Effects of Neonatal Hyperglycemia on Retinopathy of Prematurity and Visual Outcomes at 7 Years of Age: A Matched Cohort Study

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Objective To determine whether neonatal hyperglycemia is associated with retinopathy of prematurity (ROP), visual outcomes, and ocular growth at 7 years of age.

Study design Children born preterm (<30 weeks of gestational age) at a tertiary hospital in Auckland, New Zealand, who developed neonatal hyperglycemia (2 blood glucose concentrations ≥153 mg/dL [8.5 mmol/L] 4 hours apart) were matched with children who were not hyperglycemic (matching criteria: sex, gestational age, birth weight, age, socioeconomic status, and multiple birth) and assessed at 7 years of corrected age. The primary outcome, favorable overall visual outcome (visual acuity ≤0.3 logarithm of the minimum angle of resolution, no strabismus, stereoacuity ≤240 arcsec, not requiring spectacles) was compared between groups using generalized matching criteria-adjusted linear regression models.

Results Assessments were performed on 57 children with neonatal hyperglycemia (hyperglycemia group) and 54 matched children without hyperglycemia (control group). There were no differences in overall favorable visual outcome (OR 0.95, 95% CI 0.42-2.13, $P = .90$) or severe ROP incidence (OR 2.20, 95% CI 0.63-7.63, $P = .21$) between groups. Children with hyperglycemia had poorer binocular distance visual acuity (mean difference 0.08, 95% CI 0.03-0.14 logarithm of the minimum angle of resolution, $P < .01$), more strabismus (OR 6.22, 95% CI 1.31-29.45, $P = .02$), and thicker crystalline lens (mean difference 0.14, 95% CI 0.04-0.24 mm, $P < .01$). Maximum blood glucose concentration was greater in the ROP-treated group compared with the ROP-not treated and no ROP groups after adjusting for sex, gestational age, and birth weight z score ($P = .02$).

Conclusions Neonatal hyperglycemia was not associated with overall visual outcomes at 7 years of age. However, there were between-group differences for specific outcome measures relating to interocular lens growth and binocular vision. Further follow-up is required to determine implications on long-term visual outcome. *(J Pediatr 2020;223:42-50)*.

Transient neonatal hyperglycemia (blood glucose concentrations >150 mg/dL [8.3 mmol/L]) occurs in approximately 60% of infants with birth weight (BW) <1000 g.[1] Although a standard definition of neonatal hyperglycemia has not been established,[2] neonatal hyperglycemia has been associated with increased mortality[1,3] and adverse outcomes,[1,4-6] including retinopathy of prematurity (ROP).[7-10] It is unknown whether there is a causal association between hyperglycemia and these factors or whether it is purely a marker of severe illness.[2] Infants born very preterm are at increased risk of visual impairment,[11-13] but it is unclear whether neonatal hyperglycemia per se affects the development of the visual system.

ROP is a proliferative retinal vascular disease that can affect vision depending on disease severity.[14] The risk of developing ROP has been associated with the duration of hyperglycemia and increasing daily mean blood glucose concentrations in the first 30 postnatal days.[9,10,15-17] However, the current evidence does not support hyperglycemia as a definite risk factor for ROP.[7,8] Most studies reporting on the association between hyperglycemia and ROP had small sample

BW	Birth weight
CRIB-II	Clinical Risk Index for Babies II
D	Diopters
logMAR	Logarithm of the minimum angle of resolution
PIANO	Protein, Insulin and Neonatal Outcomes
ROP	Retinopathy of prematurity
SER	Spherical equivalent refraction

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sizes, used retrospective designs, and employed various definitions of neonatal hyperglycemia that are not comparable.

High blood glucose concentrations in adults with type I and II diabetes mellitus are associated with diabetic retinopathy and subsequent vision loss,[18,19] and progression is associated with longer presence of hyperglycemia.[20,21] Common signs of diabetic retinopathy include retinal thickening, microvascular changes, hemorrhages, exudates, and macula edema, with ischemia and retinal neovascularization in more severe stages.[22] Other ocular changes include the development of cataracts and loss of corneal sensitivity.[22] It is unknown whether transient hyperglycemia in infants born preterm affects visual outcomes in later childhood, either by increasing the incidence of ROP or via direct effects on the eye and visual pathway.

The aim of this study was to determine whether neonatal hyperglycemia is associated with ROP and visual outcomes at 7 years of age.

Methods

This cross-sectional, matched cohort study evaluated 7-year-old children hospitalized after birth at the neonatal intensive care unit of National Women's Health, Auckland City Hospital, New Zealand, with gestational age <30 weeks or BW < 1500 g, with or without neonatal hyperglycemia (2 consecutive blood glucose concentrations >153 mg/dL [8.5 mmol/L], ≥4 hours apart) before 36 weeks of postmenstrual age. Ethics approval was obtained from the Northern Y Regional Ethics Committee (NTY/12/05/035) of the New Zealand Ministry of Health. Written informed consent was obtained from the parents or legal guardians.

We conducted a randomized, controlled trial of tight glycemic control infants born preterm with very low BW and hyperglycemia (the Hyperglycemia and Insulin in Neonates Trial [HINT], trial registration: ACTRN12606000270516)[23] from 2005 to 2008. All surviving participants in the HINT trial were invited to take part in the Protein, Insulin and Neonatal Outcomes (PIANO) prospective observational study at 7 years of corrected age (hyperglycemia group), and each was matched with a child who was eligible for the HINT trial but did not meet the neonatal hyperglycemia criteria (control group). Matching variables were decided a priori and applied in a hierarchical order: sex, gestational age, BW, date of birth, New Zealand deprivation index[24] at pregnancy booking, multiple birth, and Clinical Risk Index for Babies II (CRIB-II) score. More than 1 matched control per case were recruited, as children who previously participated in the HINT trial were considered more likely to take part in the follow-up study. CRIB-II score matching was discontinued during recruitment because it was found to be not feasible, as hyperglycemic cases had significantly greater CRIB-II score than potential controls.

Children with gestational age <30 weeks and/or BW < 1250 g, or select infants with an unstable clinical course, underwent photo-screening for ROP at 4-6 weeks after birth.[25] ROP was graded according to the International Classification of Retinopathy of Prematurity[26] and treated according to the Early Treatment of Retinopathy of Prematurity Study recommendations.[27] Hypoglycemia was defined as blood glucose concentration <46.8 mg/dL (2.6 mmol/L).

At 7 years of corrected age, children underwent an assessment at the Liggins Institute, University of Auckland, Auckland, New Zealand. Vision assessments were performed by New Zealand registered optometrists (and included assessment of visual function, refractive error, and ocular biometry). Visual acuity was measured monocularly and binocularly using a logarithm of the minimum angle of resolution (logMAR) crowded test (Keeler Ltd, Windsor, United Kingdom) viewed at 3 meters from largest to smallest; visual acuity was recorded as the smallest page with 2 letters correct. Visual acuity was repeated with spectacles if the child had spectacles. Presenting visual acuity was defined as unaided visual acuity or spectacle visual acuity if the child had spectacles. Good distance visual acuity was defined as ≤0.30 logMAR (20/40) presenting vision in the better eye. Strabismus was defined as any manifest constant or intermittent ocular misalignment found on unilateral cover test at any distance. Other tests of binocular vision included ocular motility (dissociated Broad H test), nystagmus (observation of involuntary eye movements), binocular motor fusion (20 base out prism test), near point of convergence (Royal Air Force convergence rule),[28] and stereoacuity (test for stereoscopic vision). Normal motor fusion was defined as overcoming 20Δ base-out prism in each eye, normal near point of convergence (to ≤10 cm from the eyes) and passing stereoacuity (≤240 seconds of arc). Global motion coherence thresholds were measured with random dot kinematograms as reported previously.[29]

Autorefraction and keratometry were measured using an AR-20 Handheld Autorefractor (Nidek Inc, Gamagori, Japan) 40 minutes after instillation of one drop/eye of cyclopentolate 1% if an acceptable cycloplegic effect (pupil non-reaction to light, stable auto-refraction) was seen. Refractive error was recorded as spherical equivalent refraction (SER): spherical power + (cylindrical power/2). Refractive error was defined as any of the following: myopia SER ≤–0.50 diopters (D); significant hyperopia SER ≥+2.00 D, astigmatism cylinder ≥1.00 dioptres cylinder (DC), anisometropia inter-eye SER or cylinder difference ≥1.00 D.[30] Not requiring spectacles for refractive error (no significant refractive error) was defined as SER >–0.50 to <+2.00 D and cylinder <1.00 DC. Corneal thickness and curvature, anterior chamber depth, lens thickness, and axial length were measured before cycloplegia using a LenStar LS900 Non-contact Biometer (Haag-Streit Diagnostics, Tokyo, Japan) using optical low coherence reflectometry.[31]

The primary outcome was favorable overall visual outcome (defined as good distance visual acuity, no strabismus, passing stereoacuity, and not requiring spectacles for refractive error in either eye). Other composite visual outcomes included favorable binocular visual outcome (no strabismus or nystagmus, normal ocular motility and convergence, presence of motor fusion, and passing stereoacuity) and favorable functional visual outcome (good distance visual acuity, no

strabismus, and passing stereoacuity). An unfavorable outcome was defined as failing ≥1 test in the composite outcome irrespective of whether all components of the composite were successfully measured; nonsuccessful measurement was considered missing data. For measurements of vision in separate eyes, the results were recorded as better and poorer eye according visual acuity, least SER refractive error, and random assignment (by a random number generator) in a hierarchical order.

Statistical analyses were performed using SPSS Statistics 23 (IBM Corp, Armonk, New York). Continuous variables were reported as means (SD) or medians (IQR) and compared using the Student *t* test or Mann–Whitney *U* test. Categorical variables were summarized as counts (percentages) and compared using the χ^2 test or Fisher exact tests for small cell counts ($n < 5$).

Outcomes were evaluated using generalized linear regression models, unadjusted and adjusted for all matching variables and reported as ORs or mean differences with 95% CIs. Pairwise deletion[32] was used for missing data. A post-hoc test was used to further compare favorable overall visual outcome with a lower visual acuity threshold (better than 20/25 in the better visual acuity eye).

Exploratory regression analyses tested for associations between neonatal factors and visual outcomes at 7 years. All exposures with *P* value <.15 were further explored in multiple regression models. Outcomes were compared using no ROP/ROP and ROP-not treated/ROP-treated categories as stratification groups.

Results

Of the 88 infants who developed neonatal hyperglycemia and were randomized to the HINT trial, 57 of 77 (74% of those who survived) were included as the hyperglycemia group. Of 94 children who did not develop hyperglycemia, met matching criteria, and were selected as the control group, 54 (61% of those who survived) were assessed; a total of 111 children were assessed at 7 years of corrected age (**Figure 1**).

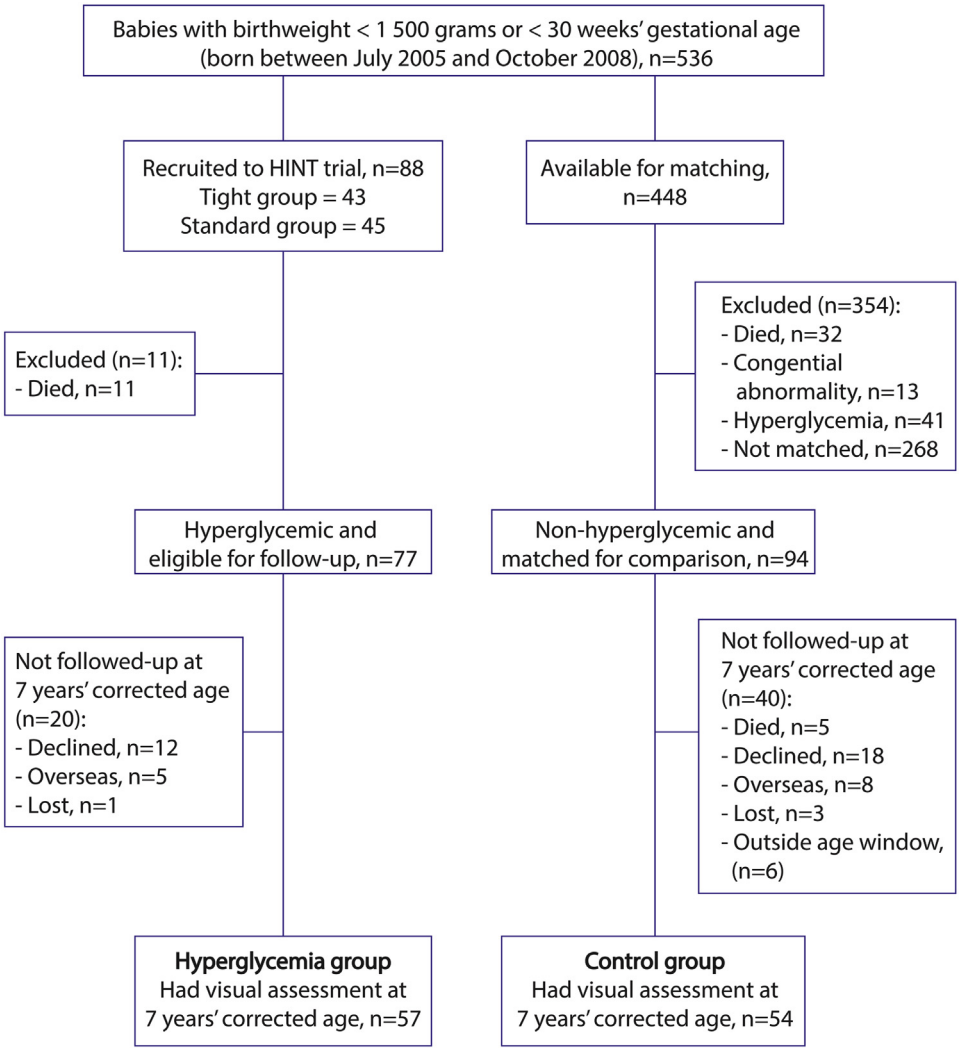

Figure 1. STROBE diagram of the neonatal hyperglycemia cohort of the PIANO study.

At birth, infants in the hyperglycemia group were born earlier and smaller, and had poorer CRIB-II scores and 1-minute Apgar scores than infants in the control group (Table I). The hyperglycemia group also had less boys and greater incidences of bronchopulmonary dysplasia, treatment with postnatal steroids, and hypoglycemia in the neonatal period. The hyperglycemia group had greater mean and maximum blood glucose concentration; only children in the hyperglycemia group received an insulin infusion for high blood glucose concentrations. The incidence of ROP was similar between groups. For both hyperglycemia and control groups, children who were eligible but not assessed did not differ significantly from those who were assessed (Table I), except that those not assessed in the hyperglycemia group had greater birth measurement z scores, and the children not assessed in the control group had fewer cases of grade I/II ROP. All assessed children underwent ROP screening.

At the time of the assessment (7.2 ± 0.1 corrected years of age), characteristics of the children were similar between the groups (Table II; available at www.jpeds.com). There were no significant differences in overall, binocular, or functional visual outcomes between children who were in the hyperglycemia group compared with those in the control

Table I. Perinatal characteristics of children eligible for the neonatal hyperglycemia cohort of the PIANO study, assessed and not assessed at 7 years of corrected age

	Hyperglycemia group			CONTROL group			Hyperglycemia vs CONTROL (assessed)
Perinatal characteristics	Assessed (n = 57)	Not assessed (n = 20)	*P* value	Assessed (n = 54)	Not assessed (n = 35)	*P* value	*P* value
Gestational age, wk	25 (25, 27)	25 (24, 26)	.29	26 (26, 28)	27 (26, 29)	.12	<.01
Boys	25 (44%)	9 (45%)	.93	34 (63%)	21 (60%)	.78	.04
Birth measurements							
Weight (g)	790 (700, 855)	851 (700, 993)	.22	988 (885, 1130)	950 (790, 1160)	.68	<.01
Weight z-score	−0.13 ± 0.91	0.47 ± 0.90	.01	0.32 ± 0.85	0.03 ± 0.97	.13	<.01
Crown–heel length, cm	33.3 (31.5, 34.4)	34.0 (31.0, 37.0)	.19	35.5 (33.5, 37.5)	35.0 (34.5, 37.0)	1.00	<.01
Length z score	−0.29 ± 1.15	0.36 ± 1.08	.04	0.26 ± 0.92	0.06 ± 1.06	.37	<.01
Head circumference, cm	23.5 (22.5, 24.8)	24.0 (22.6, 26.0)	.30	25.0 (23.7, 26.0)	24.7 (24.2, 25.8)	.99	<.01
Head circumference z score	−0.02 ± 1.14	0.67 ± 1.21	.03	0.42 ± 0.95	0.12 ± 1.19	.20	.03
Small for gestational age	8 (14%)	1 (5%)	.28	3 (6%)	4 (11%)	.32	.14
Deprivation index							
Most deprived (10)	11 (19%)	5 (25%)	.69	11 (20%)	5 (14%)	.19	.29
Least deprived (1)	6 (11%)	0 (0%)		5 (9%)	0 (0%)		
Multiple pregnancy	20 (35%)	8 (40%)	.69	13 (24%)	5 (14%)	.26	.22
CRIB-II score	11 ± 2	12 ± 3	.42	9 ± 3	9 ± 2	.64	<.01
Apgar score							
1 min	5 ± 2	6 ± 2	.29	6 ± 2	6 ± 2	.64	.02
5 min	8 ± 2	8 ± 2	.30	8 ± 2	8 ± 2	.87	.09
Neonatal complications							
NEC	1 (2%)	0 (0%)	1.00	4 (7%)	1 (3%)	.83	.15
IVH (grade III/IV)	4 (7%)	2 (10%)	.67	2 (4%)	0 (0%)	.25	.45
PVL	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–	–
ROP (grade I/II)	34 (61%)	14 (74%)	.41	36 (72%)	16 (49%)	.03	.22
ROP (grade III/IV)	9 (16%)	3 (15%)	.98	4 (7%)	1 (3%)	.35	.21
ROP treatment	8 (14%)	3 (15%)	.92	2 (4%)	1 (3%)	.85	.06
Early-onset sepsis	0 (0%)	1 (5%)	.09	1 (2%)	2 (6%)	.32	.30
Late-onset sepsis	12 (21%)	7 (35%)	.21	7 (13%)	4 (11%)	.83	.26
BPD	24 (42%)	9 (45%)	.82	12 (22%)	12 (34%)	.21	.03
Postnatal steroids	19 (35%)	7 (35%)	1.00	7 (13%)	7 (20%)	.37	<.01
Discharged with home O_2	19 (33%)	5 (25%)	.09	11 (20%)	7 (20%)	.97	.12
Major neonatal surgery	7 (12%)	2 (10%)	.79	3 (6%)	1 (3%)	.55	.22
Blood glucose status (first 28 postnatal d)							
Mean number of blood glucose readings	96 ± 54	93 ± 62	.80	39 ± 36	33 ± 22	.40	<.01
Minimum blood glucose, mg/dL	43 ± 16	47 ± 14	.63	52 ± 16	50 ± 14	.74	<.01
Mean blood glucose, mg/dL	119 ± 16	119 ± 16	.95	94 ± 11	95 ± 13	.50	<.01
Maximum blood glucose, mg/dL	259 ± 101	248 ± 83	.66	153 ± 34	160 ± 61	.54	<.01
Neonatal hyperglycemia (≥2 × blood glucose >153 mg/dL ≥4h apart)	57 (100%)	20 (100%)	–	0 (0%)	0 (0%)	–	–
Received insulin	44 (77%)	15 (75%)	.84	0 (0%)	0 (0%)	–	<.01
Hypoglycemia (blood glucose <47 mg/dL)	35 (61%)	9 (45%)	.20	17 (32%)	9 (26%)	.56	<.01
Growth velocity 28 d (g kg^{-1}.day^{-1})	11.4 ± 2.8	11.2 ± 2.5	.87	11.1 ± 4.1	8.7 ± 3.0	.09	.71
Length of neonatal stay, d	98 ± 24	111 ± 39	.09	86 ± 25	78 ± 24	.16	.01

BPD, bronchopulmonary dysplasia; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; O_2, oxygen supplementation; *PVL*, periventricular leukomalacia.
Data are n (%), mean ± SD, median (IQR).

group (Table III). Children within the hyperglycemia group had poorer presenting visual acuity in both eyes, a greater incidence of strabismus, shorter axial length, and thicker central corneas than control children. However, these differences were not significant after adjustment for matching criteria (Table III). The crystalline lens of the better eye was thicker in the hyperglycemia group (Table III). Refractive errors were similar between the groups; however, after adjustment for matching criteria, the better visual acuity eye of the control group had a greater risk of astigmatism. Of the children assessed, 14 (29%) from the hyperglycemia group had spectacles, and 8 routinely wore them, whereas in the control group, 6 (11%) had spectacles and 4 routinely wore them. Post-hoc analysis of favorable overall visual outcome with a lower visual acuity threshold (better than 20/25) was similar between the groups (53% vs 54%, aOR 1.45, 95% CI 0.35-6.02, $P = .61$), and the proportions were similar to the overall visual outcome with the greater visual acuity threshold.

Table III. Visual outcomes of children assessed in the neonatal hyperglycemic and control groups at seven years of age

Visual outcomes	Hyperglycemia group (n = 57)	CONTROL group (n = 54)	OR or mean difference (95% CI)	*P* value	aOR or mean difference (95% CI)*	*P* value
Composite visual outcomes						
Favorable overall visual outcome	26/49 (53%)	25/46 (54%)	0.95 (0.42, 2.13)	.90	1.64 (0.39, 6.80)	.50
Favorable binocular visual outcome	23/54 (43%)	22/54 (41%)	1.08 (0.50, 2.32)	.85	1.30 (0.38, 4.46)	.68
Favorable functional visual outcome	33/52 (64%)	41/54 (76%)	0.55 (0.24, 1.28)	.16	1.09 (0.25, 4.67)	.91
Visual functional outcomes						
Presenting distance visual acuity in better eye						
Equal or better than 20/40 (good visual acuity)	54/55 (98%)	54/54 (100%)	–		–	
Better than 20/25	47/55 (86%)	44/54 (82%)	1.34 (0.48, 3.69)	.58	1.37 (0.24, 7.87)	.72
LogMAR	0.00 ± 0.13	−0.04 ± 0.12	0.05 (0.00, 0.09)	.05	0.04 (−0.02, 0.09)	.18
Presenting distance visual acuity in poorer eye LogMAR	0.14 ± 0.29	0.03 ± 0.15	0.11 (0.02, 0.20)	.02	0.06 (−0.05, 0.17)	.30
Distance unaided visual acuity (logMAR)						
Better visual acuity eye	0.00 ± 0.14	−0.04 ± 0.12	0.04 (−0.10, 0.09)	.17	0.02 (−0.04, 0.08)	.48
Poorer visual acuity eye	0.09 ± 0.22	0.03 ± 0.15	0.07 (0.00, 0.14)	.06	0.02 (−0.10, 0.06)	.67
Other visual outcomes						
Presence of strabismus	11/57 (19%)	2/54 (4%)	6.22 (1.31, 29.45)	.02	2.50 (0.42, 14.71)	.32
Pass stereoacuity	36/51 (71%)	41/54 (76%)	0.76 (0.32, 1.82)	.54	0.84 (0.28, 2.54)	.76
Presence of nystagmus	2/56 (4%)	0/54 (0%)	–	–		
Normal ocular motility	48/55 (87%)	51/54 (94%)	0.40 (0.10, 1.64)	.20	0.74 (0.14, 3.97)	.73
Normal convergence	40/50 (80%)	44/52 (85%)	0.73 (0.25, 2.13)	.56	0.89 (0.22, 3.57)	.87
Presence of motor fusion	33/53 (62%)	36/53 (68%)	0.78 (0.34, 1.79)	.56	0.76 (0.27, 2.09)	.59
No spectacles needed in either eye	36/46 (78%)	33/45 (73%)	1.31 (0.50, 3.43)	.58	2.04 (0.33, 12,66)	.44
Mean global motion perception threshold	48.5 ± 21.4	46.3 ± 22.6	2.2 (−5.8, 10.3)	.59	−3.2 (−14.1, 7.6)	.55
Refractive error						
SER of the better visual acuity eye				.27		.91
Myopia	3/46 (6%)	3/45 (7%)				
Significant hyperopia	4/46 (9%)	0/45 (0%)				
Mean SER (D)	0.69 ± 1.98	0.63 ± 0.82	0.06 (−0.57, 0.69)	.85	0.21 (−0.65, 1.08)	.63
SER of the poorer visual acuity eye				.13		.29
Myopia	3/46 (7%)	5/45 (11%)				
Significant hyperopia	3/46 (7%)	1/45 (2%)				
Mean SER (D)	0.55 ± 2.23	0.64 ± 0.91	−0.10 (−0.81, 0.61)	.79	0.38 (−0.52, 1.28)	.40
Astigmatism						
Better eye	6/46 (9%)	8/45 (18%)	0.44 (0.12, 1.58)	.20	0.14 (0.02, 0.90)	.04
Poorer eye	7/46 (15%)	8/45 (18%)	0.83 (0.27, 2.52)	.74	0.36 (0.08, 1.65)	.19
Anisometropia	2/45 (4%)	0/45 (0%)	–	–		
Ocular biometry						
Central corneal thickness, μm						
Better visual acuity eye	549 ± 35	535 ± 32	14 (0.00, 27)	.05	8 (−9, 25)	.34
Poorer visual acuity eye	549 ± 40	533 ± 31	16 (1, 30)	.03	10 (−7, 27)	.26
Anterior chamber depth, mm						
Better visual acuity eye	3.34 ± 0.29	3.43 ± 0.25	−0.09 (−0.20, 0.02)	.09	−0.05 (−0.08, 0.16)	.49
Poorer visual acuity eye	3.36 ± 0.30	3.42 ± 0.26	−0.05 (−0.17, 0.06)	.36	0.00 (−0.15, 0.14)	.97
Axial length, mm						
Better visual acuity eye	22.07 ± 0.91	22.57 ± 0.75	−0.50 (−0.85, −0.15)	<.01	−0.37 (−0.79, 0.05)	.08
Poorer visual acuity eye	22.12 ± 0.99	22.59 ± 0.73	−0.46 (−0.82, −0.10)	.01	−0.35 (−0.78, 0.09)	.12
Lens thickness, mm						
Better visual acuity eye	3.83 ± 0.27	3.69 ± 0.22	0.14 (0.04, 0.24)	<.01	0.14 (0.01, 0.26)	.03
Poorer visual acuity eye	3.80 ± 0.27	3.70 ± 0.22	0.10 (0.00, 0.24)	.06	0.10 (−0.03, 0.22)	.13
Corneal curvature, mm						
Flat meridian better visual acuity eye	7.67 ± 0.26	7.73 ± 0.27	−0.06 (−0.17, 0.05)	.25	−0.03 (−0.15, 0.10)	.70
Flat meridian poorer visual acuity eye	7.68 ± 0.26	7.73 ± 0.27	−0.05 (−0.16, 0.06)	.09	−0.02 (−0.15, 0.11)	.73
Steep meridian better visual acuity eye	7.50 ± 0.28	7.61 ± 0.26	−0.11 (−0.22, 0.00)	.06	−0.05 (−0.18, 0.08)	.45
Steep meridian poorer visual acuity eye	7.51 ± 0.28	7.56 ± 0.25	−0.05 (−0.16, 0.06)	.35	−0.01 (−0.14, 0.12)	.87

Data are n (%), mean ± SD.
*Adjusted for sex (male/female), multiple birth (yes/no), gestational age, BW z score, New Zealand deprivation index at birth, and CRIB-II score.

Multiple regression analyses investigating the exposures affecting unaided visual acuity found a significant association between unaided visual acuity and lens thickness. For the eye with the better visual acuity, every increase of lens thickness by 0.1 mm was associated with a visual acuity reduction of 0.02 logMAR (adjusted R^2 = 0.14, F = 4.34, β = 0.02, 95% CI 0.01-0.03, P = .003), which is 1 logMAR letter. In a separate model investigating the exposures affecting lens thickness, there was a significant association between lens thickness and mean blood glucose concentration (adjusted R^2 = 0.23, F = 4.35, P < .001); with every 1 mmol/L (18 mg/dL) increase in mean blood glucose concentration, the lens was thicker by 0.08 mm (95% CI 0.02-0.14).

As the hyperglycemia group had more hypoglycemia, and hypoglycemia has been proposed to be associated with poorer visual outcome,[33] multiple regression was used to explore the effects of hypoglycemia on visual outcomes in this cohort. Neonatal hypoglycemia was not associated with favorable overall visual outcome (hypoglycemia vs no hypoglycemia: 52% vs 57%; OR 0.83, 95% CI 0.37-1.87, P = .65), binocular outcome (34% vs 48%, OR 0.55, 95% CI 0.25-1.20, P = .13), or functional visual outcome (34% vs 41%, OR 0.53, 95% CI 0.23-1.23, P = .14). The global motion coherence threshold tended to be greater in those who developed hypoglycemia than those who did not develop hypoglycemia (51.6 ± 22.8 vs 43.8 ± 20.6; mean difference −7.9, 95% CI −16.3 to 0.6, P = .07).

Maximum blood glucose concentration was greater in the ROP-treated group (281 ± 27 mg/dL [15.6 ± 1.5 mmol/L]) compared with the ROP-not treated (200 ± 9 mg/dL [11.1 ± 0.5 mmol/L]) and no ROP (198 ± 18 mg/dL [11.0 ± 1.0 mmol/L]) groups after adjusting for sex, gestational age, and BW z score (**Figure 2**). Within logistic regression, greater mean blood glucose concentration was associated with reduced odds of having ROP (aOR 0.58, 95% CI 0.34-0.96, P = .04, **Table IV** [available at www.jpeds.com]), whereas greater maximum blood glucose concentration was associated with increased odds of requiring ROP treatment (aOR 1.20, 95% CI 1.03-1.40, P = .02, **Table V** [available at www.jpeds.com]); no significant relationship was found between minimum blood glucose concentration and ROP. Greater gestational age was associated with reduced mean (adjusted R^2 = 0.05, χ^2 = 6.90, P = .01) and maximum (adjusted R^2 = 0.05, F = 6.40, P = .01) blood glucose concentrations and also was associated with reduced risk of ROP (OR 0.65, 95% CI 0.48-0.88, P = .005) or requiring ROP treatment (OR 0.43, 95% CI 0.22-0.82, P = .01).

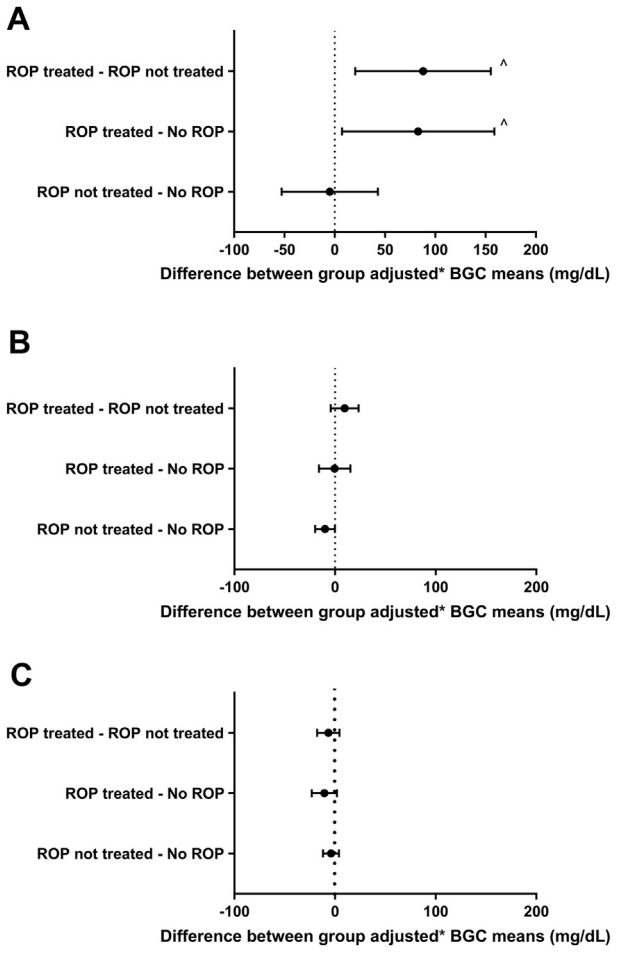

Figure 2. Mean difference in neonatal blood glucose concentration according to ROP status. Shown are the mean difference and 95% CIs for **A,** maximum; **B,** mean; and **C,** minimum neonatal blood glucose concentrations between no ROP (n = 23), ROP-not treated (n = 73), and ROP-treated groups (n = 10). *Adjusted for sex, gestational age, and BW z score. ^P = .01 for mean difference between ROP-treated vs ROP-not treated, P = .03 for ROP-treated vs No ROP on post-hoc testing. *BCG*, blood glucose concentration.

Discussion

In this matched cohort study, there were no differences in overall, binocular, and functional visual outcomes at 7 years of corrected age between children born preterm who had neonatal hyperglycemia compared with those without neonatal hyperglycemia. However, the hyperglycemia group had a thicker crystalline lens and less astigmatism in the better eye than the control group. Both groups had mean visual acuity comparable with other similar population studies of school children,[34-36] and the majority of children had presenting visual acuity equal to or better than 20/40 (0.3 logMAR) in the better eye, which would be adequate for most daily activities. Favorable overall visual outcome with a lower visual acuity threshold (better than 20/25 [0.1 logMAR]) was used in a post-hoc analysis; the proportion of favorable visual outcome was similar between the groups and similar to the primary outcome with the greater visual acuity threshold. These findings suggest that children born very preterm who developed neonatal hyperglycemia have similar visual function to those who did not develop neonatal hyperglycemia but may have some subclinical changes in visual function.

Children in the hyperglycemia group had a thicker crystalline lens than the control group. Children and adults with type 1 diabetes mellitus also have thicker crystalline lenses than those without diabetes.[37-39] In those with diabetes, lens thickness is

positively correlated with duration of diabetes. Individuals with diabetes are also likely to have a shallower anterior chamber depth, greater risk of hyperopia, and have retinal changes, findings that were not seen in our population.[39-41] However, all cases of significant hyperopia in our study were in the hyperglycemia group. Throughout childhood, the crystalline lens becomes progressively thinner as part of emmetropization process; this thinning is accentuated before myopia onset.[42] It is possible that the thickened lens seen in our cohort was due to the thinning process being halted or perhaps due to more hyperopia. However, the mean SER in our study was similar or slightly less hyperopic than other reports of children of a similar age.[43,44] Our exploratory analyses showed that greater mean blood glucose concentration in the first 28 postnatal days was associated with an increase in lens thickness, but ROP may also be associated with lens thickness. Our results suggest that neonatal hyperglycemia may have lasting effects on lens development, even though the high blood glucose concentration was experienced over a short period of time soon after birth. The implications of these changes for visual outcome in later life is unknown. A recent study in lambs has shown that lambs with hyperglycemia for 12 days after birth were at increased risk of reduced β-cell mass, with associated reduced insulin control in adulthood, which may increase the risk of diabetes.[45] In humans, many individuals with diabetes are at risk of cataractous changes in their crystalline lens.

Refractive error was similar between the groups, even though lens thickness was increased, and axial length tended to be shorter in the hyperglycemia group. The incidence of astigmatism in the better visual acuity eye was greater in the control group after adjustment for matching criteria. The main determinant of astigmatism is corneal curvature, although lens curvature and location also contribute.[46] We did not find corresponding changes in corneal curvature with astigmatism and we were unable to evaluate lens biometrics apart from lens thickness. Therefore, we were unable to confirm whether development of astigmatism was associated with hyperglycemia or other unknown factors. Although infants born preterm have been reported to be at risk of myopia and have larger variations in refractive error in childhood,[47-49] the increase in lens thickness (increasing refractive power) and trend for reduced axial length (to match the increased refractive power) in our study suggests that the visual acuity reduction experienced by the hyperglycemia group was unlikely to be due to refractive error.

Hypoglycemia, particularly over prolonged periods, has been associated previously with increased risk of visual impairment and occipital lobe damage.[33] In our cohort, children with hyperglycemia also were more likely to develop hypoglycemia associated with use of insulin, but there were no differences in any of the visual outcomes between children with and without hypoglycemia. This is similar to a study of children born at risk of hypoglycemia that reported that neonatal hypoglycemia was not associated with poorer visual outcome or global motion perception.[50] These findings suggest that neonatal hyperglycemia may have a greater effect on visual outcomes than hypoglycemia.

Several studies reporting mean blood glucose concentration in infants with different ROP status (eg, no ROP vs ROP, no to mild ROP vs moderate to severe ROP) have suggested that there is a relationship between hyperglycemia and ROP.[9,17,51] One case-control study found that infants with ROP (stage 3 or stage 4 ROP, n = 16) had significantly greater maximum, median, and mean serum, and whole blood glucose concentration compared with a control group (no ROP or stage 1 ROP, n = 31); this study did not adjust for gestational age and BW, but was reported as adequately matched.[17] However, a database review of 24 548 infants born preterm found that hyperglycemia and insulin use were not associated with severe ROP after adjustment for various neonatal factors such as gestational age, male sex, Apgar score, and ventilation.[8] Similarly, in a systemic review meta-analysis, although duration of hyperglycemia was associated with ROP (aOR 1.08, 95% CI 1.01-1.15, $P = .03$, four studies included), the association between mean blood glucose concentration and ROP was not significant (aOR 1.08, 95% CI 0.97-1.20, $P = .15$, 3 studies included).[7] Our exploratory analysis showed that although neonatal hyperglycemia, as defined in this study, was not associated with ROP, greater maximum blood glucose concentration was associated with increased odds of ROP treatment and lower mean blood glucose concentration was associated with increased odds of having any ROP. These findings are consistent with the recent reviews that have reported no association between hyperglycemia and ROP[7] or severe ROP[8] but appear to be inconsistent with retrospective studies that have shown that infants with ROP had greater mean blood glucose concentration.[17,51,52] As hyperglycemia is a spectrum, it is possible that our definition of hyperglycemia may make it difficult to detect significant differences in our logistic regression. In our cohort, although there was a significant association between lower gestational age and ROP or requiring ROP treatment, the association between greater maximum blood glucose concentration and ROP treatment persisted after adjustment for BW and gestational age. These data suggest that greater blood glucose concentration is independently associated with the development of severe ROP in infants born very preterm.

A strength of this study was that detailed glycemic status and neonatal histories were collected prospectively. This enabled an in-depth understanding of the relationships between neonatal glycemic status and outcomes in later childhood. As many infants with neonatal hyperglycemia received insulin infusion to control their hyperglycemia, the effects of insulin and hyperglycemia on visual outcomes could not be separated. However, a limitation was the observational nature of this study, which meant that causation cannot be established between neonatal hyperglycemia and visual outcomes. Also, due to the complexity of this study, many tests were performed on 1 day. Therefore, we were unable to perform additional vision tests such as contrast sensitivity or best-corrected visual acuity, which would be useful in evaluating further how the mild visual deficits we found influenced daily functioning. A relatively large number of statistical tests were used to analyze the different visual tests, which increases risks of type 1 error.

The associations between ocular growth and visual acuity are unclear, and our observational study is unable to determine causation. As yet, it is unclear how the changes in ocular growth may affect visual function in later life, but long-term follow-up is essential, as visual function for schoolwork and learning will become more important as these children grow older. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Adolescent Drug Use 50 Years Later: Marijuana's New Morbidity and Opiates Still Omnipresent

Litt IF, Cohen MI. Drug use among adolescents. J Pediatr 1970;77:195-202.

From 1967 to 1969, Litt and Cohen studied drug use among adolescents in a juvenile detention center as well as hospitalized adolescents. A history of drug abuse was established by a combination of personal report, physical signs and symptoms, and urine toxicology screening.

They found that the majority of drug-using adolescents were male. Heroin was the most common drug of abuse among both groups. The authors reported that 56% of drug-using adolescents from the detention center used heroin, and 32% sniffed glue. Nearly all adolescents who were hospitalized for a drug-related illness were heroin users with hepatitis. Marijuana use was relatively rare (5%) among adolescents in detention as well as in hospitalized adolescents.

Fifty years later, illicit drug use remains a significant health concern among adolescents, with marijuana eclipsing heroin as the most common drug of abuse. The 2019 Monitoring the Future Survey of High School Students[1] found that 36% of 12th graders used marijuana in the past year; 22% used in the past month; and 6% use daily. In the 50 years since Litt and Cohen's analysis, heroin use has fallen significantly, with less than 1% of adolescents reporting use. Opioids other than heroin grew in popularity from the 1990s to early 2000s but are now declining, with less than 3% of adolescents reporting such use.

In the early 2000s a phenomenon, cannabis hyperemesis syndrome, was described in which patients who were chronic marijuana users developed cyclic nausea and vomiting, with a learned behavior of hot bathing to relieve symptoms. It is now widely recognized throughout emergency departments and inpatient units and, in our experience, is the most common drug-related complication (not related to suicidal behavior) among hospitalized adolescents. Nationwide, hospitalizations for cannabis hyperemesis have nearly tripled in recent years, with a disproportionate impact on patients who are teens or young adults; female; and African-American or Hispanic.[2]

As laws and societal attitudes toward marijuana change, the medical community should stay vigilant in protecting the health of young people.

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Appendix

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Table II. Characteristics of children at the time of assessment in the neonatal hyperglycemic and control groups at 7 years of age

Childhood characteristics	Hyperglycemia group (n = 57)	CONTROL group (n = 54)	Hyperglycemia vs CONTROL *P* value
Age at assessment, y	7.2 ± 0.1	7.2 ± 0.1	.66
Boys	25 (44%)	34 (63%)	.04
Deprivation index			
Most deprived (10)	11 (19%)	11 (20%)	.29
Least deprived (1)	6 (11%)	5 (9%)	
Year at school	3 (1, 4)	3 (2, 3)	–
Anthropometry			
Weight, kg	23.2 (19.9, 27.0)	24.0 (22.1, 27.1)	.42
Weight z score	0.11 ± 1.58	0.17 ± 1.26	.83
Height, cm	123.1 (118.2, 127.1)	123.5 (119.7, 129.0)	.34
Height z score	0.12 ± 1.14	0.28 ± 1.29	.45
Head circumference, cm	51.5 (50.1, 52.7)	51.6 (50.8, 53.3)	.22
Head circumference z score	−1.18 ± 1.29	−0.98 ± 1.57	.47
Growth velocity, $g.kg^{-1}.d^{-1}$	1.25 ± 0.11	1.26 ± 1.0	.85

Data are n (%), mean ± SD, median (IQR).

Table IV. Logistic regression of ROP (no ROP vs ROP [reference]) in association with exposure (X), for the neonatal hyperglycemia cohort arm of the PIANO study

	OR (95% CI) for independent variables (*P* value)				
Exposure X	X*	Gestational age	BW z score	Sex (female)	Model R^2 (*P* value)
Minimum blood glucose concentration	0.67 (0.35, 1.27) (.22)	0.72 (0.49, 1.04) (.08)	1.33 (0.69, 2.58) (.40)	0.65 (0.24, 1.76) (.40)	0.15 (.03)
Mean blood glucose concentration	0.58 (0.34, 0.96) (.04)	0.59 (0.41, 0.86) (.01)	1.05 (0.59, 1.88) (.86)	0.58 (0.21, 1.61) (.30)	0.19 (.01)
Maximum blood glucose concentration	1.01 (0.90, 1.13) (.86)	0.66 (0.46, 0.95) (.02)	1.09 (0.62, 1.91) (.77)	0.64 (0.23, 1.75) (.39)	0.13 (>.05)

*Adjusted for sex, BW z core, sex (male/female) and hyperglycemic/non-hyperglycemic group. Note: for every 1 step increase in X, there is "odds" of developing ROP.

Table V. Logistic regression of ROP (ROP untreated vs ROP treatment [reference]) in association with exposure (X), for the neonatal hyperglycemia cohort of the PIANO study

	Odds ratio (95% CI) for independent variables (*P* value)				
Exposure X	X*	Gestational age	BW z score	Sex (female)	Model R^2 (*P* value)
Minimum blood glucose concentration	0.40 (0.12, 1.30) (.13)	0.44 (0.21, 0.93) (.03)	0.95 (0.29, 3.04) (.93)	1.02 (0.23, 4.56) (.98)	0.26 (.02)
Mean blood glucose concentration	1.60 (0.78, 3.25) (.19)	0.42 (0.20, 0.88) (.02)	0.50 (0.15, 1.61) (.24)	0.99 (0.22, 4.35) (.99)	0.25 (.02)
Maximum blood glucose concentration	1.20 (1.03, 1.40) (.02)	0.35 (0.16, 0.79) (.01)	0.45 (0.14, 1.52) (.20)	1.99 (0.36, 11.14) (.43)	0.34 (<.01)

*Adjusted for sex, BW z score, sex (male/female) and hyperglycemic/non-hyperglycemic group. Note: for every 1 step increase in X, there is "odds" of requiring ROP treatment.