards for *Epilepsy Currents* and *Epilepsia*. Dr. Privitera reports receiving consulting and advisory board fees from UCB, Johnson and Johnson, and Epifellows Foundation; lecture fees from Ortho-McNeil, Pfizer, GlaxoSmith Kline, Janssen, and UCB; grant support from UCB, Ortho McNeil, and American Epilepsy Society. Dr. Loring reports receiving consulting fees from UCB, NeuroPace and Sanofi-Aventis and grant support from Myriad Pharm, Sam Technology, and Novartis. No other potential conflicts of interest are reported.

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Clinical trial designs need to control for genetic and environmental influences when examining cognitive outcomes in children for whom clinical considerations preclude randomization. However, the contributions of maternal and paternal IQ and education to pediatric cognitive outcomes are uncertain in disease populations. The NEAD Study is an ongoing prospective observational multicenter study in the USA and UK, which enrolled pregnant women with epilepsy to determine if differential long-term neurodevelopmental effects exist across four commonly used antiepileptic drugs (AEDs). Here, we examined the relationship of IQ and education in both parents to child IQ at age 3 years. IQ and education for both parents were statistically correlated to child IQ. However, paternal IQ and education were not significant after accounting for maternal IQ effects. Because maternal IQ and education are independently related to child cognitive outcome, both should be assessed in studies investigating the effects of fetal drug exposures or other environmental factors that could affect the child's cognitive outcome.

Keywords

antiepileptic drugs; IQ; neurodevelopment; epilepsy

1. Introduction

Cognitive development may be affected by numerous genetic and environmental factors (e.g., drugs, other toxins, infections, anoxia, trauma, stroke, or psychosocial factors) [1]. Compared to adults, the developing brain is particularly susceptible to adverse effects from environmental toxins [1–3], and this creates significant challenges for managing the treatment of women with epilepsy who are of child-bearing potential. For example, animal studies have shown that some antiepileptic drugs (AEDs) produce widespread neuronal apoptosis in the neonatal brain which is dose dependent, occurs at therapeutically relevant blood levels, and occurs after brief AED exposure [4–10]. In humans, AEDs may be associated with reduced cognitive abilities in children exposed *in utero* [11–14].

Many AEDs commonly used in pregnancy have not been evaluated for their effects on neurodevelopment in humans. In addition, only 12 of the 3,000 chemicals produced in the highest volumes (>1 million pounds/year) have been adequately tested for their effects on the developing brain [1]. Thus, the need for additional studies assessing potential adverse effects in the developing brain is great.

Evaluation of drug and toxin effects on the immature brain in humans requires selection of appropriate outcomes and control of many potential confounding factors since these studies are observational in nature and randomization cannot be incorporated in study design [15]. The importance of parental cognitive abilities to the success of the child is highlighted by the fact that maternal cognitive scores correlate with child achievement testing ($r=.41$ to $.45$) [16]. A common behavioral outcome in drug/toxic exposure studies is IQ since it is standardized and predictive of school performance [17]. In population-based studies, maternal IQ is the single greatest predictor of child IQ [17]. Maternal IQ reflects not only genetic influences, but also incorporates environmental factors affecting the child. However, IQ may be difficult to obtain in certain circumstance, and consequently maternal education has been frequently used as a surrogate for IQ. However, it is unclear if maternal education is an adequate surrogate.

In fetal AED studies employing maternal IQ or education, paternal IQ and education have not been assessed. There is concern that maternal IQ and education might be altered by seizures, AEDs, or other factors related to epilepsy. Thus, maternal IQ and education might underestimate the genetic and environmental contributions to the child's cognitive

outcomes. If so, then paternal IQ may be an independent predictor unlike the general population where paternal IQ is not significant when maternal IQ is added to the analysis. No prior study has examined the contributions of maternal IQ and education as well as paternal IQ and education on cognitive outcomes in children of women with epilepsy who were taking an AED during pregnancy. Thus, the relative contributions of maternal and paternal IQ and education to the child's cognitive outcome are uncertain when the immature brain is exposed to AEDs. Further, it is unclear how these maternal and paternal factors are inter-related in this population. To our knowledge, the inter-relationships of maternal and parental IQ and education to child IQ have not been examined for other behavioral teratogens. The main rationale for the present analyses in the ongoing NEAD study is to provide insight into how these factors are related to the child's cognitive outcome in such a cohort in order to inform design of future studies. In the present study, we examined the relationship of maternal IQ, paternal IQ, maternal education, and paternal education to each other and to child IQ assessed at age 3 years in children with fetal AED exposure.

2. Methods

2.1 Design

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is a prospective observational study examining possible behavioral teratogenesis of AEDs. We enrolled pregnant women with epilepsy from October 1999 through February 2004, who were being treated with one of four AED monotherapies (i.e., carbamazepine, lamotrigine, phenytoin, or valproate). Subjects were recruited across 25 epilepsy centers in the USA and UK. We recently reported on preliminary findings of cognitive outcomes in the children at 3 years old [13]. Here, we examined the relationship of maternal and paternal IQ and education to child's IQ at age 3 years.

2.2 Subjects

IRBs at each center approved the study, and written informed consent was obtained prior to enrollment. Pregnant women with epilepsy on carbamazepine, lamotrigine, phenytoin, or valproate monotherapy were enrolled. These four AED monotherapies were the most frequently employed during the enrollment time period. Other AEDs were not included because of insufficient numbers. Polytherapy was not included because of its association with poorer outcomes [14]. A non-exposed control group was not included at the direction of an NIH review panel. Mothers with IQ below 70 were excluded to avoid floor effects and because maternal IQ is the major predictor of child IQ in population studies [17]. Other exclusion criteria included positive syphilis or HIV serology, progressive cerebral disease, other major disease (e.g., diabetes), exposure to teratogenic agents other than AEDs, poor AED compliance, drug abuse in the prior year, or drug abuse sequelae.

2.3 Procedures

In addition to parental IQ and education (i.e., years education), information was collected on potentially confounding variables including maternal age, employment, race, socioeconomic status [18], seizure/epilepsy types and frequency, AED dosages, compliance, UK/USA site, preconception folate use, use of alcohol, tobacco, or other drugs during pregnancy, unwanted pregnancy, abnormalities or complications in the present pregnancy or prior pregnancies, enrollment and birth gestational age, birth weight, breastfeeding, and childhood medical diseases. Separate investigations with very similar designs in the US and UK were merged after initiation. Cognitive outcomes were evaluated by assessors (blinded to AED). IQ in children was determined by the Differential Ability Scales [19] (conducted 36–45 months/old); standardized scores were calculated. Maternal IQs were determined by slightly different measures due to the later merger; these measures included the Test of Nonverbal

Intelligence (TONI) [20] in 267 mothers, Wechsler Abbreviated Scale of Intelligence (WASI) [21] in 18, and National Adult Reading Test (NART) [22] in 18. Paternal IQ was assessed using the TONI, although there were fewer fathers available for IQ assessment than mothers. Training and monitoring of neuropsychological evaluations were conducted to assure quality and consistency. Face-to-face training on all neuropsychological test batteries was performed annually. Each assessor was required to identify errors in a videotaped test session and provide appropriate correction for errors in administration and scoring. In addition, assessors submitted their own videotape and record forms using each test instrument to the Neuropsychology Core Director for review, feedback and approval. If assessors failed, they submitted additional video assessment for approval prior to testing subjects in the study. Parental education was measured as total number of years in school or post graduate training. Note that this differs from our prior publication where education was treated as a dichotomous variable (i.e., $\pm$ high school) [13].

2.4 Statistical Analysis

The primary analyses in this sub-study were correlations across maternal and paternal IQ and education as well as these factors to child IQ in the subset of families with child IQ and TONI IQ in both parents (n=140 children including 5 twin pairs, 135 mothers and 135 fathers). Secondary analyses included 1) correlations in all available subjects, by AED group and for all AEDs combined; 2) linear regression models, in the subset with child IQ and TONI IQ in both parents, to examine the effects of maternal and paternal IQ and education on age 3 child IQ adjusting for AED group, standardized AED dose, maternal and gestational age at delivery, and preconception folate. These covariates were found to be significantly related to the age 3 outcomes in our prior analysis [13]. In addition, regression analyses were conducted for all available subjects. Analyses were performed at the NEAD Data and Statistical Center using SAS 9.2.

Linear regression models were used to examine the effects of maternal and paternal IQ and education on age 3 child IQ adjusting for standardized AED dose, maternal and gestational age at delivery, and preconception folate. Additional covariates considered were: epilepsy/seizure types, seizure frequency during pregnancy, employment, race (self-reported), socioeconomic status, US/UK site, alcohol and tobacco use, birth weight, unwanted pregnancy, breastfeeding, prior pregnancy birth defects and complications, present pregnancy complications, and AED compliance. AED dose was standardized relative to ranges observed within each group: $100 \times (\text{observed dose} - \text{minimum dose})/(\text{range})$. The a priori hypothesis based on prior analysis [13] was that AED type, dose, maternal IQ, maternal and gestational age, and preconception folate were important covariates, and thus these were included as predictors in a linear model with child IQ as outcome. Other covariates were added individually to the model to investigate whether they were significant predictors of the outcome (at the .05 level of significance).

Child outcome data were available for 230 children; 140 children had all mother and father TONI IQ and education data available. All 230 children had maternal education and some form of maternal IQ data available. Of these, 216 of the mothers had a TONI score available while 14 from the UK had no TONI available. Of the 14 with missing TONI scores, the WASI IQ score was used in 11 and the NART score was used in 3. . Out of the 230 children, 15 had fathers with missing education data and 88 had fathers with missing IQ data. To eliminate concerns about possible systematic differences across the various parental IQ measures, our primary analysis focuses on the sample of n=140 with complete maternal and paternal TONI and education data. Secondary analyses consider the entire sample of 230 children with complete age 3 IQ outcome data. In this analysis, no attempt was made to consider the effect of missing data in the 81 children with missing child IQ outcome data.

See our prior analysis for further discussion [13]. Instead, we limit considerations here to the sample with complete outcome data.

3. Results

The primary analyses included 135 mothers, 135 fathers, and 140 children (5 sets of twins). Similar analyses were also conducted on all subjects available: 304 mothers, 157 fathers, and 230 children (5 sets of twins). Mean IQs (standard deviations) for the subgroups are listed in Table 1. Pearson correlation r values (95% confidence intervals (CIs)), p values, and sample sizes for parent comparisons are listed in Table 2 and for child-parent comparisons in Table 3 for both the subset with 140 children and the group with all available subjects. Both IQ and education were significantly correlated for each parent, between parents, and to child IQ. Child IQ was correlated with most parental IQ and education comparisons for carbamazepine, lamotrigine and phenytoin. In contrast, no parental IQ or educational measures were correlated with child IQ for the valproate group.

Statistical results for the secondary analyses are presented in Table 4 for the 140 child sample and in Table 5 for all subjects available. In the group with 140 children, maternal IQ was significant, but maternal education and paternal IQ and education were not. Both maternal IQ and education were independently related to child IQ in the analysis using all subject available.

5. Discussion

The present report sought to determine the relationship of maternal and paternal IQ and education to cognitive outcomes in children with fetal AED exposure. The main finding is that maternal IQ and education are independently related to child cognitive outcome, and that paternal factors add no additional predictive value. Although both the IQ and education of both parents are statistically related to the child's IQ, paternal effects are not significant after accounting for the effects of maternal IQ. There are at least three reasons why paternal IQ and education may not predict the child's cognitive outcome. First, it may be that paternal IQ and education are so closely related to maternal IQ and education that they add no additional predictive value to child cognitive outcome; this possibility is supported at least in part by our analyses. Second, the child may spend more time with the mother so that the environmental influences related to maternal IQ and education may have a greater effect. Finally, unlike maternity, absolute confirmation of paternity requires genetic testing.

Thus, clinical trial designs should include assessments of both maternal IQ and education when examining cognitive outcomes in children in observational studies when randomization cannot be incorporated into the trial design. These factors should be assessed along with other potential confounding factors. If the child outcome is not IQ, then maternal IQ may still be important, but this issue has not been directly assessed.

In the general population, IQ correlations between spouses range from .37 to .61 [23–25]; the mother-father IQ correlation in our study of .38 is at the lower end of this range. In our study, the correlations of child IQ to maternal ($r=.38$) and paternal ($r=.37$) education are similar to correlations of child IQ to maternal ($r=.41$) and paternal ($r=.35$) education in the general population [26]. IQ correlations for parents and child in the general population are approximately .42 [16], which is similar to what we found for child IQ to maternal IQ ($r=.38$ across all 4 AEDs) but greater than paternal ($r=.23$ across all 4 AEDs) IQ. When individual AEDs are examined, none of the parental factors (i.e., maternal and paternal IQ and education) were significantly related to child IQ in the valproate group. In contrast, most of the parental measures were related to child IQ in the other AED groups.

Strengths of our study include its prospective design, blinded cognitive assessments using standardized measures, and detailed monitoring of multiple potential confounding factors. However, caution is advised due to study limitations, which include a relatively small sample size, loss of enrolled subjects to analysis, lack of randomization, and lack of an unexposed control group during pregnancy. Different IQ measures were used in the child and parents similar to population studies. Other limitations are the relatively young age of the children at this planned interim analysis. However, it should be noted that the correlation of IQ at age 3 years compared to 21 years is $r=.70$ (uncorrected) and $R=.87$ (corrected for unreliability) [27].

To emphasize the importance of the issues being addressed, the potential economic impact of recent findings on valproate is highlighted. The USA National Center for Health Statistics reported 4.3 million births in 2007 [28]. Since 3 to 5 births per thousand are to women with epilepsy, there are 12,951 to 21,585 children born to women with epilepsy each year $[(3 - 5/1000) \times (4.317 \text{ million births})]$. The average incremental cost for a special education student (i.e., above and beyond the cost of a regular student) is \$7,500 per year in 2009 dollars [29]. Special education is required in 10–35% of AED-exposed children due to neurodevelopmental deficits [30]. Thus, the lifetime costs of special education costs for children born to women with epilepsy each year could reach \$793 million = $(7,554 \text{ children of women with epilepsy need special education}) \times (\$7500 \text{ special education costs/year}) \times (14 \text{ years of preschool, elementary and secondary school special education})$. When examining longer-term financial effects, each single IQ point loss is associated with a loss of income in 2009 dollars of \$17,870 (range=\$15,650–\$21,200) based upon the pediatric lead exposure literature [31].

Based on CDC data, valproate was the second most prescribed AED to women with epilepsy who were of childbearing potential from 1999 – 2006 (the last year available). Valproate comprised 20% of all AED prescriptions in 2006 to women with epilepsy. Since less than half of prescriptions for valproate are for seizures or epilepsy (i.e., most for pain and psychiatric indications), the number of children exposed would be at least doubled. Based on these facts and the data presented above, we can calculate that approximately 8,634 children are exposed *in utero* to valproate each year. Since 30% of children exposed to valproate need special education [30], the annual costs for special education in the USA each year due to valproate exposure would be \$272 million dollars. Further, the loss in lifetime earnings for children exposed each year to valproate would be \$1.08 billion based on a 7 IQ point drop and number of valproate exposures in 2006. Note that this is a conservative estimate given that the IQ drop from valproate ranged from 7–9 points in our age 3 data, 7–15 points in retrospective study, 6–12 points and 13–14 in prospective studies [11–13, 32].

Further studies are needed to confirm our findings and to extend investigations to other AEDs and environmental toxins. In addition, research is required to understand mechanisms adverse effects of AEDs and other chemicals on the immature.

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References

1. Stein J, Schetter T, Wallinga D, Valenti M. In harm's way: toxic threats to child development. *J Dev Behav Pediatr.* 2002; 23(Suppl 1):S13–22. [PubMed: 11875286]

2. Fisher JE, Vorhees C. Developmental toxicity of antiepileptic drugs: relationship to postnatal dysfunction. *Pharmacol Res.* 1992; 26(3):207–221. [PubMed: 1437987]
3. Gaily, E.; Meador, KJ. Neurodevelopmental effects. In: Engel, J.; Pedley, TA., editors. *Epilepsy: A Comprehensive Textbook.* 2. Vol. II. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1225–33.
4. Bittigau P, Siffringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci USA.* 2002; 99:15089–15094. [PubMed: 12417760]
5. Bittigau P, Siffringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. *Ann N Y Acad Sci.* 2003; 993:103–114. [PubMed: 12853301]
6. Glier C, Dzietko M, Bittigau P, et al. Therapeutic doses of topiramate are not toxic to the developing rat brain. *Exp Neurol.* 2004; 187:403–409. [PubMed: 15144866]
7. Katz I, Kim J, Gale K, Kondratyev A. Effects of lamotrigine alone and in combination with MK-801, phenobarbital, or phenytoin on cell death in the neonatal rat brain. *J Pharmacol Exp Ther.* 2007; 322:494–500. [PubMed: 17483293]
8. Kim JS, Kondratyev A, Tomita Y, Gale K. Neurodevelopmental impact of antiepileptic drugs and seizures in the immature brain. *Epilepsia.* 2007; 48 (Suppl 5):19–26. [PubMed: 17910577]
9. Manthey D, Asimiadou S, Stefovskia V, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. *Exp Neurol.* 2005; 193:497–503. [PubMed: 15869952]
10. Stefovskia VG, Uckermann O, Czuczwar M, et al. Sedative and anticonvulsant drugs suppress postnatal neurogenesis. *Ann Neurol.* 2008; 64:434–445. [PubMed: 18991352]
11. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry.* 2004; 75:1575–1583. [PubMed: 15491979]
12. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology.* 2004; 62:28–32. [PubMed: 14718692]
13. 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; 360:1597–1605. [PubMed: 19369666]
14. Harden CL, Meador KJ, Pennell PB, et al. Practice Parameter update: Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology.* 2009; 50(5):1237–46.
15. Meador KJ, Baker G, Cohen MJ, et al. Cognitive/behavioral teratogenetic effects of antiepileptic drugs. *Epilepsy Behav.* 2007; 11:292–302. [PubMed: 17996637]
16. Plomin, R.; DeFries, JC.; McClearn, GE.; McGuffin, P. *Behavioral genetics.* 4. New York: W.H. Freeman; 2001.
17. Sattler, JM. *Assessment of Children: Cognitive Foundations.* 5. Mesa, CA: Jerome M. Sattler Pub., Inc; 2008.
18. Hollingshead, AB. *Four factor index of social status.* New Haven, CT: Yale University; 1975.
19. Elliot, CD. *Differential abilities scales.* San Antonio, TX: The Psychological Corporation; 1990.
20. Brown, L.; Sherbenou, RJ.; Johnsen, SK. *Test of Non-verbal Intelligence (TONI-3).* 3. Austin, TX: Pro-Ed; 1996.
21. Wechsler, D. *Wechsler abbreviated scale of intelligence (WASI).* San Antonio, TX: Psychological Corporation; 1999.
22. Nelson, H.; Willison, J. *National adult reading test (NART).* Oxford, England: NFER-Nelson Publishing; 1991.
23. Watkins MP, Meredith W. Spouse similarity in newlyweds with respect to specific cognitive abilities, socioeconomic status, and education. *Behav Genet.* 1981; 11(1):1–21. [PubMed: 7259719]
24. Mascie-Taylor CG. Spouse similarity for IQ and personality and convergence. *Behav Genet.* 1989; 19(2):223–7. [PubMed: 2719625]
25. Watson D, Klohnen EC, Casillas A, Simms EN, Haig J, Berry DS. Match makers and deal breakers: analyses of assortative mating in newlywed couples. *J Pers.* 2004; 72(5):1029–68. [PubMed: 15335336]

26. Neiss M, Rowe DC. Parental education and child's verbal IQ in adoptive and biological families in the National Longitudinal Study of Adolescent Health. *Behav Genet.* 2000; 30(6):487–95. [PubMed: 11523707]
27. Fagan JF, Holland CR, Wheeler K. The prediction, from infancy, of adult IQ and achievement. *Intelligence.* 2007; 35:225–231.
28. Eckholm, E. '07 US births break baby boom record. 2009. http://www.nytimes.com/2009/03/19/health/19birth.html?_r=1&partner=rss&emc=rss
29. Chambers, J.; Parrish, T.; Harr, J. Special education expenditure project: what are we spending on special education services in the United States, 1999–2000?. Washington, DC: American Institutes for Research; 2002.
30. Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry.* 2001; 70:15–21. [PubMed: 11118242]
31. Grosse SD, Matte TD, Schwartz J, Jackson RJ. Economic gains resulting from the reduction in children's exposure to lead in the United States. *Environ Health Perspect.* 2002; 110:563–569. [PubMed: 12055046]
32. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L, Briggs M, Smith JC, Sin X, Baker GA. Early cognitive development in children born to women with epilepsy: A prospective report. *Epilepsia.* 2010; 51:2058–65. [PubMed: 20633039]

Appendix

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Table 1

Sample sizes and mean IQs (standard deviations, SDs) for subgroups.

Group	N	Mean IQ (SD)
Child DAS (both maternal TONI and paternal TONI available)	140 *	97.8 (18.6)
Maternal TONI (both paternal TONI and Child DAS Available)	135	99.5 (17.6)
Paternal TONI (both maternal TONI and Child DAS available)	135	101.4 (15.8)
All children (DAS)	230	98.6 (17.9)
All mothers (IQ is TONI/WAIS/NART)	304	97.9 (16.6)
All Fathers (TONI)	157	101.0 (15.8)

* Differs from n for parents since it includes 5 twins.

Table 2

Pearson correlations (95% confidence intervals), p values, and sample sizes for maternal and paternal IQ and education.

Group	Maternal & Paternal IQ	Maternal ¹ & Paternal ¹ Education	Maternal IQ & Education ¹	Paternal IQ & Education ¹
Child DAS and both parent TONIs available	0.38 (0.22–0.52) p<.0001 n=135	0.66 (0.55–0.74) p<.0001 n=135	0.60 (0.48–0.70) p<.0001 n=135	0.57 (0.45–0.68) p<.0001 n=135
All subjects available ²	0.35 (0.20–0.48) p<.0001 n=157	0.65 (0.58–0.71) p<.0001 n=276	0.55 (0.46–0.62) p<.0001 n=303	0.57 (0.45–0.67) p<.0001 n=156

¹ Total number of years of schooling reported.

² For maternal IQ, TONI was used primarily. If TONI was missing WASI or WAIS was used, and these were missing NART was used. See Methods for details.

Table 3

Pearson correlations (95% confidence intervals), p values, and sample sizes for child age 3 IQ (DAS)¹ with maternal and paternal IQ and education.

SUBSET WITH CHILD IQ AND WITH TONI FOR BOTH PARENTS				
	Maternal TONI	Paternal TONI	Maternal Education ²	Paternal Education ²
All AED Groups	0.37 (0.22–0.51) p<.0001 n=140	0.24 (0.08–0.39) p=0.0037 N=140	0.40 (0.25–0.53) p<.0001 n=140	0.39 (0.24–0.52) p<.0001 n=140
Carbamazepine	0.62 (0.37–0.79) p<.0001 n=36	0.21 (–0.13–0.50) p=.2224 N=36	0.44 (0.13–0.67) p=.0072 n=36	0.36 (0.03–0.61) p=.0326 N=36
Lamotrigine	0.18 (–0.11–0.44) p=.2258 n=48	0.31 (0.02–0.54) p=.0343 N=48	0.33 (0.05–0.56) p=.0229 n=48	0.39 (0.12–0.61) p=.0057 N=48
Phenytoin	0.56 (0.27–0.75) p=.0005 n=34	0.29 (–0.06–0.57) p=.1010 N=34	0.59 (0.32–0.78) p=.0001 N=34	0.52 (0.22–0.73) p=.0014 N=34
Valproate	–0.10 (–0.50–0.34) p=.6614 N=22	0.07 (–0.36–0.48) P=.7599 n=22	–0.23 (–0.59–0.22) P=.3162 n=22	–0.05 (–0.46–0.38) P=.8245 n=22
ALL AVAILABLE DATA				
	Maternal IQ ³	Paternal IQ	Maternal Education	Paternal Education
All AED Groups	0.38 (0.26–0.48) p<.0001 N=230	0.23 (0.07–0.38) p=.0054 n=142	0.39 (0.27–0.49) p<.0001 n=230	0.37 (0.25–0.48) p<.0001 n=215
Carbamazepine	0.56 (0.37–0.71) p<.0001 N=66	0.17 (–0.16–0.47) p=.3127 n=37	0.41 (0.18–0.59) p=.0006 N=66	0.34 (0.10–0.55) p=.0071 N=60
Lamotrigine	0.22 (–0.01–0.42) p=.0565 N=76	0.31 (0.03–0.54) p=.0322 n=49	0.27 (0.05–0.47) p=.0168 N=76	0.29 (0.06–0.49) p=.0133 N=73
Phenytoin	0.52 (0.26–0.71) p=.0003 n=42	0.29 (–0.06–0.57) p=.1010 N=34	0.60 (0.36–0.76) p<.0001 n=42	0.46 (0.17–0.67) p=.0025 N=40
Valproate	0.10 (–0.20–0.38) p=.5193 n=46	0.07 (–0.36–0.48) p=.7599 N=22	–0.07 (–0.22–0.35) p=.6380 n=46	0.27 (–0.04–0.53) p=.0845 N=42

¹ Differential Ability Scales.

² Total number of years of schooling reported.

³ For maternal IQ, TONI was used primarily. If TONI was missing WASI or WAIS was used, and these were missing NART was used. See Methods for details.

Table 4Primary model with age 3 IQ (DAS) as outcome. ($R^2=0.35$; $N=140$)

Variable	Coefficient (95% confidence interval)	F value	p value
AED ¹ (4 groups)	N/A ¹	2.97	0.0341
Maternal IQ ²	0.22 (0.03, 0.40)	5.23	0.0238
Dose ³	-0.16 (-0.31, -0.02)	4.85	0.0294
Maternal Age	0.92 (0.35, 1.50)	10.19	0.0018
Gestational Age (birth)	1.44 (0.23, 2.66)	5.51	0.0205
Folate ⁴	5.91 (-0.44, 12.25)	3.39	0.0678
Maternal Education ^{5,6,7}	0.43 (-0.63, 1.50)	0.65	0.4218

¹Least squares means (95% confidence interval) for each AED group are as follows:

CBZ: 99.7 (94.5, 104.9)

LTG: 98.6 (94.0, 103.3)

PHT: 100.7 (95.2, 106.2)

VPA: 88.6 (81.8, 95.4)

²TONI. See Methods for details.

³AED dose was standardized relative to ranges observed within each group: $100 \times (\text{observed dose} - \text{minimum dose})/(\text{range})$.

⁴Preconception folate.

⁵Total number of years of schooling reported.

⁶Model with Paternal IQ in place of maternal education: p-value for paternal IQ=0.5725.

⁷Model with years of paternal education in place of maternal education: p-value for paternal education=0.4011.

Table 5Primary model with age 3 IQ (DAS) as outcome. ($R^2=0.30$; $N=230$)

Variable	Coefficient (95% confidence interval)	F value	p value
AED ¹ (4 groups)	N/A ¹	3.46	0.0171
Maternal IQ ²	0.18 (0.03, 0.33)	5.79	0.0170
Dose ³	-0.15 (-0.26, -0.04)	6.85	0.0095
Maternal Age	0.67 (0.27, 1.06)	11.24	0.0009
Gestational Age (birth)	1.04 (0.12, 1.96)	4.94	0.0272
Folate ⁴	4.39 (-0.17, 8.95)	3.59	0.0593
Maternal Education ^{5,6,7}	0.86 (0.01, 1.72)	3.95	0.0481

¹Least squares means (95% confidence interval) for each AED group are as follows:

CBZ: 99.0 (95.3, 102.8)

LTG: 101.2 (97.7, 104.8)

PHT: 100.8 (95.8, 105.8)

VPA: 91.9 (87.2, 96.6)

²First TONI, then if TONI missing, WAIS/WASI, finally NART if all others missing. See Methods for details.

³AED dose was standardized relative to ranges observed within each group: $100 \times (\text{observed dose} - \text{minimum dose})/(\text{range})$.

⁴Preconception folate.

⁵Total number of years of schooling reported.

⁶Model with Paternal IQ in place of maternal education ($n=142$): p-value for paternal IQ=0.6513.

⁷Model with years of paternal education in place of maternal education ($n=215$): p-value for paternal education=0.1050.