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

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Abstract

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

Study design.—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.

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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 author participated.

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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 like pre-pregnancy BMI, maternal asthma. When stratified by race, variation in significant results was observed.

Conclusions.—Among children born extremely preterm, medical interventions and higher SES 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.

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 ten years of age, in the Extremely Low Gestational Age Newborn (ELGAN) study cohort of children born at less than 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 (QoL) scores (8). Notably, 32% of the cohort had none of the 11 adverse outcomes (PCHI of 100%) at age 10.

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 2002–2004, 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. 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 antecedents investigated are listed in the Supplemental Information (SI page 6).

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, 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 (GMF) impairment (7); epilepsy (5); attention-deficit/hyperactivity disorder (ADHD) (13); autism (4); anxiety; depression; asthma; and obesity (i.e., body mass index (BMI) above the 95 percentile). Based on these 11 adverse outcomes, a PCHI was generated for each child (8). Supplemental 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 Supplemental 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 Supplemental 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, presentedin 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 (GLMM) 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 (Table 1, Supplemental Table S3)

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. 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 Supplemental Table S3).

Newborn demographics and PCHI (Table 1, Supplemental Table S3)

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

Antecedents associated with higher PCHI (more positive child health) (Table 2–3, Supplemental Table S4–S7)

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 both races: cervical cerclage, during pregnancy urine, bladder, or kidney infection, and multiple gestation. Assisted reproduction and proteinuria during pregnancy were associated with more positive child health among black study participants, while receipt of antibiotics was associated with more positive child health among white participants.

Antecedents associated with lower PCHI (less positive child health) (Table 2–3, Supplemental Table S4–S7)

Eight factors were associated with less positive health health among study participants of both races in at least one model: maternal overweight or obese pre-pregnancy, maternal asthma pre-pregnancy, maternal asthma during pregnancy, maternal treatment with asthma medication during pregnancy, maternal consumption of asprin during pregnancy, and transition from private to public health insurance between the child's visits at two years of age and ten years of age. 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. In the multi-category ordinal logistic model, associations with PCHI were found for the antecedents maternal pre-pregnancy BMI, maternal use of asthma medicine during pregnancy, and multiple gestation (Tables 2 and 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, Supplemental Tables S3–S7).

DISCUSSION

The aim of this study was to identify early-life, potientally 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 both races. Among black 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) among study participants of both races; six reflect maternal health: pre-pregnacy 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 both races, transition from private to public insurance between the child's study visits at two and ten 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) as well as asthma (15) and obesity in the child (16). 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 ten 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 socio-economic 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. Fututre studies should further assess race and related socioeconomic factors in mediation analysis as potiental 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 of 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 (Supplemental Table S1 & 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 further to to promote their child's development.. pay for to interventions identify research In addition, 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, and 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Maternal and newborn demographics associated with positive child health index (PCHI) using a binary classification of PCHI. 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 less than 0.1; if that p value was ≥ 0.1, then analysis was not stratified and the interaction term was not included. Odds ratio represents the odds a child would have and disorders over the odds that a child would have no disorders for that demographic

	Overall	No Disorders (PCHI 100%)	Any Disorders (PCHI ≤ 91%)	OR (95% CI)	p-value	Stratification by Race Necessary (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)				**3.33**		0.092
Yes	121 (22%)	22 (10%)	99 (28%)	**(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	

	Overall	No Disorders (PCHI 100%)	Any Disorders (PCHI ≤ 91%)	OR (95% CI)	p-value	Stratification by Race Necessary (Interaction p-value)
Female	433 (49%)	149 (52%)	284 (47%)	1 (ref)		
Gestational Age, weeks				**0.86**		
(N=887)	26.11 ± 1.28	26.29 ± 1.20	26.03 ± 1.31	**(0.77,0.97)**	**0.013**	0.763
Birth Weight, hectograms				**0.92**		
(N=887)	8.31 ± 1.96	8.60 ± 1.86	8.18 ± 1.99	**(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

*Significant after Bonferroni correction

Table 2.

Modifiable antecedents associated with positive child health index (PCHI) with a significant ($p \leq 0.05$, bold text p-value using a binary classification of PCHI. 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 less than 0.1; if that p value was ≥ 0.1, then the analysis was not stratified and the interaction term was not included. Odds ratio represents the odds a child would have and disorders over the odds that a child would have no disorders for that demographic.

	Overall	No Disorders (PCHI 100%)	Any Disorders (PCHI ≤ 91%)	OR (95% CI)	p-value	Stratification by Race Necessary (Interaction p-value)
Prepregnancy 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 secondhand 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 Urine, 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

	Overall	No Disorders (PCHI 100%)	Any Disorders (PCHI ≤ 91%)	OR (95% CI)	p-value	Stratification by Race Necessary (Interaction p-value)
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**	

* Significant after Bonferroni correction

Table 3.

Modifiable antecedents associated with positive child health index (PCHI) with a significant ($p \leq 0.05$, bold text) p-value using a categorical classification of PCHI. 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 less than 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 odds ratio 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.).

	Overall	No Disorders (PCHI 100%)	One Disorder (PCHI ≤ 91%)	Two disorders (PCHI 82%)	Three or more disorders (PCHI < 73%)	OR (95% CI)	p-value	Stratification by Race Necessary (Interaction p-value)
Prepregnancy 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 secondhand 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	

	Overall	No Disorders (PCHI 100%)	One Disorder (PCHI ≤ 91%)	Two disorders (PCHI 82%)	Three or more disorders (PCHI < 73%)	OR (95% CI)	p-value	Stratification by Race Necessary (Interaction p-value)
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 (9%)	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	

* 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 age 10[ǂ]
Factors associated with higher PCHI	• Maternal during pregnancy urine, bladder or kidney infection[†] • 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[¶]
Factors associated with higher PCHI	• Receipt of antibiotics during pregnancy[†]

[†]no association found in analysis using a categorical classification of positive child health index

[¶]no association found in analysis using a binary classification of positive child health index

[ǂ]no association found in analysis using a categorical classification of positive child health index for black/other race