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FULL-LENGTH ORIGINAL RESEARCH

Prenatal valproate exposure and adverse neurodevelopmental outcomes: Does sex matter?

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Abstract

Objective: Prenatal exposure to the antiepileptic drug (AED) valproic acid (VPA) is associated with an increased risk of impaired postnatal neurodevelopment, including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). We aimed to evaluate the influence of sex and drug dosage on the association between prenatal VPA exposure and postnatal behavioral outcomes.

Methods: The Australian Pregnancy Register of AEDs was interrogated to identify children aged 4–11 years prenatally exposed to AEDs. Parents reported on their child's behavior using the Autism Spectrum Quotient–Children's Version and the National Institute for Children's Health Quality Vanderbilt Assessment Scale for ADHD. General linear mixed-effects models were used to investigate the relationship between clinicodemographic variables and psychometric scores.

Results: A total of 121 children were studied: 54 prenatally exposed to VPA (28 males, 26 females; mean dose ± SD: 644 ± 310 mg/day) and 67 exposed to other AEDs. There was a main effect of sex showing higher ASD scores in males compared to females ($p = .006$). An interaction between sex and VPA exposure revealed that males had higher ASD symptoms among children exposed to AEDs other than VPA ($p = .01$); however, this typical sex dynamic was not evident in VPA-exposed children. There was no evidence of any dose–response relationship between VPA

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exposure and ASD symptoms. Males had higher ADHD scores compared to females, but there was no evidence for a link between ADHD symptoms and VPA exposure.
Significance: Prenatal VPA exposure seems to negate the usual male sex-related predominance in the incidence of ASD. These initial findings deepen the concept of VPA as a "behavioral teratogen" by indicating that its effect might be influenced by sex, with females appearing particularly sensitive to the effects of VPA. No association between VPA doses and adverse postnatal behavioral outcomes was detected, possibly related to the low VPA doses used in this study.

KEYWORDS
antiepileptic drugs, attention-deficit/hyperactivity disorder, autism spectrum disorder, epilepsy, neurodevelopment

1 | INTRODUCTION

For many women with epilepsy, becoming pregnant poses a challenging need to balance between optimizing seizure control and minimizing the potentially harmful effects of antiepileptic drugs (AEDs) on the unborn child. Prenatal exposure to certain AEDs is associated with increased risks of adverse anatomical and neurodevelopmental outcomes,[1–3] with converging evidence for Valproic acid (VPA) being particularly hazardous.[3] Prenatal VPA exposure carries approximately a 10% risk of major congenital malformations,[4] including neural tube defects, cardiac anomalies, and cleft lip/palate; the risk is dose-dependent. Growing evidence suggests that children exposed to VPA, either as monotherapy or as part of AED polytherapy, are also at increased risk of adverse neurobehavioral outcomes, such as lowered intellectual ability, neurodevelopmental delay and disorders, and dyspraxia.[3,5,6] Similarly to major congenital malformations, the risk of VPA-induced adverse neurobehavioral outcomes seems to increase with higher VPA doses.[3]

There is broad consensus that neurodevelopmental disorders emerge from a complex, multifactorial interaction between genetic and environmental factors during gestation.[7,8] Exposure to VPA in utero has been found to cause defects in neural development, sometimes with behavioral effects. The prevalence of autism spectrum disorder (ASD) in children prenatally exposed to VPA has been suggested to range from 8% to 15%,[5,9–11] as opposed to a general population prevalence of .6%–1%.[12–14] In the general population, males are three to four times more likely than females to have ASD.[12,14] The relationship between prenatal VPA exposure and adverse postnatal behavioral outcomes has also been extended to attention-deficit/hyperactivity disorder (ADHD). ADHD is characterized by persistent inattention, and/or hyperactivity or impulsivity,[15] with a prevalence of 5.8% in males and 2.3% in females aged 0–14 years.[16] In children prenatally exposed to VPA, however, there is a 48% increased risk of ADHD.[17]

Key Points

- Prenatal VPA exposure seems to negate the usual male sex-related predominance in the incidence of ASD
- There was no evidence of a relationship between VPA dosage and ASD symptoms
- There was no effect of prenatal VPA exposure on ADHD symptom scores

Despite established links between increased vulnerability to neurodevelopmental disorders in males, the sex-specific effects of VPA exposure on neurodevelopmental outcomes have not been investigated. To this end, this study was designed to assess the influence of sex and drug dosage on the association between prenatal VPA exposure and postnatal behavioral outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a prospective cohort study conducted within the framework of the Raoul Wallenberg Australian Pregnancy Register of AEDs (APR). Set up in 1999, the APR was originally intended to capture the rates of major congenital malformations in relation to prenatal AED exposure. In recent years, however, the register has been extended to examine the cognitive, psychiatric, and developmental outcomes of children exposed to AEDs in utero, contributing to our growing understanding of the deleterious effects of prenatal VPA exposure on neurodevelopment.[18–20] Among these APR contributions is a study of ASD behavioral traits using the Childhood Autism Rating Scale (CARS)[21] in 105 children

aged 6–8 years, which found a positive relationship between the dose of VPA taken by the mother during pregnancy and a higher CARS score.[11] Children assessed in prior APR studies of behavioral development[11,18–20] did not overlap with the more recently recruited cohort included in the present investigation.

For this analysis, the APR was interrogated for pregnancies recorded between 2007 and 2014 to identify children who were aged 4–11 years at the time of the study. This age bracket corresponded to the target age ranges of the administered questionnaires. Children were eligible for inclusion if they had been exposed prenatally to VPA or other AEDs, and if their pregnancy had been prospectively enrolled in the APR. Participants were excluded if respondents were unable to complete questionnaires in English, if there was significant maternal illness preventing questionnaire completion, or if a maternal fatality had occurred.

The study was approved by the Melbourne Health Human Research and Ethics Committee. All participants provided written informed consent prior to study enrolment.

2.2 | Participants

Eligible children who had been prenatally exposed to VPA were first identified and then case-matched to children exposed to AEDs other than VPA. Matching was based on child's sex, child's current age (±1 year), maternal age at birth (±1 year), and exposure to either AED mono- or polytherapy. The parents of these children were then approached and asked to complete questionnaires regarding their child's behavior.

2.3 | Measures

Parents reported on their child's behavior over the preceding 6 months using the Autism Spectrum Quotient–Children's Version (AQ-Child)[22] and the National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale.[23] The questionnaires were distributed via post, by email, or through an online link to the data management service REDcap.

The AQ-Child is a parent-report measure that quantifies traits consistent with ASD in children aged 4–11 years. The underlying factor structure measures communication, attention to detail, social skills, and imagination.[22] Scores range from 0 to 150, with the maximum score indicating full endorsement of ASD traits and a score greater than 76 used to indicate provisional ASD diagnosis.[22] The scale was originally administered to a sample of 540 children with ASD and 1225 community-dwelling children. Results showed that in the normative sample of children, 4% of 1225 with no history of ASD had an AQ score greater than 76. Of the 540 children already diagnosed with ASD, 95% had an AQ score greater than 76. The measure demonstrated good reliability and validity, with high sensitivity (95%) and specificity (95%) to a clinical diagnosis of ASD in the development sample, supporting the utility of the questionnaire for research purposes.[22] The AQ-Child has also been used as a continuous measure to find large effect sizes in studies investigating ASD traits across normative samples of children.[24,25]

The NICHQ Vanderbilt Assessment Scale is a dimensional parent-report scale used to identify symptoms of ADHD in children aged 6–12 years. It measures the constructs of inattention, hyperactivity, conduct/oppositional problems, and anxiety/depression problems.[26] The scale has a maximum score of 181, and there must be six positive responses to the inattentive and/or hyperactive core symptoms to meet DSM-V criteria for diagnosis.[23] The psychometric properties of the NICHQ parent-rating scale were examined in two separate studies sampling referred ($n = 243$)[27] and community ($n = 587$)[26] populations. The scale showed acceptable reliability and validity for research purposes in both studies,[26,27] and the parent-report version demonstrated sensitivity of 49% and specificity of 81%.[26] The scale has also been used as a continuous measure in studies of ADHD symptoms in normative and ADHD-diagnosed children.[28]

2.4 | Statistical analyses

All analyses were performed using the *Jamovi*[29] and *GAMLj*[30] software packages running on top of *R*.[31] All variables were inspected for distributional assumptions prior to analyses. Generalized linear models were computed to investigate differences in sample characteristics. McDonald ω was used to access psychometric reliability. Gaussian or binomial response families were used as appropriate. General linear mixed-effects models (GLMMs) were used to investigate the relationship between clinicodemographic variables and psychometric scores. For each model, the psychometric variable was entered as the dependent variable (e.g., AQ total score). Child age, sex, VPA exposure status (exposed vs. not exposed), treatment status (monotherapy vs. polytherapy), and VPA dosage (for each pregnancy trimester) were entered as independent variables. Supplementary analyses repeated the same GLMMs for both AQ and NICHQ scores but included folic acid dosage (in micrograms), alcohol exposure during pregnancy (yes/no), nicotine exposure in pregnancy (yes/no), maternal age, and exposure to seizures since last menstrual period (yes/no) as independent variables to account for other factors known to affect postnatal behavioral outcomes.

Continuous dependent variables were centered. A random intercept was specific for each child's family to account for dependence within family groups. Gaussian response

families were selected, and all models were estimated using restricted maximum likelihood. All models were checked to ensure convergence, and model residuals were visually inspected. Marginal effects were computed to understand statistically supported effects, and simple effects analyses were performed to further explore interaction terms. Models are presented as unstandardized coefficients with 95% confidence intervals (CIs).

Power analyses were performed using the observed effect sizes to determine the required sample size for a future planned replication, and also to investigate the observed power in our study. All analyses were performed using G*Power software. An analysis of covariance (ANCOVA) model was specified to investigate the VPA by sex interaction, with $\alpha = 5\%$ and $\beta = 80\%$.

To analyze clinicodemographic variables, *t*-tests were used for comparisons of continuous data and chi-squared tests were used for comparison of dichotomous data, as appropriate. To compare the study cohort AQ scores to population data, the total AQ score was converted into a *z*-score using normative data[22] and *t*-tests were used to compare the current AQ scores to population norms.

3 | RESULTS

3.1 | Sample characteristics

A total of 158 eligible children prenatally exposed to VPA were identified and matched with 158 children exposed to other AEDs. Of these, 121 children (54 exposed to VPA, 67 exposed to other AEDs) from 91 families were included in the study, as their parents agreed to participate and returned the questionnaires.

Among eligible children exposed to VPA in utero, there were no differences in key characteristics between children included in the study ($n = 54$) and those who were not ($n = 104$), except for the former group being younger than the latter group (mean [M] = 7.24 [SD = 2.05] vs. M = 8.81 [SD = 2.21] years, $t_{146} = 4.27$, $p < .001$; Table S1). Among children exposed to other AEDs, there were no differences between children included in the study and those who were not (Table S1).

Mean age (SD) of entire sample was 7.08 (2.16) years. Most children were male ($n = 68$, 56%). Seventy-five children (62%) had been exposed prenatally to AED monotherapy and 46 (38%) to polytherapy. Demographic and clinical characteristics of the subgroup exposed to VPA and of those exposed to other AEDs are provided in Table 1. Of the 54 children exposed to VPA (28 males, 52%), dosage information (VPA dose taken at time of conception) was available for 48. In this subgroup, mean VPA dosage (SD) was 644 (310) mg. Furthermore, it was 693 (304) mg in those exposed to VPA monotherapy ($n = 30$) and 561 (311) mg in those exposed to AED polytherapy including VPA ($n = 18$).

TABLE 1 Demographic and clinical characteristics of children exposed to VPA and of those exposed to other AEDs

Characteristic	Children exposed to VPA, $n = 54$	Children exposed to other AEDs, $n = 67$
Mean age, years (SD)	7.24 (2.05)	6.96 (2.26)
Sex, *n* (%)		
Male	28 (52%)	40 (60%)
Female	26 (48%)	27 (40%)
AED therapy, *n* (%)		
Monotherapy	35 (65%)	40 (60%)
Polytherapy	19 (35%)	27 (40%)
Mean AQ overall scores (SD)	57.7 (18.90)	57.4 (23.60)
Mean NICHQ overall scores (SD)	14.2 (12.0)	16.7 (12.0)

Abbreviations: AED, antiepileptic drug; AQ, Autism Spectrum Quotient; NICHQ, National Institute for Children's Health Quality; VPA, valproic acid.

TABLE 2 General linear mixed-effects model output for Autism Spectrum Quotient overall score

Effect	*b*	SE	95% CI
Intercept	57.03	2.00	53.11 to 60.94
Sex (male)	11.03	3.93	3.32 to 18.74
VPA exposure	−.80	4.00	−8.64 to 7.04
Polytherapy	4.82	4.01	−3.03 to 12.68
Age	.82	.88	−.91 to 2.54
Sex × VPA exposure	19.45	7.83	4.11 to 34.79
Sex × polytherapy	−6.13	7.89	−21.59 to 9.33
VPA exposure × polytherapy	17.78	7.96	2.17 to 33.38

Abbreviations: CI, confidence interval; SE, standard error; VPA, valproic acid.

In the entire sample, the mean AQ score (SD) was 58.28 (21.57) and the mean NICHQ score (SD) was 15.59 (11.98). The psychometric reliability was excellent for both the AQ and NICHQ overall scores ($\omega = .93$ and .94, respectively).

3.2 | AQ overall scores (ASD symptoms)

A GLMM was computed to investigate variables associated with AQ overall scores (Akaike information criterion [AIC] = 1082.63, marginal $R^2 = .17$). As shown in Table 2, there was evidence for the main effect of sex ($b = 11.03$, 95% CI =

3.32–18.74), the interaction between sex and VPA exposure (b = 19.45, 95% CI = 4.11–34.79), and the interaction between VPA exposure and polytherapy (b = 17.78, 95% CI = 2.17–33.38). Inspection of the marginal means revealed that males had higher scores (M = 62.54, 95% CI = 57.33–67.75) compared to females (M = 51.51, 95% CI = 45.62–57.40). The interaction between sex and VPA exposure is shown in Figure 1. In the subgroup exposed to VPA, there was no evidence of difference between males and females (M_{diff} = 1.31, 95% CI = −10.38 to 12.99). In the subgroup exposed to other AEDs, however, there was strong evidence for such a difference (M_{diff} = 20.75, 95% CI = 10.50–31.00), with males having higher overall AQ scores (M = 67.00, 95% CI = 60.07–73.94) than females (M = 46.25, 95% CI = 38.50–54.01). On careful examination of the pattern of results, VPA exposure seemed to have a negative effect on ASD symptoms only in female children, who had higher scores on ASD traits than their female peers exposed to AEDs other than VPA. Males exposed to VPA evidenced instead a small relative drop in ASD symptoms compared to males exposed to other AEDs.

As shown in Figure 2, a similar interaction was observed between AED polytherapy and VPA exposure. In the subgroup exposed to VPA, there was no evidence for a difference between monotherapy and polytherapy (M_{diff} = −4.70, 95% CI = −15.85 to 7.71). In the subgroup exposed to other AEDs, there was instead evidence for a difference (M_{diff} = 13.71, 95% CI = 3.08–24.34), with those exposed to monotherapy having lower AQ scores (M = 49.77, 95% CI = 42.85–56.70) than those exposed to polytherapy (M = 63.48, 95% CI = 55.44–71.52).

A subanalysis was performed on children exposed to VPA, repeating the GLMMs with VPA dosage at each trimester of gestation as a covariate. There was no evidence of a relationship between AQ scores and VPA dosage at first trimester (b = −.004, 95% CI = −.02 to .02), second trimester (b = −.003, 95% CI = −.01 to .02), or third trimester (b = .003, 95% CI = −.01 to .02).

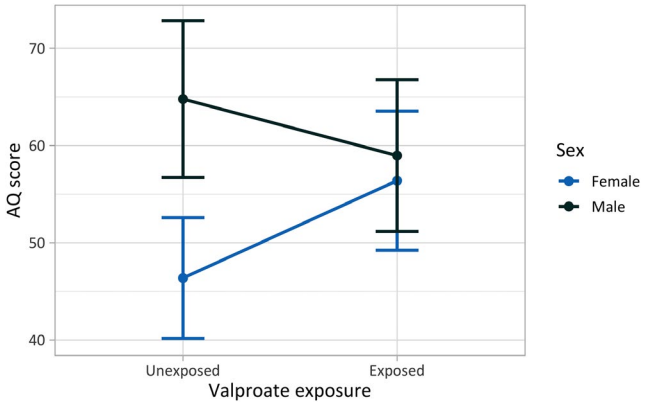

FIGURE 1 Interaction between sex (male/female) and valproate exposure (unexposed/exposed) for parent-reported Autism Spectrum Quotient (AQ) score. The AQ-Child has a minimum score of 0 and maximum score of 150 and uses a score above 76 to indicate autism spectrum disorder diagnosis. Error bars represent the 95% confidence interval

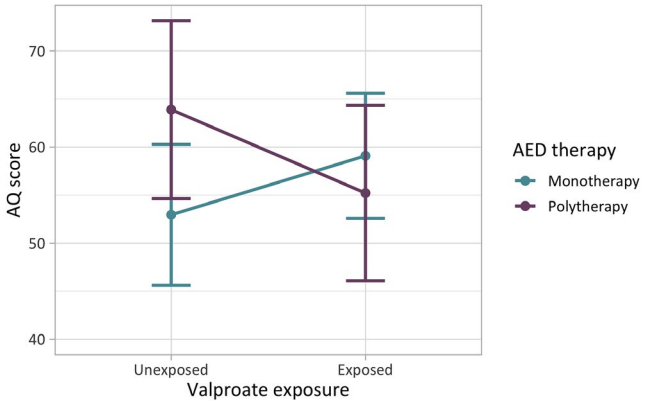

FIGURE 2 Interaction between valproate exposure (unexposed/exposed) and antiepileptic drug (AED) therapy (monotherapy/polytherapy) for parent-reported Autism Spectrum Quotient (AQ) score. The AQ-Child has a minimum score of 0 and maximum score of 150 and uses a score above 76 to indicate autism spectrum disorder diagnosis. Error bars represent the 95% confidence interval

Supplementary analyses repeated the same GLMMs but included variables known to contribute to adverse antenatal developmental outcomes, namely, folic acid dosage, alcohol exposure, nicotine exposure, maternal age, and seizure exposure as independent variables. There was no evidence of a relationship between AQ scores and folic acid dosage (b = −.001, 95% CI = −.004 to .002), alcohol exposure (b = −1.50, 95% CI = −35.63 to 32.70), nicotine exposure (b = 8.61, 95% CI = −20.62 to 37.83), maternal age (b = −.82, 95% CI = −1.70 to .06), or seizure exposure (b = 23.14, 95% CI = −65.57 to 19.29; Table S1). When accounting for these additional variables in the model, there was no significant main effect of sex on AQ scores (b = −18.42, 95% CI = −58.28 to 21.45), but there were significant interactions between sex and VPA exposure (b = −20.30, 95% CI = −37.59 to −3.02), and between AED therapy regimen and VPA exposure (b = −23.02, 95% CI = −37.75 to −6.29).

The total AQ score was converted to a z-score using normative data. Compared to the normative group of neurotypical children (aged M = 9.52 years, SD = 1.27), our cohort had higher z-scores, indicative of higher levels of autism symptomatology (M = .84, 95% CI = .64–1.09, t_{120} = 8.23, p < .001). AQ z-scores, however, did not differ significantly between the children exposed to VPA and those exposed to other AEDs (t_{119} = .57, p = .57). We also computed the number of participants who had scores commensurate with clinically significant symptomatology as defined by AQ scores cut off at >76. Twenty-four (20%) children scored greater than 76 on the AQ-Child, with no

evidence for a difference between children exposed to VPA and those exposed to other AEDs (20% vs. 19%, $\chi^2[1] = .02$, $p = .89$). Among those exposed to VPA ($n = 54$), 11 scored greater than 76 (eight males). Among children exposed to other AEDs ($n = 67$), 13 scored greater than 76 (11 males).

3.3 | AQ domain scores (specific ASD symptoms)

All GLMMs were repeated on the separate AQ domain scores. As shown in Table 3, these showed a pattern of findings revealing where the specific overall effects were maximally expressed. A main effect of sex was observed in social ($b = 3.32$, 95% CI = 1.32–5.33), communication ($b = 1.12$, 95% CI = .69–5.07), and imagination ($b = 2.44$, 95% CI = .65–4.24) domains, whereby males scored higher than females. Marginal means scores on the AQ domains are shown in Table 4. A main effect of VPA exposure was observed in the attention to detail domain, with children exposed to VPA scoring above those exposed to other AEDs ($b = 2.19$, 95% CI = .33–4.04); there was also an effect of age on attention switching ($b = .52$, 95% CI = .03–1.01). The sex by VPA exposure interaction was expressed in the imagination ($b = -4.75$, 95% CI = −8.32 to −1.18) and attention to detail ($b = -4.26$, 95% CI = −8.00 to −.55) domains, whereby males exposed to AEDs other than VPA had the highest scores on the imagination domain, whereas females exposed to VPA scored the highest on the attention to detail domain. The polytherapy by VPA interaction was observed in the attention switching ($b = -4.59$, 95% CI = −9.09 to −.08) and imagination ($b = -4.47$, 95% CI = −8.05 to −.88) domains. Those exposed to AED polytherapy not including VPA had the highest imagination domain scores. Similarly, high scores on the attention switching domain were found in children exposed to VPA monotherapy and in those exposed to AED polytherapy not including VPA.

3.4 | NICHQ overall scores (ADHD symptoms)

A GLMM was computed to investigate variables associated with NICHQ overall scores (AIC = 934.83, marginal $R^2 = .09$). As shown in Table 5, there was only evidence for an effect of sex ($b = 4.61$, 95% CI = .59–8.63). Males had higher NICHQ overall scores (M = 18.23, 95% CI = 15.20–21.26) compared to females (M = 13.62, 95% CI = 10.32–16.92). A subanalysis was performed on the VPA-exposed group, repeating the GLMMs with VPA dosage at each trimester of gestation included as a covariate. There was no evidence of a relationship between NICHQ scores and VPA dosage during first trimester ($b = -.002$, 95% CI = −.01 to .01), second trimester ($b = .002$, 95% CI = −.006 to .009), or third trimester ($b = .002$, 95% CI = −.01 to .01).

We also computed the proportion of participants who scored above the cutoff score (>6 endorsed symptoms) for hyperactive ADHD ($n = 10$, 8%), inattentive ADHD ($n = 19$, 16%), or mixed presentations ($n = 7$, 6%). There

TABLE 3 General linear mixed-effects model output for AQ domain scores

Effect	Social	Switching	Detail	Communication	Imagination
Intercept	8.57 [7.57 to 9.57]	13.33 [12.19 to 14.46]	16.28 [15.35 to 17.21]	11.24 [10.03 to 12.44]	7.56 [6.66 to 8.45]
Sex (male)	3.32 [1.32 to 5.33]	2.12 [−.06 to 4.30]	.15 [−1.71 to 2.01]	2.88 [.69 to 5.06]	2.44 [.65 to 4.24]
VPA exposure	−1.23 [−3.22 to .77]	.80 [−1.48 to 3.07]	2.19 [.33 to 4.04]	.21 [−2.20 to 2.62]	−.94 [−2.74 to .85]
Polytherapy	1.18 [−.83 to 3.20]	.59 [−1.67 to 2.86]	.24 [−1.63 to 2.11]	1.88 [−.49 to 4.26]	.88 [−.92 to 2.69]
Age	.16 [−.29 to .60]	.52 [.03 to 1.01]	.08 [−.34 to .49]	.04 [−.45 to .53]	.02 [−.38 to .42]
Sex × VPA exposure	−3.53 [−7.52 to .46]	−3.46 [−7.79 to .87]	−4.26 [−7.96 to −.55]	−2.92 [−7.28 to 1.44]	−4.75 [−8.32 to −1.17]
Sex × polytherapy	.28 [−3.76 to 4.33]	−2.54 [−6.88 to 1.80]	.08 [−3.67 to 3.84]	−1.01 [−5.34 to 3.32]	−2.53 [−6.14 to 1.09]
VPA exposure × polytherapy	−5.25 [−9.24 to −1.25]	−4.59 [−9.09 to −.08]	.14 [−3.56 to 3.85]	−3.14 [−7.86 to 1.57]	−4.47 [−8.05 to −.88]

Note: Confidence interval is given in brackets.

Abbreviation: VPA, valproic acid.

TABLE 4 Estimated marginal mean and standard error across AQ domains

Effect	Social	Switching	Detail	Communication	Imagination
Females, $n = 53$	6.88 (.75)	12.10 (.83)	15.90 (.71)	9.71 (.85)	6.34 (.67)
Males, $n = 68$	10.23 (.67)	14.40 (.76)	16.20 (.63)	12.66 (.79)	8.78 (.60)
VPA-exposed, $n = 54$	7.94 (.75)	16.60 (.85)	17.20 (.71)	11.30 (.89)	7.09 (.68)
VPA-unexposed, $n = 67$	9.17 (.66)	12.90 (.78)	15.10 (.63)	11.10 (.82)	8.03 (.60)
Monotherapy, $n = 75$	7.96 (.62)	13.0 (.71)	16.00 (.58)	10.30 (.75)	7.12 (.56)
Polytherapy, $n = 46$	9.14 (.80)	13.50 (.90)	16.20 (.75)	12.10 (.94)	8.00 (.71)

Abbreviation: VPA, valproic acid.

TABLE 5 General linear mixed-effects model output for National Institute for Children's Health Quality overall scores

Effect	*b*	SE	95% CI
Intercept	15.92	1.23	13.52 to 18.33
Sex (male)	4.61	2.05	.59 to 8.63
VPA exposure	.55	2.44	−4.24 to 5.34
Polytherapy	−3.63	2.38	−8.29 to 1.02
Age	.23	.46	−.67 to 1.14
Sex × VPA exposure	5.09	4.09	−2.93 to 13.12
Sex × polytherapy	−.32	4.02	−8.20 to 7.56
VPA exposure × polytherapy	−3.16	4.71	−12.39 to 6.08
Sex × VPA exposure × polytherapy	−14.73	7.99	−30.38 to .93

Abbreviations: CI, confidence interval; SE, standard error; VPA, valproic acid.

was no evidence for different proportions of these ADHD phenotypes between children exposed to VPA and those exposed to other AEDs (all $p > .05$). Among the 54 children exposed to VPA, four (all males) scored above the cutoff score for hyperactive ADHD, nine (six males) for inattentive ADHD, and four (all males) for mixed presentations. Among the 67 children exposed to other AEDs, six (five males) scored above the cutoff score for hyperactive ADHD, 10 (nine males) for inattentive ADHD, and three (all males) for mixed presentations.

3.5 | Power analyses

A priori power analyses were computed to determine the sample size required to confirm the observed effect sizes in future studies. For the VPA by sex interaction on the AQ total score, the observed effect size was $\eta_p^2 = .06$. Based on an ANCOVA model, 120 participants would be required for an attempted replication. The effect size for the ADHD total score was $\eta_p^2 = .01$. With the same ANCOVA parameters as above, a substantially larger sample size of 779 would be required to fully investigate this effect.

4 | DISCUSSION

Our findings suggest that prenatal VPA exposure can negate the typical male predominance of ASD traits. In the entire sample, and in the subgroup exposed to AEDs other than VPA, male children had higher ASD symptoms than females, consistent with the extensive literature showing that ASD is significantly more common in males than females. Results from meta-analyses report a male-to-female ratio of 3:1,[32] as well as sex differences in how the behavioral phenotype of ASD is expressed. Females have been found to exhibit less stereotyped behaviors than males, and increased impairments in communication and social pragmatics have been associated with intellectual disability and lower intelligence quotient.[33] Therefore, in females without intellectual impairments, the core diagnostic symptoms for ASD may appear more subtle. In our study, however, exposure to VPA in utero seemed to negate these typical sex interactions, with VPA-exposed males scoring similarly to VPA-exposed females on an ASD symptom measure, and females appearing more sensitive to the effects of prenatal VPA exposure. Overall, these findings contribute to the growing understanding of VPA as a behavioral teratogenic agent and for the first time suggest that this relationship may be influenced by sex.

Limited data are available on the role of sex in the relationship between prenatal VPA exposure and neurodevelopmental outcomes. In a population-based study, Christensen et al.[8] reported a male-to-female ratio for ASD diagnosis (identified using International Classification of Disease–10 codes) of 2.4 among children exposed to VPA in utero and of 4.4 among children not exposed to VPA. Although direct comparison of these ratios cannot be made with the current study due to differences in design and methodology (including the use of a continuous measure of ASD), the general trend in sex ratios reported in Christensen et al.[8] appears to follow the findings herein, with differences in ASD prevalence between

males and females exposed to VPA being less pronounced than is typical.[12,14]

Emerging research suggests that females recover better than males following early neuronal insult, indicating that females are "protected" from poorer cognitive outcomes following brain insult in utero.[34] In this study, VPA exposure in females resulted in a relative increase in ASD symptoms compared to males and females exposed to other AEDs, which suggests that prenatal VPA exposure may compromise the advantageous recovery typically found in females. The neuroprotective advantage found in females is hypothesized to be underpinned by multiple interacting mechanisms. Converging evidence from a variety of experimental models of brain injury and cognition has suggested a neuroprotective role for sex hormones, specifically estrogen. Estrogen appeared to act as a neuroprotectant following early brain damage in rats,[35] with data indicating that estrogen can modify brain plasticity by promoting neurogenesis, with subsequent downstream effects on neurocognitive function.[36] In early gestational periods, estrogen concentrations are equivalent regardless of fetal sex[37]; therefore, the protective advantage of estrogen level typically afforded to females perinatally may not be evident in early prenatal development when VPA exposure occurs. Although it is not possible to isolate a particular mechanism of effect in the current data, it is evident that sex-specific outcomes are a valuable area for further investigation, with interactions between sex hormones and VPA exposure on behavioral outcomes being a potential area of future research.

In contrast, sex-specific interactions were not found for ADHD symptoms. Males had higher overall ADHD scores, which is in line with research consistently demonstrating that males are more likely to be diagnosed than females.[38–40] We did not find a relationship between VPA exposure and ADHD traits, in keeping with the results of a recent meta-analysis.[41] Although a recent population-based study found that children exposed to VPA in utero had a small but significantly increased risk of ADHD,[17] our findings suggest that this relationship remains to be further elucidated, particularly at low doses of VPA such as those used in our sample. Alternatively, the lack of relationship between VPA and ADHD symptoms may indicate that VPA targets specific neurocognitive and neurobiological networks relevant to ASD rather than ADHD.

There was no impact of VPA mono- or polytherapy on overall AQ scores, and no evidence of a dose–response relationship between ASD symptoms and prenatal VPA exposure. Previous research has suggested that neurodevelopmental outcomes for mono- and polytherapy groups were driven by the absolute presence or absence of VPA,[3] but more recently, it has been understood that increased risk occurs at VPA dosage of greater than 800–1000 mg daily.[3] Of note, our sample was exposed to a mean VPA daily dosage of 644 mg, considerably lower than doses suggested to be associated with an increased risk of impaired neurodevelopmental outcomes. In keeping with the interpretation that the dosages of VPA in the current study were likely too low to have a robust impact on neural development, Rihtman et al.[42] investigated the rate of adverse neurodevelopmental outcomes following a mean VPA dosage of 546 mg and did not find evidence for a dose–response relationship. Therefore, dose–response relationships between VPA exposure and neurodevelopmental outcomes may not be evident at low doses. Of note, an earlier study that examined ASD traits using the CARS scale in children from mothers who had enrolled in the APR did find a positive dose–response relationship between VPA and higher CARS scores.[11] Of the 11 children who scored above the cutoff for ASD, seven were born to mothers who were taking VPA during the first trimester of their pregnancy, and all had taken at least 1000 mg per day (up to 3000 mg/day). However, this study was conducted on an earlier cohort, with the mothers enrolled in the register between 1999 and 2002, compared with 2007 and 2014 for the current study. The dose of VPA taken by pregnant women enrolled in the Raoul Wallenberg APR has significantly decreased over the time period between these two enrollments.[43] Consistent with this, the mean dose of VPA taken by women in this current study was 644 mg/day, compared with 961 mg/day for those on VPA monotherapy and 1589 mg/day for those on VPA polytherapy in the previous study. A lower dose cohort, such as the current study, is a useful addition to the literature investigating neurobehavioral outcomes following VPA exposure.

The risk of major congenital malformations following VPA monotherapy is similar to that of VPA in polytherapy[44] and similarly, VPA monotherapy and polytherapy carried the same risk of ASD symptoms in this study. This indicates that polytherapy does not necessarily confer a greater risk of adverse outcomes; rather, it depends on the agents included in the polytherapy.

This study has several limitations. First, we used relatively crude indices of symptoms that are suggestive of neurodevelopmental disorders including ASD and ADHD, but that cannot replace formal diagnostic interviews. As a result, this study is unable to comment on prevalence or clinical characteristics of neurodevelopmental disorders such as ASD or ADHD within this sample. However, there are some advantages to the use of screening measures. Statistical modeling techniques have shown that the clinical entities of ASD and ADHD exist at the extreme ends of their respective symptom distributions,[45,46] suggesting that subthreshold traits appear to be the most common phenotypic presentation of ASD and ADHD. Additionally, emerging research suggests that due to heterogeneity in symptom manifestations, diagnosis is delayed in females,[47] and females have a decreased likelihood of meeting diagnostic cutoffs despite presenting with high levels of symptoms.[48,49] Therefore, a continuous approach through

the use of screening measures, rather than clinical diagnosis, could be viewed as more advantageous to females and those with subthreshold conditions, and give us an enhanced ability to detect subtle sex-specific differences. Furthermore, use of a screening measure has resulted in clinical data being collected for all children and not just for a subsample who reached a clinical diagnosis of ASD or ADHD. Consequently, the current findings can be generalized to all children prenatally exposed to AEDs.

Second, parental reporting of ASD and ADHD symptoms can be unreliable in chronicling the onset and frequency of the child's symptoms.[50] Underreporting of child symptomatology may be partly due to a subset of parents having features of the broader autism phenotype themselves that might preclude their ability to recognize abnormal features in their offspring, but also may also be related to the age and developmental stage of the child when symptoms were reported in this study,[50] as distant events are recalled less accurately on retrospective interview.

Third, the opt-in rate for the current study was relatively low, that is, 34% for children prenatally exposed to VPA and 42% for children exposed to other AEDs. However, among eligible children, there were no significant differences in key demographic characteristics between children included in the study and those who were not (Table S2). The only exception was that VPA-exposed children included in the study were younger than VPA-exposed children who were not included. Despite the relatively low opt-in rate, the study was adequately powered to detect statistical effects for the hypotheses described.

Lastly, this study did not control for potential confounders such as family history of ASD and ADHD, and socioeconomic status. Given the heritability of neurodevelopmental disorders such as ASD and ADHD, clinical and demographic data regarding family history would assist in further clarifying the specific impact of VPA on neurodevelopmental outcomes, including whether children with a family history of ASD or ADHD are predisposed to developing a greater frequency of symptoms following VPA exposure compared to children exposed to other AEDs.

Neurodevelopment is a complex, dynamic process, and lack of follow-up into adolescence may lead to premature conclusions about the relationship between VPA and behavior. A prospective cohort study sampling into adolescence that uses a blinded assessor to examine symptoms of ASD and ADHD would provide more reliable data regarding neurodevelopmental outcomes and cognitive functioning following prenatal VPA exposure.

In summary, our results suggest that prenatal exposure to VPA can alter behavioral symptoms of ASD in a sex-specific manner, seeming to increase the relative rate of ASD—but not ADHD—symptoms that is typically seen in females compared to males. These initial findings deepen the conception of VPA as a behavioral teratogen by indicating that its effect might be influenced by sex. One could speculate that higher VPA doses have a more deleterious effect on neurodevelopment, and thus obscure subtle sex-specific differences that are evident at lower doses. Although no association between VPA dosage and adverse postnatal behavioral outcomes was detected, this study has shown that an increased risk of adverse outcomes is evident even at low doses. Therefore, children with any level of exposure to VPA in utero should be closely monitored to facilitate early detection and intervention for neurodevelopmental delays and disorders.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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