Pediatric RESEARCH

POPULATION STUDY ARTICLE

Early life antecedents of positive child health among 10-year-old children born extremely preterm

Jacqueline T. Bangma[1], Evan Kwiatkowski[2], Matt Psioda[2], Hudson P. Santos Jr.[3], Stephen R. Hooper[4], Laurie Douglass[5], Robert M. Joseph[6], Jean A. Frazier[7], Karl C. K. Kuban[8], Thomas M. O'Shea[9] and Rebecca C. Fry[1], for the ELGAN Investigators

BACKGROUND: To identify modifiable antecedents during pre-pregnancy and pregnancy windows associated with a positive child health at 10 years of age.

METHODS: Data on 889 children enrolled in the Extremely Low Gestational Age Newborn (ELGAN) study in 2002–2004 were analyzed for associations between potentially modifiable maternal antecedents during pre-pregnancy and pregnancy time windows and a previously described positive child health index (PCHI) score at 10 years of age. Stratification by race was also investigated for associations with investigated antecedents.

RESULTS: Factors associated with higher PCHI (more positive health) included greater gestational age, birth weight, multiple gestation, and medical interventions, including assisted reproduction and cervical cerclage. Factors associated with lower PCHI included correlates of lower socioeconomic status, pre-pregnancy chronic medical disorders in the mother such as pre-pregnancy body mass index (BMI), and maternal asthma. When stratified by race, variation in significant results was observed.

CONCLUSIONS: Among children born extremely preterm, medical interventions and higher socioeconomic status were associated with improved PCHI, while chronic illness and high BMI in the mother is associated with lower PCHI at 10 years of age. Knowledge of such antecedent factors could inform efforts to develop interventions that promote positive child health outcomes in future pregnancies.

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INTRODUCTION

Positive child health reflects the reduced presence of aberrant conditions or disease, along with positive physical, cognition, and social–emotional well-being, and serves as a foundation for adult health and wellness. Whereas traditional analyses in children's health studies generally have focused on risk for adverse outcomes, another approach is to increase understanding of what factors contribute to positive health. Preterm infants are at increased risk of a variety of adverse developmental and health outcomes.[1,2] For example, at 10 years of age, in the Extremely Low Gestational Age Newborn (ELGAN) study cohort of children born at <28 weeks gestation in the United States, 25% had moderate-to-severe cognitive impairment,[3] 7.1% had autism spectrum disorder,[4] 7.6% had epilepsy,[5] 11.4% had cerebral palsy,[6] and 4.9% had severe motor impairment.[7] We recently described a positive child health index (PCHI) based on 11 adverse outcomes and found that within the ELGAN cohort, higher values on this index were associated with higher quality of life scores.[8] Notably, 32% of the cohort had none of the 11 adverse outcomes (PCHI of 100%) at age 10 years.

Based on the premise that promoting antecedents of positive health outcomes will lead to improved long-term outcomes, the aim of this study was to identify early-life antecedents associated with positive child health outcomes at 10 years of age in the ELGAN cohort. Maternal antecedents were examined from the pre-pregnancy and pregnancy time intervals with a focus on potentially modifiable antecedents, such as maternal socioeconomic and health status. Knowledge of such antecedent factors could inform the development of educational practices and other interventions educational efforts and interventions that would increase the likelihood of positive child health outcomes in future pregnancies.

METHODS

ELGAN study participants

STROBE cohort reporting guidelines were utilized for this study.[9] From 2002 to 2004, women giving birth prior to 28 weeks gestation at one of 14 academic medical centers in five states in the United States were asked to enroll in the ELGAN study.

[1]Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [4]Department of Allied Health Sciences, University of North Carolina School of Medicine, Chapel Hill, NC, USA; [5]Department of Pediatrics, Boston Medical Center, Boston, MA, USA; [6]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, USA; [7]Eunice Kennedy Shriver Center, Department of Psychiatry, University of Massachusetts Medical School/University of Massachusetts Memorial Health Care, Worcester, MA, USA; [8]Department of Pediatrics, Division of Pediatric Neurology, Boston University Medical Center, Boston, MA, USA and [9]Department of Pediatrics, University of North Carolina, Chapel Hill, NC, USA
Correspondence: Jacqueline T. Bangma (jbangma@ad.unc.edu)
These authors contributed equally: Jacqueline T. Bangma, Evan Kwiatkowski
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Maternal consent was provided either upon hospital admission or prior to or shortly after delivery. The Institutional Review Board at each participating institution approved study procedures. Of the mothers approached, approximately 85% gave consent for participation in the original ELGAN study, resulting in a cohort of 1249 mothers and 1506 infants.

A trained research nurse interviewed mothers using a structured questionnaire shorty after time of delivery to obtain a variety of factors including sociodemographic information, such as maternal age, years of education, eligibility for public insurance, and mother's pre-pregnancy weight and height. Information on pre-pregnancy and pregnancy maternal medications and health conditions was also collected at this time. Medical records were reviewed to collect medical information about the infant and mother. All antecedents investigated in this study were obtained from the maternal interview after birth and from maternal medical records. A total of 58 antecedents of interest were identified for this study, but 13 of the 58 were excluded from analyses due to a prevalence of 5% or lower in the population of participants resulting in a set of 45 for analysis. The complete set of 45 investigated antecedents and 13 excluded antecedents are listed in the Supplementary Information (Supplementary Table S4 and SI page 6, respectively).

Within a few days before or after delivery, mothers were interviewed and asked about pre-pregnancy weight and height, from which pre-pregnancy body mass index (BMI; weight/height^2) was calculated. BMI was classified as underweight (≤18.4 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Gestational ages were estimated based on the dates of embryo retrieval, intrauterine insemination, or fetal ultrasound before the 14th week. An infant's birth weight *Z*-score is defined as the number of standard deviations (SDs) above or below the median weight of infants of the same gestational age in referent samples not delivered for preeclampsia or fetal indications.[10,11]

ELGAN 10-year follow-up

In the original ELGAN cohort, 1198 children (80% of those enrolled) survived to age 10 years. A subset of 966 eligible children were selected for follow-up at 10 years of age because neonatal blood spots had been collected from these children, as the primary goal of the ELGAN study was to evaluate associations between neonatal systemic inflammation and cognitive outcome at 10 years of age. Of the 966 children recruited, a total of 889 (92%) participated in some or all of the 10-year evaluations (Supplementary Fig. S1), which were administered in one visit of 3 to 4 hours.

Eleven adverse outcomes were assessed at the 10-year follow-up: moderate/severe cognitive impairment,[7] bilateral blindness,[12] hearing impairment,[12] gross motor function impairment,[7] epilepsy,[5] attention-deficit/hyperactivity disorder,[13] autism,[4] anxiety, depression, asthma, and obesity (i.e., BMI above the 95 percentile). Based on these 11 adverse outcomes, a PCHI was generated for each child.[8] Supplementary Table S1 compares the maternal and newborn characteristics of the 889 children who were assessed and the 77 children who were not assessed from among the 966 children eligible for study participation. The rates of missing data among the 889 ELGAN who were assessed are provided in Supplementary Table S2. Although there were some missing data for individual disorders, children were assigned a PCHI that reflected their available data. Children with no reported disorders were assigned the highest PCHI of 100%. Any additional disorder reported for a child decreased the PCHI by a percentage based on the number of disorders investigated (9% drop for each additional disorder). In the binary model, children with no disorders (100% PCHI) were compared to children with any disorders (PCHI below 100%). In the categorical model, children with no disorders (100% PCHI) were compared to children with one disorder (PCHI 91%), two disorders (PCHI 82%), and three and above disorders (PCHI ≤73%). Further details of study methods can be found in Supplementary Information Methods (SI pages 3–6).

Statistical analysis

The associations between maternal demographics/modifiable antecedents and PCHI were analyzed using logistic regression for the dichotomous classification of disorders (0 vs. 1+) and ordinal logistic regression for the categorical classification of disorders (0 vs. 1 vs. 2 vs. 3+). Each of these regression models adjusted for the potential confounders of child's sex, gestational age, and birth weight *Z*-score, public insurance, and maternal education, and a dichotomous classification of race (white vs. black/other). For the ordinal logistic regression models, the proportional odds assumption was verified to be tenable by inspecting plots of the empirical logits. To investigate whether the strength of associations between antecedents and PHCI varied by race, we performed formal tests of an interaction of antecedent and race. For cases where the interaction *p* value was or approached significance ($p < 0.10$), we conducted analyses stratified by race, presented in Tables 2 and 3. Since a large number of modifiable antecedents were considered, multiple testing was also addressed by performing Bonferroni adjustments to computed *p* values. Results that remained significant after additional Bonferroni adjustment are indicated with an asterisk in Tables 2 and 3.

Sensitivity analysis: mixed models

Generalized linear mixed models (GLMMs) were fit to account for possible dependence among children from a multiple birth. Estimates were made using Gaussian quadrature within PROC GLIMMIX with a random intercept associated with instances of a multiple birth. For each dichotomous coding of PCHI, the logistic regression model was compared with a logistic regression mixed model, and for each categorical coding of PCHI, the ordinal logistic model was compared with an ordinal logistic mixed model.

RESULTS

Maternal demographics and PCHI

Maternal characteristics of the 889 ELGAN children that were assessed for PCHI at 10 years of age using the multi-categorical logistic model are presented in Table 1 (Supplementary Table S3). Lower PCHI scores (i.e., less positive health) were found among children born to mothers who identified as black/other race and were eligible for public health insurance (i.e., Medicaid). (Results for categorical analyses can be found in Supplementary Table S3.)

Newborn demographics and PCHI

Higher gestational ages and higher birth weights were associated with higher positive child health at 10 years of age (Table 1). (Supplementary Table S3 provides results for the adjusted categorical analyses).

Antecedents associated with higher PCHI (more positive child health)

Of the 45 modifiable antecedents investigated during the pre-pregnancy and pregnancy time intervals, six were associated with more positive child health, in at least one model; among study participants of all races: cervical cerclage, during pregnancy urine, bladder, or kidney infection, and multiple gestation (Tables 2 and 3, Supplementary Table S4–S7). Assisted reproduction and proteinuria during pregnancy were associated with more positive child health among non-white study participants, while receipt of antibiotics was associated with more positive child health among white participants.

Table 1. Maternal and newborn demographics associated with PCHI using a binary classification of PCHI

	Overall	No disorders (PCHI 100%)	Any disorders (PCHI ≤91%)	OR (95% CI)	*P* value	Interaction *p* value
Maternal demographics						
Racial identity ($N = 887$)						N/A
White	562 (63%)	211 (74%)	351 (58%)	1 (ref.)		
Black	227 (26%)	49 (17%)	178 (30%)	1.48 (1.00,2.19)	0.052	
Other	98 (11%)	26 (9%)	72 (12%)	1.25 (0.75,2.07)	0.396	
Hispanic ($N = 884$)						0.340
Yes	84 (10%)	22 (8%)	62 (10%)	0.98 (0.57,1.68)	0.930	
No	800 (90%)	262 (92%)	538 (90%)	1 (ref.)		
Age (years) ($N = 887$)						0.306
<21	115 (13%)	22 (8%)	93 (15%)	1.50 (0.80,2.80)	0.204	
21–35	593 (67%)	188 (66%)	405 (67%)	1.28 (0.90,1.83)	0.173	
>35	179 (20%)	76 (27%)	103 (17%)	1 (ref.)		
Education (years) ($N = 887$)						0.817
≤12	366 (41%)	89 (31%)	277 (46%)	1.19 (0.80,1.76)	0.395	
13–15	209 (24%)	69 (24%)	140 (23%)	1.03 (0.70,1.51)	0.897	
≥16	312 (35%)	128 (45%)	184 (31%)	1 (ref.)		
Single marital status ($N = 887$)						0.858
Yes	351 (40%)	78 (27%)	273 (45%)	1.25 (0.83,1.86)	0.284	
No	536 (60%)	208 (73%)	328 (55%)	1 (ref.)		
Public insurance, stratified white ($N = 562$)						0.092
Yes	121 (22%)	22 (10%)	99 (28%)	**3.33 (1.89,5.86)**	**<0.001***	
No	441 (78%)	189 (90%)	252 (72%)	1 (ref.)		
Public insurance, stratified black/other ($N = 325$)						
Yes	193 (59%)	37 (49%)	156 (62%)	1.50 (0.83,2.70)	0.175	
No	132 (41%)	38 (51%)	94 (38%)	1 (ref.)		
Newborn demographics						
Sex ($N = 887$)						0.338
Male	454 (51%)	137 (48%)	317 (53%)	1.30 (0.97,1.73)	0.081	
Female	433 (49%)	149 (52%)	284 (47%)	1 (ref.)		
Gestational age (weeks) ($N = 887$)	26.11 ± 1.28	26.29 ± 1.20	26.03 ± 1.31	**0.86 (0.77,0.97)**	**0.013**	0.763
Birth weight (hg) ($N = 887$)	8.31 ± 1.96	8.60 ± 1.86	8.18 ± 1.99	**0.92 (0.86,0.99)**	**0.033**	0.928
Birth weight *Z*-score ($N = 887$)	−0.19 ± 1.09	−0.10 ± 1.05	−0.23 ± 1.10	0.94 (0.82,1.07)	0.338	0.918

Logistic regression models for maternal demographics adjusted for child's sex, gestational age, and birth weight *Z*-score, and maternal education, public insurance, and race; models for newborn demographics adjusted for maternal education, public insurance, and race. Stratification by race was deemed necessary when the *p* value for the interaction term between race and the modifiable antecedent was <0.1; if that *p* value was ≥0.1, then analysis was not stratified and the interaction term was not included. OR represents the odds a child would have any disorders over the odds that a child would have no disorders for that demographic

PCHI positive child health index, *hg* hectograms, *OR* odds ratio, *CI* confidence interval, *N/A* not available

Bold values indicate a *p*-value < 0.05

*Significant after Bonferroni correction

Antecedents associated with lower PCHI (less positive child health) Eight factors were associated with less positive health in at least one model; among study participants of all races: maternal overweight or obese pre-pregnancy, maternal asthma pre-pregnancy, maternal asthma during pregnancy, maternal treatment with asthma medication during pregnancy, maternal consumption of aspirin during pregnancy, and transition from private to public health insurance between the child's visits at 2 years of age and 10 years of age (Tables 2 and 3, Supplementary Tables S4–S7). Public health insurance during pregnancy, proteinuria during pregnancy, and second-hand smoke exposure during pregnancy were associated with less positive child health among white study participants.

When conservative Bonferroni adjustments were made to account for multiple association analyses, the only antecedent with a statistically significant association with PCHI modeled as a binary outcome was maternal pre-pregnancy BMI (Table 2). In the multicategory ordinal logistic model, associations with PCHI were found

Table 2. Modifiable antecedents associated with PCHI with a significant ($p \leq 0.05$, bold text) p value using a binary classification of PCHI

	Overall	No disorders (PCHI 100%)	Any disorders (PCHI ≤91%)	OR (95% CI)	*P* value	Interaction *p* value
Pre-pregnancy BMI ($N = 855$)						0.289
Underweight	68 (8%)	25 (9%)	43 (7%)	0.94 (0.54,1.65)	0.838	
Normal	429 (50%)	163 (59%)	266 (46%)	1 (ref.)		
Overweight	165 (19%)	47 (17%)	118 (20%)	1.40 (0.94,2.11)	0.101	
Obese	193 (23%)	42 (15%)	151 (26%)	**1.97 (1.31,2.97)**	**0.001***	
During pregnancy second-hand smoke						<0.001
Stratified white ($N = 552$)	117 (21%)	23 (11%)	94 (27%)	**2.25 (1.29,3.91)**	**0.004**	
Stratified black/other ($N = 312$)	94 (30%)	25 (35%)	69 (29%)	0.56 (0.30,1.04)	0.068	
Pre-pregnancy asthma ($N = 865$)	103 (12%)	22 (8%)	81 (14%)	**1.68 (1.01,2.82)**	**0.047**	0.741
During pregnancy asthma ($N = 864$)	57 (7%)	9 (3%)	48 (8%)	**2.35 (1.11,4.98)**	**0.026**	0.613
During pregnancy rine, bladder or kidney infection ($N = 864$)	119 (14%)	43 (15%)	76 (13%)	**0.65 (0.42,1.00)**	**0.049**	0.458
During pregnancy protein in your urine						0.005
Stratified white ($N = 551$)	64 (12%)	19 (9%)	45 (13%)	1.72 (0.93,3.18)	0.082	
Stratified black/other ($N = 313$)	40 (13%)	16 (23%)	24 (10%)	**0.42 (0.20,0.89)**	**0.024**	
During pregnancy antibiotic						0.013
Stratified white ($N = 550$)	148 (27%)	68 (33%)	80 (23%)	**0.52 (0.35,0.79)**	**0.002**	
Stratified black/other ($N = 313$)	115 (37%)	21 (30%)	94 (39%)	1.40 (0.78,2.50)	0.265	
During pregnancy aspirin or aspirin-containing medicine ($N = 862$)	48 (6%)	10 (4%)	38 (7%)	**2.19 (1.06,4.55)**	**0.035**	0.131
During pregnancy asthma medicine ($N = 863$)	48 (6%)	6 (2%)	42 (7%)	**3.40 (1.39,8.30)**	**0.007**	0.954
Cerclage ($N = 867$)	82 (9%)	37 (13%)	45 (8%)	**0.54 (0.33,0.87)**	**0.011**	0.415
Plurality ($N = 834$)	293 (35%)	118 (44%)	175 (31%)	**0.72 (0.53,0.99)**	**0.040**	0.454
IVF or ICSI						0.050
Stratified white ($N = 562$)	104 (19%)	46 (22%)	58 (17%)	0.89 (0.57,1.39)	0.595	
Stratified black/other ($N = 325$)	9 (3%)	6 (8%)	3 (1%)	**0.15 (0.03,0.67)**	**0.013**	
Change in insurance ($N = 887$)						0.566
No change	685 (77%)	240 (84%)	445 (74%)	1 (ref.)		
Switch from public (Yes at baseline, No at 10-year follow-up	54 (6%)	16 (6%)	38 (6%)	1.01 (0.54,1.88)	0.970	
Switch to public (No at baseline, Yes at 10-year follow-up	148 (17%)	30 (10%)	118 (20%)	**1.95 (1.25,3.02)**	**0.003**	

Logistic regression models adjusted for child's sex, gestational age, and birth weight *Z*-score, and maternal education, public insurance, and race. Stratification by race was deemed necessary when the p value for the interaction term between race and the modifiable antecedent was <0.1; if that p value was ≥0.1, then the analysis was not stratified and the interaction term was not included. OR represents the odds a child would have any disorders over the odds that a child would have no disorders for that demographic

BMI body mass index, *PCHI* positive child health index, *OR* odds ratio, *CI* confidence interval, *IVF* in vitro fertilization, *ICSI* intracytoplasmic sperm injection

*Significant after Bonferroni correction

for the antecedents maternal pre-pregnancy BMI, maternal use of asthma medicine during pregnancy, and multiple gestation (Table 3).

There was complete concordance among all maternal characteristics, newborn characteristics, and modifiable antecedents, with a statistically significant association with PCHI at the 0.05 level between the mixed models and the usual generalized linear models (Tables 1–3, Supplementary Tables S3–S7).

DISCUSSION

The aim of this study was to identify early-life, potentially modifiable antecedents that are associated with positive child health at 10 years of age among children born extremely preterm (Table 4). We identified six antecedents associated with higher PCHI (more positive health); for three of these factors (cervical cerclage, multiple gestation, and maternal during pregnancy urine, bladder, or kidney infection), the association was found among study participants of all races. Among non-white study participants, assisted reproduction and proteinuria were associated with higher PCHI, and among white participants, receipt of antibiotics was associated with higher PCHI. We identified eight antecedents associated with lower PCHI (less positive health); six reflect maternal health: pre-pregnancy overweight/obese, pre-pregnancy and pregnancy asthma, treatment with asthma medication during pregnancy, maternal consumption of aspirin during pregnancy, and second-hand tobacco smoke. Among white study participants, mother's exposure to tobacco smoke during pregnancy, proteinuria during pregnancy, and public insurance during pregnancy were associated with lower PCHI. Among study participants of all races, transition from private to

Table 3. Modifiable antecedents associated with PCHI with a significant ($p \leq 0.05$, bold text) p value using a categorical classification of PCHI

	Overall	No disorders (PCHI 100%)	One disorder (PCHI 91%)	Two disorders (PCHI 82%)	Three or more disorders (PCHI ≤73%)	OR (95% CI)	*P* value	Interaction *p* value
Pre-pregnancy BMI ($N = 855$)								0.343
Underweight	68 (8%)	25 (9%)	20 (8%)	8 (5%)	15 (8%)	0.99 (0.61,1.59)	0.951	
Normal	429 (50%)	163 (59%)	127 (53%)	67 (43%)	72 (39%)	1 (ref.)		
Overweight	165 (19%)	47 (17%)	47 (20%)	38 (25%)	33 (18%)	1.32 (0.95,1.84)	0.100	0.130
Obese	193 (23%)	42 (15%)	45 (19%)	42 (27%)	64 (35%)	**2.16 (1.57,2.97)**	**<0.001***	0.279
During pregnancy second-hand smoke ($N = 864$)								0.008
Stratified white ($N = 552$)	117 (21%)	23 (11%)	33 (21%)	26 (29%)	35 (36%)	**1.66 (1.08,2.55)**	**0.020**	
Stratified black/other ($N = 312$)	94 (30%)	25 (35%)	20 (24%)	22 (32%)	27 (30%)	0.80 (0.50,1.26)	0.331	
Pre-pregnancy asthma ($N = 865$)	103 (12%)	22 (8%)	24 (10%)	24 (15%)	33 (18%)	**1.66 (1.14,2.43)**	**0.009**	0.404
During pregnancy asthma ($N = 864$)	57 (7%)	9 (3%)	15 (6%)	14 (9%)	19 (10%)	**1.78 (1.08,2.93)**	**0.023**	0.240
During pregnancy protein in your urine ($N = 864$)								0.002
Stratified white ($N = 551$)	64 (12%)	19 (9%)	23 (14%)	8 (9%)	14 (15%)	**1.76 (1.06,2.93)**	**0.029**	
Stratified black/other ($N = 313$)	40 (13%)	16 (23%)	11 (13%)	9 (13%)	4 (4%)	**0.46 (0.24,0.88)**	**0.018**	
During pregnancy aspirin or aspirin-containing medicine ($N = 862$)	48 (6%)	10 (4%)	16 (7%)	10 (6%)	12 (6%)	**1.72 (1.01,2.93)**	**0.047**	0.244
During pregnancy asthma medicine ($N = 863$)	48 (6%)	6 (2%)	13 (5%)	9 (6%)	20 (11%)	**2.54 (1.47,4.40)**	**<0.001***	0.361
Cerclage ($N = 867$)	82 (9%)	37 (13%)	19 (8%)	15 (9%)	11 (6%)	**0.60 (0.39,0.92)**	**0.019**	0.732
Plurality ($N = 834$)	293 (35%)	118 (44%)	88 (38%)	46 (31%)	41 (22%)	**0.67 (0.51,0.88)**	**0.003**	0.210
IVF or ICSI ($N = 887$)								0.048
Stratified white ($N = 562$)	104 (19%)	46 (22%)	33 (21%)	11 (12%)	14 (14%)	0.86 (0.57,1.29)	0.459	
Stratified black/other ($N = 325$)	9 (3%)	6 (8%)	2 (2%)	1 (1%)	0 (0%)	**0.13 (0.03,0.54)**	**0.005**	
Change in insurance, stratified white ($N = 562$)								0.004
No change	451 (80%)	184 (87%)	137 (86%)	64 (70%)	66 (66%)	1 (ref.)		
Switch from public (Yes at baseline, No at 10-year follow-up)	26 (5%)	8 (4%)	8 (5%)	8 (9s%)	2 (2%)	0.99 (0.48,2.05)	0.980	
Switch to public (No at baseline, Yes at 10-year follow-up)	85 (15%)	19 (9%)	15 (9%)	19 (21%)	32 (32%)	**3.01 (1.96,4.63)**	**<0.001***	
Change in insurance, stratified black/other ($N = 325$)								
No change	234 (72%)	56 (75%)	56 (64%)	53 (75%)	69 (76%)	1 (ref.)		
Switch from public (Yes at baseline, No at 10-year follow-up)	28 (9%)	8 (11%)	8 (9%)	6 (8%)	6 (7%)	0.70 (0.35,1.42)	0.327	
Switch to public (No at baseline, Yes at 10-year follow-up)	63 (19%)	11 (15%)	24 (27%)	12 (17%)	16 (18%)	0.93 (0.56,1.54)	0.782	

Logistic regression models adjusted for child's sex, gestational age, and birth weight *Z*-score, and maternal education, public insurance, and race. Stratification by race was deemed necessary when the p value for the interaction term between race and the modifiable antecedent was <0.1; if that p value was ≥0.1, then the analysis was not stratified and the interaction term was not included. Given the assumption of proportional odds, the OR represents the odds of a higher number of disorders over the odds of the reference number of disorders or fewer; with this OR applying to each level of disorders separately (e.g., no disorders vs. one or more, 0/1 disorders vs. 2+, etc.)

BMI body mass index, *PCHI* positive child health index, *OR* odds ratio, *CI* confidence interval, *IVF* in vitro fertilization, *ICSI* intracytoplasmic sperm injection

*Significant after Bonferroni correction

Table 4. Summary of significant associations listed in Tables 1–3

Among study participants of all races	
Factors associated with lower PCHI	• Mother obese before pregnancy
	• Maternal asthma before and during pregnancy
	• Maternal consumption of aspirin during pregnancy
	• Maternal asthma medications during pregnancy
	• Switch from private to public health insurance between child's age 2 and 10 years[c]
Factors associated with higher PCHI	• Maternal during pregnancy urine, bladder or kidney infection[b]
	• Cervical cerclage
	• Multiple gestation
Among study participants of black/other race	
Factors associated with higher PCHI	• Assisted reproduction
	• Proteinuria during pregnancy
Among study participants of white race	
Factors associated with lower PCHI	• Public insurance
	• Second-hand tobacco smoke exposure during pregnancy
	• Proteinuria during pregnancy[b]
Factors associated with higher PCHI	• Receipt of antibiotics during pregnancy[a]

PCHI positive child health index
[a]No association found in analysis using a categorical classification of PCHI
[b]No association found in analysis using a binary classification of PCHI
[c]No association found in analysis using a categorical classification of PCHI for black/other race

public insurance between the child's study visits at 2 and 10 years of age was associated with lower PCHI.

Increased PCHI

The finding that multiple gestation and cerclage are associated with higher PCHI could be attributable to residual confounding by socioeconomic status. The variables that we used to adjust for socioeconomic status, maternal education and insurance status, likely do not fully capture variation in socioeconomic status, which in the ELGAN study is associated with adverse neurodevelopmental outcomes,[14,15] as well as asthma[16] and obesity in the child.[17] The more positive health of children born to mothers treated with interventions for threatened preterm delivery (cervical cerclage) might also reflect better access of such mothers and their children to health care.

Decreased PCHI

Lower positive child health was associated with chronic medical conditions in the mother, such as obesity, asthma, and diabetes. Maternal obesity is associated with neonatal inflammation[18–20] and we have previously reported associations between neonatal inflammation and adverse neurodevelopmental outcomes in the ELGAN cohort.[21,22] Asthma also has been linked to inflammatory pathways and altered placental signaling in fetal development,[23] neonatal complications.[24] Maternal diabetes prior to pregnancy is associated with macrosomia at birth and obesity in the offspring.[25] One explanation for our finding of worse health among children born to mothers who became eligible for Medicaid between their child's birth and when the child reached 10 years is that having a child increases the family's medical expenses, thus increasing the likelihood that the family will qualify for public assistance. In addition, mothers with children with disabilities are often unable to continue to work outside of the home due to the demands of caring for a child with a disability.

Stratification by race

For many antecedents of PCHI identified in this study (maternal asthma, aspirin consumption during pregnancy, cerclage, and plurality), we detected no interaction between race and the antecedent. On the other hand, assisted reproduction was associated with higher PCHI only among non-whites. A plausible explanation for this interaction of race and assisted reproduction is that assisted reproduction might be a stronger marker of socioeconomic resources among non-whites than among whites. We observed that prenatal maternal antibiotic treatment was associated with higher PCHI only among whites. Previous studies have suggested the use of antibiotics may be influenced by social and lifestyle factors.[26] We are unable to propose plausible explanations for the other interactions that we observed between race and antecedents of PCHI, such as the observation that protein in the urine was associated higher PCHI among non-white participants. Caution is appropriate when interpreting the results of stratified analyses because stratum-specific associations are based on relatively smaller sample sizes. We suggest future studies to validate and build upon results observed here. Future studies should further assess race and related socioeconomic factors in mediation analysis as potential modifiers of the effects observed in the current study.

Strengths and limitations

Strengths of this study include the large sample that was relatively diverse with respect to sociodemographic attributes. A possible limitation of this study is that the outcomes previously obtained for the PCHI were primarily neurodevelopmental outcomes, rather than a broader profile of disorders, such as cardiometabolic and respiratory illnesses. This potentially limits the generalizability of the findings to other conditions outside the neurodevelopmental outcomes at 10 years of age. Lastly, of the original 966, the 77 study participants lost to follow-up were more likely to have indicators of social disadvantage, such as eligibility for public assistance. The bias from lost-to-follow-up children would therefore be expected to result in an underestimation of adverse outcomes in the cohort. However, given the low frequency of lost-to-follow-up children (8%), the magnitude of this bias very likely was small (Supplementary Tables S1 and S2).

Implications

Several findings reported here could have implications for researchers interested in practice, policy, or programs that target improvement in child health outcomes among individuals born extremely preterm. Most notable is the finding that correlates of lower socioeconomic status (SES) early in life were associated with worse child health later in life. Irrespective of their family's household income, individuals born extremely preterm are supported by expensive medical care during their initial hospitalization (in neonatal intensive care). In about one-third of the ELGAN cohort, the cost of neonatal intensive care, which has been estimated to be around $200,000 per surviving infant for those born at 24–27 weeks of gestation, was borne by public insurance.[27] Given this large investment in survival of individuals born extremely preterm, and observed associations between indicators of low SES and worse outcomes among survivors, it is reasonable to ask whether the public should invest more in evidence-based programs.[28] This may take the form of increasing publicly funded developmental surveillance and developmentally supportive therapies for survivors of extremely preterm birth. This would serve the goal of improving child health among those individuals born into lower social economic households, which

have limited financial resources with which to pay for interventions to promote their child's development. In addition, further research to identify biosocial correlates of socioeconomic disadvantage that explain its association with reduced PCHI could identify more specific targets for interventions.

In addition to programs to support families caring for an infant discharged from neonatal intensive care, positive child health among individuals born extremely preterm might be promoted by prenatal programs to improve maternal health prior to conception and during pregnancy.[29–31] Here we report that chronic maternal illnesses, such as pre-pregnancy obesity, asthma, and tobacco smoke exposure during pregnancy were associated with reduced PCHI at 10 years of age, suggesting that interventions to improve the health of mothers, including smoking cessation and weight reduction prior to pregnancy, might benefit not only the mother but also the later life health of her offspring.

CONCLUSIONS

Among infants born extremely preterm, pre-pregnancy and perinatal factors are associated with variation in the offspring's overall health and development as much as 10 years later. Socioeconomic factors intertwined with race may also play an integral role in the associations between PCHI and antecedents, and needs to be investigated in future research. Interventions that target these early-life factors could have long-term benefits for individuals born extremely preterm.

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ELGAN-2 MEMBERS

Project Lead for ELGAN-2: Julie V. Rollins, MA.

Site Principal Investigators

Baystate Medical Center, Springfield, MA: Bhahvesh Shah, MD; Rachana Singh, MD, MS. Boston Children's Hospital, Boston, MA: Linda Van Marter, MD, MPH and Camilla Martin, MD, MPH; Janice Ware, Ph.D. Tufts Medical Center, Boston, MA: Cynthia Cole, MD; Ellen Perrin, MD. University of Massachusetts Medical School, Worcester, MA: Frank Bednarek, MD; Jean Frazier, MD. Yale University School of Medicine, New Haven, CT: Richard Ehrenkranz, MD; Jennifer Benjamin, MD. Wake Forest University, Winston-Salem, NC: T. Michael O'Shea, MD, MPH. Wake Forest University, Winston-Salem, NC: T. Michael O'Shea, MD, MPH. University of North Carolina, Chapel Hill, NC: Carl Bose, MD; Diane Warner, MD, MPH. East Carolina University, Greenville, NC: Steve Engelke, MD. Helen DeVos Children's Hospital, Grand Rapids, MI: Mariel Poortenga, MD; Steve Pastyrnak, Ph.D. Sparrow Hospital, East Lansing, MI: Padu Karna, MD; Nigel Paneth, MD, MPH; Madeleine Lenski, MPH. University of Chicago Medical Center, Chicago, IL: Michael Schreiber, MD; Scott Hunter, Ph.D; Michael Msall, MC. William Beaumont Hospital, Royal Oak, MI: Danny Batton, MD; Judith Klarr, MD.

Site Study Coordinators

Baystate Medical Center, Springfield, MA: Karen Christianson, RN; Deborah Klein, BSM, RN. Boston Children's Hospital, Boston MA: Maureen Pimental, BA; Collen Hallisey, BA; Taryn Coster, BA. Tufts Medical Center, Boston, MA: Ellen Nylen, RN; Emily Neger, MA; Kathryn Mattern, BA. University of Massachusetts Medical School, Worcester, MA: Lauren Venuti, BA; Beth Powers, RN; Ann Foley, EdM. Yale University School of Medicine, New Haven, CT: Joanne Williams, RN; Elaine Romano, APRN. Wake Forest University, Winston-Salem, NC: Debbie Hiatt, BSN (deceased); Nancy Peters, RN; Patricia Brown, RN; Emily Ansusinha, BA. University of North Carolina, Chapel Hill, NC: Gennie Bose, RN; Janice Wereszczak, MSN; Janice Bernhardt, MS, RN. East Carolina University, Greenville, NC: Joan Adams (deceased); Donna Wilson, BA, BSW. Nancy Darden-Saad, BS, RN. Helen DeVos Children's Hospital, Grand Rapids, MI: Dinah Sutton, RN; Julie Rathbun, BSW, BSN. Sparrow Hospital, East Lansing, MI: Karen Miras, RN, BSN; Deborah Weiland, MSN. University of Chicago Medical Center, Chicago, IL: Grace Yoon, RN; Rugile Ramoskaite, BA; Suzanne Wiggins, MA; Krissy Washington, MA; Ryan Martin, MA; Barbara Prendergast, BSN, RN. William Beaumont Hospital, Royal Oak, MI: Beth Kring, RN.

Psychologists

Baystate Medical Center, Springfield, MA: Anne Smith, Ph.D.; Susan McQuiston, Ph.D. Boston Children's Hospital: Samantha Butler, Ph.D.; Rachel Wilson, Ph.D.; Kirsten McGhee, Ph.D.; Patricia Lee, Ph.D.; Aimee Asgarian, Ph.D.; Anjali Sadhwani, Ph.D.; Brandi Henson, PsyD. Tufts Medical Center, Boston MA: Cecelia Keller, PT, MHA; Jenifer Walkowiak, Ph.D.; Susan Barron, Ph.D. University of Massachusetts Medical School, Worcester MA: Alice Miller, PT, MS; Brian Dessureau, Ph.D.; Molly Wood, Ph.D.; Jill Damon-Minow, Ph.D. Yale University School of Medicine, New Haven, CT: Elaine Romano, MSN; Linda Mayes, Ph.D.; Kathy Tsatsanis, Ph.D.; Katarzyna Chawarska, Ph.D.; Sophy Kim, Ph.D.; Susan Dieterich, Ph.D.; Karen Bearrs, Ph.D. Wake Forest University Baptist Medical Center, Winston-Salem NC: Ellen Waldrep, MA; Jackie Friedman, Ph.D.; Gail Hounshell, Ph.D.; Debbie Allred, Ph.D. University Health Systems of Eastern Carolina, Greenville, NC: Rebecca Helms, Ph.D.; Lynn Whitley, Ph.D. Gary Stainback, Ph.D. University of North Carolina at Chapel Hill, NC: Lisa Bostic, OTR/L; Amanda Jacobson, PT; Joni McKeeman, Ph.D.; Echo Meyer, Ph.D. Helen DeVos Children's Hospital, Grand Rapids, MI: Steve Pastyrnak, Ph.D. Sparrow Hospital, Lansing, MI: Joan Price, EdS; Megan Lloyd, MA, EdS. University of Chicago Medical Center, Chicago, IL: Susan Plesha-Troyke, OT; Megan Scott, Ph.D. William Beaumont Hospital, Royal Oak, MI: Katherine M. Solomon, Ph.D.; Kara Brooklier, Ph.D.; Kelly Vogt, Ph.D.

AUTHOR CONTRIBUTIONS

All authors listed on this manuscript contributed to all three types of substantial contributions listed in Pediatric Research instructions to authors. Bi-weekly conference calls were held throughout the processes of brainstorming, method development, writing, and reviewing of this manuscript in which all authors participated.

ADDITIONAL INFORMATION

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