

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 ^R 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 ^R 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
<u>Infant growth and lung maturation</u>										
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		
<u>Gender and ethnicity</u>										
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		
<u>Environmental and socioeconomic factors</u>										
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					
<u>Maternal factors</u>										
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 FEV₁		-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	
<u>Previous lower respiratory tract infection</u>		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 FEV₁		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	
<u>Previous lower respiratory tract infection</u>		-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)					
	Coefficient	95% CI		p-value	Coefficient	95% CI		p-value	Adj R ²	Residual Std Dev
t _{PTEF} /t _E (%)									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		
<u>Previous lower respiratory tract infection</u>	-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
<u>Infant growth and lung maturation</u>										
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		
<u>Gender and ethnicity</u>										
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		
<u>Environmental and socioeconomic factors</u>										
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					
<u>Maternal factors</u>										
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 FEV₁		-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		
<u>Previous lower respiratory tract infection</u>		-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		
<u>Previous lower respiratory tract infection</u>	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	
<u>Previous lower respiratory tract infection</u>	-0.212	-0.369	-0.056	0.008	-0.0951	-0.3001	0.1099	0.362	

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

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

LEGEND 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, t_{PTEF}/t_E , (bottom)

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, Ludermit 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



