Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
Appendix. Underlying Disorders for Valproate Use During Pregnancy Without Maternal Epilepsy Diagnosis

We assessed the underlying disorders for use of valproate in the pregnancies where the mother did not have an epilepsy diagnosis, but was taking valproate in pregnancy. We included the following ICD10 diagnoses in our assessment:

G43 Migraine (n < 5);
F00-F09 Organic, including symptomatic, mental disorders (n = 0);
F10-F19 Mental and behavioural disorders due to psychoactive substance use (n = 5);
F20-F29 Schizophrenia, schizotypal and delusional disorders (n = 5);
F30-F39 Mood [affective] disorders (n = 13);
F40-F48 Neurotic, stress-related and somatoform disorders (n = 9);
F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors (n < 5);
F60-F69 Disorders of adult personality and behavior (n = 5);
F70-F79 Mental retardation (n = 0);
F80-F89 Disorders of psychological development (n = 0);
F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence (n = 5);
F99-F99 Unspecified mental disorder (n = 5).

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**eTable 1. Risk of Intellectual Disability and Combined Outcome of Intellectual Disability and Delayed Childhood Milestones Associated With Prenatal Antiepileptic Drugs in Monotherapy Exposure vs Prenatal Lamotrigine in Monotherapy Exposure**

| Monotherapy exposure to antiepileptic drugs | Live births (Number) | Person-years at risk | ID (Number) | Incidence (Cases per 1,000 person-years (95% CI)) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|--------------------------------------------|----------------------|----------------------|-------------|--------------------------------------------------|-----------------------------|---------------------------------|
| Exposed to valproate                        | 431                  | 5,398                | 17          | 3.1 (2.0-5.1)                                     | 3.99 (1.85-8.62)            | 4.91 (2.09-11.55)               |
| Exposed to carbamazepine                    | 423                  | 5,650                | 15          | 2.7 (1.6-4.4)                                     | 3.13 (1.48-6.60)            | 3.30 (1.51-7.24)                |
| Exposed to clonazepam                       | 314                  | 3,744                | 6           | 1.6 (0.7-3.6)                                     | 2.03 (0.77-5.36)            | 1.90 (0.70-5.17)                |
| Exposed to oxcarbazepine                    | 372                  | 4,656                | 12          | 2.6 (1.5-4.5)                                     | 2.97 (1.35-6.52)            | 3.53 (1.40-8.90)                |
| Exposed to lamotrigine                      | 1,383                | 12,244               | 10          | 0.8 (0.4-1.5)                                     | 1.00 (ref)                  | 1.00 (ref)                      |

*Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity.

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**eTable 1. (Continued)**

| Monotherapy exposure to antiepileptic drugs | Live births (Number) | Person-years at risk | ID and CM (Number) | Incidence (Cases per 1,000 person-years (95% CI)) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|--------------------------------------------|----------------------|----------------------|-------------------|-----------------------------------------------|-----------------------------|---------------------------------|
| Exposed to valproate                       | 431                  | 5,184                | 38                | 7.3 (5.3-10.1)                                | 3.86 (2.40-6.23)            | 4.58 (2.68-7.81)                |
| Exposed to carbamazepine                   | 423                  | 5,582                | 18                | 3.2 (2.0-5.1)                                 | 1.69 (0.97-2.95)            | 1.77 (0.96-3.25)                |
| Exposed to clonazepam                      | 314                  | 3,648                | 15                | 4.1 (2.5-6.8)                                 | 2.09 (1.14-3.84)            | 2.00 (1.06-3.77)                |
| Exposed to oxcarbazepine                   | 372                  | 4,614                | 16                | 3.5 (2.1-5.7)                                 | 1.71 (0.96-3.05))           | 2.01 (1.01-4.00)                |
| Exposed to lamotrigine                     | 1,383                | 12,104               | 29                | 2.4 (1.7-3.4)                                 | 1.00 (ref)                  | 1.00 (ref)                      |

*Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity.
### eTable 2. Risk of Intellectual Disability and Combined Outcome of Intellectual Disability and Delayed Childhood Milestones Associated With Valproate Use During Pregnancy vs Valproate Use Prior to Pregnancy

| Valproate exposure | Live births (Number) | Person-years at risk | ID (number) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|--------------------|----------------------|----------------------|-------------|-----------------------------|--------------------------------|
| **During pregnancy** | 580 | 7,153 | 23 | 1.82 (0.96-3.46) | 1.94 (0.99-3.80) |
| **Prior to pregnancy** | 719 | 9,051 | 16 | 1.00 Ref | 1.00 Ref |

| Valproate exposure | Live births (Number) | Person-years at risk | ID and CM (number) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|--------------------|----------------------|----------------------|---------------------|-----------------------------|--------------------------------|
| **During pregnancy** | 580 | 6,816 | 58 | 2.14 (1.41-3.26) | 2.25 (1.46-3.47) |
| **Prior to pregnancy** | 719 | 8,873 | 35 | 1.00 Ref | 1.00 Ref |

*Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity.
| AED             | AED exposure | Live births (Number) | Incidence (Cases per 1,000 person-years) (95% CI) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|-----------------|--------------|-----------------------|-----------------------------------------------|----------------------------|---------------------------------|
| Valproate       | Monotherapy  | 431                   | 3.1 (2.0-5.1)                                 | 4.65 (2.89-7.49)            | 4.42 (2.75-7.11)                |
|                 | Polytherapy  | 149                   | 3.4 (1.5-7.6)                                 | 5.12 (2.28-11.50)           | 4.99 (2.21-11.30)               |
|                 | No exposure to AEDs | 899,941         | 0.7 (0.6-0.7)                                 | 1.00 (ref)                  | 1.00 (ref)                      |
| Carbamazepine   | Monotherapy  | 423                   | 2.7 (1.6-4.4)                                 | 3.88 (2.34-6.44)            | 3.84 (2.32-6.38)                |
|                 | Polytherapy  | 81                    | 1.8 (0.5-7.4)                                 | 2.73 (0.69-0.70)            | 2.60 (0.66-10.14)               |
|                 | No exposure to AEDs | 899,941         | 0.7 (0.6-0.7)                                 | 1.00 (ref)                  | 1.00 (ref)                      |
| Clonazepam      | Monotherapy  | 314                   | 1.6 (0.7-3.6)                                 | 2.41 (1.09-5.34)            | 2.41 (1.09-5.35)                |
|                 | Polytherapy  | 130                   | 4.7 (2.2-9.8)                                 | 7.04 (3.35-14.80)           | 7.70 (3.68-16.08)               |
|                 | No exposure to AEDs | 899,941         | 0.7 (0.6-0.7)                                 | 1.00 (ref)                  | 1.00 (ref)                      |
| Lamotrigine     | Monotherapy  | 1,383                 | 0.8 (0.4-1.5)                                 | 1.30 (0.70-2.42)            | 1.33 (0.71-2.48)                |
|                 | Polytherapy  | 363                   | 2.9 (1.6-5.3)                                 | 4.52 (2.50-8.16)            | 4.53 (2.52-8.15)                |
|                 | No exposure to AEDs | 899,941         | 0.7 (0.6-0.7)                                 | 1.00 (ref)                  | 1.00 (ref)                      |
| Oxcarbazepine   | Monotherapy  | 372                   | 2.6 (1.5-4.5)                                 | 3.82 (2.17-6.72)            | 3.70 (2.11-6.51)                |
|               | Polytherapy | 120 | 2.8 (1.1-7.5) | 4.21 (1.57-11.32) | 3.95 (1.47-10.63) |
|---------------|-------------|-----|---------------|-------------------|-------------------|
| No exposure to AEDs | 899,941     | 0.7 (0.6-0.7) | 1.00 (ref)     | 1.00 (ref)        |

Person-years at risk and number of persons with ID and CM omitted because some cells contained < 5 persons.

*Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity.
### Table 3. (Continued)
Hazard ratio of the combined outcome of intellectual disability (ID) and delayed childhood milestones (CM)

| AED       | AED exposure | Live births (Number) | Incidence (Cases per 1,000 person-years) (95% CI) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|-----------|--------------|----------------------|-------------------------------------------------|-----------------------------|----------------------------------|
| Valproate | Monotherapy  | 431                  | 7.3 (5.3-10.1)                                  | 5.35 (3.89-7.38)            | 5.28 (3.82-7.28)                 |
|           | Polytherapy  | 149                  | 12.3 (7.9-19.0)                                 | 8.68 (5.56-13.55)           | 8.95 (5.71-14.04)               |
|           | No exposure to AEDs | 899,941 | 1.4 (1.4-1.5)                                  | 1.00 (ref)                  | 1.00 (ref)                      |
| Carbamazepine | Monotherapy | 423                  | 3.2 (2.0-5.1)                                  | 2.42 (1.53-3.83)            | 2.49 (1.58-3.94)                |
|           | Polytherapy  | 81                   | 5.7 (2.5-12.6)                                 | 4.25 (1.89-9.58)            | 4.26 (1.90-9.58)                |
|           | No exposure to AEDs | 899,941 | 1.4 (1.4-1.5)                                  | 1.00 (ref)                  | 1.00 (ref)                      |
| Clonazepam | Monotherapy  | 314                  | 4.1 (2.5-6.8)                                  | 2.92 (1.76-4.84)            | 2.99 (1.80-4.96)               |
|           | Polytherapy  | 130                  | 10.8 (6.5-18.0)                                | 7.59 (4.54-12.67)           | 8.20 (4.88-13.76)              |
|           | No exposure to AEDs | 899,941 | 1.4 (1.4-1.5)                                  | 1.00 (ref)                  | 1.00 (ref)                      |
| Lamotrigine | Monotherapy  | 1,383                | 2.4 (1.7-3.4)                                  | 1.50 (1.04-2.16)            | 1.45 (1.01-2.09)               |
|           | Polytherapy  | 363                  | 8.7 (6.1-12.3)                                 | 5.77 (4.06-8.21)            | 5.57 (3.87-8.02)               |
|           | No exposure to AEDs | 899,941 | 1.4 (1.4-1.5)                                  | 1.00 (ref)                  | 1.00 (ref)                      |
| Oxcarbazepine | Monotherapy | 372                  | 3.5 (2.1-5.7)                                  | 2.55 (1.57-4.13)            | 2.51 (1.54-4.10)               |
|                          | Person-years at risk | Number of persons with ID and CM omitted because some cells contained < 5 persons. | *Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity. |
|--------------------------|----------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Polytherapy              | 120                  | 8.2 (4.6-14.8)                                                                  | 5.84 (3.23-10.56)                                                               | 5.27 (2.75-10.10)                                                             |
| No exposure to AEDs      | 899,941              | 1.4 (1.4-1.5)                                                                   | 1.00 (ref)                                                                      | 1.00 (ref)                                                                    |
| AED       | AED exposure       | Live births (Number) | Incidence (Cases per 1,000 person-years) (95% CI) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|-----------|--------------------|----------------------|--------------------------------------------------|-------------------------------|----------------------------------|
| Valproate | High dose (>750 mg)| 213                  | 5.5 (3.3-9.1)                                    | 8.09 (4.88-13.43)             | 7.96 (4.80-13.19)                |
|           | Low dose (≤750 mg) | 218                  | 0.7 (0.2-3.0)                                    | 1.12 (0.28-4.45)              | 1.01 (0.25-4.08)                 |
|           | No exposure        | 899,941              | 0.7 (0.6-0.7)                                    | 1.00 (ref)                    | 1.00 (ref)                      |
| Carbamazepine | High dose (>500 mg)| 259                  | 2.3 (1.1-4.5)                                    | 3.32 (1.66-6.62)              | 3.50 (1.75-6.99)                |
|           | Low dose (≤500 mg) | 164                  | 3.3 (1.6-6.9)                                    | 4.88 (2.35-10.14)             | 4.38 (2.10-9.15)                |
|           | No exposure        | 899,941              | 0.7 (0.6-0.7)                                    | 1.00 (ref)                    | 1.00 (ref)                      |
| Clonazepam | High dose (>4 mg)  | 31                   | NA                                               | NA                            | NA                              |
|           | Low dose (≤4 mg)   | 283                  | 1.8 (0.8-4.0)                                    | 2.73 (1.23-6.07)              | 2.72 (1.22-6.06)                |
|           | No exposure        | 899,941              | 0.7 (0.6-0.7)                                    | 1.00 (ref)                    | 1.00 (ref)                      |
| Lamotrigine | High dose (>150 mg)| 911                  | 0.6 (0.3-1.5)                                    | 0.98 (0.41-2.36)              | 1.04 (0.43-2.50)                |
|           | Low dose (≤150 mg) | 472                  | 1.2 (0.5-2.9)                                    | 1.94 (0.80-4.66)              | 1.85 (0.77-4.45)                |
|                          | No exposure | 899,941 | 0.7 (0.6-0.7) | 1.00 (ref) | 1.00 (ref) |
|---------------------------|-------------|---------|---------------|------------|------------|
| Oxcarbazepine             | High dose (>1,000 mg) | 212     | 2.7 (1.3-5.6) | 4.01 (1.92-8.38) | 4.14 (1.97-8.68) |
|                           | Low dose (≤1,000 mg) | 160     | 2.4 (1.0-5.9) | 3.61 (1.51-8.63) | 3.25 (1.37-7.71) |
|                           | No exposure  | 899,941 | 0.7 (0.6-0.7) | 1.00 (ref) | 1.00 (ref) |

Person-years at risk and number of persons with ID and CM omitted because some cells contained < 5 persons. NA (none exposed)

*Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity.
**eTable 4. (Continued)**

Hazard ratio of the combined outcome of intellectual disability (ID) and delayed childhood milestones (CM)

| AED       | AED exposure       | Live births (Number) | Incidence (Cases per 1,000 person-years) (95% CI) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|-----------|--------------------|----------------------|-----------------------------------------------|-----------------------------|----------------------------------|
| Valproate | High dose (>750 mg)| 213                  | 12.6 (8.9-17.8)                             | 9.23 (6.49-13.11)           | 9.47 (6.64-13.49)               |
|           | Low dose (≤750 mg) | 218                  | 2.3 (1.0-5.1)                               | 1.67 (0.75-3.70)            | 1.57 (0.70-3.50)               |
|           | No exposure        | 899,941              | 1.4 (1.4-1.5)                               | 1.00 (ref)                  | 1.00 (ref)                      |
| Carbamazepine | High dose (>500 mg)| 259                  | 2.9 (1.5-5.3)                               | 2.17 (1.17-4.03)            | 2.34 (1.26-4.34)               |
|           | Low dose (≤500 mg) | 164                  | 3.8 (1.9-7.6)                               | 2.81 (1.41-5.58)            | 2.68 (1.34-5.35)               |
|           | No exposure        | 899,941              | 1.4 (1.4-1.5)                               | 1.00 (ref)                  | 1.00 (ref)                      |
| Clonazepam | High dose (>4 mg)  | 31                   | 4.8 (1.2-19.2)                              | 3.65 (0.91-14.69)           | 4.05 (1.03-15.93)              |
|           | Low dose (≤4 mg)   | 283                  | 4.0 (2.3-6.9)                               | 2.83 (1.65-4.87)            | 2.88 (1.67-4.95)               |
|           | No exposure        | 899,941              | 1.4 (1.4-1.5)                               | 1.00 (ref)                  | 1.00 (ref)                      |
| Lamotrigine | High dose (>150 mg)| 911                  | 1.6 (0.9-2.8)                               | 1.00 (0.58-1.73)            | 1.01 (0.59-1.74)               |
|           | Low dose (≤150 mg) | 472                  | 4.0 (2.4-6.5)                               | 2.46 (1.51-4.01)            | 2.25 (1.38-3.66)               |
|           | No exposure        | 899,941              | 1.4 (1.4-1.5)                               | 1.00 (ref)                  | 1.00 (ref)                      |
| Oxcarbazepine | High dose (>1,000 mg)| 212              | 3.9 (2.1-7.2)                               | 2.79 (1.50-5.16)            | 2.89 (1.56-5.37)               |

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|                     | Person-years | ID (1.3-6.6) | CM (0.98-4.85) | ID (0.94-4.57) |
|---------------------|--------------|--------------|----------------|----------------|
| Low dose (≤1,000 mg)| 160          | 3.0          | 2.18           | 2.07           |
| No exposure         | 899,941      | 1.4          | 1.00 (ref)     | 1.00 (ref)     |

Person-years at risk and number of persons with ID and CM omitted because some cells contained < 5 persons.

*Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity.
**eTable 5. Risk of Intellectual Disability and Combined Outcome of Intellectual Disability and Delayed Childhood Milestones Associated With Prenatal Valproate Exposure Excluding Children With Congenital Malformations**

| Valproate exposure | Live births (Number) | Person-years at risk | ID (Number) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|--------------------|----------------------|----------------------|-------------|-----------------------------|---------------------------------|
| Exposed to valproate | 512 | 6,401 | 16 | 4.23 (2.59-6.92) | 4.06 (2.48-6.63) |
| Not exposed to valproate | 873,710 | 9,905,987 | 5,691 | 1.00 (ref) | 1.00 (ref) |

| Valproate exposure | Live births (Number) | Person-years at risk | ID and CM (Number) | Hazard ratio, crude (95% CI) | Hazard ratio, adjusted* (95% CI) |
|--------------------|----------------------|----------------------|---------------------|-----------------------------|---------------------------------|
| Exposed to valproate | 512 | 6,232 | 36 | 4.86 (3.50-6.75) | 4.85 (3.49-6.74) |
| Not exposed to valproate | 873,710 | 9,850,710 | 12,155 | 1.00 (ref) | 1.00 (ref) |

*Adjusted for maternal age at conception, maternal psychiatric history, maternal epilepsy status, maternal diabetes status, sex of child, year of birth of child, and parity.