Supplementary Online Content

Edwards T, Alsweiler JM, Gamble GD, et al. Neurocognitive outcomes at age 2 years after neonatal hypoglycemia in a cohort of participants from the hPOD randomized trial. JAMA Netw Open. 2022;5(10):e2235989. doi:10.1001/jamanetworkopen.2022.35989

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This supplementary material has been provided by the authors to give readers additional information about their work.
eTable 1. Maternal and infant characteristics of those included and not included in this analysis

|                        | Included Total | Not includeda Total |
|------------------------|----------------|---------------------|
| **Mothersb**           |                |                     |
| No.                    | 1180           | 164                 |
| Age, mean (SD), yearsc | 32.4 (5.3)     | 31.7 (6.0)          |
| Prioritized ethnicityd | n = 1179       | n = 155             |
| Māori                  | 213 (18.1)     | 34 (21.9)           |
| Pacific                | 103 (8.7)      | 18 (11.6)           |
| Asian                  | 187 (15.9)     | 31 (20.0)           |
| Indian                 | 156 (13.2)     | 22 (14.2)           |
| Other                  | 61 (5.2)       | 5 (3.2)             |
| European               | 459 (38.9)     | 45 (29.0)           |
| Caesarean section      | 507 (43.0)     | 67 (41.4)           |
| Mother with diabetes   | 903 (76.5)     | 118 (73.3)          |
| **Infants**            |                |                     |
| No.                    | 1194           | 165                 |
| Randomized to buccal dextrose gel | 607 (50.8) | 74 (44.9) |
| Female                 | 578 (48.4)     | 83 (50.3)           |
| Gestation, mean (SD), weeksa | 38.0 (1.2) | 38.0 (1.2) |
| Birthweight, mean (SD), gd | 3337 (647.8)  | 3276 (632.9) |
| Birthweight z-score, mean (SD) | 0.28 (1.2) | 0.17 (1.2) |
| One of Twins           | 95 (8.0)       | 9/163 (5.5)         |
| Socioeconomic decilef  | n = 1189       |                     |
| Decile 1-2 (least deprived) | 179 (15.0) |                     |
| Decile 3-4             | 228 (19.2)     |                     |
| Decile 5-6             | 252 (21.2)     |                     |
| Decile 7-8             | 279 (23.5)     |                     |
| Decile 9-10 (most deprived) | 251 (21.1) |                     |
| Primary risk factorg   |                |                     |
| Infant of mother with diabetes | 901 (75.5) | 120 (72.7) |
| Preterm                | 102 (8.5)      | 14 (8.5)            |
| Small                  | 122 (10.2)     | 19 (11.5)           |
|                          | Included Total | Not included<sup>a</sup> Total |
|--------------------------|----------------|--------------------------------|
| Large                    | 69 (5.8)       | 12 (7.3)                       |
| First blood glucose concentration, mean (SD), mg/dL<sup>h</sup> | 55.8 (13.2)    | 55.5 (13.2)                    |
| Hypoglycemia<sup>i</sup> | 490 (41.0)     | 59/157 (37.6)                  |
| Mild<sup>j</sup>         | 383 (32.1)     | 43/157 (27.4)                  |
| Severe<sup>k</sup>       | 107 (9.0)      | 16/157 (10.2)                  |
| 1-2 episodes             | 427 (35.8)     | 52/157 (33.1)                  |
| Recurrent<sup>l</sup>    | 63 (5.3)       | 7/157 (4.5)                    |
| Treatment for hypoglycemia |               |                                |
| Buccal dextrose plus feed only | 420 (35.2) | 50/163 (30.7)                  |
| Intravenous dextrose     | 36 (3.0)       | 7/163 (4.3)                    |
| Admission to NICU        | 94 (7.9)       | 11 (6.7)                       |

Data are number (%) or mean (SD). Abbreviations: SD, standard deviation; g, grams; mg/dL, milligrams per deciliter; NICU, neonatal intensive care unit.

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

<sup>a</sup>Includes 38 children not eligible for follow-up, 124 children not assessed, and three children assessed but with no blood glucose concentration data.

<sup>b</sup>Mothers included once per pregnancy because some mothers had ≥1 pregnancy and child in this cohort.

<sup>c</sup>Missing data for 2 included mother.

<sup>d</sup>Self-reported maternal ethnicity was prioritized using the New Zealand Ministry of Health classifications. “Other” included African, Canadian/Brazilian, Colombian, Fijian, Hawaiian, Indonesian, Kurdish, Latin American, Lebanese, Malaysian, Malaysian Indian, Mauritian, Middle Eastern, Nepalese, Somali, South African, and unspecified.

<sup>e</sup>Missing data for 1 included and 3 not included mothers.

<sup>f</sup>New Zealand Socioeconomic Deprivation Index (NZDep). This was not available for children not assessed.

<sup>g</sup>Primary risk factor was reported according to priority.

<sup>h</sup>Missing data for 3 included and 9 not included infants.

<sup>i</sup>Defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

<sup>j</sup>Defined as ≥1 episode of ≥36 and <47 mg/dL.

<sup>k</sup>Defined as ≥1 episode of <36 mg/dL.

<sup>l</sup>Defined as ≥3 episodes.
### Table 2. Associations between neonatal hypoglycemia and its severity and performance-based executive function tasks at 2 years

|                                | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>a</sup> (95% CI) | P value<sup>b</sup> |
|--------------------------------|---------------|----------------|-------------|-------------------------------------|---------------------|
| Simple inhibition (snack delay task) score ≤2<sup>c</sup> |               |                |             |                                     |                     |
| None (reference)               | 513/701 (73.2)|               |             |                                     | .02                 |
| Any hypoglycemia               | 371/483 (76.8)| 3.63 (-1.37 to 8.63) | 1.05 (0.98 to 1.12) | 1.03 (0.96 to 1.11) | .37                 |
| Mild hypoglycemia              | 281/377 (74.5)| 1.36 (-4.14 to 6.85) | 1.02 (0.95 to 1.10) | 1.00 (0.93 to 1.08) | .98                 |
| Severe hypoglycemia            | 90/106 (84.9) | 11.72 (4.15 to 19.30) | 1.16 (1.06 to 1.27) | 1.11 (1.01 to 1.22) | .02                 |
| Complex inhibition (fruit stroop task) score ≤2<sup>c</sup> |               |                |             |                                     | .41                 |
| None (reference)               | 351/698 (50.3)|               |             |                                     |                     |
| Any hypoglycemia               | 235/481 (48.9)| -1.43 (-7.24 to 4.38) | 0.97 (0.86 to 1.09) | 0.96 (0.86 to 1.08) | .53                 |
| Mild hypoglycemia              | 177/375 (47.2)| -3.09 (-9.36 to 3.19) | 0.94 (0.82 to 1.07) | 0.93 (0.81 to 1.06) | .26                 |
| Severe hypoglycemia            | 58/106 (54.7) | 4.43 (-5.76 to 14.62) | 1.09 (0.90 to 1.31) | 1.08 (0.89 to 1.31) | .44                 |
| Complex inhibition (reverse categorisation task) score ≤2<sup>c</sup> |               |                |             |                                     | .92                 |
| None (reference)               | 544/699 (77.8)|               |             |                                     |                     |
| Any hypoglycemia               | 372/481 (77.3)| -0.49 (-5.34 to 4.36) | 0.99 (0.93 to 1.06) | 0.99 (0.93 to 1.05) | .70                 |
| Mild hypoglycemia              | 286/375 (76.3)| -1.56 (-6.86 to 3.74) | 0.98 (0.91 to 1.05) | 0.99 (0.92 to 1.06) | .72                 |
| Severe hypoglycemia            | 86/106 (81.1) | 3.31 (-4.77 to 11.38) | 1.04 (0.94 to 1.15) | 0.99 (0.90 to 1.09) | .89                 |
| Attentional flexibility (multisearch/multilocation task) score ≤2<sup>c</sup> |               |                |             |                                     | .49                 |
| None (reference)               | 114/699 (16.3)|               |             |                                     |                     |
| Hypoglycemia                   | 80/481 (16.6) | 0.32 (-3.99 to 4.64) | 1.02 (0.79 to 1.32) | 0.93 (0.71 to 1.22) | .61                 |
| Mild hypoglycemia              | 58/375 (15.5) | -0.84 (-5.42 to 3.73) | 0.95 (0.71 to 1.27) | 0.87 (0.64 to 1.16) | .34                 |
| Severe hypoglycemia            | 22/106 (20.8) | 4.45 (-3.76 to 12.65) | 1.27 (0.85 to 1.92) | 1.09 (0.71 to 1.68) | .70                 |
Abbreviations: RD, risk difference; MD, mean difference; CI, confidence interval; RR, risk ratio. An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL. The severity of hypoglycemia was defined as none (all blood glucose concentrations ≥47 mg/dL), mild (≥1 episode of ≥36 and <47 mg/dL), and severe (≥1 episode of <36 mg/dL).

a Models compare relative risks of none vs any episode of hypoglycemia, none vs mild hypoglycemia, and none vs severe hypoglycemia. Adjustments are for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

b First P value reported in the outcome row is for the overall association between severity of hypoglycemia and outcome. P values below in the any, mild and severe rows are for the comparison between none vs any or none vs mild or none vs severe.

c Low performance defined as a score of ≤2, range 0-6, higher scores indicate better performance.
| Neurocognitive outcome                      | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD (95% CI) | P value<sup>c</sup> |
|--------------------------------------------|----------------|----------------|-------------|------------------------|-------------------|
| Moderate or severe neurosensory impairment<sup>d</sup> |                |                |             |                        | .53               |
| None (reference)                           | 20/704 (2.8)   |                |             |                        |                   |
| 1-2 episodes of hypoglycemia               | 17/424 (4.0)   | 1.17 (-1.07 to 3.41) | 1.41 (0.75 to 2.67) | 1.36 (0.71 to 2.61) | .36               |
| ≥3 episodes of hypoglycemia                | 3/63 (4.8)     | 1.92 (-3.49 to 7.33) | 1.68 (0.51 to 5.50) | 1.63 (0.49 to 5.35) | .42               |
| Cerebral palsy                             |                |                |             |                        | .21               |
| None (reference)                           | 1/700 (0.1)    |                |             |                        |                   |
| 1-2 episodes of hypoglycemia               | 1/419 (0.2)    | 0.10 (-0.45 to 0.64) | 1.67 (0.10 to 26.72) | NC                    | .84               |
| ≥3 episodes of hypoglycemia                | 1/62 (1.6)     | 1.47 (-1.68 to 4.62) | 11.29 (0.71 to 179.10) | NC                    | .10               |
| Developmental delay<sup>e</sup>            |                |                |             |                        | .12               |
| None (reference)                           | 114/701 (16.3) |                |             |                        |                   |
| 1-2 episodes of hypoglycemia               | 86/420 (20.5)  | 4.21 (-0.52 to 8.95) | 1.26 (0.98 to 1.62) | 1.24 (0.96 to 1.61) | .09               |
| ≥3 episodes of hypoglycemia                | 8/63 (12.7)    | -3.56 (-12.24 to 5.11) | 0.78 (0.40 to 1.53) | 0.75 (0.39 to 1.46) | .40               |
| Cognitive delay<sup>e</sup>                |                |                |             |                        | .28               |
| None (reference)                           | 42/703 (6.0)   |                |             |                        |                   |
| 1-2 episodes of hypoglycemia               | 33/423 (7.8)   | 1.83 (-1.28 to 4.93) | 1.31 (0.84 to 2.03) | 1.33 (0.85 to 2.08) | .21               |
| ≥3 episodes of hypoglycemia                | 2/63 (3.2)     | -2.80 (-7.48 to 1.88) | 0.53 (0.13 to 2.15) | 0.56 (0.14 to 2.25) | .41               |
| Language delay | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>b</sup> (95% CI) | P value<sup>c</sup> |
|---------------|--------------|----------------|-------------|-------------------------------------|-------------------|
| None (reference) | 104/702 (14.8) | - | - | - | .09 |
| 1-2 episodes of hypoglycemia | 79/423 (18.7) | 3.43 (-1.14 to 8.01) | 1.26 (0.97 to 1.65) | 1.25 (0.96 to 1.64) | .10 |
| ≥3 episodes of hypoglycemia | 6/63 (9.5) | -5.29 (-13.01 to 2.43) | 0.64 (0.29 to 1.41) | 0.61 (0.28 to 1.34) | .22 |

| Motor delay | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>b</sup> (95% CI) | P value<sup>c</sup> |
|---------------|--------------|----------------|-------------|-------------------------------------|-------------------|
| None (reference) | 10/702 (1.4) | - | - | - | .45 |
| 1-2 episodes of hypoglycemia | 7/420 (1.7) | 0.24 (-1.27 to 1.75) | 1.17 (0.45 to 3.05) | 1.20 (0.45 to 3.17) | .71 |
| ≥3 episodes of hypoglycemia | 2/63 (3.2) | 1.75 (-2.67 to 6.17) | 2.23 (0.50 to 9.97) | 2.42 (0.54 to 10.86) | .25 |

| Bayley-III cognitive score, mean (SD) [total] | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>b</sup> (95% CI) | P value<sup>c</sup> |
|-----------------------------------------------|--------------|----------------|-------------|-------------------------------------|-------------------|
| None (reference) | 99.0 (11.2) [n = 703] | - | - | - | .01 |
| 1-2 episodes of hypoglycemia | 97.5 (11.2) [n = 423] | -1.57 (-2.93 to -0.22) | -1.80 (-3.17 to -0.44) | .01 |
| ≥3 episodes of hypoglycemia | 100.3 (11.3) [n = 63] | 1.28 (-1.62 to 4.17) | 0.81 (-2.04 to 3.66) | .52 |

| Bayley-III language score, mean (SD) [total] | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>b</sup> (95% CI) | P value<sup>c</sup> |
|-----------------------------------------------|--------------|----------------|-------------|-------------------------------------|-------------------|
| None (reference) | 98.6 (15.0) [n = 702] | - | - | - | .04 |
| 1-2 episodes of hypoglycemia | 97.6 (15.5) [n = 423] | -1.01 (-2.86 to 0.84) | -1.18 (-3.03 to 0.67) | .21 |
| Condition                              | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MDb (95% CI) | P valuec |
|----------------------------------------|---------------|----------------|-------------|--------------------------|----------|
| ≥3 episodes of hypoglycemia            | 102.8 (16.9)  | 4.21 (0.26 to 8.16) | 3.79 (-0.05 to 7.62) | .05 |
| Bayley-III motor score, mean (SD) [total]a |               |                |             |                          | .004     |
| None (reference)                       | 104.8 (10.8)  | -2.01 (-3.29 to -0.73) | -2.23 (-3.53 to -0.92) | .001     |
| 1-2 episodes of hypoglycemia           | 102.8 (10.0)  | -0.56 (-3.29 to 2.18) | -0.77 (-3.59 to 2.05) | .59      |
| Poor executive functionf               | 36/701 (5.1)  |               |             |                          | .41      |
| Executive function total score, mean (SD) [total]g |               |                |             |                          | .71      |
| Simple inhibition (snack delay task) score ≤2h |               |                |             |                          | .16      |
| None (reference)                       | 513/701 (73.2) |                |             |                          |          |

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| Complex inhibition (fruit stroop task) score ≤2<sup>h</sup> | No./total (%) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>b</sup> (95% CI) | P value<sup>c</sup> |
|----------------------------------------------------------|----------------|----------------|-------------|----------------------------------|-----------------|
| 1-2 episodes of hypoglycemia                              | 327/420 (77.9) | 4.68 (-0.48 to 9.83) | 1.06 (0.99 to 1.14) | 1.05 (0.98 to 1.13) | .19             |
| ≥3 episodes of hypoglycemia                               | 44/63 (69.8)  | -3.34 (-15.16 to 8.48) | 0.95 (0.81 to 1.13) | 0.90 (0.76 to 1.07) | .24             |
| Complex inhibition (reverse categorisation task) score ≤2<sup>h</sup> | None (reference) | 351/698 (50.3) |                           |                  | .70             |
| 1-2 episodes of hypoglycemia                              | 207/418 (49.5) | -0.77 (-6.83 to 5.30) | 0.98 (0.87 to 1.11) | 0.97 (0.86 to 1.10) | .62             |
| ≥3 episodes of hypoglycemia                               | 28/63 (44.4)  | -5.84 (-18.68 to 7.00) | 0.88 (0.66 to 1.18) | 0.90 (0.67 to 1.19) | .46             |
| Attentional flexibility (multisearch/multilocation task) score ≤2<sup>h</sup> | None (reference) | 544/699 (77.8) |                           |                  | .92             |
| 1-2 episodes of hypoglycemia                              | 324/419 (77.3) | -0.50 (-5.56 to 4.56) | 0.99 (0.93 to 1.06) | 0.99 (0.93 to 1.06) | .76             |
| ≥3 episodes of hypoglycemia                               | 48/62 (77.4)  | -0.41 (-11.28 to 10.46) | 0.99 (0.86 to 1.14) | 1.01 (0.88 to 1.16) | .88             |

Abbreviations: RD, risk difference; MD, mean difference; CI, confidence interval; RR, risk ratio; NC, not calculated due to small numbers; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition (mean=100, SD=15, range=40-160, higher scores indicate better performance); SD, standard deviation.

<sup>a</sup> The frequency of hypoglycemia was defined as none (all blood glucose concentrations ≥47 mg/dL), 1-2 episodes of consecutive blood glucose concentrations of <47 mg/dL, and recurrent (≥3 episodes of consecutive blood glucose concentrations of <47 mg/dL).

<sup>b</sup> Adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

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First $P$ value reported in the outcome row is for the overall association between frequency of hypoglycemia and outcome. $P$ values below in 1-2 and ≥3 rows are for the comparison between none vs 1-2 episodes or none vs ≥3 episodes.

Defined as any of: blindness, hearing impairment requiring aids, moderate or severe cerebral palsy (not walking yet or permanently non-ambulant) or moderate or severe developmental delay.

One child in the hypoglycemia group was assigned a score of 49 for the Bayley-III cognitive, language and motor scales because the child was unable to finish the assessment due to severe delay. Language, cognitive and motor scales, mean 100, SD 15, higher scores indicate better performance.

Defined as an executive function total score more than 1.5 SD below the mean.

Total score range 0-24 points, higher scores indicate better performance.

Low performance defined as a score of ≤2, range 0-6, higher scores indicate better performance.
**Table 4. Interaction between treatment and the association between frequency of hypoglycemia and neurocognitive outcomes at 2 years**

| Neurosensory impairment | ≥3 episodes (N = 63) | 1-2 episodes (N = 427) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD\(^a\) (95% CI) | P value for interaction |
|-------------------------|----------------------|------------------------|----------------|-------------|-------------------------------|------------------------|
| Buccal dextrose gel plus feed | 9/51 (17.6) | 85/360 (23.6) | -5.96 (-17.34 to 5.42) | 0.75 (0.40 to 1.39) | 0.75 (0.41 to 1.38) | .78 |
| Intravenous dextrose | 3/12 (25.0) | 4/21 (19.0) | 5.95 (-24.96 to 36.86) | 1.31 (0.33 to 5.17) | 0.90 (0.00 to 366.29) |             |

**Moderate or severe neurosensory impairment**

| Buccal dextrose gel plus feed | 1/51 (2.0) | 15/360 (4.2) | -2.21 (-6.55 to 2.14) | 0.47 (0.06 to 3.51) | 0.56 (0.08 to 4.11) | .39 |
| Intravenous dextrose | 2/12 (16.7) | 1/21 (4.8) | 11.90 (-12.00 to 35.81) | 3.50 (0.32 to 38.06) | 1.31 (0.02 to 84.85) |             |

**Developmental delay\(^b\)**

| Buccal dextrose gel plus feed | 6/51 (11.8) | 72/356 (20.2) | -8.46 (-18.27 to 1.35) | 0.58 (0.27 to 1.27) | 0.57 (0.26 to 1.23) | .84 |
| Intravenous dextrose | 2/12 (16.7) | 4/21 (19.1) | -2.38 (-30.43 to 25.67) | 0.88 (0.18 to 4.35) | 0.64 (0.01 to 31.81) |             |

**Cognitive delay\(^b\)**

| Buccal dextrose gel plus feed | 1/51 (2.0) | 28/359 (7.8) | -5.84 (-10.56 to -1.12) | 0.25 (0.03 to 1.82) | 0.30 (0.04 to 2.16) | .78 |
| Intravenous dextrose | 1/12 (8.3) | 2/21 (9.5) | -1.19 (-22.06 to 19.68) | 0.88 (0.08 to 9.51) | 1.04 (0.01 to 123.21) |             |

**Language delay\(^b\)**

| Buccal dextrose gel plus feed | 4/51 (7.8) | 67/359 (18.7) | -10.82 (-19.25 to -2.39) | 0.42 (0.16 to 1.11) | 0.40 (0.15 to 1.05) | .85 |
| Intravenous dextrose | 2/12 (16.7) | 4/21 (19.1) | -2.38 (-30.43 to 25.67) | 0.88 (0.18 to 4.35) | 0.64 (0.01 to 31.81) |             |

**Motor delay\(^c\)**

| Buccal dextrose gel plus feed | 1/51 (2.0) | 6/356 (1.7) | 0.28 (-3.77 to 4.32) | 1.16 (0.14 to 9.53) | 1.20 (0.15 to 9.61) | .92 |
| Intravenous dextrose | 1/12 (8.3) | 1/21 (4.8) | 3.57 (-15.26 to 22.40) | 1.75 (0.11 to 28.44) | 1.13 (0.01 to 97.55) |             |

**Bayley-III cognitive score, mean (SD)\(^c\)**

| Buccal dextrose gel plus feed | 101.6 (11.5) [n = 51] | 97.5 (11.0) [n = 359] | 4.11 (0.86 to 7.36) | 4.18 (0.90 to 7.45) | .23 |
| Intravenous dextrose | 95.0 (9.3) [n = 12] | 98.1 (16.2) [n = 21] | -3.10 (-13.55 to 7.36) | 1.43 (-11.03 to 13.88) |             |
|                          | ≥3 episodes                  | 1-2 episodes                  | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MDa (95% CI) | P value for interaction |
|--------------------------|-----------------------------|------------------------------|----------------|-------------|--------------------------|------------------------|
| Bayley-III language score, mean (SD)b | 105.5 (16.9) [n = 51] | 97.6 (15.7) [n = 359] | 7.89 (3.23 to 12.56) | 7.80 (3.13 to 12.48) | .07 | |
| Buccal dextrose gel plus feed | 97.6 (11.5) [n = 356] | 97.3 (11.5) [n = 21] | -5.75 (-16.52 to 5.02) | -2.92 (-17.43 to 11.59) | |
| Intravenous dextrose | 105.4 (12.3) [n = 51] | 102.9 (10.2) [n = 356] | 2.49 (-0.58 to 5.57) | 2.72 (-0.39 to 5.84) | .36 | |
| Bayley-III motor score, mean (SD)b | 99.5 (9.7) [n = 12] | 100.8 (9.2) [n = 21] | -1.26 (-8.19 to 5.67) | -1.73 (-12.25 to 8.78) | |
| Buccal dextrose gel plus feed | 105.4 (12.3) [n = 51] | 102.9 (10.2) [n = 356] | 2.49 (-0.58 to 5.57) | 2.72 (-0.39 to 5.84) | .36 | |
| Intravenous dextrose | 99.5 (9.7) [n = 12] | 100.8 (9.2) [n = 21] | -1.26 (-8.19 to 5.67) | -1.73 (-12.25 to 8.78) | |
| Poor executive functionc | 2/51 (3.9) | 27/356 (7.6) | -3.66 (-9.68 to 2.35) | 0.52 (0.13 to 2.12) | 0.42 (0.10 to 1.73) | .52 | |
| Buccal dextrose gel plus feed | 1/12 (8.3) | 1/21 (4.8) | 3.57 (-15.26 to 22.40) | 1.75 (0.11 to 28.44) | 1.13 (0.01 to 97.55) | |
| Intravenous dextrose | 1/12 (8.3) | 1/21 (4.8) | 3.57 (-15.26 to 22.40) | 1.75 (0.11 to 28.44) | 1.13 (0.01 to 97.55) | |
| Executive function total score, mean (SD)d | 10.6 (4.8) [n = 51] | 10.3 (4.5) [n = 356] | 0.29 (-1.05 to 1.64) | 0.47 (-0.88 to 1.82) | .50 | |
| Buccal dextrose gel plus feed | 10.5 (5.1) [n = 12] | 9.0 (3.5) [n = 21] | 1.45 (-1.58 to 4.48) | 0.75 (-3.31 to 4.80) | |
| Intravenous dextrose | 10.6 (4.8) [n = 51] | 10.3 (4.5) [n = 356] | 0.29 (-1.05 to 1.64) | 0.47 (-0.88 to 1.82) | .50 | |

Abbreviations: RD, risk difference; CI, confidence interval; RR, risk ratio; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition (mean=100, SD=15, range=40-160, higher scores indicate better performance); SD, standard deviation.

An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

Nine children who received treatment but did not have recorded episodes of hypoglycemia were excluded.

a Generalized linear models adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

b One child in the hypoglycemia group was assigned a score of 49 for the Bayley-III cognitive, language and motor scales because the child was unable to finish the assessment due to severe delay.

c Poor executive function was defined as an executive function total score more than 1.5 SD below the mean.

d Total score range 0-24 points, higher scores indicate better performance.
| Outcome                                      | Subgroup | No. & Total (%) | Hypoglycemia \(^a\)  (n = 490) | No Hypoglycemia  (n = 704) | RD/MD  (95% CI) | RR  (95% CI) | Adjusted RR/MD\(^b\)  (95% CI) | P value for interaction |
|---------------------------------------------|----------|----------------|---------------------------------|---------------------------|-----------------|--------------|-------------------------------|------------------------|
| Neurosensory impairment                      | IDM      | 87/349 (24.9)  | 7.26 (1.71 to 12.82) | 1.41 (1.09 to 1.82) | 1.42 (1.10 to 1.83) | .18          |
|                                             | Other    | 24/138 (17.4)  | -0.67 (-9.47 to 8.12) | 0.96 (0.59 to 1.58)  | 1.00 (0.61 to 1.63) |             |
| Moderate or severe neurosensory impairment   | IDM      | 16/349 (4.6)   | 2.03 (-0.53 to 4.60) | 1.80 (0.89 to 3.64) | 1.81 (0.88 to 3.71) | .26          |
|                                             | Other    | 4/138 (2.9)    | -0.97 (-5.12 to 3.18) | 0.75 (0.21 to 2.61) | 0.74 (0.20 to 2.77) |             |
| Blindness                                   | IDM      | 1/349 (0.3)    | 0.29 (NE)                    | NE                        | NE              |             |
|                                             | Other    | 1/138 (0.7)    | 0.72 (NE)                    | NE                        | NE              |             |
| Hearing impairment                          | IDM      | 2/349 (0.6)    | 0.57 (NE)                    | NE                        | NE              |             |
|                                             | Other    | 1/138 (0.7)    | 0.72 (NE)                    | NE                        | NE              |             |
| Cerebral palsy                              | IDM      | 2/344 (0.6)    | 0.58 (NE)                    | NE                        | NE              |             |
|                                             | Other    | 0/137 (0.0)    | -0.65 (NE)                   | NE                        | NE              |             |
| Developmental delay\(^c\)                   | IDM      | 75/346 (21.7)  | 5.62 (0.29 to 10.94) | 1.35 (1.02 to 1.78) | 1.34 (1.02 to 1.77) | .12          |
|                                             | Other    | 19/137 (13.9)  | -3.13 (-11.46 to 5.21)      | 0.82 (0.47 to 1.41)     | 0.84 (0.50 to 1.44) |             |
| Cognitive delay\(^c\)                       | IDM      | 28/348 (8.1)   | 2.22 (-1.25 to 5.69)        | 1.38 (0.85 to 2.25)     | 1.42 (0.87 to 2.34) | .29          |
|                                             | Other    | 7/138 (5.1)    | -1.42 (-6.79 to 3.95)       | 0.78 (0.30 to 2.00)     | 1.02 (0.39 to 2.72) |             |
| Language delay\(^c\)                        | IDM      | 67/348 (19.3)  | 4.65 (-0.44 to 9.75)        | 1.32 (0.98 to 1.77)     | 1.31 (0.97 to 1.76) | .18          |
|                                             | Other    | 18/138 (13.0)  | -2.54 (-10.60 to 5.52)      | 0.84 (0.47 to 1.48)     | 0.97 (0.84 to 1.12) |             |
| Motor delay\(^c\)                           | IDM      | 6/346 (1.7)    | 0.46 (-1.21 to 2.13)        | 1.36 (0.46 to 4.02)     | 1.53 (0.51 to 4.62) | .90          |
|                                             | Other    | 3/137 (2.2)    | 0.23 (-3.08 to 3.53)        | 1.12 (0.23 to 5.48)     | 1.43 (0.27 to 7.62) |             |

\(^a\) Number of participants who experienced hypoglycemia.  
\(^b\) Adjusted for age, sex, race, and physician.  
\(^c\) Denotes subgroup analysis.
| Outcome                              | Subgroup | Hypoglycemia<sup>a</sup> (n = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>b</sup> (95% CI) | P value for interaction |
|--------------------------------------|----------|-----------------------------------|--------------------------|--------------|-------------|-------------------------------------|-------------------------|
| Bayley-III cognitive score, mean (SD)<sup>c</sup> | IDM      | 97.3 (11.1) [n = 348]            | 99.0 (10.9) [n = 549]    | -1.69 (-3.16 to -0.21) | 1.79 (-3.26 to -0.32) | .24                                 |
|                                      | Other    | 99.2 (11.5) [n = 138]            | 99.2 (12.4) [n = 154]    | 0.02 (-2.79 to 2.75)    | -0.63 (-3.42 to 2.17) | .13                                 |
| Bayley-III language score, mean (SD)<sup>c</sup> | IDM      | 97.3 (15.7) [n = 348]            | 98.5 (14.7) [n = 548]    | -1.21 (-3.24 to 0.82)   | -1.13 (-3.14 to 0.89) | .13                                 |
|                                      | Other    | 100.9 (15.8) [n = 138]           | 99.2 (16.1) [n = 154]    | 1.71 (-1.97 to 5.39)    | 1.17 (-2.56 to 4.89)  | .24                                 |
| Bayley-III motor score, mean (SD)<sup>c</sup> | IDM      | 102.4 (10.1) [n = 346]           | 104.7 (10.5) [n = 549]   | -2.35 (-3.74 to -0.95)  | -2.35 (-3.76 to -0.93) | .24                                 |
|                                      | Other    | 104.5 (10.4) [n = 137]           | 105.1 (12.0) [n = 153]   | -0.57 (-3.18 to 2.04)   | -1.19 (-3.84 to 1.46) | .70                                 |
| Poor executive function<sup>d</sup>  | IDM      | 24/345 (7.0) [n = 345]           | 29/548 (5.3) [n = 548]   | 1.67 (-1.61 to 4.94)    | 1.38 (0.81 to 2.35)   | .99                                 |
|                                      | Other    | 9/138 (6.5) [n = 138]            | 7/153 (4.6) [n = 153]    | 1.95 (-3.36 to 7.25)    | 1.43 (0.54 to 3.74)   | .61                                 |
| Executive function total score, mean (SD)<sup>e</sup> | IDM      | 10.2 (4.4) [n = 345]             | 10.5 (4.4) [n = 548]     | -0.37 (-0.97 to 0.22)   | -0.32 (-0.91 to 0.28) | .61                                 |
|                                      | Other    | 10.6 (4.6) [n = 138]             | 10.8 (4.5) [n = 153]     | -0.19 (-1.25 to 0.86)   | -0.06 (-1.12 to 1.00) | .46                                 |
| Simple inhibition (snack delay task) score ≤2 | IDM      | 274/345 (79.4) [n = 345]         | 407/548 (74.3) [n = 548] | 5.15 (-0.48 to 10.78)   | 1.07 (0.99 to 1.15)   | .04 (0.96 to 1.13)                 | .46                     |
|                                      | Other    | 97/138 (70.3) [n = 138]          | 106/153 (69.3) [n = 153] | 1.01 (-9.60 to 11.62)   | 1.01 (0.87 to 1.18)   | 0.96 (0.81 to 1.14)                | .61                     |
| Complex inhibition (fruit stroop task) score ≤2 | IDM      | 175/343 (51.0) [n = 343]         | 282/547 (51.6) [n = 548] | -0.53 (-7.29 to 6.22)   | 0.99 (0.87 to 1.13)   | 1.00 (0.88 to 1.14)                | .70                     |
|                                      | Other    | 60/138 (43.5) [n = 138]          | 69/151 (45.7) [n = 153]  | -2.22 (-13.73 to 9.30)  | 0.95 (0.73 to 1.23)   | 0.95 (0.73 to 1.23)                | .21                     |
| Complex inhibition (reverse categorisation task) score ≤2 | IDM      | 272/344 (79.1) [n = 344]         | 423/547 (77.3) [n = 547] | 1.74 (-3.82 to 7.30)    | 1.02 (0.95 to 1.10)   | 1.02 (0.95 to 1.09)                | .21                     |
|                                      | Other    | 100/137 (73.0) [n = 137]         | 121/152 (79.6) [n = 152] | -6.61 (-16.47 to 3.24)  | 0.92 (0.80 to 1.04)   | 0.97 (0.86 to 1.10)                | .21                     |
| Outcome | Subgroup | Hypoglycemia\(^a\) (n = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD\(^b\) (95% CI) | P value for interaction |
|---------|----------|-----------------------------|-----------------------------|----------------|------------|-----------------------------|------------------------|
| Attentional flexibility (multisearch/multilocation task) score ≤2 | IDM | 56/345 (16.2) | 87/548 (15.9) | 0.36 (-4.60 to 5.31) | 1.02 (0.75 to 1.39) | 1.00 (0.73 to 1.36) | .73 |
| | Other | 24/136 (17.7) | 27/151 (17.9) | 0.23 (-9.13 to 8.66) | 0.99 (0.60 to 1.63) | 0.87 (0.53 to 1.44) | .73 |

Abbreviations: RD, risk difference; CI, confidence interval; RR, risk ratio; NE, not estimable; Bayley-III, Bayley-Scales of Infant and Toddler Development, Third Edition (mean=100, SD=15, range=40-160, higher scores indicate better performance); SD, standard deviation.

\(^a\) An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

\(^b\) Generalized linear models adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

\(^c\) One child who became hypoglycaemic was assigned a score of 49 for the Bayley-III cognitive, language and motor scales due to severe delay.

\(^d\) Poor executive function defined as an executive function total score more than 1.5 SD below the mean.

\(^e\) Total score range 0-24 points, higher scores indicate better performance.
### eTable 6. Selected neurocognitive outcomes in boys and girls who did and did not experience hypoglycemia (subgroup analysis)

| Outcome                          | Subgroup      | Hypoglycemia (n = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD (95% CI) | P value for interaction |
|----------------------------------|---------------|------------------------|---------------------------|----------------|-------------|------------------------|-------------------------|
| **Neurosensory impairment**      | Boys          | 76/268 (28.4)          | 76/346 (22.0)             | 6.39 (-0.56 to 13.35) | 1.29 (0.98 to 1.70) | 1.27 (0.95 to 1.69)   | .85                     |
|                                  | Girls         | 35/219 (16.0)          | 49/358 (13.7)             | 2.30 (-3.74 to 8.33)  | 1.17 (0.78 to 1.74) | 1.12 (0.75 to 1.67)   |                         |
| **Moderate or severe neurosensory impairment** | Boys          | 15/268 (5.6)           | 13/346 (3.8)              | 1.84 (-1.57 to 5.25)  | 1.49 (0.72 to 3.08) | 1.60 (0.76 to 3.38)   | .70                     |
|                                  | Girls         | 5/219 (2.3)            | 7/358 (2.0)               | 0.33 (-2.12 to 2.78)  | 1.17 (0.37 to 3.64) | 0.98 (0.32 to 3.06)   |                         |
| **Blindness**                    | Boys          | 1/268 (0.4)            | 0/346 (0.0)               | 0.37 (NE)            | NE           | NE                     |                         |
|                                  | Girls         | 1/219 (0.5)            | 0/356 (0.0)               | 0.46 (NE)            | NE           | NE                     |                         |
| **Hearing impairment**           | Boys          | 2/268 (0.8)            | 0/346 (0.0)               | 0.75 (NE)            | NE           | NE                     |                         |
|                                  | Girls         | 1/219 (0.5)            | 0/356 (0.0)               | 0.46 (NE)            | NE           | NE                     |                         |
| **Cerebral palsy**               | Boys          | 0/264 (0.0)            | 1/345 (0.3)               | -0.29 (NE)           | NE           | NE                     |                         |
|                                  | Girls         | 2/217 (0.9)            | 0/355 (0.0)               | 0.92 (NE)            | NE           | NE                     |                         |
| **Developmental delay**          | Boys          | 65/266 (24.4)          | 72/345 (20.9)             | 3.57 (-3.16 to 10.29) | 1.17 (0.87 to 1.57) | 1.12 (0.83 to 1.53)   | .90                     |
|                                  | Girls         | 29/217 (13.4)          | 42/356 (11.8)             | 1.57 (-4.08 to 7.21) | 1.13 (0.73 to 1.76) | 1.06 (0.68 to 1.65)   |                         |
| **Cognitive delay**              | Boys          | 28/268 (10.5)          | 31/345 (9.0)              | 1.46 (-3.29 to 6.22) | 1.16 (0.71 to 1.89) | 1.13 (0.68 to 1.86)   | .93                     |
|                                  | Girls         | 7/218 (3.2)            | 11/358 (3.1)              | 0.14 (-2.81 to 3.09) | 1.05 (0.41 to 2.66) | 1.11 (0.43 to 2.84)   |                         |
| **Language delay**               | Boys          | 59/268 (22.0)          | 66/345 (19.1)             | 2.88 (-3.60 to 9.37) | 1.15 (0.84 to 1.57) | 1.12 (0.81 to 1.55)   | .98                     |
|                                  | Girls         | 26/218 (11.9)          | 38/357 (10.6)             | 1.28 (-4.09 to 6.66) | 1.12 (0.70 to 1.79) | 1.03 (0.65 to 1.66)   |                         |
| **Motor delay**                  | Boys          | 7/266 (2.6)            | 8/345 (2.3)               | 0.31 (-2.19 to 2.81) | 1.13 (0.42 to 3.10) | 1.29 (0.46 to 3.64)   | .88                     |
|                                  | Girls         | 2/217 (0.9)            | 2/357 (0.6)               | 0.36 (-1.13 to 1.85) | 1.65 (0.23 to 11.64)| 1.38 (0.19 to 10.16)  |                         |
| Outcome                                           | Subgroup | Hypoglycemia<sup>a</sup> (n = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD<sup>b</sup> (95% CI) | P value for interaction |
|--------------------------------------------------|----------|-----------------------------------|---------------------------|----------------|-------------|-------------------------------------|------------------------|
| Bayley-III cognitive score, mean (SD)<sup>c</sup> | Boys     | 96.3 (12.2) [n = 268]             | 97.7 (12.0) [n = 345]     | -1.37 (-3.31 to 0.56) | -1.72 (-3.68 to 0.25) | -0.87 (-2.56 to 0.83) | .63 |
|                                                  | Girls    | 99.7 (9.5) [n = 218]              | 100.3 (10.4) [n = 358]    | -0.63 (-2.33 to 1.06)  | -1.68 (-4.18 to 0.82) | .19 |
| Bayley-III language score, mean (SD)<sup>c</sup> | Boys     | 95.1 (16.0) [n = 268]             | 96.3 (14.9) [n = 345]     | -1.15 (-3.60 to 1.31)  | -1.58 (-3.32 to 3.85) | .63 |
|                                                  | Girls    | 102.2 (14.7) [n = 218]            | 100.9 (14.9) [n = 357]    | 1.29 (-1.21 to 3.78)   | 1.36 (-1.13 to 3.85)  | .63 |
| Bayley-III motor score, mean (SD)<sup>c</sup>    | Boys     | 101.7 (10.4) [n = 266]            | 103.6 (11.3) [n = 345]    | -1.96 (-3.71 to -0.21) | -2.45 (-4.25 to -0.65) | .35 |
|                                                  | Girls    | 104.6 (9.9) [n = 217]             | 105.9 (10.2) [n = 357]    | -1.35 (-3.06 to 0.35)  | -1.58 (-3.32 to 0.16) | .19 |
| Poor executive function<sup>d</sup>              | Boys     | 22/266 (9.0) [n = 268]            | 16/344 (4.7) [n = 345]    | 3.62 (-0.38 to 7.62)   | 1.94 (1.05 to 3.58)   | 1.76 (0.93 to 3.35)   | .09 |
|                                                  | Girls    | 9/217 (4.2) [n = 217]             | 20/357 (5.6) [n = 357]    | -1.46 (-5.03 to 2.12)  | 0.74 (0.34 to 1.60)   | 0.77 (0.36 to 1.67)   | .63 |
| Executive function total score, mean (SD)<sup>e</sup> | Boys     | 9.8 (4.5) [n = 266]               | 10.3 (4.5) [n = 344]      | -0.56 (-1.28 to 0.15)  | -0.38 (-1.11 to 0.35) | .35 |
|                                                  | Girls    | 10.9 (4.4) [n = 217]              | 10.8 (4.4) [n = 357]      | 0.09 (-0.65 to 0.83)   | 0.18 (-0.56 to 0.93)  | .64 |
| Simple inhibition (snack delay task) score ≤2   | Boys     | 210/266 (79.0) [n = 268]          | 263/344 (76.5) [n = 345]  | 2.49 (-4.16 to 9.15)   | 1.03 (0.95 to 1.12)   | 0.99 (0.89 to 1.10)   | .22 |
|                                                  | Girls    | 161/217 (74.2) [n = 217]          | 250/357 (70.0) [n = 357]  | 4.17 (-3.37 to 11.70)  | 1.06 (0.95 to 1.18)   | 1.05 (0.95 to 1.17)   | .10 |
| Complex inhibition (fruit stroop task) score ≤2 | Boys     | 140/264 (53.0) [n = 268]          | 169/342 (49.4) [n = 344]  | 3.62 (-4.42 to 11.65)  | 1.07 (0.92 to 1.25)   | 1.06 (0.90 to 1.24)   | .45 |
|                                                  | Girls    | 95/217 (43.8) [n = 217]           | 182/356 (51.1) [n = 357]  | -7.35 (-15.76 to 1.07) | 0.86 (0.71 to 1.03)   | 0.84 (0.70 to 1.01)   | .10 |
| Complex inhibition (reverse categorisation task) score ≤2 | Boys     | 205/265 (77.4) [n = 268]          | 272/343 (79.3) [n = 345]  | -1.94 (-8.57 to 4.69)  | 0.98 (0.90 to 1.06)   | 0.97 (0.88 to 1.07)   | .10 |
|                                                  | Girls    | 167/216 (77.3) [n = 217]          | 272/356 (76.4) [n = 357]  | 0.91 (-6.22 to 8.04)   | 1.01 (0.92 to 1.11)   | 1.03 (0.94 to 1.13)   | .64 |
| Attentional flexibility (multisearch/multilocation task) score ≤2 | Boys     | 48/265 (18.1) [n = 268]           | 55/343 (16.0) [n = 345]   | 2.08 (-3.98 to 8.14)   | 1.13 (0.79 to 1.61)   | 0.97 (0.66 to 1.41)   | .64 |
|                                                  | Girls    | 32/216 (14.8) [n = 217]           | 59/356 (16.6) [n = 357]   | -1.76 (-7.88 to 4.37)  | 0.89 (0.60 to 1.33)   | 0.85 (0.57 to 1.27)   | .64 |
Abbreviations: RD, risk difference; CI, confidence interval; RR, risk ratio; NE, not estimable; Bayley-III, Bayley-Scales of Infant and Toddler Development, Third Edition (mean=100, SD=15, range=40-160, higher scores indicate better performance); SD, standard deviation.

a An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

b Generalized linear models adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

c One child who became hypoglycaemic was assigned a score of 49 for the Bayley-III cognitive, language and motor scales due to severe delay.

d Poor executive function defined as an executive function total score more than 1.5 SD below the mean.

e Total score range 0-24 points, higher scores indicate better performance.
### Table 7. Selected neurocognitive outcomes in children who did and did not experience hypoglycemia, excluding children with postneonatal diagnoses likely to affect the outcome (sensitivity analysis)

| Analysis group                                           | No./total (%)                  | Hypoglycemiaa (N = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MDb (95% CI) | P value |
|----------------------------------------------------------|--------------------------------|--------------------------|---------------------------|----------------|-------------|--------------------------|---------|
| Neurosensory impairment                                  |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 111/487 (22.8)                 | 125/704 (17.8)           | 5.04 (0.36 to 9.72)       | 1.28 (1.02 to 1.61) | 1.28 (1.01 to 1.60) | .04          |
| Diagnoses excluded                                       | 110/484 (22.7)                 | 123/698 (17.6)           | 5.11 (0.42 to 9.79)       | 1.29 (1.02 to 1.62) | 1.29 (1.02 to 1.62) | .03          |
| Moderate or severe neurosensory impairment               |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 20/487 (4.1)                   | 20/704 (2.8)             | 1.27 (-0.88 to 3.42)      | 1.45 (0.79 to 2.66) | 1.41 (0.76 to 2.62) | .28          |
| Diagnoses excluded                                       | 19/484 (3.9)                   | 18/698 (2.6)             | 1.35 (-0.75 to 3.44)      | 1.52 (0.81 to 2.87) | 1.53 (0.80 to 2.92) | .20          |
| Cerebral palsy                                           |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 2/481 (0.4)                    | 1/700 (0.1)              | 0.27 (-0.37 to 0.91)      | 2.91 (0.26 to 32.09) | 2.44 (0.20 to 29.14) | .48          |
| Diagnoses excluded                                       | 2/478 (0.4)                    | 1/694 (0.1)              | 0.27 (-0.37 to 0.92)      | 2.90 (0.26 to 32.01) | 2.44 (0.20 to 29.14) | .48          |
| Developmental delayc                                      |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 94/483 (19.5)                  | 114/701 (16.3)           | 3.20 (-1.27 to 7.67)      | 1.20 (0.93 to 1.53) | 1.18 (0.92 to 1.51) | .19          |
| Diagnoses excluded                                       | 93/480 (19.4)                  | 112/695 (16.1)           | 3.26 (-1.21 to 7.73)      | 1.20 (0.94 to 1.54) | 1.19 (0.93 to 1.53) | .17          |
| Cognitive delayc                                         |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 35/486 (7.2)                   | 42/703 (6.0)             | 1.16 (-1.72 to 4.03)      | 1.21 (0.78 to 1.86) | 1.22 (0.79 to 1.89) | .37          |
| Diagnoses excluded                                       | 34/483 (7.0)                   | 41/697 (5.9)             | 1.16 (-1.72 to 4.03)      | 1.20 (0.77 to 1.86) | 1.23 (0.79 to 1.92) | .37          |
| Language delayc                                          |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 85/486 (17.5)                  | 104/702 (14.8)           | 2.68 (-1.61 to 6.96)      | 1.18 (0.91 to 1.53) | 1.16 (0.89 to 1.52) | .26          |
| Diagnoses excluded                                       | 84/483 (17.4)                  | 102/696 (14.7)           | 2.74 (-1.55 to 7.02)      | 1.19 (0.91 to 1.55) | 1.18 (0.90 to 1.54) | .23          |
| Motor delayc                                             |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 9/483 (1.9)                    | 10/702 (1.4)             | 0.44 (-1.05 to 1.93)      | 1.31 (0.54 to 3.20) | 1.38 (0.56 to 3.42) | .48          |
| Diagnoses excluded                                       | 8/480 (1.7)                    | 8/696 (1.2)              | 0.52 (-0.88 to 1.91)      | 1.45 (0.55 to 3.84) | 1.61 (0.60 to 4.34) | .35          |
| Bayley-III cognitive score, mean (SD)c                   |                                |                          |                           |                |             |                           |         |
| Whole cohort                                             | 97.8 (11.2) [n = 486]          | 99.0 (11.2) [n = 703]    | -1.20 (-2.50 to 0.10)     | -1.48 (-2.79 to -0.18) | -1.50 (-2.80 to -0.21) | .03          |
| Diagnoses excluded                                       | 97.9 (11.1) [n = 483]          | 99.1 (11.1) [n = 697]    | -1.20 (-2.49 to 0.10)     | -1.50 (-2.80 to -0.21) | -1.50 (-2.80 to -0.21) | .02          |
| Analysis group       | Hypoglycemia\(^a\) (N = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD\(^b\) (95% CI) | P value |
|----------------------|-------------------------------|---------------------------|---------------|------------|------------------|---------|
| Bayley-III language score, mean (SD)\(^c\) |                               |                           |               |            |                  |         |
| Whole cohort         | 98.3 (15.8) [n = 486]         | 98.6 (15.0) [n = 702]     | -0.33 (-2.11 to 1.44) | -0.51 (-2.29 to 1.28) | .58              |         |
| Diagnoses excluded  | 98.3 (15.7) [n = 483]         | 98.7 (14.9) [n = 696]     | -0.36 (-2.13 to 1.42) | -0.56 (-2.34 to 1.22) | .54              |         |
| Bayley-III motor score, mean (SD)\(^d\) |                               |                           |               |            |                  |         |
| Whole cohort         | 103.0 (10.3) [n = 483]        | 104.8 (10.8) [n = 702]    | -1.82 (-3.05 to -0.59) | -2.05 (-3.30 to -0.79) | .001             |         |
| Diagnoses excluded  | 103.0 (10.2) [n = 480]        | 104.9 (10.6) [n = 696]    | -1.88 (-3.09 to -0.67) | -2.14 (-3.38 to -0.90) | .001             |         |
| Poor executive function\(^d\) | 33/483 (6.8) | 36/701 (5.1) | 1.70 (-1.09 to 4.48) | 1.33 (0.84 to 2.10) | 1.31 (0.82 to 2.10) | .25 |
| Diagnoses excluded  | 32/480 (6.7) | 34/695 (4.9) | 1.78 (-0.98 to 4.53) | 1.36 (0.85 to 2.18) | 1.37 (0.85 to 2.21) | .20 |
| Executive function total score, mean (SD)\(^e\) |                               |                           |               |            |                  |         |
| Whole cohort         | 10.3 (4.5) [n = 483]          | 10.6 (4.4) [n = 701]      | -0.30 (-0.82 to 0.22) | -0.19 (-0.70 to 0.33) | .48              |         |
| Diagnoses excluded  | 10.3 (4.5) [n = 480]          | 10.6 (4.4) [n = 695]      | -0.31 (-0.83 to 0.21) | -0.20 (-0.72 to 0.32) | .45              |         |

Abbreviations: RD, risk difference; CI, confidence interval; RR, risk ratio; Bayley-III, Bayley-Scales of Infant and Toddler Development, Third Edition (mean=100, SD=15, range=40-160, higher scores indicate better performance); SD, standard deviation.

Excluded 9 children with a post-neonatal diagnoses likely to affect the outcome including: 3 in the hypoglycemia group (1 meningitis, 1 near drowning, 1 genetic condition) and 6 in the normoglycemia group (3 meningitis, 1 congenital abnormality, 2 genetic conditions).

\(^a\) An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

\(^b\) Generalized linear models adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

\(^c\) One child who became hypoglycaemic was assigned a score of 49 for the Bayley-III cognitive, language and motor scales due to severe delay.

\(^d\) Poor executive function defined as an executive function total score more than 1.5 SD below the mean.

\(^e\) Composite score range 0-24 points, higher scores indicate better performance.

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### eTable 8. Selected neurocognitive outcomes in children who did and did not experience hypoglycemia, excluding children assessed outside of the intended assessment window of 23 to 25 months’ corrected age (sensitivity analysis)

| Outcome                              | Analysis group     | No./total (%) | Hypoglycemia\(^a\) (N = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD\(^b\) (95% CI) | P value |
|--------------------------------------|--------------------|---------------|-------------------------------|---------------------------|----------------|-------------|--------------------------------|---------|
| Neurosensory impairment              | Whole cohort       | 111/487 (22.8) | 125/704 (17.8)               | 5.04 (0.36 to 9.72)       | 1.28 (1.02 to 1.61) | 1.28 (1.01 to 1.60) | .04               |
|                                      | Within window      | 92/411 (22.4)  | 98/578 (17.0)                | 5.43 (0.36 to 10.49)      | 1.32 (1.02 to 1.70) | 1.32 (1.02 to 1.71) | .04               |
| Moderate or severe neurosensory      | Whole cohort       | 20/487 (4.1)   | 20/704 (2.8)                 | 1.27 (-0.88 to 3.42)      | 1.45 (0.79 to 2.66) | 1.41 (0.76 to 2.62) | .28               |
| impairment                           | Within window      | 15/411 (3.7)   | 15/578 (2.6)                 | 1.05 (-1.18 to 3.29)      | 1.41 (0.69 to 2.85) | 1.27 (0.61 to 2.61) | .52               |
| Cerebral palsy                       | Whole cohort       | 2/481 (0.4)    | 1/700 (0.1)                  | 0.27 (-0.37 to 0.91)      | 2.91 (0.26 to 32.09) | 2.44 (0.20 to 29.14) | .48               |
|                                      | Within window      | 2/408 (0.5)    | 1/576 (0.2)                  | 0.32 (-0.44 to 1.08)      | 2.82 (0.26 to 31.13) | 2.41 (0.20 to 28.37) | .49               |
| Developmental delay\(^c\)            | Whole cohort       | 94/483 (19.5)  | 114/701 (16.3)              | 3.20 (-1.27 to 7.67)      | 1.20 (0.93 to 1.53) | 1.18 (0.92 to 1.51) | .19               |
|                                      | Within window      | 79/410 (19.3)  | 90/576 (15.6)                | 3.64 (-1.20 to 8.48)      | 1.23 (0.94 to 1.62) | 1.23 (0.93 to 1.62) | .15               |
| Cognitive delay\(^c\)                | Whole cohort       | 35/486 (7.2)   | 42/703 (6.0)                 | 1.16 (-1.72 to 4.03)      | 1.21 (0.78 to 1.86) | 1.22 (0.79 to 1.89) | .37               |
|                                      | Within window      | 30/410 (7.3)   | 32/577 (5.6)                 | 1.77 (-1.37 to 4.91)      | 1.32 (0.81 to 2.14) | 1.32 (0.81 to 2.16) | .27               |
| Language delay\(^c\)                 | Whole cohort       | 85/486 (17.5)  | 104/702 (14.8)               | 2.68 (-1.61 to 6.96)      | 1.18 (0.91 to 1.53) | 1.16 (0.89 to 1.52) | .26               |
|                                      | Within window      | 72/410 (17.6)  | 83/576 (14.4)                | 3.15 (-1.52 to 7.83)      | 1.22 (0.91 to 1.63) | 1.22 (0.91 to 1.64) | .19               |
| Motor delay\(^c\)                    | Whole cohort       | 9/483 (1.9)    | 10/702 (1.4)                 | 0.44 (-1.05 to 1.93)      | 1.31 (0.54 to 3.20) | 1.38 (0.56 to 3.42) | .48               |
|                                      | Within window      | 7/410 (1.7)    | 7/577 (1.2)                  | 0.49 (-1.05 to 2.04)      | 1.41 (0.50 to 3.99) | 1.43 (0.49 to 4.14) | .51               |
| Bayley-III cognitive score, mean (SD)\(^c\) | Whole cohort | 97.8 (11.2) [n = 486] | 99.0 (11.2) [n = 703] | -1.20 (-2.50 to 0.10) | -1.48 (-2.79 to -0.18) | -1.48 (-2.79 to -0.18) | .03 |
|                                      | Within window      | 98.3 (11.5) [n = 410] | 99.4 (11.1) [n = 577] | -1.12 (-2.55 to 0.31) | -1.36 (-2.81 to -0.08) | -1.36 (-2.81 to -0.08) | .06 |
| Bayley-III language score, mean (SD)\(^c\) | Whole cohort | 98.3 (15.8) [n = 486] | 98.6 (15.0) [n = 702] | -0.33 (-2.11 to 1.44) | -0.51 (-2.29 to 1.28) | -0.51 (-2.29 to 1.28) | .58 |
|                                      | Within window      | 98.8 (15.9) [n = 410] | 98.9 (15.2) [n = 567] | -0.04 (-2.00 to 1.93) | -0.25 (-2.24 to 1.74) | -0.25 (-2.24 to 1.74) | .81 |
| Bayley-III motor score, mean (SD)\(^c\) | Whole cohort | 103.0 (10.3) [n = 483] | 104.8 (10.8) [n = 702] | -1.82 (-3.05 to -0.59) | -2.05 (-3.30 to -0.79) | -2.05 (-3.30 to -0.79) | .001 |
|                                      | Within window      | 103.2 (10.0) [n = 410] | 104.9 (10.4) [n = 577] | -1.77 (-3.07 to -0.47) | -1.95 (-3.29 to -0.62) | -1.95 (-3.29 to -0.62) | .004 |

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| Outcome | Analysis group     | Hypoglycemia\(a\) \((N = 490)\) | No hypoglycemia \((n = 704)\) | RD/MD \((95\% CI)\) | RR \((95\% CI)\) | Adjusted RR/MD\(b\) \((95\% CI)\) | \(P\) value |
|---------|-------------------|-------------------------------|-----------------------------|-----------------------|-----------------|---------------------------------|-------------|
| Poor executive function\(d\) | Whole cohort | 33/483 (6.8) | 36/701 (5.1) | 1.70 (-1.09 to 4.48) | 1.33 (0.84 to 2.10) | 1.31 (0.82 to 2.10) | .25 |
|         | Within window     | 27/408 (6.6) | 30/576 (5.2) | 1.41 (-1.61 to 4.43) | 1.27 (0.77 to 2.11) | 1.25 (0.75 to 2.11) | .39 |
| Executive function total score, mean \((SD)^e\) | Whole cohort | 10.3 (4.5) \([n = 483]\) | 10.6 (4.4) \([n = 701]\) | -0.30 (-0.82 to 0.22) | -0.19 (-0.70 to 0.33) | -0.05 (-0.60 to 0.51) | .48 |
|         | Within window     | 10.2 (4.4) \([n = 408]\) | 10.4 (4.3) \([n = 576]\) | -0.16 (-0.71 to 0.39) | -0.05 (-0.60 to 0.51) | -0.05 (-0.60 to 0.51) | .87 |

Abbreviations: RD, risk difference; CI, confidence interval; RR, risk ratio; Bayley-III, Bayley-Scales of Infant and Toddler Development, Third Edition (mean = 100, SD = 15, range = 40-160, higher scores indicate better performance); SD, standard deviation.

Within window = excluded 202 children (76 in the hypoglycemia group and 126 in the normoglycemia group) assessed outside the intended study window period.

\(a\) An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

\(b\) Generalized linear models adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

\(c\) One child who became hypoglycaemic was assigned a score of 49 for the Bayley-III cognitive, language and motor scales due to severe delay.

\(d\) Poor executive function defined as an executive function total score more than 1.5 SD below the mean.

\(e\) Composite score range 0-24 points, higher scores indicate better performance.
eTable 9. Selected neurocognitive outcomes in children who did and did not experience hypoglycemia, excluding children whose first language was not English (sensitivity analysis)

| Outcome                        | Analysis group            | Hypoglycemiaa (N = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MDb (95% CI) | P value |
|--------------------------------|---------------------------|--------------------------|---------------------------|----------------|-------------|--------------------------|---------|
| Neurosensory impairment        | Whole cohort              | 111/487 (22.8)          | 125/704 (17.8)            | 5.04 (0.36 to 9.72) | 1.28 (1.02 to 1.61) | 1.28 (1.01 to 1.60) | .04     |
|                                | First language English    | 57/321 (17.8)           | 62/445 (13.9)             | 3.82 (-1.46 to 9.11) | 1.27 (0.92 to 1.77) | 1.26 (0.90 to 1.76) | .18     |
| Moderate or severe neurosensory impairment | Whole cohort              | 20/487 (4.1)            | 20/704 (2.8)              | 1.27 (-0.88 to 3.42) | 1.45 (0.79 to 2.66) | 1.41 (0.76 to 2.62) | .28     |
|                                | First language English    | 12/321 (3.7)            | 12/445 (2.7)              | 1.04 (-1.53 to 3.61) | 1.39 (0.63 to 3.05) | 1.17 (0.53 to 2.60) | .69     |
| Cerebral palsy                 | Whole cohort              | 2/481 (0.4)             | 1/700 (0.1)               | 0.27 (-0.37 to 0.91) | 2.91 (0.26 to 32.09) | 2.44 (0.20 to 29.14) | .48     |
|                                | First language English    | 2/316 (0.6)             | 1/443 (0.2)               | 0.41 (-0.57 to 1.39) | 2.80 (0.25 to 30.90) | 2.40 (0.21 to 26.92) | .48     |
| Developmental delayc           | Whole cohort              | 94/483 (19.5)           | 114/701 (16.3)            | 3.20 (-1.27 to 7.67) | 1.20 (0.93 to 1.53) | 1.18 (0.92 to 1.51) | .19     |
|                                | First language English    | 45/319 (14.1)           | 57/442 (12.9)             | 1.21 (-3.73 to 6.15) | 1.09 (0.76 to 1.57) | 1.04 (0.72 to 1.50) | .85     |
| Cognitive delayc               | Whole cohort              | 35/486 (7.2)            | 42/703 (6.0)              | 1.16 (-1.72 to 4.03) | 1.21 (0.78 to 1.86) | 1.22 (0.79 to 1.89) | .37     |
|                                | First language English    | 17/320 (5.3)            | 23/444 (5.2)              | 0.13 (-3.08 to 3.35) | 1.03 (0.56 to 1.89) | 0.91 (0.49 to 1.69) | .77     |
| Language delayc               | Whole cohort              | 85/486 (17.5)           | 104/702 (14.8)            | 2.68 (-1.61 to 6.96) | 1.18 (0.91 to 1.53) | 1.16 (0.89 to 1.52) | .26     |
|                                | First language English    | 40/320 (12.5)           | 52/443 (11.7)             | 0.76 (-3.95 to 5.47) | 1.06 (0.72 to 1.57) | 1.00 (0.68 to 1.49) | .98     |
| Motor delayc                  | Whole cohort              | 9/483 (1.9)             | 10/702 (1.4)              | 0.44 (-1.05 to 1.93) | 1.31 (0.54 to 3.20) | 1.38 (0.56 to 3.42) | .48     |
|                                | First language English    | 4/319 (1.3)             | 7/443 (1.6)               | -0.33 (-2.01 to 1.36) | 0.79 (0.23 to 2.69) | 0.80 (0.23 to 2.75) | .72     |
| Bayley-III cognitive score, mean (SD)c | Whole cohort              | 97.8 (11.2)             | 99.0 (11.2)               | -1.20 (-2.50 to 0.10) | -1.48 (-2.79 to 0.18) |                       | .03     |
|                                | First language English    | 99.2 (11.1)             | 100.3 (11.5)              | -1.05 (-2.68 to 0.58) | -1.36 (-2.99 to 0.28) |                       | .10     |
| Bayley-III language score, mean (SD)c | Whole cohort              | 98.3 (15.8)             | 98.6 (15.0)               | -0.33 (-2.11 to 1.44) | -0.51 (-2.29 to 1.28) |                       | .58     |
|                                | First language English    | 101.3 (15.9)            | 101.2 (15.5)              | 0.07 (-2.18 to 2.33) | -0.16 (-2.42 to 2.11) |                       | .89     |

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| Outcome | Analysis group | Hypoglycemia\(^a\) (N = 490) | No hypoglycemia (n = 704) | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD\(^b\) (95% CI) | P value |
|---------|----------------|------------------------------|------------------------|----------------|-------------|-------------------------------|---------|
| Bayley-III motor score, mean (SD)\(^c\) | Whole cohort | 103.0 (10.3) [n = 483] | 104.8 (10.8) [n = 702] | -1.82 (-3.05 to -0.59) | -2.05 (-3.30 to -0.79) | 0.001 |
| First language English | 103.7 (10.0) [n = 319] | 105.2 (10.9) [n = 443] | -1.54 (-3.06 to -0.02) | -1.86 (-3.42 to -0.30) | 0.02 |
| Poor executive function\(^d\) | Whole cohort | 33/483 (6.8) | 36/701 (5.1) | 1.70 (-1.09 to 4.48) | 1.33 (0.84 to 2.10) | 1.31 (0.82 to 2.10) | 0.25 |
| First language English | 15/318 (4.7) | 17/443 (3.8) | 0.88 (-0.02 to 3.82) | 1.23 (0.62 to 2.43) | 1.28 (0.64 to 2.55) | 0.49 |
| Executive function total score, mean (SD)\(^e\) | Whole cohort | 10.3 (4.5) [n = 483] | 10.6 (4.4) [n = 701] | -0.30 (-0.82 to 0.22) | -0.19 (-0.70 to 0.33) | 0.48 |
| First language English | 10.8 (4.3) [n = 318] | 10.9 (4.4) [n = 443] | -0.06 (-0.69 to 0.57) | 0.00 (-0.64 to 0.64) | 1.00 |
| Complex inhibition (fruit stroop task) score ≤2 | Whole cohort | 235/481 (48.9) | 351/698 (50.3) | -1.43 (-7.24 to 4.38) | 0.97 (0.86 to 1.09) | 0.96 (0.86 to 1.08) | 0.53 |
| First language English | 148/317 (46.7) | 212/440 (48.2) | -1.49 (-8.71 to 5.73) | 0.97 (0.83 to 1.13) | 0.96 (0.82 to 1.11) | 0.57 |
| Complex inhibition (reverse categorisation task) score ≤2 | Whole cohort | 372/481 (77.3) | 544/699 (77.8) | -0.49 (-5.34 to 4.36) | 0.99 (0.93 to 1.06) | 0.99 (0.93 to 1.05) | 0.70 |
| First language English | 238/317 (75.1) | 331/441 (75.1) | 0.02 (-6.23 to 6.28) | 1.00 (0.92 to 1.09) | 0.97 (0.89 to 1.06) | 0.56 |

Abbreviations: RD, risk difference; CI, confidence interval; RR, risk ratio; Bayley-III, Bayley-Scales of Infant and Toddler Development, Third Edition (mean=100, SD=15, range=40-160, higher scores indicate better performance); SD, standard deviation.

First language English = excluded 425 children (166 in the hypoglycemia group and 259 in the normoglycemia group).

\(^a\) An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

\(^b\) Generalized linear models adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

\(^c\) One child who became hypoglycaemic was assigned a score of 49 for the Bayley-III cognitive, language and motor scales due to severe delay.

\(^d\) Poor executive function defined as an executive function total score more than 1.5 SD below the mean.

\(^e\) Composite score range 0-24 points, higher scores indicate better performance.
**eTable 10. The primary outcome of neurosensory impairment in children who did and did not experience hypoglycemia, excluding children randomized to prophylactic buccal dextrose gel (sensitivity analysis)**

|                          | No./total (%) | RD (95% CI) | RR (95% CI) | Adjusted RR<sup>a</sup> (95% CI) | P value |
|--------------------------|---------------|-------------|-------------|----------------------------------|---------|
| Normoglycemia (reference)<sup>b</sup> | 49/329 (14.9) |             |             |                                  |         |
| Hypoglycemia<sup>c</sup>  | 61/258 (23.6) | 8.75 (2.28 to 15.22) | 1.59 (1.13 to 2.23) | 1.55 (1.10 to 2.18) | .01     |
| Mild hypoglycemia<sup>d</sup> | 42/204 (20.6) | 5.70 (-1.07 to 12.46) | 1.38 (0.95 to 2.01) | 1.34 (0.92 to 1.97) | .13     |
| Severe hypoglycemia<sup>e</sup> | 19/54 (35.2)  | 20.29 (6.94 to 33.64) | 2.36 (1.51 to 3.69) | 2.39 (1.49 to 3.84) | <.001   |
| 1-2 episodes of hypoglycemia | 53/224 (23.7) | 8.77 (1.99 to 15.55) | 1.59 (1.12 to 2.25) | 1.58 (1.10 to 2.26) | .01     |
| ≥3 episodes of hypoglycemia | 8/34 (23.5)   | 8.64 (-6.18 to 23.45) | 1.58 (0.82 to 3.06) | 1.33 (0.69 to 2.55) | .39     |

Abbreviations: RD, risk difference; CI, confidence interval; RR, risk ratio.

Excluded 604 children randomized to prophylactic buccal dextrose gel (229 in the hypoglycemia group and 375 in the normoglycemia group).

<sup>a</sup>Generalized linear models adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth and multiple births.

<sup>b</sup>Normoglycemia was defined as all blood glucose concentrations ≥47 mg/dL.

<sup>c</sup>An episode of hypoglycemia was defined as ≥1 episode of consecutive blood glucose concentrations of <47 mg/dL.

<sup>d</sup>Mild hypoglycemia was defined as ≥1 episode of ≥36 and <47 mg/dL.

<sup>e</sup>Severe hypoglycemia was defined as ≥1 episode of <36 mg/dL.