**A randomized controlled trial investigating the impact of maternal dietary supplementation with pomegranate juice on brain injury in infants with IUGR**

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# Supplementary Information

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**S1 Table.** Brain volumes by study arm

| | Group Comparisons | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | **MODIFIED INTENTION-TO-TREAT** (Placebo, *n*=27; POM, *n*=24) | | | | **PER-PROTOCOL** (Placebo Metabolite -ve, *n*=16; POM Metabolite +ve, *n*=15) | | | |
| | **Estimate (95% CI)** | **SE** | **z** | ***P-value*** | **Estimate (95% CI)** | **SE** | **z** | ***P-value*** |
| GM | 5.46 (-8.26, 19.19) | 7.00 | 0.78 | 0.435 | 4.36 (-17.31, 26.03) | 11.06 | 0.39 | 0.693 |
| WM | -6.62 (-14.35, 1.10) | 3.94 | -1.68 | 0.093 | 3.49 (-14.30, 21.29) | 9.08 | 0.38 | 0.700 |
| CSF | -2.14 (-16.22, 11.93) | 7.18 | -0.30 | 0.765 | -8.02 (-27.34, 11.30) | 9.86 | -0.81 | 0.416 |
| DGM | 0.19 (-1.61, 1.99) | 0.92 | 0.21 | 0.837 | 0.45 (-0.91, 1.81) | 0.69 | 0.65 | 0.515 |
| Hippocampus | 0.09 (-0.83, 1.00) | 0.47 | 0.18 | 0.854 | -0.01 (-0.77, 0.76) | 0.39 | -0.01 | 0.988 |
| Amygdala | 0.26 (-0.10, 0.63) | 0.19 | 1.41 | 0.160 | -0.08 (-0.44, 0.28) | 0.18 | -0.45 | 0.654 |
| Cerebellum | -0.71 (-3.49, 2.07) | 1.42 | -0.50 | 0.617 | -0.82 (-3.85, 2.21) | 1.55 | -0.53 | 0.596 |
| Brainstem | 0.00 (-0.78, 0.78) | 0.40 | 0.00 | 0.999 | -0.48 (-2.36, 1.40) | 0.96 | -0.50 | 0.615 |
| Total tissue | -9.87 (-34.56, 14.83) | 12.60 | -0.78 | 0.434 | 8.21 (-17.99, 34.41) | 13.37 | 0.61 | 0.539 |
| ICV | -17.68 (-50.84, 15.48) | 16.92 | -1.05 | 0.296 | -15.87 (-76.97, 45.22) | 31.17 | -0.51 | 0.611 |
| *Adjusted for ICV* | | | | | | | | |
| GM | 5.01 (-5.31, 15.33) | 5.26 | 0.95 | 0.342 | 6.42 (-13.24, 26.07) | 10.03 | 0.64 | 0.522 |
| WM | -3.30 (-9.90, 3.30) | 3.37 | -0.98 | 0.327 | -2.44 (-14.90, 10.01) | 6.36 | -0.38 | 0.701 |
| CSF | -1.17 (-11.01, 8.67) | 5.02 | -0.23 | 0.816 | -5.04 (-18.05, 7.96) | 6.63 | -0.76 | 0.447 |
| DGM | 0.18 (-1.42, 1.78) | 0.82 | 0.22 | 0.823 | 0.49 (-0.84, 1.82) | 0.68 | 0.72 | 0.473 |
| Hippocampus | 0.05 (-0.81, 0.91) | 0.44 | 0.12 | 0.903 | -0.11 (-0.79, 0.58) | 0.35 | -0.30 | 0.762 |
| Amygdala | 0.15 (-0.32, 0.62) | 0.24 | 0.61 | 0.542 | -0.09 (-0.41, 0.24) | 0.17 | -0.52 | 0.607 |
| Cerebellum | -1.01 (-4.00, 1.97) | 1.52 | -0.67 | 0.505 | -0.27 (-3.57, 3.04) | 1.69 | -0.16 | 0.875 |
| Brainstem | 0.00 (-1.10, 1.11) | 0.56 | 0.00 | 0.998 | 0.03 (-1.51, 1.58) | 0.79 | 0.04 | 0.968 |
| Total tissue | 1.17 (-8.67, 11.01) | 5.02 | 0.23 | 0.816 | 5.04 (-7.96, 18.05) | 6.63 | 0.76 | 0.447 |

Group comparisons evaluated using median regression adjusted for intrafamilial correlation among twins, as well as for potential confounding by maternal BMI at enrollment, PMA at MRI scan, infant sex and SGA status (placebo = reference).

GM – cortical grey matter; CSF – cerebrospinal fluid; DGM – deep grey matter; ICV – intracranial volume; POM – pomegranate; WM – white matter

**S2 Table.** DTI measures by study arm

| | | MODIFIED INTENTION-TO-TREAT (Placebo, n=19; POM, n=18) | | | | PER-PROTOCOL (Placebo Metabolite –ve, n=8; POM Metabolite +ve, n=11) | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Tract** | | **Estimate (95% CI)** | **SE** | **z** | **P-value** | **Estimate (95% CI)** | **SE** | **z** | **P-value** |
| *L ALIC* | FA | -0.01 (-0.05, 0.04) | 0.02 | -0.37 | 0.711 | 0.05 (-0.01, 0.10) | 0.03 | 1.76 | 0.079 |
| | MD | -0.09 (-0.39, 0.21) | 0.15 | -0.58 | 0.565 | 0.66 (-0.62, 1.94) | 0.66 | 1.01 | 0.314 |
| | AD | 0.19 (-1.04, 1.41) | 0.63 | 0.30 | 0.763 | 1.17 (-0.93, 3.26) | 1.07 | 1.09 | 0.276 |
| | RD | 0.18 (-0.23, 0.58) | 0.21 | 0.84 | 0.399 | 0.38 (-0.58, 1.33) | 0.49 | 0.77 | 0.442 |
| *R ALIC* | FA | -0.02 (-0.08, 0.04) | 0.03 | -0.65 | 0.515 | 0.03 (-0.02, 0.08) | 0.03 | 1.27 | 0.203 |
| | MD | 0.13 (-0.25, 0.51) | 0.20 | 0.66 | 0.507 | -0.24 (-0.49, 0.00) | 0.12 | -1.97 | 0.049[1] |
| | AD | 0.00 (-1.11, 1.10) | 0.56 | 0.00 | 0.999 | 0.17 (-1.42, 1.76) | 0.81 | 0.21 | 0.833 |
| | RD | 0.19 (-0.32, 0.71) | 0.26 | 0.74 | 0.461 | -0.38 (-1.45, 0.69) | 0.55 | -0.70 | 0.485 |
| *L PLIC* | FA | -0.02 (-0.07, 0.03) | 0.03 | -0.67 | 0.504 | 0.04 (-0.03, 0.11) | 0.04 | 1.01 | 0.315 |
| | MD | 0.17 (-0.27, 0.60) | 0.22 | 0.76 | 0.444 | -0.25 (-1.66, 1.15) | 0.72 | -0.35 | 0.725 |
| | AD | -0.20 (-1.10, 0.70) | 0.46 | -0.44 | 0.661 | 0.61 (-0.63, 1.85) | 0.63 | 0.96 | 0.336 |
| | RD | 0.15 (-0.45, 0.75) | 0.31 | 0.48 | 0.632 | -0.44 (-1.52, 0.63) | 0.55 | -0.81 | 0.419 |
| *R PLIC* | FA | -0.02 (-0.07, 0.02) | 0.02 | -1.00 | 0.319 | 0.03 (-0.07, 0.14) | 0.06 | 0.62 | 0.537 |
| | MD | 0.17 (-0.19, 0.52) | 0.18 | 0.91 | 0.364 | -0.24 (-1.24, 0.76) | 0.51 | -0.47 | 0.636 |
| | AD | -0.20 (-1.09, 0.68) | 0.45 | -0.45 | 0.652 | 0.99 (-2.78, 4.75) | 1.92 | 0.51 | 0.607 |
| | RD | 0.49 (-0.16, 1.14) | 0.33 | 1.48 | 0.138 | -0.34 (-1.51, 0.92) | 0.60 | -0.57 | 0.566 |
| *L OR* | FA | 0.01 (-0.03, 0.05) | 0.02 | 0.56 | 0.573 | 0.03 (-0.02, 0.07) | 0.02 | 1.16 | 0.247 |
| | MD | 0.11 (-0.78, 1.00) | 0.45 | 0.24 | 0.812 | 1.69 (-1.40, 4.78) | 1.58 | 1.07 | 0.284 |
| | AD | 0.54 (-0.65, 1.71) | 0.60 | 0.89 | 0.374 | 1.29 (-0.28, 2.86) | 0.80 | 1.61 | 0.107 |
| | RD | 0.02 (-1.03, 1.07) | 0.54 | 0.03 | 0.977 | 0.98 (-1.28, 3.24) | 1.15 | 0.85 | 0.395 |
| *R OR* | FA | -0.02 (-0.08, 0.03) | 0.03 | -0.85 | 0.396 | -0.02 (-0.09, 0.05) | 0.04 | -0.62 | 0.537 |
| | MD | 0.11 (-0.92, 1.14) | 0.53 | 0.21 | 0.834 | 0.59 (-1.07, 2.26) | 0.85 | 0.70 | 0.485 |
| | AD | 0.40 (-0.69, 1.50) | 0.56 | 0.72 | 0.470 | 0.46 (-0.93, 1.85) | 0.71 | 0.65 | 0.515 |
| | RD | 0.30 (-0.76, 1.36) | 0.54 | 0.56 | 0.576 | 0.62 (-1.18, 2.41) | 0.92 | 0.67 | 0.501 |
| *L Frontal* | FA | 0.00 (-0.04, 0.04) | 0.02 | 0.14 | 0.891 | -0.02 (-0.09, 0.05) | 0.03 | -0.61 | 0.543 |
| | MD | -0.76 (-1.97, 0.46) | 0.62 | -1.22 | 0.223 | 0.14 (-1.97, 2.24) | 1.08 | 0.13 | 0.900 |
| | AD | -0.48 (-1.72, 0.75) | 0.63 | -0.77 | 0.442 | -0.10 (-2.51, 2.30) | 1.23 | -0.08 | 0.932 |
| | RD | -0.98 (-2.60, 0.64) | 0.83 | -1.19 | 0.234 | 0.03 (-2.56, 2.62) | 1.32 | 0.02 | 0.984 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *R Frontal* | FA | 0.02 (0.00, 0.05) | 0.01 | 1.66 | 0.098 | 0.02 (-0.01, 0.05) | 0.02 | 1.30 | 0.194 |
| | MD | -0.24 (-1.48, 0.99) | 0.63 | -0.39 | 0.699 | -0.43 (-3.33, 2.46) | 1.48 | -0.29 | 0.770 |
| | AD | 0.10 (-0.97, 1.17) | 0.55 | 0.18 | 0.856 | 0.09 (-3.45, 3.63) | 1.81 | 0.05 | 0.960 |
| | RD | -0.32 (-1.73, 1.10) | 0.72 | -0.44 | 0.662 | -0.45 (-3.14, 2.25) | 1.37 | -0.33 | 0.745 |
| *L Occipital* | FA | -0.01 (-0.04, 0.01) | 0.01 | -1.23 | 0.217 | -0.03 (-0.06, 0.00) | 0.01 | -2.06 | 0.039[1] |
| | MD | -0.29 (-1.56, 0.99) | 0.65 | -0.44 | 0.661 | -1.36 (-4.65, 1.93) | 1.68 | -0.81 | 0.419 |
| | AD | -0.48 (-1.68, 0.72) | 0.61 | -0.79 | 0.429 | -2.22 (-5.63, 1.20) | 1.74 | -1.27 | 0.203 |
| | RD | -0.26 (-1.27, 0.76) | 0.52 | -0.50 | 0.618 | -1.49 (-4.69, 1.71) | 1.63 | -0.91 | 0.362 |
| *R Occipital* | FA | -0.01 (-0.03, 0.02) | 0.01 | -0.45 | 0.652 | 0.01 (0.00, 0.02) | 0.01 | 1.30 | 0.192 |
| | MD | 0.28 (-0.30, 0.87) | 0.30 | 0.95 | 0.340 | 0.04 (-2.98, 3.06) | 1.54 | 0.03 | 0.980 |
| | AD | 0.33 (-1.12, 1.77) | 0.74 | 0.44 | 0.659 | 0.21 (-2.50, 2.93) | 1.39 | 0.15 | 0.877 |
| | RD | 0.19 (-0.43, 0.80) | 0.32 | 0.59 | 0.554 | -0.03 (-2.82, 2.75) | 1.42 | -0.02 | 0.981 |

Group comparisons evaluated using median regression adjusted for intrafamilial correlation among twins, as well as for potential confounding by maternal BMI at enrollment, PMA at MRI scan, infant sex and SGA status (placebo = reference).

[1] Did not survive FDR correction for multiple comparisons

AD – axial diffusivity; ALIC – anterior limb of internal capsule; FA – fractional anisotropy; Frontal – frontal lobe; L – left; OR – optic radiation; MD – mean diffusivity; Occipital – occipital lobe; PLIC – posterior limb of internal capsule; POM – pomegranate; R – right; RD – radial diffusivity; MD/AD/RD values are x10$^{-4}$

**S3 Table.** Continuous brain injury measures by study arm

| | Placebo (n=31) | | | POM (n=25) | | | MODIFIED INTENTION-TO-TREAT[1] | | | | MODIFIED INTENTION-TO-TREAT[2] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25th | 50th | 75th | 25th | 50th | 75th | Estimate (95% CI) | SE | z | P-value | Estimate (95% CI) | SE | z | P-value |
| DGM (cm²) | 11.25 | 12.10 | 13.20 | 11.50 | 12.22 | 12.60 | 0.12 (-0.82, 1.06) | 0.48 | 0.25 | 0.803 | 0.33 (-0.95, 1.61) | 0.65 | 0.51 | 0.612 |
| BPD (mm) | 78.07 | 82.01 | 88.83 | 75.80 | 79.50 | 83.70 | -2.51 (-7.75, 2.73) | 2.67 | -0.94 | 0.348 | 1.63 (-4.32, 7.59) | 3.04 | 0.54 | 0.591 |
| IHD (mm) | 1.80 | 2.56 | 4.00 | 0.97 | 1.96 | 2.40 | -0.60 (-1.52, 0.32) | 0.47 | -1.28 | 0.200 | -0.51 (-1.44, 0.42) | 0.47 | -1.08 | 0.280 |
| rLVD (mm) | 4.57 | 5.80 | 6.90 | 5.00 | 5.33 | 6.32 | -0.47 (-1.67, 0.74) | 0.61 | -0.76 | 0.447 | 0.71 (-0.83, 2.25) | 0.79 | 0.91 | 0.364 |
| lLVD (mm) | 4.76 | 5.60 | 7.90 | 5.00 | 5.70 | 6.94 | 0.10 (-1.23, 1.43) | 0.68 | 0.15 | 0.883 | 0.34 (-1.17, 1.85) | 0.77 | 0.45 | 0.655 |
| TCD (mm) | 50.23 | 53.37 | 56.40 | 49.63 | 51.50 | 53.40 | -1.87 (-4.62, 0.88) | 1.40 | -1.33 | 0.182 | 0.54 (-3.53, 4.61) | 2.08 | 0.26 | 0.794 |
| | Placebo Metabolite –ve (n=17) | | | POM Metabolite +ve (n=16) | | | PER PROTOCOL[1] | | | | PER PROTOCOL[2] | | | |
| | 25th | 50th | 75th | 25th | 50th | 75th | Estimate (95% CI) | SE | z | P-value | Estimate (95% CI) | SE | z | P-value |
| DGM (cm²) | 10.90 | 12.10 | 13.30 | 11.88 | 12.40 | 12.85 | 0.30 (-1.04, 1.64) | 0.68 | 0.44 | 0.661 | 1.22 (-0.45, 2.88) | 0.85 | 1.43 | 0.152 |
| BPD (mm) | 79.71 | 83.71 | 88.83 | 74.96 | 82.69 | 83.68 | -1.21 (-8.45, 6.03) | 3.69 | -0.33 | 0.743 | 1.12 (-6.47, 8.71) | 3.87 | 0.29 | 0.772 |
| IHD (mm) | 2.30 | 2.63 | 4.22 | 0.82 | 1.55 | 2.54 | -0.93 (-2.22, 0.35) | 0.66 | -1.42 | 0.154 | -0.68 (-1.81, 0.45) | 0.58 | -1.18 | 0.240 |
| rLVD (mm) | 4.49 | 5.22 | 6.90 | 4.60 | 5.20 | 5.89 | -0.02 (-1.95, 1.91) | 0.99 | -0.02 | 0.985 | 1.13 (-0.87, 3.12) | 1.01 | 1.10 | 0.269 |
| lLVD (mm) | 4.76 | 5.55 | 8.52 | 4.92 | 5.68 | 6.35 | 0.12 (-1.51, 1.74) | 0.83 | 0.14 | 0.890 | -0.90 (-2.90, 1.10) | 1.02 | -0.88 | 0.380 |
| TCD (mm) | 49.63 | 53.90 | 56.31 | 49.00 | 52.09 | 54.17 | -1.22 (-5.80, 3.36) | 2.34 | -0.52 | 0.602 | 1.73 (-4.31, 7.76) | 3.08 | 0.56 | 0.575 |

[1] Group comparisons evaluated using median regression adjusted for intrafamilial correlation among twins (placebo = reference).

[2] Group comparisons evaluated using median regression adjusted for intrafamilial correlation among twins, as well as for potential confounding by maternal BMI at enrollment, PMA at MRI scan, infant sex and SGA status (placebo = reference).

BPD – biparietal diameter; DGM – deep grey matter (total basal ganglia area); IHD – interhemispheric distance; lLVD – left lateral ventricle diameter; rLVD – right lateral ventricle diameter; POM – pomegranate; TCD – transverse cerebellar diameter

**S4 Table.** Brain injury scores by study arm – modified intent-to-treat (mITT) analysis.

| | Score | Placebo (n=31) | | POM (n=26) | |
|---|---|---|---|---|---|
| | | *n* | *%* | *n* | *%* |
| **WM cystic lesions** | | | | | |
| | 0 | 31 | 100.0 | 26 | 100.0 |
| | ≥ 1 | 0 | 0.0 | 0 | 0.0 |
| **WM focal signal abnormality** | | | | | |
| | 0 | 23 | 74.2 | 19 | 73.1 |
| | 1 | 5 | 16.1 | 4 | 15.4 |
| | 2 | 3 | 9.7 | 3 | 11.5 |
| **WM myelination delay** | | | | | |
| | 0 | 22 | 71.0 | 22 | 84.6 |
| | 1 | 9 | 29.0 | 4 | 15.4 |
| **WM volume reduction[1]** | | | | | |
| | 0 | 24 | 77.4 | 18 | 72.0 |
| | 1 | 6 | 19.4 | 3 | 12.0 |
| | 2 | 1 | 3.2 | 3 | 12.0 |
| | 3 | 0 | 0.0 | 1 | 4.0 |
| **Dilated ventricles[1]** | | | | | |
| | 0 | 21 | 67.7 | 20 | 80.0 |
| | 1 | 5 | 16.1 | 3 | 12.0 |
| | 2 | 5 | 16.1 | 2 | 8.0 |
| **IVH** | | | | | |
| | 0 | 30 | 96.8 | 26 | 100.0 |
| | 1 | 1 | 3.2 | 0 | 0.0 |
| **GM signal abnormality** | | | | | |
| | 0 | 31 | 100.0 | 26 | 100.0 |
| | > 0 | 0 | 0.0 | 0 | 0.0 |
| **GM gyral maturation** | | | | | |
| | 0 | 24 | 77.4 | 24 | 92.3 |
| | 1 | 6 | 19.4 | 2 | 7.7 |
| | 2 | 1 | 3.2 | 0 | 0.0 |
| **DGM signal abnormality** | | | | | |
| | 0 | 30 | 96.8 | 26 | 100.00 |
| | 1 | 1 | 3.2 | 0 | 0.00 |
| **DGM volume reduction[1]** | | | | | |
| | 0 | 31 | 100.0 | 25 | 100.0 |
| | 1 | 0 | 0.0 | 0 | 0.0 |
| **Increased extra-axial space[1]** | | | | | |
| | 0 | 23 | 74.2 | 25 | 100.0 |
| | 1 | 4 | 12.9 | 0 | 0.0 |
| | 2 | 4 | 12.9 | 0 | 0.0 |
| **CB signal abnormality** | | | | | |

| | | | | |
|---|---|---|---|---|
| **0** | 29 | 93.6 | 26 | 100.0 |
| **1** | 2 | 6.5 | 0 | 0.0 |
| **CB volume reduction[1]** | | | | |
| **0** | 24 | 77.4 | 16 | 64.0 |
| **1** | 6 | 19.4 | 8 | 32.0 |
| **2** | 1 | 3.2 | 1 | 4.0 |
| **Total WM score** | | | | |
| **0** | 9 | 29.0 | 13 | 50.0 |
| **1** | 7 | 22.6 | 2 | 7.7 |
| **2** | 9 | 29.0 | 5 | 19.2 |
| **3** | 6 | 19.4 | 4 | 15.4 |
| **4** | 0 | 0.0 | 1 | 3.9 |
| **5** | 0 | 0.0 | 1 | 3.9 |
| **Total DGM Score** | | | | |
| **0** | 30 | 96.8 | 26 | 100.0 |
| **1** | 1 | 3.2 | 0 | 0.0 |
| **Total GM Score** | | | | |
| **0** | 20 | 64.5 | 24 | 92.3 |
| **1** | 5 | 16.1 | 2 | 7.7 |
| **2** | 3 | 9.7 | 0 | 0.0 |
| **3** | 3 | 9.7 | 0 | 0.0 |
| **Total CB Score** | | | | |
| **0** | 23 | 74.2 | 17 | 65.4 |
| **1** | 7 | 22.6 | 8 | 30.8 |
| **2** | 0 | 0.0 | 1 | 3.9 |
| **3** | 1 | 3.2 | 0 | 0.0 |
| **Global Abnormality Score** | | | | |
| **0** | 5 | 16.1 | 11 | 42.3 |
| **1** | 6 | 19.4 | 3 | 11.5 |
| **2** | 8 | 25.8 | 3 | 11.5 |
| **3** | 5 | 16.1 | 5 | 19.2 |
| **4** | 2 | 6.5 | 0 | 0.0 |
| **5** | 2 | 6.5 | 3 | 115 |
| **6** | 2 | 6.5 | 1 | 3.9 |
| **8** | 1 | 3.2 | 0 | 0.0 |

[1] Metric-based data missing for 1 POM infant, percentages calculated for total number of infants for whom data were available

CB – cerebellum; DGM – deep grey matter; GM – cortical grey matter; IVH – intraventricular hemorrhage; POM – pomegranate; WM – white matter

**S5 Table.** Brain injury scores by study arm – per protocol (PP) analysis.

| | Score | Placebo Metabolite –ve (n=17) | | POM Metabolite +ve (n=17) | |
|---|---|---|---|---|---|
| | | *n* | *%* | *n* | *%* |
| **WM cystic lesions** | | | | | |
| | 0 | 17 | 100.0 | 17 | 100.0 |
| | ≥ 1 | 0 | 0.0 | 0 | 0.0 |
| **WM focal signal abnormality** | | | | | |
| | 0 | 12 | 70.6 | 15 | 88.2 |
| | 1 | 3 | 17.7 | 1 | 5.9 |
| | 2 | 2 | 11.8 | 1 | 5.9 |
| **WM myelination delay** | | | | | |
| | 0 | 12 | 70.6 | 16 | 94.1 |
| | 1 | 5 | 29.4 | 1 | 5.9 |
| **WM volume reduction[1]** | | | | | |
| | 0 | 14 | 82.4 | 12 | 75.0 |
| | 1 | 3 | 17.7 | 1 | 6.3 |
| | 2 | 0 | 0.0 | 3 | 18.8 |
| | 3 | 0 | 0.0 | 0 | 0.00 |
| **Dilated ventricles[1]** | | | | | |
| | 0 | 10 | 58.8 | 15 | 93.8 |
| | 1 | 5 | 29.4 | 1 | 6.3 |
| | 2 | 2 | 11.8 | 0 | 0.0 |
| **IVH** | | | | | |
| | 0 | 16 | 94.1 | 17 | 100.0 |
| | 1 | 1 | 5.9 | 0 | 0.0 |
| **GM signal abnormality** | | | | | |
| | 0 | 17 | 100.0 | 17 | 100.0 |
| | ≥ 1 | 0 | 0.0 | 0 | 0.0 |
| **GM gyral maturation** | | | | | |
| | 0 | 12 | 70.6 | 17 | 100.0 |
| | 1 | 4 | 23.5 | 0 | 0.0 |
| | 2 | 1 | 5.9 | 0 | 0.0 |
| **DGM signal abnormality** | | | | | |
| | 0 | 16 | 94.1 | 17 | 100.0 |
| | 1 | 1 | 5.9 | 0 | 0.0 |
| **DGM volume reduction[1]** | | | | | |
| | 0 | 17 | 100.0 | 16 | 100.0 |
| | 1 | 0 | 0.0 | 0 | 0.0 |
| **Increased extra-axial space[1]** | | | | | |
| | 0 | 12 | 70.6 | 16 | 100.0 |
| | 1 | 1 | 5.9 | 0 | 0.0 |
| | 2 | 4 | 23.5 | 0 | 0.0 |
| **CB signal abnormality** | | | | | |
| | 0 | 16 | 94.1 | 17 | 100.0 |

| | | | | | |
|---|---|---|---|---|---|
| | **1** | 1 | 5.9 | 0 | 0.0 |
| **CB volume reduction[1]** | | | | | |
| | **0** | 11 | 64.7 | 10 | 62.5 |
| | **1** | 5 | 29.4 | 5 | 31.3 |
| | **2** | 1 | 5.9 | 1 | 6.3 |
| **Total WM Score** | | | | | |
| | **0** | 3 | 17.7 | 11 | 64.7 |
| | **1** | 6 | 35.3 | 2 | 11.8 |
| | **2** | 6 | 35.3 | 2 | 11.8 |
| | **3** | 2 | 11.8 | 2 | 11.8 |
| | **4** | 0 | 0.0 | 0 | 0.0 |
| | **5** | 0 | 0.0 | 0 | 0.0 |
| **Total DGM Score** | | | | | |
| | **0** | 16 | 94.1 | 17 | 100.0 |
| | **1** | 1 | 5.9 | 0 | 0.0 |
| **Total GM Score** | | | | | |
| | **0** | 10 | 58.8 | 17 | 100.0 |
| | **1** | 2 | 11.8 | 0 | 0.0 |
| | **2** | 2 | 11.8 | 0 | 0.0 |
| | **3** | 3 | 17.7 | 0 | 0.0 |
| **Total CB Score** | | | | | |
| | **0** | 11 | 64.7 | 11 | 64.7 |
| | **1** | 5 | 29.4 | 5 | 29.4 |
| | **2** | 0 | 0.0 | 1 | 5.9 |
| | **3** | 1 | 5.9 | 0 | 0.0 |
| **Global Abnormality Score** | | | | | |
| | **0** | 0 | 0.0 | 9 | 52.9 |
| | **1** | 6 | 35.3 | 3 | 17.7 |
| | **2** | 4 | 23.5 | 1 | 5.9 |
| | **3** | 2 | 11.8 | 3 | 17.7 |
| | **4** | 1 | 5.9 | 0 | 0.0 |
| | **5** | 1 | 5.9 | 1 | 5.9 |
| | **6** | 2 | 11.8 | 0 | 0.0 |
| | **8** | 1 | 5.9 | 0 | 0.0 |

[1] Metric-based data missing for 1 POM infant, percentages calculated for total number of infants for whom data were available

CB – cerebellum; DGM – deep grey matter; GM – cortical grey matter; IVH – intraventricular hemorrhage; POM – pomegranate; WM – white matter

**S6 Table.** Brain injury scores by study arm – per protocol (PP) analysis, excluding infants born to mothers who were metabolite positive at enrollment

| | Score | Placebo Metabolite –ve n=16 | | POM Metabolite +ve n=9 | |
|---|---|---|---|---|---|
| | | *n* | *%* | *n* | *%* |
| **WM cystic lesions** | | | | | |
| | 0 | 16 | 100.0 | 9 | 100.0 |
| | ≥ 1 | 0 | 0.0 | 0 | 0.0 |
| **WM focal signal abnormality** | | | | | |
| | 0 | 12 | 75.0 | 9 | 100.0 |
| | 1 | 2 | 12.5 | 0 | 0.0 |
| | 2 | 2 | 12.5 | 0 | 0.0 |
| **WM myelination delay** | | | | | |
| | 0 | 12 | 75.0 | 8 | 88.9 |
| | 1 | 4 | 25.0 | 1 | 11.1 |
| **WM volume reduction[1]** | | | | | |
| | 0 | 13 | 81.3 | 6 | 75.0 |
| | 1 | 3 | 18.8 | 1 | 12.5 |
| | 2 | 0 | 0.0 | 1 | 12.5 |
| | 3 | 0 | 0.0 | 0 | 0.0 |
| **Dilated ventricles[1]** | | | | | |
| | 0 | 9 | 56.3 | 8 | 100.0 |
| | 1 | 5 | 31.3 | 0 | 0.0 |
| | 2 | 2 | 12.5 | 0 | 0.0 |
| **IVH** | | | | | |
| | 0 | 15 | 93.8 | 9 | 100.0 |
| | 1 | 1 | 6.3 | 0 | 0.0 |
| **GM signal abnormality** | | | | | |
| | 0 | 16 | 100.0 | 9 | 100.0 |
| | ≥ 1 | 0 | 0.0 | 0 | 0.0 |
| **GM gyral maturation** | | | | | |
| | 0 | 11 | 68.8 | 9 | 100.0 |
| | 1 | 4 | 25.0 | 0 | 0.0 |
| | 2 | 1 | 6.3 | 0 | 0.0 |
| **Increased extra-axial space[1]** | | | | | |
| | 0 | 11 | 68.8 | 8 | 100.0 |
| | 1 | 1 | 6.3 | 0 | 0.0 |
| | 2 | 4 | 25.0 | 0 | 0.0 |
| **DGM signal abnormality** | | | | | |
| | 0 | 15 | 93.8 | 9 | 100.0 |
| | 1 | 1 | 6.3 | 0 | 0.0 |
| **DGM volume reduction[1]** | | | | | |
| | 0 | 16 | 100.0 | 8 | 100.0 |
| | 1 | 0 | 0.0 | 0 | 0.0 |

| | | | | | |
|---|---|---|---|---|---|
| **CB signal abnormality** | | | | | |
| | 0 | 15 | 93.8 | 9 | 100.0 |
| | 1 | 1 | 6.3 | 0 | 0.0 |
| **CB volume reduction[1]** | | | | | |
| | 0 | 10 | 62.5 | 5 | 62.5 |
| | 1 | 5 | 31.3 | 2 | 25 |
| | 2 | 1 | 6.3 | 1 | 12.5 |
| **Total WM Score** | | | | | |
| | 0 | 3 | 18.8 | 7 | 77.8 |
| | 1 | 6 | 37.5 | 1 | 11.1 |
| | 2 | 5 | 31.3 | 0 | 0.0 |
| | 3 | 2 | 12.5 | 1 | 11.1 |
| | 4 | 0 | 0.0 | 0 | 0.0 |
| | 5 | 0 | 0.0 | 0 | 0.0 |
| **Total DGM Score** | | | | | |
| | 0 | 15 | 93.8 | 9 | 100.0 |
| | 1 | 1 | 6.3 | 0 | 0.0 |
| **Total GM Score** | | | | | |
| | 0 | 9 | 56.3 | 9 | 100.0 |
| | 1 | 2 | 12.5 | 0 | 0.0 |
| | 2 | 2 | 12.5 | 0 | 0.0 |
| | 3 | 3 | 18.8 | 0 | 0.0 |
| **Total CB Score** | | | | | |
| | 0 | 10 | 62.5 | 6 | 66.7 |
| | 1 | 5 | 31.3 | 2 | 22.2 |
| | 2 | 0 | 0.0 | 1 | 11.1 |
| | 3 | 1 | 6.3 | 0 | 0.0 |
| **Global Abnormality Score** | | | | | |
| | 0 | 0 | 0.0 | 6 | 66.7 |
| | 1 | 6 | 37.5 | 1 | 11.1 |
| | 2 | 3 | 18.8 | 1 | 11.1 |
| | 3 | 2 | 12.5 | 0 | 0.0 |
| | 4 | 1 | 6.3 | 0 | 0.0 |
| | 5 | 1 | 6.3 | 1 | 11.1 |
| | 6 | 2 | 12.5 | 0 | 0.0 |
| | 8 | 1 | 6.3 | 0 | 0.0 |

[1] Metric-based data missing for 1 POM infant, percentages calculated for total number of infants for whom data were available

CB – cerebellum; DGM – deep grey matter; GM – cortical grey matter; IVH – intraventricular hemorrhage; POM – pomegranate; WM – white matter

**S7 Table.** Brain injury and study arm, stratified by obesity status for infants with increased extra-axial space in modified intent-to-treat (mITT) analysis, and dilated ventricles in per protocol (PP) analysis

| mITT – Juice association with extra-axial space, by obesity status[1] | | | | |
|---|---|---|---|---|
| | POM (*n*=25)[2] | | Placebo (*n*=31) | |
| | Obese (*n*=6) | Non-Obese (*n*=19) | Obese (*n*=16) | Non-Obese (*n*=15) |
| Increased extra-axial space, *n (%)* | 0 (0) | 0 (0) | 6 (37.5) | 2 (13.3) |
| **PP – Juice association with enlarged ventricles, by obesity status[1]** | | | | |
| | POM Metabolite +ve (*n*=16)[2] | | Placebo Metabolite –ve (*n*=17) | |
| | Obese (*n*=4) | Non-obese (*n*=12) | Obese (*n*=10) | Non-obese (*n*=7) |
| Dilated ventricles, *n (%)* | 1 (25) | 0 (0) | 6 (60) | 1 (14.3) |

[1] Percentages shown are for infants with injury only, stratified by obesity status (cutoff, BMI > 30)

[2] Metric-based data missing for 1 POM infant, percentages calculated for total number of infants for whom data were available