Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
**Table 1.** Participant Characteristics at Baseline and Age 10 Years: The ELGAN Cohort Study (2002-2020)

| Characteristic                     | Enrolled at birth (n=1506) | Survived to 24 months (n=1198) | Age 10 years (n=889) |
|------------------------------------|----------------------------|--------------------------------|----------------------|
| Gestational age at delivery - mean (SD) | 25.9 (1.3)              | 26.1 (1.3)                      | 26.1 (1.3)           |
| Sex – n (%)                        |                            |                                |                      |
| Male                               | 799 (53.0%)                | 621 (51.8%)                    | 455 (51.2%)          |
| Female                             | 707 (47.0%)                | 577 (48.2%)                    | 434 (48.8%)          |
| Weight for gestational age at delivery z-score - mean (SD) | -0.27 (1.12)              | -0.16 (1.06)                   | -0.19 (1.09)         |
| Chronic lung disease – n (%)       |                            |                                |                      |
| Neither O2 nor Ventilator at 36 weeks | 597 (48.1%)                | 590 (49.7%)                    | 421 (47.7%)          |
| O2 at 36 weeks                     | 520 (41.9%)                | 498 (41.9%)                    | 380 (43.1%)          |
| Ventilator at 36 weeks             | 124 (10.0%)                | 100 (8.4%)                     | 81 (9.2%)            |
| White matter damage – n (%)        | 347 (23.9%)                | 242 (20.2%)                    | 188 (21.2%)          |
| Maternal race – n (%)              |                            |                                |                      |
| Black                              | 427 (28.9%)                | 322 (27.3%)                    | 227 (25.6%)          |
| White                              | 866 (58.5%)                | 706 (59.9%)                    | 562 (63.4%)          |
| Other                              | 187 (12.7%)                | 151 (12.8%)                    | 98 (11.1%)           |
| Maternal ethnicity – n (%)         |                            |                                |                      |
| Hispanic                           | 179 (12.0%)                | 147 (12.3%)                    | 86 (9.7%)            |
| Non-Hispanic                       | 1313 (88.0%)               | 1045 (87.7%)                   | 800 (90.3%)          |
| Maternal education (years) at Birth – n (%) | <=12 633 (45.2%)        | 506 (43.9%)                    | 355 (41.1%)          |
|                                   | >12 - <16 340 (24.3%)     | 270 (23.4%)                    | 202 (23.4%)          |
|                                   | >=16 428 (30.6%)           | 376 (32.6%)                    | 306 (35.5%)          |
| Public insurance – n (%)           |                            |                                |                      |
| No                                 | 841 (58.6%)                | 709 (60.4%)                    | 568 (64.9%)          |
| Yes                                | 594 (41.4%)                | 464 (39.6%)                    | 307 (35.1%)          |
| Feeding difficulties at 12 months – n (%) | Missing* 481 (31.9%) | 179 (14.9%)                    | 93 (10.5%)           |
|                                   | No 749 (49.7%)             | 746 (62.3%)                    | 574 (64.6%)          |
|                                   | Yes 276 (18.3%)            | 273 (22.8%)                    | 222 (25.0%)          |
| Cerebral Palsy – n (%)**           |                            |                                |                      |
| Quad                               | 64 (6.1%)                  | 63 (6.0%)                      | 48 (5.7%)            |
| Di                                 | 37 (3.5%)                  | 37 (3.5%)                      | 29 (3.4%)            |
| Hemi                               | 19 (1.8%)                  | 19 (1.8%)                      | 16 (1.9%)            |
| None                               | 936 (88.6%)                | 936 (88.7%)                    | 756 (89.1%)          |

*Participants that died prior to the 12 month follow-up visit have this data missing

**Collected at 24 months of age

**Table 2.** Acid Suppression and Neurocognitive and Neurodevelopmental Outcomes by Outcome Severity at Age 10: The ELGAN Cohort Study (2002-2020)

| Outcome                  | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------|-------------------|----------------------|
|                          | Impaired (≤ −2)   | Low Normal (−2 < − ≤ −1) | Referent > -1    | Impaired (≤ −2)   | Low Normal (−2 < − ≤ −1) | Referent > -1    |
|                          |                   | (n=1743)             | (n=1423)          |                   | (n=1743)             | (n=1423)          |
| DAS verbal IQ            | 2.0 (1.3, 2.8)    | 1.2 (0.9, 1.8)       | Referent          | 1.8 (1.2, 2.7)    | 1.3 (0.9, 1.9)       | Referent          |
| DAS non-verbal IQ        | 2.0 (1.4, 3.0)    | 1.4 (1.0, 2.0)       | Referent          | 1.9 (1.3, 2.9)    | 1.5 (1.0, 2.1)       | Referent          |
| DAS Full Scale IQ        | 2.0 (1.4, 2.9)    | 1.6 (1.1, 2.3)       | Referent          | 1.8 (1.2, 2.8)    | 1.8 (1.2, 2.6)       | Referent          |

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| Neurocognitive function composite | 2.5 (1.5, 4.2) | 1.7 (1.2, 2.6) | Referent | 2.2 (1.2, 3.8) | 1.7 (1.1, 2.6) | Referent |
|----------------------------------|----------------|----------------|----------|----------------|----------------|----------|
| DAS working memory               | 1.8 (1.2, 2.6) | 1.3 (0.9, 1.9) | Referent | 1.7 (1.2, 2.6) | 1.3 (0.9, 1.9) | Referent |
| NEPSY inhibition inhibition      | 1.3 (1.0, 1.8) | 1.0 (0.7, 1.4) | Referent | 1.3 (0.9, 1.8) | 1.0 (0.7, 1.5) | Referent |
| NEPSY inhibition switching       | 1.4 (1.0, 2.0) | 1.0 (0.7, 1.4) | Referent | 1.4 (1.0, 2.0) | 1.0 (0.7, 1.4) | Referent |
| SCI (DSM-5 Compatible Scores)    | 1.1 (0.5, 2.1) | 0.7 (0.4, 1.2) | Referent | 0.9 (0.5, 1.9) | 0.7 (0.4, 1.2) | Referent |
| RRB (DSM-5 Compatible Scores)    | 1.6 (0.8, 3.1) | 1.2 (0.6, 2.3) | Referent | 1.6 (0.8, 3.1) | 1.1 (0.6, 2.1) | Referent |

*Adjusted for sex, insurance, maternal education, white matter damage, and chronic lung disease (missing covariates were multiple imputed)

Table 3. Likelihood Ratio Test for Model Selection Comparing PPI and H2RA Combined vs PPI and H2RA as Separate Covariates: The ELGAN Cohort Study (2002-2020)

|                          | Full -2 Log Likelihood (PPI only + H2RA Only) | Reduced Model -2 Log Likelihood (PPI and H2RA combined) | Chi-Square | df | p-value |
|--------------------------|-----------------------------------------------|----------------------------------------------------------|------------|----|---------|
| Neurocognitive function composite | 976.9904                                      | 976.1424                                                  | 0.848      | 1  | 0.3571  |
| Autism                   | 394.8026                                      | 394.7584                                                  | 0.0442     | 1  | 0.8335  |
| ADHD                     | 767.3418                                      | 767.4678                                                  | 0.126      | 1  | 0.7226  |
| Generalized Anxiety      | 719.1986                                      | 719.8618                                                  | 0.6632     | 1  | 0.4154  |
| Depression               | 398.894                                       | 398.4812                                                  | 0.4128     | 1  | 0.5206  |

Table 4. Acid Suppressant Use and Neurocognitive, Neurodevelopmental, and Psychiatric Outcomes at Age 10 With Inverse Probability Weighting: The ELGAN Cohort Study (2002-2020)

|                          | aRR (95% CI) |
|--------------------------|--------------|
| Neurocognitive function composite | Referent     |
| Normal or low normal      | Referent     |
| Moderate or severe        | 1.33 (1.04, 1.68) |
| Autism                    | No           |
| Referent                  | Referent     |
| Outcome | Level            | RR         | aRR         | Parametric P-value * |
|---------|------------------|------------|-------------|----------------------|
| **Epilepsy** |                  |            |             |                      |
| No      | Referent         | Yes        | 1.97 (1.19, 3.24) |                      |
| Yes     |                  |            |             |                      |
| **ADHD** |                  |            |             |                      |
| No      | Referent         | Yes        | 0.88 (0.65, 1.19) |                      |
| Yes     |                  |            |             |                      |
| **Anxiety** |                |            |             |                      |
| No      | Referent         | Yes        | 0.99 (0.72, 1.38) |                      |
| Yes     |                  |            |             |                      |
| **Depression** |              |            |             |                      |
| No      | Referent         | Yes        | 1.10 (0.65, 1.84) |                      |
| Yes     |                  |            |             |                      |

*Adjusted for sex, insurance, maternal education, white matter damage, and chronic lung disease

**eTable 5. Propensity Score Matching Analysis of Acid Suppressant Exposure at Age 10: The ELGAN Cohort Study (2002-2020)**

| Outcome                        | Level              | RR        | aRR        | Parametric P-value * |
|--------------------------------|--------------------|-----------|------------|----------------------|
| DAS verbal IQ                  | ≤ -2               | 1.58 (1.06, 2.36) | 1.68 (1.08, 2.61) | 0.0215               |
|                                | > -2, ≤ -1         | 1.31 (0.87, 1.97) | 1.34 (0.88, 2.05) | 0.1664               |
|                                | > -1, ≤ 1          |           |            |                      |
|                                | >1                 | 1.18 (0.64, 2.16) | 1.17 (0.62, 2.18) | 0.6291               |
| DAS non-verbal IQ              | ≤ -2               | 1.69 (1.10, 2.59) | 1.74 (1.09, 2.75) | 0.0191               |
|                                | > -2, ≤ -1         | 1.36 (0.94, 1.96) | 1.38 (0.94, 2.01) | 0.0962               |
|                                | > -1, ≤ 1          |           |            |                      |
|                                | >1                 | 1.54 (0.77, 3.11) | 1.53 (0.75, 3.14) | 0.2419               |
| DAS full scale IQ              | ≤ -2               | 1.61 (1.07, 2.44) | 1.69 (1.08, 2.66) | 0.0223               |
|                                | > -2, ≤ -1         | 1.66 (1.10, 2.50) | 1.70 (1.11, 2.59) | 0.0138               |
|                                | > -1, ≤ 1          |           |            |                      |
|                                | >1                 | 1.47 (0.67, 3.22) | 1.40 (0.62, 3.14) | 0.4134               |
| Neurocognitive function composite | Normal          |            |            |                      |
| Low normal                     | 0.69 (0.48, 0.98) | 0.69 (0.48, 1.00) | 0.0529               |

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|                      | Moderate | Severe     |   |   |
|----------------------|----------|------------|---|---|
|                      | 1.16 (0.74, 1.81)| 1.18 (0.73, 1.92)| 0.4979   |
|                      | 1.37 (0.78, 2.42)| 1.39 (0.74, 2.61)| 0.3124   |
| DAS working memory   | 1.40 (0.94, 2.09)| 1.43 (0.93, 2.22)| 0.1058   |
| ≤ -2                 | 1.23 (0.82, 1.84)| 0.88 (0.40, 1.93)| 0.7558   |
| > -2, ≤ -1           | 0.92 (0.61, 1.39)| 0.92 (0.61, 1.39)| 0.6902   |
| > -1, ≤ 1            | 0.92 (0.61, 1.39)| 0.92 (0.61, 1.39)| 0.6902   |
| NEPSY inhibition     | 1.06 (0.74, 1.52)| 1.05 (0.73, 1.53)| 0.7821   |
| ≤ -2                 | 0.92 (0.61, 1.39)| 0.92 (0.61, 1.39)| 0.6902   |
| > -2, ≤ -1           | 0.92 (0.61, 1.39)| 0.92 (0.61, 1.39)| 0.6902   |
| > -1, ≤ 1            | 0.92 (0.61, 1.39)| 0.92 (0.61, 1.39)| 0.6902   |
| NEPSY inhibition     | 1.14 (0.78, 1.69)| 1.11 (0.73, 1.68)| 0.6257   |
| switching            | 0.89 (0.61, 1.32)| 0.87 (0.58, 1.30)| 0.4986   |
| > -2, ≤ -1           | 0.89 (0.61, 1.32)| 0.87 (0.58, 1.30)| 0.4986   |
| > -1, ≤ 1            | 0.89 (0.61, 1.32)| 0.87 (0.58, 1.30)| 0.4986   |
| SCI (DSM-5 Compatible Scores) |          |            |   |   |
| Normal               | 1.73 (1.03, 2.91)| 1.69 (1.00, 2.85)| 0.0497   |
| Mild                 | 1.07 (0.68, 1.70)| 1.05 (0.65, 1.68)| 0.8394   |
| Moderate             | 1.70 (0.89, 3.25)| 1.75 (0.90, 3.40)| 0.0961   |
| Severe               | 1.64 (0.96, 2.82)| 1.65 (0.96, 2.85)| 0.0710   |
| RRB (DSM-5 Compatible Scores) |          |            |   |   |
| Normal               | 1.20 (0.99, 1.45)| 1.17 (0.97, 1.40)| 0.0952   |
| Mild                 | 1.10 (0.90, 1.34)| 1.07 (0.88, 1.30)| 0.4837   |
| Moderate             | 1.14 (0.90, 1.44)| 1.10 (0.88, 1.38)| 0.3944   |
| Severe               | 1.14 (0.90, 1.44)| 1.10 (0.88, 1.38)| 0.3944   |
| Autism spectrum      | 1.76 (1.06, 2.93)| 1.71 (1.04, 2.83)| 0.0361   |
| disorder             | 2.27 (1.31, 3.96)| 2.17 (1.28, 3.66)| 0.0037   |

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|                  | None                        | NICU Only Beta (95% CI) | Post Discharge Only Beta (95% CI) | NICU + Post Discharge Only Beta (95% CI) |
|------------------|-----------------------------|-------------------------|----------------------------------|------------------------------------------|
| DAS-II verbal IQ z-score | Referent                    | -0.19 (-0.41, 0.04)    | -0.53 (-0.82, -0.23)             | -0.46 (-0.85, -0.07)                   |
| DAS-II non-verbal IQ z-score | Referent                    | -0.06 (-0.26, 0.15)    | -0.48 (-0.76, -0.20)             | -0.29 (-0.62, 0.04)                   |
| DAS-II Full Scale IQ z-score | Referent                    | -0.13 (-0.34, 0.07)    | -0.50 (-0.77, -0.23)             | -0.39 (-0.72, -0.06)                   |
| DAS-II Working Memory z-score | Referent                    | -0.12 (-0.36, 0.11)    | -0.40 (-0.67, -0.12)             | -0.47 (-0.87, -0.06)                   |
| NEPSY-II Inhibition Inhibition z-score | Referent                    | -0.21 (-0.41, -0.01)   | -0.34 (-0.59, -0.10)             | -0.12 (-0.46, 0.22)                    |
| NEPSY-II Inhibition Switching z-score | Referent                    | -0.09 (-0.29, 0.12)    | -0.24 (-0.49, 0.00)              | -0.09 (-0.44, 0.27)                    |
| Neurocognitive function composite (LPA) | Referent                    | 1.24 (0.93, 1.66)      | 1.60 (1.24, 2.08)                | 1.45 (0.98, 2.16)                      |
| Autism spectrum disorder | Referent                    | 1.85 (1.07, 3.20)      | 1.66 (0.90, 3.09)                | 1.56 (0.70, 3.49)                      |
| Epilepsy | Referent                    | 1.64 (0.91, 2.96)      | 2.46 (1.39, 4.35)                | 1.99 (0.89, 4.44)                      |
| ADHD | Referent                    | 0.85 (0.59, 1.22)      | 0.94 (0.61, 1.44)                | 1.02 (0.59, 1.76)                      |
| Anxiety | Referent                    | 0.92 (0.61, 1.38)      | 1.17 (0.75, 1.83)                | 1.23 (0.67, 2.28)                      |
| Depression | Referent                    | 0.65 (0.31, 1.38)      | 2.41 (1.32, 4.42)                | 0.66 (0.17, 2.57)                      |

Adjusted Beta Coefficients and 95% CI for Verbal IQ, non-verbal IQ, full scale IQ, working memory, inhibition inhibition, inhibition switching
Adjusted RR and 95% CI for Neurocognitive function composite, Autism spectrum disorder, epilepsy, ADHD, Anxiety, Depression
*Adjusted for sex, insurance, maternal education, white matter damage, and chronic lung disease (missing covariates were multiple imputed)

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Table 7. Acid suppressant use within subset of participants without cerebral palsy and without tube feedings: The ELGAN Cohort Study (2002-2020)

|                                | No Cerebral Palsy Beta (95% CI) | No Tube Feeding Beta (95% CI) |
|--------------------------------|---------------------------------|------------------------------|
| DAS-II verbal IQ               | -0.32 (-0.50,-0.14)            | -0.27 (-0.47,-0.08)         |
| DAS-II non-verbal IQ           | -0.19 (-0.36,-0.03)            | -0.21 (-0.40,-0.03)         |
| DAS-II Full Scale IQ           | -0.26 (-0.41,-0.10)            | -0.25 (-0.43,-0.07)         |
| DAS-II Working Memory          | -0.21 (-0.39,-0.03)            | -0.26 (-0.45,-0.06)         |
| NEPSY-II Inhibition Inhibition | -0.25 (-0.42,-0.08)            | -0.18 (-0.36,-0.01)         |
| NEPSY-II Inhibition Switching  | -0.08 (-0.26, 0.09)            | -0.07 (-0.25, 0.11)         |
| **aRR (95% CI)**                | **1.45 (1.11,1.90)**           | **1.31 (1.02,1.69)**        |
| Neurocognitive function composite (LPA) |                                  |                              |
| Autism spectrum disorder       | 1.96 (1.19,3.23)               | 1.83 (1.10,3.03)            |
| Epilepsy                       | 2.78 (1.55,4.98)               | 2.37 (1.42,3.94)            |
| ADHD                           | 0.94 (0.69,1.27)               | 0.97 (0.71,1.33)            |
| Anxiety                        | 0.96 (0.69,1.34)               | 0.95 (0.66,1.34)            |
| Depression                     | 1.05 (0.61,1.80)               | 0.92 (0.53,1.58)            |

*Adjusted for sex, insurance, maternal education, white matter damage, and chronic lung disease (missing covariates were multiple imputed)
eFigure. Directed Acyclic Graph