

On line supplement: Determinants of early life lung function in African infants

Diane Gray MD¹, Lauren Willemse B.Cur¹, Ane Alberts B.Tech¹, Dorottya Czövek MD², Polite Nduru Mphil³, Aneesa Vanker MD¹, Dan J. Stein MD⁴, Nastassja Koen MD⁴, Peter D. Sly MD², Zoltán Hantos PhD⁵, Graham L. Hall PhD^{6#}, Heather J. Zar MD^{1#}

¹Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and MRC Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa;

²Children's Lung, Environment and Asthma Research, Child Health Research Centre, University of Queensland, Brisbane, Australia;

³Division of Epidemiology and Biostatistics, Department of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa;

⁴Department of Psychiatry and MRC Unit on Anxiety and Stress Disorder, University of Cape Town, Cape Town, South Africa;

⁵Department of Medical Physics and Informatics, University of Szeged, Szeged, Hungary;

⁶Telethon Kids Institute, Perth, Australia Centre for Child Health Research, University of Western Australia, School of Physiotherapy and Exercise Science, Faculty of Health Sciences, Curtin University, Perth, Australia;

Table S1 Methodological detail of study measurements

Measurement	Definition	Collected
Birth-weight for gestational age z-score	Z-score calculated using the Fenton New-born growth charts	At birth
Weight and height for age z-scores	Z-scores calculated using the WHO Child Growth Standards. Age corrected for prematurity (<37 weeks)	On day of lung function test (6 week study visit)
Gestational age	Assessed by antenatal ultrasound or combination of last menstrual period, antenatal examination of pubic symphysis fundal height and birth weight, when ultrasound was not available	Antenatal 2 nd trimester ultrasound/examination
Maternal smoking	Urine cotinine: the highest value from two visits used to classify as active smoker (cotinine >500 ng.ml ⁻¹), passive smoker (10-500 ng.ml ⁻¹) or non-smoker (<10 ng.ml ⁻¹). ¹	Antenatal study visit (28-32 weeks gestation) and at birth; using the IMMULITE [®] 1000 Nicotine Metabolite Kit ¹
Household benzene	Categorized as above threshold if benzene >5mcg/m ³ ; based on the 2015 South African National Ambient Air Quality Standards (SANAAQ).	Antenatal home visit using a Markes [®] thermal desorption tube left in the home for two weeks
Socioeconomic status	Composite variable, placing participants into relative quartiles. Score is derived from employment status and standardized scores of: educational attainment, household income, assets and market access. ²	Based on questionnaire information collected at antenatal study visit (28-32 weeks).
Maternal distress	Defined as high risk if WHO endorsed Self Reporting Questionnaire (SRQ) score ≥8.	Antenatal study visit (28-32 wk), SRQ-20 questionnaire. ^{3,4}
Maternal alcohol dependence/high risk	Daily and/or weekly use of alcohol in the preceding 3 months.	Antenatal visit (28-32 wk) Alcohol, Smoking and Substance Test questionnaire. ^{3,4}
Maternal respiratory health	Maternal recurrent respiratory symptoms: chronic cough or recurrent wheeze in previous 12 months, doctor diagnosed asthma, bronchiectasis or chronic obstructive pulmonary disease ever. Low FEV ₁ : < -2 SD predicted using the Global Lung Initiative multi-ethnic equations ⁵	Antenatal study visit (28-32 weeks) and 6 week visit questionnaire
Infant feeding	Exclusive breastfeeding: breast-milk only; Mixed feeding: mixture of breast-milk and infant formulas; No breastfeeding: infant formula only.	6 week study visit questionnaire, questions related to the previous 6-10 weeks feeding practices
HIV status	Mothers: point of care rapid HIV antibody test, positive test confirmed with laboratory based combined antibody and antigen test. Infants of HIV positive mothers: HIV PCR test	Mothers: pregnancy booking and labour Exposed infants: birth and 4 weeks

Table S2: Lung function outcomes

Lung function variable	Median	IQR	CV [#] mean (SD)
Tidal breathing n=649			
Respiratory rate n.min ⁻¹	47	41; 55	8.8 (2.9)
Tidal volume mL	34.2	30.0; 38.6	8.8 (3.4)
t _{PTEF} /t _E * %	38.6	30.2; 46.2	23.0 (9.3)
t _I /t _{TOT} * %	45.2	42.0; 48.8	6.6 (2.4)
t _E /t _{TOT} *%	54.8	51.2; 58.0	5.5 (2.1)
Multiple breath washout n=614			
Functional residual capacity (FRC) mL	74.5	65.5; 86.3	5.8 (3.5)
Lung clearance index n turnovers	7.1	6.9; 7.4	4.3 (2.5)
Forced oscillation technique n=508			
Resistance (R _{rs}) cmH ₂ O.s.L ⁻¹	45.0	37.5; 55.8	6.4 (4.2)
Compliance (C _{RS}) mL.cmH ₂ O ⁻¹	0.88	0.67; 1.14	13.1 (12.4)

[#]Intra-subject coefficient of variation *t_{PTEF}/t_E: time to peak tidal expiratory flow over total expiratory time; t_I/t_{TOT}: inspiratory time over total breath time; t_E/t_{TOT}: expiratory time over total breath time

Table S3: Univariate and multivariate analysis of respiratory rate

	Univariate (n=654)				Multivariate model (n=459)				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev	
Respiratory rate (n.min ⁻¹)							7%	10.94	
Infant growth and lung maturation									
Weight-for-age z score	-1.621	-2.420	-0.822	<0.001	0.347	-0.962	1.656	0.603	
Gestation	-0.653	-1.091	-0.215	0.004	-0.949	-1.596	-0.302	0.004	
Birth weight z score	-1.937	-2.775	-1.099	<0.001	-2.717	-4.120	-1.314	<0.001	
Gender and ethnicity									
Male gender	0.381	-1.424	2.186	0.679	-1.109	-3.190	0.972	0.295	
Ethnicity Black African	2.764	0.974	4.555	0.003	3.580	1.047	6.113	0.006	
Environmental and socioeconomic factors									
Smoking: Non smoker									
Passive	-1.910	-4.288	0.468	0.115	-0.622	-3.294	2.050	0.647	
Active	-0.418	-2.936	2.099	0.744	1.869	-1.307	5.045	0.248	
Benzene	-1.025	-3.072	1.021	0.325	-1.779	-3.832	0.275	0.089	
Social Economic Status: Highest quartile									
Lowest quartile	0.375	-2.121	2.872	0.768					
Low-moderate quartile	1.380	-1.198	3.958	0.294					
Moderate-high quartile	0.058	-2.571	2.687	0.965					
Maternal factors									
Maternal stress	-1.050	-3.302	1.202	0.360					
Feeding choice: Exclusive breastfeeding									
Mixed feeding	-0.116	-2.035	1.803	0.906					
No breastfeeding	0.390	-2.581	3.361	0.797					
Maternal recurrent respiratory symptoms, low FEV ₁	-0.674	-3.381	2.033	0.625					
Maternal HIV infection	0.699	-1.621	3.020	0.554	-0.214	-3.165	2.737	0.887	
Maternal alcohol	-2.692	-7.102	1.718	0.231	-7.199	-12.627	-1.771	0.009	
Previous lower respiratory tract infection	2.698	-1.301	6.697	0.186	2.797	-1.762	7.356	0.229	

Table S4: Univariate and multivariate analysis of tidal volume

Univariate (n=654)				Multivariate model (n=459)				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev
Tidal volume (mL)							33%	5.14
<u>Infant growth and lung maturation</u>								
Weight-for-age z score	2.863	2.487	3.239	<0.001	2.492	1.876	3.109	<0.001
Gestation	0.670	0.438	0.902	<0.001	0.454	0.149	0.759	0.004
Birth weight z score	1.803	1.368	2.239	<0.001	0.492	-0.171	1.155	0.146
<u>Gender and ethnicity</u>								
Male gender	1.323	0.356	2.289	0.007	2.416	1.438	3.395	<0.001
Ethnicity	1.076	0.109	2.043	0.029	-0.804	-2.011	0.403	0.191
<u>Environmental and socioeconomic factors</u>								
Smoking: Non smoker								
Passive	-0.170	-1.446	1.107	0.794	-0.553	-1.811	0.705	0.388
Active	-2.491	-3.842	-1.139	<0.001	-1.549	-3.045	-0.053	0.042
Benzene	0.467	-0.648	1.583	0.411	0.803	-0.168	1.775	0.105
Social Economic Status: highest quartile								
Lowest quartile	-1.059	-2.401	0.283	0.122				
Low-moderate quartile	-0.070	-1.456	1.316	0.921				
Moderate-high quartile	0.171	-1.242	1.584	0.812				
<u>Maternal factors</u>								
Maternal stress	-0.599	-1.800	0.603	0.328				
Feeding choice: Exclusive breastfeeding								
Mixed feeding	0.577	-0.452	1.606	0.271	0.747	-0.279	1.773	0.153
No breastfeeding	1.746	0.153	3.339	0.032	1.499	-0.351	3.349	0.112
Maternal recurrent respiratory symptoms, low FEV ₁	0.256	-1.201	1.713	0.731				
Maternal HIV infection	1.686	0.442	2.929	0.008	1.679	0.059	3.300	0.042
Maternal alcohol	-1.118	-3.472	1.237	0.352	2.955	0.403	5.506	0.023
Previous lower respiratory tract infection	-2.033	-4.182	0.117	0.064	-1.025	-3.170	1.120	0.348

Table S5: Univariate and multivariate analysis of the ratio of time to peak tidal expiratory flow over total expiratory time (tPTEF/tE)

	Univariate (n=654)				Multivariate model (n=459)				Adj R ²	Residual Std Dev
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev		
tPTEF/tE (%)							10%	11.87		
<u>Infant growth and lung maturation</u>										
Weight-for-age z score	0.023	-0.833	0.880	0.957	-0.913	-2.327	0.500	0.205		
Gestation	0.379	-0.087	0.845	0.111	0.287	-0.412	0.987	0.420		
Birth weight z score	-0.021	-0.922	0.880	0.964	0.602	-0.920	2.123	0.437		
<u>Gender and ethnicity</u>										
Male gender	-2.750	-4.650	-0.850	0.005	-3.196	-5.440	-0.952	0.005		
Ethnicity	3.971	2.087	5.854	<0.001	4.414	1.648	7.179	0.002		
<u>Environmental and socioeconomic factors</u>										
Smoking: Non smoker										
Passive	-2.014	-4.543	0.514	0.118	-0.127	-3.012	2.758	0.931		
Active	-3.139	-5.815	-0.462	0.022	-0.036	-3.465	3.393	0.984		
Benzene	-1.706	-3.893	0.482	0.126	-2.931	-5.158	-0.704	0.010		
Social Economic Status: highest quartile										
Lowest quartile	0.764	-1.881	3.410	0.571						
Low-moderate quartile	-0.364	-3.095	2.367	0.794						
Moderate-high quartile	0.399	-2.387	3.184	0.779						
<u>Maternal factors</u>										
Maternal stress	0.774	-1.629	3.177	0.527						
Feeding choice: Exclusive breastfeeding										
Mixed feeding	-2.322	-4.333	-0.311	0.024	-2.192	-4.544	0.160	0.068		
No breastfeeding	3.018	-0.096	6.132	0.057	1.086	-3.158	5.330	0.615		
Maternal recurrent respiratory symptoms, low FEV ₁	-2.419	-5.278	0.441	0.097	-2.422	-5.816	0.973	0.162		
Maternal HIV infection	3.218	0.773	5.664	0.010	-1.503	-5.232	2.225	0.429		
Maternal alcohol	-6.201	-10.879	-1.523	0.009	-8.485	-14.359	-2.612	0.005		
Previous lower respiratory tract infection	-3.984	-8.211	0.243	0.065	-1.647	-6.569	3.275	0.511		

Table S6: Univariate and multivariate analysis of the ratio of inspiratory time over total breath time (t_i/t_{TOT})

	Univariate (n=654)				Multivariate model (n=457)				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev	
t _i /t _{TOT} (%)							3%	4.60	
Infant growth and lung maturation									
Weight-for-age z score	-0.245	-0.575 0.085	0.145	-0.016	-0.564 0.531	0.954			
Gestation	-0.150	-0.329 0.029	0.100	-0.086	-0.357 0.184	0.532			
Birth weight z score	-0.293	-0.636 0.051	0.095	-0.351	-0.938 0.237	0.241			
Gender and ethnicity									
Male gender	-0.436	-1.167 0.295	0.242	-0.542	-1.412 0.329	0.222			
Ethnicity	1.697	0.977 2.416	<0.001	1.275	0.203 2.348	0.020			
Environmental and socioeconomic factors									
Smoking: Non smoker									
	Passive	-0.437	-1.392 0.517	0.369	-0.106	-1.224 1.012	0.852		
	Active	-0.852	-1.863 0.159	0.098	-0.260	-1.589 1.069	0.701		
Benzene		0.049	-0.778 0.875	0.908	-0.213	-1.072 0.647	0.627		
Social Economic Status: highest quartile									
	Lowest quartile	0.356	-0.651 1.364	0.488					
	Low-moderate quartile	0.045	-1.001 1.091	0.933					
	Moderate-high quartile	0.587	-0.478 1.653	0.279					
Maternal factors									
Maternal stress		-0.634	-1.561 0.294	0.180					
Feeding choice: Exclusive									
	Mixed feeding	-0.089	-0.866 0.687	0.822					
	None	0.090	-1.126 1.306	0.885					
Maternal recurrent respiratory symptoms, low FEV ₁	-0.540	-1.640 0.560	0.336						
Maternal HIV infection	0.434	-0.507 1.374	0.366	-0.389	-1.623 0.846	0.537			
Maternal alcohol	-0.565	-2.348 1.218	0.534	-1.499	-3.770 0.773	0.195			
Previous lower respiratory tract infection	0.167	-1.462 1.796	0.841	0.964	-0.943 2.872	0.321			

Table S7: Univariate (n=654) and multivariate (n=459) analysis of the ratio of expiratory time over total breath time (t_E/t_{TOT})

	Univariate (n=654)				Multivariate (n=459) model				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev	
t_E/t_{TOT} (%)							3%	4.620	
<u>Infant growth and lung maturation</u>									
Weight-for-age z score	0.245	-0.085 0.575	0.145	0.016	-0.531 0.564	0.954			
Gestation	0.150	-0.029 0.329	0.100	0.086	-0.184 0.357	0.532			
Birth weight z score	0.293	-0.051 0.636	0.095	0.351	-0.237 0.938	0.241			
<u>Gender and ethnicity</u>									
Male gender	0.436	-0.295 1.167	0.242	0.542	-0.329 1.412	0.222			
Ethnicity	-1.697	-2.416 -0.977	<0.001	-1.275	-2.348 -0.203	0.020			
<u>Environment and socioeconomic factors</u>									
Smoking: Non smoker									
	Passive	0.437	-0.517 1.392	0.369	0.106	-1.012 1.224	0.852		
	Active	0.852	-0.159 1.863	0.098	0.260	-1.069 1.589	0.701		
Benzene		-0.049	-0.875 0.778	0.908	0.213	-0.647 1.072	0.627		
Social Economic Status: highest quartile 4									
	Lowest quartile	-0.356	-1.364 0.651	0.488					
	Low-moderate quartile	-0.045	-1.091 1.001	0.933					
	Moderate-high quartile	-0.587	-1.653 0.478	0.279					
<u>Maternal factors</u>									
Maternal stress		0.634	-0.294 1.561	0.180					
Feeding choice: Exclusive									
	Mixed feeding	0.089	-0.687 0.866	0.822					
	None	-0.090	-1.306 1.126	0.885					
Maternal recurrent respiratory symptoms, low FEV ₁	0.540	-0.560 1.640	0.336						
Maternal HIV infection	-0.434	-1.374 0.507	0.366	0.389	-0.846 1.623	0.537			
Maternal alcohol	0.565	-1.218 2.348	0.534	1.499	-0.773 3.770	0.195			
Previous lower respiratory tract infection	-0.167	-1.796 1.462	0.841	-0.964	-2.872 0.943	0.321			

Table S8: Univariate and multivariate (n=435) analysis of the functional residual capacity (FRC)

Univariate (n=563)				Multivariate model (n=435)				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev
FRC (mL)							10%	15.90
<u>Infant growth and lung maturation</u>								
Weight-for-age z score	3.645	2.526	4.765	<0.001	0.228	-1.731	2.187	0.819
Gestation	1.205	0.593	1.817	<0.001	1.308	0.350	2.266	0.008
Birth weight z score	2.981	1.802	4.160	<0.001	3.965	1.839	6.091	<0.001
<u>Gender and ethnicity</u>								
Male gender	-2.338	-4.880	0.205	0.071	-0.194	-3.323	2.936	0.903
Ethnicity	2.710	0.173	5.248	0.036	2.764	-1.214	6.742	0.173
<u>Environmental and socioeconomic factors</u>								
Smoking: Non smoker								
Passive	-1.987	-5.355	1.381	0.247	-1.995	-6.037	2.046	0.332
Active	-4.676	-8.228	-1.124	0.010	-2.684	-7.521	2.154	0.276
Benzene	-0.517	-3.516	2.482	0.735	-0.436	-3.517	2.645	0.781
Social Economic Status: highest quartile								
Lowest quartile	-3.658	-7.177	-0.138	0.042	-2.540	-7.138	2.057	0.278
Low-moderate quartile	-2.770	-6.401	0.861	0.135	-0.696	-5.169	3.777	0.760
Moderate-high quartile	-3.726	-7.420	-0.031	0.048	-2.925	-7.403	1.553	0.200
<u>Maternal factors</u>								
Maternal stress	-1.365	-4.571	1.841	0.403				
Feeding choice: Exclusive								
Mixed feeding	-0.027	-2.736	2.681	0.984				
None	2.736	-1.435	6.907	0.198				
Maternal recurrent respiratory symptoms, low FEV ₁	0.670	-3.144	4.484	0.730				
Maternal HIV infection	2.415	-0.833	5.663	0.145	0.556	-3.850	4.962	0.804
Maternal alcohol	1.012	-5.345	7.369	0.755	5.298	-2.869	13.466	0.203
Previous lower respiratory tract infection	-3.207	-8.867	2.453	0.266	0.269	-6.674	7.212	0.939

Table S9: Univariate and multivariate analysis of the lung clearance index (LCI)

Univariate (n=563)				Multivariate model (n=435)				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev
LCI (n FRC turnovers)							4%	0.44
<u>Infant growth and lung function</u>								
Weight-for-age z score	-0.012	-0.044	0.020	0.456	-0.015	-0.069	0.039	0.585
Gestation	-0.007	-0.024	0.010	0.404	0.006	-0.021	0.032	0.667
Birth weight z score	0.006	-0.027	0.039	0.739	0.013	-0.045	0.071	0.664
<u>Gender and ethnicity</u>								
Male gender	0.035	-0.035	0.105	0.324	0.069	-0.016	0.154	0.111
Ethnicity	0.007	-0.062	0.077	0.837	0.085	-0.020	0.189	0.114
<u>Environmental and socioeconomic factors</u>								
Smoking: Non smoker								
Passive	0.060	-0.031	0.151	0.196	0.057	-0.052	0.166	0.304
Active	0.113	0.017	0.209	0.021	0.139	0.011	0.268	0.034
Benzene	0.071	-0.011	0.152	0.088	0.054	-0.031	0.138	0.213
Social Economic Status: Highest quartile								
Lowest quartile	0.000	-0.097	0.096	0.996				
Low-moderate quartile	0.035	-0.065	0.135	0.491				
Moderate-high quartile	0.029	-0.073	0.130	0.579				
<u>Maternal factors</u>								
Maternal stress	0.057	-0.030	0.145	0.198				
Feeding choice: Exclusive breastfeeding								
Mixed feeding	-0.023	-0.097	0.051	0.540				
No breastfeeding	-0.012	-0.126	0.103	0.840				
Maternal recurrent respiratory symptoms, low FEV ₁	0.011	-0.093	0.116	0.832				
Maternal HIV infection	-0.005	-0.094	0.084	0.908	-0.031	-0.151	0.090	0.614
Maternal alcohol	-0.093	-0.266	0.080	0.290	-0.222	-0.446	0.002	0.052
Previous lower respiratory tract infection	0.105	-0.050	0.260	0.182	0.120	-0.070	0.310	0.214

Table S10: Univariate and multivariate analysis of resistance (R_{RS})

Univariate (n=568)				Multivariate model (n=393)				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev
R_{RS} cmH₂O.L.s⁻¹							4%	15.33
<u>Infant growth and lung maturation</u>								
Weight-for-age z score	0.077	-1.059	1.212	0.895	0.858	-1.115	2.832	0.393
Gestation	-0.391	-1.021	0.239	0.224	-0.778	-1.787	0.231	0.130
Birth weight z score	-0.778	-1.964	0.407	0.198	-1.537	-3.644	0.571	0.152
<u>Gender and ethnicity</u>								
Male gender	3.491	0.963	6.020	0.007	4.137	1.005	7.270	0.010
Ethnicity	-0.820	-3.368	1.728	0.528	-0.952	-4.821	2.918	0.629
<u>Environmental and socioeconomic factors</u>								
Smoking: Non smoker								
Passive	0.583	-2.847	4.012	0.739	-1.549	-5.626	2.528	0.456
Active	-0.372	-3.971	3.227	0.839	-4.716	-9.533	0.100	0.055
Benzene	-0.019	-3.013	2.976	0.990	0.412	-2.676	3.500	0.793
Social Economic Status: highest quartile								
Lowest quartile	0.175	-3.342	3.692	0.922				
Low-moderate quartile	-1.444	-5.063	2.175	0.434				
Moderate-high quartile	-0.033	-3.757	3.690	0.986				
<u>Maternal factors</u>								
Maternal stress	-0.592	-3.748	2.564	0.713				
Feeding choice: Exclusive breastfeeding								
Mixed feeding	-2.151	-4.833	0.532	0.116				
No breastfeeding	-2.731	-7.111	1.649	0.221				
Maternal recurrent respiratory symptoms, low FEV ₁	3.117	-0.652	6.886	0.105				
Maternal HIV infection	-1.853	-5.125	1.420	0.267	-1.356	-5.833	3.121	0.552
Maternal alcohol	0.300	-5.825	6.424	0.923	2.098	-5.710	9.905	0.598
Previous lower respiratory tract infection	1.211	-4.873	7.295	0.696	-3.459	-10.992	4.075	0.367

Table S11: Univariate and multivariate analysis of tidal compliance (C_{rs})

	Univariate (n=568)				Multivariate model (n=393)				
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value	Adj R ²	Residual Std Dev	
C _{rs} (mL.cmH ₂ O ⁻¹)							4%	0.42	
<u>Infant growth and lung maturation</u>									
Weight-for-age z score	0.037	0.008	0.066	0.014	-0.0254	-0.0791	0.0282	0.352	
Gestation	0.029	0.013	0.046	<0.001	0.0332	0.0058	0.0605	0.017	
Birth weight z score	0.033	0.002	0.064	0.037	0.0620	0.0047	0.1194	0.034	
<u>Gender and ethnicity</u>									
Male gender	-0.101	-0.166	-0.036	0.003	-0.1162	-0.2018	-0.0305	0.008	
Ethnicity	0.046	-0.020	0.112	0.169	-0.0258	-0.1361	0.0844	0.645	
<u>Environmental and socioeconomic factor</u>									
Smoking: Non smoker									
Passive	-0.030	-0.119	0.059	0.504	0.0108	-0.1024	0.1240	0.852	
Active	-0.117	-0.210	-0.024	0.014	-0.0692	-0.2037	0.0653	0.312	
Benzene	0.076	-0.004	0.156	0.063	0.0679	-0.0163	0.1522	0.114	
Social Economic Status: Highest quartile									
Lowest quartile	-0.092	-0.182	-0.001	0.048	-0.0727	-0.2002	0.0547	0.263	
Low-moderate quartile	-0.049	-0.143	0.044	0.298	-0.0344	-0.1545	0.0857	0.574	
Moderate-high quartile	-0.005	-0.101	0.091	0.918	0.0310	-0.0924	0.1543	0.622	
<u>Maternal factors</u>									
Maternal stress	-0.026	-0.108	0.056	0.534					
Feeding choice: Exclusive breastfeeding									
Mixed feeding	-0.002	-0.072	0.067	0.948					
No breastfeeding	0.074	-0.040	0.187	0.204					
Maternal recurrent respiratory symptoms, low FEV ₁	-0.022	-0.120	0.075	0.651					
Maternal HIV infection	0.054	-0.031	0.138	0.213	0.0570	-0.0650	0.1790	0.359	
Maternal alcohol	-0.096	-0.255	0.063	0.235	-0.0834	-0.2955	0.1286	0.440	
Previous lower respiratory tract infection	-0.212	-0.369	-0.056	0.008	-0.0951	-0.3001	0.1099	0.362	

References:

- 1 Siemens. Immulite 1000 Nicotine Metabolite. UK, 2009.
- 2 Myer L, Stein DJ, Grimsrud A, Seedat S, Williams DR. Social determinants of psychological distress in a nationally-representative sample of South African adults. *Soc Sci Med*. 2008; **66**: 1828-40.
- 3 Stein DJ, Koen N, Donald KA, Adnams CM, Koopowitz S, Lund C, Marais A, Myers B, Roos A, Sorsdahl K, Stern M, Tomlinson M, van der Westhuizen C, Vythilingum B, Myer L, Barnett W, Brittain K, Zar HJ. Investigating the psychosocial determinants of child health in Africa: The Drakenstein Child Health Study. *Journal of neuroscience methods*. 2015.
- 4 Harpham T, Reichenheim M, Oser R, Thomas E, Hamid N, Jaswal S, Ludermir A, Aidoo M. Measuring mental health in a cost-effective manner. *Health policy and planning*. 2003; **18**: 344-9.
- 5 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, Initiative ERSGLF. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012; **40**: 1324-43.

FIGURE S1: Directed acyclic graph constructed to select minimum set of adjustment variables

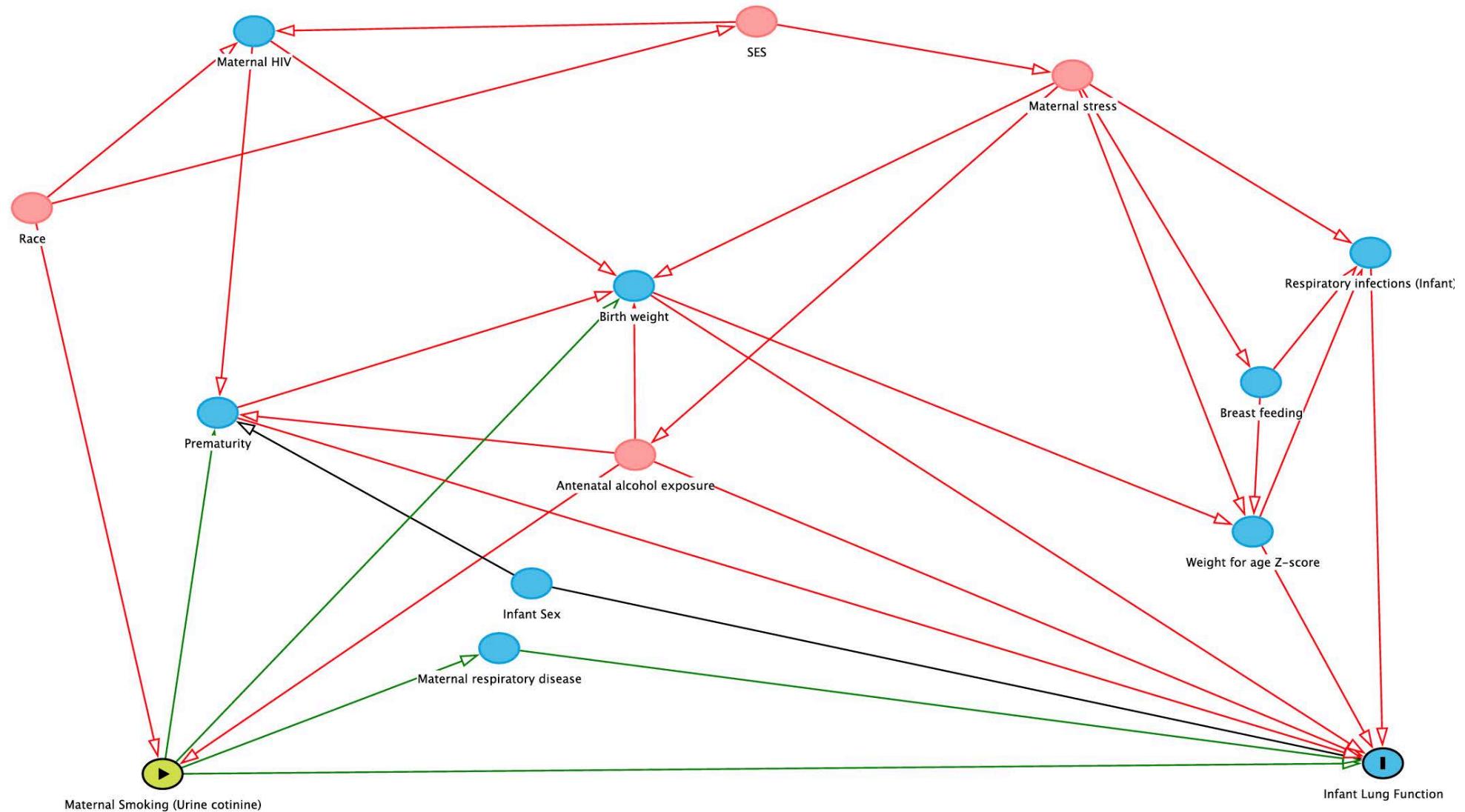


FIGURE S2: Household benzene exposure and ratio of time to peak tidal expiratory flow over total expiratory time, t_{PTEF}/t_E ,

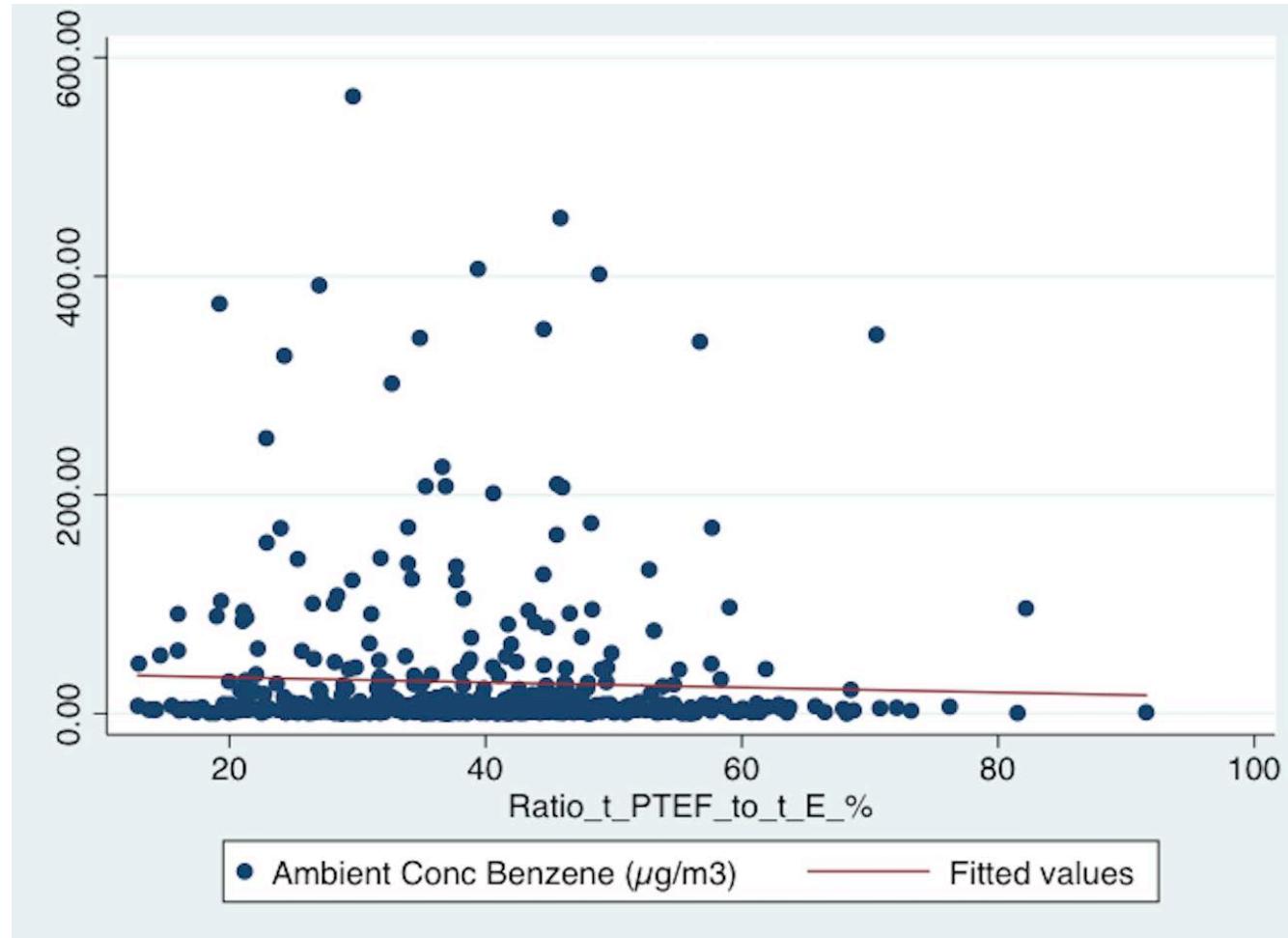


FIGURE S3: Alcohol exposure and tidal volume (top left), respiratory rate (top right) and ratio of time to peak tidal expiratory flow over total expiratory time, tPTEF/TE, (bottom)

