Supplementary Material

eTable 1. Search terms

eTable 2. Measurement tools

eTable 3. Newcastle - Ottawa Quality Assessment Scale modified for cohort studies

eTable 4. Newcastle - Ottawa Quality Assessment Scale modified for case-control studies

eTable 5. Newcastle - Ottawa Quality Assessment Scale adapted for cross-sectional studies

eTable 6. Summary of study sample characteristics, study design, and key statistics

eTable 7. Results of study quality appraisal of included cohort studies

eTable 8. Results of study quality appraisal of included case-control studies

eTable 9. Results of study quality appraisal of included cross-sectional studies

### eTable 1. Search terms

|  |  |  |
| --- | --- | --- |
| Term Group | Search String | Number of results on June 10, 2024 |
| Final Search | (Valproate OR Valproic Acid OR Fetal Valproate Syndrome OR Fetal Valproate Spectrum Disorder) AND (Major Congenital Malformation OR Congenital Malformation OR Congenital Anomaly OR Neurodevelopment OR Cognitive Development OR Prenatal Exposure OR Fetus OR Embryo OR Folic Acid OR Folate) AND (Cohort Study OR Retrospective Study OR Longitudinal Study OR Case Control Study OR Observational Study) | 795 |

### 

### 

### eTable 2. Newcastle - Ottawa Quality Assessment Scale modified for cohort studiesa

|  |  |  |
| --- | --- | --- |
| Selection (Maximum 2 stars) |  |  |
|  | Representativeness of the exposed cohort | a. Truly representative of target population (e.g., nation-wide database)\*  b. Somewhat representative of target population (e.g., city, hospital/hospital system, social media survey)\*  c. Selected groups of participants (i.e., by subgroup: sex, race, occupation, insurance coverage, disease severity, ICU treatment status, pre-existing condition). Restricting inclusion criteria to adults does not count as a subgroup.  d. No description of the derivation of the cohort |
|  | Selection of the non-exposed cohort | a. Drawn from the same community/database/hospital as the exposed cohort\*  b. Drawn from a different source  c. No description of the derivation of the non-exposed cohort  d. No non-exposed cohort included |
|  | Ascertainment of Exposure | a. Validated measurement tool, or secure medical/hospital records indicative of diagnosis\*  b. Diagnosis based upon clinical judgement, or record-linkage (e.g., ICD)\*  c. Parental/personal recall only (self-report of test positivity) |
|  | Demonstration That Outcome of Interest Was Not Present at Start of Study | a. Yes\*  b. No |
| Comparability (Maximum 2 stars) |  |  |
|  | Comparability of Cohorts on the Basis of the Design or Analysis | a. Controls/adjusts and/or matches and/or regression analysis for both age and sex\*  b. Controls/adjusts and/or matches and/or regression analysis for additional confounders\* |
| Outcome (Maximum 3 stars) |  |  |
|  | Assessment of Outcome | a. Validated objective assessment tool or clinical diagnosis for at least 1 outcome of interest\*  b. Structured/systematic interview or questionnaire conducted by trained healthcare or research professional\*  c. Unstructured self-report (i.e., open question regarding symptoms) and/or not conducted by trained healthcare or research professional (i.e., self-administered) or not stated  d. No description |
|  | Was Follow-Up Long Enough for Outcomes to Occur? | a. Yes\*  b. Not stated  c. No |
|  | Adequacy of Follow Up of Cohorts | a. Complete follow up; all subjects accounted for\*  b. Subjects lost to follow up unlikely to introduce bias: ≤10% of initial sample size lost, or description provided of those lost\*  c. Lost >10 % of initial sample size during follow up, and no description of those lost  d. No statement |

a Maximum: 9 stars. Methodological quality rank: high=7-9 stars, moderate=5-6 stars, low=4 or fewer stars.

### eTable 3. Newcastle - Ottawa Quality Assessment Scale modified for case-control studiesa

|  |  |  |
| --- | --- | --- |
| Selection (Maximum 4 stars) |  |  |
|  | Is the Case Definition Adequate? | a. Validated objective assessment tool or clinical diagnosis for at least 1 outcome of interest\*  b. Structured/systematic interview or questionnaire conducted by trained healthcare or research professional\*  c. Unstructured self-report (i.e., open question regarding symptoms) and/or not conducted by trained healthcare or research professional (i.e., self-administered) or not stated  d. No description |
|  | Sample size | a. Consecutive or obviously representative series of cases (all eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area/hospital/healthcare organization, or a random sample of those cases)\*  b. Not satisfying requirements in part a (i.e., potential for selection biases), or not stated |
|  | Selection of Controls | a. Community controls (i.e., same community or database as cases and would be cases if had outcome)\*  b. Hospital controls within same community as cases (i.e., not another city) but derived from a hospitalized population  c. No description |
|  | Definition of Controls | a. If cases are the first occurrence of outcome, then it must explicitly state that controls have no history of this outcome (endpoint). If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded\*  b. No mention of history of outcome |
| Comparability (Maximum 2 stars) |  |  |
|  | Comparability of Cases and Controls on the Basis of the Design or Analysis | a. Controls/adjusts and/or matches and/or regression analysis for both age & sex\*  b. Controls/adjusts and/ or matches and/or regression analysis for additional confounders\* |
| Exposure (Maximum 2 stars) |  |  |
|  | Ascertainment of Exposure | a. Validated measurement tool (laboratory testing), or secure medical/hospital records indicative of test positivity\*  b. Diagnosis based upon clinical judgement, or record-linkage (e.g., ICD)  c. Parental/personal recall only (self-report of test positivity |
|  | Non-Response Rate | a. Yes\*  b. Not stated  c. No |

a Maximum: 8 stars. Methodological quality rank: high=7-8 stars, moderate=5-6 stars, low=4 or fewer stars.

### eTable 4. Newcastle - Ottawa Quality Assessment Scale adapted for cross-sectional studiesa

|  |  |  |
| --- | --- | --- |
| Selection (Maximum 5 stars) |  |  |
|  | Representativeness of the Sample | a. Truly representative of the average in the target population (all subjects or random sampling)\*  b. Somewhat representative of the average in the target population (non-random sampling)\*  c. Selected group of users/convenience sample  d. No description of the derivation of the included subjects |
|  | Sample Size | a. Justified and satisfactory (including pre-determined sample size calculation)\*  b. Not justified (not pre-determined through calculation)  c. No information provided |
|  | Non-Respondents | a. Comparability between respondents and non-respondents is established, and the response rate is satisfactory (>60%) or proportion of target sample recruited attains pre-specified target\*  b. Unsatisfactory recruitment rate, no summary data on non-respondents, or the comparability between respondents and non-respondents is unsatisfactory  c. No description of the response rate or the characteristics of the responders and non-responders |
|  | Ascertainment of Exposure | a. Validated measurement tool, or secure medical/hospital records indicative of test positivity\*\*  b. Diagnosis based upon clinical judgement, or record-linkage (e.g., ICD)\*  c. Parental/personal recall only (self-report of test positivity) |
| Comparability (Maximum 2 stars) |  |  |
|  | Comparability of Subjects in Different Outcome Groups on the Basis of the Design or Analysis | a. Data/ results controlled/adjusted for both age and sex, or separate proportions/analyses reported for each age group and sex\*  b. Data/results controlled/adjusted for additional confounders, or separate proportions/analyses reported for additional confounders identified\* |
| Outcome (Maximum 2 stars) |  |  |
|  | Assessment of Outcome | a. Validated objective assessment tool or clinical diagnosis for at least 1 outcome of interest\*  b. Structured/systematic interview or questionnaire conducted by trained healthcare or research professional\*  c. Unstructured self-report (i.e., open question regarding symptoms) and/or not conducted by trained healthcare or research professional (i.e., self-administered) or not stated  d. No description |
|  | Statistical Methodology | a. Statistical test used to analyze the data clearly described\*  b. Statistical test not appropriate, not described or incomplete |

a Maximum: 9 stars. Methodological quality rank: high=7-9 stars, moderate=5-6 stars, low=4 or fewer stars.

### 

### eTable 5. Summary of study sample characteristics, study design, and key statisticsa

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Lead Author/Year | Country/Region | Study Design | Investigated Domain | Sample Size  (n =) | Maternal Characteristics (At Pregnancy) | Sample Characteristics (Offspring) | Sample Source | Assessment Tool(s) | Follow-Up Duration | Key Statistics | Key Finding(s) |
| Adab et al., 2001 | UK | Retrospective Cohort Study | -Behavioural  -Cognitive | 721 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: 8.95 +/-5.18  -Sex (%Female/%Male): NR | Mersey Regional Epilepsy Clinic | N/A | NR | -OR (Additional educational needs VPA monotherapy vs. controls): 3.40 (1.63–7.10)  -OR (Additional educational needs VPA polytherapy vs. controls): 2.51 (1.04–6.07) | -Prenatal VPA exposure (monotherapy or polytherapy) is associated with child development risks. |
| Adab et al., 2004 | UK | Retrospective Cohort Study | -Cognitive | 375 | -Age Range: NR  -Mean Age: 26.1 +/- 4.8 | -Age Range: 6-16  -Mean Age: 7.7 +/- 4.3  -Sex (%Female/%Male): NR | Mersey Regional Epilepsy Clinic | -Wechsler Intelligence Test  for Children, Third Edition (WISC-III)  -Schedule of Growing Skills II (SGS-II) - psychomotor and cognitive development | 16 years | VIQ Comparisons (Student's t test) (Mean Difference in IQ, 95% CI, p value):  -VPA exposed vs unexposed -5.9 (211.2 to 20.6) p = 0.030  -VPA monotherapy vs. CBZ monotherapy: 210.5 (217.3 to 23.6) p = 0.003  -VPA monotherapy vs. PHT monotherapy: 214.9 (224.1 to 25.6) p=0.002  -VPA monotherapy vs. unexposed: 27.3 (213.6 to 20.9) p=0.025  -OR (VIQ of 69 or less VPA monotherapy vs. unexposed controls): 3.5, 95% CI 1.1 to 10.6)  -Correlation (VIQ and VPA dose in the first trimester): Spearman’s p -0.399, p = 0.011  -Among those exposed to VPA monotherapy, the proportion of children scoring in the low (20%) and exceptionally low range (22%) was significantly greater than in the CBZ exposed group (x² for trend 8.431, df 1, p = 0.004).  -Mean VIQ in first born children exposed to VPA (n = 27, 82.7, 95% CI 75.6 to 90.0) was significantly lower than the unexposed group (n = 53, 94.1, 95% CI 89.7 to 98.5, p = 0.006) and those exposed to CBZ (n = 27, 95.5, 95% CI 87.9 to 103.0, p = 0.006) | -Prenatal VPA exposure is associated with increased risk of developmental delay and cognitive impairment. |
| Almgren et al., 2009 | Sweden | Prospective Cohort Study | -Anatomical | 2,526 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Swedish Medical Birth Registry (SMBR) | NR | NR | -VPA monotherapy and mean bw - adj - HC: SDS = 0.10, t = 2.1, p = 0.04 | -VPA monotherapy is associated with a reduced mean bw - adj - HC. |
| Aratma et al., 2005 | Finland | Retrospective Cohort Study | -Anatomical | 20,101 | -Age Range: NR  -Mean Age: 27.5 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | National Medical Birth Registry (Finland) | NR | NR | -Risk of congenital malformations in offspring increased with the daily VPA dose: (p for trend < 0.0001):  OR (<1500 mg/day): 3.68 (1.97-6.86)  OR (>1500mg/day): 10.89 (2.9-34.3)  -OR (Malformations VPA monotherapy vs. unexposed controls): 4.18; 95% CI: 2.31, 7.57  -OR (Malformations VPA polytherapy vs. controls): 3.54; 95% CI: 1.42, 8.11 | -Prenatal VPA exposure is associated with an increased risk of CM (Dose-dependent). |
| Baker et al., 2015 | UK | Prospective Cohort Study | -Cognitive | 530 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | 11 national health service hospitals in the UK | -Differential Ability Scales | 6 years | -aRR (impairment (IQ <85) high doses of VPA vs. controls): 8.6, 95% CI 3.1–18.8; p < 0.001  -VPA (Coefficient (SE) 95%CI, p value)  -FSIQ (>800mg VPA): -9.7 (2.5) -14.6 to -4.9 p<0.001  -Verbal IQ (>800mg VPA): -9.4 (2.5) -14.2 to -4.6 p<0.001  -Non Verbal IQ(>800mg VPA) -7.6 (2.8) -13.1 to -2.0 p = 0.007  -Spatial IQ >800mg VPA: -9.7 (3.0) -15.5 to -3.9 p=0.001  -Verbal IQ (<800mg VPA): -5.6 (2.8) -11.1 to -0.1 p=0.04  Additional educational needs:  -(<800mg VPA): OR 6.6 (1.5-30.4), RR 5.9 (1.4 to 18.0) (p<0.01)  -(>800mg VPA): OR:9.6 2.6-35.7, RR: 8.0 (2.5-19.7) (p<0.001)  CBZ vs <800mg VPA:  -Nonverbal: 8.3 (3.6) (1.2-15.4) (p=0.02)  CBZ vs >800mg VPA:  -FSIQ: 9.7 (2.9) (4.0-15.3) (p<0.001)  -Nonverbal IQ: 10.5 (3.3) (4.1-16.9) p=0.001)  -Spatial IQ: 9.5 (3.4) (2.8-16.2) (p=0.006)  LTG vs. >800mg VPA  -FSIQ: 6.8 (3.3)(0.4-13.2) (p=0.04)  -Verbal IQ: 6.6 (3.2) (0.3-12.9) (p=0.04)  -Spatial IQ: 9.0 (3.9)(1.4-16.6) (p=0.02) | -School-aged children exposed to VPA at maternal doses more than 800 mg daily experience poorer cognitive development than control children or children exposed to LTG or CBZ. |
| Ban et al., 2015 | UK | Prospective Cohort Study | -Anatomical  -Folic Acid | 258,591 | -Age Range: 15-44  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | The Health Improvement Network | N/A | NR | -aOR Monotherapy >5mg folic acid daily: 1.56, 0.83–2.92 (any major anomaly)  -aOR Polytherapy >5mg folic acid daily: 2.54, 0.99–6.54 (any major anomaly)  -aOR Monotherapy <5mg folic acid daily (any major anomaly): 1.71,0.98–2.96  -aOR Polytherapy <5mg folic acid daily (any major anomaly): 3.22, 1.23–8.44  -aOR (CAs valproate vs. controls): 2.63, 95%CI 1.46–4.73) | -Folic acid supplementation is not associated with a reduced CA risk in AED exposed pregnancies. |
| Bansal et al., 2018 | India | Retrospective Cohort Study | -Anatomical | 99 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Medical-surgical disorder antenatal clinic of the department of obstetrics and gynecology at a tertiary care teaching hospital and referral center in North India | N/A | NR | -Risk of MCM in VPA exposed children (13.3%, P=0.1) | -Prenatal VPA exposure is associated with an increased risk of MCM relative to LEV (Not statistically significant). |
| Barton et al., 2018 | Australia | Prospective Cohort Study | -Cognitive | 86 | -Age Range: NR  -Mean Age: NR | -Age Range: 6-8  -Mean Age: NR  -Sex (%Female/%Male): 52.3/47.7 | Australian Pregnancy Register | -Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) - full scale IQ, working memory  -Clinical Evaluation of Language Fundamentals—Fourth Edition—Australian standardization (CELF-IV)  -NEPSY-II - list memory, narrative memory, memory for designs  -The Rey Complex Figure - visual memory, visuospatial constructional ability, and organizational ability | NR | -There was a significant effect of child FSIQ (F(3, 90) = 7.04, p < 0.001, η2 = 0.19) and WMI (F(3, 89) = 3.77, p = 0.013, η2 = 0.11) in AED-exposed children, with the lowest scores associated with VPA exposure.  -Core Language varied across AED-exposed children (F(3, 90) = 7.82, p < 0.001, η2 = .21), with VPA polytherapy exposed children performing most poorly.  -For narrative memory, children exposed to VPA polytherapy performed significantly below the expected test mean of 10, t(13) = −3.685, p = 0.003, d = −0.98.  -Performance on List Memory was significantly below the expected mean in children exposed to both VPA monotherapy, t(20) = −2.90, p = 0.009, d = −0.63, and VPA polytherapy, t(8) = −1.88, p = 0.046, d = −0.63.  -Significantly more children than expected demonstrated weaker performance on Narrative Memory (35%; χ2 = 6.70, p = 0.010) and List Memory (43%; χ2 = 11.27, p < 0.001) in the VPA monotherapy group.  -In Narrative Memory Free Recall (F(3, 86) = 4.62, p = 0.005, η2 = 0.14), the VPA polytherapy group performed significantly below the CBZ monotherapy (p = 0.003) and non-VPA polytherapy groups (p = 0.048).  -There was a significant difference between VPA polytherapy and CBZ monotherapy (p = 0.024) for Narrative Memory Recognition (F(3, 86) = 3.21, p = 0.027, η2 = 0.10).  -Children in the VPA polytherapy group consistently performed below the CBZ monotherapy group after correction for multiple comparisons (Total Learning p = 0.007, Retroactive Interference, p = 0.015, Delay p = 0.024).  -On Narrative Memory measures, there was a significant negative relationship between mean VPA dose and Free Recall, r = −0.402, p = 0.006 and Recognition, r = −0.292, p = 0.038.  -VPA dose was negatively correlated with List Memory Total Learning, r = −0.428, p = 0.003 and Delay, r = −0.473, p = 0.001. | -Prenatal VPA exposure is associated with impaired memory skills.  -Higher doses of prenatal VPA exposure is associated with poorer cognitive functioning. |
| Battino et al., 1992 | Italy | Prospective Cohort Study | -Anatomical | 315 | -Age Range: 16-42  -Mean Age: 26.6 +/- 4.7 years | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Milan Collaborative Study on Epilepsy and Pregnancy | NR | 1 year | -Percentage of malformations was significantly higher in VPA exposed children than controls: chi square = 5.2, p < 0.02  -Percentage of minor anomalies was significantly higher in VPA polytherapy exposed children than controls: chi square = 4.2, p < 0.04  -Percentage of minor anomalies was significantly higher in VPA exposed children than controls: (chi square = 4.4, p<0.03) | -Prenatal VPA exposure is associated with a higher incidence of malformation. |
| Battino et al., 2024 | Americas: 1.1%  Europe: 86.0%  Eastern Mediterranean: 0.3%  Southeast Asia: 4.2%  Western Pacific: 8.5% | Prospective Cohort Study | -Anatomical | 9,840 | -Age Range: 14.1-55.2  -Mean Age: 30.1 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 48.3/51.1 | EURAP Study Group | N/A | 1 year | -aOR (MCM risk in VPA exposed vs. unexposed children): 2.44, 95% CI = 1.80–3.30 | -Prenatal VPA exposure is associated with increased risk of MCM. |
| Bech et al., 2018 | Denmark | Prospective Case-Control Study | -Cognitive | 1,070 | -Age Range: 25.0 - 33.0  -Mean Age: 29.0 | -Age Range: NR  -Mean Age: 6.1  -Sex (%Female/%Male): 44.3/55.7 | Danish nationwide register | N/A | 5 years | -OR (Learning disabilities VPA exposed children vs. controls): 4.67, 95% CI 1.73-12.59 | -Prenatal VPA exposure iss associated with an increased risk of learning disabilities. |
| Blotiere et al., 2019 | France | Retrospective Cohort Study | -Anatomical | 1,886,825 | -Age Range: <25 to >35  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | French National Health Insurance claims information system (Système national d'information interrégimes de l'Assurance maladie) | N/A | 2 years | Prenatal VPA exposure was associated with increased risks of:  -spina bifida (aOR 19.4, 95% CI 8.6–43.5)  -ventricular (aOR 4.0, 95% CI 2.1–7.8)  -atrial septal defects (aOR 9.0, 95% CI 5.4–15.0)  -pulmonary valve atresia (OR 27.8, 95% CI 3.3–102.5)  -hypoplastic left heart syndrome (OR 19.6, 95% CI 2.4–71.7)  -cleft palate (OR 5.4, 95% CI 1.1–15.8)  -anorectal atresia (OR 11.7, 95% CI 2.4–34.4)  -hypospadias (aOR 4.8, 95% CI 2.4–9.8) | -Prenatal VPA exposure is associated with increased risk of MCM. |
| Blotiere et al., 2020 | France | Prospective Cohort Study | -Behavioural  -Cognitive | 9,034 | -Age Range: <25 to >35  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 48.7/51.3 | French national health insurance database (Système national d’information interrégimes de l’Assurance maladie (SNIIRAM)) and the French hospital discharge database (Programme de médicalisation des systèmes d'information (PMSI)) | N/A | Unlimited | HR VPA (compared to LTG)  -NDD2.7 (1.8 to 4.0)  -PDD 4.4 (2.1 to 9.3)  -Mental retardation: 3.1 (1.5 to 6.2)  -Visits to a speech therapist: 1.5 (1.1 to 1.9)  HR VPA sensitivity analysis (children of women with epilepsy): (compared to lamotrigine)  -NDD: 3.5 (2.3 to 5.4)  -PDD: 4.7 (1.9 to 11.4)  -Mental retardation: 4.0 (1.9 to 8.6)  -Visits to a speech therapist:1.5 (1.1 to 1.9)  HR VPA dose analysis (compared to LTG)  -NDD: <700: 1.5 (1.1 to 1.9), 700-1500 mg 2.7 (1.6 to 4.6) ,>1500 8.7 (5.2 to 14.6)  -PDD: 2.7 (0.7 to 11.4),3.0 (1.0 to 8.9), 15.4 (5.7 to 41.1)  -Mental retardation: 1.6 (0.4 to 6.7), 2.6 (1.0 to 6.7), 8.4 (3.4 to 20.4)  -Visits to a speech therapist: 0.5 (0.3 to 0.9),1.5 (1.1 to 2.1),2.7 (1.8 to 4.1)  HR VPA dose analysis (main analysis) (compared to LTG):  -NDD: 1.3 (0.6 to 2.8), 2.1 (1.3 to 3.5),7.0 (4.3 to 11.5)  -PDD: 2.2 (0.5 to 8.5), 2.7 (1.0 to 7.1), 14.7 (6.2 to 34.7)  -Mental Retardation: 1.5 (0.4 to 5.9), 1.8 (0.7 to 4.9), 7.3 (3.0 to 17.7)  -Visits to a speech therapist: 0.6 (0.3 to 1.0), 1.6 (1.2 to 2.1), 2.6 (1.7 to 4.0) | -Prenatal VPA exposure is associated with an increased risk of an adverse neurodevelopmental outcome relative to LTG (Dose-dependent). |
| Bluett-Duncan et al., 2023 | UK, Ireland, New Zealand and Australia | Cross-Sectional Study | -Behavioural  -Cognitive | 146 | -Age Range: NR  -Mean Age: NR | -Age Range: <10 to 39  -Mean Age: NR  -Sex (%Female/%Male): 78.4/17.6 | Participating charities based in the UK, Ireland, New Zealand and Australia | -MacArthur Health Behaviour Questionnaire (HBQ) - physical health, social functioning, and academic performance  -Standardised EUROCAT list of malformations  -Subscales: Neurodevelopmental Disorder Checklist (NDD), Service Utilisation Checklist, Academic Competence Subscale  -Pediatric Symptoms Checklist – 17 (PSC-17) - psychosocial problems  -Patient Reported Outcomes Measurement – Perceived Cognitive Function (PROMIS-PCF)  -Bespoke Set of Questions - sensory issues | N/A | Individuals with a diagnosis of FVSD showed:  -Higher levels of moderate (43.4%) and severe (14.4%) cognitive impairment relative to VPA inexposure (p = 0.003)  -High levels of required formal educational support (77.6%), and poorer academic competence relative to VPA inexposure (p = 0.001)  -Overall psychosocial problems (p = 0.02), internalizing problems (p = 0.05) and attention problems (p = 0.001) | -FVSD is associated with higher levels of moderate and severe cognitive impairment, required formal educational support, and poorer academic competence.  -FVSD is associated with overall psychosocial problems, internalizing problems, and attention problems.  -FVSD phenotype is associated with neurodevelopmental disorders such as autism and sensory problems.  -Neurodevelopmental impairment in FVSD occurs commonly in the absence of physical impairment. |
| Bjork et al., 2018 | Norway | Prospective Cohort Study | -Folic Acid | 104,946 | -Age Range: NR  -Mean Age: 29.8 +/- 4.6 | -Age Range:NR  -Mean Age: NR  -Sex (%Female/%Male): NR | Norwegian Mother and Child Cohort Study (MoBa) | -Modified Checklist for Autism in Toddlers (M-CHAT) - autistic traits  -Social Communication Questionnaire (SCQ) - autistic traits | 3 years | -aOR (Autistic Traits Without Folic Acid Supplementation vs. With, Children Aged 18 Months and Exposed to AEDs): 5.9 (95% CI, 2.2-15.8)  -aOR: (Autistic Traits Without Folic Acid Supplementation vs. With, Children Aged 36 Months and Exposed to AEDs): 7.9 (95% CI, 2.5-24.9)  -aOR: (Autistic Traits Without Folic Acid Supplementation vs. With, Children Aged 18 Months and Exposed to AEDs, Mothers with Epilepsy Subgroup): 1.3 (95% CI, 1.2-1.4)  -aOR: (Autistic Traits Without Folic Acid Supplementation vs. With, Children Aged 36 Months and Exposed to AEDs, Mothers with Epilepsy Subgroup): 1.7 (95% CI, 1.5-1.9)  -Correlation (Social Communication Questionnaire Score and Maternal Folate Intake, AED Exposed Children): -0.03 (r2 - 0.52)  -Correlation (Social Communication Questionnaire Score and Maternal Folate Concentration, Multiple Linear Regression Analysis, AED Exposed Children): −0.25 (p = 0.03)  -Social Communication Score: Low (< 24.20 nmol/L ) vs. High Maternal Plasma Folate Concentration (≥ 85.18 nmol/L.): 7.91 (4.3) vs. 5.79 (3.2) (p=0.04)  -Adjusted Beta (Prepregnancy Use and Degree of Autistic Traits at 36 Months): -0.27 (p=0.007)  -Adjusted Beta (1st Trimester Folate Acid Dose and Degree of Autistic Traits at 36 Months): -0.45 (p<0.001)  -Adjusted Beta (2nd Trimester Folate Acid Dose and Degree of Autistic Traits at 36 Months): -0.31 (p=0.02)  -Adjusted Beta (3rd Trimester Folate Acid Dose and Degree of Autistic Traits at 36 Months): -0.25 (p=0.04)  -Odds Ratio (Autistic Traits with Folic Acid Supplementation Valproate Exposed vs. AED Exposed Children with Mothers Without Epilepsy): 1.6 (0.6-4.5)  -Odds Ratio (Autistic Traits without Folic Acid Supplementation Valproate Exposed vs. AED Exposed Children with Mothers Without Epilepsy): 3.2 (0.6-16.5)  -Late Folic Acid Supplementation is Associated with an Increased Likelihood of Autistic Traits: AED Exposed Children - 18 Months of Age (P = .007), AED Exposed Children - 36 Months of Age (P = .01)  -Correlation (Social Communication Questionnaire Score vs. AED + Folic Acid Supplementation: B = -3.13 (SE = 1.07) (Beta = -0.42) (p<0.004) | -Periconceptual folic acid supplementation is associated with a reduced risk of autistic traits in AED exposed children (Includes VPA). |
| Bjork et al., 2022 | Denmark, Finland, Iceland,, Norway, Sweden | Prospective Cohort Study | -Behavioural  -Cognitive | 4,494,926 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 48.7/51.3 | Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) | N/A | 8 years | -aHR (Neurodevelopmental Disorder (ASD, ID or Global Developmental Delay) in VPA Exposed vs. AED Unexposed Children (Children with Epileptic Mothers Subgroup)): 2.44 (1.93-3.07)  -aHR (Neurodevelopmental Disorder (ASD, ID or Global Developmental Delay) in VPA Exposed vs. AED Unexposed Children (Total Cohort): 3.87 (3.36-4.47)  -aHR (Autism in VPA Exposed vs. AED Unexposed Children (Children with Epileptic Mothers Subgroup)): (2.4 (95% CI, 1.7-3.3)  -aHR (Autism in VPA Exposed vs. AED Unexposed Children (Total Population): 3.44 (2.77-4.28)  -aHR (Neurodevelopmental Disorder (ASD, ID or Global Developmental Delay) in <750 mg Daily Valproate Exposed vs. AED Unexposed Children (Total Cohort)): 2.3 (95% CI, 1.9-2.8)  -aHR (Neurodevelopmental Disorder (ASD, ID or Global Developmental Delay) in >750 mg Daily Valproate vs. AED Unexposed Children (Total Cohort)): 5.6 (95% CI, 4.7-6.8)  -aHR (Intellectual Disability (ID) in VPA Exposed vs. Unexposed Children (Children with Epileptic Mothers)): 2.4 (1.73-3.30)  -aHR (ID in VPA Exposed vs. Unexposed Children (Total Population): 4.77 (1.70-3.69)  -aHR (ID in VPA Exposed 90 days Before Last Menstrual Period and Birth vs. AED Unexposed Children (Total Population)): 4.04 (3.19-5.13)  -aHR (ID in VPA Exposed Children with >2 Exposures vs. AED Unexposed (Total Population )): 4.24 (3.07-5.86)  -aHR (ID in VPA Exposed vs. AED Unexposed Children (Total Population, Fine Stratification Weighted Analysis): 4.93 (4.04-6.01) | -Prenatal VPA exposure is associated with an increased risk of ASD, global developmental delay, and ID. |
| Bromley et al., 2013 | UK | Prospective Cohort Study | -Behavioural | 214 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: 74 months  -Sex (%Female/%Male): 45.6/54.4 | Antenatal clinic in England | N/A | NR | -OR (Neurodevelopmental disorder VPA monotherapy vs. controls): 6.05 (1.65, 24.53) p= 0.007  -OR (Neurodevelopmental disorder VPA polytherapy vs. controls): 9.97 (1.82, 49.40) p=0.005 | -Prenatal VPA exposure is associated with an increased risk of neurodevelopmental disorder. |
| Bromley et al., 2016 | UK | Cross-Sectional Study | -Cognitive | 185 | -Age Range: NR  -Mean Age: 32.9 | -Age Range:NR  -Mean Age: NR  -Sex (%Female/%Male): 45.4/54.6 | United Kingdom Epilepsy and Pregnancy Register (UK-EPR) | -Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)  -Wechsler Preschool and Primary Scale of Intelligence–Third Edition  -NEPSY: A Developmental Neuropsychological Assessment, 2nd edition  -Clinical Evaluation of Language Fundamentals–Fourth Edition  -Behavior Assessment System for Children, Second Edition | NR | Increasing dose of VPA was associated with poorer:  -Full-Scale IQ (−10.6, 95% CI−16.3 to −5.0, p < 0.001)  -Verbal Abilities (−11.2, 95% CI −16.8 to −5.5, p < 0.001)  -Non-Verbal Abilities (−11.1, 95% CI −17.3 to −4.9, p < 0.001)  -Expressive Language Ability (−2.3, 95% CI −3.4 to −1.6, p < 0.001) | -Prenatal VPA exposure is associated with poorer FSIQ, verbal abilities, and expressive language abilities (Dose-dependent). |
| Bromley et al., 2019 | UK | Cross-Sectional Study | -Cognitive | 31 | -Age Range:NR  -Mean Age: NR | -Age Range: 6-27  -Mean Age: 14.97  -Sex (%Female/%Male): 42/58 | Manchester University NHS Foundation Trust's Genomic Medicine Department and two UK based charities | -Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) - full-scale IQ, verbal comprehension index, perceptual reasoning index, working memory index, and processing speed index  -Wechsler Adult Intelligence Scale - full-scale IQ, verbal comprehension index, perceptual reasoning index, working memory index, and processing speed index | N/A | -Mean Difference in IQ (Controls vs. FVS) (19.55, 95% CI −24.94 to 14.15)  -Mean Difference in Verbal Comprehension (Controls vs. FVS) (21.07, 95% CI −25.84 to −16.29)  -Mean Difference in Working Memory (Controls vs. FVS) (19.77, 95% CI −25.00 to −14.55)  -Mean Difference in Processing Speed (Controls vs. FVS) (16.87, 95% CI −22.24 to −11.50)  -IQ scores <70 were present in 26% of FVS subjects  -Requirement for educational intervention in FVS subjects: 74% | -Intellectual difficulties are a central feature of FVS.  -Individuals with FVS with the characteristic facial presentation are at high risk of cognitive difficulties regardless of VPA dose or MCM presence. |
| Burger et al., 2022 | South Africa | Cross-Sectional Study | -Behavioural | 112 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 55.5/54.5 | Maternal and Infant Mental Health (MIMH) study | -General Movement Assessment (GMA)  -Motor Optimality Score-Revised (MOS-R) | NR | -No significant differences were found between VPA exposed infants (median MOS-R: 26; IQR: 24–26) vs. infants with exposed to LTG, CBZ or lithium (median MOS-R: 24; IQR: 22–26) (Wilcoxon Two-Sample p = 0.283). | -Prenatal VPA exposure is not associated with impaired infant motor behavior at 10-20 weeks post-term age. |
| Campbell et al., 2013 | UK | Prospective Cohort Study | NR | 1,534 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | United Kingdom Epilepsy and Pregnancy Register | N/A | NR | -RR (VPA and recurrent malformation): 1.47, 95% CI 0.68–3.20 (No statistical significance) | -Prenatal VPA exposure is associated with an increased risk of recurrent malformations (Not statistically significant). |
| Campbell et al., 2014 | UK | Prospective Cohort Study | -Anatomical  -Folic Acid | 5,206 | -Age Range: NR  -Mean Age: 28.3 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 49.18/50.81 | UKEPR | N/A | NR | -OR (MCM VPA monotherapy vs. LTG monotherapy): 3.0 (95% CI 2.1 to 4.3, p<0.0001)  -OR (MCM VPA monotherapy vs. CBZ monotherapy): 2.7 (1.9 to 3.9, p<0.0001)  -Mean VPA daily dose MCM vs. absence: 1031.2 mg vs. 897.9 mg, p=0.02  -OR (Neural tube defects & facial clefts VPA vs CBZ): 4.45; 95% CI 1.45 to 13.69, p=0.009  -OR (Neural tube defects & facial clefts VPA vs LTG): 11.29; 95% CI 2.54 to 50.12, p=0.0002  -OR (Hypospadias and genitourinary defects VPA vs. CBZ): 4.11; 95% CI 1.49 to 11.35, p=0.006  -OR (Hypospadias and genitourinary defects VPA vs. LTG): 2.60; 95% CI 1.16 to 5.81, p=0.03  -OR (Skeletal defects VPA vs. CBZ): 3.41; 95% CI 1.07 to 10.91  -OR (Skeletal defects VPA vs. LTG): 5.77; 95% CI 1.59 to 21.02, p=0.007  -OR (Cardiac defects VPA vs. LTG): 2.69; 95% CI 1.16 to 6.25, p=0.03)  -MCM rate absence of folic acid vs. folic acid supplementation: 3.6% (95% CI 3.1 to 4.2) vs. with 2.7% (95% CI 1.5 to 4.8) (p=0.39)  -MCM (periconceptual folic acid first trimester vs. absence): p=0.23  -Neural tube defects (periconceptual folic acid first trimester vs. absence): 0.9% vs. 1.2% (p=0.78) | -Prenatal VPA exposure is associated with increased risk of MCM relative to lamotrigine and carbamazepine.  -Folic acid supplementation is not effective in reducing risk of VPA associated MCM. |
| Charleton et al., 2017 | UK | Prospective Cohort Study | -Behavioural | 7,210 | -Age Range: NR  -Mean Age: 28.9 | -Age Range: NR  -Mean Age: 6 years and 3 months  -Sex (%Female/%Male): 49.8/50.2 | UK Clinical Practice Research Datalink (CPRD) | N/A | NR | -aRR (Neurodevelopmental disorder VPA exposed children vs. controls): 2.02 (0.52–7.86) p=0.5 | -Prenatal VPA exposure is associated with an increased risk of neurodevelopmental disorder (Not statistically significant). |
| Christensen et al., 2013 | Denmark | Prospective Cohort Study | -Behavioural | 655,615 | -Age Range: <21 to >36  -Mean Age: NR | -Age Range: 4-14  -Mean Age: 8.84  -Sex (%Female/%Male): NR | Danish Prescription Register | N/A | Unlimited | -HR (ASD VPA exposed vs. controls, epileptic mother): 1.7 (0.9-3.2)  -HR (ASD VPA exposed vs. controls, non epileptic mother): 4.4 (1.4-13.6)  -HR (Childhood autism VPA exposed vs. controls, epileptic mother): 2.9 (1.4-6.0)  -HR (Childhood autism VPA exposed vs. controls, non-epileptic mother): 3.9 (0.5-28.9)  -HR (ASD VPA exposed vs. controls, total population): 2.9 (1.7-4.9)  -HR (Childhood autism VPA exposed vs. controls, total population): 5.2 (2.7-10.0) | -Prenatal VPA exposure is associated with increased risk of ASD and childhood autism. |
| Christensen et al., 2015 | Denmark | Retrospective Cohort Study | -Anatomical | 677,021 | -Age Range: <21 to >36  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Danish Medical Birth Registry | NR | NR | -RR (VPA & low apgar score): 1.85 (95% CI 1.04 to 3.30) | -Prenatal VPA exposure is associated with increased risk of being born with a low Apgar score. |
| Christensen et al., 2019 | Denmark | Prospective Cohort Study | -Behavioural  -Cognitive | 913,302 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: 10.1  -Sex (%Female/%Male): 48.7/51.3 | The Danish National Prescription Registry | N/A | Unlimited | -aHR (ADHD in VPA Exposed vs Unexposed Children): 1.48; 95% CI, 1.09-2.00 (N = 580 vs. 912 722)  -aHR (ADHD in VPA Exposed vs. Unexposed Children (Epilepsy Born Subgroup) ): 1.39; 95% CI, 1.00-1.93 (N = 516 vs. 7104)  -aHR (ADHD in VPA Monotherapy Exposed vs. Anti Epileptic Drug (AED) Unexposed: 1.52; 95% CI, 1.05-2.19 (N = 431 vs. 899 941)  -aHR (ADHD in VPA Exposed vs. Valporate Ceased (Prior to Pregnancy): 1.66; 95% CI, 1.05-2.62 (N = 580 vs. 719)  -aHR (ADHD in VPA Polytherapy vs. AED Unexposed): 1.43 (95% CI, 0.75-2.70) (N = 149 vs. 719)  -aHR (ADHD in High Dose VPA (>750 mg/d) vs AED Unexposed) 1.68; 95% CI, 1.04-2.71 (N = 204 vs. 899 941)  -aHR (ADHD in VPA Exposed vs. Unexposed Children): 1.47; 95% CI, 1.06-2.05 (N= 512 vs. 873 710, Congenital Malformation Patients Excluded)  -aHR (ADHD in VPA Exposed vs. Unexposed Children): 1.53 (95% CI, 1.05-2.23) (N= 519 vs. 903 016, Children with Epilepsy Excluded)  -aHR (ADHD in VPA Exposed vs. Unexposed Children): 1.56 (95% CI, 1.10-2.21)) (N= 580 vs. 911 382, Mothers with ADHD Excluded)  -aHR (ADHD in VPA Exposed 90 Days Before Birth vs. Unexposed Children): 1.48; 95% CI, 1.05-2.07 (N = 637 vs. 912 665)  -aHR (ADHD in VPA Exposed (& Follow Up Started at 3 years of Age) vs. Unexposed Children): 1.93 (95% CI, 1.28-2.91 (N= 419 vs. 883 311)  -aHR (ADHD in VPA Exposed vs. Lamotrigine): 2.16; 95% CI, 1.34-3.48 (N = 419 vs. 1355)  -aHR (ADHD in VPA Exposed vs. Carbamazepine): 1.79; 95% CI, 1.06-3.04 (N = 419 vs. 413)  -aHR (ADHD in VPA Exposed vs. Clonazepam): 1.96; 95% CI, 1.09-3.50 (N = 419 vs. 306) | -Prenatal VPA exposure is associated with increased risk of ADHD. |
| Christensen et al., 2021 | Denmark | Prospective Cohort Study | -Anatomical | 895,507 | -Age Range: 20-40+  -Mean Age: 30.02 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 48.7/51.3 | Danish National Prescription Registry | N/A | 1 year | -aOR (Risk of MCMs in VPA Exposed vs. Unexposed Children): 2.44, 95% CI = 1.80–3.30) | -Prenatal VPA exposure is associated with increased risk of MCM. |
| Christensen et al., 2021 | Denmark, Finland, Iceland, Norway, and Sweden | Prospective Cohort Study | -Anatomical | 4,494,918 | -Age Range: <20 - >40  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 49/51 | Denmark, Finland, Iceland, Norway, and Sweden–the SCAN-AED project | N/A | 1 year | -aOR (VPA and small gestational size): 1.07 (0.95–1.21) (ASM exposed vs. unexposed)  -aOR (VPA and small gestational size): 1.07 (0.90–1.26) (mothers with epilepsy group)  -aOR (VPA and microcephaly): 1.08 (0.85–1.37)  -aOR (VPA and microcephaly): 1.06 (0.78–1.45) (mothers with epilepsy group) | -Prenatal VPA exposure is not associated with small gestational age and microcephaly. |
| Cohen et al., 2011 | USA, UK | Prospective Cohort Study | -Behavioral  -Cognitive | 229 | -Age Range: NR  -Mean Age: 30 | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | -Motor Scale from the Bayley Scales of Infant Development - Second Edition (BSID – II) - motor outcomes  -Adaptive Behavior Assessment System – Second Edition (ABAS – II) - emotional/behavioral functioning  -Behavior Assessment System for Children (BASC) - emotional/behavioral functioning | 3 years | -BSID – II Motor Index and VPA correlation:-0.60 (p=<0.0001)  -ABAS – II General Adaptive Composite and VPA correlation: -0.54 (p=0.0002) | -Prenatal VPA exposure is associated with lower verbal and non-verbal abilities (Dose-dependent). |
| Cohen et al., 2013 | USA, UK | Prospective Cohort Study | -Behavioural  -Cognitive | 195 | -Age Range: NR  -Mean Age: 30 | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | -Adaptive Behavior Assessment System—Second Edition (ABAS-II) - adaptive functioning  -Behavior Assessment System for Children (BASC) - emotional/behavioral functioning | 6 years | -Lower ABAS scores were observed for LTG (p=0.0252 ) and PHT (0.0014) vs. VPA  -% of children with ADHD VPA exposed: 21.43 95% CI 8.30-40.95, p=0.0028 | -Prenatal VPA exposure is associated with lower General Adaptive Composite scores relative to LTG and PHT (Dose-dependent).  -Prenatal VPA exposure is associated with an increased risk of atypical behavior and inattention relative to LTG and PHT.  -Prenatal VPA exposure is associated with an increased risk of ADHD. |
| Cohen et al., 2019 | USA, UK | Prospective Cohort Study | -Cognitive | 221 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 51/49 | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study | -Wechsler Intelligence Scale for Children, Third Edition (WISC-III)  -Differential Ability Scales - intelligence | 6 years | Correlation VPA dose:  -Age 6 IQ: r = -0.45 p = 0.0013  -Attention: r = -0.38 p = 0.0075  -Verbal immediate: r =-0.3 p=0.0424  -Verbal delayed: -0.32 p=0.0348  -Delayed recognition:-0.43 p=0.003  -Visual Immediate: -0.3 p=0.0433 | -Prenatal VPA exposure is associated with difficulties in learning and working memory (Dose-dependent). |
| Cohen et al., 2023 | Denmark, Finland, Iceland, Norway, Sweden | Retrospective Cohort Study | -Anatomical | 2,031 | -Age Range: <25 - >40  -Mean Age: 30.98 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | National health register data from Denmark, Finland, Iceland,Norway, and Sweden | N/A | 1 year | -aRR (Malformation VPA vs. LTG): aRR = 2.05, 95% CI = 1.70-2.46  -aRR (Multiple malformations VPA exposed vs. ASM unexposed children): 1.86, 95% CI = 0.97 - 3.57  -aRR (Hypospadias VPA exposed vs. ASM unexposed children): 6.47, 95% CI = 4.32 - 9.69 | -Prenatal VPA exposure is associated with increased risk of MCM. |
| Cohen et al., 2023 | Denmark, Finland, Iceland, Norway, and Sweden, United States and Australia | Prospective Cohort Study | -Anatomical | 50,905 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | International Pregnancy Safety Study (InPreSS) Consortium | NR | 1.5 years | -RR (LTG-LEV duotherapy vs. VPA monotherapy): 0.41 (0.24-0.69)  -aRR (LTG-LEV duotherapy vs. VPA monotherapy): 0.38 (0.23-0.63) | -VPA monotherapy is associated with a 60% increased risk of MCM relative to lamotrigine-levetiracetam duotherapy. |
| Coste et al., 2020 | France | Retrospective Cohort Study | -Behavioural  -Cognitive | 1,721,990 | -Age Range: <25 to >35  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 48.9/51.1 | French national health data system (SNDS) | N/A | 5 years | -aHR (Mental and Behavioral Disorders in VPA Exposed vs. Unexposed Children): 3.7 [2.8–4.9]  -aHR (Pervasive Developmental Disorders in VPA Exposed vs. Unexposed Children): 4.6 [2.9–7.5]  -aHR (Mental Retardation in VPA Exposed vs. Unexposed Children):5.1 [3.1–8.5]  -aHR (Disorders of Psychological Development in First Trimester VPA exposed vs. Unexposed Children): 4.7 [3.5–6.4]  -aHR (Speech Therapy in First Trimester VPA Exposed vs. Unexposed Children): 1.7 [1.4–2.1]  -aHR (Mental and Behavioral Disorders in First Trimester VPA Exposed vs. Unexposed Children): 5.5 [4.0–7.4]  -aHR (Pervasive Developmental Disorders in First Trimester VPA Exposed vs.VPA Unexposed Children): 7.0 [4.1–11.8]  -aHR (Mental Retardation in First Trimester VPA Exposed vs.VPA Unexposed Children): 6.0 [3.2–11.1]  -aHR (Disorders of Psychological Development in First Trimester VPA Exposed vs.VPA Unexposed Children): 6.9 [4.9–9.7]  -aHR (Speech Therapy in First Trimester VPA Exposed vs. VPA Unexposed Children): 2.2 [1.8–2.8]  -aHR (Orthopedic Usage in First Trimester VPA Exposed vs.VPA Unexposed Children): 1.3 [1.0–1.5] (p = 0.03)  -aHR (Mental and Behavioral Disorders in 2nd or 3rd Trimester VPA Exposed vs.VPA Unexposed Children): 3.0 [1.3–6.6]  -aHR (Mental Retardation in First Trimester 2nd or 3rd Trimester VPA Exposed vs.VPA Unexposed children): 6.8 [2.2–21.1]  -aHR (Disorders of Psychological Development in 2nd or 3rd Trimester VPA Exposed vs.VPA Unexposed Children): 4.4 [2.0–9.9] | -Prenatal VPA exposure is associated with a 4-5 fold increased risk of ND. |
| Cummings et al., 2011 | Ireland | Retrospective Case-Control Study | -Behavioural  -Cognitive | 210 | -Age Range: 16-49  -Mean Age: NR | -Age Range: 9-60 months  -Mean Age: 35.1  -Sex (%Female/%Male): 54/46 | UK Epilepsy and Pregnancy Register | -Bayley Scales of Infant Development  -Griffiths Scale of Infant Development | N/A | -OR (Detrimental neurodevelopment VPA exposed children vs. controls): 26.1 (4.9 to 139) (vs. controls) (p<0.001) | -Prenatal VPA exposure is associated with an increased risk of detrimental neurodevelopment. |
| Daugaard et al., 2020 | Denmark | Prospective Cohort Study | -Behavioural  -Cognitive | 913,302 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: 10 +/ 4.4  -Sex (%Female/%Male): 48.7/51.3 | The Danish Prescription Register | N/A | 18 years | -aHR (ID) in VPA Exposed vs.Unexposed Children): 4.48; 95% CI, 2.97-6.76 (N = 580 vs. 912 722)  -aHR (ID in VPA Exposed vs.Unexposed Children): 6.07; 95% CI, 4.67-7.89 (N = 580 vs. 912 722)  -aHR (ID in VPA Exposed vs.Unexposed Children): 1.95; 95% CI, 1.21-3.14 (Mothers with Epilepsy) (N = 516 vs. 7104)  -aHR (ID with Delayed Milestones (Combined Outcome) in VPA Exposed vs. Unexposed Children): 3.07; 95% CI, 2.24-4.20 (Mothers with Epilepsy) (N = 516 vs. 7104)  -aHR (ID in VPA Monotherapy vs. AED Unexposed Children): 4.42; 95% CI, 2.75-7.11 (N = 431 vs. 899 941)  -aHR (Combined Outcome in Valproate Monotherapy vs. Anti Epileptic Drug (AED) Unexposed Children): 5.28; 95% CI, 3.82-7.28 (N = 431 vs. 899 941)  -aHR (ID in VPA Polytherapy vs. AED Unexposed Children): aHR, 4.99; 95% CI, 2.21-11.30 (N = 149 vs. 899 941)  -aHR (ID in VPA vs. Lamotrigine): 4.91; 95% CI, 2.09-11.55 ( N = 431 vs. 1383)  -aHR (ID in VPA Exposed vs. Unexposed Children): 4.06; 95% CI, 2.48-6.63 (Excluding Children with Congenital Malformations) (N = 512 vs. 873 710)  -aHR (Combined Outcome in Valproate Exposed vs. Unexposed Children): 4.85; 95% CI, 3.49-6.74 (Excluding Children with Congenital Malformations) (N = 512 vs. 873 710)  -aHR (ID in High Dose (>750 mg) Valporate vs.Unexposed Children): 7.96; 95% CI, 4.80-13.19 (N = 213 vs. 899 941)  -Cumulative Incidence of ID: 5.99% (95% CI, 3.43%-9.52%) in Children with Prenatal Valproate Exposure.  -At age 18 years, Cumulative Incidence of Combined Outcome 12.03% (95% CI, 8.81%-15.79%) in Children with Prenatal VPA Exposure. | -Prenatal VPA exposure is associated with increased risk of ID and delayed childhood milestones. |
| Deshmukh et al., 2016 | USA, Canada | Prospective Cohort Study | -Behavioural | 252 | -Age Range: NR  -Mean Age: NR | -Age Range: 3-6  -Mean Age: NR  -Sex (%Female/%Male): NR | North American Antiepileptic Drug (AED) Pregnancy Registry | -Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) - child's self-sufficiency and adaptive functioning in the domains of communication, daily living, socialization, and motor skills | NR | -Mean ABC score for VPA-exposed children was 95.6 (95% CI [91, 101]), versus 100.8 (95% CI [98, 103]) and 103.5 (95% CI [101, 106]) for CBZ- and LTG-exposed children respectively (ANOVA; p = 0.017).  -Significant differences were observed among the three drug groups in the ABC (p = 0.017), socialization (p = 0.026), and motor (p = 0.018) domains, with a trend toward significance in the communication domain (p = 0.053). VPA-exposed children scored lowest and LTG-exposed children scored highest in every category. | -Prenatal VPA exposure is associated with adaptive behavior impairments (Socialization and motor function) (Dose-dependent).  -Prenatal VPA exposure is associated with a weakness in communication relative to LTG and CBZ. |
| Diav-Citrin et al., 2008 | Israel | Prospective Cohort Study | -Anatomical | 1,469 | -Age Range: 26-34  -Mean Age: 29 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Israeli Teratology Information Service  (TIS) | NR | 1.5 years | -RR (Major anomalies VPA exposed vs. controls): 2.66, 95% CI 1.25, 5.65  -OR (VPA >1000mg polytherapy & major anomalies): 20.53, 95% CI 5.46, 77.21; p < 0.001  -OR (VPA >1000mg monotherapy & major anomalies): 6.08, 95% CI 1.25, 29.66 p = 0.026  -RR (VPA exposure & cardiovascular anomalies): 6.44, 95% CI 2.14, 19.37 | -Prenatal VPA exposure is associated with an increased risk of CA. |
| Dreier et al., 2023 | Denmark, Finland, Iceland, Norway, and Sweden | Prospective Cohort Study | -Cognitive | 38,661 | -Age Range: <20 to >45  -Mean Age: NR | -Age Range: NR  -Mean Age: 7.5  -Sex (%Female/%Male): 48.7/51.3 | Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) project | N/A | 15 years | -aHR (Combined Psychiatric End Point (Risk of 1/13 Psychiatric Conditions) in VPA Monotherapy vs. ASM Unexposed Children):1.80 [95% CI, 1.60-2.03]  -aHR (Combined Psychiatric End Point in VPA Polytherapy vs. ASM Unexposed Children): 1.85; 95% CI, 1.56-2.18  -aHR (ID VPA Monotherapy vs. VPA Unexposed Children): 2.70; 95% CI, 1.94-3.74  -aHR (ASD VPA Monotherapy vs. VPA Unexposed Children): 2.45; 95% CI, 1.84-3.26  -aHR (Other Developmental Disorder (Ex. Speech, Scholastic Skills, and Motor Function) VPA Monotherapy vs. VPA Unexposed Children): 2.76; 95% CI, 2.27-3.36  -aHR (ADHD VPA Monotherapy vs. VPA Unexposed Children): 1.41; 95% CI, 1.10-1.81  -aHR (Attachment Disorder VPA Monotherapy vs. VPA Unexposed Children): 1.91; 95% CI, 1.15-3.18  -aHR (Tic Disorder VPA Monotherapy vs. VPA Unexposed Children): 1.56 (0.91-2.68)  -Cumulative Incidence (Combined Psychiatric End Point VPA Monotherapy vs. ASM Unexposed Children, Age 10): 27.2 (24.9-29.4)  -Cumulative Incidence (Combined Psychiatric End Point VPA Monotherapy vs. ASM Unexposed Children, Age 18): 42.1% (95% CI, 38.2%-45.8%)  -Cumulative Incidence (Any Psychiatric Disorder VPA Monotherapy vs. ASM unexposed, age 15): 34.8 (31.9- 37.6)  -Cumulative Incidence (ADHD VPA Monotherapy vs. ASM Unexposed, Age 15): 9.6%; 95% CI, 7.8%-11.7%  -Cumulative Incidence (ASD VPA Monotherapy vs.ASM Unexposed, Age 15): 6.8%; 95% CI, 5.4%-8.5%  -Cumulative Incidence (ID VPA Monotherapy vs. ASM Unexposed, Age 15): 5.2%; 95% CI, 4.1%-6.5%  -Cumulative Incidence (Other Developmental Disorder VPA Monotherapy vs. ASM Unexposed, Age 15): 18.2 (16.1-20.3)  -Cumulative Incidence (ADHD VPA Monotherapy vs. ASM Unexposed, Age 15): 9.6 (7.8-11.7)  -Cumulative Incidence (ASD Valproate Monotherapy vs. ASM Unexposed, Age 15): 6.8 (5.4-8.5)  -Cumulative Incidence (ID Valproate Monotherapy vs. ASM Unexposed, Age 15): 5.2 (4.1-6.5) | -Prenatal VPA exposure is associated with an increased risk of psychiatric disorders. |
| Dreier et al., 2024 | Denmark, Finland, Iceland, Norway, and Sweden | Prospective Cohort Study | -Anatomical  -Behavioural  -Cognitive | 38,663 | -Age Range: <20 to >40  -Mean Age: NR | -Age Range: 0-22  -Mean Age: 7.2  -Sex (%Female/%Male): 48.8/52.2 | Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) project | NR | 22 years | -aHR (Epilepsy VPA exposed children vs. unexposed sibling): 0.58; 95% CI, 0.23-1.46  -aHR (Epilepsy VPA exposed children vs. VPA exposed sibling, including exposure to other ASMs, 0.95; 95% CI, 0.50-1.82 | -Prenatal VPA exposure is not associated with epilepsy.  -Prenatal Valproate exposure is associated with ASD and MCM (Dose-dependent). |
| Elkjaer et al., 2018 | Denmark | Prospective Cohort Study | -Cognitive | 479,027 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 49.1/50.9 | Danish Register of Medicinal Product Statistics | -2nd, 4th, 6th, and 8th grade Danish  -3rd and 6th grade math | 14 years | -Z-Score Difference (4th Grade Danish in VPA Exposed Children vs. AED Unexposed Children): -0.33 (-0.52 to - 0.14) (p<0.001)  -Z-Score Difference (6th Grade Danish in VPA Exposed Children vs. AED Unexposed Children): -0.27 (-0.42 to - 0.12) (p<0.001)  -Z-Score Difference (8th Grade Danish in VPA Exposed Children vs. AED Unexposed Children): -0.22 (-0.41 to -0.03) (p=0.027)  -Z-Score Difference (6th Grade Mathematics in VPA Exposed Children vs. AED Unexposed Children): -0.33 (-0.47 to - 0.19) (p<0.001)  -Z-Score Difference (4th Grade Danish in VPA Exposed Children vs. LTG Exposed Children): -0.36 (-0.59 to -0.13) (p=0.003)  -Z-Score Difference (6th Grade Danish in VPA Exposed Children vs. LTG Exposed Children): -0.33 (-0.60 to -0.06) (p=0.02)  -Z-Score Difference (8th Grade Danish in VPA Exposed Children vs. LTG Exposed Children): -0.39 (-0.77 to 0.00) (p=0.048)  -Z-Score Difference (6th Grade Mathematics in VPA Exposed Children vs. LTG Exposed Children): -0.48 (-0.70 to - 0.25) (p<0.001) | -Prenatal VPA exposure is associated with impaired school performance in both primary and lower secondary schooling compared with AED-unexposed children and LTG. |
| Erikkson et al., 2005 | Finland | Prospective Cohort Study | -Cognitive | 39 | -Age Range: NR  -Mean Age: 28.2 +/-4.4 | -Age Range: 6.6–13.4 years  -Mean Age: 9.7  -Sex (%Female/%Male): 53.8/46.2 | Kuopio University Hospital | -Wechsler Adult Intelligence Scale (WAIS)  -NEPSY Neuropsychological Development | NR | -Memory of faces: 7.3 ± 4.2 (10) , (p = 0.016) VPA < CBZ  -List learning: 11.0 ± 3.5 (9) , (p= 0.008) VPA/CBZ < no AED  -Digit Symbols: 6.3 ± 2.6 (12) (p= 0.044) VPA < CBZ. VPA < no AED | -Prenatal VPA exposure is associated with poorer cognitive development. |
| Foch et al., 2018 | France | Retrospective Case-Control Study | -Anatomical | 29,291 | -Age Range: 27-34  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 49/51 | EFEMERIS database | NR | 2 years | -aOR (Hearing impairment VPA exposed vs. unexposed): 6.88 95% CI [2.53–18.71] | -Prenatal VPA exposure is associated with an increased risk of hearing loss. |
| Gopinath et al., 2015 | India | Prospective Case-Control Study | -Cognitive | 339 | -Age Range: NR  -Mean Age: NR | -Age Range: 10-12  -Mean Age: NR  -Sex (%Female/%Male): 47.5 + 52.5 | Kerala Registry of Epilepsy and Pregnancy (KREP) | -Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)  -Wechsler Memory Scale-Visual Reproduction (WMS-VR) - verbal learning and memory  -Rey Auditory Verbal Learning Test (RAVLT) - verbal learning and memory  -Trail Making Test (TMT) - attention | 12 years | -The FSIQ mean ± SD; prescribed daily dose/daily-defined dose ratio and number of monotherapy exposure for different AEDs drugs: phenobarbital: (74.5 ± 14; 1.1 ± 0.8; 22), valproate: (82.8 ± 12.4; 0.3 ± 0.1; 36), carbamazepine: (82.2 ± 13.9; 0.6 ± 0.3; 41), phenytoin: (82.6 ± 13.5; 0.8 ± 0.3; 11) | -VPA monotherapy is associated with lower IQ relative to phenobarbital. |
| Guveli et al., 2017 | Turkey | Retrospective Cohort Study | -Anatomical | 117 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate-10  -Mean Age: NR  -Sex (%Female/%Male): 53/47 | Epilepsy outpatient clinics of Department of Neurology, Istanbul Faculty of Medicine, Istanbul University; or Department of Neurology, Bakirkoy Research and Training Hospital for Psychiatry, Neurology, and Neurosurgery; | NR | NR | -OR (MM folic acid + AED vs. controls): 3.48; 95% CI 0.67–18.0, p >0.05  -Dysmorphic features was associated with VPA exposure (p<0.05)  -VPA dose was not associated with increased risk of malformation (p>0.05) | -Prenatal VPA exposure is associated with an increased risk of malformation.  -Folic acid supplementation is not effective in reducing AED-associated malformations. |
| Hernandez-Diaz et al., 2024 | USA | Retrospective Cohort Study | -Behavioural | 4,208,611 | -Age Range: 12-55  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | Medicaid Analytic eXtract–Transformed Medicaid Statistical Information System Analytic Files | N/A | 8 years | -HR (ASD prenatal VPA exposed vs. ASM unexposed children, mothers with epilepsy): 2.67 (1.69-4.20)  -HR (ASD VPA monotherapy vs. ASM unexposed children): 2.96 (1.79-4.89)  -HR (ASD high dose VPA vs. ASM unexposed children): 4.38 (2.42 - 7.93)  -HR (ASD early exposure VPA vs. ASM unexposed children): 2.35 (1.57-3.50)  -HR (ASD VPA vs. LTG): 1.79 (1.12-2.87) | -Prenatal VPA exposure is associated with increased risk of ASD (Dose-dependent). |
| Holmes et al., 2011 | US, Canada | Prospective Cohort Study | -Anatomical | 7,298 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | North American AED Pregnancy Registry | NR | 3 months | -OR (MCM VPA polytherapy vs. controls): 5.0 (1.5-14.0)  -OR (MCM polytherapy without VPA vs. controls): 1.5 (0.7-3.0) | -VPA polytherapy is associated with increased risk of MCM. |
| Honybun et al., 2021 | Australia | Prospective Cohort Study | -Behavioural | 121 | -Age Range: NR  -Mean Age: NR | -Age Range: 4-11  -Mean Age: 7.08 +/- 2.16  -Sex (%Female/%Male): 43.8/51.2 | Australian Pregnancy Register | -Autism Spectrum Quotient–Children's Version (AQ-Child)  -National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale | NR | -Sex typical dynamic of males having higher ASD symptoms was found for all AEDs except VPA (p = .01). | -Prenatal VPA exposure may negate the male sex-related predominance of incidence of ASD. |
| Huber-Mollema et al., 2019 | Netherlands | Prospective Cohort Study | -Behavioural | 181 | -Age Range: NR  -Mean Age: NR | -Age Range: 6-8 years  -Mean Age: NR  -Sex (%Female/%Male): 47/53 | Dutch EURAP & Development study | -Child Behavior Checklist (CBCL) - child behavioral problems  -Social Emotional Questionnaire - child behavioral problems | NR | -Z Score (Conduct Disorder in VPA Exposed Children Relative to Population Norm): -3.8958 (p=0.0001)  -Z Score (Autism in VPA Exposed Children Relative to Population Norm): -2.5358 (p=0.01) | -Prenatal VPA exposure is associated with clinical behavioral problems (Conduct Disorder, autism). |
| Huber-Mollema et al., 2020 | Netherlands | Prospective Cohort Study | -Cognitive | 161 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 48.5/51.5 | Dutch EURAP & Development study | -Wechsler Intelligence Scale for Children (WISC-III-NL) - full-scale IQ (FSIQ), verbal IQ (VIQ), performance IQ (PIQ) and the processing speed index (PSI)  -The Developmental Neuropsychological Assessment (NEPSY-II-NL) - inhibition of learned and automated responses; monitoring and self-regulation; alertness, selective and sustained attention; ability to establish maintain and change responses; nonverbal problem solving, planning and organizing a complex response; and production of patterns, speeded naming, comprehension of instructions, and word generation, short and long-term memory, fine motor skills, visuospatial skills  -Visual Sky Search Task of the Test of Everyday Attention for Children (Tea-CH) - visual attention  -Peabody Picture Vocabulary Test (PPVT-III-NL) - vocabulary  -Lindeboom - verbal fluency | 7 years | Mean (SD):  -Inhibition-name timing score: 9.9 (3.1) (VPA), 11.0 (2.3) (CBZ), 11.4 (2.1) (LTG), 11.5 (2.4) (LEV) (p=0.069)  -Statue: 6.8 (2.0) (VPA), 8.6 (2.5) (CBZ), 9.0 (3.2) (LTG), 8.6 (2.9) (LEV) (p=0.052)  -Comprehension of instructions: 9.2 (2.1) (VPA), 10.6 (2.3)(CBZ), 11.2 (3.0) (LTG) ,12.0 (3.5) (LEV) (p = 0.004)  -Visuomotor precision total errors: 6.5 (2.6) (VPA), 8.4 (2.1) (CBZ), 8.7 (2.5) (LTG), 7.5 (2.3) (LEV) (p=0.004)  -Verbal IQ: 100.6 (14.9) (Range 70–126 4) (percentage of children scoring below 85: 18.2%) (VPA), 106.2 (14.2) 86–138 0 (0%) (CBZ), 109.7 (15.7) 64–150 6 (7.3%) (LTG) ,114.0 (13.1) 88–140 0 (0%) (LEV) (p=0.014)  Adjusted Mean (SD) 95% CI:  -Verbal IQ: 100.5 (2.9) 95–106 (VPA), 107.9 (2.5) 103–111 (CBZ), 109.6 (1.5) 107–113 (LTG) , 112.3 (2.9) 107–118 (LEV)  Intelligence (VPA as reference group) (B (SE) 95% CI, p value):  -VIQ CBZ: 9.1 (4.0), 1.3–17.0 , p=0.023  -VIQ LTG: 10.3 (3.5) , 3.4–17.3 , p=0.004  -VIQ LEV: 13.4 (4.2) , 5.2–21.6 , p=0.002  -LTG FSIQ: 7.5 (3.5), 0.6–14.4, p=0.033  VPA vs LTG (B (SE) 95% CI, p value):  -Verbal IQ: -8.5 (3.4) -15.3 to -1.8, p= .014  -Statue: -2.1 (0.8) -3.7 to -0.4, p=.014  -Design fluency: -2.0 (1.0) -3.9 to -0.1, p= .041  -Inhibition - name timing score :-1.4 (0.6) -2.5 to -0.3, p= .015  -Comprehension of instructions: -2.0 (0.7) -3.3 to -0.6, p=.005  -Word generation; -1.9 (0.8) -3.4 to -0.3,p= .019  -Visuomotor precision total errors: -2.3 (0.6) -3.5 to -1.2, p=.000  -Fingertapping series with dominant hand: -1.5 (0.6) -2.6 to -0.4, p= .011  -Arrows: -1.7 (0.8) -3.3 to -0.2, p=.029  -Design copying: -1.0 (0.5) -2.0 to 0.01, p= .052  -The effect of VPA dose was significant for statue (p = 0.032), phoneme deletion (p = 0.017), memory for names (p = 0.032), memory for names delayed (p = 0.029), and narrative memory (p = 0.025). | -Prenatal VPA exposed children performed poorer on all neurocognitive domains (attention, executive function, language, memory, sensorimotor, visuospatial processing) relative to CBZ, LTG, and LEV. |
| Husebye et al., 2018 | Norway | Prospective Cohort Study | -Cognitive  -Folic Acid | 104,577 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | Norwegian Mother and Child Cohort Study (MoBa) | -Ages and Stages Questionnaires (ASQ) - global language delay, expressive language delay | 3 years | -Correlation: Maternal Valproate Concentration and Global Language Score: (r = −0.50, p = 0.04)  -OR (Language Delay at 18 Months in AED Exposed Children vs Controls): 3.9 (95% Confidence Interval [CI] 1.9–7.8, p < 0.001)  -OR (Language Delay at 36 Months in AED Exposed Children vs Controls): 4.7 (95% CI 2.0–10.6, p < 0.001)  -OR (Language Delay at 18 Months in AED Exposed Children + Periconceptional Folic Acid Supplementation vs Controls): 1.7 (95% CI 1.2–2.6, p = 0.01)  -OR (Language Delay at 36 Months in AED Exposed Children + Periconceptional Folic Acid Supplementation vs Controls): 1.7 (95% CI 0.9–3.2, p = 0.13) | -Prenatal VPA exposure is associated with low language scores at 18 months of age (Dose-dependent).  -Periconceptional folic acid supplementation is associated with a reduction in AED-associated language delay (Not specific to VPA). |
| Husebye et al., 2019 | Norway | Prospective Cohort Study | -Cognitive  -Folic acid | 114,408 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age:NR  -Sex (%Female/%Male): 41/59 | Norwegian Mother and Child Cohort Study (MoBa) | -Ages and Stages Questionnaires (ASQ)  -Speech and Language Assessment Scale (SLAS)  -Norwegian Instrument Twenty Statements about Language-related Difficulties (Language 20) | 8 years | -OR (Periconceptional Folic Acid Use and Language Impairment (AED exposed children of mothers with epilepsy): 0.4 (0.2–0.9) p<0.05  -Maternal Plasma VPA Concentration and ASQ Score in children at 5 years: Spearman’s rho −0.77, P = 0.02, n = 9  -Maternal Plasma VPA Concentration and Language 20 Score in children at 5 years: Spearman’s rho 0.82, P = 0.01, n = 9  -VPA monotherapy and Language 20 score 8 years (mean (SD, 95 CI)): 13.0 (6.4) 9.6–16.4) (p<0.05)  -VPA monotherapy SLAS score 5 years: Mean: 3.1 (SD: 0.6, 2.8–3.5) (p<0.05)  -ASQ Score at age 5 (Periconceptional folic acid use and AED exposure): P = 0.009, standardized beta 0.03  -The aORs for language impairment in AED-exposed children compared to control children with no folic acid use were 10.5 (CI 1.9–56.3, P = 0.006) at age 5 years and 3.8 (CI 1.6–9.1, P = 0.003) at age 8 years, respectively. When the mothers were using periconceptional folic acid supplement, the corresponding aORs for language impairment were 1.4 (CI 0.9–2.2, P = 0.14) at age 5 years and 1.7 (CI 1.1–2.6, P = 0.02) at age 8 years, respectively. | -Periconceptional folic acid supplementation protects against AED-associated language impairment.  -Prenatal AED exposure is associated with an increased risk of language impairment in children aged 5 and 8 years.  -Prenatal VPA exposure is associated with an increased risk of language impairment in children at 5 and 8 years. |
| Jentik et al., 2010 | Netherlands | Prospective Case-Control Study | -Folic Acid | 5165 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | Eurocat Northern Netherlands | NR | NR | -Folic acid significantly decreased the risk for spina bifida with 50% (OR: 0.5 [0.3–0.7]) in AED exposed pregnancies, but not VPA exposed (OR: 1.0 [0.1–7.6]). | -Folic acid supplementation reduced the risk of spina bifida in AED exposed pregnancies, but not VPA exposed pregnancies (Low power). |
| Jonge et al., 2013 | Netherlands | Prospective Case-Control Study | -Anatomical | 32,435 | -Age Range: 15-50  -Mean Age: 30.4 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | EUROCAT NNL | N/A | NR | -RR (VPA and heart anomalies): 5.98 (95 % CI 2.66–13.44)  -RR (VPA and anomalies of the nervous system): 15.05 (96 % CI 5.09–44.51) | -Prenatal VPA exposure is associated with an increased risk of heart and CNS anomalies. |
| Kaaja et al., 2003 | Helsinki | Prospective Cohort Study | -Anatomical | 770 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male):NR | Department of Obstetrics and Gynecology of Helsinki University Central Hospital | N/A | NR | -aOR: MCM and VPA exposure: 4.1 (1.6-10.5) p=0.003 | -Prenatal VPA exposure is associated with increased risk of MCM. |
| Kaneko et al., 1988 | Japan | Prospective Cohort Study | -Anatomical | 172 | -Age Range: 18-46  -Mean Age: 26.0 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Hirosaki University Hospital, Nagasaki University Hospital, and Fukushima Medical College Hospital | NR | NR | Wilcoxon Sum Test:  -VPA Z score: -2.101 (p=0.036)  -Drug score: VPA polytherapy daily dosage: Z = -2.587 (p = 0.010) | -Polypharmacy with high dose VPA is associated with increased risk of CM. |
| Kaneko et al., 1999 | Japan, Italy, Canada | Prospective Cohort Study | -Anatomical | 983 | -Age Range: NR  -Mean Age: 27 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Japanese Association of Obstetricians for Maternal Welfare | N/A | 1 month | -VPA dose and malformation occurrence: regression coefficient = 0.0021, p=0.0075  -OR (Malformation VPA exposed offspring vs. unexposed): 4.0, p=0.039  -VPA level in maternal blood and malformation occurrence: regression coefficient=0.052, p = 0.005)  -VPA level in maternal blood and malformation occurrence: regression coefficient=0.035, p = 0.001) | -VPA dose and level are positively correlated with CM incidence. |
| Kasradze et al., 2017 | US | Prospective Cohort Study | -Cognitive | 100 | -Age Range: NR  -Mean Age: 30.5 | -Age Range: 36 - 72 months  -Mean Age: 52.5 months  -Sex (%Female/%Male): 60/40 | Georgian National AED-Pregnancy Registry | -Wechsler Adult Intelligence Scale – Revised (WAIS-R)  -Wechsler Preschool and Primary Scale of Intelligence (WPPSI-4) | NR | VPA mean scores and confidence intervals:  -Full Scale IQ (FSIQ): 82.3 (75.5; 89.2) p<0.001  -Verbal comprehension (VCI): 82.6 (75.4; 89.8) p<0.001  -Visual Spatial (VSI): 87.2 (79.4; 94.9) p<0.001  -FSIQ (VPA>800 mg): 80.3 (72.9; 87.6) p<0.001  -VCI (VPA>800mg): 83.0 (75.2; 90.8) p<0.05  -VSI: 85.3 (74.7; 95.8) p<0.05  -Exposure to VPA was associated with FSIQ in children (β, − 12.04; p = 0.006) and Verbal Comprehension Intelligence (β, − 8.89; p = 0.019). | -Prenatal VPA exposure is associated with decreased cognitive performance. |
| Kawai et al., 2023 | Japan | Prospective Cohort Study | -Anatomical | 91,664 | -Age Range: <25 - >40  -Mean Age: 23.11 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Japan Environmental and Children's Study (JECS) Group | N/A | 2 years | -aOR (Valproic acid and CHD): 4.86 [95% CI, 1.51–15.64]) p = 0.008  -Multivariable sensitivity analysis (VPA and CHD): 5.15 (1.60–16.58) p = 0.006 | -Prenatal VPA exposure is associated with CHDs. |
| Keni et al., 2018 | India | Prospective Cohort Study | -Anatomical | 1,688 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Kerala Registry of Epilepsy and Pregnancy (KREP) | N/A | 1 year | -RR (MCM VPA dual therapy vs LTG monotherapy): 5.43, 95% CI 0.72–40.81  -RR (MCM VPA monotherapy vs LTG monotherapy): 1.76, 95% CI 1.11–2.80  -RR (MCM VPA and phenobarbitone dual therapy vs. LTG monotherapy): 12.7, 95% CI 1.64–97.55  -RR (MCM VPA and clobazam dual therapy vs. LTG monotherapy): 7.6, 95% CI 0.56–103.78  -RR (MCM AED dual therapy vs. LTG monotherapy, excluding VPA and topiramate): 1.78, 95% CI 1.00–3.15 | -VPA dual therapy is associated with increased risk of MCM. |
| Kini et al., 2006 | UK | Retrospective Cohort Study | -Anatomical  -Cognitive | 375 | -Age Range: NR  -Mean Age: NR | -Age Range: 6 months - 16 years  -Mean Age: NR  -Sex (%Female/%Male): NR | Central Manchester Maternity Hospital | -Wechsler Intelligence Scale for Children (WISC‐III) | NR | -OR (VPA and Major Malformations): 4.04 (1.19 to 13.74)  -OR (VPA and Deformations): 1.65 (0.46 to 5.96)  -Verbal IQ and dysmorphic features in VPA exposed children (Spearman's ρ  =  −0.436, p  =  0.007) | -In VPA exposed children, verbal intelligence quotient is negatively correlated with dysmorphic facial features. |
| Kishk et al., 2019 | Egypt | Cross-Sectional Study | -Cognitive | 80 | -Age Range: NR  -Mean Age: 33.18 | -Age Range: 5-16  -Mean Age: 8.8  -Sex (%Female/%Male): NR | Cairo University Epilepsy Unit and Kasr Al Ainy Child Psychiatry Unit | -Arabic Version of Child Behavior Checklist (CBCL) - emotional/behavioral functioning | N/A | Linear regression analysis (VPA and IQ):  -Beta: -1.578 (p=0.039)  -OR (vs. controls): 0.206 (0.046 - 0.926)  VPA is associated with a lower (Mean (SD) exposure vs. inexposure):  -Verbal IQ: 80.15 (19.6) vs. 88.38 (4.15) (p=0.005)  -Performance IQ: 84.26 (12.57 vs. 101.62 (10.1) (p<0.001)  -Global IQ: 80.44 (10.34) vs. 92.77 (6.1) (p=0.001) | -Prenatal VPA exposure is associated with lower IQ. |
| Li et al., 2023 | China | Prospective Case-Control Study | -Anatomical  -Behavioural  -Cognitive  -Folic Acid | 781 | -Age Range: 20-45  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Chinese Clinical Trial Registry | -Child Neuropsychological Development Scale-Revised 2016 (CNBS-R2016) | 1 year | -VPA and Low Birth Weight: OR 3.141 (1.703-5.794), Kappa: 0.147 (< 0.001), χ2: 14.623(< 0.001)  -VPA and Neuropsychiatric Developmental Delay: OR 2.535 (1.202-5.348), Kappa 0.099, χ2: 5.158 (p=0.023)  -Folic acid dosage and adverse outcome (r = −0.102, P = 0.004) | -Prenatal VPA exposure is associated with low birth weight and neuropsychiatric developmental delay.  -Folic acid supplementation is inversely correlated with adverse outcomes in pregnancy (Not specific to AED associated outcomes). |
| Mahwhinny et al., 2012 | UK | Prospective Cohort Study | -Anatomical | 1,109 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | UK Epilepsy and Pregnancy Register | NR | NR | -MCM rate and VPA exposures: 6.7% (95% CI: 5.2–8.2%)  -mCMs rate and VPA exposure: 7.7% (95% CI: 6.1–9.3%) | -Prenatal VPA exposure is associated with an increased risk of malformation. |
| Mahwhinny et al., 2013 | UK, Ireland | Prospective Cohort Study | -Anatomical  -Folic Acid | 671 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 44.7/44.4 (10.9% missing) | UK and Ireland Epilepsy and Pregnancy Registers | NR | 3 months | -RR (MCM VPA exposed vs. controls): 1.41 (95 CI 1.9–22.0)  -AED monotherapy: 50% of MCM took folic acid, 61% without MCM took folic acid (p=1.00)  -AED polytherapy: 55% of MCM took folic acid, 52.5% without MCM took folic acid (p=0.81) | -Prenatal VPA exposure is associated with an increased risk of MCM.  -Folic acid supplementation is not effective in reducing AED polytherapy associated MCM. |
| Maskova et al., 2011 | Czech Republic | Retrospective Case-Control Study | -Anatomical | 14,428 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Czech National Registry of Congenital Abnormalities | NR | NR | -OR VPA (CAs and deformities in the musculoskeletal system): 3.6 1.1 -12 (p<0.05) | -Prenatal VPA exposure is associated with CA and deformities in the musculoskeletal system. |
| Mastroiacovo et al., 1988 | Italy | Prospective Cohort Study | -Anatomical | 349 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Italian Multicentric Registry on Birth Defects (IPIMC) | NR | NR | VPA (P>0.05):  -Birthweight: 3.177 +/- 377  -Head Circumference: 34.2 +/- 0.8  -Length: 47.1 +/- 4.1 | -Prenatal VPA exposure is associated with a lower mean birth weight and small head circumference (Not statistically significant). |
| Mavrogenis et al., 2013 | Hungary | Prospective Case Control Study | -Anatomical | 38,948 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Hungarian Congenital Abnormality Registry | N/A | 3 months | -OR (Isolated hypospadias VPA exposed vs. controls): 1.97, 95% CI 1.07-3.61 | -Prenatal VPA exposure is associated with increased risk of isolated hypospadias. |
| Mawer et al., 2013 | UK | Prospective Cohort Study | -Anatomical | 512 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Antenatal clinics at 11 National Health Service (NHS) hospitals within Merseyside and Greater Manchester | N/A | 6 years | -OR (VPA monotherapy and MCM): 5.94 (1.84 – 19.19), p =0.01  -OR (VPA polytherapy and MCM): 9.30 (2.43 – 35.66), p= 0.004  -OR (VPA and MCM): 6.94 (2.44 – 16.20), p= 0.001  -OR (MCM in AED exposed + folic acid vs. controls): 0.99, CI 0.32–3.07, p = 1.00 | -Prenatal VPA exposure is associated with increased risk of MCM.  -Folic acid supplementation is not associated with a reduced risk of MCM. |
| McVearry et al., 2009 | USA | Prospective Cohort Study | -Cognitive | 42 | -Age Range: 18–35  -Mean Age: NR | -Age Range: 3.5 – 5.5  -Mean Age: 4.2 years +/- 0.5  -Sex (%Female/%Male): 45.3/54/7 | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | -Torrance Thinking Creatively in Action and Movement - cognitive fluency and originality  -Differential Abilities Scale (DAS-II Preschool Version) - psychometric intelligence, convergent intelligence | 4.5 years | -Fluency was lower in the VPA group (mean=76.3; SD=7.53) vs. LTG (mean=93.76; SD=13.5; ANOVA p<0.0015) and CBZ (mean=95.5; SD=18.1; ANOVA p<0.003).  -Originality was lower in the VPA group (mean=84.2; SD=3.23) vs. LTG (mean=103.1; SD=14.8; ANOVA p<0.002) and CBZ (mean=99.4; SD=17.1; ANOVA p<0.01). | -Prenatal VPA exposure is associated with impaired fluency and originality relative to other AEDs. |
| Meador et al., 2006 | USA, UK:  -80% Caucasian  -4% Black  -10% Hispanic  -5% Other | Prospective Cohort Study | -Anatomical | 333 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study | N/A | 6 years | -(MCM prevalence and VPA) (p ≤ 0.0003)  -RR (CM VPA vs CBZ): 4.59 (1.58, 15.34)  -RR (CM VPA vs LTG): 22.82 (4.25, 424.20)  -RR (CM VPA vs PHT): 2.87 (0.91, 11.02) | -Prenatal VPA exposure is associated with increased risk of MCM relative to CBZ, LTG, and PHT. |
| Meador et al., 2009 | USA, UK | Prospective Cohort Study | -Cognitive | 258 | -Age Range: NR  -Mean Age: NR | -Age Range: 2-3 years  -Mean Age: NR  -Sex (%Female/%Male): NR | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | -Mental Developmental Index of the Bayley Scales of Infant Development, second edition - cognitive outcomes  -Differential Ability Scales - cognitive outcomes | 3 years | -On average, children exposed to VPA had an IQ score 9 points lower than the score of those exposed to LTG (95% confidence interval [CI], 3.1 to 14.6; P = 0.009), 7 points lower than the score of those exposed to PHT (95% CI, 0.2 to 14.0; P = 0.04), and 6 points lower than the score of those exposed to CBZ (95% CI, 0.6 to 12.0; P = 0.04).  -In analyses assessing associations between the average dose of an antiepileptic drug in pregnancy and a child’s IQ at the age of 3 years, only the doses of VPA was significantly correlated with IQ (r = −0.38, P = 0.005). | -Prenatal VPA exposure is associated with an increased risk of impaired cognitive function at 3 years of age relative to other commonly used AEDs. |
| Meador et al., 2012 | USA, UK:  -80% Caucasian  -4% Black  -10% Hispanic  -5% Other | Prospective Cohort Study | -Cognitive | 203 | -Age Range: NR  -Mean Age: 30 | -Age Range: 51 - 61 months  -Mean Age: NR  -Sex (%Female/%Male): NR | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | -Differential Ability Scales (DAS)  -Bayley Scales of Infant Development (BSID) | 4.5 years | -From age 3 to 4.5, IQ improved for CBZ (p = 0.008), LTG (p < 0.0001), and PHT (p = 0.002), but not VPA (p = 0.57).  -At age 4.5, 10% of children exposed to VPA had marked intellectual impairment compared to 0%–4% for other AEDs (p = 0.0064).  -Difference in verbal vs. nonverbal scores VPA: 10.6 (5.5-15.7) (p<0.0001) | -Prenatal VPA exposure is associated with poorer IQ and intellectual impairment. |
| Meador et al., 2011 | USA, UK:  -82% Caucasian  -4% Black  -9% Hispanic  -5% Other | Prospective Cohort Study | -Cognitive  -Folic Acid | 211 | -Age Range: NR  -Mean Age: 30 | -Age Range: 36–45 months  -Mean Age: NR  -Sex (%Female/%Male): NR | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | -Differential Ability Scales  -Preschool Language Scale (4th edition)  -Peabody Picture Vocabulary Test (fourth edition)  -Developmental Test of Visual-Motor Integration (fifth edition) | 3 years | -Mean differences (95% CI) between non-verbal and verbal indices for valproate (Using a linear model controlling for maternal IQ, dose, age of mother, alcohol use, race and folate): 14.6 (9.3, 19.8), p < 0.0001.  - Mean verbal and non-verbal index scores for children exposed in utero to valproate were significantly lower than all other AEDs combined (P ≤  0.0001) and across all individual pairwise comparisons: carbamazepine (P = 0.0009), lamotrigine (P ≤ 0.0001) and phenytoin (P = 0.0006).  -Valproate pearson correlation: Verbal Index −0.48 (0.001), Non Verbal Index: 0.39 (0.010)  Valproate Partial Pearson Correlations:  -Preschool Language Scale (expressive communication): −0.41 (0.006)  -Preschool Language Scale (auditory comprehension): −0.51 (0.0004)  -Differential Ability Scales (naming vocabulary): −0.45 (0.003)  -Differential Ability Scales (verbal comprehension): −0.38 (0.01)  -Peabody Picture Vocabulary: −0.39 (0.01)  -Differential Ability Scales (block building) : −0.47 (0.002)  -Preconception Folate and Verbal and Non Verbal Index Scores (Not specific to AED or VPA exposure): F value: 3.33, df: 2 , p=0.0379 | -Prenatal VPA exposure is associated with poor non-verbal and verbal performance (Dose-dependent).  -Preconceptional folate may improve cognitive outcomes (Not specific to AED or VPA exposed pregnancies). |
| Meador et al., 2013 | USA, UK:  -80% Caucasian  -5% Black  -10% Hispanic  -5% Other | Prospective Cohort Study | -Cognitive  -Folic Acid | 311 | -Age Range: NR  -Mean Age: NR | -Age Range: 70-87 months  -Mean Age: 74 months  -Sex (%Female/%Male): NR | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | -Differential Ability Scales (DAS)  -Bayley Scales of Infant Development (BSID)  -Children’s Memory Scale (CMS)  -The Behavior Rating Inventory of Executive Function (BRIEF)  -The Developmental Neuropsychological Assessment (NEPSY)  -The Expressive One-Word Picture Vocabulary Test  -The Developmental Test of Visual Motor Integration (DTVMI) | 6 years | -Multivariate analysis of all children showed that age-6 IQ was lower after exposure to valproate (mean 97, 95% CI 94–101) than to carbamazepine (105, 102–108; p=0·0015), lamotrigine (108, 105–110; p=0·0003), or phenytoin (108, 104–112; p=0·0006).  -High doses of valproate were negatively associated with IQ (r=–0·56, p<0·0001), verbal ability (r=–0·40, p=0·0045), non-verbal ability (r=–0·42, p=0·0028), memory (r=–0·30, p=0·0434), and executive function (r=–0·42, p=0·0004), BRIEF parent index (r=0·35, p=0·0212 [higher score is worse for BRIEF]).  -Right-handedness was less frequent in valproate groups (38 [79%] of 40; p=0·0089). Right-handed frequency was lower for valproate than carbamazepine (54 [93%] of 58 were right-handed; p=0·0284), but not statistically lower than for phenytoin (34 [89%] of 38; p=0·0641).  Mean IQ Difference from VPA:  -CBZ: 7 (3–12) 0·0015  -LTG: 10 (6–15) 0·0003  -Phenytoin: 10 (5–16) 0·0006  -Adjusted mean relative to VPA  -Verbal index CBZ: 104 (102–107) p= 0·0005  -Verbal Index LTG: 105 (102–107) P= 0·0003  -Verbal Index PHE: 106 (102–109) p=0·0005  -Non verbal index LTG: 108 (105–110) p= 0·0015  -Non verbal minue verbal LTG: 2·82 (0·31 to 5·33) p=0·0280  -Non verbal - verbal VPA 4·37 (1·24 to 7·49) p=0·0063  -General memory index: 104  (100–108) p = 0·0010  General memory index LTG: 106  (102–110) p = 0·0003  General memory index PHE: 101  (96–107) p = 0·0260  Executive index LTG: 107  (104–109) p = 0·0078  Linear Regression Analysis:  -Verbal Index: valproate worse than carbamazepine (p=0·0005), lamotrigine (p=0·0003), and phenytoin (p=0·0005).  -Non-verbal Index: valproate worse than lamotrigine (p=0·0015) with trends toward worse than carbamazepine (p=0·0818) and phenytoin (p=0·0514).  -Mean child IQ (periconceptional folate + VPA exposure): 98 (95% CI 94–103)  -Mean child IQ (VPA exposure): 96 (95% CI 91–102) | -Prenatal VPA exposure is associated with reduced cognitive abilities (IQ, verbal ability, non-verbal ability, executive function) (Dose-dependent).  -Periconceptual folate is associated with a higher mean IQ (Not AED specific). |
| Medveczky et al., 2004 | Hungary | Retrospective Case-Control Study | -Anatomical | 61,828 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) | NR | 1 year | OR (VPA and NTD): 3.9 (1.0-16.1) (Patient controls)  OR (VPA and NTD): 11.1 (2.2-57.5) (Population controls) | -Prenatal VPA exposure is associated with an increased risk of NTD. |
| Morrow et al., 2005 | UK | Prospective Cohort Study | -Anatomical | 3,607 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | UK Epilepsy and Pregnancy Register | N/A | 3 months | -aOR (MCM VPA exposed vs. controls): 2.97 (1.65 to 5.35) p<0.001  -OR (MCM VPA polytherapy vs. controls): 2.49 (1.31 to 4.70) | -VPA polytherapy is associated with increased risk of MCM. |
| Morrow et al., 2008 | UK | Prospective Cohort Study | -Folic Acid | 4,680 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | UK Epilepsy and Pregnancy Register | NR | 3 months | -MCM prevalence + preconceptual folic acid: 3.9%; 95% CI 3.1 to 4.9  -NTD prevalence + preconceptual folic acid: 0.4%; 95% CI 0.2 to 0.8  -MCM prevalence + late folic acid administration: 2.2%; 95% CI 1.7 to 2.9  -NTD prevalence + late folic acid administration: 0.34%; 95% CI 0.2 to 0.7  -NTD prevalence (VPA + periconceptual folic acid): 0.8% (95% CI 0.3–2.2)  -NTD prevalence (VPA) 1.7% (95% 0.7–3.4)  -MCM prevalence (VPA + periconceptual folic acid): 5.3% (95% CI 3.5–8.0)  -MCM prevalence (VPA): 4.3% (95% CI 2.8–6.8) | -Folic acid supplementation did not reduce risk of fetal malformations in monotherapy with commonly used AEDs. |
| Nadebaum et al., 2011 | Australia | Prospective Cohort Study | -Cognitive | 57 | -Age Range: NR  -Mean Age: NR | -Age Range: 6-8  -Mean Age: NR  -Sex (%Female/%Male): 47.3/52.7 | Australian Pregnancy Register | -Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) | 8 years | -Mean Full-Scale IQ scores in the VPA monotherapy (M = 94.3, SD = 13.1) and VPA polytherapy (M = 81.0, SD = 17.5) fell significantly below the test mean, p < .05.  -Working Memory index scores fell below the expected level for VPA polytherapy and monotherapy , p ≤ .031.  -VPA polytherapy demonstrated significantly impaired scores on the Processing Speed Index (p = .005).  -There was a significant negative correlation between mean VPA dose and Verbal Comprehension scores, r = −0.265, p = 0 .046. | -Prenatal VPA exposure is associated with negative impact of verbal abilities (dose-dependent), and may also affect working memory. |
| Nadebaum et al., 2011 | Australia | Prospective Cohort Study | -Cognitive | 57 | -Age Range: NR  -Mean Age: NR | -Age Range: 6-8  -Mean Age: NR  -Sex (%Female/%Male): 47.3/52.7 | Australian Pregnancy Register | -Wechsler Intelligence Scale for Children, Fourth Edition (WISC - IV)  -Wechsler Abbreviated Score of Intelligence (WASI) | 8 years | -Full-Scale IQ scores in the VPA monotherapy (M = 94.3, SD = 13.1), and VPA polytherapy (M = 81.0, SD = 17.5) fell significantly below the test mean (p < .05).  -VPA dose and Verbal Comprehension scores: r = −0.265, p = 0.046 | -Prenatal VPA exposure is associated with impaired verbal intellectual abilities and working memory (Dose-dependent). |
| Nadebaum et al., 2011 | Australia | Prospective Cohort Study | -Cognitive | 100 | -Age Range: NR  -Mean Age: NR | -Age Range: 6-8 years  -Mean Age: 7.4 +/- 0.6  -Sex (%Female/%Male): 46/54 | Australian Pregnancy Register | -Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) | 8 years | -The proportion of language delay was highest in the VPA polytherapy group (60%). This was significantly higher than the general population rate of 16%( p < 0.001).  -Mean score of children exposed to VPA was significantly lower than expected (91.5 ± 17.0; t = −2.39, p = 0.026).  -The poorest core language scores were obtained by children in the VPA polytherapy group (73.4 ± 22.3; t = −4.63, p < 0.001),  -Children exposed to VPA monotherapy scored lower than children exposed to LTG monotherapy: ( F 1,30 = 5.54, p = 0.025)  -There was a significant negative correlation between mean first trimester VPA dose and core language scores in the children exposed to VPA (monotherapy or polytherapy): r = −0.46, p = 0.005.  -Group comparisons showed that first trimester VPA dose was higher in the VPA polytherapy group (1,527 ± 654 mg/day) than the VPA monotherapy group (952 ± 997 mg/day), F 1,36 = 5.10, p = 0.030.  -Linear regression analysis (adjusted R 2 = 0.23, F 7,90 = 5.17, p < 0.001) showed that core language scores were significantly predicted by first trimester VPA. | -Prenatal VPA exposure is associated with an increased risk of language impairment. |
| Pekoz et al., 2023 | Turkey | Prospective Cohort Study | -Anatomical | 759 | -Age Range: 19.0-47.0  -Mean Age: 31 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 48/49.4 (2.6% Missing Information) | Turkish Neurology Outpatient Clinics | N/A | 3 months | -OR (congenital malformation high dose VPA polytherapy vs. other high dose ASMs: 2.62, 95% CI: 0.97–7.06, p = .056  -OR (congenital malformation normal dose VPA polytherapy vs. other normal dose ASMs: 4.17, 95% CI: 0.80–21.77, p = .090  -OR (congenital malformation VPA monotherapy vs. other ASMs): 3.20 (1.02–9.99) (0.045) (congenital malformation)  -Multivariate Logistical Regression analysis CM and VPA Monotherapy >750mg: 4.10 (1.18–14.11), p = 0 .025  -Multivariate Logistical Regression analysis CM and VPA Polytherapy: 5.76 (1.51–22.10), p=0.011 | -Prenatal VPA exposure is associated with increased risk of CM. |
| Pennell et al., 2012 | USA, UK | Prospective Cohort Study | -Anatomical | 329 | -Age Range: NR  -Mean Age: 29.8 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 53/47 | Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study | N/A | 3 years | -The percent of neonates that had a 1-minute Apgar score less than seven differed by AED group (Fisher’s exact test; p=0.0015), poorest for VPA and best for LTG. | -Prenatal VPA exposure is associated with a transiently reduced Apgar score, and small birth size for gestational age. |
| Ren et al., 2023 | Denmark | Prospective Cohort Study | -Cognitive | 370,859 | -Age Range: <20 to >35  -Mean Age: NR | -Age Range:NR  -Mean Age: 16.1  -Sex (%Female/%Male): 49.9/50.1 | The Danish National Prescription Registry | -9th grade Danish and math scores | 16 years | Adjusted Z score (relative to ASM unexposed children):  -Danish: -0.13 (-0.23 to -0.03)  -Math:-0.08 (-0.20 to 0.03)  -Danish: -0.03 (-0.22 to -0.17) (mother's without epilepsy)  -Danish: -0.16 ((-0.28 to -0.05) (mother's with epilepsy)  -Math -0.13 (-0.27 to 0.00) mother's with epilepsy) | -Prenatal VPA exposure is associated with poor academic performance in adolescence. |
| Richards et al., 2019 | New Zealand | Retrospective Cohort Study | -Behavioural  -Cognitive | 606 | -Age Range: NR  -Mean Age: 29 | -Age Range: NR  -Mean Age:  -Sex (%Female/%Male): 48.6/51.1 | Three of New Zealand's administrative databases:  -The Pharmaceutical Collection  -The National Minimum Dataset (NMDS; hospital events)  -The B4SC database | -Parent-Completed Parental Evaluation of Developmental Status (PEDS) Questionnaire  -Strengths and Difficulties Questionnaire (SDQ) - Parent Completed (SDQP) | NR | -aRR (Strengths and Difficulties Questionnaire, Parent Completed (SDQP) VPA exposed vs. AED unexposed controls): 2.11 (1.23–3.63)  -aRR (Conduct >5 VPA exposed vs. AED unexposed controls): 1.87 (1.17–3.00) | -Prenatal VPA exposure is associated with an increased risk of abnormal behavioral development. |
| Rihtman et al., 2013 | Israel | Prospective Cohort Study | -Behavioural  -Cognitive | 124 | -Age Range: NR  -Mean Age: NR | -Age Range: 37-83 months  -Mean Age: NR  -Sex (%Female/%Male): 48.7/51.3 | Israeli Teratogen Information Service | -Stanford-Binet Intelligence Scales, Fifth Edition (SB5) - non-verbal IQ [NVIQ] and verbal IQ [VIQ]) and a full-scale general IQ score (GIQ)  -Developmental Coordination Questionnaire 2007 (DCDQ’07) - motor coordination  -Little Developmental Coordination Disorder Questionnaire (Little DCDQ) - motor coordination  -Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition (Beery) - visual-motor skills (for ages 2–18), visual motor integration (VMI), visual perception (VP) and motor coordination (MC)  -Miller Function & Participation Scales (M-FUN) - visual motor (VM), fine motor (FM) and gross motor (GM) score  -Sensory Profile (SP) - sensory processing abilities (for ages 3–10)  -Short Sensory Profile (SSP) - sensory processing abilities (for ages 3–10)  -Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) - executive functioning (EF) of children aged 2–5  -Behavior Rating Inventory of Executive Function (BRIEF) - executive functioning (EF) of children aged 5-18  -Conners’ Rating Scales–Revised (Conners’) - problem behaviors and attention (for ages 3–17) | NR | VPA:  -Berry score (MC): 29; 25.54 (26.54)  -MFUN score (FM): 29; 31.30 (24.18)  -MFUN score (GM): 29; 31.30 (24.18)  -SP registration: 29; 64.59 (7.72)  -SP Seeking: 29; 109.28 (9.95)  -SP sensitivity: 29; 85.83 (8.71)  -SP avoiding: 29; 117.41 (11.60)  -SSP total score: 29; 159.10 (15.34)  -BRIEF parent GEC: 28; 47.96 (10.12)  -Conners parent ADHD index: 29; 54.32 (32.13)  -Conner's parent CGI total: 29; 56.66 (30.02)  Correlation VPA:  -SP registration: −0.16 (p=0.43)  -MFUN GM: −0.46 (p=0.02)  -DCDQ total z score: −0.38 (p=0.06) | -Prenatal VPA exposure is associated with poor cognitive, motor, sensory, and behavioral function scores relative to lamotrigine. |
| Rodriguez-Pinilla et al., 2000 | Spain | Retrospective Case-Control Study | -Anatomical | 51,293 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Spanish Collaborative Study of Congenital Malformations (ECEMC) | N/A | N/A | -OR (Limb deficiencies VPA exposed vs. unexposed): 6.17 [CI 1.28–29.66, P = 0.023]  -OR (Limb anomalies VPA first trimester exposed vs. unexposed, non neural defect subgroup): 3.95 ( 1.24–13.94 ) p=0.015  -OR (Limb deficiencies VPA first trimester exposed vs. controls: :5.2 (1.04–23.41) p=0.04  -Logistic Regression Analysis: OR (Limb anomalies VPA exposed vs. unexposed): 3.59 (CI 1.10–11.78, P = 0.035)  -Logistic Regression Analysis: OR (Limb deficiencies VPA exposed vs. unexposed): 6.17 (CI 1.28–29.66, P = 0.023) | -Prenatal VPA exposure is associated with increased risk of CM. |
| Rodríguez-Pinilla et al., 2008 | Spain | Prospective Case-Control Study | -Anatomical | 46,846 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Spanish Collaborative Study of Congenital Malformations (ECEMC) | N/A | NR | -OR (VPA and hypospadias, multiple regression analysis): 5.71; 95% CI 1.78-18.36; p = 0.003) | -Prenatal VPA exposure is associated with an increased risk of hypospadia. |
| Samren et al., 2001 | Netherlands | Retrospective Cohort Study | -Anatomical | 1,411 | -Age Range: <20 - 35  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 47.8/52.1 | Four university hospitals and 24 non-university hospitals in the Netherlands | N/A | NR | -RR (Neural tube defect VPA vs 6 other antiepileptic drugs): 5.4; p = 0.004  -RR (Neural tube defect VPA vs 2 other antiepileptic drugs): 4.0; p = 0.03  -RR (Neural tube defect VPA vs carbamazepine)): 8.1; p=0.01  -RR (Hypospadias VPA vs 6 other antiepileptic drugs): 4.8; p=0.03  -RR (Hypospadias VPA vs 2 other antiepileptic drugs): 4.8; p =0.05 | -VPA monotherapy is associated with an increased risk of MCM (Dose-dependent). |
| Seshachala et al., 2021 | India | Retrospective Cohort Study | -Anatomical | 865 | -Age Range: 21.78- 30.58  -Mean Age: 26.18 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Kerala Registry of Epilepsy and Pregnancy (KREP) | N/A | 1 year | -MCM rate: VPA exposed: 20 (10.36) vs unexposed: 39 (4.99) (p=0.005)  -RR (MCM in VPA exposed vs. unexposed infants): 2.08, 95% confidence interval [CI] = 1.24–3.48  -Absolute risk (MCM in VPA exposed vs. unexposed infants): 5.37  -NNT (use non-VPA AED rather than VPA to avoid MCM): 19 (95% CI = 9–71) | -Prenatal VPA exposure is associated with increased risk of MCM. |
| Shalcross et al., 2011 | UK | Prospective Cohort Study | -Cognitive | 155 | -Age Range: NR  -Mean Age: NR | -Age Range: 3-24 months  -Mean Age: 14 months  -Sex (%Female/%Male): NR | UKEPR | -Griffiths Mental Development Scale (GMDS) | NR | Children exposed in utero to LEV had a higher mean score on the below scales when compared to children exposed to VPA:  -locomotor skills (p < 0.001)  -hand and eye coordination (p < 0.001)  -performance skills (p < 0.001)  -hearing and language (p = 0.01).  -overall developmental ability (p < 0.001) | -Prenatal VPA exposure is associated with a lower developmental quotient relative to LEV. |
| Shalcross et al., 2014 | UK | Cross-Sectional Study | -Behavioural  -Cognitive | 197 | -Age Range: NR  -Mean Age: 30.3 +/- 5.2 | -Age Range: 36-54 months  -Mean Age: 42 months  -Sex (%Female/%Male): 51.3/48.7 | UKEPR | -Griffiths Mental Development Scales (GMDS) - child development (locomotor, personal and social, eye and hand coordination, performance, and practical reasoning abilities)  -Reynell Developmental Language Scales (RDLS) - verbal comprehension and expressive language | N/A | Coefficient (SE) (95CI) VPA:  -Gross motor (vs. non-AED-exposed controls): -11.7 (3.9) (-19.4 to -4.1) (p=0.003)  -Gross motor (vs. LEV): -15.8 (4.4) (-24.1 to -7.1) p<0.001  -Language comprehension (vs. non-AED-exposed controls): -8.7 (2.1) ( -12.9 to -4.5) p<0.001  -Language comprehension (vs. LEV): -6.4 (2.3) (-11.0 - -1.8) p=0.005  -Expressive language (vs. LEV): -9.5 (2.6) (-14.7 to - 4.4) p<0.001 | -Prenatal VPA exposure is associated with poorer language and motor development scores relative to LEV. |
| Shi et al., 2022 | China | Retrospective Cohort Study | -Folic Acid | 123 | -Age Range: 25-29  -Mean Age: 27 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Xijing Hospital in Shaanxi Province, China | NR | 3 months | -OR (Adverse pregnancy outcomes folic acid supplementation vs. controls, univariate analysis): 0.335; 95 %CI, 0.147–0.764; p = 0.009  -OR (Adverse pregnancy outcomes folic acid supplementation vs. controls, multivariate analysis): 0.892; 95 % CI, 0.317–2.512; p = 0.829  -OR (Adverse pregnancy outcomes VPA vs. controls): 4.441; 95 % CI, 1.165–16.934; p = 0.029 | -VPA polytherapy is associated with an increased risk of adverse pregnant outcomes (Including spontaneous fetal loss, induced abortion, and MCM).  -Folic acid supplementation does not protect against adverse pregnancy outcomes. |
| Syvänen et al., 2020 | Finland | Prospective Case-Control Study | -Anatomical | 115 | -Age Range: <25 to 35>  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 45.6/54.4 | National Register of Congenital Malformations, the Medical Birth Register, and the Register on Induced Abortions, all maintained by the Finnish Institute for Health and Welfare | NR | NR | -Valproic acid was a risk factor for RRD (p = .002). | -Prenatal VPA exposure in the first trimester is associated with an increased risk of RDD. |
| Tennis & Eldridge, 2002 | -USA: (24%)  -UK (21%)  -Sweden (9%)  -Denmark (8%)  -Australia (6%)  -Remaining countries: Austria, Belgium, Canada, Czech Republic, Finland, France, Germany, Greece, Netherlands, Iran, Ireland, Israel, Italy, Lebanon, Malta, New Zealand, Norway, Poland, South Africa, Spain, and Turkey. | Prospective Cohort Study | -Anatomical | 492 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | The International Lamotrigine Pregnancy Registry | NR | NR | -Birth defects (VPA + lamotrigine polytherapy): 10%, 95% CI, 3.7–22.6%  -Birth defects, Lamotrigine polytherapy without VPA): 4.3%, 95% CI, 1.6–10.3% | -Prenatal LTG-VPA exposure is associated with increased risk of BD relative to LTG polytherapy without VPA and LTG monotherapy. |
| Thomas et al., 2008 | India | Prospective Cohort Study | -Anatomical | 462 | -Age Range: NR  -Mean Age: 25.6 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 47.4/52.6 | Kerala Registry of Epilepsy and Pregnancy (KREP) | N/A | 6 years | N/A | -Prenatal VPA exposure was associated with increased risk of CM relative to other AEDs (Not statistically significant). |
| Thomas et al., 2008 | India | Prospective Cohort Study | -Behavioural  -Cognitive | 395 | -Age Range: NR  -Mean Age: NR | -Age Range: 13.7 - 167.9 months  -Mean Age: 15.3 ± 4.4 months  -Sex (%Female/%Male): 47.9/52.1 | Kerala Registry of Epilepsy and Pregnancy (KREP) | -Developmental Assessment Scale for Indian Infants | NR | -MoDQ VPA (Infants with mothers with epilepsy): 86.1 (79.3–92.9) , p=0.031  -Pearson correlation coefficient (VPA monotherapy and MoDQ): –0.239, p = 0.042  -Pearson’s correlation coefficient (VPA monotherapy and MeDQ): = –0.093, p = 0.432 | -Folic acid supplementation during pregnancy does not influence infant mental (MeDQ) and motor (MoDQ) development quotients (Not specific to AED-exposed pregnancies).  -VPA monotherapy is associated with lower MoDQ in IME. |
| Thomas et al., 2017 | India | Prospective Cohort Study | -Anatomical | 1,688 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Selected Centers in Kerala, India | N/A | 1 year | -MCM prevalence & valproate dose: ≤400 mg/day: 3.2% , 401–800 mg/day: 10.1% , 801 + mg/day: 33.3% (p=0.001) | -Prenatal VPA exposure is associated with an increased risk of MCM (Dose-dependent). |
| Thomas et al., 2021 | India | Prospective Cohort Study | -Anatomical | 2,328 | -Age Range: 21.6-30.6  -Mean Age: 26.1 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Kerala Registry of Epilepsy and Pregnancy (KREP) | N/A | 1 year | -Incidence Rate Ratio: MCM and poly-therapy with high dose valproate: 4.12 ( 2.2–7.8 ) p <0.001 | -Polytherapy with high-dose valproate during the first trimester of pregnancy is associated with higher incidence of CM. |
| Tomsen et al., 2011 | Americas: 1%  Europe: 86%  Southeast Asia: 3%  Western Pacific: 10% | Prospective Cohort Study | -Anatomical | 4,424 | -Age Range: 14·1–44·3  -Mean Age: 29·7 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 49/49 (3% missing) | EURAP Study Group | N/A | 1 year | OR VPA vs. <300 LTG daily:  -Valproic acid (<700 mg per day): 2·8 (1·46–5·30) p=0·0019  -Valproic acid (≥700 to <1500 mg per day): 5·8 (3·27–10·13) p <0·0001  -Valproic acid (≥1500 mg per day): 16·1 (8·22–31·54) p <0·0001  -Valproic acid (≥700 to <1500 vs <700 mg per day): 2·1 (1·25–3·43) p= 0·0047  -Valproic acid (≥1500 vs <700 mg per day) 5·8 (3·07–10·92) p<0·0001 | -Prenatal VPA exposure is associated with an increased risk of malformation (Dose-dependent). |
| Tomson et al., 2015 | Europe, Asia, Australia, Americas | Prospective Cohort Study | -Anatomical | 1,558 | -Age Range: 14.1-45.8  -Mean Age: 29.04 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 49/51 | EURAP Study Group | N/A | 1 year | -MCM frequency: 10.0% for VPA monotherapy, 11.3% for VPA + LTG, and 11.7% for VPA + another (non-LTG) AED.  VPA dose is positively associated with MCM frequency:  - <700 mg/d: 5.9% for monotherapy, 7.0% for VPA + LTG, and 5.4% for VPA + other AEDs  - ≥1,500 mg/d: 24.0% for monotherapy, 31.0% for VPA + LTG, and 19.2% for VPA + other AEDs | -VPA dose is positively associated with MCM risk. Both in the presence and absence of a concomitant AED. |
| Tomson et al., 2018 | Americas: 1%  Europe: 87%  Southeast Asia: 3%  Western Pacific: 9% | Prospective Cohort Study | -Anatomical | 7,355 | -Age Range: 24.9-34.7  -Mean Age: 29·8 (SD 4.9) | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 49/51 | EURAP Study Group | N/A | 1 year | -Prevalence (MCM in Valproate Exposed (100-3000mg/d) vs. Controls): 9.9 (8.5-11.5)  -OR (MCM in 650-1450mg Valproate vs. <650mg): 2.06 (1.38-3.07) (p=0.001)  -OR (MCM in >1450 mg Valproate vs. <650mg): 5.63 (3.31 - 9.58) (p<0.001)  -OR (MCM in >1450 mg Valproate vs. 650-1450 mg): 2.74(1.68-4.44) (p<0.001)  Valproate Dose Dependency Analysis (p<0.001):  -OR (MCM in Valproate Exposed (<650mg) vs. Controls): 6.0 (4.4-8.0)  -OR (MCM in Valproate Exposed (650-1450mg) vs. Controls): 11.1 (8.9-13.6)  -OR (MCM in Valproate Exposed (>1450mg) vs. Controls): 25.2 (17.8-33.8) | -VPA at doses of 650 mg/day or less is associated with increased risk of MCM compared with levetiracetam at doses of 250–4000 mg/day. |
| Unnikrishnan et al., 2020 | India | Prospective Cohort Study | -Cognitive | 335 | -Age Range: NR  -Mean Age: 25.9 | -Age Range: 9-13  -Mean Age: NR:11.0  -Sex (%Female/%Male):48.2/51.2 | Kerala Registry of Epilepsy and Pregnancy (KREP) | -Developmental Assessment Scale for Indian Infants  -Wechsler Intelligence Scale for Children Version IV (WISC-IV)  -Malayalam Language Test | 6 years | -Intrauterine exposure to valproate (monotherapy or polytherapy) showed a negative effect on language performance (CLSS) in Children with Mothers with Epilepsy (CWE): −7.8, 95% CI = −13.3 to −2.2, p = .006.  -Valproate monotherapy showed a negative effect on CLSS in CWE: −6.3, 95% CI = −12.3 to −0.3, p = .04) showed a negative effect on CLSS.  -Valproate monotherapy was associated with lower CLSS score relative to healthy controls: −10.28, 95% CI = −14.4 to −6.2, p < .001. | -Prenatal VPA exposure impairs language development in children of women with epilepsy, with effects persisting into the second decade. |
| Vajda et al., 2003 | Australia | Prospective Cohort Study | -Anatomical  -Folic Acid | 292 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Australian Centre for Clinical Neuropharmacology, Raoul Wallenberg Centre, at St. Vincent’s Hospital Melbourne | NR | 9 months | -Incidence of folate supplementation being taken prior to conception did not differ for pregnancy outcomes with or without BD (70% vs. 66%, p=0.82).  -Valproate dose was higher in pregnancies with BD compared to those without (mean 2081 mg vs. 1149 mg, p<0.0001).  -Incidence of BD (birth defect) was non-significantly associated with VPA exposure (p=0.19). | -Pre-conception folic acid supplementation is not protective against AED-associated BDs.  -Prenatal VPA exposure is associated with an increased risk of BD (Dose-dependent). |
| Vajda et al., 2003 | Australia | Prospective Cohort Study | -Anatomical  -Folic Acid | 630 | -Age Range: NR  -Mean Age: 30.2 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Australian Pregnancy Registry | NR | 1 year | -VPA dose >1100mg/day & birth defects: b (regression coefficient) =2.0 , OR 7.3 (2.7–19.5), p<0.0001  -VPA >1100 mg/day & FM incidence (vs. no AED exposure): 15/39 (38.5%), p=0.000051  -The incidence of FMs in relation to folate is not statistically significantly different between folate exposed and not exposed groups (5.75% vs. 6.74%, difference = 0.998%, 95% CI=−3.40 to 5.38%). | -Prenatal VPA exposure in doses > 1100 mg/day is associated with increased risk of FM relative to other AEDs.  -Folate supplementation does not decrease AED-associated FM. |
| Vajda et al., 2004 | Australia | Prospective Cohort Study | -Anatomical | 403 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Australian Centre for Clinical Neuropharmacology, Raoul Wallenberg Centre, at St. Vincent's Hospital Melbourne | NR | 1 year | -The FM rate was greater in pregnancies exposed to sodium valproate (VPA) in the first trimester (16.0%) compared with those exposed to all other AEDs (16.0% vs. 2.4%, P<0.01) or no AEDs (16.0% vs. 3.1%, P<0.01).  -The mean daily dose of VPA taken in pregnancy with FMs was significantly greater than in those without (1975 mg vs. 1128 mg, P<0.01).  -The incidence of FM with VPA doses ⩾1100 mg was 30.2%, vs. 3.2% with doses <1100 mg (P<0.01). | -Prenatal VPA exposure is associated with an increased risk of FM relative to other AEDs (Dose-dependent). |
| Vajda et al., 2013 | Australia | Prospective Cohort Study | -Anatomical | 1,243 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Australian Register of Antiepileptic Drugs in Pregnancy | N/A | 1 year | -OR (Fetal malformation VPA vs.other AEDs: 3.24; 95% CI 2.03–5.15  -OR (Fetal malformation first postindex pregnancies VPA vs.other AEDs): 6.07; 95% CI 1.7–21.7  -OR (Fetal malformations first postindex pregnancies VPA vs. controls, (index resulted in fetal malformation subgroup): 17.8; 95% CI 2.7-119.1  -OR (Fetal malformations VPA exposed vs. AED unexposed children): 6.80, 95% CI 2.08–22.2 | -Prenatal VPA exposure is associated with increased risk of FM. |
| Vajda et al., 2013 | Australia | Prospective Cohort Study | -Anatomical | 1,705 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | Australian Register of Antiepileptic Drugs in Pregnancy | N/A | 1 year | -Mean dose of valproate taken during the first trimester was higher in mothers whose offspring had spina bifida (2,000 ± 707 vs 1,257 ± 918 mg/d, p < 0.05) and hypospadias (2,417 ± 1,320 vs 1,235 ± 715 mg/d, p < 0.05). | -Reduction in VPA dose in early pregnancy is protective against spina bifida and hypospadias relative to other forms of fetal malformation (Ex. cleft lip, heart septal defect). |
| Vajda et al., 2018 | Australia | Prospective Cohort Study | -Anatomical  -Folic Acid | 2,148 | -Age Range: 26.31 - 35.61  -Mean Age: 30.96 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Australian Pregnancy Register (APR) | N/A | 1 year | -Logistic regression partial correlation coefficients (VPA and spina bifida): +0.0010, p <0.01  -OR (Fetal malformation and AED exposure, excluding VPA and topiramate): 0.53; 95% C.I. 0.27, 1.01  -RR: (Malformation rate and preconception folate): 1.02; 95% C.I. 0.69, 1.55 | -Pre-conception folate is not effective in reducing AED-associated teratogenicity.  -VPA is associated with increased risk of MCM (Dose-dependent).  -AED polytherapy does not increase malformation risk without VPA and topiramate. |
| Vajda et al., 2019 | Australia | Prospective Cohort Study | -Anatomical | 602 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | Australian Pregnancy Register (APR) | N/A | 1 year | -Multivariable logistical regression analysis: Fetal malformations and VPA dose (P<0.05) | -Prenatal VPA exposure is associated with increased risk of CM. |
| Vajda et al., 2020 | Australia | Retrospective Cohort Study | -Anatomical | 580 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Australian Pregnancy Register (APR) | NR | 1 year | -HR (Fetal Malformation Rate VPA Changed Dosage vs. VPA Unchanged Dosage): 0.412, 95% CI 0.190-0.892  -HR (Fetal Malformation Rate VPA Ceased Pregnancies vs. VPA Reduced Pregnancies (VPA Changed Dosage Subgroup): 0.262, 95% CI 0.083-0.826)  -HR (Seizures VPA Changed Dosage vs. VPA Unchanged Dosage): 1.500, 95% CI 1.203- 1.870 | -Prepregnancy reduction in VPA dosage reduced the hazard of FM.  -Ceasing or reducing VPA dose is associated with decreased epileptic control of prepregnancy seizures. |
| Vajda et al., 2021 | Australia | Prospective Cohort Study | -Folic Acid | 2,104 | -Age Range: 16-48 years  -Mean Age: 31.01 ± 4.58 years | -Age Range: NR  -Mean Age:NR  -Sex (%Female/%Male): NR | Australian Pregnancy Register (APR) | NR | NR | -Multiple variable logistic regression failed to demonstrate any statistically significant effect of folic acid dosage in reducing overall fetal malformation rates in women taking folic acid either before and during pregnancy (P = 0.640) or during early pregnancy only (P = 0.801), and in reducing spina bifida occurrence rates (P = 0.409). | -Folic acid supplementation failed to demonstrate a significant effect in reducing VPA-associated fetal malformations. |
| Vegrim et al., 2022 | Denmark, Norway, Sweden | Prospective Cohort Study | -Folic Acid | 3,379,171 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): 48.6/51.4 | National Medical Birth Registers in Denmark, Norway, and Sweden | -International Classification of Childhood Cancer, Third Edition - cancer diagnosis | NR | -aHR (Cancer Risk in High Dose Folic Acid Exposed Mothers With Epilepsy vs. Unexposed): 2.7 (95% CI, 1.2-6.3)  -Absolute Risk if Exposed to High Dose Folic Acid, Children Born to Mothers with Epilepsy + Anti Seizure Medication (ASM): 1.4% (95% CI, 0.5%-3.6%)  -Absolute Risk if Unexposed to High Dose Folic Acid, Children Born to Mothers with Epilepsy + ASM: 0.6% (95% CI, 0.3%-1.1%) | -Prenatal exposure to high-dose folic acid is associated with increased risk of cancer in children of mothers with epilepsy. |
| Veiby et al., 2013 | Norway | Prospective Cohort Study | -Behavioural | 503 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: NR  -Sex (%Female/%Male): NR | Norwegian Mother and Child Cohort Study (MoBa) (Norwegian Institute of Public Health) | -Ages and Stages Questionnaire - motor skills, communication skills  -Ages and Stages Questionnaire + Items from the Bayley Scales of Infant Development - social skills  -Infant Characteristics Questionnaire - difficult temperament  -Modified Checklist for Autism in Toddlers - autism  -Social Communication Score - autism  -Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) - ADHD  -Child Behavior Checklist - aggression, ADHD  -MoBA Checklist - ADHD | NR | N/A | -Prenatal VPA exposure is not significantly associated with fine motor impairment, gross motor impairment, or social impairment. |
| Veiby et al., 2013 | Norway | Prospective Cohort Study | -Behavioural | 107,597 | -Age Range: NR  -Mean Age: NR | -Age Range: N/A  -Mean Age: 18 or 36 months  -Sex (%Female/%Male): NR | Norway Medical Birth Registry | -Ages and Stages Questionnaire (ASQ)  -MoBa Questionnaire - mothers’ reports on motor development, language, and social behaviour  -Modified Checklist for Autism in Toddlers (M-CHAT)  -14-item Early Screening of Autistic Traits questionnaire (ESAT)  -Child Behaviour Checklist - aggression, ADHD  -ADHD criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) | 3 years | -OR (Gross mother skills at 18 months, children of epileptic mothers): 7.0 (2.4–21.0) (p<0.05)  -OR (Sentence skills at 36 months, children of non- epileptic mothers): 3.4 (1.0–12.0) (p<0.05) | -Prenatal VPA exposure is associated with adverse developmental outcomes (Gross motor skills, sentence skills). |
| Veiby et al., 2014 | Norway | Retrospective Cohort Study | -Anatomical | 776,098 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): NR | Medical Birth Registry of Norway | N/A | NR | -OR (VPA Monotherapy and MCM): 2.47 (1.58–3.84) p<0.001  -OR (VPA polytherapy and MCM): 2.03 (0.74–5.56) p= 0.17 | -VPA monotherapy was associated with increased risk of MCM, but not polytherapy. |
| Videman et al., 2016 | Finland | Prospective Cohort Study | -Cognitive | 123 | -Age Range: NR  -Mean Age: NR | -Age Range: 6.50-8.25 months  -Mean Age: 7.25 months  -Sex (%Female/%Male): NR | Helsinki University Hospital | -Griffiths Mental Developmental Scale - developmental status | 7 months | -VPA and mean VIQ: 109, range: 87–122, SD: ± 14, p = 0.59  -VPA and mean PIQ 113, 100–119, ± 9, p = 0.07  -VPA and hearing and speech: 79 (65–89, 10, p = 0.005)  -VPA and general quotient (general development): 88 (77–96, 9,p = 0.008) | -Prenatal VPA exposure is associated with impaired language abilities, observable at 7 months of age. |
| Vinten et al., 2005 | UK | Retrospective Cohort Study | -Cognitive | 256 | -Age Range: NR  -Mean Age: NR | -Age Range: 6-16  -Mean Age: 10.4  -Sex (%Female/%Male): 46/54 | Specialist epilepsy clinics and obstetric clinics from the Liverpool and Manchester region | -The Wechsler Intelligence Scale for Children III (WISC-III)  -Rivermead Behavioral Memory Test for Children (RMBTC) | 16 years | -OR (Impaired VIQ VPA exposed vs. controls): 3.47 (1.14-10.56)  -Multiple regression analysis VPA and Verbal IQ (VIQ) association: ( p = 0.017)  -Children exposed to VPA in utero had a lower VIQ compared to CBZ ( p = 0.003), PHT (p = 0.002), and the non-exposed group ( p < 0.001).  -VPA group scored lower on the verbal comprehension subscale than the non-exposed group ( p = 0.02), CBZ ( p = 0.07), and PHT ( p = 0.04).  -The VPA group scored lower on the freedom from distractibility subscale than CBZ ( p = 0.01) and PHT (0.03).  -The differences between VPA and the other groups for the number of children classified in the mentally impaired range (IQ below 69) were significant (χ 2 for trend 8.431, df 1, p = 0.004). | -Prenatal VPA exposure is associated with harmful effects on neuropsychological development. |
| Wen et al., 2017 | USA | Retrospective Cohort Study | -Anatomical | 47,139 | -Age Range: 19.5-32.3  -Mean Age: 25.9 | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 51/49 | Florida Medicaid claims, Florida Birth Vital Statistics, Florida Birth Anomalies, and Florida Hospital Discharge Inpatient and Outpatient records | N/A | NR | -VPA rate of birth defects (BD) vs AED unexposed children (20% vs. 10.5%, p < .0001). | -Prenatal VPA exposure is associated with BD. |
| Wiggs et al., 2020 | Sweden |  | -Behavioural  -Cognitive | 6,428 | -Age Range: NR  -Mean Age: NR | -Age Range: NR  -Mean Age: 4  -Sex (%Female/%Male): NR | Swedish Register Data | N/A | NR | -aHR (ASD Valproic Acid Exposed vs. Controls): 2.66 (1.82-3.89)  -aHR (ADHD Valproic Acid Exposed vs. Controls): 1.77 (1.31-2.39)  -aHR (ASD Valproate Monotherapy vs. Controls): 2.30 (1.53-3.47)  -aHR (ADHD Valproate Monotherapy vs. Controls): 1.74 (1.28-2.38) | -Prenatal VPA exposure is associated with an increased risk of ASD and ADHD. |
| Wood et al., 2015 | Australia | Prospective Cohort Study | -Behavioural  -Folic Acid | 105 | -Age Range: NR  -Mean Age: NR | -Age Range: 6-8  -Mean Age: NR  -Sex (%Female/%Male): NR | Australian Pregnancy Register | -Childhood Autism Rating Scale (CARS) - autism | NR | -CARS (Childhood Autism Rating Scale) score linear regression, folic acid first trimester: B coefficient (std error): −8.631 (2.830), t: −3.05 (p = 0.003)  -CARS score linear regression (Mean Valproate Dose): B (SE): 0.002 (0.001), t: 3.20 (p = 0.002)  -Children exposed to polytherapy with valproate scored significantly higher than all other groups (range of mean differences 7.55–9.42, p < 0.001).  -There was a significant relationship between CARS score and valproate monotherapy (r = 0.61, p = 0.001), but not polytherapy (r = −0.06, p > 0.1).  -Mothers of AED exposed children with autistic traits were less likely to have taken folic acid supplements in the first trimester (p = 0.028, Fisher's exact test). | -Periconceptional folic acid is associated with lower risk of autism in AED exposed children (Dose-dependent). |
| Wyszynski et al., 2005 | USA | Prospective Case-Control Study | -Anatomical | 3,441 | -Age Range: NR  -Mean Age: NR | -Age Range: Neonate  -Mean Age: Neonate  -Sex (%Female/%Male): 46.3/53.7 | North American Antiepileptic Drug Pregnancy Registry | N/A | 7 months | -RR (Malformation prenatal VPA exposure): 7.3 (95% CI: 4.4 to 12.2; p < 0.001) | -Prenatal VPA exposure during the first trimester is associated with an increased risk of malformation. |

a Abbreviations: ABAS = Adaptive Behavior Assessment System; ABC = Adaptive Behavior Composite; AED = Antiepileptic Drug; ADHD = Attention Deficit/ Hyperactivity Disorder; aHR = Adjusted Hazard Ratio; ANOVA = Analysis of Variance; aOR = Adjusted Odds Ratio; ASD = Autism Spectrum Disorder; ASM = Anti Seizure Medication; ASQ = Ages and Stages Questionnaires; b = regression coefficient; BASC = Behavior Assessment System for Children; Beery = Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition; BD = Birth Defect; BRIEF-P = Behavior Rating Inventory of Executive Function-Preschool Version; BSID - II = Bayley Scales of Infant Development - Second Edition (BSID – II); bw-adj-HC = birth-weight-adjusted mean head circumference; CA = Congenital Anomaly; CARS = Childhood Autism Rating Scale; CBCL = Child Behavior Checklist; CBZ = Carbamazepine; CELF-IV = Clinical Evaluation of Language Fundamentals—Fourth Edition; CGI = Conner’s Global Index; CLSS = Core Language Scaled Score; CMS = children’s memory scale; CHD= Congenital Heart Defect; Conners = Conners’ Rating Scales–Revised - Problem behaviors and attention; CI = Confidence Interval; CM = Congenital Malformation; CWE = Children with Mothers with Epilepsy; DAS = Differential ability scales; DCDQ = Developmental Coordination Questionnaire; df = Degrees of Freedom; DTVMI = developmental test of visual motor integration; F value = F statistic for Wilk’s Lambda; FM = Fetal Malformation; FSIQ = Full Scale IQ; FVS = Fetal Valproate Syndrome; GIQ = General IQ; ID = Intellectual Disability; IME = Infants of Mothers with Epilepsy; IQ = Intelligence Quotient; Language 20 = Norwegian instrument Twenty Statements about Language-related Difficulties; LEV = levetiracetam; LTG = Lamotrigine; M = mean; MC = Motor Coordination; MCM = Major Congenital Malformations; mCM = minor congenital malformation; MeDQ = Mental Developmental Quotient; MFUN = Miller Function & Participation Scales; MM = Major Malformation; MoDQ = Motor Developmental Quotient; N/A = Not Applicable; NDD = Neurodevelopmental Disorder; NEPSY = The developmental neuropsychological assessment; NNT = Number needed to Treat; NR = Not Reported; NTD = Neural Tube Defect; NVIQ = Non- Verbal IQ; p = p value; PDD = Pervasive Developmental Disorder; PHT = Phenytoin; r = correlation coefficient; RR = Risk Ratio; RRD = Radial Ray Deficiency; SCQ = Social Communication Score; SD = Standard Deviation; SDQP = Strengths and Difficulties Questionnaire, Parent Completed; SDS = Standard Deviation Score; SLAS = Speech and Language Assessment Scale; SP = Sensory Profile; SSP = Short Sensory Profile; t = t test; VCI = Verbal Comprehension Index; VIQ= Verbal IQ; VMI = Visual Motor Integration; VP = Visual Perception; VPA = Valproate; WISC - IV = Wechsler Intelligence Scale for Children—Fourth Edition

### 

### eTable 6. Measurement toolsa

|  |  |
| --- | --- |
| Measured Domain | Measurement Tools |
| Behaviour | Modified Checklist for Autism in Toddlers (M-CHAT), 14-item Early Screening of Autistic Traits Questionnaire (ESAT), Autism Spectrum Quotient–Children's Version (AQ-Child), National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale, General Movement Assessment (GMA), Motor Optimality Score-Revised (MOS-R), Parent-completed Parental Evaluation of Developmental Status (PEDS) questionnaire, Developmental Coordination Questionnaire (DCDQ), Developmental Test of Visual-Motor Integration, Fifth Edition (Beery), Miller Function & Participation Scales (M-FUN), Little Developmental Coordination Disorder Questionnaire (Little DCDQ), Behavior Rating Inventory of Executive Function (BRIEF), Childhood Autism Rating Scale (CARS), Motor Developmental Quotient (MoDQ), MoBA Questionnaire, Sensory Issues (Bespoke Set of Questions), Trail Making Test (TMT), The Developmental Test of Visual Motor Integration (DTVMI), Developmental Assessment Scale for Indian Infants |
| Cognitive | Modified Checklist for Autism in Toddlers (M-CHAT), 14-item Early Screening of Autistic Traits Questionnaire (ESAT), Autism Spectrum Quotient–Children's Version (AQ-Child), National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale, General Movement Assessment (GMA), Motor Optimality Score-Revised (MOS-R), Parent-completed Parental Evaluation of Developmental Status (PEDS) questionnaire, Developmental Coordination Questionnaire (DCDQ), Developmental Test of Visual-Motor Integration, Fifth Edition (Beery), Miller Function & Participation Scales (M-FUN), Little Developmental Coordination Disorder Questionnaire (Little DCDQ), Behavior Rating Inventory of Executive Function (BRIEF), Childhood Autism Rating Scale (CARS), Motor Developmental Quotient (MoDQ), MoBA Questionnaire, Sensory Issues (Bespoke Set of Questions), Trail Making Test (TMT), The Developmental Test of Visual Motor Integration (DTVMI), Developmental Assessment Scale for Indian Infants |
| Behaviour and Cognitive | Child Neuropsychological Development Scale-Revised 2016 (CNBS-R2016), Ages and Stages Questionnaire (ASQ), Reynell Developmental Language Scales (RDLS), Diagnostic and Statistical Manual of Mental Disorders – the fifth revision (DSM-5), Differential Ability Scales (DAS), Bayley Scales of Infant Development, Child Behaviour Checklist (CBCL), Speech and Language Assessment Scale (SLAS), Strengths and Difficulties Questionnaire (SDQ) - Parent Completed (SDQP), Conners’ Rating Scales–Revised (Conners’), Social Emotional Questionnaire, Adaptive Behavior Assessment System—Second Edition (ABAS-II), Behavior Assessment System for Children - second edition (BASC-II), Schedule of Growing Skills II (SGSII), Vineland Adaptive Behavior Scales, Second Edition (Vineland-II), MacArthur Health Behaviour Questionnaire (HBQ) ,The Developmental Neuropsychological Assessment (NEPSY), Griffiths Mental Development Scale (GMDS), Peabody Picture Vocabulary Test (fourth edition), Lindeboom, Malayalam Language Test, The Expressive One-Word Picture Vocabulary Test, Clinical Evaluation of Language Fundamentals—Fourth Edition (CELF-IV), Norwegian instrument Twenty Statements about Language-related Difficulties (Language 20) |

a Number of scales = 62

### eTable 7. Results of study quality appraisal of included cohort studies

| Study | Selection |  |  |  | Comparability | Outcome |  |  | Score /9 | Quality Rating |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Representativeness of the Exposed Cohort | Selection of the Non-Exposed Cohort | Ascertainment of Exposure | Demonstration That Outcome of Interest Was Not Present at Start of Study | Comparability of Cohorts on the Basis of the Design or Analysis | Assessment of Outcome | Was Follow-Up Long Enough for Outcomes to Occur? | Adequacy of Follow Up of Cohorts |  |  |
| Adab et al., 2001 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Adab et al., 2004 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Almgren et al., 2009 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Aratma et al., 2005 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Baker et al., 2015 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | High |
| Ban et al., 2015 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Bansal et al., 2018 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Barton et al., 2018 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Battino et al., 1992 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Battino et al., 2024 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Bjork et al., 2018 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Bjork et al., 2022 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Blotiere et al., 2019 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Blotiere et al., 2020 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Bromley et al., 2013 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Campbell et al., 2013 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Campbell et al., 2014 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Charleton et al., 2017 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Christensen et al., 2013 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | High |
| Christensen et al., 2015 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Christensen et al., 2019 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Christensen et al., 2021 | \* | \* | \* |  | \* | \* | \* | \* | 8/9 | High |
| Christensen et al., 2024 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | High |
| Cohen et al., 2011 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Cohen et al., 2013 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Cohen et al., 2019 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Cohen et al., 2023 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | High |
| Coste et al., 2020 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | High |
| Daugaard et al., 2020 | \* | \* | \* |  | \*\* | \* | \* | \* | 8/9 | High |
| Deshmukh et al., 2016 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Diav-Citrin et al., 2008 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Dreier et al., 2023 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Dreier et al., 2024 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | High |
| Elkjaer et al., 2018 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Erikkson et al., 2005 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Guveli et al., 2017 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Hernandez-Diaz et al., 2024 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Holmes et al., 2011 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Honybun et al., 2021 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Huber-Mollema et al., 2019 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Huber-Mollema et al., 2020 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Husebye et al., 2018 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Husebye et al., 2019 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Kaaja et al., 2003 | \* | \* | \* |  | \* | \* | \* |  | 5/9 | Moderate |
| Kaneko et al., 1988 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Kaneko et al., 1999 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Kasradze et al., 2017 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | High |
| Kawai et al., 2023 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Keni et al., 2018 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Kini et al., 2006 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Laiber et al., 2012 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Mahwhinny et al., 2012 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Mahwhinny et al., 2013 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Mastroiacovo et al., 1988 | \* | \* | \* |  | \* | \* | \* |  | 5/9 | Moderate |
| Mawer et al., 2013 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| McVearry et al., 2009 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Meador et al., 2006 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Meador et al., 2009 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Meador et al., 2011 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Meador et al., 2023 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Morrow et al., 2005 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Morrow et al., 2008 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Nadebaum et al., 2011 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Nadebaum et al., 2011 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Nadebaum et al., 2011 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Pekoz et al., 2023 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Pennell et al., 2012 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Ren et al., 2023 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Richards et al., 2019 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Rihtman et al., 2013 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Samren et al., 2001 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Seshachala et al., 2021 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Shalcross et al., 2011 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Shi et al., 2022 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Tennis & Eldridge, 2002 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Thomas et al., 2008 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Thomas et al., 2008 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Thomas et al., 2017 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Thomas et al., 2021 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Tomsen et al., 2011 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Tomson et al., 2015 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Tomson et al., 2021 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Unnikrishnan et al., 2020 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Vajda et al., 2003 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Vajda et al., 2003 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Vajda et al., 2004 | \* | \* | \* |  |  | \* | \* | \* | 6/9 | Moderate |
| Vajda et al., 2013 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Vajda et al., 2013 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Vajda et al., 2018 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Vajda et al., 2019 | \* | \* | \* |  |  | \* | \* | \* | 6/9 | Moderate |
| Vajda et al., 2020 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Vajda et al., 2021 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Veeranki et al., 2015 | \* | \* | \* |  | \*\* | \* | \* |  | 8/9 | High |
| Vegrim et al., 2022 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Veiby et al., 2013 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Veiby et al., 2013 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Veiby et al., 2014 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Videman et al., 2016 | \* | \* | \* |  | \*\* | \* | \* |  | 7/9 | Moderate |
| Vinten et al., 2005 | \* | \* | \* |  |  | \* | \* |  | 5/9 | Moderate |
| Wen et al., 2017 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Wiggs et al., 2020 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |
| Wood et al., 2015 | \* | \* | \* |  | \* | \* | \* |  | 6/9 | Moderate |

### eTable 8. Results of study quality appraisal of included case-control studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Selection |  |  |  | Comparability | Exposure |  | Score /8 | Quality Rating |
|  | Is the Case Definition Adequate? | Representativeness of Cases | Selection of Controls | Definition of Controls | Comparability of Cases and Controls on the Basis of the Design or Analysis | Ascertainment of Exposure | Non-Response Rate |  |  |
| Bech et al., 2018 | \* | \* | \* | \* | \* | \* | \* | 7/8 | High |
| Cummings et al., 2011 | \* | \* | \* | \* | \* | \* | \* | 7/8 | High |
| Foch et al., 2018 | \* | \* | \* | \* | \* | \* | \* | 7/8 | High |
| Gopinath et al., 2015 | \* | \* | \* | \* | \* | \* | \* | 7/8 | High |
| Jentik et al., 2010 | \* | \* | \* | \* | \*\* | \* | \* | 8/8 | High |
| Jonge et al., 2013 | \* | \* | \* | \* |  | \* | \* | 6/8 | Moderate |
| Li et al., 2023 | \* | \* | \* |  |  | \* | \* | 5/8 | Moderate |
| Maskova et al., 2011 | \* | \* | \* | \* |  | \* | \* | 6/8 | Moderate |
| Mavrogenis et al., 2013 | \* | \* | \* |  | \* | \* | \* | 6/8 | Moderate |
| Medveczky et al., 2004 | \* | \* | \* | \* | \* | \* | \* | 7/8 | High |
| Syanen et al., 2020 | \* | \* | \* | \* | \* | \* | \* | 7/8 | High |
| Rodriguez-Pinilla et al., 2000 | \* | \* | \* |  | \* | \* | \* | 6/8 | Moderate |
| Rodríguez-Pinilla et al., 2008 | \* | \* | \* | \* | \* | \* | \* | 7/8 | High |
| Wyszynski et al., 2005 | \* | \* | \* | \* |  | \* | \* | 6/8 | Moderate |

### 

### eTable 9. Results of study quality appraisal of included cross-sectional studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Selection |  |  |  | Comparability | Outcome |  | Score /9 | Quality Rating |
|  | Representativeness of the Sample | Sample Size | Non-Respondents | Ascertainment of Exposure | Comparability of Subjects in Different Outcome Groups on the Basis of the Design or Analysis | Assessment of the Outcome | Statistical Methodology |  |  |
| Bluett-Duncan et al., 2023 | \* | \* | \* | \*\* |  | \* | \* | 7/9 | High |
| Bromley et al., 2016 | \* | \* | \* | \*\* | \* | \* | \* | 8/9 | High |
| Bromley et al., 2019 | \* | \* | \* | \*\* | \* | \* | \* | 8/9 | High |
| Burger et al., 2022 | \* | \* | \* | \*\* | \* | \* | \* | 8/9 | High |
| Kishk et al., 2019 | \* | \* | \* | \*\* | \* | \* | \* | 8/9 | High |
| Shallcross et al., 2014 | \* | \* | \* | \*\* | \* | \* | \* | 8/9 | High |