Revisión Bibliográfica

Enero – Abril 2020

- NEJM
- Lancet
- Jama
- BMJ

Dr. Javier Cifuentes.
09 de abril 2020.

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Un Nuevo Concepto en Medicina Perinatal

Neo Red

A Randomized Trial of Erythropoietin for Neuroprotection in Preterm Infants.

Juul S. et al for the PENUT Trial Consortium. DOI: 10.1056/NEJMoa1907423

- **BACKGROUND**
- High-dose erythropoietin has been shown to have a neuroprotective effect in preclinical models of neonatal brain injury, and phase 2 trials have suggested possible efficacy; however, the benefits and safety of this therapy in extremely preterm infants have not been established.
- RN 24 0/7 – 27 – 6/7
- Randomización:
  - Estratificada (24 0/7 – 25 6/7 y 26 0/7 – 27 6/7)
  - Enrolamiento y primera dosis: < 24 h de vida
  - Dosis:
    - EPO 1000 u/kg cada 48 h por 6 IV
    - 400 U/kg 3/s SC hasta las 32 6/7 s

http://clinicaltrials.gov/show/NCT01378273

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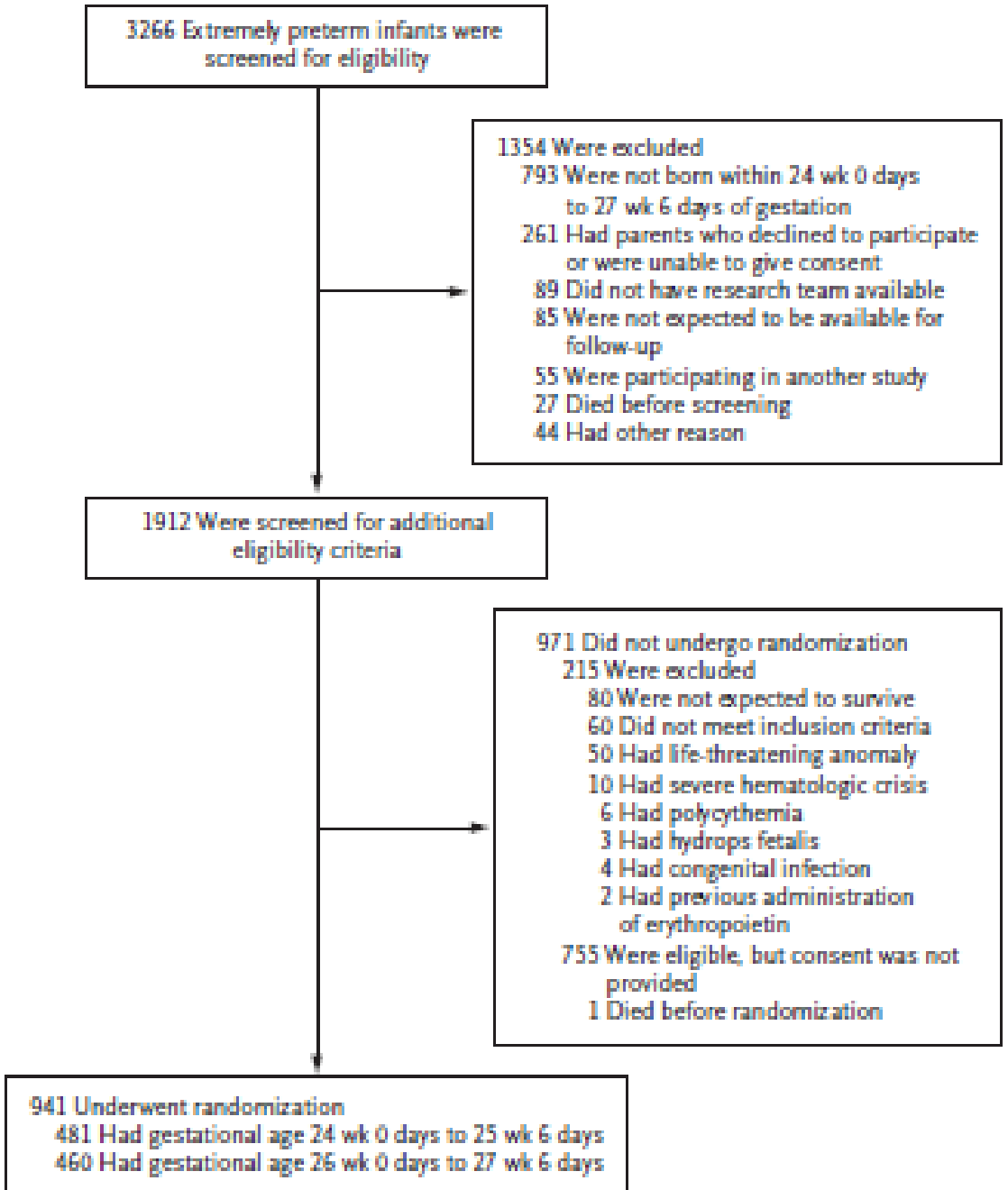
- Eco cerebral antes de inicia tratamiento, 7-9 día y 36s EGC (220 RN RNM)
- LM o fórmula prematuro
- Fe (enteral):
  - 3 mg/kg/d con vol 60 cc/kg/d y ≥ 7 d.
  - 6 mg/kg/d con Volumen 100 – 120 cc/kg/d
  - Fe iv: 1,5 mg/kg 2 v/s según ferritina o zinc protoporfirina / heme
- Transfusiones: según prácticas locales
- Outcome:
  - Primario: Muerte o Compromiso neurológico severo (PC o BIII m BIII c < 70)
  - Secundario: Muerte o Compromiso neurológico moderado o severo (PC o BIII m BIII c < 85)
  - Estadísticas: 18% mortalidad y 30% v/s 40 % de CNS. N: 856 RN


3266 Extremely preterm infants were screened for eligibility
1354 Were excluded
793 Were not born within 24 wk 0 days to 27 wk 6 days of gestation
261 Had parents who declined to participate or were unable to give consent
89 Did not have research team available
85 Were not expected to be available for follow-up
55 Were participating in another study
27 Died before screening
44 Had other reason
1912 Were screened for additional eligibility criteria
971 Did not undergo randomization
215 Were excluded
80 Were not expected to survive
60 Did not meet inclusion criteria
50 Had life-threatening anomaly
10 Had severe hematologic crisis
6 Had polycythemia
3 Had hydrops fetalis
4 Had congenital infection
2 Had previous administration of erythropoietin
755 Were eligible, but consent was not provided
1 Died before randomization
941 Underwent randomization
481 Had gestational age 24 wk 0 days to 25 wk 6 days
460 Had gestational age 26 wk 0 days to 27 wk 6 days

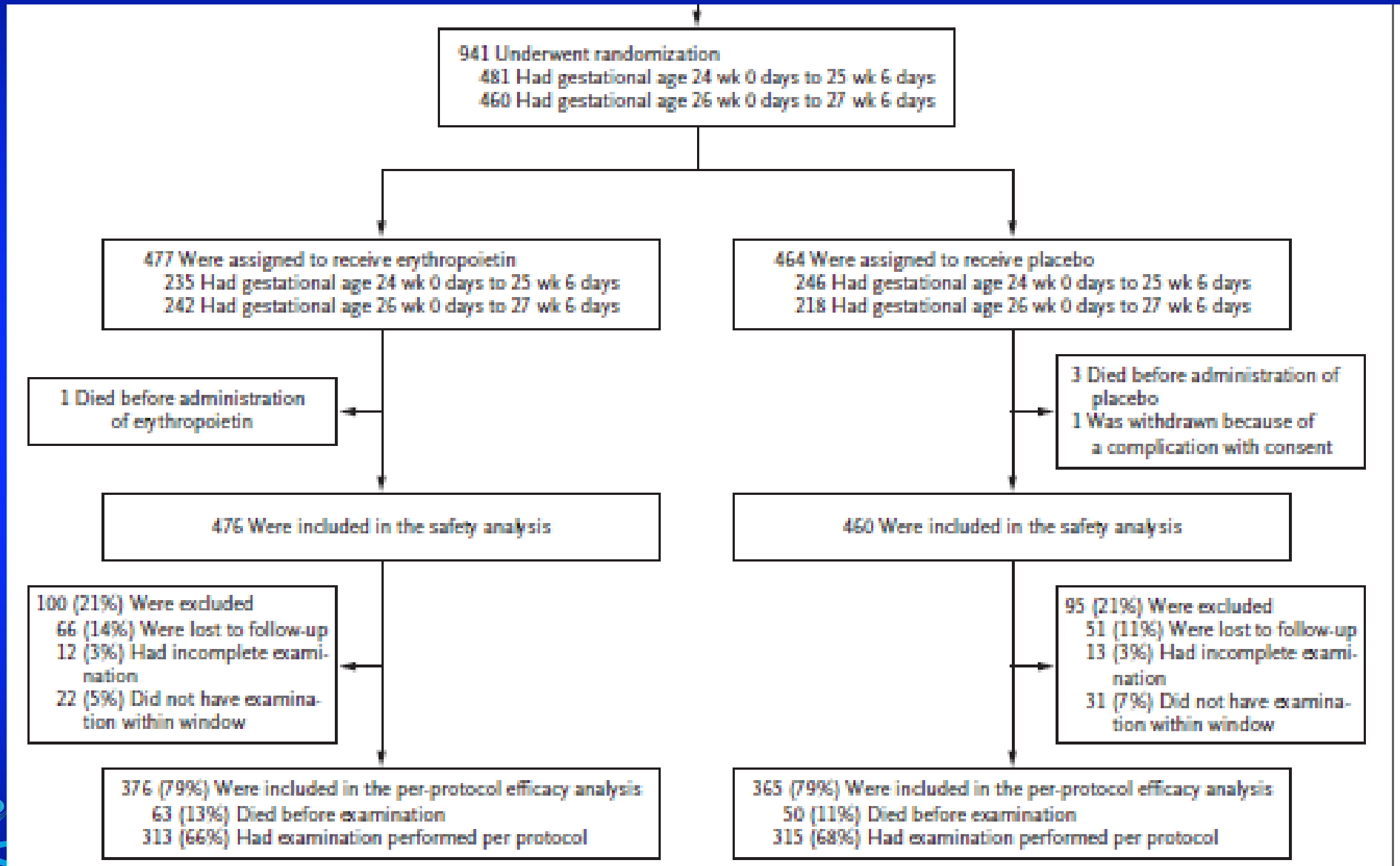
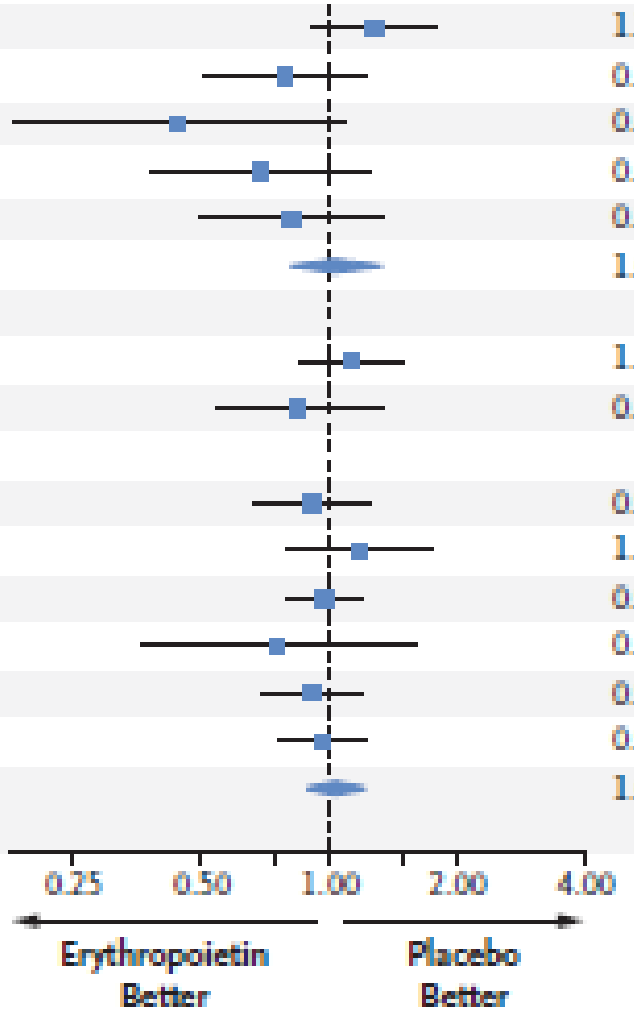


Figure 1. Screening, Randomization, and Follow-up.

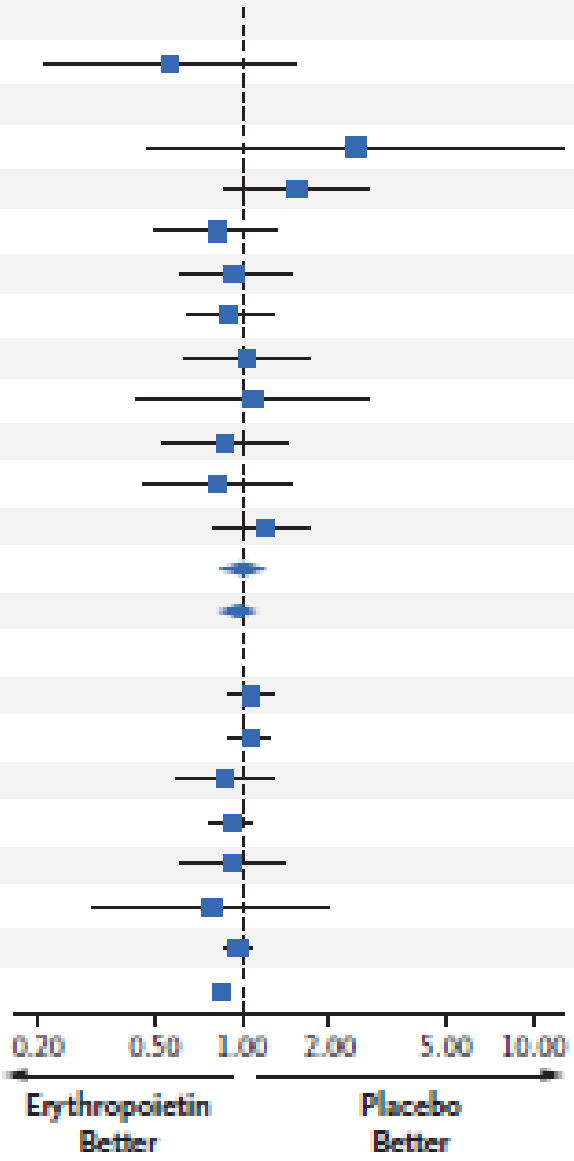
Table 1. Maternal, Pregnancy, and Infant Characteristics at Enrollment.*

Characteristic	Erythropoietin (N=476)	Placebo (N=460)
Maternal characteristics		
Age — yr	29.1±6.2	28.8±6.2
Prenatal glucocorticoid use — no. (%)	430 (90)	412 (90)
Prenatal magnesium sulfate use — no. (%)	374 (79)	375 (82)
Delivery complications — no. (%)¶	79 (17)	70 (15)
Cesarean delivery — no. (%)	337 (71)	314 (68)
Delayed cord clamping — no./total no. (%)	171/346 (49)	147/334 (44)
Pregnancy with multiple fetuses — no. (%)	125 (26)	118 (26)
Infant characteristics		
Female sex — no. (%)	219 (46)	229 (50)
Gestational age at birth — no. (%)		
24 wk	113 (24)	119 (26)
25 wk	121 (25)	124 (27)
26 wk	103 (22)	118 (26)
27 wk	139 (29)	99 (22)
Mean gestational age at birth — wk	26.0±1.2	25.8±1.1
Weight — g	806.4±194.6	792.9±182.2
Weight <10th percentile for gestational age — no. (%)	69 (14)	78 (17)
Head circumference <10th percentile — no. (%)	80 (17)	81 (18)
Apgar score at 5 min	6.1±2.2	6.2±2.1
Apgar score <5 at 5 min — no. (%)	104 (22)	85 (18)
Intracranial hemorrhage before first infusion — no. (%)	100 (21)	94 (20)
Median age at first infusion (interquartile range) — hr	21.1 (15.3–23.5)	20.0 (14.8–23.3)

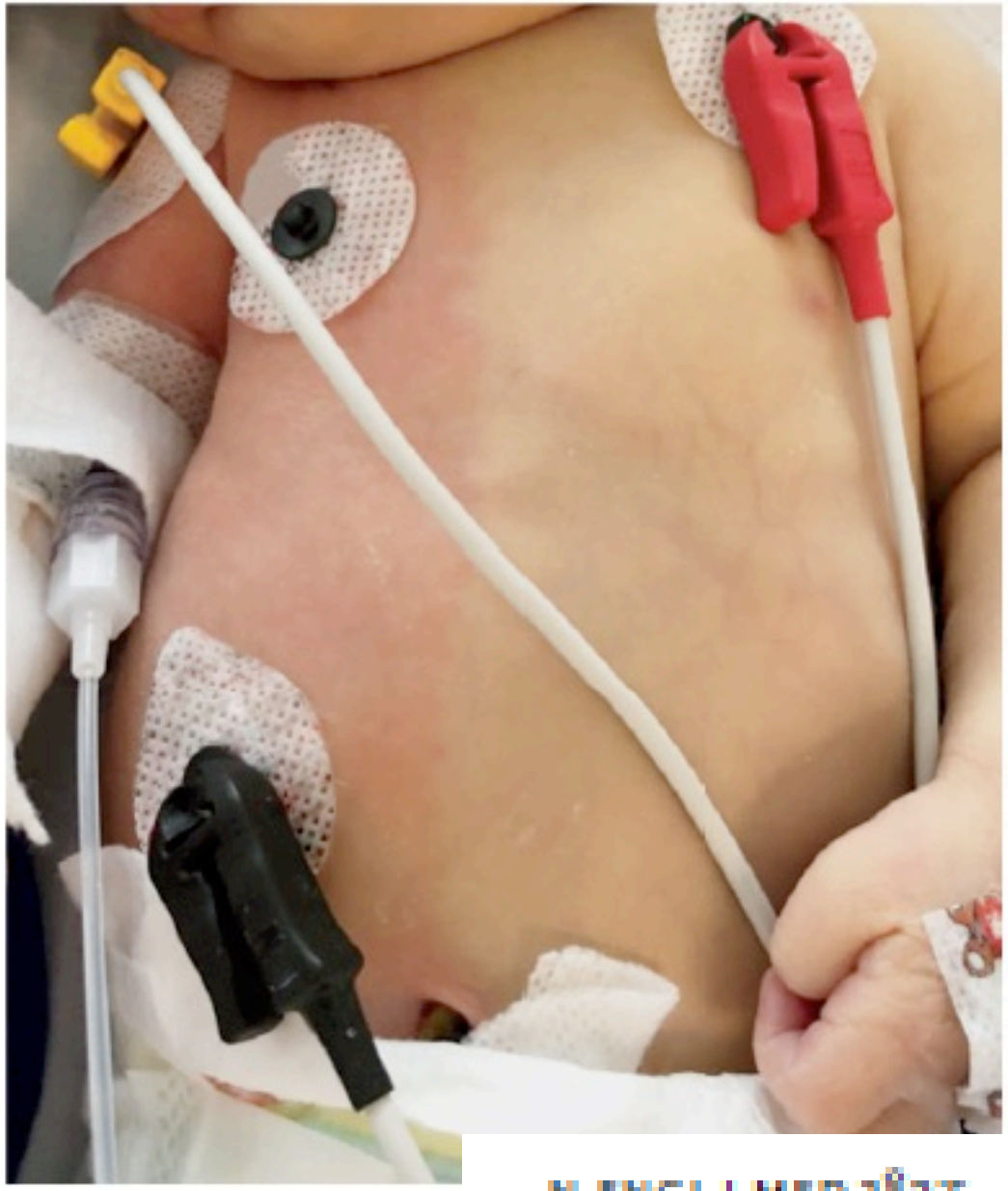
Outcome	Erythropoietin	Placebo	Relative Risk (95% CI)
	no. of events/total no. (%)		
Death	63/476 (13)	50/460 (11)	1.27 (0.91–1.79)
Severe neurodevelopmental impairment	34/313 (11)	44/315 (14)	0.79 (0.51–1.22)
Severe cerebral palsy	8/313 (3)	18/315 (6)	0.44 (0.18–1.08)
Bayley-III composite cognitive score <70	19/311 (6)	28/314 (9)	0.69 (0.38–1.23)
Bayley-III composite motor score <70	28/310 (9)	36/314 (11)	0.81 (0.50–1.32)
Death or severe neurodevelopmental impairment	97/376 (26)	94/365 (26)	1.03 (0.81–1.32)
Gestational age at birth			
24 wk 0 days to 25 wk 6 days	67/190 (35)	62/197 (31)	1.12 (0.84–1.50)
26 wk 0 days to 27 wk 6 days	30/186 (16)	32/168 (19)	0.84 (0.54–1.33)
Sex			
Male	59/201 (29)	57/183 (31)	0.91 (0.67–1.24)
Female	38/175 (22)	37/182 (20)	1.17 (0.79–1.75)
Moderate-to-severe neurodevelopmental impairment	118/312 (38)	120/314 (38)	0.97 (0.79–1.18)
Moderate-to-severe cerebral palsy	13/311 (4)	18/315 (6)	0.75 (0.36–1.57)
Bayley-III composite cognitive score <85	77/311 (25)	87/314 (28)	0.91 (0.69–1.18)
Bayley-III composite motor score <85	95/310 (31)	96/314 (31)	0.96 (0.76–1.21)
Death or moderate-to-severe neurodevelopmental impairment	181/375 (48)	170/365 (47)	1.03 (0.88–1.21)



Event	Erythropoietin (N=476)	Placebo (N=460)	Relative Risk (95% CI)
	no. of events (%)		
Serious adverse events			
Hypertension	6 (1)	10 (2)	0.57 (0.21–1.53)
Polycythemia	2 (<1)	1 (<1)	—
Major venous or arterial thrombosis	5 (1)	2 (<1)	2.46 (0.48–12.7)
Severe pulmonary hemorrhage	30 (6)	19 (4)	1.54 (0.88–2.71)
Necrotizing enterocolitis, stage 2b or 3	28 (6)	36 (8)	0.82 (0.51–1.31)
Severe sepsis	35 (7)	38 (8)	0.94 (0.61–1.46)
Intracranial hemorrhage, grade III or IV	57 (12)	64 (14)	0.90 (0.65–1.26)
Severe retinopathy of prematurity	30 (6)	30 (7)	1.04 (0.64–1.70)
Nonfatal cardiac arrest	9 (2)	8 (2)	1.09 (0.43–2.74)
Other unexpected life-threatening event	27 (6)	31 (7)	0.87 (0.53–1.44)
Spontaneous intestinal perforation	19 (4)	23 (5)	0.83 (0.46–1.49)
Death	53 (11)	45 (10)	1.19 (0.81–1.73)
Total serious adverse events	282 (59)	284 (62)	1.01 (0.83–1.22)
Infants with at least one serious adverse event	175 (37)	185 (40)	0.97 (0.84–1.13)
Complications of prematurity			
Severe bronchopulmonary dysplasia	172 (36)	161 (35)	1.07 (0.91–1.26)
Treated patent ductus arteriosus	178 (37)	172 (37)	1.07 (0.91–1.25)
Necrotizing enterocolitis, all grades	46 (10)	53 (12)	0.87 (0.60–1.27)
Intracranial hemorrhage, all grades	168 (35)	181 (39)	0.92 (0.78–1.08)
Periventricular leukomalacia	41 (9)	43 (9)	0.92 (0.61–1.39)
Cerebral hemorrhage	8 (2)	10 (2)	0.79 (0.31–2.00)
Retinopathy of prematurity, all grades	244 (51)	258 (56)	0.97 (0.87–1.08)
One or more blood transfusions	341 (72)	401 (87)	0.85 (0.80–0.90)



Harlequin Color Change in a Neonate



Lower versus Traditional Treatment Threshold for Neonatal Hypoglycemia.

van Kempen A, et al for the HypoEXIT Study Group. DOI: 10.1056/NEJMoa1905593

- **BACKGROUND**
- Worldwide, many newborns who are preterm, small or large for gestational age, or born to mothers with diabetes are screened for hypoglycemia, with a goal of preventing brain injury. However, there is no consensus on a treatment threshold that is safe but also avoids overtreatment.
- On the basis of expert opinion, a concept of operational thresholds was developed that considered glucose concentrations between 36 mg per deciliter (2.0 mmol per liter) and 47 mg per deciliter (2.6 mmol per liter) to be acceptable for short periods of time.
- The HypoEXIT (Hypoglycemia–Expectant Monitoring versus Intensive Treatment) trial was a multicenter, randomized, controlled, noninferiority trial

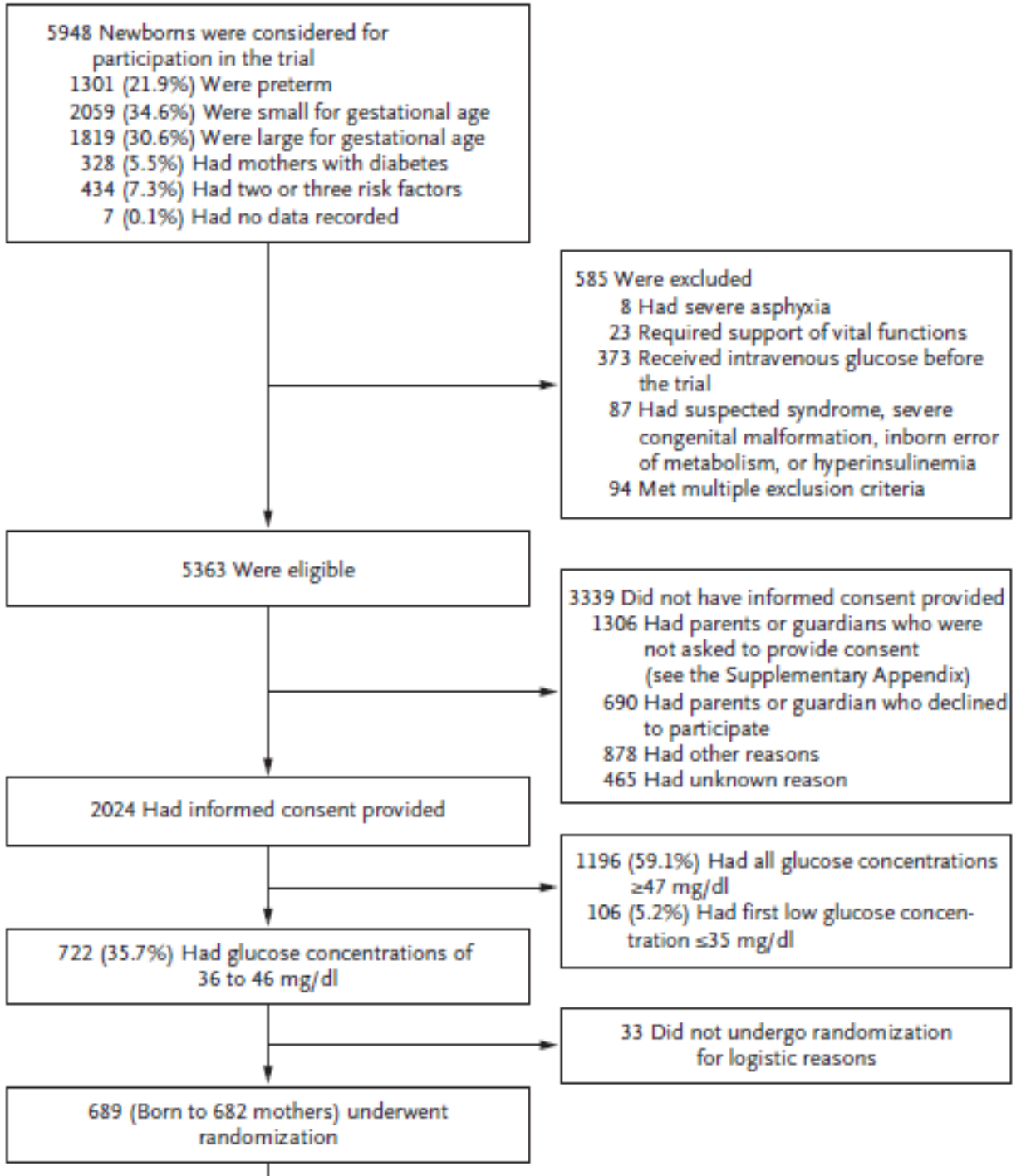
- Patients: 35 weeks or more of gestation, had a birth weight of 2000 g or more, and had an indication for routine screening for hypoglycemia.
- The participants were newborns in four subgroups at high risk for hypoglycemia — late-preterm infants (gestational age from 35 to 37 weeks), newborns who were small (below the 10th percentile) or large (above the 90th percentile) for gestational age, and infants of mothers with diabetes.
- The participants were all otherwise healthy newborns without initial severe hypoglycemia (defined as plasma glucose concentrations of ≤35 mg per deciliter [1.9 mmol per liter]

- Newborns found to have asymptomatic moderate hypoglycemia between 3 and 24 hours after birth were randomly assigned in a 1:1 ratio (with the use of Webbased block randomization) to receive treatment when the glucose concentration was lower than 36 mg per deciliter (lower-threshold group) or to receive treatment when the glucose concentration was lower than 47 mg per deciliter (traditional-threshold group).
- In the lower-threshold group, the aim was to maintain the infants' glucose concentration at 36 mg per deciliter or greater. In the traditionalthreshold group, the aim was to attain a glucose concentration of 47 mg per deciliter or greater and then maintain that level

- Treatment interventions, which were similar in the two groups, were supplemental oral feeding, tube feeding, or intravenous glucose administration.

- If an infant's glucose concentration fell below the prespecified threshold, the carbohydrate intake was increased by 1 to 2 mg per kilogram of body weight per minute. The glucose concentration was checked 1 hour after each increase, and, if necessary, the infant's carbohydrate intake was further adjusted.

Primary outcome: The primary outcome was psychomotor development at 18 months, as measured by the Bayley Scales of Infant and Toddler Development, third edition, Dutch version (Bayley-III-NL)


5948 Newborns were considered for participation in the trial
1301 (21.9%) Were preterm
2059 (34.6%) Were small for gestational age
1819 (30.6%) Were large for gestational age
328 (5.5%) Had mothers with diabetes
434 (7.3%) Had two or three risk factors
7 (0.1%) Had no data recorded
585 Were excluded
8 Had severe asphyxia
23 Required support of vital functions
373 Received intravenous glucose before the trial
87 Had suspected syndrome, severe congenital malformation, inborn error of metabolism, or hyperinsulinemia
94 Met multiple exclusion criteria
5363 Were eligible
3339 Did not have informed consent provided
1306 Had parents or guardians who were not asked to provide consent (see the Supplementary Appendix)
690 Had parents or guardian who declined to participate
878 Had other reasons
465 Had unknown reason
2024 Had informed consent provided
1196 (59.1%) Had all glucose concentrations ≥47 mg/dl
106 (5.2%) Had first low glucose concentration ≤35 mg/dl
722 (35.7%) Had glucose concentrations of 36 to 46 mg/dl
33 Did not undergo randomization for logistic reasons
689 (Born to 682 mothers) underwent randomization

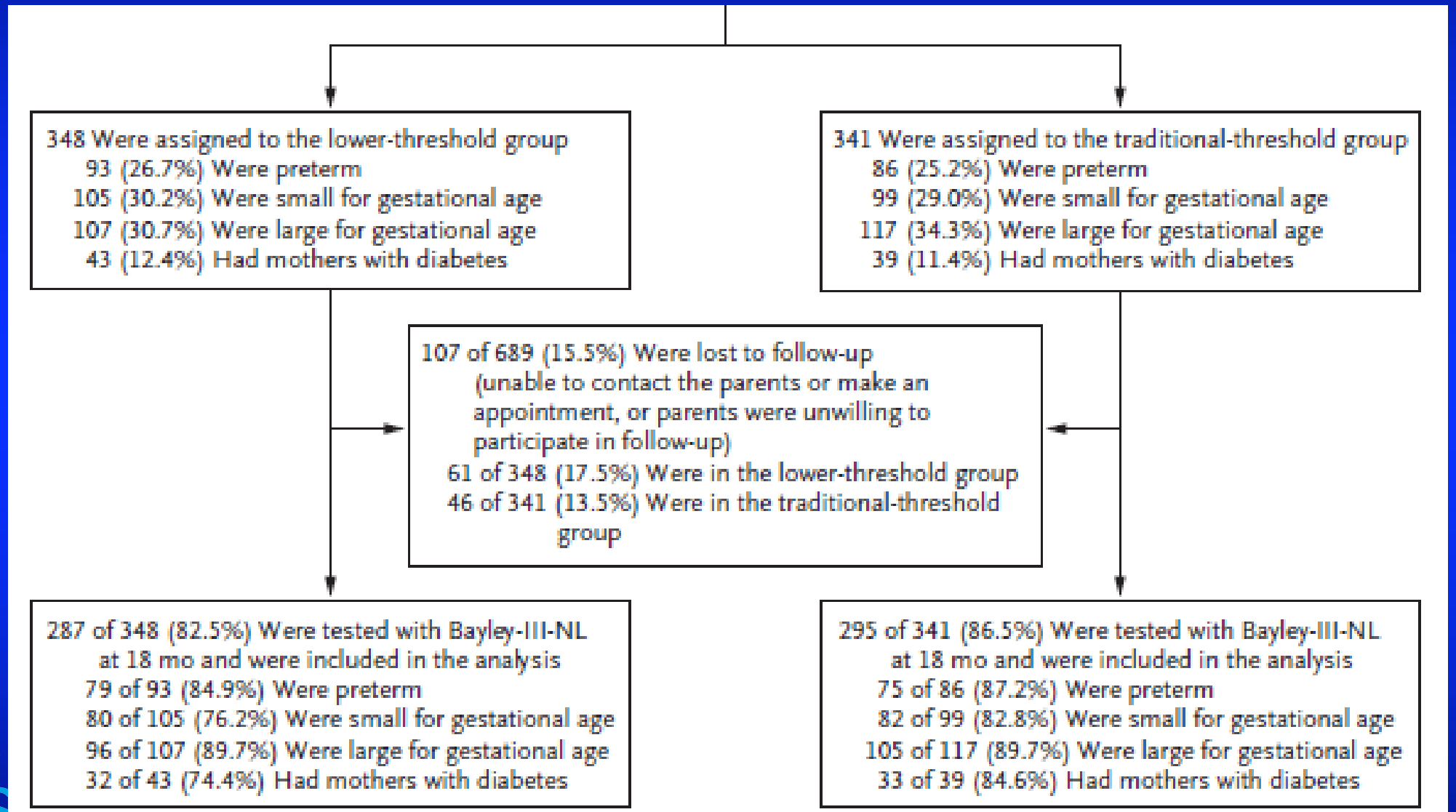


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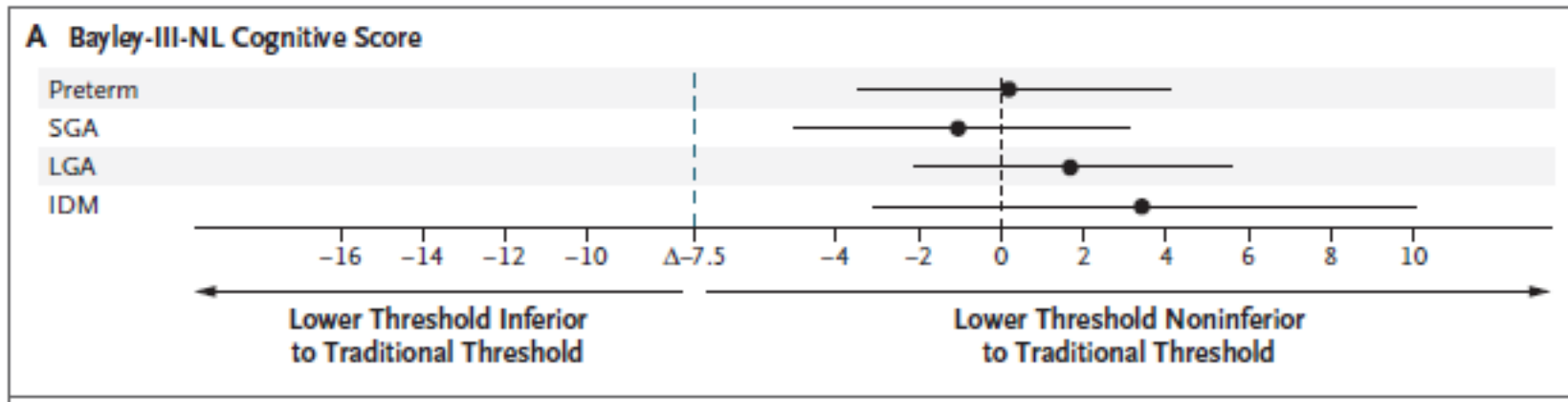
Table 1. Characteristics of Participants at Baseline.*

Characteristic	Lower-Threshold Group	Traditional-Threshold Group
Newborns — no.	348	341
Gestational age — wk	38.6±0.1	38.7±0.1
Birth weight — g	3316±47	3354±46
Male sex — no. (%)	202 (58)	185 (54)
Singleton birth — no. (%)	324 (93)	324 (95)
Apgar score at 5 min	9.6±0.04	9.6±0.04
Age at randomization — hr	6.4±0.2	6.9±0.2
Glucose at randomization — mg/dl	41.4±0.2	41.2±0.2



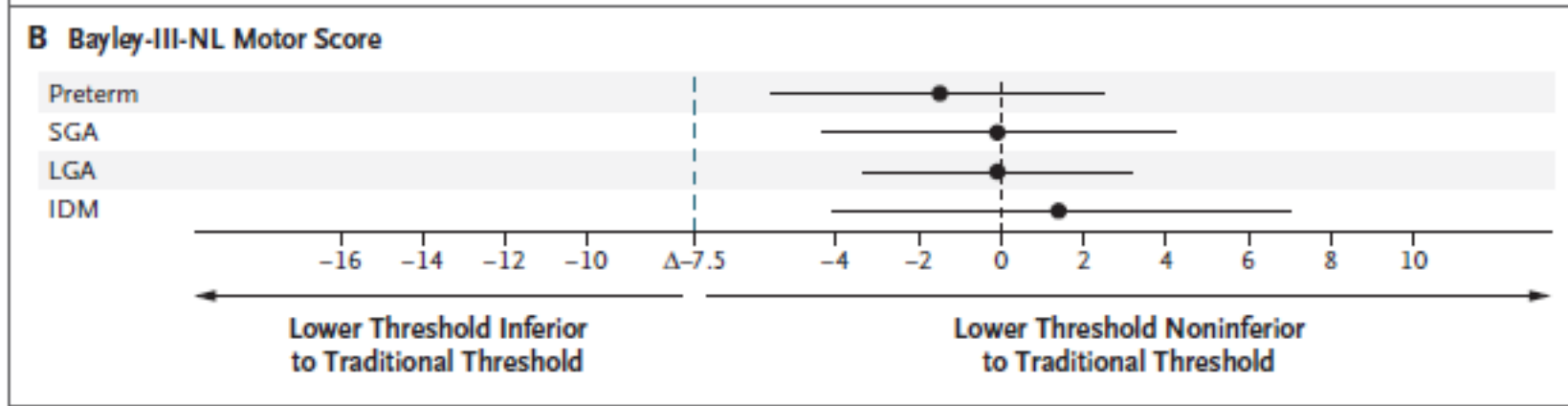


Figure 2. Effect Sizes in Relation to the Noninferiority Margin.

Shown are mean absolute differences between newborns assigned to the lower-threshold group and those assigned to the traditional-threshold group with respect to cognitive scores (Panel A) and motor scores (Panel B) on the Bayley-III-NL, in relation to the prespecified noninferiority margin of –7.5 points, indicated by a vertical dashed line. Horizontal bars show 97.5% confidence intervals. IDM denotes infants of mothers with diabetes mellitus, LGA large for gestational age, and SGA small for gestational age.

Table 2. Bayley-III-NL Outcome Scores at 18 Months of Corrected Age.*

Group	Lower-Threshold Group	Traditional-Threshold Group	Mean Difference (97.5% CI)
Total trial population tested — no./total no. (%)	287/348 (82.5)	295/341 (86.5)	
Bayley-III-NL cognitive score	102.9±0.7	102.2±0.7	0.7 (–1.5 to 2.9)
Missing data — no. (%)	61 (18)	46 (13)	
Bayley-III-NL motor score	104.6±0.7	104.9±0.7	–0.3 (–2.4 to 1.8)
Missing data — no. (%)	64 (18)	51 (15)	
Preterm infants — no./total no. (%)	79/93 (84.9)	75/86 (87.2)	
Bayley-III-NL cognitive score	104.3±1.2	103.9±1.2	0.3 (–3.5 to 4.2)
Missing data — no. (%)	14 (15)	11 (13)	
Bayley-III-NL motor score	105.0±1.3	106.5±1.3	–1.5 (–5.7 to 2.6)
Missing data — no. (%)	15 (16)	11 (13)	
Infants small for gestational age — no./total no. (%)†	80/105 (76.2)	82/99 (82.8)	
Bayley-III-NL cognitive score	97.5±1.3	98.5±1.3	–1.0 (–5.1 to 3.2)
Missing data — no. (%)	25 (24)	17 (17)	
Bayley-III-NL motor score	102.4±1.3	102.5±1.4	–0.1 (–4.4 to 4.3)
Missing data — no. (%)	26 (25)	20 (20)	
Infants large for gestational age — no./total no. (%)‡	96/107 (89.7)	105/117 (89.7)	
Bayley-III-NL cognitive score	105.4±1.3	103.7±1.1	1.7 (–2.1 to 5.5)
Missing data — no. (%)	11 (10)	12 (10)	
Bayley-III-NL motor score	106.0±1.2	106.0±0.9	–0.1 (–3.4 to 3.2)
Missing data — no. (%)	12 (11)	13 (11)	
Infants of mothers with diabetes — no./total no. (%)	32/43 (74.4)	33/39 (84.6)	
Bayley-III-NL cognitive score	106.5±1.8	103.1±2.3	3.4 (–3.2 to 10.0)
Missing data — no. (%)	11 (26)	6 (15)	
Bayley-III-NL motor score	105.7±1.5	104.2±2.0	1.4 (–4.1 to 7.0)
Missing data — no. (%)	11 (26)	7 (18)	

Table 3. Secondary Outcomes.*

Variable	Lower-Threshold Group (N=348)	Traditional-Threshold Group (N=341)	Mean Difference (95% CI)
No. of glucose measurements	6.4±0.1	7.0±0.2	−0.7 (−1.0 to −0.3)
Missing data — no. (%)	3 (0.9)	4 (1.2)	
Glucose concentration — mg/dl†	57±0.4	61±0.5	−4.4 (−5.6 to −3.1)
Missing data — no. (%)	3 (0.9)	4 (1.2)	
Infants with hypoglycemic episodes after randomization — no. (%)	197 (57)	160 (47)	9.7 (2.2 to 17.0)‡
No. of hypoglycemic episodes — no. (%)			
0 or 1	244 (70)	280 (82)	−12.0 (−18.2 to −5.6)‡
2 or 3	73 (21)	54 (16)	5.1 (−0.7 to 10.9)‡
4 or more	31 (9)	7 (2)	6.9 (3.5 to 10.5)‡
Severity of hypoglycemia — no. (%)§			
No hypoglycemia	151 (43)	181 (53)	−9.7 (−17.0 to −2.2)‡
Moderate	164 (47)	142 (42)	5.5 (−1.9 to 12.8)‡
Severe or both moderate and severe¶	33 (10)	18 (5)	4.2 (0.3 to 8.2)‡

Variable	Lower-Threshold Group (N=348)	Traditional-Threshold Group (N=341)	Mean Difference (95% CI)
Infants who received supplemental oral feeding — no. (%)	275 (79)	332 (97)	−18.3 (−23.1 to −13.8)
Missing data — no. (%)	5 (1.4)	4 (1.2)	
No. of supplemental oral feedings	5±0.2	7±0.2	−2.2 (−2.8 to −1.7)
Missing data — no. (%)	10 (3)	7 (2)	
Volume of supplemental oral feeding — ml	86±5	157±6	−71 (−86 to −56)
Missing data — no. (%)	10 (3)	7 (2)	
Tube feeding — no. (%)	17 (5)	44 (13)	−8.0 (−12.4 to −3.8)‡
Missing data — no. (%)	3 (0.9)	3 (0.9)	
Continuous IV glucose — no. (%)	21 (6)	70 (21)	−14.5 (−19.5 to −9.5)‡
Missing data — no. (%)	2 (0.6)	2 (0.6)	
Bolus glucose IV — no. (%)	6 (1.8)	12 (3.4)	−1.8 (−4.5 to 0.7)‡
Missing data — no. (%)	2 (0.6)	2 (0.6)	
Hospital stay for newborn — days	4.6±0.2	4.7±0.2	−0.1 (−0.6 to 0.4)
Missing data — no. (%)	2 (0.6)	1 (0.3)	
Hospital stay for mother — days	3.8±0.1	4.0±0.1	−0.2 (−0.5 to 0.02)
Missing data — no. (%)	2 (0.6)	1 (0.3)	
Duration of breast-feeding — no. (%)			
Never or <2 wk	96 (28)	75 (22)	5.6 (−0.9 to 12.0)‡
2 wk to <3 mo	98 (28)	101 (30)	−1.5 (−8.2 to 5.3)‡
≥3 mo	74 (21)	99 (29)	−7.8 (−14.2 to −1.3)‡
Missing data	80 (23)	66 (19)**	

JAMA | Original Investigation

Diagnostic Yield of Newborn Screening for Biliary Atresia Using Direct or Conjugated Bilirubin Measurements

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JAMA March 24/31, 2020 Volume 323, Number 12

IMPORTANCE Treating biliary atresia in newborns earlier can delay or prevent the need for liver transplant; however, treatment typically occurs later because biliary atresia is difficult to detect during its early stages.

OBJECTIVE To determine the diagnostic yield of newborn screening for biliary atresia with direct or conjugated bilirubin measurements and to evaluate the association of screening implementation with clinical outcomes.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional screening study of 124 385 infants born at 14 Texas hospitals between January 2015 and June 2018; and a pre-post study of 43 infants who underwent the Kasai portoenterostomy as treatment for biliary atresia at the region's largest pediatric hepatology center before (January 2008-June 2011) or after (January 2015-June 2018) screening implementation. Final follow-up occurred on July 15, 2019.

EXPOSURES Two-stage screening with direct or conjugated bilirubin measurements. In stage 1, all newborns were tested within the first 60 hours of life, with a positive screening result defined as bilirubin levels exceeding derived 95th percentile reference intervals. In stage 2, infants who had a positive screening result in stage 1 were retested at or before the 2-week well-child visit, with a positive screening result defined as bilirubin levels greater than the stage 1 result or greater than 1 mg/dL.

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MAIN OUTCOMES AND MEASURES The primary outcomes of the screening study were sensitivity, specificity, positive predictive value, and negative predictive value based on infants testing positive in both stages. The reference standard was biliary atresia diagnosed at the region's pediatric hepatology centers. The primary outcome of the pre-post study was the age infants underwent the Kasai portoenterostomy for treatment of biliary atresia.

RESULTS Of 124 385 newborns in the screening study, 49.2% were female, 87.6% were of term gestational age, 70.0% were white, and 48.1% were Hispanic. Screening identified the 7 known infants with biliary atresia with a sensitivity of 100% (95% CI, 56.1%-100.0%), a specificity of 99.9% (95% CI, 99.9%-99.9%), a positive predictive value of 5.9% (95% CI, 2.6%-12.2%), and a negative predictive value of 100.0% (95% CI, 100.0%-100.0%). In the pre-post study, 24 infants were treated before screening implementation and 19 infants were treated after screening implementation (including 6 of 7 from the screening study, 7 from screening at nonstudy hospitals, and 6 from referrals because of clinical symptoms). The age infants underwent the Kasai portoenterostomy was significantly younger after screening was implemented (mean age, 56 days [SD, 19 days] before screening implementation vs 36 days [SD, 22 days] after screening implementation; between-group difference, 19 days [95% CI, 7-32 days]; *P* = .004).

CONCLUSIONS AND RELEVANCE Newborn screening with direct or conjugated bilirubin measurements detected all known infants with biliary atresia in the study population, although the 95% CI around the sensitivity estimate was wide and the study design did not ensure complete ascertainment of false-negative results. Research is needed in larger populations to obtain more precise estimates of diagnostic yield and to better understand the clinical outcomes and cost-effectiveness of this screening approach.

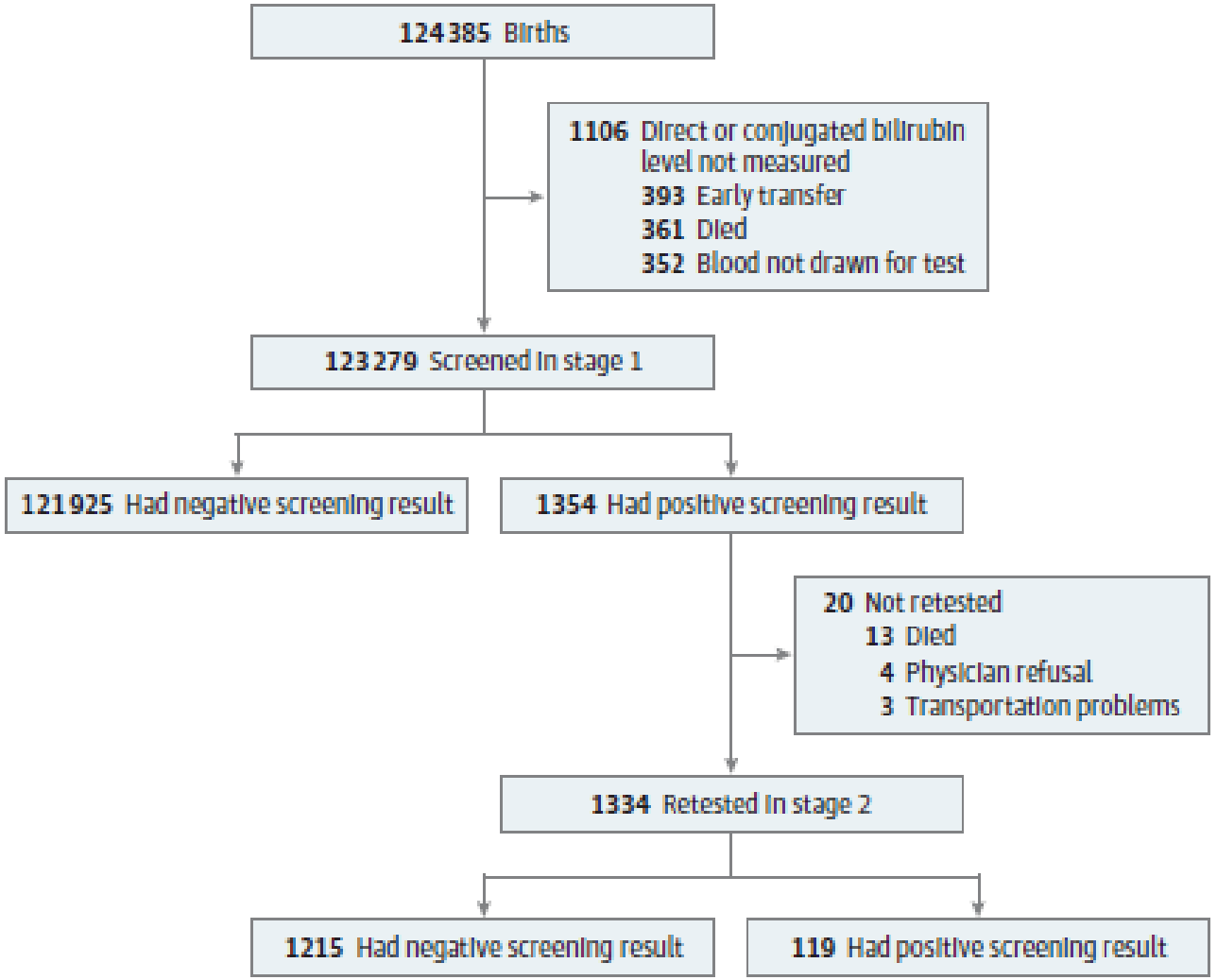
Key Points

Question What is the diagnostic yield of newborn screening for biliary atresia using direct or conjugated bilirubin measurements?

Findings In this study that involved 124 385 newborns, a 2-stage screening approach based on direct or conjugated bilirubin measurements identified the 7 known infants with biliary atresia with a sensitivity of 100.0% and a specificity of 99.9%, although the 95% CI around the sensitivity was wide and the study design did not ensure complete ascertainment of false-negative results.

Meaning These findings may help inform decision-making about newborn screening for biliary atresia, although further research is needed from larger populations to obtain more precise estimates of diagnostic yield and to better understand clinical outcomes and cost-effectiveness of this screening approach.

Figure 1. Patient Flow for the 2-Stage Screening Study for Biliary Atresia



Stage 1 testing occurred within the first 60 hours of life. Stage 2 testing occurred at or before the 2-week well-child visit.

Figure 2. Newborn Direct or Conjugated Bilirubin Screening for Biliary Atresia

Stage 1	Positive screening result	Negative screening result	Total No.
Positive	7	1347	1354
Negative	0	121925	121925
Total	7	123272	123279

Stage 2	Positive screening result	Negative screening result	Total No.
Positive	7	112	119
Negative	0	1215	1215
Total	7	1327	1334[a]

Total	Positive screening result	Negative screening result	Total No.
Positive	7	112	119
Negative	0	123140	123140
Total	7	123252	123259

	% (95% CI)
Sensitivity	100.0 (56.1-100.0)
Specificity	99.9 (99.9-99.9)
PPV	5.9 (2.6-12.2)
NPV	100.0 (100.0-100.0)

NPV indicates negative predictive value; PPV, positive predictive value.

[a] There were 20 newborns who were not retested in stage 2 because 13 died, the physician refused to test in 4, and there were transportation problems for 3.

Table 2. Diagnoses and Evaluation for False-Positive Screening Results (n = 112)

Description of diagnosis and evaluation	No. (%)
Type of diagnosis	
Not determined	59 (52.7)
Cholestasis-associated conditions[a]	17 (15.2)
Heterozygosity in cholestasis-related genes[b]	12 (10.7)
Cholestatic liver diseases[c]	9 (8.0)
Congenital infections[d]	8 (7.1)
Excessive red blood cell clearance	7 (6.3)
Type of evaluation performed	
Additional direct or conjugated bilirubin testing only	28 (25.0)
Additional laboratory testing	25 (22.3)
Additional noninvasive imaging	38 (33.9)
Liver biopsy with or without percutaneous transhepatic cholangiogram	20 (17.9)
Intraoperative cholangiogram	1 (0.9)

[a] Included trisomy 21 (5 cases), gastroschisis (4 cases), trisomy 18 (3 cases), portosystemic shunt (2 cases), maternal lupus (1 case), omphalocele (1 case), and panhypopituitarism (1 case).

[b] The gene names appear in eTable 7 in the Supplement.

[c] Included Alagille syndrome (4 cases), α_1 antitrypsin deficiency (3 cases), *ABCB11* deficiency (1 case), and choledochal cyst (1 case).

[d] Included cytomegalovirus (3 cases), syphilis (3 cases), coxsackievirus (1 case), and rubella (1 case).

IMPORTANCE Reducing neonatal mortality is a national health care priority. Understanding the association between neonatal mortality and antenatal transfer of pregnant women to a level III perinatal hospital for delivery of infants who are very preterm (VPT) may help identify opportunities for improvement.

OBJECTIVE To assess whether antenatal transfer to a level III hospital is associated with neonatal mortality in infants who are VPT.

DESIGN, SETTING, AND PARTICIPANTS This population-based cross-sectional study included infants who were born VPT to Illinois residents in Illinois perinatal-network hospitals between January 1, 2015, and December 31, 2016, and followed up for 28 days after birth. Data analysis was conducted from June 2017 to September 2018.

EXPOSURES Delivery of an infant who was VPT at a (1) level III hospital after maternal presentation at that hospital (reference group), (2) a level III hospital after antenatal (in utero) transfer from another hospital, or (3) a non–level III hospital.

MAIN OUTCOMES AND MEASURES Neonatal mortality.

RESULTS The study included 4817 infants who were VPT (gestational age, 22-31 completed weeks) and were born to Illinois residents in 2015 and 2016. Of those, 3302 infants (68.5%) were born at a level III hospital after maternal presentation at that hospital, 677 (14.1%) were born at a level III hospital after antenatal transfer, and 838 (17.4%) were born at a non–level III hospital. Neonatal mortality for all infants who were VPT included in this study was 573 of 4817 infants (11.9%). The neonatal mortality was 10.7% for the reference group (362 of 3302 infants), 9.8% for the antenatal transfer group (66 of 677 infants), and 17.3% for the non–level III birth group (145 of 838 infants). When adjusted for significant social and medical characteristics, infants born VPT at a level III hospital after antenatal transfer from another facility had a similar risk of neonatal mortality as infants born at a level III hospital (odds ratio, 0.79 [95% CI, 0.56-1.13]) after maternal presentation at the same hospital. Infants born at a non–level III hospital had an increased risk of neonatal mortality compared with infants born at a level III hospital after maternal presentation to the same hospital (odds ratio, 1.52 [95% CI, 1.14-2.02]).

CONCLUSIONS AND RELEVANCE The risk of neonatal mortality was similar for infants who were VPT, whether women initially presented at a level III hospital or were transferred to a level III hospital before delivery. This suggests that the increased risk of mortality associated with delivery at a non–level III hospital may be mitigated by optimizing opportunities for early maternal transfer to a level III hospital.

Neonatal Mortality After Interhospital Transfer of Pregnant Women for Imminent Very Preterm Birth in Illinois

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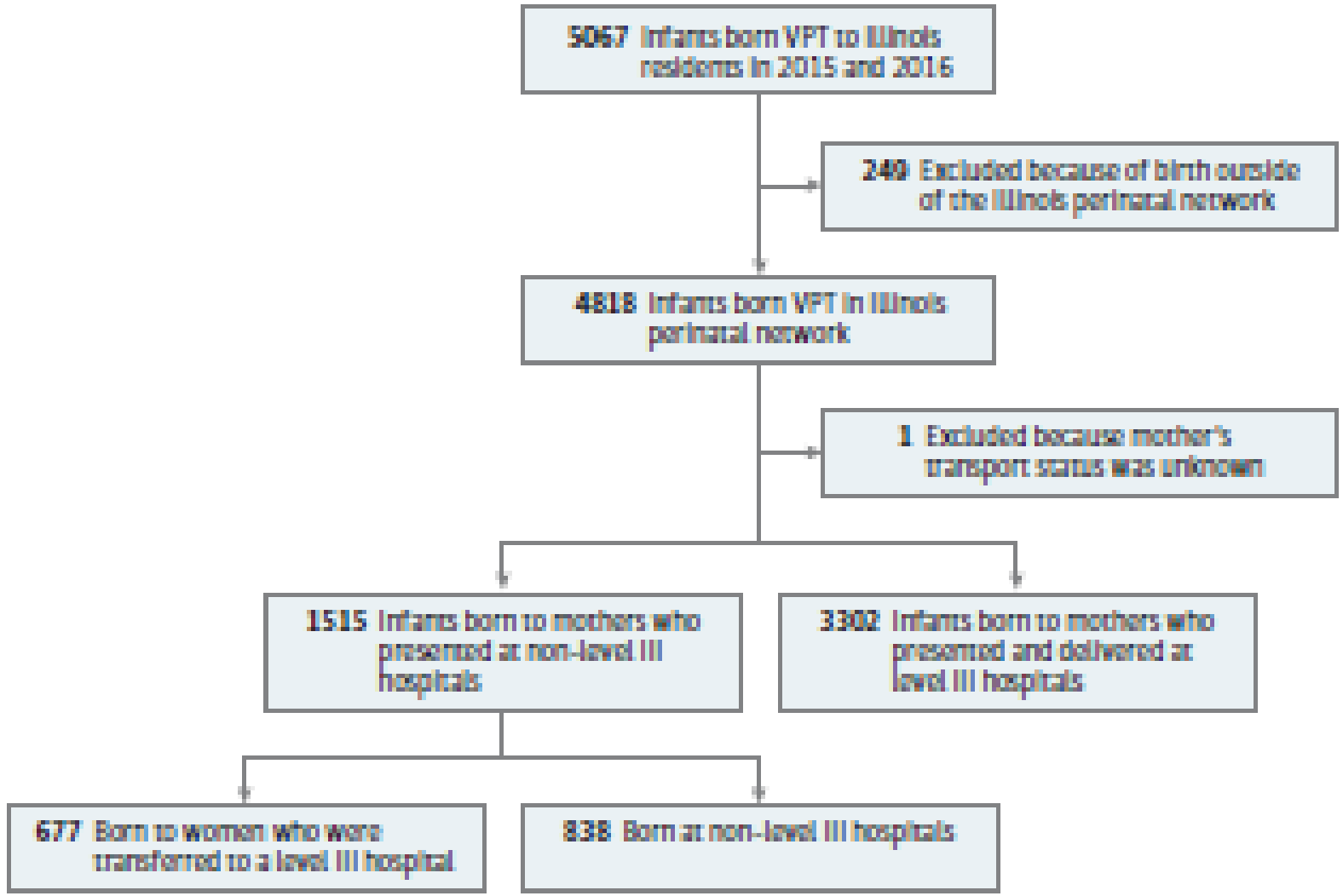
Key Points

Question Is antenatal transfer to a level III hospital prior to very preterm delivery associated with neonatal mortality?

Findings In this cross-sectional study, neonates born very preterm in level III hospitals had similar odds of mortality, regardless of whether women presented directly or were transferred to the level III hospital prior to delivery. Neonates born very preterm in non–level III hospitals had higher odds of mortality than when women presented for delivery at level III hospitals.

Meaning Increasing antenatal transfers to level III hospitals for women with threatened very preterm delivery may be one means to lessen neonatal mortality in infants who are very preterm.

Figure. Study Groups of Very Preterm (VPT) Births in Illinois in 2015 and 2016



The reference group is the 3302 infants born to mothers who presented and delivered at level III hospitals. The antenatal transfer group includes the 677 infants born to women who were transferred to a level III hospital. The non–level III hospital group includes the 838 infants born at non–level III hospitals. The reference, antenatal transfer, and non–level III birth groups represent the study groups. Together, the reference and antenatal transfer group represent inborn infants who were VPT.