Supplementary Online Content

Supplement to: Campbell MS, Bastarache LA, et al. PheWAS Analysis of Perinatal Exposures Associates with Bronchopulmonary Dysplasia in Preterm Infants

This appendix has been provided by the authors to give readers additional information about their work.

eTable 1. Missing Data from 20 Variables in NICU Registry and 5 Variables in Base Model that was reconciled by manual chart review

Variable	Initial Missing (N)	Missing Information	Final Missing (N)
Mom age	14	14	0
Baby gender	3	3	0
Mom race	8	7	1
Gestational age	0	0	0
Birth year	0	0	0
Birth weight	0	0	0
Multiple gestation	0	0	0
Prenatal care	22	0	22
Vaginal bleeding	0	0	0
Chorioamnionitis	3	3	0
Oligohydramnios	0	0	0
Polyhydramnios	0	0	0
Diabetes	0	0	0
Chronic hypertension	0	0	0
Maternal Illicit drug	0	0	0
Antenatal steroids	92	7	85
C-Section	0	0	0
Vertex presentation	0	0	0
Anesthesia	51	31	20
Gestational	20	0	20
Vaginal bleeding	2	0	2
Meconium	0	0	0
Gravida	16	9	7

Variable	Initial Missing (N)	Missing Information	Final Missing (N)
Reason for Preterm	34	0	34
Rupture of membranes	78	0	78

eTable 2. List of phenotypes used in PheWAS analysis

Maternal Phenotype	OR	p-value	Cases	Controls	FDR
Polyhydramnios	4.72	3.4×10^{-9}	130	1831	3.2×10^{-7}
Problems associated with amniotic	2.35	2.2×10^{-7}	480	1481	1.0×10^{-5}
Known or suspected fetal	1.94	2.5×10^{-5}	1208	753	7.8×10^{-4}
Oligohydramnios	1.83	7.6×10^{-4}	356	1605	0.018
Asthma	2.47	9.9×10^{-4}	148	1813	0.019
Poor fetal growth and uterine size	1.68	5.3×10^{-3}	495	1466	0.084
Placental disorders	1.50	0.018	440	1521	0.246
Mood [affective] disorders	1.72	0.026	196	1765	0.309
Abnormalities of gravid uterus	0.54	0.043	131	1830	0.449
Maternal care for abnormality of	0.71	0.076	338	1623	0.711
Preeclampsia and eclampsia	0.76	0.135	485	1476	0.846
Major depressive disorder	1.55	0.138	130	1831	0.846
Maternal care for breech	1.28	0.146	415	1546	0.846
Abnormalities of breathing	1.52	0.152	141	1820	0.846
Malposition and malpresentation of	1.24	0.158	654	1307	0.846
Severe pre-eclampsia or HELLP	0.73	0.164	253	1708	0.846
Headache	0.72	0.166	233	1728	0.846
Hemolytic anemias	0.64	0.170	145	1816	0.846
Intrinsic (hereditary) hemolytic	0.65	0.179	144	1817	0.846
Antepartum hemorrhage	1.33	0.180	240	1721	0.846
Other conditions or status of the	1.21	0.195	976	985	0.871
Headache	0.74	0.222	207	1754	0.946
Cytology and pathology findings	1.35	0.244	170	1791	0.946

Maternal Phenotype	OR	p-value	Cases	Controls	FDR
Spotting complicating pregnancy	0.67	0.252	109	1852	0.946
Anemia	0.82	0.261	447	1514	0.946
Premature rupture of membranes	1.21	0.268	432	1529	0.946
Abdominal pain	0.81	0.278	431	1530	0.946
Premature separation of placenta	1.28	0.291	183	1778	0.946
Substance dependence	1.33	0.321	119	1842	0.946
False labor	0.78	0.326	214	1747	0.946
Abnormality in fetal heart rate or	1.16	0.333	724	1237	0.946
Umbilical cord complications	1.25	0.342	185	1776	0.946
Mental disorders complicating	1.21	0.343	311	1650	0.946
Substance abuse, dependence, and	1.27	0.352	151	1810	0.946
Endocrine, nutritional and metabolic	0.78	0.367	145	1816	0.946
Infection of amniotic cavity	0.84	0.382	296	1665	0.946
Preterm labor (including history of)	0.87	0.392	1269	692	0.946
Dyspnea	1.31	0.406	104	1857	0.946
Tachycardia	1.27	0.419	126	1835	0.946
Tobacco use during pregnancy	1.18	0.420	283	1678	0.946
Tobacco use	1.17	0.422	327	1634	0.946
Anemia secondary to chronic	0.86	0.443	293	1668	0.946
Anemia in pregnancy	0.86	0.443	293	1668	0.946
Morbid obesity	1.17	0.490	237	1724	0.946
Type 2 diabetes	1.24	0.491	127	1834	0.946
Other behavioral problems	1.14	0.492	353	1608	0.946
Diabetes mellitus	1.13	0.521	400	1561	0.946
Delayed delivery after spontaneous	1.13	0.527	400	1561	0.946
Nausea	0.83	0.532	163	1798	0.946
Hypothyroidism	0.83	0.540	115	1846	0.946
Drugs and alcohol during pregnancy	1.12	0.552	318	1643	0.946
Infections of genitourinary tract in	1.14	0.568	264	1697	0.946

Maternal Phenotype	OR	p-value	Cases	Controls	FDR
Nausea and vomiting	0.85	0.568	170	1791	0.946
Substance related disorders	1.17	0.580	114	1847	0.946
Threatened abortion	0.88	0.591	200	1761	0.946
Hypertension	1.11	0.607	330	1631	0.946
Chest pain	1.17	0.618	111	1850	0.946
Pre-existing hypertension	1.10	0.632	371	1590	0.946
Diabetes mellitus in pregnancy,	1.09	0.635	401	1560	0.946
Other viral infections	0.85	0.637	104	1857	0.946
Acute posthemorrhagic anemia	0.87	0.641	101	1860	0.946
Complications of labor and delivery	0.88	0.651	136	1825	0.946
Other symptoms/disorders or the	0.88	0.654	144	1817	0.946
Bleeding in pregnancy	1.07	0.676	480	1481	0.946
Disorders of thyroid gland	1.11	0.687	149	1812	0.946
Vomiting	0.87	0.697	122	1839	0.946
Obesity	1.07	0.698	599	1362	0.946
Edema, proteinuria and	0.94	0.705	685	1276	0.946
Disorders of menstruation and other	1.12	0.723	112	1849	0.946
Obesity or excessive weight gain in	1.06	0.724	595	1366	0.946
Viral diseases complicating	1.12	0.737	100	1861	0.946
Cervical shortening and	0.94	0.760	257	1704	0.946
Inflammatory diseases of female	1.07	0.782	197	1764	0.946
Essential hypertension	1.06	0.793	300	1661	0.946
Cardiac arrhythmia	1.06	0.794	206	1755	0.946
Reaction to severe stress, and	1.08	0.797	111	1850	0.946
Back pain	0.92	0.805	136	1825	0.946
Hemorrhage in early pregnancy	0.95	0.806	302	1659	0.946
Inflammatory disease of cervix,	0.94	0.821	144	1817	0.946
Vaginitis and vulvovaginitis	0.94	0.823	127	1834	0.946
Infections and carrier state in	0.97	0.826	683	1278	0.946

Maternal Phenotype	OR	p-value	Cases	Controls	FDR
Abnormal forces of labor	1.04	0.835	460	1501	0.946
Gastro-esophageal reflux disease	1.07	0.836	121	1840	0.946
Dysuria	0.94	0.864	105	1856	0.963
Overweight and obesity	1.02	0.890	625	1336	0.963
Excessive vomiting in pregnancy	0.97	0.894	224	1737	0.963
Abnormal glucose complicating	0.97	0.911	273	1688	0.963
Decreased fetal movements,	0.97	0.916	179	1782	0.963
Placenta previa	1.03	0.917	143	1818	0.963
Anxiety disorders	1.03	0.922	123	1838	0.963
Urinary tract infection	0.99	0.955	213	1748	0.972
Abnormal glucose tolerance in	0.99	0.957	299	1662	0.972
Gestational (pregnancy-induced)	0.99	0.964	233	1728	0.972
Preterm labor	1.01	0.972	1217	744	0.972

eTable 3. Data dictionary of the variables included in the database

Field Caption	Explanation	Rules
Multiple gestation	Multiple births	Range: 0, 1, 9; Codes: 0=No, 1=Yes, 9=Unknown
Prenatal Care	Prenatal care	Range: 0, 1, 9; Codes: 0=No, 1=Yes, 9=Unknown
Vaginal Bleeding	Vaginal bleeding prior to delivery	Range: 0, 1; Codes: 0=No, 1=Yes
Chorioamnionitis	Maternal infection diagnosed clinically prior to delivery	Range: 0, 1; Codes: 0=No, 1=Yes
Oligohydramnios	Oligohydramnios diagnosed by ultrasound criteria	Range: 0, 1; Codes: 0=No, 1=Yes
Polyhydramnios	Polyhydramnios diagnosed by ultrasound criteria	Range: 0, 1; Codes: 0=No, 1=Yes
Diabetes (all types)	Included gestational diabetes, type 1 diabetes and type 2 diabetes	Range: 0, 1; Codes: 0=No, 1=Yes
Chronic Hypertension	Maternal chronic hypertension	Range: 0, 1; Codes: 0=No, 1=Yes
Maternal Drug Use	Maternal substance abuse	Range: 0, 1; Codes: 0=No, 1=Yes
Antenatal Steroids	Antenatal steroids	Range: 0, 1, 9; Codes: 0=No, 1=Yes, 9=Unknown
Mode of delivery	Delivery type	Range: 0, 1, 9; Codes: 0=C-section, 1=Vaginal, 9=Unknown
Vertex Presentation	Vertex presentation	Range: 0, 1; Codes: 0=No, 1=Yes
Anesthesia used in labor	Included use of epidural, spinal anesthesia, regional anesthesia or general anesthesia	Range: 0, 1, 2, 3, 4; Codes: 0=None, 1=Epidural, 2=Spinal, 3=Regional, 4=General
Pregnancy induced hypertension	Included pre-eclampsia, HELLP and eclampsia	Range: 0 ,1, 2, 3; Codes: 0=No, 1=Pre-eclampsia, 2=HELLP, 3=Eclampsia
Vaginal bleeding type	Reason for bleeding	Range: 1, 2, ; Codes: 1=Unknown origin, 2= Abruption, 3=Placenta previa
Meconium	Meconium stained amniotic fluid present at the time of delivery	Range: 0, 1; Codes: 0=No, 1=Yes
Mom Age	Mother's age at the time of delivery	Range: Minimum 12, Maximum 50
Gravida	Number of previous pregnancies	Range: Minimum 1, Maximum 20

Field Caption	Explanation	Rules
Reason for Preterm Labor	Included premature labor, preterm premature rupture of membranes, pregnancy induced hypertension, multiple gestation, chorioamnionitis, abruption, incompentent cervix, trauma, maternal diabetes, and medically indicated for maternal or infant heath	Range 1,2,3,4,5,6,7,8,9,10, 99: Code 1=Premature Labor, 2=Preterm Premature Rupture of Membranes, 3=Pregnancy Induced Hypertension, 4=Multiple Gestation, 5=Chorioamionintis, 6=Abruption, 7=Incompentent Cervix, 8=Trauma, 9=Maternal Diabetes, 10= Medically Indicated for Maternal or Infant Heath, 99=Unknown
Rupture of membranes	Number of days the membranes were ruptured prior to delivery	Range: Minimum 0, Maximum 270 days

eTable 4. Sensitivity analysis: Base model with maternal diabetes

Pregnancy Exposures and Complications	BPD (%)	Controls (%)	a*OR	95% CI	p-value
Polyhydramnios, N (%)	23 (2%)	40 (1%)	5.66	2.75-11.64	<0.001

a*OR controlling for diabetes in addition to variables in our base model

eTable 5. Sensitivity analysis: Base model with congenital malformations

Pregnancy Exposures and Complications	BPD (%)	Controls (%)	a*OR	95% CI	p-value
Polyhydramnios, N (%)	23 (2%)	40 (1%)	4.01	1.93-8.33	<0.001

a*OR controlling for congenital malformations in addition to variables in our base model

eTable 6. Sensitivity analysis: Base model with multiple gestation

Pregnancy Exposures and Complications	BPD (%)	Controls (%)	a*OR	Robust Std. Err.	95% CI	p-value
Polyhydramnios, N (%)	23 (2%)	40 (1%)	5.58	2.36	2.44-12.77	<0.001

a*OR controlling for multiple gestation in addition to variables in our base model

eTable 7. Comparison of variables used in both PheWAS and logistic regression from the NICU Registry

Variables	PheWAS						NICU Registry			
	Cases	Controls	OR	*p*-value	FDR	Bonferroni	n	aOR	95% CI	*p*-value
Bleeding in pregnancy	480	1481	1.0729	0.676	0.946	1	754	1.04	0.81-1.34	0.73
Premature separation of placenta	183	1778	1.2769	0.291	0.946	1	489	1.14	0.85 - 1.52	0.38
Preeclampsia and eclampsia	485	1476	0.7629	0.135	0.846	1	1136	1.07	0.85 - 1.34	0.59
Polyhydramnios	130	1831	4.7164	3.4×10^{-9}	3.2×10^{-7}	3.2×10^{-7}	63	5.70	2.78 - 11.44	1.4×10^{-6}
Oligohydramnios	356	1605	1.8325	7.6×10^{-4}	0.018	0.072	198	2.19	1.42 - 3.34	3.3×10^{-4}
Drugs and alcohol during pregnancy	318	1643	1.1219	0.552	0.946	1	1189	0.85	0.68 - 1.05	0.123

eTable 8. Variables known to be associated with increased BPD risk or protective affect in PheWAS group

	All subjects (N=1961)	with BPD (N=531)	without BPD (N=1430)
Birthweight Mean (range)[a]	1546g (340-3960g)	1033g (340-3005g)	1737g (560-3960)
Gestational age	30 weeks (22-33weeks)	27 weeks (22-33weeks)	31 weeks (25-33weeks)

Mean (range)[b]			
Sex	Male: 1069 (54.5%) Female: 892 (45.5%)	Male: 301 (56.7%) Female: 230 (43.3%)	Male: 768 (53.7%) Female: 662 (46.3%)
Birth year (range)	2012 (2005-2017)	2012 (2005-2017)	2012 (2006-2017)
Maternal race/ethnicity[c]	White, non-Hispanic 1133 (57.8%) African-American 457 (23.3%) Hispanic 200 (10.2%) Other 92 (4.7%) Unknown 79 (4.0%)	White, non-Hispanic 306 (57.6%) African-American 122 (23.0%) Hispanic 51 (9.6%) Other 32 (6.0%) Unknown 20 (3.8%)	White, non-Hispanic 827 (57.8%) African-American 335 (23.4%) Hispanic 149 (10.4%) Other 60 (4.2%) Unknown 59 (4.1%)

eFigure 1. Receiver Operating Characteristic (ROC) curve for base model

Area under ROC curve = 0.9162